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REVIEW ARTICLE: SYNTHESIS, CHARACTERISATION AND INVITRO ANTI- MICROBIAL SCREENING OF NOVEL SCHIFF BASES

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ABSTRACT

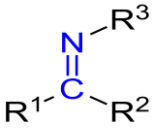
A literature Survey of hydrazide Schiff bases showed that the Schiff bases were reported as more potent Anti-Microbial agent. The aim of work is to Synthesize new hydrazide Schiff bases and evaluate Anti-Bacterial activity. The derivatives are synthesized by equimolar quantities of ethyl-4-bromo benzoate, hydrazine hydrate and the resultant mixture is reacts with aldehyde leads to the formation of Schiff Bases. The substitute Schiff base moieties are previously different biological activities. Here we have synthesised some novel Schiff bases. The characterization and structural elucidation of these novel Compounds were carried by using spectral techniques like IR. The anti-Microbial Screening results presented in all the synthesised hydrazide Schiff bases exhibited significant anti-bacterial activity against the microbial Strains. All the synthesised Compounds were active against all tested micro organisms with a range of minimum inhibitory concentration (MIC) values. The results from anti bacterial screening clearly indicated that the compounds synthesised have shown good anti-bacterial activity with the standard drugs.

INTRODUCTION

Schiff bases are formed typically by the condensation of a primary amine and an aldehydes/ketones. The resultant compound, R1R2C=NR3 is called a Schiff base, where R1

is an aryl group, R2 is a hydrogen atom and R3 is either an alkyl or aryl group. However usually compounds where R3 is an alkyl or aromatic group are also regarded as Schiff bases. Schiff bases that contain aryl substituents are substantially more stable and readily synthesised, while those which contain alkyl substituents are relatively unstable. Schiff bases of aliphatic aldehyde are relatively unstable and readily polymerizable, While those of aromatic aldehyde have effective conjugation are more stable.

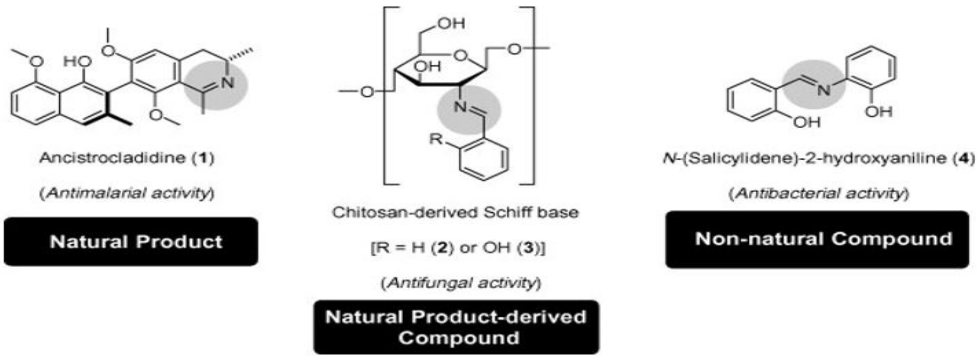
Schiff bases, named after Hugo Schiff are formed when any primary amine reacts with aldehyde or a ketone under specific conditions. Structurally, a Schiff base is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (c=o) has been replaced by an imines or azomethine group.



R^1, R^2 and R^3=aryl or alkyl group

General structure of schiff bases

Schiff bases are some of the most widely used organic compounds. They are used as pigments and dyes, catalyst, intermediates in organic synthesis and as polymer stabilisers. Schiff bases have also been shown to exhibit a broad range of biological activities, including anti fungal, anti bacterial, anti malarial, anti proliferative, anti inflammatory, anti viral and anti pyretic properties. Imine or azomethine groups are present in various natural, natural derived, and non-natural compounds and has been shown to be critical to their biological activities.



Classification of Schiff bases

The Schiff bases have more than two positions through which covalent or coordinate linkage can be established with the metal ion. These molecules which have two and three sites for chelation are called bi and tridentate ligands respectively. The Schiff bases may be classified on the basis of the type and the functional groups which is present in the molecules.

For example, the bidentate ligands are divided into three classes

a) Those containing two acidic groups.
b) Those containing one acidic and one basic groups like -COOH and NH2.

Schiff bases and their complexes with metals are classified on the basis of donor atoms present in the ligands. Thus there are large numbers of organic and inorganic ligands containing donor atoms like O,N & S etc.

Synthesis of schiff bases

The first preparation of imines was reported in the 19th century by Schiff (1864). Since then a variety of methods for the synthesis of imines have been described. The classical synthesis reported by Schiff involves the condensation of a carbonyl compound with an amine under azeotropic distillation. Molecular sieves are then used to completely remove water formed in the system.

Biological activity of schiff bases

Anti-malarial activity

Malaria is a neglected disease that still causes serious public health problems. Schiff bases have been shown to be interesting moieties for the design of antimalarial agents. Ancistroclandidine is a secondary metabolite produced by plants from the families Ancistrocladaceae and Dionophyllaceae that present an imine group in its. The minimum inhibitory concentrations (MIC values) of ancistrocladidine necessary to completely abolish P.Falciparum K1 and 3D7 growth were 0.3 and 1.9 µg/ml, respectively.

Anti-bacterial activity

The development of new antibacterial agents with novel and more efficient mechanisms of action is definitely an urgent medical need. The Schiff bases presented MIC values in the range of 1.6-5.7 µg/ml against Escherichia coli, while the MIC value for kanamycin was 3.9 µg/ml. Isatin-derived Schiff bases have also been reported to possess antibacterial activity. The isoniazid-derived Schiff base was against M.Tuberculosis H37Rv, exhibiting an MIC

value of 0.03mg/l. Schiff bases with a 2,4-dichloro-5-flourophenyl moiety are also effective in the inhibition of bacterial growth.

Anti-fungal activity

The search and development of more effective antifungal agents are mandatory, and some Schiff bases are known to be promising antifungal agents. Schiff bases with a 2,4-dichloro-5-flourophenyl moiety have been demonstrated to inhibit the growth of fungi of clinical interest, such as Aspergillus fumigatus, Aspergillus flavus, Trichophyton mentagrophytes and penicillium marneffei. The MIC values for these compounds were in the range of 6.3-12.5 µg/ml, indicating that they are potent as the reference fluconazole.

Anti-viral activity

Although there are many therapeutic options for viral infections, currently available antiviral agents are not yet fully effective, probably due to the high rate of virus mutation. They may also present any of a number of side effects. Salicylaldehyde Schiff bases of 1-amino-3-hydroguanidine tosylate are a good platform for the design of new antiviral agents. In fact, from a set different 1-amino-3-hydroxyguanidine tosylate derived Schiff bases, compound shown to be very effective against mouse hepatitis virus (MHV), inhibiting its growth by 50% when employed at concentrations as low as 3.2µm.

Biological importance of schiff bases

Many biological important Schiff bases have been reported in the literature possessing antimicrobial, antibacterial, anti-inflammatory, anticonvulsant, antitumor and anti HIV activities. Another important role of Schiff base structure is in transamination. Schiff base formation is also involved in the chemistry of vision, where the reaction occurs between the aldehyde function of 11-cis-retinal and amino group of the protein (opsin).

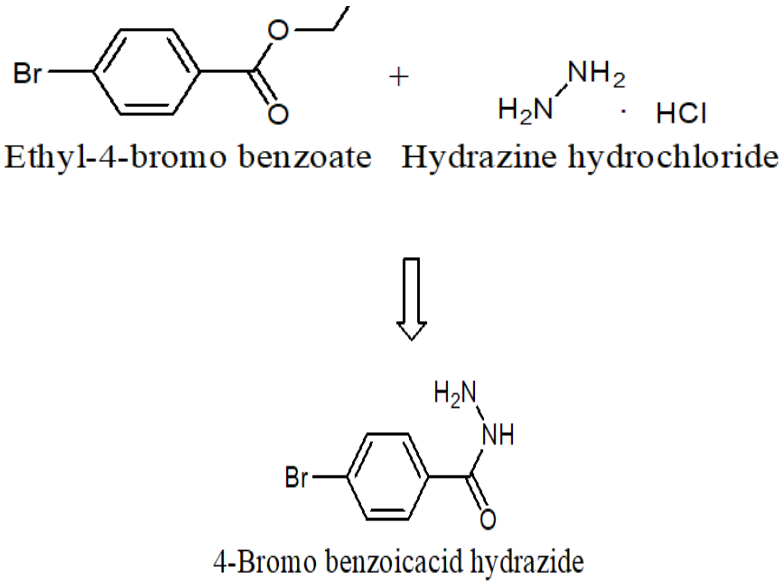
Uses of schiff bases

Schiff bases are tremendously used in different fields such as agriculture, industries, pharmaceuticals, medicine and so on. Schiff bases are extremely useful in analytical methods, such as condensation reaction of amines and aldehyde or ketones compounds in which the azomethine linkage is formed. Usefulness of Schiff base compounds in biological, analytical and industrial application of their complexes makes additional investigations in this part highly beneficial.

Experimental work

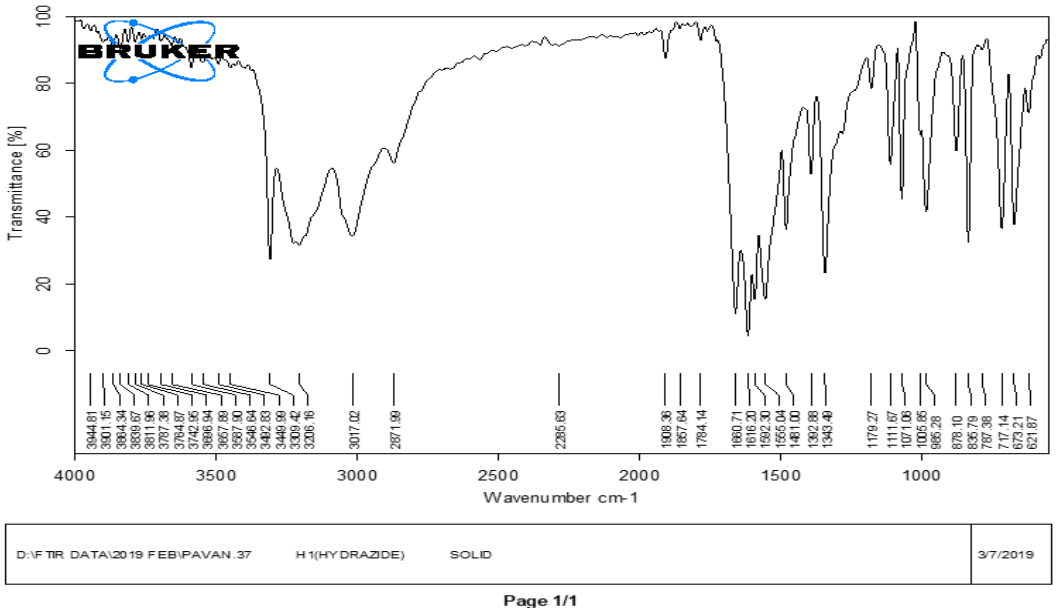
Synthesis of ethyl-4-bromo benzoate

General procedure: The synthetic strategy leading to the target compounds are illustrated in scheme 1. The derivatives are synthesized by equimolar quantities of Ethyl-4-bromo benzoate (0.001 mol), hydrazine hydrate (0.001 mol) in 30 ml of ethanol and refluxed on sand bath for 8 hrs and cool the mixture at room temperature. Filter and vacuum dry the residue.



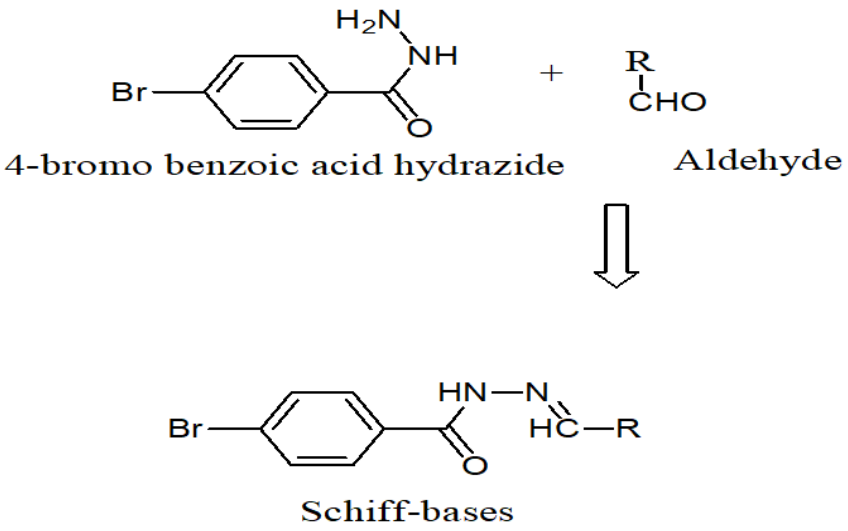
Scheme- 1.

IR of 4- bromo benzoicacid hydrazide



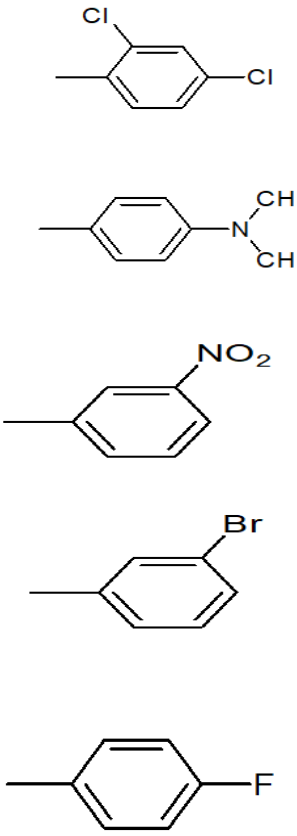
Synthesis of schiff bases

A mixture of equimolar quantities of Ethyl-4-bromo benzoate (0.001 mol) and aldehyde (4-Nitro benzaldehyde, 2,4-Dichloro benzaldehyde,4-Dimethyl amino benzaldehyde, 3-Nitro benzaldehyde, 3-Bromo benzaldehyde, 3,4,5-Tri methoxy benzaldehyde, 4-Hydroxy benzaldehyde, 4-FLouro benzaldehyde, 4-Methoxy benzaldehyde, 3-Ethoxy-4-hydroxy benzaldehyde) in 15ml of ethanol were refluxed for 3 hrs and cooled the mixture at room temperature. Filter and vacuum dried.

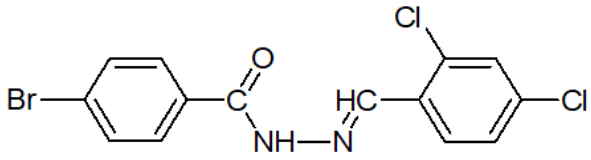


Scheme- 2.

R=



BBAH-1



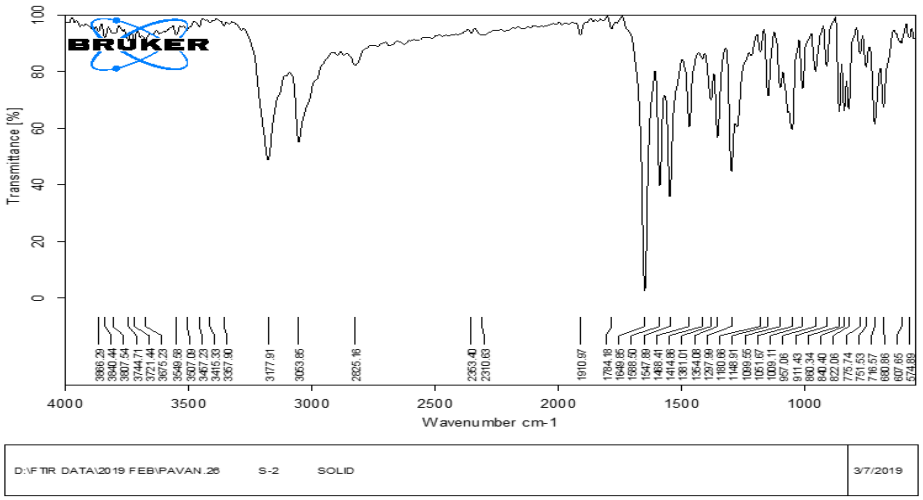
4-Bromo-benzoic acid (2,4-dichloro-benzylidene)-hydrazide

M.P(°C)	112˚C
Molecular weight	370gm/mol
Molecular formula	$C_{14}H_8ON_2BrCl_2$
%yield	97%

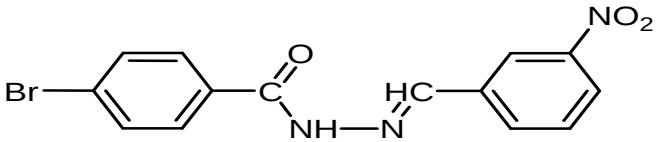
IR (KBr):

Functional group	Absorption maximum (cm^{-1})
N-H	3177.91
C-H	2825.16
C=C	1649.85
C=N	1354.08
Ar-Cl	716.57
Ar-Br	680.86

IR of 4-Bromo-benzoic acid (2, 4-dichloro-benzylidene)-hydrazide



BBAH-2



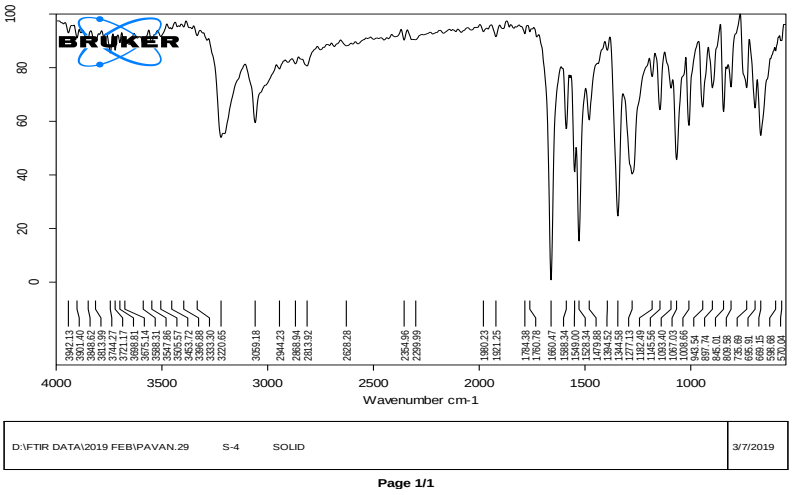
4-Bromo-benzoic acid (3-nitro-benzylidene)-hydrazide

M.P(ºC)	**111˚C**
Molecular weight	346gm/mol
Molecular formula	$C_{14}H_8O_3N_3Br$
%yield	92%

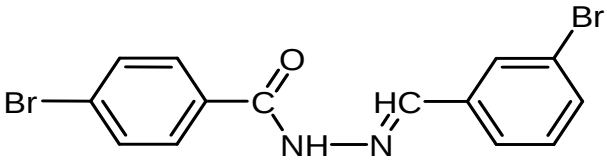
IR (KBr):

Functional group	Absorption maximum (cm^{-1})
N-H	3220.65
C-H	2813.92
C=O(Amide)	1660.47
Ar- NO_2	1528.34
C=N	1344.58
Ar-Br	669.15

IR of 4-Bromo-benzoic acid (3-Nitro-benzylidene)-hydrazide



BBAH-3.

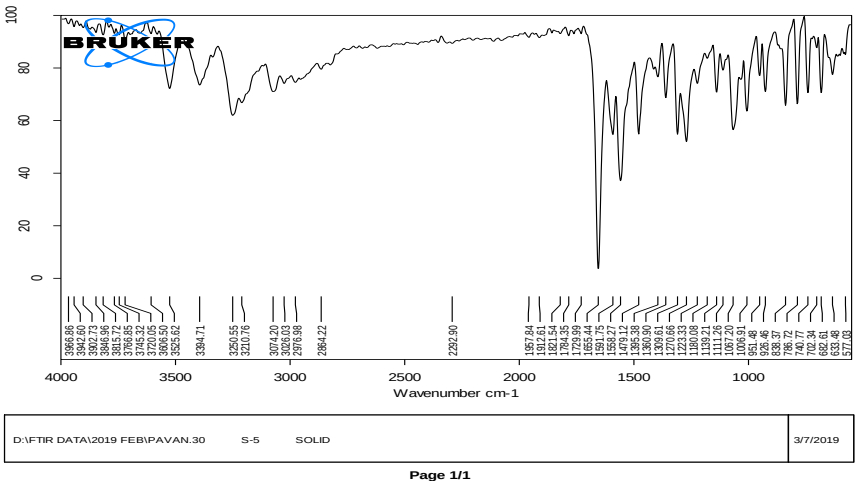


4-Bromo-benzoic acid (3-bromo-benzylidene)-hydrazide

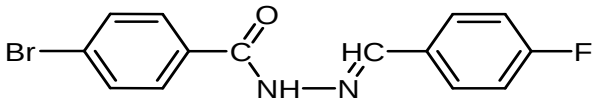
IR (KBr):

Functional group	Absorption maximum (cm^{-1})
N-H	3250.55
C-H	2976.98
C=O(Amide)	1655.44
C=C	1558.27
C=N	1309.67
Ar-Br	633.48

IR of 4-Bromo-benzoic acid (3-Bromo-benzylidene)-hydrazide.



BBAH-4



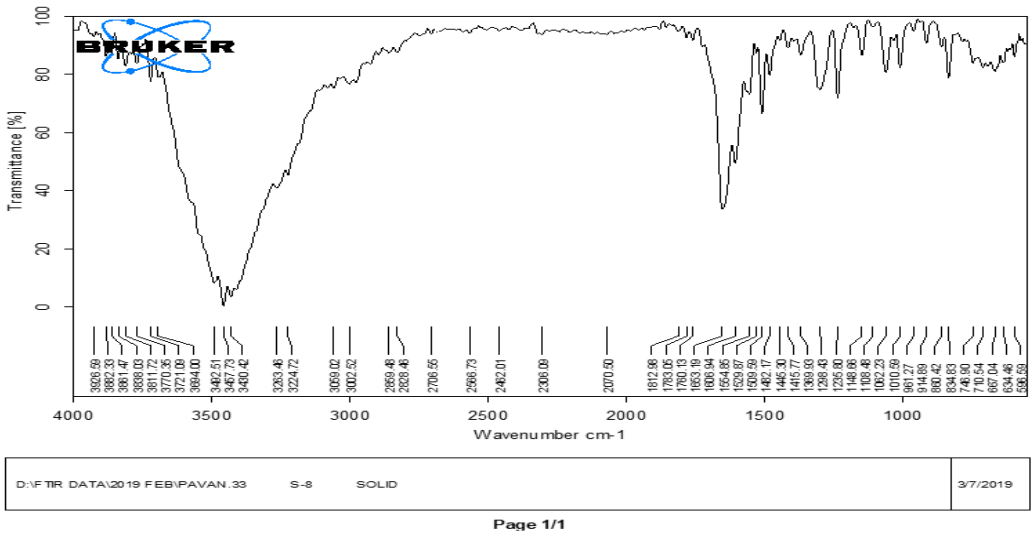
4-Bromo-benzoic acid (4-fluoro-benzylidene)-hydrazide

M.P(ºC)	100.5ºC
Molecular weight	319
Molecular formula	$C_{14}H_8ON_2BrF$
%yield	92%

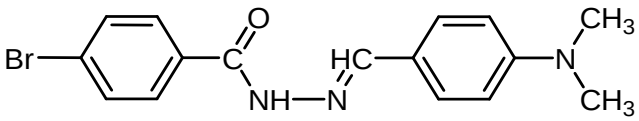
IR (KBr):

Functional group	Absorption maximum (cm^{-1})
N-H	3263.46
C=O(Amide)	1653.19
C=N	1482.17
Ar-F	1010.59
Ar-Br	667.04

IR of 4-Bromo-benzoic acid (4-Flouro-benzylidene)-hydrazide.



BBAH-5



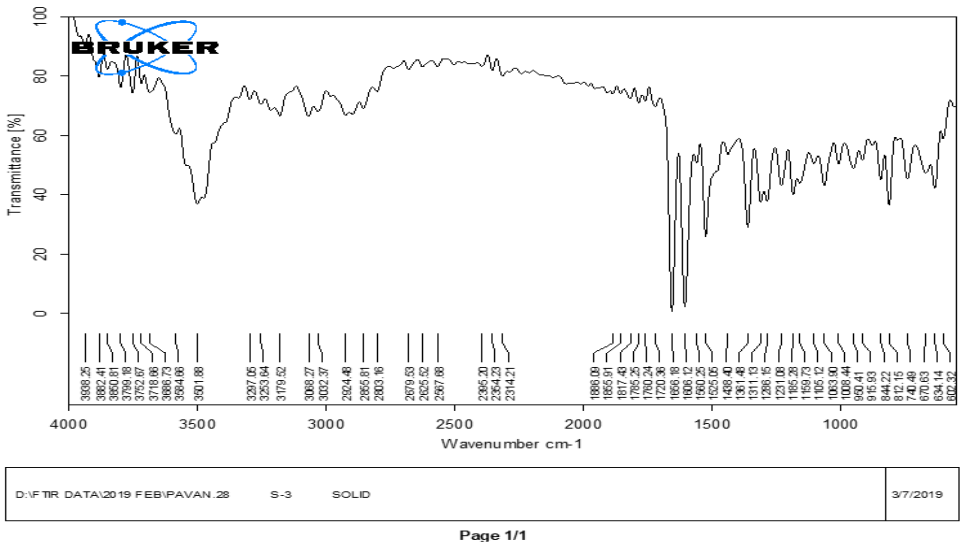
4-Bromo-benzoic acid (4-dimethylamino-benzylidene)-hydrazide

M.P(ºC)	100˚C
Molecular weight	344 gm/mol
Molecular formula	$C_{16}H_{14}ON_3Br$
%yield	91%

IR (KBr):

Functional group	Absorption maximum (cm^{-1})
N-H	3179.52
C=O	1656.18
C=C	1606.12
C=N	1361.48
Ar-NH_3	1311.13
Ar-Br	634.14

IR of 4-Bromo-benzoic acid (4-dimethylamino-benzylidene)-hydrazide



Biological evoluation

Based on literature review, the Novel Hydrazide Schiff bases posses anti bacterial activity. So present work is to test the synthesized compounds for their anti bacterial activity.

Anti-bacterial studies

The anti-bacterial activity was tested by cup-plate method. The anti-microbial activity of hydrazide Schiff bases were tested and compared with the standard (Amoxicillin) Solution at concentration of 100 µg/ml. Dimethyl sulfoxide (DMSO) was used as a solvent and control.

Organism

Gram positive bacteria: Staphylococcus aureus

Gram negative bacteria: Escherichia Coli

Experimental procedure

The test organisms were sub cultured using nutrient agar medium. The tubes containing sterilized medium were inoculated with the respective bacterial strain. After inoculation at $37^0C \pm 1^0C$ for 18 hours, they were stored in a refrigerator.

Nutrient agar was dissolved and distributed in 25ml quantities in 100ml conical flasks. The nutrient agar medium was sterilized by autoclaving at 121^0C (15lb/sq.,inch) for 15 mins. The petri plates, tubes and flasks plugged with cotton were sterilized in hot air oven at 160^0C for an hour. Into each sterilized petri plate (4 inches diameter) about 25ml of molten nutrient medium which was already inoculated with the respective strain of bacteria was poured (5ml of inoculums to 250ml of nutrient agar medium) aseptically.

The plates were left at room temperature aseptically to allow to solidification. After solidification, cups of each of 8mm diameter were made by scooping out medium with a sterilized cork borer from a petri dish and labelled accordingly.

Each test compound (0.01mg) was dissolved in dimethyl sulfoxide (DMSO 10ml, Analar grade) to give a concentration 10,000µg/ml. Amoxicillin solution was also prepared to give a concentration of 10,000µg/ml in DMSO. All compounds were tested at dose levels of 100 µg/ml (0.01ml) and DMSO was used as control. The solution of each test compound, control and reference standard (0.01ml) was added separately in the cups and the plates were kept undistributed for at least 2 hours in a refrigerator to allow diffusion properly into nutrient agar medium. Petri plates were subsequently incubated at 37 ± 1^0C for 24 hours after incubation, the petri dishes were removed and zones are measured with the help of anti biotic zone reader. All the experiment was carried out in triplicates.

The results were

Table 1:

S.No	Name of the compound	Concentration of the drug	Zone of inhibition (Gram +ve) S.aureus
	Amoxicillin (standard)	100 µg/ml	35mm
1	BBAH-1	100µg/ml	25mm
2	BBAH-2	100µg/ml	20mm
3	BBAH-3	100µg/ml	25mm
4	BBAH-4	100µg/ml	22mm
5	BBAH-5	100 µg/ml	12mm

Table 2:

S.No	Name of the compound	Concentration of the drug	Zone of inhibition (Gram -ve) E.coli
	Amoxicillin (standard)	100 µg/ml	42mm
1	BBAH-1	100 µg/ml	27mm
2	BBAH-2	100 µg/ml	15mm
3	BBAH-3	100 µg/ml	28mm
4	BBAH-4	100 µg/ml	19mm
5	BBAH-5	100 µg/ml	13mm

RESULTS AND DISCUSSION

Hydrazide Schiff bases have been synthesized. The data of physio-chemical parameters of Schiff bases are given in table.

The characterization and structural elucidation of these novel compounds were carried by using spectral techniques like IR.

The results of anti-bacterial activity of newer compounds are given in table 1 (gram positive) and table 2 (gram negative). The anti-microbial screening results were presented in the above table reveal that all the synthesized hydrazide Schiff bases exhibited significant anti-bacterial activity against the microbial strains.

All the synthesized compounds were active against all tested micro organisms with a range of minimum inhibitory concentration (MIC) values.

Compound 1: ***4-Bromo benzoic acid (2,4-dichloro benzylidene) hydrazide***

It exhibited significant anti-microbial activity at MIC (100 µg/ml) against E.coli (Gram negative) and S.aureus (Gram positive)

Compound 2: ***4-Bromo benzoic acid (3-Nitro benzylidene) hydrazide***

It exhibited significant anti-microbial activity at MIC (100 µg/ml) against E.coli (Gram negative) and S.aureus (Gram positive)

Compound 3: ***4-Bromo benzoic acid (3-Bromo benzylidene) hydrazide***

It exhibited significant anti-microbial activity at MIC (100 µg/ml) against E.coli (Gram negative) and S.aureus (Gram positive)

Compound 4: ***4-Bromo benzoic acid (4-flouro benzylidene) hydrazide***

It exhibited significant anti-microbial activity at MIC (100 µg/ml) against E.coli (Gram negative) and S.aureus (Gram positive)

Compound 5: ***4-Bromo benzoic acid (4-dimethyl-amino- benzylidene) hydrazide***

It exhibited significant anti-microbial activity at MIC (100 µg/ml) against E.coli (Gram negative) and S.aureus (Gram positive).

CONCLUSION

The data from anti-bacterial activity clearly concluded that the synthesized compounds are significant and good anti-bacterial agents. The substitute Schiff base moieties are previously known for different biological activities. Here we have synthesized some novel Schiff bases.

The results from anti-bacterial screening clearly indicated that the compounds synthesized have shown good anti-bacterial activity with the standard drugs. Among all the synthesized compounds, the agents containing -Cl, -Br and -F (within the aldehyde) atoms showed more activity than remaining agents. Nitro group containing compound has showed more activity on gram positive bacteria than the gram negative bacteria. Therefore, in search of new active compounds, the possibility is by introducing different functional groups may result into better active agents.

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