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Research

Synthesis, Characterization and Biological evaluation of New Schiff's Base Derivatives

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Abstract

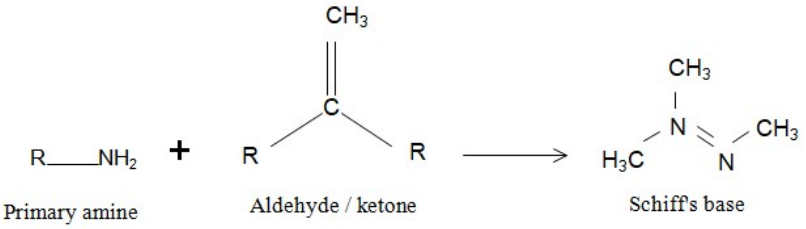
This manuscript presents the synthesis, characterization, and biological evaluation of novel Schiff's base derivatives derived from aromatic aldehydes and amino acids. Schiff bases, known for their biological relevance and stability when linked to aryl groups, were synthesized using a condensation reaction facilitated by mildly acidic conditions to ensure optimal yields without compromising the nucleophilicity of the amines. The synthesized compounds were rigorously characterized using melting point determination, thin-layer chromatography (TLC), and infrared spectroscopy (IR). Their biological efficacy was assessed through in vitro antibacterial and antifungal assays, demonstrating considerable activity against common pathogenic strains such as Escherichia coli, Bacillus subtilis, and Candida albicans. The compounds exhibited a range of activities, with some showing comparable efficacy to standard antibiotics and antifungals. These findings suggest that Schiff's bases could be potent candidates for drug development, offering a scaffold for further chemical enhancement and therapeutic application.

Keywords: Schiff's bases, Aromatic aldehydes, Antibacterial activity, Antifungal activity, Synthesis and characterization.

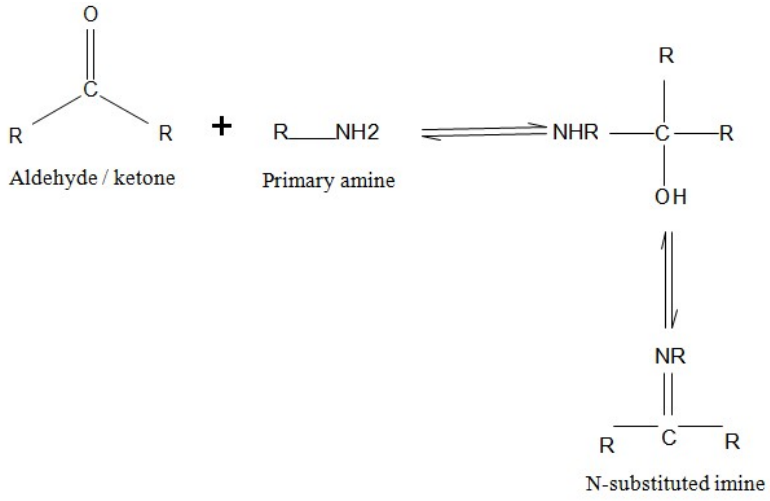
INTRODUCTION

Formation of Schiff bases

A Schiff bases is nitrogen analog of an aldehyde or ketone in which the C=O is replaced by C=N- R group[1-5]. It is usually formed by condensation of an aldehyde or ketone with a primary amine according to the following scheme



Where R may be an alkyl or aryl group. Schiff bases that contain aryl substituent's are substantially more stable and more readily synthesized, while those which contain alkyl substituents are relatively unstable. Schiff basely polymers of aliphatic aldehydes are relatively unstable and readily polymerized[5,6] while those of aromatic aldehydes having effective conjugation are more stable[6,7]. The formation of a Schiff bases from an aldehydes or ketones is a reversible reaction and generally takes place under acid or base catalyst upon heating. The formation is generally driven to the completion by separation of the product or removal of water or both. Many Schiff bases's can be hydrolyzed back to their aldehydes or ketones and amines by aqueous acid or base. The mechanism of Schiff bases formation is another variation on the theme of neuclophilic addition to the carbonyl group. In this case, the neuclophile is the amine. In the first part of the mechanism the amine reacts with the aldehyde or ketone to give a stable addition compound called carbinolamine.



The carbinolamine loses water by either acid- or base- catalyzed pathway[8]. Since the carbinolamine is an alcohol it undergoes acid- catalyzed dehydration. Typically the dehydration of the carbinolamine is the ratedetermining step of Schiff base formation and this is why the reaction is catalyzed by acids. Yet the acid concentration cannot be too high because amines are basic compounds. If the amines are protonated and become non-nucleophilic, equilibrium is pulled to the left and cabinolamine formation cannot occur. Therefore, many Schiff bases syntheses are best carried out at mildly acidic pH. The dehydration of carbinolamine[9] is also catalyzed by base. This reaction is somewhat analogous to the E_2 elimination of alkyl halides except that it is not a concerted reaction. It proceeds in two steps through an anionic intermediate. The Schiff base formation is really a sequence of two types of reaction, i.e. addition followed by elimination[10].

Biological importance of schiff's bases

Schiff bases appear to be important intermediate in a number of enzymatic reactions involving interaction of the amino group of an enzyme usually that of a lysine residue with a carbonyl group of the substrate[11].

Stereo chemical investigations[12] carried out with the aid of molecular models showed that Schiff bases formed between methylglyoxal and the amino group of the lysine chain of the proteins can bean back in such a way towards the N atom of peptide groups that a charge transfer can occur between these groups and the oxygen atoms of the Schiff bases.

Schiff bases derived from pyridoxal (the active form of vitamin B_6) and amino acids are considered as very important ligands from biological point of view. Transition metal complexes of such ligands are important enzyme models. The rapid development of these ligands resulted in an enhanced research activity in the field of coordination chemistry leading to very interesting conclusions.

Many biologically important Schiff bases have been reported in the literature possessing antibacterial[13], antifungal[14,15], anticonvulsant[16], anti HIV[16], anti-inflammatory[17] and antitumor[18] activities. Also certain polymeric Schiff bases have the highest degree of hydrolysis at pH 5 and the solubility in water is also highest at this pH. The antitumor activity of Schiff bases towards ascetic tumors increases considerably with the slight increase in the water solubility.

Another important role of Schiff bases structure is in transamination[19]. Transamination reactions are catalysed by a class of enzymes called transaminases or aminotransferases. Transaminases are found in mitochondria and cytosol of eukaryotic cells. All the transaminases appear to have the same prosthetic group, i.e. pyridoxal phosphate, which is covalently attached to them via an imine or Schiff base. Schiff bases formation also involved in the chemistry of vision, where the reaction occurs between the aldehyde function of 11-cisretinal and amino group of the protein (opsin)[20].

The biosynthesis of porphyrin, for which glycine is a precursor is another important pathway, which involves the intermediate formation of Schiff base between keto group of one molecule of δ-aminolevulinic acid and ε-amino group of lysine residue of an enzyme.

MATERIALS AND METHODS

List of chemicals used

S.No.	CHEMICALS
1.	Glacial acetic acid
2.	Methanol
3.	Sodium hydroxide
4.	Benzaldehyde
5.	Salicylaldehyde
6.	Alanine
7.	Lycine
8.	Glycine
9.	Phenylalanine

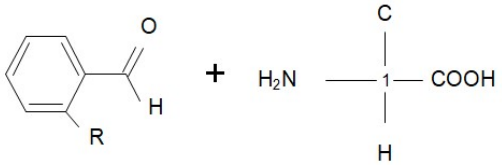
All the chemicals were used only analytical Reagent grade. The chemicals were purchased in Poonmani Chemicals, Coimbatore.

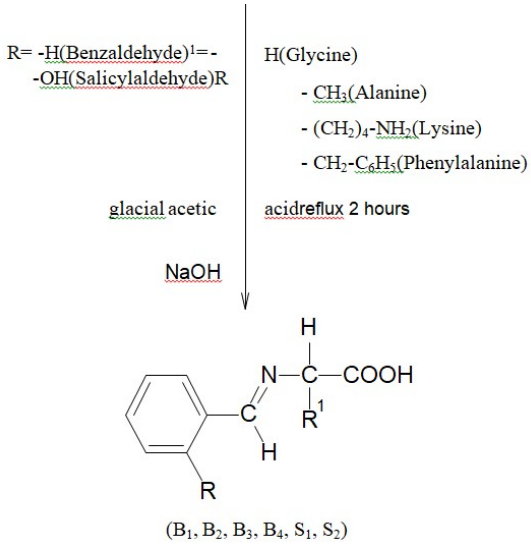
List of instruments used

1. Digital balance
2. Reflex Condenser
3. Hot Air Oven
4. Scientific Melting Point Apparatus
5. SHIMADZU UV Spectrophotometer
6. SHIMADZU IR Spectrophotometer

Experimetal work

Scheme





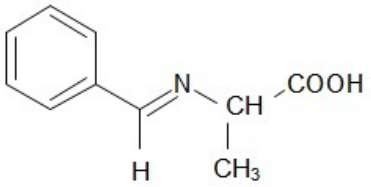
(B_1, B_2, B_3, B_4, S_1, S_2)

Procedure

A mixture of 0.01mole of different amino acids (Alanine, Lysine, Glysine and Phenylalanine) and 0.01mole of aromatic aldehydes[40] (Benzaldehyde & Salicilaldehyde) was taken in a clean and dry round bottom flask containing 25ml of methanol and 4 to 5 drops of glacial acetic acid and add the reaction mixture 0.01mole of sodium hydroxide as a catalyst. Then the reaction mixture was refluxed for 2 hours. The solid that separated on cooling was filtered and re-crystalysed with a little amount of cold methanol and dried. The structures of these Schiff's bases are confirmed by using physical methods, namely, melting points or boiling point, TLC and IR spectra.

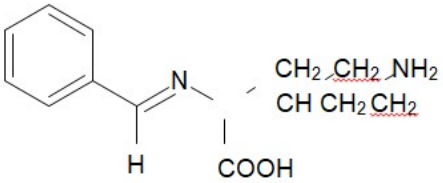
Characterization of synthesized compounds

Phenylmethylideneaminopropanoic acid(B_1)



Mol. Formula : C10H11NO2
Mol.Weight : 177.19984
Solubilty : Chloroform
R_f Value : 0.7
Yield : 80%
Melting Point : 280^{O}C
IR(in KBr cm^{-}) : O-H 3394cm^{-1}(stretch)
C=O 1635cm^{-1}(stretch)
C=N 1539 cm^{-1}(stretch)
C-H 427 cm^{-1}(stretch)

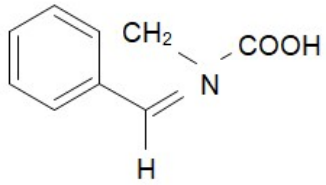
6-amino-2-{[(*E*)-phenylmethylidene]amino}hexanoic acid(B_2)



Mol. Formula : C13H18N2O2
Mol.Weight : 234.29422
Solubilty : Chloroform

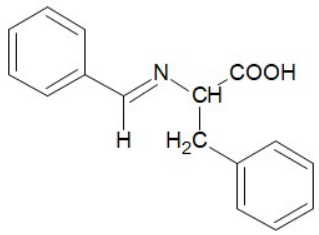
R_f Value	: 0.761
Yield	: 80%
Melting Point	: 222-225^{O}C
IR(in KBr cm^{-})	: O-H 3387 cm^{-1}(stretch)
	C=O 1641 cm^{-1}(stretch)
	C=N 1605 cm^{-1}(stretch)
	C-H 445 cm^{-1}(stretch)

Phenylmethylideneaminoacetic acid(B_3)



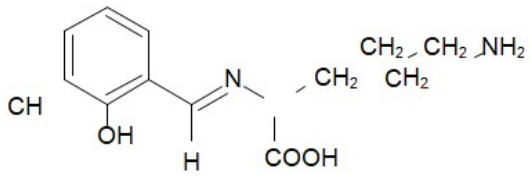
Mol. Formula	: $C_9H_9NO_2$
Mol.Weight	: 163.17326
Solubilty	: Chloroform
R_f Value	: 0.8
Yield	: 75%
Melting Point	: 208-210^{O}C
IR(in KBr cm^{-})	: O-H 3386 cm^{-1}(stretch)
	C=O 1639 cm^{-1}(stretch)
	C=N 1541 cm^{-1}(stretch)
	C-H 423 cm^{-1}(stretch)

3-phenyl-2-{[(*E*)-phenylmethylidene]amino}propanoic acid(B_4)



Mol. Formula	: C16H15NO2
Mol.Weight	: 253.2958
Solubilty	: Chloroform
R_f Value	: 0.9
Yield	: 70%
Melting Point	: 255-230^{O}C
IR(in KBr cm^{-})	:O-H 3457 cm^{-1}(stretch)
	C=O 1633 cm^{-1}(stretch)
	C=N 1534 cm^{-1}(stretch)
	C-H 432 cm^{-1}(stretch)

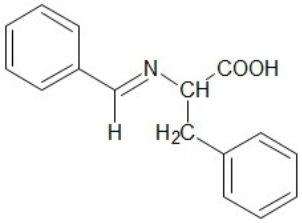
6-amino-2-{[(*E*)-(2 hydroxyphenyl)methylidene]amino}hexanoic acid(S_1)



Mol. Formula	: C13H18N2O3
Mol.Weight	: 250.29362
Solubilty	: Chloroform
R_f Value	: 0.9
Yield	: 80%

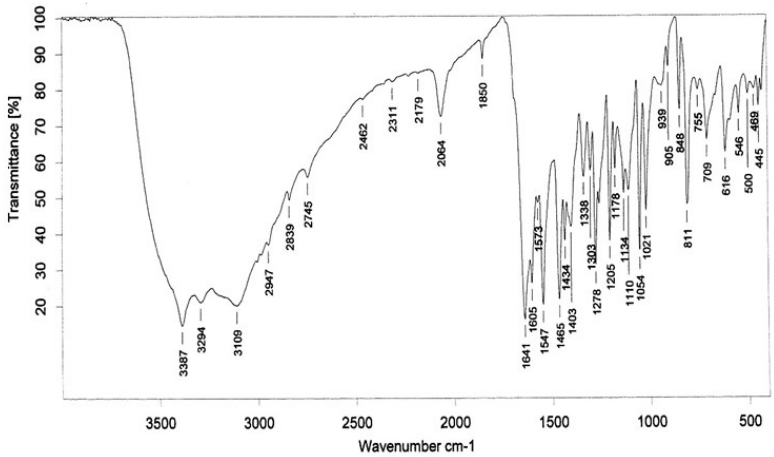
Melting Point : 228-230^{O}C
IR(in KBr cm^{-}) :O-H 3394 cm^{-1}(stretch)
C=O 1677 cm^{-1}(stretch)
C=N 1607 cm^{-1}(stretch)
C-H 494 cm^{-1}(stretch)

(2-hydroxyphenyl)methylidene amino acetic acid(S_2)

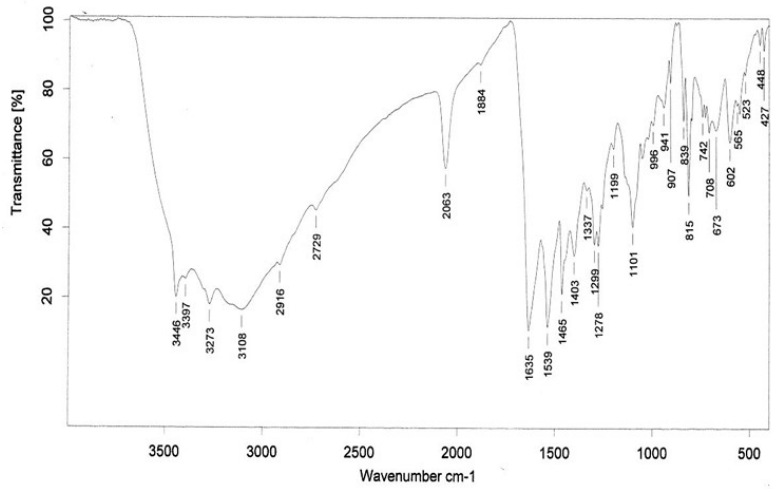


Solubility : Chloroform
R_f Value : 0.8
Yield : 75%
Melting Point : 266-270^{O}C
IR(in KBr cm^{-}) : O-H 3417 cm^{-1}(stretch)
C=O 1605 cm^{-1}(stretch)
C=N 1572 cm^{-1}(stretch)
C-H 498 cm^{-1}(stretch)

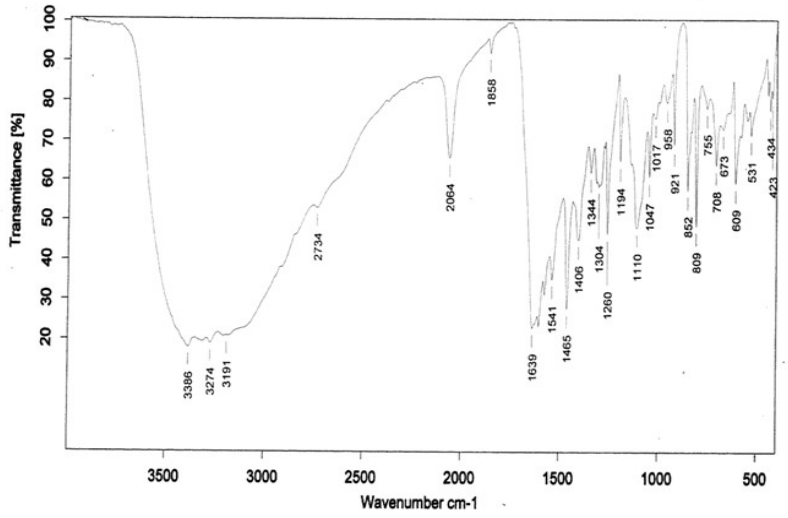
B_1



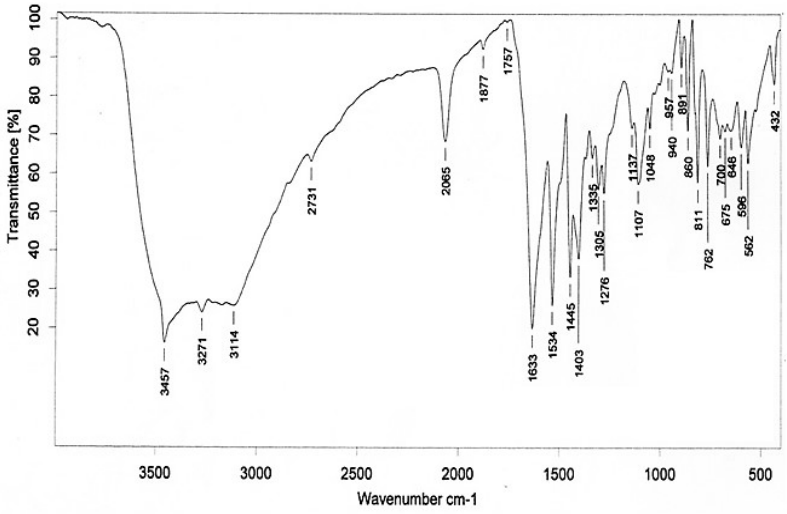
B_2



B_3


Transmittance [%]
Wavenumber cm-1
3386
3274
3191
2734
2064
1858
1639
1541
1465
1406
1344
1304
1260
1194
1110
1047
1017
958
921
852
809
755
708
673
609
531
434
423

B_4


Transmittance [%]
Wavenumber cm-1
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3271
3114
2731
2065
1877
1757
1633
1534
1445
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1335
1305
1276
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940
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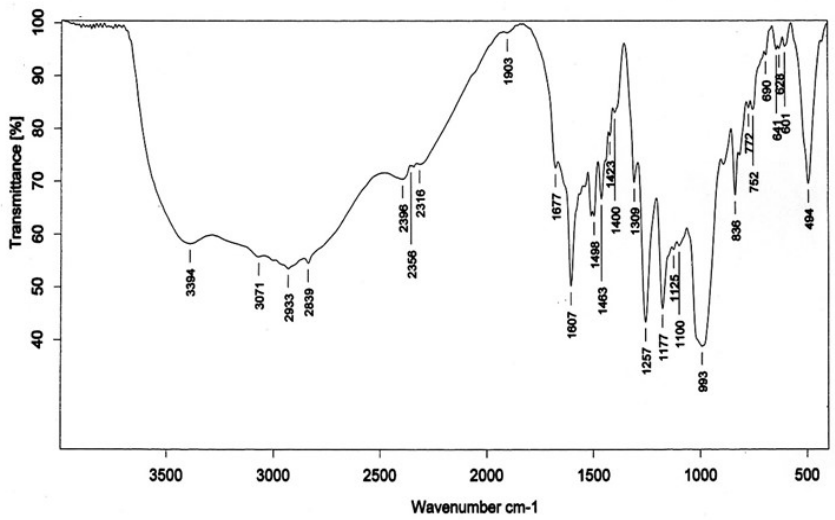
860
811
762
700
675
646
596
562
432

S_1


Transmittance [%]
Wavenumber cm-1
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3071
2933
2839
2396
2356
2316
1903
1677
1607
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1257
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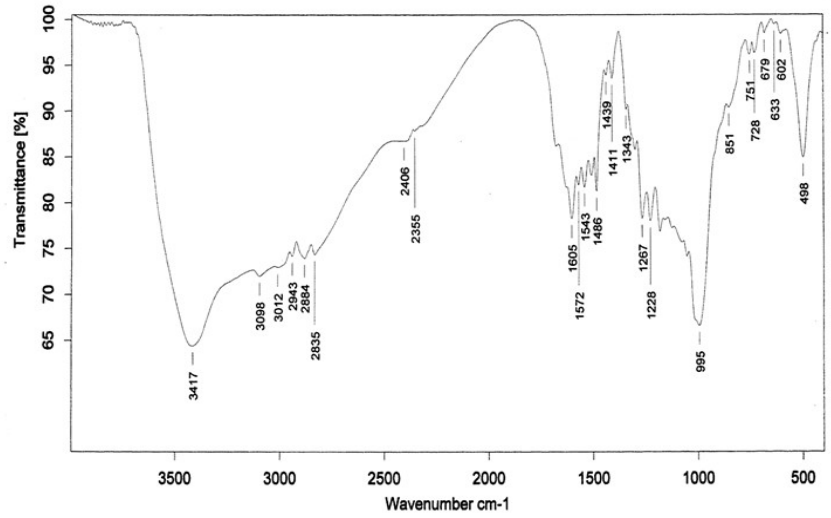
1125
1100
993
836
772
752
690
641
601
626
494

S_2



Biological evaluation

Antibacterial activity[41]

The bacterial strains used in the present study were obtained from National Chemical Laboratory (NCL). The bacterial strains comprised: *Escherichia coli* and*Bacillus subtilis.*

Preparation of inoculums

The bacteria were maintained in Mueller-Hinton Agar (MH). Inoculam- were prepared by adding an overnight culture of the organisms in Nutrient broth to obtain an OD_{600} 0.1. The cells were allowed to grow until they obtain the McFarland standard 0.5 (approximately 10^8 CFU/ml). The suspensions were then diluted to 1:100 in NAM broth to obtain 10^6 CFU/ml.

Anti bacterial assay

The medium was prepared by dissolving all the ingredients in distilled water and subjected to sterilization in an autoclave at 121^0C for 15minutes. The Petri plates were washed thoroughly and sterilized in hot air oven at 160^0C for 1 ½ hours. 30ml of sterile molten agar medium was seeded by organisms (about 2 ml according to McFarland's standard), in semi hot conditions (40^0C) was poured aseptically in sterile Petri plate and allowed to solidify at room temperature. Bores were made on the medium using sterile borer and 0.1 ml of synthesized compounds at 1mg/ml concentration in DMSO were added to respective bores and 0.1ml of the standard Rifamycin used at a concentration of 50µg/ml was used as standard. The Petri plates seeded with organisms, containing extracts and the standard were kept in a refrigerator at 40ºC for 1 hour to facilitate the diffusion of the extracts and the standard in to the media. After diffusion the Petri plates were incubated at 37 ± 10^0C for 24 hours in an incubator and later the zone of inhibition was observed and measured using a scale.

Mueller Hinton Agar (MHA)

Component	**g/l**
Beef, dehydrated infusion	2
Casein hydrolysate	17.5
Starch	1.5
Agar	17
Final pH at 25°C	7.4 ± 0.2

Nutrient Broth (NB)

Component	**g/l**
Beef extract	3
Sodium chloride	5
Yeast extract	1.5
Peptone	5.0
Final pH at 25°C	7.2 ± 0.2

Table 1: Zone of inhibition of compounds

S.No.	Compound code	Zone of inhibition (in mm)	
		Bacillus subtillis	***Escherichia coli***
1	B1	10	03
2	B2	19	20
3	B_3	05	07
4	B_4	12	05
5	S1	15	15
6	S2	19	09
Standard	Rifamacin	20	25

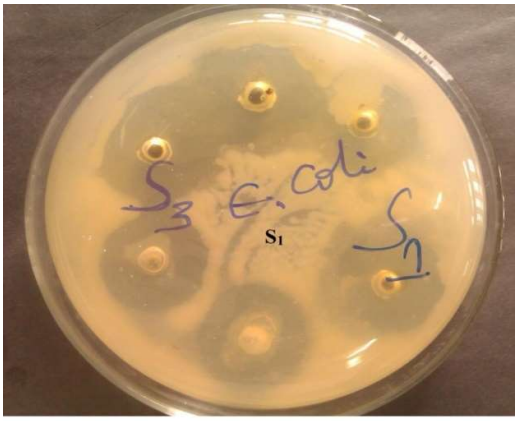


Fig 1: Zone of inhibition of compounds (Antibacterial activity)

Antifungal activity[42]

The fungal strains used in the present study were obtained from National Chemical Laboratory (NCL). The fungal strains comprised:

Preparation of inoculums

The fungi were maintained in potato dextrose agar. Inoculamwere prepared by adding an overnight culture of the organisms in Nutrient broth to obtain an OD_{600} 0.1. The cells were allowed to grow until they obtain the McFarland standard 0.5 (approximately 10^8 CFU/ml). The suspensions were then diluted to 1:100 in NAM broth to obtain 10^6 CFU/ml.

Antifungal assay

The medium was prepared by dissolving all the ingredients in distilled water and subjected to sterilization in an autoclave at 121^0C for 15minutes. The Petri plates were washed thoroughly and sterilized in hot air oven at 160^0C for 1 ½ hours. 30ml of sterile molten agar medium was seeded by organisms (about 2 ml according to McFarland's standard), in semi hot conditions (28^0C) was poured aseptically in sterile Petri plate and allowed to solidify at room temperature. Bores were made on the medium using sterile borer and 0.1ml of the extracts at 1mg/ml concentration in DMSO were added to respective bores and 0.1ml of the standard Clarithroycin at a concentration 50µg/ml was used as standard. The Petri plates seeded with organisms, containing extracts and the standard were kept in a refrigerator at 40ºC for 1hour to facilitate the diffusion of the extracts and the standard in to the media. After diffusion the Petri plates were incubated at 37 ± 10^0C for 7 days in an incubator and later the zone of inhibition was observed and measured using a scale.

Potato Dextrose Agar (PDA)

Component	**g/l**
Beef, dehydrated infusion	2
Casein hydrolysate	17.5
Starch	1.5
Agar	17
Final pH at 25°C	7.4 ± 0.2

Nutrient Broth (NB)

Component	**g/l**
Beef extract	3
Sodium chloride	5
Yeast extract	1.5
Peptone	5.0
Final pH at 25°C	7.2 ± 0.2

Table 2: Zone of inhibition of compounds

S.no	Compondcode	Zone of inhibition(in mm) of *Candida albicans*
1	B1	09
2	B_2	06
3	B_3	01
4	B_4	1.5
5	S1	10
6	S2	09
Standard	Clarithromycin	10

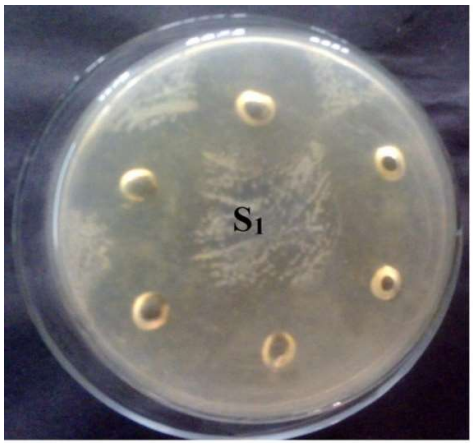


Fig 2: Zone of inhibition of compounds (Antifungalactivity)

RESULTS AND DISCUSSION

New substituted Schiff's bases analogues were synthesized as mentioned in the scheme, and all the synthesized compounds were obtained in good yields were mentioned in experimental section. The synthesized substituted Schiff's bases were characterized by both physical and spectral data like FT-IR. All the synthesized compounds were evaluated for their antibacterial and antifungal activities.

Antibacterial activity

All the six compounds showed antibacterial activity against Bacillus subtilis and Escherichia coli using Rifamacin as a standard drug. From the data presented in table(1), it is clear that all the compounds were found to possess excellent to moderate activity against all the micro organisms. Compounds B_1, B_2 , B_4 and S_1 exhibited Excellent activity against all bacterial strains.

Anti fungal activity

Synthesized compounds were tested for antifungal activity against Candida albaicans. The tested compounds were shown promising results against these organisams presented in table(2). Compounds B_1, S_1 and S_2 showed good activity but not very much significant when compared with the activity shown by the standard drug Clarithromycin.

CONCLUSION

The objective of the present work was to synthesize, purify,characterize and evaluate the antimicrobial activity of new schiff's bases. The yields of different synthesized compounds were found to be in therange of 60-80% and the characterization was done by melting pointand TLC. Characteristic IR bands show several functional vibrationalmodes which confirm the completion of reaction. All the test compounds showed antibacterial activity against both gram positive and gram negative bacteria in a concentration of 50g/ml. Best result in terms of antimicrobial activity, were shown by B_1, B_2, B_4 and S_1 for both gram positive and gram negative organisms. The close observation of the antifungal activity of all the test compounds showed mild to moderate anti-fungal activity.

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