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Synthesis characterization and antibacterial studies of 4-aminoantipyrine schiff's bases

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synthesis; characterization; 4-aminoantipyrine; Schiff bases; antibacterial activity;

ABSTRACT:

Aim: To synthesize and evaluate 4-aminoantipyrine related schiff's bases as antibacterial agents.
Objective: To synthesize, purify, characterize and evaluate 4-aminoantipyrine.
Method: Schiff bases derived from 4-aminoantipyrine play a vital role in biological and pharmacological activities. Knowing the importance of 4-aminoatipyrine schiff bases and their analogues wide varieties of bioactivities like analgesic, antiviral, antipyretic, anti-rheumatic, antimicrobial and anti-inflammatory activities have been widely studied. 4-aminoantipyrine compounds C_1 (anisaldehyde), C2 (p-hydroxybenzaldehyde) and C_3(vanillin) were prepared by condensation between 4-amino antipyrine and substituted aromatic benzaldehydes. The products were purified by recrystallization by using ethanol, characterized by IR spectroscopy. The N-H stretching in 4-aminoantipyrine is shown at 3430 cm^{-1}&-3325 cm^{-1}. The -HC=N- stretching is observed in the range of 1508-1504 cm^{-1} The $–OCH_3$ stretching is found at 1888 cm^{-1}. 4-amino antipyrine related schiff's bases evaluated their activity as antimicrobials in-vitro by spread plate method against *E.coli*. Schiff bases have potent antibacterial activity with gram negative bacteria E.coli.
Results: Synthesis and characterization of a schiff bases derived from substituted benzaldehydes and 4-aminoantipyrine was evaluated and characterized with the IR spectroscopic techniques and schiff bases have shown potent antibacterial activity against E.Coli.

1. Introduction

4-Aminoantipyrine (4-Amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one) is a heterocyclic compound containing pyrazole ring. Its broad bioactivities are anticancer (Sigroha et al., 2012), analgesic (Turan Zitouni et al., 2001), anti-inflammatory (Lutsevich et al., 1995), antimicrobial (Bondock et al., 2008). 4-Aminoantipyrine was 1st synthesized by Knorrin 1883. It was the 1st pyarzolone derivative used in the management of pain and inflammation.

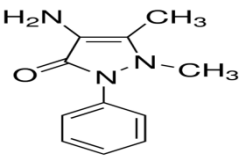
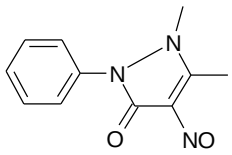
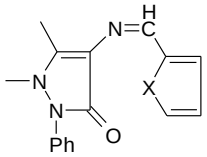
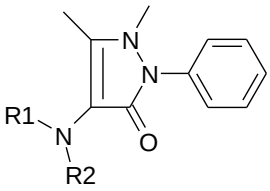


Figure 1: 4 Aminoantipyrine

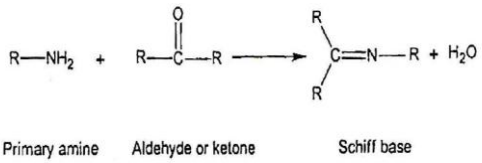
4-aminoantipyrine has an N phenyl group and a -CH_2 group on either side of a polar carbonyl group, thus resembles to N-substituted amides. The carbonyl group in 4- aminoantipyrine is a potential donor due to the large dipole moment and strong basic characters. Generally, the electron withdrawing and electron releasing nature and the position of substituents present in the phenyl ring affect the antimicrobial activities (Bondock et al., 2008); the presence of substituents at the *o*-position lowers the antimicrobial activity whereas the substituents at the *p*-position give higher antimicrobial activity. Inhibition is enhanced with the introduction of an electron withdrawing nitro group in the phenyl ring.

Table 1: Structures showing biological activity

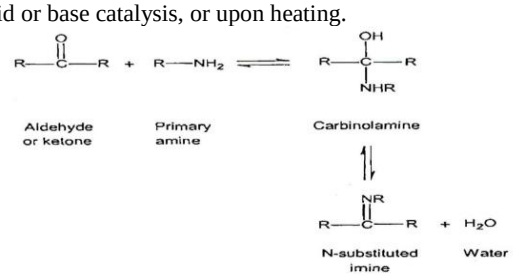
Activity	Structure
Analgesic	
Antibacterial	 X=S;X=O
Anti-inflammatory	 R1=R2= H → 4-Aminoantipyrine; CH_3 → 4-(N-Methyl)-aminoantipyrine; CH_3 → 4-(N,N-Dimethyl)-aminoantipyrine

1.1 Schiff bases

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

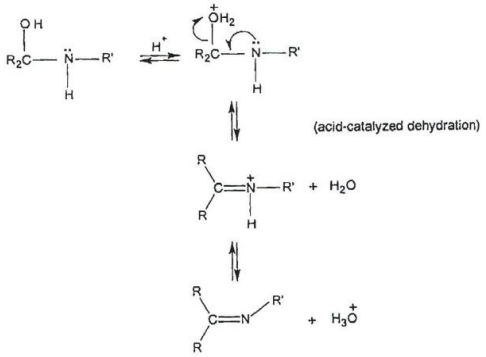


Where R, may be an alkyl or an aryl group. Schiff bases that contain aryl substituents are substantially more stable and more readily synthesized, while those which contain alkyl substituents are relatively unstable. Schiff bases of aliphatic aldehydes are relatively unstable and readily polymerizable while those of aromatic aldehydes having effective conjugation are more stable. The formation of a Schiff base from an aldehydes or ketones is a reversible reaction and generally takes place under acid or base catalysis, or upon heating.



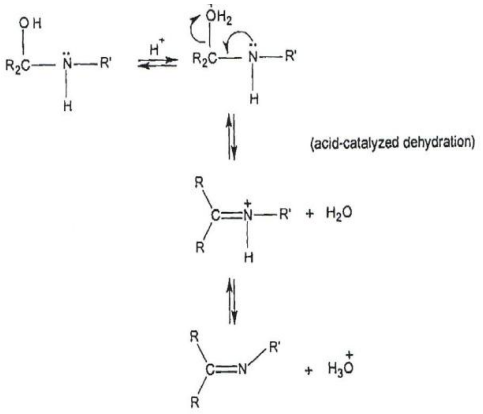
The formation is generally driven to the completion by separation of the product or removal of water, or both. Many Schiff bases can be hydrolyzed back to their aldehydes or ketones and amines by aqueous acid or base. The mechanism of Schiff base formation is another variation on the theme of nucleophilic addition to the carbonyl group. In this case, the nucleophile is the amine.

In the first part of the mechanism, the amine reacts with the aldehyde or ketone to give an unstable addition compound called carbinolamine. The carbinolamine loses water by either acid or base catalyzed pathways. Since the carbinolamine is an alcohol, it undergoes acid catalyzed dehydration.



Typically the dehydration of the carbinolamine is the rate-determining step of schiff base formation and that is why the reaction is catalyzed by acids. Yet the acid concentration cannot be too high because amines are basic compounds. If the amine is protonated and becomes non-nucleophilic, equilibrium is pulled to the left and carbinolamine formation cannot occur.

Therefore, many schiff bases synthesis are best carried out at mildly acidic pH. The dehydration of carbinolamines 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 a sequence of two types of reactions, i.e. addition followed by elimination (S. Patai et al., 1970, N. Raman et al., 2009, Rosu T et al., 2006, D Ortegon-Reyna et al., 2014).

1.2 Chemistry and Biological Importance of Schiff bases

Schiff bases have a large number of synthetic uses in organic chemistry. Acylation of schiff's bases by acid anhydrides, acid chlorides and acyl cyanides is initiated by attack at the nitrogen atom and leads to net addition of the acylating agent to the carbon-nitrogen double bond (Joseph et al., 2013). Reactions of this type have been put to good use in natural product synthesis. Schiff bases appear to be an important intermediate in a number of enzymatic reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate.

The rapid development of these ligands resulted in an enhance research activity in the field of coordination chemistry leading to very interesting conclusions. The carbon-nitrogen double bond of Schiff bases like the carbon-oxygen double bond is readily reduced by complex metal hydrides. Reduction of this type is probably the most efficient and convenient method for the conversion of C=N into amino compounds (Vaghasiya et al., 2004, S. Patai et al., 1970).

Schiff bases derived from heterocyclic ring with carbonyl compounds has its important special center of attraction in many areas like biological, clinical, medicinal, analytical and pharmacological field. Among them 4-aminoantipyrine based heterocycles had a great importance as it is abundant in nature and have wide pharmacological activities, 4-Aminoantipyrine is a temperature reducing pyrazole derivative (Jungreis et al., 1969).

Schiff bases and metal complexes of 4-aminoantipyrine are also known for their great variety of applications in the area of catalysis and biological activity ranging from anti-tumor (Y. Dong Dong et al., 2001), fungicide, bactericide (V. Prakash et al., 2013), anti-inflammatory and antiviral activities (V. Anandhi et al., 2008). Reports on drugs showed increased activity when administered as metal complexes rather than as organic compounds. Investigation on the interaction of DNA with small molecules is also important in the design of new types of pharmaceutical molecules (Bernardo et al., 1996, Spichiger-Keller et al., 1998, T Gabriela et al., 2014).

2. Materials and methods

2.1 Chemicals & Reagents:

The chemicals and reagents of Analytical and Laboratory grade from Asha Chemicals, Seth Chemicals, Prince trading company, Hyderabad.

Table 2: Chemicals and Reagents

Agar
4-Amino antipyrine
Anisaldehyde
Dimethyl sulfoxide
Ethanol
Distilled water
Sodium chloride
Sodium hydroxide
Peptone
p- Hydroxybenzaldehyde
Vanillin

2.2 Analytical techniques

I. Physical Data:

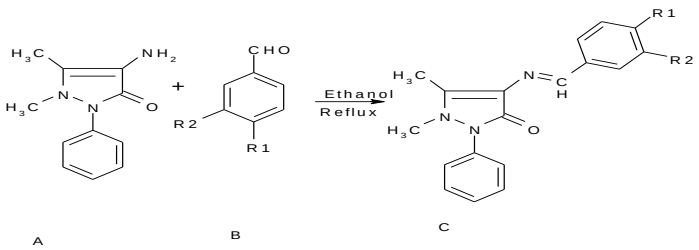
The melting points of the synthesized products were determined by melting point apparatus (open capillary tube method) and all the compounds gave sharp melting points and were uncorrected.

II. Thin Layer Chromatography:

Purity of the compounds was ascertained by thin layer chromatography using silica gel-G as stationary phase and appropriate mixtures of the following Solvents as mobile phase Methanol and chloroform. The spots resolved were visualized using iodine chamber and UV chamber (Lawrence et al., 1976).

2.3 Preparation of Schiff's bases

Reaction:



A B C

Chemicals used: Anisaladehyde-1.36g, Para hydroxybenzaldehyde-1.22g, Vanillin-1.5 g, Ethanol-10ml.

Procedure: 2.03g of 4-amino antipyrine was dissolved in 10ml of ethanol in a beaker. 1.36g of aryl benzaldehyde was dissolved in 10ml of ethanol in a round bottomed flask. These two mixtures were mixed together and kept for reflex for 5hrs with stirring. The mixture was cooled and pour into crushed ice and the precipitate obtained was filtered, dried and recrystallized with ethanol.

Table 3: Amino anti-pyrine Schiff's bases

S.No	Aldehyde name	Yield (%)	R_f solvent system used (chloroform: methanol;1:1)	R^1	R^2	M.P(°C)
C_1	Anisaldehyde	84.5	0.88	OCH_3	H	166-170
C_2	P- hydroxybenzaldehyde	81.2	0.91	OH	H	165-168
C_3	Vanillin	80	0.4	OH	OCH_3	170-173

2.4 Biological Evaluation

Preparation of Nutrient Agar media

Table 4: Composition of Nutrient Agar media

Ingredients	Gms / Litre
Peptone	5.000
Sodium chloride	5.000
Beef extract	1.500
Yeast extract	1.500
Agar	15.000
Final pH (at 25°C)	7.4±0.2

Procedure:

Suspend 28 grams in 1000 ml distilled water. Heat to boiling to dissolve the medium completely. Dispense as desired and sterilize by autoclaving at 15 lbs pressure (121°C) for 15 minutes. Mix well before pouring.

3. Results

3.1 Physical data of the synthesized compounds C_1-3

Table 5: Physical data of the synthesized compounds C_1-3

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C_2	P-hydroxybenzaldehyde	81.2	0.91	OH	H	165-168
C_3	Vanillin	80	0.4	OH	OCH_3	170-173

3.2 Spectral data of the synthesized compounds

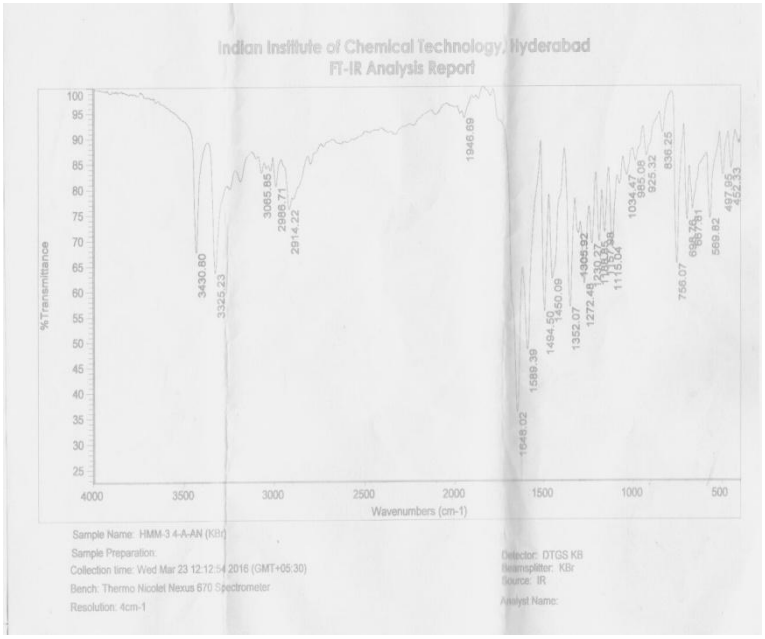
Table 6: Spectral data of the synthesized compounds

S.No	Compound	IR Spectra values (cm^{-1})
1	A	$-NH_2$ (3430, 3325)
2	C_1	-CH=N (1504) , $-OCH_3$ (1888)

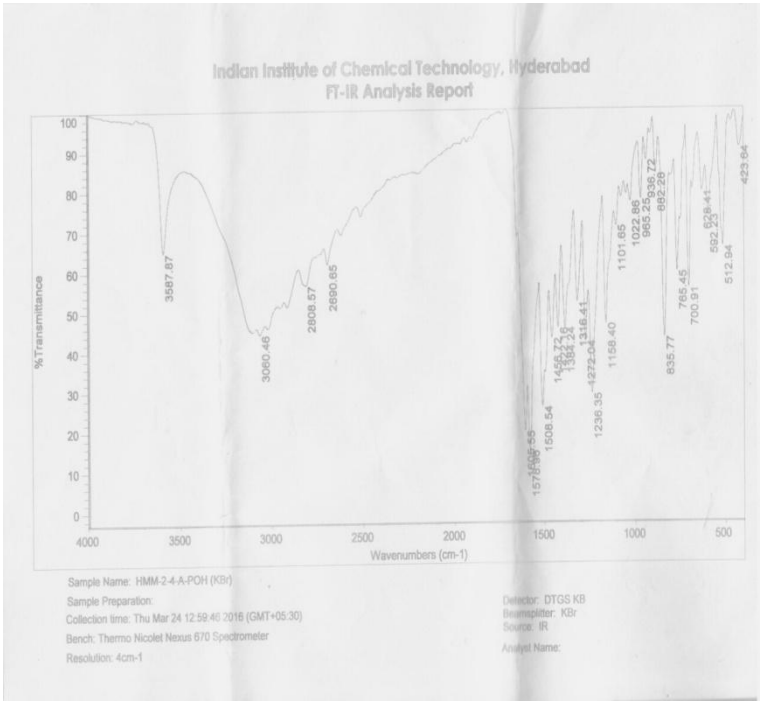
3	C_2	-CH=N (1508), Phenolic - OH (3587)

3.3 IR Spectra of 4-Aminoantipyrin

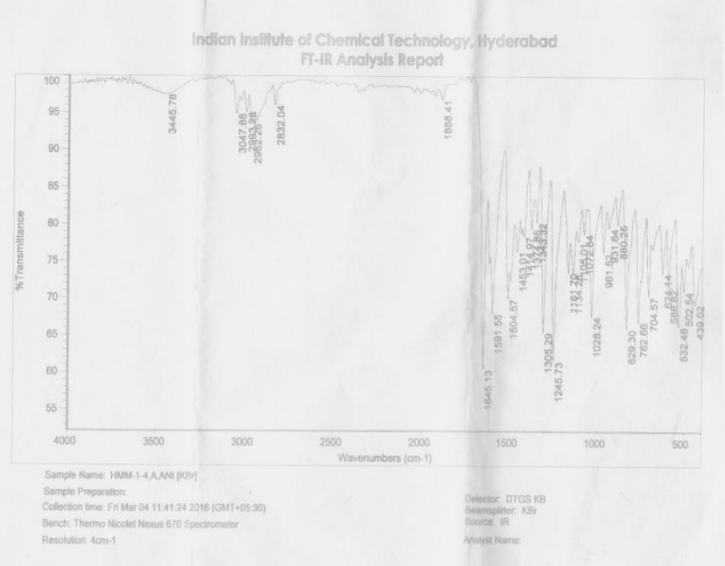
3.3.1 IR Spectra of compound C_1



3.3.2 IR Spectra of compound C_2



3.3.3 IR Spectra of compound C3



3.4 Antibacterial Activity:

Table 7: Antibacterial activity against E.coli

Sample	Concentration	Inhibition zone(mm)
Compound C_1	30µg	5
Compound C_2	30µg	7
Compound C_3	30 µg	8
Ampicillin	30µg	4
Cefotaxime	30µg	15

4. Discussion

Results of our study demonstrated that Schiff bases were synthesized and characterized. Schiff bases derived from 4-aminoantipyrine have potent antibacterial activity. Compounds C_1, C2 and C_3 were prepared by condensation between 4-aminoantipyrine and substituted aromatic benzaldehydes. The products were purified by recrystallization by using ethanol, characterized by IR spectroscopy. The N-H stretching in 4-aminoantipyrine is shown at 3430 cm^{-1}&-3325 cm^{-1}. The -HC=N- stretching is observed in the range of 1508-1504 cm^{-1} The $–OCH_3$ stretching is found at 1888 cm^{-1}. In the view of synthesizing new antimicrobials, the synthesized Schiff bases from 4-aminoantipyrine having antimicrobial activity through in-vitro by spread plate method against *E.coli* (gram negative) bacteria.

5. Conclusion

In this work the synthesis and characterization of a Schiff bases derived from substituted benzaldehydes and 4-aminoantipyrine is reported. The synthesized Schiff's bases were characterized by IR spectroscopic techniques. The antibacterial studies are also reported.The yield of the products ranged from 80-85%. The purity of the compounds was checked by TLC. With these encouraging results, all the synthesized compounds can be further explored for structural modification and detailed microbiological investigations to arrive at possibly newer potent antibacterial agent with various other activities.

Conflict of Interest:

Authors have no conflict of interest from any point of view.

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