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SYNTHESIS OF SOME NEW PARACETAMOL INCORPORATED SHIFF BASES AND THEIR ANTIMICROBIAL ACTIVITY

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ABSTRACT

Some new Schiff bases are synthesized from condensation of 4-acetamidophenoxyacetyl-Hydrazide with various aldehyde. The entire synthesized compound characterized by physical and analytical data. The chemical structures of synthesized compound were confirmed by means of IR, 1HNMR and MS. Antimicrobial activity of synthesized compounds evaluated by cup-plate method. Synthesized compound showed good antimicrobial activity.

KEYWORDS: Antimicrobial, Paracetamol, Schiff bases.

INTRODUCTION

A Schiff base, named after Hugo Schiff, is a compound with a functional group that contains a carbon-nitrogen double bond with the nitrogen atom connected to an aryl or alkyl group, not hydrogen. Schiff bases in a broad sense have the general formula $R^1R^2C=NR^3$, where R is an organic side chain. In this definition, Schiff base is synonymous with azomethine. Although deaths from bacterial and fungal infection have dropped currently, still those are the major cause of death in the world. [1] Over the few past decades the bacterial resistance to antibiotics, anti-fungal and anti-tuberculotic drugs has become one of the most challenging problem in the infections treatments. Several research has been done and currently in progress to develop new and better chemical entity against infections. Literature survey reveals that Schiff bases form a significant class of compounds in medicinal and pharmaceutical chemistry with several biological applications that include antibacterial, antifungal and antitumor activity.

MATERIAL AND METHOD

All the raw material used in synthesis receives from Loba Chemie Pvt. Ltd. Mumbai, India. Melting point is determine by open capillary tube method and uncorrected. The IR spectrum was recorded by using KBr disc on FTIR 8010 Shimadzu model. The ^{1}H-NMR spectra of the synthesized compounds were recorded on Brucker Spectrospin DPX 300 spectrophotometer. The solutions of the test compounds were prepared in dimethyl sulfoxide DMSO-d_6. Tetra Methyl Silane (TMS) was used as internal standard. Molecular weight weights of the synthesized compounds were identified by Mass Spectrophotometer, LC-MSD-TrapSL (6300 Series Ion Trap LC/MS). Completion of reaction is monitored by thin layer chromatography (TLC) carried out on activated silica gel coated plates with the solvent system glacial acetic acid: chloroform: methanol (6:2:2).

Procedure for the Synthesis of Ethyl-4-Acetamidophenoxyacetate

A mixture of paracetamol (1.51g, 0.01mol) and ethylchloroacetate (1.22ml, 0.01mol) was refluxed in dry acetone in presence of anhydrous K_2CO_3 (1.38g, 0.01mol) for 6 hr and was then poured onto the crushed ice. Solid product obtained was crystallized from ethanol.

Percentage yield: 80%, Melting point: 197- 199 ^{O}C

Procedure for the Synthesis of 4-acetamidophenoxyacetylhydrazide

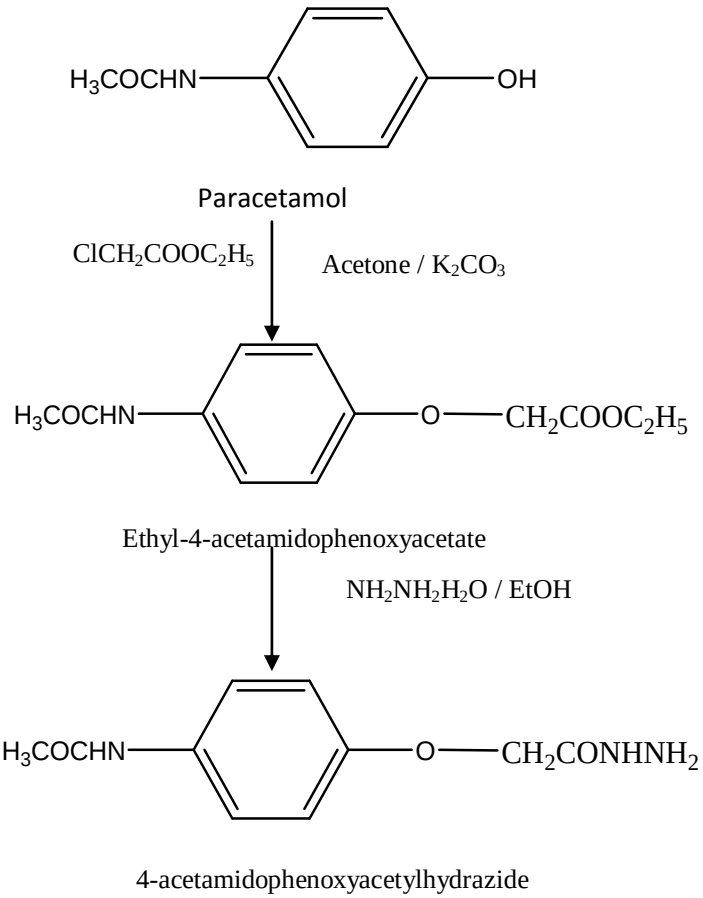
A mixture of ethyl-4-acetamidophenoxyacetate (2.835g, 0.01mol) and hydrazine hydrate (2.0 ml, 0.04 mol) in ethanol was refluxed for 5 hr. The solution was then poured onto crushed ice. The separated solid was crystallized from ethanol.

Percentage yield: 70%, Melting point: 155- 157 ^{0}C

Procedure for Synthesis of Schiff bases: (IIa-IIe)

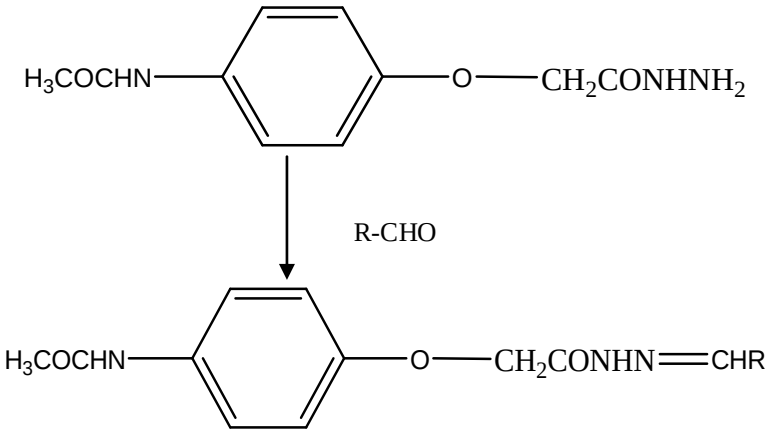
In a round bottomed flask, 4-acetamidophenoxyacetylhydrazide (2.23 gm, 0.01mol), various aldehyde (5 ml) and ehanol (30-35 ml) was taken and refluxed for three hours. The solution was cooled at room temperature and allowed to stand for 5 hours. Solid product was separated out, filtered, washed with ice cooled distilled water, dried and crystallized with ethanol. The Schiff Base was obtained.

SCHEME



Step I: Synthesis of 4-acetamidophenoxyacetylhydrazide

Step II: Synthesis of Schiff bases



R = Various aromatic aldehyde

Physical Characterization

Table: 1 Physical characteristics of synthesized compounds

Compound	R	Molecular Formula	Yield (%)	M. P. (°C)	Molecular Weight	Rf
IIa	CH_3	$C_{12}H_{15}N_3O_2$	58	235	215	0.6
IIb	C_6H_5	$C_{17}H_{17}N_3O_2$	62	242	279	0.4
IIc	$C_6H_4OCH_3$	$C_{18}H_{19}N_3O_3$	71	295	309	0.7
IId	p-OHC_6H_4	$C_{17}H_{17}N_3O_3$	74	286	295	0.7
IIe	p-$NO_2C_6H_4$	$C_{15}H_{11}N_4O_4$	73	172	324	0.6

Spectral Data of the Synthesized Compounds

IIa: IR- 3350 (N-H Stre. Secondary Amide), 3020 (Aromatic -C-H Stre.), 1690 (cyclic C=O Stre), . ^{1}HNMR- 11.88 (1H, s, HC=N), 8.1 (s, 1H, NH amide), 7.7-7.2 (m, 8H, Ar-CH), 3.3 (2H, -CH_2 - aromatic), 2.5 (1H, aromatic –CH-), 2.2 (3H, CH_3). MS – 213 (M^+)

IIb: IR- 3320 (N-H Stre. Secondary Amide), 3020 (C-H Stre phenyl), 1633 (cyclic C=O Stre).^{1}HNMR- 10.32 (1H, s, HC=N), 8.1 (s, 1H, NH amide), 7.7-7.2 (m, 8H, Ar-CH), 3.1 (2H, -CH_2 - aromatic), 2.4 (3H, CH_3). MS- 278 (M^+)

IIc: IR- 3330 (N-H Stre. Secondary Amide), 3040 (C-H Stre phenyl), 2820 (C-H Stre OCH_3), 1690 (cyclic C=O Stre). ^{1}HNMR- 11.34 (1H, s, HC=N), 8.1 (s, 1H, NH amide), 7.7-7.2 (m, 8H, Ar-CH), 3.3 (2H, -CH_2 - aromatic), 3.1 (3H, OCH_3), 2.5 (1H, aromatic –CH-). MS – 292 (M^+)

IId: IR- 3410 (O-H), 3250 (N-H Stre. Secondary Amide), 3020 (C-H Stre phenyl), 1640 (cyclic C=O Stre).^{1}HNMR- : 10.37 (1H, s, HC=N), 8.1 (s, 1H, NH amide), 7.7-7.2 (m, 8H, Ar-CH), 5.2 (s, 1H, OH), 3.3 (2H, -CH_2 - aromatic), 2.5 (1H, aromatic –CH-). MS – 295 (M^+)

IIe: IR- 3350 (N-H Stre. Secondary Amide), 3040 (C-H Stre phenyl), 1690 (cyclic C=O Stre), 1470 (O-NO_2 Stre.),. ^{1}HNMR- 10.52 (1H, s, HC=N), 8.1 (s, 1H, NH amide), 7.7-7.2 (m, 8H, Ar-CH), 3.2 (2H, -CH_2 - aromatic), 2.5 (1H, aromatic –CH-). MS – 324 (M^+)

Antimicrobial Activity

All the synthesized compounds were evaluated for their invitro antimicrobial activity against gram positive bacteria *staphylococcus aureus* (ATCC-24392), the gram negative bacteria *Echerichia coli* (ATCC-24391) in nutrient agar media, fungi *C Albicans* (ATCC-436) and *Aspergillus niger* in sabouraud dextrose medium. The zone of inhibition values were determined and compared with well known (standard) antibacterial Ofloxacin and antifungal Ketoconazole drugs. Table: 2 shows data obtained from the biological screening of synthesized compounds and reference drugs.

Table: 2 Antimicrobial screening data of synthesized compounds

Compounds	Zone of Inhibition (in mm) at concentration of 20 µg/mL)			
	S. aureus	***E. Coli***	***C. Albicans***	***Aspergillus niger***
IIa	09	13	22	24
IIb	12	15	24	23
IIc	11	14	26	27
IId	18	22	23	27
IIe	21	18	22	28
Ofloxacin	23	26	-----	-----
Ketoconazole	-----	-----	26	28

RESULT AND DISCUSSION

The present study reports the synthesis of some paracetamol incorporated Schiff bases derivatives. The synthesized compound were re-crystallized and identified by TLC, the R_f values were calculated and tabulated. The melting point of the product were found and are presented uncorrected in the table. Synthesized compound confirm by IR, NMR & Mass data. The compounds IIa-IIe has been investigated for their antibacterial activity against *S. aureus*, *E. Coli* and antifungal activity against *Aspergillus niger* and *C. albicans.* Ofloxacin and Ketoconazole were used as standards for antibacterial and antifungal activity respectively. Compound IId and IIe shows good activity against bacterium strain whereas compound IIc and IId shows good activity against fungal strain.

CONCLUSION

A series of paracetamol contending Schiff bases derivatives (IIa-IIe) were synthesized and characterized by analytical and spectral studies. The newly synthesized compounds were evaluated for antibacterial & antifungal. The present study showed that the antimicrobial activity of newly synthesized compounds may change by introduction or elimination of a specific group. Hence further structural modifications and screening is to be required to confirm the more and still better activity.

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