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Original Article

Synthesis and Antimicrobial Activity of Some New 5-Oxo-Imidazolidine Derivatives

Vivek Gupta[1]*, A. Pandurangan[2]

[1]Charak Institute of Pharmacy, Mandleshwar Dist. Khargone (M.P.)
[2]College of Pharmacy, MM University, Mullana, Ambala (Haryana)

Address for Correspondence
Charak Institute of Pharmacy,
Mandleshwar Dist.
Khargone (M.P.)
Tel. +91-9302255204
E-mail: Vivekg_srm06@yahoo.co.in

ABSTRACT

Schiff bases are synthesized from paracetamol. 4-acetamidophenoxyacetylhydrazide is synthesized from paracetamol, which on reaction with various aldehydes gives Schiff bases. Schiff bases treated with amino-acetic acid to produce Imidazolidine derivatives. 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**[1]. Some restrict the term to the secondary aldimines (azomethines where the carbon is connected to a hydrogen atom), thus with the general formula RCH=NR. Schiff bases derived from aromatic amines and aromatic aldehydes have a wide variety of applications in many fields, e.g., biological, inorganic and analytical chemistry[1-5]. Application of many new analytical devices requires the presence of organic reagents as essential compounds of the measuring system. They are used in optical and electrochemical sensors, as well as in various chromatographic methods, to enable detection of enhance selectivity and sensitivity[6-8]. Imidazole nucleus has proved to be a versatile moiety for a number of medicinal agents. The various activities associated with the imidazole nucleus are antiprotozoal, mutagenic properties, anticancer, antiviral, enzyme inhibition and broad spectrum antibacterial and antifungal activities. The aim of present study to make an efficient and less toxic antimicrobial agent with converting Schiff bases into imidazolone[9].

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MATERIALS AND METHODS

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).

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, 0.04mol) 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: (1a-1l)

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.

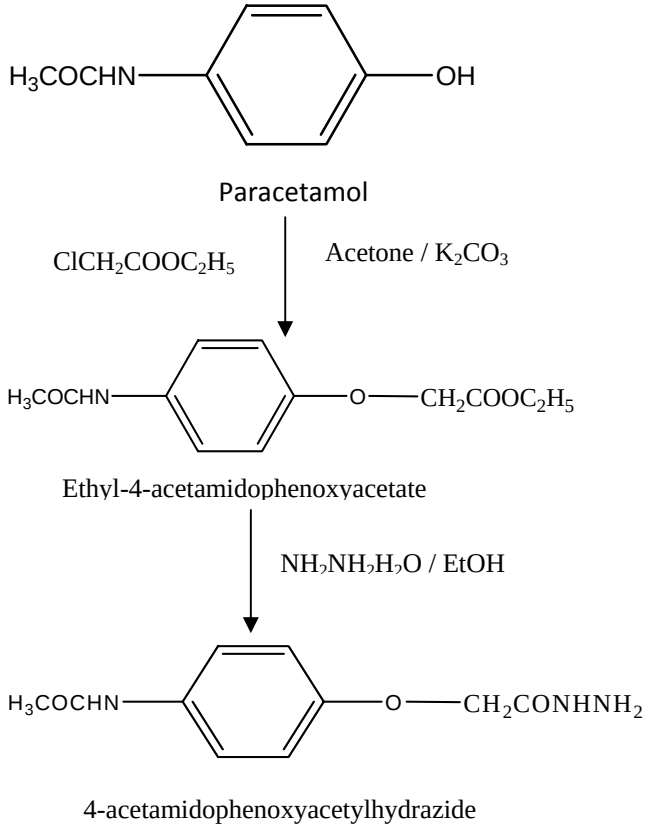
Percentage yield: 78%, melting point : 146- 148^{O}C

Procedure for Synthesis of 5-Oxo-Imidazolidine derivatives (2a-2l)

Schiff bases (1a-1l) (0.01 mol) and amino acetic acid (0.75gm, 0.01 mol) was dissolved in 1:4 dioxane (25ml) with constant stirring. The content was transferred to round bottom flask and heated under reflux for 5 hours. The mixture was allowed to cool at room temperature. The solid product was filtered, washed with ice cold water, dried and re-crystallised from ethanol.

SCHEME

Step I: Synthesis of 4-acetamidophen-oxyacetylhy-drazide



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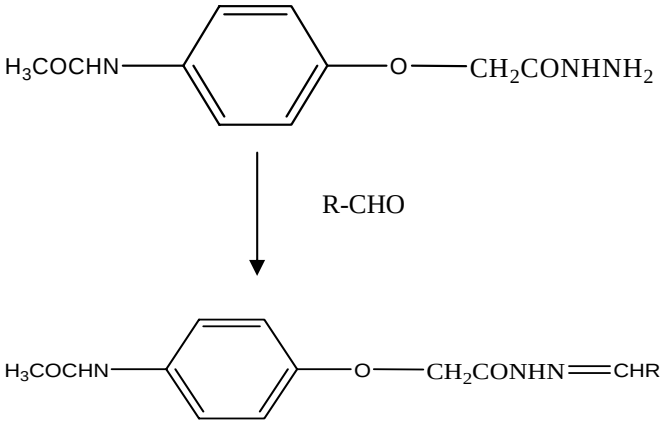
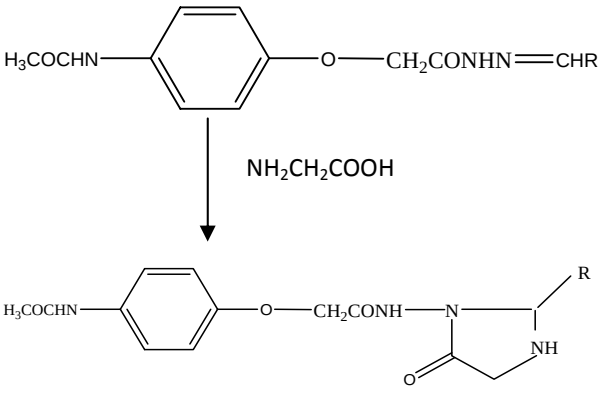
Step II: Synthesis of Schiff bases



Step- III: Synthesis of N-(5-oxo-2-aryl-imidazolidine-1-yl) 4-acetamidophen-oxyacetamide derivatives



2a-2l
R = Various aromatic aldehyde

Thin layer chromatography

The purity of synthesized compound was ascertained by TLC

Absorbent - Precoated silica gel plate
Mobile phase - Carbon tetra chloride:Chloroform: Methanol (6:2:2 v/v)
Detecting agent - Iodine vapour

R_f = Distance run by solute / Distance run by solvent

See Table 2

Spectral data of the synthesized compounds

2a: IR- 3390 (N-H Stre. Secondary Amide), 3350 (N-H Stre imidazolidine), 3050 (Aromatic -C-H Stre.), 1610 (acyclic C=O stre.), 1340 (C-NH imidazolidine).

^{1}HNMR- 9.6 (m, 1H NH cyclic), 8.1 (s, 1H, NH amide), 7.6-7.2 (m, 8H, Ar-CH), 3.3 (d, 2H, -CH_2- aromatic), 2.5 (m, 1H, aromatic –CH-).

MS - 367(M^+)

2b: IR- 3360 (O-H Stre.), 3340 (N-H Stre imidazolidine), 3040 (Aromatic -C-H Stre.), 1610 (acyclic C=O stre.), 1340 (C-NH imidazolidine).

^{1}HNMR- 9.6 (m, 1H NH cyclic), 8.1 (s, 1H, NH amide), 7.6-7.3 (m, 8H, Ar-CH), 5.2 (s, 1H, OH), 3.3 (d, 2H, -CH_2- aromatic), 2.2 (s, 3H, CH_3).

MS- 384 (M^+)

2c: IR- 3370 (N-H Stre. Secondary Amide), 3350 (N-H Stre imidazolidine), 3020 (Aromatic -C-H Stre.), 1610 (acyclic C=O stre.), 1340 (C-NH imidazolidine), 810 (C-Cl).

^{1}HNMR- 9.6 (m, 1H NH cyclic), 8.1 (s, 1H, NH amide), 7.6-7.2 (m, 8H, Ar-CH), 3.3 (2H, -CH_2- aromatic), 2.5 (1H, aromatic –CH-), 2.2 (3H, CH_3).

MS – 401.1(M^+)

2d: IR- 3430 (N-H Stre of Primary Amine), 3390 (N-H Stre. Secondary Amide), 3350 (N-H Stre imidazolidine), 3050 (Aromatic -C-H Stre.),1610 (acyclic C=O stre.), 1490 (CH_2 bend.), 1340 (C-NH imidazolidine).

^{1}HNMR- : 9.6 (s, 1H, NH cyclic), 8.1 (s, 1H, NH amide), 7.6-7.2 (m, 8H, Ar-CH), 5.0 (d, 2H, NH_2), 3.3 (2H, -CH_2- aromatic), 2.5 (1H, aromatic –CH-).

MS – 383 (M^+)

2e: IR- 3360 (N-H Stre. Secondary Amide), 3310 (N-H Stre imidazolidine), 3040

(Aromatic -C-H Stre.), 2815 (C-H Stre OCH_3), 1710 (acyclic C=O stre.), 1360 (C-NH imidazolidine).

^{1}HNMR- 9.6 (s, 1H NH cyclic), 8.1 (s, 1H, NH amide), 7.6-7.2 (m, 8H, Ar-CH), 4.1 (t, 3H, OCH_3), 3.3 (2H, -CH_2 - aromatic), 2.5 (1H, aromatic –CH-).

MS – 396 (M^+)

2f: IR- 3360 (N-H Stre. Secondary Amide), 3310 (N-H Stre imidazolidine), 3010 (Aromatic -C-H Stre.), 2920 (Aliphatic C-H Stre.), 1610 (acyclic C=O stre.), 1340 (C-NH imidazolidine).

^{1}HNMR- 9.6 (s, 1H NH cyclic), 8.1 (s, 1H, NH amide), 7.6-7.2 (m, 8H, Ar-CH), 3.3 (t, 3H, -CH_3), 2.5 (1H, aromatic –CH-).

MS – 381 (M^+)

2g: IR- 3360 (N-H Stre. Secondary Amide), 3320 (N-H Stre imidazolidine), 3040 (Aromatic -C-H Stre.), 1610 (acyclic C=O Stre.), 1490 (N-O Stre.), 1340 (C-NH imidazolidine).

^{1}HNMR- 9.6 (s, 1H NH cyclic), 8.1 (s, 1H, NH amide), 7.6-7.2 (m, 4H, Ar-CH), 3.3 (2H, -CH_2 - aromatic), 2.5 (1H, aromatic –CH-).

MS – 381 (M^+)

2h: IR- 3410 (O-H Stre.), 3370 (N-H Stre. Secondary Amide), 3310 (N-H Stre imidazolidine), 3050 (Aromatic -C-H Stre.), 1610 (acyclic C=O stre.), 1340 (C-NH imidazolidine).

^{1}HNMR- 9.6 (s, 1H NH cyclic), 8.1 (s, 1H, NH amide), 7.6-7.2 (m, 7H, CH), 5.2 (d, 2H, OH), 3.3 (2H, -CH_2 - aromatic), 2.5 (1H, aromatic –CH-).

MS – 399 (M^+)

2i: IR- 3390 (N-H Stre. Secondary Amide), 3330 (N-H Stre imidazolidine), 3020 (Aromatic -C-H Stre.), 1610 (acyclic C=O stre.), 1340 (C-NH imidazolidine), 810 (C-Cl Stre).

^{1}HNMR- 9.6 (s, 1H NH cyclic), 8.1 (s, 1H, NH amide), 7.6-7.2 (m, 8H, Ar-CH), 3.3 (2H, -CH_2 - aromatic), 2.5 (1H, aromatic –CH-).

MS – 432 (M^+)

2j: IR- 3390 (N-H Stre. Secondary Amide), 3350 (N-H Stre imidazolidine), 3050 (Aromatic -C-H Stre.), 1610 (acyclic C=O stre.), 1340 (C-NH imidazolidine).

^{1}HNMR- 9.6 (s, 1H NH cyclic), 8.1 (s, 1H, NH amide), 7.6-7.2 (m, 8H, Ar-CH), 5.0 (s, 4H, NH_2), 3.3 (2H, -CH_2 - aromatic), 2.5 (1H, aromatic –CH-).

MS – 396 (M^+)

2k: IR- 3360 (N-H Stre. Secondary Amide), 3310 (N-H Stre imidazolidine), 3020 (Aromatic -C-H Stre.), 1610 (acyclic C=O stre.), 1490 (N-O Stre), 1340 (C-NH imidazolidine).

^{1}HNMR- 9.6 (s, 1H NH cyclic), 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-).

MS – 457 (M^+)

2l: IR- 3390 (N-H Stre. Secondary Amide), 3350 (N-H Stre imidazolidine), 3050 (Aromatic -C-H Stre.), 1610 (acyclic C=O stre.), 1350 (C-NH imidazolidine), 820 (C-Cl Stre.)

^{1}HNMR- 9.6 (s, 1H NH cyclic), 8.1 (s, 1H, NH amide), 7.7-6.8 (m, 8H, Ar-CH), 3.3 (2H, -CH_2 - aromatic), 2.5 (1H, aromatic –CH-).

MS – 401 (M^+)

Antimicrobial Method

The *in vitro* antimicrobial activity was carried out against 24 h old cultures of two bacteria and two fungi by cup-plate method. The compounds **2a-2l** has been investigated for their antibacterial activity against *S. aureus, E. Coli, Pseudomonas aeruginosa* and *Staphylococcus aureus* and antifungal activity against *Aspergillus niger* and *C. albicans*. Chloramphenicol and fluconazole were used as standards 20µg/mL for antibacterial and antifungal activity respectively. The compounds were tested at a concentration of 20µg/mL in DMF against all organisms. The zone of inhibition was

compared with the standard drug after 24 h of incubation at 25°C for antibacterial activity and 48 h at 30°C for antifungal activity.

RESULT AND DISCUSSION

The present study reports the synthesis of some paracetamol incorporated N-(5-oxo-2-aryl-imidazolidine-1-yl) 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 **2a**-**2l** has been investigated for their antibacterial activity against *S. aureus*, *E. Coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* and antifungal activity against *Aspergillus niger* and *C. albicans*. Chloramphenicol and fluconazole were used as standards for antibacterial and antifungal activity respectively. Compound 2c, 2e and 2f shows good activity against bacterium strain.

CONCLUSION

A series of paracetamol containing 5-oxo- imidazolidine derivatives **(2a-2l)** 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. Thus, the imidazole derivatives could be powerful and elegant factor to stimulate major advances in chemotherapeutic agents of remarkable significance in medicine, biology and pharmacy. The results obtained here indicated, that ring systems enhances the activity to a considerable extent. In many cases, presence of electron withdrawing group results in increase of activity. Hence further structural modifications and screening has to be done to confirm the more and still better activity.

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Table 1. Physical characterization

Compound	% Yeild	Appearance	Melting Point (°C)	Molecular Formula	Molecular Weight
2a	73	White Crystals	286-287	$C_{19}H_{20}O_4N_4$	368
2b	76	White Crystals	283-284	$C_{19}H_{20}O_5N_4$	384
2c	71	Yellowish crystals	247-249	$C_{19}H_{19}O_4N_4Cl$	402
2d	73	White Crystals	242-244	$C_{19}H_{21}O_4N_5$	383
2e	69	Radish brown crystals	232-233	$C_{20}H_{22}O_5N_4$	398
2f	72	White Crystals	247-249	$C_{20}H_{22}O_4N_4$	382
2g	75	Greenish white crystals	251-252	$C_{19}H_{19}O_6N_5$	413
2h	68	Light yellow crystals	267-268	$C_{19}H_{20}O_6N_4$	400
2i	63	Brown Crystals	258-259	$C_{19}H_{18}O_4N_4Cl_2$	436
2j	64	White Crystals	271-272	$C_{19}H_{22}O_4N_6$	398
2k	74	White Crystals	268-269	$C_{19}H_{18}O_8N_6$	458
2l	73	Brown crystals	271-272	$C_{19}H_{19}O_4N_4Cl$	402

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Table 2. R_f Value of the synthesized compounds

S. No.	Code of compounds	R_f Value
1.	2a	0.61
2.	2b	0.67
3.	2c	0.56
4.	2d	0.59
5.	2e	0.62
6.	2f	0.57
7.	2g	0.62
8.	2h	0.58
9.	2i	0.65
10.	2j	0.57
11.	2k	0.64
12.	2l	0.69

Table 3. Zone of inhibition of the synthesized compounds
(Antibacterial screening data of compound 2a-2l)

Compounds	Zone of Inhibition (in mm) at concentration of 20µg/mL)			
	S. aureus	*E. coli*	*P. aeruginosa*	*K. pneumonia*
2a	14	18	24	23
2b	17	19	23	15
2c	22	19	25	23
2d	18	17	26	22
2e	22	24	26	24
2f	22	21	24	24
2g	19	18	25	25
2h	21	24	17	09
2i	19	20	13	12
2j	13	12	12	21
2k	15	17	11	16
2l	19	19	18	23
Chloramphenicol	24	28	27	28

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(Antifungal screening data of compounds 2a-2l)

Comp.	Std.	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	2k	2l
C. albicans	28	11	14	21	13	23	24	14	21	16	13	11	11
A. niger	27	12	14	22	20	16	22	19	15	14	-	13	12