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Research Paper

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF MANNICH BASES OF 7-HYDROXY-4-METHYL COUMARIN

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The attempt to synthesize mannich bases of 7-hydroxy-4-methyl coumarin were successfully carried out as per the scheme mentioned. The entire synthesized compounds are primarily characterized by running T.L.C. and melting point analysis.The structures of the compounds synthesized are confirmed by I.R.,NMR and Mass spectrum. The Anti-inflammatory activity was determined by in vivo using carrageenan-induced paw edema test using diclofenac sod. (25mg/kg) as standard drug. All compounds showed mild to moderate activity. The compounds (2b,2d,2e,2i,2j) showed excellent activity as compared to standard diclofenac sodium.

Key Words: Diclofenac sodium, I.R.,NMR and Mass spectrum

INTRODUCTION

Coumarin is used in the pharmaceutical industry as a precursor molecule in the synthesis of a number of synthetic anticoagulantdicoumarol, notably warfarin (which has a common and confusing brand name *Coumadin*) and some even more potent rodenticides that work by the same anticoagulant mechanism.

Coumarin has clinical medical value by itself, as an edema modifier i.e. anti-inflammatory activity. Coumarin and other benzopyrones, such as 5,6benzopyrone, 1,2 benzopyrone, diosmin and others are known to stimulate macrophages to degrade extracellular albumin, allowing faster resorption of edematous fluids

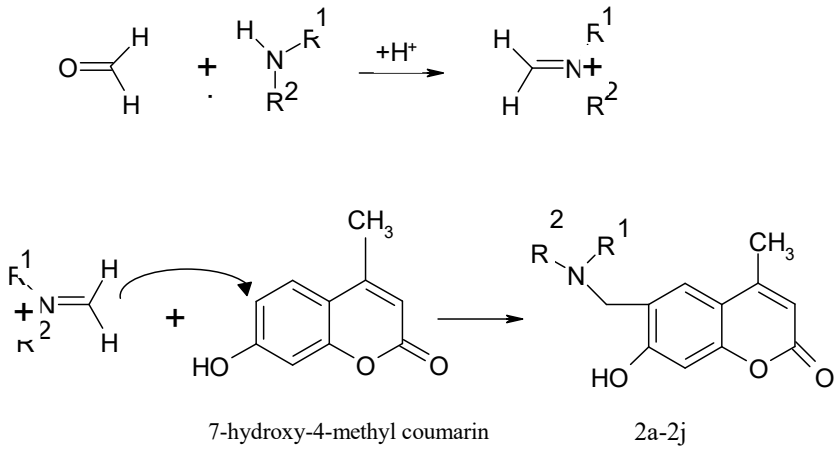

Fig. 1: Scheme for synthesis of mannich bases of 7-hydroxy-4-methyl coumarin

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In vitro Antibacterial screening

The synthesized compound s were subjected to antibacterial screening by cup plate method for zone inhibition and by estimating the minimum inhibitory concentration (MIC) by adopting two –fold serial dilution technique.

Materials:

Microorganisms used:

Selected bacterial Strains: *Bacillus Subtillis, Klebsiella Pneumoniae* (gram positive),E.coli , Pseudomonas aeruginasa (gram negative).

Drug (Control):

Standard drug: Ciprofloxin (Antibacterial Agent)

Solvent (Control); DMSo(200µl)

Title Compounds:

2a) 6-[(dimethylamino)methyl]-7-hydroxy-4-methyl-2*H*-chromen-2-one

2b) 7-hydroxy-4-methyl-6-(morpholin-4-yl methyl)-2*H*-chromen-2-one

2c) 7-hydroxy-4-methyl-6-(piperidin-1-ylmethyl)-2*H*-chromen-2-one

2d) 6-[(diethylamino)methyl]-7-hydroxy-4-methyl-2*H*-chromen-2-one

2e) 6-[(diphenylamino)methyl]-7-hydroxy-4-methyl-2*H*-chromen-2-one

2f) 6-(1*H*-benzimidazol-1-ylmethyl)-7-hydroxy-4-methyl-2*H*-chromen-2-one

2g) 6-(1*H*-benzotriazol-1-ylmethyl)-7-hydroxy-4-methyl-2*H*-chromen-2-one

2h) 7-hydroxy-6-{[(1-hydroxy-1-phenylpropan-2-yl)(methyl)amino]methyl}-4-methyl-2*H*-chromen-2-one

Culture Media: Nutrient broth

Testing for Anti-bacterial activity by cup plate mehod

Requirements:

Nutrient broth

Petri dishes

Standardized culture of test organisms

Sterile Pipettes

Test drug

Standard drug

Gram +ve bacteria		Gram –ve bacteria	
Bacillus subtillis	Klebsiella Pneumoniae	E. coli	Pseudomonas aeruginasa

Method:

1) Sterile nutrient broth plates were be prepared by pouring the sterile agar into petri dishes in aseptic conditions. 0.1 ml of each standardized test organism arespreaded into agar plates.

2) Holes were prepared by using a sterile borer of diameter 6 mm. The test drug as well as the standard drug and the solvent control were placed in each hole separately.

3) Then the plates were maintained at+4°C for 1 hr to allow the diffusion of solution into the medium.

4) All the bacterial plates will be incubated at 37°C for 24 hrs.

5) The zone of inhibition will be measured in mm.

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Table1: In vitro Antibacterial Activity of the synthesized compound

Sample no.	Gram +ve bacteria		Gram –ve bacteria	
	Bacillus subtillis	Klebsiella Pneumoniae	E.coli	Pseudomonas aeruginasa
	Z.O.I.	Z.O.I.	Z.O.I.	Z.O.I.
2a	19mm	12mm	12mm	13mm
2b	20mm	13mm	11mm	14mm
2c	19mm	11mm	15mm	14mm
2d	17mm	11mm	11mm	16mm
2e	18 mm	18mm	13mm	11mm
2f	16mm	12mm	17mm	12mm
2g	17mm	15mm	14mm	15mm
2h	20mm	14mm	16mm	17mm
Std.	35mm	35mm	35mm	35mm

	Gram +ve bacteria		Gram –bacteria	
	Bacillus subtillis	Klebsiella Pneumoniae	E.coli	Pseudomonas aeruginasa
	% inhi.	% inhi.	% inhi.	% inhi.
2a	54.28	34.29	34.29	37.43
2b	57.14	37.14	31.43	40.0
2c	54.28	31.43	42.86	40.0
2d	48.57	31.43	31.43	45.75
2e	51.0	51.0	37.43	31.43
2f	46.0	34.29	49.0	34.29
2g	49.0	42.86	40.0	42.86
2h	57.0	40.0	45.75	49.0
Std.	100	100	100	100

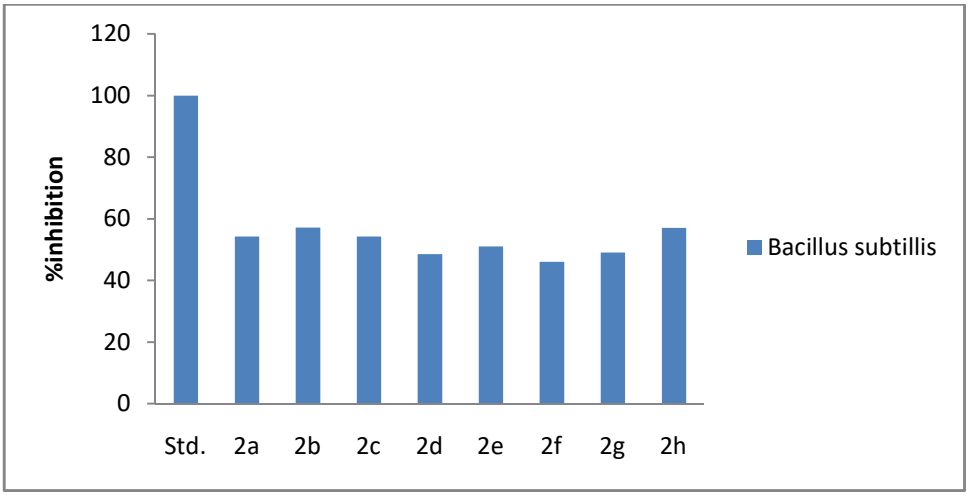

Fig. 1: The percentage inhibition of title compound on Bacillus subtillis

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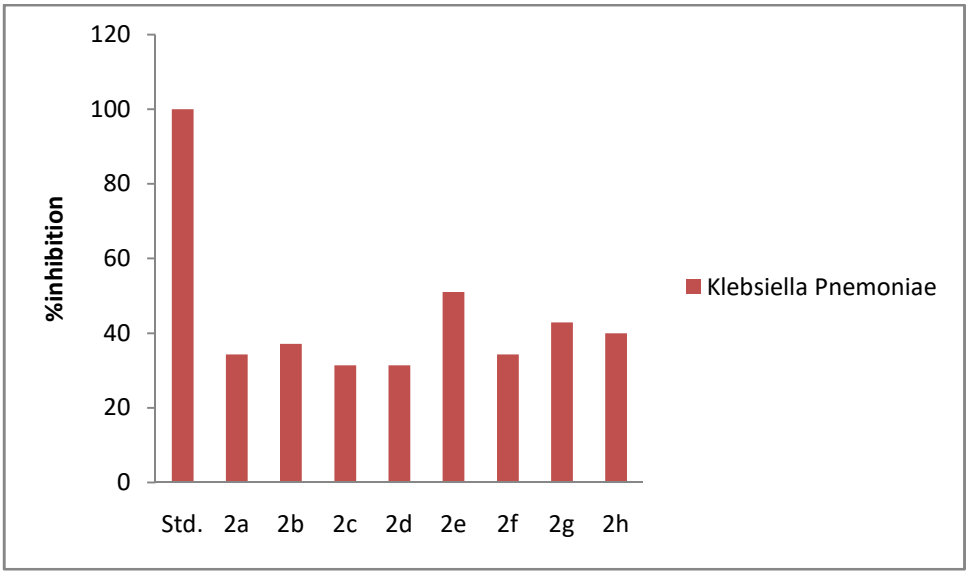

Fig. 2: Percentage inhibition of title compound on Klebsiella Pnemoniae

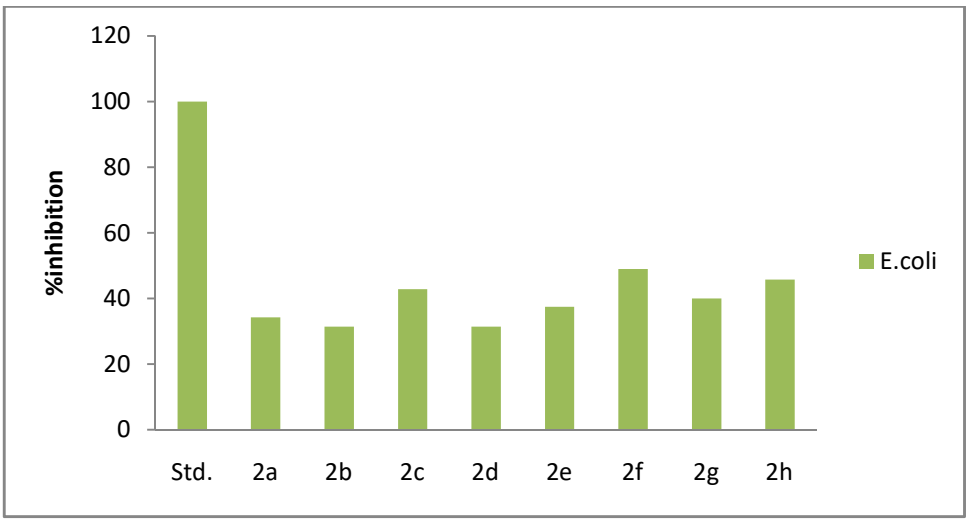

Fig3: The percentage inhibition of title compound on E.coli

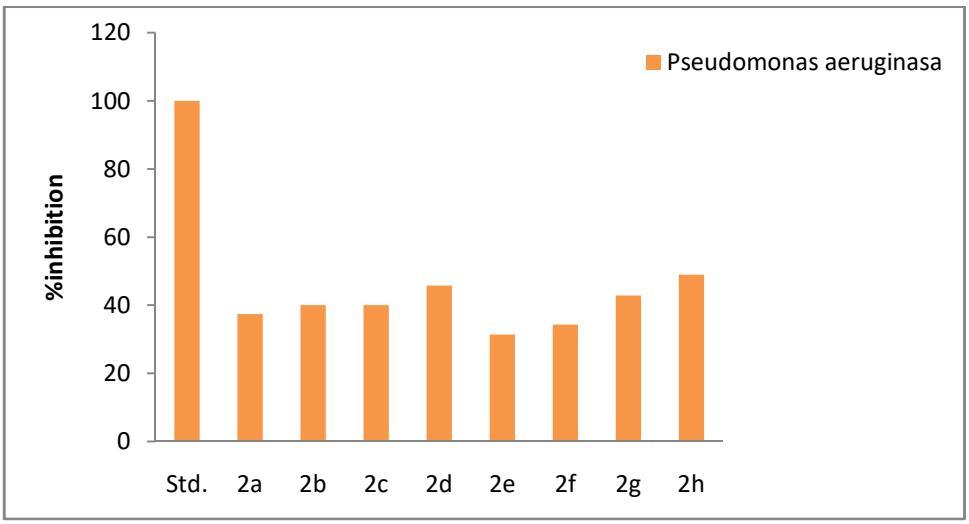

Fig. 4: The percentage inhibition of title compound on Pseudomonas aeruginasa

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Animals

Adult albino mice (25-32 g)[38] of both sexes may used. Animals were housed in steel cages under standard conditions and fed with standard pellets and water *ad libitum*[39]. The mice were obtained from the Department of Pharmacology, B.N.College of Pharmacy, Udaipur, Rajasthan, India. The animals are divided into groups of four each and fasted for 12 hr before the experiment. The ethical guidelines prescribed for the investigation of animals used in experiments were followed in all the tests.

Anti-inflammatory activity

Anti-inflammatory activity was determined *in vivo* using the carrageenan-induced mice paw edema test[40-42]. Animals of either sex were divided into ten groups of four each. A solution of 0.1 ml of 1% carrageenan[43] in saline was injected subplantarly into the right hind paw of the mice 1 h after i.p. administration of the compounds. Paw thickness was measured from the ventral to the dorsal surfaces immediately prior to carrageenan injection and then at each hour, up to three hours after the subplantar injection. Edema was calculated as the thickness variation between the carrageenan and control treated paws. Anti-inflammatory activity expressed as the percent of inhibition of the edema when compared with the control group and was calculated by using the formula.

$\Delta V = V_t - V_o$

= Mean paw volume

% inhibition of edema = [1 – (ΔV experimental / ΔV control)] × 100

Where, V_t and V_c are the paw volumes of the test and control groups, respectively.

RESULT AND DISCUSSION

The attempt to synthesize mannich bases of 7-hydroxy-4-methyl coumarin were successfully carried out as per the scheme mentioned. The entire synthesized compounds are primarily characterized by running T.L.C. and melting point analysis.

The structures of the compounds synthesized are confirmed by I.R., NMR and Mass spectrum.

Anti bacterial Activity-

All the compounds have shown good activity against *Basillussubtilis,* In case of *KlebsiellaPneumoniae* compound show moderate activity. Compound 2b show excellent activity against *Bacillus subtilis*in comparison of others.Whereas other compound possess mild to moderate activity in comparison with the standard i.e. Ciprofloxacin.

Anti inflammatory Activity-

The Anti-inflammatory activity was determined by in vivo using carrageenan-induced paw edema test using diclofenac sod. (25mg/kg) as standard drug. All compounds showed mild to

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moderate activity. The compounds (2b,2d,2e,2i,2j) showed excellent activity as compared to standard diclofenac sodium.

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