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Synthesis of some azetidinones with coumarinyl moiety and their antimicrobial activity

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ABSTRACT

Compounds bearing azetidinone moiety having β-lactam ring which is an antibiotic still in the list of the prescription[1] are endowed with a variety of biological activities such as sedative, hypnotic, anticonvulsant[2,3], herbicidal[4] and antibacterial[5]. Looking over to these properties it was contemplated to synthesis some Azetidinones having coumarin moiety type(II) which may enhance the biological activity with least side effect. The structures of type (II) have been characterized by the elemental analysis and the spectral data. The compounds were screened for their antimicrobial activity using different strains of Bacteria's and Fungi.

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KEYWORDS

Schiff's base;
Azetidinones;
Antimicrobial activity.

INTRODUCTION

Benzopyrones forms a fascinating group of the compounds occurring widely both in free and combined states. Benzo-α pyrones so called coumarin is a mile stone in a path of natural chemistry; due to its varied biochemical & analytical applications[6].

Due to its varied industrial use in perfumery, backery, beverages, soap, tobacco, rubber and plastic industries, a considerable amount of work has been some coumarins & has been reviewed by a number of workers[7,8].

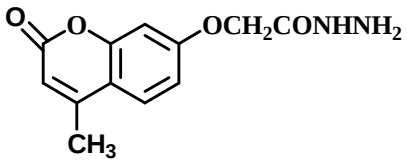
Coumarin derivatives are reported to have an excellent biological activity such as anthelmintic[9], antiallergic, antiarthritic[10], antibacterial[11], anticancerous [12], anticoagulant[13], antifungal[14], antiinflamatory[15], antimalarial[16], antinaphylactic[10], antiproliferative [17], antispasmodic[18], hypnotic[19], hypolipidimic[20], hypotensive[21], insecticidal [22], antifertility[23], potential nervous system depressant sedative[24].

It would enhance the therapeutic activity, if the coumarinyl moiety is joined with the moiety having β-lactam ring. During synthesis of substituted azetidinones, we came across different synthetic routes adopted by different workers.Parikh[25] and Joshi[26] synthesized azetidinones requiring 5 hour stirring and keeping reaction mixture for 3 days for the reaction of acetyl chloride or chloroacetylchloride with Schiff's base using Dioxane as solvent and Triethyl amine as the catalyst reporting 65% yield.

The starting compound i.e. Schiff's base 7-(4'-methoxybenzal hydrazino carbonyl methoxy)-4-methyl coumarin was characterized by elemental analysis as well as various spectroscopic data.

EXPERIMENTAL

All the melting points are taken in an open capillary tube and all uncorrected I.R spectra (KBr) were recorded on Perkin Elmer spectrometer and 1H NMR spectrometer at 300MHz. the purity of compound was checked by TLC using Silica gel-G.



Preparation of the Schiff base[7-(substituted benzal hydrazinocarbonylmethoxy)-4-methylcoumarin]

(A) Preparation of 4-methyl-7-hydrazinocarbonylmethoxycoumarin[27]

The 7-Hydroxy-4-methyl coumarin was esterified stirring for 12 hrs. with ethylchloroacetate in acetone and refluxed. The ester formed was then taken in rectified spirit to which hydrazinehydrate was added and further refluxed for 8Hrs. then after it is cooled and poured in ice to give crystalline product with (m.p. - 115ºC).yield 75%

(Found C-58.06%, H-4.83% and N-11.29%; Calculated C - 58.10%, H-4.78% and N-11.33%) For C_{12} H_{12} N_2O_4.

(B) Preparation of Schiff's Base[4-methyl-7-(substituted benzylhydrazinocarbonylmethoxy) coumarin][27]

A mixture of hydrazine (0.01M, 2.48 gm) was dissolved in alcohol then p-Anisaldehyde (0.01 M, 1.36 gm) was added to it, refluxed for four hours. The reaction mixture was cooled and the product was isolated as well as crystallized in DMF to give shinning white crystal (m.p 248ºC) Yield 75% , (Found C-65.52% , H-4.9% and N-7.62%; Calculated C-65.57%, H-4.9% and N-7.65%) For C_{20} H_{18} N_2 O_5.

Similarly other Schiff bases were prepared.The physical constants are recorded in TABLE 1.

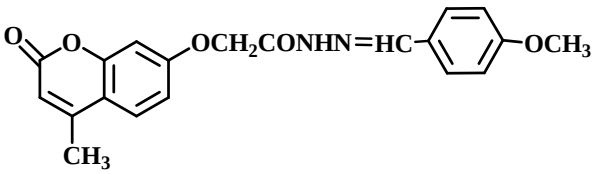


TABLE 1

(A) 4-methyl-7-[(4'-methoxybenzyl hydrazinocarbonylmethoxy] coumarin

Sr. no.	R.	Mol. Form.	m.p ºC	Ppercentage % Yield	N Calc.	N found
1	Phenyl	$C_{19}H_{16}N_2O_4$	254	70	8.30	8.28
2	3-Aminophenyl	$C_{19}H_{17}N_3O_4$	256	65	11.97	11.94
3	4-Aminophenyl	$C_{19}H_{17}N_3O_4$	225	65	11.97	11.95
4	5-bromo-4-hydroxy-3-methoxyphenyl	$C_{20}H_{17}N_2O_6Br$	250	70	6.07	6.06
5	2-chlorophenyl	$C_{19}H_{15}N_2O_4Cl$	263	70	7.56	7.54
6	5-chlorophenyl	$C_{19}H_{15}N_2O_4Cl$	218	70	7.56	7.52
7	3,4-dibromo-2-hyroxy phenyl	$C_{19}H_{14}N_2O_5Br_2$	268	65	5.50	5.52
8	3,4-dichlorophenyl	$C_{19}H_{14}N_2O_4Cl_2$	265	65	6.93	6.92
9	3,4-dimethoxyphenyl	$C_{21}H_{20}N_2O_6$	270	65	7.07	7.08
10	3,4-dimethoxy-5-nitrophenyl	$C_{21}H_{19}N_3O_8$	175	75	9.52	9.52
11	4-Methoxyphenyl	$C_{20}H_{18}N_2O_5$	248	75	7.65	7.62

(B) N.M.R spectral data

Signle no.	δ p.p.m	No.of protons	Multiplicity	Inference
1	2.35	3H	Singlet	-CH3
2	3.75	3H	Singlet	-OCH3
3	4.60	2H	Singlet	-OCH2-
4	6.80	1H	Singlet	-N=CH-Ar
5	6.9	1H	Singlet	-CH-coumarin
6	7.5-7.9	8H	Multiplet	Aromatic H
7	8.1	1H	Singlet	-CO-NH-N=

(C) IR Spectral study (SHIMADZU-2245)

Type	Vibration mode	Freq in cm^{-1} Obs.	Reported	Ref.
Alkane	-C-H str.(asym)	2950	2975-2950	[28-29]
$-CH_3$	-C-H str. (sym)	2855	2880-2860	-
$-CH_2$	-C-H str.(asym)	2935	2940-2915	-
	-C-H str. (sym)	2875	2890-2845	-
	-C-H str.	3050	3080-3030	-
Aromatic (1-4-isubst.)	-C=C- str.	1620	1612-1600	-
		1580	1585-1573	-
		1500	1520-1480	-
		1405	1417-1401	-
	-N-H. str. (asym.)	3455	3550-3250	-
	-N-H. str. (sym.)	3310	3450-3250	-
Amide	-N-H. def,	1550	1650-1580	-
-CO-NH-N-	-C-N. str.	1120	1220-1020	-
	-C=O str.	1690	1680-1630	-
	Schiffbase linkage	1630	1690-1580	-
-CH3	-C-O-C-(asym.)	1275	1275-1200	-
	-C-O-C(sym.)	1050	1075-1020	-
Coumarin moiety	-C=O	1725	1725-1730	-
		1275	1275-1200	-

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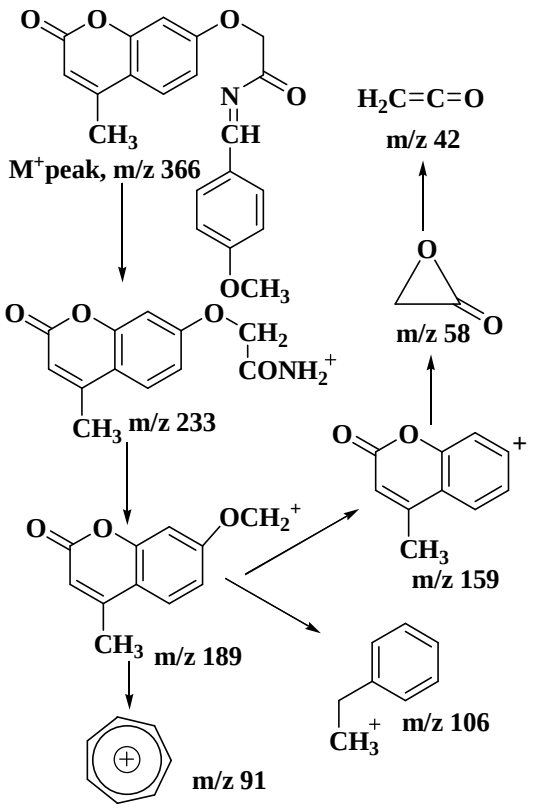
(D) Mass Fragmantation



2. Preparation of 4-(4″ methoxyphenyl)-3-chloro-1-(4′ methyl-7'-carbamoylmethoxycoumarinyl)-2-azetidinones

Schiff's base (0.01M 3.66gm) was taken in Dioxan (60ml0, to it chloroacetyl chloride (0.01M 0.079 ml) was addedslowly at the room temperature with constant stirring, then triethylamine was added (0.01 M,1.39ml) the whole mixture was stirred at 80ºC temperature for about 8 hours a and was left over for crystalisation for 2-3 days . the excess of the solvent was distilled off and the product was isolated and recrystalised in dioxin Yield -55%; m.p.-218ºC, elemental analysis found was C-59.71%; H-4.29%; N-6.28% and Calculated C-59.68%, H-4.3% and N-6.43%).

TABLE 2: 4-(4″ methoxyphenyl)-3-chloro-1-(4′ methyl-7′-carbamoylmethoxy-coumarinyl)-2-azetidinones

(a) Physical constants

Sr. no.	R.	Mol. form.	M.p ºC	Percentage % Yield	N Calc	N found
1	Phenyl	$C_{21}H_{17}N_2O_5Cl$	225	55	6.79	6.79
2	3-Aminophenyl	$C_{21}H_{18}N_3O_5Cl$	180	60	9.83	9.83
3	4-Aminophenyl	$C_{21}H_{18}N_3O_5Cl$	260	50	9.83	9.83

(A) Physical constants

Sr. no.	R.	Mol. form.	m.p ºC	Percentage % Yield	N Calc	N found
4	5-Bromo-4-hydroxy-3-methoxyphenyl	$C_{22}H_{18}N_2O_7Cl\ Br$	195	45	5.21	5.21
5	2-Chlorophenyl	$C_{21}H_{16}N_2O_5Cl_2$	185	40	6.27	6.27
6	5-Chlorophenyl	$C_{21}H_{16}N_2O_5Cl_2$	175	55	6.27	6.27
7	3,4-Dibromo-2-hyroxy phenyl	$C_{21}H_{15}N_2O_6ClBr_2$	180	60	4.90	4.91
8	3,4-Dichlorophenyl	$C_{21}H_{15}N_2O_5Cl_3$	150	70	5.83	5.83
9	3,4-Dimethoxyphenyl	$C_{23}H_{21}N_2O_7Cl$	205	50	5.93	5.93
10	3,4-Ddimethoxy-5-nitrophenyl	$C_{23}H_{20}N_3O_9Cl$	165	50	8.12	8.12
11	4-Methoxyphenyl	$C_{22}H_{19}N_2O_6Cl$	218	55	6.43	6.28

(B) N.M.R spectral data

Signal no.	δ p.p.m	No.of protons	Multiplicity	Inference
1	2.35	3H	Singlet	$-CH_3$
2	4.01	3H	Singlet	$-OCH_3$
3	4.6	2H	Singlet	$-OCH_2-$
4	6.01	1H	Singlet	-CH-Azet.
5	6.8	1H	Doublet	-CH-Cl
6	6.95	1H	Singlet	-CH-Coumarin
7	7.5-7.7	4H	Multiplet	
8.	7.9	1H	Singlet	-CO-NH-N=

(C) IR spectral study (SHIMADZU-2245)

Type	Vibration mode	Freq in cm^{-1} Obs.	Reported	Ref.
Alkane $-CH_3$	-C-H str.(asym)	2955	2975-2950	[28-29]
	-C-H str. (sym)	2865	2880-2860	-
$-CH_2$	-C-H str.(asym)	2850	2850-2765	-
	-C-H sci.	1440	1480-1440	-
	-C-H twisting	1255	1250	-
Aromatic (1-4-disubst.)	-C-H str.	3075	3080-3030	-
	-C=C- str.	1612	1612-1600	-
		1575	1585-1573	-
		1485	1520-1480	-
		1401	1417-1401	-
	-C-H (oop) def.	830	832-802	-
Amide -CO-NH-N-	-N-H.str.(asym.)	3450	3550-3250	-
	-N-H. str.(sym.)	3250	3350-3250	-
	-C-N. str. + -N-H def II band	1550	1570-1580	-
	-C-N. str. + -N-H def III band	1305	1305-1200	-
Ether linkage	-C=O str.2º	1650	1680-1630	-
	-C-O-C-(asym.)	1210	1275-1200	-
	-C-O-C(sym.)	1075	1075-1020	--
Coumarin moiety	-C=O	1725	1725-1730	-
	α-lactonic ring	1260	1220-1260	-
	C=O (str.)	1715	1760-1660	-

(D) Mass Spectra

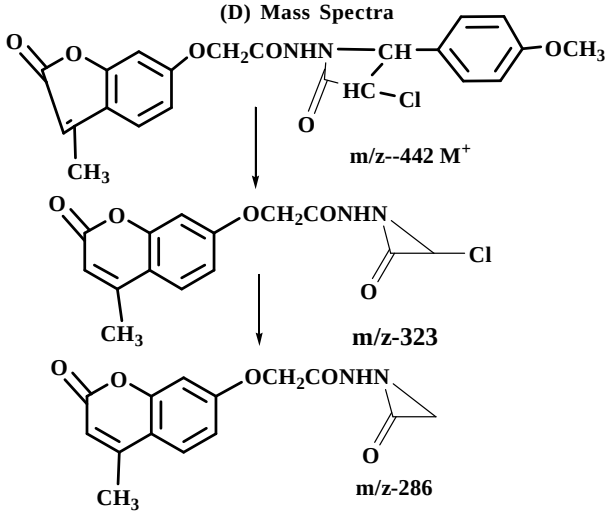


TABLE 3: Anti microbial activity of 4-(Substituted phenyl)-3-chloro-1-(4′ methyl-7′-carbamoylmethoxycoumarinyl)-2-azetidinones

Sr. no.	Compound	Zone of inhibition in mm.				
		Bacteria				Fungi
		B.maget	*S.Citrus*	*E.coli*	*S.Typhosa*	*A.Niger*
1	Phenyl	15	15	16	21	16
2	3-Aminophenyl	13	15	18	14	18
3	4-Aminophenyl	19	16	10	18	15
4	5-bromo-4-hydroxy-3-methoxyphenyl	16	17	18	18	16
5	2-chlorophenyl	13	13	10	20	16
6	5-chlorophenyl	16	20	15	13	16
7	3,4-dibromo-2-hyroxy phenyl	17	19	16	14	14
8	3,4-dichlorophenyl	16	16	10	10	14
9	3,4-dimethoxyphenyl	15	14	20	10	16
10	3,4-dimethoxy-5-nitrophenyl	14	13	12	15	16
11	4-Methoxyphenyl	13	12	17	17	19
12	Ampicillin	23	26	24	25	-
13	Chloramphenicol	27	22	21	23	-
14	Norfloxacin	22	27	25	27	-
15	Griseofulvin	-	-	-	-	24

The azetidinones were characterized by elemental analysis as well as supported by its various spectroscopic data as shown in TABLE 2.

Antimicrobial activity 4-(4′′methoxyphenyl)-3-chloro-1-(4′ methyl-7′-carbamoylmethoxy-coumarinyl)-2-azetidinones

Method :	Cup-plate method[29,30]
Gram positive bacteria	Bacillus Mageterium (2087) Staphylococcus citrus
Gram negative bacteria	Escherecia Coli Salmonella Typhosa
Fungus	Aspergillus niger
Concentration	50µ gm
Solvent used	Dimethyl Formamide
Standard Drugs	Ampicilin; Chloramphenicol Norfloxacin; Griseofulvin

The nutrient agar broth and sterilized sabouraud's agar prepared by the usual method, was inocculated aseptically with 0.5ml of 24 hour old subculture of various bacteria in separate conical flasks at 40-50ºC and mixed well by gentle shaking . About 25 ml of agar broth was poured and evenly spread over sterilized Petri dish (13 cm in diameter) and allowed to set for 2 hours. The cups (10mm in diameter) were formed by help of the cork borer in agar medium and inoculated with various bacteria and fungi separately the cups were filled with 0.05ml (1mg/ml) of all the test samples of azetidinones in DMF solution the plates were incubated at 37ºC for 24 hours and the control was also maintained with 0.05 ml of DMF in same way the Zones of inhibition were measured in mm. and recorded in TABLE 3.

RESULTS AND DICUSSIONS

The compounds were screened for both gram positive and gram negative bacterias and fungus by the Cup-plate method[27,34].

The compound no-**(1)** and **(5)** were considerably active against S.Typhosa as compared with the standard drugs, for *E.coli* compound no. **(2)** and **(4)** are moderately active and compound no- **(9)** shows similar activity as compared to standard drug. For gram positive bacteria *S.citrus* bacteria compound **(6)** and **(7)**. And for *B.mageterium* compound **(3)** showed moderate activity as compared to standard drug.

In case of antifungal activity against *A.niger* almost all the compounds showed low activity other than compound no-**(2)** and **(11)** showed preferable activity report comparing with the standard drug.

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