Chapter - IV
Part - I
Synthesis of amides and anilides of coumarin derivatives

SYNTHESIS OF AMIDES AND ANILIDES OF COUMARIN DERIVATIVES

INTRODUCTION

Anilides and amides are known to have diverse physiological activity. Phenacetin (1) is proven analgesic and antipyretic. 2-Butoxy nupercaine (2), potent anaesthetic and a narcotic drug, was discovered while searching for other coumpounds as antipyretics in the acetanilide series. Other compounds such as oxindole (3) and its ring homologues and dihydrocarbostynil (4) were also examined for their activity as local anaesthetics.

A number of publications in recent years suggested that anilides and amides of coumarin derivatives have been found to have antibacterial and antifungal activity. A brief survey has been mentioned here.

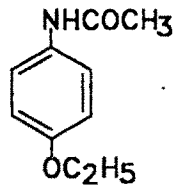
Werder[1] reported the sedative and toxic properties of N,N-diallyl coumarin-3-carboxamides. R.O.Clinton and S.C.Laskowski[2] reported some simple and substituted coumarin-3-carboxamides (5) from coumarin-3-carbonylchloride and diallylaminoamine Genshan Sunagawa and Hideo Nakao[3] synthesised various 8-methoxy-3-coumarin carboxamides (6).

L Reppel and W.Schmollack[4] prepared number of 3-monoacylamino-4-hydroxycoumarin (7) and N-(4-hydroxy-3-coumarinyl)urea (8) for their biological evaluation.

Number of carboxamides derivatives (9) had been synthesised by LIPHA[5] from 3-carbethoxy-4-hydroxycoumarin and $nC_7H_{12}NH_2$, 4-hydroxycoumarin and $nC_7H_{15}NCO$, 4-hydroxycoumarin and pyridine-3-carboxylic acid azide. These compounds showed antibacterial and antifungal activity.

J.R. Geigy A.G.[6] prepared coumarin carboxamides (10) from N-acylation of 3-phenyl-7-aminocoumarin or its derivatives which were used as optical brighteners

LIPHA[7] also reported synthesis of 4-hydroxycoumarin-3-carboxylic acid-N-(aminoalkyl) amides (11) by condensing alkyl-4-hydroxy-coumarin-3-carboxylates with alkylene diamine. These compounds were used as anaesthetics and as fibrinolytic, antiinflammatory, analgesic and antitussive agents.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OC2H5

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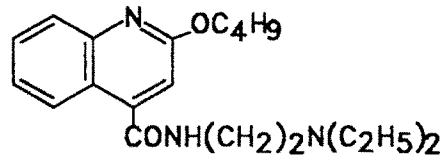
N
OC4H9
CONH(CH2)2N(C2H5)2

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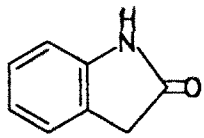
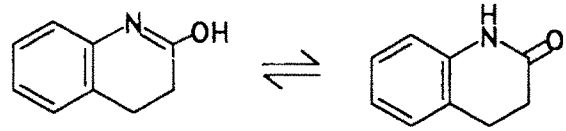
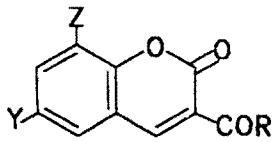

H
N
O

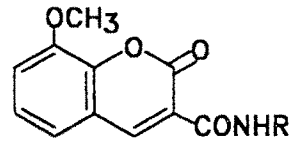
(3)


N
OH
H
N
O

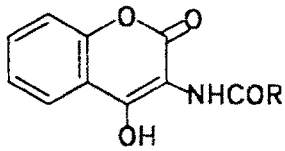
(4)


Z
O
O
Y
COR

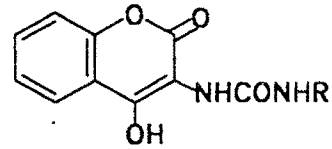
(5)


OCH3
O
O
CONHR

(6)


O
O
NHCOR
OH

(7)


O
O
NHCONHR
OH

(8)

Kento Okumura et al[8-10] showed the bactericidal activity of 3-carbamoyl-4,7-dihydroxy coumarin which were synthesised from $PhNH_2$ and Et-4,7-dihydroxycoumarin-3-carboxylate. They also reported number of 3-N-substitutedcarbamoyl-4-hydroxycoumarin (13) and 3-alkylcarbamoyl-4-hydroxy-7-aminocoumarin (14) which were useful as bactericides and antituberculous agents.

Ichikawa Masutaka and Ichibagase Hisashi[11] prepared N-substituted-6-nitro-, and 7-nitro-3-coumarincarboxamides. N-(2-pyridyl)-7-nitro-8-hydroxy and N-(2-pyridyl)-7-nitro-8- methoxy-3-coumarin carboxamides. They reported that some N-(2-pyridyl) amide and nitro fufurylidene derivatives showed strong activity against tubercle bacilli.

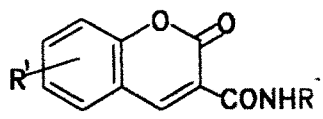
The bactericidal and fungicidal activities of 3-[(aminoalkyl and aminoaryl) carbamoyl)]-4-hydroxycoumarin (17) was reported by McIntyre Johns et al.[12,13] . They prepared 3-(alkoxyphenyl carbamoyl)-4-hydroxycoumarin (18) from 4-hydroxycoumarin and phenylisocynate.

Mamta Agrawal, S.B.Bansal and O.P. Singhal[14] reported coumarin carboxamides (19) by condensing malon-o-phenetidic, 3-chloro-2-methyl, 3-chloro-2-methoxy anilic acids and thiazole-2-malonamic acid with salicylaldehyde and substituted salicylaldehyde. They showed that the compound 6-bromocoumarin-3-phenetidine was active against the bacteria B.Subtilis and the fungi T. mentagrophytes, A .niger, 6-chlorocoumarin-3-carboxy-(3-chloro-2-methyl) anilide was active against bacteria S.aureus, B.subtilis and fungi A niger, 6,8-dibromocoumarin-3-carboxy-(3-chloro-2-methoxy)anilide was active against bacteria V.comma and fungi T.rubram.

Smidrkal Jan and Hedrlin Ivo[15] prepared 8-ethoxycoumarin-3-carboxamide (20) from 8-ethoxycoumarin-3-carboxylate and $H_2NCH_2CH_2NMe_2$ which was potentially effective components of creams protective against UV radiation.

Sonal Shah and R.H.Mehta[16] reported synthesis and antifungal activity of 8-methoxycoumarin-3-carboxanilides(21) and amides (22).

El-Farargy A.F., Soliman A.Y., El-Mobayed M and El-Essers[17] prepared carbamoylcoumarin (23) and showed their reactions with active methylene compounds, ketones, grignard and aromatic amines.



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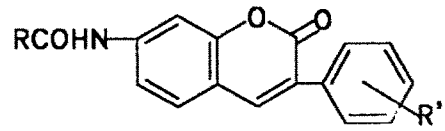

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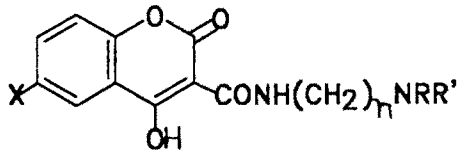

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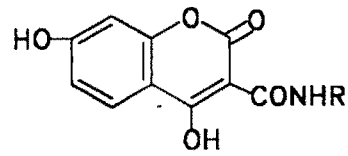

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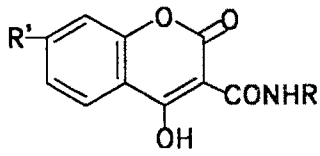

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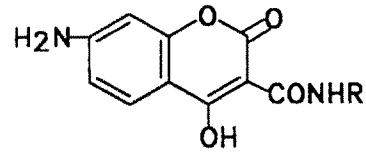

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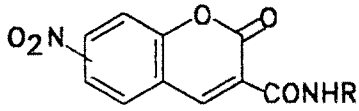

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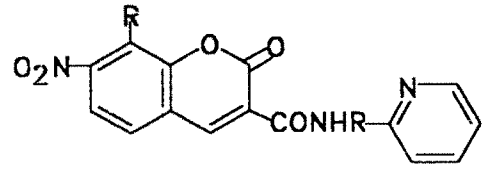


(16)

A novel one pot synthesis of 3-(acylamino)coumarins (24) was reported by Archana Jain and Aryak Mukerjee.[18]

Bozhilova, A, Ivanova D.[19] reported synthesis of some basic 3-(1-acylaminobenzyl) 2H-1-benzopyran-2-ones. The reaction of 3-(1-propanoyloxy benzyl) -2H-1-benzopyran-2-one with nitriles of 4-(dimethyl amino)benzoic, 4-(diethyl amino) benzoic, nicotinic, isonicotinic, 3-(dimethyl) amino propionic acid in concentrated H_2SO_4 gave (25).

Meguro, Kanji Tawada Hiroyuki and Ikeda Hitoshi[20] reported synthesis of (26) which showed 99% inhibition of cholesterol acyltransferase.

M.R. Selim[21] reported condensation of 3-carboethoxy-6-bromo- and 6,8-dibromo coumarin with aniline derivatives which gave (27), exhibited various biological activities.

Pradeep K. Tripathy[22] prepared 3-N-acylaminocoumarins by triethylamine mediated condensation of salicylaldehyde or o-hydroxy acetophenone and or their N-substituted imine with 2-N-substituted 2-oxazoline-5-ones, e.g. (28) in benzene gives 3-N-acylamino coumarin(29) exclusively.

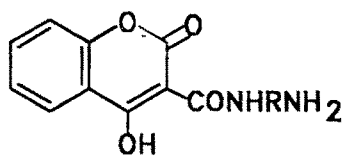
L Bonsignove, G. Loy, D. Secci and A. Calignono[23] synthesised 2-oxo-(2H)-1-benzopyran-3-carboxamides (30). They have reported diuretic, analgesic and myorelaxant activity of (30).

Reaction of 3,5-dichlorosalicylaldehyde with acyl glycine derivative afforded exclusively acylamino coumarin (31) which was reported by Ismail M. Hohsen and Kanded M.M.[24]

Ogiso Akira, Misawa Tsutami, Imai Rihoko and Itoh Hisato[25] reported synthesis of N-(4-alkoxy carbonyl phenyl) coumarin-3-carboxamides (32). Coumarin-3-carboxylic acid was amidated by 4-$(NH_2)C_6H_4COOEt$ to get (32) and used in thermoplastic resins

Present Work

The literature survey also revealed that haloacetamides [26,27] possess amoebicidal activity and substituted acetamides [28-30] have local anaesthetic property. With a view to prepare better therapeutically active compounds the present work is undertaken.



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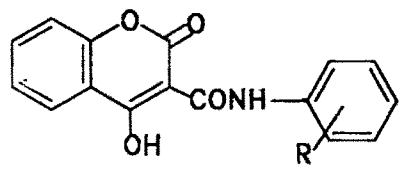

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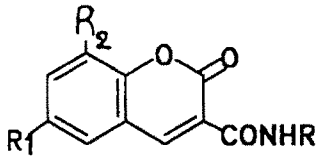

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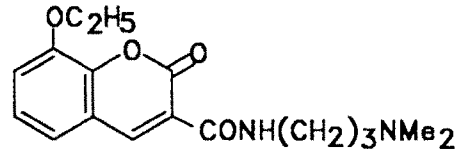

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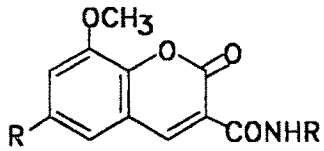

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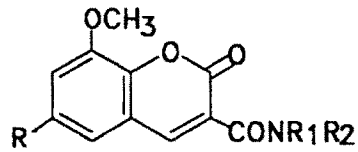

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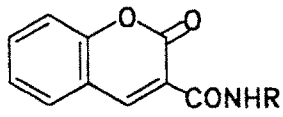

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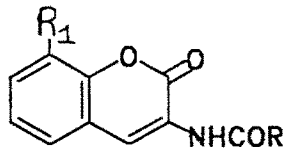

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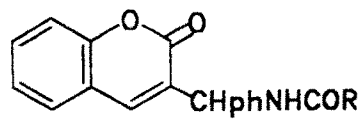

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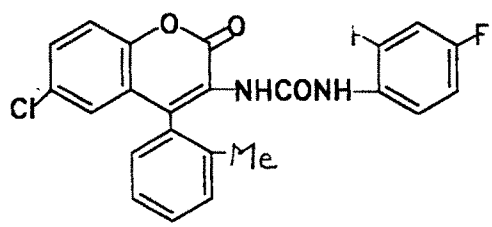

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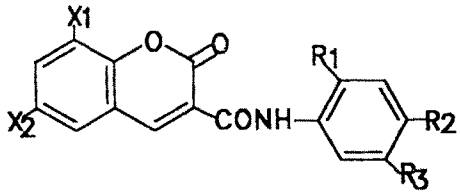

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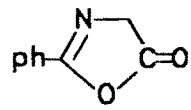

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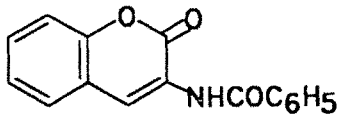

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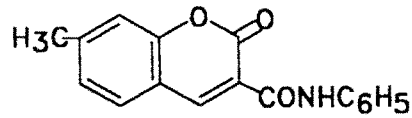

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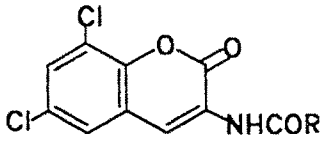

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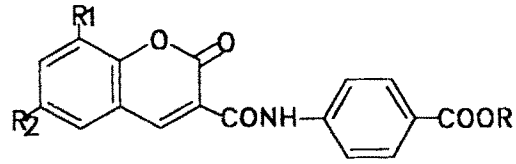

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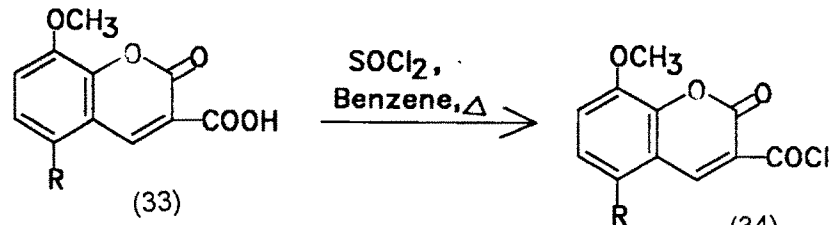
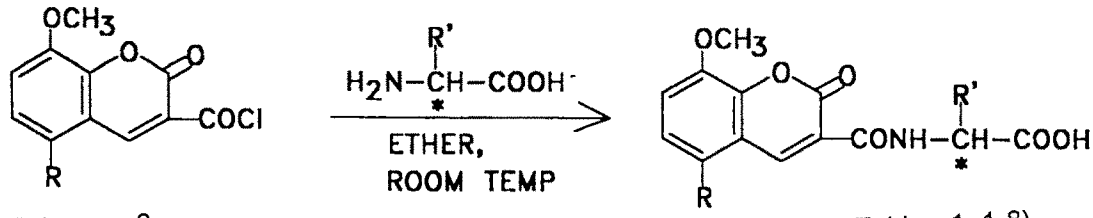


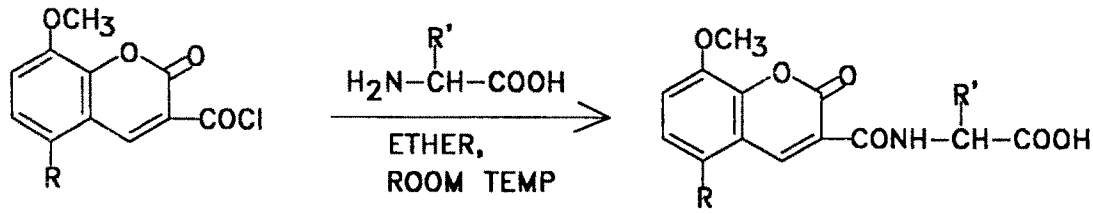
R=Br.H

Scheme - 1



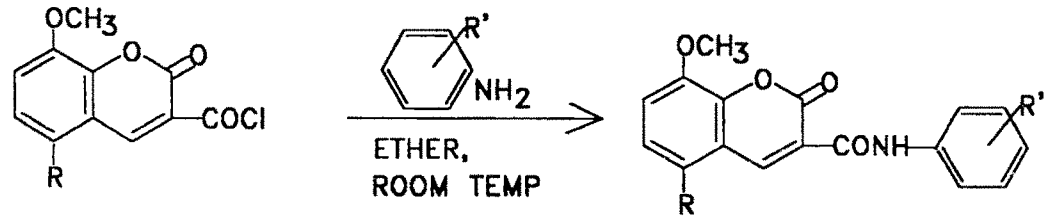
Scheme - 2

(35, Table - 1, 1-8)



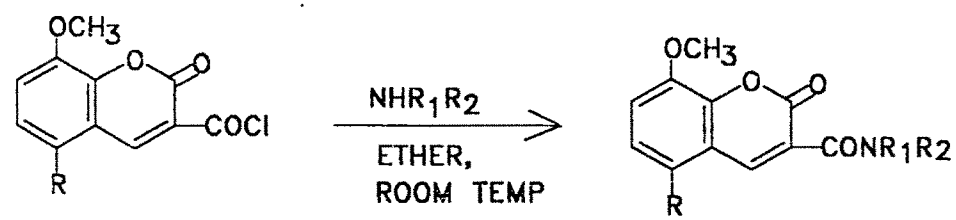
Scheme - 3

(36, Table - 2, 1-7)



(37, Table - 3, 1-15)

Scheme - 4



(38, Table - 4, 1-7)

General Method of Preparation

8-Methoxy-, 8-methoxy-5-bromocoumarin-3-carboxamides and anilides.

The acid chloride was prepared by treating 8-methoxy-,8-methoxy-5-bromo-coumarin-3-carboxylic acid with thionylchloride. These acid chlorides were treated with various L- and DL- aminoacids and primary and secondary amines.

General Discussion of IR Spectra

The IR spectra showed characteristic absorption band of N-H stretching at 3400 cm^{-1}(broad), 1720 cm^{-1} for lactonic C=O of coumarin and 1600 cm^{-1} for aromatic C=C ring stretch cm^{-1}, an amide band I at 1670-1650 cm^{-1} and amide band II at 1560-1540 cm^{-1} were also observed, C-O-C absorption bands were observed at 1280, 1110 cm^{-1}.

The method of synthesis and spectral data of some individual compounds have been given here to support the structure assigned to the compound.

N-(8-Methoxy-3-coumarinoyl) L-valine (35, Table-1,2) Scheme-1

8-Methoxycoumarin-3-carbonyl chloride (34) was treated with L-valine in dry ether to obtain N(8-methoxy-3-coumarinoyl) L-valine. The structure was established by IR and PMR spectra.

The IR (KBr) spectrum exhibited bands at 3350, 1715, 1660,1605,1540,1275 and 1100 cm^{-1}. (Fig. 1)

The PMR spectrum in CF_3COOH showed following signals :a doublet at δ 1 0 for six protons of two methyl groups of isopropyl function; a multiplet at δ 2.35 for one methyne proton of isopropyl function, $C\underline{H}(CH_3)_2$; a singlet at δ 4.0 for three protons of $OC\underline{H}_3$ group at C-8; a multiplet at δ 4.61 for one proton, $C\underline{H}$-COOH; a multiplet in region of δ 7 2-7 5 for three aromatic protons; a singlet at δ 8.8 for one proton at C-4 and a doublet at δ 9.2 for one NH proton was observed. (Fig.2)

Other L-aminoacids were condensed in similar way (Table-1,1-8).

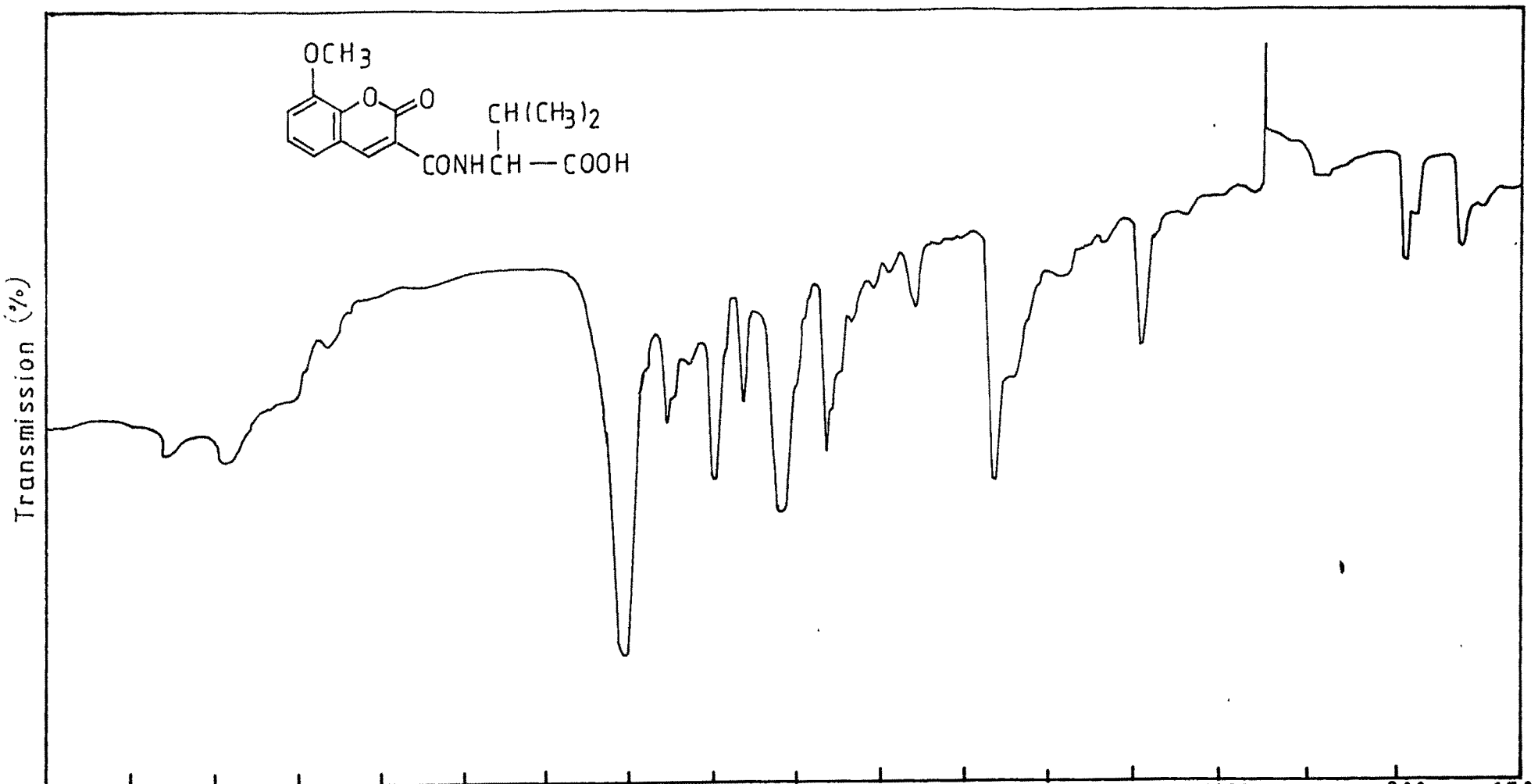

OCH3
O
O
CH(CH3)2
CONHCH—COOH
Transmission (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
650
Wavenumber cm-1

FIG. 1

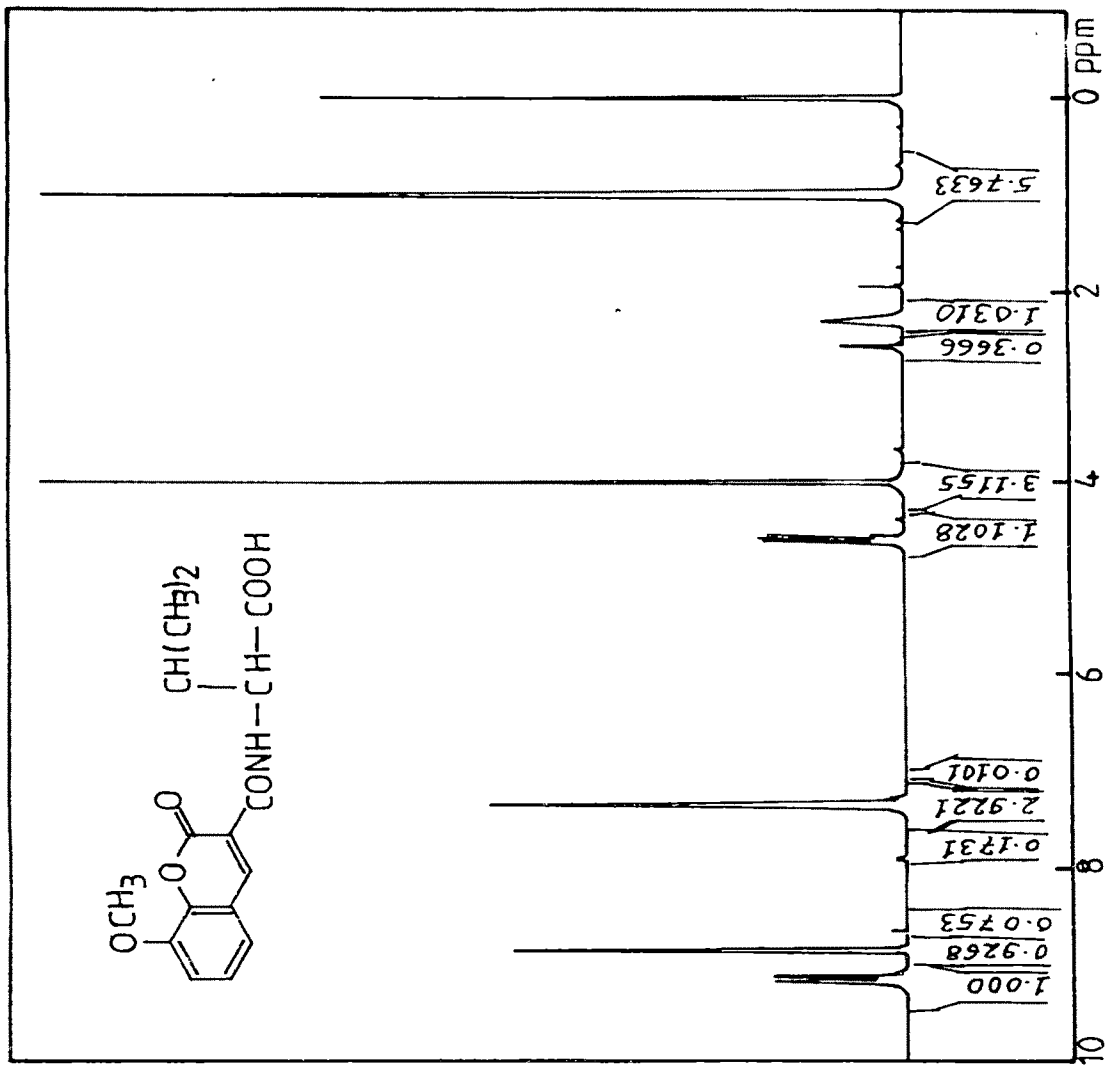

5.7633
1.0310
0.3666
3.1155
1.1028
0.0101
2.9221
0.1731
0.0753
0.9268
1.000
0 ppm
2
4
6
8
10
CH(CH3)2
CONH—CH—COOH
OCH3
O

FIG. 2

N-(8-Methoxy-3-coumarinoyl)DL-valine (36, Table-2,2) (Scheme - 2)

8-Methoxycoumarin-3-carbonyl chloride(34) was treated with DL-valine to get above compound. The structure of the compound was proved by IR and PMR spectra.

The IR(KBr) spectrum showed following bands; 3350, 1715, 1665, 1610, 1540, 1280, 1105 cm^{-1}.

The PMR spectrum in CF_3COOH exhibited signals : a doublet at δ 1.0 for six protons of two methyl groups of isopropyl function $CH(C\underline{H}_3)_2$; a multiplet at δ 2.35 for one methyne proton of isopropyl group $C\underline{H}(CH_3)_2$; a singlet at 3.85 for three protons of $OC\underline{H}_3$ group at C-8; a multiplet at δ 4.6 for one proton C<u>H</u>-COOH. In aromatic region a multiplet at δ 7.1-7.5 for aromatic protons; a singlet at δ 8.85 for one proton at C-4 was obtained. (Fig. 4).

Other DL-amino acids and β-alanine were condensed in similar way(Table-2,1-7)

N-(8-Methoxy-5-bromo-3-coumarinoyl) β-alanine (36,Table-2,7) Scheme-2

When 8-methoxy-5-bromocoumarin-3-carbonyl chloride was condensed with β-alanine it furnished N-(8-Methoxy-5-bromo-3-coumarinoyl) β-alanine. This structure was established on basis of PMR spectrum.

The PMR spectrum in CF_3COOH exhibited signals ; a singlet at δ 4.0 for three protons of $OC\underline{H}_3$ group at C-4; a multiplet at δ 4.3 for two protons of methylene group attached to carboxylate group; another multiplet at δ 4.5 of two protons of another methylene group attached to nitrogen; aromatic protons were observed between δ 7 3 - 7.7 and a singlet for C-4 proton at δ 9.4 (Fig. 5).

8-Methoxy-5-bromocoumarin-3-carboxy(4'-carbethoxy) anilide (37,Table-3,2) Scheme-3

The above compound was obtained by condensing 8-methoxy-5-bromocoumarin-3-carbonyl chloride with benzocaine in dry ether. The assigned structure was proved by IR and PMR spectra.

The IR (KBr) spectrum exhibited bands at 3250 (broad), 1710, 1665, 1600, 1560, 1280 and 1100 cm^{-1} (Fig. 6).

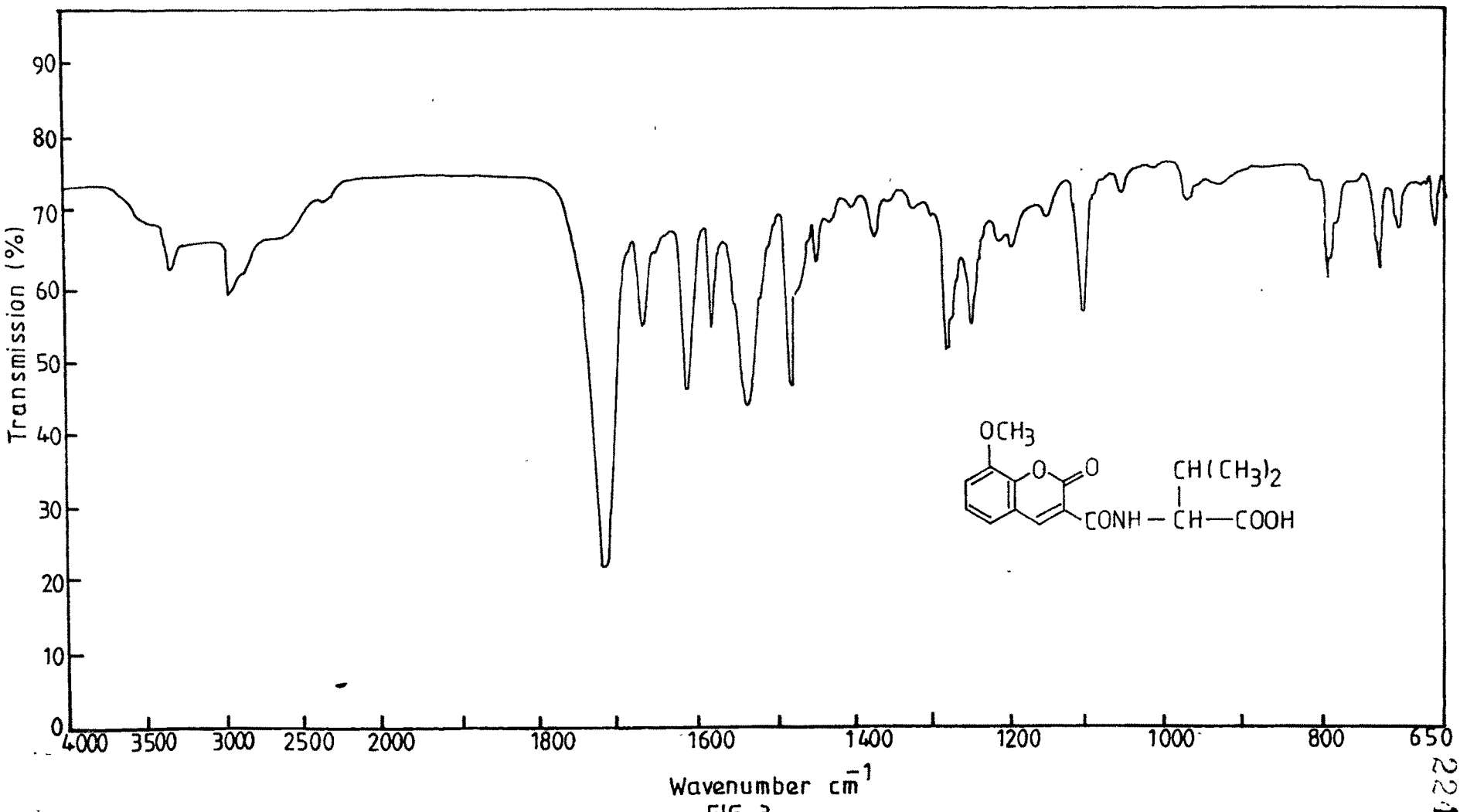

Transmission (%)
90
80
70
60
50
40
30
20
10
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
650
Wavenumber cm⁻¹
OCH3
O
O
CH(CH3)2
CONH — CH — COOH

FIG. 3

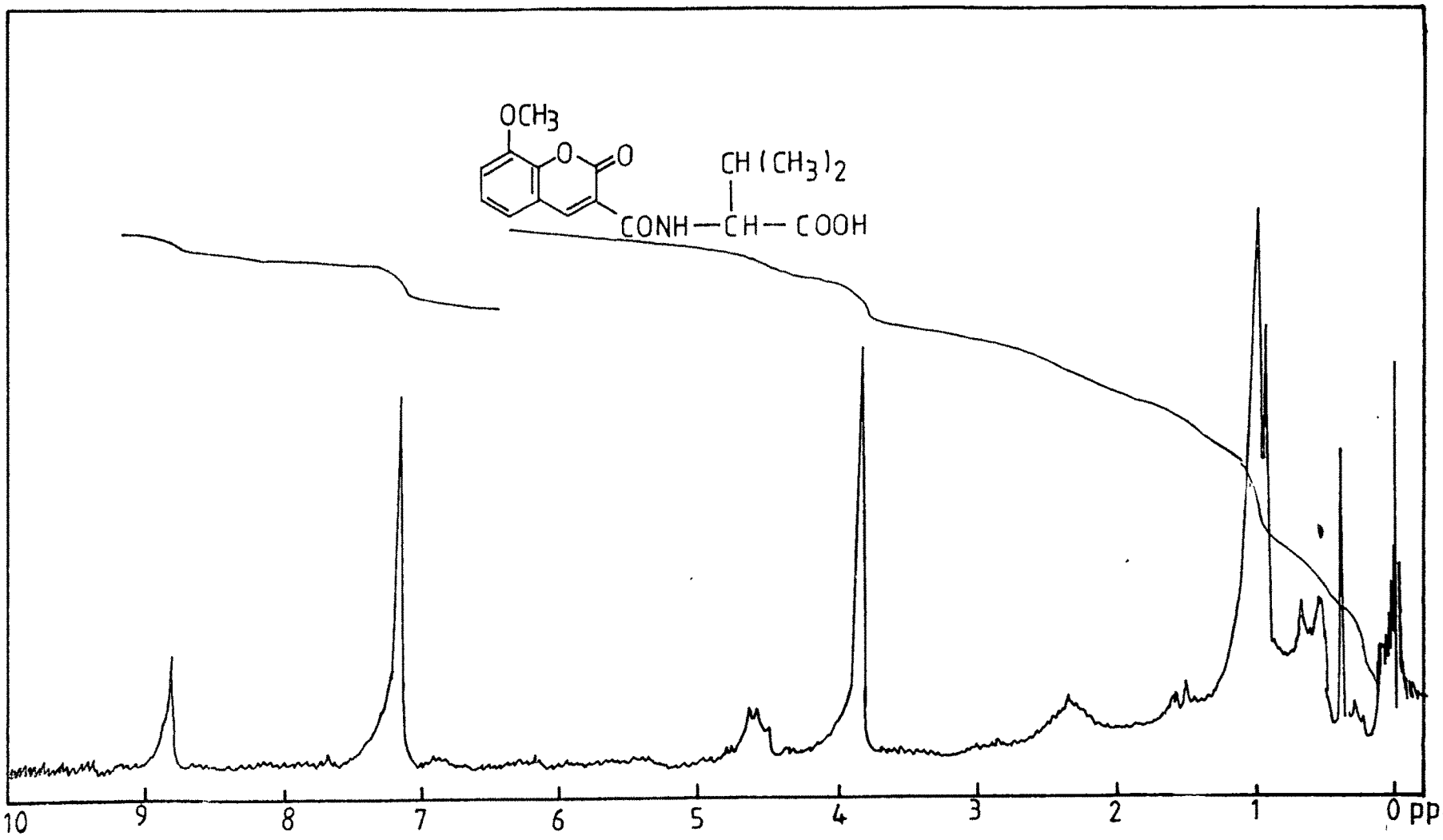


FIG. 4

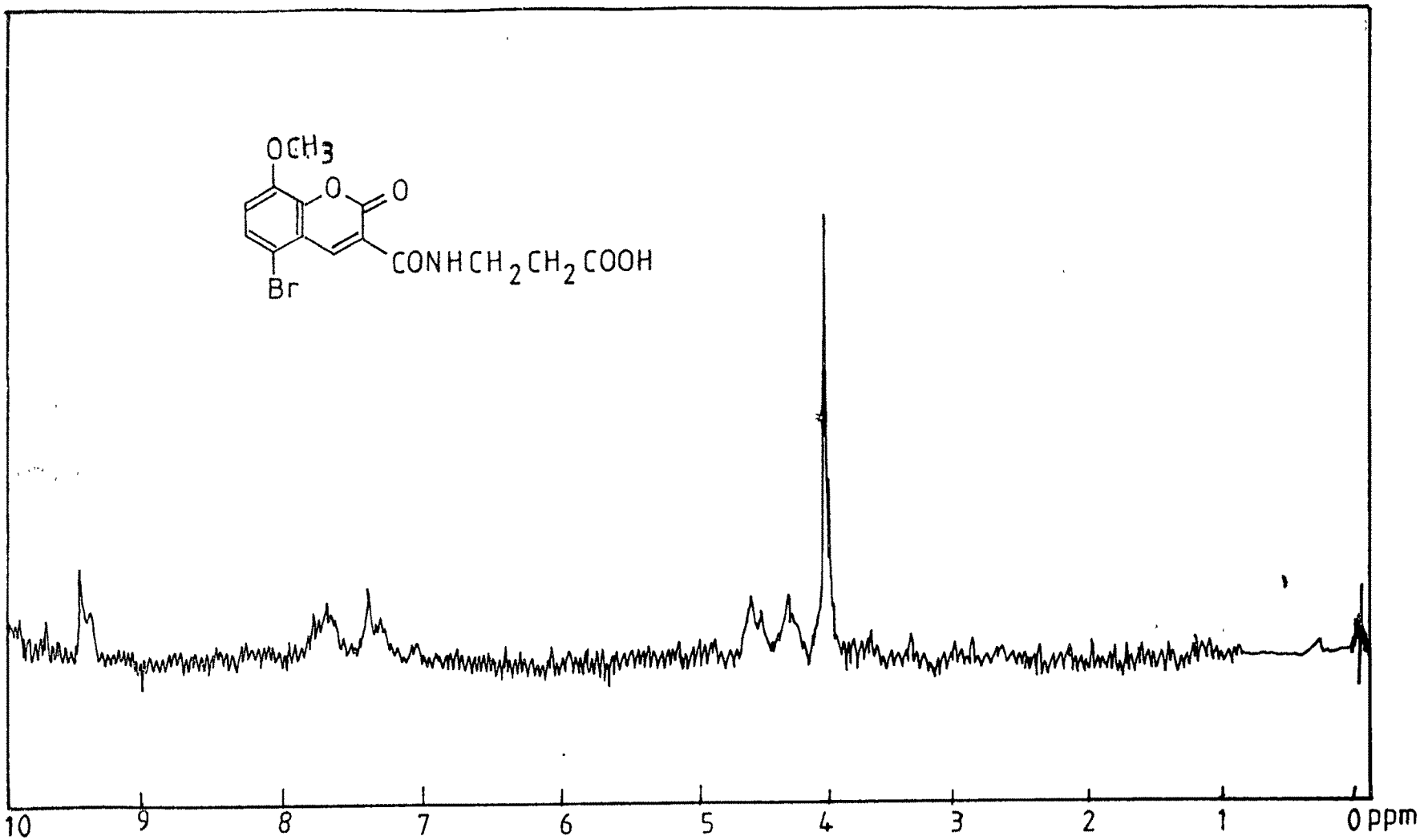


FIG. 5

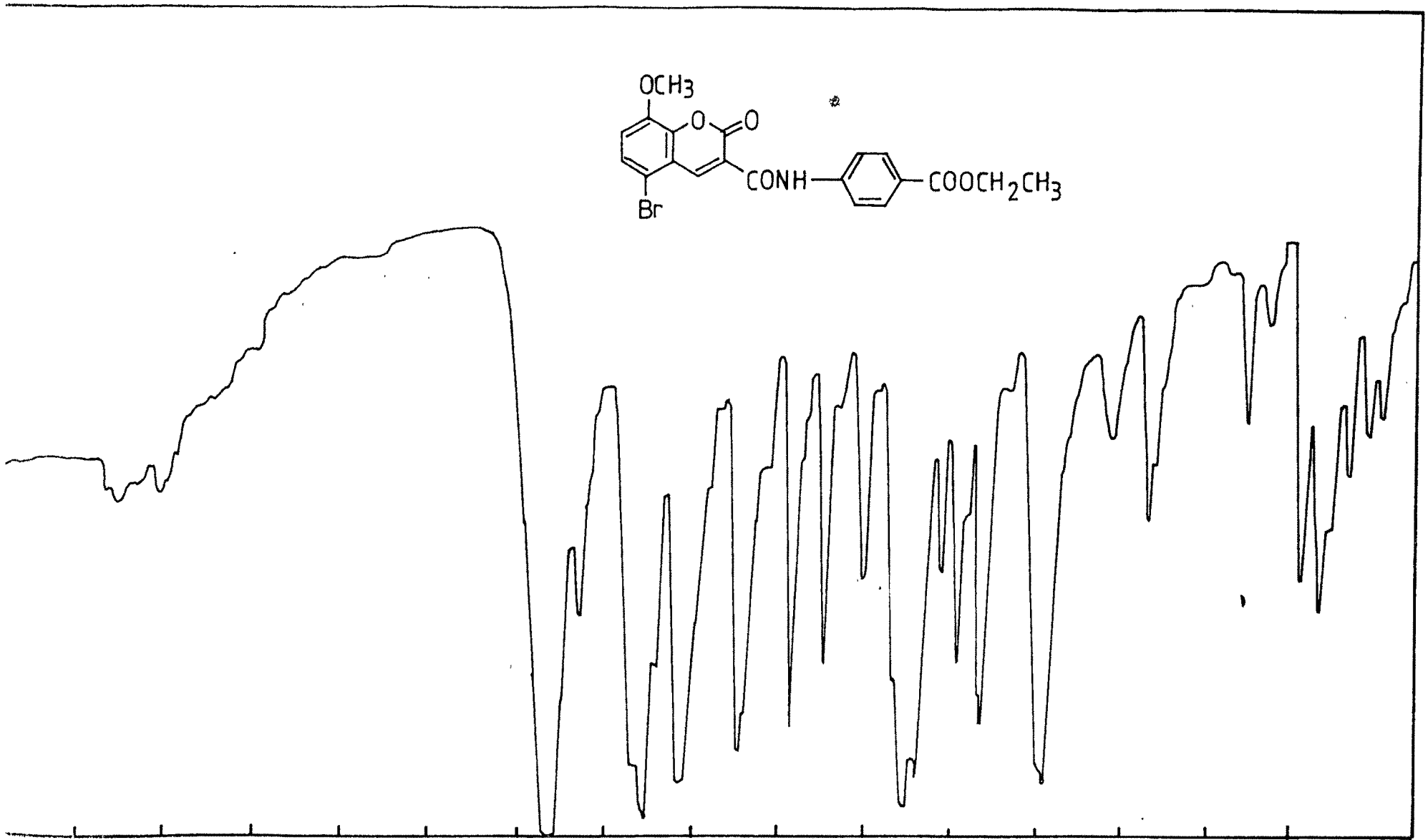

OCH3
O
O
CONH
COOCH2CH3
Br
0
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
650
Wavenumber cm-1

FIG. 6

The PMR spectrum in CF_3COOH showed following signals : a triplet at δ 1.5 for three protons of methyl group of carbethoxy group, $COOCH_2C\underline{H}_3$; a singlet at δ 4.0 for three protons of $OC\underline{H}_3$ group at C-8; a quartet at δ 4.4 for two protons of methylene group of carbethoxy group, $COOC\underline{H}_2CH_3$; a doublet at δ 7.1 (J=9Hz) for C-7 proton and a doublet at δ 7.55 (J=9Hz) for C-6 proton. Other two doublets at δ 7.7 (J=9Hz) and at δ 8.1 (J=9Hz) for other four aromatic protons of amine component and a singlet at δ 9.2 for C-4 proton (Fig. 7).

The mass spectra showed following m/z peaks, 445 (M+ peak, 63.06%), 447 (M+2 Peak, 61.98%) and 283 (Base Peak, 100%) (Fig. 8).

8-Methoxycoumarin-3-carboxy (2'methyl)anilide (37, Table-3,15) Scheme-3

8-Methoxycoumarin-3-carbonyl chloride was condensed with toludine to get above product.

The PMR spectrum in CF_3COOH exhibited following signals : a singlet at δ 2.2 for three protons of methyl group of o-toluidine function; another singlet at δ 4.0 for three protons of $OC\underline{H}_3$ group at C-8; a multiplet for aromatic protons at δ 7.4-8.3 and a singlet at δ 9.0 for one proton at C-4. (Fig.9)

Other primary aromatic amines were condensed in similar way(Table-3,1-15).

8-Methoxy -5-bromocoumarin-3-carboxy (N-phenylpiperazinyl) amide (38,Table-4,5)

8-Methoxy-5-bromocoumarin-3-carbonyl chloride was condensed with N-phenyl piperazine to obtain above product. The structure was assigned on the basis of PMR spectrum.

In $CDCl_3$ it exhibited following signals, a multiplet at δ 3.1 for four protons of two methylene groups of N-phenylpiperazine function; another multiplet at δ 3.6 for four protons of other two methylene groups attached to nitrogen adjecent to carbonyl at C-3, a singlet at δ 4.0 for three protons of methoxy group at C-8 In aromatic region, a multiplet

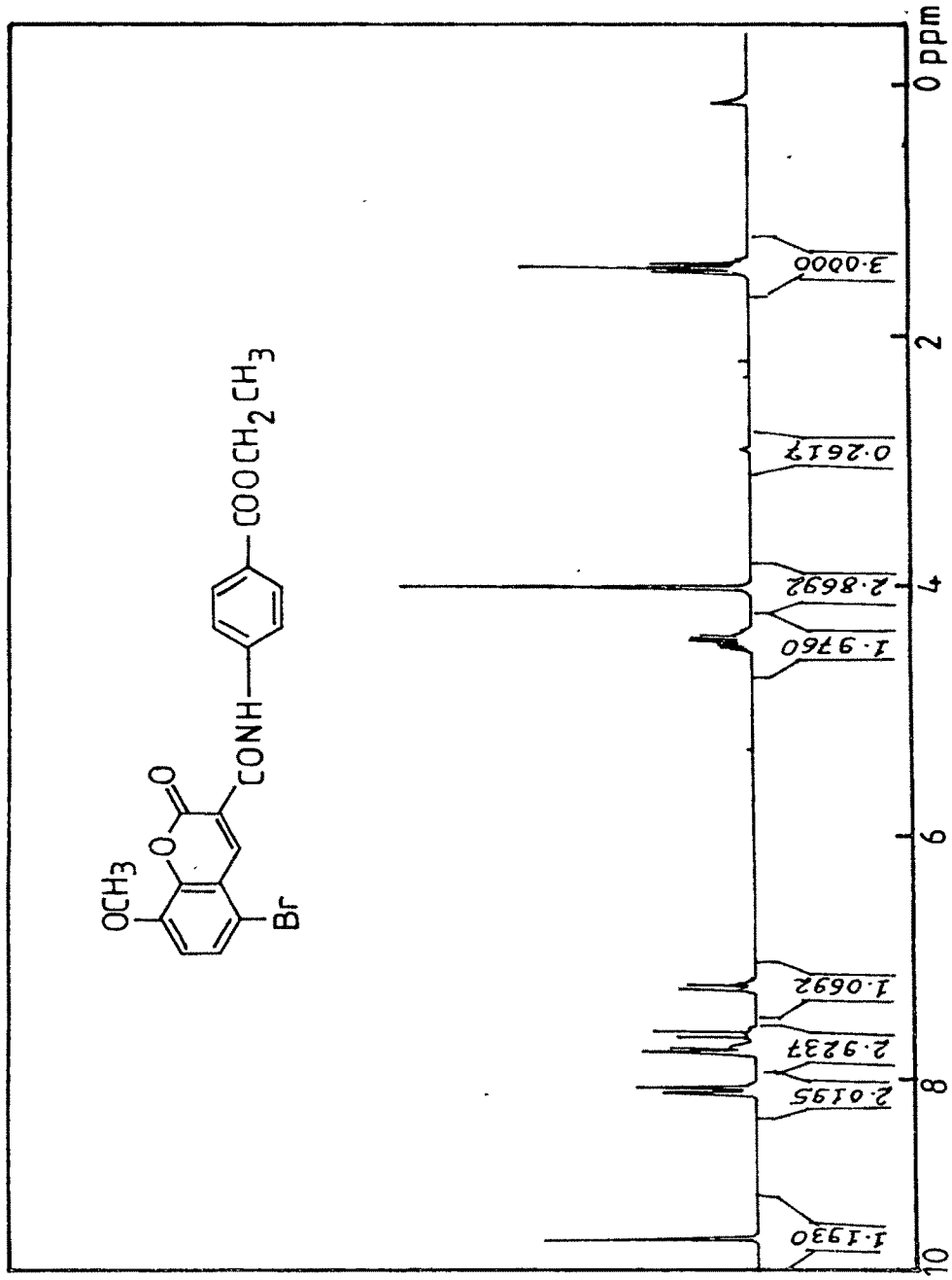

0 ppm
2
4
6
8
10
3.0000
0.2617
2.8692
1.9760
1.0692
2.9237
2.0195
1.1930
COOCH2CH3
CONH
O
O
OCH3
Br

FIG 7

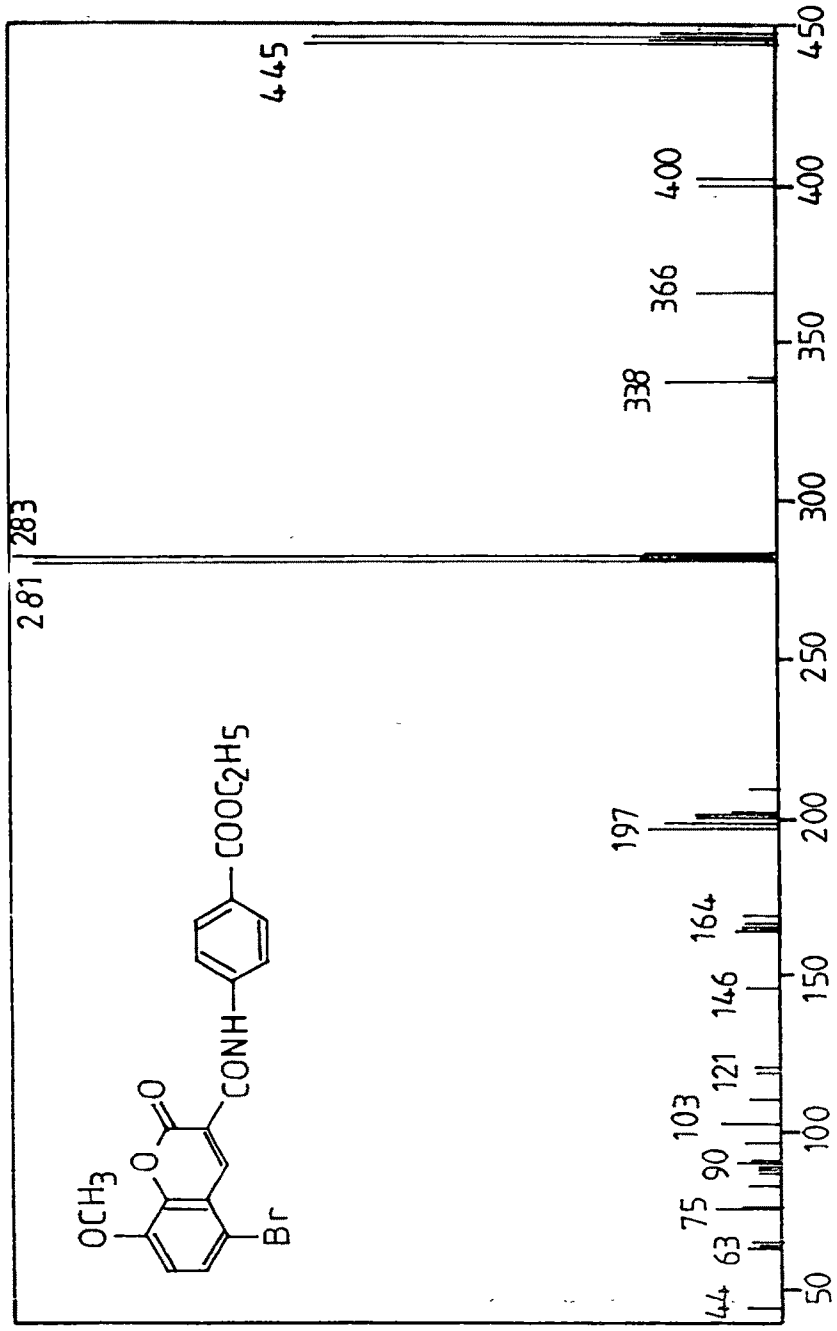

445
400
366
338
283
281
197
164
146
121
103
90
75
63
44
450
400
350
300
250
200
150
100
50
OCH3
O
O
CONH
COOC2H5
Br

FIG. 8

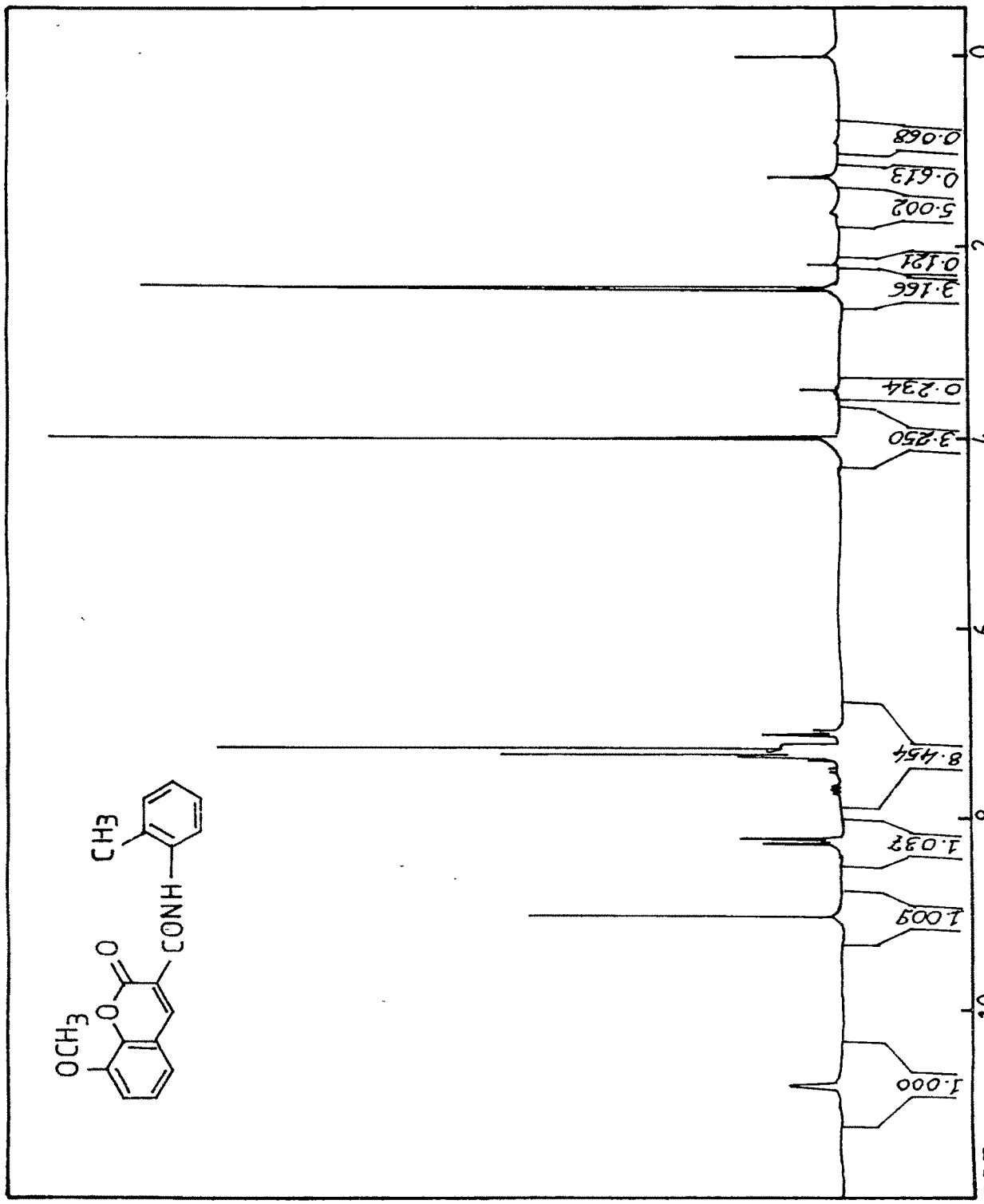

CH3
CONH
O
O
OCH3
ppm
0
2
4
6
8
10
1.000
1.009
1.037
8.454
3.250
0.234
3.166
0.121
5.002
0.613
0.068

FIG. 9

at δ 6.8-7.5 for aromatic protons was observed and a singlet at δ 8.3 for C-4 proton. (Fig.10)

Other secondary amines were condensed in similar way. (Table-4,1-7)

Antibacterial activity

All the synthesised compounds were tested for their antibacterial activity at 100 and 500 ppm concentrations against strains E.coli and S.aureus. Screening report is mentioned in chapter-V.

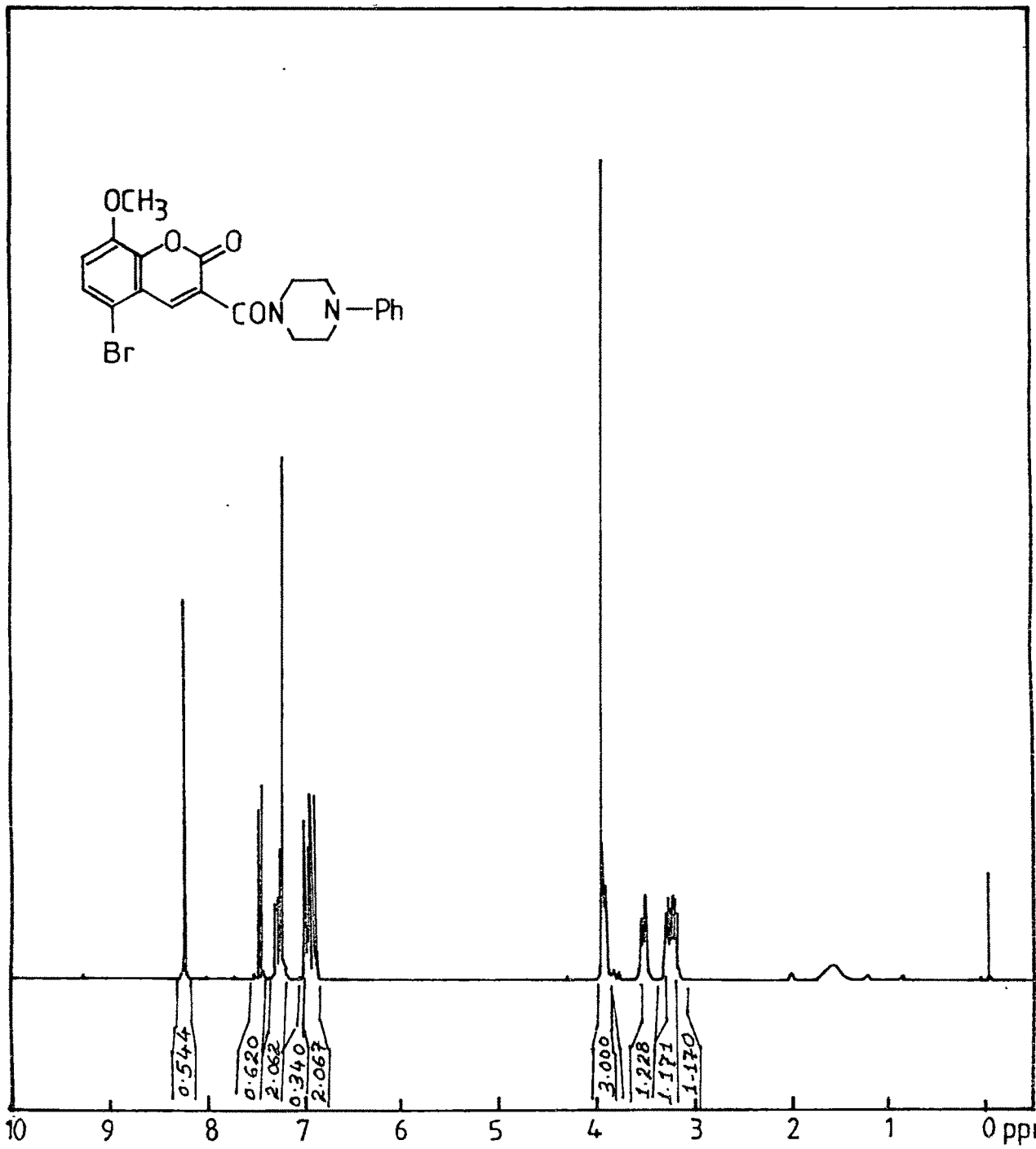

OCH3
O
O
CON
N—Ph
Br
0·544
0·620
2·062
0·340
2·067
3·000
1·228
1·171
1·170
10
9
8
7
6
5
4
3
2
1
0 ppm

FIG. 10

EXPERIMENTAL

All melting points were uncorrected. Microanalysis were performed on a coleman instrument. IR spectra (KBr) were taken on a shimadzu 408 spectrometer. PMR spectra were recorded on Perkin-Elmer R-32 spectrometer at 90 MHz and dpx spectrometer at 200 MHz, using TMS as the internal standard. The chemical shifts are measured in δ ppm. The specific rotations were measured on Jesco-Dip ^{37o}D digital polarimeter.

N-(8-Methoxy-3-coumarinoyl)L-valine (35,Table-1,2)

A mixture of 3-methoxy coumarin-3-carbonyl chloride (0.01 mol) and L-valine (0.01 mol) was stirred in dry ether (30-40 ml) at room temperature for 3 hrs. The resulting product was filtered dried and washed with water. It was crystallised from mixture of glacialacetic acid and water. M.p 178-80°C, Yield 90%.

Analysis	:	Found	:	C, 59.76;	H, 5.73; N, 4.70%
$C_{16}H_{17}O_6N$	:	Required	:	C, 60.18;	H, 5.32; N, 4.38%

N-(8-Methoxy-3-coumarinoyl)DL-valine (36, Table-2,2)

8-Methoxycoumarin-3-carbonyl chloride (0.01 mol), DL-valine (0.01 mol) were mixed in dry ether (30 ml) and stirred at room temperature for 3 hrs. The separated product was worked up as usual. M.p. 227°C, Yield 86%.

Analysis	:	Found	:	C, 59.97;	H, 5.01; N, 4.02%
$C_{16}H_{17}O_6N$	:	Required	:	C, 60.18;	H, 5 32; N, 4.38%

N-(8-Methoxy-5-bromo-3-coumarinoyl) β-alanine (36, Table-2,7)

A mixture of 8-methoxy-5-bromocoumarin-3-carbonyl chloride (0.01 mol) and β-alanine (0.01 mol) were stirred in dry ether (30 ml) for 3 hrs. The product was worked up as usual. M.p. 170°C, Yield 70%.

Analysis	:	Found	:	C, 45.42;	H, 3.25; N, 3.55%
$C_{14}H_{12}O_6NBr$	:	Required	:	C, 45.40;	H, 3.24; N, 3.78%

8-Methoxycoumarin-3-carboxy(4'-carbethoxy)anilide (37, Table-3,2)

A mixture of 8-methoxy-5-bromocoumarin-3-carbonyl chloride (0.01 mol) and benzocane (0.01 mol) in dry ether (30 ml) was stirred for 3 hrs. The separated product was filtered, dried and crystallised from benzene. M.p. 245°C, Yield 82%

Analysis	:	Found	:	C, 53.41;	H, 3.13; N, 3.47%
$C_{20}H_{16}O_6NBr$	.	Required	:	C, 53.81;	H, 3.58; N, 3.13%

8-Methoxycoumarin-3-carboxy (2'methyl) anilide (37, Table-3,15)

8-Methoxycoumarin-3-carbonyl chloride (0.01 mol) and o-toluidine (0.01 mol) were taken in dry ether (30 ml) and stirred for 3 hrs at room temperature. The separated product was worked up as usual. M.p 241° C, Yield 73%

Analysis	:	Found	:	C, 69.81;	H, 4.95; N, 4.91%
$C_{18}H_{15}O_4N$	:	Required	:	C, 69.90,	H, 4.85; N, 4.53%

8-Methoxy-5-bromocoumarine-3-carboxy(N-phenylpiperazinyl)amide (38, Table-4,5)

A mixture of 8-methoxy-5-bromocoumarine-3-carbonyl chloride(0.01 mol) and N-phenyl piperazine(0.01 mol) in dry ether (30 ml) was stirred for 3 hrs. The separated product was worked up as usual. M.p 187° C, Yield 75%

Analysis	:	Found	:	C, 57.30;	H, 4 04; N, 6.40%
$C_{21}H_{19}O_4N_2Br$	:	Required	:	C, 56.88;	H, 4 28; N, 6.32%

Table - 1 : Analytical and Physical Data of Compounds (35)

Sr. No.	R	R'	M.P.* in °C	%Yield	Molecular Formula	Elemental Analysis Found / Required			Specific Rotation $[\alpha]_{25}^{D}$
						%C	%H	%N	
1.	H	CH_3	250^{A}	72	$C_{14}H_{13}O_6N$	57.75 57.73	4.88 4.46	4.41 4.81	+ 58.70°
2.	H	$CH(CH_3)2$	180^{G+W}	90	$C_{16}H_{17}O_6N$	59.74 60.18	5.73 5.32	4.70 4.38	+ 30.61°
3.	H	$CH_2CH_2SCH_3$	190^{A}	76	$C_{16}H_{17}O_6NS$	54.23 54.70	5.17 4.84	3.89 3.98	+ 27.62°
4.	H	CH_2OH	250^{A}	70	$C_{14}H_{13}O_7N$	54.31 54.72	4.63 4.23	4.92 4.56	+ 28.95°
5.	H	$CH(OH)CH_3$	$259\text{-}60^{A}$	65	$C_{15}H_{15}O_7N$	55.71 56.07	5.12 4.67	4.56 4.36	+ 38.83
6	Br	CH_3	185^{A}	72	$C_{14}H_{12}O_6NBr$	44.99 45.40	3.54 3.24	3.52 3.78	- 10.16
7.	Br	$CH(CH_3)_2$	212^{G}	70	$C_{16}H_{16}O_6NBr$	47.89 48.24	3.66 4.02	3.33 3.54	- 29.76
8.	Br	$CH(OH)CH_3$	220^{A}	65	$C_{15}H_{14}O_7NBr$	45.32 45.00	3.61 3.50	3.36 3.50	+ 10.54

* Solvent of crystallisation, A = Alcohol, G = Acetic acid, W = Water

Table - 2. : Analytical and Physical Data of Compound (36)

Sr. No.	R	R'	M.P.* in °C	%Yield	Molecular Formula	Elemental Analysis Found / Required		
						%C	%H	%N
1.	H	CH_3	230^{A+W}	80	$C_{13}H_{11}O_6N$	57.75 57.73	4.88 4.46	4.75 4.81
2.	H	$CH(CH_3)_2$	227^{A+W}	86	$C_{16}H_{17}O_6N$	59.97 60.18	5.01 5.32	4.02 4.38
3.	H	$CH_2CH_2SCH_3$	220^{A+W}	79	$C_{16}H_{17}O_6NS$	54.94 54.70	4.50 4.84	3.66 3.98
4	H	$CH_2C_6H_5$	175^{A+W}	83	$C_{16}H_{17}O_6N$	64.94 65.39	4.50 4.63	3.55 3.81
5.	H	β-alanine	215^{D+W}	73	$C_{14}H_{13}O_6N$	57.45 57.73	4.86 4.46	5.20 4.81
6.	H	H	242^{A}	71	$C_{13}H_{11}O_6N$	55.95 56.17	4.41 3.97	5.14 5.05
7	Br	β-alanine	170^{D+W}	70	$C_{14}H_{12}O_6NBr$	45.42 45.40	3.25 3.24	3.55 3.78

Solvent of crystallisation, A = Alcohol, D = DMF, W = Water

Table - 3. : Analytical and Physical Data of Compounds (37)

Sr. No.	R	R'	M.P.* in ^{o}C	%Yield	Molecular Formula	Elemental Analysis Found / Required		
						%C	%H	%N
1.	Br	H	244^{B}	75	$C_{17}H_{12}O_4NBr$	55.00 54.54	3.38 3.32	3.42 3.74
2.	Br	$4COOC_2H_5$	230^{B}	82	$C_{20}H_{16}O_6NBr$	53.41 53.81	3.13 3.58	3.47 3.13
3.	Br	$4\text{-}CH_3$	234^{B}	80	$C_{18}H_{14}O_4NBr$	55.27 55.67	3.20 3.60	4.08 3.60
4.	Br	$2\text{-}CH_3$	250^{D}	70	$C_{18}H_{14}O_4NBr$	55.24 55.67	3.74 3.60	3.30 3.60
5.	Br	$4\text{-}NO_2$	284^{B+D}	72	$C_{17}H_{11}O_6N_2Br$	48.49 48.68	2.20 2.62	6.62 6.68
6.	Br	$3\text{-}NO_2$	$275\text{-}76^{D}$	65	$C_{17}H_{11}O_6N_2Br$	48.31 48.68	2.18 2.62	7.03 6.68
7.	Br	$2,4\text{-}Cl_2$	285^{B+D}	81	$C_{17}H_{10}O_4NBrCl_2$	46.48 46.04	2.20 2.25	3.43 3.16
8	Br	$3,4\text{-}Cl_2$	290^{B+D}	83	$C_{17}H_{10}O_4NBrCl_2$	46.50 46.04	1.84 2.25	3.28 3.16

Contd... Table - 3. Analytical and Physical Data of Compounds (37)

Sr. No.	R	R'	M.P.* in°C	%Yield	Molecular Formula	Elemental Analysis Found / Required		
						%C	%H	%N
9.	Br	3-$COCH_3$	294^D	67	$C_{19}H_{14}O_5NBr$	55.14 54.80	3.75 3.36	3.11 3.36
10.	Br	4-$COCH_3$	280^D	65	$C_{19}H_{14}O_5NBr$	55.21 54.80	3.72 3.36	2.95 3.36
11.	Br	4-OCH_3	250^D	65	$C_{18}H_{14}O_5NBr$	53.60 53.46	3.89 3.46	3.71 3.46
12.	Br	4-Br	280^{D+W}	69	$C_{17}H_{11}O_4NBr_2$	45.50 45.03	2.83 2.42	3.29 3.09
13.	Br	2-Naphthyl	259^{B+D}	60	$C_{21}H_{14}O_4NBr$	59.64 59.43	3.57 3.30	3.67 3.30
14	H	2-NO_2	$255\text{-}56^D$	70	$C_{18}H_{12}O_6N_2$	60.33 60.00	3.88 3.50	7.80 8.40
15.	H	2-CH_3	241^D	73	$C_{18}H_{15}O_4N$	69.81 69.90	4.95 4.85	4.91 4.53

Solvent of crystallisation, D = DMF, B = Benzene

Table - 4. : Analytical and Physical Data of Compound (38)

Sr. No.	R_1	R_2	M.P.* in°C	%Yield	Molecular Formula	Elemental Analysis Found / Required		
						%C	%H	%N
1.	$-CH_3$,	C_6H_5	210^d	69	$C_{18}H_{14}O_4NBr$	55.39 55.67	4.01 3.60	4.01 3.60
2.	$-C_2H_5$,	C_6H_5	204^{d+w}	65	$C_{19}H_{16}O_4NBr$	56.29 56.71	4.21 3.98	3.93 3.48
3.	C_6H_5	C_6H_5	204^{d+w}	72	$C_{23}H_{16}O_4NBr$	60.90 61.33	3.49 3.55	2.64 3.11
4	Morpholine		245^{d+a}	79	$C_{15}H_{14}O_5NBr$	49.90 48.91	4.21 3.80	3.66 3.80
5.	N-Phenylpiperazine		187^{d+a}	75	$C_{21}H_{19}O_4N_2Br$	57.30 56.88	4.04 4.28	6.40 6.32
6.	4-CH_3-piperidine		195^d	70	$C_{17}H_{18}O_4NBr$	53.24 53.68	4.30 4.73	3.67 3.68
7.	3-CH_3 piperidine		152^d	66	$C_{17}H_{18}O_4NBr$	53.67 53.68	4.63 4.73	3.47 3.68

Solvent of crystallisation, d = DMF, W = Water, A = Alcohol

Chapter - IV
Part - II
Synthesis of sulfonamides of coumarin derivatives

SYNTHESIS OF SULFONAMIDES OF COUMARIN DERIVATIVES

INTRODUCTION

It is well-known that sulfanilamide and certain related substituted amides are of considerable medical importance as the sulfa drugs. The antibacterial activity of these drugs stems from a rather simple fact, enzymes in the bacteria confuse it for p-amino benzoic acid, which is an essential metabolite. In what is known as metabolite antagonism, the sulfanilamide competes with p-aminobenzoic acid for reactive sites on the enzymes; deprived of the essential metabolite, the organism fails to reproduce and dies.

Some research reports on synthesis of sulfonamido derivatives of coumarin compounds and their physiological properties have been briefly reviewed here.

Robert F.Meyer[1] prepared 3-allyl-4-hydroxy-7-chlorocoumarin-6-sulfonamides (1) by condensing 3-allyl-4-hydroxy-7-chloro 6-sulfonylchloride coumarin with ammonia. These compounds possessed diuretic activity.

Haruo Kitagawa and Riichiro Iwaki[2] synthesised substituted 6-(p-tolylsulfonamido) coumarin, 6-(p-acetamidosulfonamido)coumarin and 6-(p-aminosulfonamido)coumarin (2) from 6-aminocoumarin and substituted sulfonylchloride. They reported that 6-(p-acetamido sulfonamido)coumarin derivative possessed greater tuberculostatic activity.

L.Reppel and W.Schmollack[3] had also reported synthesis of sulfanilamido coumarin (3) from 3-amino-, 6-amino-, 8-amino-, 3-amino-6-nitro-, 3-amino-8-nitrocoumarin and p-Ac-$NH_6CH_4SO_2Cl$.

3(p-acetamidosulfonamido)7-hydroxycoumarin (4) (R'=H) was reported by Chakravarti and R.Das[4] by condensing p-acetamidobenzene sulfonylchloride with 3-amino-7-hydroxy coumarin.They also prepared 8-methoxy-3-(p-acetamidosulfonamido) coumarin.

M.Dazelic and co-workers[5] synthesised 3-sulfonamido-4-hydroxy 6-bromocoumarin (5) by refluxing 3-amino-4-hydroxy-6-bromocoumarin with p-acetamido benzene sulfonylchloride followed by removal of acetyl group.

Condensation of 3,7-diamino-4-hydroxycoumarin with p-substituted benzenesulfonyl chloride to give 7-amino-4-hydroxy-3-sulfonamidocoumarin (6) was reported by Ichikawa Masataka and Ichibagase Hisashi[6,7] (6) was active against mycobacterium tuberculosis in vitro with MIC of 6.3 μg/ml. They observed that activity was not affected by acetylation of aminogroup of the sulfanilamide but was greatly reduced by acetylation of amino group in the 7-position of the coumarin ring.

Bachman Gerald[8] reported synthesis of various sulfonamido coumarin (7) by condensing aniline or aminocoumarin with a halogenated coumarin sulfonylchloride. They synthesised 6-(3,4-dichlorophenyl sulfonamido) 3,4-dichlorocoumarin and other halo derivatives. These compounds were active against gram positive bacteria.

K.A. Thaker and N.R.Manjarkar[9] reported 4-methyl-5-hydroxycoumarin derivatives of 2-(N-4-acetylsulfanilamido) thiazole (8). Some of these compounds inhibited the growth of fungi and inhibited mustard seed germination.

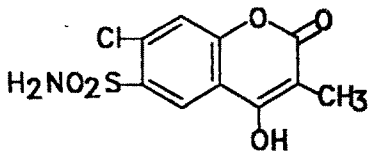
Daiichi Seiyaky Co.Ltd.[10] prepared 4-hydroxy-7-amino-3-sulfanilamidocoumarin (9) which was useful as a bactericides.

A.M. Islam and Coworkers[11] synthesised coumarin sulfonamides (10) by condensing coumarin-6-sulfonylchloride with primary aliphatic, aromatic and secondary aliphatic amines. They also reported synthesis of bromo and nitrocoumarin sulfonamido derivatives (11). Some of the compounds were found to be active against S.aureus

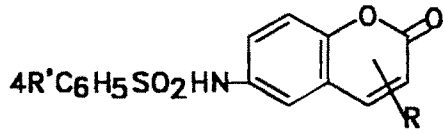
Number of substituted 4-sulfonamido methylcoumarins (12) were prepared by Hanmatgad Shrikant et al.[12] They were active against S.aureus and E.coli.

Sulfanilamido derivatives of 3-amino-5-nitro-8-methoxy (13), 3-acetylamino-5-amino-8-methoxy- (14), 3-amino-8-hydroxy- and 3-amino-7,8-dihydroxycoumarin were prepared by Antonello cipriano.[13] They tested their antibacterial activity.

Cremlyn Richard and Clowes sally[14] synthesised sulfonyl coumarin derivatives from 6-(chlorosulfonyl)coumarin and various amines. Some of them showed fungicidal activity



(1)



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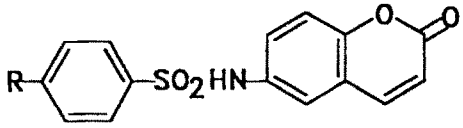
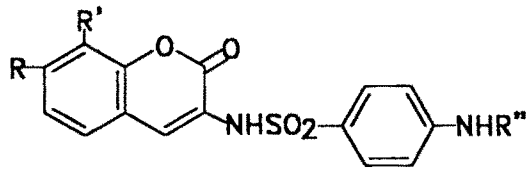


(3)



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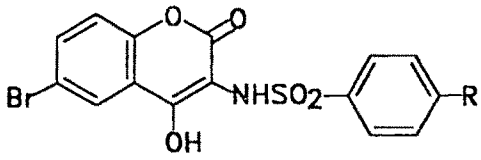
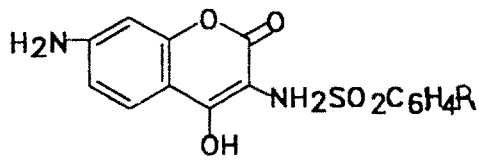
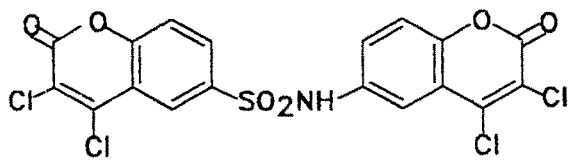


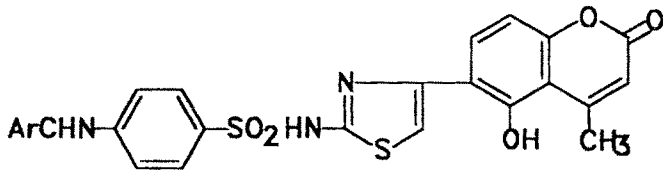
(5)



(6)



(7)



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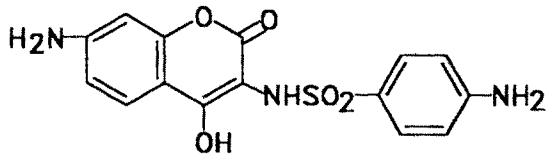

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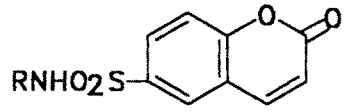

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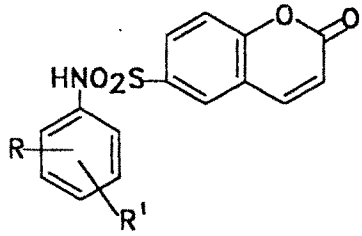

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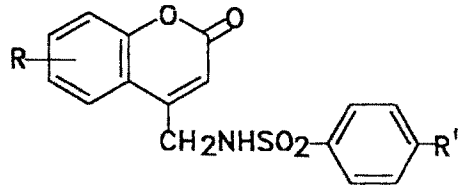


(12)

M.M. Badran, L.N. Soliman, El.Gendy A.A., El.Assi H.R.[15] reported synthesis of (15),7-hydroxy-4-methylcoumarin was chlorosulfonated and then treated with piperazine derivative to get (15).

M.M. Badran, El.ansari A.K., E' Meligie, S.[16] condensed 4-hydroxycoumarin with some sulfa drugs to get (16). Some of these compounds showed moderate antibacterial activity.

Some coumarin-3-(4-aminosulfonyl) carbanilides (17) were prepared by Moustafa M A.A.[17] These compounds had bactericidal activity but they did not show fungicidal activity in standard disk test.

Chandrashekhar D. Lakkqhnavar, Manohar D. Kulkarni and Vemanna P. Patil[18] reported synthesis of (18) and (19). (18) (R=4ACNH,2,5- Br_2) showed partial inhibition against S.aureus, B.aureus but inactive against E.coli while (19) (R=H, 4-NHAC, 2,5 Br_2) showed partial inhibition of S.aureus, E.coli but inactive against B.aureus. (18) (R= 4' Br) and (19) (R=H) showed considerable inhibition of fungicide Aniger None of above compounds were active against Cl albicans.

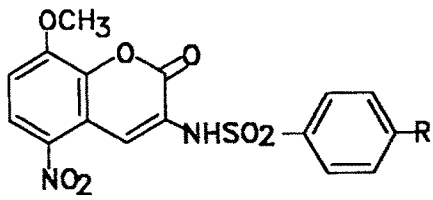
Synthesis of some phthalimido and tosylamino coumarin derivatives and N-(7-hydroxy-4-methylcoumarin-6-sulfonyl) aminoacids were prepared by Ibrahim Tarek, El-Gazzar Mohmed M and Shedid Saied A.[19] (20,21)

A.M. Shalaby, A.H. Mandour and H.A. Farrag[20] reported reaction of 6-coumarinsulfonyl chloride with aminoacid ester which gave N-(coumarinyl)sulfonyl glycine hydrazide (22). (R=alkyl, benzyl etc.)

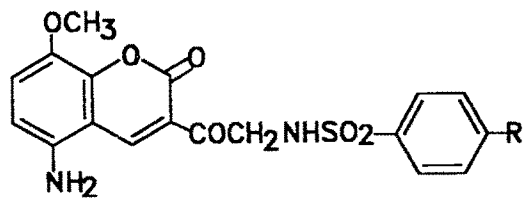
Adel Berg, Hamed M. Abelil, A.H. Aleem and Ismail I Imam[21] showed reaction of coumarin 6-sulfonylchloride with 4-aminobenzosulfonamide. They reported mono and di-sulfonamides (23) and (24) respectively.

N.D. Shinde, D.B. Shinde and M.S. Shingare[22] synthesised substituted sulfonamides alkenes (25).

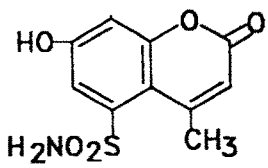
A.S. Gupta and Manjnder sing Phull[23] reported a convenient one pot synthesis of sulphonilamino derivatives (26) by condensing salicyldehyde derivatives with sodium salt of p-acetamidobenzosulfonyl glycine. They were screened for antitubercular activity


OCH3
O
O
NHSO2
R
NO2

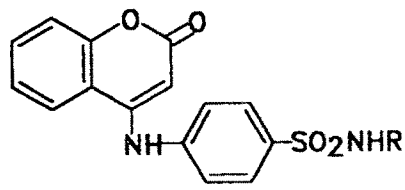
(13)


OCH3
O
O
COCH2NHSO2
R
NH2

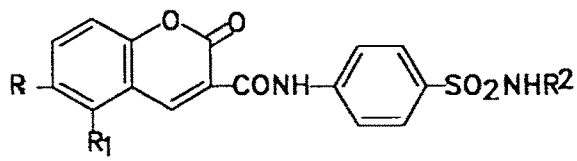
(14)


HO
O
O
H2NO2S
CH3

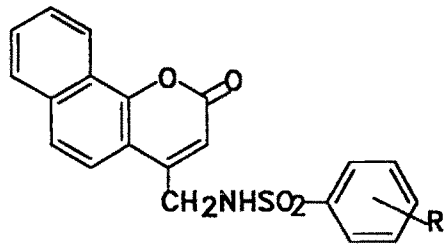
(15)


O
O
NH
SO2NHR

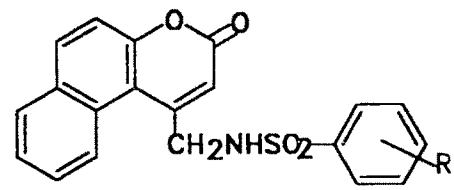
(16)


R
O
O
CONH
SO2NHR2
R1

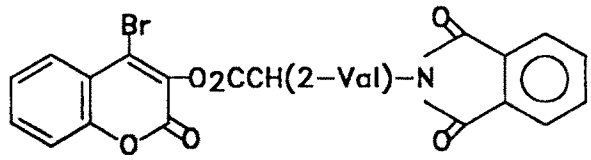
(17)



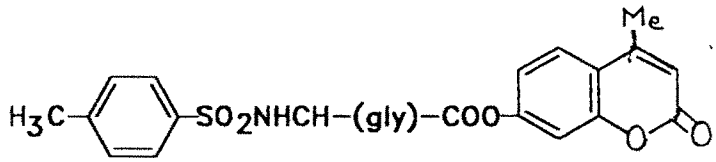
(18)



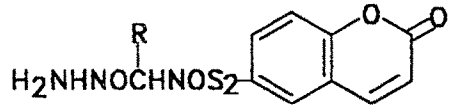
(19)



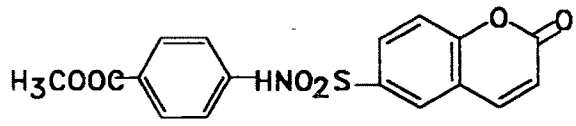
(20)



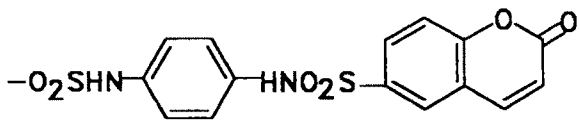
(21)



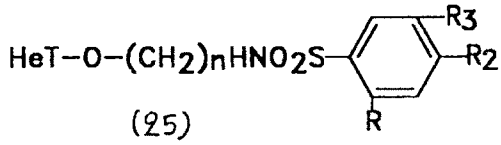
(22)



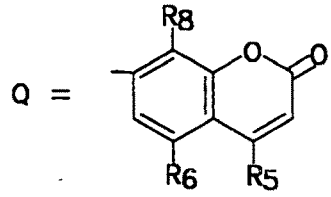
(23)

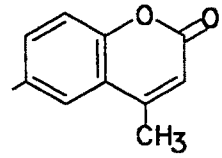


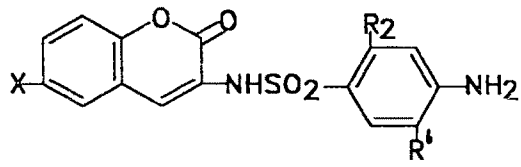
(24)



(25)







(26)

PRESENT WORK

References quoted in the earlier paragraphs reveal that introduction of SO_2 NH group in the substrate molecule like coumarin derivatives induces biological activities. In search of potent drug, it was therefore thought of interest to prepare sulfonamido derivatives by condensing 8-methoxycoumarin-3-carbonyl chloride and 8-methoxy-5-bromocoumarin-3-carbonyl chloride with various sulfonamides and to observe if the products could display any antibacterial activity.

8-Methoxycoumarin-3-carboxy [4'-(N-ethyl-N-phenylsulfonyl)] anilide. (27, Table-1,2) Scheme-1

8-Methoxycoumarin-3-carboxylic acid was converted into its acidchloride using thionylchloride which was treated with N-ethyl-N-phenyl sulfanilamide to get above product. The structure of this compound was established on the basis of IR, PMR and mass spectral data.

IR (Nujol) exhibited bands in region 3200-3100 cm^{-1}, due to SO_2NH and NH stretching, 1710cm^{-1} due to lactonic C=O, 1670 cm^{-1} due to CONH, 1600 cm^{-1} due to aromatic C=C, 1280 and 1100 cm^{-1} for C-O-C linkage (Fig. 1).

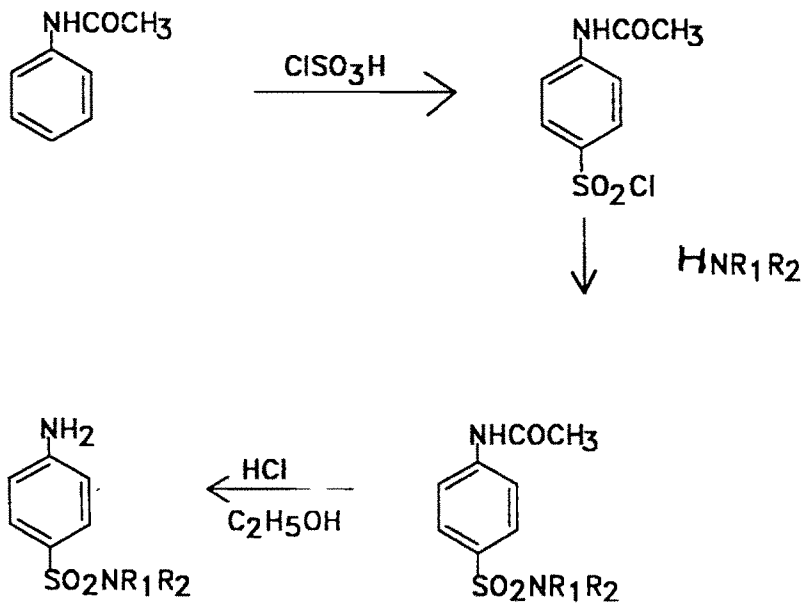
The PMR spectra in (CF_3COOH + $CDCl_3$) exhibited following signals, a triplet at δ 1.1 for three protons of methyl group of $CH_2\underline{CH_3}$ function; a quarlet at δ 3.7 for two protons of methylene group of $\underline{CH_2}CH_3$ function; a singlet at δ 4.05 for three protons of $O\underline{CH_3}$ group at C-8, aromatic protons appeared as multiplet in the region δ 7.0 - 7.9 and a singlet at δ 9.3 for C-4 proton (Fig. 2).

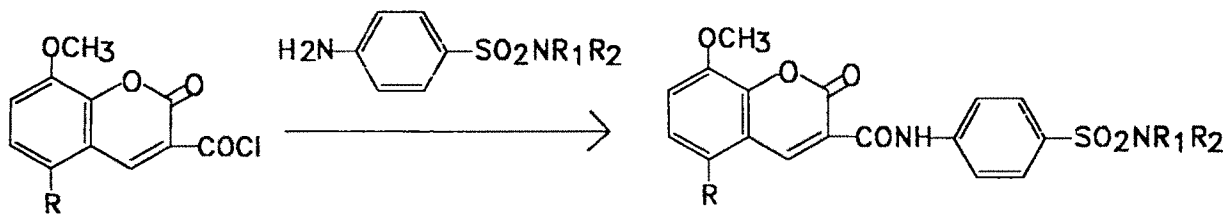
The mass spectra showed following prominent m/z peaks, 478 (M^+ peak,24.1%) and 414 (Base peak, 100%) (Fig.3)

8-Methoxy-5-bromocoumarin-3-carboxy[4'-(4"-methyl piperidinosulfonyl)] anilide (27, Table-1,12) Scheme-1

8-Methoxy-5-bromocoumarin-3-carbonyl chloride was condensed with 4-methylpiperidino sulfonyl anilide in dry ether to get above product. The structure was established on basis of IR and PMR spectra.

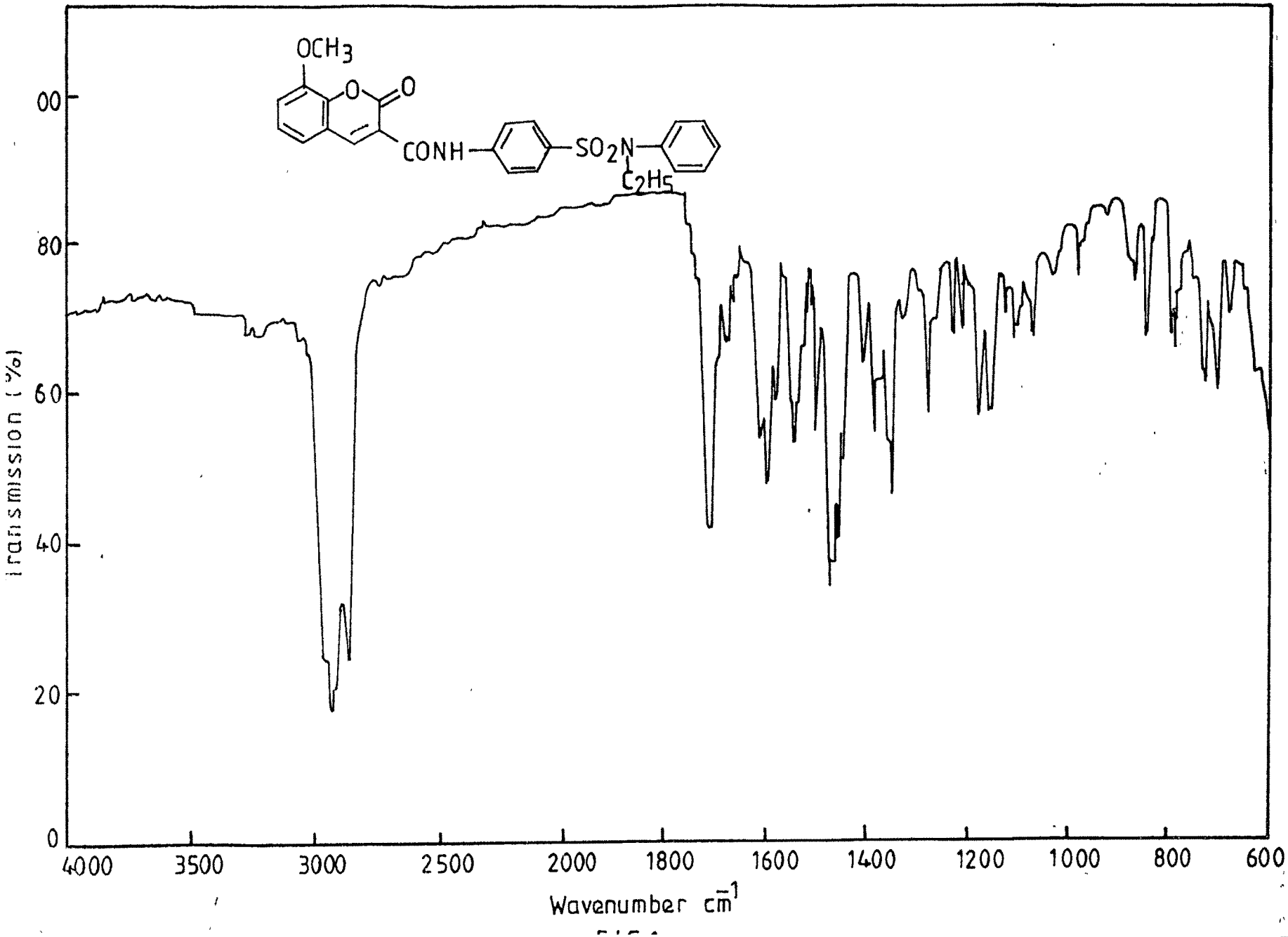
Scheme - 1





R=H, Br

(27, Table - 1, 1-15)


OCH3
O
O
CONH
SO2N
C2H5
Transmission (%)
00
80
60
40
20
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
Wavenumber cm-1

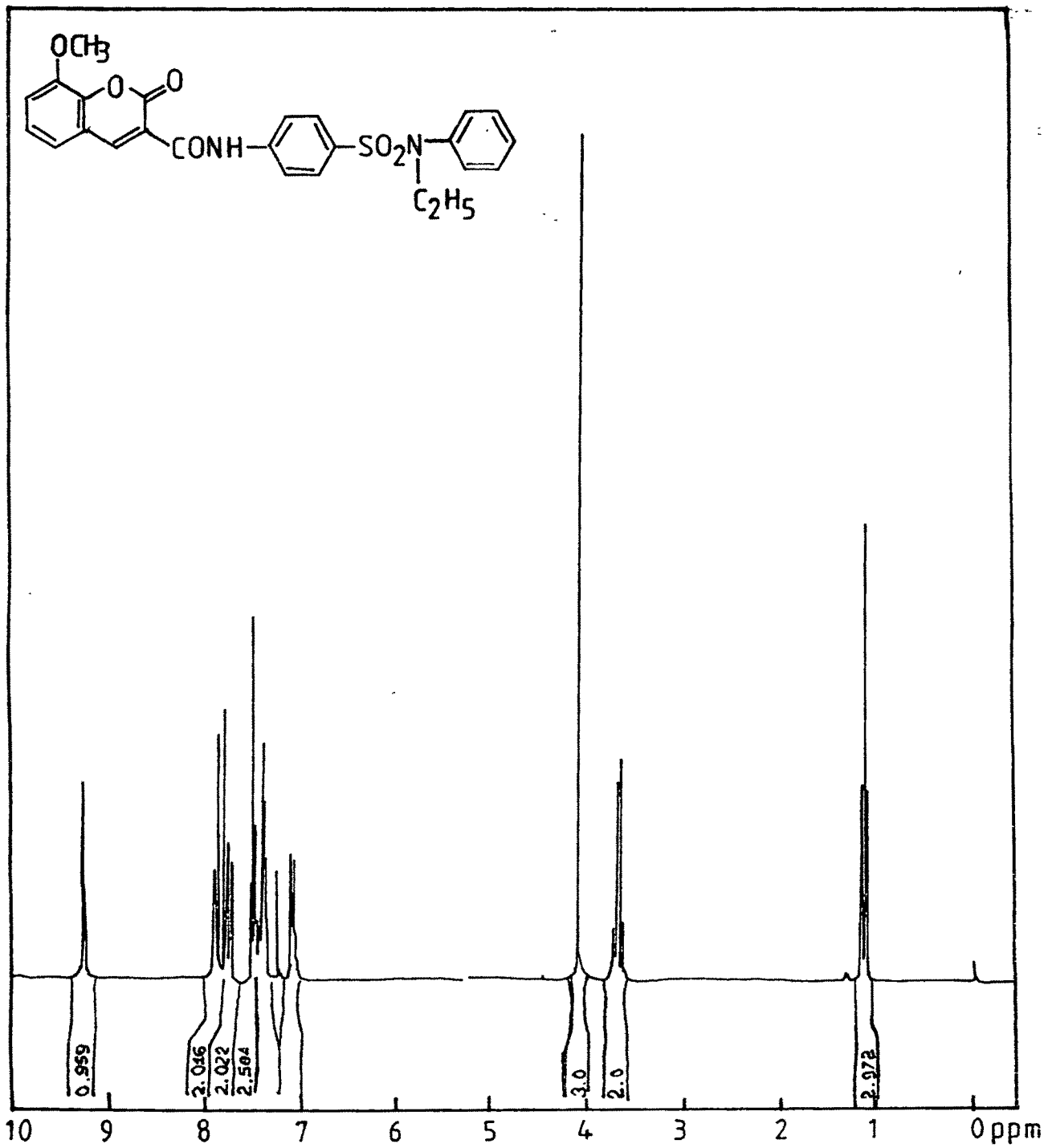

OCH3
O
O
CONH
SO2N
C2H5
0.959
2.046
2.022
2.504
3.0
2.0
2.972
10
9
8
7
6
5
4
3
2
1
0 ppm

FIG. 2

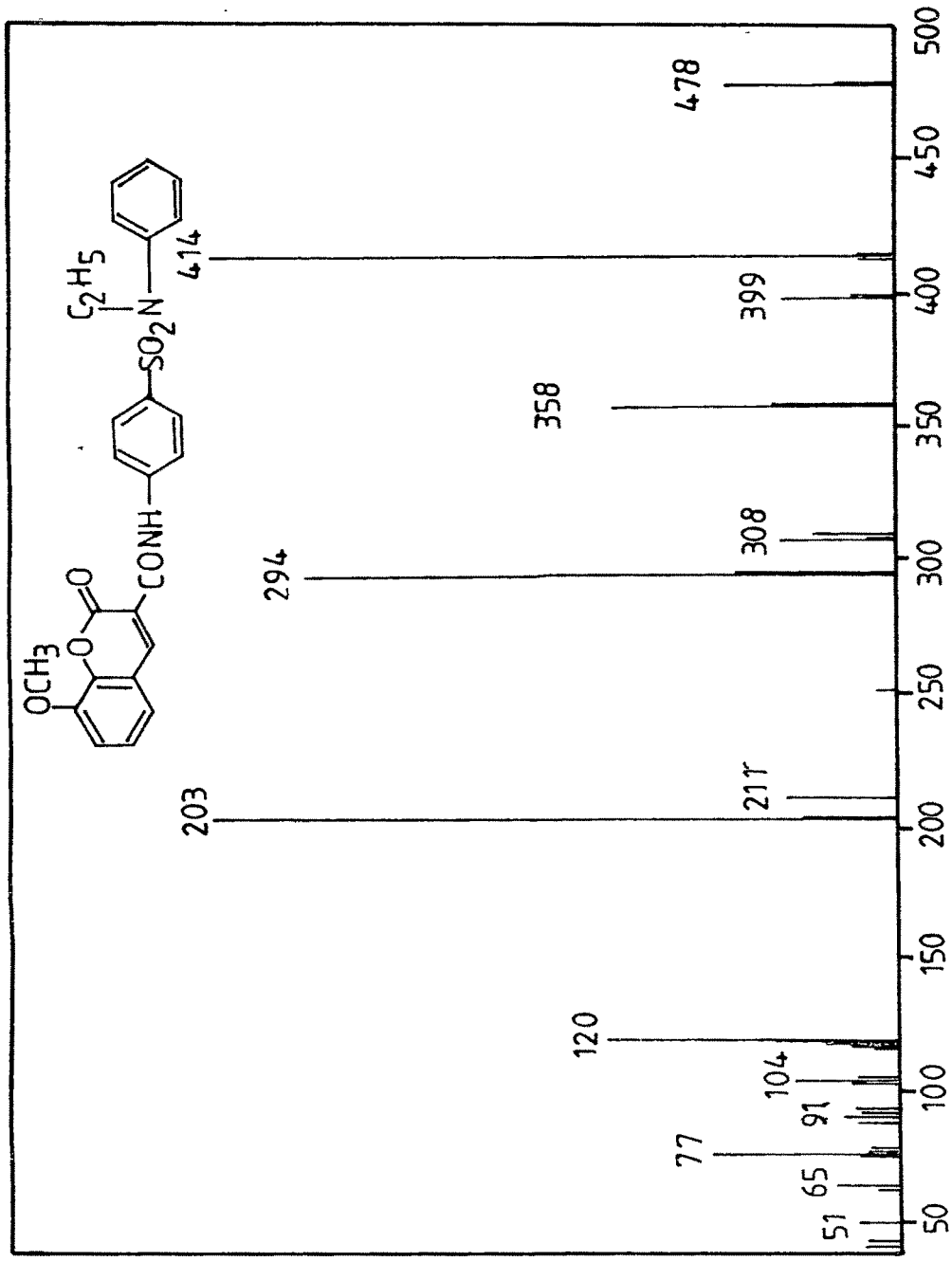

OCH3
O
O
CONH
SO2N
C2H5
414
478
399
358
308
294
211
203
120
104
91
77
65
51
50
100
150
200
250
300
350
400
450
500

FIG.3

The IR (KBr) exhibited bands in region of 3300-3200 cm^{-1} due SO_2NH and NH stretching, 1710 cm^{-1} due to lactonic C=O, 1600 cm^{-1} due to C=C, 1270 and 1100 cm^{-1} due to C-O-C (Fig. 4).

The PMR spectra in ($CDCl_3$ +DMSO) exhibited following signals : a doublet at δ 0.9 for three protons of CH_3 group of 4-methyl piperidine moiety; two multiplets at δ 1.2 and δ 1 6 for rest of nine protons of 4-methyl piperidine moiety; a singlet at δ 4.0 for three protons of $OC\underline{H}_3$ group at C-8. In aromatic region four doublets were observed, a doublet at δ 7.1 (J=9Hz) for one proton at C-7 of coumarin ring and other doublet at δ 7.5 (J=9Hz) for one proton at C-8 position, other two doublets at δ 7 6 (J=9Hz) and δ 7.8 (J=9Hz) for four protons of phenyl ring attached to SO_2 group and one singlet at δ 9.2 for C-4 proton (Fig 5).

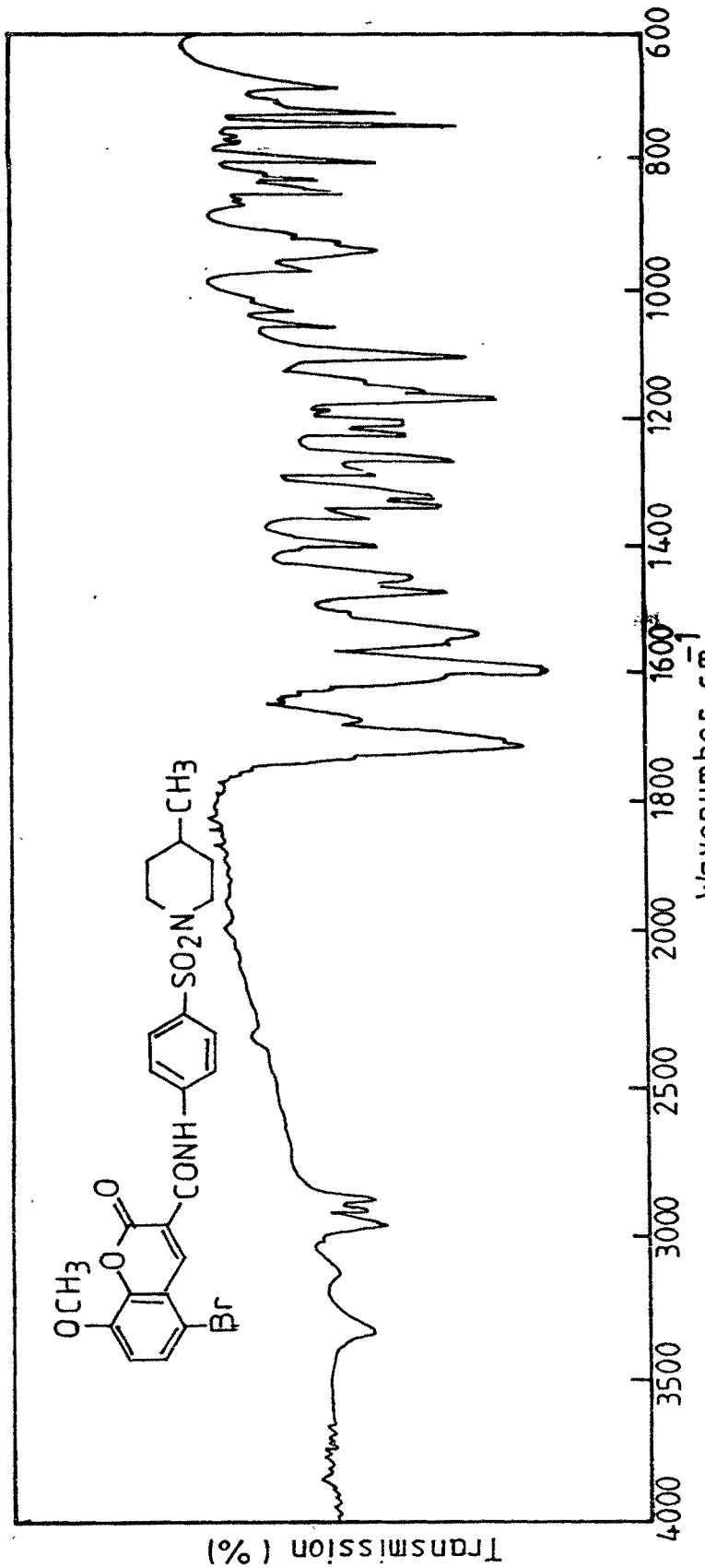

Transmission (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
Wavenumber cm⁻¹
OCH3
O
O
CONH
SO2N
CH3
Br

FIG. 4

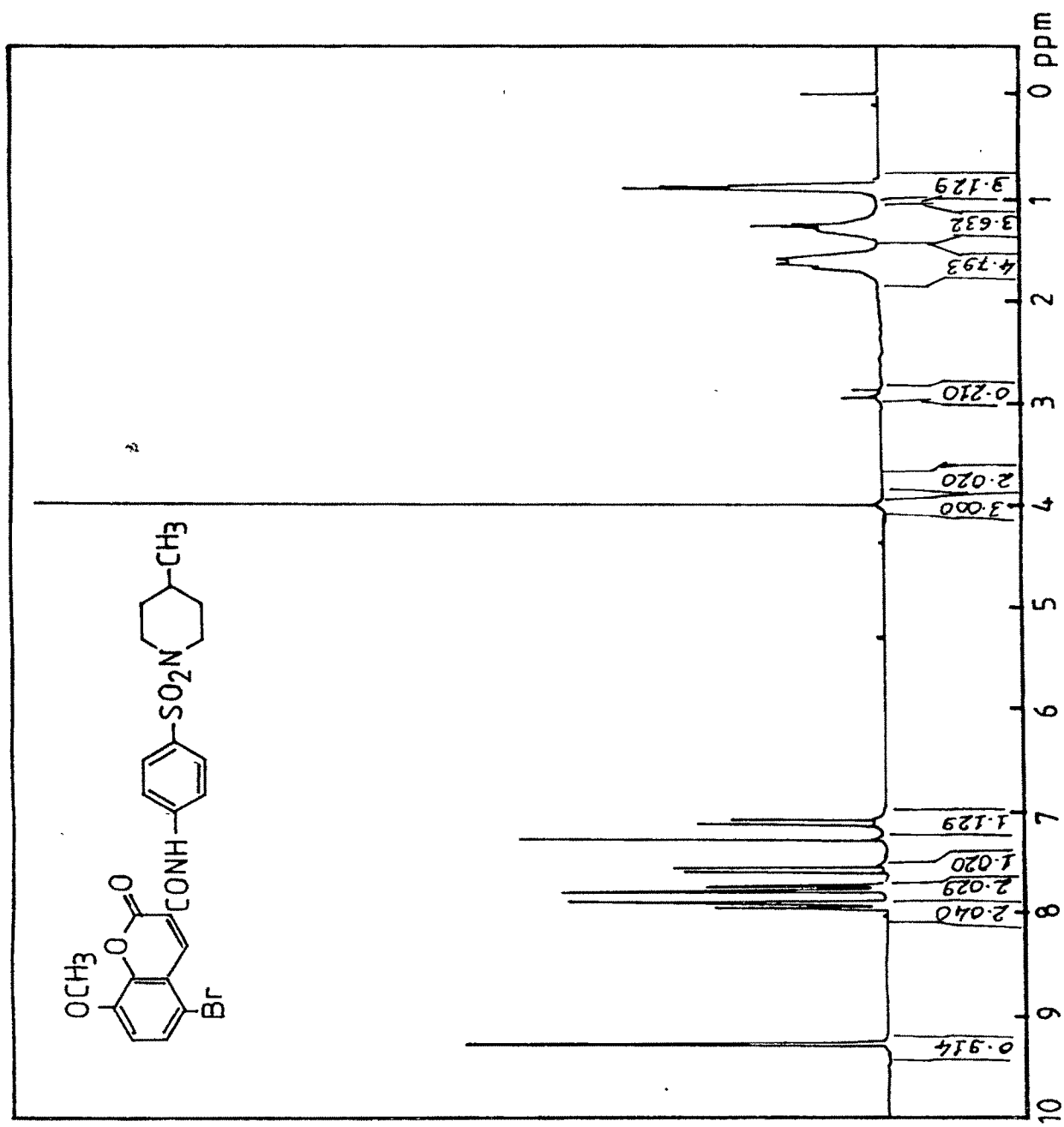

0 ppm
1
2
3
4
5
6
7
8
9
10
3.129
3.632
4.793
0.210
2.020
3.000
1.129
1.020
2.029
2.040
0.914
OCH3
O
O
CONH
SO2N
CH3
Br

FIG. 5

Experimental

8-Methoxycoumarin-3-carboxy [4'(N-ethyl-N-phenylsulfonyl)] anilide (27, Table-1,2)

A mixture of 8-methoxycoumarin-3-carbonyl chloride (0.01 mol) and N-ethyl-N-phenyl sulfanilamide (0.01 mol) was taken in 30-35 ml dry, diethylether and stirred at room temperature for 5 hrs. The product was filtered, dried and crystallised from DMF, M.p. 247° C, Yield 75%.

Analysis	:	Found	:	C, 62.77;	H, 4.82; N, 5.78%
$C_{25}H_{22}O_6N_2S$	:	Required	:	C, 62.76;	H, 4.60; N, 5.88%

8-Methoxy-5-bromocoumarin-3-carboxyl-[4'-(4"-methylpiperidinosulfonyl)]anilide

(27, Table-1,12)

8-Methoxy-5-bromocoumarin-3-carbonyl chloride (0.01 mol) and 4-methylpiperidino sulfanilamide (0.01 mol) was stirred in 30-35 ml of dry ether for 5 hrs. The product separated was worked up as usual. M.p. 245°C, Yield 73%.

Analysis	:	Found	:	C, 51.18;	H, 4.27, N, 5.61%
$C_{23}H_{23}O_6N_2SBr$	:	Required	:	C, 51.58;	H, 4.29; N, 5.23%

Table - 1. Analytical and Physical Data of Compound (27)

Sr. No.	R	R_1	R_2	M.P.* in °C	%Yield	Molecular Formula	Elemental Analysis Found / Required		
							%C	%H	%N
1.	H	CH_3	C_6H_5	256^{D+A}	65	$C_{24}H_{20}O_6N_2S$	61.67 62.06	4.37 4.31	5.79 6.03
2.	H	C_2H_5	C_6H_5	247^{D}	75	$C_{25}H_{22}O_6N_2S$	62.77 62.76	4.82 4.60	5.78 5.88
3.	H	Piperidino		284^{D}	70	$C_{22}H_{22}O_6N_2S$	59.47 59.27	5.10 4.97	5.98 6.33
4.	H	4-Methylpiperidino		239^{D}	72	$C_{23}H_{24}O_6N_2S$	60.66 60.52	5.68 5.26	5.79 6.14
5.	H	3-Methylpiperidino		216^{D}	60	$C_{23}H_{24}O_6N_2S$	60.93 60.52	5.48 5.26	6.15 6.14
6.	H	2-Methylpiperidino		250^{D+A}	55	$C_{23}H_{24}O_6N_2S$	61.08 60.52	5.41 5.26	6.62 6.14
7.	H	Morpholino		272^{D}	75	$C_{21}H_{20}O_7N_2S$	56.31 56.75	4.94 4.50	6.73 6.30
8.	H	N-phenylpiperazino		280^{D}	62	$C_{27}H_{26}O_6N_3S$	62.94 62.42	5.23 4.87	8.30 8.09

Solvent of crystallisation, A = Alcohol, D = DMF, W = Water

Contd... Table - 1. Analytical and Physical Data of Compound (27)

Sr. No.	R	R_1	R_2	M.P.* in°C	%Yield	Molecular Formula	Elemental Analysis Found / Required		
							%C	%H	%N
9.	Br	CH_3	C_6H_5	211^{D+W}	60	$C_{24}H_{19}O_6N_2SBr$	53.47 53.03	3.66 3.49	4.93 5.15
10.	Br	C_2H_5	C_6H_5	205^{D}	64	$C_{25}H_{21}O_6N_2SBr$	53.42 53.85	3.80 3.77	5.37 5.02
11.	Br	Piperidino		207^{D}	70	$C_{22}H_{21}O_6N_2SBr$	50.24 50.67	4.21 4.03	4.79 5.07
12.	Br	4-Methylpiperidino		245^{D}	73	$C_{23}H_{23}O_6N_2SBr$	51.18 51.58	4.27 4.29	5.61 5.23
13.	Br	3-Methylpiperidino		216^{D}	62	$C_{23}H_{23}O_6N_2SBr$	51.72 51.58	4.50 4.29	4.87 5.23
14.	Br	Morpholino		240^{D}	60	$C_{21}H_{19}O_7N_2SBr$	48.29 48.18	30 3.63	5.26 5.35
15.	Br	N-phenylpiperazino		270^{D}	56	$C_{27}H_{25}O_6N_3SBr$	53.79 54.18	4.48 4.01	7.51 7.03

Solvent of crystallisation, D = DMF, A = Alcohol, W = Water

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