List of Publications

1. Synthesis of Some Mannich Bases from coumarin derivatives and their antibacterial activities.
   Devki Desai and R. H. Mehta*.
   Indian Journal of Heterocyclic Chemistry, Vol. 5. April - June 1996, pp 319-320.

2 Synthesis and antibacterial activity of substituted coumarins.
   Devki Desai and R. H. Mehta*
   Indian Journal of Heterocyclic Chemistry, Vol. 6, Jan - March - 1997, pp 241-244.

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Synthesis and antibacterial activity of sulfonamido derivatives and amides of coumarin compounds. Sonal Shah, Devki Desai and R. H. Mehta*, Journal of Indian Chemical Society.

Under Publications

1. Synthesis and Antibacterial activity of some 7,8-dimethoxy-4-amino-methylcoumarins.

2. Synthesis and antibacterial activity of some Schiff bases, hydrazides and oxadiazoles of coumarin compounds.

3. Synthesis and antibacterial activity of sulfonamides of coumarin derivatives.

Indian Journal of Heterocyclic Chemistry
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SYNTHESIS OF SOME MANNICH BASES FROM COUMARIN DERIVATIVES AND THEIR ANTIBACTERIAL ACTIVITIES*

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Mannich bases from 7-hydroxy coumarins have been prepared and tested for their antibacterial activity

In continuation of our work on Mannich compounds from coumarin derivatives and DL-α-amino carboxylic acids[1,2] we now report Mannich bases from L-aminoacids as L-aminoacids are mostly found in natural proteins and antibodies. All the compounds were found to have optical activity and their specific rotations have been determined. All the compounds have been screened for their antibacterial activity(Scheme-1).

Antibacterial activity

All the synthesized compounds were tested at 100 and 500 ppm concentrations for their antibacterial activity by cup-plate method[3] in DMF *in vitro* against *E coli* and *B subtilis* using ampicillin as standard drug All the compounds were less active against these microorganisms in comparison to ampicillin. They are even less active than the Mannich products obtained from DL-aminoacids [1,2]

Anticancer and Anti-HIV activity

Some selected compounds (except compound. 3, 6, 8 and 14) have been evaluated for anticancer and anti-HIV activity by National Cancer Institute, U.S.A. and were inactive.

Experimental

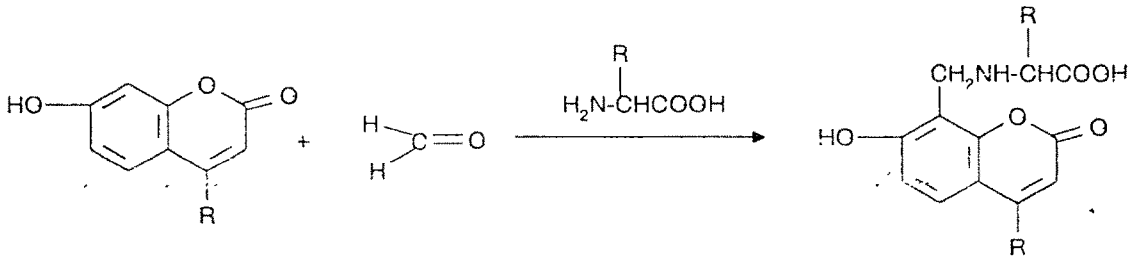
Melting points were determined in open capillaries and are uncorrected. Microanalyses were performed on a Coleman instrument IR spectra (KBr) were recorded on a Shimadzu-408 spectrometer. PMR spectra (TFA) were recorded on a Perkin Elmer R-32 Spectrometer at 90 MHz using TMS as the internal standard. The Mass spectra were recorded on a GCMS model HP 5985 at 70 eV. The specific rotations were determined on the Jasco-Dip-370-D digital polarimeter taking DMSO as solvent The homogeneity and purity of the compounds were tested by TLC.

N-(7-Hydroxy-8-coumarinyl) L-alanine (13)

A mixture of 7-hydroxycoumarin (0.01 mol), L-alanine (0 01 mol) and formalin (1 2 ml) in 80% ethanol (50 ml), was refluxed for 3 hr The product separated during reflux was then filtered, extracted with ethanol to remove unreacted coumarin and then crystallised from DMF All other compounds were prepared similarly (Table-1)

IR of compound **1** to **18** 3500-2100 (broad, phenolic-OH, -NH and -COOH hydroxyl)-1730-1705 (lactonic C=O of coumarin ring system skeletal vibration involving C-C stretch within aromatic ring) - 1600-1500 (Carboxylate anion), 1395-1240 (C-N and carboxylate anion)

PMR data Compound 1 -1.5 (d, 3H, $CHCH_3$), 2 2 (s, 3H, C-4-CH_3), 4 05 (q, 1H, J=7Hz, NH $CH(CH_3)$), 4 5 (broad, 2H, -CH_2-NH), 6.1 (s, 1H, C-3 proton), 7.5 (d, 1H, C-5 proton).



SCHEME-1 COMPOUNDS [1 TO 18]

*Presented at the international Symposium on perspective in Bioorganic Chemistry. 1994, New Delhi

Table-1

Analytical and physical data of compounds prepared

Compd	R	R	M.P. (°C)	Yield (%)	Specific* Rotation (α) D^{25}
1.	$-CH_3$	$-CH_3$	248-50d	70	-1.2005°
2.	$-CH_3$	$-CH_2C_6H_5$	235d	75	-1.2005°
3.	$-CH_3$	$-CH_2CH_2SCH_3$	264-65d	80	+1.4010°
4.	$-CH_3$	$-CH_2OH$	249-50d	75	-2.4010°
5.	$-CH_3$	$-CH(OH)CH_3$	245d	60	-+12.0400°
6.	$-CH_3$	$-CH(CH_3)_2$	248d	80	+13.2050°
7.	$-CH_3$	$-CH_2CH(CH_3)$	242-43d	80	+12.0400°
8.	$-CH_3$	-H	207-9d	70	No Chiral Center
9.	$-C_6H_5$	$-CH_3$	268-70d	75	+7.2029°
10.	$-C_6H_5$	$-CH_2C_6H_5$	246-46d	70	-6.0024°
11.	$-C_6H_5$	$-CH_2CH_2SCH_3$	243-44d	75	+12.0050°
12.	$-C_6H_5$	$-CH(CH_3)_2$	239-49d	80	+10.8040°
13.	-H	$-CH_3$	250d	70	+3.6014°
14	-H	$-CH_2C_6H_5$	210d	70	+6.0200°
15.	-H	$-CH_2CH_2SCH_3$	230d	75	+1.2005°
16.	-H	$-CH_2OH$	221d	65	+24.0900°
17.	-H	$-CH(CH_3)_2$	240-42d	75	+25.2100°
18.	-H	$-CH_2CH(CH_3)_2$	212-14d	80	+84 3300°

*D line of sodium, 5893° A. All compounds gave correct CHN analyses.

3: 1.85 (s, 3H, $-CH_2-S-CH_3$),2 25 (s, 3H, C-4 -CH_3), 2.55 (m, 2H, $-CH_2-CH_2-S-CH_3$), 2.9 (m, 2H, $-CH_2-CH_2-SCH_3$), 4.25 (m, 1H, -NH-CH-COOH), 4.6 (broad, 2H, $-CH_2$-NH)-6.2 (s, 1H, C-3 proton), 6.9 (d, 1H, J=10Hz C-6 proton), 7 6 (d, 1H, J=10Hz C-5 proton).

9: 1 6 (d, 3H, -NHCH (CH_3)), 4 6 (m, 1H, -NH-CH-COOH), 5.0 (s, 2H, $-CH_2$-NH), 6 25 (d, 1H, C-3 proton), 6.80 (d, 1H, J=9Hz, C-6 proton), 7 2(m, Ar-H of C-4 phenyl ring), 7.5 (d, 1H, J=9Hz, C-5 proton)

11: 2.1 (s, 3H, $-CH-S-CH_3$), 2.3 (m, 2H, $-CH_2-CH_2-S-CH_3$), 2.65 (m, 2H, $-CH_2-CH_2-S-CH_3$), 4.75 (broad, 2H, $-CH_2$-NH), 6.32 (s, 1H, C-3 proton), 6.90 (d, 1H, J=10Hz, C-6 proton), 7.60 (d, 1H, J=10Hz C-5 proton), 7.30 (broad, C-4-C_6H_5)

13: 1 7 (d, 3H, $-CH_3$-CH-COOH), 4.35 (m, 1H, -NH-CH-COOH), 4 78 (broad, 2H, $-CH_2$-NH), 6 5 (d, 1H, J=10Hz, C-3 proton), 7 72 (d, 1H, J-10Hz, C-4 proton), 7 15 (d, 1H, J=10Hz, C-6 proton), 8.08 (d, 1H, J=10Hz, C-5 proton).

15 2 0 (s, 3H, $-CH_2-S-CH_3$), 2 35 (m, 2H, $-CH_2-CH_2-S-CH_3$), 2.70 (m, 2H, $-CH_2-CH_2-S-CH_3$), 4 3 (m, 1H, -NH-CH-COOH), 4.8 (broad, 2H, $-CH_2$-NH), 6 5 (d, 1H, J=10Hz, C-3 proton), 7.65 (d, 1H, J=10Hz, C-4 proton), 7.10 (d, 1H, J=8Hz, C-6 proton), 8.00 (d, 1H, J=8Hz, C-5 proton).

MS: **6**, m/z : 305 (M+) · 149, 72 (base peak), 57.

MS: 11, m/z : 399 (M+): 129 (base peak), 102, 57.

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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SUBSTITUTED COUMARINS

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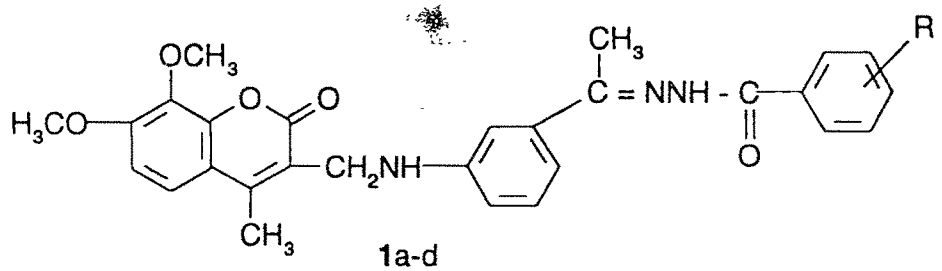
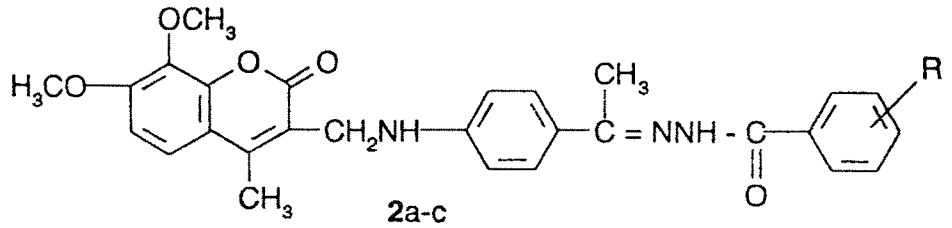
Synthesis of a number of substituted coumarins has been reported. Their stuctures have been established on the basis of spectral and elemental analyses. Some of the compounds synthesised showed significant antibacterial activity.

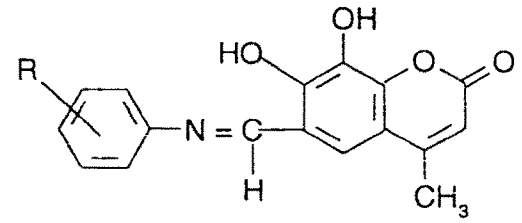
In continuation of our earlier work on synthesis of new coumarin derivatives[1,2] we report herein the condensation of 7,8-dihydroxy-6-formyl-4-methyl coumarin; 7,8-dimethoxy-3-(3′-acetyl phenyl aminomethyl)-4-methyl coumarin; 7,8-dimethoxy-3-(4′-acetyl phenyl aminomethyl)—4-methyl coumarin and 6′-hydroxy -5′-formyl-4-methyl-7,8-benzocoumarin with various primary aromatic amines and substituted



1a-d



2a-c



3a-d

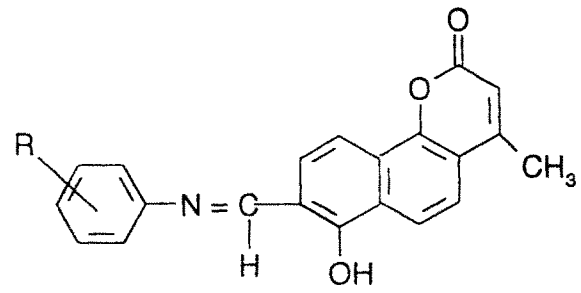
Table-1

Analytical and physical data of compounds (1 to 4)

Compd	R	M.P. (°C)	Yield (%)
1a	2-NO_2	252	60
1b	3-Cl	196	65
1c	4-Cl	208	65
1d	3-Br	195	60
2a	4-Cl	266	60
2b	2-Cl	276	70
2c	2-NO_2	290	55
3a	4-CH_3	255	65
3b	4-COOEt	255	75
3c	3,4-Cl_2	215	70
3d	2,4-Cl_2	245	65
4a	-H	>310(d)	60
4b	4-CH_3	>310(d)	65
4c	3,4-Cl_2	>310(d)	65
4d	2,4-Cl_2	>310(d)	60
4e	4-Br	>300(d)	70
4f	4-NO_2	>310(d)	65
4g	4-COOEt	275(d)	55

Satisfactory CHN analyses were obtained for all the compounds.

Compd : 1c, 2b, 3a-d, 4b, 4d and 4f were crystallised from DMF + water and rest were crystallised from DMF.



4a-g

benzoyl hydrazides with a view to screening them for antibacterial activity.

The structures of the compounds (Table-1) were assigned on the basis of their elemental analysis, IR PMR, and mass spectral data.

Antibacterial activity

All the synthesised compounds were screened for their antibacterial activity at 500 ppm concentration by cup-plate method[3] in *vitro* against *E. coli* (gram negative) and *S. aureus* (gram positive) in DMF solvent. Ampicillin was used as a standard drug, it showed 22 mm zone of inhibition against *E.coli* and 35 mm zone of inhibition against *S. aureus*. DMF also showed 10 mm zone of inhibition against both bacteria.

From the results, it seems that azomethine linkage is perhaps an essential structural requirement for such activity. Results are given in Table-2.

Experimental

Melting points were determined in open capillaries and are uncorrected. Microanalyses were performed on a Coleman instrument. IR spectra (KBr) were recorded on a Shimadzu 408 spectrometer. PMR spectra (CF_3COOH) were recorded on a Perkin-Elmer R-32 spectrometer at 90MHz using tetramethyl silane as the internal standard and chemical shifts are measured in δ ppm

The homogeneity and purity of the compounds were tested by TLC using silica gel G

7,8-Dimethoxy-3-[3'-yl-ethyliden(substituted benzoic acid hydrazide)-phenyl aminomethyl]-4-methyl coumarin [1 a-d] and 2a-c.

A mixture of 7,8-dimethoxy-3-(3'-acetyl phenyl

Table-2
Antibacterial activity of compounds (1a-d), (2a-c), (3a-d) and (4a-g)

Compd	Zone of inhibition *E. coli*	*S. aureus*
1a	++	++
1b	++	++
1c	++	++
1d	+	+
2a	-	-
2b	++	++
2c	+	++
3a	++	++
3b	++	++
3c	+	+
3d	++	++
4a	-	-
4b	-	-
4c	+	+
4d	-	-
4e	-	-
4f	-	-
4g	+	+

(-) - Indicates no inhibition.

(+) - Indicates zone diameter between 11mm-14 mm

(++) - Indicates zone diameter between 15mm-20mm

aminomethyl) -4-methyl coumarin[4] (0.01 mol) and various substituted benzoic acid hydrazides (0.01 mol) in 50 ml of ethanol (95%) and a few drops of acetic acid was refluxed for 1 hr. The separated solids were crystallised from appropriate solvents.

6-(Substituted-phenyl imino methyl)7, 8-dihydroxy-4-methyl coumarin [3a-d] and 4a-g

7,8-Dihydroxy-6-formyl-4-methyl coumarin[4] (0.01 mol) dissolved in 20 ml of 95% ethanol and various primary aromatic amines (0.01 mol) in 10 ml of ethanol were mixed and refluxed for 1.5 hr.

The excess of the solvent was then removed by distillation and the remaining liquid was cooled, the scarlet red solid separated on cooling was filtered, washed with ethyl alcohol then crystallised from mixture of DMF + water.

The analytical and physical data are given in Table-1

IR : The IR spectra of compounds (1a-d) and (2a-c) exhibited characteristic absorption bands at 3400 (NH) 1730-1705 (lactonic >C=O) 1600 (aromatic C=C ring stretch) 1670-1650 (amide band-I), 1560-1540 (amide band -II), 1390-1155 (C=N) and 1100 cm^{-1} (C-O-C) and that of (3a-d) and (4a-g) exhibited at 1730-1705 (lactonic >C=O), 1600-(aromatic C=C ring), 1390-1160 (C=N) and 1100 (C-O-C).

^1H NMR . ^1H NMR spectra exhibited following signals

1a · 2.3 (3H,s, $-CH_3$ at C-4). 2.6 (3H, s, = $C-CH_3$), 3 8 (6H, s, 2 x OCH_3 at C-7 and C-8), (2H, s, $-CH_2$ -NH), 6 75 (1H, d, C-6 proton), 7.9 (1H, d, C-5 proton), 7-1-7.7 (m, aromatic protons).

2c 2.5 (3H, s, $-CH_3$ at C-4), 2.80 (3H, s, $=C=CH_3$), 3.95 (6H, s, 2 x OCH_3 at C-7 and C-8); 4.9 (2H, s, $-CH_2$ -NH), 7.1 (1H, d, C-6 proton), 8.05 (1H, d, C-5 proton) and 7.4 to 7.8 (m, aromatic protons).

3a · 2 35 (3H, s, $-CH_3$ at C-4), 2 55 (3H, s, $-CH_3$ at aromatic ring para to -C = N-), 6.45 (1H, s, C-3 proton), 7 23-7-6 (m, aromatic protons), 7.9 (1H, s, C-5 proton) and 9 05 (1H, s, =C-H)

4a · 2 3 (3H, s, $-CH_3$ at C-4), 6.4 (1H, s, C-3 proton), 7 2-7 8 (m, aromatic protons) and 8.9 (1H, s, =C-H).

4c : 2.35 (3H, s, $-CH_3$ at C-4), 2 7 (3H, s, $-CH_3$ at aromatic ring para to -C=N-), 6.8 (1H, s, C-3 proton), 7 3-8.5 (m, aromatic protons) and 9.05 (1H, s, =C-H)

2c : MS : m/z : 530 (M^+, 11.6%), 233 (Base peak).

3a : MS · m/z : 309 (M^+, and Base peak).

4c: MS m/z : 398 (M^+, 18.6%), 149 (Base peak).

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