Med Chem Res (2011) 20:535–541
DOI 10.1007/s00044-010-9347-9

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

7-Hydroxy-coumarin derivatives: synthesis, characterization and preliminary antimicrobial activities

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Received: 9 November 2009 / Accepted: 3 March 2010 / Published online: 19 March 2010

Abstract A new series of 7-*O*-coumarinyl alkenoates were synthesized from 7-hydroxyl-coumarin and fatty acids using DCC and DMAP as catalyst. The synthesized compounds were characterized on the basis of their spectral data. All the target compounds were evaluated for their in vitro antimicrobial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Streptococcus pyogene*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Escherichia coli* and fungal cultures of *Candida albicans*, *Candida krusei*, *Candida parapsilosis* and *Cryptococcus neoformans.* The minimum inhibitory concentration (MIC) was determined for the test compounds as well as for reference standards. Among the tested compounds, 7-*O*-coumarinyl (9*Z*, 12*R*)-12-hydroxyoctadec-9-enoate and 7-*O*-coumarinyl (12*Z*, 9*R*)-9-hydroxyoctadec-12-enoate showed the most potent antifungal as well as antibacterial activities.

Keywords 7-Hydroxy-coumarin · Fatty acids · DCC · DMAP · Antimicrobial activity

Abbreviations

FA	Fatty acid
7-HC	7-Hydroxy-coumarin
DCC	*N*,*N*′-Dicyclohexylcarbodiimide
DMAP	4-Dimethylaminopyridine

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Introduction

Morbidity and mortality because of enteric bacterial infection are the major health problems in some areas like Indian subcontinent, portions of South America and tropical fraction of Africa (Qadri *et al*., 2005; Devasia *et al.,* 2006). Every year millions of people are being killed by some or the other Gram-positive and Gram-negative strains of bacteria. These bacteria mostly lead to food poisoning, rheumatic, salmonellosis and diarrhoea (Khan *et al.,* 2008). In addition, drug resistance is being developed by these bacteria against the commonly used antimicrobial agents which are being extensively used for the treatment of above diseases. Furthermore, the pharmacological drugs available are either too expensive or have undesirable side effects or contraindications (Berger, 1985). Many traditional plant treatments for the antimicrobial infections exist, and there lies a hidden wealth of potentially useful natural products for the control of microbial diseases (Gray and Flatt, 1997). Natural plant drugs are frequently considered to be less toxic and free from side effects than synthetic ones (Morin, 1987). Among the most significant classes of natural compounds, an important position is occupied by oxygen-containing heterocyclic compounds. 7-Hydroxy coumarin (7-HC) is a benzopyrone in nature, which is a major human metabolite and plays a role as dietary antioxidant in the human diet (fruits and vegetables). 7-HC has been reported to have antitumor (Kofinas *et al*., 1998), aldose reductase inhibitor (Okada *et al.,* 1995) and xanthine oxidase inhibitor (Mills and Bone 2000) activities. The parent compound coumarin has been reported to reduce blood glucose levels (Marles and Farnsworth, 1996). A number of natural and synthetic coumarin (2-oxo-2*H*-chromene) derivatives have been reported to exert antimicrobial (Czerpack and Skolska, 1982; Jund *et al.*, 1971), antifungal (El-Ansary

et al., 1992; Reddy and Somayojulu, 1981), antiamoebic (Iqbal *et al*., 2009) and tuberculostatic (Abd Allah, 2000) activities. Moreover, the antibiotic novobiocin belongs to the hydroxy coumarin series. Coumarin may be a prodrug and 7-HC is the pharmacologically active agent (Ritschel *et al*., 1981). Many seed oils, fatty acids (FA) and their derivatives are known for their antimicrobial (Rauf and Parveen, 2005; Kabara *et al*., 1972), antifungal (Ahmed *et al.,* 1985) and pesticidal (Khan *et al*., 1983) activities. A number of investigations have demonstrated that a variety of modified FA are promising molecules in cancer prevention and have potential in the treatment of cancers (Mujeebur-Rahman *et al.,* 2005; Nagao *et al.,* 1991; Lie Ken Jie *et al.,* 1990). FA-ester analogs have received very little attention despite the fact that such molecules have been found to be associated with diverse biological activities such as antioxidant (Viklund *et al*., 2003), antifeedant (Mallavadhani *et al*., 2003), anti-inflammatory (Feng *et al*., 2009), antiparasitic (Grunberg *et al*., 1973), antimicrobial (Mod *et al*., 1975) and neuroprotective (Takahashi *et al*., 2003). Some fatty esters have been found to be very effective for the treatment of dermatitis (Csóka *et al*., 2007) cardiovascular, hepatic and renal disorders (Greelings *et al*., 2003). Thus, FA-esters may lead to a new route to potential pharmaceutical molecules. Literature reveals that long-chain fatty acids have not been esterified with 7-HC in presence of DCC and DMAP.

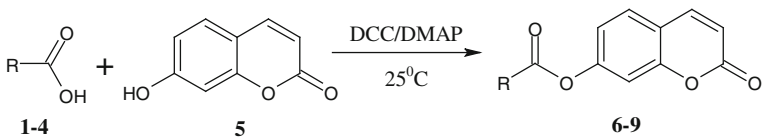
The purpose of this study is to find the novel bioactivity of 7-HC esters. As discussed, the coumarin derivatives possess antimicrobial activity and in view of the significance of long-chain FA as potential pharmacophores; we herein report the synthesis and spectral studies of new coumarin derivatives containing C11 and C18 FA chain. These derivatives were further tested for their in vitro antimicrobial activity against a panel of Gram-positive, Gram-negative strains of bacteria and selected strains of fungus. FA incorporated at the C7 hydroxy group of coumarin are undec-10-enioc, (9*Z*)-octadec-9-enoic, (9*Z*, 12*R*)-12-hydroxyoctadec-9-enoic (ricinoleic) and (9*R*, 12*Z*)-9-hydroxyoctadec-12-enoic (isoricinoleic) acids (Scheme 1).

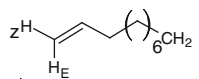
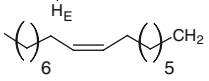
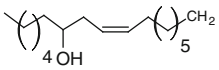
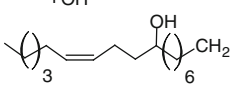
Results and discussion

Chemistry

FA and their derivatives have been reported as antimicrobial agents. It is expected that the incorporation of the hydroxyl and non-hydroxyl FA chain may increase the antimicrobial activity of certain organic moieties. This study is based on the synthesis, characterization and evaluation of antimicrobial activities of 7-HC derivatives derived from different FA. 7-Hydroxy coumarin reacts with fatty acid in the presence of DCC and 4-dimethyl aminopyridine (DMAP) in dichloromethane by stirring at room temperature. The completion of the reaction was checked by thin layer chromatography (TLC). The reaction time varied from 2 to 3 h. The purity of the compounds was checked by TLC and the compounds under the study were characterized by the spectral data. In general, the IR spectra showed ester peak at 1729 cm^{-1} and CH_2 (methylene) peak at 2921 and 2849 cm^{-1}. In the ^{1}H-NMR spectra, the signals of the respective protons of the prepared derivatives were verified on the basis of their chemical shifts, multiplicities and coupling constants. The spectra of all the compounds showed peaks at δ 6.39–7.69 ppm corresponding to the protons of 7-hydroxy coumarin. The ^{13}C-NMR spectra of all the compounds were also in good agreement. Characteristic molecular ion peaks [M + Na] was observed for all the compounds under study. A detailed spectral description for compound **6** is discussed below.

Scheme 1 Synthetic route for the target compounds



Compound	R
1,6	
2,7	
3,8	
4,9	

IR spectrum of compound **6** revealed characteristic band at 1729 cm^{-1} (ester C–O stretching). In the ^{1}H-NMR the olefinic protons, $C_{11'}H_2{=}C_{10'}H$ were observed at δH 5.81 (tdd, 1H, $J_{10'-9'} = 6.8$, $J_{10'-H_Z} = 16.8$, $J_{10'-H_E} = 10.4$, CH_2=CH–), 4.99 (dd, 1H, $J_{H_Z-10'} = 16.8$, $J_{H_Z-H_E} = 3.2$, H_ZC=CH), 4.93 (dd, 1H, $J_{H_E-10'} = 10.4$, $J_{H_E-H_Z} = 3.2$, H_EC=CH–) and were correlated with observations in the ^{13}C-NMR which gave signals at δC 139.18 and 114.24, respectively. Besides these a characteristic carbon signal for the fatty acid chain at δC 171.68 ($C_{1'}$, ester C=O) was recorded. Similarly other compounds were characterized from their spectral data. Spectral studies have illustrated that the change in the nature of FA at C_7 has not significantly influenced the pattern of proton and carbon signals of the 7-HC moiety.

Pharmacology

A variety of acylated 7-hydroxycoumarins were investigated in the early 1970s for antibiotic and antifungal activities (Jund *et al*., 1971). Acyl groups in the study included acetyl, propanoyl and butanoyl. These compounds were found to possess activity against a number of fungal strains (MIC approximately 125 μg/ml) and Gram-negative bacteria (MIC sub 500 μg/ml). It was observed that the ester derivatives of 7-hydroxycoumarins increased the antimicrobial activity of 7-hydroxycoumarin. Thus, it is expected that the use of long-chain hydroxyl and non-hydroxyl fatty acid groups can further increase the antimicrobial potency of the coumarin ester derivatives.

The determination of MIC of synthesized compounds against bacterial and fungal strains was performed by macro dilution test and the results were recorded visually and spectrophotometrically. The investigation of antibacterial screening data (Table 5) revealed that all the tested compounds showed moderate to good bacterial inhibition. Compound **9** showed good inhibition against *S. pyogens*, *S. aureus* and *E. coli* species at 32 μg/ml where as compound **8** showed good inhibition against *S. aureus* at 32 μg/ml concentrations. Compounds **8** and **9** showed good antibacterial activity nearly equivalent to that of standard drug (Chloramphenicol) against most of the bacterial strains.

The investigation of antifungal screening data revealed that all the tested compounds showed moderate to good fungal inhibition. Compound **8** showed good antifungal activity against all strains of fungi. Compound **9** exhibited antifungal activities nearly equivalent to that of standard drug (Fluconazole) against *C. parapsilosis* at 8 μg/ml, against *C. neoformans* at 16 μg/ml and *C. albicans* at 2 μg/ml.

One of the reasons for activity difference may be based on the several unique characteristics of Gram-negative bacteria such as the structure of the outer membrane. The outer leaflet of the membrane comprises a complex lipopolysaccharide whose lipid portion acts as an endotoxin. This outer membrane protects the bacteria from several antibiotics, dyes and detergents which would normally damage the inner membrane or cell wall (peptidoglycan). The outer membrane provides these bacteria with resistance to lysozyme and penicillin. That is why most of the times Gram-negative bacteria have higher MIC values as compared to Gram-positive bacteria. In case of antifungal activity, *Candida albicans* are generally susceptible for most of the antifungals while non-albicans like *Candida krusei*, *Candida parapsilosis*, *Cryptococcus neoformans* are resistant to most of the antifungal drugs. Furthermore, the compounds having a hydroxyl group in the alkenyl side chain showed greater activity.

Experimental

Chemicals and instruments

Undec-10-enioc (purity 98%) and (9*Z*)-octadec-9-enoic (97%) acids were purchased from Fluka Chemicals (Bucks, Switzerland). (9*Z*, 12*R*)-12-Hydroxyoctadec-9-enoic (ricinoleic, 98%) acid and (9*R*, 12*Z*)-9-hydroxyoctadec-12-enoic (isoricinoleic, 98%) acid were isolated from *Ricinus communis* and *Wrightia tinctoria* seed oils, respectively, following Gunstone's (1954) partition procedure. 7-Hydroxy-coumarin was purchased from S-d fine-chem. (Mumbai, India). Thin layer chromatography was done on glass plates (20 × 5 cm) with a layer of silica gel G (Merck, Mumbai, India, 0.5-mm thickness). Mixture of petroleum ether–ethyl acetate–acetic acid (50:50:1, v/v) were used as developing solvents. Column chromatography was carried out on silica gel (Merck, Mumbai, India, 60–120 mesh). ^{1}H NMR was recorded with Bruker DRX 400 spectrometer at 400 MHz and ^{13}C NMR was recorded at 100 MHz in $CDCl_3$. Chemical shifts (δ) are quoted in ppm. Melting points were taken in open capillary and are uncorrected.

Chemistry: synthesis of fatty acid derivatives of 7-hydroxy-coumarin

A solution of FA (5 mmol), DCC (5.5 mmol) and 7-hydroxy-coumarin (5 mmol) in dichloromethane (50 ml) with catalytic amount of DMAP were stirred mechanically at room temperature until esterification was complete. The *N*,*N*-dicyclohexylurea was filtered off and the filtrate was washed with water (3 × 50 ml), 5% acetic acid (3 × 50 ml) again with water (3 × 50 ml) and then dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to give the esters **6**–**9** (Scheme 1)

which were chromatographed over a column of silica gel using *n*-hexane–ethyl acetate (94:6, v/v) as eluent. All these novel compounds were characterized from their spectral data. ^{1}H, ^{13}C NMR and COSY spectra of synthesized compounds shown in Tables 1, 2, 3, 4.

*7-O-Coumarinyl undec-10-enoate (**6**)*

White powder; Yield: 91%; mp: 168°C; Rf: 0.59; IR (KBr): 3080 (C=C aromatic ring), 2921 (C–H asymm.), 2849 (C–H symm.), 1729 (C=O ester), 1624 (C=O coumarin

Table 1 ^{1}H-NMR, ^{13}C-NMR and COSY data of (**6**) in $CDCl_3$

H number	δ (ppm)	Integration	Multiplicity	J (Hz)	COSY	C number	δ (ppm)
4	7.69	1H	d	9.6	H-3	4	142.96
5	7.49	1H	d	8.4	H-6	5	118.50[a]
8	7.10	1H	s			8	110.46
6	7.04	1H	d	8.4	H-5	6	116.61[a]
3	6.39	1H	d	9.2	H-4	3	116.03[a]
10′	5.81	2H	tdd	$J_{10'-9'} = 6.8, J_{10'-H_Z} = 16.8, J_{10'-H_E} = 10.4$	H-11′	10′	139.18
11′(H_Z)	4.99	1H	dd	$J_{H_Z-10'} = 16.8, J_{H_Z-H_E} = 3.2$	H-10′	11′	114.24
11′(H_E)	4.93	1H	dd	$J_{H_E-10'} = 10.4, J_{H_E-H_Z} = 3.2$	H-10′		
2′	2.59	2H	t	7.6	H-3′	2′	33.02[a]
9′	2.03	2H	qd	7.2	H-10′	9′	34.35[a]
3′	1.75	2H	q	12.4	H-2′	3′–8′	29.30–24.79
4′–8′	1.45–1.32	5 × 2H	br. s				
						10	128.58
						9	153.31[a]
						7	154.70[a]
						2	160.44
						1′	171.68

[a] Assignments may be reversed

Table 2 ^{1}H-NMR, ^{13}C-NMR and COSY data of (**7**) in $CDCl_3$

H number	δ (ppm)	Integration	Multiplicity	J (Hz)	COSY	C number	δ (ppm)
4	7.70	1H	d	9.6	H-3	4	142.91
5	7.49	1H	d	8.4	H-6	5	127.76[a]
8	7.09	1H	s			8	115.76
6	7.03	1H	d	8.4	H-5	6	118.34[a]
3	6.37	1H	d	9.6	H-4	3	116.44[a]
9′–10′	5.35	2H	m			10′	130.07[a]
						9′	129.84[a]
2′	2.59	2H	t	7.6	H-3′	2′	34.17[a]
8′, 11′	2.03	4H	m		H-9′-10′	9′	31.79[a]
						11′	31.40[a]
3′	1.75	2H	q	11.6	H-2′	3′–7′, 12′–17′	29.64–22.57
4′–7′, 12′–17′	1.41–1.26	10 × 2H	br. s				
18′	0.87	3H	dist. t			18′	14.03
						10	127.75[a]
						9	153.15[a]
						7	154.48[a]
						2	160.31
						1′	171.47

[a] Assignments may be reversed

Table 3 ^{1}H-NMR, ^{13}C-NMR and COSY data of (**8**) in $CDCl_3$

H number	δ (ppm)	Integration	Multiplicity	J (Hz)	COSY	C number	δ (ppm)
4	7.61	1H	d	9.6	H-3	4	142.97
5	7.40	1H	d	8.4	H-6	5	125.18[a]
8	7.03	1H	s			8	115.99[a]
6	6.97	1H	d	8.4	H-5	6	118.49[a]
3	6.31	1H	d	$J = 9.6$	H-4	3	116.60[a]
9′	5.33	1H	m		H-10′, H-8′	9′	128.57[a]
10′	5.48	1H	m		H-11′, H-9′	10′	133.31[a]
12′	3.55	1H	q	8.4	H-11′	12′	71.57
2′	2.51	2H	t	7.6	H-3′	2′	35.32[a]
11′	2.14	2H	t	7.2	H-12′, H-10′	11′	36.81[a]
8′	1.97	2H	qd	7.6	H-9′	8′	34.31[a]
3′	1.68	2H	q	11.2	H-2′	3′–7′, 13′–17′	31.84–24.69
OH	1.55	1H	br. m				
4′–7′, 13′–17′	1.43–1.21	9 × 2H	br. s				
18′	0.80	3H	dist. t			18′	14.11
						10	125.28[a]
						9	153.29[a]
						7	154.66[a]
						2	160.50
						1′	171.65

[a] Assignments may be reversed

Table 4 ^{1}H-NMR, ^{13}C-NMR and COSY data of (**9**) in $CDCl_3$

H number	δ (ppm)	Integration	Multiplicity	J (Hz)	COSY	C number	δ (ppm)
4	7.73	1H	d	9.6	H-3	4	143.37
5	7.55	1H	d	8.8	H-6	5	128.90[a]
8	7.02	1H	s			8	110.19[a]
6	6.98	1H	d	8.4	H-5	6	116.61[a]
3	6.30	1H	d	9.6	H-4	3	115.75[a]
12′–13′	5.27	1H	m		H-11′, H-14′	12′	129.99[a]
						13′	129.61[a]
9′	3.44	1H	q	8.4		9′	70.53
2′	2.52	2H	t	7.6	H-3′	2′	33.88[a]
11′, 14′	2.02	2 × 2H	m		H-12′–13′	14′	34.18[a]
3′	1.67	2H	q	12.0	H-2	3′–7′, 11′, 15′–17′	30.95–22.50
OH	1.55	1H	br. m			11′	22.50
4′–8′, 10′, 15′–17′	1.40–1.02	9 × 2H	br. s			10′	37.39[a]
18′	0.80	3H	dist. t			18′	14.11
						8′	39.83[a]
						9	153.23[a]
						7	154.51[a]
						2	160.24
						1′	171.52

[a] Assignments may be reversed

carbonyl), 1400 (C–O), 1269 (C=C), 1122 (C–H aromatic ring) cm^{-1}. ESI–MS found $[M + Na]^+$ 351.2; $C_{20}H_{24}O_4$ $[M + Na]^+$ requires 351.17.

*7-O-Coumarinyl (9Z)-octadec-9-enoate (**7**)*

Viscous solid; Yield: 89%; Rf: 0.57; IR (KBr): 3120 (C=C aromatic ring), 2921 (C–H asymm.), 2849 (C–H symm.), 1728 (C=O ester), 1651 (C=O coumarin carbonyl), 1405 (C–O), 1270 (C=C), 1122 (C–H aromatic ring) cm^{-1}. ESI–MS found $[M + Na]^+$ 449.3; $C_{27}H_{38}O_4$ $[M + Na]^+$ requires 449.28.

*7-O-Coumarinyl (9Z, 12R)-12-hydroxyoctadec-9-enoate (**8**)*

Viscous solid; Yield: 85%; Rf: 0.52; IR (KBr): 3384 (O–H), 3080 (C=C aromatic ring), 2920 (C–H asymm.), 2858 (C–H symm.), 1732 (C=O ester), 1618 (C=O coumarin carbonyl), 1401 (C–O), 1267 (C=C), 1122 (C–H aromatic ring) cm^{-1}. ESI–MS found $[M + Na]^+$ 465.3; $C_{27}H_{38}O_5$ $[M + Na]^+$ requires 465.27.

*7-O-Coumarinyl (12Z,9R)-9-hydroxyoctadec-12-enoate (**9**)*

Viscous solid; Yield: 87%; Rf: 0.53; IR (KBr): 3421 (O–H), 3002 (C=C aromatic ring), 2920 (C–H asymm.), 2852 (C–H symm.), 1736 (C=O ester), 1639 (C=O coumarin carbonyl), 1396 (C–O), 1270 (C=C), 1122 (C–H aromatic ring) cm^{-1}. ESI–MS found $[M + Na]^+$ 465.3; $C_{27}H_{38}O_5$ $[M + Na]^+$ requires 465.27.

Pharmacology

Antibacterial studies

The minimum inhibitory concentration (MIC) was assessed by the macro dilution test using standard inoculums of 5×10^5 c.f.u./ml. Initially, the compounds were dissolved in DMSO after that serial dilution of the test compounds were set to final concentrations of 512, 256, 128, 64, 32, 16, 8, 4, 2 and 1 μg/ml. To each tube was added 100 μl of 24-h old inoculums. The growth was monitored visually and spectrophotometrically. The lowest concentration (highest dilution) required to arrest the growth of bacteria was regarded as minimum inhibitory concentration (MIC). The minimum inhibitory concentrations are given in Table 5.

Antifungal studies

The minimum inhibitory concentration (MIC) was assessed by the macro dilution test using standard inoculums of 1.6×10^4-6×10^4 c.f.u./ml. Initially, the compounds were dissolved in DMSO after that serial dilution of the test compounds were set to final concentrations of 512, 256, 128, 64, 32, 16, 8, 4, 2 and 1 μg/ml. To each tube was added 100 μl of 48–72-h-old inoculums. The growth was monitored visually and spectrophotometrically. The lowest concentration (highest dilution) required to arrest the growth of fungi was regarded as minimum inhibitory concentration (MIC). The minimum inhibitory concentrations are given in Table 5.

Table 5 Minimum inhibition concentration (MIC) fatty acid analogs of 7-hydroxy coumarin

Strains	Compounds						
	6 MIC (μg/ml)	**7**	**8**	**9**	Chloram.	Fluconazol	DMSO
Gram positive							
B. subtilis	64	64	64	64	32	NT	–
S. Pyogenes	64	128	64	32	32	NT	–
S. aureus	128	128	32	32	32	NT	–
Gram negative							
P. aeruginosa	128	128	128	128	64	NT	–
S. typhimurium	64	128	64	64	32	NT	–
E. coli	128	128	64	32	32	NT	–
Fungi							
C. albicans	4	8	4	2	NT	1.0	–
C. krusei	256	512	256	256	NT	64.0	–
C. parapsilosis	32	64	16	16	NT	8.0	–
C. neoformans	16	32	16	8	NT	8.0	–

NT not tested, *Chloram.* chloramphenicol

Conclusion

It is conceivable that these derivatives showing antimicrobial activity can be further modified to exhibit better potency than the standard drugs. Compound **9** showed good antibacterial activity nearly equivalent to that of chloramphenicol. The varied divergence in the antimicrobial activity of these compounds validates the reason of this study. Compounds **8** and **9** showed good antifungal activity against all strains of fungi. The importance of such kind of work lies in the possibility that the new compounds might be more efficient against bacteria for which a thorough study regarding the structure–activity relationship, toxicity and in their biological effects would be helpful in designing more effective antimicrobial agents.

Acknowledgements The authors thank the Chairman, Department of Chemistry, AMU, Aligarh, for providing necessary facilities and SAIF Panjab University, Chandigarh for recording the spectra.

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