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Research Article

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Evaluation of 4-Hydroxy-Coumarin Derivatives as Antimicrobial Agents

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ABSTRACT

Synthesis of a series of 4-hydroxy-6-methyl-3-(substituted methyl)-2H-chromen-2-one (4h-m) was achieved from different secondary amine, Formaldehyde and 4-Hydroxy-6-methyl-2H-chromen-2-one using Con. HCl added refluxed within 8 hrs with good yield. The structures of the products were supported by FTIR, PMR and Mass Spectra data.

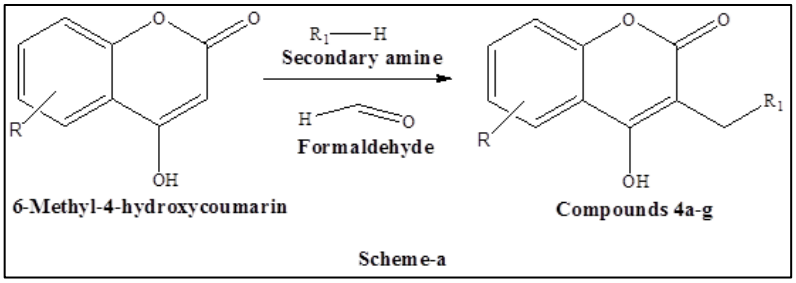
Keywords: 4-hydroxy-6-methyl-3-(substituted-methyl)-2H-chromen-2-one, Secondary amine, Formaldehyde, 4-Hydroxy-6-methyl-2H-chromen-2-one.

INTRODUCTION

Coumarin is a freedom gallows among Hetero-cycles and is known to possess a wide range of biological activities including antibiotic, anti-malarial, antifungal, anti-viral, and cytotoxic [1-8]. In finicky, the 4-Hydroxy-coumarins and its derivatives (3-alkylated) have stir up a great deal of interest due to their utility as 'anticoagulant rodenticides as well as antithrombotic agents' such as brodifacoum, difethialone, bromadiolone, coumatetralone, and flocoumafen [9] and also as non-peptide human immunodeficiency virus (*HIV*) protease inhibitors [10]. The C3 or O-alkylation of 4-Hydroxycoumarin is undoubtedly one of the most important and challenging reactions in synthetic chemistry due to its pharmaceutical utility as mentioned above and also can be diversified to synthesize 3,4-substituted compounds [11-14]. In continuation of our interest in developing novel synthetic methodologies, particularly carbon-carbon, carbon-heteroatom bond formations to synthesize pharmaceutically relevant heterocycles [15], we have very recently reported SnO_2-catalyzed C3-alkylation of 4-Hydroxycoumarin with secondary benzyl alcohols and O-alkylation with O-acetyl compounds [16].
To avoid these problems, we have developed a new etiquette for the synthesis of novel 4-hydroxy-6-methyl-3-(substituted methyl)-2H-chromen-1 (4a-g) with the benefit of superior yield and environmentally friendliness (as Scheme-a).

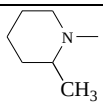
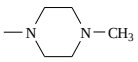
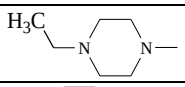
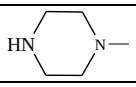
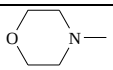
EXPERIMENTAL SECTION

In a 50 ml single neck round bottom flask 15 ml IPA was charged and then, to this 5,8-Dimethyl-4-hydroxycoumarin (0.0026 mol), secondary amine (0.0026 mol) and 40% aq. solution of formaldehyde (0.00312 mol) were added. Add 1 ml conc. HCl to the reaction mass and refluxed for 8-10 hrs. Reaction mass wash, cooled to room temperature, poured on to crushed ice and neutralized with aq.$NaHCO_3$ solution. Obtained solid was filtered and wash with Methanol, it give pure product as 4-hydroxy-6-methyl-3-(substituted methyl)-2H-chromen-2-one.



Scheme-a

Table 1: synthesized compounds

Code	R_1	Molecular Formula	M.W.	Code	R_1	Molecular Formula	M.W.
4a		$C_{17}H_{21}NO_3$	287	4e		$C_{18}H_{23}NO_3$	301
4b		$C_{17}H_{22}N_2O_3$	302	4f		$C_{16}H_{15}NO_3$	269
4c		$C_{18}H_{24}N_2O_3$	316	4g		$C_{16}H_{20}N_2O_3$	288
4d		$C_{16}H_{19}NO_4$	289	R= 5,8-Dimethyl			

4-Hydroxy-5,8-dimethyl-3-((piperidin-1-yl)methyl)-2H-chromen-2-one

Yield: 62%; mp 218-222 ºC; IR (cm^{-1}): 3461 and 3360 (-O-H stretching of hydroxyl group), 3060 (-C-H stretching of aromatic ring), 2970 (-C-H asymmetrical stretching of $-CH_3$ group), 2831 (-C-H symmetrical stretching of $-CH_3$ group), 1689 (-C=O stretching of coumarin), 1523, 1500 and 1422 (-C=C stretching of aromatic ring), 1387 (-C-H asymmetrical deformation of $-CH_3$ group), 1320 (-C-H symmetrical deformation of $-CH_3$ group), 1050 (-C-O-C stretching); MS: *m/z* 287; Anal. Calcd. for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87; O, 16.70; Found: C, 71.01; H, 7.27; N, 4.67; O, 16.60%.

4-Hydroxy-5,8-dimethyl-3-((4-methyl-piperazin-1-yl)methyl)2H-chromen-2-one

Yield: 67%; mp 210-215 ºC; IR (cm^{-1}): 3423 and 3357 (-O-H stretching of hydroxyl group), 3054 (-C-H stretching of aromatic ring), 2965 (-C-H asymmetrical stretching of $-CH_3$ group), 2807 (-C-H symmetrical stretching of $-CH_3$ group), 1700 (>C=O stretching of coumarin), 1552, 1500 and 1432 (-C=C stretching of aromatic ring), 1388 (-C-H asymmetrical deformation of $-CH_3$ group), 1337 (-C-H symmetrical deformation of $-CH_3$ group), 1050 (-C-O-C stretching); MS: *m/z* 302; Anal. Calcd. for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26; O, 15.87; Found: C, 67.03; H, 7.03; N, 9.06; O, 15.27%.

3-((4-Ethyl-piperazin-1-yl)methyl)-4-hydroxy-5,8-dimethyl-2H-chromen-2-one

Yield: 67%; mp 240-242 ºC; IR (cm^{-1}): 3473 and 3377 (-O-H stretching of hydroxyl group), 3064 (-C-H stretching of aromatic ring), 2985 (-C-H asymmetrical stretching of $-CH_3$ group), 2837 (-C-H symmetrical stretching of $-CH_3$ group), 1701 (>C=O stretching of coumarin), 1554, 1502 and 1442 (-C=C stretching of aromatic ring), 1398 (-C-H asymmetrical deformation of $-CH_3$ group), 1317 (-C-H symmetrical deformation of $-CH_3$ group),1050 (-C-O-C stretching); ^{1}HNMR (DMSO-d_6) δ ppm: 0.96 (t, 3H), 1.97 (s, 3H), 2.14 (s, 3H), 2.36 (m, 4H), 2.43 (t, 2H), 3.02 (t, 2H), 3.22 (t, 2H), 4.06 (s, 2H), 6.75(d, 1H) and 7.08 (d, 1H), 10.20 (s, 1H) MS: *m/z* 316; Anal. Calcd. For $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85; O, 15.17; Found: C, 68.13; H, 7.55; N, 8.80; O, 15.10%.

4-Hydroxy-5,8-dimethyl-3-(morpholino-methyl)-2H-chromen-2-one

Yield: 72%; mp 231-235 ºC; IR (cm^{-1}): 3473 and 3377 (-O-H stretching of hydroxyl group), 3064 (-C-H stretching of aromatic ring), 2985 (-C-H asymmetrical stretching of $-CH_3$ group), 2837 (-C-H symmetrical stretching of $-CH_3$ group), 1701 (>C=O stretching of coumarin), 1554, 1502 and 1442 (-C=C stretching of aromatic ring), 1398 (-C-H asymmetrical deformation of $-CH_3$ group), 1317 (-C-H symmetrical deformation of $-CH_3$ group), 1050 (-C-O-C

stretching); ^{1}HNMR (DMSO-d_6) δ ppm: 1.97 (s, 3H), 2.11 (s, 3H), 2.21 (t, 2H), 2.88 (t, 2H), 3.79 (t, 4H), 4.02 (s, 2H), 6.80(d, 1H)and 7.11 (d, 1H), 10.00 (s, 1H) MS: *m/z* 289; Anal. Calcd. $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84; O, 22.12; Found: C, 66.32; H, 6.12; N, 4.24; O, 22.00%.

4-Hydroxy-5,8-dimethyl-3-((2-methyl-piperidin-1-yl)methyl)-2H-chromen-2-one

Yield: 70%; mp 230-235 ºC; IR (cm^{-1}): 3464 and 3368 (-O-H stretching of hydroxyl group), 3055 (-C-H stretching of aromatic ring), 2972 (-C-H asymmetrical stretching of -CH_3 group), 2822 (-C-H symmetrical stretching of -CH_3 group), 1700 (>C=O stretching of coumarin), 1527, 1500 and 1433 (-C=C stretching of aromatic ring), 1377 (-C-H asymmetrical deformation of -CH_3 group), 1307 (-C-H symmetrical deformation of -CH_3 group), 1050 (-C-O-C stretching); MS: *m/z* 301; Anal. Calcd. $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65; O, 15.93; Found: C, 71.71; H, 7.61; N, 4.62; O, 15.90%.

3-((1H-pyrrol-1-yl)methyl)-4-hydroxy-5,8-dimethyl-2H-chromen-2-one

Yield: 64%; mp 232-235 ºC; IR (cm^{-1}): 3462 and 3328 (-O-H stretching of hydroxyl group), 3042 (-C-H stretching of aromatic ring), 2962 (-C-H asymmetrical stretching of -CH_3 group), 2835 (-C-H symmetrical stretching of -CH_3 group), 1682 (>C=O stretching of coumarin), 1522, 1500 and 1430 (-C=C stretching of aromatic ring), 1373 (-C-H asymmetrical deformation of -CH_3 group), 1317 (-C-H symmetrical deformation of -CH_3 group), 1050 (-C-O-C stretching); MS: *m/z* 269; Anal. Calcd. $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20; O, 17.82; Found: C, 71.26; H, 5.51; N, 5.10; O, 17.72%.

4-Hydroxy-5,8-dimethyl-3-((piperazin-1-yl)methyl)-2H-chromen-2-one

Yield:55%; mp 250-255 ºC; IR (cm^{-1}): 3454 and 3358 (-O-H stretching of hydroxyl group), 3065 (-C-H stretching of aromatic ring), 2952 (-C-H asymmetrical stretching of -CH_3 group), 2852 (-C-H symmetrical stretching of -CH_3 group), 1705 (>C=O stretching of coumarin), 1525, 1505 and 1435 (-C=C stretching of aromatic ring), 1375 (-C-H asymmetrical deformation of -CH_3 group), 1305 (-C-H symmetrical deformation of -CH_3 group), 1050 (-C-O-C stretching); MS: *m/z* 288; Anal. Calcd. $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72; O, 16.65; Found: C, 66.55; H, 6.89; N, 9.62; O, 16.55%.

RESULT AND DISCUSSION

Melting points were measured in open capillaries and are uncorrected. 1HNMR spectra were recorded on BRUKUR spectrophotometer (400MHz). Chemical shifts are expressed in units relative to TMS signal as internal reference. IR spectra were recorded on FT-IR SHIMADZU -FT-IR 8400 spectrophotometer on KBr pallets. Mass spectra were recorded on GCMS QP2010 Gas Chromatograph SHIMADZU. Thin Layer Chromatography (TLC) was performed on silica gel-G using hexane: ethyl-acetate solvent system.

Table 2: Antimicrobial Screening Activity for Compounds 4a-g

Compound	Minimal inhibition concentration (µg mL^{-1})					
	Gram-positive		Gram-negative		Fungal species	
	Staphylococcus aureus	*Streptococcus pyogenes*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Candida albicans*	*Aspergillus clavatus*
4a	500	500	500	500	250	500
4b	500	1000	1000	1000	>1000	>1000
4c	100	100	250	200	1000	500
4d	1000	500	1000	1000	1000	1000
4e	200	100	100	200	250	1000
4f	1000	1000	500	500	250	1000
4g	500	500	250	250	250	1000
Gentamycin	0.25	0.5	0.05	1	-	-
Ampicillin	250	100	100	100	-	-
Chloramphenicol	50	50	50	50	-	-
Ciprofloxacin	50	50	25	25	-	-
Norfloxacin	10	10	10	10	-	-
Nystatin	-	-	-	-	100	100
Gresiofulvin	-	-	-	-	500	100

All of the synthesized substances were tested for their antibacterial and antifungal activity in vitro by broth dilution method with two gram positive bacteria Staphylo-coccusaureus & Streptococcus pyogenes, two gram negative bacteria Escheric-hia coli & Pseudomon-as aeruginosa, and two fungal species Candida albicans & Aspergil-lusclavatus. Gentamycin, Ampicillin, Chloramphenicol, Ciprofloxacin, Norfloxacin, Nystatin, and Gresiofulvin are used as standard drugs for this antimicrobial screening.
All the compounds possess better antifungal activity than antibacterial, so that most of the compounds are more toxic against fungi. Compound-4e has good activity against bacteria as well as fungi. Compound 4a, 4e, 4f, and 4g have given some good result against fungi.

CONCLUSION

Various 3-Substituted 4-Hydroxy-coumarin derivatives were prepared by reaction of different secondary amine, Formaldehyde and. The compounds prepared in this paper possess Chromen nucleus and has substitution at C3 position. And these compounds have good yields with biological activity.

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