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RESEARCH ARTICLE

Synthetic Advances and Biological Activities of 4-Hydroxy Coumarin Derivatives

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ABSTRACT

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

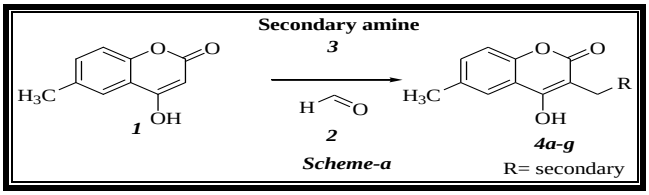
KEYWORDS

4-hydroxy-6-methyl-3-(substituted methyl)-2H-chromen-2-one; secondary amine, 2-Aformaldehyde, only refluxed

INTRODUCTION

Coumarin is a freedom gallows among heterocycles 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-hydroxycoumarins 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 warfarin, brodifacoum, difethialone, bromadiolone, coumatetralone, and flocoumafen[9] and also as nonpeptide 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-substitued compounds[11,12,13,14]. 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 SO42-/SnO2-catalyzed C3-alkylation of 4-hydroxycoumarin with secondary benzyl alcohols and O-alkylation with O-acetyl compounds[16].

To evade these problems, we have developed a new etiquette for the synthesis of novel 4-hydroxy-6-methyl-3-(substituted methyl)-2H-chromen-2-one (4a-g) with the advantage of good yield and environmentally friendliness (Scheme-a).



Scheme-a

Experimental

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Typical Experimental Procedure for the Synthesis of 4-Hydroxy Coumarins

In a 50 ml singal neck round bottom flask 15 ml Isopropyl alcohol was added and then, to this 6-methyl 4-hydroxy coumarin (0.0026 mole), secondary amine (0.0026 mole) and aq. Solution of formaldehyde (0.00312 mole) were added. To this solution 1 ml con HCl was added and then reaction mass refluxed for 8-10 hours. Reaction mass was cooled to room temperature, poured on to crushed ice and neutralized with aq.NaHCO3 solution. Obtained solid was filtered and was with methanol to give pure product.to crushed ice and neutralized with aq.NaHCO3 solution. Obtained solid was filtered and was with methanol to give pure product. 4-hydroxy-6-dimethyl-3-((subtituted)methyl)-2H-chromen-2-one.

4-hydroxy-6-methyl-3-((piperidin-1-yl)methyl)-2H-chromen-2-one. Yield: 57%; mp 210-220 ºC; IR (cm^{-1}): 3460 and 3355 (O-H stretching of hydroxyl group), 3050 (C-H stretching of aromatic ring), 2961 (C-H asymmetrical stretching of CH_3 group), 2861(C-H symmetrical stretching of CH_3 group), 1710 (C=O stretching of coumarin), 1527, 1499 and 1444 (C=C stretching of aromatic ring), 1367 (C-H asymmetrical deformation of CH_3 group), 1387 (C-H symmetrical deformation of CH_3 group), 823 (C-O-C stretching); 1H NMR (DMSO-d6) δ ppm: 1.57 (m, 6H), 2.14 (s, 3H), 2.36 (m, 4H), 4.06 (s, 2H), 6.75 and 7.08 (two d, 3H); MS: m/z 273; Anal. Calcd. $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12; O, 17.56; Found: C, 70.24; H, 7.00; N, 5.10; O, 17.52%.

4-hydroxy-6-methyl-3-((4-methylpiperazin-1-yl)methyl)-2H-chromen-2-one. Yield: 59%; mp 215-225 ºC; IR (cm^{-1}): 3456 and 3367 (O-H stretching of hydroxyl group), 3056 (C-H stretching of aromatic ring), 2953 (C-H asymmetrical stretching of CH_3 group), 2872 (C-H symmetrical stretching of CH_3 group), 1709 (C=O stretching of coumarin), 1527, 1499 and 1437 (C=C stretching of aromatic ring), 1359 (C-H asymmetrical deformation of CH_3 group), 1376 (C-H symmetrical deformation of CH_3 group), 835 (C-O-C stretching); 1H NMR (DMSO-d6) δ ppm: 1.57 (m, 6H), 2.14 (s, 3H), 2.36 (m, 4H), 4.06 (s, 2H), 6.75 and 7.08 (two d, 3H); 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, 66.60; H, 6.89; N, 9.66; O, 16.64%.

4-hydroxy-6-methyl-3-((4-phenylpiperazin-1-yl)methyl)-2H-chromen-2-one. Yield: 51%; mp 203-207 ºC; IR (cm-1): 3451 and 3379 (O-H stretching of hydroxyl group), 3076 (C-H stretching of aromatic ring), 2973 (C-H asymmetrical stretching of CH_3 group), 2877 (C-H symmetrical stretching of CH_3 group), 1714 (C=O stretching of coumarin), 1537, 1497 and 1439 (C=C stretching of aromatic ring), 1351 (C-H asymmetrical deformation of CH_3 group), 1367 (C-H symmetrical deformation of CH_3 group), 831 (C-O-C stretching); MS: m/z 350; Anal. Calcd. $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99; O, 13.70; Found: C, 71.68; H, 6.14; N, 7.79; O, 13.61%.

3-((4-benzylpiperazin-1-yl)methyl)-4-hydroxy-6-methyl-2H-chromen-2-one. Yield: 54%; mp 203-207 ºC; IR (cm^{-1}): 3451 and 3379 (O-H stretching of hydroxyl group), 3076 (C-H stretching of aromatic ring), 2973 (C-H asymmetrical stretching of CH_3 group), 2877 (C-H symmetrical stretching of CH_3 group), 1714 (C=O stretching of coumarin), 1537, 1497 and 1439 (C=C stretching of aromatic ring), 1351 (C-H asymmetrical deformation of CH_3 group), 1367 (C-H symmetrical deformation of CH_3 group), 831 (C-O-C stretching); MS: m/z 350; Anal. Calcd. $C_{22}H_{24}N_2O_3$: C, 71.98; H, 6.33; N, 7.99; O, 13.70; Found: C, 71.68; H, 6.14; N, 7.79; O, 13.61%.

3-((4-ethylpiperazin-1-yl)methyl)-4-hydroxy-6-methyl-2H-chromen-2-one. Yield: 50%; mp 220-223 ºC; IR (cm-1): 3433 and 3359 (O-H stretching of hydroxyl group), 3071 (C-H stretching of aromatic ring), 2969 (C-H asymmetrical stretching of CH_3 group), 2867 (C-H symmetrical stretching of CH_3 group), 1706 (C=O stretching of coumarin), 1523, 1487 and 1421 (C=C stretching of aromatic ring), 1345 (C-H asymmetrical deformation of CH_3 group), 1352 (C-H symmetrical deformation of CH_3 group), 827 (C-O-C stretching); MS: m/z

302; Anal. Calcd. $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26; O, 15.87; Found: C, 67.43; H, 7.13; N, 9.16; O, 15.67%.

4-hydroxy-6-methyl-3-(morpholinomethyl)-2H-chromen-2-one. Yield: 52%; mp 200-205 ºC; IR (cm^{-1}): 3433 and 3345 (O-H stretching of hydroxyl group), 3065 (C-H stretching of aromatic ring), 2962 (C-H asymmetrical stretching of CH3 group), 2860 (C-H symmetrical stretching of CH_3 group), 1702 (C=O stretching of coumarin), 1543, 1484 and 1441 (C=C stretching of aromatic ring), 1344 (C-H asymmetrical deformation of CH_3 group), 1354 (C-H symmetrical deformation of CH_3 group), 824 (C-O-C stretching); MS: m/z 275; Anal. Calcd. $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09; O, 23.25; Found: C, 65.34; H, 6.20; N, 5.07; O, 23.05%.

4-hydroxy-6-methyl-3-((piperazin-1-yl)methyl)-2H-chromen-2-one. Yield: 70%; mp 224-230 ºC; IR (cm-1): 3398 and 3295 (O-H stretching of hydroxyl group), 3102 (C-H stretching of aromatic ring), 2945 (C-H asymmetrical stretching of CH_3 group), 2847 (C-H symmetrical stretching of CH_3 group), 1654 (C=O stretching of coumarin), 1584, 1512 and 1432 (C=C stretching of aromatic ring), 1378 (C-H asymmetrical deformation of CH_3 group), 1307 (C-H symmetrical deformation of CH_3 group), 837 (C-O-C stretching); MS: m/z 301; Anal. Calcd. $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21; O, 17.50; Found: C, 65.38; H, 6.41; N, 10.01; O, 17.40%.

Table 1: Antimicrobial activity of compounds 3a-g

Compound	Antibacterial activity				Antifungal activity	
	Gram +ve		Gram -ve			
	S. aureus	S. pyrogenes	E. Cali	P. aeruginosa	C. albicans	A. clavatus
3a	100	100	200	250	1000	500
3b	62.5	1000	200	1000	500	>1000
3c	150	250	100	150	500	500
3d	1000	500	62.5	62.5	>1000	>1000
3e	200	200	100	100	>1000	1000
3ef	500	1000	500	500	500	>1000
3g	150	250	100	150	500	500
Gentamycin	0.25	0.5	0.05	1	-	-
Ampicillin	250	100	100	100	-	-
Chloramphenicol	50	50	50	50	-	-
Iprofloxacin	50	50	25	25	-	-
Norfloxacin	10	10	10	10	-	-
Nystatin	-	-	-	-	100	100
Greseofulvin	-	-	-	-	500	100

CONCLUSION

Various 3 substituted 4 Hydroxy Coumarin derivatives were prepared by reaction of different secondary Amines with the formaldehyde. The compounds prepared in this article possess Chromene nucleus and has substitution at C3 position. And this compound is good yield with biological activity.

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