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 floucmufen [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 pharmacologically relevant heterocycles [15], we have very recently reported SnO2-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.NaHCO3 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.
4-Hydroxy-5,8-dimethyl-3-((piperidin-1-yl)methyl)-2H-chromen-2-one
Yield: 62%; mp 218-222 °C; 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 -CH₃ group), 2831 (C-H symmetrical stretching of -CH₃ group), 1689 (C=O stretching of coumarin), 1523, 1500 and 1422 (C=C stretching of aromatic ring), 1387 (C-H asymmetrical deformation of -CH₃ group), 1320 (C-H symmetrical deformation of -CH₃ group), 1050 (C-O-C stretching); MS: m/z 287; Anal. Calcd. for C₁₇H₁₈NO₅: 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 °C; 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 -CH₃ group), 2807 (C-H symmetrical stretching of -CH₃ group), 1700 (C=O stretching of coumarin), 1552, 1500 and 1432 (C=C stretching of aromatic ring), 1388 (C-H asymmetrical deformation of -CH₃ group), 1337 (C-H symmetrical deformation of -CH₃ group), 1050 (C-O-C stretching); MS: m/z 302; Anal. Calcd. for C₁₇H₂₁NO₅: 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 °C; 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 -CH₃ group), 2837 (C-H symmetrical stretching of -CH₃ group), 1701 (C=O stretching of coumarin), 1554, 1502 and 1442 (C=C stretching of aromatic ring), 1398 (C-H asymmetrical deformation of -CH₃ group), 1317 (C-H symmetrical deformation of -CH₃ group), 1050 (C-O-C stretching); ¹H NMR (DMSO-d₆) 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 C₁₉H₂₄N₅O₂: 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 °C; 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 -CH₃ group), 2837 (C-H symmetrical stretching of -CH₃ group), 1701 (C=O stretching of coumarin), 1554, 1502 and 1442 (C=C stretching of aromatic ring), 1398 (C-H asymmetrical deformation of -CH₃ group), 1317 (C-H symmetrical deformation of -CH₃ group), 1050 (C-O-C stretching).
4-Hydroxy-5,8-dimethyl-3-(2-methyl-piperidin-1-yl)methyl)-2H-chromen-2-one

Yield: 70%; mp 230-235 °C; 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 -CH₃ group), 2822 (-C-H symmetrical stretching of -CH₃ group), 1700 (>C=O stretching of coumarin), 1527, 1500 and 1433 (-C=C stretching of aromatic ring), 1377 (-C-H asymmetrical deformation of -CH₃ group), 1307 (-C-H symmetrical deformation of -CH₃ group), 1050 (-C-O-C stretching); MS: m/z 289; Anal. Calcd. C₁₆H₁₉NO₄; 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%.

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

Yield: 64%; mp 232-235 °C; 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 -CH₃ group), 2835 (-C-H symmetrical stretching of -CH₃ group), 1682 (>C=O stretching of coumarin), 1522, 1500 and 1430 (-C=C stretching of aromatic ring), 1373 (-C-H asymmetrical deformation of -CH₃ group), 1317 (-C-H symmetrical deformation of -CH₃ group), 1050 (-C-O-C stretching); MS: m/z 269; Anal. Calcd. C₁₆H₁₉NO₃; C: 71.71; H: 7.61; 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 °C; 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 -CH₃ group), 2852 (-C-H symmetrical stretching of -CH₃ group), 1705 (>C=O stretching of coumarin), 1525, 1505 and 1435 (-C=C stretching of aromatic ring), 1375 (-C-H asymmetrical deformation of -CH₃ group), 1305 (-C-H symmetrical deformation of -CH₃ group), 1050 (-C-O-C stretching); MS: m/z 288; Anal. Calcd. C₁₆H₂₁NO₃; 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. ¹H NMR spectra were recorded on BRUKER 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

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<th>Streptococcus pyogenes</th>
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<th>Pseudomonas aeruginosa</th>
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All of the synthesized substances were tested for their antibacterial and antifungal activity in vitro by broth dilution method with two gram positive bacteria Staphylococcus aureus & Streptococcus pyogenes, two gram negative bacteria Escherichia coli & Pseudomonas aeruginosa, and two fungal species Candida albicans & Aspergillus niger. 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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REFERENCES