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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NEW CONDENSED COUMARIN 4-ACETOHYDRAZIDE

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ABSTRACT

Synthesis of a series of 4-(2-(2-(substitutedbenzylidene)hydrazinyl)-2-oxoethyl)-2-oxo-2H-chromen-7-yl acetate. **(3a-l)** was achieved from different substituted 2-(7-Hydroxy-2-oxo-2H-chromen-4-yl) acetohydrazide, acetic anhydride and using few drops H_2SO_4 added and string with DCM. The structures of the products were supported by FTIR, PMR and mass spectral data.

Key words: 4-(2-(2-(Substitutedbenzylidene)hydrazinyl)-2-oxoethyl)-2-oxo-2H-chromen-7-yl acetate, Different substituted 2-(7-Hydroxy-2-oxo-2H-chromen-4-yl) acetohydrazide, Anhydrous acetic acid, H_2SO_4 only string.

INTRODUCTION

Coumarin and its derivatives from natural products, either semi-synthetic or synthetic, represent one of the most active classes of compounds exhibiting a wide spectrum of biological activity. Additionally, coumarin derivatives are used as additives in food and cosmetic industry. Due to the significance of these compounds, the quest for efficient syntheses of coumarin ring compounds[1] as well as new bioactive derivatives from known coumarins[2] is topic.

There are a number of reports that natural and synthetic coumarin derivatives posse's antimicrobial activity[3-6]. It was found that when one biodynamic heterocyclic system was coupled with another heterocyclic system, enhanced biological activity was produced. Compounds containing azomethine group (-CH=N-) is known as Schiff bases. Day by day Schiff bases are more frequently applied for the betterment of human welfare. The importance of the Schiff base is due its versatile nature. Literature survey shows that many Schiff bases exhibit biological activities such as antifungal, antibacterial, antitumor, anti-inflammatory, and Anticonvulsant[7-11].

To evade these problems, we have developed a new etiquette for the synthesis of novel 4-(2-(2-(substitutedbenzylidene)hydrazinyl)-2-oxoethyl)-2-oxo-2H-chromen-7-yl acetate **(3a-l)** with the benefit of good quality yield and environmentally friendliness (**Scheme 1**).

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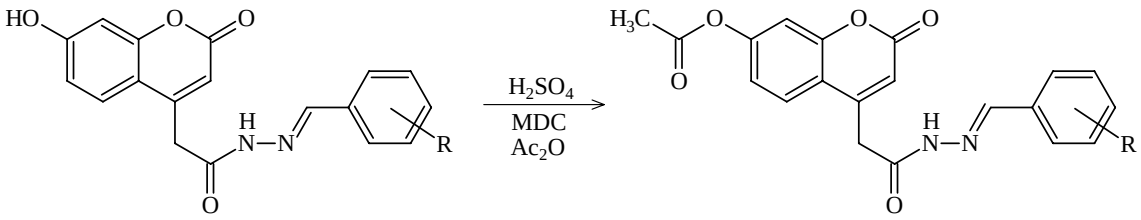

Scheme 1

EXPERIMENTAL

Typical experimental procedure for the synthesis of Coumarin 4-acetohydrazide

In a 50 mL single neck round bottom flask above 0.005 mole hydrazide derivative of coumarine was taken in 20 mL MeOH. To this 0.005 mole of various substituted aldehydes and 2 drops of glacial acetic acid were added, and then the reaction mass was refluxed for two hours. The completion of reaction was monitored by TLC. Reaction mass was cooled to room temperature and obtained solid was filtered and wash with MeOH to give pure product with good yield.

3a. 4-(2-(2-Benzylidenehydrazinyl)-2-oxoethyl)-2-oxo-2H-chromen-7-yl acetate

Yield: 64%; MP 252-254ºC; MS: m/z M+1 365 and M-1 363; IR (cm^{-1}): 3032 (C-H stretching of aromatic ring), 2965 (C-H asymmetrical stretching of alkane group), 1670, 1606 (C=O stretching), 1562 (C=C stretching of aromatic ring), 1394 and 1325 (C-H asymmetrical deformation of CH3 group), 1263 (C-N starching), 1143, 1062, 837 (C-O-C stretching);); ^{1}H NMR: 2.28 (s, 3H), 3.21 (s, 2H), 6.10 (s, 1H), 7.00 (s, 1H), 7.11 (d, 1H), 7.39 (d, 2H), 7.73 (s, 1H), 7.90 (d, 2H) 8.20 (d, 1H), 11.49 (s, 1H (NH)), Anal. Calcd. $C_{20}H_{16}N_2O_5$, C, 65.93; H, 4.43; N, 7.69; Found: C, 65.81; H, 4.29; N, 7.58%.

3b. 4-(2-(2-(2-Bromobenzylidene)hydrazinyl)-2-oxoethyl)-2-oxo-2H-chromen-7-yl acetate

Yield: 56%; MP 240-250ºC; MS: m/z 443; IR (cm^{-1}): 3044 (C-H stretching of aromatic ring), 2965 (C-H asymmetrical stretching of alkane group), 1674, 1602 (C=O stretching), 1542 (C=C stretching of aromatic ring), 1384 and 1305 (C-H asymmetrical deformation of CH3 group), 1260 (C-N starching), 964 (C-Br starching), 1153, 1072, 831(C-O-C stretching)); Anal. Calcd. $C_{20}H_{15}BrN_2O_5$, C, 54.19; H, 3.41; Br, 18.03; N, 6.32; O, 18.05 Found: C, 54.00; H, 3.01; Br, 17.90; N, 6.01; O, 17.75%.

3c. 4-(2-(2-(4-Bromobenzylidene)hydrazinyl)-2-oxoethyl)-2-oxo-2H-chromen-7-yl acetate

Yield: 50%; MP 240-243ºC; MS: m/z 443; IR (cm^{-1}): 3067 (C-H stretching of aromatic ring), 2961 (C-H asymmetrical stretching of alkane group), 1671, 1600 (C=O stretching), 1522 (C=C stretching of aromatic ring), 1354 and 1301 (C-H asymmetrical deformation of CH_3 group), 1220 (C-N starching), 961 (C-Br starching), 1150, 1012, 866 (C-O-C stretching)); Anal. Calcd. $C_{20}H_{15}BrN_2O_5$, C, 54.19; H, 3.41; Br, 18.03; N, 6.32; O, 18.05, Found: C, 53.68; H, 3.11; Br, 17.94; N, 6.10; O, 17.19%.

3d. 4-(2-(2-(2-Chlorobenzylidene)hydrazinyl)-2-oxoethyl)-2-oxo-2H-chromen-7-yl acetate

Yield: 52%; MP 235-240ºC; MS: m/z 398; IR (cm^{-1}): 3060 (C-H stretching of aromatic ring), 2960 (C-H asymmetrical stretching of alkane group), 1671, 1608 (C=O stretching), 1528 (C=C stretching of aromatic ring), 1354 and 1301 (C-H asymmetrical deformation of CH_3 group), 1224 (C-N starching), 868 (C-Cl starching), 1152, 1014, 860 (C-O-C stretching); Anal. Calcd. $C_{20}H_{15}ClN_2O_5$, C, 60.23; H, 3.79; Cl, 8.89; N, 7.02; O, 20.06, Found: C, 60.03; H, 3.61; Cl, 8.54; N, 6.87; O, 19.85%.

3e. 4-(2-(2-(4-Chlorobenzylidene)hydrazinyl)-2-oxoethyl)-2-oxo-2H-chromen-7-yl acetate

Yield: 45%; MP 235-238ºC; MS: m/z 398; IR (cm^{-1}): 3089 (C-H stretching of aromatic ring), 2987 (C-H asymmetrical stretching of alkane group), 1675, 1665 (C=O stretching), 1520 (C=C stretching of aromatic ring), 1376 and 1311 (C-H asymmetrical deformation of CH_3 group), 1234 (C-N starching), 828 (C-Cl starching), 1159, 1014, 843 (C-O-C stretching); Anal. Calcd. $C_{20}H_{15}ClN_2O_5$, C, 60.23; H, 3.79; Cl, 8.89; N, 7.02; O, 20.06, Found: C, 60.00; H, 3.41; Cl, 8.50; N, 6.80; O, 19.56%.

3f. 4-(2-(2-(2-Methylbenzylidene)hydrazinyl)-2-oxoethyl)-2-oxo-2H-chromen-7-yl acetate

Yield: 68%; MP 210-212ºC; MS: m/z M+1 379 and M-1 377; IR (cm^{-1}): 3058 (C-H stretching of aromatic ring), 2970 (C-H asymmetrical stretching of alkane group), 1683, 1648 (C=O stretching), 1467 and 1394 (C-H asymmetrical deformation of CH_3 group), 1267 (C-N starching), 1147, 1026, 857 (C-O-C stretching)); ^1H NMR: 2.027 (s, 3H), 2.241 (s, 3H), 4.215 (s, 2H), 6.238 (s, 1H), 6.785 (m, 2H), 7.256 (t, 2H), 7.602 (m, 3H), 8.017 (s, 1H), 8.198 (s, 1H (NH)), Anal. Calcd. $C_{21}H_{18}N_2O_5$, C, 66.66; H, 4.79; N, 7.40; Found: C, 66.21; H, 4.53; N, 7.18%.

3g. 4-(2-(2-(4-Methylbenzylidene)hydrazinyl)-2-oxoethyl)-2-oxo-2H-chromen-7-yl acetate

Yield: 64%; MP 208-210ºC; MS: m/z M+1 379 and M-1 377; IR (cm^{-1}): 3054 (C-H stretching of aromatic ring), 2974 (C-H asymmetrical stretching of alkane group), 1684, 1644 (C=O stretching), 1464 and 1395 (C-H asymmetrical deformation of CH_3 group), 1267 (C-N starching), 1144, 1024, 854 (C-O-C stretching)); Anal. Calcd. $C_{21}H_{18}N_2O_5$, C, 66.66; H, 4.79; N, 7.40; Found: C, 66.24; H, 4.56; N, 7.14%.

3h. 4-(2-(2-(2,4-Dimethylbenzylidene)hydrazinyl)-2-oxoethyl)-2-oxo-2H-chromen-7-yl acetate

Yield: 62%; MP 200-205ºC; MS: m/z 392; IR (cm^{-1}): 3054 (C-H stretching of aromatic ring), 2978 (C-H asymmetrical stretching of alkane group), 1688, 1647 (C=O stretching), 1464 and 1395 (C-H asymmetrical deformation of CH_3 group), 1260 (C-N starching), 1140, 1024, 850 (C-O-C stretching)); Anal. Calcd. $C_{22}H_{20}N_2O_5$, C, 67.34; H, 5.14; N, 7.14; O, 20.39; Found: C, 67.22; H, 5.12; N, 7.13; O, 20.36%.

3i. 4-(2-(2-(2,3-Dimethylbenzylidene)hydrazinyl)-2-oxoethyl)-2-oxo-2H-chromen-7-yl acetate

Yield: 55%; MP 199-200ºC; MS: m/z 392; IR (cm^{-1}): 3050 (C-H stretching of aromatic ring), 2970 (C-H asymmetrical stretching of alkane group), 1670, 1653 (C=O stretching), 1460 and 1390 (C-H asymmetrical deformation of CH_3 group), 1269 (C-N starching), 1149, 1029, 859 (C-O-C stretching)); Anal. Calcd. $C_{22}H_{20}N_2O_5$, C, 67.34; H, 5.14; N, 7.14; O, 20.39; Found: C, 67.311; H, 5.10; N, 7.13; O, 20.31%.

3j. 4-(2-(2-(2,6-Difluorobenzylidene)hydrazinyl)-2-oxoethyl)-2-oxo-2H-chromen-7-yl acetate

Yield: 51%; MP 232-234ºC; MS: m/z M+1 401 and M-1 399; IR (cm^{-1}): 3042 (C-H stretching of aromatic ring), 2945, 2860 (C-H asymmetrical stretching of alkane group), 1647, 1587 (C=O stretching), 1467 and 1394 (C-H asymmetrical deformation of CH_3 group), 1267 (C-N starching), 1147, 1026, 857 (C-O-C stretching)); Anal. Calcd. $C_{20}H_{14}F_2N_2O_5$, C, 60.00; H, 3.52; F, 9.49; N, 7.00; Found: C, 59.81; H, 3.23; N, 6.67%.

3k. 4-(2-(2-(3-Nitrobenzylidene)hydrazinyl)-2-oxoethyl)-2-oxo-2H-chromen-7-yl acetate

Yield: 64%; MP 200-202ºC; MS: m/z 409; IR (cm^{-1}): 3040 (C-H stretching of aromatic ring), 2956 (C-H asymmetrical stretching of alkane group), 1664, 1629 (C=O stretching), 1544 (N-O stretching of NO_2), 1426 and 1345 (C-H asymmetrical deformation of CH_3 group), 1269 (C-N starching), 1134, 1005, 805 (C-O-C stretching); Anal. Calcd. $C_{20}H_{15}N_3O_7$, C, 58.68; H, 3.69; N, 10.27; O, 27.36; Found: C, 58.45; H, 3.14; N, 10.12; O, 27.11%.

3l. 4-(2-(2-(4-Nitrobenzylidene)hydrazinyl)-2-oxoethyl)-2-oxo-2H-chromen-7-yl acetate

Yield: 54%; MP 205-210ºC; MS: m/z 409; IR (cm^{-1}): 3064 (C-H stretching of aromatic ring), 2957 (C-H asymmetrical stretching of alkane group), 1664, 1629 (C=O stretching), 1548 (N-O stretching of NO_2), 1427 and 1347 (C-H asymmetrical deformation of CH_3 group), 1267 (C-N starching), 1134, 1005, 805 (C-O-C stretching)); Anal. Calcd. $C_{20}H_{15}N_3O_7$, C, 58.68; H, 3.69; N, 10.27; O, 27.36; Found: C, 58.40; H, 3.04; N, 10.02; O, 27.22%.

Table 1: Antimicrobial activity of compounds 3a-l

Compound	Antibacterial activity				Antifungal activity	
	Gram +ve		Gram -ve			
	S. aureus	***S. pyrogenes***	***E. Coli***	***P. aeruginosa***	***C. albicans***	***A. clavatus***
3a	240	450	450	450	250	350
3b	450	350	350	350	550	550
3c	100	100	250	200	350	450
3d	350	450	350	350	350	450
3e	200	100	100	200	250	350
3f	350	90	450	450	250	350
3g	450	450	250	250	250	350
3h	100	100	200	250	350	450
3i	350	350	200	350	450	550
3j	150	250	100	150	450	450
3k	350	450	90	90	550	550
3l	200	200	100	100	550	350
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

We have synthesized a library of acylhydrazones using simple and convenient method. This method produces these products in good yields, with a short reaction time and easy workup. Product is isolated by simple vaccum filteration. The isolated products are very pure and do not need any column purification. This study opens up a new area of cost-effective synthesis of potentially biologically active acylhydrazone compounds.

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