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Synthesis and Characterization of Some Coumarin Derivatives

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Abstract: ***A series of coumarin derivatives were synthesized.The present study reveals the synthesis of coumarin derivative in which 4-hydroxycoumarin was reacted with chloroethylacetate in presence of K_2CO_3 to form an intermediate which was further treated with hydrazine hydrate to form hydrazino derivative of coumarin and finally the intermediate is condensed by substituted isothiocynate derivatives to form final compound, the synthesized compounds were then Characterized by using FT-IR, ^{1}H-NMR and Mass spectrophotometer, All the compounds were screened for their anti-microbial activity. It was found that the derivatives showed moderate activity as compared to standard***

Keywords: Coumarin, anti-microbial activity

1. Introduction

Coumarin is a heterocyclic ring system consisting of a benzene ring fused to a pyran ring. Coumarin constitute the basic backbone of various types of polyphenols and widely found in natural alkaloids, tocopherols, flavonoids, and anthocyanins (Qiao Ren *et.al.,* 2011). It is known that certain natural and synthetic chromene derivatives possess important biological activities such as antimicrobial (Chetan BS *et.al.,* 2012), antioxidant (Milan M *et.al.,* 201), antifungal (Suresh T *et.al.,* 2010), anti-inflammatory (Nitin K *et.al.,* 2012) activity. Since varying substituent's is a common method for drug design in medicinal chemistry and a useful medical value of substituted isothiocynate derivatives, we aimed to synthesize coumarin derivatives and to investigate their biological activities.

2. Material and Method

All raw materials used in the synthesis have been obtained from M/S Fluka AG (Bachs, Switzerland) and M/S Sigma-Aldrich chemicals and Co. Inc. (Milwoukee, WI,USA). Melting points were recorded on a Thermonik Melting point Apparatus (Campbell Electronics, Mumbai, India) and are uncorrected. IR spectra were recorded on a IR-Affinity, Shimadzu using DRS system. ^{1}H-NMR spectra have been recorded on a JEOL AL-400 FT-NMR spectrometer (400 MHz, JEOL Ltd., Tokyo, Japan), using TMS as internal standard in solvent DMSO. Mass data have been recorded on Agilent GC-MS Elemental analysis has been carried out on a C, H, and N Elemental Analyzer (Thermo-Finnigan Flash EA 1112, Italy) GC-MS is carried on GC7890 MS 200 of Agilent

3. Experimental 3.1 Synthesis of ethyl [(2-oxo-2H-chromen-4-yl)oxy]acetate

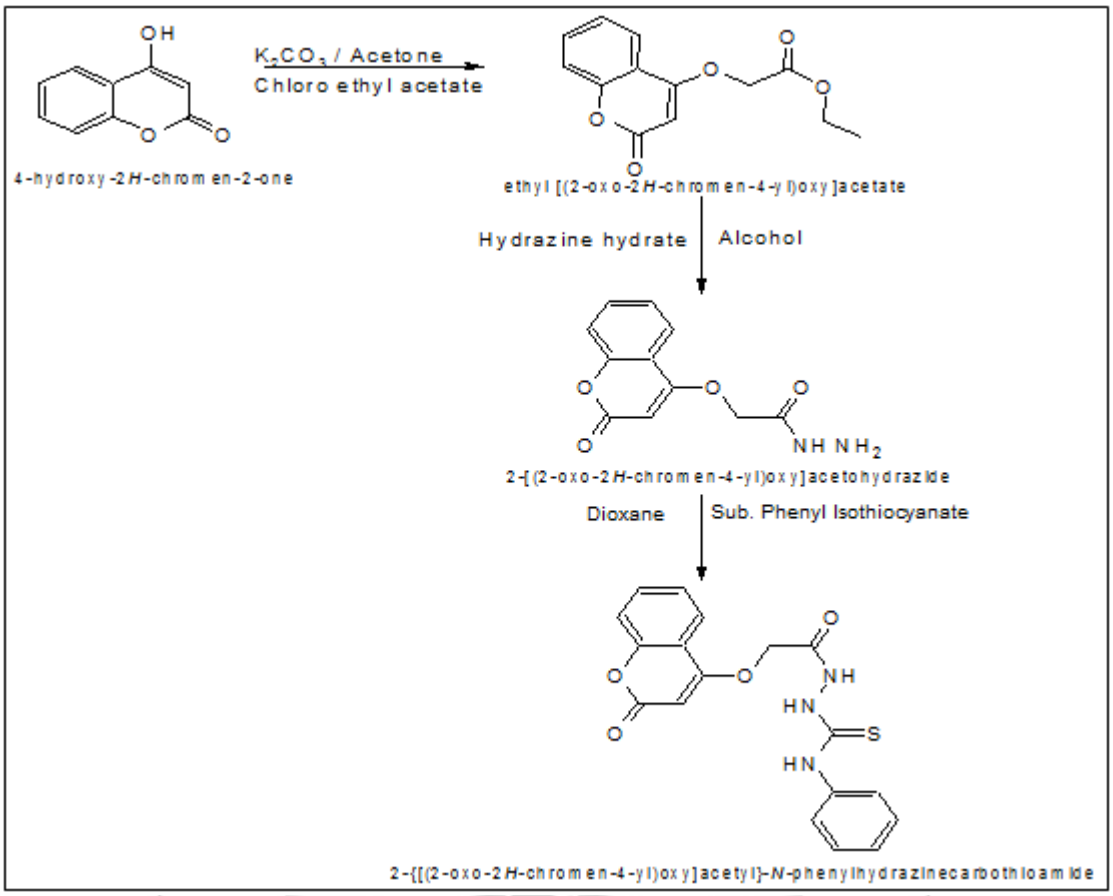
4-Hydroxy coumarin (0.01 mol), ethyl chloro acetate (0.01 mol) and anhydrous K_2CO_3 was dissolved in dry acetone was refluxed on water bath for 24 hrs. The resulting reaction mixture was cooled and filtered. The acetone was removed from the filtrate by distillation the remaining filtrate was poured into well stirred, ice-cold water. The organic layer was extracted with diethyl ether. The ether was then removed by evaporation on a water bath and the remaining liquid vacuum distilled to afford pure product. M.P 95^{0}C, Yield 74%, Colour buff, FT-IR cm^{-1} KBr: 1753.29 (-C=O), 1116.78 (-O-)

3.2 Synthesis of 2-[2-oxo-2H-chromen-4-yl)oxy]acetohydrazide (Compound 3)

Crystallized product of III-A.1 (ethyl [(2-oxo-2*H*-chromen-4-yl)oxy]acetate) was dissolved in alcohol reflux the reaction mixture. To this solution Hydrazine hydrate was added and refluxes the reaction mixture for 5 hours. Reaction was monitoring by TLC technique. From the resulting mixture, the excess of ethanol was removed by distillation. On cooling, white, needle-like crystals of the required products separated, which were collected. The product was dried and recrystallized by ethanol.
M.P 168^{0}C, Yield 72%, Colour brown, FT-IR cm^{-1} KBr: 3325.28 (-NH), 1058.92 (-O-), 1554.63 (-C-O)

3.3 Synthesis of 2-({[(2-oxo-2*H*-chromen-4-yl)oxy]acetyl}-*N*-phenyl hydrazine carbothioamide

An equimolar solution of crystallized product III-A.2 (2-[2-oxo-2H-chromen-4-yl)oxy] acetohydrazide) (0.02 mol) was dissolved in dry benzene and to this solution substituted Phenyl isothiocyanate in equimolar quantity (0.02 mol) was added, this reaction mixture is kept under reflux for 10 hrs. Reaction was monitoring by TLC technique. After completion of reaction excess of solvent was removed by distillation. The solid material obtained, was filtered off and recrystallized from methanol.



4. Tables

Table 1: Characterization Table

Code	*^{1}H NMR (400 MHz, DMSO-δ6) δ (ppm)*	*IR (KBr) cm^{-1}*	*MS (m/z)*
2	3.2 (s, 2H), 3.5 (q, 2H), 3.8 (t, 3H) 7.11-8.28 (m, 5H, Ar-H)	1116.78 (C-O), 1753.29 (C=O)	369[M$^+$], 92
3	5.4 (s, 2H), 6.1(s, 1H), 3.2(s, 2H), 7.12-8.48 (m, 5H, Ar-H)	3325.28(-NH), 1058.92 (-O-) 1553.23(-C-O)	402 [M$^+$], 92
4a	4.4 (s, 2H), 5.2 (s,1H), 8.2 (s,1H), 8.6 (s, 1H) 7.29-8.27 (m, 10H, Ar-H)	1637(CONH), 1072(-O-), 2600(C=S)	389 [M$^+$],92
4b	4.3 (s, 2H), 5.8 (s,1H), 8.4 (s,1H), 1H) 7.19-8.17 (m, 9H, Ar-H)	1636(CONH), 1096(-O-), 2624(C=S)	438 [M$^+$],90
4c	4.7 (s, 2H), 5.8 (s,1H), 8.4 (s,1H), 1H) 7.19-8.17 (m, 10H, Ar-H)	1653(CONH), 1103(-O-), 2741(C=S	389 [M$^+$], 137
4d	4.3 (s, 2H), 5.9 (s,1H), 8.7 (s,1H), 1H) 7.20-8.27 (m, 8H, Ar-H)	1603(CONH), 1096(-O-), 2592(C=S	438 [M$^+$], 92
3e	4.2 (s, 2H), 5.2 (s,1H), 8.2 (s,1H), 1H) 7.20-8.27 (m, 8H, Ar-H)	1649(CONH), 1096(-O-), 2745(C=S	437 [M$^+$], 161

Table 2: Biological Activity

Sr. No.	*Comp. code*	*R*	*Anti-Microbial Activity(10 mg/ml)*		
			Bacterial strains		*Fungal strains*
			E. coli	*S. aureus*	*C. albicans*
1	4a	H	-ve	-ve	-ve
2	4b	4-Cl	-ve	-ve	-ve
3	4c	4-F	-ve	-ve	-ve
4	4d	2,4-DiCl	-ve	+ve (13 mm)	-ve
5	4e	4-CF_3	-ve	+ve (23 mm)	-ve
6	Positive control Ampicillin	-	+ve (24 mm)	+ve (24 mm)	-
7	Positive control Ketonazole	-	-	-	+ve (24 mm)
8	Negative control 15%DMSO in water	-	-ve	-ve	-ve

5. Result and Discussion

Synthesized compound were screened for anti-microbial activity. The compound was tested on Bacterial stains *E. coli*, *S. aureus*, *Fungal Stains C.Albicans*. The activity was then monitored for 24-48 hours and the data is presented in the Table 2. the compounds showed mild to moderate anti-microbial activity. Compound 4c has shown low activity for all the microbial stains but the compound 4c has shown moderate activity for *Vibrio chlorae*, while the compound has not shown much activity for other bacterial and fungal stains.

6. Conclusion

The series of derivatives of coumarin were synthesized and evaluated for anti-microbial activity. Among which all compound showed moderate activity towards specific bacteria as compared with standard

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