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Synthesis of substituted Coumarin derivatives and their spectral Characterization

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Abstract: *A series of some coumarin derivative have been synthesized by the interaction of 4-hydroxy coumarin with substituted benzaldehyde. The identities of these synthesized compounds have been established on the basis of chemical transformation and IR, [1]H NMR and Mass spectral studies. In the present study synthesized compounds were studied for their in-vitro anti inflammatory activity by using HRBC membrane stabilization method, all compounds studied shows satisfactory results*
Keywords: *Coumarin, Anti-inflammatory, etc*

I. Introduction

Inflammatory diseases are becoming common in aging society throughout the world. Recent studies indicate that the mediators and cellular effectors of inflammation are important constituents of the local environment of tumors [1]. Inflammation in the body's response to noxious or injurious stimuli, characterized by warmth, redness of the skin, pain, swelling and loss of function. It is a part of host defense mechanism. There are several tissue factors that are known to be involved in the inflammatory reactions such as release of histamines, bradykinin and prostaglandins [2.] Coumarins (2H-1-benzopyran-2-ones) are important oxygen containing fused heterocycles used in drugs and dyes [3]. Coumarins be bound their class name to 'coumarou' the vernacular name of the Tonka bean (Dipteryx odorata willd, Fabaceae), from which coumarin itself was isolated in 1820[4]. They are the family of lactones containing benzopyrone skeletal framework that have enjoyed isolation from plant as well as total synthesis in the laboratory[5]. The incorporation group as a fused component into parent coumarin alters the property of parent coumarin and converts it into a more useful product[6]. Coumarin is plant flavonoids widely distributed in nature. Natural coumarins are known to have antidiabetic activity [7], anabolic antioxidant and hepato protective activities [8]. Substituted coumarins derivatives have been reported to have variety of biological activities. The potent antibiotics like Novobiocin, Coumaromycin and Chartesium are coumarin derivatives. Recently, the interest on these compounds has been revived owing to their use as fluorescent markers in the biochemical determination of enzymes. Introduction of fluoro and sulfonamide moieties into coumarin side chain hoping for an improvement of biological activity because incorporation of fluorine to various heterocycles is known to influence the biological activity[9] and the sulfonamide moiety itself possesses important antibacterial[10] and antitumor activity[11]. Specifically 1, 5 substituted benzothiazepine[12] are well known compounds for diverse therapeutically properties ike antimicrobial[13], antihypertensive[14], calcium channel blocker[15], blood platelet aggregation inhibitory[16] and coronary vasodilatory effects[17]. In the present study, we have evaluated the anti-inflammatory and antibacterial activity of some newly synthesized coumarin derivatives.

II. Materials and methods

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-300 FT-NMR spectrometer (300 MHz, JEOL Ltd., Tokyo, Japan), using TMS as internal standard in solvent DMSO. Masss datahave 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).

1.1 Experimental

1.1.1 Preparation of ethyl [(2-oxo-2H-chromen-4-yl)oxy]acetate (Compound 1)

4-Hydroxy Coumarin (2.0 mol) in dry acetone was dissolved and Potassium carbonate (1.0 mol) was added, the reaction mixture was refluxed for 6 hours and then Ethychlorolacetate was added and the reaction mixture was refluxed for another 6 hours the reaction mass then was neutralized by using glacial acetic acid and then extraction was given by using diethylether. The completion of the reaction was mentioned by TLC. Yield

74%; Buff colour solid; mp;95^{0}C. ^{1}H NMR(400 MHz, DMSO-δ6) δ (ppm) 2.30 (t, 3H), 3.18 (q, 2H), 4.13 (s, 2H), 7.18-8.26 (m, 5H, Ar-H) Anal. calcd for $C_{13}H_{12}O_5$:C, 62.90; H, 4.87; Found: C, 62.37; H, 4.16. IR (KBr) cm^{-1}: 2943(-CH_3), 1719(C=O), 1214 (C-O) . MS (m/z): 248[M^+] ($C_{13}H_{12}O_5^+$), 203($C_{11}H_7O_4$), 175($C_{10}H_7O_3$), 145($C_9H_5O_2$).

2.1.2 PREPARATION OF 2-[(2-OXO-2H-CHROMEN-4-YL)OXY]ACETOHYDRAZIDE(COMPOUND 2)

Compound 1(1 mol) dissolve in ethanol treated with mixture of hydrazine hydrate hydrochloride solution (1 mol) was refluxed for 6 hrs. The reaction was cooled, poured into ice cold water. Solid product was filtered, dried and Recrystallized from ethanol. Yield 72%; brown colour solid; mp;168^{0}C; ^{1}H NMR(400 MHz, DMSO-δ6) δ (ppm) 6.98-7.65 (m, 5H Ar-H), 10.35 (s, 1H), 5.89 (s, 2H), 4.12 (s, 2H) Anal. calcd for $C_{11}H_{10}N_2O_4$:C, 56.41; H, 4.30; N, 11.96 Found: C, 56.37; H, 4.16; N, 11.40. IR (KBr) cm^{-1}: 1645(C-O-C), 2953(-CH3), 1720(C=O), 3342 (N-H), MS (m/z): 234 [M^+] ($C_{11}H_{10}N_2O_4^+$), 218 ($C_{11}H_8NO_4$),203 ($C_{11}H_7O_4$), 175 ($C_{10}H_7O_3$), 145 ($C_9H_5O_2$)

2.1.3 PREPARATION OF 4-[(5-METHOXY-1,3-BENZOTHIAZOL-2-YL)SULFANYL]-2H-CHROMEN-2-ONE (COMPOUND 3A)

Compound 2(1 mol) dissolve in ethanol to this substituted Benzaldehyde (1 mol) few drops of glacial acetic acid was added and refluxed for 2 hrs. The reaction was cooled, poured into ice cold water. Solid product was filtered, dried and Recrystallized from ethanol.; ^{1}H NMR(400 MHz, DMSO-δ6) δ (ppm) 7.12-8.16 (m, 10H Ar-H), 3.18 (s, 2H), 5.34 (s, 1H), 2.84 (s, 1H) Anal. calcd for $C_{18}H_{14}O_4N_2$:C, 67.07; H,4.38; N,8.69. Found: C, 67.37; H, 4.16; N,8.60IR (KBr) cm^{-1}: 1615(C-O-C), 2943(-CH3), 1745(C=O), 3344 (N-H). MS (m/z): 322 [M^+] ($C_{18}H_{14}O_4N_2^+$), 245 ($C_{12}H_9N_2O_4$),218 ($C_{11}H_8NO_4$), 203 ($C_{11}H_7O_4$), 175 ($C_{10}H_7O_3$), 145 ($C_{10}H_5O_2$)

2.1.4 Preparation of N'-[(E)-(4-chlorophenyl)methylidene]-2-[(2-oxo-2H-chromen-4yl)oxy]acetohydrazide (Compound 3b)^{1}H NMR(400 MHz, DMSO-d6) d (ppm) 7.22-8.36 (m, 19H Ar-H), 3.56 (s, 2H), 5.84 (s, 1H), 2.94 (s, 1H) Anal. calcd for $C_{18}H_{14}N_2O_3S$:C, 63.89; H, 4.17, N, 8.28; Found: C, 63.81; H, 4.16. N, 8.82 IR (KBr) cm^{-1} 2943(-CH3), 1745(C=O),1214 (C-O)
MS (m/z): 356 [M^+] ($C_{18}H_{13}N_2O_4Cl^+$), 321 ($C_{18}H_{13}N_2O_4$), 245 ($C_{12}H_9N_2O_4$),218 ($C_{11}H_8NO_4$), 203 ($C_{11}H_7O_4$), 175 ($C_{10}H_7O_3$), 145 ($C_{10}H_5O_2$)

2.1.4.3Preparation of 4N'-[(E)-(4-fluorophenyl)methylidene]-2-[(2-oxo-2H-chromen-4-yl)oxy]acetohydrazide (Compound 3c)
^{1}H NMR(400 MHz, DMSO- δ6) δ (ppm) 7.36-8.26 (m, 9H Ar-H), 3.10 (s, 2H), 5.44 (s, 1H), 2.01 (s, 1H) Anal. calcd for $C_{18}H_{13}N_2O_4F$:C, 63.53; H, 3.85; N, 8.23; Found: C, 63.72; H, 3.16, N, 8.79
IR (KBr) cm^{-1}: 2943(-CH3), 1785(C=O),1294 (C-O)
MS (m/z):): 340 [M^+] ($C_{18}H_{13}N_2O_4F^+$), 321 ($C_{18}H_{13}N_2O_4$), 245 ($C_{12}H_9N_2O_4$),218 ($C_{11}H_8NO_4$), 203 ($C_{11}H_7O_4$), 175 ($C_{10}H_7O_3$), 145 ($C_{10}H_5O_2$)

2.1.4.4Preparation of N'-[(E)-(2,4-dihydroxyphenyl)methylidene]-2-[(2-oxo-2H-chromen-4-yl)oxy]acetohydrazide (Compound 3d)
^{1}H NMR(400 MHz, DMSO- δ 6) δ (ppm) 7.02-8.60 (m, 8H Ar-H), 3.28 (s, 2H), 5.41 (s, 1H), 2.94 (s, 1H), 6.34 (s, 1H), 6.74 (s, 1H) Anal. calcd for $C_{18}H_{14}N_2O_6$:C, 61.02; H, 3.98, N, 7.91; Found: C, 61.17; H, 3.46. N, 7.32 IR (KBr) cm^{-1}: 3235 (-NH), 1725(C=O),1394 (C-O)
MS (m/z):): 354 [M^+] ($C_{18}H_{14}N_2O_6^+$), 337 ($C_{18}H_{13}N_2O_5$) 321 ($C_{18}H_{13}N_2O_4$), 245 ($C_{12}H_9N_2O_4$),218 ($C_{11}H_8NO_4$), 203 ($C_{11}H_7O_4$), 175 ($C_{10}H_7O_3$), 145 ($C_{10}H_5O_2$)

2.1.4.4Preparation of N'-[(E)-(4-nitrophenyl)methylidene]-2-[(2-oxo-2H-chromen-4-
^{1}H NMR(400 MHz, DMSO- δ 6) δ (ppm) 7.32-8.56 (m, 9H Ar-H), 3.01 (s, 2H), 5.04 (s, 1H), 2.04 (s, 1H) Anal. calcd for $C_{18}H_{13}N_3O_6$:C, 58.86; H, 3.57, N, 11.44; Found: C, 58.17; H, 3.46. N, 11.32. IR (KBr) cm^{-1}: 3235 (-NH), 1725(C=O),1394 (C-O) MS (m/z):): 367 [M^+] ($C_{18}H_{13}N_3O_6^+$), 321 ($C_{18}H_{13}N_2O_4$), 245 ($C_{12}H_9N_2O_4$),218 ($C_{11}H_8NO_4$),203 ($C_{11}H_7O_4$), 175 ($C_{10}H_7O_3$), 145 ($C_{10}H_5O_2$)

Table 1: Schematic Representation of Titled Compounds

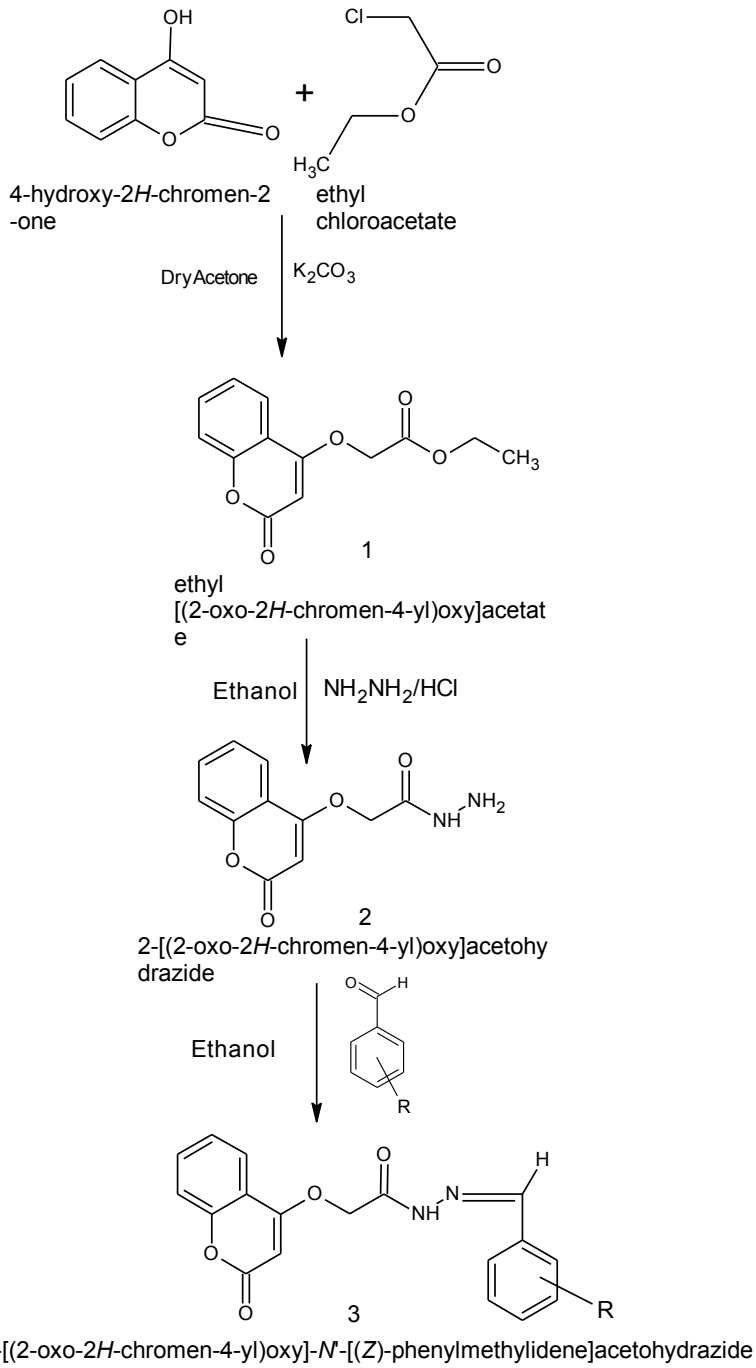

Table 2: Substitution table

Compounds	Substitution	Yield	M.P/B.P	Nature	Colour
3a	H	60	116	Crystalline	White
3b	4-Cl	72	176	Amorphorous	buff
3c	4-F	77	182	Amorphorous	white
3d	2,4-Di OH	56	119	Amorphorius	Pale yellow
3e	4-NO_2	64	189	liquid	Reddis brown

Table 3: Substitution table Anti- inflammatory results %inhibition

Concentration	3a	%inh	3b	%inh	3c	%inh	3d	%inh	3e	%inh
6.25	0.370	68.80	0.415	76.61	0.400	77.46	0.288	75.71	0.242	79.59
12.5	0.357	69.89	0.305	82.81	0.352	80.16	0.263	77.82	0.200	83.13
25	0.314	73.52	0.301	83.04	0.349	80.33	0.256	78.41	0.196	83.47
50	0.272	77.06	0.294	83.44	0.342	80.73	0.227	80.86	0.184	84.48
100	0.255	78.49	0.288	83.77	0.338	80.95	0.214	81.95	0.162	86.34
Positive control	1.186		1.775		1.775		1.186		1.186	

III. Results

The activity of coumarin derivatives was studied for in vitro anti-inflammatory Activity by HRBC membrane stabilization method. Among all the concentrations 100 µg/ml showed significant anti-inflammatory activity and 86.34% protection of HRBC in hypotonic solution. Results were compared with standard Diclofenac which showed 90% protection. The Coumarin derivative exhibited membrane stabilization effect by inhibiting hypotonicity induced lyses of RBC membrane. The RBC membrane is analogous to the lysosomal membrane and its stabilization implies that the extract may as well stabilize lysosomal membranes. Stabilization of lysosomal membrane is play an important role in limiting the inflammatory response by preventing the release of lysosomal constituents of activated neutrophile such as bactericidal enzymes and proteases, which cause further tissue inflammation and damage upon extra cellular release

IV. Conclusion

In vitro anti-inflammatory study reveals that the activity of the drugs under test was satisfactory as compared to that of standard DFS i.e. the coumarin derivatives were found out to be potent enough to suppress haemolysis. However, the % inhibition of haemolysis in case of DFS treated RBC's was slightly high as compared to that of the % inhibition provided by the test drugs.

Also within the series of test drugs, (i.e. various coumarin derivatives) those which were substituted with electron donating groups showed an enhancement of anti-inflammatory activity while those derivatives which were formed by substituting an electron withdrawing moiety were found to be showing a drastic reduction of anti-inflammatory activity.

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