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CHARACTERIZATION BY SPECTRAL ANALYSIS OF SOME SYNTHESIZED COUMARIN DERIVATIVE AND THEIR BIOLOGICAL APPLICATIONS.

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ABSTRACT

A series of some coumarin derivative have been synthesized by the interaction of 4-hydroxy coumarin with chloroethylacetate to form ester derivative of coumarin. Further treatment with hydrazine hydrate leads to formation of hydrazone derivative which was further treated with substituted benzaldehyde to form schiff base and finally on treatment with thioglycolic acid in presence of alcohol forms thiadiazole derivative of coumarin. The identities of these synthesized compounds have been established on the basis of chemical transformation and FT- IR, ^{1}H NMR and Mass spectral studies. In the present study synthesized compounds were studied for their *in vitro* anti inflammatory activity, anti-oxidant and anti microbial activity. all compounds studied shows satisfactory results.

KEYWORDS: Coumarin, Anti-inflammatory, Anti-oxidant, Anti microbial activity.

INTRODUCTION

Coumarins owe their class name to ‘Coumarou’, the vernacular name of the Tonka bean (Dipteryx odorata Willd, Fabaceae), from which Coumarin itself was isolated in 1820.[1]

Coumarin is classified as a member of the Benzopyrone family of compounds, all of which consist of a benzene ring joined to a pyrone ring.[2] The Benzopyrone can be subdivided into the benzo-a-pyrones to which the Coumarins belong and the benzo-g-pyrones, of which the flavonoids are principal members. Due to biochemical properties of coumarin was proposed for use in clinical medicine. A recent study investigated the efficacy of coumarin/troxerutine combination therapy for the protection of salivary glands and mucosa in patients undergoing head and neck radiotherapy. The results suggest that coumarin/troxerutine have a favourable effect in the treatment of radiogenic sialadentis and mucositis.[3] The interest in coumarin and 7-hydroxycoumarin as anti-cancer agents, arose from reports that these agents had achieved objective responses in some patients with advanced malignancies 4-Thiazolidinones[4] are well known for their versatile pharmacological activities. The nucleus is also known as wonder nucleus because it gives out different derivatives with all different types of biological activities. The presence of N-C-S linkage in the compounds has been shown to have hypnotic[5] and anti-cancer[6] activities. Some 4-thiazolidinones have been assessed for their cardiovascular[7] and antioxidant[8] activities. The methylene carbon atom at the position 5 of 4-thiazolidinone possesses nucleophilic activity. Coumarin and coumarin-related compounds have proved for many years to have significant therapeutic potential. This review provides an overview of the synthesis and reactivity of coumarin and their derivatives. We intend to outline the general methods by which substituted coumarin derivatives are synthesized and check for their biological evaluation.

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. 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 Agilent).

Experimental

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 ethylchloroacetate 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 diethyl ether. 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($C_9H_5O_2$).

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 ($C_9H_5O_2$).

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.

Yield 62%, Pale yellow colour solid, mp;172^{0}C ^{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 ($C_{10}H_5O_2$).

Characterization of N'-[(E)-(4-chlorophenyl)methylidene]-2-[(2-oxo-2H-chromen-4yl)oxy]acetohydrazide (Compound 3b)

Yield 71%, Brown colour solid, mp; 228^{0}C ^{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 ($C_{10}H_5O_2$).

Characterization of 4N'-[(E)-(4-fluorophenyl)methylidene]-2-[(2-oxo-2H-chromen-4-yl)oxy]acetohydrazide (Compound 3c)

Yield 67%, Yellow colour solid, mp;218^{0}C ^{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 ($C_{10}H_5O_2$).

Characterization of N'-[(E)-(2,4-dihydroxyphenyl)methylidene]-2-[(2-oxo-2H-chromen-4-yl)oxy]acetohydrazide (Compound 3d)

Yield 73%, Brown colour solid, mp;126^{0}C ^{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 ($C_{10}H_5O_2$).

Characterization of N'-[(E)-(4-nitrophenyl)methylidene]-2-[(2-oxo-2H-chromen-4-yl)oxy]acetohydrazide (Compound 3e)

Yield 67%, Yellow colour solid mp;123^{0}C ^{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 ($C_{10}H_5O_2$).

Preparation of 2-[(2-oxo-2*H*-chromen-4-yl)oxy]-*N*-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)acetamide (Compound 4a)

Compound 3a-e (0.1mol)was dissolved in DMF to this mixture thioglycolic acid is added drop wise with dropping funnel the mixture was constantly stirred and refluxed for 3hours, Completion of reaction was regularly monitored with definite interval by TLC, after completion of reaction the mixture was poured in ice cold water. The mixture was extracted by chloroform, the product obtained was then dried and excess amount of chloroform was remover by using rotary evaporator.

Yield 58%, yellow colour liquid, bp;223^{0}C, ^{1}H NMR(400 MHz, DMSO- δ 6) δ (ppm) 7.12-8.16 (m, 10H Ar-H), 3.11 (s, 2H), 5.64 (s, 1H), 3.98(s, 2H,), 2.16 (s, 1H) Anal. calcd for $C_{20}H_{16}N_2O_5S$:C, 60.60; H, 4.07, N, 7.07; Found: C, 60.27; H, 4.46. N, 7.32. IR (KBr) cm^{-1}: 3335 (-NH), 1795(C=O),1204 (C-O). MS (m/z): 396[M$^+$] ($C_{20}H_{16}N_2O_5S$ $^+$), 320 ($C_{14}H_{12}N_2O_5S$), 204 ($C_{11}H_8O_4$) , 145 ($C_{10}H_5O_2$).

Characterization of *N*-[2-(4-chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-[(2-oxo-2*H*-chromen-4-yl)oxy]acetamide (Compound 4b)

Yield 52%, Brown colour liquid, bp;245^{0}C ^{1}H NMR(400 MHz, DMSO- δ 6) δ (ppm) 7.22-8.56 (m, 9H Ar-H), 3.42 (s, 2H), 5.68 (s, 1H), 3.62(s, 2H,), 2.76 (s, 1H) Anal. calcd for $C_{20}H_{15}N_2O_5SCl$:C, 55.75; H, 3.51, N, 6.50; Found: C, 55.17; H, 3.26. N, 6.55. IR (KBr) cm^{-1}: 3635 (-NH), 1725(C=O),1233 (C-O) .MS (m/z): 430.86 [M$^+$] ($C_{20}H_{15}N_2O_5SCl$ $^+$), 396 ($C_{20}H_{16}N_2O_5S$), 320 ($C_{14}H_{12}N_2O_5S$), 204 ($C_{11}H_8O_4$) , 145 ($C_{10}H_5O_2$).

Characterization of *N*-[2-(4-fluorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-[(2-oxo-2*H*-chromen-4-yl)oxy]acetamide (Compound 4c)

Yield 64%, yellow colour liquid, bp;216^{0}C ^{1}H NMR(400 MHz, DMSO- δ 6) δ (ppm) 7.19-8.66 (m, 9H Ar-H), 3.63 (s, 2H), 5.91 (s, 1H), 3.44(s, 2H,), 2.12 (s, 1H) Anal. calcd for $C_{20}H_{15}N_2O_5SF$:C, 57.97; H, 3.65, N, 6.76; Found: C, 57.21; H, 3.62. N, 6.21. IR (KBr) cm^{-1}: 3315 (-NH), 1620(C=O),1293 (C-O) .MS (m/z): 414.86 [M$^+$] ($C_{20}H_{15}N_2O_5SF$ $^+$), 396 ($C_{20}H_{16}N_2O_5S$), 320 ($C_{14}H_{12}N_2O_5S$), 204 ($C_{11}H_8O_4$) , 145 ($C_{10}H_5O_2$).

Characterization of *N*-[2-(2,4-dihydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-[(2-oxo-2*H*-chromen-4-yl)oxy]acetamide (Compound 4d)

Yield 61%, yellow colour liquid, bp;217^{0}C ^{1}H NMR(400 MHz, DMSO- δ 6) δ (ppm) 7.20-8.16 (m, 8H Ar-H), 3.46 (s, 2H), 5.64 (s, 1H), 3.21 (s, 2H,), 2.12 (s, 1H) 4.02(s, 1H), 4.25

(s,1H) Anal. calcd for $C_{20}H_{16}N_2O_7S$:C, 56.07; H, 3.76, N, 6.54; Found: C, 56.41; H, 3.15. N, 6.66. IR (KBr) cm^{-1}: 3305 (-NH),3012 (-OH), 1640(C=O),1303 (C-O) .MS (m/z): 428 [M^+] ($C_{20}H_{16}N_2O_7S^+$), 396 ($C_{20}H_{16}N_2O_5S$), 320 ($C_{14}H_{12}N_2O_5S$), 204 ($C_{11}H_8O_4$) , 145 ($C_{10}H_5O_2$).

Characterization of *N*-[2-(4-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-[(2-oxo-2*H*-chromen-4-yl)oxy]acetamide (Compound 4e)

Yield 52%, yellow colour solid, bp;228^{0}C ^{1}H NMR(400 MHz, DMSO- δ 6) δ (ppm) 7.19-8.66 (m, 9H Ar-H), 3.63 (s, 2H), 5.91 (s, 1H), 3.44(s, 2H,), 2.12 (s, 1H) Anal. calcd for $C_{20}H_{15}N_3O_7S$:C, 54.42; H, 3.43, N, 9.52; Found: C, 54.21; H, 3.62. N, 9.21. IR (KBr) cm^{-1}: 3316 (-NH), 1640(C=O),1333 (C-O) .MS (m/z): 441 [M^+] ($C_{20}H_{15}N_3O_7S^+$), 396 ($C_{20}H_{16}N_2O_5S$), 320 ($C_{14}H_{12}N_2O_5S$), 204 ($C_{11}H_8O_4$) , 145 ($C_{10}H_5O_2$).

Anti-microbial Activity

The benzothiazole derivatives were screened for *in vitro* antimicrobial activity against a panel of selected Bacteria and fungi and the minimal inhibitory concentrations that inhibited the growth of the tested microorganisms (MIC) were detected. In order to elucidate the kind of the exhibited antimicrobial activity, when MIC values were lower than 100 µg/mL, the minimal bactericidal concentrations (MBCs) and the minimal fungicidal concentrations (MFCs) were determined. The results of antimicrobial testing are reported in Table I and are compared with those of standards Ampicillin, Trimethoprim and Miconazole.

Table No. I:- Anti-Microbial activity of synthesized compounds

Sr. No	Code	R	Anti-Microbial Activity (µg/ml) [MIC]						
			Bacterial strains					Fungal strains	
			E. coli	***S. typhi***	***P. aeroginosa***	***Kleb Pneumoniae***	***Vibrio chlorae***	***C. albican***	***A. niger***
1	4a	-H	100	100	200	200	200	200	200
2	4b	-Cl	100	100	100	200	100	100	200
3	4c	-F	100	200	100	200	100	100	200
4	4d	-OH	50	25	50	50	50	25	50
5	4e	$-NO_2$	200	200	N.A	200	200	N.A	200

1. Ampicillin (MIC-0.04 µg/ml) used as standard against *S. aureus, Kleb pneumonia, Vibrio chlorae.*
2. Trimethoprim (MIC 0.01 µg/ml) used as standard against *S. typhi, P. aeroginosa,*
3. Miconazole (MIC 6.25 µg/ml) as standard against *C. albicans* and *A. niger.*

Anti-Oxidant Activity & Anti Inflammatory Activity

Anti-oxidant is done by using Free radical Scavenging method[13] and readings were taken on 517nm of UV-Visible Spectrophotometer.[10]

Anti-inflammatory is done by using HRBC-Membrane Stabilization method[12] and readings were taken on 560nm of UV-Spectrophotometer.[11]

Table No. II:- Result for Anti-oxidant and Anti-Inflammatory activity of Synthesized Compounds

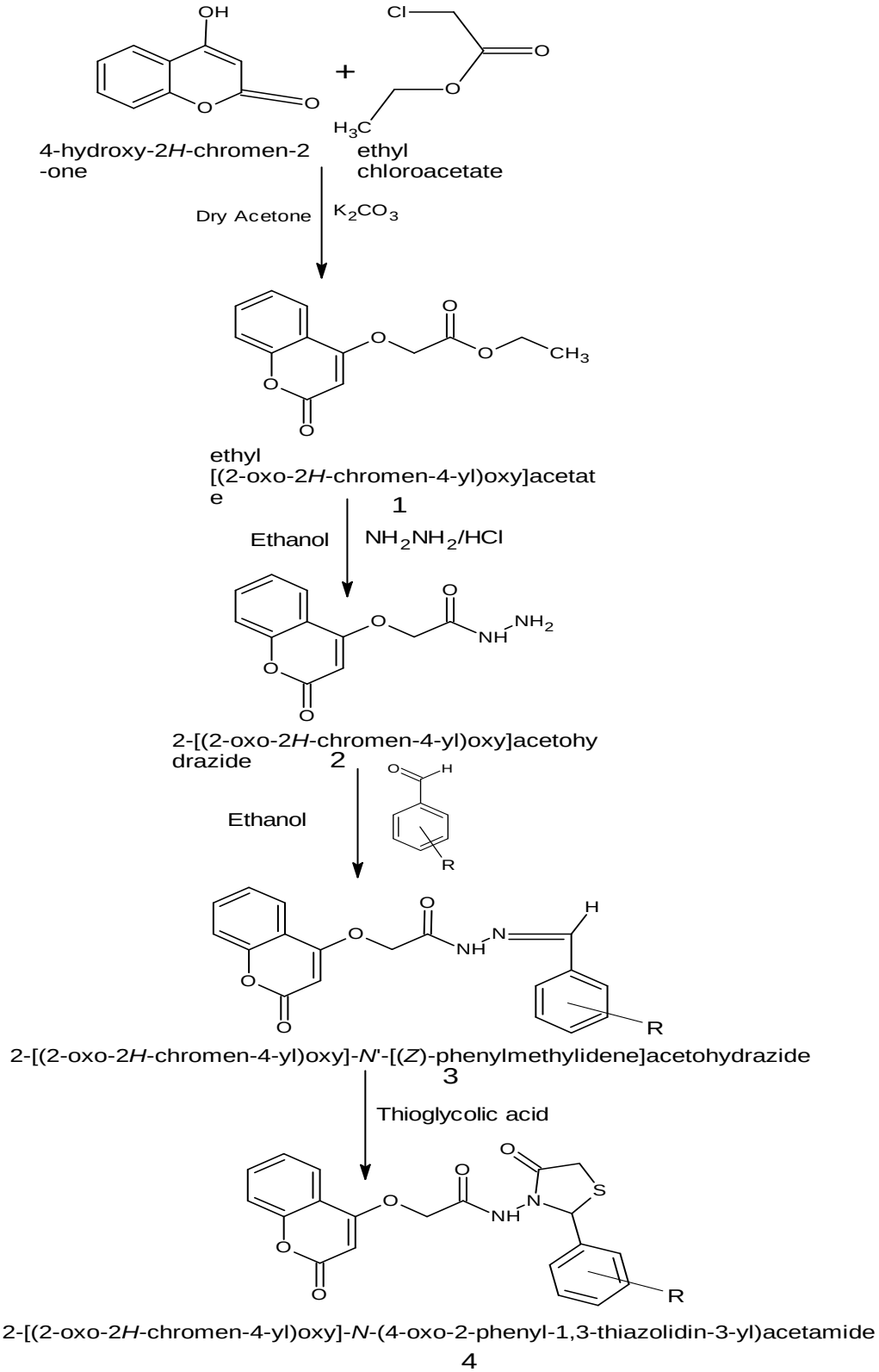
Sr. no.	Code	R	Anti-oxidant	Anti-inflammatory
			IC_{50}±SD	IC_{50}±SD
1	4a	-H	32.25±0.131	54.16±0.034
2	4b	-Cl	38.68±0.324	62.31±0.128
3	4c	-F	32.34±0.238	68.29±0.894
4	4d	-OH	22.64±0.236	38.64±0.635
5	4e	$-NO_2$	28.94±0.147	22.94±0.337
9	Std.	-	8.25±0.336	11.27±0.261

1. Standard for Anti-oxidant is Butyrate Hydrogen Toluene(BHT)
2. Standard for Anti-Inflammatory Sodium Diclofenac

RESULT AND DISCUSSION

The compound were tested on Bacterial stains *E. coli, S. typhi, P. aeroginosa, Kleb Pneumoniae, Vibrio chlorae,* Fungal Stains *C.Albicans, A.niger.* Each test compound were tested against each strain. The activity was then monitored for 24-48 hours and the data is presented in the Table I. The compounds showed mild to moderate anti-microbial activity. Compound with substituted electron donating group has shown better activity than electron withdrawing group for all the microbial stains as compared with standard. Anti-oxidant activity done by DPPH method, standard drug BHT shows IC_{50} at 8.25µg/mL. All Synthesized compounds compared with standard, we observed that comp. 4d and 4e has comparatively shown better activity. In Anti-inflammatory activity done by Human Red Blood Cell (HRBC) membrane stabilization method, standard drug shows IC_{50} at 11.70µg/mL. Compound 4e has shown enhancing result then other compounds as compared with standard.

Schematic Representation



CONCLUSION

The series of derivatives of Coumarin were synthesized and evaluated for anti-microbial activity, anti-inflammatory and anti-oxidant activity. Among which for antimicrobial electron

donating group has shown better results, while for anti-inflammatory and anti oxidant activity compounds has shown much moderate results as compared to standard.

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