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Synthesis and study of (5*Z*)-5-[(4-oxo-4*H*-chromen-3-yl) methylidene]-1, 3-thiazolidine-2, 4-dione derivative

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ABSTRACT

Thiazolidinone was synthesized by using Thiourea and chloroethylacetate. Chromene derivative were synthesized by Vilsmeier-Hack reaction using substituted Hydroxy Benzoic Acid. Initially synthesized Thiazolidinone and Chromene derivative were condensed using alcohol as a solvent. Further synthesized compounds were characterized by elemental & spectroscopic analysis. Compounds were further evaluated for in-vitro Anti-Inflammatory activity.

Keywords: Thiazolidinone, Chromene, Vilsmeier-Hack Reaction, Anti-Inflammatory activity.

INTRODUCTION

Thiazolidines are a class of heterocyclic organic compounds with a 5-membered saturated ring with a thioether group and an amine group. It is a sulfur analogue of oxazolidine. The drug pioglitazone contains a thiazolidine ring. It is a drug usually indicated in cases of type II diabetes for decreasing blood sugar. It also decreases triglycerides and C-reactive protein levels. It lowers blood pressure and increases levels of HDL. Another drug which contains a thiazolidine ring is the antibiotic drug penicillin. Thiazolidinones gives good pharmacological properties[1]. Thiazolidinones known to exhibit anti-tubercular[2] antibacterial[3], anticonvulsant[4], antifungal [5], anti-thyroid [6] activities.

Coumarins and their derivatives have engrossed substantial attention from organic and medicinal chemists for many years as they belong to a class of compounds with proven utility in medicinal chemistry. Coumarin is an important scaffold since several coumarin derivatives have wide range of biological activities. Coumarin is a fragrant chemical compound in the benzo-pyrone chemical class, found in many plants. Coumarin is used in the pharmaceutical industry as a precursor molecule in the synthesis of a number of synthetic anticoagulant pharmaceuticals. Coumarin is a fragrant chemical compound in the benzo-pyrone chemical class found in many plants. Coumarin is used in the pharmaceutical industry as a precursor molecule in the synthesis of a number of synthetic anticoagulant pharmaceuticals. Coumarins containing a Schiff base are expected to have enhanced anti tumor and other biological activities [7].Coumarin derivatives have been of great interest because of their role n natural and synthetic organic chemistry. Many products which contains a coumarin subunit exhibit biological activity such as anti-coagulant, molluscicides [8], insecticidal [9] activity.

A Schiff base, named after Hugo Schiff, is a compound with a functional group that contains a carbon-nitrogen double bond with the nitrogen atom connected to an aryl or alkyl group, not hydrogen.[10] Schiff bases and their biologically active complexes have been studied extensively over the past decade day by day Schiff bases are more frequently applied for the betterment of human welfare. The importance of Schiff base is due to its versatile

nature. Literature surveys shows that many Schiff bases exhibit biological activities such as antifungal, antitumor, anti-inflammatory and antipoetic among others

These results prompted us to synthesize a series of 3-[(4-oxotetrahydrothiophen-3-yl) methyl]-4*H*-chromen-4-one derivatives containing chromen-4-one ring and Thiazolidinones that would act as potent anti-inflammatory agent.

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. Elemental analysis has been carried out on a C, H, and N Elemental Analyzer (Thermo-Finnigan Flash EA 1112, Italy).

Preparation of 1, 3-thiazolidine-2, 4-dione (1)
Equimolar quantities of thiourea and chloroethyl acetate were gently refluxed in absolute alcohol over a period of 3 hr. the reaction mixture was then allowed to cool to room temperature. The HCl salt of 2-iminothiazolidinne-4-one was filtered from the solution of CH_3COONa, which precipitated 2-iminothiazolidine-4-one on cooling. The product was filtered and dried at 60^0C. This was hydrolyzed with 2N HCl in alcohol by refluxing for 15 hr. the reaction mixture was then cooled and neutralized with saturated solution of $NaHCO_3$(10%). The crude product 2, 4-thiazolidinedione was separated as solid. This was recrystallized from ethanol: water (40:60) mixture. On drying a white crystalline powder was obtained. (Compound 1)

Yield 74%; Cream colour solid; mp;142^{o}C; **^{1}H NMR**(400 MHz, DMSO-d6) d (ppm): 10.0 (s, 1H), 4.13-4.24 (s, 2H); **Anal. calcd for $C_2H_3NO_2$**: C, 30.76; H, 2.565; N 11.36 Found: C, 30.37; H, 2.16; N, 12.03.; **IR (KBr) cm^{-1}:** 3415(-NH), 2943 (-CH3), 1719(C=O),

Preparation of 4-oxo-4*H*-chromene-3-carbaldehyde (2)
Different Substituent's of (0.1mol) 2-Hydroxy Acetophenone was dissolved in DMF and is kept in ice cold condition. To this Vilsmeier Haack reagent [0.1 mol of $POCl_3$ was added drop by drop with stirring in 5mL/gm of DMF] is added with stirring at room temperature for 4 hrs then content was poured into crushed ice. Further it was neutralized with liquor NH_3 solid separates out which was filter washed with water, dried and recrystallized from ethanol.

Preparation of 4-oxo-4*H*-chromene-3-carbaldehyde (2a)
Yield- 62%; white colour, solid; mp: 158^{o}C; **^{1}H NMR**(400 MHz, DMSO-d6) d (ppm) :6.98-7.65 (m, 5H Ar-H), 10.35 (s, 1H); **Anal. calcd for $C_{10}H_6O_3$**:C, 68.96; H, 3..44; Found: C, 67.37; H, 2.16; **IR (KBr) cm^{-1}:** 1645(C-O-C), 2960 (-CH3), 1720(C=O).

Preparation of 7-Chloro-4-oxo-4*H*-chromene-3-carbaldehyde (2b)
Yield52%; Pale yellow colour solid; mp: 210^{o}C; **^{1}H NMR** (400 MHz, DMSO-d6) d (ppm): 6.45-7.65 (m, 5H Ar-H), 11.20 (s, 1H)); **Anal. calcd for $C_{10}H_6O_3Cl$** :C, 57.27; H, 2.86; Found: C, 55.37; H, 3.16.; **IR (KBr) cm^{-1}:** 1675(C-O-C), 2943(-CH3), 1745(C=O), 785(C-Cl).

Preparation of 7-Floro-4-oxo-4*H*-chromene-3-carbaldehyde (2c)
Yield48%; Brown colour solid; mp: 202^{o}C; **^{1}H NMR** (400 MHz, DMSO-d6) d (ppm) 7.85-8.21 (m, 5H Ar-H), 9.23 (s, 1H)); **Anal. calcd for $C_{10}H_6O_3F$** :C, 62.50; H, 3.125; Found: C, 62.07; H,3.16.; **IR (KBr) cm^{-1}:** 1673(C-O-C), 2352(-CH3), 1705(C=O).

Preparation of 7-Nitro-4-oxo-4*H*-chromene-3-carbaldehyde (2d)
Yield-48%; yellow colour solid; mp: 222^{o}C; **^{1}H NMR** (400 MHz, DMSO-d6) d (ppm) 7.65-8.01 (m, 5H Ar-H), 9.23 (s, 1H)); **Anal. calcd for $C_{10}H_6O_5N$** :C, 54.54; H, 2.727;N,6.33 Found: C, 55.07; H,2.16; N ; 6.23; **IR (KBr) cm^{-1}:** 1643(C-O-C), 2582(-CH3), 1745(C=O).

Preparation of 7-Hydroxy-4-oxo-4*H*-chromene-3-carbaldehyde (2e)
Yield71%; white colour solid; mp: 188^{o}C; **^{1}H NMR**(400 MHz, DMSO-d6) d (ppm) 6.45-7.65 (m, 5H Ar-H), 10.20 (s, 1H),5.34 (s, 1H); **Anal. calcd for $C_{10}H_6O_4$**:C, 63.15; H, 3.15; Found: C, 62.37; H, 3.16.; **IR (KBr) cm^{-1}:** 1625(C-O-C), 2943(-CH3), 1745(C=O), 3103(-OH).

Preparation of 7-methyl 4-oxo-4*H*-chromene-3-carbaldehyde (2f)
Yield 69%; light yellow colour, solid; mp; 174^{o}C; **^{1}H NMR**(400 MHz, DMSO-d6) d (ppm): 6.45-7.65 (m, 5H Ar-H), 10.35 (s, 1H),2.34 (s, 3H); **Anal. calcd for $C_{11}H_8O_3$**:C, 70.25; H, 4.25; Found: C, 69.37; H, 4.16; **IR (KBr) cm^{-1}:** 1615(C-O-C), 2943(-CH3), 1745(C=O)

Preparation of (5*Z*)-5-[(4-oxo-4*H*-chromen-3-yl) methylidene]-1, 3-thiazolidine-2, 4-dione (3)
A mixture of (0.025mol)compound 1 and (0.0025 mol) compound 2 was dissolve in ethanol was heated about 8 hrs. Completion of reaction was monitored by TLC. The resulted mixture was cooled, poured into ice cold water. Resulted product was recrystallized from ethanol

Preparation of (5*Z*)-5-[(4-oxo-4*H*-chromen-3-yl) methylidene]-1, 3-thiazolidine-2, 4-Dione (3a)
Yield 79%; brown colour solid; mp:143^{o}C; **^{1}H NMR** (400 MHz, DMSO-d6) d (ppm) 7.47-8.08 (m,5H,Ar-H); 7.43 (1H,s); 10.0(1H, s); **Anal. calcd for $C_{13}H_7O_3NS$**:C, 60.70; H, 2.72;N, 5.44 Found: C, 61.00; H, 2.98; N, 5.46; **IR (KBr) cm^{-1}:** 3327(-NH), 3263(-CH3), 1692 (C=O),1200 (C-O)

Preparation of 7-Chloro-(5*Z*)-5-[(4-oxo-4*H*-chromen-3-yl) methylidene]-1, 3-thiazolidine-2, 4-dione (3b)
Yield 79%; brown colour solid; mp: 211^{o}C; **^{1}H NMR**(400 MHz, DMSO-d6) d (ppm) 6.72-7.66(m, 4H Ar-H), 6.72 (s, 1H); 10.05 (s, 1H, -NH),7.43(s.1H); **Anal. calcd for $C_{13}H_7O_3NSCl$** :C, 53.33; H, 2.39; N, 4.78 Found: C, 53.37; H2.38, N, 4.51; **IR (KBr) cm^{-1}:** 3331(-NH), 2879(-CH3), 1625(C=O),1237 (C-O), 550 (C-Cl)

Preparation of 7-Floro-(5*Z*)-5-[(4-oxo-4*H*-chromen-3-yl) methylidene]-1, 3-thiazolidine-2, 4-dione (3c)
Yield 64%; Brown colour solid; mp153^{o}C; **^{1}H NMR**(400 MHz, DMSO-d6) d (ppm): 6.32-8.7(m, 4H Ar-H),6.58(s,1H); **Anal. calcd for $C_{14}H_{10}OFS$** :C, 68.85; H, 4.09; Found: C, 67.37; H, .4.16; **IR (KBr) cm^{-1}:** 2860(-CH3), 1775(C=O),1207 (C-O).

Preparation of 7-Nitro-(5*Z*)-5-[(4-oxo-4*H*-chromen-3-yl) methylidene]-1, 3-thiazolidine-2, 4-dione (3d)
Yield 64%; yellow colour solid; mp; 243^{o}C; **^{1}H NMR**(400 MHz, DMSO-d6) d (ppm) 6.72-8.01(m, 4H Ar-H),7.58(s,1H); **Anal. calcd for $C_{14}H_{10}O_3NS$** :C, 61.76; H, 3.67; N, 5.14 Found: C, 61.37; H, .3.16, N, 4.11; **IR (KBr) cm^{-1}:** 3323 (-NH), 2879(-CH3), 1725(C=O),1297 (C-O).

Preparation of 7-Hydroxy-(5*Z*)-5-[(4-oxo-4*H*-chromen-3-yl) methylidene]-1, 3-thiazolidine-2, 4-dione (3e)
Yield82%; yellow colour solid; mp: 189^{o}C; **^{1}H NMR**(400 MHz, DMSO-d6) d (ppm) 6.72-7.60 (m, 4H Ar-H), 6.72 (s, 1H); 10.05 (s, 1H, -NH),7.43(s.1H); **Anal. calcd for $C_{13}H_8O_4NS$** :C, 56.93; H, 2.91; N, 5.10 Found: C, 56.37; H, 2.16, N, 4.98; **IR (KBr) cm^{-1}:** 3331(-NH), 2879(-CH3), 1625(C=O),1237 (C-O).

Preparation of 7-Methyl-(5*Z*)-5-[(4-oxo-4*H*-chromen-3-yl) methylidene]-1, 3-thiazolidine-2, 4-dione (3f)
Yield 56%; reddish brown colour solid; mp:168^{o}C; **^{1}H NMR**(400 MHz, DMSO-d6) d (ppm): 6.72-7.60 (m, 4H Ar-H), 2.34 (s, 3H); 10.05 (s, 1H); **Anal. calcd for $C_{14}H_{10}O_3NS$** :C, 61.76; H, 3.67; N, 5.14 Found: C, 61.37; H, .3.16, N, 4.11; **IR (KBr) cm^{-1}:** 3234(-NH), 2893(-CH3), 1845(C=O),1257 (C-O).

Table 1.1: Anti-Inflammatory Activity of Synthesized compound

Sr. no.	Comp	Subs.	Concentration					
			6.25	12.5	25	50	100	IC_{50}
1	3a	H	32.33	44.32	49.59	57.36	60.30	46
2	3b	Cl	76.31	78.59	80.37	83.37	85.48	23
3	3c	F	78.28	80.57	83.33	85.43	87.67	18
4	3d	NO_2	72.98	76.59	80.36	84.36	85.30	30
5	3e	OH	40.85	55.36	59.35	62.36	65.66	36
6	3f	CH_3	37.78	45.78	46.79	55.87	60.48	40
7	1	DFS	99.25	99.38	99.52	99.69	99.88	**6.25**

Standard DFS- Diclofenac Sodium
MIC of Standard is 6.25µg.

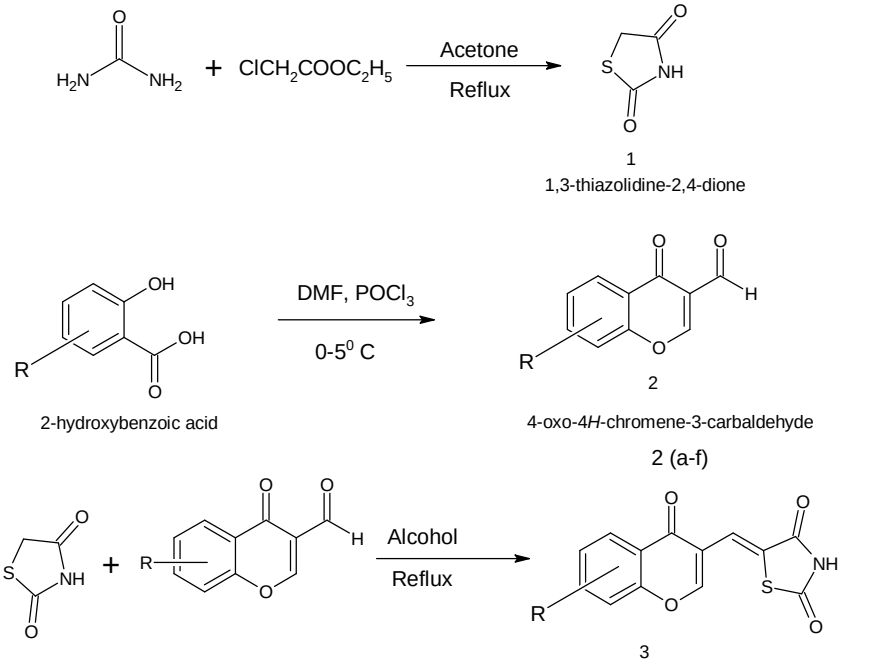
Anti-inflammatory test
The present study was undertaken to evaluate the efficiency of title compound for anti-inflammatory activity by consuming HRBC membrane stabilization method. The HRBC are used as their membrane stabilization method. The HRBC are used as their membrane is similar to lysosomal membrane which influence in the process if inflammation Diclofenac sodium was used as standard [11,12,13]

$$\% \text{ inhibition} = \frac{(\text{O.D of Control} - \text{O.D of Sample})}{\text{O.D of Control}}$$

RESULTS AND DISCUSSION

- Based on the results it can be concluded that the heterocyclic derivatives of substituted formyl chromene significant anti-inflammatory activity.
- Additions of different functional groups have varying effects. Significant increase in anti-inflammatory effect of compound 3c was observed with fluoro substitution.
- While a good activity is shown by 3b with chloro substitution, IC_{50} of better result is shown by nitro and methoxy substitution, methyl substituted shows comparable activity.

Table No. 2:- Schematic Representation



CONCLUSION

- When compared with standard i.e. DFS (Diclofenac Sodium) chromene derivative was found to be less potent, as percentage inhibition in case of DFS treated RBC'S was very high (more than 99%) whereas on the other hand chromene derivatives treated RBC'S suffered much more heamolysis i.e. the percentage inhibition was comparatively less (less than 90%).
- However, with the increase in concentration of chromene derivative its membrane stabilizing activity was more enhanced
- Further studies to determine the relevance of this finding in biological model should be undertaken that might result in the development of potent anti-inflammatory agent with low toxicity and better therapeutic index.

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