

Synthesis and biological evaluation of some triazole integrated Schiff Base as antioxidant and anti-inflammatory agents

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Abstract

A series of some 2-[(Z)-[(3-Methyl-5-sulfanyl-4H-1,2,4-triazol-4-yl)imino]methyl]-4H-chromen-4-ones were synthesized by reaction of substituted 4-oxo-4H-1-benzopyran-3-carbaldehyde with 4-amino-5-methyl-4H-1,2,4-triazole-3-thiol in acidic medium. The synthesized compounds were characterized by proton NMR, ¹³C NMR, IR and mass spectroscopy techniques. The products were screened for their antioxidant and anti-inflammatory activities. Compound MP 2 and MP 6 demonstrate excellent antioxidant activity while remaining compounds show moderate activity. Compounds MP 2 and MP 3 demonstrate excellent anti-inflammatory activity while compounds MP 4, MP 6 and MP 8 show moderate activity.

Keywords Aldehydes, Biological activities, Heterocycles, Schiff bases, 1,2,4 triazole.

1.0 Introduction

Benzopyran and its derivatives belonging to significant oxygen containing heterocyclic compound occurs in most of the naturally occurring plants [1]. Most of the synthetic as well as naturally occurring derivative of chromones own excellent biological activities [2]. Chromones also acts as synthetic intermediate in many new heterocyclic compounds [3-5]. From last few year 3-formyl chromones plays a significant role in highly reactive compounds [6]. 3-Formylchromone with suitable substituent shows antifungal [7-8], antibacterial [9-11], anticancer [12-14], anti-HIV [15-17] activities. Hence it has been called as promising moiety in drug chemistry. Amongst the heterocyclic compounds, triazoles are one of the most important heterocycles demonstrating notable pharmacological properties [18]. The derivative of 1, 2, 4 triazole exhibits insecticidal [19], anti-inflammatory [20], antidepressant [21], anticancer [22-23], antifungal [24-26] and antibacterial [27-30] activities. Schiff bases have impressive importance due to its wide spectrum in biological activities such as antitubercular [31], antioxidant [32] and analgesic [33-34].

In view of these applications of 3-formyl chromones and 1, 2, 4 triazole, we thought to explore the chemistry of these moieties, to accomplish this we have carried out synthesis of some Schiff base derivatives by condensation of these moieties and also screened for anti inflammatory and antioxidant activities.

2.0 Experimental

2.1 Material and method:

All the chemicals were purchased from commercial suppliers of Sigma Aldrich and used without further purification. Melting points of synthesized compounds were taken by open tube capillary method and are uncorrected. The proton NMR spectra were recorded on a Bruker 400 MHz spectrometer using tetramethyl silane (TMS) as an internal standard. The Infra-red (IR)

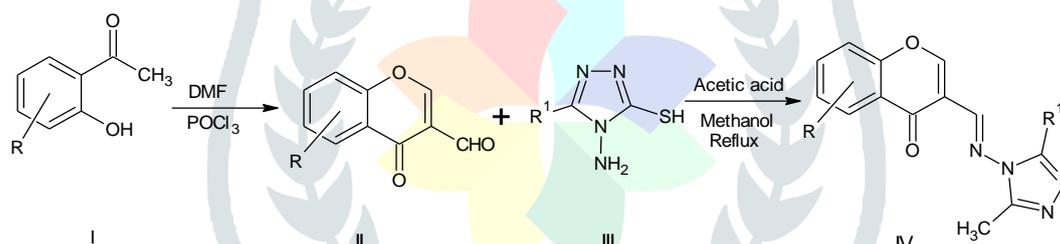
spectra were recorded on Thermo Fisher IR instrument by ATR technique. The mass spectra were recorded on Thermo Scientific Q-Exactive, Accela 1250 pump. The completion of reaction and purity of the synthesized compounds were checked by TLC on silica coated aluminium plates.

2.1.1 General procedure for Synthesis of 4-[[*(Z)*-(1,3-diphenyl-1*H*-pyrazol-4-yl)methylidene]amino]-5-methyl-4*H*-1,2,4-triazole-3-thiols (C):

Substituted 4-oxo-4*H*-1-benzopyran-3-carbaldehydes were synthesized by reaction of different substituted ortho hydroxy acetophenone with dimethyl formamide (DMF) through Vilsmeier Haack reaction [35]. 4-Amino-5-methyl-4*H*-1,2,4-triazole-3-thiols were synthesized by reaction of hydrazine hydrate and carbon disulphide followed by reaction with acetic acid [36]. Substituted 4-oxo-4*H*-1-benzopyran-3-carbaldehyde (1 mmol) and equimolar amount of the 4-amino-5-methyl-4*H*-1,2,4-triazole-3-thiol were condensed by refluxing the mixture for 3-4 hrs in acetic acid-methanol mixture. The reaction was monitored by Thin Layer Chromatography (TLC). After completion of reaction, the mixture was poured on crushed ice. The separated solid product was recrystallized from ethanol. Yield of the products ranges between 73 to 83 % with good purity.

Owing to, significant pharmaceutical activities of 1, 2, 4 triazole, its derivatives and chromones, we have synthesised various Schiff bases by condensation of different substituted 3-formyl chromones with 1, 2, 4 triazole-3- thiol using acetic acid as a catalyst (Scheme 1).

Scheme I:



R= CH₃

R¹= 6 OCH₃, 6 CH₃, 6 Cl, 6 NO₂, 6 F, 5,7 di Cl, naphto, 4 H

In this protocol 2-[(*Z*)-[(3-methyl-5-sulfanyl-4*H*-1,2,4-triazol-4-yl)imino]methyl]-4*H*-chromen-4-one derivatives were synthesized by condensation of 4-oxo-4*H*-1-benzopyran-3-carbaldehyde (II) i.e. 3-formyl chromones with 4-amino-5-methyl-4*H*-1,2,4-triazole-3-thiol (III) using acetic acid as a catalyst in methanol at reflux temperature.

2.2 Spectroscopic characterization for derivative of 4-[[*(Z)*-(1,3-diphenyl-1*H*-pyrazol-4-yl)methylidene]amino]-5-methyl-4*H*-1,2,4-triazole-3-thiols:

2.2.1 6-Methoxy-3-[(*E*)-[(3-methyl-5-sulfanyl-4*H*-1,2,4-triazol-4-yl)imino]methyl]-4*H*-1 benzopyran-4-one (MP 1), white solid, MP. 219-220 °C; IR (cm⁻¹): 3070 (C-H str), 1642 (CH=N str), 1277 (C-S str), 1604 (C=C str); ¹H NMR (d₆-DMSO 400 MHz): δ 2.32 (s, 3H,CH₃), 3.83 (s, 3H,OCH₃), 7.26-7.62 (m, 3H, Ar-H), 10.36 (s, 1H, N=CH), 8.72 (s,1H C2), 13.47 (s, 1H, SH); ¹³C NMR (100 MHz, d₆-DMSO): 11.12, 21.05, 117.76, 118.47, 125.13, 135.89, 136.42, 148.68, 154.48, 154.98, 156.16, 161.85, 174.99; HRMS m/z calculated for C₁₄H₁₂N₄O₃S (M+ H)⁺ 316.33; found 318.2996.

2.2.2 6-Methyl-3-[(*E*)-[(3-methyl-5-sulfanyl-4*H*-1,2,4-triazol-4-yl)imino]methyl]-4*H*-1-benzopyran-4-one (MP 2), white solid, MP. 224-226 °C; IR (cm⁻¹): 3066 (C-H str), 1649 (CH=N str), 1275 (C-S str), 1597 (C=C str), 2755 (-SH); ¹H NMR (d₆-

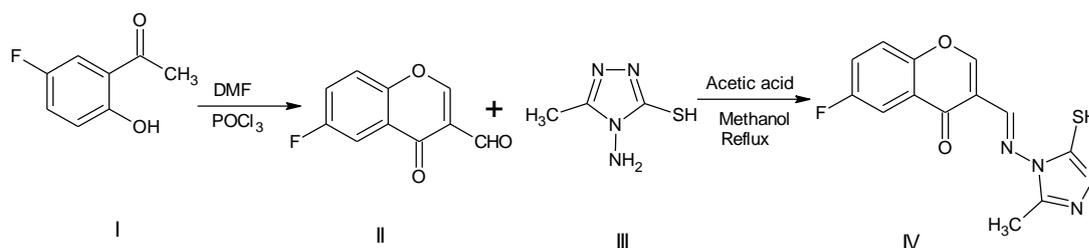
- DMSO 400 MHz): δ 2.33 (s, 3H,CH₃), 2.41 (s, 3H,CH₃), 7.43-7.89 (m, 3H, Ar-H), 10.36 (s, 1H,N=CH), 8.76 (s,1H C2), 13.52 (s, 1H, SH); ¹³C NMR (100 MHz, d₆-DMSO): 11.12, 56.00, 105.43, 117.14, 120.14, 124.09, 124.77, 148.66, 150.95, 155.19, 155.92, 157.65, 161.86, 174.82; HRMS m/z calculated for C₁₄H₁₂N₄O₂S (M+ H)⁺ : 300.3357; found 301.0746.
- 2.2.3 *6-Chloro-3-((E)-[(3-methyl-5-sulfanyl-4H-1,2,4-triazol-4-yl)imino]methyl)-4H-1-benzopyran-4-one (MP 3)*, yellow solid, MP. 230-231 °C; IR (cm⁻¹): 3067 (C-H str), 1651 (CH=N str), 1244 (C-S str), 1598 (C=C str), 2755 (-SH); ¹H NMR (d₆-DMSO 400 MHz): δ 2.33 (s, 3H,CH₃), 7.61-8.04 (m, 3H, Ar-H), 10.43 (s, 1H,N=CH), 8.86 (s,1H C2), 13.61 (s, 1H, SH), ¹³C NMR (100 MHz, d₆-DMSO): 11.12, 118.05, 120.91, 125.00, 131.89, 134.87, 148.77, 153.71, 154.59, 156.58, 161.79, 173.87.
- 2.2.4 *3-((E)-[(3-Methyl-5-sulfanyl-4H-1,2,4-triazol-4-yl)imino]methyl)-6-nitro-4H-1-benzopyran-4-one (MP 4)*, yellow solid, MP. 240-242 °C; IR (cm⁻¹): 3064 (C-H str), 1626 (CH=N str), 1245 (C-S str), 1554 (C=C str), 2759 (-SH); ¹H NMR (d₆-DMSO 400 MHz): δ 2.34 (s, 3H,CH₃), 7.67-8.82 (m, 3H, Ar-H), 10.56 (s, 1H,N=CH), 8.95 (s,1H C2), 13.23 (s, 1H, SH).
- 2.2.5 *6-Fluoro-3-((E)-[(3-methyl-5-sulfanyl-4H-1,2,4-triazol-4-yl)imino]methyl)-4H-1-benzopyran-4-one (MP 5)*, faint yellow solid, MP. 251-252 °C; IR (cm⁻¹): 3065 (C-H str), 1625 (CH=N str), 1242 (C-S str), 1531 (C=C str), 2760 (-SH); ¹H NMR (d₆-DMSO 400 MHz): δ 2.33 (s, 3H,CH₃), 7.42-7.79 (m, 3H, Ar-H), 10.43 (s, 1H,N=CH), 8.70 (s,1H C2), 13.36 (s, 1H, SH); ¹³C NMR (100 MHz, d₆-DMSO): 11.10, 110.65, 110.88, 117.49, 121.08, 121.16, 122.72, 122.97, 125.25, 125.33, 148.69, 152.46, 154.23, 156.24, 158.72, 161.19, 161.90, 174.34; HRMS m/z calculated for C₁₃H₉FN₄O₂S (M+ H)⁺ : 304.2996; found 305.0495.
- 2.2.6 *5,7-Dichloro-3-((E)-[(3-methyl-5-sulfanyl-4H-1,2,4-triazol-4-yl)imino]methyl)-4H-1-benzopyran-4-one (MP 6)*, faint yellow solid, MP. 235-237 °C; IR (cm⁻¹): 3057 (C-H str), 1654 (CH=N str), 1238 (C-S str), 1599 (C=C str), 2757 (-SH); ¹H NMR (d₆-DMSO 400 MHz): δ 2.32 (s, 3H,CH₃), 7.60-8.02 (m, 3H, Ar-H), 10.53 (s, 1H,N=CH), 8.80 (s,1H C2), 13.49 (s, 1H, SH).
- 2.2.7 *3-((E)-[(3-Methyl-5-sulfanyl-4H-1,2,4-triazol-4-yl)imino]methyl)-4H-aphtho[1,2-b]pyran-4-one (MP 7)*, faint yellow solid, MP. 221-222 °C; IR (cm⁻¹): 3068 (C-H str), 1643 (CH=N str), 1234 (C-S str), 1589 (C=C str); ¹H NMR (d₆-DMSO 400 MHz): δ 2.33 (s, 3H,CH₃), (7.53-7.70 (m, 3H, Ar-H), 7.72-8.14 (m 2H), 10.54 (s, 1H,N=CH), 9.90 (s,1H C2), 13.42 (s, 1H, SH), ¹³C NMR (100 MHz, d₆-DMSO): 10.75, 11.17, 117.86, 120.39, 126.76, 128.77, 129.62, 131.01, 136.67, 148.79, 149.17, 153.98, 154.69, 157.68, 165.73, 176.63.
- 2.2.8 *3-((E)-[(3-Methyl-5-sulfanyl-4H-1,2,4-triazol-4-yl)imino]methyl)-4H-1-benzopyran-4-one (MP 8)*, white solid, MP. 211-212 °C; IR (cm⁻¹): 3058 (C-H str), 1621 (CH=N str), 1231 (C-S str), 1606 (C=C str), 2754 (-SH); ¹H NMR (d₆-DMSO 400 MHz): δ 2.33 (s, 3H,CH₃), 7.42-7.74 (m, 4H, Ar-H), 10.39 (s, 1H,N=CH), 8.73 (s,1H C2), 13.44 (s, 1H, SH); ¹³C NMR (100 MHz, d₆-DMSO): 11.13, 21.05, 117.98, 118.73, 124.00, 125.82, 126.43, 134.78, 148.72, 154.58, 156.17, 156.31, 161.85, 174.95; HRMS m/z calculated for C₁₃H₁₀N₄O₂S (M+ H)⁺ : 286.3091; found 287.0591.

3.0 Results and discussion

In trial case, the reaction between 6-fluoro-4-oxo-4H-1-benzopyran-3-carbaldehyde (2) (1 mmol) and 4-amino-5-methyl-4H-1, 2, 4-triazole-3-thiol (3) (1 mmol) was carried out in presence of acetic acid as a catalyst in methanol by refluxing at 80 °C

for 3-4 hrs. (Scheme 2). The completion of reaction was monitored by TLC. The product was obtained with 82.56 % yield (Table 2 entry MP 5).

Scheme 2.

R= CH₃R'= 6 OCH₃, 6 CH₃, 6 Cl, 6 NO₂, 6 F, 5,7 di Cl, naphto, 4 H

For the selection of most appropriate solvent, we have carried out the reaction with different catalyst as well as solvents and the optimization of reaction conditions is as shown in Table 1.

Table 1 Optimization of reaction condition for synthesis of 6-fluoro-3-[(E)-[(3-methyl-5-sulfanyl-4H-1,2,4-triazol-4-yl)imino]methyl]-4H-1-benzopyran-4-one

Entry	Catalyst	Solvent	Time (h)	Yield ^b (%)
1	-	Absolute ethanol	5-6	-
2	-	Toluene	2-3	-
3	NH ₄ OH	H ₂ O	3-4	-
4	NH ₄ OH	50% C ₂ H ₅ OH	3-4	T _c
5	NH ₄ OH	Absolute ethanol	5-6	T _c
6	NH ₄ OH	Toluene	2-3	31
7	H ₂ SO ₄	H ₂ O	5-6	-
8	H ₂ SO ₄	50% EtOH	2-3	45
9	H ₂ SO ₄	Absolute ethanol	4-5	73-82
10	CH ₃ COOH	Absolute ethanol	4-5	72-83
11	H ₂ SO ₄	Toluene	1-2	66-81
12	CH ₃ COOH	Toluene	1-2	65-79
13	CH ₃ COOH	Methanol	3-4	74-86

^{Tc}Trace amount, ^bIsolated yield

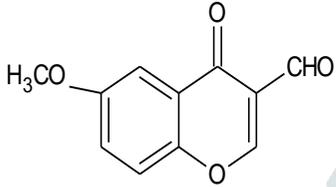
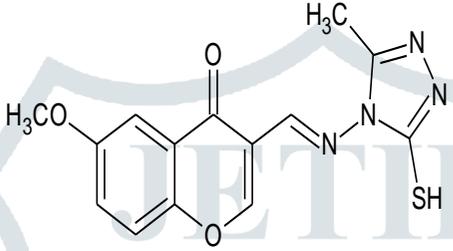
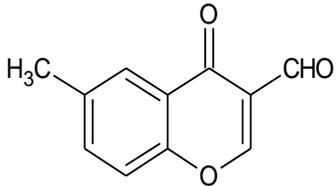
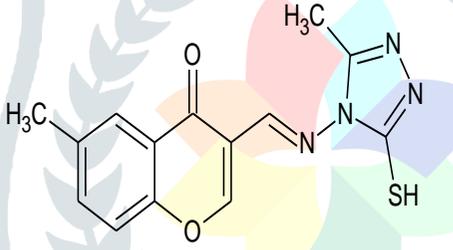
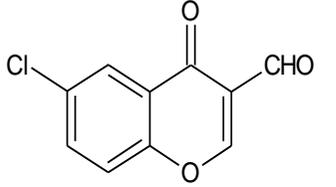
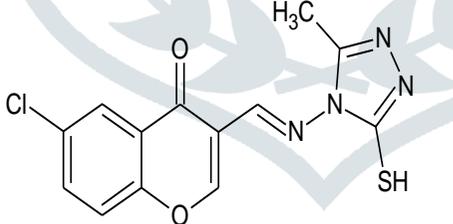
It was noticed that in the absence of catalyst, reaction could not proceed (Table 1 entries-1, 2) which indicates the need of catalyst for this transformation. To accomplish this we have used different catalyst. Satisfactory yield was obtained when the reaction is carried out in methanol as a solvent and acetic acid as a catalyst (Table 1 entry-13). Furthermore, when the reaction was carried out in ethanol as a solvent and acetic acid as a catalyst, good yield was obtained (Table 1 entry-10). It has been also found that in presence of NH₄OH or H₂SO₄ as a catalyst and water as solvent reaction did not get any product after refluxing for 2-6 hrs (Table 1 entries- 3, 7). If the reaction is carried out in presence of NH₄OH as a catalyst and 50% ethanol or absolute ethanol afforded

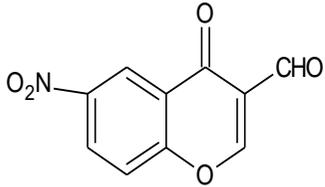
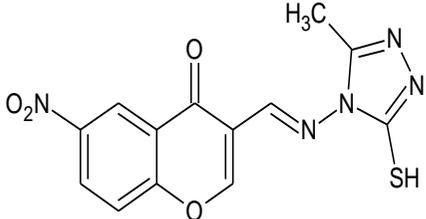
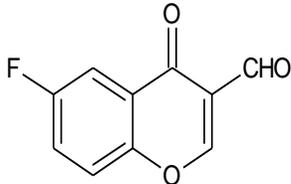
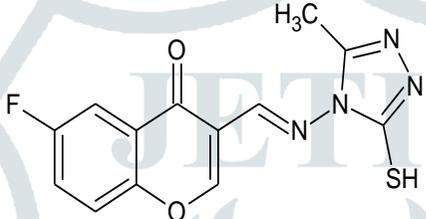
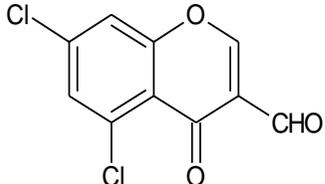
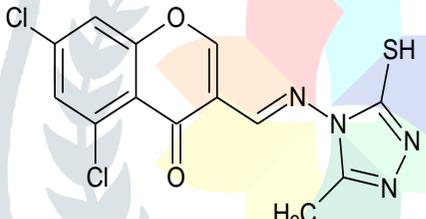
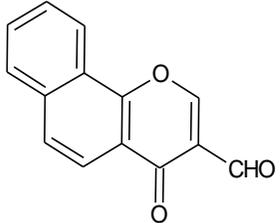
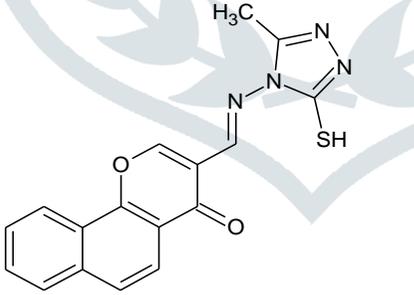
trace amount of yield (Table 1 entries-4 ,5). However good yield was obtained when the reaction is carried out in presence of H_2SO_4 or CH_3COOH as a catalyst and toluene as a solvent (Table 1 entries-11, 12). Though good yield is obtained when the reaction is carried out in presence of H_2SO_4 as a catalyst and absolute ethanol as a solvent (Table 1 entry-9), but on the basis of time required and hazards of H_2SO_4 , we have selected acetic acid as a catalyst and methanol as a solvent (Table 1 entry-13). Low yield was observed when the reaction is carried out in toluene in presence of NH_4OH catalyst (Table 1, entry 6). However moderate yield was observed by performing the reaction in 50% ethanol using H_2SO_4 catalyst (Table 1, entry 8).

Moreover, increase in reaction time did not show any effect on the yield of the product. In our protocol, we initiated our studies by employing a trial reaction in which the condensation reaction was carried out by reacting 6-fluoro-4-oxo-4*H*-1-benzopyran-3-carbaldehyde (1 mmol) with 4-amino-5-methyl-4*H*-1, 2, 4-triazole-3-thiol (1 mmol) in presence of acetic acid as a catalyst and methanol as a solvent by refluxing for 3 hrs. The formation of title compound MP-5 was confirmed by IR, ^{13}C NMR and mass spectra. IR spectrum shows the peaks at 3065 cm^{-1} is due to (C-H str), 1625 cm^{-1} due to (CH=N str), 1242 cm^{-1} due to (C-S str), 1531 cm^{-1} due to (C=C str) and 2760 cm^{-1} is due to (-SH). In 1H NMR spectrum shows chemical shifts at δ 2.33 (s, 3H, CH_3), 7.42-7.79 (m, 3H, Ar-H), 10.43 (s, 1H, N=CH), 8.70 (s, 1H, CH), 13.36 (s, 1H, SH). In ^{13}C NMR spectrum chemical shifts at δ 11.10, 110.65, 110.88, 117.49, 121.08, 121.16, 122.72, 122.97, 125.25, 125.33, 148.69, 152.46, 154.23, 156.24, 158.72, 161.19, 161.90, 174.34 were observed. Appearance of $[M+H]^+$ at m/z 305.0495 in mass spectrum was also in good agreement with the proposed structure.

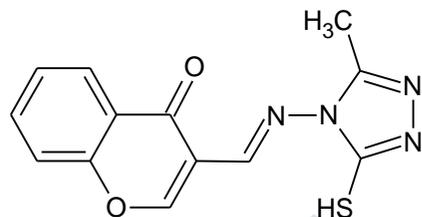
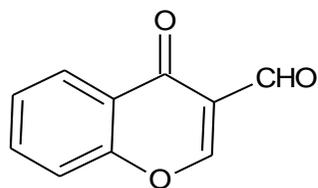
To ensure the scope and utility of catalyst and solvent for the synthesis of derivative of 4-oxo-4*H*-1-benzopyran-3-carbaldehyde, the reaction were carried out between different substituted 4-oxo-4*H*-1-benzopyran-3-carbaldehyde with 4-amino-5-methyl-4*H*-1, 2, 4-triazole-3-thiol using acetic acid as a catalyst in methanol at reflux temperature and the physical data is summarized in **Table 2**.

Table 2 Physical data of derivative of 4-oxo-4H-1-benzopyran-3-carbaldehyde

Entry	Aldehyde	Product	Time (min)	Yield (%)	M.P. (°C)
MP 1			240	80.53	219-220
MP 2			240	81.66	224-226
MP 3			190	81.42	230-231

MP 4			180	86.10	240-242
MP 5			180	82.56	251-252
MP 6			180	83.06	235-237
MP 7			210	78.40	221-222

MP 8



200

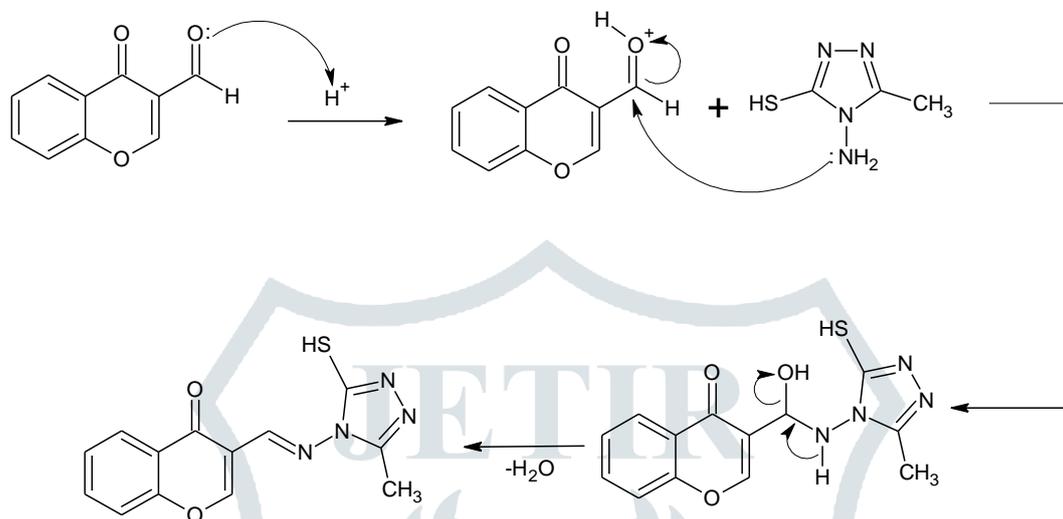
74.67

211-212



From the analysis of reaction data (Table 2), it is found that electron withdrawing group on aldehyde is favorable for this transformation because they exhibit higher yield of product and also require less time for completion of reaction. However, electron donating group on aldehyde exhibit slightly lower yield and also require more time for completion of reaction. The entire synthesized compounds were characterized by ^1H NMR, IR, ^{13}C NMR and mass spectroscopic techniques. The plausible reaction mechanism for formation of Schiff base is shown in Scheme 3.

Scheme 3



3.1 Pharmacology

3.1.1 *In vitro* anti-inflammatory activity

The anti-inflammatory activity was measured by protein denaturation method. The reaction mixture (10 mL) consists of 0.4 mL of egg albumin (from fresh hen egg), 5.6 mL of phosphate buffered saline (PBS, pH 6.4) and 4 mL of synthetic derivatives (1 mM). Similar volume of double-distilled water was used as control. Then the mixtures were incubated at $(37\text{ }^\circ\text{C} \pm 2)$ in an incubator for 15 minutes and then heated at $70\text{ }^\circ\text{C}$ for 5 minutes. After cooling, the absorbance was measured at 660 nm. Diclofenac sodium (1 mM) was used as reference drug and treated similarly for determination of absorbance. The percentage inhibition of protein denaturation was calculated by using the formula,

$$\% \text{ Inhibition} = 100 \times \frac{V_t}{V_c - 1}$$

Where,

V_t = absorbance of test sample.

V_c = absorbance of control.

Anti-inflammatory activities of 4-oxo-4H-1-benzopyran-3-carbaldehyde derivatives

The graphical representation of in-vitro anti-inflammatory activities for derivatives of 4-oxo-4H-1-benzopyran-3-carbaldehyde at (1mM) is shown in fig. 1. From fig. 1 it is found that compounds MP 2 and MP 3 demonstrate excellent activity while compounds MP 4, MP 6 and MP 8 show moderate activity. It reveals that methyl or chloro group at para position exhibit excellent activity.

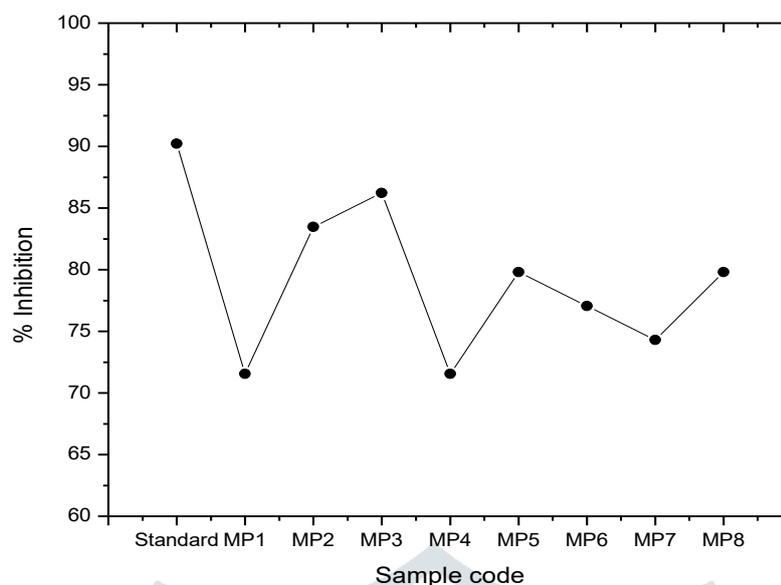


Fig. 1 Graphical representation of in-vitro anti-inflammatory activities for derivatives of 4-oxo-4H-1-benzopyran-3-carbaldehyde at (1mM)

3.1.2 Antioxidant activity

The molecule 1, 1-diphenyl-2-picrylhydrazyl (a,a-diphenyl-bipicrylhydrazyl; DPPH) is characterized as a stable free radical by virtue of the delocalization of the spare electron over the molecule as a whole, so that the molecule does not dimerize, as would be the case with most other free radicals. The delocalization of electron also gives rise to the deep violet color, characterized by an absorption band in ethanol solution centered at about 517 nm. When a solution of DPPH is mixed with that of a substrate (AH) that can donate a hydrogen atom, then this gives rise to the reduced form with the loss of this violet color. The ability of synthesized compounds to scavenge DPPH radical was assessed using reported method [37, 38] with modification. Briefly, 1 ml of synthesized compounds as 1 mM was mixed with 3.0 mL DPPH (0.5 mmol/L in methanol), the resultant absorbance was recorded at 517 nm after 30 minutes incubation at 37°C. The percentage of scavenging activity was derived using the formula,

$$\% \text{ inhibition} = \frac{A_{\text{control}} - A_{\text{sample}}}{A_{\text{control}}} \times 100$$

Where,

A control - absorbance of DPPH

A sample - absorbance of reaction mixture (DPPH with Sample).

Antioxidant activity of 4-oxo-4H-1-benzopyran-3-carbaldehyde derivatives

The graphical representation of in-vitro antioxidant activity for derivative of 4-oxo-4H-1-benzopyran-3-carbaldehyde at (1mM) is shown in fig. 2. From fig. 2 it is found that compounds MP 2 and MP 6 demonstrate excellent activity while remaining compounds shows moderate activity.

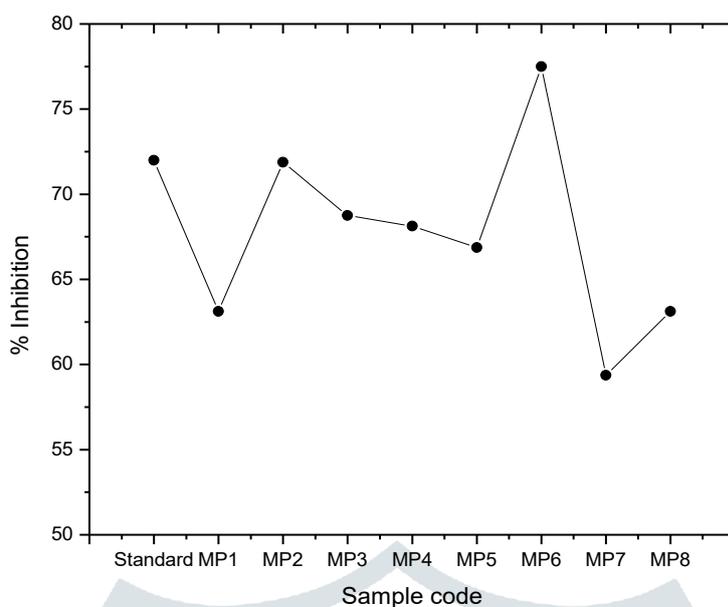


Fig. 2 Graphical representation of in-vitro anti-oxidant activity for derivatives of 4-oxo-4H-1-benzopyran-3-carbaldehyde at (1mM).

4.0 Conclusion

A series of some 2-*[(Z)-[(3-methyl-5-sulfanyl-4H-1,2,4-triazol-4-yl)imino]methyl]-4H-chromen-4-ones* were synthesized and characterized by proton NMR, ¹³C NMR, IR, mass spectroscopy technique. The synthesized compounds were screened for their antioxidant and anti-inflammatory activities. Compounds MP 2 and MP 6 demonstrate excellent antioxidant activity while remaining compounds show moderate activity. Compounds MP 2 and MP 3 demonstrate excellent anti-inflammatory activity while compounds MP 4, MP 6 and MP 8 show moderate activity. The compounds having methyl or chloro group at para position exhibit excellent activity. 1,2,4-Triazole is one of the biological nucleus moiety present in all molecule contributing to the net biological activities of synthesized compounds.

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