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Synthesis and anti-inflammatory activity of 2-oxo-2*H*-chromenyl and 2*H*-chromenyl-5-oxo-2,5-dihydrofuran-3-carboxylates

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ABSTRACT

Cycloaddition reaction of 4-chloro-2-oxo-2*H*-chromene-3-carbaldehydes (**3a-g**) and 4-chloro-2*H*-chromene-3-carbaldehydes (**7a-h**) with activated alkynes (**4a-b**) provided the 2-oxo-2*H*-chromenyl-5-oxo-2,5-dihydrofuran-3-carboxylates (**5a-n**) and 2*H*-chromenyl-5-oxo-2,5-dihydrofuran-3-carboxylates (**8a-p**). All the prepared compounds were screened for anti-inflammatory activity. In vitro anti-inflammatory activity data demonstrated that the compounds **5g**, **5i**, **5k-l** and **8f** are effective among the tested compounds against TNF-α (1.108±0.002, 0.423±0.022, 0.047±0.001, 0.070±0.002 and 0.142±0.001 µM) in comparison with standard compound Prednisolone (0.033±0.002 µM). Based on *in vitro* results, three compounds (**5i**, **5k** and **8f**) have been selected for *in vivo* experiments and these compounds are identified as better compounds with respect to anti-inflammatory activity in LPS induced mice model. Compound **5i** was identified as potent and showed significant reduction in TNF-α and IL-6.

Furanones (butenolides) are important heterocyclic compounds[1-2] having unsaturated γ-lactone ring system found to be an essential subunit in natural products (Fig.1). These compounds have been displayed broad range of medicinal and pharmaceutical properties such as anti-microbial, anti-cancer, anti-inflammatory, anti-malarial, anti-viral, anti-oxidant, anti-convulsant, anti-ulcerative, anti-psychotic and anti-tuberculosis. Geiparvarin, Ascorbic acid, Inotilone, Rubrolide-O, Firocoxib and Rofecoxib are important molecules having furanone moiety (Fig.1) displayed anti-tumor, anti-oxidant and anti-inflammatory activities[1]. Therefore, the furanone moiety had the immense importance and the preparations of furanone containing novel heterocyclic compounds are worth to carry out the research.

On the other hand, coumarins are important natural products[3] and privileged heterocyclic compounds associated with various biological activities namely anti-coagulant, anti-cancer, anti-viral, anti-oxidant, anti-microbial and anti-inflammatory properties[4-9]. Due to the importance of coumarins, our research group focused work on coumarins and prepared various novel coumarin heterocyclic compounds[10-13]. The author research group

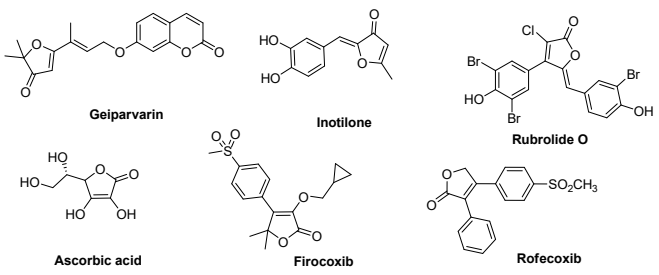

Figure 1. Important molecules with Furanone moiety.

prepared 4-chloro-2-oxo-2*H*-chromene-3-carbaldehydes based compounds such as *Knoevenagel* derivatives, 6*H*-chromenoquinolinones[14] and 2-oxo-2*H*-chromenylpyrazolecarboxylates[10]. We identified 2*H*-chromenylpyrazolecarboxylate compounds as potential anti-cancer agents with better photophysical properties[10]. Author research group also worked on 4-chloro-2*H*-chromene-3-carbaldehydes and prepared useful heterocyclic compounds such as 2*H*-chromenylphenyloxazolones[15], 2*H*-chromenylmethylene benzohydrazides[16] and chromenyldihydropyridines[17].

The furanone moieties coupled with the coumarins to obtain novel heterocyclic compounds have not been explored and moreover, biological profiles of these compounds are also had not been studied. Therefore, the present research work has been

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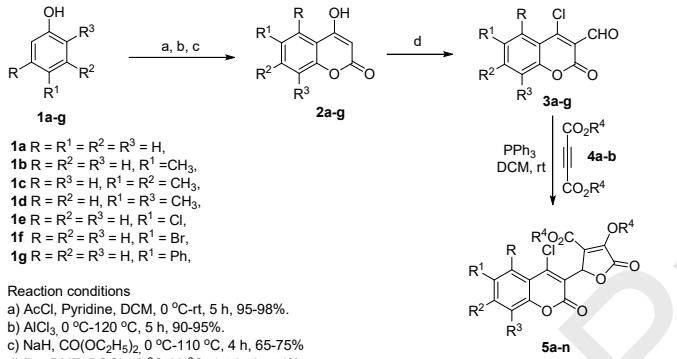
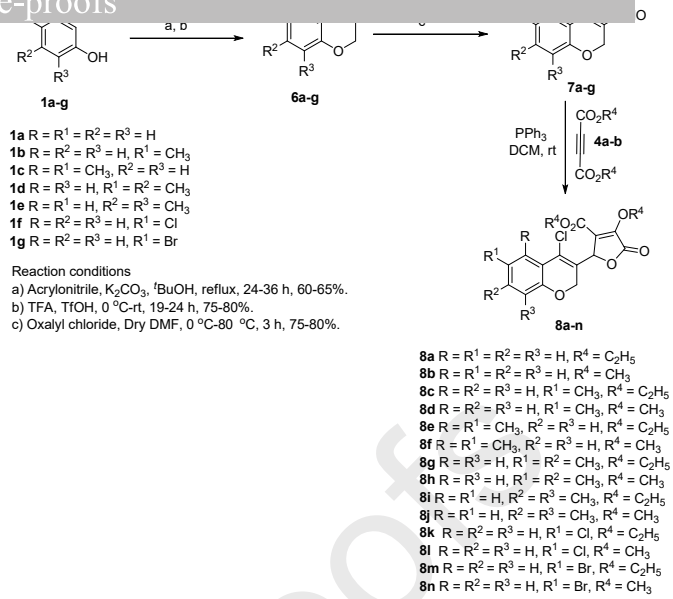
cycloaddition reaction of 4-chloro-2-oxo-2*H*-chromene-3-carbaldehydes[10,18] and 4-chloro-2*H*-chromene-3-carbaldehydes[15-17] with activated alkynes. The target compounds were evaluated for anti-inflammatory activity for the first time and the results were discussed below.

Scheme I describes the preparation of target compounds 2-oxo-2*H*-chromenyl-5-oxo-2,5-dihydrofuran-3-carboxylates **5a-n**. The required starting materials 4-chloro-2-oxo-2*H*-chromene-3-carbaldehydes **3a-g** were prepared starting from phenols **1a-g**. The acetylation of phenols **1a-g** with acetyl chloride in the presence of pyridine in dry DCM provided the phenyl acetates. The Fries rearrangement of phenyl acetates in presence of $AlCl_3$ at 120 °C and subsequent reaction with diethyl carbonate in the presence of NaH in one-step provided the 4-hydroxycoumarins **2a-g**. Vilsmeier-Haack reaction (VH) of **2a-g** in the presence of $POCl_3$ and dry DMF provided 4-chloro-2-oxo-2*H*-chromene-3-carbaldehydes **3a-g**. [3+2] Cycloaddition reaction[19-20] of **3a-g** with activated alkynes **4a-b** in the presence of PPh_3 in dry DCM provided the series of target compounds **5a-n** (Table 1, Scheme I).[21] All the prepared compounds are unknown and characterized by spectral data (SI).



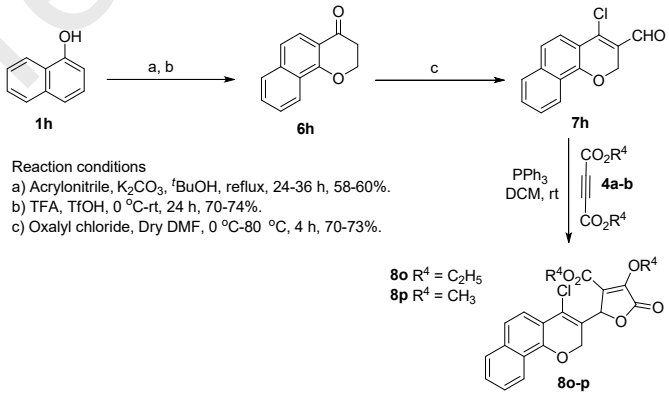
Scheme 1 Preparation of 2-oxo-2*H*-chromenyl-5-oxo-2,5-dihydrofuran-3-carboxylates **5a-n**.

Next, we have prepared another set of target compounds 2*H*-chromenyl-5-oxo-2,5-dihydrofuran-3-carboxylates **8a-p** and depicted in scheme II (Table 2). The Michael addition of phenols **1a-g** with acrylonitrile in the presence of K_2CO_3 in *tert*.butanol under reflux conditions and subsequent reaction with trifluoroacetic acid in presence of trifluoromethanesulfonic acid at room temperature provided the corresponding chroman-4-ones **6a-g**. Chroman-4-ones **6a-g** under VH reaction conditions with oxalyl chloride in dry DMF provided the corresponding 4-chloro-2*H*-chromene-3-carbaldehydes **7a-g**. Thus obtained carbaldehydes **7a-g** were subjected to [3+2] cycloaddition reaction with activated alkynes **4a-b** and provided the target compounds **8a-n** (Scheme II, Table 2).



Scheme 2 Preparation of 2*H*-chromenyl-5-oxo-2,5-dihydrofuran-3-carboxylates **8a-n**.

Further, the naphthyl based target compounds **8o-p** also prepared as per the Scheme III under our optimized reaction conditions starting from naphthalen-1-ol **1h** (Table 2).[22] All the prepared compounds **8a-p** are unknown and characterized by spectral data (see SI).



Scheme 3 Preparation of 2*H*-benzochromenyl-5-oxo-2,5-dihydrofuran-3-carboxylates **8o-p**.

Thus prepared target compounds **5a-n** and **8a-p** were evaluated for anti-inflammatory activity based on inhibition of TNF-α and IL-6 (enzyme-linked immunosorbent assay, ELISA).[23] From the *in vitro* anti-inflammatory activity profiles of the target compounds, two compounds of 2-oxo-2*H*-chromenyl-5-oxo-2,5-dihydrofuran-3-carboxylates **5i**, **5k** and one 2*H*-chromenyl-5-oxo-2,5-dihydrofuran-3-carboxylate **8f** compound have been chosen for *in vivo* animal experiments using LPS induced mice model. The biological activity results were discussed below.

In vitro anti-inflammatory activity results of 2-oxo-2*H*-chromenyl-5-oxo-2,5-dihydrofuran-3-carboxylates **5a-n** were tabulated in Table 1 and were compared with the standard drug prednisolone. The percent viability of the tested compounds **5a-n** were assessed at 20 μM on U937 cell line, which displayed

viab ... sent compounds **5a-n** were measured at 20 µM on TNF-α and IL-6. The compounds have shown inhibition of TNF-α in the range of 14.8-97.1% with respect to prednisolone (98.0%), whereas, we could not observe the inhibition against IL-6. The IC_{50} values were calculated for five compounds **5g** and **5i-l** based on % inhibition and were found to be in the range of 0.047-6.243 µM with respect to prednisolone (IC_{50} 0.033 µM).

The structure activity relationships of the target compounds denoted that the compounds **5a-f** could not show the activity which may be due to the presence of methyl groups present on coumarin at 6th and 8th positions displayed the activity (**5g,** IC_{50} 1.108 µM). It is also observed that the ethoxy group present on furanone **5g** has shown the activity when compared to methoxy group **5h**. The chloro substitution on coumarin with ethoxy group on furanone **5i** (IC_{50} 0.423 µM) has displayed better activity when compared to methoxy compound **5j** (IC_{50} 6.243 µM). The bromo substituted coumarin compounds **5k** (IC_{50} 0.047 µM) and **5l** (IC_{50} 0.070 µM) have shown potent activity in comparison with the standard prednisolone (IC_{50} 0.033 µM). The phenyl

Table 1 2-Oxo-2*H*-chromenyl-5-oxo-2,5-dihydrofuran-3-carboxylates and anti-inflammatory activity profiles of **5a-n.**

S.No.	Compound	R	R^1	R^2	R^3	R^4	Yield (%)	U937 Cellline	TNF-α	
								%Viability at 20 µM	% Inhibition at 20 µM	**IC_{50} (µM)**
1	**5a**	H	H	H	H	C_2H_5	68	75.9	40.7	---
2	**5b**	H	H	H	H	CH_3	64	78.3	27.1	---
3	**5c**	H	CH_3	H	H	C_2H_5	65	79.8	32.3	---
4	**5d**	H	CH_3	H	H	CH_3	64	84.3	14.8	---
5	**5e**	H	CH_3	CH_3	H	C_2H_5	69	79.0	26.8	---
6	**5f**	H	CH_3	CH_3	H	CH_3	71	75.9	34.9	---
7	**5g**	H	CH_3	H	CH_3	C_2H_5	63	96.8	80.2	1.108 ± 0.002
8	**5h**	H	CH_3	H	CH_3	CH_3	66	86.1	44.9	---
9	**5i**	H	Cl	H	H	C_2H_5	46	90.7	97.1	0.423 ± 0.022
10	**5j**	H	Cl	H	H	CH_3	49	93.1	75.0	6.243 ± 0.120
11	**5k**	H	Br	H	H	C_2H_5	48	83.0	91.0	0.047 ± 0.001
12	**5l**	H	Br	H	H	CH_3	41	85.3	76.9	0.070 ± 0.002
13	**5m**	H	Ph	H	H	C_2H_5	62	83.1	20.0	---
14	**5n**	H	Ph	H	H	CH_3	64	82.3	44.2	---
	Prednisolone (1µM)								**98.0**	**0.033 ±0.0021**

Table 2 2*H*-Chromenyl-5-oxo-2,5-dihydrofuran-3-carboxylates and anti-inflammatory activity profiles of **8a-p.**

S.No.	Compound	R	R^1	R^2	R^3	R^4	Yield (%)	U937 Cellline	TNF-α	
								%Viability at 20 µM	% Inhibition at 20 µM	**IC_{50} (µM)**
1	**8a**	H	H	H	H	C_2H_5	76	88.9	50.6	---
2	**8b**	H	H	H	H	CH_3	74	88.1	95.5	18.67 ± 0.01
3	**8c**	H	CH_3	H	H	C_2H_5	79	81.6	6.40	---
4	**8d**	H	CH_3	H	H	CH_3	75	88.5	35.6	---
5	**8e**	CH_3	CH_3	H	H	C_2H_5	76	85.2	29.7	---
6	**8f**	CH_3	CH_3	H	H	CH_3	73	92.1	70.4	0.142 ± 0.001
7	**8g**	H	CH_3	CH_3	H	C_2H_5	81	93.4	96.1	11.19 ± 1.26
8	**8h**	H	CH_3	CH_3	H	CH_3	78	90.7	49.7	---
9	**8i**	H	H	CH_3	CH_3	C_2H_5	82	89.9	23.3	---
10	**8j**	H	H	CH_3	CH_3	CH_3	79	93.8	45.7	---
11	**8k**	H	Cl	H	H	C_2H_5	67	79.4	75.9	10.612 ± 0.025
12	**8l**	H	Cl	H	H	CH_3	65	84.6	19.4	---
13	**8m**	H	Br	H	H	C_2H_5	67	87.2	73.3	3.261 ± 0.23
14	**8n**	H	Br	H	H	CH_3	63	94.3	80.2	13.026 ± 1.56
15	**8o**	---	---	---	---	C_2H_5	78	83.6	4.10	---
16	**8p**	---	---	---	---	CH_3	76	80.2	29.1	---
	Prednisolone (1µM)								**98.0**	**0.033 ±0.0021**

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activity. Based on above observations, the electron withdrawing groups present on coumarin **5i**, **5k-l** displayed potent anti-inflammatory activity when compared to electron donating groups **5g**.

In vitro anti-inflammatory activity results of 2*H*-chromenyl-5-oxo-2,5-dihydrofuran-3-carboxylates **8a-p** were tabulated in Table 2 and were compared along with standard drug prednisolone. The % viability of all the target compounds was measured at 20 µM on U937 cell line which displayed the viability ranging from 79.4 to 94.3%. The % inhibitions of the compounds **8a-p** were measured at 20 µM on TNF-α and IL-6. The compounds have shown the anti-inflammatory activity for TNF-α in the range of 4.1-95.5% with respect to prednisolone (98.0%), whereas we could not observe the activity on IL-6. The IC_{50} values were calculated for six compounds **8b, 8f-g**, **8k** and **8m-n** based on % inhibition and were found to be in the range of 0.142-18.67 µM with respect to prednisolone (IC_{50} 0.033 µM). The structure activity relationships of the target compounds denoted that the compound **8b** (IC_{50} 18.67 µM) has shown moderate activity due to the presence of methoxy group present on furanone moiety when compared to **8a**. The methyl group present on coumarins **8c-d** at 6th position could not show the activity. The methyl groups present on coumarin **8f** at 5th and 6th positions and methoxy group present on furanone (IC_{50} 0.142 µM) have shown potent anti-inflammatory activity when compared to its ethoxy group **8e**. The methyl groups present on coumarin at 6th and 7th positions **8g-h** and the change of methyl position at 7th and 8th **8i-j** could not show the activity, however compound **8g** (IC_{50} 11.19 µM) has shown moderate activity. The chloro substitution on coumarin with ethoxy group present on furanone **8k** (IC_{50} 10.612 µM) has shown moderate activity when compared to methoxy group **8l**. The bromo substituted coumarin compound **8m** (IC_{50} 3.261 µM) having ethoxy group on furanone has shown potent activity when compared to methoxy group **8n** (IC_{50} 13.026 µM). The 2*H*-benzo[*h*]chromen-3-ylcompounds **8o** and **8p** could not show the activity. The electron donating groups present on coumarin **8f** has shown the potent activity when compared to electron withdrawing group **8m**.

Having achieved the *in vitro* results, next, we carried out the *In vivo* anti-inflammatory activity on the identified compounds employing LPS challenged mouse model. LPS has been implicated as an important pathogenic factor for the induction of sepsis, which is characterized by an inflammatory cytokine storm.[24-26] Hence, *in vivo* anti-inflammatory activity of compounds **5i, 5k** and **8f** were evaluated against LPS induced cytokine expression in Balb/c mice. The challenge with LPS in mice showed significant (P<0.001) increase in TNF-α (Fig.2) and IL-6 (Fig.3) levels in LPS alone group compared to the vehicle control group of animals (P<0.001). In the treatment groups, mice were pre-treated with the test compounds **5i, 5k** and **8f** at a dose of 100 mg/kg for three consecutive days followed by LPS challenge (10 mg/kg, IP).

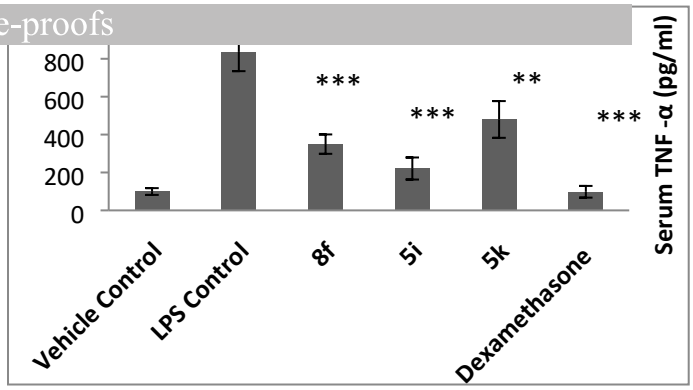

Figure 2. Effect of test compounds on LPS induced serum inflammatory cytokine expression. Graph represents the serum TNF-α level of different test groups in balb/c mice. All values are expressed as mean ± S.E.M, n = 5.
P<0.001compared to Vehicle control,
*** P<0.001compared to LPS Control,
** P<0.001compared to LPS Control.

The results indicated that the test compounds **5i** and **8f** have displayed significant (P<0.001) inhibition in the TNF-α levels and in IL-6 levels (P<0.001) when compared to those in LPS control animals. Hence, based on *in vivo* experiments, compound **5i** is considered as promising lead molecule to treat the inflammatory disease in present series of the compounds.

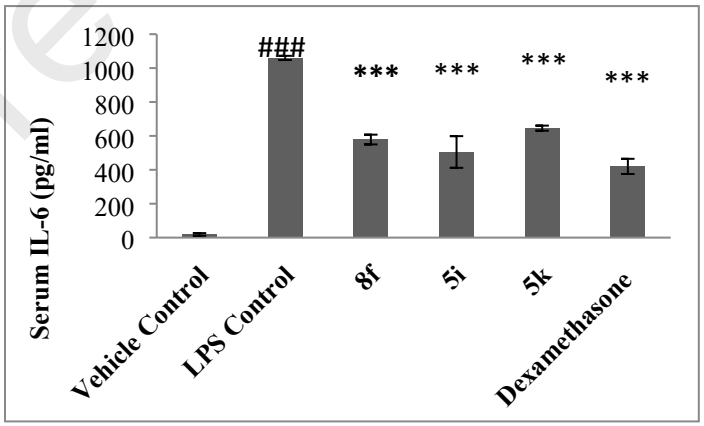

Figure 3. Effect of test compounds on LPS induced serum inflammatory cytokine IL-6. Graph represents the serum IL-6 level of different test groups in balb/c mice. All values are expressed as mean ± S.E.M, n = 5.
P<0.001compared to Vehicle control
*** P<0.001compared to LPS Control

Over all, among the present series of compounds, compounds **5g** and **8f** were having the methyl substitution and compounds **5i**, **5k-l** and **8m** having chloro/bromo substitutions have shown the anti-inflammatory activity (in vivo) and among these, **5i** was identified as the most potent compound. Four compounds in 5 series and 2 compounds in 8 series have shown the activity. It is observed that the 2-oxo-2*H*-chromenyl-5-oxo-2,5-dihydrofuran-3-carboxylates were identified as better compounds when compared to 2*H*-chromenyl-5-oxo-2,5-dihydrofuran-3-carboxylates.

In conclusion, two series of compounds such as 2-oxo-2*H*-chromenyl-5-oxo-2,5-dihydrofuran-3-carboxylates **5a-n** and 2*H*-

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prepared by cycloaddition reaction. These compounds were not reported earlier in the literature with synthetic methodology and the assignment of the in vitro and in vivo anti-inflammatory activity to all of the target compounds in this report is new aspect. In vitro anti-inflammatory activity data demonstrated that the compounds **5g**, **5i**, **5k-l** and **8f** are effective among the tested compounds against TNF-α. Three compounds (**5i**, **5k** and **8f**) are identified as better compounds with respect to anti-inflammatory activity in LPS induced mice model. The compound **5i** was identified as the most effective in the LPS induced sepsis model in mice which has demonstrated significant reduction in both TNF-α and IL-6 levels. Therefore, we consider the coumarin coupled with furanone moiety as a lead compound for anti-inflammatory activity which can be explored further.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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21. *General procedure for the preparation of ethyl 2-(4-chloro-2-oxo-2H-chromen-3-yl)-4-ethoxy-5-oxo-2,5-dihydrofuran-3-carboxylates* (**5a-n**): Diethyl but-2-ynedioate (**4a**, 1.5 equiv.) was added to a stirred solution of the 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde (**3a**, 1 equiv.) in DCM at room temperature and followed by Triphenylphosphine (1.5 equiv.). The contents were stirred at room temperature and the reaction was monitored by TLC (2 h). After completion of the reaction, the solvent was removed under reduced pressure. The residue was purified by column chromatography using silica gel (60:120, ethyl acetate/hexane 5:95) afforded compound **5a** in 68% as colourless solid. The remaining 2-oxo-2*H*-chromenyl-2,5-dihydrofuran-3-carboxylates **5b-n** were prepared by the reaction of 4-chloro-2-oxo-2*H*-chromene-3-carbaldehydes **3b-g** with diethyl/methyl but-2-ynedioate **4a-b** under our optimized reaction conditions. The newly prepared compounds **5a-n** have been characterized by spectral data. *Ethyl 2-(4-chloro-2-oxo-2H-chromen-3-yl)-4-ethoxy-5-oxo-2,5- dihydrofuran-3-carboxylate* (**5a**): Yield: 68%; 2 h; colourless solid; mp 156-158 °C. IR (KBr): 3420, 2924, 2854, 1740, 1724, 1651, 1600, 1565, 1427, 1386, 1297, 1181, 1015 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.96 (t, J = 8.8 Hz, 1H, aromatic), 7.65 (t, J = 7.7 Hz, 1H, aromatic), 7.41 (t, J = 7.6 Hz, 1H, aromatic), 7.38-7.34 (m, 1H, aromatic), 6.59 (s, 1H, CH), 4.95-4.62 (m, 2H, OCH_2), 4.18 (q, J = 7.1 Hz, 2H, OCH_2), 1.45 (t, J = 7.0 Hz, 3H, CH_3), 1.20 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.60, 160.91, 156.97, 152.14, 150.06, 149.88, 133.72, 126.28, 125.06, 119.36, 118.99, 117.88, 116.83, 73.98, 69.06, 61.20, 15.52, 13.92 ppm. MS (ESI): (*m/z*) 379 $[M+H]^+$. HRMS (ESI): (*m/z*)calcd for $C_{18}H_{16}O_7Cl$ $[M+H]^+$ 379.0585, Found: 379.0564.
22. *General procedure for the preparation of ethyl 2-(4-chloro-2H-chromen-3-yl)-4-ethoxy-5-oxo-2,5-dihydrofuran-3-carboxylate* (**8a-p**): Diethyl but-2-ynedioate (**4a**, 1.5 equiv.) was added to a stirred solution of 4-chloro-2*H*-chromene-3-carbaldehyde (**7a**, 1 equiv.) in DCM at room temperature followed by Triphenylphosphine (1.5 equiv.). The contents were stirred at room temperature and the reaction was monitored by TLC (2 h). After completion of the reaction, the solvent was removed under reduced pressure. The residue was purified by column chromatography using silica gel (60:120, ethyl acetate/hexane 5:95) afforded compound **8a** in 76% as colourless solid. The remaining target4-chloro-2*H*-chromenyl-2,5-dihydrofuran-3-carboxylates **8b-p** were prepared by the reaction of 4-chloro-chromene-3-arbaldehydes **7b-h** with diethyl/methyl but-2-ynedioate **4a-b** under our optimized reaction conditions. The newly prepared compounds **8a-p** were characterized by spectral data. *Ethyl 2-(4-chloro-2H-chromen-3-yl)-4-ethoxy-5-oxo-2,5-dihydrofuran-3-carboxylate* (**8a**): Yield: 76%; 2 h; colourless solid; mp 170-172 °C. IR (KBr): 2983, 2926, 1776, 1721, 1649, 1610, 1565, 1465, 1346, 1297, 1214, 1116 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.55 (dd, J = 7.8, 1.5 Hz, 1H, aromatic), 7.26-7.25 (m, 1H, aromatic), 7.02-6.85 (m, 1H, aromatic), 6.85 (dd, J = 8.1, 0.9 Hz, 1H, aromatic), 6.34 (s, 1H, CH), 4.74-4.65 (m, 2H, OCH_2), 4.46-4.49 (m, 2H, OCH_2), 4.22 (q, J = 7.1 Hz, 2H, OCH_2), 1.43 (t, J = 7.0 Hz, 3H, CH_3), 1.22 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.12, 160.58, 154.52, 148.65, 131.29, 130.29, 125.56, 121.94, 121.23, 121.18, 119.47, 116.00, 75.36, 69.17, 63.99, 61.54, 15.37, 13.93 ppm. MS (ESI): (*m/z*) 365 $[M+H]^+$. HRMS (ESI): (*m/z*)calcd for $C_{18}H_{18}O_6Cl$ $[M+H]^+$ 365.0792, Found: 365.0786.
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Synthesis and anti-inflammatory activity of 2-oxo-2*H*-chromenyl and 2*H*-chromenyl-5-oxo-2,5-dihydrofuran-3-carboxylates

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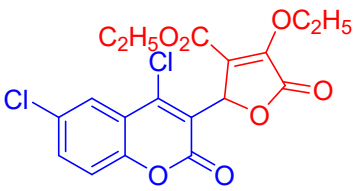
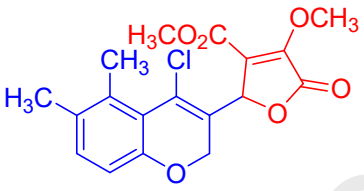


5i, IC_{50} 0.423±0.022 μM



8f, IC_{50} 0.142±0.001 μM

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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