# An Organo-Catalyst Mediated Synthesis of Chalcones of Dehydroacetic Acid and Determination of Their Anti-Oxidant Activity.

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**Abstract:**

A diverse series of chalcones of dehydroacetic acid were synthesized and subjected to antioxidant activity. Highest DPPH scavenging effect was observed in case of HR **4** displaying $IC_{50}$ of 4.18 mg/ml in comparison to the standard ascorbic acid ($IC_{50}$ 0f 4.04 mg/ml). However, the highest hydroxyl radical scavenging effect was displayed by **HR 25** exhibiting ($IC_{50}$ 10.21). Keeping in view the very low cytotoxicity issues of most of the chalcone derivatives of dehydroacetic acid, this study provides an important aspect with regard to the use of dehydroacetic acid-based derivatives as antioxandts.

**Keywords:** Dehydoacetic acid, Chalcone, Anti-Oxidant, Cytotoxicity, DPPH.

## Introduction:

4-Hydroxy-2-pyrones are the most abundant and biologically most significant class of 2-pyrones [1-3] *e.g.,* Fusapyrone and Deoxyfusapyrone (Figure 1), isolated from the rice cultures of *Fusarium semitectum* [4]. They show considerable anti-fungal activity with high selectivity and low toxicity [5]. 4-Hydroxy-2pyrone represents the active component of naturally isolated anti-TB agents like Pseudo pyronine B [6,7] and Myxopyronin [8,9] and clinically approved anti-HIV agent like Tipranavir [10,11] (Figure 1).

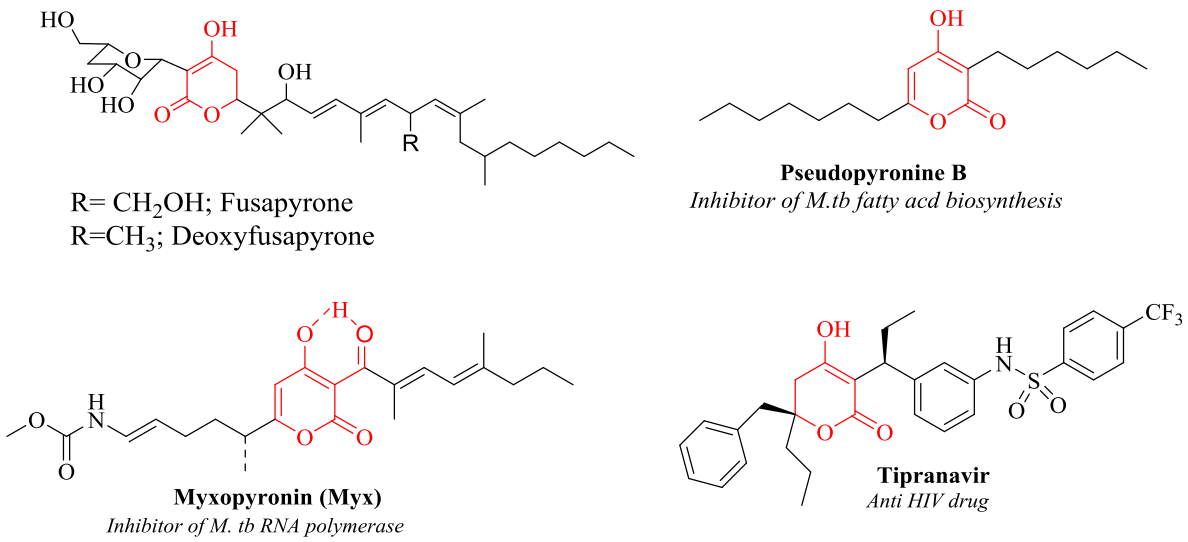



**Figure 1: Some biologically significant 4-hydroxy-2-pyrones**

Chalcones of dehydroacetic acid are well known for their anti-TB [12], anti-cancer[13,14], and anti-microbial [15] and anti-HIV [16] activities. Because of the above-mentioned biological properties, it is envisaged that the chalcone serivatives of dehyroacetic acid could be further investigated to explore its additional biological properties. A thorough literature survey revealed that anti-oxidant properties of chalcones of dehydroacetic acid were yet to be investigated. Keeping this fact in mind as well as our previous work on 2-pyrones [17-20], we directed our studies towards the syntheis of a diverse series of chalcones of dehydroacetic acid of biological interest. All the synthesized analogs were subjected to DPPH and hydroxyl radical scavenging assay to check their anti-oxidant potential. This work provides a report on SAR of chalcones of dehyroacetic acid to come up with analogs having better activity, and improved selectivity.

**Results and discussion**

Chalcones of 3-Acetyl-4-hydroxy-6-methyl-2-pyrone (**1**) were synthesized by classical Clasein Schmidt condensation in good to excellent yields by treating 1 equivalent of (**1**) with aromatic aldehydes (1.1 equiv.) in ethanol in prence of catalytic amount of piperidine. The reaction mixture was heated at 60 $^0$C for 1-4 hours (Figure 2).

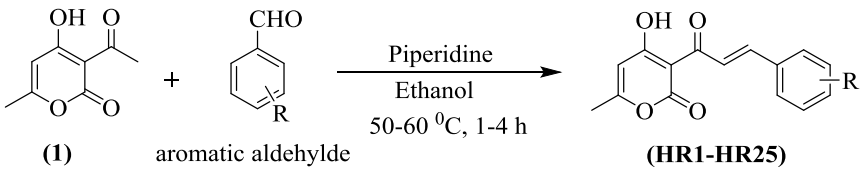
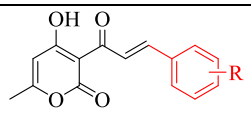
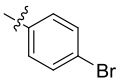
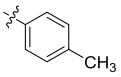
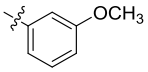
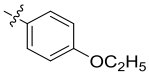
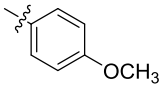
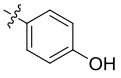
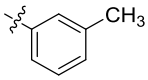
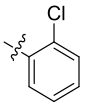
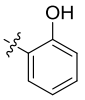
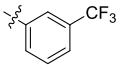
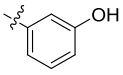
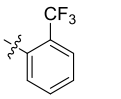
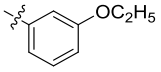
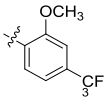
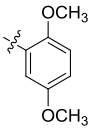
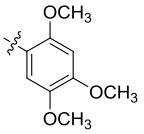
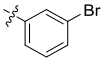
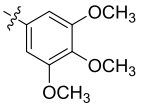
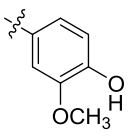



**Figure 2: general reaction for the synthesis of chalcones**

Completion of the reaction was monitored of TLC. After the completion, the desired product was purified by column chromatography technique using Hexane: Ethylacetate as eluent. A library of 25 chalcones (**HR1-HR25**) enlisted in **(Table 1**) were synthesized for biological screening. The products formed were easily confirmed by $^{1}H$ and $^{13}CNMR$ spectra.




Chalcones of 4-Hydroxy pyrones **(HR1-HR25)**

| Compound | Yield (%) | Structure | Compound | Yield (%) | Structure |
|---|---|---|---|---|---|
| **HR 1** | 85 |  | **HR 14** | 77 |  |
| **HR 2** | 81 |  | **HR 15** | 81 |  |
| | 79 |  | **HR 16** | 82 |  |
| **HR 3** | 80 |  | **HR 17** | 79 |  |
| **HR 4** | 78 |  | **HR 18** | 82 |  |
| | 82 |  | | | |
| **HR 5** | 77 |  | **HR 19** | 82 |  |
| | | | **HR 20** | 78 | |
| **HR 6** | 80 |  | **HR 21** | 83 |  |
| **HR 7** | 81 |  | **HR 22** | 80 |  |
| **HR 8** | 82 |  | **HR 23** | 81 |  |
| | 79 |  | **HR 24** | 83 |  |
| **HR 9** | 78 |  | **HR 25** | 80 |  |
| | 80 | | | | |
| **HR 10** | | | | |  |

| | | | | | |
|---|---|---|---|---|---|
| **HR 11**<br><br>**HR 12**<br><br>**HR 13** | | | | | |

**Table 1: Library of synthesized chalcones of 3-Acetyl-4-hydroxy-6-methyl-2-pyrone.**

All the synthesized derivatives were subjected to antioxidant activity using DPPH scavenging assay and Hydroxy radical scavenging assay. To evaluate their DPPH scavenging effect, the derivatives were screened at different concentrations to obtain their $IC_{50}$ values, as shown (Table 2).

Ascorbic acid was used as positive control in this assay. Amongst the synthesied derivatives a notable difference in DPPH scavenging was observed which may be attributed to the type of the aldeyde and position and the type of substituent in the aldehyde used. Amongst the derivatives **HR 4** (4- Hydroxy aldehyde analog) was found to be most active with an $IC_{50}$ of 4.58 although less than the control used but still very comperative. The *ortho*-hydrxy benzaldehyde derivate **HR 19** and *meta*-hydroxy benzaldehyde derivative **HR 20** were less active displaying $IC_{50}$ values of 5.1 mg/ml and 6.9 mg/ml respectively. The next active analog of the series was found to be **HR 25** with an $IC_{50}$ value 4.69. The effect of substituents had hardly any effect on the antioxidant activity. However, the hydroxyl benzaldehyde derivatives were found to comparatively more active than other analogs of aromatic aldehydes. The results have been summed up in table 2.

| S. No | Compound | DPPH Assay<br>$IC_{50}$ (µg/ml) | OH Radical Assay<br>$IC_{50}$ (µg/ml) |
|---|---|---|---|
| 01 | **HR 1** | 8.06 | 82.4 |
| 02 | **HR 2** | 12.23 | 45.4 |
| 03 | **HR 3** | 15.22 | 62.3 |
| 04 | **HR 4** | 4.58 | 13.4 |
| 05 | **HR 5** | 16.7 | 21.2 |
| 06 | **HR 6** | 22.32 | 15.2 |
| 07 | **HR 7** | 15.42 | 23.3 |
| 08 | **HR 8** | 8.67 | 25.4 |
| 09 | **HR 9** | 6.53 | 69.7 |
| 10 | **HR 10** | 10.43 | 56.6 |
| 11 | **HR 11** | 6.33 | 12.3 |
| 12 | **HR 12** | 25.4 | 17.6 |
| 13 | **HR 13** | 6.67 | 19.3 |

| | | | |
|---|---|---|---|
| 14 | **HR 14** | 12.32 | 16.7 |
| 15 | **HR 15** | 9.82 | 66.9 |
| 16 | **HR 16** | 6.34 | 82.3 |
| 17 | **HR 17** | 7.21 | 15.2 |
| 16 | **HR 18** | 5.69 | 36.4 |
| 19 | **HR 19** | 5.14 | 13.5 |
| 20 | **HR 20** | 6.89 | 15.3 |
| 21 | **HR 21** | 7.22 | 35.9 |
| 22 | **HR 22** | 8.21 | 21.4 |
| 23 | **HR 23** | 8.78 | 12.4 |
| 24 | **HR 24** | 8.67 | 13.2 |
| 25 | **HR 25** | 4.69 | 10.2 |

**Table 2. DPPH and OH radical scavenging potential of derivatives of dehydro acetic acid**

These derivatives were further subjected to hydroxyl scavenging effect at different concentrations, the $IC_{50}$ values are shown in (**Table 2**). Again, ascorbic acid was taken as control in this assay. 4-Hydroxy 3- methoxy benzaldehyde derivate **HR 25** of dehyroacetic acid displayed the highest hydroxyl radical scavenging activity with an $IC_{50}$ of 10.21 which is in comparative to the OH radical scavenging value of ascorbic acid. From the table it is clear that the hydroxyl radical scavenging capacity is independent of the nature and position of the substituents. However, it is clear that the hydroxy benzaldehyde substituents have displayed better ability of hydroxyl radical scavenging. All the results have been summed in **Table 2** above.

**Conclusion:**

In coclusion, a diverse series of chalcones of dehroacetic acid (DHA) has been developed using piperidine as catalyst. Among all the derivatives, (E)-4-hydroxy-3-(3-(4-hydroxyphenyl)acryloyl)-6-methyl-2H-pyran-2-one (HR 4) showed the highest DPPH scavenging ($IC_{50}$ of 4.58), while as (E)-4-hydroxy-3-(3-(4-hydroxy-3-methoxyphenyl)acryloyl)-6-methyl-2H-pyran-2-one (HR 25) displayed the best OH radical scavenging with $IC_{50}$

of 10.21 which is very close to the $IC_{50}$ values of ascorbic acid used as standard. Owing to the fact that these chalcones exhibit very low cytotoxity, they show a promising potential in getting expored in food industry.

**Supporting Information:**

Experimental section including synthesis and antioxidant activity of chalcones of dehydroacetic acid, $^{1}H$ and $^{13}CNMR$ spectra of the synthesised compounds can be found associated with this article as supplementary data.

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**Supporting Information**

**General experimental procedures**

All the solvents and reagents for the preparation of the extracts, chemical synthesis and biological assays were purchased from Sigma Aldrich. The chemical reactions were monitored using F254 silica gel TLC plates (E. Merck) with ceric ammonium sulphate as charring agent and UV chamber (366 and 254 nm) for the detection of spots. The synthesized products were purified using column chromatography on silica gel (60–120 mesh). 1H NMR and 13C NMR spectra (chemical shifts expressed in ppm and coupling constants in Hertz) were recorded on Bruker DPX 400 instrument using MeOD as the solvent with TMS as the internal standard. IR was recorded on Cary 630 FT-IR Spectrometer and Mass spectra were carried out on LC–MS 8030 tandem mass spectrometer manufactured by Shimadzu Corporation, Kyoto, Japan. All the compounds were analysed in full scan mode with nitrogen serving as interface gas. Detection was done in ESI mode having probe voltage of 180.0 V, with probe temperature of 400 C.

**Chemicals used:** 2, 2-diphenyl-1-picryl hydrazyl (DPPH), ascorbic acid, dry ferric chloride, ferric nitrate, Potassium ferricyanide (1% w/v), phosphate buffer (0.2 M, pH 6.6), TCA, trichloro acetic acid (10%), ferric chloride (0.1%).

**General procedure for the synthesis of pyrone based chalcone derivatives:**

To a mixture of 3-acetyl-6-methypyron-2-one (1 equiv) and aromatic aldehyde (1 equiv) in ethanol (2 mL), catalytic amount of piperidine was added. The reaction mixture was allowed to stir at 60 $^{o}$C for 1 to 4 hrs. The progress of the reaction was monitored using TLC. After the completion of the reaction as monitored by TLC, ethanol was evaporated and the crude mixture was subjected to column chromatography (petroleum ether/EtOAc) to obtain the desired product.

**Spectral analysis:**

**3-cinnamoyl-4-hydroxy-6-methyl-2H-pyran-2-one (HR 1):**

$^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 15.7 Hz, 1H), 7.94 (d, J = 15.8 Hz, 1H), 7.67 (dd, J=6.5, 2.8 Hz, 2H), 7.39 (dd, J = 11.3, 7.7 Hz, 3H), 5.94 (s, 1H), 2.26 (s, 3H). $^{13}$C NMR (101 MHz,$CDCl_3$) δ 193.04, 183.40, 168.90, 161.44, 146.56, 134.97, 131.33, 129.42 (2 x C), 129.18 (2 xC), 123.25, 102.62, 99.70, 20.87. ESI MS (m/z): 256 $[M+Na]^+$. Anal. Calc. for $C_{15}H_{12}O_4$: C,70.31; H, 4.72; Found C,70.38; H, 4.68.

**(E)-4-hydroxy-6-methyl-3-(3-(p-tolyl)acryloyl)-2H-pyran-2-one (HR 2):**

$^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 15.7 Hz, 1H), 7.98 (d, J = 15.7 Hz, 1H), 7.61 (d, J=7.8 Hz, 2H), 7.32 – 7.22 (m, 2H), 5.97 (s, 1H), 2.42 (s, 3H), 2.30 (s, 3H). $^{13}$C NMR (101 MHz,$CDCl_3$) δ 192.96, 183.50, 168.70, 161.49, 146.83, 142.12, 132.30, 129.95 (2 x C), 129.52 (2 xC), 122.10, 102.71, 99.64, 77.55, 77.23, 76.92, 21.84, 20.84. ESI MS (m/z): 270 $[M+Na]^+$. Anal.Calc. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22; Found C,71.17; H, 5.27.

**(E)-3-(3-(4-ethoxyphenyl)acryloyl)-4-hydroxy-6-methyl-2H-pyran-2-one (HR 3):**

$^{1}$H NMR (400 MHz, CDCl3) δ 8.18 (d, *J* = 15.6 Hz, 1H), 7.94 (d, *J* = 15.7 Hz, 1H), 7.63 (t, *J* =7.8 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.91 (d, *J* = 2.6 Hz, 1H), 4.11 – 4.02 (m, 2H), 2.25 (s, 3H),1.45 – 1.37 (m, 3H). $^{13}$C NMR (101 MHz, CDCl3) δ 192.92, 183.35, 168.68, 161.59, 159.53,146.37, 136.32, 130.10, 123.59, 122.08, 117.89, 114.54, 102.79, 99.82, 63.83, 20.83, 14.98. ESI MS (m/z): 300 $[M+Na]^+$. Anal. Calc. for C17H16O5: C, 67.99; H, 5.37; Found C,70.38; H, 4.68

**(E)-4-hydroxy-3-(3-(4-hydroxyphenyl)acryloyl)-6-methyl-2H-pyran-2-one (HR 4):**

$^{1}$H NMR (400 MHz, DMSO) δ 10.29 (s, 1H, -OH), 8.03 (d, *J* = 15.7 Hz, 1H), 7.90 (d, *J* = 15.7Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.27 (s, 1H), 2.26 (s, 3H). $^{13}$C NMR (101 MHz, DMSO) δ 191.58, 182.76, 169.51, 161.10, 160.59, 146.54, 131.39 (2 x C), 125.41, 118.69, 116.23 (2 x C), 102.03, 98.69, 20.01. ESI MS (m/z): 272 $[M+Na]^+$. Anal. Calc. for C15H12O5: C, 66.17; H, 4.44; Found C,66.12; H, 4.40.

**(E)-3-(3-(furan-2-yl)acryloyl)-4-hydroxy-6-methyl-2H-pyran-2-one (HR 5):**

$^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 15.4 Hz, 1H), 7.70 (d, J = 15.4 Hz, 1H), 7.56 (s, 1H), 6.78 (d, J = 2.3 Hz, 1H), 6.50 (s, 1H), 5.92 (s, 1H), 2.25 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 192.35, 183.41, 168.71, 161.32, 152.07, 146.30, 132.17, 120.68, 117.70, 113.13, 102.68, 99.0, 77.55, 77.23, 76.91, 20.84. C13H10O5 246. ESI MS (m/z): 246 $[M+Na]^+$. Anal. Calc. for $C_{13}H_{10}O_5$: C, 63.42; H, 4.09; Found C,63.47; H, 4.03.

**(E)-4-hydroxy-6-methyl-3-(3-(thiophen-3-yl)acryloyl)-2H-pyran-2-one (HR 6):**

$^{1}$H NMR (400 MHz, CDCl3) δ 8.09 (d, *J* = 15.6 Hz, 1H), 7.93 (d, *J* = 15.6 Hz, 1H), 7.65 (s, 1H), 7.46 (d, *J* = 4.2 Hz, 1H), 7.34 (s, 1H), 5.92 (s, 1H), 2.25 (s, 3H). $^{13}$C NMR (101 MHz, CDCl3) δ 193.10, 183.40, 168.73, 161.44, 139.82, 138.61, 130.69, 127.27, 126.19, 122.90, 102.67, 99.61, 20.83. C13H10O4S 262. ESI MS (m/z): 262 $[M+Na]^{+}$. Anal. Calc. for C13H10O4S: C, 59.53; H, 3.84; Found C,59.58; H, 3.88.

**(E)-4-hydroxy-3-(3-(2-methoxyphenyl)acryloyl)-6-methyl-2H-pyran-2-one (HR 7):**

$^{1}$HNMR (400 MHz, CDCl3) δ 8.35 (s, 2H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.2 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 5.92 (s, 1H), 3.91 (s, 3H), 2.25 (s, 3H). $^{13}$CNMR (101 MHz, CDCl3) δ 193.20, 183.59, 168.55, 161.49, 159.34, 141.96, 132.79, 129.79, 124.01, 123.22, 121.04, 111.42, 102.76, 101.66, 55.78, 20.81. ESI MS (m/z): 268 $[M+Na]^{+}$. Anal. Calc. for C16H14O5: C, 67.13; H, 4.93; Found C,67.17; H, 4.90.

**(E)-4-hydroxy-6-methyl-3-(3-(2-(trifluoromethyl)phenyl)acryloyl)-2H-pyran-2-one (HR 8):**

$^{1}$H NMR (400 MHz, CDCl3) δ 8.27 (bs, 2H), 7.93 (d, *J* = 7.4 Hz, 1H), 7.70 (d, *J* = 7.3 Hz, 1H), 7.59 (t, *J* = 7.0 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 5.96 (s, 1H), 2.27 (s, 3H). $^{13}$CNMR (101 MHz, CDCl3) δ 192.79, 183.15, 169.35, 161.45, 141.05, 132.39, 130.33 (2 x C), 128.84 (2 x C), 127.29, 126.45, 126.39, 102.44, 99.87, 20.92. ESI MS (m/z): 324 $[M+Na]^{+}$. Anal. Calc. for C16H11F3O4: C, 59.27; H, 3.42; Found C,59.21; H, 3.48.

**(E)-4-hydroxy-6-methyl-3-(3-(3-(trifluoromethyl)phenyl)acryloyl)-2H-pyran-2-one (HR 9):**

$^{1}$H NMR (400 MHz, CDCl3) δ 8.32 (d, *J* = 15.8 Hz, 1H), 7.91 (d, *J* = 15.0 Hz, 1H), 7.85 (d, *J* = 7.1 Hz, 2H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 5.96 (s, 1H), 2.27 (s, 3H). $^{13}$CNMR (101 MHz, CDCl3) δ 192.85, 183.17, 169.34, 161.40, 144.15, 135.77, 131.86, 129.70, 127.48, 127.44, 126.10, 126.06, 125.20, 102.44, 99.81, 20.91. ESI MS (m/z): 324 $[M+Na]^{+}$. Anal. Calc. for C16H11F3O4: C, 59.27; H, 3.42; Found C,59.22; H, 3.46.

**(E)-4-hydroxy-6-methyl-3-(3-(4-(trifluoromethyl)phenyl)acryloyl)-2H-pyran-2-one(HR 10):**

$^{1}$HNMR (400 MHz, CDCl3) δ 8.34 (d, *J* = 15.7 Hz, 1H), 7.89 (d, *J* = 15.7 Hz, 1H), 7.75 (d, *J* = 7.2 Hz, 2H), 7.64 (d, *J* = 7.1 Hz, 2H), 5.96 (s, 1H), 2.27 (s, 3H). $^{13}$C NMR (101 MHz, CDCl3) δ 192.87, 183.17, 169.41, 161.39, 143.98, 138.31, 129.34 (2 x C), 126.15, 126.12, 126.08, 126.04, 125.85, 102.43, 99.86, 20.92. ESI MS (m/z): 324 $[M+Na]^{+}$. Anal. Calc. for C16H11F3O4: C, 59.27; H, 3.42; Found C,59.30; H, 3.44.

**(E)-4-hydroxy-3-(3-(2-methoxy-4-(trifluoromethyl)phenyl)acryloyl)-6-methyl-2H-pyran-2-one (HR 11):**

$^{1}$H NMR (400 MHz, CDCl3) δ 8.39 (d, *J* = 15.9 Hz, 1H), 8.24 (d, *J* = 16.0 Hz, 1H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 7.4 Hz, 2H), 7.11 (s, 1H), 5.95 (s, 1H), 3.95 (s, 3H), 2.27 (s, 3H). $^{13}$CNMR (101 MHz, CDCl3) δ 193.17, 183.33, 169.08, 161.44, 158.97, 139.69, 129.88 (2 x C), 127.34, 125.76 (2 x C), 117.72, 108.23, 102.56, 99.86, 56.12, 20.89. ESI MS (m/z): 354 [M+Na]$^{+}$. Anal. Calc. for C17H13F3O5: C, 70.3157.63; H, 3.70; Found C,57.67; H, 3.75.

**(E)-3-(3-(4-bromothiophen-2-yl)acryloyl)-4-hydroxy-6-methyl-2H-pyran-2-one (HR 12):**

$^{1}$H NMR (400 MHz, CDCl3) δ 7.95 (q, *J* = 15.4 Hz, 2H), 7.13 (d, *J* = 3.6 Hz, 1H), 7.04 (d, *J* = 3.7 Hz, 1H), 5.93 (s, 1H), 2.26 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 192.09, 183.27, 168.94, 161.36, 142.36, 137.68, 133.13, 131.72, 122.27, 118.57, 102.59, 99.87, 20.89. ESI MS (m/z): 341 [M+Na]$^{+}$. Anal. Calc. for C13H9BrO4S: C, 45.76; H, 2.66; Found C,45.79; H, 2.60.

**(E)-3-(3-(3-bromophenyl)acryloyl)-4-hydroxy-6-methyl-2H-pyran-2-one (HR 13):**

$^{1}$H NMR (400 MHz, CDCl3) δ 8.25 (d, *J* = 15.7 Hz, 1H), 7.88 – 7.74 (m, 2H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.32 – 7.20 (m, 1H), 5.95 (s, 1H), 2.26 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 192.83, 183.22, 169.22, 161.38, 144.42, 137.07, 133.94, 131.94, 130.64, 127.79, 124.71, 123.31, 102.48, 99.78, 20.91. ESI MS (m/z): 335 [M+Na]$^{+}$. Anal. Calc. for C15H11BrO4: C, 53.76; H, 3.31; Found C,53.70; H, 3.30.

**(E)-3-(3-(4-bromophenyl)acryloyl)-4-hydroxy-6-methyl-2H-pyran-2-one (HR 14):**

$^{1}$H NMR (400 MHz, CDCl3) δ 8.27 (d, *J* = 15.7 Hz, 1H), 7.84 (d, *J* = 15.7 Hz, 1H), 7.52 (s, 4H), 5.94 (s, 1H), 2.26 (s, 2H). 13C NMR (101 MHz, CDCl3) δ 192.84, 183.27, 169.08, 161.41, 144.86, 133.88 (2 x C), 132.44, 130.65 (2 x C), 125.70, 123.90, 102.53, 99.72, 20.88. ESI MS (m/z): 335 [M+Na]$^{+}$. Anal. Calc. for C15H11BrO4: C, 53.76; H, 3.31; Found C,53.72; H, 3.30.

**(E)-4-hydroxy-3-(3-(3-methoxyphenyl)acryloyl)-6-methyl-2H-pyran-2-one (HR 15):**

$^{1}$H NMR (400 MHz, CDCl3) δ 8.28 (t, *J* = 15.5 Hz, 1H), 7.89 (d, *J* = 15.7 Hz, 1H), 7.35 – 7.22 (m, 2H), 7.14 (d, *J* = 16.7 Hz, 1H), 6.92 (dd, *J* = 20.2, 8.0 Hz, 1H), 5.93 (s, 1H), 3.82 (s, 3H), 2.25 (s, 3H). $^{13}$C NMR (101 MHz, CDCl3) δ 192.93, 183.32, 168.90, 161.37, 160.12, 146.39, 136.29, 130.11, 123.48, 122.11, 117.37, 113.94, 102.55, 99.67, 55.53, 20.81. ESI MS (m/z): 286 [M+Na]$^{+}$. Anal. Calc. for C16H14O5: C, 67.13; H, 4.93; Found C,67.16; H, 4.90.

**(E)-4-hydroxy-3-(3-(4-methoxyphenyl)acryloyl)-6-methyl-2H-pyran-2-one (HR 16):**

$^{1}$H NMR (400 MHz, CDCl3) δ 8.18 (d, *J* = 15.6 Hz, 1H), 7.93 (d, *J* = 15.7 Hz, 1H), 7.63 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.92 (s, 1H), 3.84 (s, 3H), 2.25 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 192.65, 183.61, 168.47, 162.54, 161.56, 146.72, 131.43, 127.82, 120.56, 114.70, 102.83, 99.51, 55.66, 29.90, 20.80. ESI MS (m/z): 286 [M+Na]$^{+}$. Anal. Calc. for C16H14O5: C, 67.13; H, 4.93; Found C,67.15; H, 4.96.

**(E)-4-hydroxy-6-methyl-3-(3-(m-tolyl)acryloyl)-2H-pyran-2-one (HR 17):**

$^{1}$H NMR (400 MHz, CDCl3) δ 8.31 (d, *J* = 15.7 Hz, 1H), 7.95 (d, *J* = 15.7 Hz, 1H), 7.57 – 7.47 (m, 2H), 7.29 (dt, *J* = 16.7, 7.5 Hz, 2H), 5.97 (s, 1H), 2.41 (s, 3H), 2.29 (s, 3H). $^{13}$C NMR (101 MHz, CDCl3) δ 192.94, 183.38, 168.78, 161.40, 146.81, 138.83, 134.86, 132.21, 129.81, 129.01, 126.78, 122.90, 102.60, 99.63, 21.46, 20.79. ESI MS (m/z): 270 [M+Na]$^{+}$. Anal. Calc. for C16H14O4: C, 71.10; H, 5.22; Found C,71.14; H, 5.27.

**(E)-3-(3-(2-chlorophenyl)acryloyl)-4-hydroxy-6-methyl-2H-pyran-2-one (HR 18):**

$^{1}$H NMR (400 MHz, CDCl3) δ 8.29 (d, *J* = 15.8 Hz, 1H), 8.20 (d, *J* = 15.7 Hz, 1H), 7.77 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.29 – 7.17 (m, 2H), 5.89 (s, 1H), 2.20 (s, 3H). $^{13}$C NMR (101 MHz, CDCl3) δ 192.83, 183.20, 169.12, 161.37, 141.65, 136.10, 133.09, 131.88, 130.37, 128.62, 127.36, 125.56, 102.47, 99.77, 20.85. ESI MS (m/z): 290 [M+Na]$^{+}$. Anal. Calc. for C15H11ClO4: C, 61.98; H, 3.81; Found C,61.92; H, 3.86

**(E)-4-hydroxy-3-(3-(2-hydroxyphenyl)acryloyl)-6-methyl-2H-pyran-2-one (HR 19):**

$^{1}$H NMR (400 MHz, DMSO) δ 10.49 (s, 1H, -OH), 8.29 (d, *J* = 15.9 Hz, 1H), 8.18 (d, *J* = 15.9 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.02 – 6.85 (m, 2H), 6.29 (s, 1H), 3.32 (s, 1H, -OH), 2.27 (s, 3H). $^{13}$C NMR (101 MHz, DMSO) δ 192.24, 182.70, 169.73, 160.47, 157.86, 141.67, 132.90, 129.36, 121.90, 121.12, 119.66, 116.45, 101.94, 98.91, 20.04. ESI MS (m/z): 272 [M+Na]$^{+}$. Anal. Calc. for C15H12O5: C, 66.17; H, 4.44; Found C,66.12; H, 4.40.

**(E)-4-hydroxy-3-(3-(3-hydroxyphenyl)acryloyl)-6-methyl-2H-pyran-2-one (HR 20):**

$^{1}$H NMR (400 MHz, DMSO) δ 9.73 (s, 1H, -OH), 8.13 (d, *J* = 15.8 Hz, 1H), 7.83 (d, *J* = 15.8 Hz, 1H), 7.34 – 7.23 (m, 1H), 7.14 (d, *J* = 6.6 Hz, 2H), 6.95 – 6.87 (m, 1H), 6.31 (s, 1H), 2.28 (s, 3H). $^{13}$C NMR (101 MHz, DMSO) δ 192.03, 182.46, 170.08, 160.62, 157.86, 145.66, 135.53, 130.28, 122.67, 120.62, 118.79, 114.27, 101.85, 99.10, 20.09. ESI MS (m/z): 272 [M+Na]$^{+}$. Anal. Calc. for C15H12O5: C, 66.17; H, 4.44; Found C,66.16; H, 4.41.

**(E)-3-(3-(3-ethoxyphenyl)acryloyl)-4-hydroxy-6-methyl-2H-pyran-2-one (HR 21):**

$^{1}$H NMR (400 MHz, CDCl3) δ 8.26 (t, *J* = 16.0 Hz, 1H), 7.87 (d, *J* = 15.7 Hz, 1H), 7.26 (dt, *J* = 7.4, 5.8 Hz, 2H), 7.15 (s, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 5.92 (s, 1H), 4.06 (p, *J* = 7.0 Hz, 2H), 2.24 (s, 3H), 1.40 (t, *J* = 7.0 Hz, 3H). $^{13}$C NMR

(101 MHz, CDCl3) δ 192.92, 183.35, 168.68, 161.59, 159.53, 146.37, 136.32, 130.10, 123.59, 122.08, 117.89, 114.54, 102.79, 99.82, 63.83, 20.83, 14.98. ESI MS (m/z): 300[M+Na]$^+$. Anal. Calc. for C17H16O5: C, 67.99; H, 5.37; Found C,67.92; H, 5.31.

**(E)-3-(3-(2,5-dimethoxyphenyl)acryloyl)-4-hydroxy-6-methyl-2H-pyran-2-one (HR 22):**

$^1$H NMR (400 MHz, CDCl3) δ 8.37 – 8.25 (m, 2H), 7.29 – 7.18 (m, 1H), 6.94 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.84 (d, *J* = 9.0 Hz, 1H), 5.92 (s, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 2.25 (s, 3H). $^{13}$C NMR (101 MHz, CDCl3) δ 193.11, 183.54, 168.60, 161.49, 153.99, 153.79, 141.69, 124.50, 123.41, 119.00, 113.57, 112.76, 102.74, 99.70, 56.36, 56.07, 20.81. ESI MS (m/z): 316 [M+Na]$^+$. Anal. Calc. for C17H16O6: C, 64.55; H, 5.10; Found C,64.51; H, 5.14.

**(E)-4-hydroxy-6-methyl-3-(3-(2,4,5-trimethoxyphenyl)acryloyl)-2H-pyran-2-one (HR 23):**

$^1$H NMR (400 MHz, CDCl3) δ 8.41 (d, *J* = 15.8 Hz, 1H), 8.26 (d, *J* = 15.7 Hz, 1H), 7.24 (s, 1H), 6.54 (s, 1H), 5.97 (s, 1H), 3.99 (s, 2H), 3.96 (s, 3H), 3.95 (s, 3H), 2.30 (s, 3H). $^{13}$C NMR (101 MHz, CDCl3) δ 192.52, 183.85, 168.09, 161.75, 155.68, 153.87, 143.74, 141.97, 119.98, 115.83, 111.39, 103.09, 99.48, 96.76, 56.72, 56.60, 56.33, 20.78. ESI MS (m/z): 346 [M+Na]$^+$. Anal. Calc. for C18H18O7: C, 62.42; H, 5.25; Found C,62.47; H, 5.20.

**(E)-4-hydroxy-6-methyl-3-(3-(3,4,5-trimethoxyphenyl)acryloyl)-2H-pyran-2-one (HR 24):**

$^1$H NMR (400 MHz, CDCl3) δ 8.19 (d, *J* = 15.6 Hz, 1H), 7.86 (d, *J* = 15.6 Hz, 1H), 7.25 (d, *J* = 4.3 Hz, 1H), 6.88 (s, 2H), 5.94 (s, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 2.26 (s, 1H). $^{13}$C NMR (101 MHz, CDCl3) δ 192.69, 183.43, 168.78, 161.58, 153.67, 146.69, 141.34, 130.45, 122.36, 106.65, 102.71, 99.64, 61.23, 56.46, 20.85. ESI MS (m/z): 346 [M+Na]$^+$. Anal. Calc. for C18H18O7: C, 62.42; H, 5.25; Found C,62.45; H, 5.22.

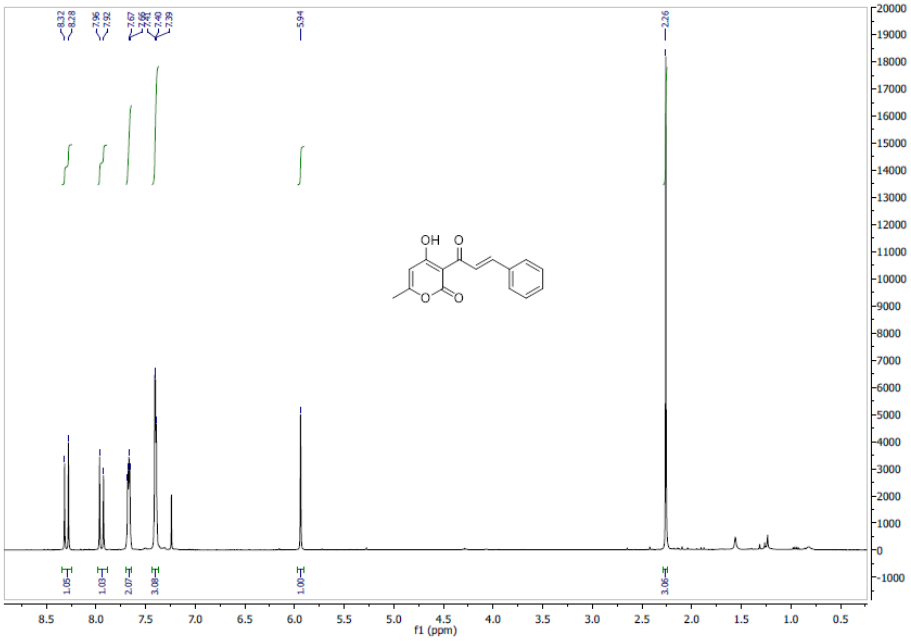
**(E)-4-hydroxy-3-(3-(4-hydroxy-3-methoxyphenyl)acryloyl)-6-methyl-2H-pyran-2-one (HR 25):**

**1**H NMR (400 MHz, CDCl3) δ 8.16 (d, *J* = 15.6 Hz, 1H), 7.88 (d, *J* = 15.6 Hz, 1H), 7.31 (t, *J* = 6.0 Hz, 1H), 7.20 (dd, *J* = 8.4, 1.8 Hz, 1H), 5.92 (s, 1H), 5.62 (s, 1H, -OH), 3.93 (s, 3H), 2.25 (s, 3H). $^{13}$C NMR (101 MHz, CDCl3) δ 192.71, 183.60, 168.58, 161.51, 149.64, 146.84, 146.17, 128.79, 123.53, 121.28, 114.52, 110.81, 102.80, 99.59, 56.30, 20.85. ESI MS (m/z): 302 [M+Na]$^+$. Anal. Calc. for C16H14O6: C, 63.57; H, 4.67; Found C,63.52; H, 4.61.

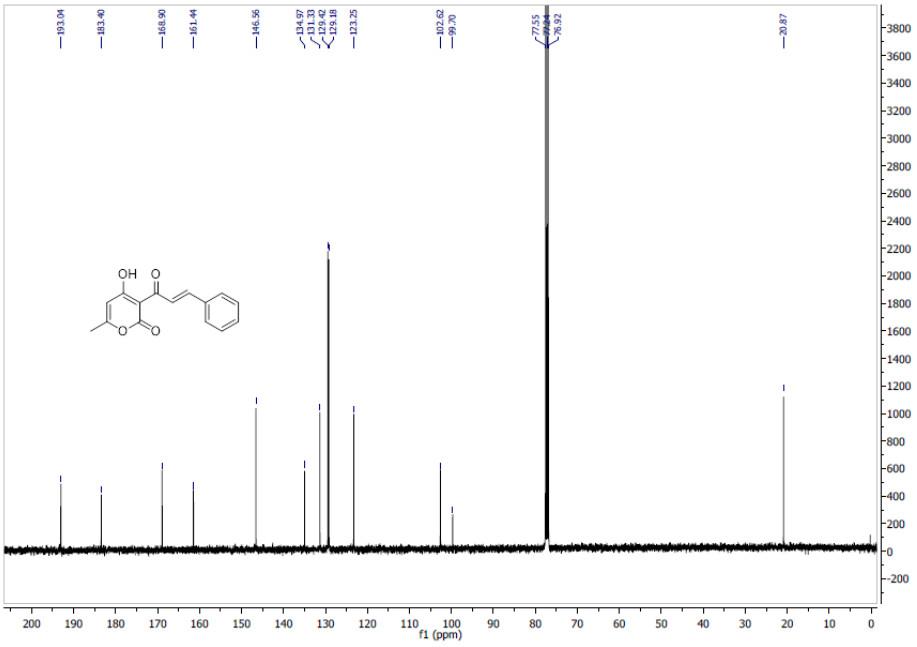
**Representative Specctra**

$^1$HNMR and $^{13}$CNMR of 3-cinnamoyl-4-hydroxy-6-methyl-2H-pyran-2-one

$^1$HNMR of

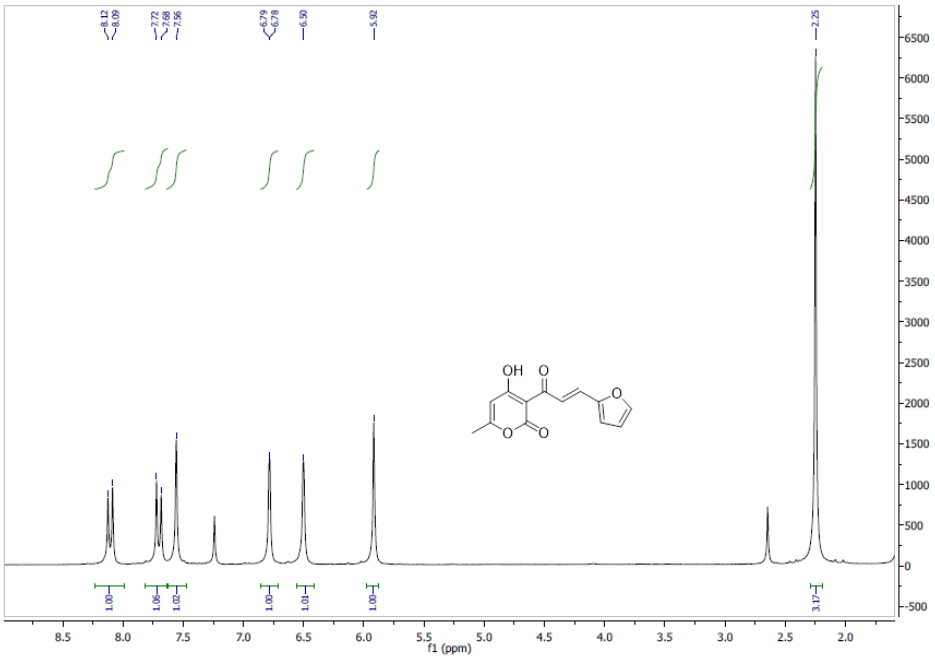



$^{13}$CNMR




$^{1}$HNMR and $^{13}$CNMR of (E)-3-(3-(furan-2-yl)acryloyl)-4-hydroxy-6-methyl-2H-pyran-2-one

$^{1}$HNMR

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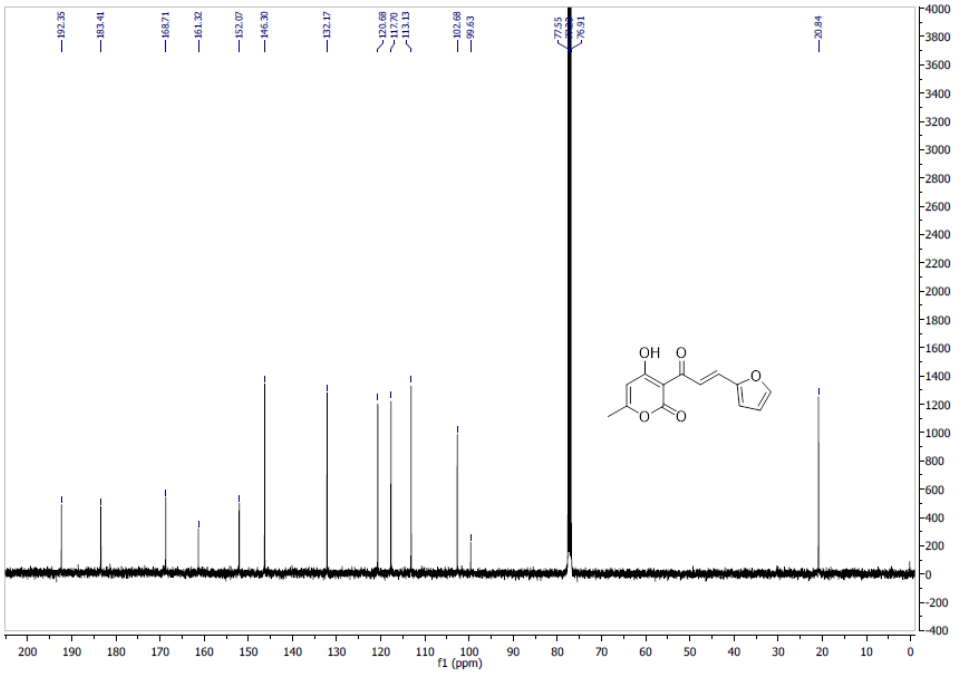
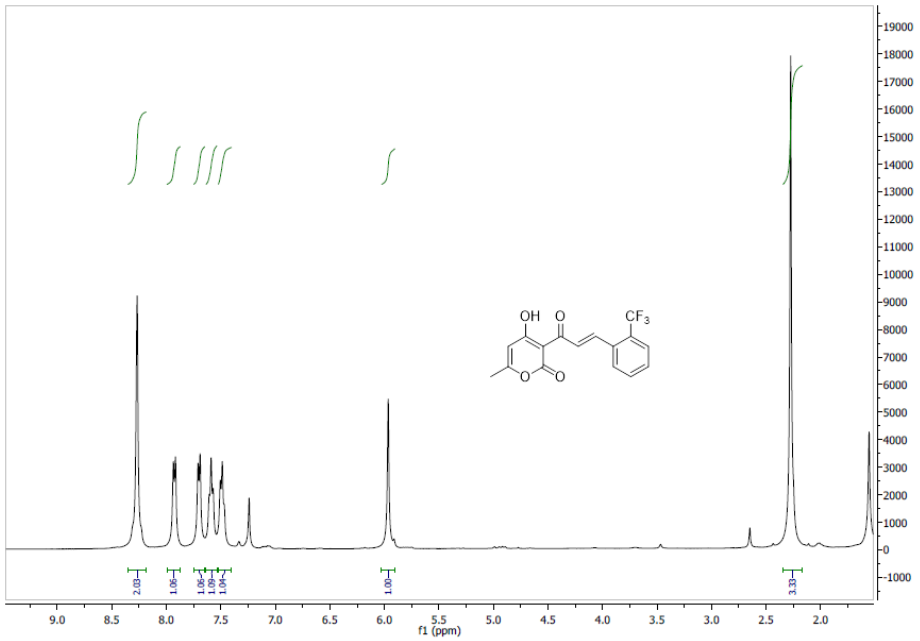



$^{1}$HNMR and $^{13}$CNMR of (E)-4-hydroxy-6-methyl-3-(3-(2-(trifluoromethyl)phenyl)acryloyl)-2H-pyran-2-one

HNMR

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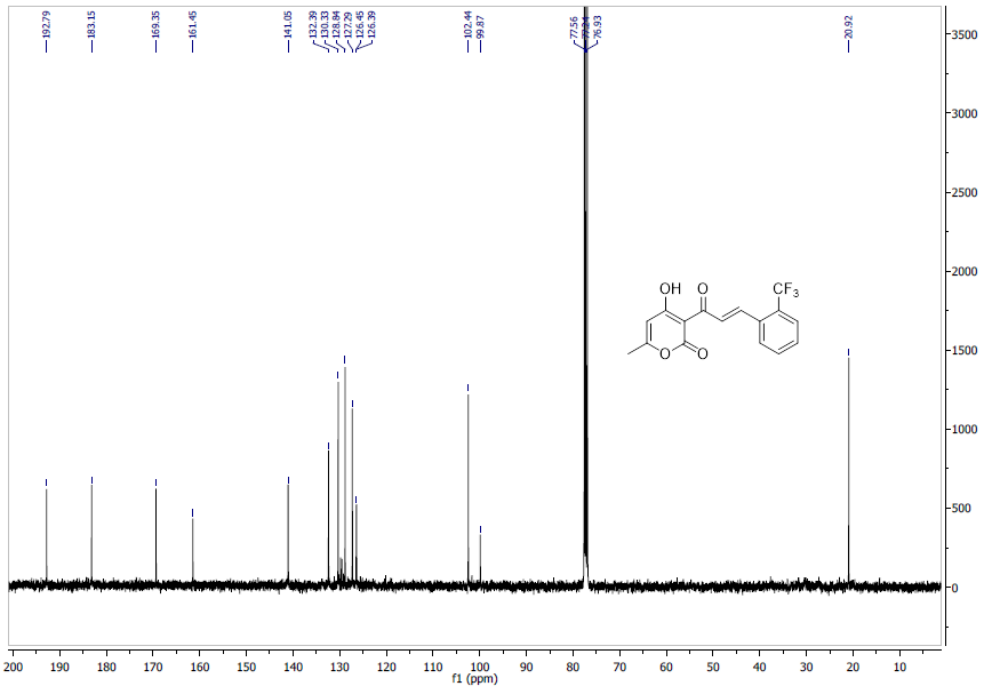
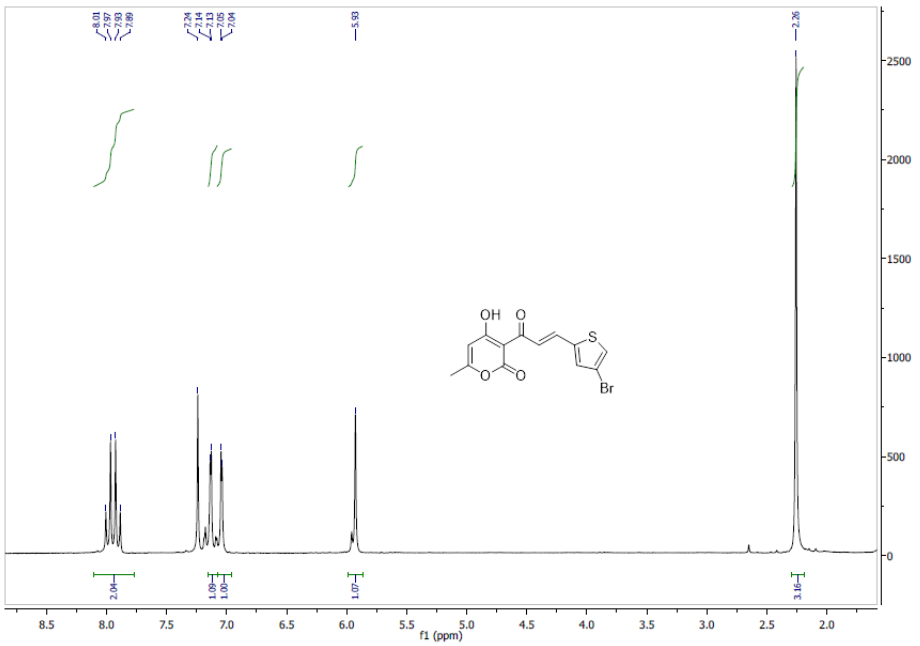



$^{1}$HNMR and $^{13}$CNMR of (E)-3-(3-(4-bromothiophen-2-yl)acryloyl)-4-hydroxy-6-methyl-2H-pyran-2-one

$^{1}$HNMR

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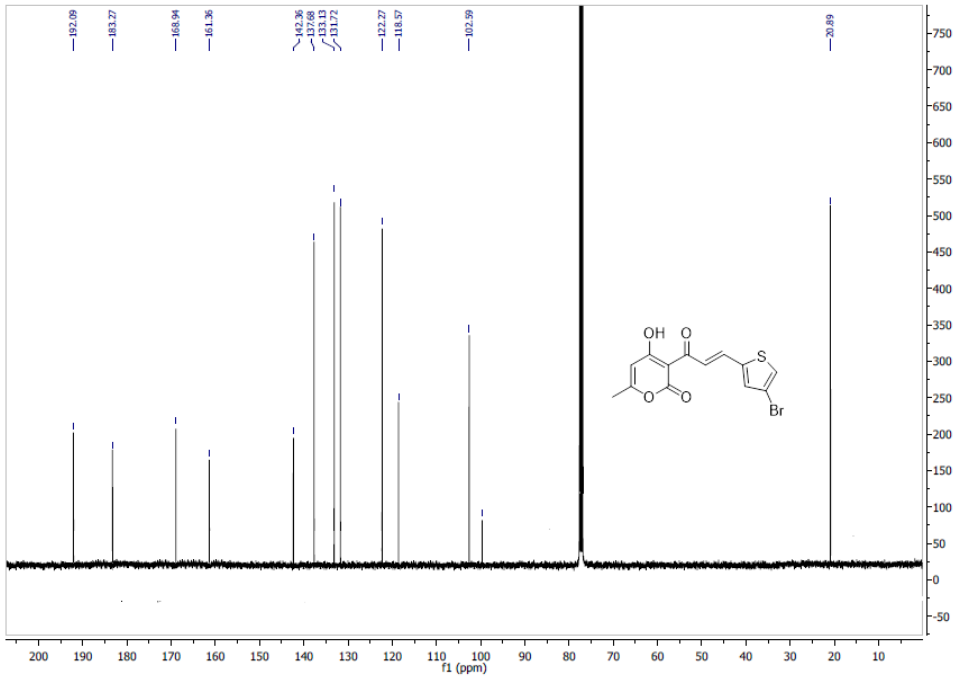
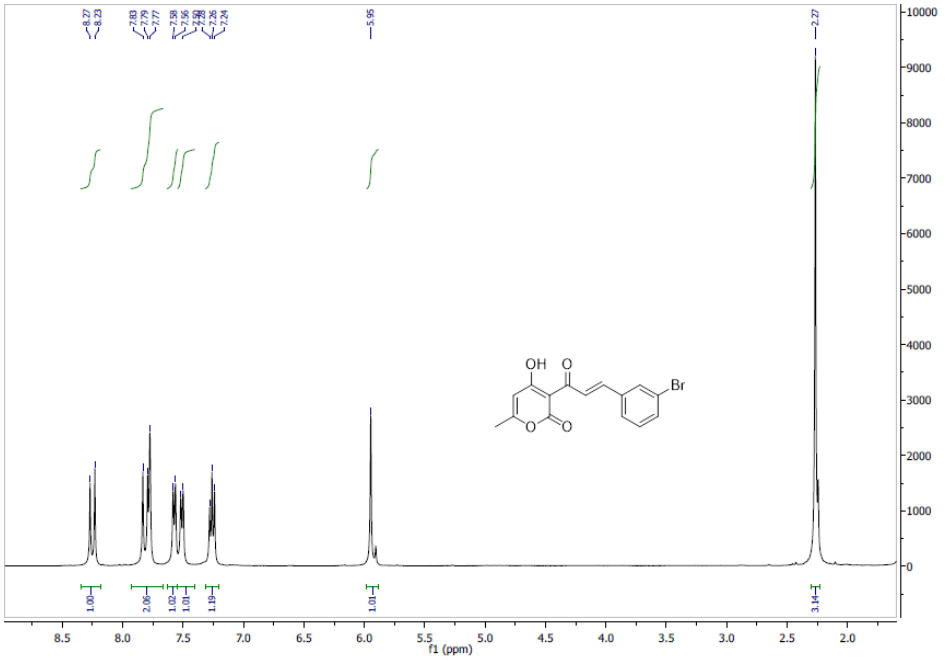



HNMR and CNMR of (E)-3-(3-(3-bromophenyl)acryloyl)-4-hydroxy-6-methyl-2H-pyran-2-one

$^{1}$HNMR

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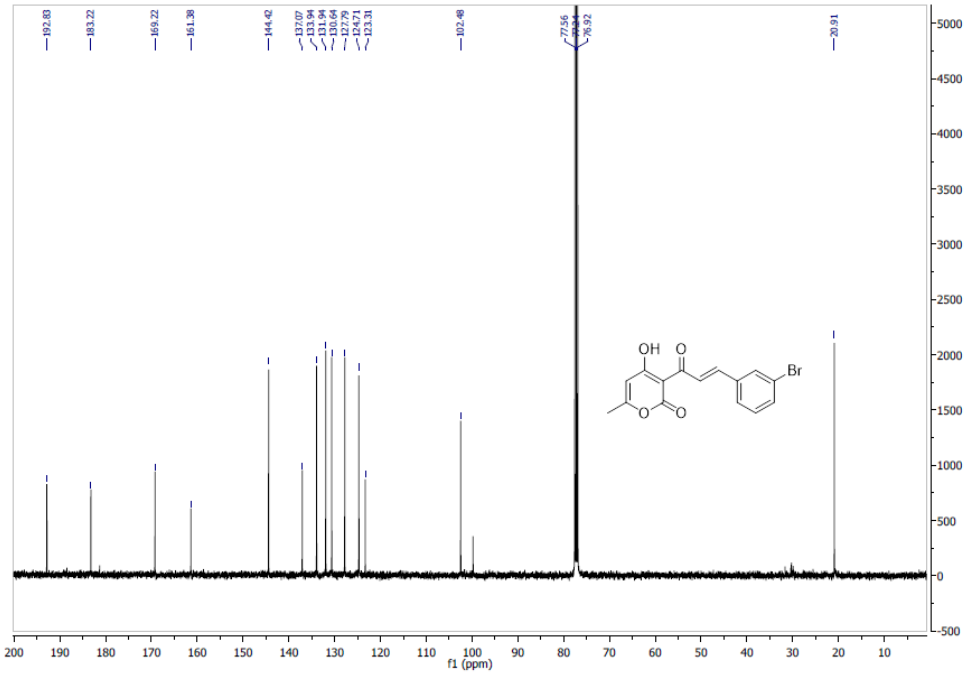
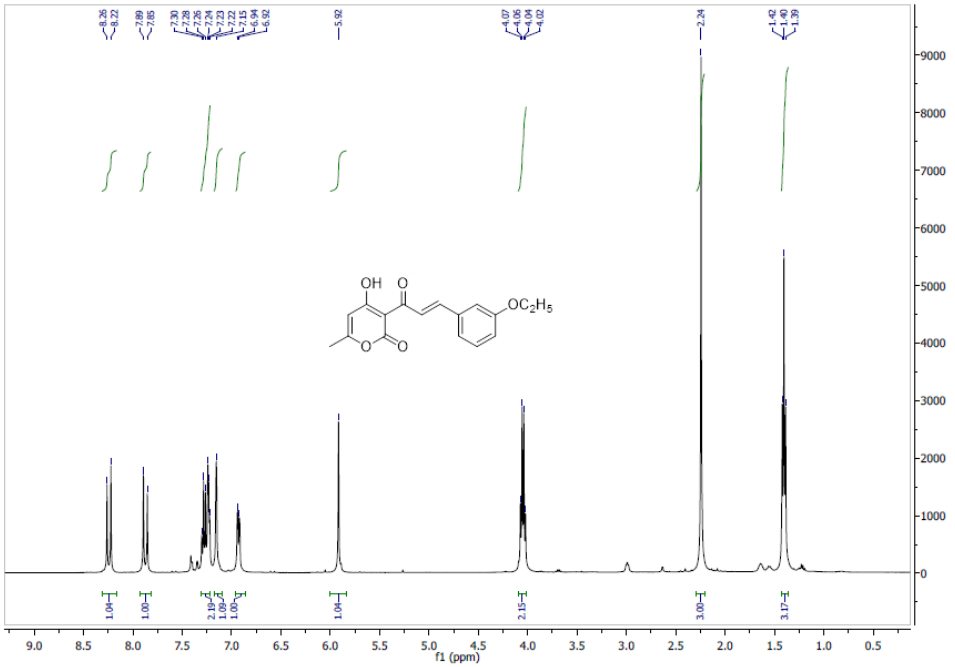
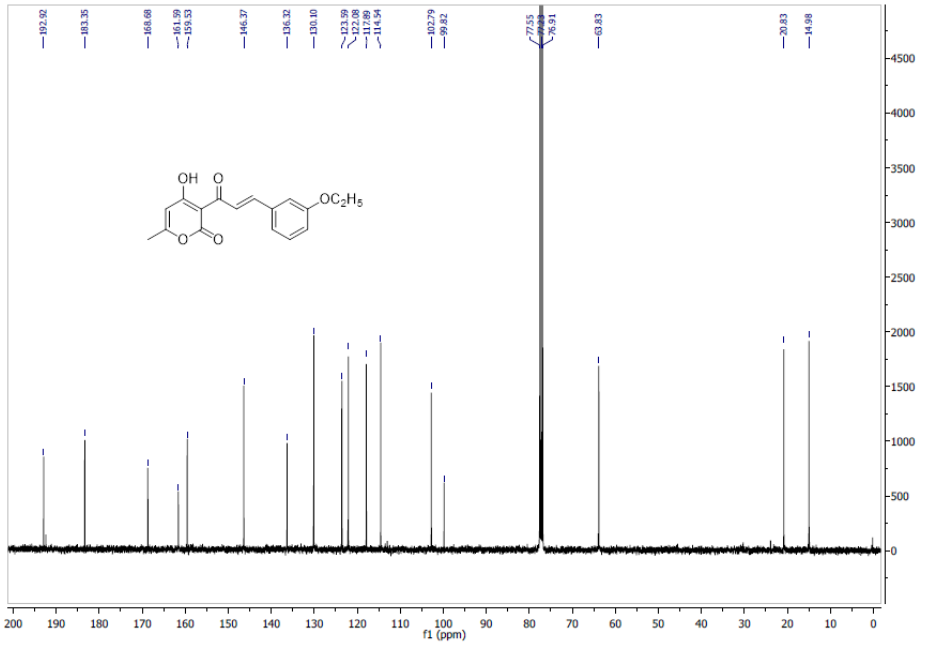



$^{1}$HNMR and $^{13}$CNMR of (E)-3-(3-(3-ethoxyphenyl)acryloyl)-4-hydroxy-6-methyl-2H-pyran-2-one

$^{1}$HNMR

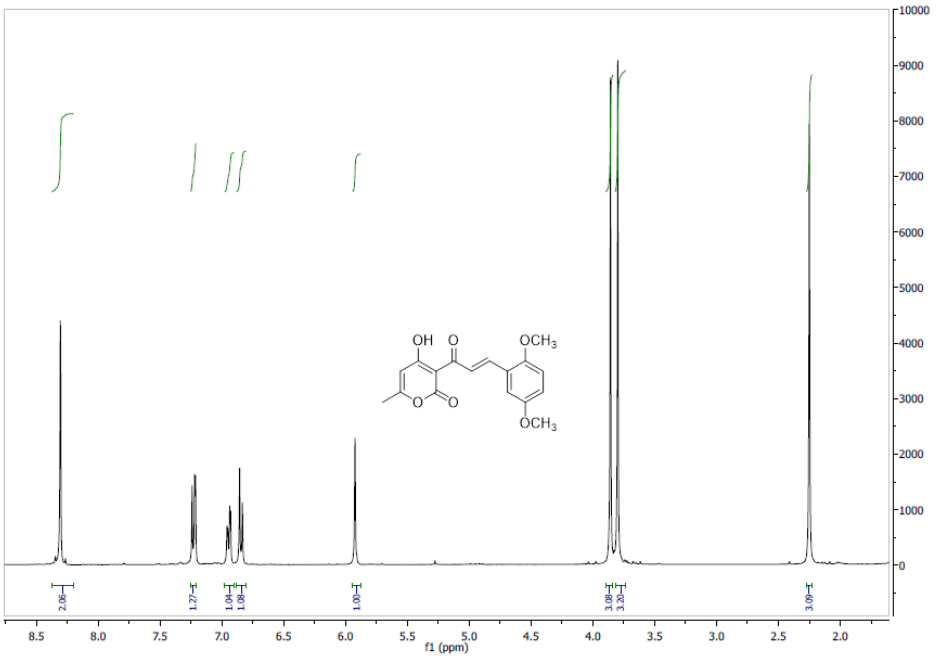



$^{13}$CNMR

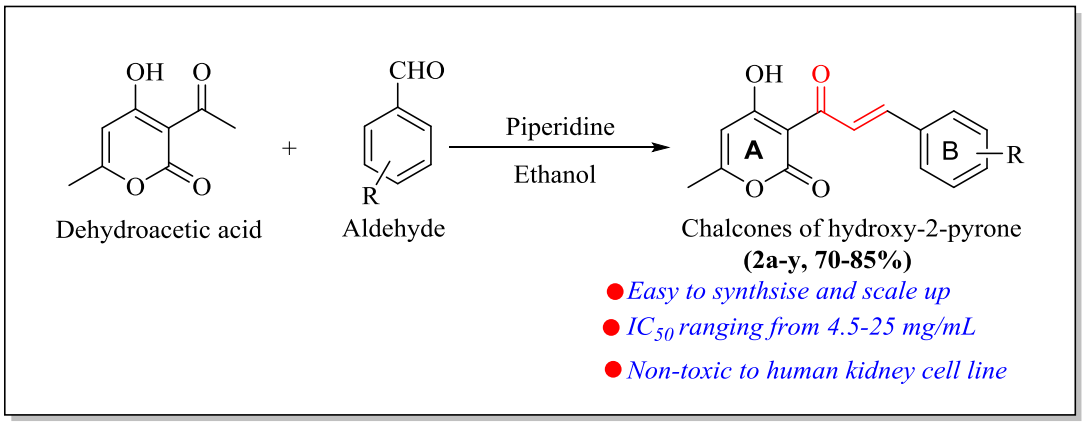



$^{1}$HNMR and $^{13}$CNMR of (E)-3-(3-(2,5-dimethoxyphenyl)acryloyl)-4-hydroxy-6-methyl-2H-pyran-2-one

$^{1}$HNMR


OH
O
OCH3
OCH3
O
O
f1 (ppm)

$^{13}$CNMR


OH
O
O
O
+
CHO
R
Piperidine
Ethanol
OH
O
A
B
R
O
O
Dehydroacetic acid
Aldehyde
Chalcones of hydroxy-2-pyrone
(2a-y, 70-85%)
Easy to synthsise and scale up
IC50 ranging from 4.5-25 mg/mL
Non-toxic to human kidney cell line