Supporting Information

Expeditious access of chromone analogues via a Michael addition-driven multicomponent reaction

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Table of Contents

<table>
<thead>
<tr>
<th>Table of Contents</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Experimental</td>
<td>2</td>
</tr>
<tr>
<td>General procedures for compounds 5 and 6</td>
<td>2</td>
</tr>
<tr>
<td>General procedures for compounds 9</td>
<td>2</td>
</tr>
<tr>
<td>General procedures for compounds 19</td>
<td>3</td>
</tr>
<tr>
<td>General procedures for compounds 20</td>
<td>3</td>
</tr>
<tr>
<td>General procedures for compounds 21</td>
<td>3</td>
</tr>
<tr>
<td>General procedures for compounds 22</td>
<td>3</td>
</tr>
<tr>
<td>Gram scale for compound 9g</td>
<td>4</td>
</tr>
<tr>
<td>Electrostatic potential (ESP) calculations</td>
<td>5</td>
</tr>
<tr>
<td>Cell lines and culture and MTT assay</td>
<td>7</td>
</tr>
<tr>
<td>NMR Characterization Data and Figures of Products</td>
<td>9-62</td>
</tr>
<tr>
<td>X-ray of Compounds 6g and 9a</td>
<td>63</td>
</tr>
</tbody>
</table>
General Experimental

$^1$H and $^{13}$C NMR were recorded on a Bruker 400 spectrometer. $^1$H NMR data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant (Hz), relative intensity. $^{13}$C NMR data are reported as follows: chemical shift in ppm (δ). LC/MS analyses were performed on a Shimadzu-2020 LC-MS instrument using the following conditions: Shim-pack VP-ODS C18 column (reverse phase, 150 x 4.6 mm); a linear gradient from 10% water and 90% acetonitrile to 75% acetonitrile and 25% water over 6.0 min; flow rate of 0.5 mL/min; UV photodiode array detection from 200 to 400 nm. High-resolution mass spectra (HRMS) were recorded on Thermo Scientific Exactive Plus System. The products were purified by Biotage Isolera™ Spektra Systems and hexane/EtOAc solvent systems. All reagents and solvents were obtained from commercial sources and used without further purification.

General procedures for compounds 5 and 6.

A solution of acid (0.3 mmol), isocyanide (0.3 mmol), amine (0.3 mmol) and aldehyde (0.3 mmol) was stirred in 2,2,2-trifluoroethanol (TFE, 2.0 mL) for 2 h. The reaction mixture was monitored by TLC. When the reaction was completed, the solvent was removed under reduced pressure. Then the reaction mixture was diluted with EtOAc (15.0 mL), washed with sat. Na$_2$CO$_3$ and brine. The organic layer was dried over MgSO$_4$ and concentrated. The residue was purified by silica gel column chromatography using a gradient of ethyl acetate/hexane (0-100%) to afford the relative targeted product.

General procedures for compound 9.

A solution of trimethylsilyl azide (0.3 mmol), isocyanide (0.3 mmol), amine (0.3 mmol) and aldehyde (0.3 mmol) was stirred in TFE, 2.0 mL for 2 h. The reaction mixture was monitored by TLC. When the reaction was completed, the solvent was removed under reduced pressure. Then the reaction mixture was diluted with EtOAc (15.0 mL), washed with sat. Na$_2$CO$_3$ and brine. The organic layer was dried over MgSO$_4$ and concentrated. The residue was purified by silica gel column chromatography using a gradient of ethyl acetate/hexane (0-100%) to afford the relative targeted product.
General procedure for compound 19

In a solution of compound 9 (0.2 mmol) in DCM (3.0 mL), [bis(trifluoroacetoxy)iodo]benzene (PIFA, 0.2 mmol) and trifluoroacetic acid (TFA, 0.2 mmol) were added and stirred at room temperature for 6 h. When the reaction was completed, the reaction mixture was diluted with EtOAc (15.0 mL), washed with sat. Na₂CO₃ and brine. The organic layer was dried over MgSO₄ and concentrated. The residue was purified by silica gel column chromatography using a gradient of ethyl acetate/hexane (0-100%) to afford the relative targeted products 19a-c.

General procedure for compound 20

In a solution of compound 9b (0.2 mmol) in EtOH (3.0 mL), hydroxylamine hydrochloride (0.2 mmol) was added and stirred under reflux overnight. When the reaction was completed, the reaction mixture was diluted with EtOAc (15.0 mL), washed with sat. Na₂CO₃ and brine. The organic layer was dried over MgSO₄ and concentrated. The residue was purified by silica gel column chromatography using a gradient of ethyl acetate/hexane (0-100%) to afford the relative targeted product 20 in 78% yield.

General procedure for compound 21

In a solution of compound 9i (0.2 mmol) in AcOH (3.0 mL), 3-amino-5-methylpyrazole (0.2 mmol) was added and stirred under reflux for 2 h. When the reaction was completed, the reaction mixture was diluted with EtOAc (15.0 mL), washed with sat. Na₂CO₃ and brine. The organic layer was dried over MgSO₄ and concentrated. The residue was purified by silica gel column chromatography using a gradient of ethyl acetate/hexane (0-100%) to afford the relative targeted product 21 in 83% yield.

General procedure for compound 22

In a solution of compound 9i (0.2 mmol) in EtOH (3.0 mL), guanidine hydrochloride (0.2 mmol) and EtONa (0.4 mmol) were added and stirred under reflux for 16 h. When the reaction was completed, the reaction mixture was diluted with EtOAc (15.0 mL), washed with sat. Na₂CO₃ and brine. The organic layer was dried over MgSO₄ and concentrated. The residue was purified by silica gel column chromatography using a
gradient of ethyl acetate/hexane (0-100%) to afford the relative targeted product 22 in 84% yield.

**Gram scale for compound 9g**

![Diagram of the synthesis of compound 9g](image)

**Scheme S1.** Gram scale for compound 9g.

The mixture of 6-bromo-4-oxo-4H-chromene-3-carbaldehyde (3.0 mmol) and tert-butyl amine (3.0 mmol) was stirred in TFE, 10.0 mL under room temperature for 10 min. Then trimethylsilyl azide (3.0 mmol) and tert-octylisocyanide (3.0 mmol) were added dropwise, respectively. When the addition was completed, the reaction was stirred under room temperature for 6 h. When the reaction was completed, the solvent was removed under reduced pressure. Then the reaction mixture was diluted with EtOAc (100.0 mL), washed with sat. Na₂CO₃ and brine. The organic layer was dried over MgSO₄ and concentrated. The residue was purified by silica gel column chromatography using a gradient of ethyl acetate/hexane (0-100%) to afford 9g in yield of 80%.
Electrostatic potential (ESP) calculations

Geometry optimization and electrostatic potential (ESP) calculations for compounds 13 and 14 are performed and no much more difference was found on the calculation of the molecular ESP energy surfaces.

Figure 1. The electrostatic potentials (ESPs) are mapped onto the electron density surface. Red is more electropositive (cationic) while blue is lower (relatively polar).
Table S1. The electron negativity calculation of the corresponding iminium ion.

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Cell lines and culture

The human tumor cells MCF-7, Hela, A549, HCT116, BxPC3 and PC-3 were obtained from American Type Culture Collection (ATCC, Manassas, VA, USA). The MCF-7, Hela, HCT116 and BxPC3 cells were cultured in high-glucose DMEM (Hyclone, SH30022.01, USA) medium supplemented with 10% fetal bovine serum (FBS, Gibco, 10099, Australia origin). The A549 and PC3 cells were cultured with the Ham's F-12K (Kaighn's) Medium (GIBCO, 21127022, USA) supplemented with 10% FBS. The cells were cultured in the incubator at the 37°C and 5% CO2 with humidified atmosphere.

MTT assay

The effect of compound 9g to the human tumor cells viability were measured by 3-(4,5-dimethyl-2-thiazoly)-2,5-diphenyl-2-H-tetrazolium bromide (MTT, Beyotime, ST316, Shanghai, China) assay. The tumor cells were counted and seeded into the 96-well plate containing 100 µL complete medium, the MCF-7 Hela, A549, HCT116, BxPC-3 and PC-3 with a density 4 × 10³ cells per well and the other cells with a density 1 × 10³ cells per well. After incubation for 24 h, added another 100 µL complete medium containing 10 µM compounds and incubated another 48 h. To further measured the IC₅₀ of compound 10 h, tumor cells were incubated with various concentrations (0, 1.25, 2.5, 5, 10 µM) of compound 10 h for 48 h. After that, 20 µL MTT (5 mg/mL) was added to each well and incubated another 4 h. After incubation, removed the medium and added 200 µL DMSO into each well to dissolve the formazan product. The absorbance was measured at 570 nm (Bio-Tek, Winooski, VT, USA) and the inhibition values of compounds or IC₅₀ values were analyzed by GraphPad Prism 8. (Positive control sample paclitaxel was only measured in HCT116 with IC₅₀ = 0.14 ± 0.05 µM)
Table S2. Screening and antiproliferative viability of small molecular inhibitors in different human tumor cells.

(Inhibition values%) 10 µM concentration of compounds was used for the following cell lines.

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NMR Characterization Data and Figures of Products

**N-(2,6-dimethylphenyl)-2-(N-(2,6-dimethylphenyl)-2-(4-nitrophenyl)acetamido)-2-(4-oxo-4H-chromen-3-yl)acetamide**

5a white solid, 29% (EA/Hex = 20%, Rf = 0.35), $^1$H NMR (400 MHz, CDCl$_3$) δ 8.18 (d, $J = 8.0$ Hz, 1H), 8.08 (t, $J = 7.6$ Hz, 2H), 7.97 (s, 1H), 7.84 (d, $J = 2.6$ Hz, 1H), 7.65 (t, $J = 7.5$ Hz, 1H), 7.37 (dt, $J = 14.3$, 6.9 Hz, 2H), 7.20 (t, $J = 7.0$ Hz, 2H), 7.18 – 7.08 (m, 2H), 7.08 – 6.96 (m, 3H), 6.92 (d, $J = 4.4$ Hz, 1H), 6.64 (d, $J = 5.3$ Hz, 1H), 3.48 (dt, $J = 15.0$, 12.3 Hz, 2H), 2.47 (s, 3H), 2.12 (s, 6H), 1.85 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 175.67, 171.29, 167.98, 158.28, 155.60, 147.03, 141.89, 138.72, 138.30, 137.01, 135.40, 134.15, 133.46, 130.40, 129.42, 129.25, 129.14, 128.17, 127.31, 126.19, 125.75, 123.42, 123.18, 118.25, 117.17, 54.95, 41.25, 18.76, 18.38. HRMS (ESI) m/z calcd for C$_{35}$H$_{32}$N$_3$O$_6$ (M+H)$^+$ 590.2286, found 590.2286.

**(Z)-N-(2,6-dimethylphenyl)-3-(((2,6-dimethylphenyl)amino)methylene)-N-(2-(4-nitrophenyl)acetyl)-4-oxochromane-2-carboxamide**

6a light yellow solid, 57% (EA/Hex = 20%, Rf = 0.3), $^1$H NMR (400 MHz, CDCl$_3$) δ 11.49 (d, $J = 12.5$ Hz, 1H), 7.93 (dd, $J = 8.5$, 4.9 Hz, 2H), 7.88 (dd, $J = 5.5$, 2.2 Hz, 1H), 7.40 (dd, $J = 11.0$, 4.5 Hz, 1H), 7.24 (d, $J = 5.8$ Hz, 1H), 7.16 (dt, $J = 7.3$, 4.6 Hz, 1H), 7.13 – 7.06 (m, 4H), 7.06 – 6.94 (m, 5H), 6.49 (s, 1H), 3.58 (q, $J = 15.8$ Hz, 2H), 2.28 (s, 6H), 2.01 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 181.71, 173.07, 172.59, 159.32, 150.07, 147.25, 140.20, 137.78, 136.74, 135.73, 134.76, 131.39, 130.33, 129.65, 129.43, 129.19, 126.35, 123.56, 122.48, 121.58, 116.85, 97.45, 78.78, 43.39, 18.73, 17.90. HRMS (ESI) m/z calcd for C$_{35}$H$_{32}$N$_3$O$_6$ (M+H)$^+$ 590.2286, found 590.2285.
(Z)-3-((tert-butylamino)methylene)-N-(2,6-dimethylphenyl)-N-(2-(4 nitrophenyl)-acetyl)-4-oxochromane-2-carboxamide

6b, light yellow solid, 74% (EA/Hex = 20%, Rf = 0.3), \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 10.39 (d, \(J = 12.9\) Hz, 1H), 8.18 – 8.04 (m, 2H), 7.81 (d, \(J = 7.7\) Hz, 1H), 7.35 (dd, \(J = 10.4, 4.9\) Hz, 1H), 7.28 – 7.22 (m, 1H), 7.24 – 7.13 (m, 3H), 7.11 (d, \(J = 6.9\) Hz, 2H), 6.99 – 6.91 (m, 2H), 6.25 (s, 1H), 3.65 (d, \(J = 11.0\) Hz, 2H), 1.99 (s, 6H), 1.27 (s, 9H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 180.41, 173.30, 172.38, 158.93, 148.53, 147.30, 140.53, 136.70, 135.88, 134.16, 130.63, 129.60, 129.50, 129.23, 126.57, 125.95, 121.40, 116.62, 95.11, 79.10, 52.75, 43.52, 29.99, 17.99. HRMS (ESI) m/z calcd for C\(_{31}\)H\(_{32}\)N\(_3\)O\(_6\)\(^+\) (M+H\(^+\)) 542.2286 found 542.2285.

(Z)-3-((tert-butylamino)methylene)-N-(2-(2,4-dichlorophenyl)acetyl)-N-(2,6-dimethylphenyl)-4-oxochromane-2-carboxamide

6c light green solid, 65% (EA/Hex = 20%, Rf = 0.3), \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 10.43 (d, \(J = 13.4\) Hz, 1H), 7.79 (dd, \(J = 7.9, 1.4\) Hz, 1H), 7.38 (d, \(J = 2.1\) Hz, 1H), 7.36 – 7.28 (m, 1H), 7.22 – 7.15 (m, 2H), 7.10 (dd, \(J = 8.3, 6.9\) Hz, 3H), 7.01 (d, \(J = 8.2\) Hz, 1H), 6.97 – 6.88 (m, 2H), 6.43 (s, 1H), 3.50 (t, \(J = 11.2\) Hz, 2H), 2.16 (s, 3H), 2.08 (s, 3H), 1.26 (s, 9H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 180.36, 173.30, 171.81, 159.11, 148.89, 136.62, 135.82, 135.62, 135.35, 134.10, 134.03, 132.48, 130.41, 129.39, 127.16, 125.95, 122.83, 121.18, 116.51, 95.20, 79.22, 52.73, 41.56, 29.95, 17.97, 17.84. HRMS (ESI) m/z calcd for C\(_{31}\)H\(_{31}\)N\(_2\)O\(_4\)\(^+\) (M+H\(^+\)) 565.1655, found 565.1663.

(Z)-6-bromo-3-((tert-butylamino)methylene)-N-(2,6-dimethylphenyl)-N-(2-(4-fluorophenyl)acetyl)-4-oxochromane-2-carboxamide

6d light green solid, 61% (EA/Hex = 20%, Rf = 0.3), \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 10.44 (d, \(J = 13.5\) Hz, 1H), 7.87 (d, \(J = 2.5\) Hz, 1H), 7.38 (dd, \(J = 8.7, 2.5\) Hz, 1H), 7.19
(dd, J = 14.5, 7.2 Hz, 2H), 7.07 (d, J = 7.6 Hz, 2H), 6.97 – 6.87 (m, 4H), 6.81 (d, J = 8.7 Hz, 1H), 6.51 (s, 1H), 3.43 – 3.33 (m, 2H), 1.98 (s, 3H), 1.90 (s, 3H), 1.26 (s, 9H). 

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 178.81, 173.54, 173.26, 163.34, 160.89, 158.12, 149.22, 136.71, 136.48, 135.59, 131.13, 129.40, 129.03, 128.60, 124.30, 118.53, 115.44, 113.70, 94.92, 79.27, 52.88, 42.64, 29.91, 17.85, 17.73. HRMS (ESI) m/z calcd for C$_{31}$H$_{21}$BrFN$_2$O$_4$+ (M+H)$^+$ 593.1446, found 593.1452.

(Z)-6-bromo-N-(2-(4-bromophenyl)acetyl)-3-((tert-butylamino)methylene)-N-(2,6-dimethylphenyl)-4-oxochromane-2-carboxamide

6e light green solid, 73% (EA/Hex = 20%, $R_f$ = 0.3), $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.43 (d, J = 13.6 Hz, 1H), 7.87 (d, J = 2.5 Hz, 1H), 7.40 – 7.35 (m, 3H), 7.18 (dt, J = 10.7, 5.3 Hz, 2H), 7.07 (d, J = 7.5 Hz, 2H), 6.82 (dd, J = 12.6, 8.6 Hz, 3H), 6.48 (s, 1H), 3.37 (t, J = 11.3 Hz, 2H), 1.99 (s, 3H), 1.91 (s, 3H), 1.26 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 178.80, 173.22, 173.16, 158.09, 149.18, 136.68, 136.49, 135.84, 135.57, 131.77, 131.55, 131.24, 129.44, 129.06, 128.60, 124.29, 121.50, 118.52, 113.72, 94.87, 79.27, 52.89, 42.85, 29.91, 17.88, 17.76. HRMS (ESI) m/z calcd for C$_{31}$H$_{31}$Br$_2$N$_2$O$_4$+ (M+H)$^+$ 655.0625, found 655.0629.

(Z)-3-((tert-butylamino)methylene)-N-(1-(4-chlorophenyl)cyclopropane-1-carbonyl)-N-(2,6-dimethylphenyl)-4-oxochromane-2-carboxamide

6f light green solid, 83% (EA/Hex = 20%, $R_f$ = 0.3), $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.45 (d, J = 13.4 Hz, 1H), 7.75 (dd, J = 7.8, 1.6 Hz, 1H), 7.32 (ddd, J = 8.2, 7.3, 1.8 Hz, 1H), 7.07 – 6.95 (m, 2H), 6.97 – 6.87 (m, 4H), 6.68 (d, J = 7.3 Hz, 1H), 6.62 (d, J = 8.3 Hz, 2H), 6.05 (s, 1H), 1.92 (s, 2H), 1.91 – 1.82 (m, 1H), 1.55 – 1.49 (m, 1H), 1.37 (s, 9H), 1.23 – 1.13 (m, 1H), 0.82 (ddd, J = 9.4, 7.2, 3.9 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 180.52, 177.01, 158.74, 148.86, 137.36, 136.73,
136.61, 135.01, 133.93, 132.67, 128.82, 128.65, 128.46, 127.97, 125.93, 123.13, 121.35, 117.04, 95.91, 79.48, 52.80, 32.33, 30.09, 18.26, 18.06, 17.71. HRMS (ESI) m/z calcd for C_{33}H_{34}ClN_{2}O_{4}^{+} (M+H)^{+} 557.2202, found 557.2201.

(Z)-N-(2,6-dimethylphenyl)-3-(((2-methylbut-3-yn-2-yl)amino)methylene)-N-(2-(4-nitrophenyl)acetyl)-4-oxochromane-2-carboxamide

6g light yellow solid, 72% (EA/Hex = 20%, Rf = 0.3), \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 10.37 (d, \(J = 12.7\) Hz, 1H), 8.12 (d, \(J = 8.6\) Hz, 2H), 7.82 (d, \(J = 7.7\) Hz, 1H), 7.37 (t, \(J = 7.7\) Hz, 1H). 7.31 (s, 1H), 7.22 (t, \(J = 8.9\) Hz, 3H), 7.10 (d, \(J = 7.6\) Hz, 2H), 7.04-6.87 (m, 2H), 6.29 (s, 1H), 3.69 (s, 2H), 2.48 (s, 1H), 1.98 (s, 6H), 1.59 (s, 3H), 1.55 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 181.13, 173.19, 172.38, 159.03, 148.48, 147.28, 140.47, 136.63, 135.95, 135.69, 134.49, 130.64, 129.63, 129.46, 129.27, 126.14, 123.55, 122.60, 121.48, 116.78, 96.44, 84.79, 78.79, 73.55, 43.57, 31.28, 30.99, 17.96. HRMS (ESI) m/z calcd for C_{32}H_{30}N_{3}O_{6}^{+} (M+H)^{+} 552.2129, found 552.2130. CCDC 1852172.

(Z)-N-(2,6-dimethylphenyl)-N-isobutyryl-3-(((2-methylbut-3-yn-2-yl)amino)methylene)-4-oxochromane-2-carboxamide

6h white solid, 59% (EA/Hex = 20%, Rf = 0.3), \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 10.42 (d, \(J = 12.6\) Hz, 1H), 7.81 (d, \(J = 7.7\) Hz, 1H), 7.48 (d, \(J = 12.7\) Hz, 1H), 7.42 - 7.30 (m, 1H), 7.17 - 7.09 (m, 1H), 7.05 (t, \(J = 5.9\) Hz, 2H), 6.96 (dd, \(J = 14.0\), 7.5 Hz, 2H), 6.54 (s, 1H), 2.58 (s, 1H), 2.46 (dd, \(J = 12.8\), 6.4 Hz, 1H), 2.03 (d, \(J = 18.7\) Hz, 6H), 1.60 (d, \(J = 16.8\) Hz, 6H), 1.04 (dd, \(J = 8.7\), 3.2 Hz, 6H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 181.28, 180.70, 173.85, 159.40, 149.10, 136.65, 136.33, 135.81, 134.39, 129.16, 128.91, 126.06, 122.76, 121.29, 116.94, 96.99, 84.72, 79.35, 73.75, 51.20, 34.36, 31.59, 30.95, 19.91, 19.34. HRMS (ESI) m/z calcd for C_{28}H_{31}N_{2}O_{6}^{+} (M+H)^{+} 459.2278, found 459.2277.
(Z)-N-(2,6-dimethylphenyl)-3-(((2-methylbut-3-yn-2-yl)amino)methylene)-N-(2-nitrobenzoyl)-4-oxochromane-2-carboxamide

6i light yellow solid, 68% (EA/Hex = 20%, Rf = 0.3), 1H NMR (400 MHz, CDCl3) δ 10.20 (d, J = 12.6 Hz, 1H), 8.12 (d, J = 8.1 Hz, 1H), 7.73 (dd, J = 7.7, 1.4 Hz, 1H), 7.52 (t, J = 7.3 Hz, 1H), 7.43 (dd, J = 9.8, 5.8 Hz, 1H), 7.36 – 7.27 (m, 3H), 7.28 – 7.17 (m, 2H), 6.92 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.53 (d, J = 12.4 Hz, 1H), 5.16 (s, 1H), 2.54 (s, 3H), 2.33 (s, 3H), 1.60 (s, 3H), 1.49 (s, 3H).

13C NMR (100 MHz, CDCl3) δ 181.06, 170.78, 167.70, 147.63, 144.83, 137.42, 136.98, 134.82, 134.25, 134.04, 129.94, 129.69, 129.44, 126.12, 124.80, 122.80, 121.54, 116.69, 95.01, 84.41, 73.95, 60.42, 51.34, 31.43, 30.92, 18.50, 18.44. HRMS (ESI) m/z calcd for C31H28N3O6+(M+H)+ 538.1973, found 538.1973.

(Z)-6-bromo-N-(1-(4-chlorophenyl)cyclopropane-1-carbonyl)-N-(2,6-dimethylphenyl)-3-(((2-methylbut-3-yn-2-yl)amino)methylene)-4-oxochromane-2-carboxamide

6j light green solid, 79% (EA/Hex = 20%, Rf = 0.3), 1H NMR (400 MHz, CDCl3) δ 10.00 (d, J = 12.3 Hz, 1H), 7.85 (d, J = 2.5 Hz, 1H), 7.43 – 7.37 (m, 1H), 7.05 (t, J = 7.5 Hz, 1H), 6.95 (t, J = 8.8 Hz, 4H), 6.84 – 6.76 (m, 2H), 6.69 (d, J = 8.2 Hz, 2H), 5.83 (s, 1H), 3.48 (dd, J = 13.2, 6.7 Hz, 1H), 2.10 (s, 1H), 1.94 (s, 3H), 1.88 – 1.81 (m, 1H), 1.56 – 1.51 (m, 2H), 1.35 (d, J = 6.5 Hz, 3H), 1.26 (d, J = 6.6 Hz, 3H), 0.90 – 0.82 (m, 2H). 13C NMR (100 MHz, CDCl3) δ 179.03, 177.02, 157.72, 151.14, 137.21, 136.81, 134.97, 132.81, 132.34, 130.89, 129.40, 128.98, 128.58, 128.05, 127.97, 124.50, 118.93, 113.84, 94.92, 79.00, 50.80, 32.51, 29.68, 24.09, 23.35, 18.37, 17.70. HRMS (ESI) m/z calcd for C34H31BrClN2O6+(M+H)+ 645.1150, found 645.1153.

(Z)-N-(2-(2,4-dichlorophenyl)acetyl)-N-(2,6-dimethylphenyl)-3-((isopropylamino)methylene)-4-oxochromane-2-carboxamide
6k light green solid, 70% (EA/Hex = 20%, Rf = 0.3), $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.06 (dd, $J = 12.4, 7.7$ Hz, 1H), 7.79 (d, $J = 8.0$ Hz, 1H), 7.39 (d, $J = 1.8$ Hz, 1H), 7.34 (t, $J = 7.7$ Hz, 1H), 7.23 – 7.15 (m, 2H), 7.10 (d, $J = 7.5$ Hz, 2H), 7.02 (d, $J = 8.2$ Hz, 1H), 6.97 – 6.90 (m, 2H), 6.85 (d, $J = 10.3$ Hz, 1H), 6.37 (s, 1H), 3.53 (q, $J = 17.9$ Hz, 2H), 3.40 (td, $J = 13.4, 6.7$ Hz, 1H), 2.14 (s, 3H), 2.10 (s, 3H), 1.27 (d, $J = 6.5$ Hz, 3H), 1.19 (d, $J = 6.5$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 186.81, 179.48, 178.27, 165.52, 157.35, 143.09, 142.06, 141.64, 140.47, 138.78, 136.85, 135.73, 135.39, 133.56, 132.30, 129.04, 127.51, 122.84, 85.36, 56.90, 48.16, 30.50, 29.62, 24.29, 24.18. HRMS (ESI) m/z calcd for C$_{30}$H$_{29}$Cl$_2$N$_2$O$_4$+ (M+H)$^+$ 551.1499, found 551.1509.

(Z)-N-(2-(4-bromophenyl)acetyl)-N-(2,6-dimethylphenyl)-3-((isopropylamino)methylene)-4-oxochromane-2-carboxamide

6l white solid, 75% (EA/Hex = 20%, Rf = 0.3), $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.02 (dd, $J = 12.8, 7.4$ Hz, 1H), 7.78 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.41 – 7.36 (m, 2H), 7.33 (ddd, $J = 8.2, 7.3, 1.8$ Hz, 1H), 7.21 – 7.15 (m, 1H), 7.06 (d, $J = 7.6$ Hz, 2H), 6.97 – 6.90 (m, 2H), 6.90 – 6.84 (m, 2H), 6.79 (d, $J = 12.5$ Hz, 1H), 6.29 (s, 1H), 3.52 – 3.40 (m, 2H), 3.39 – 3.27 (m, 1H), 1.97 (s, 3H), 1.94 (s, 3H), 1.23 (d, $J = 6.5$ Hz, 3H), 1.19 (d, $J = 6.5$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 180.47, 173.39, 159.06, 150.71, 136.88, 135.89, 134.11, 132.08, 131.54, 131.23, 129.31, 128.98, 125.97, 122.71, 121.43, 116.62, 95.18, 78.99, 50.47, 43.05, 24.00, 23.40, 17.83. HRMS (ESI) m/z calcd for C$_{30}$H$_{30}$BrN$_2$O$_4$+ (M+H)$^+$ 561.1383, found 561.1286.

N-(4-chlorophenyl)-N-(2-((2,6-dimethylphenyl)amino)-2-oxo-1-(4-oxo-4H-chromen-3-yl)ethyl)-2-(4-nitrophenyl)acetamide

5m white solid, 82% (EA/Hex = 20%, Rf = 0.3), $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.13 (s, 1H), 8.11 (dd, $J = 8.3, 1.4$ Hz, 1H), 8.03 (d, $J = 8.7$ Hz, 2H), 7.97 (s, 1H), 7.68 – 7.61 (m, 1H), 7.41 – 7.34 (m, 2H), 7.18 (d, $J = 8.5$ Hz, 4H), 7.09 (dd, $J = 8.7, 6.0$ Hz, 2H),
N-(2,6-dimethylphenyl)-2-(N-(3,5-dimethylphenyl)-2-(4-nitrophenyl)acetamido)-2-(4-oxo-4H-chromen-3-yl)acetamide

5n white solid, 87% (EA/Hex = 30%, Rf = 0.25), \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.32 (s, 1H), 8.12 – 8.04 (m, 2H), 8.00 (s, 1H), 7.65 – 7.56 (m, 1H), 7.32 (dd, \(J = 13.0, 8.1\) Hz, 2H), 7.14 (d, \(J = 8.5\) Hz, 2H), 7.05 (dt, \(J = 14.0, 6.0\) Hz, 3H), 6.81 (s, 1H), 6.63 (s, 1H), 6.45 (s, 1H), 3.54 (s, 2H), 2.18 (s, 11H), \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 176.08, 170.54, 168.15, 157.85, 155.75, 146.64, 142.82, 138.87, 135.42, 133.98, 133.46, 130.38, 130.04, 128.15, 127.37, 125.70, 125.47, 123.56, 123.27, 118.38, 118.15, 55.12, 41.70, 18.51. HRMS (ESI) m/z calcd for C\(_{35}\)H\(_{32}\)N\(_3\)O\(_6\)\(^{+}\) (M+H)\(^{+}\) 590.2286, found 590.2286.

2-((2,6-dimethylphenyl)amino)-2-oxo-1-(4-oxo-4H-chromen-3-yl)ethyl benzo[d]-[1,3]dioxole-5-carboxylate

7 white solid, 67% (EA/Hex = 20%, Rf = 0.35), \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.38 (d, \(J = 0.6\) Hz, 1H), 8.26 (dd, \(J = 8.0, 1.7\) Hz, 2H), 7.79 – 7.69 (m, 2H), 7.53 (t, \(J = 5.2\) Hz, 2H), 7.46 (dd, \(J = 11.4, 4.3\) Hz, 1H), 7.09 – 6.98 (m, 3H), 6.85 (d, \(J = 8.2\) Hz, 1H), 6.50 (s, 1H), 6.04 (s, 2H), 2.18 (s, 6H), \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 176.50, 165.74, 164.57, 156.30, 155.35, 152.22, 147.87, 135.48, 134.39, 133.09, 128.07, 127.25, 125.97, 125.82, 123.72, 122.97, 119.60, 118.38, 109.68, 108.16,
HRMS (ESI) m/z calcd for C_{27}H_{22}NO_7^+ (M+H)^+ 472.1391, found 472.1388.

(Z)-3-((tert-butylamino)methylene)-2-(1-(2,6-dimethylphenyl)-1H-tetrazol-5-yl)chroman-4-one

9a yellow solid, 82% (EA/Hex = 20%, R_f = 0.2), ^1^H NMR (400 MHz, CDCl_3) δ 10.54 (d, J = 13.0 Hz, 1H), 7.70 (dd, J = 7.8, 1.5 Hz, 1H), 7.28 – 7.25 (m, 1H), 7.23 (dd, J = 6.8, 1.3 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.95 (ddd, J = 7.8, 7.3, 1.0 Hz, 1H), 6.85 (d, J = 13.3 Hz, 1H), 6.56 (dd, J = 8.2, 0.7 Hz, 1H), 6.23 (d, J = 0.5 Hz, 1H), 1.85 (s, 3H), 1.79 (s, 3H), 1.27 (s, 9H). ^1^C NMR (100 MHz, CDCl_3) δ 179.13, 156.28, 155.91, 147.53, 135.75, 135.64, 133.79, 130.83, 128.77, 128.67, 125.95, 122.29, 122.00, 116.63, 94.89, 71.89, 52.99, 29.88, 17.46, 17.29. HRMS (ESI) m/z calcd for C_{23}H_{26}N_5O_2^+ (M+H)^+ 404.2081, found 404.2081. CCDC 1962910.

(Z)-2-(1-(tert-butyl)-1H-tetrazol-5-yl)-3-((tert-butylamino)methylene)chroman-4-one

9b yellow solid, 93% (EA/Hex = 20%, R_f = 0.2), ^1^H NMR (400 MHz, CDCl_3) δ 10.56 (d, J = 13.1 Hz, 1H), 7.91 (dd, J = 7.8, 1.7 Hz, 1H), 7.27 (ddd, J = 8.3, 7.3, 1.8 Hz, 1H), 7.01 (td, J = 7.8, 1.0 Hz, 1H), 6.83 – 6.73 (m, 2H), 6.38 (s, 1H), 1.81 (s, 9H), 1.27 (s, 9H). ^1^C NMR (100 MHz, CDCl_3) δ 180.30, 155.33, 153.41, 146.91, 133.59, 126.53, 124.12, 122.52, 116.75, 96.70, 71.61, 62.61, 52.74, 29.97. HRMS (ESI) m/z calcd for C_{19}H_{26}N_5O_2^+ (M+H)^+ 356.2081, found 356.2086.

(Z)-3-((tert-butylamino)methylene)-2-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)chroman-4-one
9c yellow solid, 85% (EA/Hex = 20%, Rf = 0.2), $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.54 (d, $J$ = 13.0 Hz, 1H), 7.93 (dt, $J$ = 7.8, 1.9 Hz, 1H), 7.34 – 7.25 (m, 1H), 7.08 – 6.95 (m, 1H), 6.77 (dd, $J$ = 7.8, 5.1 Hz, 2H), 6.46 (s, 1H), 2.06 (q, $J$ = 15.2 Hz, 2H), 1.88 (d, $J$ = 7.8 Hz, 6H), 1.25 (s, 9H), 0.78 (s, 9H). 13C NMR (100 MHz, CDCl$_3$) $\delta$ 180.43, 155.71, 153.42, 146.79, 133.59, 126.49, 124.06, 122.46, 116.83, 96.74, 71.59, 65.94, 53.94, 52.72, 31.73, 30.76. HRMS (ESI) m/z calcd for C$_{23}$H$_{34}$N$_{5}$O$_{2}$ (M+H)$^+$ 412.2707, found 412.2704.

(Z)-6-bromo-3-((tert-butylamino)methylene)-2-(1-cyclohexyl-1H-tetrazol-5-yl)-chroman-4-one

9d yellow solid, 88% (EA/Hex = 20%, Rf = 0.2), $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.67 (d, $J$ = 13.1 Hz, 1H), 8.01 (d, $J$ = 2.5 Hz, 1H), 7.42 (dd, $J$ = 8.6, 2.5 Hz, 1H), 6.72 (d, $J$ = 8.7 Hz, 1H), 6.64 (d, $J$ = 13.3 Hz, 1H), 6.42 – 6.38 (m, 1H), 4.58 (tt, $J$ = 11.4, 4.0 Hz, 1H), 2.11 – 1.97 (m, 4H), 1.92 (d, $J$ = 9.7 Hz, 4H), 1.74 (s, 1H), 1.37 – 1.29 (m, 3H), 1.26 (s, 9H). 13C NMR (100 MHz, CDCl$_3$) $\delta$ 178.40, 155.16, 152.28, 147.19, 136.43, 129.25, 125.27, 118.69, 115.47, 95.52, 71.91, 59.07, 53.14, 33.21, 32.79, 29.86, 25.26, 24.74. HRMS (ESI) m/z calcd for C$_{21}$H$_{27}$BrN$_{5}$O$_{2}$ (M+H)$^+$ 460.1343, found 460.1341.

(Z)-6-bromo-3-((tert-butylamino)methylene)-2-(1-(2,6-dimethylphenyl)-1H-tetrazol-5-yl)chroman-4-one

9e yellow solid, 79% (EA/Hex = 20%, Rf = 0.2), $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.57 (d, $J$ = 13.1 Hz, 1H), 7.75 (s, 1H), 7.29 (dd, $J$ = 15.1, 8.1 Hz, 2H), 7.11 (d, $J$ = 7.5 Hz, 1H), 7.00 (d, $J$ = 7.6 Hz, 1H), 6.86 (d, $J$ = 13.4 Hz, 1H), 6.49 (d, $J$ = 8.7 Hz, 1H), 6.27 (s, 1H), 1.82 (s, 3H), 1.78 (s, 3H), 1.27 (s, 9H). 13C NMR (100 MHz, CDCl$_3$) $\delta$ 177.42, 155.77, 155.04, 148.03, 136.21, 135.67, 130.88, 128.86, 128.77, 128.55, 123.59, 118.46, 114.59, 109.75, 94.33, 71.94, 53.25, 29.83, 17.48, 17.24. HRMS (ESI) m/z calcd for C$_{23}$H$_{25}$BrN$_{5}$O$_{2}$ (M+H)$^+$ 482.1186, found 482.1184.
(Z)-6-bromo-2-(1-(tert-butyl)-1H-tetrazol-5-yl)-3-((tert-butylamino)methylene)chroman-4-one

9f yellow solid, 86% (EA/Hex = 20%, R_f = 0.2), ^1H NMR (400 MHz, CDCl_3) δ 10.58 (d, J = 13.2 Hz, 1H), 8.03 (s, 1H), 7.36 (d, J = 8.6 Hz, 1H), 6.83 (d, J = 13.3 Hz, 1H), 6.66 (d, J = 8.7 Hz, 1H), 6.36 (s, 1H), 1.82 (s, 9H), 1.30 (s, 9H). ^13C NMR (100 MHz, CDCl_3) δ 178.78, 154.12, 153.17, 147.29, 136.15, 129.31, 125.61, 118.67, 115.30, 96.17, 71.65, 62.62, 53.00, 29.94. HRMS (ESI) m/z calcd for C_{19}H_{25}BrN_5O_2+ (M+H)^+ 434.1186, found 434.1181.

(Z)-6-bromo-3-((tert-butylamino)methylene)-2-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)chroman-4-one

9g yellow solid, 86% (EA/Hex = 20%, R_f = 0.2), ^1H NMR (400 MHz, CDCl_3) δ 10.57 (d, J = 13.3 Hz, 1H), 8.05 (d, J = 2.5 Hz, 1H), 7.43 – 7.33 (m, 1H), 6.79 (d, J = 13.3 Hz, 1H), 6.67 (d, J = 8.7 Hz, 1H), 6.45 (s, 1H), 2.07 (dd, J = 33.2, 15.2 Hz, 2H), 1.90 (d, J = 8.3 Hz, 6H), 1.28 (s, 9H), 0.80 (s, 9H). ^13C NMR (100 MHz, CDCl_3) δ 178.92, 154.50, 153.18, 147.10, 136.15, 129.29, 125.57, 118.74, 115.24, 96.23, 71.64, 65.94, 54.05, 52.96, 31.76, 30.78, 30.40, 29.92. HRMS (ESI) m/z calcd for C_{23}H_{33}BrN_5O_2+ (M+H)^+ 490.1812, found 490.1811.

(Z)-2-(1-(tert-butyl)-1H-tetrazol-5-yl)-3-((isopropylamino)methylene)chroman-4-one

9h yellow solid, 78% (EA/Hex = 20%, R_f = 0.2), ^1H NMR (400 MHz, CDCl_3) δ 10.22 (d, J = 7.3 Hz, 1H), 7.92 (dd, J = 7.8, 1.5 Hz, 1H), 7.35 – 7.26 (m, 1H), 7.03 (t, J = 7.5 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 6.69 (d, J = 12.9 Hz, 1H), 6.39 (s, 1H), 3.43 (dq, J = 13.3, 6.6 Hz, 1H), 1.82 (s, 9H), 1.24 (dd, J = 6.5, 3.5 Hz, 6H). ^13C NMR (100 MHz, CDCl_3) δ 180.49, 155.51, 153.28, 149.14,
133.67, 126.58, 124.03, 122.56, 116.78, 96.69, 71.49, 62.60, 50.66, 30.02, 23.86, 23.54. HRMS (ESI) m/z calcd for C₁₈H₂₃N₅O₂⁺ (M+H)⁺ 342.1925, found 342.1922.

(Z)-3-((isopropylamino)methylene)-2-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)chroman-4-one

9i yellow solid, 78% (EA/Hex = 20%, Rf = 0.2), ¹H NMR (400 MHz, CDCl₃) δ 10.18 (dd, J = 12.4, 7.5 Hz, 1H), 7.92 (dd, J = 7.8, 1.6 Hz, 1H), 7.29 (ddd, J = 8.3, 7.4, 1.7 Hz, 1H), 7.02 (td, J = 7.8, 0.9 Hz, 1H), 6.76 (dd, J = 8.2, 0.6 Hz, 1H), 6.67 (d, J = 12.9 Hz, 1H), 6.46 (s, 1H), 3.40 (dq, J = 13.3, 6.6 Hz, 1H), 2.07 (dd, J = 38.9, 15.1 Hz, 2H), 1.88 (d, J = 17.3 Hz, 6H), 1.20 (dd, J = 6.5, 4.9 Hz, 6H), 0.79 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 180.57, 155.77, 153.35, 149.07, 133.64, 126.52, 124.00, 122.47, 116.84, 96.75, 71.47, 66.01, 53.88, 50.63, 31.72, 30.76, 30.51, 30.16, 23.84, 23.50. HRMS (ESI) m/z calcd for C₂₂H₃₂N₅O₂⁺ (M+H)⁺ 398.2551, found 398.2555.

(Z)-2-(1-cyclohexyl-1H-tetrazol-5-yl)-3-((isopropylamino)methylene)chroman-4-one

9j yellow solid, 74% (EA/Hex = 20%, Rf = 0.2), ¹H NMR (400 MHz, CDCl₃) δ 10.35 – 10.19 (m, 1H), 7.91 (dd, J = 7.8, 1.7 Hz, 1H), 7.35 (ddd, J = 8.2, 7.4, 1.7 Hz, 1H), 7.13 – 7.03 (m, 1H), 6.88 – 6.78 (m, 1H), 6.50 (d, J = 12.9 Hz, 1H), 6.44 (s, 1H), 4.63 (tt, J = 11.6, 3.8 Hz, 1H), 3.39 (td, J = 13.3, 6.6 Hz, 1H), 2.05 (dd, J = 11.9, 3.2 Hz, 2H), 1.92 (dd, J = 10.7, 8.6 Hz, 3H), 1.72 (s, 2H), 1.32 (ddd, J = 10.0, 9.3, 6.7 Hz, 3H), 1.21 (dd, J = 7.9, 6.6 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 180.14, 156.51, 152.44, 148.96, 133.97, 126.51, 123.68, 122.74, 116.79, 96.05, 71.75, 59.06, 50.84, 33.24, 32.70, 25.23, 24.77, 23.66. HRMS (ESI) m/z calcd for C₂₀H₂₆N₅O₂⁺ (M+H)⁺ 368.2081, found 368.2085.

(Z)-2-(1-(2,6-dimethylphenyl)-1H-tetrazol-5-yl)-3-((isopropylamino)methylene) chroman-4-one
9k yellow solid, 88% (EA/Hex = 20%, Rf = 0.2), 1H NMR (400 MHz, CDCl₃) δ 10.19 – 10.00 (m, 1H), 7.69 (dd, J = 7.8, 1.7 Hz, 1H), 7.29 – 7.23 (m, 1H), 7.09 (d, J = 7.3 Hz, 1H), 7.03 (dd, J = 7.6, 0.6 Hz, 1H), 6.93 (ddd, J = 8.2, 7.5, 1.0 Hz, 1H), 6.68 – 6.55 (m, 2H), 6.15 (d, J = 1.8 Hz, 1H), 3.33 (dq, J = 13.6, 6.6 Hz, 1H), 1.82 (s, 3H), 1.78 (s, 3H), 1.21 (d, J = 6.5 Hz, 3H). 13C NMR (100 MHz, CDCl₃) δ 179.34, 156.42, 155.87, 149.76, 135.73, 133.89, 132.30, 130.81, 128.77, 128.65, 125.97, 122.31, 122.02, 116.78, 94.86, 71.80, 50.73, 23.91, 23.25, 17.42, 17.28. HRMS (ESI) m/z calcd for C₂₂H₂₄N₅O₂⁺ (M+H)⁺ 390.1925, found 390.1923.

(Z)-3-((sec-butylamino)methylene)-2-(1-cyclohexyl-1H-tetrazol-5-yl)chroman-4-one

9l yellow solid, 82% (EA/Hex = 20%, Rf = 0.2), 1H NMR (400 MHz, CDCl₃) δ 10.28 (d, J = 17.8 Hz, 1H), 7.92 (d, J = 6.4 Hz, 1H), 7.40 – 7.33 (m, 1H), 7.12 – 7.05 (m, 1H), 6.84 (dd, J = 8.2, 3.6 Hz, 1H), 6.47 (d, J = 12.0 Hz, 2H), 4.64 (dd, J = 15.4, 7.7, 3.9 Hz, 1H), 3.08 (td, J = 14.6, 7.7 Hz, 1H), 2.06 (d, J = 9.4 Hz, 3H), 1.91 (d, J = 8.5 Hz, 4H), 1.53 – 1.46 (m, 2H), 1.32 (dd, J = 15.6, 5.6 Hz, 3H), 1.19 (dd, J = 8.4, 6.8 Hz, 3H), 0.91 – 0.84 (m, 3H). 13C NMR (101 MHz, CDCl₃) δ 180.08, 149.82, 133.98, 126.50, 125.76, 125.43, 123.69, 122.75, 118.25, 116.83, 95.94, 71.75, 59.07, 57.18, 33.27, 32.70, 30.54, 25.22, 21.40, 10.28. HRMS (ESI) m/z calcd for C₂₁H₂₈N₅O₂⁺ (M+H)⁺ 382.2238, found 382.2236.

(Z)-3-((cyclopropylamino)methylene)-2-(1-(2,6-dimethylphenyl)-1H-tetrazol-5-yl)chroman-4-one

9m yellow solid, 51% (EA/Hex = 20%, Rf = 0.2), 1H NMR (400 MHz, CDCl₃) δ 10.04 (d, J = 12.2 Hz, 1H), 7.72 (dd, J = 7.8, 1.7 Hz, 1H), 7.28 (dd, J = 8.6, 6.7 Hz, 1H), 7.10 (dd, J = 17.7, 7.6 Hz, 2H), 7.00 – 6.88 (m, 1H), 6.69 (d, J = 12.6 Hz, 1H), 6.60 (d, J = 8.3 Hz, 1H), 6.12 (s, 1H), 2.69 (dt, J = 6.8, 3.2 Hz, 1H), 1.85 (s, 3H), 1.80 (s, 3H), 0.78 – 0.68 (m, 2H), 0.64 – 0.52 (m, 2H). 13C
NMR (100 MHz, CDCl₃) δ 179.77, 156.50, 155.71, 151.69, 135.74, 134.13, 132.29, 130.85, 128.80, 128.69, 126.17, 122.30, 122.11, 116.90, 96.06, 71.74, 29.37, 17.44.

HRMS (ESI) m/z calcd for C₂₂H₂₂N₅O₂⁺ (M+H)⁺ 388.1768, found 388.1762.

(Z)-2-(1-(tert-butyl)-1H-tetrazol-5-yl)-3-((cyclobutylamino)methylene)chroman-4-one

9n yellow solid, 60% (EA/Hex = 20%, Rₛ = 0.2), ¹H NMR (400 MHz, CDCl₃) δ 10.43 – 10.26 (m, 1H), 7.92 (d, J = 7.7 Hz, 1H), 7.28 (dd, J = 10.6, 4.9 Hz, 1H), 7.02 (td, J = 7.7, 0.9 Hz, 1H), 6.80 – 6.72 (m, 1H), 6.63 (d, J = 12.8 Hz, 1H), 6.36 (s, 1H), 3.75 (dd, J = 16.3, 8.2 Hz, 1H), 2.28 (dt, J = 14.1, 4.9 Hz, 2H), 2.04 (dd, J = 19.7, 10.0 Hz, 2H), 1.85 – 1.76 (m, 9H), 1.79 – 1.49 (m, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 180.66, 155.49, 153.29, 148.77, 133.73, 126.61, 123.98, 122.56, 116.80, 96.75, 71.36, 62.58, 53.75, 31.70, 31.48, 29.99, 14.41. HRMS (ESI) m/z calcd for C₁₉H₂₄N₅O₂⁺ (M+H)⁺ 354.1925, found 354.1926.

3-((1-(tert-butyl)-1H-tetrazol-5-yl)(butylamino)methyl)-4H-chromen-4-one

10o white solid, 77% (EA/Hex = 20%, Rₛ = 0.25), ¹H NMR (400 MHz, CDCl₃) δ 8.21 – 8.17 (m, 2H), 7.66 (ddd, J = 8.7, 7.2, 1.6 Hz, 1H), 7.47 – 7.37 (m, 2H), 5.82 (s, 1H), 2.62 (dt, J = 10.9, 7.1 Hz, 1H), 2.51 (dt, J = 10.9, 7.2 Hz, 1H), 1.75 (s, 9H), 1.44 (dt, J = 14.7, 7.3 Hz, 2H), 1.35 – 1.19 (m, 3H), 0.84 (t, J = 7.3 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 176.08, 156.26, 155.98, 155.23, 134.07, 125.97, 125.46, 123.61, 122.62, 118.26, 61.65, 48.02, 47.75, 31.98, 29.89, 20.25, 13.84. HRMS (ESI) m/z calcd for C₁₉H₂₆N₅O₂⁺ (M+H)⁺ 356.2081, found 356.2063.

3-((1-(tert-butyl)-1H-tetrazol-5-yl)(phenylamino)methyl)-4H-chromen-4-one
10p white solid, 84% (EA/Hex = 20%, R<sub>f</sub> = 0.25), ¹H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.27 (d, J = 0.9 Hz, 1H), 8.15 (dd, J = 8.0, 1.7 Hz, 1H), 7.67 (ddd, J = 8.7, 7.2, 1.7 Hz, 1H), 7.47 – 7.37 (m, 2H), 7.17 (t, J = 7.9 Hz, 2H), 6.77 (t, J = 7.4 Hz, 1H), 6.69 – 6.63 (m, 2H), 6.48 (d, J = 8.5 Hz, 1H), 4.45 (t, J = 8.4 Hz, 1H), 1.83 (s, 9H). ¹³C NMR (100 MHz, CDCl<sub>3</sub>) δ 176.83, 156.49, 155.53, 154.18, 144.70, 134.09, 129.67, 125.59, 123.48, 121.64, 119.38, 118.33, 113.44, 62.24, 45.15, 29.98. HRMS (ESI) m/z calcd for C<sub>21</sub>H<sub>22</sub>N<sub>5</sub>O<sub>2</sub>+(M+H)<sup>+</sup> 376.1768, found 376.1725.

2-(1-(tert-butyl)-1H-tetrazol-5-yl)-4-oxo-4H-chromene-3-carbaldehyde

19a white solid, 63% (EA/Hex = 25%, R<sub>f</sub> = 0.3), ¹H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.37 (s, 1H), 8.33 (d, J = 7.9 Hz, 1H), 7.86 – 7.79 (m, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 1.70 (s, 9H). ¹³C NMR (100 MHz, CDCl<sub>3</sub>) δ 187.95, 175.76, 156.48, 155.69, 146.93, 135.80, 127.50, 126.36, 124.63, 121.16, 118.41, 63.10, 29.69. HRMS (ESI) m/z calcd for C<sub>15</sub>H<sub>15</sub>N<sub>4</sub>O<sub>3</sub>+(M+H)<sup>+</sup> 299.1139, found 299.1134.

2-(1-cyclohexyl-1H-tetrazol-5-yl)-4-oxo-4H-chromene-3-carbaldehyde

19b white solid, 54% (EA/Hex = 25%, R<sub>f</sub> = 0.3), ¹H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.94 (s, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.75 (t, J = 7.8 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.48 (dd, J = 7.9, 7.2 Hz, 1H), 4.98 – 4.85 (m, 1H), 2.18 (d, J = 12.6 Hz, 2H), 2.06 – 1.92 (m, 5H), 1.76 (d, J = 13.3 Hz, 1H), 1.48 – 1.43 (m, 2H). ¹³C NMR (100 MHz, CDCl<sub>3</sub>) δ 179.46, 173.80, 162.43, 155.61, 149.43, 134.82, 126.71, 126.55, 124.94, 122.62, 118.37, 60.16, 32.91, 25.20, 24.87. HRMS (ESI) m/z calcd for C<sub>17</sub>H<sub>17</sub>N<sub>4</sub>O<sub>3</sub>+(M+H)<sup>+</sup> 325.1295, found 325.1291.

4-oxo-2-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)-4H-chromene-3-carbaldehyde
19c white solid, 71% (EA/Hex = 25%, Rf = 0.3), $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.36 (s, 1H), 8.34 (dd, $J$ = 8.0, 1.6 Hz, 1H), 7.83 (ddd, $J$ = 8.7, 7.3, 1.7 Hz, 1H), 7.59 (td, $J$ = 7.7, 1.0 Hz, 1H), 7.50 – 7.46 (m, 1H), 2.11 (s, 2H), 1.70 (s, 6H), 0.86 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 187.96, 175.76, 156.73, 155.59, 146.04, 135.85, 127.52, 124.62, 121.18, 118.24, 66.59, 54.62, 31.66, 30.72, 29.35. HRMS (ESI) m/z calcd for C$_{19}$H$_{23}$N$_4$O$_3$+ (M+H)$^+$ 355.1765, found 355.1782.

4-(1-(tert-butyl)-1H-tetrazol-5-yl)-4H-chromeno[4,3-c]isoxazole

20 white solid, 78% (EA/Hex = 30%, Rf = 0.2), $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.64 – 8.59 (m, 1H), 7.96 (dd, $J$ = 7.6, 1.4 Hz, 1H), 7.39 (ddd, $J$ = 8.6, 4.7, 1.3 Hz, 1H), 7.17 (t, $J$ = 7.6 Hz, 1H), 7.07 – 7.00 (m, 1H), 6.64 (d, $J$ = 1.3 Hz, 1H), 1.88 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 154.57, 153.31, 152.75, 150.61, 132.37, 125.07, 123.88, 117.61, 114.42, 110.54, 65.56, 63.32, 29.86. HRMS (ESI) m/z calcd for C$_{15}$H$_{16}$N$_5$O$_2$+ (M+H)$^+$ 298.1299, found 298.1297.

6-(1-cyclohexyl-1H-tetrazol-5-yl)-2-methyl-6H-chromeno[3,4-e]pyrazolo[1,5-a]pyrimidine

21 white solid, 83% (EA/Hex = 30%, Rf = 0.2), $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.51 (d, $J$ = 8.0 Hz, 1H), 8.03 (s, 1H), 7.44 (t, $J$ = 7.7 Hz, 1H), 7.28 (t, $J$ = 7.8 Hz, 1H), 6.97 (d, $J$ = 8.1 Hz, 1H), 6.82 (s, 1H), 6.60 (s, 1H), 4.72 – 4.56 (m, 1H), 2.60 (s, 3H), 2.13 – 1.95 (m, 5H), 1.76 (s, 2H), 1.35 (t, $J$ = 8.6 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 156.16, 153.82, 151.15, 151.08, 144.32, 135.55, 133.71, 130.70, 123.56, 117.06, 115.73, 107.82, 97.02, 67.39, 59.25, 33.25, 25.25, 24.71, 14.90. HRMS (ESI) m/z calcd for C$_{21}$H$_{22}$N$_7$O$^+$ (M+H)$^+$ 388.1880, found 388.1883.
5-(1-cyclohexyl-1H-tetrazol-5-yl)-5H-chromeno[4,3-d]pyrimidin-2-amine

22 white solid, 84% (EA/Hex = 35%, Rf = 0.2), $^1H$ NMR (400 MHz, CDCl$_3$) δ 8.17 (dd, $J = 7.8$, 1.5 Hz, 1H), 7.83 (s, 1H), 7.38 (td, $J = 8.2$, 1.7 Hz, 1H), 7.13 (dd, $J = 11.0$, 4.1 Hz, 1H), 6.89 (d, $J = 8.2$ Hz, 1H), 6.69 (s, 1H), 5.32 (s, 2H), 4.61 – 4.45 (m, 1H), 2.02 (dd, $J = 18.4$, 8.7 Hz, 3H), 1.97 – 1.86 (m, 3H), 1.71 (s, 1H), 1.30 (s, 3H). $^{13}C$ NMR (100 MHz, CDCl$_3$) δ 163.63, 155.97, 154.80, 154.47, 151.43, 133.61, 125.43, 123.44, 120.64, 117.05, 111.32, 68.33, 59.23, 33.23, 32.75, 25.23, 24.72. HRMS (ESI) m/z calcd for C$_{18}$H$_{20}$N$_7$O$^+$ (M+H)$^+$ 350.1724, found 350.1717.
NMR Characterization Data and Figures of Products

$^1$H NMR and $^{13}$C NMR spectrum of 5a
$^1$$H$ NMR and $^{13}$$C$ NMR spectrum of 6a
$^1$H NMR and $^{13}$C NMR spectrum of 6b
$^1$H NMR and $^{13}$C NMR spectrum of 6c.
$^1$H NMR and $^{13}$C NMR spectrum of 6d
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$^1$H NMR and $^{13}$C NMR spectrum of 20
$^{1}\text{H NMR}$ and $^{13}\text{C NMR}$ spectrum of 21
$^1$H NMR and $^{13}$C NMR spectrum of 22
checkCIF/PLATON report

You have not supplied any structure factors. As a result the full set of tests cannot be run.

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No syntax errors found. CIF dictionary Interpreting this report

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<th>Alert Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLAT003_ALERT_2_C</td>
<td>Number of Uiso or Uij Restrained non-H Atoms 2 Report</td>
</tr>
<tr>
<td>PLAT005_ALERT_5_G</td>
<td>No Embedded Refinement Details Found in the CIF Please Do !</td>
</tr>
<tr>
<td>PLAT066_ALERT_1_G</td>
<td>Predicted and Reported Tmin&amp;Tmax Range Identical ? Check</td>
</tr>
<tr>
<td>PLAT230_ALERT_2_G</td>
<td>Hirshfeld Test Diff for C28 -- C31 7.4 s.u.</td>
</tr>
<tr>
<td>PLAT343_ALERT_2_G</td>
<td>Unusual sp? Angle Range in Main Residue for C32 Check</td>
</tr>
<tr>
<td>PLAT793_ALERT_4_G</td>
<td>Model has Chirality at C18 (Centro SPGR) R Verify</td>
</tr>
<tr>
<td>PLAT860_ALERT_3_G</td>
<td>Number of Least-Squares Restraints 1 Note</td>
</tr>
<tr>
<td>PLAT899_ALERT_4_G</td>
<td>SHELXL97 is Deprecated and Succeeded by SHELXL 2018 Note</td>
</tr>
</tbody>
</table>

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9 ALERT level G = General information/check it is not something unexpected

2 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
12 ALERT type 2 Indicator that the structure model may be wrong or deficient
2 ALERT type 3 Indicator that the structure quality may be low
2 ALERT type 4 Improvement, methodology, query or suggestion
2 ALERT type 5 Informative message, check
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**PLATON version of 23/04/2018; check.def file version of 23/04/2018**
checkCIF/PLATON report

Structure factors have been supplied for datablock(s) a

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found.  CIF dictionary  Interpreting this report

Datablock: a

Bond precision:  C-C = 0.0061 Å  Wavelength=0.71073 Å

Cell:  
    a=10.815(8)  b=25.531(17)  c=15.619(11)  
    alpha=90  beta=90.186(14)  gamma=90

Temperature:  293 K

Calculated  Reported
Volume  4313(5)  4313(5)
Space group  P 21/c  P 1 21/c 1
Hall group  -P 2ybc  -P 2ybc
Moiety formula  C23 H25 N5 O2  C23 H25 N5 O2
Sum formula  C23 H25 N5 O2  C23 H25 N5 O2
Mr  403.48  403.48
Dx,g cm-3  1.243  1.243
Z  8  8
Mu (mm-1)  0.082  0.082
F000  1712.0  1712.0
F000’  1712.64
h,k,lmax  12,30,18  12,30,18
Nref  7600  7588
Tmin,Tmax  0.977,0.984  0.977,0.984
Tmin’  0.977

Correction method= # Reported T Limits: Tmin=0.977 Tmax=0.984
AbsCorr = NONE

Data completeness= 0.998  Theta(max)= 25.000
R(reflections)= 0.0767(3484)  wr2(reflections)= 0.1816(7588)
S = 1.039  Npar= 541

The following ALERTS were generated. Each ALERT has the format
   test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.
Alert level B

PLAT242_ALERT_2_B Low ‘MainMol’ Ueq as Compared to Neighbors of C19 Check

Alert level C

ABSTY03_ALERT_1_C The _exptl_absorpt_correction_type has been given as none. However values have been given for Tmin and Tmax. Remove these if an absorption correction has not been applied.

From the CIF: _exptl_absorpt_correction_T_min 0.977
From the CIF: _exptl_absorpt_correction_T_max 0.984

RINTA01_ALERT_3_C The value of Rint is greater than 0.12
Rint given 0.150

PLAT020_ALERT_3_C The Value of Rint is Greater Than 0.12 ......... 0.150 Report

PLAT220_ALERT_2_C Non-Solvent Resd 1 C Ueq(max)/Ueq(min) Range 4.8 Ratio

PLAT221_ALERT_2_C Non-Solvent Resd 2 C Ueq(max)/Ueq(min) Range 3.9 Ratio

PLAT232_ALERT_2_C Non-Solv. Resd 1 H Uiso(max)/Uiso(min) Range 5.4 Ratio

PLAT233_ALERT_2_C Non-Solv. Resd 2 H Uiso(max)/Uiso(min) Range 4.6 Ratio

PLAT234_ALERT_4_C Large Hirshfeld Difference C19 --C22 . 0.16 Ang.

PLAT242_ALERT_2_C Low ‘MainMol’ Ueq as Compared to Neighbors of C42 Check

PLAT244_ALERT_2_C Low ‘MainMol’ Ueq as Compared to Neighbors of C42 Check

PLAT250_ALERT_2_C Large Average Ueq of Residue Including 01 0.083 Check

PLAT250_ALERT_2_C Large Average Ueq of Residue Including 03 0.081 Check

PLAT334_ALERT_2_C Small Aver. Benzene C-C Dist C2 -C8 1.37 Ang.

PLAT334_ALERT_2_C Small Aver. Benzene C-C Dist C13 -C18 1.37 Ang.

PLAT334_ALERT_2_C Small Aver. Benzene C-C Dist C24 -C30 1.37 Ang.

PLAT334_ALERT_2_C Small Aver. Benzene C-C Dist C35 -C40 1.37 Ang.

PLAT340_ALERT_3_C Low Bond Precision on C-C Bonds ............... 0.00607 Ang.

Alert level G

PLAT003_ALERT_2_G Number of Uiso or Uij Restrained non-H Atoms ... 1 Report

PLAT007_ALERT_5_G Number of Unrefined Donor-H Atoms ............... 2 Report

PLAT066_ALERT_1_G Predicted and Reported Tmin/Tmax Range Identical? Check

PLAT186_ALERT_4_G The CIF-Embedded .res File Contains ISOR Records 1 Report

PLAT199_ALERT_1_G Reported _cell_measurement_temperature ..... (K) 293 Check

PLAT200_ALERT_1_G Reported _diffrn_ambient_temperature ..... (K) 293 Check

PLAT380_ALERT_4_G Incorrectly? Oriented X(sp2)-Methyl Moiety ..... C1 Check

PLAT380_ALERT_4_G Incorrectly? Oriented X(sp2)-Methyl Moiety ..... C5 Check

PLAT380_ALERT_4_G Incorrectly? Oriented X(sp2)-Methyl Moiety ..... C23 Check

PLAT380_ALERT_4_G Incorrectly? Oriented X(sp2)-Methyl Moiety ..... C27 Check

PLAT793_ALERT_4_G Model has Chirality at C10 (Centro SPGR) R Verify

PLAT793_ALERT_4_G Model has Chirality at C32 (Centro SPGR) R Verify

PLAT860_ALERT_3_G Number of Least-Squares Restraints ............... 6 Note

PLAT913_ALERT_3_G Missing # of Very Strong Reflections in FCF ..... 1 Note

PLAT933_ALERT_2_G Number of OMIT Records in Embedded .res File ... 6 Note

PLAT961_ALERT_5_G Dataset Contains no Negative Intensities ....... Please Check

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PLATON version of 06/01/2019; check.def file version of 19/12/2018