

## An easy synthesis of diversely functionalized 2*H*-chromenes and amido amines by an enol-Ugi reaction

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Dedicated to Prof. Oleg Rakitin on the occasion of his 65<sup>th</sup> birthday

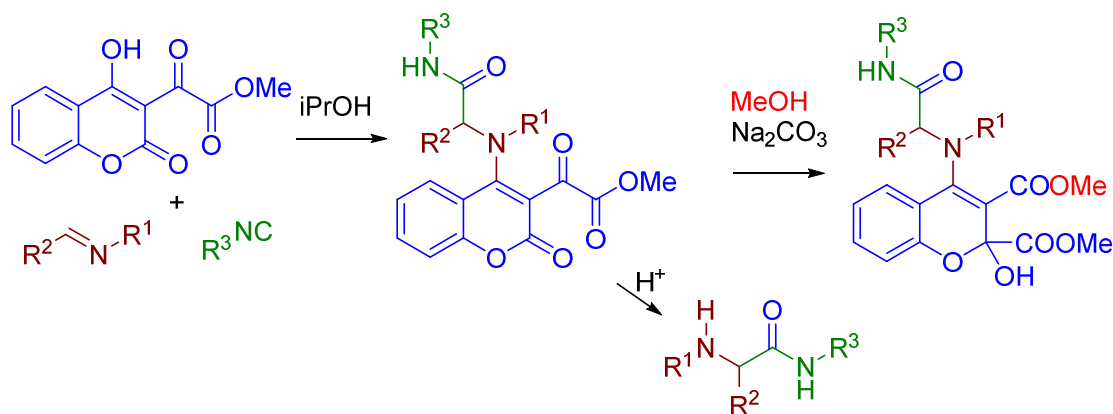
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### Abstract

The first synthesis of methyl 2-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxoacetate is described. This compound has been successfully used in a multicomponent enol-Ugi condensation with imines and isocyanides affording 4-aminoacyl-coumarin enamines in a highly atom-economic and convergent process. Furthermore, the post-condensation transformation of these adducts allows the straightforward synthesis of both unprotected amino amides and as yet unknown 2-hydroxychromenyl enamines.



**Keywords:** Multicomponent reactions, enols, benzopyrans, coumarins, natural products, combinatorial chemistry

## Introduction

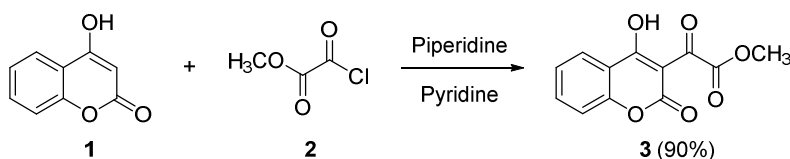
The 2*H*-chromene structure is the core motif of a large diversity of natural and synthetic compounds possessing important biological activities.<sup>1,2</sup> In addition, many 2*H*-chromenes have utility as photochromic materials<sup>3-6</sup> and as intermediates in the synthesis of more complex polycyclic heterocycles.<sup>7-11</sup> These important applications have stimulated the development of diverse synthetic approaches to 2*H*-chromenes; however, new efficient strategies leading to novel substitution patterns are still required. With this aim, we have effectively used multicomponent reactions of isocyanides for the one-pot synthesis of several chromene scaffolds.<sup>12-17</sup> In particular, we have synthesized biologically interesting 4-amino-2*H*-chromenes through the novel enol-Ugi reaction<sup>18</sup> of electron-deficient 4-hydroxycoumarins.<sup>19</sup>

We reasoned that the introduction of a strongly electron-withdrawing  $\alpha$ -ketoester group into the 3-position of 4-hydroxycoumarin would have the double effect of facilitating the enol-Ugi reaction of this enol and opening the possibility of performing post-condensation transformations leading to new chromene scaffolds.

Here we report the enol-Ugi reactions of methyl 2-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxoacetate to give the corresponding 4-aminoacyl-coumarins, and their further transformation into 4-amino-2-hydroxy-2*H*-chromenes (**8**). Although 2-hydroxy-2*H*-chromenes can be synthesized from salicylaldehydes and dimethyl acetylenedicarboxylate in particular conditions,<sup>20-23</sup> there is only one report in which a simple aromatic amine substituent is introduced on position 4, with loss of the double bond.<sup>24</sup> Chromene-substituted amino amides are privileged structures, as combine the possibility of forming conformationally diverse peptides with the ability of the heterocycle to bind to biological targets. The direct introduction of complex aminoacyl substituents in a combinatorial way would provide a powerful strategy to modulate the biological or physical properties of these chromene derivatives.

## Results and Discussion

It is known that 3-acyl-4-hydroxycoumarins can be prepared by the reaction of 4-hydroxycoumarin with different acylating agents.<sup>25</sup> Basing on these precedents, we could readily synthesize the hitherto unknown 2-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxoacetate, in a 90% yield, by the acylation of 4-hydroxy-2*H*-chromen-2-one with methyl 2-chloro-2-oxoacetate, followed by a Fries rearrangement (Scheme 1).



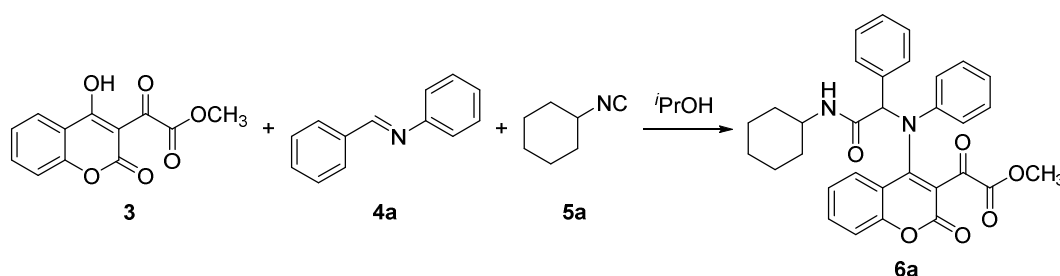
**Scheme 1.** Synthesis of 2-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxoacetate.

We then performed the enol-Ugi reaction of 2-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxoacetate with *N*,1-diphenylmethanimine and cyclohexyl isocyanide in methanol, the usual solvent for this type of reaction. Unfortunately, although the formation of a main product was detected by tlc, only a complex mixture of products was obtained after the workup. We thus explored the use of other solvents (Table 1). Successfully,

when the reaction was performed in isopropanol at room temperature (Table 1, entry 7), the expected adduct **6a** precipitated from the reaction medium and could be isolated by simple filtration in 64% yield (Scheme 2).

**Table 1.** Effect of the solvent in the enol-Ugi reaction of enol **3**

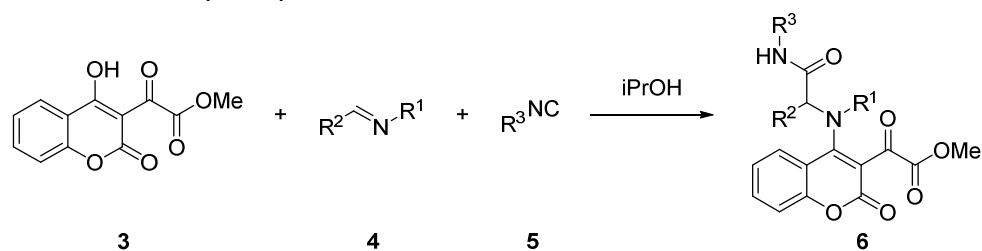
Entry	Solvent	% Yield
1	Methanol	Complex mixture
2	CH <sub>2</sub> Cl <sub>2</sub>	44%
3	Toluene	No reaction
4	Hexane	No reaction
5	CH <sub>3</sub> CN	30%
7	Isopropanol	64%



**Scheme 2.** Enol-Ugi reaction with hydroxycoumarin **3**.

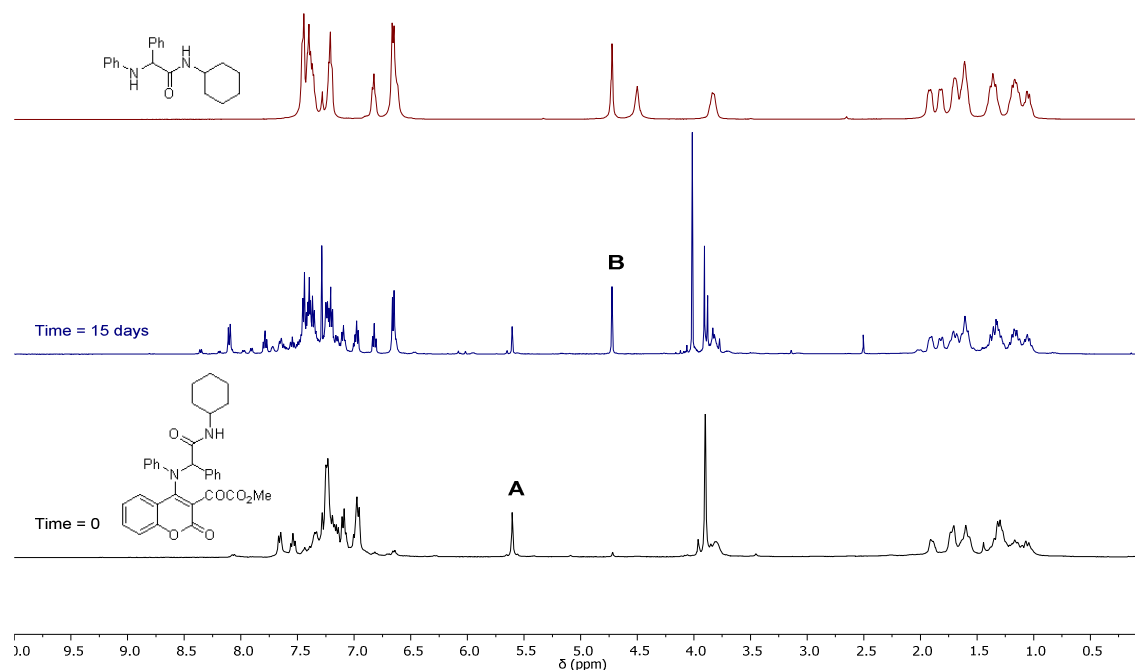
In order to explore the scope of the reaction, enol **3** was reacted in isopropanol with different imines (**4**) and isocyanides (**5**). In all the cases a stable precipitate corresponding to the adduct **6b-f** is formed in moderate to good yields (Table 2).

4-Aminocoumarins **6a-f** were always obtained as stable solids, which were characterized by the usual spectroscopic techniques. However tlc analysis showed that these adducts slowly decompose in solution. Thus, when a CDCl<sub>3</sub> solution of **6a** was measured by NMR at different times (Figure 1), a gradual decrease of the signal at 5.6 ppm (**A**), corresponding to H  $\alpha$  to the amide group, was observed and a new peak at 4.7 ppm (**B**) simultaneously emerged. Variation of the aromatic and methoxide signals was also apparent. This instability of **6a** in solution can be explained due to the highly electrophilic character of coumarin carbon 4, which is prone to the addition of nucleophiles. Thus, nucleophilic attack of a water molecule would cause breakage of the C4-N bond with release of aminoamide **7a** (Scheme 3). Comparison of the NMR spectra of **6a** and **7a** allowed to unequivocally identify one of the products in which **6a** is transformed in CDCl<sub>3</sub> solution as **7a** (Figure 1). Other adducts of 2-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-oxoacetate showed a similar behaviour. The instability of enol-Ugi adducts **6**, explains that complex mixtures are obtained when their synthesis is attempted in solvents such as dichloromethane or methanol, and the better results obtained in isopropanol, in which these products are scarcely soluble.

**Table 2.** Enol-Ugi reaction with hydroxycoumarin **3**

Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	<b>6</b> (% Yield)
1	Ph	Ph	cC <sub>6</sub> H <sub>11</sub>	<b>6a</b> (64)
2	Ph	Ph	tBu	<b>6b</b> (39)
3	Ph	<i>p</i> MePh	cC <sub>6</sub> H <sub>11</sub>	<b>6c</b> (60)
4	Ph	<i>p</i> MePh	CH <sub>2</sub> Ph	<b>6d</b> (87)
5	CH <sub>2</sub> Ph	Ph	cC <sub>6</sub> H <sub>11</sub>	<b>6e</b> (63)
6	CH <sub>2</sub> Ph	Ph	tBu	<b>6f</b> (49)
7	3,4-(OCH <sub>2</sub> O)C <sub>6</sub> H <sub>3</sub>	Ph	cC <sub>6</sub> H <sub>11</sub>	<b>6g</b> (61) <sup>a</sup>

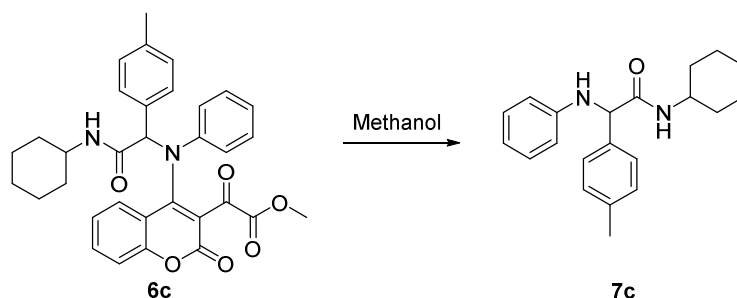
<sup>a</sup>The reaction was performed in dichloromethane.



**Figure 1.** NMR spectra of **6a** recently dissolved and after 15 days in solution, and comparison with spectrum of **7a**.

This behaviour of enol-Ugi adducts (**6**) is in sharp contrast with the lack of reactivity of the products of the Ugi four-component condensation. In fact, although this classical reaction is a powerful strategy for the synthesis of  $\alpha$ -amido amides, deacylation of Ugi adducts usually requires harsh conditions that lead to

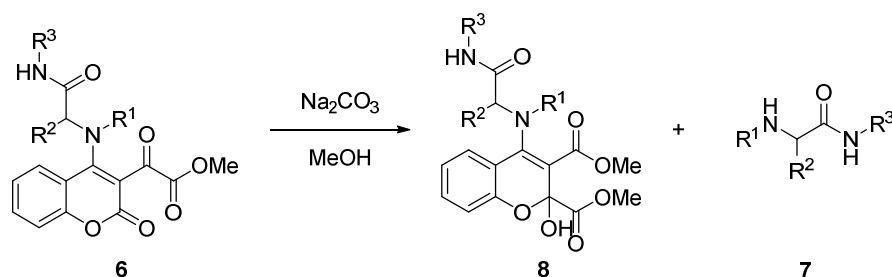
mixtures of products.<sup>26</sup> Aminoamides are interesting synthetic targets, since they possess useful therapeutic properties.<sup>13,27</sup> Thus, development of simple straightforward and flexible syntheses of unprotected  $\alpha$ -amino amides is still a challenging task. We believe that the apparently simple hydrolysis of enol-Ugi adducts **6** could provide a useful method for the synthesis of unprotected  $\alpha$ -amino amides. With this idea, we treated adduct **6c** with a slight excess of acetic acid in methanol. Under these conditions amino amide **7c** is readily formed, and can be isolated in a 62% yield after 4 days of reaction. Surprisingly, the same product is formed in a comparable yield in methanol solution, with no need of adding acid (Scheme 3). Other enol-Ugi adducts (**6**) showed a similar behaviour, readily giving the corresponding amino amides (**7**) either in acid, basic or neutral media (results not shown).



**Scheme 3.** Solvolysis of enol-Ugi adduct **6c**.

Importantly, when adduct **6c** was treated with 1 equivalent of  $\text{Na}_2\text{CO}_3$  in methanol, a new product, different from the fragmentation products previously obtained in acidic and neutral solutions, was formed. After chromatographic purification this compound was characterized as the dimethyl ester **8c** (Table 3; entry 3).

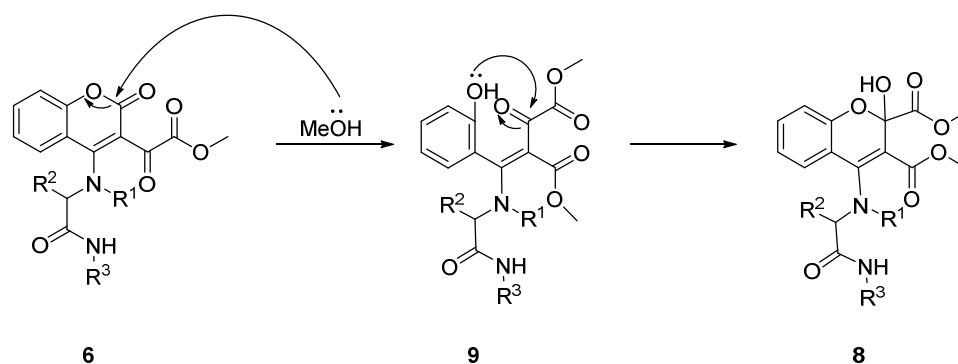
**Table 3.** Addition of methanol to enol-Ugi adducts **6**



Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	<b>7</b> (% Yield)	<b>8</b> (% Yield)
1	Ph	Ph	cC <sub>6</sub> H <sub>11</sub>	<b>7a</b> (8)	<b>8a</b> (40)
2	Ph	Ph	tBu	<b>7b</b> (36)	<b>8b</b> (38)
3	Ph	pMePh	cC <sub>6</sub> H <sub>11</sub>	<b>7c</b> (traces)	<b>8c</b> (55)

A plausible mechanism for this transformation is shown in Scheme 4. We hypothesize that the nucleophilic attack of a methanol molecule to coumarin C2 carbonyl would lead to the opening of the pyran ring, affording phenol intermediate **9**. Then an isomerisation of the double bond must take place, in order to

allow the addition of the phenol group onto the carbonyl of the oxoester. This is only possible when both phenol and oxoester groups are in a *cis* configuration.



**Scheme 4.** Proposed mechanism for the synthesis of 2-hydroxychromenes **8**.

Interestingly, Maiti and co-workers reported the formation of 2-oxo-2-(2-oxo-2*H*-chromen-3-yl)acetates by the reaction of relatively electron-rich salicylaldehydes with acetylenic diesters, while they obtain 2-hydroxy-2*H*-chromene-2,3-dicarboxylates when electron-deficient salicylaldehydes are used.<sup>21</sup> These authors do not postulate the mechanism for these transformations, suggesting that the two types of products should be formed through separated mechanistic pathways. In the view of our results, it is conceivable that 2-oxo-2-(2-oxo-2*H*-chromen-3-yl)acetates are formed in all the cases, but the electrophilic coumarins obtained from electron-deficient salicylaldehydes further react with methanol byproduct to give the observed 2-hydroxy-2*H*-chromenes.

The reaction of 4-amino-chromones (**6**) with methanol seems to be general, as other adducts **6** also suffered addition of methanol to give the corresponding diesters (**8**), together with variable amounts of amino amides (**7**; Table 3).

## Conclusions

In conclusion, methyl 2-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxoacetate has proved to be a suitable acidic component in the enol-Ugi multicomponent condensation with imines and isocyanides. The reaction takes place readily in isopropanol at room temperature, affording 4-coumarin enamines in a highly convergent manner. In contrast with other previously reported coumarin enamines, these adducts show a unique reactivity that permits their easy transformation in the corresponding 2-hydroxychromenyl enamines by the addition of methanol in basic conditions. On the other hand, the labile bond between coumarin C4 and nitrogen permits the solvolysis of enamines **6** in mild neutral conditions. This makes the enol-Ugi reaction of methyl 2-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxoacetate a feasible method for the straightforward synthesis of unprotected  $\alpha$ -amino amides.

## Experimental Section

**General.** Melting points are uncorrected. IR spectra were recorded as KBr pellets. Proton and carbon-13 nuclear magnetic resonance (<sup>1</sup>H NMR or <sup>13</sup>C NMR) spectra were obtained on a 400 or 500 MHz spectrometer. The assignments of signals in <sup>13</sup>C NMR were made using DEPT. Mass spectra (MS) and High Resolution Mass

Spectra (HRMS) were recorded using Chemical Ionization (CI) with CH<sub>4</sub> or ESI-qTOF. Liquid reagents were measured using positive-displacement micropipettes with disposable tips and pistons.

**Synthesis of 2-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-oxoacetate.** It was prepared according to the method described by Eisenhauer for the synthesis of 3-acyl-4-hydroxycoumarins.<sup>25</sup>

Methyl 2-chloro-2-oxoacetate (**2**) (5 mmol) was slowly added to a cooled (ice bath) solution of 4-hydroxycoumarin (**1**) (486 mg, 3 mmol) in anhydrous pyridine (4 mL). A drop of piperidine was then added, and the resulting mixture was stirred 48 h at 37 °C under nitrogen atmosphere. Then it was poured on ice-water and acidified with 10% HCl up to pH 2. The resulting light brown precipitate was filtered under vacuum and washed with cold water to give enol **3** (671 mg, 90%).

Obtained as a light brown solid. m.p.: 148-150 °C; IR (cm<sup>-1</sup>) 3340, 1755, 1728, 1609, 1556, 1491, 1455, 1272, 1225, 1090, 999, 772; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.10 (dd, *J* 7.9, 1.1 Hz, 1H), 7.79 (t, *J* 7.9 Hz, 1H), 7.43 (t, *J* 7.6 Hz, 1H), 7.38 (d, *J* 8.4 Hz, 1H), 4.02 (s, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 191.30 (C), 177.69 (C), 163.17 (C), 159.30 (C), 155.74 (C), 137.41 (CH), 125.69 (CH), 125.19 (CH), 117.72 (CH), 114.29 (C), 99.17 (C), 53.31 (CH<sub>3</sub>); MS (qTOF) *m/z* (%) 249 (M<sup>+</sup> +1, 100), 189 (22); HRMS (qTOF) Calcd for C<sub>12</sub>H<sub>9</sub>O<sub>6</sub>: 249.0399. Found: 249.0399.

**Synthesis of the Ugi adducts.** The imine **4** (0.5 mmol) was suspended in 0.5 mL of *i*PrOH and 0.5 mmol of isocyanide **5** and 0.5 mmol of methyl 2-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-oxoacetate **3** were successively added. After 48-96 hours stirring at room temperature, a precipitate was formed, which was filtered and washed with *i*-Pr<sub>2</sub>O and hexane, yielding **6** as an almost pure solid.

**Methyl 2-(4-((2-(cyclohexylamino)-2-oxo-1-phenylethyl)(phenyl)amino)-2-oxo-2H-chromen-3-yl)-2-oxoacetate (6a).** Obtained as a red solid (64%); m.p.: 144-146 °C; IR (cm<sup>-1</sup>) 3305, 2932, 2855, 1757, 1714, 1654, 1604, 1555, 1499, 1373, 1260, 1313, 1004, 762; <sup>1</sup>H RMN (400 MHz, CDCl<sub>3</sub>) δ (ppm): 7.66 (d, *J* 7.9 Hz, 1H), 7.54 (t, *J* 7.7 Hz, 1H), 7.45 – 7.13 (m, 8H), 7.10 (m, 2H), 6.97 (m, 3H), 5.60 (s, 1H), 3.90 (s, 3H), 3.85 – 3.71 (m, 1H), 1.96 – 1.01 (m, 10H); <sup>13</sup>C RMN (101 MHz, CDCl<sub>3</sub>) δ (ppm): 184.17 (C), 168.49 (C), 162.83 (C), 160.81 (C), 160.54 (C), 154.43 (C), 145.37 (C), 134.62 (CH), 133.25 (C), 130.09 (CH), 129.70 (CH), 129.29 (CH), 128.70 (CH), 128.58 (CH), 122.62 (CH), 121.69 (C), 119.67 (C), 117.75 (CH), 117.52 (CH), 114.07 (CH), 71.19 (CH), 53.42 (CH<sub>3</sub>), 48.81 (CH), 32.79 (CH<sub>2</sub>), 32.54 (CH<sub>2</sub>), 25.54 (CH<sub>2</sub>), 24.99 (CH<sub>2</sub>), 24.89 (CH<sub>2</sub>); MS (CI) *m/z* (%) 539 (M<sup>+</sup> +1, < 5), 396 (33), 411 (49), 328 (18), 364 (100), 181 (43), 83 (83); HRMS (CI) Calcd for C<sub>32</sub>H<sub>31</sub>N<sub>2</sub>O<sub>6</sub>: 539.2182. Found: 539.2177.

**Methyl 2-(4-((2-(tert-butylamino)-2-oxo-1-phenylethyl)(phenyl)amino)-2-oxo-2H-chromen-3-yl)-2-oxoacetate (6b).** Obtained as a red solid (39%); m.p.: 138-140 °C; IR (cm<sup>-1</sup>) 3557, 2970, 1762, 1713, 1669, 1604, 1556, 1493, 1454, 1213, 1009, 760; <sup>1</sup>H RMN (400 MHz, CDCl<sub>3</sub>) δ (ppm): 7.71 – 6.89 (m, 15H), 5.50 (s, 1H), 3.89 (s, 3H), 1.30 (s, 9H); <sup>13</sup>C RMN (101 MHz, CDCl<sub>3</sub>) δ (ppm): 184.05 (C), 168.43 (C), 163.05 (C), 161.09 (C), 160.63 (C), 154.39 (C), 145.39 (C), 134.53 (CH), 133.49 (C), 130.09 (CH), 129.91 (CH), 129.66 (CH), 129.25 (CH), 128.65 (CH), 128.59 (CH), 124.97 (CH), 122.82 (CH), 119.73 (C), 118.23 (CH), 117.50 (CH), 71.88 (CH), 53.39 (CH<sub>3</sub>), 51.88 (C), 28.52 (CH<sub>3</sub>); MS (CI) *m/z* (%) 513 (M<sup>+</sup> + 1, <5), 364 (16), 189 (49), 162 (67), 57 (100).

**Methyl 2-(4-((2-(cyclohexylamino)-2-oxo-1-(*p*-tolyl)ethyl)(phenyl)amino)-2-oxo-2H-chromen-3-yl)-2-oxoacetate (6c).** Obtained as a red solid (60%); m.p.: 152-154 °C; IR (cm<sup>-1</sup>) 3377, 2931, 2855, 1728, 1692, 1667, 1603, 1552, 1366, 1309, 1213, 1010, 755; <sup>1</sup>H RMN (500 MHz, CDCl<sub>3</sub>) δ (ppm): 7.64 (d, *J* 7.9 Hz, 1H), 7.52 (t, *J* 7.5 Hz, 1H), 7.30 – 7.13 (m, 4H), 7.09 (d, *J* 7.7 Hz, 2H), 7.01 – 6.91 (m, 4H), 6.86 (d, *J* 7.7 Hz, 2H), 5.54 (s, 1H), 3.88 (s, 3H), 3.81 – 3.74 (m, 1H), 2.18 (s, 3H), 1.92 – 0.97 (m, 10H); <sup>13</sup>C RMN (126 MHz, CDCl<sub>3</sub>) δ (ppm): 184.11 (C), 168.70 (C), 162.85 (C), 160.91 (C), 160.60 (C), 154.45 (C), 145.49 (C), 139.21 (C), 134.56 (CH), 130.18 (C), 129.99 (CH), 129.69 (CH), 129.30 (CH), 128.63 (CH), 125.03 (CH), 122.49 (CH), 119.77 (C), 117.63 (CH), 117.52

(CH), 70.99 (CH), 53.38 (CH<sub>3</sub>), 48.78 (CH), 32.81 (CH<sub>2</sub>), 32.56 (CH<sub>2</sub>), 27.12 (CH<sub>2</sub>), 25.00 (CH<sub>2</sub>), 24.91 (CH<sub>2</sub>), 21.27 (CH<sub>3</sub>); MS (CI) *m/z* (%) 553 (M<sup>+</sup> + 1, <5), 378 (12), 189 (19), 83 (100); HRMS (qTOF) Calcd for C<sub>32</sub>H<sub>33</sub>N<sub>2</sub>O<sub>6</sub>: 553.2339. Found: 553.2344.

**Methyl 2-(4-((2-(benzylamino)-2-oxo-1-(*p*-tolyl)ethyl)(phenyl)amino)-2-oxo-2H-chromen-3-yl)-2-oxoacetate (6d).** Obtained as a red solid (87%); m.p.: 119-121 °C; IR (cm<sup>-1</sup>) 3296, 3062, 3024, 2945, 2926, 1757, 1717, 1662, 1604, 1555, 1499, 1376, 1259, 1003, 756, 697; <sup>1</sup>H RMN (400 MHz, CDCl<sub>3</sub>) δ (ppm): 7.78 (d, *J* 8.0 Hz, 1H), 7.61 (d, *J* 5.7 Hz, 1H), 7.55 (t, *J* 9.63 Hz, 1H), 7.37 – 7.15 (m, 7H), 7.15 – 7.03 (m, 3H), 6.98 (t, *J* 7.3 Hz, 2H), 6.94 (d, *J* 8.0 Hz, 2H), 6.88 (d, *J* 7.9 Hz, 2H), 5.65 (s, 1H), 4.53 (d, *J* 5.9 Hz, 1H), 4.49 (d, *J* 6.0 Hz, 1H), 3.85 (s, 3H), 2.21 (s, 3H); <sup>13</sup>C RMN (101 MHz, CDCl<sub>3</sub>) δ (ppm): 184.13 (C), 169.97 (C), 162.70 (C), 160.98 (C), 160.60 (C), 154.42 (C), 145.41 (C), 139.37 (C), 138.02 (C), 134.62 (CH), 130.05 (CH), 129.76 (CH), 129.69 (C), 129.33 (CH), 128.73 (CH), 128.69 (CH), 127.81 (CH), 127.47 (CH), 125.07 (CH), 122.60 (CH), 119.85 (C), 117.89 (CH), 117.48 (CH), 70.77 (CH), 53.35 (CH<sub>3</sub>), 43.82 (CH<sub>2</sub>), 21.28 (CH<sub>3</sub>); MS (CI) *m/z* (%) 576 (M<sup>+</sup> + CH<sub>4</sub>, <5), 561 (M<sup>+</sup> + 1, <5), 501 (12), 433 (100), 378 (11), 194 (77).; HRMS (qTOF) Calcd for C<sub>34</sub>H<sub>29</sub>N<sub>2</sub>O<sub>6</sub>: 561.2026. Found: 561.2021.

**Methyl 2-(4-(benzyl(2-(cyclohexylamino)-2-oxo-1-phenylethyl)amino)-2-oxo-2H-chromen-3-yl)-2-oxoacetate (6e).** Obtained as a yellow solid (63%); m.p.: 160-161 °C; IR (cm<sup>-1</sup>) 3382, 2927, 2852, 1746, 1690, 1594, 1542, 1407, 1298, 1269, 1214, 1073, 1042, 761; <sup>1</sup>H RMN (500 MHz, CDCl<sub>3</sub>) δ (ppm): 7.98 (d, *J* 7.7 Hz, 1H), 7.55 (t, *J* 7.4 Hz, 1H), 7.30 – 7.17 (m, 10H), 7.09 (d, *J* 6.1 Hz, 2H), 6.29 (d, *J* 6.2 Hz, 1H), 5.10 (s, 1H), 4.82 (d, *J* 14.8 Hz, 1H), 4.42 (d, *J* 14.7 Hz, 1H), 3.73 (s, 3H), 3.71 – 3.64 (m, 1H), 1.89 – 1.55 (m, 5H), 1.37 – 1.03 (m, 5H); <sup>13</sup>C RMN (126 MHz, CDCl<sub>3</sub>) δ (ppm): 184.57 (C), 168.15 (C), 162.96 (C), 162.70 (C), 161.70 (C), 154.14 (C), 135.19 (C), 134.93 (C), 134.05 (CH), 129.21 (CH), 129.18 (CH), 129.03 (CH), 128.80 (CH), 128.76 (CH), 128.50 (CH), 124.50 (CH), 119.33 (C), 117.88 (CH), 111.55 (C), 71.48 (CH), 58.86 (CH<sub>2</sub>), 53.07 (CH<sub>3</sub>), 49.05 (CH), 32.79 (CH<sub>2</sub>), 32.70 (CH<sub>2</sub>), 27.13 (CH<sub>2</sub>), 25.55 (CH<sub>2</sub>), 25.00 (CH<sub>2</sub>), 24.90 (CH<sub>2</sub>); MS (CI) *m/z* (%) 553 (M<sup>+</sup> + 1, <5), 321 (9), 196 (26), 173 (79), 59 (100); HRMS (CI) Calcd for C<sub>33</sub>H<sub>33</sub>N<sub>2</sub>O<sub>6</sub>: 553.2339. Found: 553.2338.

**Methyl 2-(4-(benzyl(2-(*tert*-butylamino)-2-oxo-1-phenylethyl)amino)-2-oxo-2H-chromen-3-yl)-2-oxoacetate (6f).** Obtained as a yellow solid (49%); m.p.: 165-167 °C; IR (cm<sup>-1</sup>) 3382, 2972, 1747, 1696, 1607, 1535, 1455, 1406, 1266, 1214, 1074, 760; <sup>1</sup>H RMN (500 MHz, CDCl<sub>3</sub>) δ (ppm): 8.02 (d, *J* 7.9 Hz, 1H), 7.58 (t, *J* 7.8 Hz, 1H), 7.39 – 7.20 (m, 12H), 6.06 (s, 1H), 5.11 (s, 1H), 4.89 (d, *J* 14.9 Hz, 1H), 4.47 (d, *J* = 14.9 Hz, 1H), 3.73 (s, 3H), 1.28 (s, 9H); <sup>13</sup>C RMN (126 MHz, CDCl<sub>3</sub>) δ (ppm): <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 183.92 (C), 167.98 (C), 162.88 (C), 162.78 (C), 161.52 (C), 153.87 (C), 135.04 (C), 134.59 (C), 133.78 (CH), 128.93 (CH), 128.86 (CH), 128.77 (CH), 128.58 (CH), 128.41 (CH), 128.25 (CH), 124.28 (CH), 119.11 (C), 117.73 (CH), 110.45 (C), 71.81 (CH), 58.53 (CH<sub>2</sub>), 52.80 (CH<sub>3</sub>), 51.91 (C), 28.39 (CH<sub>3</sub>); MS (CI) *m/z* (%) 527 (M<sup>+</sup> + 1, 13), 426 (14), 367 (37), 321 (14), 173 (33), 162 (80), 91 (100); HRMS (CI) Calcd for C<sub>31</sub>H<sub>31</sub>N<sub>2</sub>O<sub>6</sub>: 527.2182. Found: 527.2172.

**Methyl 2-(4-((benzo[*d*][1,3]dioxol-5-ylmethyl)(2-(cyclohexylamino)-2-oxo-1-phenylethyl)amino)-2-oxo-2H-chromen-3-yl)-2-oxoacetate (6g).** Obtained as a yellow solid (61%); m.p.: 166-168 °C; IR (cm<sup>-1</sup>) 3445, 3370, 2923, 2856, 1745, 1702, 1680, 1607, 1408, 1298, 1239, 1040, 757; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.03 (d, *J* 7.9 Hz, 1H), 7.57 (t, *J* 7.9 Hz, 1H), 7.33 – 7.20 (m, 7H), 6.67 (d, *J* 7.9 Hz, 1H), 6.63 (d, *J* 1.4 Hz, 1H), 6.53 (dd, *J* 7.9, 1.4 Hz, 1H), 6.27 (d, *J* 6.7 Hz, 1H), 5.94 (d, *J* 1.2 Hz, 2H), 5.14 (s, 1H), 4.74 (d, *J* 14.7 Hz, 1H), 4.30 (d, *J* 14.7 Hz, 1H), 3.77 (s, 3H), 3.85 – 3.63 (m, 1H), 1.91 – 1.54 (m, 5H), 1.40 – 1.04 (m, 5H); <sup>13</sup>C RMN (126 MHz, CDCl<sub>3</sub>) δ (ppm): <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 184.37 (C), 168.14 (C), 161.58 (C), 154.08 (C), 148.02 (C), 147.77 (C), 134.91 (C), 133.97 (CH), 129.12 (CH), 128.98 (CH), 128.95 (CH), 128.78 (C), 128.61 (CH), 124.49 (CH), 123.00 (CH), 119.21 (C), 117.82 (CH), 111.61 (C), 109.32 (CH), 108.23 (CH), 101.28 (CH<sub>2</sub>), 71.37 (CH), 58.25 (CH<sub>2</sub>), 52.98 (CH<sub>3</sub>), 48.99 (CH), 32.75 (CH<sub>2</sub>), 32.66 (CH<sub>2</sub>), 25.47 (CH<sub>2</sub>), 24.93 (CH<sub>2</sub>), 24.83 (CH<sub>2</sub>); MS (qTOF) *m/z* (%) 597 (M<sup>+</sup> + 1, 100), 566 (6), 463 (20), 282 (22); HRMS (qTOF) Calcd for C<sub>34</sub>H<sub>33</sub>N<sub>2</sub>O<sub>8</sub>: 597.2237. Found: 597.2225.



**Addition of methanol to the enol-Ugi adducts.** Enol-Ugi adduct **6** (0.1 mmol) was suspended in a solution of anhydrous Na<sub>2</sub>CO<sub>3</sub> (0.1 mmol) in MeOH (1 mL). After 1-5 hours stirring at room temperature, the reaction was diluted with ethyl acetate (10 mL), washed with 10% HCl (1 mL) and H<sub>2</sub>O (10 mL), dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by flash column chromatography (hexane to hexane-EtOAc 7:3) to afford the corresponding adducts **8a-c** and amido amides **7a-c**.

**Dimethyl 4-[[2-(cyclohexylamino)-2-oxo-1-phenylethyl](phenyl)amino]-2-hydroxy-2H-chromene-2,3-dicarboxylate (8a).** Obtained as a yellow solid (49%); m.p.: 107-109 °C; IR (cm<sup>-1</sup>) 33001, 2928, 2853, 1768, 1714, 1655, 1599, 1542, 1498, 1454, 1254, 1144, 758, 698; <sup>1</sup>H RMN (500 MHz, CDCl<sub>3</sub>) δ (ppm): 9.03 (d, *J* 6.1 Hz, 0.6H), 8.29 (bs, 0.14H), 7.36 – 6.67 (m, 14H), 5.62 (bs, 0.2H), 5.23 (s, 0.6H), 4.82 (bs, 0.6H), 3.91 (s, 3H), 4.00 – 3.62 (m, 1H), 3.81 (s, 3H), 2.00 – 1.48 (m, 5H), 1.46 – 0.77 (m, 5H); <sup>13</sup>C RMN (126 MHz, CDCl<sub>3</sub>) δ (ppm): 170.03 (C), 169.40 (C), 163.40 (C), 152.13 (C), 147.89 (C), 146.20 (C), 133.81 (C), 132.24 (CH), 130.19 (CH), 129.51 (CH), 129.21 (CH), 128.32 (CH), 127.55 (CH), 126.97 (CH), 122.28 (CH), 120.11 (CH), 119.98 (C), 117.31 (CH), 117.12 (CH), 114.06 (CH), 94.81 (C), 77.23 (CH), 71.20 (CH), 53.96 (CH<sub>3</sub>), 53.88 (CH<sub>3</sub>), 52.11 (CH<sub>3</sub>), 51.93 (CH<sub>3</sub>), 48.14 (CH), 32.58 (CH<sub>2</sub>), 32.33 (CH<sub>2</sub>), 25.57 (CH<sub>2</sub>), 25.50 (CH<sub>2</sub>), 24.90 (CH<sub>2</sub>), 24.72 (CH<sub>2</sub>); MS (qTOF) *m/z* (%) 571 (M<sup>+</sup> + 1, 100), 553 (74), 282 (7); HRMS (qTOF) Calcd for C<sub>33</sub>H<sub>35</sub>N<sub>2</sub>O<sub>7</sub>: 571.2444. Found: 571.2465.

**Dimethyl 4-((2-(tert-butylamino)-2-oxo-1-phenylethyl)(phenyl)amino)-2-hydroxy-2H-chromene-2,3-dicarboxylate (8b).** Obtained as a yellow solid (38%); m.p.: 165-166 °C; IR (cm<sup>-1</sup>) 3450, 2920, 1765, 1718, 1663, 1498, 1253, 1143, 1118, 761, 699; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.88 (bs, 0.6H), 8.19 (bs, 0.1H), 7.35 – 6.69 (m, 14H), 5.50 (bs, 0.2H), 5.11 (s, 0.7H), 4.80 (bs, 0.5H), 3.92 (s, 3H), 3.78 (s, 3H), 1.36 (s, 6H), 1.34 (s, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 170.18 (C), 169.40 (C), 163.23 (C), 152.10 (C), 147.83 (C), 146.29 (C), 133.98 (C), 132.19 (CH), 130.21 (CH), 129.47 (CH), 128.27 (CH), 127.54 (CH), 126.98 (CH), 122.30 (CH), 120.08 (C), 119.98 (C), 117.29 (CH), 117.12 (CH), 114.13 (CH), 94.78 (C), 77.23 (CH), 72.01 (CH), 53.97 (CH<sub>3</sub>), 52.00 (CH<sub>3</sub>), 51.05 (C), 28.29 (CH<sub>3</sub>); MS (qTOF) *m/z* (%) 545 (M<sup>+</sup> + 1, 100), 527 (70), 356 (5); HRMS (qTOF) Calcd for C<sub>31</sub>H<sub>33</sub>N<sub>2</sub>O<sub>7</sub>: 545.2288. Found: 545.2298.

**Dimethyl 4-((2-(cyclohexylamino)-2-oxo-1-(*p*-tolyl)ethyl)(phenyl)amino)-2-hydroxy-2H-chromene-2,3-dicarboxylate (8c).** Obtained as a yellow solid (55%); m.p.: 114-116 °C; IR (cm<sup>-1</sup>) 3431, 2929, 1756, 1715, 1655, 1604, 1499, 1454, 1254, 1143, 1107, 753; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.99 (d, *J* 7.2 Hz, 0.5H), 8.26 (bs, 0.22H), 7.38 – 6.62 (m, 13H), 5.58 (bs, 0.3H), 5.20 (s, 0.6H), 4.84 (bs, .5H), 4.06 – 3.64 (m, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 2.26 (s, 1H), 2.20 (s, 2H), 1.98 – 1.52 (m, 5H), 1.42 – 0.87 (m, 5H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 170.21 (C), 169.47 (C), 163.40 (C), 152.13 (C), 147.98 (C), 146.25 (C), 137.88 (C), 132.19 (CH), 129.47 (CH), 129.19 (CH), 128.31 (CH), 126.99 (CH), 122.23 (CH), 120.03 (CH), 117.32 (CH), 117.06 (CH), 114.09 (CH), 94.80 (C), 77.23 (CH), 70.85 (CH), 53.88 (CH<sub>3</sub>), 52.09 (CH<sub>3</sub>), 51.95 (CH<sub>3</sub>), 48.08 (CH), 47.95 (CH), 32.84 (CH<sub>2</sub>), 32.58 (CH<sub>2</sub>), 32.33 (CH<sub>2</sub>), 25.57 (CH<sub>2</sub>), 25.50 (CH<sub>2</sub>), 24.90 (CH<sub>2</sub>), 24.71 (CH<sub>2</sub>), 21.19 (CH<sub>3</sub>), 21.16 (CH<sub>3</sub>); MS (qTOF) *m/z* (%) 585 (M<sup>+</sup> + 1, 100), 567 (65), 398 (34), 282 (32); HRMS (qTOF) Calcd for C<sub>34</sub>H<sub>37</sub>N<sub>2</sub>O<sub>7</sub>: 585.2601. Found: 585.2629.

***N*-cyclohexyl-2-phenyl-2-(phenylamino)acetamide (7a).** Obtained as a white solid (10%); m.p.: 174-176 °C; IR (cm<sup>-1</sup>) 3404, 3321, 2930, 2852, 1650, 1603, 1542, 1504, 1450, 1315, 748, 693; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.45 (d, *J* 7.0 Hz, 2H), 7.40 (t, *J* 7.2 Hz, 2H), 7.38 – 7.33 (m, 1H), 7.21 (t, *J* 7.9 Hz, 2H), 6.83 (t, *J* 7.3 Hz, 1H), 6.66 (d, *J* 7.9 Hz, 2H), 6.63 (d, *J* 8.1 Hz, 1H), 4.73 (s, 1H), 4.51 (bs, 1H), 3.89 – 3.78 (m, 1H), 1.96 – 1.56 (m, 5H), 1.42 – 1.00 (m, 5H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 170.02 (C), 146.78 (C), 139.10 (C), 129.29 (CH), 129.19 (CH), 128.51 (CH), 127.39, 119.11 (CH), 113.90 (CH), 64.40 (CH), 48.12 (CH), 33.00 (CH<sub>2</sub>), 32.75 (CH<sub>2</sub>), 25.44 (CH<sub>2</sub>), 24.76 (CH<sub>2</sub>), 24.63 (CH<sub>2</sub>); HRMS (qTOF) Calcd for C<sub>20</sub>H<sub>25</sub>N<sub>2</sub>O: 309.1967. Found: 309.1967.

***N*-(tert-butyl)-2-phenyl-2-(phenylamino)acetamide (7b).** Obtained as a white solid (36%); m.p.: 114-118 °C; IR (cm<sup>-1</sup>) 3409, 3290, 2963, 2920, 2847, 1721, 1646, 1602, 1558, 1508, 1225, 745, 693; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

$\delta$  7.47 – 7.35 (m, 5H), 7.24 – 7.18 (m, 2H), 6.83 (t,  $J$  7.4 Hz, 1H), 6.68 – 6.66 (dd,  $J$  8.6, 1.0 Hz, 2H), 6.54 (bs, 1H), 4.63 (s, 1H), 4.51 (bs, 1H), 1.34 (s, 9H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.25 (C), 146.81 (C), 139.30 (C), 129.29 (CH), 129.22 (CH), 128.46 (CH), 127.33 (CH), 119.09 (CH), 113.91 (CH), 64.91 (CH), 51.20 (C), 28.56 ( $\text{CH}_3$ ); MS (qTOF)  $m/z$  (%) 283 ( $\text{M}^+$ , +1, 100), 182 (<5); HRMS (qTOF) Calcd for  $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}$ : 283.1810. Found: 283.1810.

***N*-cyclohexyl-2-(phenylamino)-2-(*p*-tolyl)acetamide (7c).** Obtained as a white solid (64%); m.p.: 101-103 °C; IR ( $\text{cm}^{-1}$ ) 3387, 2927, 2853, 1647, 4604, 1505, 1259, 1178, 748, 691;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33 (d,  $J$  8.0 Hz, 2H), 7.23 – 7.19 (m, 4H), 6.82 (t,  $J$  7.4 Hz, 1H), 6.65 (d,  $J$  7.7 Hz, 2H), 6.62 (bs, 1H), 4.68 (s, 1H), 4.47 (bs, 1H), 3.87 – 3.78 (m, 1H), 2.37 (s, 3H), 1.95 – 1.56 (m, 5H), 1.43 – 1.00 (m, 5H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  170.23 (C), 146.85 (C), 138.30 (C), 136.10 (C), 129.84 (CH), 129.27 (CH), 127.26 (CH), 119.04 (CH), 113.88 (CH), 64.12 (CH), 48.08 (CH), 33.02 ( $\text{CH}_2$ ), 32.77 ( $\text{CH}_2$ ), 25.45 ( $\text{CH}_2$ ), 24.79 ( $\text{CH}_2$ ), 24.66 ( $\text{CH}_2$ ), 21.16 ( $\text{CH}_3$ ); HRMS (qTOF) Calcd for  $\text{C}_{21}\text{H}_{27}\text{N}_2\text{O}$ : 323.2123. Found: 323.2118.

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