Supporting Information

One-pot construction of functionalized aziridines and maleimides via a novel pseudo-Knoevenagel cascade reaction†

Jie Lei,Gui-Ting Song,Liu-Jun He,Ya-Fei Luo,Dian-Yong Tang,Hui-Kuan Lin,Brendan Frett,Hong-yu Li,Zhong-Zhu Chen,Zhi-Gang Xu

College of Pharmacy, Chongqing University of Arts and Sciences, 319 Honghe Ave., Yongchuan, Chongqing, 402160 China. Email: 18883138277@163.com; xzg@cqwu.edu.cn

Department of Pharmaceutical Sciences, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205, USA. Email: HLi2@uams.edu

Department of Cancer Biology, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, North Carolina 27157, USA. Email: hulin@wakehealth.edu

Table of Contents

| General Experimental | 2 |
| Optimization and general procedures for compounds cis-6 | 3 |
| Optimization and general procedures for compounds trans-7 | 4 |
| Optimization for synthesizing compound 8a | 5 |
| General procedures for compounds 8 | 5 |
| General procedures for compounds 9 | 6 |
| Density functional theory (DFT) calculations | 6-8 |
| Cell lines and culture and MTT assay | 8-10 |
| NMR Characterization Data and Figures of Products | 11-60 |
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 ($\delta$), 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 ($\delta$). 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. All microwave irradiation experiments were carried out in a Biotage® Initiator Classic microwave apparatus with continuous irradiation power from 0 to 400W with utilization of the standard absorbance level of 250W maximum power. The reactions were carried out in 10 mL glass tubes, sealed with microwave cavity. The reaction was irradiated at a required ceiling temperature using maximum power for the stipulated time. Then it was cooled to 50 °C with gas jet cooling.
Table S1. Optimization for synthesizing compound cis-6a.

<table>
<thead>
<tr>
<th>entry</th>
<th>solvt.</th>
<th>cat.</th>
<th>eq.</th>
<th>temp. (°C)</th>
<th>time (min)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>DBU</td>
<td>2.0</td>
<td>MW 150</td>
<td>10</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>Et3N</td>
<td>2.0</td>
<td>MW 110</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>TEOA</td>
<td>2.0</td>
<td>MW 110</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>DMF</td>
<td>TEOA</td>
<td>2.0</td>
<td>MW 130</td>
<td>10</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>TEOA</td>
<td>5.0</td>
<td>MW 130</td>
<td>10</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>DMF</td>
<td>TEOA</td>
<td>8.0</td>
<td>MW 130</td>
<td>10</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>DMF</td>
<td>TEOA</td>
<td>5.0</td>
<td>MW 150</td>
<td>10</td>
<td>33</td>
</tr>
<tr>
<td>8</td>
<td>DMF</td>
<td>TEOA</td>
<td>5.0</td>
<td>MW 170</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>MeCN</td>
<td>TEOA</td>
<td>5.0</td>
<td>MW 130</td>
<td>10</td>
<td>29</td>
</tr>
<tr>
<td>10</td>
<td>DMSO</td>
<td>TEOA</td>
<td>5.0</td>
<td>MW 130</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>11</td>
<td>THF</td>
<td>TEOA</td>
<td>5.0</td>
<td>MW 130</td>
<td>10</td>
<td>NR</td>
</tr>
<tr>
<td>12</td>
<td>DCE</td>
<td>TEOA</td>
<td>5.0</td>
<td>MW 130</td>
<td>10</td>
<td>NR</td>
</tr>
</tbody>
</table>

*aYield of isolated product. MW = microwave irradiation. Reaction conditions: 5a (0.2 mmol), base (relative equiv.) in solvent (1.0 mL) under microwave irradiation.

General procedures for compound cis-6.

A solution of benzoylformic acid (1.0 mmol), isocyanide (1.0 mmol), aniline (1.0 mmol) and ethyl glyoxylate (2.0 mmol) was stirred overnight in MeOH (2.0 mL) at room temperature. The reaction mixture was monitored by TLC. When the reaction was completed, the solvent was removed under reduced pressure. Then the crude residue was subjected to triethanolamine (TEOA) (5.0 equiv.) and DMF (3.0 mL) solution under microwave irradiation condition at 130 °C for 10 min. After the microwave vial was cooled to room temperature, 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 cis-6.
Table S2. Optimization for synthesizing compound 7a.

```
<table>
<thead>
<tr>
<th>entry</th>
<th>solvt.</th>
<th>cat.</th>
<th>eq.</th>
<th>temp. (°C)</th>
<th>time (min)</th>
<th>yield (%) 7a†</th>
<th>yield (%) 6a†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>TEOA</td>
<td>5.0</td>
<td>MW 130</td>
<td>10</td>
<td>12</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>TEOA</td>
<td>2.0</td>
<td>MW 130</td>
<td>10</td>
<td>43</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>TEOA</td>
<td>2.0</td>
<td>MW 140</td>
<td>10</td>
<td>37</td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>DMF</td>
<td>TEOA</td>
<td>1.0</td>
<td>MW 140</td>
<td>10</td>
<td>32</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>TEOA</td>
<td>2.0</td>
<td>MW 150</td>
<td>10</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>DMSO</td>
<td>TEA</td>
<td>2.0</td>
<td>MW 140</td>
<td>10</td>
<td>36</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>DCE</td>
<td>TEA</td>
<td>2.0</td>
<td>MW 140</td>
<td>Trace</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>MeCN</td>
<td>TEA</td>
<td>2.0</td>
<td>MW 140</td>
<td>10</td>
<td>68</td>
<td>9</td>
</tr>
<tr>
<td>9</td>
<td>MeCN</td>
<td>TEA</td>
<td>2.0</td>
<td>MW 140</td>
<td>20</td>
<td>61</td>
<td>17</td>
</tr>
<tr>
<td>10</td>
<td>MeCN</td>
<td>TEA</td>
<td>2.0</td>
<td>MW 150</td>
<td>10</td>
<td>50</td>
<td>14</td>
</tr>
<tr>
<td>11</td>
<td>MeCN</td>
<td>DIPEA</td>
<td>2.0</td>
<td>MW 140</td>
<td>10</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>12</td>
<td>MeCN</td>
<td>DIPA</td>
<td>2.0</td>
<td>MW 140</td>
<td>10</td>
<td>37</td>
<td>51</td>
</tr>
</tbody>
</table>

†Yield of isolated product. MW = microwave irradiation. Reaction conditions: 5a (0.2 mmol), base (relative equiv.) in solvent (1.0 mL) under microwave irradiation.
```

General procedures for compound trans-7.

A solution of benzoxyllformic acid (1.0 mmol), isocyanide (1.0 mmol), aniline (1.0 mmol) and ethyl glyoxylate (2.0 mmol) was stirred overnight in MeOH (2.0 mL) at room temperature. The reaction mixture was monitored by TLC. When the reaction was completed, the solvent was removed under reduced pressure. Then the crude residue was subjected to TEA (2.0 equiv.) and MeCN (3.0 mL) solution under microwave irradiation condition at 140 °C for 10 min. After the microwave vial was cooled to room temperature, 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.
trans-7.

**Table S3.** Optimization for synthesizing compound 8a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvt.</th>
<th>Cat.</th>
<th>Eq.</th>
<th>Temp. (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>10% TFA/DCE</td>
<td>MW 120</td>
<td>10</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>10%HCl/AcOH</td>
<td>MW 120</td>
<td>10</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>K₂CO₃</td>
<td>2.0</td>
<td>MW 120</td>
<td>10</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>DMF</td>
<td>EtONa</td>
<td>2.0</td>
<td>MW 120</td>
<td>30</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>NaOH</td>
<td>2.0</td>
<td>MW 120</td>
<td>10</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>DMF</td>
<td>KOAc</td>
<td>2.0</td>
<td>MW 120</td>
<td>10</td>
<td>NR</td>
</tr>
<tr>
<td>7</td>
<td>DMF</td>
<td>DIPA</td>
<td>2.0</td>
<td>MW 120</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>DMF</td>
<td>DIPEA</td>
<td>2.0</td>
<td>MW 120</td>
<td>10</td>
<td>32</td>
</tr>
<tr>
<td>10</td>
<td>DMF</td>
<td>DABCO</td>
<td>2.0</td>
<td>MW 120</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>11</td>
<td>DMF</td>
<td>DBU</td>
<td>2.0</td>
<td>MW 120</td>
<td>10</td>
<td>57</td>
</tr>
<tr>
<td>12</td>
<td>DMF</td>
<td>DBU</td>
<td>2.0</td>
<td>MW 120</td>
<td>10</td>
<td>63</td>
</tr>
<tr>
<td>13</td>
<td>DMF</td>
<td>DBU</td>
<td>2.0</td>
<td>MW 140</td>
<td>10</td>
<td>75</td>
</tr>
<tr>
<td>14</td>
<td>DMF</td>
<td>DBU</td>
<td>2.0</td>
<td>MW 150</td>
<td>10</td>
<td>60</td>
</tr>
</tbody>
</table>

*Yield of isolated product. MW = microwave irradiation. Reaction conditions: 5a (0.2 mmol), base (0.4 mmol) in DMF (1.0 mL) under microwave irradiation. b The solvent was used as 1.0 mL.*

**General procedure for compound 8a from compound cis-6a**

In a solution of compound cis-6a (86 mg, 0.2 mmol) in DMF (3.0 mL), DBU (60 mg, 0.4 mmol) was added and treated in microwave at 170 °C for 10 min. After the microwave vial was cooled to room temperature, 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 8a with 81% yield.

**General procedures for compound 8.**

A solution of benzyolformic acid (1.0 mmol), isocyanide (1.0 mmol), aniline (1.0 mmol) and ethyl glyoxylate (2.0 mmol) was stirred overnight in MeOH (2.0 mL) at room temperature. The reaction mixture was monitored by TLC. When no isonitrile
was left, the solvent was removed under nitrogen blowing and the crude residue was dissolved in DBU (2.0 equiv.) and DMF (3.0 mL) solution and treated in microwave at 140 °C for 10 min. After the microwave vial was cooled to room temperature, 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 8.

**General procedures for compound 10.**

A solution of benzoylformic acid (1.0 mmol), benzyl isocyanide (1.0 mmol), 4-bromoaniline (1.0 mmol) and cyclohexanone (1.0 mmol) was stirred overnight in MeOH (2.0 mL) at room temperature. The reaction mixture was monitored by TLC. When the reaction was completed, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using a gradient of ethyl acetate/hexane (0-20%) to afford the relative targeted product 10 with 67% yield.

**Density functional theory (DFT) calculations**

The mechanism was investigated via DFT using the B3LYP functional with the 6-31G* basis set as implemented in Gaussian 09 package, which was used in the geometric optimizations of intermediates (IMs) and transition states (TSs). To considerate the weak interaction, the D3 version of Grimme’s dispersion with Becke-Johnson damping were employed during the optimization. To check the IMs and TSs structures, vibrational frequency calculations at the same level of theory were performed. Intrinsic reaction coordinates (IRC) were performed to confirm the transition states connecting with the corresponding reactant and product intermediates. According to reaction conditions, the solvent effect of N, N-dimethylformamide (ε = 37.2) was evaluated using the Polarizable Continuum Model (PCM). Natural charges were calculated via natural population analysis at the same level as that used for geometry optimization.
As shown in Figure 1, carbanion formation is exothermic (-11.12 kcal/mol), while amide anionic formation is endothermic (+4.90 kcal/mol). Further, the energy barrier for carbanion formation (4.07 kcal/mol) is lower than that of amide anionic formation (5.61 kcal/mol). Therefore, the formation of the carbanion is favourable thermodynamically and kinetically. The negative charge of the carbanion can delocalize between two adjacent carbonyls, while the amide anion can only delocalize to one carbonyl. Most importantly the α-amino group of compound 5 is neutralized with the substitutions of two adjacent carbonyl and a benzyl functional groups, which would further stabilize the enolate ion (carbanion). For the formation of the 4-membered azetidin-2-one ring 11, the energy barrier of isomer IM3 (R, R) (0.06 kcal/mol) is lower than another IM3’ (R, S) (7.98 kcal/mol). Therefore, the DFT results supported the formation of IM3 (R, R) would be the major pathway and also proved the reversible formation of compound cis-6.
Materials and methods

1. cell lines and culture

The human tumor cells (Huh-7, Hep3B, A549, H460, LN229, DU145, PC3, MDA-MB-468, MCF-7, PANC, SW1990, HCT116, SW620, Hela) were purchased from American Type Culture Collection (ATCC, Manassas, VA, USA). The Huh-7, Hep3B, LN229, DU145, MDA-MB-468, MCF-7, SW1990, SW620 and Hela cells were cultured with 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 in the Ham's F-12K (Kaighn's) Medium (GIBCO, 21127022, USA) with 10% FBS. The H460 and PANC cells were cultured with the RPMI 1640 Medium (GIBCO, 61870044, USA) added with 10% FBS. The cells were cultured in an incubator at the 37 °C and 5% CO₂ with humidified atmosphere.

2. MTT assay

The anticancer activity and the IC₅₀ value of compound 8i in the human tumor cells were measured by 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide (MTT, Beyotime, ST316, Shanghai, China) assay. Briefly, the tumor cells were counted and seeded into the 96-well plate with density of 1 × 10³ cells per well
containing 100 µL complete medium. After incubation for 24 h, added another 100 µL complete medium containing 10 µM compounds and incubated with 3 days for the initial screening. To further evaluate the IC\textsubscript{50} of compound 8i, tumor cells were incubated with various concentrations (0, 2.5, 5, 10, 20, 40, 80, 160, 320 µM) of compound 8i for 7 days. Then, 20 µL MTT (5 mg/mL) was added to each well and incubated with 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 IC\textsubscript{50} values were analyzed by GraphPad Prism 8.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Entry name</th>
<th>Huh7</th>
<th>Hep3B</th>
<th>A549</th>
<th>H460</th>
<th>LN229</th>
<th>DU145</th>
<th>PC3</th>
<th>MDA-MB-468</th>
<th>MCF7</th>
<th>PAN</th>
<th>SW1990</th>
<th>HCT116</th>
<th>SW620</th>
<th>Hela</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8a</td>
<td>6.6</td>
<td>17.9</td>
<td>14.8</td>
<td>11.5</td>
<td>13.8</td>
<td>6.7</td>
<td>11.6</td>
<td>5.0</td>
<td>19.4</td>
<td>16.8</td>
<td>25.4</td>
<td>12.7</td>
<td>24.0</td>
<td>29.7</td>
</tr>
<tr>
<td>2</td>
<td>8b</td>
<td>22.4</td>
<td>7.8</td>
<td>12.1</td>
<td>22.6</td>
<td>5.8</td>
<td>10.5</td>
<td>9.8</td>
<td>15.9</td>
<td>24.3</td>
<td>28.9</td>
<td>21.5</td>
<td>17.7</td>
<td>6.9</td>
<td>26.1</td>
</tr>
<tr>
<td>3</td>
<td>8c</td>
<td>20.5</td>
<td>14.5</td>
<td>18.9</td>
<td>28.6</td>
<td>15.8</td>
<td>13.1</td>
<td>9.4</td>
<td>24.0</td>
<td>23.5</td>
<td>22.5</td>
<td>12.2</td>
<td>26.0</td>
<td>20.6</td>
<td>22.2</td>
</tr>
<tr>
<td>4</td>
<td>8d</td>
<td>5.1</td>
<td>10.4</td>
<td>17.6</td>
<td>26.4</td>
<td>7.4</td>
<td>18.9</td>
<td>27.6</td>
<td>5.8</td>
<td>24.0</td>
<td>23.5</td>
<td>15.0</td>
<td>15.4</td>
<td>23.9</td>
<td>17.4</td>
</tr>
<tr>
<td>5</td>
<td>8e</td>
<td>13.7</td>
<td>10.7</td>
<td>29.3</td>
<td>19.0</td>
<td>10.9</td>
<td>15.8</td>
<td>21.2</td>
<td>21.2</td>
<td>13.4</td>
<td>29.2</td>
<td>27.6</td>
<td>20.7</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>8f</td>
<td>15.3</td>
<td>18.9</td>
<td>28.2</td>
<td>15.7</td>
<td>12.7</td>
<td>10.5</td>
<td>27.5</td>
<td>8.2</td>
<td>23.9</td>
<td>16.6</td>
<td>9.0</td>
<td>21.2</td>
<td>10.6</td>
<td>15.9</td>
</tr>
<tr>
<td>7</td>
<td>8g</td>
<td>15.4</td>
<td>8.0</td>
<td>11.0</td>
<td>27.1</td>
<td>13.4</td>
<td>13.9</td>
<td>24.0</td>
<td>11.3</td>
<td>24.9</td>
<td>11.2</td>
<td>24.0</td>
<td>24.0</td>
<td>12.2</td>
<td>9.4</td>
</tr>
<tr>
<td>8</td>
<td>8h</td>
<td>18.5</td>
<td>6.6</td>
<td>10.9</td>
<td>20.5</td>
<td>6.4</td>
<td>11.0</td>
<td>24.9</td>
<td>6.4</td>
<td>17.4</td>
<td>18.0</td>
<td>18.1</td>
<td>15.9</td>
<td>24.0</td>
<td>9.8</td>
</tr>
<tr>
<td>9</td>
<td>8i</td>
<td>56.2</td>
<td>50.3</td>
<td>28.1</td>
<td>12.9</td>
<td>11.8</td>
<td>13.8</td>
<td>5.7</td>
<td>17.0</td>
<td>13.9</td>
<td>29.2</td>
<td>23.8</td>
<td>24.9</td>
<td>25.9</td>
<td>11.6</td>
</tr>
<tr>
<td>10</td>
<td>8l</td>
<td>29.2</td>
<td>5.2</td>
<td>11.6</td>
<td>8.3</td>
<td>17.3</td>
<td>6.7</td>
<td>8.2</td>
<td>18.9</td>
<td>24.5</td>
<td>25.7</td>
<td>17.3</td>
<td>27.5</td>
<td>26.4</td>
<td>24.0</td>
</tr>
<tr>
<td>11</td>
<td>8m</td>
<td>13.6</td>
<td>13.0</td>
<td>8.4</td>
<td>4.7</td>
<td>13.1</td>
<td>18.5</td>
<td>15.9</td>
<td>10.5</td>
<td>5.7</td>
<td>25.6</td>
<td>24.3</td>
<td>8.2</td>
<td>23.6</td>
<td>27.5</td>
</tr>
<tr>
<td>12</td>
<td>8n</td>
<td>7.8</td>
<td>23.5</td>
<td>15.2</td>
<td>9.8</td>
<td>10.4</td>
<td>6.7</td>
<td>16.1</td>
<td>22.7</td>
<td>9.8</td>
<td>25.1</td>
<td>17.4</td>
<td>19.7</td>
<td>21.6</td>
<td>30.1</td>
</tr>
</tbody>
</table>
Figure 2. Anticancer activities IC₅₀ (µM) of compound 8i. A) Screening and activity analysis of compound 8i in cancer cell lines using MTT assay for 3 days. B) The IC₅₀ values of compound 8i against Huh-7 and Hep3B (7 days). C) Data Compare. 7

NMR Characterization Data and Figures of Products

**Ethyl 3-(benzylamino)-2-(N-(4-bromophenyl)-2-oxo-2-phenylacetamido)-3-oxopropanoate**

Compound 5a (white solid, 520 mg, yield 78%, $R_f = 0.29$ (EA/Hex=25%)). $^1$H NMR (400 MHz, $d_6$-DMSO) $\delta$ 9.06 (t, $J = 5.6$ Hz, 1H), 7.91 (d, $J = 8.0$ Hz, 2H), 7.71 (t, $J = 7.4$ Hz, 1H), 7.56 (t, $J = 7.7$ Hz, 2H), 7.43 (d, $J = 8.7$ Hz, 2H), 7.38-7.19 (m, 5H), 7.13 (d, $J = 7.9$ Hz, 2H), 5.71 (s, 1H), 4.33-4.16 (m, 4H), 1.22 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) $\delta$ 190.4, 167.1, 167.0, 163.5, 138.6, 136.8, 135.8, 132.8, 132.5, 131.9, 129.7, 129.6, 128.7, 127.8, 127.4, 122.7, 64.3, 62.4, 43.2, 14.3. HRMS (ESI) m/z calcd for C$_{26}$H$_{24}$BrN$_2$O$_5$ $(M+H)^+$ 523.0863, found 523.0864.

**3-benzyl-6-(4-bromophenyl)-1-phenyl-3,6-diazabicyclo[3.1.0]hexane-2,4-Dione**

Compound cis-6a (white solid, 290 mg, yield 67%, $R_f = 0.35$ (EA/Hex=15%)). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.55 (dd, $J = 6.6$, 3.1 Hz, 2H), 7.47-7.40 (m, 3H), 7.24 (d, $J = 7.5$ Hz, 1H), 7.14 (t, $J = 7.6$ Hz, 2H), 7.08 (d, $J = 8.7$ Hz, 2H), 6.92 (d, $J = 7.4$ Hz, 2H), 6.70 (d, $J = 8.7$ Hz, 2H), 4.37 (s, 2H), 3.75 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 168.74, 167.53, 142.61, 133.62, 131.38, 129.10, 128.26, 127.80, 127.75, 127.51, 126.78, 126.52, 119.99, 116.65, 51.19, 46.71, 41.00. HRMS (ESI) m/z calcd for C$_{23}$H$_{18}$BrN$_2$O$_2$ $(M+H)^+$ 433.0546, found 433.0544.

**6-(4-Bromophenyl)-1-(4-methoxyphenyl)-3-(4-methylbenzyl)-3,6-diazabicyclo[3.1.0]hexane-2,4-dione**

Compound cis-6b (white solid, 331 mg, yield 72%, $R_f=0.33$ (EA/Hex=15%)). $^1$H NMR (400 MHz,
CDCl$_3$ δ 7.49-7.44 (m, 2H), 7.23 (d, $J = 7.4$ Hz, 1H), 7.13 (t, $J = 7.6$ Hz, 2H), 7.09-7.04 (m, 2H), 6.94 (t, $J = 5.8$ Hz, 2H), 6.91 (d, $J = 7.4$ Hz, 2H), 6.69 (t, $J = 5.8$ Hz, 2H), 4.36 (s, 2H), 3.83 (s, 3H), 3.71 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 170.07, 168.72, 160.39, 143.79, 134.70, 132.38, 129.16, 128.76, 128.52, 127.52, 121.93, 121.02, 117.57, 114.31, 55.41, 52.02, 47.57, 41.98. HRMS (ESI) m/z calcd for C$_{24}$H$_{20}$BrN$_2$O$_3$+ (M+H)$^+$ 463.0652, found 463.0649.

3-Benzyl-1,6-diphenyl-3,6-diazabicyclo[3.1.0]hexane-2,4-dione

Compound cis-6c (white solid, 212 mg, yield 60%, R$_f$ = 0.34 (EA/Hex=15%)). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.63-7.54 (m, 2H), 7.43 (dd, $J = 5.0$, 2.3 Hz, 3H), 7.13 (ddd, $J = 15.8$, 8.2, 5.7 Hz, 6H), 6.99-6.87 (m, 5H), 4.27 (s, 2H), 3.77 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 170.17, 169.01, 144.69, 135.03, 130.50, 129.52, 129.15, 128.76, 128.56, 127.91, 127.48, 124.68, 119.44, 52.34, 47.93, 41.87. HRMS (ESI) m/z calcd for C$_{23}$H$_{19}$N$_2$O$_2$+ (M+H)$^+$ 355.1441, found 355.1442.

3-Benzyl-6-(3-chlorophenyl)-1-phenyl-3,6-diazabicyclo[3.1.0]hexane-2,4-dione

Compound cis-6d (white solid, 252 mg, yield 65%, R$_f$ = 0.30 (EA/Hex=15%)). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.54 (dd, $J = 6.6$, 3.1 Hz, 2H), 7.43 (dd, $J = 5.1$, 1.9 Hz, 3H), 7.18-7.09 (m, 3H), 6.97 (dd, $J = 6.4$, 2.9 Hz, 2H), 6.93-6.83 (m, 2H), 6.80-6.69 (m, 2H), 4.35 (s, 2H), 3.74 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 169.80, 168.57, 145.74, 135.04, 134.96, 130.44, 130.02, 129.32, 128.84, 128.50, 127.86, 127.68, 125.16, 119.55, 117.66, 52.07, 47.64, 41.91. HRMS (ESI) m/z calcd for C$_{23}$H$_{17}$ClN$_2$O$_2$+ (M+Na)$^+$ 411.0871, found 411.0969.

3-Benzyl-6-(3-bromophenyl)-1-phenyl-3,6-diazabicyclo[3.1.0]hexane-2,4-dione

Compound cis-6e (white solid, 260 mg, yield 60%, R$_f$ = 0.34 (EA/Hex=15%)). $^1$H NMR (400 MHz, CDCl$_3$) δ
7.54 (dd, $J = 6.5$, 3.0 Hz, 2H), 7.49-7.40 (m, 3H), 7.19-7.12 (m, 3H), 7.01 (s, 1H), 6.97 (dd, $J = 6.4$, 2.6 Hz, 2H), 6.92 (d, $J = 7.9$ Hz, 1H), 6.83 (t, $J = 7.9$ Hz, 1H), 6.77 (d, $J = 8.1$ Hz, 1H), 4.36 (s, 2H), 3.75 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 169.77, 168.53, 145.83, 134.93, 130.67, 129.99, 129.32, 128.84, 128.51, 128.08, 127.84, 127.67, 123.07, 122.37, 118.09, 52.06, 47.64, 41.91. HRMS (ESI) m/z calcd for C$_{23}$H$_{18}$BrN$_2$O$_2^+$ (M+H)$^+$ 433.0546, found 433.0613.

3-Benzyl-6-(4-chlorophenyl)-1-phenyl-3,6-diazabicyclo[3.1.0]hexane-2,4-dione

Compound cis-6f (white solid, 264 mg, yield 68%, $R_f = 0.31$ (EA/Hex=15%)). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.55 (dd, $J = 6.6$, 3.0 Hz, 2H), 7.46-7.40 (m, 3H), 7.23 (t, $J = 7.4$ Hz, 1H), 7.13 (t, $J = 7.6$ Hz, 2H), 6.96-6.86 (m, 4H), 6.75 (d, $J = 8.7$ Hz, 2H), 4.37 (s, 2H), 3.75 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 169.80, 168.59, 143.13, 134.66, 130.16, 129.83, 129.51, 129.28, 128.82, 128.48, 127.82, 127.51, 120.63, 52.26, 47.79, 42.00. HRMS (ESI) m/z calcd for C$_{23}$H$_{18}$ClN$_2$O$_2^+$ (M+H)$^+$ 389.1051, found 389.1045.

3-Benzyl-1-phenyl-6-(3-(trifluoromethyl)phenyl)-3,6-diazabicyclo[3.1.0]hexane-2,4-dione

Compound cis-6g (white solid, 282 mg, yield 67%, $R_f = 0.30$ (EA/Hex=15%)). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.56 (dd, $J = 6.5$, 3.1 Hz, 2H), 7.44 (dd, $J = 5.0$, 1.8 Hz, 3H), 7.13-7.03 (m, 6H), 6.99 (dd, $J = 5.5$, 3.4 Hz, 1H), 6.96-6.90 (m, 2H), 4.33 (s, 2H), 3.79 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 169.71, 168.45, 145.10, 134.87, 129.97, 129.40, 128.89, 128.55, 127.81, 127.60, 124.80, 122.55, 121.52, 116.30, 52.10, 47.70, 41.89. HRMS (ESI) m/z calcd for C$_{24}$H$_{18}$F$_3$N$_2$O$_2^+$ (M+H)$^+$ 423.1315, found 423.1307.

3-Benzyl-1,6-bis(4-bromophenyl)-3,6-diazabicyclo[3.1.0]hexane-2,4-dione
Compound cis-6h (white solid, 312 mg, yield 61%, R_f = 0.33 (EA/Hex=15%)). 1H NMR (400 MHz, CDCl_3) δ 7.57 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 7.5 Hz, 1H), 7.14 (t, J = 7.6 Hz, 2H), 7.07 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 7.5 Hz, 2H), 6.67 (d, J = 8.6 Hz, 2H), 4.36 (s, 2H), 3.73 (s, 1H). 13C NMR (100 MHz, CDCl_3) δ 169.36, 168.19, 143.31, 134.50, 132.47, 132.03, 129.41, 129.25, 128.79, 128.57, 127.62, 123.60, 120.95, 117.89, 51.60, 47.91, 42.08. HRMS (ESI) m/z calcd for C_{23}H_{17}BrN_2O^+ (M+H)^+ 510.9651, found 510.9653.

6-(4-Bromophenyl)-3-phenethyl-1-phenyl-3,6-diazabicyclo[3.1.0]hexane-2,4-dione

Compound cis-6i (white solid, 280 mg, yield 63%, R_f = 0.32 (EA/Hex=15%)). 1H NMR (400 MHz, CDCl_3) δ 7.57-7.49 (m, 3H), 7.44 (dd, J = 5.0, 1.9 Hz, 3H), 7.39 (d, J = 8.7 Hz, 2H), 7.25 (s, 1H), 7.21 (d, J = 7.2 Hz, 1H), 7.08 (d, J = 7.0 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 3.76 (s, 1H), 3.38 (ddd, J = 9.4, 7.1, 3.8 Hz, 2H), 2.13 (td, J = 7.1, 4.6 Hz, 2H). 13C NMR (100 MHz, CDCl_3) δ 169.78, 168.67, 144.44, 137.45, 132.55, 131.52, 129.31, 128.85, 128.57, 127.78, 126.67, 121.52, 117.28, 52.42, 47.97, 39.04, 32.96. HRMS (ESI) m/z calcd for C_{24}H_{20}BrN_2O_2^+ (M+H)^+ 447.0703, found 447.0702.

6-(4-Bromophenyl)-3-(4-methylbenzyl)-1-phenyl-3,6-diazabicyclo[3.1.0]hexane-2,4-dione

Compound cis-6j (white solid, 315 mg, yield 71%, R_f = 0.31 (EA/Hex=15%)). 1H NMR (400 MHz, CDCl_3) δ 7.55-7.52 (m, 2H), 7.43 (dd, J = 5.0, 1.7 Hz, 3H), 7.10 (d, J = 8.6 Hz, 2H), 6.96 (d, J = 7.8 Hz, 2H), 6.81 (d, J = 7.9 Hz, 2H), 6.71 (d, J = 8.6 Hz, 2H), 4.33 (s, 2H), 3.74 (s, 1H), 2.34 (s, 3H). 13C NMR (100 MHz, CDCl_3) δ 169.82, 168.64,
6-(4-Bromophenyl)-3-(4-chlorobenzyl)-1-phenyl-3,6-diazabicyclo[3.1.0]hexane-2,4-dione

Compound cis-6k (white solid, 270 mg, yield 58\%, \( R_f = 0.33 \) (EA/Hex=3\%)). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.54 (dd, \( J = 6.5, 3.2 \) Hz, 2H), 7.44 (dd, \( J = 5.0, 1.9 \) Hz, 3H), 7.08 (d, \( J = 8.8 \) Hz, 3H), 6.96 (m, 1H), 6.75-6.61 (m, 4H), 4.36 (s, 2H), 3.76 (s, 1H). \(^1\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 169.69, 168.43, 143.50, 136.90, 132.34, 130.10, 129.36, 128.86, 127.79, 124.50, 120.97, 52.16, 47.65, 41.32. HRMS (ESI) m/z calcd for C\(_{24}\)H\(_{20}\)BrN \( \Omega^+ \) (M+H\(^+\)) 447.0703, found 447.0701.

3-cyclohexyl-6-(3,5-dimethylphenyl)-1-phenyl-3,6-diazabicyclo[3.1.0]hexane-2,4-dione

Compound cis-6l (light yellow solid, 259 mg, yield 71\%, \( R_f = 0.35 \) (EA/Hex=15\%)). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.58 – 7.52 (m, 2H), 7.42 (tt, \( J = 6.6, 3.4 \) Hz, 3H), 6.67 (s, 1H), 6.58 (s, 2H), 3.62 (d, \( J = 0.9 \) Hz, 1H), 3.59 – 3.48 (m, 1H), 2.21 (s, 6H), 1.72 – 1.58 (m, 4H), 1.51 (s, 1H), 1.06 (t, \( J = 10.2 \) Hz, 3H), 0.86 (d, \( J = 10.9 \) Hz, 1H), 0.76 (d, \( J = 12.7 \) Hz, 1H). \(^1\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 170.29, 169.39, 145.06, 139.26, 130.93, 128.90, 128.64, 127.87, 125.87, 117.60, 109.99, 51.69, 51.19, 47.75, 28.58, 28.32, 25.79, 25.75, 24.87, 21.14. HRMS (ESI) m/z calcd for C\(_{24}\)H\(_{27}\)N\(_2\)O\(_2\) \( \Omega^+ \) (M+H\(^+\)) 375.2067, found 375.2072.

Ethyl 3-(benzylcarbamoyl)-1-(4-bromophenyl)-3-phenylaziridine-2-carboxylate
Compound trans-7a (white solid, 325 mg, yield 68%, R_f = 0.18 (EA/Hex=20%). 1H NMR (400 MHz, CDCl_3) δ 7.56 (dd, J = 7.5, 1.8 Hz, 2H), 7.48-7.37 (m, 3H), 7.31-7.26 (m, 5H), 7.05 (dd, J = 6.8, 2.5 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 6.07 (t, J = 5.7 Hz, 1H), 4.43 (dd, J = 14.8, 6.5 Hz, 1H), 4.24 (s, 1H), 4.17 (dd, J = 14.8, 5.6 Hz, 1H), 4.07-3.85 (m, 2H), 0.93 (t, J = 7.1 Hz, 3H). 13C NMR (100 MHz, CDCl_3) δ 166.84, 164.46, 146.63, 137.45, 133.15, 131.93, 129.38, 129.01, 128.68, 127.78, 121.05, 116.06, 61.26, 56.01, 47.23, 44.35, 13.81. HRMS (ESI) m/z calcd for C_{25}H_{24}BrN_2O_3+ (M+H)+ 479.0965, found 479.0960.

Ethyl 3-(benzylcarbamoyl)-1,3-diphenylaziridine-2-carboxylate

Compound trans-7c (white solid, 245 mg, yield 61%, R_f = 0.21 (EA/Hex=20%). 1H NMR (400 MHz, CDCl_3) δ 7.59 (d, J = 7.4 Hz, 2H), 7.40 (t, J = 6.6 Hz, 3H), 7.26 (d, J = 13.0 Hz, 5H), 7.06 (dd, J = 9.9, 4.6 Hz, 3H), 6.96 (d, J = 7.5 Hz, 2H), 6.03 (t, J = 5.5 Hz, 1H), 4.43 (dd, J = 14.8, 6.5 Hz, 1H), 4.29 (s, 1H), 4.18 (dd, J = 14.9, 5.5 Hz, 1H), 3.96 (ddd, J = 34.8, 10.8, 7.1 Hz, 2H), 0.93 (d, J = 7.1 Hz, 3H). 13C NMR (100 MHz, CDCl_3) δ 167.09, 164.94, 147.54, 137.76, 133.81, 129.21, 128.97, 128.94, 128.87, 127.89, 127.51, 123.23, 119.45, 61.37, 55.54, 46.84, 43.88, 13.48. HRMS (ESI) m/z calcd for C_{25}H_{25}N_2O_3+ (M+H)+ 401.1859, found 401.1859.

Ethyl 3-(benzylcarbamoyl)-1-(3-bromophenyl)-3-phenylaziridine-2-carboxylate

Compound trans-7e (white solid, 286 mg, yield 60%, R_f = 0.19 (EA/Hex=20%). 1H NMR (400 MHz, CDCl_3) δ 7.56 (dd, J = 7.5, 1.5 Hz, 2H), 7.41 (q, J = 7.1 Hz, 3H), 7.31-7.26 (m, 5H), 7.07 (dd, J = 6.8, 2.5 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 6.07 (t, J = 5.7 Hz, 1H), 4.43 (dd, J = 14.8, 6.5 Hz, 1H), 4.26 (s, 1H), 4.17 (dd, J = 14.8, 5.6 Hz, 1H), 4.07-3.85 (m, 2H), 0.93 (t, J = 7.1 Hz, 3H). 13C NMR (100 MHz, CDCl_3) δ 166.84, 164.46, 146.63, 137.45, 133.81, 129.21, 128.97, 128.94, 128.87, 127.89, 127.51, 123.23, 119.45, 61.37, 55.54, 46.84, 43.88, 13.81. HRMS (ESI) m/z calcd for C_{25}H_{25}N_2O_3+ (M+H)+ 401.1859, found 401.1859.
5.3 Hz, 3H), 7.33 – 7.21 (m, 4H), 7.17 (d, J = 8.5 Hz, 1H), 7.10 (dd, J = 7.1, 5.7 Hz, 3H), 6.88 (d, J = 8.1 Hz, 1H), 6.13 (t, J = 5.6 Hz, 1H), 4.46 (dd, J = 14.9, 6.6 Hz, 1H), 4.25 (s, 1H), 4.19 (dd, J = 14.9, 5.4 Hz, 1H), 4.03 – 3.85 (m, 2H), 0.93 (t, J = 7.1 Hz, 3H). 13C NMR (100 MHz, CDCl3) δ 166.98, 162.36, 149.28, 137.23, 132.87, 130.38, 129.48, 129.23, 128.50, 128.29, 127.74, 126.35, 122.95, 122.42, 118.56, 118.35, 61.47, 55.88, 47.41, 44.27, 13.74. HRMS (ESI) m/z calcd for C25H24BrN2O3+ (M+H)+ 479.0965, found 479.0981.

**Ethyl 3-(benzylcarbamoyl)-3-phenyl-1-(3-(trifluoromethyl)phenyl)aziridine-2-carboxylate**

![Diagram of compound](image)

Compound trans-7g (white solid, 318 mg, yield 68%, Rf = 0.16 (EA/Hex=20%)). 1H NMR (400 MHz, CDCl3) δ 7.61-7.54 (m, 2H), 7.43 (q, J = 5.4 Hz, 3H), 7.35 (t, J = 7.8 Hz, 1H), 7.32-7.27 (m, 3H), 7.21 (s, 1H), 7.13-7.04 (m, 3H), 6.11 (t, J = 5.5 Hz, 1H), 4.38 (dd, J = 14.9, 6.2 Hz, 1H), 4.29 (s, 1H), 4.25 (dd, J = 14.9, 5.6 Hz, 1H), 4.06-3.89 (m, 2H), 0.94 (t, J = 7.1 Hz, 3H). 13C NMR (100 MHz, CDCl3) δ 166.69, 164.35, 148.27, 137.24, 132.88, 129.55, 129.09, 128.74, 127.70, 122.49, 120.08, 116.07, 61.35, 55.94, 47.46, 44.37, 13.81. HRMS (ESI) m/z calcd for C26H23F3N2O+ (M+H)+ 469.1734, found 469.1734.

**Ethyl 3-(benzylcarbamoyl)-1,3-bis(4-bromophenyl)aziridine-2-carboxylate**

![Diagram of compound](image)

Compound trans-7h (white solid, 320 mg, yield 58%, Rf = 0.20 (EA/Hex=20%)). 1H NMR (400 MHz, CDCl3) δ 7.56 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.30 (dd, J = 6.4, 1.8 Hz, 5H), 7.06 (d, J = 9.3 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 6.00 (s, 1H), 4.44 (dd, J = 14.7, 6.6 Hz, 1H), 4.24 (s, 1H), 4.16 (dd, J = 14.7, 5.5 Hz, 1H), 4.07 – 3.89 (m, 2H),
1.00 (t, J = 7.1 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.45, 163.34, 146.54, 137.65, 132.58, 132.37, 131.65, 130.94, 129.27, 128.28, 127.83, 123.51, 121.35, 60.82, 54.81, 46.41, 43.76, 13.27. HRMS (ESI) m/z calcd for C$_{23}$H$_{23}$Br$_2$NO$^+$ (M+H)$^+$ 557.0070, found 557.0077.

**Ethyl 1-(4-bromophenyl)-3-((4-methylbenzyl)carbamoyl)-3-phenylaziridine-2-carboxylate**

Compound *trans*-7j (white solid, 295 mg, yield 60%, R$_f$ = 0.15 (EA/Hex=20%)). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.57 (d, J = 30.0 Hz, 2H), 7.41 (d, J = 19.2 Hz, 3H), 7.28 (dd, J = 10.9, 8.0 Hz, 2H), 7.09 (d, J = 7.8 Hz, 2H), 6.99 – 6.88 (m, 2H), 6.81 (t, J = 5.7 Hz, 2H), 6.04 (s, 1H), 4.38 (dd, J = 14.7, 6.5 Hz, 1H), 4.26 (s, 1H), 4.12 (dd, J = 14.6, 5.4 Hz, 1H), 4.06 – 3.83 (m, 2H), 2.36 (s, 3H), 0.94 (t, J = 4.2 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 167.65, 164.17, 146.02, 137.05, 134.60, 132.60, 131.91, 131.57, 129.35, 129.11, 128.15, 127.62, 121.17, 116.45, 60.79, 55.52, 47.59, 44.64, 20.26, 12.54. HRMS (ESI) m/z calcd for C$_{26}$H$_{26}$BrN$_2$O$^+$ (M+H)$^+$ 493.1121, found 493.1129.

**Ethyl 1-(4-bromophenyl)-3-((4-chlorobenzyl)carbamoyl)-3-phenylaziridine-2-carboxylate**

Compound *trans*-7k (white solid, 328 mg, yield 64%, R$_f$ = 0.22 (EA/Hex=20%)). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.57 (dd, J = 7.5, 1.8 Hz, 2H), 7.47-7.39 (m, 3H), 7.32 (d, J = 8.7 Hz, 2H), 7.26-7.19 (m, 1H), 6.96 (td, J = 8.4, 2.1 Hz, 1H), 6.87-6.72 (m, 4H), 6.09 (t, J = 5.9 Hz, 1H), 4.42 (dd, J = 15.0, 6.6 Hz, 1H), 4.23 (s, 1H), 4.15 (dd, J = 15.0, 5.8 Hz, 1H), 3.90-4.03 (m, 2H), 0.93 (t, J = 7.1 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.77, 164.64, 146.52, 140.03, 133.07, 131.98, 129.47, 129.09, 123.30, 121.03, 116.18, 114.73, 61.30, 55.93, 47.20, 43.77,
13.81. HRMS (ESI) m/z calcd for C_{25}H_{23}BrClNO^{+} (M+H)^+ 513.0575, found 513.0600.

**1-Benzyl-3-((4-bromophenyl)amino)-4-phenyl-1H-pyrrole-2,5-dione**

Compound 8a (yellow solid, 307 mg, yield 71%, R_f = 0.27 (EA/Hex=15%)) \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.47-7.41 (m, 2H), 7.38-7.27 (m, 3H), 7.21-7.17 (m, 2H), 7.16-7.11 (m, 3H), 7.03 (dd, \(J = 8.1, 1.5\) Hz, 2H), 6.48 (d, \(J = 8.7\) Hz, 2H), 4.78 (s, 2H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 171.54, 168.08, 136.44, 135.56, 135.44, 131.31, 129.77, 129.04, 128.70, 127.86, 127.80, 127.50, 122.76, 117.36, 103.71, 41.91. HRMS (ESI) m/z calcd for C_{25}H_{21}BrN_{2}O^{+} (M+H)^+ 433.0546, found 433.0546.

**1-Benzyl-3-((4-bromophenyl)amino)-4-(4-methoxyphenyl)-1H-pyrrole-2,5-dione**

Compound 8b (yellow solid, 345 mg, yield 75%, R_f = 0.24 (EA/Hex=15%)) \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.47-7.38 (m, 2H), 7.36-7.27 (m, 3H), 7.16 (d, \(J = 8.8\) Hz, 2H), 7.12 (s, 1H), 7.06-6.94 (m, 2H), 6.77-6.65 (m, 2H), 6.49 (d, \(J = 8.8\) Hz, 2H), 4.76 (s, 2H), 3.77 (s, 2H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 171.81, 168.35, 159.27, 136.52, 135.64, 134.34, 131.34, 131.13, 128.70, 127.84, 122.51, 121.50, 117.01, 113.10, 104.22, 55.32, 41.88. HRMS (ESI) m/z calcd for C_{24}H_{19}BrN_{2}O^{+} (M+H)^+ 463.0652, found 463.0653.

**1-Benzyl-3-phenyl-4-(phenylamino)-1H-pyrrole-2,5-dione**

Compound 8c (light yellow solid, 260 mg, yield 73%, R_f = 0.23 (EA/Hex=15%)) \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.45 (d, \(J = 7.0\) Hz, 2H), 7.38-7.27 (m, 3H), 7.15 -7.06 (m, 3H), 7.05-6.95 (m, 5H), 6.62 (d, \(J = 7.6\) Hz, 2H), 4.78 (s, 2H). \(^{13}\)C
NMR (100 MHz, CDCl₃) δ 171.81, 168.25, 136.59, 136.28, 136.13, 129.74, 129.32, 128.69, 128.67, 128.31, 127.81, 127.34, 127.27, 124.55, 121.55, 102.79, 41.87. HRMS (ESI) m/z calcd for C_{34}H_{26}N₂O₂⁺ (M+H)⁺ 355.1441, found 355.1441.

1-Benzyl-3-((3-chlorophenyl)amino)-4-phenyl-1H-pyrrole-2,5-dione

Compound 8d (white solid, 325 mg, yield 61%, Rf = 0.20 (EA/Hex=15%)). ¹H NMR (400 MHz, CDCl₃) δ 7.44 (d, J = 6.9 Hz, 2H), 7.38-7.28 (m, 3H), 7.21-7.14 (m, 3H), 7.04 (dd, J = 8.0, 1.5 Hz, 2H), 6.97-6.91 (m, 2H), 6.58 (s, 1H), 6.52 (dt, J = 6.7, 2.3 Hz, 1H), 4.78 (s, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 171.51, 168.08, 137.46, 136.43, 135.50, 134.23, 129.72, 129.20, 129.02, 128.70, 128.64, 127.90, 127.86, 127.48, 124.36, 121.79, 119.32, 104.25, 41.93. HRMS (ESI) m/z calcd for C_{23}H_{18}ClN₂O₂⁺ (M+H)⁺ 389.1051, found 389.1051.

1-Benzyl-3-((3-bromophenyl)amino)-4-phenyl-1H-pyrrole-2,5-dione

Compound 8e (white solid, 325 mg, yield 75%, Rf = 0.20 (EA/Hex=15%)) ¹H NMR (400 MHz, CDCl₃) δ 7.47-7.41 (m, 2H), 7.38-7.27 (m, 3H), 7.22-7.16 (m, 3H), 6.89 (t, J = 8.0 Hz, 1H), 6.73 (t, J = 1.9 Hz, 1H), 6.58 (dd, J = 8.1, 1.6 Hz, 1H), 4.78 (s, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 171.51, 168.07, 137.54, 136.43, 135.42, 129.74, 129.46, 128.99, 128.71, 127.98, 127.52, 127.27, 124.72, 122.10, 119.74, 104.29, 41.94. HRMS (ESI) m/z calcd for C_{23}H_{18}BrN₂O₂⁺ (M+H)⁺ 433.0546, found 433.0546.

1-Benzyl-3-((4-chlorophenyl)amino)-4-phenyl-1H-pyrrole-2,5-dione

Compound 8f (yellow solid, 264 mg, yield 68%, Rf = 0.28 (EA/Hex=15%)) ¹H NMR (400 MHz, CDCl₃) δ 7.44 (d, J = 7.0 Hz, 2H), 7.37-7.28 (m, 3H), 7.21 (s, 1H), 7.20-7.12
(m, 3H), 7.02 (dd, J = 7.9, 1.3 Hz, 2H), 6.98 (d, J = 8.7 Hz, 2H), 6.54 (d, J = 8.7 Hz, 2H), 4.78 (s, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 171.57, 168.09, 136.46, 135.69, 134.93, 129.79, 129.77, 129.05, 128.71, 128.67, 128.37, 127.87, 127.77, 127.48, 122.49, 103.54, 41.91. HRMS (ESI) m/z calcd for C$_{23}$H$_{18}$ClN$_2$O $^+$ (M+H)$^+$ 389.1051, found 389.1051.

1-Benzyl-3-phenyl-4-((3-(trifluoromethyl)phenyl)amino)-1$H$-pyrrole-2,5-dione

Compound 8g (yellow solid, 330 mg, yield 78%, R$_f$ = 0.29 (EA/Hex=15%)). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.44 (d, J = 7.1 Hz, 2H), 7.33 (dd, J = 13.9, 6.6 Hz, 3H), 7.22-7.09 (m, 5H), 7.02 (d, J = 6.9 Hz, 2H), 6.92-6.84 (m, 1H), 6.75 (s, 1H), 4.79 (s, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 171.43, 168.07, 136.85, 136.39, 135.31, 131.02, 130.69, 129.67, 128.96, 128.68, 128.01, 127.91, 127.56, 124.69, 124.01, 120.78, 118.00, 117.97, 104.69, 41.97. HRMS (ESI) m/z calcd for C$_{24}$H$_{18}$F$_3$N$_2$O$_2$ $^+$ (M+H)$^+$ 423.1315, found 423.1315.

1-Benzyl-3-(4-bromophenyl)-4-((4-bromophenyl)amino)-1$H$-pyrrole-2,5-dione

Compound 8h (light yellow solid, 285 mg, yield 56%, R$_f$ = 0.31 (EA/Hex=15%)). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.42 (d, J = 7.6 Hz, 2H), 7.36-7.27 (m, 5H), 7.20 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 6.51 (d, J = 8.7 Hz, 2H), 4.76 (s, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 171.24, 167.78, 136.78, 135.70, 135.21, 131.57, 131.22, 130.66, 128.73, 127.94, 122.88, 122.00, 117.87, 102.34, 41.99. HRMS (ESI) m/z calcd for C$_{23}$H$_{17}$Br$_2$N$_2$O $^+$ (M+H)$^+$ 510.9651, found 510.9649.

3-((4-Bromophenyl)amino)-1-phenethyl-4-phenyl-1$H$-pyrrole-2,5-dione

Compound 8i (light yellow solid, 320 mg, yield 72%, R$_f$ = 0.20 (EA/Hex=15%)). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.32-7.27 (m, 3H), 7.19 (s, 2H), 7.16 (dd, J = 10.0, 8.2 Hz,
5H), 7.03 (dd, J = 8.0, 1.5 Hz, 2H), 6.49 (d, J = 8.7 Hz, 2H), 3.89-3.83 (dd, J = 8.6, 6.9 Hz, 2H), 3.08-2.89 (m, 2H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 171.74, 168.19, 138.11, 135.52, 131.32, 129.78, 129.12, 128.89, 128.59, 127.80, 127.53, 126.67, 122.74, 117.31, 103.68, 39.62, 34.79. HRMS (ESI) m/z calcd for C\(_{24}\)H\(_{20}\)BrN\(_2\)O\(_2\)\(^{+}\) (M+H)\(^{+}\) 447.0703, found 447.0703.

1-cyclohexyl-3-((3,5-dimethylphenyl)amino)-4-phenyl-1H-pyrrole-2,5-dione

Compound 8l (yellow solid, 243 mg, yield 69%, \(R_f= 0.40\) (EA/Hex=15%)) \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.13 (dd, J = 5.2, 2.1 Hz, 3H), 7.02 – 6.97 (m, 2H), 6.57 (s, 1H), 6.21 (s, 2H), 4.06 – 3.95 (m, 1H), 2.11 (dt, J = 15.7, 10.9 Hz, 2H), 1.98 (s, 6H), 1.84 (d, J = 13.4 Hz, 2H), 1.75 (d, J = 10.7 Hz, 2H), 1.67 (d, J = 12.0 Hz, 2H), 1.35 (dd, J = 13.1, 3.1 Hz, 2H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 172.23, 168.34, 137.98, 135.91, 135.76, 129.92, 128.64, 127.87, 127.09, 127.02, 125.83, 119.41, 117.59, 50.81, 30.10, 25.99, 25.14, 20.88. HRMS (ESI) m/z calcd for C\(_{24}\)H\(_{27}\)N\(_2\)O\(_2\)\(^{+}\) (M+H)\(^{+}\) 375.2067, found 375.2071.

1-Benzyl-3-((2-fluorophenyl)amino)-4-phenyl-1H-pyrrole-2,5-dione

Compound 8m (yellow solid, 257 mg, yield 69%, \(R_f= 0.26\) (EA/Hex=15%)) \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.48-7.42 (m, 2H), 7.37-7.28 (m, 3H), 7.15-7.10 (m, 3H), 7.06-7.01 (m, 2H), 7.01-6.96 (m, 1H), 6.96-6.89 (m, 1H), 6.60 (t, J = 7.7 Hz, 1H), 6.28 (td, J = 8.2, 1.4 Hz, 1H), 4.78 (s, 2H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 171.51, 168.34, 155.72, 153.26, 136.49, 135.77, 129.65, 128.97, 128.69, 127.84, 127.62, 127.38, 125.36, 115.36, 115.17, 104.35, 41.90. HRMS (ESI) m/z calcd for C\(_{23}\)H\(_{18}\)FN\(_2\)O\(_2\)\(^{+}\) (M+H)\(^{+}\) 373.1347, found 373.1347.

1-Benzyl-3-((4-bromophenyl)amino)-4-(furan-2-yl)-1H-pyrrole-2,5-dione
Compound 8n (white solid, 300mg, yield 71%, R$_f$ = 0.24 (EA/Hex=15%)) $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.42-7.37 (m, 2H), 7.33-7.27 (m, 5H), 7.20 (d, $J$ = 1.7 Hz, 1H), 6.84-6.77 (m, 2H), 6.74 (d, $J$ = 3.4 Hz, 1H), 6.42 (dd, $J$ = 3.4, 1.8 Hz, 1H), 4.72 (s, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 169.48, 167.19, 144.26, 142.59, 136.90, 136.32, 134.52, 131.62, 128.71, 128.55, 127.88, 123.07, 118.00, 111.76, 111.44, 97.65, 41.77. HRMS (ESI) m/z calcd for C$_{21}$H$_{16}$BrN$_2$O$_3$+(M+H)$^+$ 423.0339, found 423.0331.

1-Cyclohexyl-3-phenyl-4-(phenylamino)-1H-pyrrole-2,5-dione

Compound 8o (light yellow solid, 266 mg, yield 77%, R$_f$ = 0.28 (EA/Hex=15%)) $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.30 (d, $J$ = 12.0 Hz, 1H), 7.06 (d, $J$ = 12.6 Hz, 7H), 6.64 (s, 2H), 4.02 (s, 1H), 2.13 (d, $J$ = 10.4 Hz, 2H), 1.75 (m, 5H), 1.32 (m, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.12, 168.40, 136.53, 135.96, 129.78, 129.59, 128.22, 127.21, 127.17, 124.31, 121.51, 102.27, 50.95, 30.16, 26.04, 25.20. HRMS (ESI) m/z calcd for C$_{22}$H$_{23}$N$_2$O$_2$+(M+H)$^+$ 347.1754, found 347.1752.

$N$-benzyl-$1-(N$-(4-bromophenyl)$)-2$-oxo$-2$-phenylacetamido)cyclohexanecarboxamide, Compound 9 (white solid, 350 mg, yield 67%, R$_f$ = 0.42 (EA/Hex=20%)) $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.78 – 7.69 (m, 2H), 7.52 (t, $J$ = 7.4 Hz, 1H), 7.43 – 7.35 (m, 6H), 7.31 – 7.26 (m, 5H), 6.76 (t, $J$ = 5.1 Hz, 1H), 4.62 (d, $J$ = 5.6 Hz, 2H), 2.27 – 2.20 (m, 2H), 1.93 – 1.86 (m, 2H), 1.53 – 1.52 (m, 4H), 1.40 – 1.24 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 189.7, 173.1, 168.6, 138.2, 135.7, 134.3, 133.7, 133.1, 131.8, 129.5, 128.8, 128.7, 127.9, 127.5, 123.3, 66.7, 44.3, 33.5, 25.2, 22.5. HRMS (ESI) m/z calcd for C$_{28}$H$_{28}$BrN$_2$O$_3$+(M+H)$^+$ 519.1278, found 519.1274.
NMR spectrum of 5a.

\[ \text{H NMR spectrum of 5a} \]

\[ \text{C NMR spectrum of 5a} \]
DEPT (135°) spectrum of 5a

$^1$H-$^1$H COSY spectrum of 5a
$^1$H-$^1$H NOESY spectrum of 5a

$^{13}$C-$^1$H HMOC spectrum of 5a
$^{13}$C-$^1$H HMBC spectrum of 5a
$^1$H NMR and $^{13}$C NMR spectrum of cis-6a.
$^{1}H$ NMR and $^{13}C$ NMR spectrum of cis-6b.
$^1$H NMR and $^{13}$C NMR spectrum of cis-6c.
$^1$H NMR and $^{13}$C NMR spectrum of cis-6d.
$^1$H NMR and $^{13}$C NMR spectrum of cis-6e.
$^1$H NMR and $^{13}$C NMR spectrum of cis-6f.
$^1$H NMR and $^{13}$C NMR spectrum of cis-6g.
$^1$H NMR and $^{13}$C NMR spectrum of cis-6h.
$^1$H NMR and $^{13}$C NMR spectrum of cis-6i.
$^1$H NMR and $^{13}$C NMR spectrum of cis-6j.
$^1$H NMR and $^{13}$C NMR spectrum of cis-6k.
$^1$H NMR and $^{13}$C NMR spectrum of cis-6l.
$^1$H NMR and $^{13}$C NMR spectrum of trans-7a.
$^1$H NMR and $^{13}$C NMR spectrum of trans-7c.
$^1$H NMR and $^{13}$C NMR spectrum of trans-7e.
$^1$H–$^1$H COSY spectrum of \textit{trans}-7e

$^1$H–$^1$H NEOSY spectrum of \textit{trans}-7e
$^{13}$C-$^1$H HMQC spectrum of trans-7e

$^{13}$C-$^1$H HMBC spectrum of trans-7e
$^1$H NMR and $^{13}$C NMR spectrum of trans-7g.
$^1$H NMR and $^{13}$C NMR spectrum of trans-7h.
$^1$H NMR and $^{13}$C NMR spectrum of trans-7j.
$^1$H NMR and $^{13}$C NMR spectrum of trans-7k.
$^1$H NMR and $^{13}$C NMR spectrum of 8a.
$^1$H NMR and $^{13}$C NMR spectrum of 8b.
$^1$H NMR and $^{13}$C NMR spectrum of 8c.
$^1$H NMR and $^{13}$C NMR spectrum of 8d.
$^1$H NMR and $^{13}$C NMR spectrum of 8e.
$^1$H NMR and $^{13}$C NMR spectrum of 8f.
$^1$H NMR and $^{13}$C NMR spectrum of 8g.
$^1$H NMR and $^{13}$C NMR spectrum of 8h.
$^1$H NMR and $^{13}$C NMR spectrum of 8i.
$^1$H NMR and $^{13}$C NMR spectrum of 81.
$^1$H NMR and $^{13}$C NMR spectrum of 8m.
$^1$H NMR and $^{13}$C NMR spectrum of 8n.
$^1$H NMR and $^{13}$C NMR spectrum of 80.
$^1$H NMR and $^{13}$C NMR spectrum of 9.