Supplementary Information

α-Chymotrypsin-Catalyzed Povarov Reaction: One-Pot Synthesis of Tetrahydroquinoline Derivatives

Ling-Po Li\textsuperscript{a,d}, Xin Cai\textsuperscript{b,c,d}, Yang Xiang\textsuperscript{a}, Yong Zhang\textsuperscript{a}, Jian Song\textsuperscript{a}, Da-Cheng Yang\textsuperscript{a}, Zhi Guan\textsuperscript{a*} and Yan-Hong He\textsuperscript{a*}

\textsuperscript{a}Key Laboratory of Applied Chemistry of Chongqing Municipality, School of Chemistry and Chemical Engineering, Southwest University, Chongqing 400715, PR China

\textsuperscript{b}School of Chemical Engineering, Sichuan University, Chengdu 610065, PR China

\textsuperscript{c}MolDesigner Co. Ltd

\textsuperscript{d}Ling-Po Li and Xin Cai contributed equally to this work.

Fax: +86-23-68254091; E-mails: guanzhi@swu.edu.cn (for Z. Guan); heyh@swu.edu.cn (for Y.-H. He)

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1. Materials and Methods

1.1 Materials

The α-chymotrypsin from bovine pancreas (BPC) preparation [Type II, lyophilized powder, molecular weight 25 kDa, product No: C4129, lot No: 060M7007V, 94.1% protein (UV); 45.2 units/mg protein; One unit will hydrolyze 1.0 μmol of BTEE (N-benzoyl-L-tyrosine ethyl ester) per min at pH 7.8 at 25°C; Another BPC preparation (alternative name: TLCK-chymotrypsin) [TLCK treated to inactivate residual trypsin activity, Type VII, molecular weight 25 kDa, essentially salt-free, lyophilized powder, 94% protein (UV); 64 units/mg protein; product No: C3142; lot No: SLBK5967V]; α-Amylase from hog pancreas [product No: 10080, lot No: BCBK7223V, 48.6 U/mg, 1 U corresponds to the amount of enzyme which liberates 1 μmol maltose per minute at pH 6.9 at 25 °C (starch acc. to Zulkowsky, Fluka No. 85642, as substrate.]); β-Glucanase from trichoderma longibriatum [product No: G4423, lot No: 089K1700, 3.1 U/mg solid, one unit will liberate 1.0 μmol of glucose from cellulose in 1 h at pH 5.0 at 37 °C.]; Lipase from Candida rugosa [product No: 62316, 4.28 U/mg, 1 U corresponds to the amount of enzyme which liberates 1 μmol oleic acid per minute at pH 8.0 at 40°C.]; Lipase, immobilized on immobead 150, from Psedomnas cepacia [product No: 54327, lot No: 1388464V, 941 U/g, 1 U corresponds to the amount of enzyme which liberates 1 μmol butyric acid per minute at pH 7.5 at 40°C. Glyceryl tributyrate, Fluka No. 91010, as substrate.]; Trypsin, from porcine pancreas [product No. 93615, lot No. 1434759V, 1460 U/mg) [1 U corresponds to the amount of enzyme which increases the absorbance at 253 nm by 0.001 per minute at pH 7.6 at 25°C. (N-benzoyl-L-arginine ethyl ester, Fluka No. 12880, as substrate)]; Proteinase, from Aspergillus melleus [product No: P4032, lot No:080M1456V, Type XXIII, ≥3 U/mg solid. 1 U will hydrolyze casein to produce color equivalent to 1.0 μmole (181 μg) of tyrosine per minute at pH 7.5 at 37°C (color by Folin & Ciocalteu’s reagent)]; Papain, from Carica Papaya [product No: 76220, lot No: BCBD3116V, 3.6 U/mg, 1 U corresponds to the amount of enzyme which hydrolyzes 1 μmol N-benzoyl-L-arginine ethyl ester (BAEE, Fluka No. 12880) per minute at pH 6.2 at 25 °C] were purchased from Sigma-Aldrich. Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification.

1.2 General methods
NMR spectra were recorded on a 300 MHz spectrometer (Bruker AVANCE DMX300). Routine monitoring of reaction was performed by TLC using pre-coated Haiyang GF254 silica gel TLC plates. All the column chromatography separations were done by silica gel (200-300 mesh) at increased pressure. Evaporation of solvents was performed at reduced pressure. The crude products were purified by column chromatography with petroleum ether/ethyl acetate as eluent.

1.3 Molecular Docking

AutoDock (V4.2) was used with an empirical free-energy function to evaluate binding free energies and the Lamarckian genetic algorithm (LGA) to search for favorable binding positions. The empirical scoring function which contains hydrogen bonding, electrostatics, conform, torsion and solvent terms, was trained to calculate the affinity between ligand and protein. It was used to dock compounds into BPC protein. The grid maps defining the search region and representing the protein in the docking process were calculated with AutoGrid and had dimensions of 40 Å × 40 Å × 40 Å centered by ser195, with a spacing of 0.375 Å between the grid points. The LGA parameters were accepted as number of GA runs 100, population size 150, maximum number of evals 2,500,000 generations and others parameters were left at the default values.

1.4 Energy calculation of quantum chemistry

Gaussview5 was used to generate structures. Energy calculation of the two compounds were performed with Gaussian09 using semi-empirical theory with the PM6 method and density functional theory (DFT) at the B3LYP level of theory and the 6-31G* basis set.

2. Optimization of reaction conditions for the BPC-catalyzed Povarov reaction.

2.1. Effect of solvents on the BPC-catalyzed Povarov reaction
### 2.2. Effect of water contents on the BPC-catalyzed Povarov reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>MeCN (mL)</th>
<th>water (mL)</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>dr (trans/cis)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>0</td>
<td>38</td>
<td>76/24</td>
</tr>
<tr>
<td>2</td>
<td>0.9</td>
<td>0.1</td>
<td>50</td>
<td>82/18</td>
</tr>
<tr>
<td>3</td>
<td>0.85</td>
<td>0.15</td>
<td>50</td>
<td>90/10</td>
</tr>
<tr>
<td>4</td>
<td>0.8</td>
<td>0.2</td>
<td>51</td>
<td>91/9</td>
</tr>
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<td>0.75</td>
<td>0.25</td>
<td>52</td>
<td>89/11</td>
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<tr>
<td>6</td>
<td>0.7</td>
<td>0.3</td>
<td>52</td>
<td>82/18</td>
</tr>
<tr>
<td>7</td>
<td>0.65</td>
<td>0.35</td>
<td>57</td>
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<td>51</td>
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<td>0.5</td>
<td>47</td>
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</tr>
<tr>
<td>10</td>
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<td>0.6</td>
<td>47</td>
<td>75/25</td>
</tr>
<tr>
<td>11</td>
<td>0.3</td>
<td>0.7</td>
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<tr>
<td>12</td>
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<sup>a</sup> Unless otherwise noted, reaction conditions: 1a (0.5 mmol), 2 (1.0 mmol), 3 (4.5 mmol), and BPC (25 mg) in MeCN and deionized water at 30 °C for 120 h. <sup>b</sup> Yield of the isolated products (4a + 5a) after silica gel chromatography. <sup>c</sup> Calculated according to the isolated weights of 4a and 5a.

### 2.3. Effect of BPC concentration on the BPC-catalyzed Povarov reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>BPC concentration (mg/mL)</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>dr (trans/cis)&lt;sup&gt;c&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>40</td>
<td>89/11</td>
</tr>
<tr>
<td>Entry</td>
<td>Temperature (°C)</td>
<td>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>dr (trans/cis)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------</td>
<td>-------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>14</td>
<td>71/29</td>
</tr>
<tr>
<td>2</td>
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</tr>
<tr>
<td>8</td>
<td>60</td>
<td>72</td>
<td>77/23</td>
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</tbody>
</table>

<sup>a</sup> Unless otherwise noted, reaction conditions: 1a (0.5 mmol), 2 (1.0 mmol), 3 (4.5 mmol), and BPC (50 mg) in MeCN (0.8 mL) and deionized water (0.2 mL) at 30°C for 120 h. <sup>b</sup> Yield of the isolated products (4a + 5a) after silica gel chromatography. <sup>c</sup> Calculated according to the isolated weights of 4a and 5a.

### 2.4. Effect of temperature on the BPC-catalyzed Povarov reaction<sup>a</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Phosphate buffer pH</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>dr (trans/cis)&lt;sup&gt;c&lt;/sup&gt;</th>
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</tr>
<tr>
<td>7</td>
<td>9.21</td>
<td>59</td>
<td>90/10</td>
</tr>
<tr>
<td>8</td>
<td>11.20</td>
<td>43</td>
<td>88/12</td>
</tr>
<tr>
<td>9</td>
<td>None (deionized water)</td>
<td>80</td>
<td>89/11</td>
</tr>
</tbody>
</table>

<sup>a</sup> Unless otherwise noted, reaction conditions: 1a (0.5 mmol), 2 (1.0 mmol), 3 (4.5 mmol), and BPC (50 mg) in MeCN (0.8 mL) and phosphate buffer solution (0.2 mL) at 38°C for 120 h. <sup>b</sup> Yield of the isolated products (4a + 5a) after silica gel chromatography. <sup>c</sup> Calculated according to the isolated weights of 4a and 5a.

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*Unless otherwise noted, reaction conditions: 1a (0.5 mmol), 2 (1.0 mmol), 3 (4.5 mmol), and BPC in MeCN (0.8 mL) and deionized water (0.2 mL) at 30°C for 120 h. Yield of the isolated products (4a + 5a) after silica gel chromatography. Calculated according to the isolated weights of 4a and 5a.*
5a) after silica gel chromatography. Calculated according to the isolated weights of 4a and 5a.

2.6 Time course of the BPC-catalyzed Povarov reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>dr (trans/cis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>17</td>
<td>82/18</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>40</td>
<td>82/18</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>70</td>
<td>81/19</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>72</td>
<td>87/13</td>
</tr>
<tr>
<td>5</td>
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<td>89/11</td>
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<td>6</td>
<td>72</td>
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<td>81</td>
<td>89/11</td>
</tr>
<tr>
<td>9</td>
<td>120</td>
<td>80</td>
<td>88/12</td>
</tr>
</tbody>
</table>

Unless otherwise noted, reaction conditions: 1a (0.5 mmol), 2 (1.0 mmol), 3 (4.5 mmol), and BPC (50 mg) in MeCN (0.8 mL) and deionized water (0.2 mL) at 38°C for specified time. Yield of the isolated products (4a + 5a) after silica gel chromatography. Calculated according to the isolated weights of 4a and 5a.

3. The kinetics of BPC catalyzed-hydrolysis of BTEE

![UV spectrophotometric determination of the kinetics of BPC catalyzed-hydrolysis of BTEE.](image)

S-Fig. 1 UV spectrophotometric determination of the kinetics of BPC catalyzed-hydrolysis of BTEE.

Reaction conditions: a solution of Tris-HCl buffer (80 mM, 1.42 mL, pH 7.8), BTEE (1.18 mM, 1.40 mL), calcium chloride (2 M, 0.08 mL) and BPC (0.1 mg/mL, 0.1 mL) was added to the cuvette and measured at 256 nm for 360 s by UV spectrophotometric. Curve a: BPC. Curve b, c, d: the mixture of BPC (50 mg) in MeCN (0.8 mL) and deionized water (0.2 mL) was stirred at 38 °C for 24 h (for curve b), 60 h (for curve c), 120 h (for curve d), and then BPC was collected through filtration which was used for the kinetics test. Curve e: urea-denatured BPC.
Curve f: PMSF-inhibited BPC. Curve g: blank.

4. Kcat for the BPC- or Asp-catalyzed Povarov reaction

\[
\text{CHO} \quad \text{or} \quad \text{Imine} \quad \text{OH} \\
1a \quad 2 \quad 3 \\
\rightarrow \quad \text{BPC or Asp} \quad \text{MeCN/H2O, 30 °C} \\
\text{cis} \quad 4a \quad \text{trans} \quad 5a
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Kcat (h(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BPC</td>
</tr>
<tr>
<td>1(^b)</td>
<td>benzaldehyde (1a)</td>
<td>9.62</td>
</tr>
<tr>
<td>2(^c)</td>
<td>2-aminophenol (2)</td>
<td>5.60</td>
</tr>
<tr>
<td>3(^d)</td>
<td>2,3-dihydropyran (3) (reacting with 1a and 2)</td>
<td>9.08</td>
</tr>
<tr>
<td>4(^e)</td>
<td>Imine</td>
<td>24.02</td>
</tr>
</tbody>
</table>

\(^a\) The reaction was carried out in MeCN (0.9 mL) and deionized water (0.1 mL) at 30 °C. The kinetic parameters were obtained as final BPC concentration as 0.998 mM (for entries 1 and 2) and 0.941 mM (for entries 3 and 4), and final Asp concentration as 50 mM (for entries 1-4). The experiments were based on HPLC determination of the products. \(^b\) Concentration of 1a varied from 0.25 M to 1.5 M, with 2 (0.5 M) and 3 (4.5 M). \(^c\) Concentration of 2 varied from 0.25 M to 1.5 M, with 1a (0.5 M) and 3 (4.5 M). \(^d\) Concentration of 3 varied from 0.5 M to 4.5 M, with 1a (0.5 M) and 2 (1.0 M). \(^e\) Concentration of imine varied from 0.25 M to 1.5 M, with 3 (4.5 M).

5. SDS-PAGE analysis of BPC
6. Enzymatic assay of BPC


6.2. Methods: Continuous spectrophotometric rate determination

6.3. Reagents:

6.3.1. 80 mM Tris-HCl buffer, pH 7.8 at 25 °C.
Prepare a 9.69 mg/mL solution in purified water using Trizma base, and adjust the pH of this solution to 7.8 at 25 °C by HCl.

6.3.2. N-benzoyl-L-tyrosine ethyl ester solution (BTEE).
Weigh 37 mg of N-benzoyl-L-tyrosine ethyl ester into a 100 mL volumetric flask. Dilute the BTEE in 63.4 mL of methanol and bring to volume by purified water. Invert the flask several times to ensure complete mixing.

6.3.3. Calcium chloride solution (CaCl$_2$)
Dissolve 2.94 g of calcium chloride dehydrate in 10 mL of purified water.

6.3.4. Hydrochloric acid solution
Add 0.10 mL of concentrated hydrochloric acid to purified water, then dilute to 100 mL. Mix by inversion and place on ice.

6.3.5. BPC solution.
Weigh 10 mg of BPC into a 100 mL volumetric flask. Dilute the enzyme to volume by cold hydrochloric acid solution (4.3.4). Invert the flask several times to ensure complete mixing.

6.4. General procedure:
Pipette the following reagents into quartz cuvettes, then immediately mix by inversion and record the increase in A_{256nm} for 6 minutes:

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Blank (mL)</th>
<th>Test (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tris-HCl buffer (4.3.1)</td>
<td>1.42</td>
<td>1.42</td>
</tr>
<tr>
<td>BTEE (4.3.2)</td>
<td>1.40</td>
<td>1.40</td>
</tr>
<tr>
<td>CaCl$_2$ (4.3.3)</td>
<td>0.08</td>
<td>0.08</td>
</tr>
<tr>
<td>Hydrochloric acid solution (4.3.4)</td>
<td>0.10</td>
<td>--</td>
</tr>
<tr>
<td>BPC solution (4.3.5)</td>
<td>--</td>
<td>0.10</td>
</tr>
</tbody>
</table>
7. Characterization of Povarov products

**Compound 4a: 5-phenyl-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinolin-7-ol (cis)**

White solid, $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta =$ 9.30 (s, 1H), 7.45-7.26 (m, 5H), 6.75 (d, $J = 7.5$ Hz, 1H), 6.61 (d, $J = 6.6$ Hz, 1H), 6.53 (t, $J = 7.6$ Hz, 1H), 5.24 (d, $J = 5.4$ Hz, 1H), 4.64 (d, $J = 1.47$ Hz, 1H), 4.52 (s, 1H), 3.49-3.46 (m, 1H), 3.29-3.21 (m, 1H), 2.04 (s, 1H), 1.36 (s, 3H), 1.11 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta =$ 142.0, 141.1, 134.2, 128.3, 127.4, 126.8, 121.1, 119.8, 117.1, 113.1, 72.8, 60.8, 59.0, 38.8, 25.3, 18.0.

**Compound 5a: 5-phenyl-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinolin-7-ol (trans)**

White solid, $^1$H NMR (300 MHz, CDCl$_3$) $\delta =$ 7.34-7.19 (m, 5H), 6.72 (t, $J = 3.9$ Hz, 1H), 6.39 (d, $J = 3.8$ Hz, 2H), 6.20-5.34 (brs, 1H), 4.56 (d, $J = 10.6$ Hz, 1H), 4.34-4.28 (m, 2H), 4.03 (m, 1H), 3.63 (td, $J_1 =$ 11.5 Hz, $J_2 =$ 2.0 Hz, 1H), 2.02-1.97 (m, 1H), 1.84-1.68 (m, 1H), 1.61-1.49 (m, 1H), 1.40-1.35 (m, 1H), 1.26-1.22 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta =$ 142.2, 142.0, 134.6, 128.5, 127.9, 127.8, 127.7, 122.8, 120.7, 116.5, 114.8, 74.6, 68.6, 54.5, 38.8, 24.1, 22.0.

**Compound 4b: 5-phenyl-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline (cis)**

White solid, $^1$H NMR (300 MHz, CDCl$_3$) $\delta =$ 7.44-7.28 (m, 6H), 7.10 (t, $J = 7.4$ Hz, 1H), 6.80 (t, $J = 7.4$ Hz, 1H), 6.61 (d, $J = 7.9$ Hz, 1H), 5.33 (d, $J = 5.4$ Hz, 1H), 4.69 (d, $J = 2.1$ Hz, 1H), 3.88 (br,
Compound 5b: 5-phenyl-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline (trans)

viscous oil, $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 7.44-7.29 (m, 5H), 7.24-7.21 (m, 1H), 7.10 (dt, $J_1$ = 8.0 Hz, $J_2$ = 1.4 Hz, 1H), 6.70 (t, $J$ = 7.4 Hz, 1H), 6.51 (d, $J$ = 8.0 Hz, 1H), 4.71 (d, $J$ = 10.8 Hz, 1H), 4.38 (d, $J$ = 2.6 Hz, 1H), 4.13-4.08 (m, 2H), 3.71 (td, $J_1$ = 11.5 Hz, $J_2$ = 2.5 Hz, 1H), 2.12-2.05 (m, 1H), 1.93-1.77 (m, 1H), 1.71-1.59 (m, 1H), 1.49-1.44 (m, 1H), 1.36-1.26 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ = 144.8, 142.4, 130.9, 129.4, 128.7, 127.9, 127.9, 120.6, 117.4, 114.2, 74.5, 68.6, 54.8, 38.9, 24.2, 22.1.

Compound 4c: 5-(4-nitrophenyl)-3, 4, 4a, 5, 6, 10b-hexahydro-2H-pyrano [3, 2-c] quinolin-7-ol (cis)

Yellow solid, $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ = 9.32 (s, 1H), 8.23 (d, $J$ = 8.6 Hz, 2H), 7.70 (d, $J$ = 8.6 Hz, 2H), 6.73 (d, $J$ = 7.4 Hz, 1H), 6.61 (d, $J$ = 7.0 Hz, 1H), 6.53 (t, $J$ = 7.6 Hz, 1H), 5.23 (d, $J$ = 5.2 Hz, 1H), 4.84 (s, 1H), 4.74 (s, 1H), 3.45 (d, $J$ = 10.7 Hz, 1H), 3.27-3.19 (m, 1H), 2.16-2.10 (m, 1H), 1.33 (s, 3H), 1.01-0.98 (m, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ = 150.5, 146.8, 144.5, 134.2, 128.3, 123.6, 120.4, 117.6, 117.4, 113.0, 72.1, 60.2, 57.9, 38.4, 25.2, 18.3.
Compound 5c: 5-(4-nitrophenyl)-3, 4, 4a, 5, 6, 10b-hexahydro-2H-pyrano [3, 2-c] quinolin-7-ol (trans)\(^7\)

Yellow solid, \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta = 9.28\) (s, 1H), 8.23 (d, \(J = 8.5\) Hz, 2H), 7.69 (d, \(J = 8.5\) Hz, 2H), 6.64 (d, \(J = 7.6\) Hz, 2H), 6.45 (t, \(J = 7.6\) Hz, 1H), 5.09 (s, 1H), 4.67 (d, \(J = 9.4\) Hz, 1H), 4.30 (d, \(J = 2.4\) Hz, 1H), 3.84 (d, \(J = 11.0\) Hz, 1H), 3.59 (t, \(J = 9.7\) Hz, 1H), 2.03-2.00 (m, 1H), 1.76-1.63 (m, 2H), 1.34-1.16 (m, 2H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta = 151.8, 147.2, 143.8, 134.0, 129.2, 123.8, 121.0, 120.7, 116.2, 113.6, 73.0, 66.8, 54.3, 38.5, 24.2, 22.5.

Compound 4d: 5-(4-chlorophenyl)-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinolin-7-ol (cis)\(^7\)

White solid, \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta = 9.32\) (s, 1H), 7.48-7.41 (m, 4H), 6.75 (d, \(J = 7.4\) Hz, 1H), 6.63 (d, \(J = 7.8\) Hz, 1H), 6.54 (t, \(J = 7.6\) Hz, 1H), 5.24 (d, \(J = 5.3\) Hz, 1H), 4.63-4.61 (m, 2H), 3.49-3.45 (m, 1H), 3.29-3.21 (m, 1H), 2.03-1.99 (m, 1H), 1.37-1.26 (m, 3H), 1.12-1.07 (m, 1H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta = 144.4, 141.1, 134.4, 131.7, 128.9, 128.4, 120.4, 117.5, 117.4, 112.9, 72.3, 60.2, 57.6, 38.6, 25.3, 18.3.

Compound 5d: 5-(4-chlorophenyl)-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinolin-7-ol (trans)\(^7\)
White solid, $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ = 9.25 (s, 1H), 7.45-7.42 (m, 4H), 6.63 (d, $J$ = 7.5 Hz, 2H), 6.44 (t, $J$ = 7.7 Hz, 1H), 4.80 (s, 1H), 4.54 (d, $J$ = 10.0 Hz, 1H), 4.29 (d, $J$ = 2.7 Hz, 1H), 3.86 (d, $J$ = 11.2 Hz, 1H), 3.57 (t, $J$ = 10.1 Hz, 1H), 1.99-1.93 (m, 1H), 1.71-1.57 (m, 2H), 1.27 (d, $J$ = 10.1, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ = 143.7, 142.4, 134.2, 132.2, 129.8, 128.7, 121.3, 120.9, 116.1, 113.6, 73.5, 67.3, 53.9, 38.6, 24.2, 22.3.

**Compound 4e: 5-(4-fluorophenyl)-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinolin-7-ol (cis)**

White solid, $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ = 9.28 (s, 1H), 7.44 (t, $J$ = 6.9 Hz, 2H), 7.17 (t, $J$ = 8.8 Hz, 2H), 6.72 (d, $J$ = 7.4 Hz, 1H), 6.59 (d, $J$ = 7.2 Hz, 1H), 6.51 (t, $J$ = 7.6 Hz, 1H), 5.21 (d, $J$ = 5.2 Hz, 1H), 4.61 (s, 1H), 4.53 (s, 1H), 3.46-3.43 (m, 1H), 3.24-3.18 (m, 1H), 1.99-1.97 (m, 1H), 1.33-1.29 (m, 3H), 1.12-1.07 (m, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ = 163.2, 160.0, 144.3, 138.2, 138.1, 134.4, 128.9, 128.8, 120.3, 117.5, 117.4, 115.3, 115.0, 112.9, 72.3, 60.2, 57.6, 38.6, 25.3, 18.2. HRMS (ESI-TOF) calcd for C$_{18}$H$_{17}$FNO$_2$ ([M-H$^+$]), 298.1249, Found 298.1245.

**Compound 5e: 5-(4-fluorophenyl)-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinolin-7-ol (trans)**

White solid, $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ = 9.20 (s, 1H), 7.43 (t, $J$ = 6.9 Hz, 2H), 7.17 (t, $J$ = 8.7 Hz, 2H), 6.60 (d, $J$ = 7.6 Hz, 2H), 6.40 (t, $J$ = 7.6 Hz, 1H), 4.71 (s, 1H), 4.53 (d, $J$ = 10.1 Hz, 1H), 4.27 (d, $J$ = 2.2 Hz, 1H), 3.85 (d, $J$ = 10.9 Hz, 1H), 3.56 (t, $J$ = 10.2 Hz, 1H), 1.97-1.92 (m, 1H), 1.70-1.60 (m, 2H), 1.26-1.18 (m, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ = 163.5, 160.3, 143.6, 139.4, 134.3, 129.9, 129.9, 121.4, 121.0, 116.0, 115.6, 115.3, 113.6, 73.6, 67.4, 53.7, 38.6,
24.2, 22.2. HRMS (ESI-TOF) calcd for C_{18}H_{17}FNO (\text{[M-H]}^{-}), 298.1249, Found 298.1244.

**Compound 4f: 5-(p-tolyl)-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinolin-7-ol (cis)**

White solid, $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ = 9.30 (s, 1H), 7.31 (d, $J = 8.0$ Hz, 2H), 7.18 (d, $J = 7.9$ Hz, 2H), 6.75 (d, $J = 7.4$ Hz, 1H), 6.62 (d, $J = 6.9$ Hz, 1H), 6.53 (t, $J = 7.6$ Hz, 1H), 5.23 (d, $J = 5.4$ Hz, 1H), 4.59 (s, 1H), 4.45 (s, 1H), 3.48-3.45 (m, 1H), 3.26-3.21 (m, 1H), 2.31 (s, 3H), 2.10-1.99 (m, 1H), 1.37-1.32 (m, 3H), 1.18-1.12 (m, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ = 144.2, 138.9, 136.5, 134.6, 129.1, 126.9, 120.3, 117.6, 117.2, 112.9, 72.4, 60.2, 58.0, 38.8, 25.4, 21.1, 18.3. HRMS (ESI-TOF) calcd for C_{19}H_{20}NO (\text{[M-H]}^{-}), 294.1499, Found 294.1495.

**Compound 5f: 5-(p-tolyl)-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinolin-7-ol (trans)**

White solid, $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ = 9.21 (s, 1H), 7.29 (d, $J = 7.9$ Hz, 2H), 7.17 (d, $J = 6.1$ Hz, 2H), 6.62 (d, $J = 7.5$ Hz, 2H), 6.42 (t, $J = 7.6$ Hz, 1H), 4.61 (s, 1H), 4.50 (d, $J = 10.2$ Hz, 1H), 4.29 (d, $J = 2.6$ Hz, 1H), 3.87 (d, $J = 11.1$ Hz, 1H), 3.57 (t, $J = 9.93$ Hz, 1H), 2.30 (s, 3H), 1.99-1.92 (m, 1H), 1.72-1.55 (m, 2H), 1.32-1.23 (m, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ = 143.5, 140.1, 137.0, 134.4, 129.4, 127.9, 121.5, 121.0, 115.8, 114.9, 113.6, 73.8, 67.5, 54.1, 38.6, 24.2, 22.2, 21.1. HRMS (ESI-TOF) calcd for C_{19}H_{20}NO (\text{[M-H]}^{-}), 294.1499, Found 294.1489.
Compound 4g: 9-methyl-5-phenyl-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline (cis)§
White solid, $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 7.40-7.19 (m, 6H), 6.90 (d, $J = 7.9$ Hz, 1H), 6.50 (d, $J = 8.0$ Hz, 1H), 5.28 (d, $J = 5.4$ Hz, 1H), 4.60 (d, $J = 1.4$ Hz, 1H), 3.75 (s, 1H), 3.59-3.55 (m, 1H), 3.42 (td, $J_1 = 11.0$ Hz, $J_2 = 2.1$ Hz, 1H), 2.26 (s, 3H), 2.14-2.11 (m, 1H), 1.61-1.42 (m, 3H), 1.29-1.27 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ = 142.8, 141.3, 128.7, 128.3, 127.8, 127.4, 126.8, 119.8, 114.6, 72.8, 60.7, 59.4, 39.1, 25.4, 20.7, 17.9.

![Diagram of Compound 4g]

Compound 5g: 9-methyl-5-phenyl-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline (trans)§
Viscous liquid, $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 7.41-7.27 (m, 5H), 7.03 (s, 1H), 6.89 (d, $J = 7.8$ Hz, 1H), 6.42 (d, $J = 8.1$ Hz, 1H), 4.65 (d, $J = 10.8$ Hz, 1H), 4.34 (d, $J = 2.3$ Hz, 1H), 4.10-4.07 (m, 1H), 3.94 (s, 1H), 3.70 (td, $J_1 = 11.5$ Hz, $J_2 = 2.0$ Hz, 1H), 2.22 (s, 3H), 2.07-2.03 (m, 1H), 1.90-1.74 (m, 1H), 1.67-1.56 (m, 1H), 1.46-1.42 (m, 1H), 1.32-1.28 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ = 142.4, 131.0, 130.1, 128.6, 127.8, 126.6, 120.6, 114.2, 74.6, 68.6, 54.9, 39.0, 24.1, 22.0, 20.4.

![Diagram of Compound 5g]

Compound 4h: 4-phenyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-c]quinoline (cis)§
White solid, $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 7.46-7.28 (m, 6H), 7.08 (t, $J = 7.8$ Hz, 1H), 6.80 (t, $J = 7.3$ Hz, 1H), 6.58 (d, $J = 7.9$ Hz, 1H), 5.26 (d, $J = 7.9$ Hz, 1H), 4.67 (d, $J = 2.4$ Hz, 1H), 3.84-3.65 (m, 3H), 2.81-2.72 (m, 1H), 2.26-2.13 (m, 1H), 1.55-1.45 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ = 144.9, 142.2, 130.1, 128.6, 128.3, 127.6, 126.5, 122.7, 119.1, 114.9, 75.9, 66.8, 57.5, 45.7, 24.6.

![Diagram of Compound 4h]
Compound 5h: 4-phenyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-c]quinoline (trans)⁶
Viscous liquid, \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 7.46-7.35\) (m, 6H), 7.13 (t, \(J = 7.9\) Hz, 1H), 6.81 (t, \(J = 7.3\) Hz, 1H), 6.63 (d, \(J = 8.0\) Hz, 1H), 4.61 (d, \(J = 5.0\) Hz, 1H), 4.16 (s, 1H), 4.08-4.00 (m, 1H), 3.89-3.79 (m, 2H), 2.51-2.43 (m, 1H), 2.08-1.96 (m, 1H), 1.77-1.70 (m, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 145.4, 141.6, 131.2, 128.9, 128.6, 128.2, 128.1, 118.3, 114.6, 76.2, 65.2, 57.7, 43.3, 28.7.

Compound 4i: 8-methyl-4-phenyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-c]quinoline (cis)⁹
White solid, \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 7.47-7.27\) (m, 5H), 7.16 (s, 1H), 6.90 (d, \(J = 8.0\) Hz, 1H), 6.52 (d, \(J = 8.1\) Hz, 1H), 5.24 (d, \(J = 8.0\) Hz, 1H), 4.63 (d, \(J = 2.2\) Hz, 1H), 3.83 (td, \(J_1 = 8.3\) Hz, \(J_2 = 3.0\) Hz, 1H), 3.73-3.65 (m, 2H), 2.81-2.72 (m, 1H), 2.26 (s, 3H), 2.20-2.14 (m, 1H), 1.55-1.45 (m, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 142.6, 142.3, 130.3, 129.1, 128.6, 128.4, 127.6, 126.5, 122.6, 115.0, 76.0, 66.9, 57.8, 45.9, 24.6, 20.5.

Compound 5i: 8-methyl-4-phenyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-c]quinoline (trans)⁹
Viscous liquid, \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 7.44-7.32\) (m, 5H), 7.21 (s, 1H), 6.93 (d, \(J = 8.0\) Hz, 1H), 6.53 (d, \(J = 8.0\) Hz, 1H), 4.57 (d, \(J = 5.0\) Hz, 1H), 4.02-3.97 (m, 2H), 3.85-3.72 (m, 2H),
2.45-2.41 (m, 1H), 2.26 (s, 3H), 2.05-1.93 (m, 1H), 1.74-1.65 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) 
$\delta$ = 143.1, 141.8, 131.3, 129.6, 128.6, 128.2, 128.0, 127.6, 120.1, 114.7, 76.2, 65.2, 58.0, 43.5, 28.8, 20.4.

8. References

9. $^1$H NMR and $^{13}$C NMR spectra of Povarov products and HRMS for new compounds

$^1$H NMR Spectrum (DMSO-$d_6$) of 4a

$^{13}$C NMR Spectrum (CDCl$_3$) of 4a
$^1$H NMR Spectrum (CDCl$_3$) of 5a

$^{13}$C NMR Spectrum (CDCl$_3$) of 5a
$^1$H NMR Spectrum (CDCl$_3$) of 4b

$^{13}$C NMR Spectrum (CDCl$_3$) of 4b
$^1$H NMR Spectrum (CDCl$_3$) of 5b

$^{13}$C NMR Spectrum (CDCl$_3$) of 5b
$^1$H NMR Spectrum (DMSO-d$_6$) of 4c

$^{13}$C NMR Spectrum (DMSO-d$_6$) of 4c
$^1$H NMR Spectrum (DMSO-$d_6$) of 5c

$^{13}$C NMR Spectrum (DMSO-$d_6$) of 5c
$^1$H NMR Spectrum (DMSO-$d_6$) of 4d

$^{13}$C NMR Spectrum (DMSO-$d_6$) of 4d
$^1$H NMR Spectrum (DMSO-$d_6$) of 5d

$^{13}$C NMR Spectrum (DMSO-$d_6$) of 5d
$^1$H NMR Spectrum (DMSO-d$_6$) of 4e

$^{13}$C NMR Spectrum (DMSO-d$_6$) of 4e
$^1$H NMR Spectrum (DMSO-d$_6$) of 5e

$^{13}$C NMR Spectrum (DMSO-d$_6$) of 5e
$^1$H NMR Spectrum (DMSO-d$_6$) of 4f

$^{13}$C NMR Spectrum (DMSO-d$_6$) of 4f
$^1$H NMR Spectrum (DMSO-d$_6$) of 5f

$^{13}$C NMR Spectrum (DMSO-d$_6$) of 5f
$^1$H NMR Spectrum (CDCl$_3$) of $4g$

$^{13}$C NMR Spectrum (CDCl$_3$) of $4g$
$^1$H NMR Spectrum (CDCl$_3$) of 5g
$^1$H NMR Spectrum (CDCl$_3$) of 4h

$^{13}$C NMR Spectrum (CDCl$_3$) of 4h
$^1$H NMR Spectrum (CDCl$_3$) of 5h

$^{13}$C NMR Spectrum (CDCl$_3$) of 5h
$^1$H NMR Spectrum (CDCl$_3$) of $4i$

$^{13}$C NMR Spectrum (CDCl$_3$) of $4i$
$^1$H NMR Spectrum (CDCl$_3$) of 5i

$^{13}$C NMR Spectrum (CDCl$_3$) of 5i
HRMS spectra of new products 4e

HRMS spectra of new products 5e
HRMS spectra of new products 4f

HRMS spectra of new products 5f