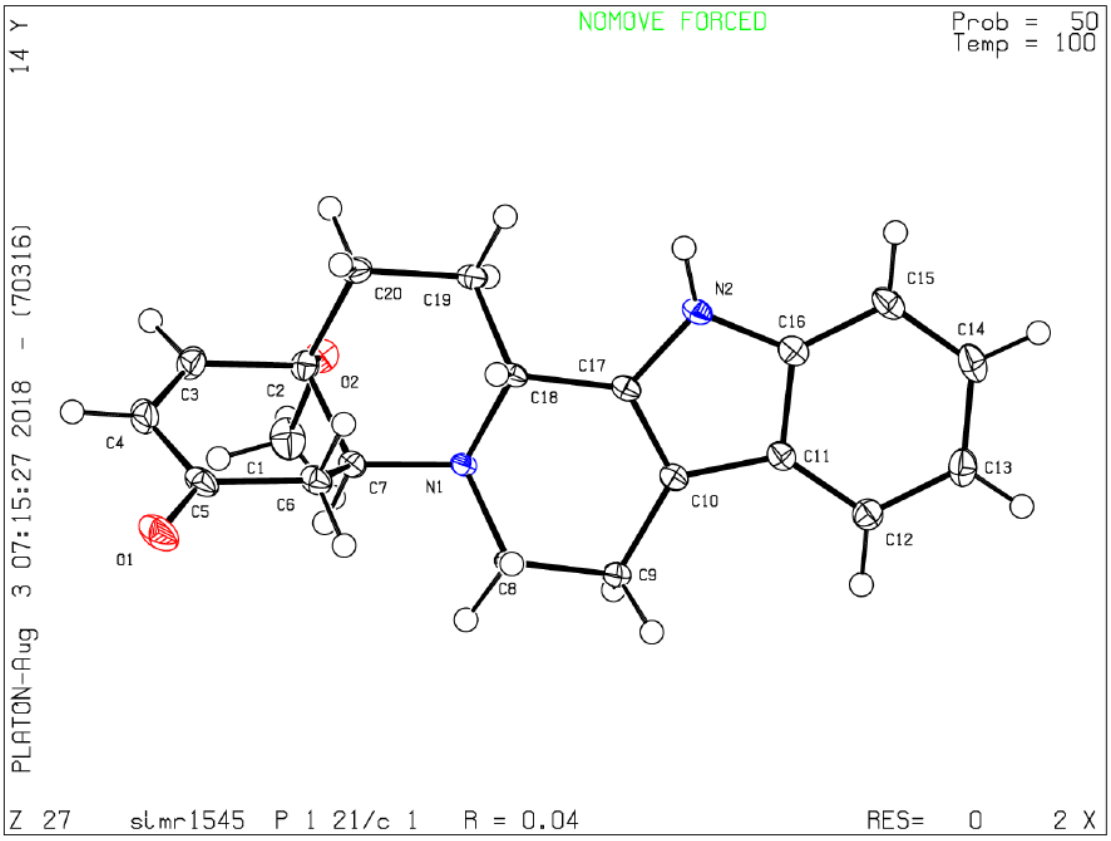
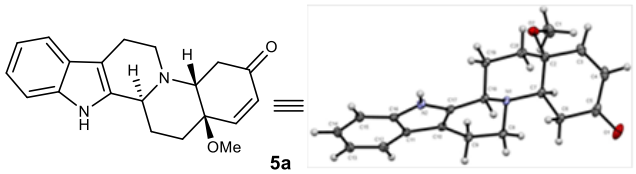
# Multidirectional Desymmetrization of Pluripotent Building Block *en Route* to Diastereoselective Synthesis of Complex Nature-Inspired Scaffolds

*Vunnam et al.*

## Supplementary Tables



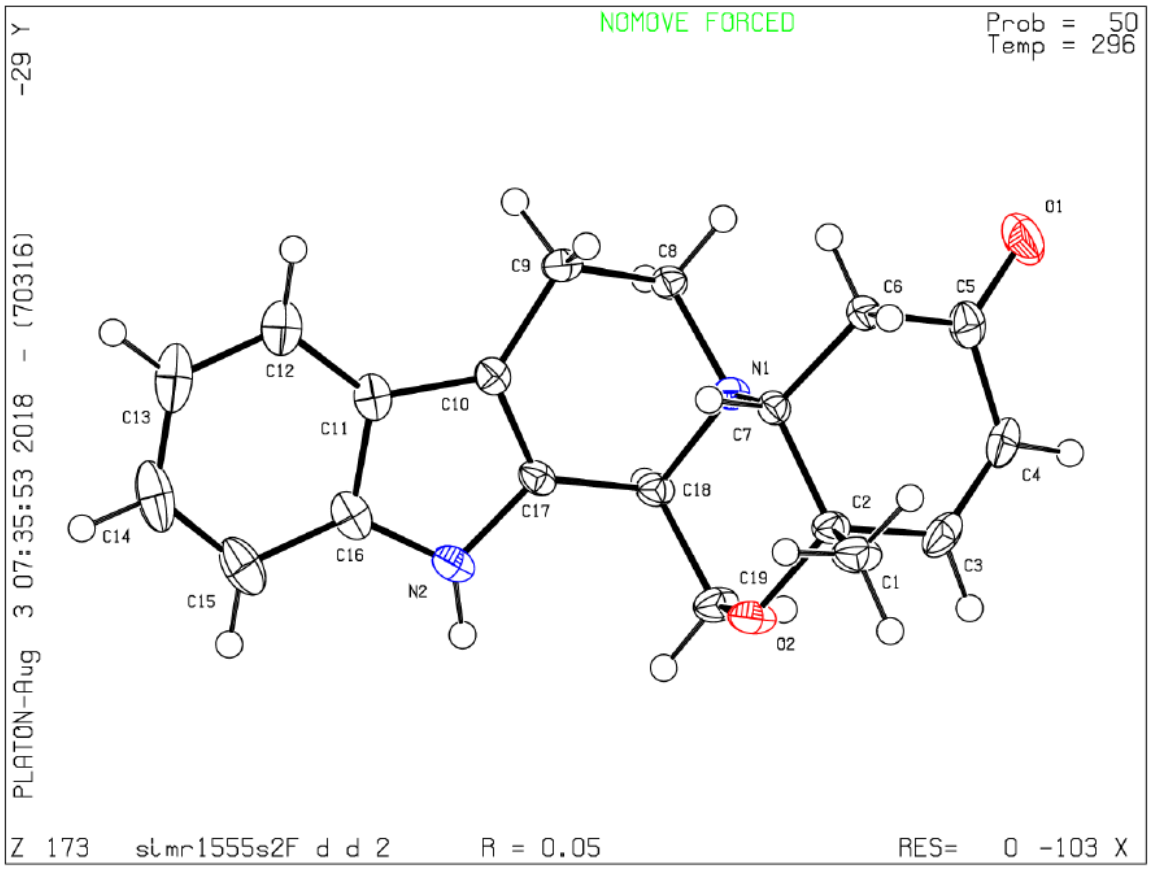



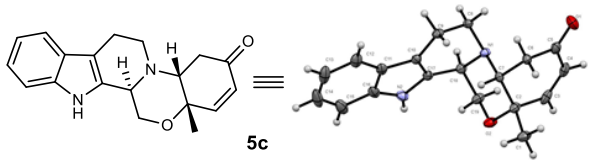

**5a**

| | | |
|---|---|---|
| Identification code | SIMR-1545 | |
| Empirical formula | $C_{20}H_{22}N_2O_2$ | |
| Formula weight | 322.39 | |
| Temperature | 100(2) K | |
| Wavelength | 0.71073Å | |
| Crystal system | Monoclinic | |
| Space group | $P_12_1/c_1$ | |
| Unit cell dimensions | a = 10.612(5) Å | α = 90° |
| | b = 16.433(7) Å | β = 114.413(7) |

| | |
|---|---|
| | c = 10.452(5) Å γ = 90° |
| Volume | 1659.8(13) $Å^3$ |
| Z | 4 |
| Density (calculated) | 1.290 g $cm^{-3}$ |
| Absorption coefficient | 0.084 $mm^{-1}$ |
| F(000) | 688 |
| Crystal size | 0.2 × 0.05 × 0.05 $mm^3$ |
| Reflections collected | 39285 |
| Independent reflections | 4184 [R(int) = 0.0355] |
| Absorption correction | multi-scan |
| Max. and min. transmission | 0.7137and 0.7457 |
| Refinement method | Least Squares minimization |
| Data / restraints / parameters | 4184 / 0 / 218 |
| Goodness-of-fit on F2 | 0.916 |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.0385, $wR_2$ = 0.0965 |
| R indices (all data) | $R_1$ = 0.0473, $wR_2$ = 0.1041 |
| Largest diff. peak and hole | 0.38 and –0.23 e.$Å^{-3}$ |

**Supplementary Table 1** X-ray crystal structure and crystallographic data for compound **5a**



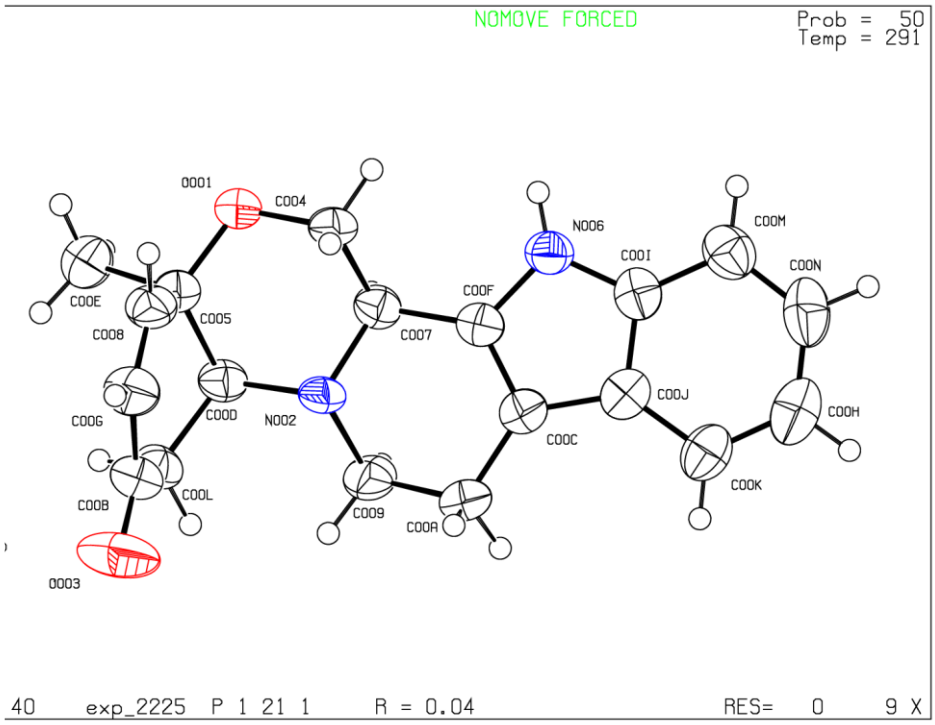



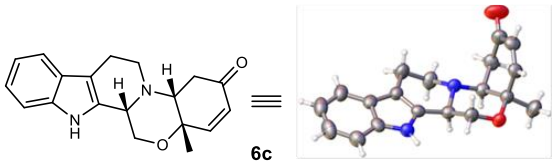

**5c**

| | |
|---|---|
| Identification code | SIMR-1555s2 |
| Empirical formula | $C_{19}H_{20}N_2O_2$ |
| Formula weight | 308.37 |
| Temperature | 296(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Orthorhombic |
| Space group | $Fdd_2$ |
| Unit cell dimensions | a = 28.514(6) Å α = 90° |
| | b = 31.144(7) Å β = 90° |
| | c = 7.0650(15) Å γ = 90° |

| | |
|---|---|
| Volume | 6274(2) $Å^3$ |
| Z | 16 |
| Density (calculated) | 1.306 g $cm^{-3}$ |
| Absorption coefficient | 0.085 $mm^{-1}$ |
| F(000) | 2624 |
| Crystal size | 0.4 × 0.1 × 0.1 $mm^3$ |
| Reflections collected | 31030 |
| Independent reflections | 3901 [R(int) = 0.1374] |
| Absorption correction | multi-scan |
| Max. and min. transmission | 0.6670 and 0.7457 |
| Refinement method | Least Squares minimization |
| Data / restraints / parameters | 3901 / 0 /209 |
| Goodness-of-fit on F2 | 1.012 |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.0532, $wR_2$ = 0.0915 |
| R indices (all data) | $R_1$ = 0.1074, $wR_2$ = 0.1094 |
| Largest diff. peak and hole | 0.21 and –0.23 e.$Å^{-3}$ |

**Supplementary Table 2** X-ray crystal structure and crystallographic data for compound **5c**



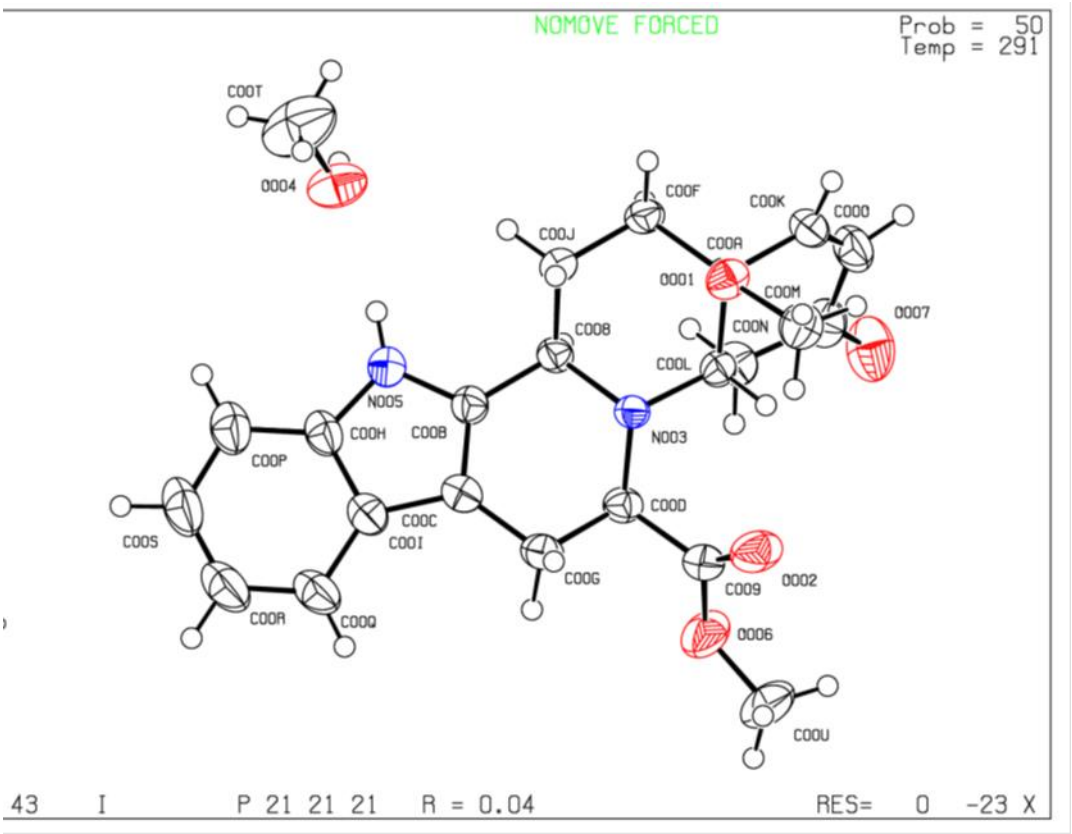



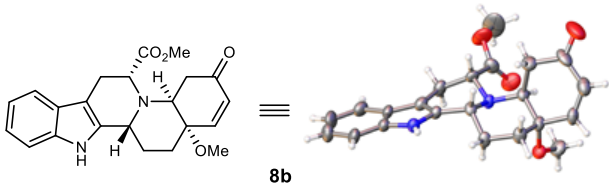

**6c**

| | |
|---|---|
| Identification code | exp_2225 |
| | SIMR-1555 |
| Empirical formula | $C_{19}H_{20}N_2O_2$ |
| Formula weight | 308.38 |
| Temperature | 291(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Monoclinic |
| Space group | $P2_1$ |
| Unit cell dimensions | a = 9.9579(11) Å α = 90° |
| | b = 9.2394(6) Å β = 119.203(16)° |
| | c = 10.0669(12) Å γ = 90° |
| Volume | 808.48(19) $Å^3$ |

| | |
|---|---|
| Z | 2 |
| Density (calculated) | 1.2667 g $cm^{-3}$ |
| Absorption coefficient | 0.083 $mm^{-1}$ |
| F(000) | 328.1 |
| Crystal size | 0.8 × 0.2 × 0.1 $mm^3$ |
| Theta range for data collection | 6.4 to 58.64°. |
| Index ranges | $-11 \leq h \leq 13$, $-12 \leq k \leq 7$, $-7 \leq l \leq 12$ |
| Reflections collected | 2626 |
| Independent reflections | 2051 [R(int) = 0.0170] |
| Absorption correction | multi-scan |
| Max. and min. transmission | 0.210 and 1.000 |
| Refinement method | Least Squares minimization |
| Data / restraints / parameters | 4630 / 0 /275 |
| Goodness-of-fit on F2 | 1.028 |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.0420, $wR_2$ = 0.0981 |
| R indices (all data) | $R_1$ = 0.0574, $wR_2$ = 0.1083 |
| Largest diff. peak and hole | 0.12 and –0.13 e.$Å^{-3}$ |

**Supplementary Table 3** X-ray crystal structure and crystallographic data for compound **6c**



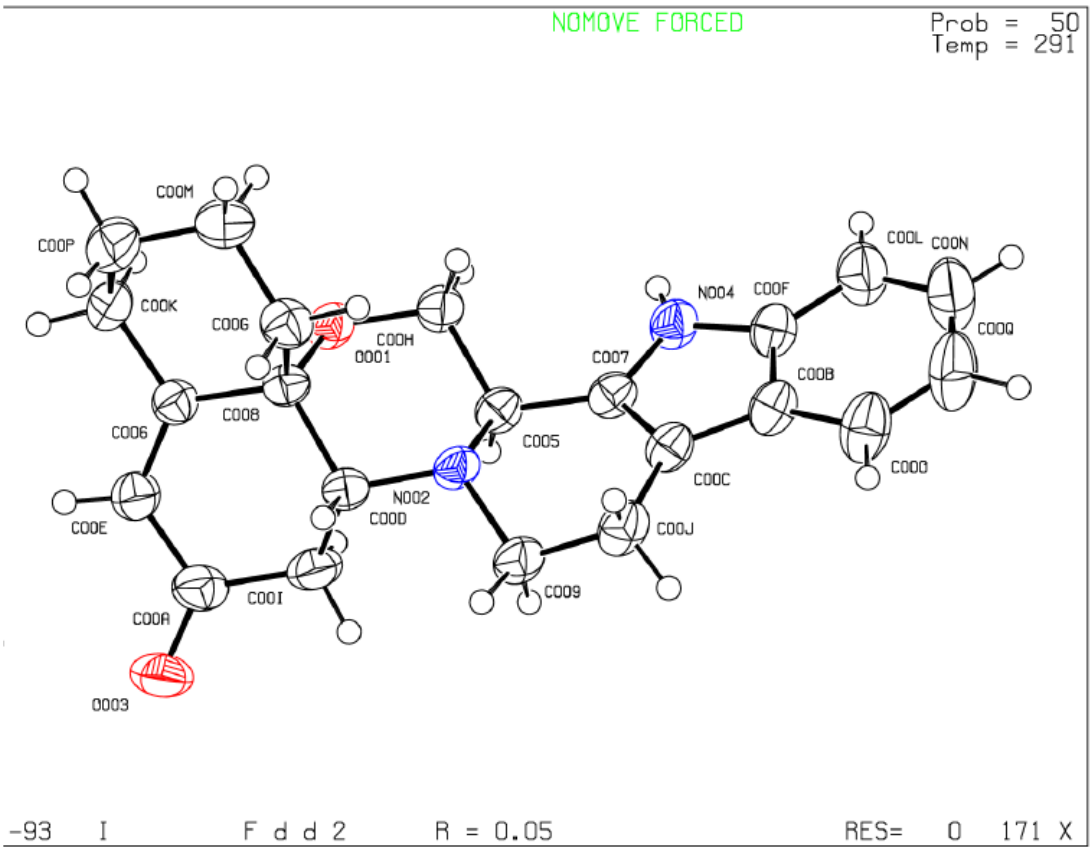



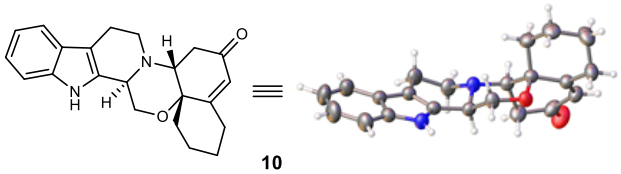

**8b**

| | | |
|---|---|---|
| Identification code | exp_2229 | |
| | SIMR-1549 | |
| Empirical formula | $C_{22}H_{24}N_2O_4 \cdot CH_4O$ | |
| Formula weight | 412.49 | |
| Temperature | 291(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | orthorhombic | |
| Space group | $P2_12_12_1$ | |
| Unit cell dimensions | a = 7.0712(7) Å | α = 90° |
| | b = 8.8316(9) Å | β = 90° |
| | c = 34.544(3) Å | γ = 90° |

| | |
|---|---|
| Volume | 2157.3(4) $Å^3$ |
| Z | 4 |
| Density (calculated) | 1.2699 g $cm^{-3}$ |
| Absorption coefficient | 0.090 $mm^{-1}$ |
| F(000) | 880.5 |
| Crystal size | 0.8 × 0.4 × 0.2 $mm^3$ |
| Theta range for data collection | 2.297 to 28.349°. |
| Index ranges | $8 \leq h \leq 9$, $-10 \leq k \leq 12$, $-43 \leq l \leq 44$ |
| Reflections collected | 8073 |
| Independent reflections | 4630 [R(int) = 0.0166] |
| Completeness to theta = 29.25° | 99.9 % |
| Absorption correction | multi-scan |
| Max. and min. transmission | 0.724 and 1.000 |
| Refinement method | Least Squares minimization |
| Data / restraints / parameters | 4630 / 0 /275 |
| Goodness-of-fit on F2 | 1.069 |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.0428, $wR_2$ = 0.0966 |
| R indices (all data) | $R_1$ = 0.0530, $wR_2$ = 0.1026 |
| Largest diff. peak and hole | 0.38 and –0.23 e.$Å^{-3}$ |

**Supplementary Table 4** X-ray crystal structure and crystallographic data for compound **8b**



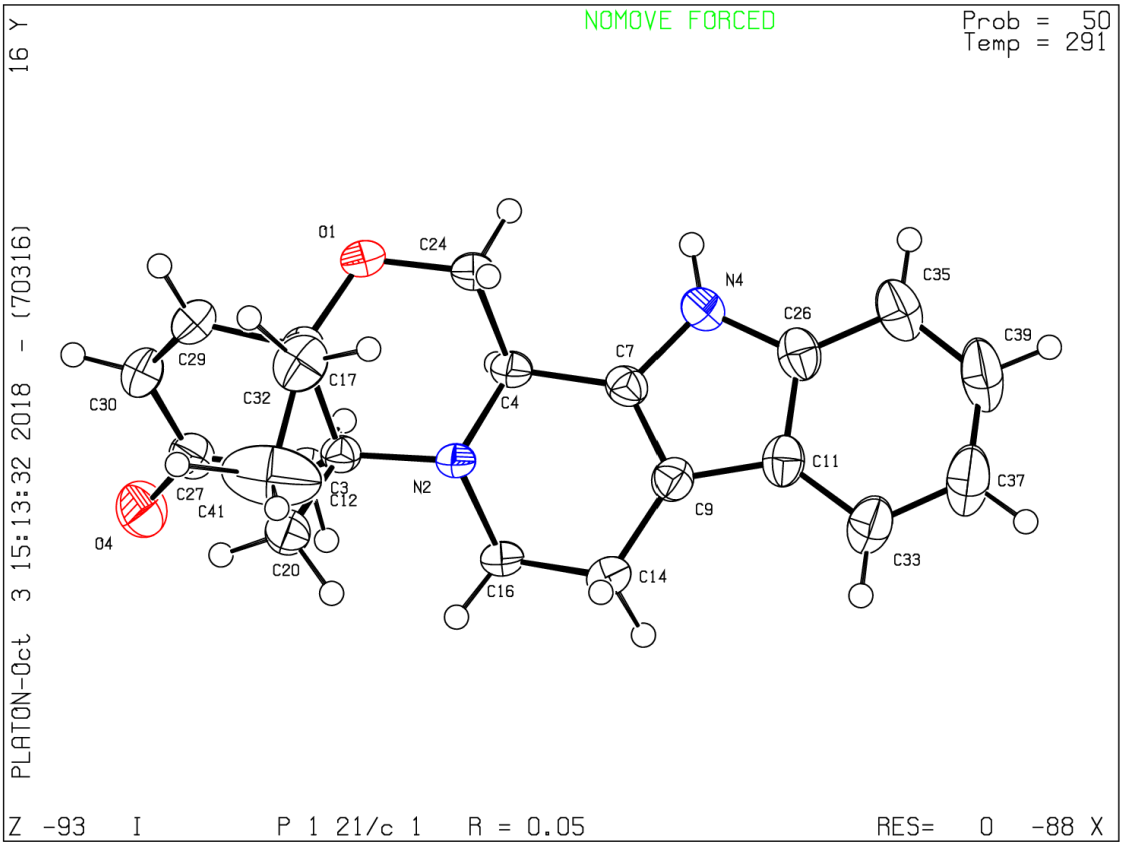



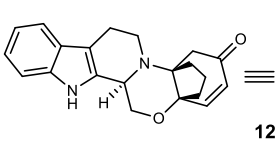
10

| | |
|---|---|
| Identification code | exp_2239 |
| | SIMR-1805 |
| Empirical formula | $C_{22}H_{24}N_2O_2$·solvent |
| Formula weight | 348.43 |
| Temperature | 291(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | monoclinic |
| Space group | $P2_1/c$ |
| Unit cell dimensions | a = 13.4439(9) Å α = 90° |
| | b = 9.8893(6) Å β = 108.931(7) ° |

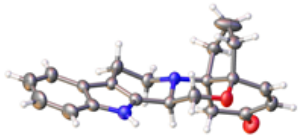
| | |
|---|---|
| | c = 17.2687(11) Å  γ = 90° |
| Volume | 2171.7(3)Å$^3$ |
| Z | 4 |
| Density (calculated) | 1.066 g cm$^{-3}$ |
| Absorption coefficient | 0.069 mm$^{-1}$ |
| F(000) | 744.0 |
| Crystal size | 0.6 × 0.2 × 0.04 mm$^3$ |
| Theta range for data collection | 6.408 to 58.694°. |
| Index ranges | -17 ≤ h ≤ 16, -13 ≤ k ≤ 11, -23 ≤ l ≤ 22 |
| Reflections collected | 10757 |
| Independent reflections | 5072 [R(int) = 0.0233] |
| Absorption correction | multi-scan |
| Max. and min. transmission | 0.800 and 1.000 |
| Refinement method | Least Squares minimization |
| Data / restraints / parameters | 5072 / 0 /236 |
| Goodness-of-fit on F2 | 1.005 |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.0486, $wR_2$ = 0.1359 |
| R indices (all data) | $R_1$ = 0.0795, $wR_2$ = 0.1518 |
| Largest diff. peak and hole | 0.18 and –0.17 e.Å$^{-3}$ |

**Supplementary Table 5** X-ray crystal structure and crystallographic data for compound **10**



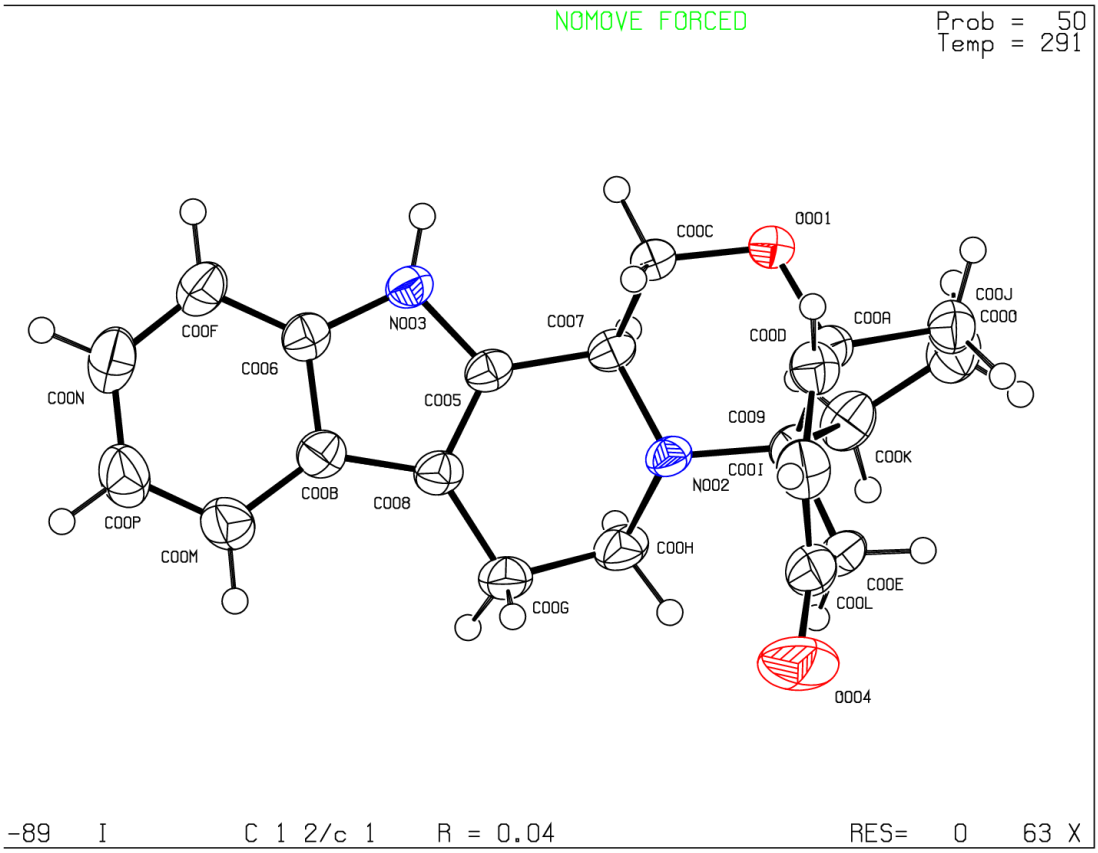

12

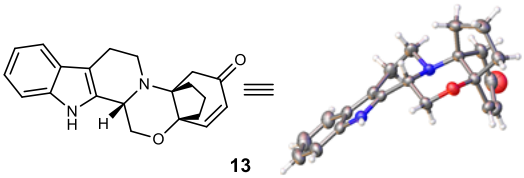


| | | |
|---|---|---|
| Identification code | exp_2222 | |
| | SIMR-1811 | |
| Empirical formula | $C_{21}H_{22}N_2O_2$ | |
| Formula weight | 334.40 | |
| Temperature | 291(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | monoclinic | |
| Space group | $P2_1/c$ | |
| Unit cell dimensions | a = 7.0056(3) Å | α = 90.002(6)° |
| | b = 13.8119(9) Å | β = 90.041(5)° |

| | |
|---|---|
| | c = 18.7722(17)Å γ = 103.969(5)° |
| Volume | 1762.7(2)Å$^3$ |
| Z | 4 |
| Density (calculated) | 1.260 g cm$^{-3}$ |
| Absorption coefficient | 0.082 mm$^{-1}$ |
| F(000) | 712.3 |
| Crystal size | 0.8 × 0.4 × 0.2 mm$^3$ |
| Theta range for data collection | 6.02 to 58.84°. |
| Index ranges | $-9 \leq h \leq 9$, $-15 \leq k \leq 24$, $-17 \leq l \leq 12$ |
| Reflections collected | 8619 |
| Independent reflections | 4115 [R(int) = 0.0175] |
| Absorption correction | multi-scan |
| Max. and min. transmission | 0.902 and 1.000 |
| Refinement method | Least Squares minimization |
| Data / restraints / parameters | 4115/ 0 /234 |
| Goodness-of-fit on F2 | 1.035 |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.0459, $wR_2$ = 0.1208 |
| R indices (all data) | $R_1$ = 0.0596, $wR_2$ = 0.1306 |
| Largest diff. peak and hole | 0.34 and –0.22 e.Å$^{-3}$ |

**Supplementary Table 6** X-ray crystal structure and crystallographic data for compound **12**



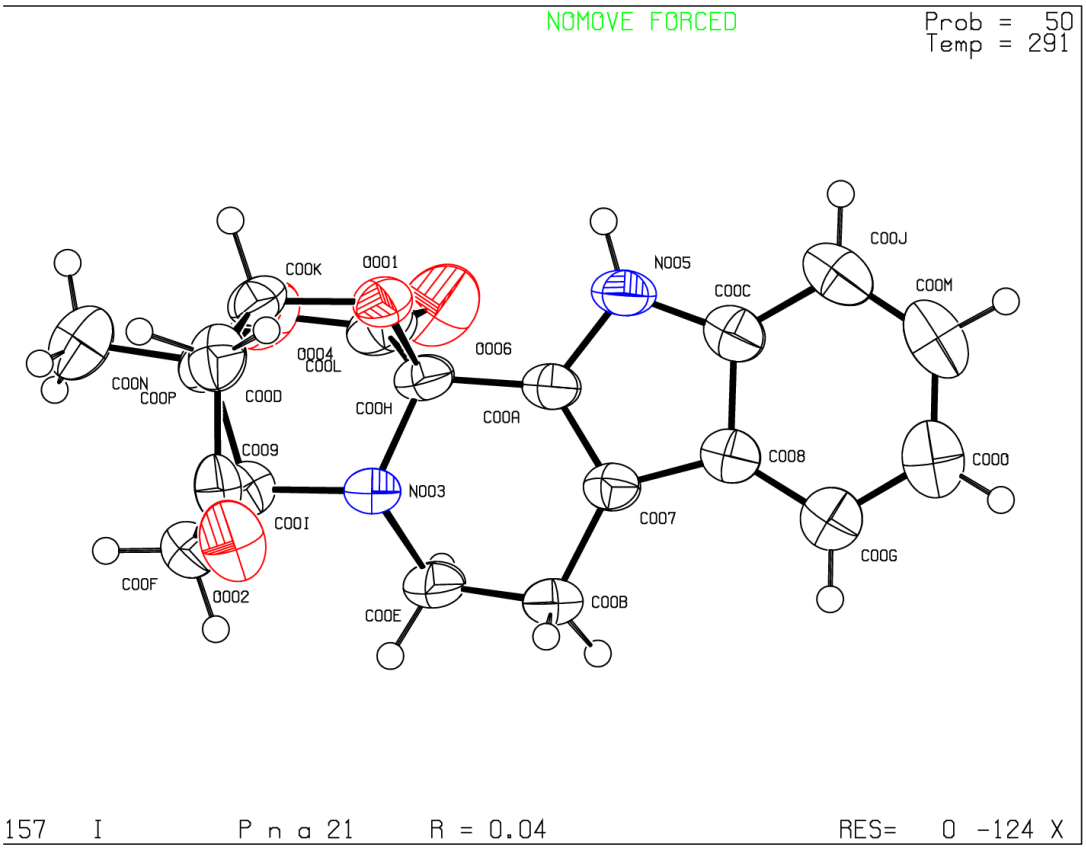



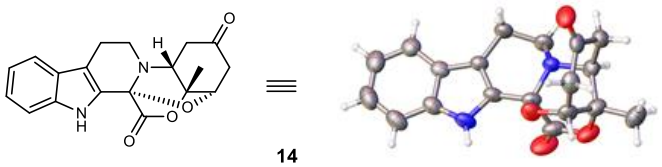

13

| | | |
|---|---|---|
| Identification code | exp_2227 | |
| | SIMR-1813 | |
| Empirical formula | $C_{21}H_{22}N_2O_2$ | |
| Formula weight | 334.40 | |
| Temperature | 291(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | monoclinic | |
| Space group | C2/c | |
| Unit cell dimensions | a = 18.3021(11) Å | α = 90 ° |
| | b = 9.0743(5) Å | β = 90.400(6)° |

| | |
|---|---|
| | c = 20.5335(13) Å  γ = 90° |
| Volume | 3410.1(4)Å$^3$ |
| Z | 8 |
| Density (calculated) | 1.303 g cm$^{-3}$ |
| Absorption coefficient | 0.084 mm$^{-1}$ |
| F(000) | 1424.0 |
| Crystal size | 0.8 × 0.4 × 0.1 mm$^3$ |
| Theta range for data collection | 6.382 to 58.49°. |
| Index ranges | -23 ≤ h ≤ 22, -12 ≤ k ≤ 10, -27 ≤ l ≤ 16 |
| Reflections collected | 6251 |
| Independent reflections | 3633 [R(int) = 0.0130] |
| Absorption correction | multi-scan |
| Max. and min. transmission | 0.836 and 1.000 |
| Refinement method | Least Squares minimization |
| Data / restraints / parameters | 3633/ 0 /226 |
| Goodness-of-fit on F2 | 1.051 |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.0446, w$R_2$ = 0.1075 |
| R indices (all data) | $R_1$ = 0.0583, w$R_2$ = 0.1160 |
| Largest diff. peak and hole | 0.22 and –0.21 e.Å$^{-3}$ |

**Supplementary Table 7** X-ray crystal structure and crystallographic data for compound **13**



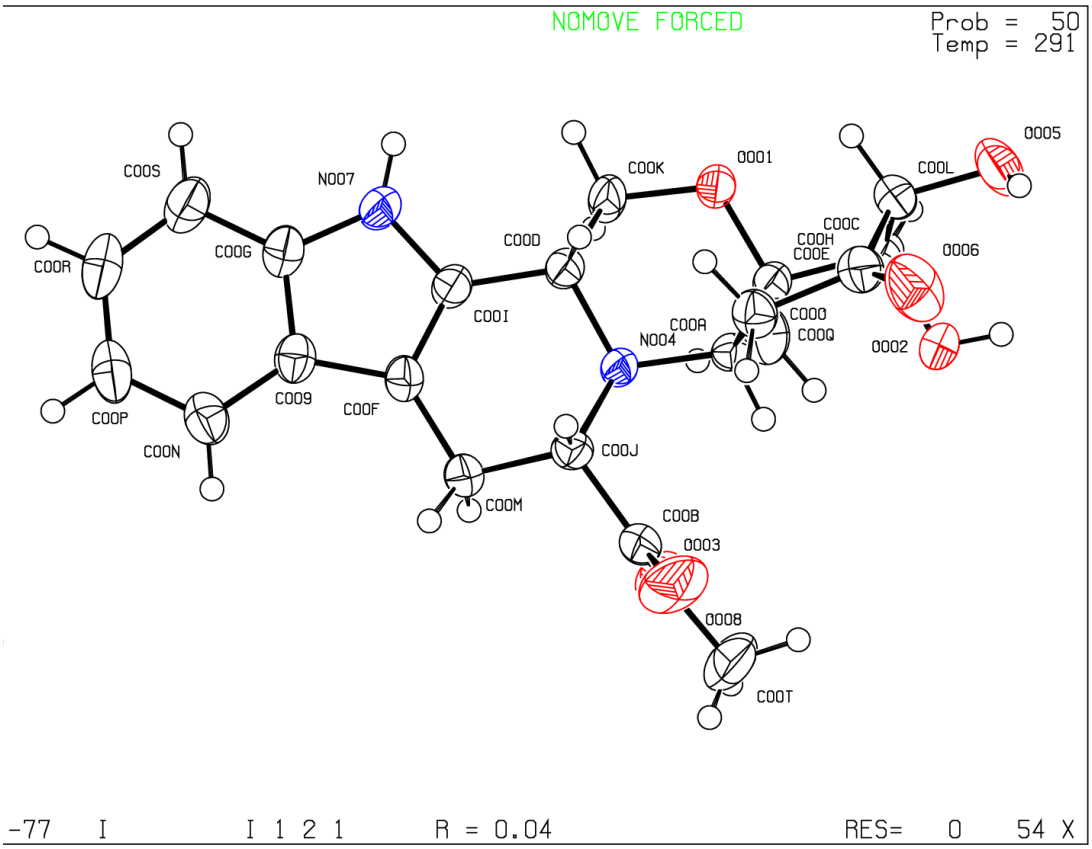



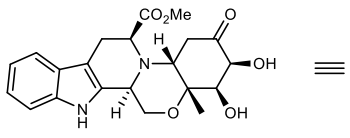
**14**

| | |
|---|---|
| Identification code | exp_2268 |
| | SIMR-1870 |
| Empirical formula | $C_{19}H_{18}N_2O_4$· |
| Formula weight | 338.35 |
| Temperature | 291(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | orthorhombic |
| Space group | $Pna2_1$ |
| Unit cell dimensions | a = 12.0313(8) Å α = 90 ° |
| | b = 17.8969(12) Å β = 90° |
| | c = 7.7473(5) Å γ = 90° |

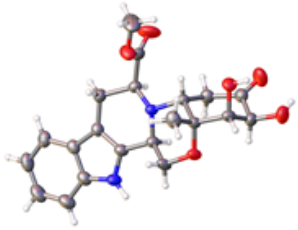
| | |
|---|---|
| Volume | 1668.17(19)Å$^3$ |
| Z | 4 |
| Density (calculated) | 1.347 g cm$^{-3}$ |
| Absorption coefficient | 0.096 mm$^{-1}$ |
| F(000) | 712.0 |
| Crystal size | 0.4 × 0.2 × 0.1 mm$^3$ |
| Theta range for data collection | 6.656 to 58.596°. |
| Index ranges | $-13 \leq h \leq 15$, $-20 \leq k \leq 23$, $-6 \leq l \leq 10$ |
| Reflections collected | 4992 |
| Independent reflections | 2952 [R(int) = 0.0172] |
| Absorption correction | multi-scan |
| Max. and min. transmission | 0.928 and 1.000 |
| Refinement method | Least Squares minimization |
| Data / restraints / parameters | 2952/ 1 /227 |
| Goodness-of-fit on F2 | 1.081 |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.0416, $wR_2$ = 0.0829 |
| R indices (all data) | $R_1$ = 0.0524, $wR_2$ = 0.0878 |
| Largest diff. peak and hole | 0.14 and –0.14 e.Å$^{-3}$ |

**Supplementary Table 8** X-ray crystal structure and crystallographic data for compound **14**



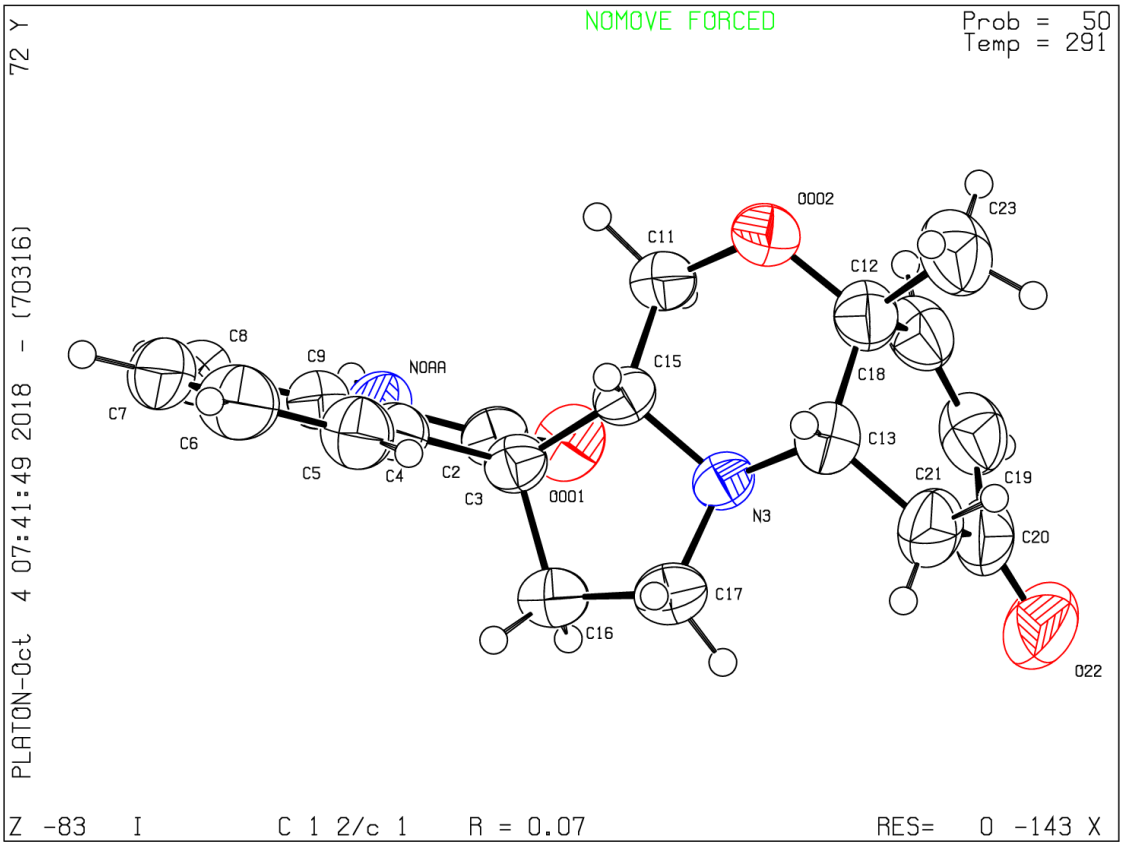

16

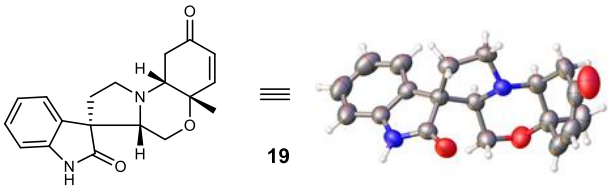


| | |
|---|---|
| Identification code | exp_2305 |
| | SIMR-1984 |
| Empirical formula | $C_{21}H_{24}N_2O_6$ |
| Formula weight | 400.42 |
| Temperature | 291(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | monoclinic |
| Space group | I2 |
| Unit cell dimensions | a = 9.7616(6) Å α = 90 ° |

| | |
|---|---|
| | b = 8.9376(4) Å β = 97.650(5)° |
| | c = 23.1897(12) Å γ = 90° |
| Volume | 2005.18(19)Å$^3$ |
| Z | 4 |
| Density (calculated) | 1.326 g cm$^{-3}$ |
| Absorption coefficient | 0.098 mm$^{-1}$ |
| F(000) | 848.0 |
| Crystal size | 0.8 × 0.6 × 0.2 mm$^3$ |
| Theta range for data collection | 6.206 to 58.174°. |
| Index ranges | $-13 \leq h \leq 9$, $-7 \leq k \leq 11$, $-31 \leq l \leq 25$ |
| Reflections collected | 4932 |
| Independent reflections | 3397 [R(int) = 0.0152] |
| Absorption correction | multi-scan |
| Max. and min. transmission | 0.959 and 1.000 |
| Refinement method | Least Squares minimization |
| Data / restraints / parameters | 3397/ 1 /267 |
| Goodness-of-fit on F2 | 1.042 |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.0350, $wR_2$ = 0.0836 |
| R indices (all data) | $R_1$ = 0.0429, $wR_2$ = 0.0889 |
| Largest diff. peak and hole | 0.18 and –0.16 e.Å$^{-3}$ |

**Supplementary Table 9** X-ray crystal structure and crystallographic data for compound **16**



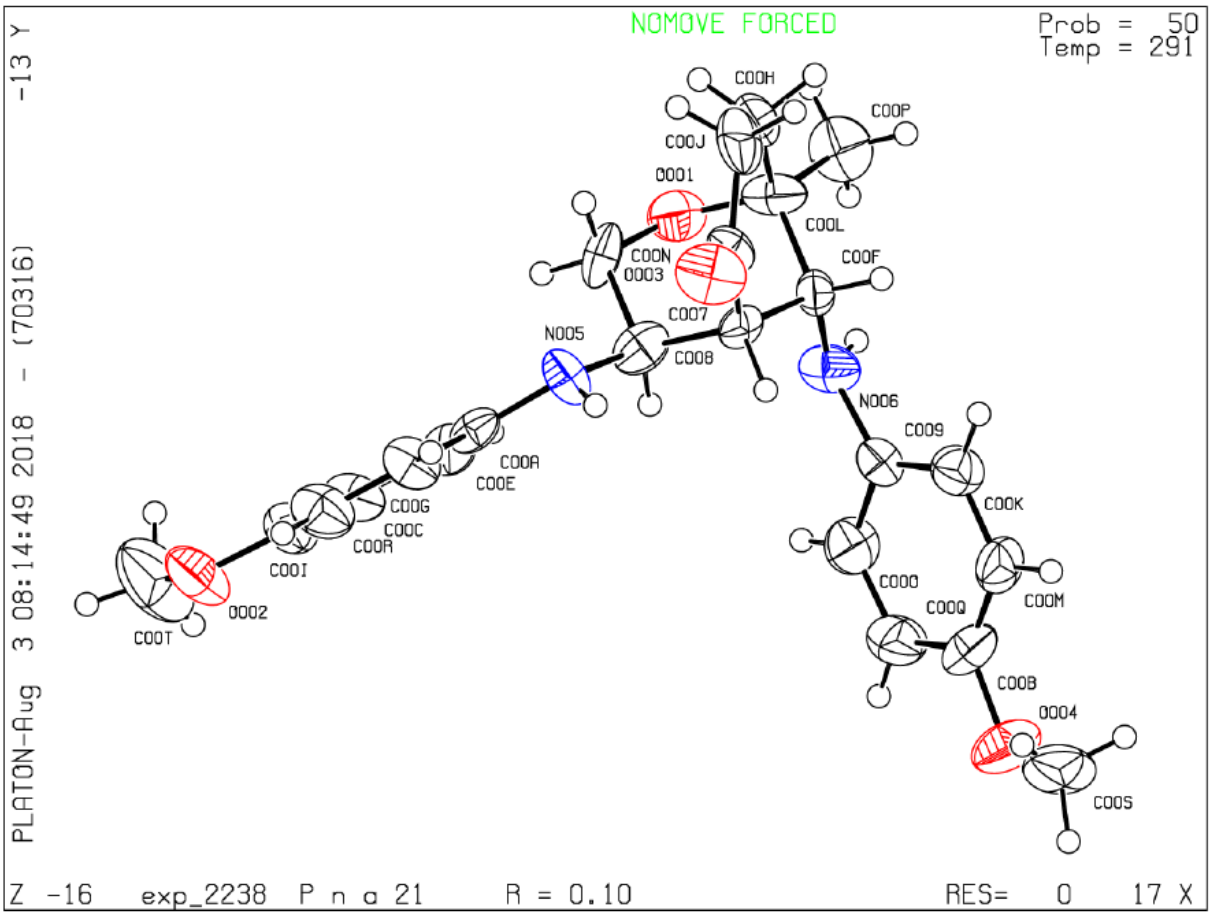



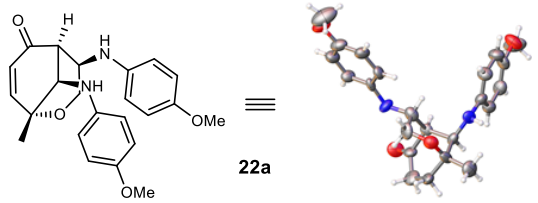

**19**

| | | |
|---|---|---|
| Identification code | exp_2276 | |
| | SIMR-1890 | |
| Empirical formula | $C_{19}H_{20}N_2O_3$ | |
| Formula weight | 324.37 | |
| Temperature | 291(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | C2/c | |
| Unit cell dimensions | a = 21.571(4) Å | α = 90 ° |
| | b = 8.7569(9) Å | β = 125.59(3)° |

| | |
|---|---|
| | c = 21.547(4) Å  γ = 90° |
| Volume | 3310.0(13)Å$^3$ |
| Z | 8 |
| Density (calculated) | 1.302 g cm$^{-3}$ |
| Absorption coefficient | 0.089 mm$^{-1}$ |
| F(000) | 1376.0 |
| Crystal size | 0.4 × 0.08 × 0.04 mm$^3$ |
| Theta range for data collection | 7.358 to 58.59°. |
| Index ranges | -28 ≤ h ≤ 18, -11 ≤ k ≤ 11, -28 ≤ l ≤ 29 |
| Reflections collected | 8640 |
| Independent reflections | 3863 [R(int) = 0.0366] |
| Absorption correction | multi-scan |
| Max. and min. transmission | 0.953 and 1.000 |
| Refinement method | Least Squares minimization |
| Data / restraints / parameters | 3863/ 0 /280 |
| Goodness-of-fit on F2 | 1.022 |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.0713, w$R_2$ = 01754 |
| R indices (all data) | $R_1$ = 0.1355, w$R_2$ = 0.2141 |
| Largest diff. peak and hole | 1.02  and –0.15 e.Å$^{-3}$ |

**Supplementary Table 10** X-ray crystal structure and crystallographic data for compound **19**



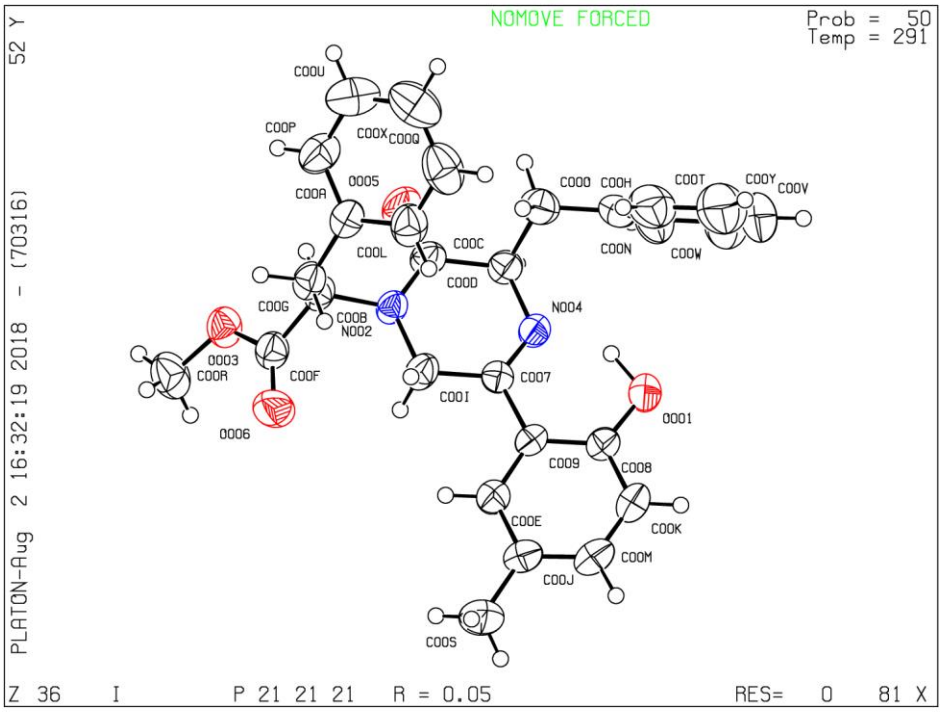



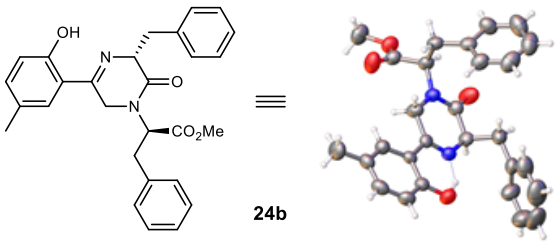

**22a**

| | |
|---|---|
| Identification code | exp_2238 |
| | SIMR-1769 |
| Empirical formula | $C_{23}H_{28}N_2O_4$ |
| Formula weight | 396.49 |
| Temperature | 291(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Orthorhombic |
| Space group | $Pna2_1$ |

| | |
|---|---|
| Unit cell dimensions | a = 15.718(5) Å α = 90° |
| | b = 19.298(6) Å β = 90° |
| | c = 6.748(3) Å γ = 90° |
| Volume | 2047.0(12)Å$^3$ |
| Z | 4 |
| Density (calculated) | 1.2865 g cm$^{-3}$ |
| Absorption coefficient | 0.088 mm$^{-1}$ |
| F(000) | 848.4 |
| Crystal size | 0.4 × 0.08 × 0.02 mm$^3$ |
| Theta range for data collection | 6.4 to 58.3°. |
| Index ranges | -19 ≤ h ≤ 21, -24 ≤ k ≤ 24, -9 ≤ l ≤ 7 |
| Reflections collected | 7059 |
| Independent reflections | 4142 [R(int) = 0.1449] |
| Absorption correction | multi-scan |
| Max. and min. transmission | 0.551 and 1.000 |
| Refinement method | Least Squares minimization |
| Data / restraints / parameters | 4142/ 1 /265 |
| Goodness-of-fit on F2 | 1.002 |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.0976, w$R_2$ = 0.1168 |
| R indices (all data) | $R_1$ = 0.4177, w$R_2$ = 0.2082 |
| Largest diff. peak and hole | 1.37 and –1.45 e.Å$^{-3}$ |

**Supplementary Table 11** X-ray crystal structure and crystallographic data for compound **22a**




**24b**

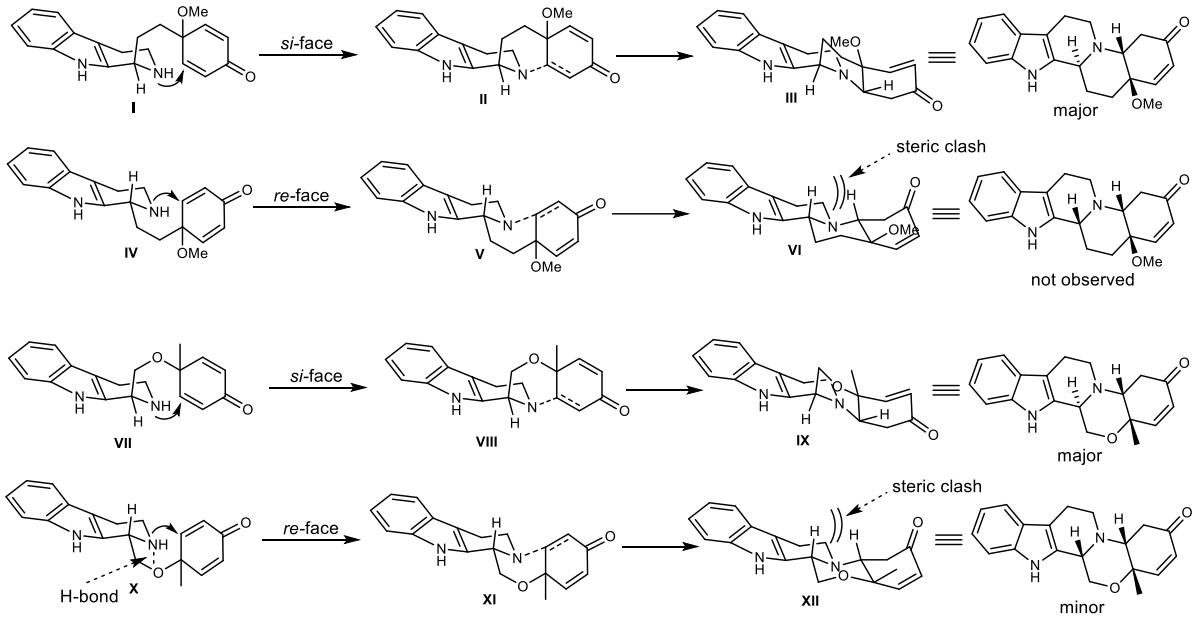
| | | |
|---|---|---|
| Identification code | exp_2236 | |
| | SIMR-1774 | |
| Empirical formula | $C_{28}H_{28}N_2O_4$ | |
| Formula weight | 456.55 | |
| Temperature | 291(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Orthorhombic | |
| Space group | $P2_12_12_1$ | |
| Unit cell dimensions | a = 5.9593(8) Å | α = 90° |
| | b = 17.479(2) Å | β = 90° |

| | |
|---|---|
| | c = 23.174(3) Å  γ = 90° |
| Volume | 2413.8(5)Å$^3$ |
| Z | 4 |
| Density (calculated) | 1.2562 g cm$^{-3}$ |
| Absorption coefficient | 0.084 mm$^{-1}$ |
| F(000) | 968.5 |
| Crystal size | 0.6 × 0.04 × 0.02 mm$^3$ |
| Theta range for data collection | 7.04 to 58.18°. |
| Index ranges | $-8 \leq h \leq 7$, $-18 \leq k \leq 23$, $-30 \leq l \leq 19$ |
| Reflections collected | 7968 |
| Independent reflections | 5177 [R(int) = 0.0237] |
| Absorption correction | multi-scan |
| Max. and min. transmission | 0.959 and 1.000 |
| Refinement method | Least Squares minimization |
| Data / restraints / parameters | 5177/ 0 /348 |
| Goodness-of-fit on F2 | 1.035 |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.0492, $wR_2$ = 0.0879 |
| R indices (all data) | $R_1$ = 0.0924, $wR_2$ = 0.1037 |
| Largest diff. peak and hole | 0.21 and –0.28 e.Å$^{-3}$ |

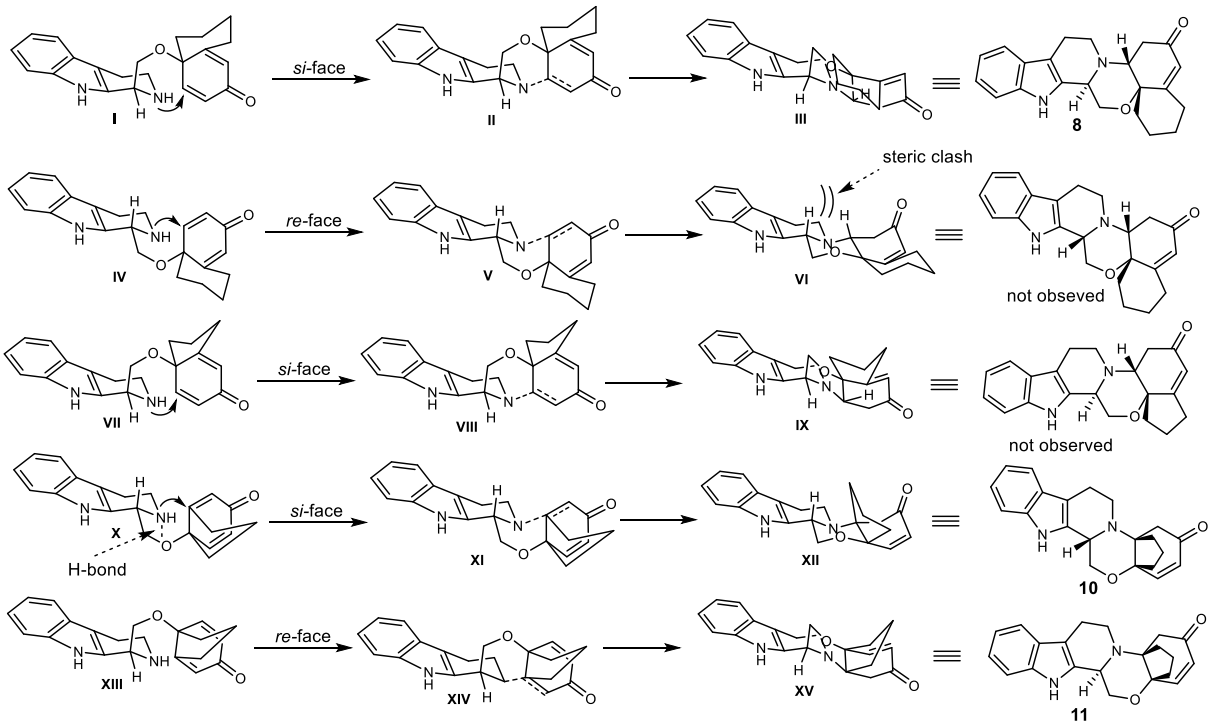
**Supplementary Table 12** X-ray crystal structure and crystallographic data for compound **24b**

| Compound | ATP content (Normalized luminescence units) | MMP (Normalized fluorescence units) | ROS content (Normalized fluorescence units) | Cytotoxicity (Percentage*) | Redox potential (Normalized fluorescence units) | Cell proliferation (Normalized colorimetric absorbance) |
|---|---|---|---|---|---|---|
| **5a** | 0.84 | 0.59 | 1.20 | -0.14 | 1.50 | 0.56 |
| **5c** | 0.67 | 0.27 | 0.98 | 0.14 | 3.14 | 0.21 |
| **8a** | 1.47 | 0.70 | 0.54 | -2.98 | 1.31 | 0.48 |
| **8b** | 1.22 | 0.68 | 1.14 | -2.44 | 1.46 | 0.75 |
| **8d** | 0.83 | 0.57 | 0.87 | 0.90 | 2.10 | 0.45 |
| **26c** | 0.62 | 0.13 | 0.89 | -0.28 | 3.06 | 0.46 |
| **26d** | 0.66 | 0.48 | 0.99 | -0.17 | 2.13 | 0.71 |

**Supplementary Table 13** Biological assays results for the tested compounds. Hepatoma cells (Hepa1.6 cell line) were incubated for 24 h (72 h in case of proliferation assay) with the indicated compounds at a final concentration of 10 µM. **ATP content** was measured using a luminescence based detection method and results were normalized to the DMSO control and oligomycin treated (ATP depleted) controls. **Mitochondrial membrane potential (MMP)** was determined using the TMRE fluorophore and results were normalized to the DMSO control and FCCP treated (MMP uncoupled) controls. **ROS content** was measured using the MitoSOX fluorescent probe and results were normalized to the DMSO control and FCCP treated (MMP uncoupled) controls. **Cytotoxicity** was determined by measuring the release of the enzyme LDH into the culture medium and was detected by a colorimetric assay. Results were expressed as percentage* compared to the maximum LDH content in the cells (*background signal of spontaneous LDH release in healthy cells was subtracted). Cellular **Redox potential** was determined using the Alamar blue (resazurin) fluorophore and were normalized to the DMSO control and oligomycin treated controls. **Cell proliferation** was assessed after a 72 h incubation period by assessing BrdU incorporation and colorimetric detection. Results were normalized to the DMSO control and FCCP treated (non-proliferating) controls. Data were normalized as: $(x-\mu_{FCCP/oligomycin})/(\mu_{DMSO}-\mu_{FCCP/oligomycin})$.




**Supplementary Figure 1** Proposed stereochemical analysis of the intramolecular aza-Michael addition

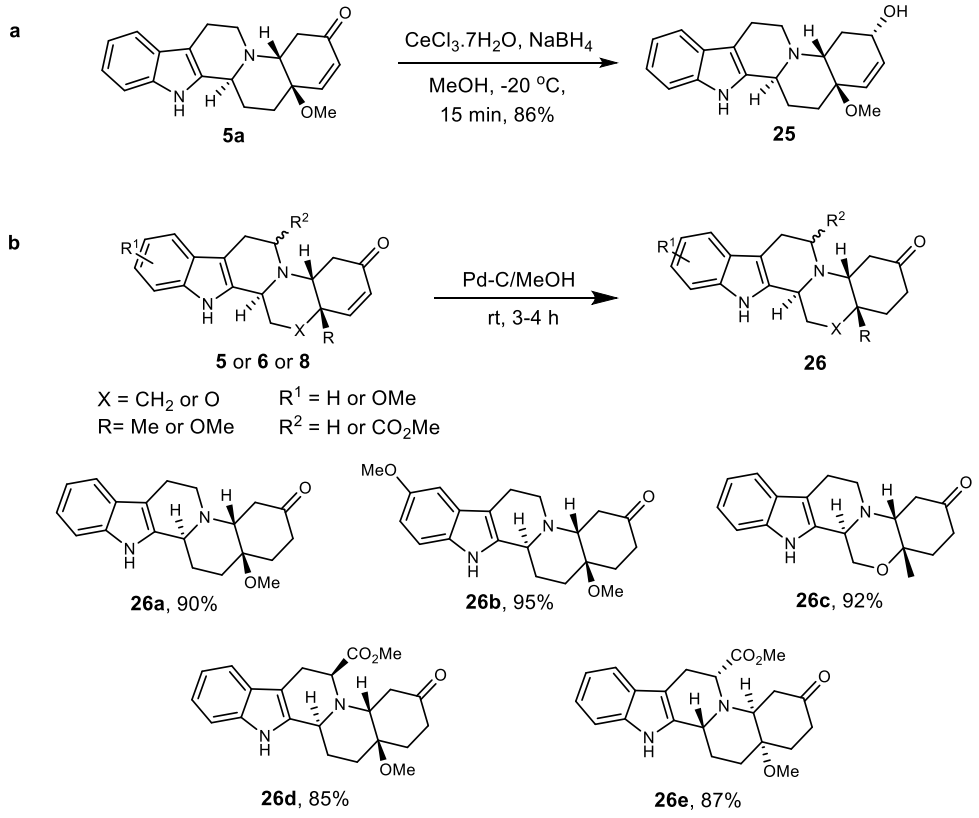



**Supplementary Figure 2** Proposed stereochemical analysis of the intramolecular aza-Michael addition

## Supplementary Discussion

To grow the pilot library with increased chirality, the carbonyl group of compound **5a** was reduced employing $CeCl_3.7H_2O$ and $NaBH_4$ at -20 °C to deliver the alcohol **25** as a single diastereoisomer in 86% yield (Supplementary Figure 3a). The stereochemistry of **25** was confirmed from its 1D- and 2D-NMR analysis (Supplementary Figures 169-177).

To further increase the diversity of the pilot library, representative examples of saturated cyclohexanone subunit containing products were synthesized. This was achieved by subjecting the α,β-unsaturated functionality contained in the THCs to conventional hydrogenation reaction using Pd/C. Thus the five saturated anologues **26a-26e** were synthesized in high yields (Supplementary Figure 3b).




**Supplementary Figure 3 Post-pairing transformations**. **a** Reduction of the carbonyl group. **b** Reduction of α,β-unsaturated double bond

## Supplementary Methods

### Chemicals and cell culture

The tested compounds were dissolved in DMSO at a concentration of 100 mM and further diluted in PBS supplemented with 10% (v/v) DMSO. When necessary dissolution was enhanced by incubation at 50 °C and sonication at maximum output for 10 min. Hepa1.6 cell line (#CRL-1830, ATCC) was cultured in DMEM culture medium containing 1g $L^{-1}$ glucose, 10% fetal bovine serum, 2mM glutamine, 100 U $mL^{-1}$ Penicilin and 100 µg $mL^{-1}$ Streptomycin and 30 µM oleic acid. Cells were seeded at a density of 20000 cells per well in 96 well plates and incubated for several hours to allow the cells to attach at 37 °C with 5% $CO_2$. Cells were then supplemented with the test substances at indicated concentrations (0.01-50 µM) and incubated for indicated time periods (24-48 h).

For all assays the tested substances were further diluted in 10% DMSO/PBS and added to the cells at the indicated concentrations with a final DMSO concentration of 0.01%. Negative vehicle controls were treated with 0.01% DMSO. Positive control was treated with 10 µM oligomycin or 10 µM FCCP (Carbonyl cyanide-4-(trifluoromethoxy) phenylhydrazone).

### Cytotoxicity

Cytotoxicity was assessed using the Pierce LDH Cytotoxicity Assay Kit (#88953, Thermo Fisher). After cells were culture with the test substances for 24 h 20µL of the cell culture medium were transferred to a new 96 well plate and the cytotoxicity assay was performed as per the manufacturer's instructions. Absorbance was measure at 490 nm and background at 680 nm. The signal intensity of untreated cells was considered as the background signal of spontaneous LDH release and subtracted from all measurements. Cytotoxicity was expressed as the percentage of maximum signal intensity observed in freshly lysed cells.

### Mitochondrial membrane potential

Mitochondrial membrane potential ($\Delta\Psi m$) was assessed using the tetramethylrhodamine (TMRE) fluorophore. The cells were incubated with the test substances for 24 h and then loaded with TMRE at a final concentration of 200 nM for 45 min at 37 °C. Positive control wells were treated with 10µM FCCP 30 min before loading the cells with TMRE. The medium was removed and the cells were washed with PBS and supplemented with fresh culture medium. Fluorescence intensity of TRME was immediately measured (ex/em: 545/580 nm) using a plate

reader spectrophotometer. The results were normalized to the fluorescence intensity measured in mock treated negative controls and the positive controls treated with 10 µM FCCP.

**ATP content**

Cells were treated for 24 h with the test substances at the indicated concentrations. The cellular ATP content was assessed using the CellTiter-Glo Assay (#G7571, Promega) as per the manufacturer's instructions. Luminescence was detected in a plate reader spectrophotometer. The results were normalized to the luminescence intensity measured in mock treated negative controls and the positive controls treated with 10 µM oligomycin.

**Cellular Redox potential**

Cells were treated for 24 h with the test substances or controls (0.1 % DMSO, 10 µM FCCP and 10 µM oligomycin). AlamarBlue reagent (resazurin, #BUF012A, Bio-Rad) was added to the cells in an amount equal to 10 % of the culture medium per well during the last 4 h of incubations. Fluorescence was measured at ex/em: 550/590 nm. Results were normalized to the fluorescence intensity measured in blank wells and wells containing fully reduced AlamarBlue reagent. Results were expressed relative to the mock treated negative controls.

**BrdU incorporation/cell proliferation assay proliferation assay**

Cells were incubated for a total of 48 h with the tested substances. During the last 12 h the cells were supplemented with 200 µM BrdU (#ab126556, Abcam). After the incubation period cells were washed with PBS. Following that the cells fixed and permeabilized using the reagents of the kit and labeled for 1 h with anti-BrdU antibodies conjugated with peroxidase. After washing the fixed cells 5 times with PBS the wells were incubated with peroxidase substrate TMB. The reaction was stopped after 30 min. The signal intensity was measure at absorbance 450 nm. Results were normalized to controls samples treated with vehicle (0.01% DMSO, negative control) or 10 µM oligomycin.

**Lymphocyte and splenocyte preparation**

Spleen and lymph nodes were collected from C57BL/6J mice and stored in RPMI medium on ice until further processing. Further procedures were performed using a laminar flow hood. Single cell suspensions were created by shearing the organs between two microscopy slides. Cell suspensions were passed through a 70 µm cell strainer to exclude remaining tissue chunks. Cells were washed in PBS and centrifuged at 300 g for 5min at 4 °C. During the preparation of splenic single cell suspension, erythrocytes were removed by incubating the cells for 5 min at rt in RBC

lysis buffer followed by extensive washing in PBS. Cells were resuspended in RPMI medium and cell count was determined. Lymphocytes were kept on ice until further use.

**T cell enrichment from splenocytes**

T cell was enriched from the splenocytes by negative selection using magnetic bead separation (Pan T cell isolation kit II, mouse, #130-095-130, Miltenyi) achieving more than 90% purity. The cells were kept in RPMI medium until further use.

**Activation induced immune cell proliferation in T cells and lymphocytes**

A total $17x10^6$ cells were suspended in 15 mL Krebs Ringer buffer (with HEPES, 1g $L^{-1}$ glucose, 1mM pyruvate), supplemented with 30 µL of Cytopainter blue stock solution (500x) (#ab176726, Abcam) and incubated for 30 min at 37 °C to let the CFSE analog accumulate in the cells. The remaining Cytopainter reagent that was not incorporated into the cells was quenched by addition of 10 mL FCS and incubated for 5 min at rt. Another 25 mL of PBS were added and cells were centrifuged at 300 g for 5 min at rt. The cells were then suspended in 12.75 mL of complete RPMI culture medium. $2x10^5$ cells in a volume of 150 µL were added to the wells of 96 well plates. The cytopainter-loaded cells were supplemented with the test substances, or DMSO as a negative control and oligomycin as a positive control.

Cytopainter loaded T cells were stimulated using two different approaches. Either T cells stimulated by plate bound anti-CD3 antibodies (coated at 1µg/mL) and soluble anti-CD28 antibodies (at a final concentration of 0.2 µg $mL^{-1}$), or in separate replicates by addition of the cytokines IL-2 (50 ng $mL^{-1}$) and IL-7 (10 ng $mL^{-1}$) to stimulate T cells proliferation and survival.

Cytopainter loaded lymphocytes were stimulated with PMA (15 ng $mL^{-1}$) and Ionomycin (0.5 µg $mL^{-1}$). All cells were incubated for 60 h at 37 °C, 5% $CO_2$. Lymphocytes were then washed with 2% FBS in PBS, supplemented with anti-CD16/CD32 antibodies (to block unspecific Fc-receptor binding) and incubated for 10 min at 4 °C. Subsequently cells were incubated for 20 min at 4 °C with anti-CD3 antibodies conjugated to FITC (clone:145-2C11, #11-0031-82, eBioscience) and anti-B220 antibodies conjugated to PerCP-Cy5.5 (clone:RA3-6B2, #45-0452-82, eBioscience) to label T cells and B cells, respectively. Cells were subsequently washed with 2% FBS in PBS analyzed.

Cell proliferation was then analyzed by assessing the fluorescence intensity of cytopainter in the cells by flow cytometry. Reduced intensity of cytopainter dye indicates cells that have undergone

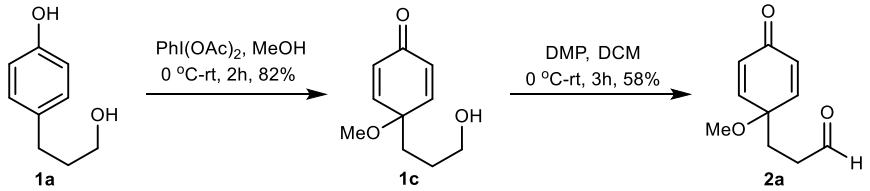
cell division. Data was analyzed using FlowJo v10.4.2. Proliferation parameters were derived using the FlowJo Proliferation Tool. The Expansion index determines the fold-expansion of the overall culture. The Division index expresses the average number of cell divisions that a cell in the original population has undergone and also includes the cells that have never divided.

Statistical analysis was performed using Graph Pad Prism v6.07. Comparison of the test substances was performed by ANOVA with Dunnett's post hoc test unless otherwise stated. Non-linear regression was fitted to the data points using Graph Pad.

**X-Ray diffraction studies**

Data collection, reduction, and cell refinement were performed using the software package CrysAlisPro[1]. Analytical absorption corrections were applied using spherical harmonics implemented in SCALE3 (ABSPACK) scaling algorithm. Using Olex2[2] program, the structures were solved with SHELXL-97[3] and/or ShelXT[4] structure solution programs, using direct method or intrinsic phasing and refined with Olex2 refine[5] refinement package using Gauss-Newton or Least Squares minimization. Anisotropic least-squares refinement of non-H atoms was applied. All crystallographic plots were obtained using the Olex2 program.

**Experimental procedures and characterization data**

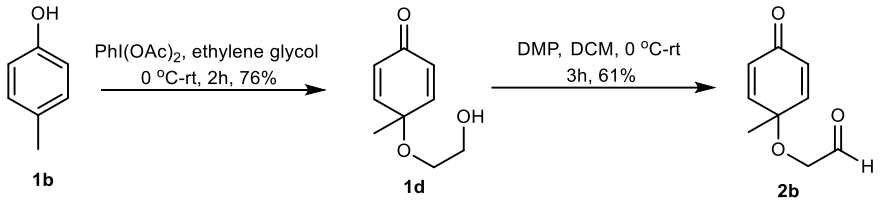



**Supplementary Figure 4** Reaction scheme for the preparation of compound **2a**

**Reaction procedure for the preparation of 4-(3-hydroxypropyl)-4-methoxycyclohexa-2,5-dien-1-one (1c):** Phenol (**1a,** 1.0 mmol)) was dissolved in MeOH (5.0 mL) and a solution of $PhI(OAc)_2$ (1.2 mmol) in methanol (5.0 mL) was added dropwise at 0 °C over a period of 1h and stirring was continued at rt for another 1h. After completion, methanol was removed; the crude was dissolved in EtOAc (50 mL) and washed with water (2 x 50 mL). The organic layer was separated, dried over $Na_2SO_4$ and concentrated under vacuum. The crude product was purified on flash chromatography using 60 % EtOAc in hexane to obtain the compound (**1c)** as colorless liquid: 149 mg, 82% yield; $R_f$ = 0.45 (silica gel, hexane/EtOAc 1:4); $^1$H NMR (500 MHz,

DMSO-$d_6$): δ 6.91 – 6.85 (m, 2H), 6.36 – 6.30 (m, 2H), 4.44 (t, *J* = 5.2 Hz, 1H), 3.35 – 3.30 (m, 2H), 3.12 (s, 3H), 1.75 – 1.67 (m, 2H), 1.37 – 1.27 (m, 2H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 184.9, 151.8, 130.8, 75.3, 60.5, 52.4, 35.2, 26.7; HRMS (m/z): $[M+H]^+$ calcd. for $C_{10}H_{15}O_3$, 183.1021, found 183.1013.

**Reaction procedure for the preparation of 3-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)propanal (2a):** Compound **1c** (0.5 mmol) was dissolved in DCM (5.0 mL) and added DMP (0.75 mmol) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirring continued for 3h. After completion, the reaction mixture was passed through the pad of celite and collected the superintendent. This organic layer was concentrated and purified on filter column using 100% DCM to obtain the compound **2a** as colorless liquid; 53 mg, 58% yield; $R_f$ = 0.55 (silica gel, hexane/EtOAc 1:1); $^1$H NMR (500 MHz, $CDCl_3$): δ 9.75 (t, *J* = 1.2 Hz, 1H), 6.78 – 6.72 (m, 2H), 6.43 – 6.38 (m, 2H), 3.23 (s, 3H), 2.51 (td, *J* = 7.5, 1.2 Hz, 2H), 2.10 (t, *J* = 7.5 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 200.4, 185.0, 150.2, 131.9, 74.8, 53.3, 38.3, 31.5; HRMS (m/z): $[M+Na]^+$ calcd. for $C_{10}H_{12}O_3Na$, 203.0684, found 203.0678.



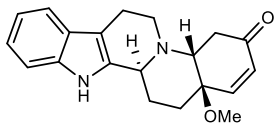

**Supplementary Figure 5** Reaction scheme for the preparation of compound **2b**

**Reaction procedure for the preparation of 4-(2-hydroxyethoxy)-4-methylcyclohexa-2,5-dien-1-one (1d):** Phenol (**1b,** 1.0 mmol)) was dissolved in DCM (0.2 mL) and added ethylene glycol (30 mmol) at 0 °C. Next, a solution of $PhI(OAc)_2$ (1.2 mmol) in DCM (4.0 mL) was added dropwise at 0 °C over a period of 1h and stirring was continued at rt for another 1h. After completion, the crude was diluted with DCM (50 mL) and washed with water (2 x 50 mL). The organic layer was separated, dried over $Na_2SO_4$ and concentrated under vacuum. The crude product was purified on flash chromatography using 50 % EtOAc in hexane to obtain the compound (**1d)** as colorless liquid: 127 mg, 76% yield; $R_f$ = 0.5 (silica gel, hexane/EtOAc 1:4); $^1$H NMR (500 MHz, DMSO-$d_6$): δ 7.01 – 6.90 (m, 2H), 6.31 – 6.21 (m, 2H), 4.60 (t, *J* = 5.4 Hz, 1H), 3.45 (q, *J* = 5.1 Hz, 2H), 3.26 (t, *J* = 5.3 Hz, 2H), 1.37 (s, 3H); $^{13}$C NMR (125 MHz,

DMSO-$d_6$) δ 185.1, 153.3, 129.7, 72.5, 67.4, 61.0, 26.3; HRMS (m/z): $[M+H]^+$ calcd. for $C_9H_{13}O_3$, 169.0864, found 169.0852.

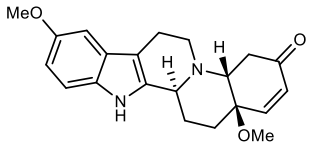
**Reaction procedure for the preparation of 2-((1-methyl-4-oxocyclohexa-2,5-dien-1-yl)oxy)acetaldehyde (2b):** Compound **1d** (0.5 mmol) was dissolved in DCM (5.0 mL) and added DMP (0.75 mmol) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirring continued for 3h. After completion, the reaction mixture was passed through the pad of celite and collected the superintendent. This organic layer was concentrated and purified on filter column using 100% DCM to obtain the compound **2b** as colorless liquid; 51 mg, 61% yield; $R_f$ = 0.55 (silica gel, hexane/EtOAc 1:1); $^1$H NMR (500 MHz, $CDCl_3$): δ 9.66 (s, 1H), 6.82 – 6.76 (m, 2H), 6.40 – 6.28 (m, 2H), 3.99 (d, *J* = 0.6 Hz, 2H), 1.57 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 199.3, 184.8, 150.0, 131.0, 73.3, 71.3, 26.1; HRMS (m/z): $[M+H]^+$ calcd. for $C_9H_{11}O_3$, 167.0708, found 167.0697.

**General reaction procedure for the preparation of compounds 5a-f:** Aldehyde (**2**, 0.5 mmol) was dissolved in DCM (2 mL) and a solution of amine (**3**, 0.5 mmol) in DCM (2.0 mL) was added dropwise at -78 °C. Then, a solution of TFA (1.0 mmol) in DCM (1 mL) was added dropwise at -78 °C and slowly warmed to room temperature and stirring was continued for 2-4 h. After completion, the reaction mixture was diluted with DCM (30 mL) and washed with saturated sodium bicarbonate solution (2 x 20 mL). The organic layer was separated, dried over $Na_2SO_4$ and concentrated under vacuum. The crude was purified on flash chromatography, using EtOAc/hexane as an eluent to produce the title compounds **5a-f**.

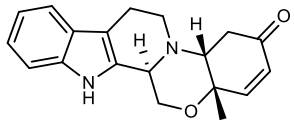



**(2aR,6aR,14bS)-2a-Methoxy-2,2a,6,6a,8,9,14,14b-octahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5(1H)-one (5a):** Off-white solid, 107 mg, 67% yield; mp: 204–207 °C; $R_f$ = 0.45 (silica gel, hexane/EtOAc 1:1); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 8.4 Hz, 1H), 7.19 – 7.09 (m, 2H), 6.86 (d, *J* = 10.3 Hz, 1H), 6.12 (d, *J* = 10.3 Hz, 1H), 3.96 (d, *J* = 10.0 Hz, 1H), 3.83 – 3.74 (m, 1H), 3.32 (s, 3H), 3.11 – 3.05 (m, 1H), 3.03 – 2.90 (m, 2H), 2.85 – 2.73 (m, 3H), 2.09 – 1.97 (m, 2H), 1.95 – 1.83 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 199.4, 155.5, 136.2, 134.5, 130.6, 127.3, 121.5, 119.5, 118.2, 110.7, 108.6,

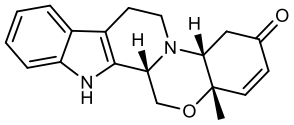
74.7, 59.1, 50.7, 50.4, 49.3, 35.3, 30.3, 24.9, 22.1; HRMS (m/z): $[M+H]^+$ calcd. for $C_{20}H_{23}N_2O_2$, 323.1759; found 323.1764.



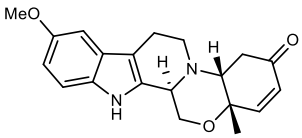

**(2aR,6aR,14bS)-2a,11-Dimethoxy-2,2a,6,6a,8,9,14,14b-octahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5(1H)-one (5b):** Off-white solid, 121 mg, 69% yield; mp: 216–218 °C; $R_f$ = 0.4 (silica gel, hexane/EtOAc 1:1); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.21 (d, *J* = 8.7 Hz, 1H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.88 – 6.79 (m, 2H), 6.11 (d, *J* = 10.3 Hz, 1H), 3.92 (d, *J* = 10.7 Hz, 1H), 3.87 (s, 3H), 3.77 (t, *J* = 8.6 Hz, 1H), 3.33 (s, 3H), 3.11 – 3.04 (m, 1H), 3.02 – 2.86 (m, 2H), 2.80 (d, *J* = 8.6 Hz, 2H), 2.72 (d, *J* = 14.3 Hz, 1H), 2.10 – 1.96 (m, 2H), 1.93 – 1.80 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 199.3, 155.5, 154.1, 135.4, 131.2, 130.6, 127.7, 111.4, 111.2, 108.5, 100.5, 74.7, 59.1, 55.9, 50.7, 50.5, 49.3, 35.3, 30.4, 24.9, 22.2; HRMS (m/z): $[M+H]^+$ calcd. for $C_{21}H_{25}N_2O_3$, 353.1865, found 353.1871.



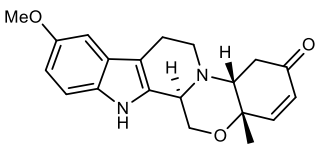

**(2aS,6aR,14bR)-2a-Methyl-6,6a,8,9,14,14b-hexahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (5c):** White solid, 80 mg, 52% yield; mp: 217–219 °C; $R_f$ = 0.45 (silica gel, hexane/EtOAc 1:1); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.23 – 7.17 (m, 1H), 7.17 – 7.12 (m, 1H), 6.70 (d, *J* = 10.6 Hz, 1H), 6.13 (d, *J* = 10.6 Hz, 1H), 4.27 – 4.14 (m, 2H), 4.10 – 4.01 (m, 1H), 3.32 (d, *J* = 4.4 Hz, 2H), 3.09 – 2.93 (m, 3H), 2.72 (d, *J* = 14.9 Hz, 1H), 2.64 (dd, *J* = 16.0, 3.5 Hz, 1H), 1.51 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ $^{13}$C NMR (125 MHz, $CDCl_3$) δ 198.9, 151.4, 136.1, 130.8, 129.9, 127.3, 121.9, 119.7, 118.1, 111.0, 109.7, 72.2, 63.5, 59.0, 52.1, 48.0, 46.1, 23.6, 19.3; HRMS (m/z): $[M+H]^+$ calcd. for $C_{19}H_{21}N_2O_2$, 309.1603, found 309.1607.



**(2aS,6aR,14bS)-2a-Methyl-6,6a,8,9,14,14b-hexahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (6c):** White solid, 32 mg, 21% yield; mp: 226–228 °C; $R_f$ = 0.5 (silica gel, hexane/EtOAc 1:1); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.66 (s, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.19 – 7.13 (m, 1H), 7.11 (dd, *J* = 11.0, 3.9 Hz, 1H), 6.64 (dd, *J* = 10.1, 2.1 Hz, 1H), 6.06 (d, *J* = 10.1 Hz, 1H), 4.09 (d, *J* = 7.9 Hz, 1H), 3.81 – 3.71 (m, 2H), 3.54 (dd, *J* = 11.3, 4.5 Hz, 1H), 3.11 – 3.02 (m, 2H), 2.89 – 2.79 (m, 1H), 2.79 – 2.67 (m, 2H), 2.34 (td, *J* = 11.3, 3.9 Hz, 1H), 1.58 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 196.7, 153.2, 136.2, 130.4, 130.2, 127.0, 121.9, 119.7, 118.3, 110.8, 110.1, 74.7, 66.3, 66.1, 58.4, 46.1, 40.1, 25.6, 22.0; HRMS (m/z): $[M+H]^+$ calcd. for $C_{19}H_{21}N_2O_2$, 309.1603, found 309.1611.

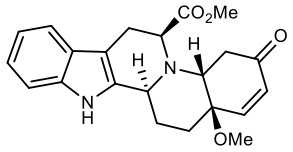


**(2aS,6aR,14bR)-11-methoxy-2a-methyl-6,6a,8,9,14,14b-hexahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (5d):** Off-white solid, 89 mg, 53% yield; mp: 230–232 °C; $R_f$ = 0.4 (silica gel, hexane/EtOAc 1:1); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.73 (s, 1H), 7.24 (d, *J* = 8.7 Hz, 1H), 6.97 (d, *J* = 1.7 Hz, 1H), 6.85 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.70 (d, *J* = 10.2 Hz, 1H), 6.12 (d, *J* = 10.2 Hz, 1H), 4.22 – 4.09 (m, 2H), 4.00 (dd, *J* = 11.4, 6.0 Hz, 1H), 3.88 (s, 3H), 3.29 (d, *J* = 4.8 Hz, 2H), 3.09 – 2.90 (m, 3H), 2.70 – 2.59 (m, 2H), 1.52 (s, 3H); $^{13}$C NMR (125 MHz, $CD_3OD$): δ 199.9, 153.6, 152.6, 131.9, 131.7, 129.3, 127.3, 111.6, 110.8, 107.9, 99.9, 72.0, 63.1, 58.8, 55.5, 53.3, 52.4, 35.6, 23.1, 18.9; HRMS (m/z): $[M+H]^+$ calcd. for $C_{20}H_{23}N_2O_3$, 339.1708, found 339.1719.

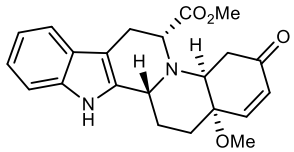


**(2aS,6aR,14bS)-11-Methoxy-2a-methyl-6,6a,8,9,14,14b-hexahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (6d):** Off-white solid, 34 mg, 20% yield; mp: 243–246 °C; $R_f$ = 0.4 (silica gel, hexane/EtOAc 1:1); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.54 (s, 1H), 7.20 (d, *J* = 8.7 Hz, 1H), 6.92 (d, *J* = 1.9 Hz, 1H), 6.81 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.64 (d, *J* = 9.8 Hz, 1H), 6.05 (d, *J* = 10.3 Hz, 1H), 4.07 (d, *J* = 6.9 Hz, 1H), 3.85 (s, 3H), 3.75 (d, *J* = 5.9 Hz, 2H), 3.53 (dd, *J* = 11.2, 5.2 Hz, 1H), 3.05 (d, *J* = 13.5 Hz, 2H), 2.86 – 2.74 (m, 3H), 2.38 – 2.30 (m, 1H), 1.57 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 196.7, 154.2, 153.2, 131.3, 130.4, 130.3, 127.5, 111.8, 111.5, 110.0, 100.4, 74.7, 66.3, 66.0, 58.5, 55.9, 46.2, 40.1, 25.6, 22.0; HRMS (m/z): $[M+H]^+$ calcd. for $C_{20}H_{23}N_2O_3$, 339.1708, found 339.1715.

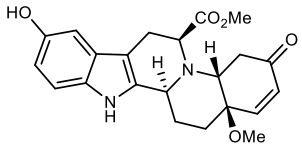
**General reaction procedure for the preparation of compounds 8a-e:** Aldehyde (**2**, 0.5 mmol) was dissolved in DCM (2 mL) and a solution of amine (**5**, 0.5 mmol) in DCM (2.0 mL) was added dropwise at -78 °C. Then, a solution of TFA (1.0 mmol) in DCM (1 mL) was added dropwise at -78 °C and slowly warmed to room temperature and stirring was continued for 6 h. After completion, the reaction mixture was diluted with DCM (30 mL) and washed with saturated sodium bicarbonate solution (2 x 20 mL). The organic layer was separated, dried over $Na_2SO_4$ and concentrated under vacuum. The crude was purified on flash chromatography, using EtOAc/hexane as an eluent to deliver the title compounds **8a-e**.



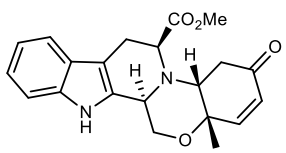

**Methyl (2aR,6aR,8S,14bS)-2a-methoxy-5-oxo-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinoline-8-carboxylate (8a):** Pinkish solid, 120 mg, 63 % yield; mp: 159–161 °C; $R_f$ = 0.4 (silica gel, hexane/EtOAc 1:2); $[\alpha]_D$ = -275.0 (0.0047 M in acetone); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.44 (d, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.21 – 7.08 (m, 2H), 6.85 (d, *J* = 10.3 Hz, 1H), 6.10 (d, *J* = 10.3 Hz, 1H), 4.01 (d, *J* = 11.3 Hz, 1H), 3.93 (dd, *J* = 10.6, 7.2 Hz, 1H), 3.83 (s, 3H), 3.75 (dd, *J* = 10.6, 3.9 Hz, 1H), 3.37 (s, 3H), 3.19 – 3.12 (m, 1H), 3.05 – 2.99 (m, 1H), 2.85 – 2.75 (m, 2H), 2.17 – 1.98 (m, 3H), 1.92 – 1.81 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 198.6, 173.1, 156.6, 136.3, 133.2, 130.9, 126.9, 122.0, 119.9, 118.2, 110.9, 106.4, 74.8, 60.9, 54.8, 52.4, 51.0, 50.4, 34.0, 30.7, 27.1, 25.9; HRMS (m/z): $[M+H]^+$ calcd. for $C_{22}H_{25}N_2O_4$, 381.1814, found 381.1815.



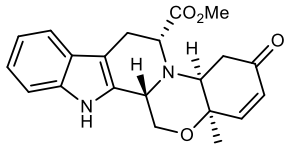

**Methyl (2aS,6aS,8R,14bR)-2a-methoxy-5-oxo-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinoline-8-carboxylate (8b):** Off-white solid, 104 mg, 55% yield; mp: 158–160 °C; $R_f$ = 0.4 (silica gel, hexane/EtOAc 1:2); $[\alpha]_D$ = +280.7 (0.0034 M in acetone); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.16 (t, *J* = 7.3 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 10.3 Hz, 1H), 6.08 (d, *J* = 10.3 Hz, 1H), 3.92 (dd, *J* = 10.8, 6.2 Hz, 2H), 3.83 (s, 3H), 3.72 (dd, *J* = 10.6, 3.8 Hz, 1H), 3.35 (s, 3H), 3.19 – 3.11 (m, 1H), 3.02 (dd, *J* = 14.8, 2.6 Hz, 1H), 2.79 – 2.68 (m, 2H), 2.11 – 1.93 (m, 3H), 1.85 – 1.71 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 198.6, 173.0, 156.6, 136.3, 133.3, 130.8, 126.9, 121.9, 119.8, 118.2, 111.0, 106.2, 74.8, 60.9, 54.8, 52.4, 51.0, 50.4, 34.0, 30.6, 27.1, 25.9; HRMS (m/z): $[M+H]^+$ calcd. for $C_{22}H_{25}N_2O_4$, 381.1814, found 381.1823.



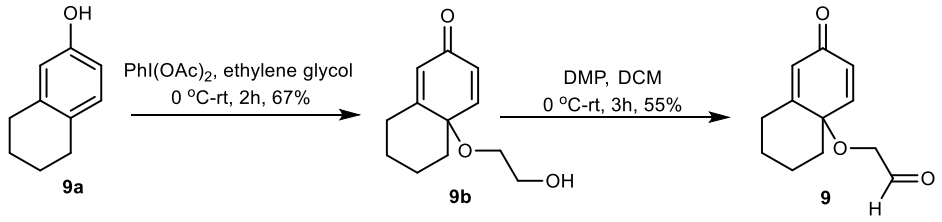

**Methyl (2aR,6aR,8S,14bS)-11-hydroxy-2a-methoxy-5-oxo-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinoline-8-carboxylate (8c):** Brownish solid, 79 mg, 40% yield; mp: 165–167 °C; $R_f$ = 0.35 (silica gel, hexane/EtOAc 1:2); $[\alpha]_D$ = -214.2 (0.0017 M in acetone); $^1$H NMR (500 MHz, $CD_3OD$): δ 7.13 (d, *J* = 8.6 Hz, 1H), 6.90 (dd, *J* = 10.4, 3.6 Hz, 1H), 6.76 (d, *J* = 2.3 Hz, 1H), 6.64 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.05 (d, *J* = 10.3 Hz, 1H), 3.95 – 3.86 (m, 1H), 3.87 – 3.79 (m, 4H), 3.69 (dd, *J* = 10.5, 3.9 Hz, 1H), 3.31 (s, 3H), 3.04 – 2.95 (m, 1H), 2.95 – 2.82 (m, 2H), 2.72 – 2.63 (m, 1H), 2.13 (d, *J* = 6.7 Hz, 1H), 1.99 – 1.84 (m, 3H); $^{13}$C NMR (125 MHz, $CD_3OD$): δ 199.5, 173.2, 156.5, 150.0, 134.4, 131.6, 129.8, 127.1, 110.9, 110.4, 103.7, 101.7, 74.9, 61.1, 55.2, 51.3, 50.4, 49.7, 33.5, 29.8, 26.4, 25.0; HRMS (m/z): $[M+H]^+$ calcd. for $C_{22}H_{25}N_2O_5$, 397.1763, found 397.1774.



**Methyl (2aS,6aR,8S,14bR)-2a-methyl-5-oxo-2a,5,6,6a,8,9,14,14b-octahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-8-carboxylate (8d):** Off-white solid, 78 mg, 43% yield; mp: 150–153 °C; $R_f$ = 0.45 (silica gel, hexane/EtOAc 1:1); $[\alpha]_D$ = -252.4 (0.0054 M in acetone); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.25 – 7.19 (m, 1H), 7.16 (dd, *J* = 11.0, 3.9 Hz, 1H), 6.73 (d, *J* = 10.2 Hz, 1H), 6.08 (d, *J* = 10.2 Hz, 1H), 4.36 – 4.29 (m, 1H), 4.17 (dd, *J* = 11.2, 2.8 Hz, 1H), 3.99 (dd, *J* = 11.2, 9.1 Hz, 1H), 3.86 – 3.76 (m, 4H), 3.46 – 3.38 (m, 1H), 3.22 – 3.12 (m, 1H), 3.11 – 2.94 (m, 2H), 2.58 (dd, *J* = 15.9, 3.7 Hz, 1H), 1.60 (d, *J* = 10.6 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 198.6, 172.8, 151.0, 136.4, 129.6, 126.8, 122.7, 120.1, 118.3, 111.2, 108.1, 76.9, 71.6, 64.0, 60.7, 56.9, 52.5, 52.0, 33.9, 25.0, 22.9; HRMS (m/z): $[M+H]^+$ calcd. for $C_{21}H_{23}N_2O_4$, 367.1657, found 367.1660.




**Methyl (2aR,6aS,8R,14bS)-2a-methyl-5-oxo-2a,5,6,6a,8,9,14,14b-octahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-8-carboxylate (8e):** Off-white solid, 95 mg, 52% yield; mp: 150–152 °C; $R_f$ = 0.45 (silica gel, hexane/EtOAc 1:1); $[\alpha]_D$ = +250.0 (0.0027 M in acetone); $^1$H NMR (500 MHz, Acetone-$d_6$): δ 10.06 (s, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.11 – 7.05 (m, 1H), 7.05 – 6.99 (m, 1H), 6.72 (d, *J* = 10.2 Hz, 1H), 5.93 (d, *J* = 10.2 Hz, 1H), 4.36 (d, *J* = 9.2 Hz, 1H), 4.27 (dd, *J* = 11.2, 3.5 Hz, 1H), 3.89 (t, *J* = 9.7 Hz, 1H), 3.83 – 3.74 (m, 4H), 3.35 (dd, *J* = 11.4, 3.8 Hz, 1H), 3.13 – 2.93 (m, 2H), 2.81 (t, *J* = 10.1 Hz, 1H), 2.53 (dd, *J* = 15.5, 3.8 Hz, 1H), 1.59 (s, 3H); $^{13}$C NMR (125 MHz, Acetone-$d_6$): δ 198.7, 173.3, 151.4, 137.7, 137.6, 131.3, 129.6, 127.7, 122.2, 119.9, 118.6, 111.9, 107.3, 71.7, 64.4, 61.5, 57.8, 52.4, 33.7, 30.3, 22.7; HRMS (m/z): $[M+H]^+$ calcd. for $C_{21}H_{23}N_2O_4$, 367.1657, found 367.1649.



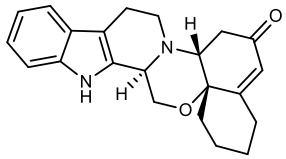
**Supplementary Figure 6** Reaction scheme for the preparation of compound **9**

**Reaction procedure for the preparation of 4a-(2-hydroxyethoxy)-5,6,7,8-tetrahydronaphthalen-2(4aH)-one (9b):** Phenol (**9a**, 1.0 mmol)) was dissolved in DCM (0.2 mL) and added ethylene glycol (30 mmol) at 0 °C. Next, a solution of $PhI(OAc)_2$ (1.2 mmol) in DCM (4.0 mL) was added dropwise at 0 °C over a period of 1h and stirring was continued at rt for another 1h. After completion, the crude was diluted with DCM (50 mL) and washed with water (2 x 50 mL). The organic layer was separated, dried over $Na_2SO_4$ and concentrated under vacuum. The crude product was purified on flash chromatography using 55 % EtOAc in hexane to obtain the compound **9b** as colorless liquid: 139 mg, 67% yield; $R_f$ = 0.5 (silica gel, hexane/EtOAc 1:4); $^1$H NMR (500 MHz, DMSO-$d_6$) δ 6.84 (d, *J* = 10.0 Hz, 1H), 6.24 (dd, *J* = 10.0, 2.0 Hz, 1H), 6.17 (t, *J* = 1.7 Hz, 1H), 4.62 (t, *J* = 5.7 Hz, 1H), 3.49 – 3.44 (m, 2H), 3.17 – 3.12 (m, 1H), 3.05 – 3.00 (m, 1H), 2.48 – 2.40 (m, 1H), 2.36 – 2.28 (m, 1H), 2.15 – 2.09 (m, 1H), 1.98 – 1.84 (m, 2H), 1.56 – 1.50 (m, 1H), 1.33 – 1.22 (m, 2H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 185.3, 163.7, 152.1, 129.8, 125.5, 72.9, 65.7, 60.3, 38.6, 31.6, 27.6, 19.9; HRMS (m/z): $[M+H]^+$ calcd. for $C_{12}H_{16}O_3$, 209.1177, found 209.1167.

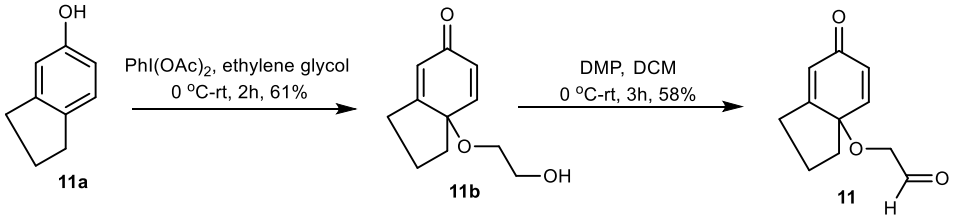
**Reaction procedure for the preparation of 2-((7-oxo-1,3,4,7-tetrahydronaphthalen-4a(2H)-yl)oxy)acetaldehyde (9):** Compound **9b** (0.5 mmol) was dissolved in DCM (5.0 mL) and added DMP (0.75 mmol) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirring continued for 3h. After completion, the reaction mixture was passed through the pad of celite and collected the superintendent. This organic layer was concentrated and purified on filter column using 100% DCM to obtain the compound **9** as colorless liquid; 57 mg, 55% yield; $R_f$ = 0.55 (silica gel, hexane/EtOAc 1:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 9.68 (s, 1H), 6.71 (d, *J* = 10.0 Hz, 1H), 6.34 (dd, *J* = 10.0, 1.9 Hz, 1H), 6.25 (d, *J* = 1.4 Hz, 1H), 3.87 – 3.76 (m, 2H), 2.45 – 2.27 (m, 3H), 2.10 – 1.99 (m, 2H), 1.73 – 1.66 (m, 1H), 1.49 – 1.37 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 199.2, 185.8, 161.4, 149.6, 131.3, 127.2, 74.3, 70.1, 39.1, 32.6, 28.0, 20.4; HRMS (m/z): $[M+H]^+$ calcd. for $C_{12}H_{15}O_3$, 207.1021, found 207.1012.

**Reaction procedure for the preparation of (2aS,9aR,17bR)-3,4,5,6,9,9a,11,12,17,17b-Decahydro-1H,8H-naphtho[1'',8a'':5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-8-one**

**(10):** Aldehyde (**9**, 0.5 mmol) was dissolved in DCM (2 mL) and a solution of amine (**3a**, 0.5 mmol) in DCM (2.0 mL) was added dropwise at -78 °C. Then, a solution of TFA (1.0 mmol) in DCM (1 mL) was added dropwise at -78 °C and slowly warmed to room temperature and stirring was continued for 12 h. After completion, the reaction mixture was diluted with DCM (30 mL) and washed with saturated sodium bicarbonate solution (2 x 20 mL). The organic layer was separated, dried over $Na_2SO_4$ and concentrated under vacuum. The crude was purified on flash chromatography, using 42 %EtOAc in hexane as an eluent to produce the title compound **10**.



White solid, 88 mg, 55% yield; mp: 232–235 °C; $R_f$ = 0.45 (silica gel, hexane/EtOAc 1:1); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.22 – 7.09 (m, 2H), 5.91 (s, 1H), 4.16 (d, *J* = 8.4 Hz, 1H), 4.05 (dd, *J* = 10.6, 2.8 Hz, 1H), 3.84 (t, *J*= 10.6 Hz, 1H), 3.21 – 3.12 (m, 2H), 3.12 – 3.02 (m, 1H), 3.11 – 2.92 (m, 3H), 2.80 – 2.70 (m, 1H), 2.68 – 2.51 (m, 2H), 2.36 (d, *J* = 13.9 Hz, 1H), 1.94 (d, *J* = 12.2 Hz, 1H), 1.73 – 1.57 (m, 2H), 1.53 – 1.39 (m, 1H), 1.21 (t, *J* = 12.9 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 199.6, 162.5, 136.3, 130.7, 127.1, 125.2, 121.9, 119.7, 118.2, 110.9, 109.8, 72.5, 63.2, 60.6, 50.6, 48.9, 32.6, 32.2, 32.1, 26.9, 21.4, 20.2; HRMS (m/z): $[M+H]^+$ calcd. for $C_{22}H_{25}N_2O_2$, 349.1916, found 349.1910.



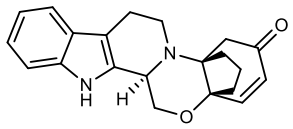

**Supplementary Figure 7** Reaction scheme for the preparation of compound **11**

**Reaction procedure for the preparation of 7a-(2-hydroxyethoxy)-1,2,3,7a-tetrahydro-5H-inden-5-one (11b):** Phenol (**11a**, 1.0 mmol)) was dissolved in DCM (0.2 mL) and added ethylene glycol (30 mmol) at 0 °C. Next, a solution of $PhI(OAc)_2$ (1.2 mmol) in DCM (4.0 mL)

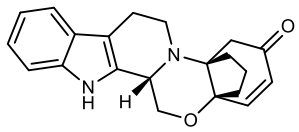
was added dropwise at 0 °C over a period of 1h and stirring was continued at rt for another 1h. After completion, the crude was diluted with DCM (50 mL) and washed with water (2 x 50 mL). The organic layer was separated, dried over $Na_2SO_4$ and concentrated under vacuum. The crude product was purified on flash chromatography using 57 % EtOAc in hexane to obtain the compound **11b** as colorless liquid: 119 mg, 61% yield; $R_f$ = 0.5 (silica gel, hexane/EtOAc 1:4); $^1$H NMR (500 MHz, DMSO-$d_6$) δ 6.94 (d, *J* = 10.0 Hz, 1H), 6.23 (dd, *J* = 10.0, 1.8 Hz, 1H), 6.16 (dd, *J* = 3.3, 2.0 Hz, 1H), 4.56 (t, *J* = 5.6 Hz, 1H), 3.46 – 3.38 (m, 2H), 3.19 – 3.13 (m, 1H), 3.08 – 3.02 (m, 1H), 2.73 – 2.62 (m, 1H), 2.49 – 2.39 (m, 1H), 2.16 – 1.99 (m, 2H), 1.91 – 1.80 (m, 1H), 1.60 – 1.52 (m, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 185.5, 167.2, 146.1, 130.7, 124.2, 77.7, 65.3, 60.2, 34.8, 28.0, 21.3; HRMS (m/z): $[M+H]^+$ calcd. for $C_{11}H_{15}O_3$, 195.1021, found 195.1015.

**Reaction procedure for the preparation of 2-((6-oxo-1,2,3,6-tetrahydro-3aH-inden-3a-yl)oxy)acetaldehyde (11):** Compound **11b** (0.5 mmol) was dissolved in DCM (5.0 mL) and added DMP (0.75 mmol) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirring continued for 3h. After completion, the reaction mixture was passed through the pad of celite and collected the superintendent. This organic layer was concentrated and purified on filter column using 100% DCM to obtain the compound **11** as colorless liquid; 56 mg, 58% yield; $R_f$ = 0.55 (silica gel, hexane/EtOAc 1:1); $^1$H NMR (500 MHz, $CDCl_3$) δ 9.62 (s, 1H), 6.83 (d, *J* = 9.9 Hz, 1H), 6.32 (dd, *J* = 9.9, 1.7 Hz, 1H), 6.22 (s, 1H), 3.85 (q, *J* = 17.9, 0.6 Hz, 2H), 2.80 – 2.66 (m, 1H), 2.57 – 2.45 (m, 1H), 2.38 – 2.22 (m, 2H), 2.07 – 1.92 (m, 1H), 1.82 – 1.68 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 199.3, 185.9, 165.4, 143.9, 132.3, 125.8, 79.4, 69.8, 35.5, 28.8, 21.7; HRMS (m/z): $[M+H]^+$ calcd. for $C_{11}H_{13}O_3$, 193.0864, found 193.0854.

**Reaction procedure for the preparation of compounds 12 and 13:** Aldehyde (**11**, 0.5 mmol) was dissolved in DCM (2 mL) and a solution of amine (**3a**, 0.5 mmol) in DCM (2.0 mL) was added dropwise at -78 °C. Then, a solution of TFA (1.0 mmol) in DCM (1 mL) was added dropwise at -78 °C and slowly warmed to room temperature and stirring was continued for 12 h. After completion, the reaction mixture was diluted with DCM (30 mL) and washed with saturated sodium bicarbonate solution (2 x 20 mL). The organic layer was separated, dried over $Na_2SO_4$ and concentrated under vacuum. The crude was purified on flash chromatography, using 45 % EtOAc in hexane as an eluent to deliver the title compounds **12** and **13**.



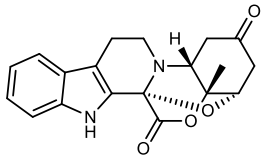
**(2aS,6aR,14bR)-8,9,14,14b-Tetrahydro-1H-2a,6a-propanobenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(6H)-one (12):** Off-white solid, 50 mg, 30% yield; mp: 126–228 °C; $R_f$ = 0.5 (silica gel, hexane/EtOAc 1:1); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.84 (s, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.16 (dt, *J* = 26.8, 7.2 Hz, 2H), 6.62 (t, *J* = 12.2 Hz, 1H), 6.08 (d, *J* = 10.1 Hz, 1H), 4.17 – 4.06 (m, 2H), 3.93 (t, *J* = 10.6 Hz, 1H), 3.32 (d, *J* = 7.3 Hz, 1H), 3.03 (d, *J* = 15.6 Hz, 1H), 2.91 – 2.80 (m, 2H), 2.61 – 2.45 (d, *J* = 14.3 Hz, 1H), 2.62 – 2.43 (m, 2H), 2.22 (t, *J* = 9.7 Hz, 1H), 1.98 – 1.87 (m, 1H), 1.64 – 1.44 (m, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ: 200.1, 150.4, 136.3, 130.9, 128.9, 127.0, 121.9, 119.7, 118.2, 110.9, 110.4, 80.3, 63.5, 62.5, 51.8, 43.1, 35.8, 33.8, 30.4, 22.6, 19.0; HRMS (m/z): $[M+H]^+$ calcd. for $C_{21}H_{23}N_2O_2$, 335.1759, found 335.1754.



**(2aS,6aR,14bS)-8,9,14,14b-Tetrahydro-1H-2a,6a-propanobenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(6H)-one (13):** Off-white solid, 50 mg, 30% yield; mp: 200–202 °C; $R_f$ = 0.55 (silica gel, hexane/EtOAc 1:1); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.72 (s, 1H), 7.53 – 7.41 (m, 1H), 7.36 – 7.25 (m, 1H), 7.19 – 7.06 (m, 2H), 6.67 (d, *J* = 10.2 Hz, 1H), 6.08 (d, *J* = 10.2 Hz, 1H), 4.15 (d, *J* = 9.7 Hz, 1H), 4.06 (dd, *J* = 10.8, 3.0 Hz, 1H), 3.69 (t, *J* = 10.8 Hz, 1H), 3.47 (dd, *J* = 11.3, 4.8 Hz, 1H), 2.94 (d, *J* = 16.0 Hz, 1H), 2.85 – 2.74 (m, 1H), 2.67 (d, *J* = 14.9 Hz, 1H), 2.60 – 2.47 (m, 2H), 2.41 (td, *J* = 11.5, 3.4 Hz, 1H), 2.24 – 1.99 (m, 3H), 1.97 – 1.85 (m, 1H), 1.48 – 1.35 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 197.8, 150.5, 136.2, 130.9, 130.8, 127.1, 121.7, 119.7, 118.2, 110.8, 110.2, 83.2, 71.5, 65.7, 51.9, 45.8, 43.5, 36.6, 25.7, 22.6, 20.5; HRMS (m/z): $[M+H]^+$ calcd. for $C_{21}H_{23}N_2O_2$, 335.1759, found 335.1755.

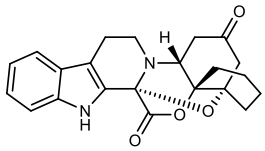
**Reaction procedure for the preparation of (2aR,3S,6aR,14bS)-2a-methyl-3,4,6,6a,9,14-hexahydro-1H,8H-3,14b-epoxybenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-1,5(2aH)-dione (14):** Compound **5c/6c** (0.1 mmol) was dissolved in degassed acetone (0.3 mL) and a

solution of NMO (0.2 mmol) in degassed water (0.2 mL) was added at rt. Then, $OsO_4$ (10 mol%, 2.5 wt% in tert-Butanol) solution was added dropwise and stirring was continued for 14 h. After completion, the reaction mixture was quenched with saturated solution of $Na_2S_2O_3.5H_2O$ and stirring was continued for another 30 min. Then, the reaction mixture was passed through a celite pad and the filtrate was concentrated. Then, the crude was dissolved with DCM (30 mL) and washed with water (2 x 20 mL). The organic layer was separated, dried over $Na_2SO_4$ and concentrated under vacuum. The crude was purified on flash chromatography, using 55% EtOAc in hexane as an eluent to produce the title compound **14**.



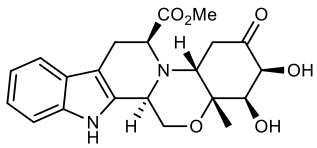

Off-white solid, 25 mg, 76% yield; mp: 163–166 °C; $R_f$ = 0.45 (silica gel, hexane/EtOAc 1:4); $^1$H NMR (500 MHz, $CD_3OD$): δ 7.50 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.21 – 7.15 (m, 1H), 7.10 – 7.02 (m, 1H), 4.55 – 4.51 (m, 1H), 3.33 – 3.31 (m, 1H), 3.25 – 3.18 (m, 1H), 3.01 – 2.61 (m, 8H), 1.79 (s, 3H); $^{13}$C NMR (125 MHz, $CD_3OD$): δ 205.7, 167.5, 137.2, 126.1, 125.6, 122.2, 118.8, 118.4, 111.5, 111.4, 80.8, 79.0, 76.3, 62.2, 47.2, 44.2, 43.1, 21.2, 18.9; HRMS (m/z): $[M+H]^+$ calcd. for $C_{19}H_{19}N_2O_4$, 339.1344, found 339.1346.

**Reaction procedure for the preparation of (2aR,6aS,9aR,17bS)-3,4,5,6,9,9a,12,17-Octahydro-1H,11H-6a,17b-epoxynaphtho[1'',8a'':5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-1,8(7H)-dione (15):** Compound **10** (0.1 mmol) was dissolved in degassed acetone (0.3 mL) and a solution of NMO (0.2 mmol) in degassed water (0.2 mL) was added at rt. Then, $OSO_4$ (10 mol%, 2.5 wt% in tert-Butanol) solution was added dropwise and stirring was continued for 17 h. After completion, the reaction mixture was quenched with saturated solution of $Na_2S_2O_3.5H_2O$ and stirring was continued for 30 min. Then, the reaction mixture was passed through a celite pad and the filtrate was concentrated. Then, the crude was dissolved with DCM (30 mL) and washed with water (2 x 20 mL). The organic layer was separated, dried over $Na_2SO_4$ and concentrated under vacuum. The crude was purified on flash chromatography, using 52% EtOAc in hexane as an eluent to produce the title compound **15**.



Off-white solid, 24 mg, 65% yield; mp: 185–187 °C; $R_f$ = 0.55 (silica gel, hexane/EtOAc 1:3); $^1$H NMR (500 MHz, Acetone-$d_6$): δ 7.49 (d, *J* = 7.9 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.19 – 7.11 (m, 1H), 7.07 – 6.99 (m, 1H), 3.31 c 3.21 (m, 2H), 3.07 (d, *J* = 16.9 Hz, 1H), 3.01 – 2.70 (m, 6H), 2.36 (dd, *J* = 17.0, 2.2 Hz, 1H), 2.33 – 2.24 (m, 1H), 1.89 – 1.72 (m, 4H), 1.71 – 1.64 (m, 1H), 1.59 – 1.47 (m, 1H); $^{13}$C NMR (125 MHz, Acetone-$d_6$): δ 205.1, 167.4, 138.1, 138.0, 127.8, 127.6, 126.8, 123.1, 119.8, 119.4, 112.5, 112.3, 80.7, 79.1, 63.2, 48.4, 48.1, 44.3, 34.5, 22.5, 22.3, 20.7; HRMS (m/z): $[M+H]^+$ calcd. for $C_{22}H_{23}N_2O_4$, 379.1657, found 379.1666.

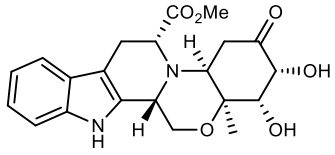
**Reaction procedure for the preparation of methyl (2aR,3R,4S,6aR,8S,14bR)-3,4-dihydroxy-2a-methyl-5-oxo-2a,3,4,5,6,6a,8,9,14,14b-decahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-8-carboxylate (16):** Compound **8d** (0.1 mmol) was dissolved in degassed acetone (0.3 mL) and a solution of NMO (0.2 mmol) in degassed water (0.2 mL) was added at rt. Then, $OSO_4$ (10 mol%, 2.5 wt% in tert-Butanol) solution was added dropwise and stirring was continued for 16 h. After completion, the reaction mixture was quenched with saturated solution of $Na_2S_2O_3.5H_2O$ and stirring was continued for another 30 min. Then, the reaction mixture was passed through a celite pad and the filtrate was concentrated. Then, the crude was dissolved with DCM (30 mL) and washed with water (2 x 20 mL). The organic layer was separated, dried over $Na_2SO_4$ and concentrated under vacuum. The crude was purified on flash chromatography, using EtOAc in hexane as an eluent to produce the title compound **16**.



White solid, 20 mg, 52% yield; mp: 228–230 °C; $R_f$ = 0.55 (silica gel, hexane/EtOAc 1:4); $[\alpha]_D$ = -100.0 (0.001 M in acetone); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.73 (s, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.25 – 7.18 (m, 1H), 7.18 – 7.12 (m, 1H), 4.76 – 4.66 (m, 1H), 4.38 (d, *J* = 8.5 Hz, 1H), 4.18 – 4.11 (m, 1H), 4.09 – 3.98 (m, 2H), 3.84 (s, 3H), 3.72 – 3.62 (m,

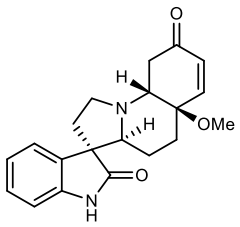
2H), 3.48 – 3.39 (m, 1H), 3.25 – 3.12 (m, 2H), 3.07 – 2.96 (m, 1H), 2.69 (dd, *J* = 13.7, 5.8 Hz, 1H), 2.51 (s, 1H), 1.70 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 208.7, 172.2, 136.3, 129.1, 126.5, 122.3, 120.1, 118.2, 111.0, 107.5, 77.5, 76.5, 74.3, 64.2, 60.6, 57.5, 52.4, 49.6, 32.0, 26.8, 18.5; HRMS (m/z): $[M+H]^+$ calcd. for $C_{21}H_{25}N_2O_6$, 401.1712, found 401.1711.

**Reaction procedure for the preparation of methyl (2aS,3S,4R,6aS,8R,14bS)-3,4-dihydroxy-2a-methyl-5-oxo-2a,3,4,5,6,6a,8,9,14,14b-decahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-8-carboxylate (17):** Compound **8e** (0.1 mmol) was dissolved in degassed acetone (0.3 mL) and a solution of NMO (0.2 mmol) in degassed water (0.2 mL) was added at rt. Then, $OSO_4$ (10 mol%, 2.5 wt% in tert-Butanol) solution was added dropwise and stirring was continued for 16 h. After completion, the reaction mixture was quenched with saturated solution of $Na_2S_2O_3.5H_2O$ and stirring was continued for another 30 min. Then, the reaction mixture was passed through a celite pad and the filtrate was concentrated. Then, the crude was dissolved with DCM (30 mL) and washed with water (2 x 20 mL). The organic layer was separated, dried over $Na_2SO_4$ and concentrated under vacuum. The crude was purified on flash chromatography, using EtOAc in hexane as an eluent to deliver the title compound **17**.

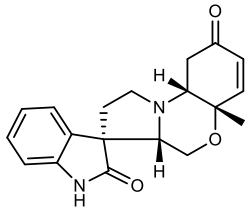



White solid, 17.5 mg, 44% yield; mp: 228–230 °C; $R_f$ = 0.55 (silica gel, hexane/EtOAc 1:4); $[\alpha]_D$ = +105.5 (0.0022 M in acetone); $^1$H NMR (500 MHz, $CDCl_3$) δ: 7.71 (s, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 4.71 – 4.66 (m, 1H), 4.38 (d, *J* = 10.6 Hz, 1H), 4.14 (dd, *J* = 11.0, 4.0 Hz, 1H), 4.06 (t, *J* = 11.0 Hz, 1H), 4.03 – 3.98 (m, 1H), 3.84 (s, 3H), 3.69 – 3.62 (m, 2H), 3.43 (dd, *J* = 10.9, 5.8 Hz, 1H), 3.23 – 3.12 (m, 2H), 3.05 – 2.98 (m, 1H), 2.73 – 2.65 (m, 1H), 2.49 (d, *J* = 1.5 Hz, 1H), 1.71 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 209.0, 172.4, 136.5, 129.3, 126.6, 122.4, 120.1, 118.3, 111.1, 107.5, 77.70, 76.6, 74.5, 64.3, 60.7, 57.6, 52.5, 49.7, 32.2, 26.9, 18.6. HRMS (m/z): $[M+H]^+$ calcd. for $C_{21}H_{25}N_2O_6$, 401.1712, found 401.1710.

**General reaction procedure for the preparation of compounds 18-20:** Compound (**5a/6c/8a**, 0.1 mmol) was dissolved in THF:AcOH:water (0.4:0.4:0.4 mL) and *N*-bromosuccinamide (0.1 mmol) was added slowly at -10 °C. The reaction mixture was slowly warmed to room temperature and stirring continued for 2 h. After completion, the reaction mixture was quenched slowly with saturated sodiumbicarbonate solution at 0 °C. Then, the reaction mixture was diluted with DCM (30 mL) and washed with water (2 x 20 mL). The organic layer was separated, dried over $Na_2SO_4$ and concentrated under vacuum. The crude was purified on flash chromatography, using EtOAc in hexane as an eluent to obtain the title compounds **18-20**.

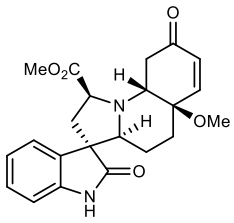



**(3S,3a'S,5a'R,9a'R)-5a'-Methoxy-1',2',3a',4',5',5a',9',9a'-octahydro-8'H-spiro[indoline-3,3'-pyrrolo[1,2-a]quinoline]-2,8'-dione (18):** Off-white solid, 17 mg, 51% yield; mp: 213–215 °C; $R_f$ = 0.4 (silica gel, hexane/EtOAc 1:4); $^1$H NMR (500 MHz, Acetone-$d_6$): δ 9.35 (s, 1H), 7.39 (d, *J* = 7.3 Hz, 1H), 7.18 (td, *J* = 7.7, 1.1 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 6.82 (d, *J* = 10.3 Hz, 1H), 5.97 (d, *J* = 10.3 Hz, 1H), 4.05 – 3.98 (m, 1H), 3.31 (s, 3H), 3.20 – 3.11 (m, 1H), 3.09 – 3.01 (m, 2H), 2.72 (d, *J* = 8.8 Hz, 2H), 2.32 – 2.23 (m, 1H), 1.98 – 1.88 (m, 1H), 1.77 – 1.63 (m, 2H), 1.40 – 1.27 (m, 2H), 1.03 – 0.95 (m, 1H); $^{13}$C NMR (125 MHz, Acetone-$d_6$): δ 198.8, 180.4, 156.7, 142.3, 134.5, 131.2, 128.3, 125.9, 122.4, 109.9, 75.4, 62.4, 57.1, 55.1, 50.7, 46.9, 35.4, 33.4, 30.4, 21.3; HRMS (m/z): $[M+H]^+$ calcd. for $C_{20}H_{23}N_2O_3$, 339.1708, found 339.1715.



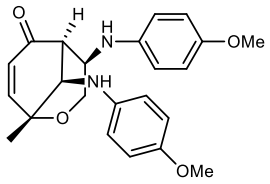

(3S,3aS,5aS,9aR)-5a-Methyl-1,2,3a,4,9,9a-hexahydrospiro[benzo[b]pyrrolo[1,2-d][1,4]oxazine-3,3'-indoline]-2',8(5aH)-dione (**19**): Off-white solid, 17 mg, 52% yield; mp: 215–217 °C; $R_f$ = 0.45 (silica gel, hexane/EtOAc 1:4); $^1$H NMR (500 MHz, $CD_3OD$): δ 7.31 (d, *J* = 7.4 Hz, 1H),

7.22 (t, *J* = 7.7 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 6.67 (d, *J* = 10.8 Hz, 1H), 6.03 (d, *J* = 10.8 Hz, 1H), 3.70 (t, *J* = 10.5 Hz, 1H), 3.49 (t, *J* = 8.3 Hz, 1H), 3.28 (dd, *J* = 10.5, 2.5 Hz, 1H), 2.88 – 2.80 (m, 2H), 2.77 (t, *J* = 9.1 Hz, 1H), 2.69 (dd, *J* = 10.1, 2.2 Hz, 1H), 2.49 (dd, *J* = 17.4, 8.5 Hz, 1H), 2.28 (dt, *J* = 13.0, 9.0 Hz, 1H), 2.07 – 2.01 (m, 1H), 1.43 (s, 3H) $^{13}$C NMR (125 MHz, $CD_3OD$): δ 199.2, 181.9, 155.6, 142.6, 134.4, 130.9, 129.4, 124.1, 123.8, 110.6, 74.4, 72.6, 69.7, 64.8, 55.7, 52.7, 41.3, 35.4, 24.9; HRMS (m/z): $[M+H]^+$ calcd. for $C_{19}H_{21}N_2O_3$, 325.1552, found 325.1555.

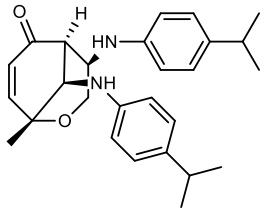



**Methyl (1'S,3S,3a'S,5a'R,9a'R)-5a'-methoxy-2,8'-dioxo-1',2',3a',4',5a',8',9',9a'-octahydro-5'H-spiro[indoline-3,3'-pyrrolo[1,2-a]quinoline]-1'-carboxylate (20):** Off-white solid, 19 mg, 48% yield; mp: 246–248 °C; $R_f$ = 0.4 (silica gel, hexane/EtOAc 1:4); $[\alpha]_D$ = -12.5 (0.002 M in acetone); $^1$H NMR (500 MHz, Acetone-$d_6$): δ 8.78 (s, 1H), 7.34 (d, *J* = 7.3 Hz, 1H), 7.11 (td, *J* = 7.7, 0.9 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 6.52 (dd, *J* = 10.2, 2.1 Hz, 1H), 6.08 (d, *J* = 10.2 Hz, 1H), 4.07 (dd, *J* = 9.0, 1.5 Hz, 1H), 3.74 (s, 3H), 3.44 (dd, *J* = 10.1, 3.6 Hz, 1H), 3.27 (s, 3H), 3.20 (d, *J* = 2.3 Hz, 1H), 3.03 (dd, *J* = 16.4, 3.0 Hz, 1H), 2.56 – 2.49 (m, 1H), 2.12 (d, *J* = 9.3Hz, 1H), 1.46 – 1.25 (m, 3H); $^{13}$C NMR (125 MHz, Acetone-$d_6$): δ 197.9, 179.8, 173.8, 148.0, 141.4, 132.5, 132.1, 128.0, 123.8, 122.3, 109.1, 71.5, 69.0, 62.0, 60.5, 55.6, 51.3, 50.5, 38.4, 37.9, 32.2, 21.5.HRMS (m/z): $[M+H]^+$ calcd. for $C_{22}H_{25}N_2O_5$, 397.1763, found 397.1774.

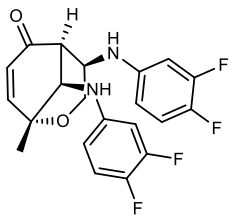
**General reaction procedure for the preparation of 22a-d:** Aldehyde (**2b**, 0.5 mmol) was dissolved in DCM (0.5 mL) and molecular sieves were added at -78 °C. Then, a solution of amine (**21**, 0.5 mmol) in DCM (0.5 mL) was added dropwise and stirring was continued at -78 °C. After 45 min, a second equivalent of solution of amine (**21**, 0.5 mmol) in DCM (0.5 mL) was added dropwise and stirring was continued at -78 °C for 2 h. Then, the reaction mixture was slowly warmed to rt and stirring was continued at room temperature for 10h. After completion, DCM was removed under vacuum and the crude was purified on flash chromatography, using EtOAc in hexane as eluent to produce the title compounds **22a-d**.



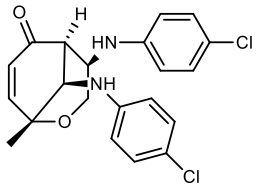

**(1R,4R,5S,9R)-4,9-Bis((4-methoxyphenyl)amino)-1-methyl-2-oxabicyclo[3.3.1]non-7-en-6-one (22a):** White solid, 124 mg, 63% yield; mp: 158–160 °C; $R_f$ = 0.45 (silica gel, hexane/EtOAc 1:1); $^1$H NMR (500 MHz, $CDCl_3$): δ 6.85 – 6.79 (m, 2H), 6.76 – 6.69 (m, 2H), 6.68 – 6.62 (m, 3H), 6.55 – 6.49 (m, 3H), 4.06 (dd, *J* = 12.0, 5.8 Hz, 1H), 3.98 – 3.91 (m, 1H), 3.84 (d, *J* = 3.2 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.31 (t, *J* = 12.0 Hz, 1H), 3.21 – 3.15 (m, 1H), 1.50 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 200.3, 152.7, 147.6, 140.0, 134.3, 115.3, 115.1, 115.0, 114.8, 71.1, 64.0, 56.4, 55.8, 55.7, 49.3, 46.4, 23.7; HRMS (m/z): $[M+H]^+$ calcd. for $C_{23}H_{27}N_2O_4$, 395.1970, found 395.1969.




**(1R,4R,5S,9R)-4,9-Bis((4-isopropylphenyl)amino)-1-methyl-2-oxabicyclo[3.3.1]non-7-en-6-one (22b):** White solid, 127 mg, 67% yield; mp: 124–126 °C; $R_f$ = 0.5 (silica gel, hexane/EtOAc 1:1); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.08 (t, *J* = 5.5 Hz, 2H), 7.00 (t, *J* = 8.8 Hz, 2H), 6.67 (d, *J* = 9.9 Hz, 1H), 6.65 – 6.59 (m, 2H), 6.56 – 6.46 (m, 3H), 4.09 (dd, *J* = 12.0, 5.9 Hz, 1H), 4.05 – 3.97 (m, 1H), 3.91 (d, *J* = 3.2 Hz, 1H), 3.32 (t, *J* = 11.9 Hz, 1H), 3.20 (t, *J* = 3.9 Hz, 1H), 2.87 – 2.75 (m, 2H), 1.52 (s, 3H), 1.24 (d, *J* = 6.9 Hz, 6H), 1.19 (d, *J* = 6.9 Hz, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ: 200.4, 147.7, 143.7, 139.0, 138.7, 134.3, 127.6, 127.2, 113.3, 113.2, 71.0, 64.0, 55.5, 49.3, 45.5, 33.2, 33.1, 24.2, 24.2, 24.1, 23.7; HRMS (m/z): $[M+H]^+$ calcd. for $C_{27}H_{35}N_2O_2$, 419.2698, found 419.2697.

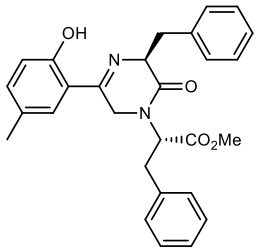


**(1R,4R,5S,9R)-4,9-Bis((3,4-difluorophenyl)amino)-1-methyl-2-oxabicyclo[3.3.1]non-7-en-6-one (22c):** White solid, 117 mg, 58% yield; mp: 160–163 °C; $R_f$ = 0.55 (silica gel, hexane/EtOAc 1:1); $^1$H NMR (500 MHz, Acetone-$d_6$): δ 7.14 – 7.06 (m, 1H), 7.04 – 6.95 (m, 1H), 6.94 – 6.86 (m, 1H), 6.75 – 6.70 (m, 2H), 6.51 – 6.44 (m, 1H), 6.42 (d, *J*= 10.0 Hz, 1H), 6.39 – 6.33 (m, 1H), 5.69 (d, *J* = 10.0 Hz, 1H), 4.53 (d, *J* = 9.3 Hz, 1H), 4.22 – 4.12 (m, 2H), 3.87 (dd, *J* = 11.8, 6.0 Hz, 1H), 3.38 (t, *J* = 11.8 Hz, 1H), 3.12 – 3.06 (m, 1H), 1.46 (s, 3H); $^{13}$C NMR (125 MHz, Acetone-$d_6$): δ 198.2, 151.64 (dd), 149.72 (dd) 146.7, 144.74 (d), 144.40 (d),143.34 (dd), 141.48 (dd), 133.94, 117.47 (dd), 108.86 (dd), 108.52 (dd), 101.78 (d), 101.18 (d), 70.9, 62.5, 54.9, 48.5, 45.2, 23.0; HRMS (m/z): $[M+H]^+$ calcd. for $C_{21}H_{19}F_4N_2O_2$, 407.1382, found 407.1379.

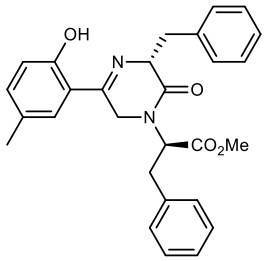



**(1R,4R,5S,9R)-4,9-Bis((4-chlorophenyl)amino)-1-methyl-2-oxabicyclo[3.3.1]non-7-en-6-one (22d):** Off-white solid, 116 mg, 58% yield; mp: 200–202 °C; $R_f$ = 0.55 (silica gel, hexane/EtOAc 1:1); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.20 – 7.16 (m, 2H), 7.11 – 7.06 (m, 2H), 6.68 (d, *J*= 9.9 Hz, 1H), 6.63 – 6.59 (m, 2H), 6.54 (dd, *J* = 9.9, 1.0 Hz, 1H), 6.46 (d, *J*= 8.8 Hz, 2H), 4.05 (dd, *J* = 12.1, 5.9 Hz, 1H), 3.96 (dt, *J* = 11.1, 5.4 Hz, 1H), 3.87 (d, *J* = 3.3 Hz, 1H), 3.30 (t, *J* = 12.0 Hz, 1H), 3.16 (t, *J* = 3.9 Hz, 1H), 1.50 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 199.7, 147.5, 144.4, 134.4, 129.6, 129.3, 123.2, 114.5, 114.4, 71.0, 63.5, 55.5, 49.0, 45.4, 23.7. HRMS (m/z): $[M+H]^+$ calcd. for $C_{21}H_{21}Cl_2N_2O_2$, 403.0980, found 403.0981.

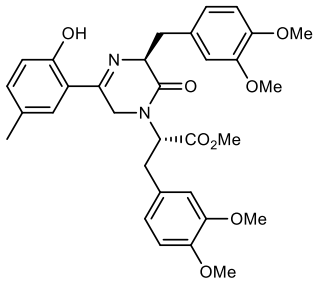
**General reaction procedure for the preparation of 24a-f:** Aldehyde (**2b**, 0.5 mmol) was dissolved in DCM (0.5 mL) and molecular sieves were added at -78 °C. Then, a solution of amine (**23**, 0.5 mmol) in DCM (0.5 mL) was added dropwise and stirring was continued at -78 °C. After 45 min, a second equivalent of solution of amine (**23**, 0.5 mmol) in DCM (0.5 mL) was added dropwise and stirring was continued at -78 °C for 2h. Then, the reaction mixture was slowly warmed to rt and stirring was continued for 10h. After completion, DCM was removed under vacuum and the crude was purified on flash chromatography, using EtOAc in hexane as eluent to deliver the title compounds **24a-d**.



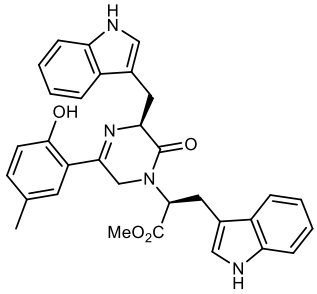

**Methyl (S)-2-((S)-3-benzyl-5-(2-hydroxy-5-methylphenyl)-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-phenylpropanoate (24a):** Yellowish solid, 148 mg, 68% yield; mp: 120–123 °C; $R_f$ = 0.6 (silica gel, hexane/EtOAc 1:1); $[\alpha]_D$ = -39.5 (0.0052 M in acetone); $^1$H NMR (500 MHz, Acetone-$d_6$): δ 13.39 (s, 1H), 7.34 – 7.15 (m, 12H), 6.79 (d, *J* = 8.4 Hz, 1H), 5.36 (dd, *J* = 10.3, 5.7 Hz, 1H), 4.69 – 4.63 (m, 1H), 4.51 – 4.45 (m, 1H), 4.39 – 4.33 (m, 1H), 3.76 (s, 3H), 3.47 – 3.40 (m, 1H), 3.31 – 3.23 (m, 2H), 3.02 – 2.95 (m, 1H), 2.26 (s, 3H); $^{13}$C NMR (125 MHz, $CD_3OD$): δ 170.2, 168.2, 166.0, 158.4, 136.7, 136.4, 133.5, 129.4, 128.6, 128.3, 127.9, 127.4, 126.7, 126.6, 126.4, 117.1, 115.8, 61.9, 58.9, 51.6, 47.3, 38.7, 33.7, 19.1; HRMS (m/z): $[M+H]^+$ calcd. for $C_{28}H_{29}N_2O_4$, 457.2127, found 457.2129.




**Methyl (R)-2-((R)-3-benzyl-5-(2-hydroxy-5-methylphenyl)-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-phenylpropanoate (24b):** Yellowish solid, 148 mg, 65% yield; mp: 121–123 °C; $R_f$ = 0.6 (silica gel, hexane/EtOAc 1:1); $[\alpha]_D$ = -35.7 (0.0015 M in acetone); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.25 (m, 3H), 7.24 – 7.18 (m, 6H), 7.16 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.13 – 7.09 (m, 2H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.82 – 6.80 (d, *J* = 1.0 Hz, 1H), 5.43 (dd, *J* = 8.9, 6.8 Hz, 1H), 4.73 – 4.68 (m, 1H), 4.26 (dd, *J* = 17.2, 2.8 Hz, 1H), 3.76 – 3.70 (m, 4H), 3.35 – 3.24 (m, 2H), 3.07 – 2.96 (m, 2H), 2.29 (s, 3H); $^{13}$C NMR (125 MHz, Acetone-$d_6$): δ 170.2, 166.7, 166.4, 137.5, 137.2, 133.6, 129.5, 128.9, 128.5, 128.1, 127.2, 126.9, 126.7, 126.4, 117.5, 116.1, 61.7, 57.6, 51.7, 45.6, 38.8, 33.9, 19.6; HRMS (m/z): $[M+H]^+$ calcd. for $C_{28}H_{29}N_2O_4$, 457.2127, found 457.2128.

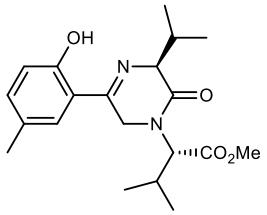



**Methyl (S)-2-((S)-3-(3,4-dimethoxybenzyl)-5-(2-hydroxy-5-methylphenyl)-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-(3,4-dimethoxyphenyl)propanoate (24c):** Yellowish solid, 158 mg, 58% yield; mp: 155–158 °C; $R_f$ = 0.45 (silica gel, hexane/EtOAc 1:1); $[\alpha]_D$ = -22.2 (0.0048 M in acetone); $^1$H NMR (500 MHz, Acetone-$d_6$): δ 7.20 (s, 1H), 7.16 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.84 (d, *J* = 1.6 Hz, 1H), 6.80 – 6.71 (m, 5H), 6.62 (dd, *J* = 8.1, 1.9 Hz, 1H), 5.28 (dd, *J* = 10.5, 5.5 Hz, 1H), 4.64 – 4.56 (m, 1H), 4.38 (dd, *J* = 17.6, 2.8 Hz, 1H), 4.21 (dd, *J* = 17.6, 1.9 Hz, 1H), 3.75 (s, 6H), 3.70 (s, 3H), 3.67 (s, 3H), 3.64 (s, 3H), 3.30 (dd, *J* = 14.6, 5.5 Hz, 1H), 3.18 (dt, *J* = 14.6, 8.2 Hz, 2H), 2.98 – 2.90 (s, 1H), 2.23 (s, 3H); $^{13}$C NMR (125 MHz, Acetone-$d_6$): δ 170.3, 166.9, 166.6, 159.3, 149.5, 149.0, 148.4, 148.3, 133.6, 129.7, 129.3, 127.2, 126.9, 121.5, 121.0, 117.5, 116.2, 113.7, 112.6, 112.0, 111.8, 62.0, 57.6, 55.1 (2C), 55.0, 54.8, 51.7, 45.6, 38.3, 33.5, 19.6; HRMS (m/z): $[M+H]^+$ calcd. for $C_{32}H_{37}N_2O_8$, 577.2549, found 577.2550.

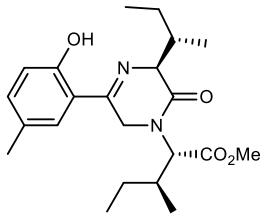



**Methyl (S)-2-((S)-3-((1H-indol-3-yl)methyl)-5-(2-hydroxy-5-methylphenyl)-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-(1H-indol-3-yl)propanoate (24d):** Yellowish solid, 28 mg, 48% yield; mp: 138–140 °C; $R_f$ = 0.4 (silica gel, hexane/EtOAc 1:3); $[\alpha]_D$ = +45.5 (0.0020 M in acetone); $^1$H NMR (500 MHz, Acetone-$d_6$): δ 9.98 (bs, 2H), 7.61 – 7.53 (m, 2H), 7.40 – 7.34 (m, 2H), 7.14 – 7.02 (m, 5H), 6.99 – 6.94 (m, 1H), 6.93 – 6.88 (m, 2H), 6.77 – 6.73 (m, 1H), 5.43 (dd, *J* = 8.7, 6.6 Hz, 1H), 4.77 – 4.71 (m, 1H), 4.48 – 4.41(m, 1H), 3.96 – 3.89 (m, 1H), 3.64 (s, 3H), 3.41 – 3.30 (m, 2H), 3.24 – 3.17 (m, 1H), 3.07 – 2.99 (m, 1H), 2.14 (s, 3H); $^{13}$C

NMR (125 MHz, Acetone-$d_6$): δ 170.8, 166.9, 165.9, 159.4, 136.6, 136.5, 133.4, 127.7, 127.3, 126.9, 126.7, 124.0, 123.2, 121.4, 121.3, 118.9, 118.8, 118.6, 118.3, 117.4, 116.2, 111.4, 111.2, 110.0, 109.8, 61.2, 56.1, 51.5, 45.0, 29.2, 23.8, 19.6; HRMS (m/z): $[M+H]^+$ calcd. for $C_{32}H_{31}N_4O_4$, 535.2345, found 535.2345.



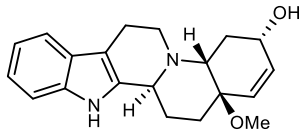

**Methyl (S)-2-((S)-5-(2-hydroxy-5-methylphenyl)-3-isopropyl-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-methylbutanoate (24e):** Colorless oil, 99 mg, 55% yield; $R_f$ = 0.55 (silica gel, hexane/EtOAc 2:1); $[\alpha]_D$ = -25.0 (0.0038 M in acetone); $^1$H NMR (500 MHz, Acetone-$d_6$): δ 13.9 (s, 1H), 7.47 (s, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 4.99 – 4.72 (m, 3H), 4.25 (d, *J* = 2.1 Hz, 1H), 3.69 (s, 3H), 2.62 – 2.39 (m, 2H), 2.28 (s, 3H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.89 (dd, *J* = 11.2, 6.8 Hz, 6H); $^{13}$C NMR (125 MHz, Acetone-$d_6$): δ 171.5, 167.5, 167.5, 160.5, 134.6, 128.2, 127.9, 118.5, 117.2, 66.2, 62.1, 52.2, 45.5, 32.2, 27.8, 20.5, 20.2, 20.1 19.5, 17.7; HRMS (m/z): $[M+H]^+$ calcd. for $C_{20}H_{29}N_2O_4$, 361.2127, found 361.2135.




**Methyl (2S,3S)-2-((S)-3-((S)-sec-butyl)-5-(2-hydroxy-5-methylphenyl)-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-methylpentanoate (24f):** Colorless oil, 100 mg, 52% yield; $R_f$ = 0.55 (silica gel, hexane/EtOAc 2:1); $[\alpha]_D$ = +8.6 (0.0059 M in acetone); $^1$H NMR (500 MHz, Acetone-$d_6$): δ 13.9 (s, 1H), 7.47 (s, 1H), 7.21 – 7.18 (m, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 4.99 (d, *J* = 10.7 Hz, 1H), 4.93 (dd, *J* = 18.0, 3.1 Hz, 1H), 4.74 (dd, *J* = 18.0, 2.0 Hz, 1H), 4.32 – 4.25 (m, 1H), 3.69 (s, 3H), 2.32 – 2.24 (s, 5H), 1.53 – 1.42 (m, 2H), 1.22 – 1.08 (m, 5H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.93 – 0.84 (m, 6H); $^{13}$C NMR (125 MHz, Acetone-$d_6$): δ 171.8, 167.6, 167.4, 160.4,

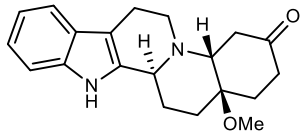
134.6, 128.1, 127.9, 118.4, 117.2, 66.0, 60.1, 52.2, 45.1, 38.0, 33.4, 25.9, 25.8, 20.5, 16.6, 16.1, 12.0, 10.4; HRMS (m/z): $[M+H]^+$ calcd. for $C_{22}H_{33}N_2O_4$, 389.2440, found 389.2445.

**Reaction procedure for the preparation of (2aR,5S,6aR,14bS)-2a-methoxy-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5-ol (25):** Compound **5a** (0.1 mmol) was dissolved in methanol (2.0 mL) and $CeCl_3.7\ H_2O$ (0.1 mmol) was added at -20 °C. Then, $NaBH_4$ (0.11 mmol) was added slowly and stirring was continued at -20 °C for 115 min. After completion, the reaction mixture was quenched with ice at 0 °C. Then, the reaction mixture was diluted with EtOAc (30 mL) and washed with water (2 x 20 mL). The organic layer was separated, dried over $Na_2SO_4$ and concentrated under vacuum. The crude was purified on flash chromatography, using 60 % EtOAc in hexane as an eluent to produce the title compound **25**.

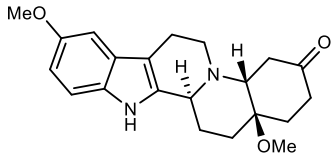



Half white solid, 26 mg. 86% yield; mp: 240–242 °C; $R_f$ = 0.5 (silica gel, hexane/EtOAc 0:1); $^1$H NMR (500 MHz, $CD_3OD$): δ 7.30 (d, *J* = 7.7 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 6.95 (t, *J* = 7.3 Hz, 1H), 6.88 (t, *J* = 7.3 Hz, 1H), 5.72 (d, *J* = 10.3 Hz, 1H), 5.46 (dd, *J* = 10.3, 1.5 Hz, 1H), 4.34 – 4.23 (m, 1H), 3.89 (d, *J* = 10.8 Hz, 1H), 3.32 – 3.20 (m, 1H), 3.13 (s, 3H), 3.08 – 2.94 (m, 2H), 2.92 – 2.80 (m, 1H), 2.66 (d, *J* = 14.8 Hz, 1H), 2.27 (d, *J* = 8.7 Hz, 1H), 1.98 – 1.92 (m, 1H), 1.90 – 1.71 (m, 4H); $^{13}$C NMR (125 MHz, $CD_3OD$): δ 136.7, 134.9, 133.8, 132.5, 126.9, 120.6, 118.4, 117.4, 110.6, 106.7, 74.9, 67.6, 58.3, 51.5, 49.4, 49.1, 31.8, 29.3, 25.2, 21.4. HRMS (m/z): $[M+H]^+$ calcd. for $C_{20}H_{25}N_2O_2$, 325.1916, found 325.1922.

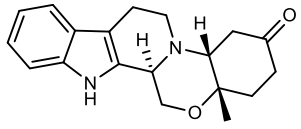
**General reaction procedure for the preparation of 26a-e:** Compound (**5/6/8**, 0.2 mmol) was dissolved in methanol (1.0 mL) and 10 wt% Pd/C (5 mol%) was added and stirring was continued under hydrogen atmosphere for 3-4 h at rt. After completion, the reaction mixture was filtered through a celite pad and the filtrate was concentrated. The crude was purified on flash chromatography, using EtOAc in hexane as an eluent to produce the title compounds **26a-e**.



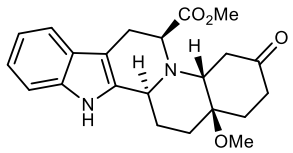
**(2aR,6aR,14bS)-2a-Methoxy-2,2a,3,4,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5(1H)-one (26a):** Off-white solid, 58 mg, 90% yield; mp: 183–185 °C; $R_f$ = 0.45 (silica gel, hexane/EtOAc 1:1); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.20 – 7.09 (m, 2H), 4.29 – 4.21 (m, 1H), 3.48 – 3.36 (m, 1H), 3.28 – 3.21 (m, 4H), 3.05 – 2.96 (m, 1H), 2.87 (t, *J* = 13.0 Hz, 2H), 2.62 (d, *J* = 13.0 Hz, 2H), 2.53 – 2.37 (m, 2H), 2.36 – 2.27 (m, 1H), 2.15 – 2.05 (m, 2H), 2.03 – 1.88 (m, 2H), 1.70 – 1.59 (s, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 211.1, 135.9, 133.2, 127.8, 121.6, 119.7, 118.2, 110.9, 109.0, 73.6, 61.0, 53.5, 48.6, 48.2, 38.3, 37.2, 28.5, 27.3, 24.6, 18.8; HRMS (m/z): $[M+H]^+$ calcd. for $C_{20}H_{25}N_2O_2$, 325.1916, found 325.1908.



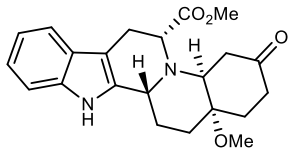
**(2aR,6aR,14bS)-2a,11-dimethoxy-2,2a,3,4,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5(1H)-one (26b):** Off-white solid, 67 mg, 95% yield; mp: 180–183 °C; $R_f$ = 0.4 (silica gel, hexane/EtOAc 1:1); $^1$H NMR (500 MHz, Acetone): δ 9.73 (s, 1H), 7.17 (t, *J* = 10.1 Hz, 1H), 6.91 (d, *J* = 2.4 Hz, 1H), 6.68 (dd, *J* = 8.7, 2.4 Hz, 1H), 4.21 – 4.12 (m, 1H), 3.78 (s, 3H), 3.30 (dd, *J*= 12.8, 4.6 Hz, 1H), 3.24 – 3.17 (m, 4H), 2.95 – 2.88 (m, 1H), 2.85 – 2.69 (m, 3H), 2.64 (dd, *J* = 13.8, 7.0 Hz, 1H), 2.55 – 2.49 (m, 1H), 2.38 – 2.30 (m, 1H), 2.25 (dt, *J* = 16.0, 5.3 Hz, 2H), 2.18 – 2.12 (m, 1H), 2.11 – 2.07 (m, 1H), 1.91 (dd, *J* = 12.3, 6.3 Hz, 1H), 1.59 – 1.50 (m, 1H); $^{13}$C NMR (125 MHz, Acetone): δ 209.6, 154.8, 136.1, 132.3, 128.9, 112.3, 111.3, 108.3, 100.7, 74.3, 61.8, 55.8, 54.0, 48.9, 48.4, 38.6, 37.7, 29.2, 28.2, 25.1, 20.1; HRMS (m/z): $[M+H]^+$ calcd. for $C_{21}H_{27}N_2O_3$, 355.2021, found 355.2029.



**(2aS,6aR,14bR)-2a-Methyl-3,4,6,6a,8,9,14,14b-octahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (26c):** Off-white solid, 57 mg, 92% yield; mp: 236–238 °C; $R_f$ = 0.5 (silica gel, hexane/EtOAc 1:1); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.11 (t, *J* = 7.3 Hz, 1H), 4.17 – 4.05 (m, 2H), 3.89 (t, *J* = 10.6 Hz, 1H), 3.13 – 3.02 (m, 2H), 3.01 – 2.91 (m, 1H), 2.90 – 2.81 (m, 2H), 2.81 – 2.67 (m, 2H), 2.44 (d, *J* = 9.2 Hz, 1H), 2.19 (d, *J* = 11.9 Hz, 2H), 1.80 – 1.71 (m, 1H), 1.49 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 211.7, 136.4, 131.0, 127.1, 121.9, 119.8, 118.3, 111.0, 109.7, 72.2, 64.6, 64.5, 49.8, 49.3, 36.7, 36.6, 35.8, 22.7, 22.1. HRMS (m/z): $[M+H]^+$ calcd. for $C_{19}H_{23}N_2O_2$, 311.1759, found 311.1755.

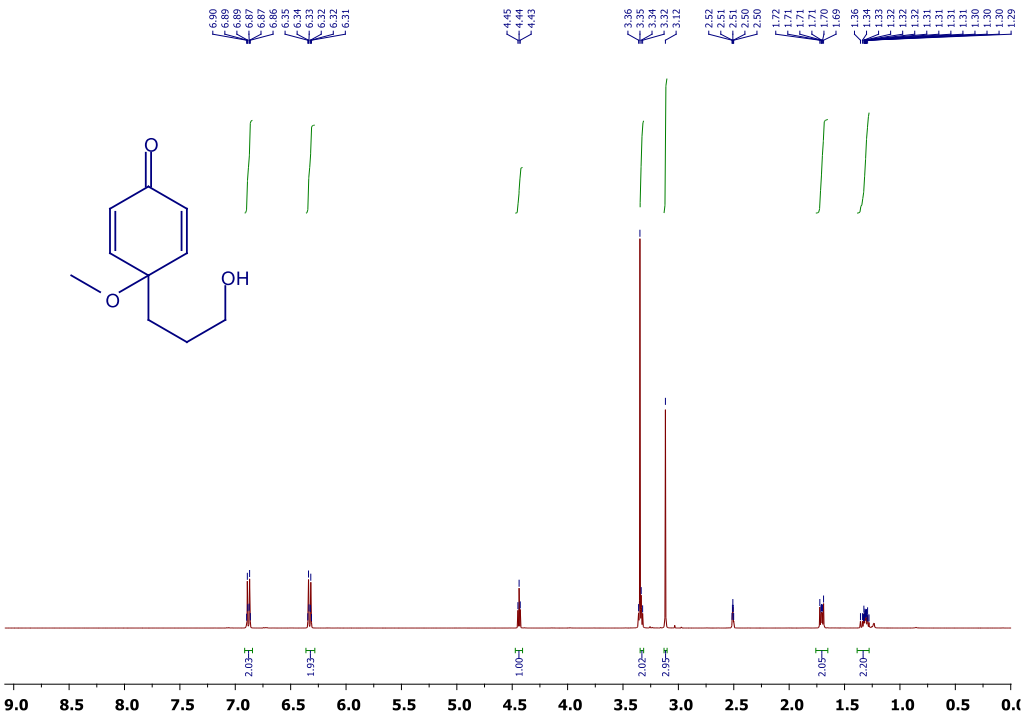



**Methyl (2aR,6aR,8S,14bS)-2a-methoxy-5-oxo-1,2,2a,3,4,5,6,6a,8,9,14,14b-dodecahydroindolo[2',3':3,4]pyrido[1,2-a]quinoline-8-carboxylate (26d):** Off-white solid, 64 mg, 85% yield; mp: 114–116 °C; $R_f$ = 0.4 (silica gel, hexane/EtOAc 1:2); $[\alpha]_D$ = -92.8 (0.0018 M in acetone); $^1$H NMR (500 MHz, Acetone) δ: 10.03 (s, 1H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 10.0 Hz, 1H), 7.07 (t, *J* = 6.0 Hz, 1H), 7.00 (t, *J* = 6.0 Hz, 1H), 4.16 – 4.08 (m, 1H), 3.78 (s, 3H), 3.69 (dd, *J* = 10.8, 3.8 Hz, 1H), 3.47 (dd, *J* = 10.8, 5.0 Hz, 1H), 3.25 (s, 3H), 3.08 – 2.98 (m, 1H), 2.96 – 2.78 (m, 2H), 2.58 – 2.43 (m, 2H), 2.37 – 2.28 (m, 1H), 2.27 – 2.16 (m, 2H), 2.17 – 2.09 (m, 1H), 2.04 – 1.95 (m, 1H), 1.90 – 1.81 (m, 1H), 1.68 – 1.59 (m, 1H); $^{13}$C NMR (125 MHz, Acetone): δ 208.6, 173.6, 137.6, 137.4, 135.4, 127.8, 121.7, 119.7, 118.4, 111.8, 106.2, 73.9, 62.7, 58.7, 52.2, 48.2, 38.1, 37.1, 30.6, 28.5, 26.6, 26.5; HRMS (m/z): $[M+H]^+$ calcd. for $C_{22}H_{27}N_2O_4$, 383.1970, found 383.1981.

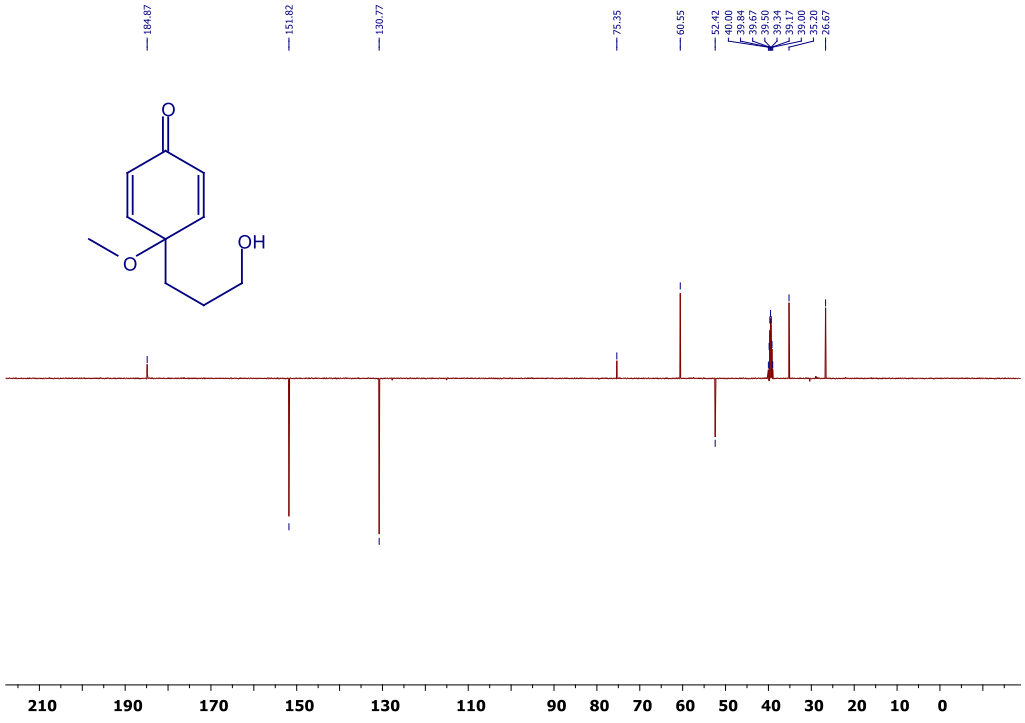



**Methyl (2aS,6aS,8R,14bR)-2a-methoxy-5-oxo-1,2,2a,3,4,5,6,6a,8,9,14,14b-dodecahydroindolo[2',3':3,4]pyrido[1,2-a]quinoline-8-carboxylate (26e):** Off-white solid, 66 mg, 87% yield; mp: 113–16 °C; $R_f$ = 0.4 (silica gel, hexane/EtOAc 1:2); $[\alpha]_D$ = +95.2 (0.0005 M

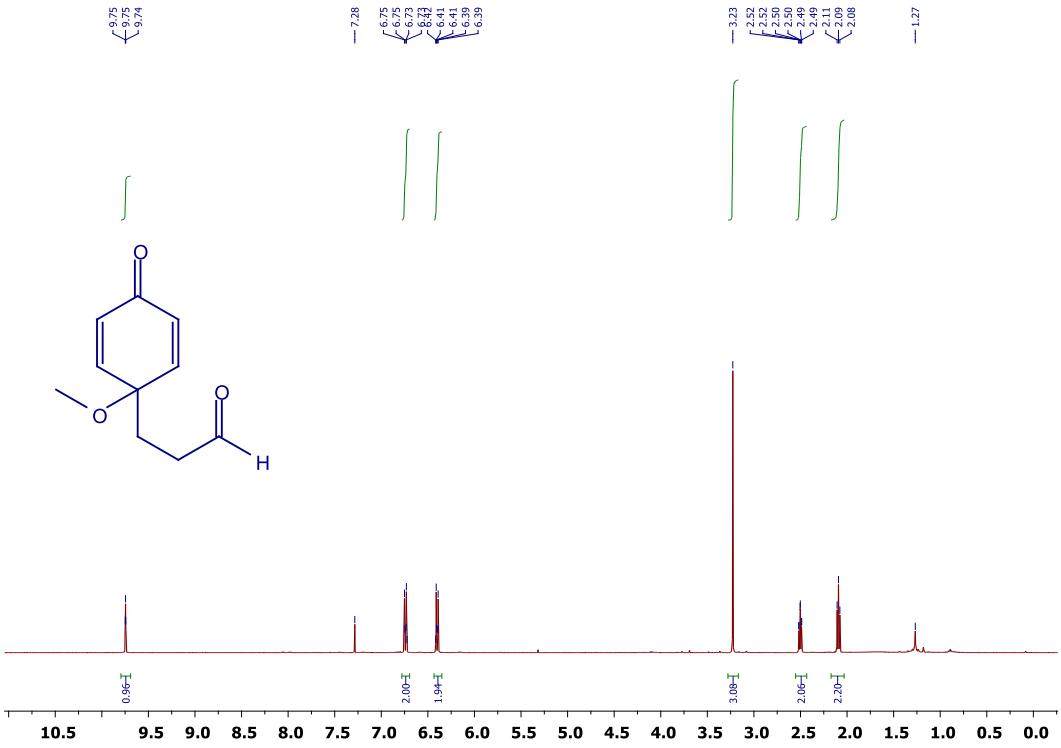
in acetone); $^{1}$H NMR (500 MHz, Acetone): δ 9.99 (s, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.00 (t, *J* = 7.1 Hz, 1H), 4.17 – 4.07 (m, 1H), 3.79 (s, 3H), 3.69 (dd, *J* = 10.6, 3.2 Hz, 1H), 3.47 (dd, *J* = 10.6, 4.8 Hz, 1H), 3.25 (s, 3H), 3.07 – 2.99 (m, 1H), 2.94 – 2.88 (m, 1H), 2.85 – 2.80 (m, 1H), 2.59 – 2.43 (m, 2H), 2.38 – 2.27 (m, 1H), 2.27 – 2.18 (m, 2H), 2.17 – 2.09 (m, 1H), 2.05 – 1.96 (m, 1H), 1.90 – 1.80 (m, 1H), 1.68 – 1.60 (m, 1H); $^{13}$C NMR (125 MHz, Acetone): δ 208.6, 173.6, 137.6, 135.4, 127.8, 121.7, 119.7, 118.4, 111.8, 106.2, 73.9, 62.7, 58.7, 52.3, 52.2, 48.2, 38.1, 37.1, 30.6, 28.5, 26.6, 26.5; HRMS (m/z): $[M+H]^+$ calcd. for $C_{22}H_{27}N_2O_4$, 383.1970, found 383.1964.



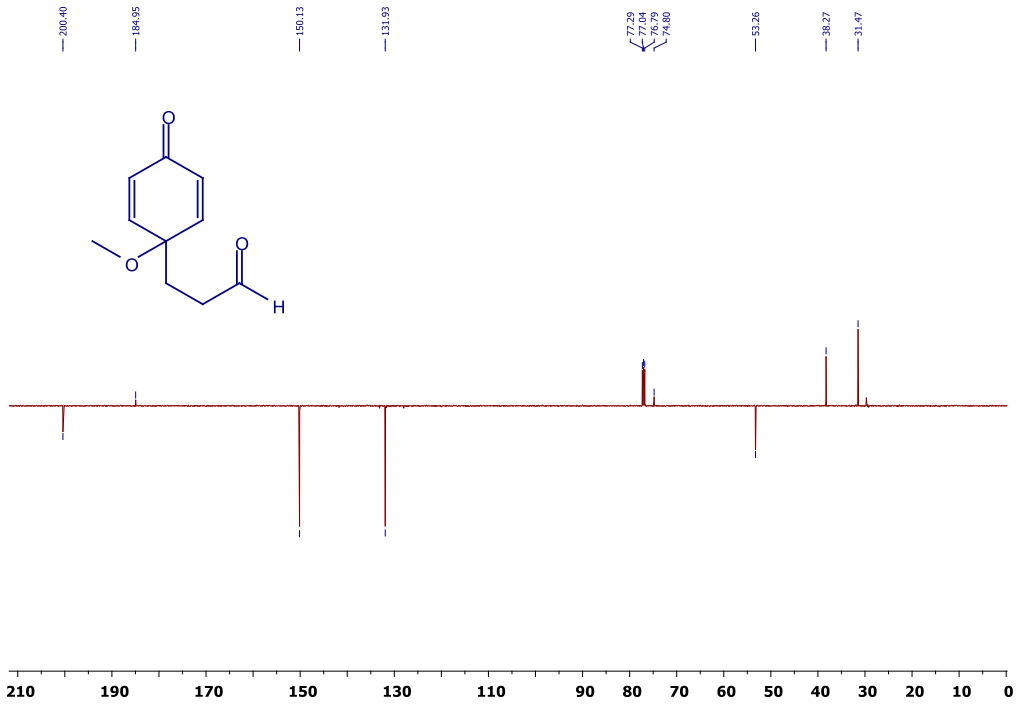

**Supplementary Figure 8** $^{1}$H NMR (500 MHz, DMSO-$d_6$) spectrum of 4-(3-hydroxypropyl)-4-methoxycyclohexa-2,5-dien-1-one (**1c**)



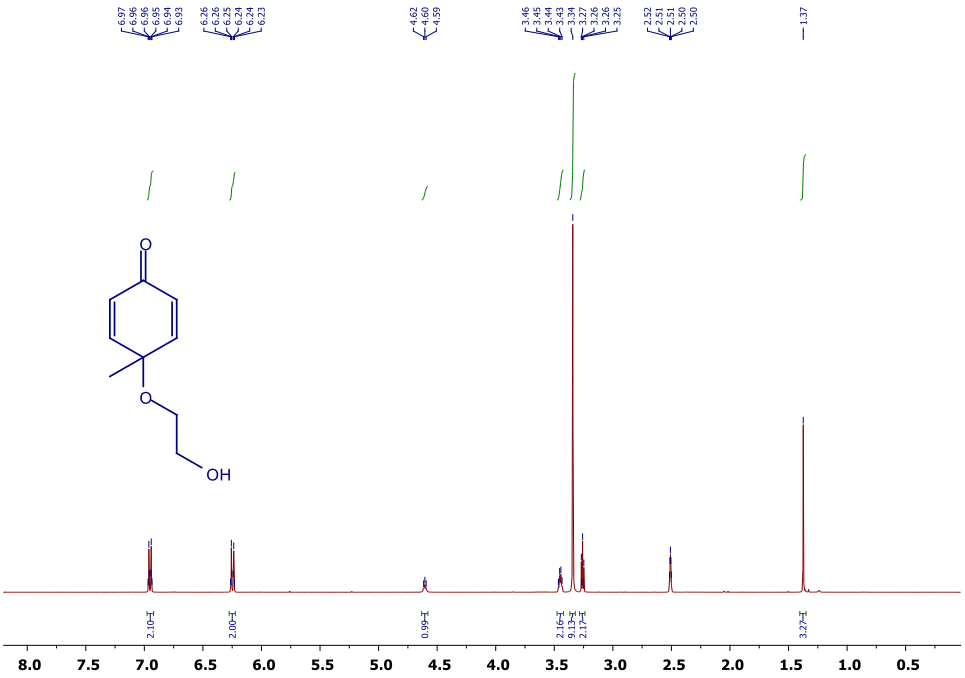

**Supplementary Figure 9** APT NMR (125 MHz, DMSO-$d_6$) spectrum of 4-(3-hydroxypropyl)-4-methoxycyclohexa-2,5-dien-1-one (**1c**)



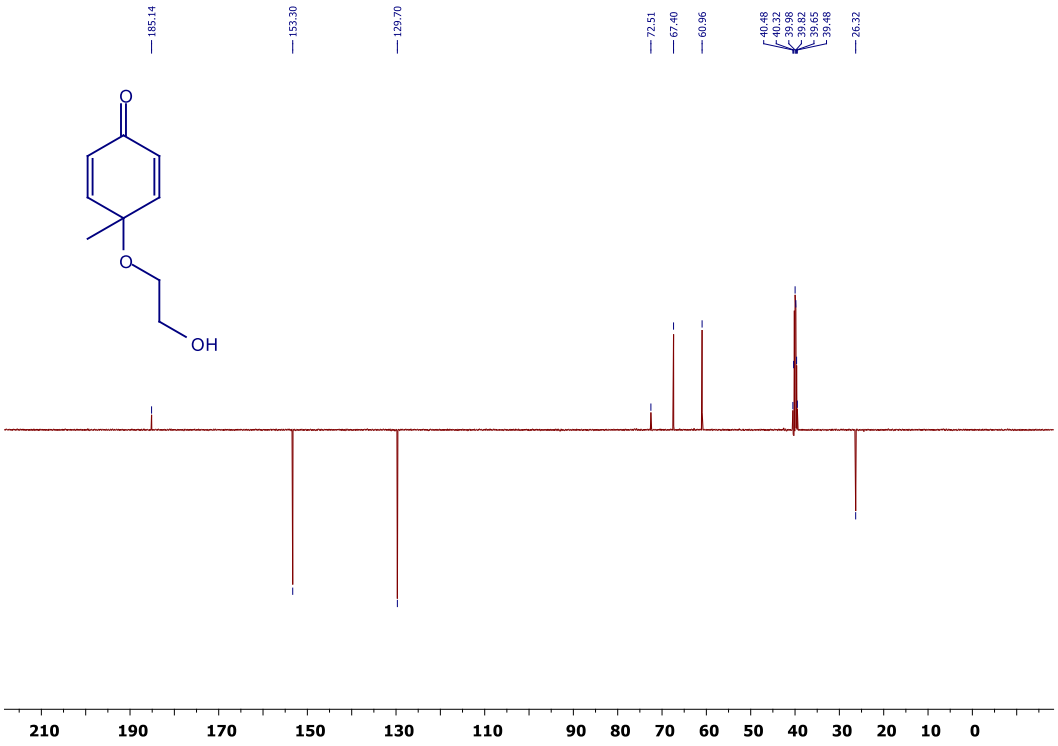

**Supplementary Figure 10** $^{1}$H NMR (500 MHz, $CDCl_3$) spectrum of 3-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)propanal (**2a**)



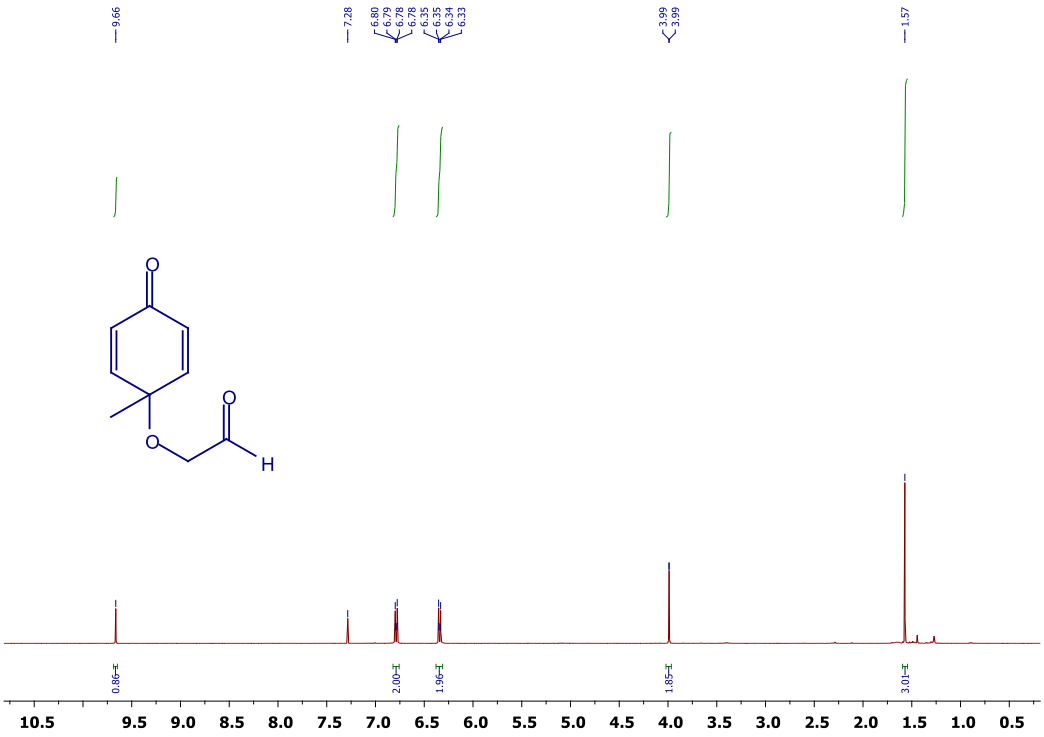

**Supplementary Figure 11** APT NMR (125 MHz, $CDCl_3$) spectrum of 3-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)propanal (**2a**)



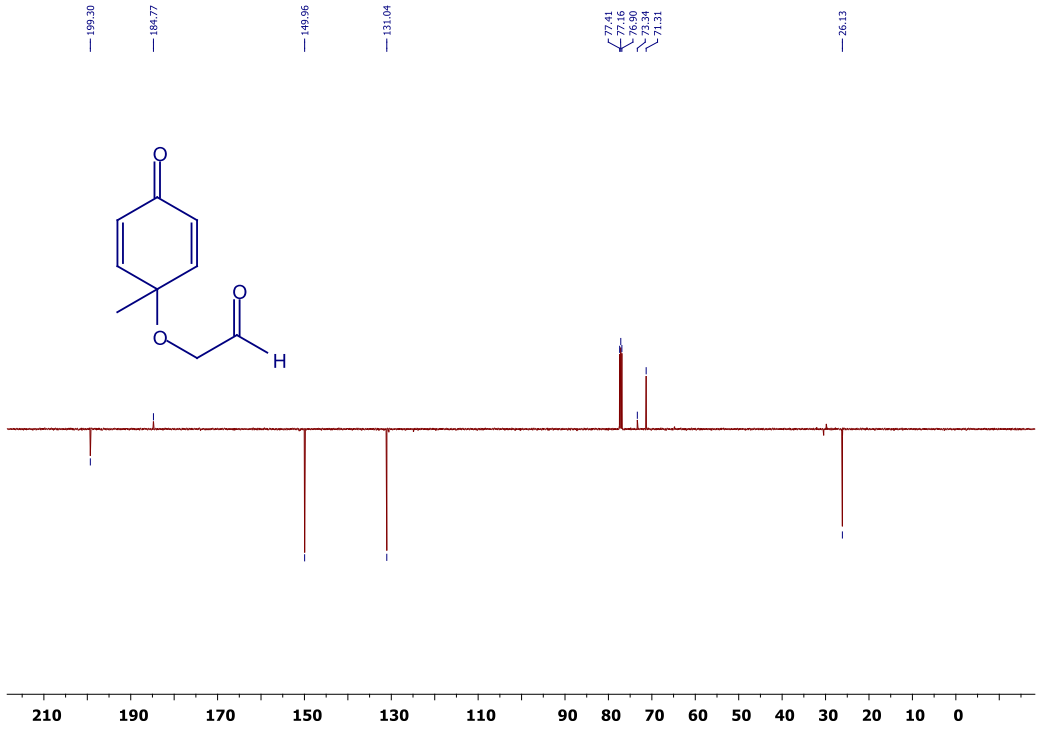

**Supplementary Figure 12** $^{1}$H NMR (500 MHz, DMSO-$d_6$) spectrum of 4-(2-hydroxyethoxy)-4-methylcyclohexa-2,5-dien-1-one (**1d**)



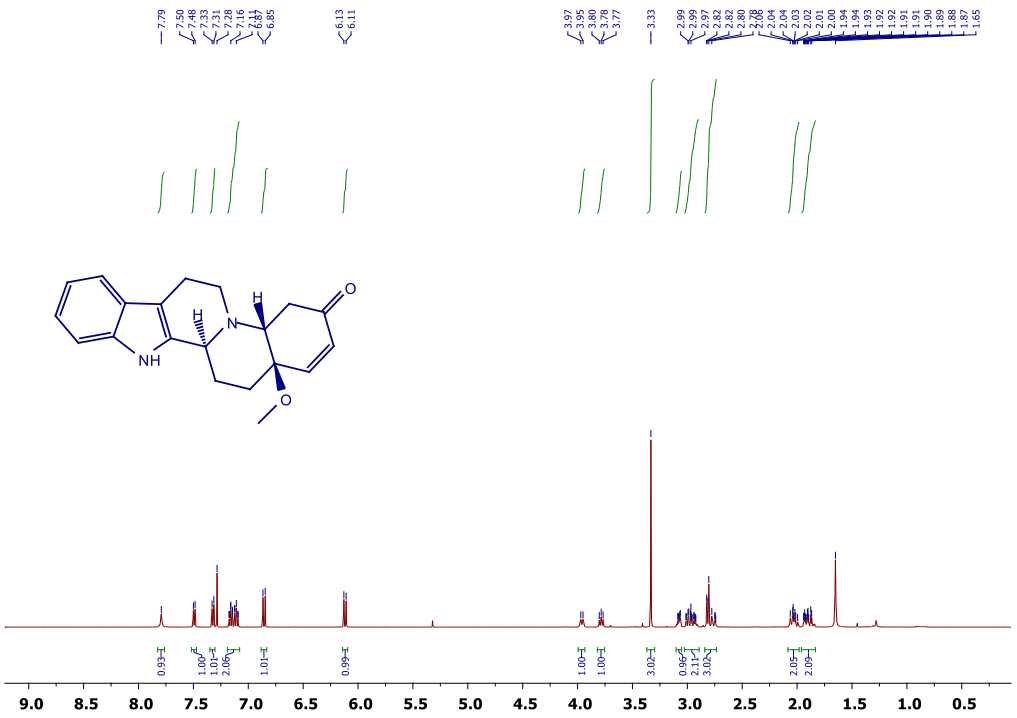

**Supplementary Figure 13** APT NMR (125 MHz, DMSO-$d_6$) spectrum of 4-(2-hydroxyethoxy)-4-methylcyclohexa-2,5-dien-1-one (**1d**)



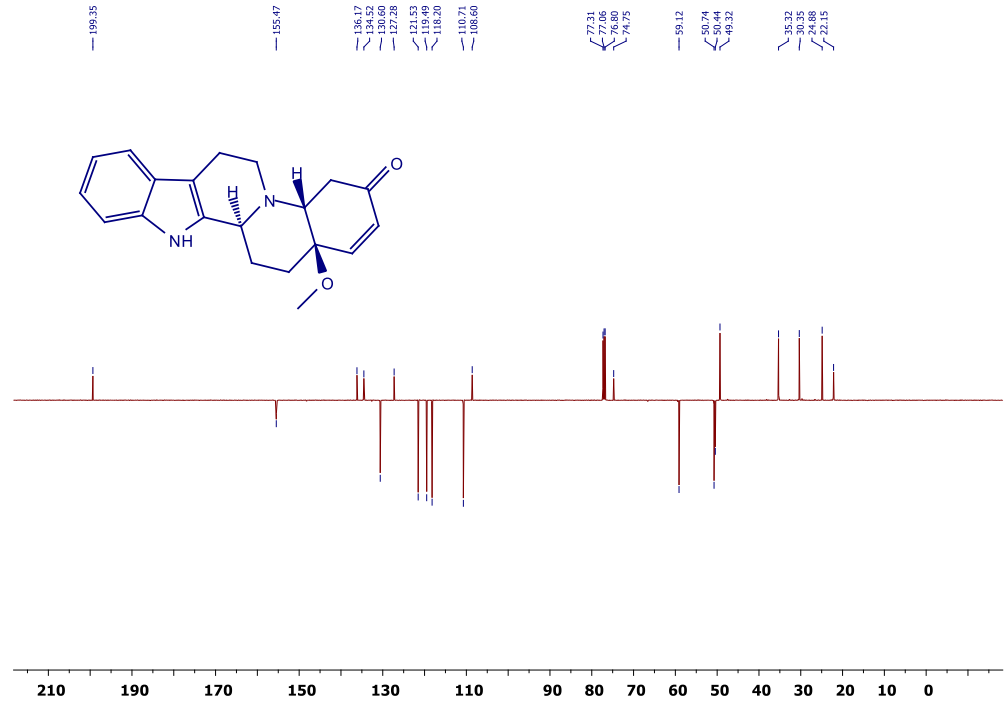

**Supplementary Figure 14** $^{1}H$ NMR (500 MHz, $CDCl_3$) spectrum of 2-((1-methyl-4-oxocyclohexa-2,5-dien-1-yl)oxy)acetaldehyde (**2b**)



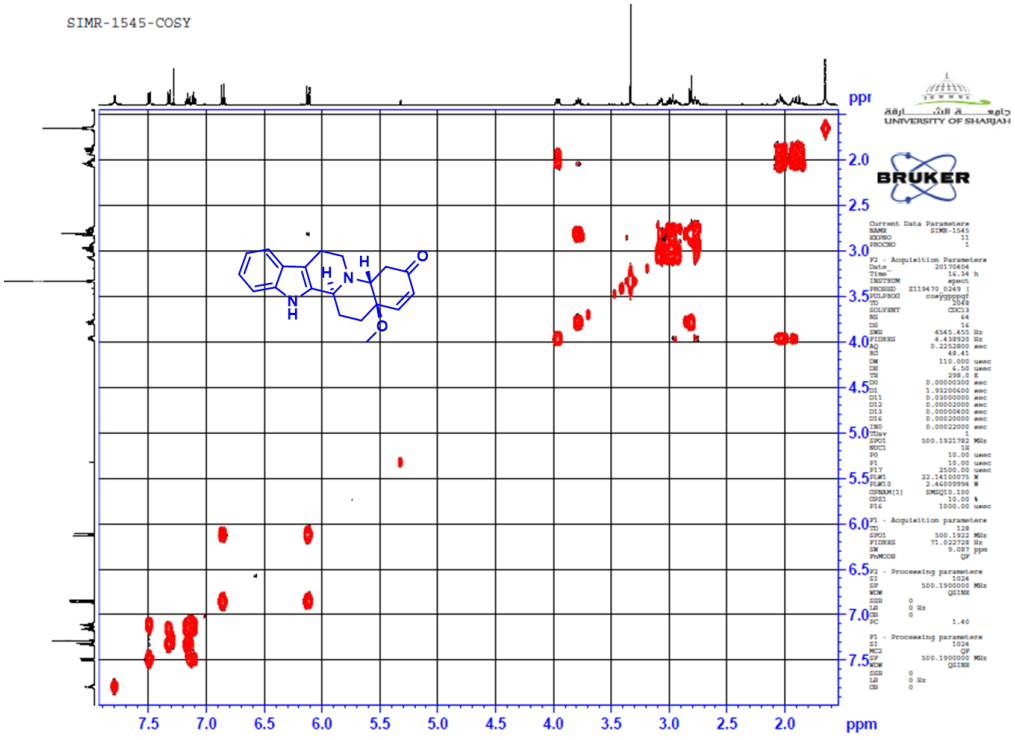

**Supplementary Figure 15** APT NMR (125 MHz, $CDCl_3$) spectrum of 2-((1-methyl-4-oxocyclohexa-2,5-dien-1-yl)oxy)acetaldehyde (**2b**)



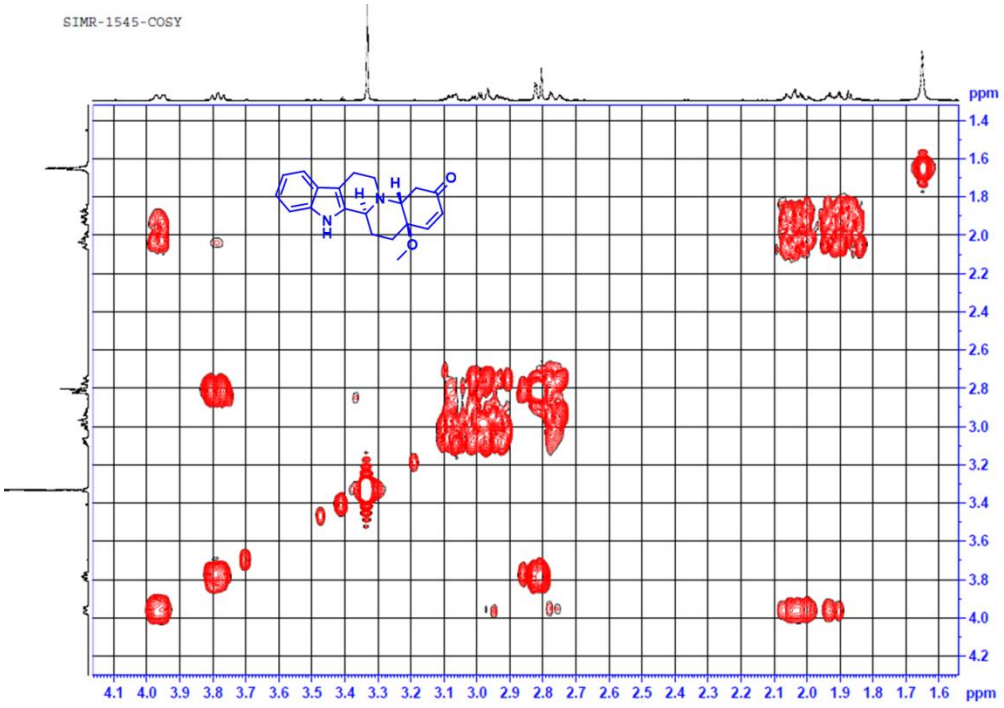
**Supplementary Figure 16** $^{1}$H NMR (500 MHz, $CDCl_3$) spectrum of (2aR,6aR,14bS)-2a-methoxy-2,2a,6,6a,8,9,14,14b-octahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5(1H)-one (**5a**)



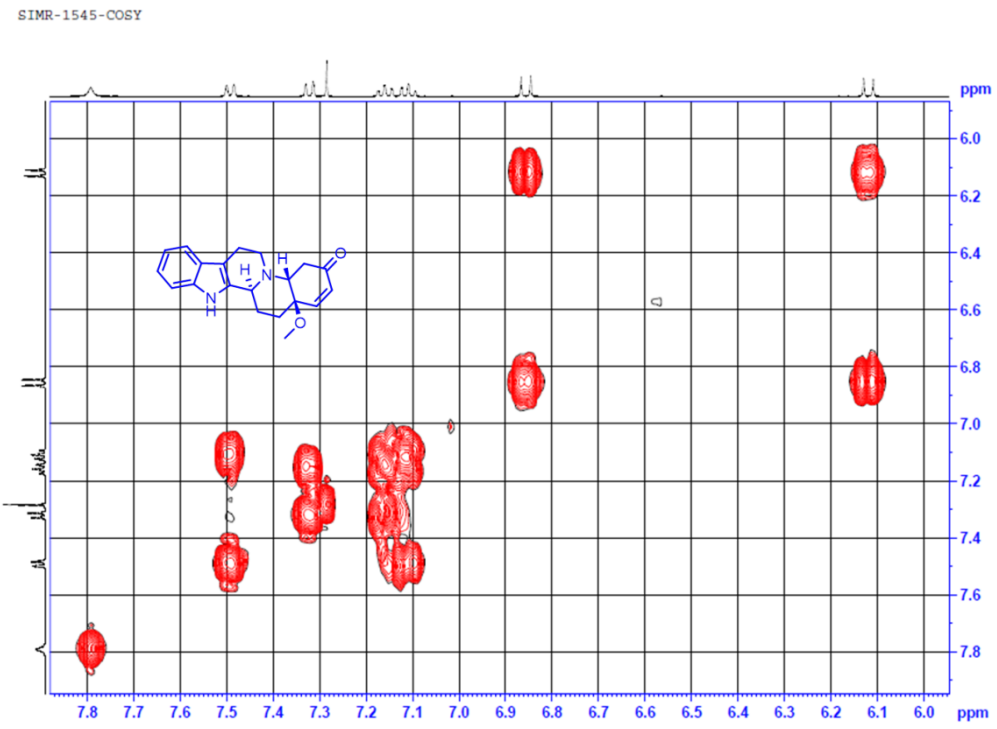
**Supplementary Figure 17** APT NMR (125 MHz, $CDCl_3$) spectrum of (2aR,6aR,14bS)-2a-methoxy-2,2a,6,6a,8,9,14,14b-octahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5(1H)-one (**5a**)



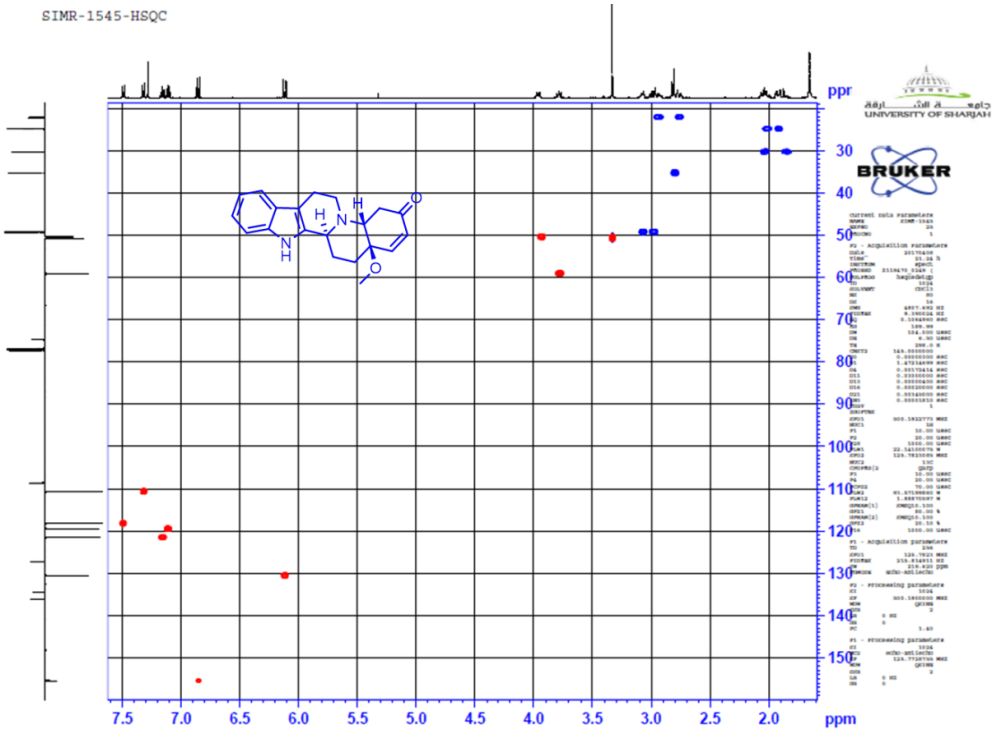

**Supplementary Figure 18** COSY (500 MHz, $CDCl_3$) spectrum of (2aR,6aR,14bS)-2a-methoxy-2,2a,6,6a,8,9,14,14b-octahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5(1H)-one (**5a**)



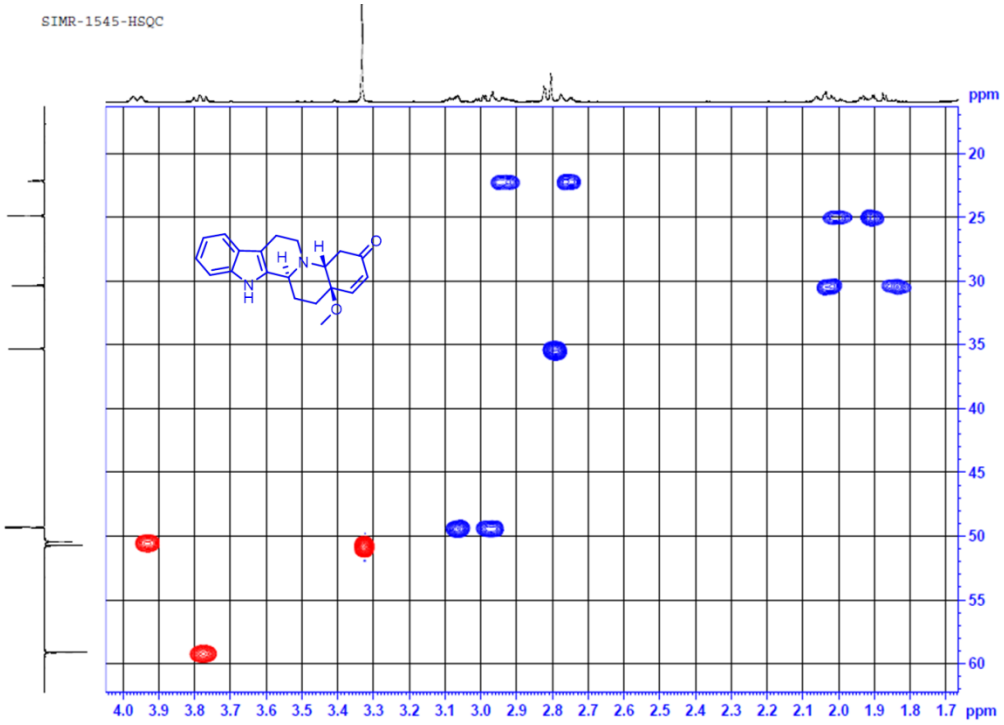

**Supplementary Figure 19** COSY (Expansion) spectrum of (2aR,6aR,14bS)-2a-methoxy-2,2a,6,6a,8,9,14,14b-octahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5(1H)-one (**5a**)



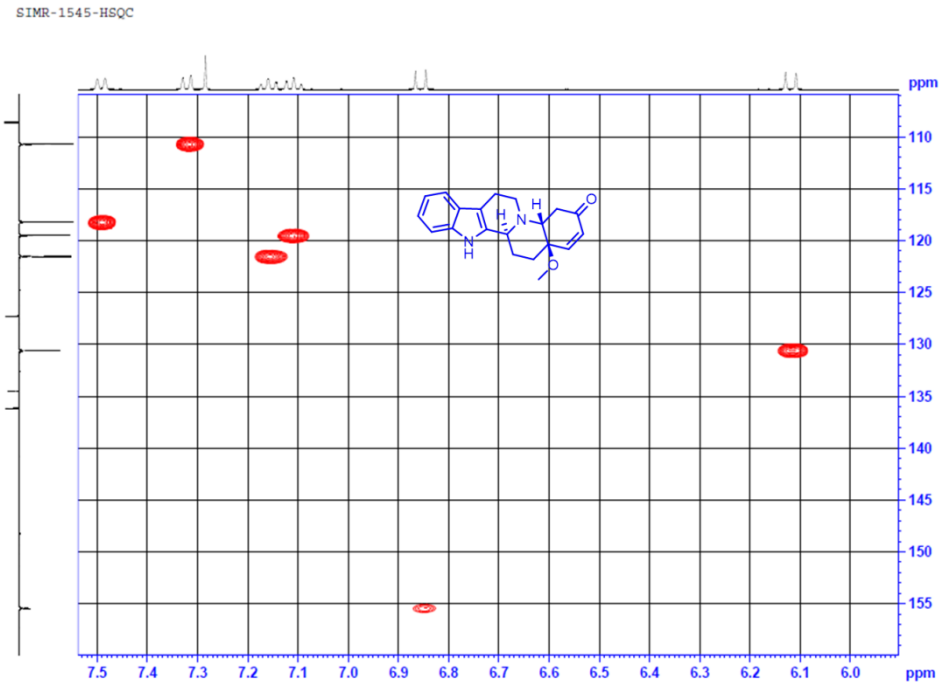

**Supplementary Figure 20** COSY (Expansion) spectrum of (2aR,6aR,14bS)-2a-methoxy-2,2a,6,6a,8,9,14,14b-octahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5(1H)-one (**5a**)



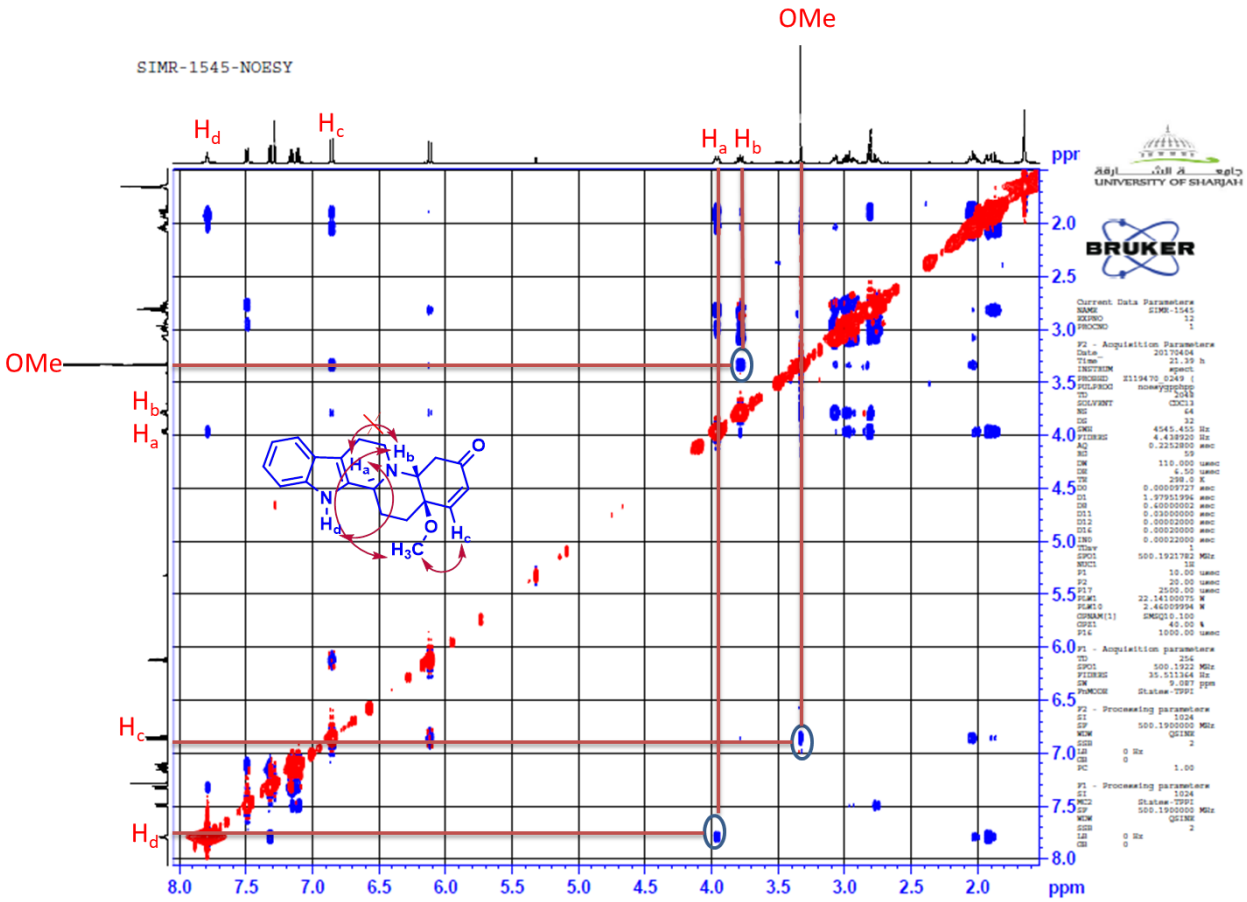

**Supplementary Figure 21** HSQC (500 MHz, $CDCl_3$) spectrum of (2aR,6aR,14bS)-2a-methoxy-2,2a,6,6a,8,9,14,14b-octahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5(1H)-one (**5a**)



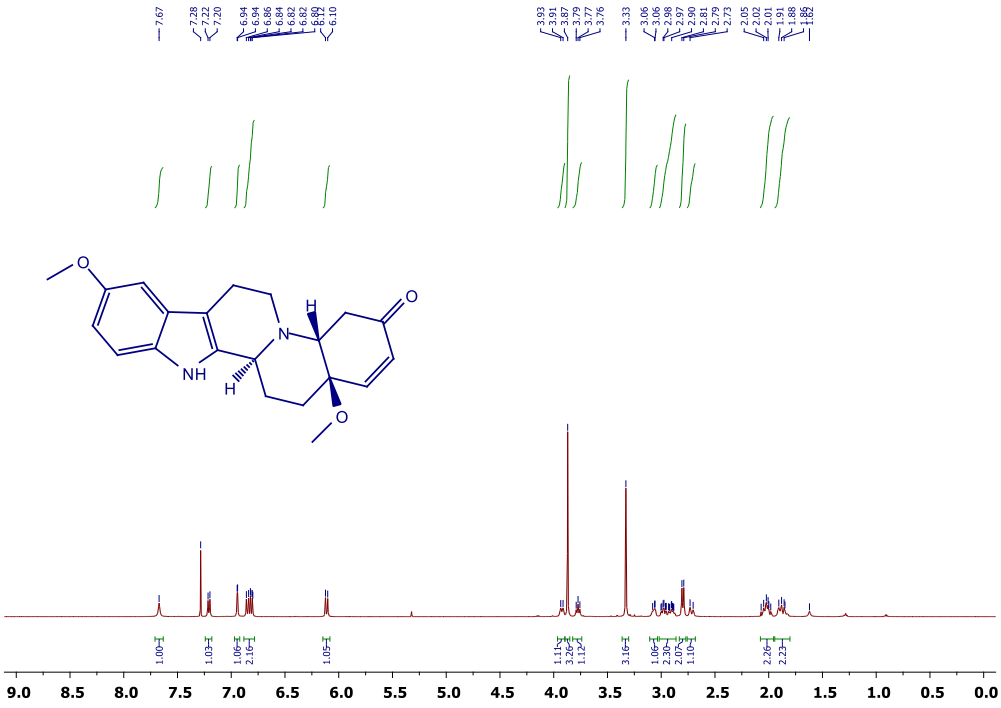

**Supplementary Figure 22** HSQC (Expansion) spectrum of (2aR,6aR,14bS)-2a-methoxy-2,2a,6,6a,8,9,14,14b-octahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5(1H)-one (**5a**)



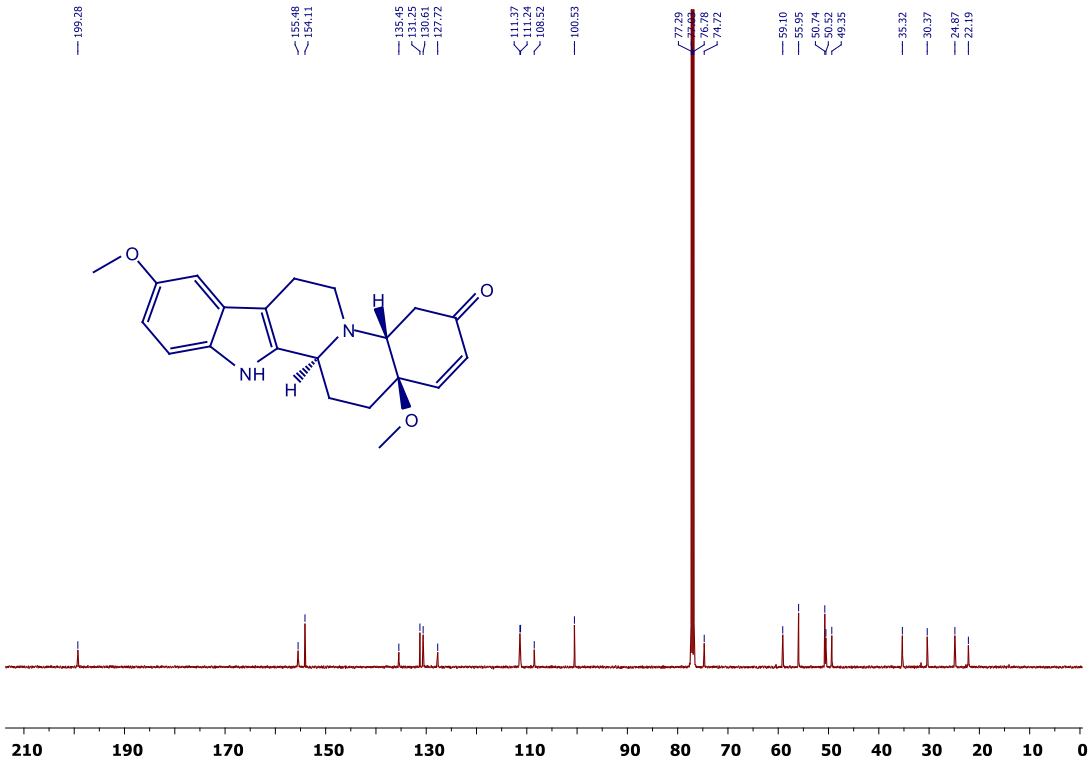

**Supplementary Figure 23** HSQC (Expansion) spectrum of (2aR,6aR,14bS)-2a-methoxy-2,2a,6,6a,8,9,14,14b-octahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5(1H)-one (**5a**)



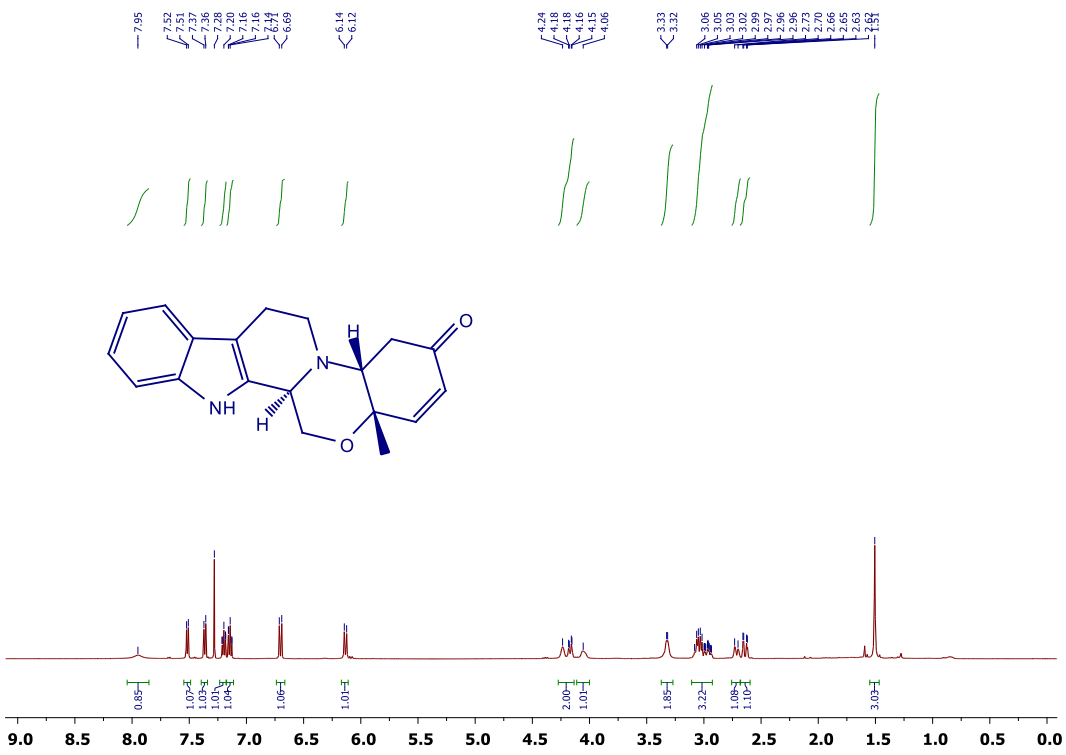

**Supplementary Figure 24** NOESY (500 MHz, $CDCl_3$) spectrum of (2aR,6aR,14bS)-2a-methoxy-2,2a,6,6a,8,9,14,14b-octahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5(1H)-one (**5a**)



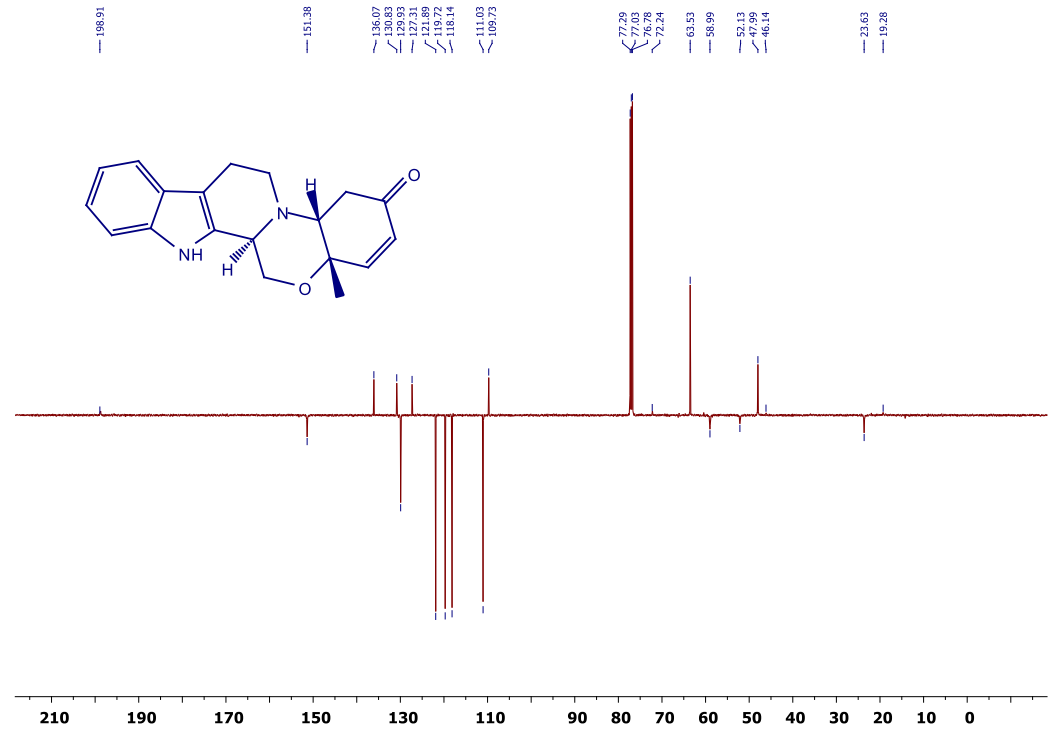
**Supplementary Figure 25** $^{1}$H NMR (500 MHz, $CDCl_3$) spectrum of (2aR,6aR,14bS)-2a,11-dimethoxy-2,2a,6,6a,8,9,14,14b-octahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5(1H)-one (**5b**)



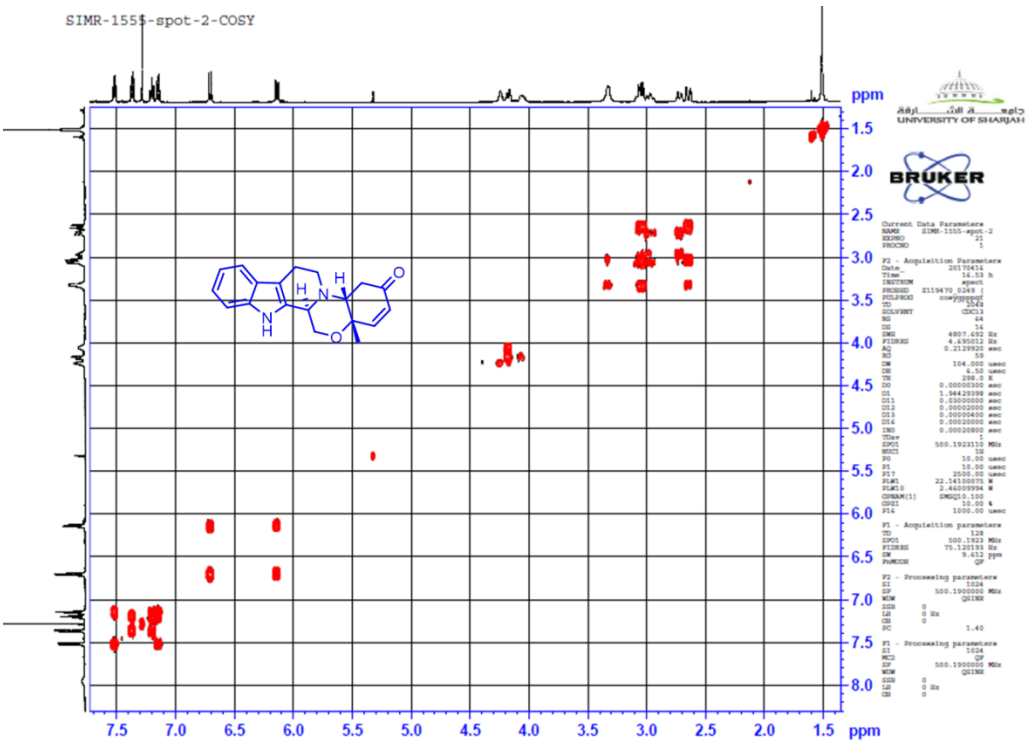
**Supplementary Figure 26** $^{13}$C NMR (125 MHz, $CDCl_3$) spectrum of (2aR,6aR,14bS)-2a,11-dimethoxy-2,2a,6,6a,8,9,14,14b-octahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5(1H)-one (**5b**)



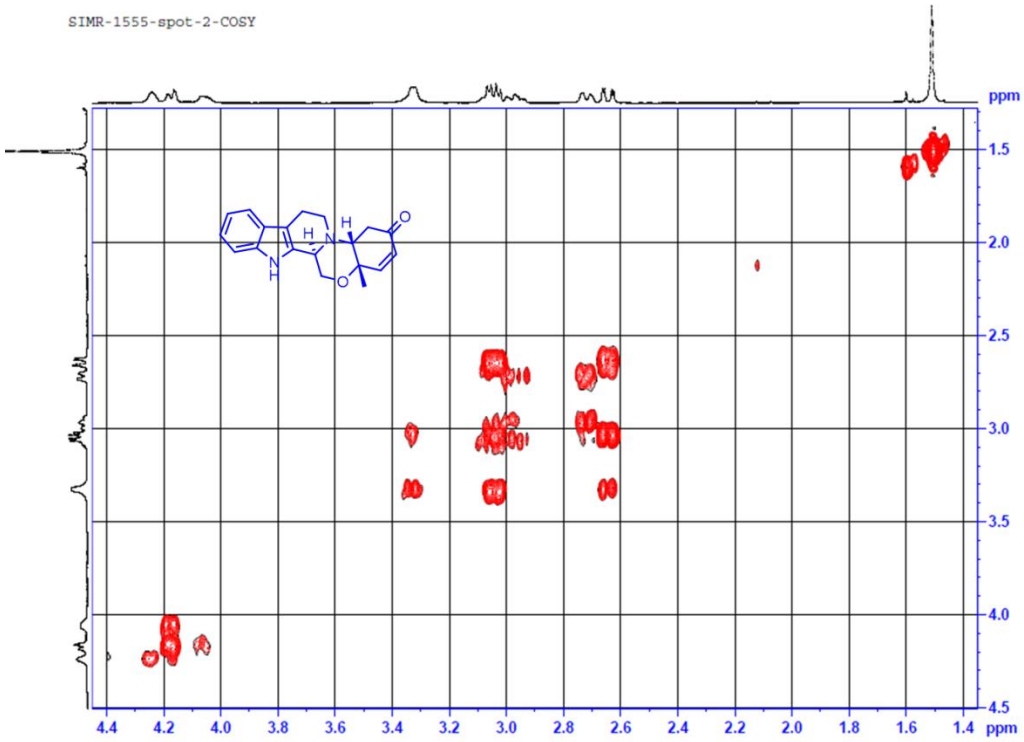
**Supplementary Figure 27** $^{1}$H NMR (500 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bR)-2a-methyl-6,6a,8,9,14,14b-hexahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (**5c**)



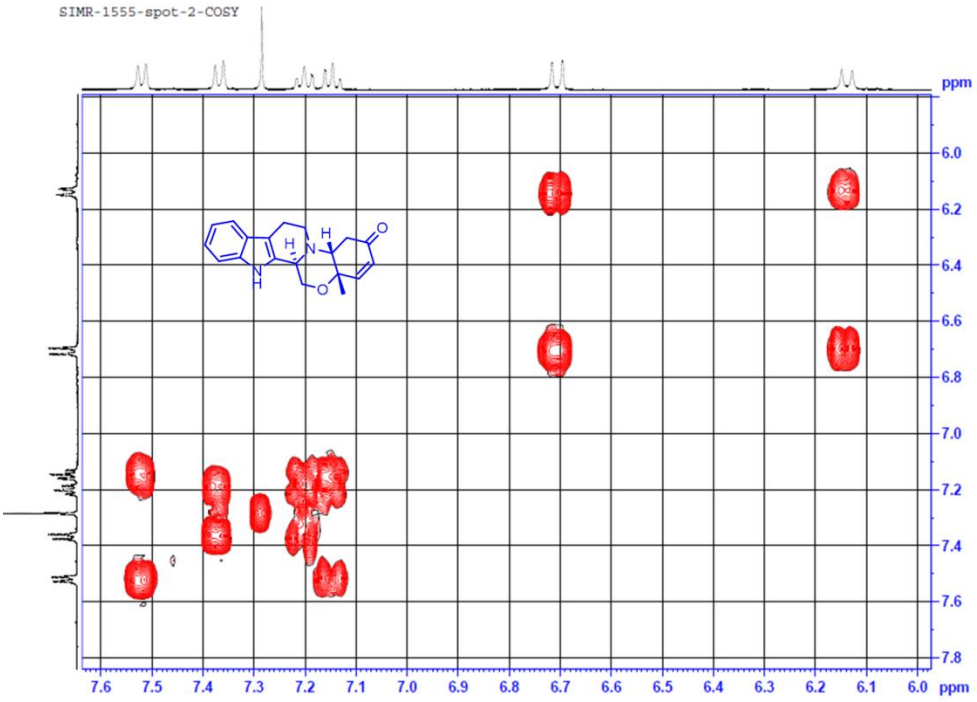
**Supplementary Figure 28** APT NMR (125 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bR)-2a-methyl-6,6a,8,9,14,14b-hexahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (**5c**)



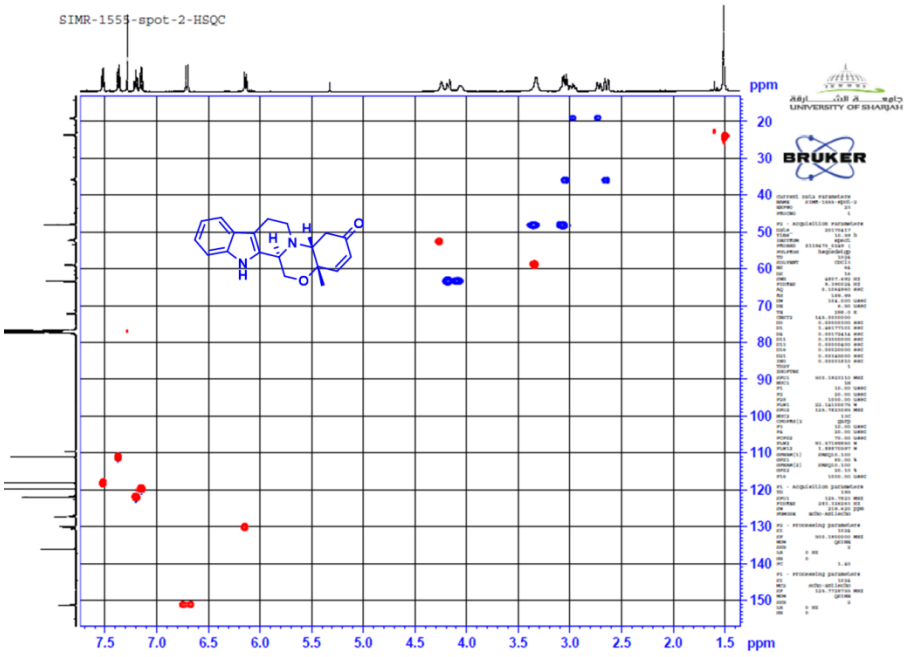

**Supplementary Figure 29** COSY (500 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bR)-2a-methyl-6,6a,8,9,14,14b-hexahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (**5c**)



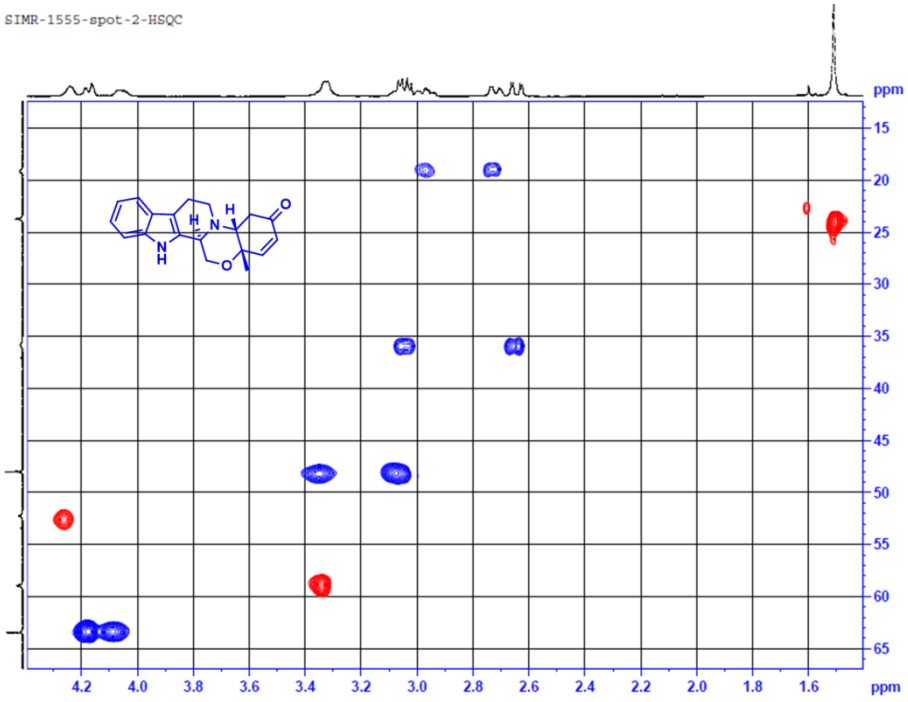

**Supplementary Figure 30** COSY (Expansion) spectrum of (2aS,6aR,14bR)-2a-methyl-6,6a,8,9,14,14b-hexahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (**5c**)



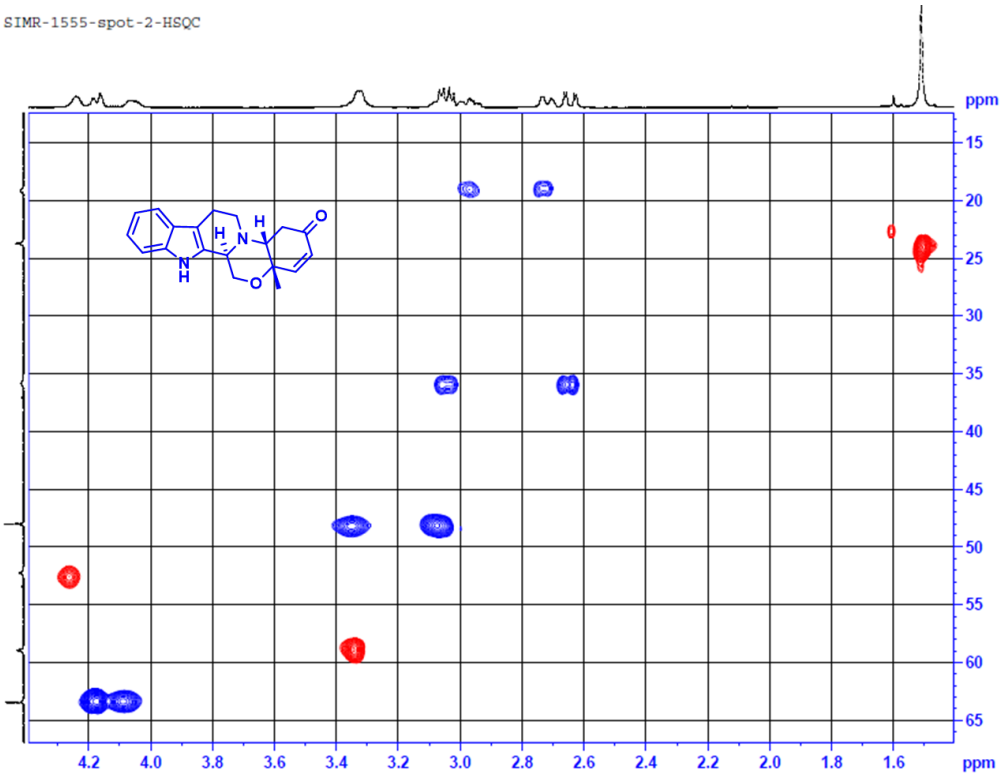

**Supplementary Figure 31** COSY (Expansion) spectrum of (2aS,6aR,14bR)-2a-methyl-6,6a,8,9,14,14b-hexahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (**5c**)



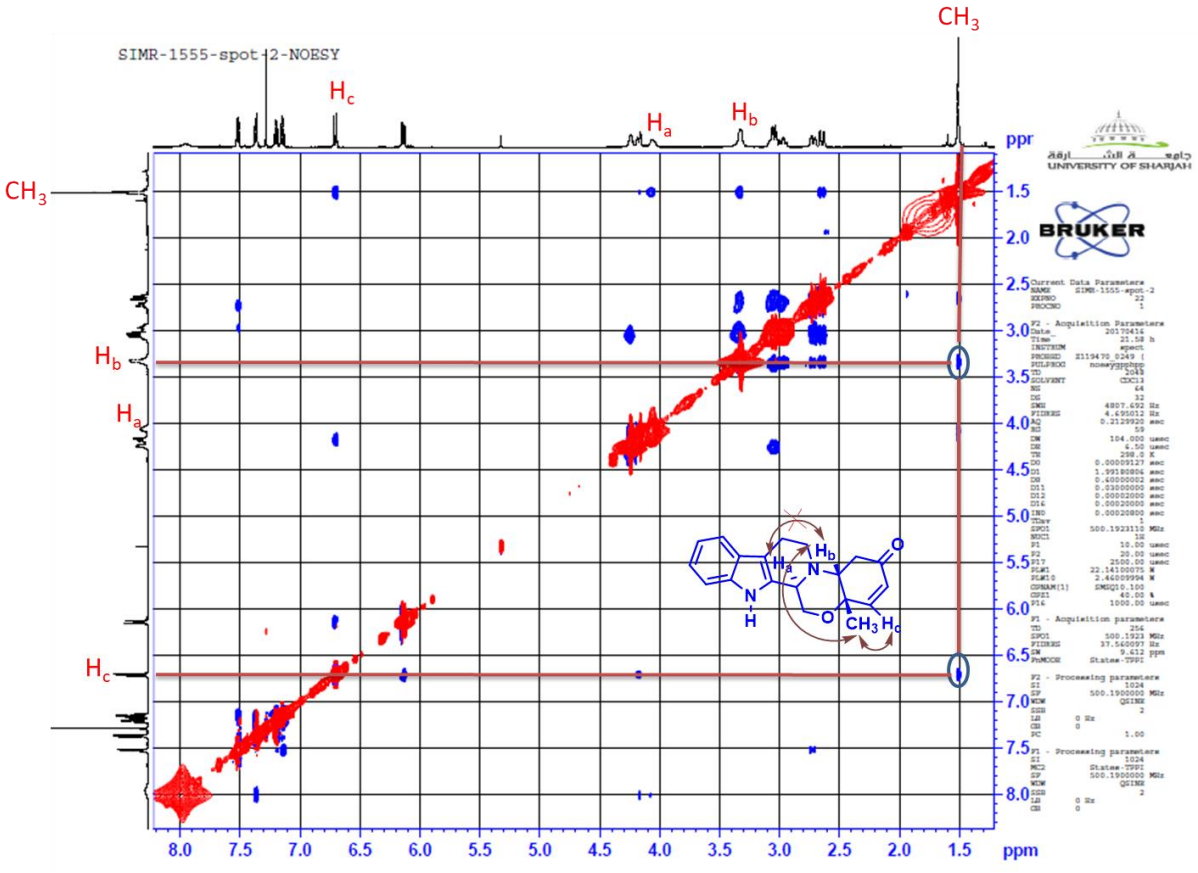

**Supplementary Figure 32** HSQC (500 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bR)-2a-methyl-6,6a,8,9,14,14b-hexahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (**5c**)



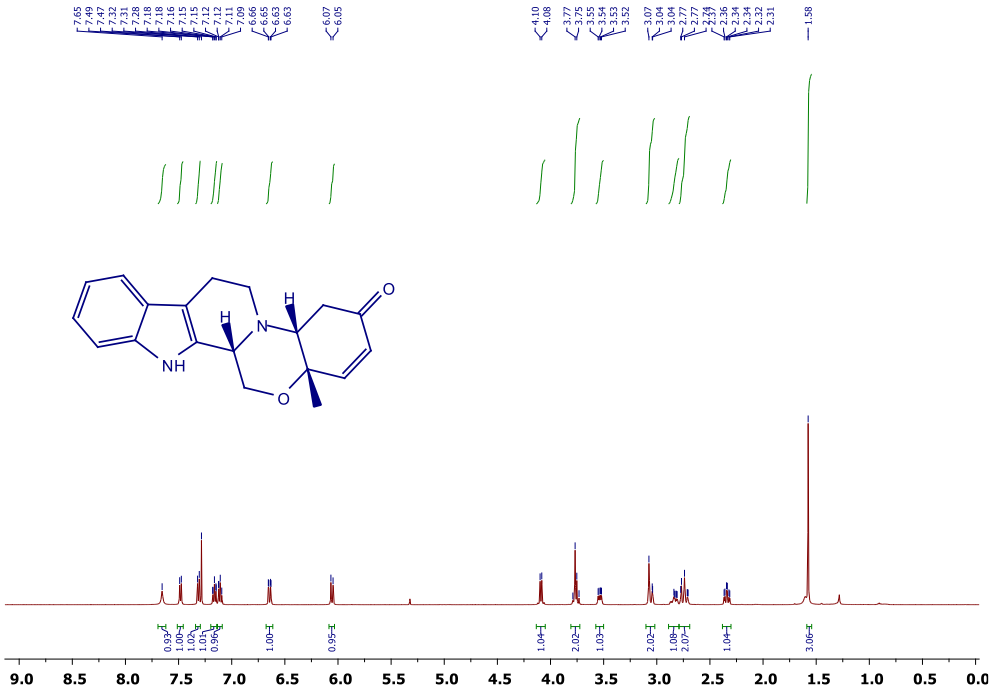

**Supplementary Figure 33** HSQC (Expansion) spectrum of (2aS,6aR,14bR)-2a-methyl-6,6a,8,9,14,14b-hexahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (**5c**)



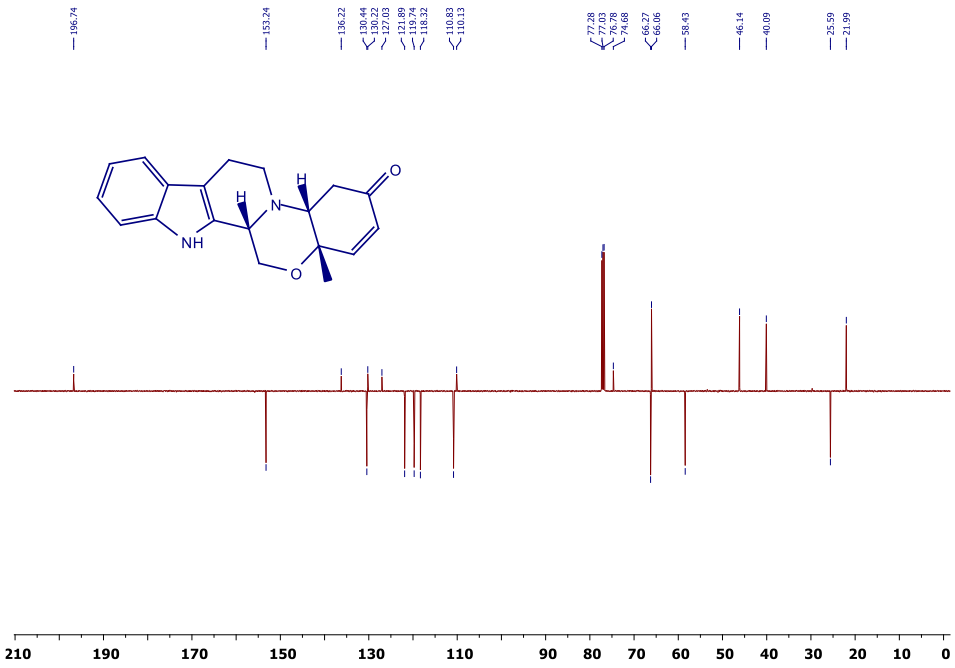

**Supplementary Figure 34** HSQC (Expansion) spectrum of (2aS,6aR,14bR)-2a-methyl-6,6a,8,9,14,14b-hexahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (**5c**)



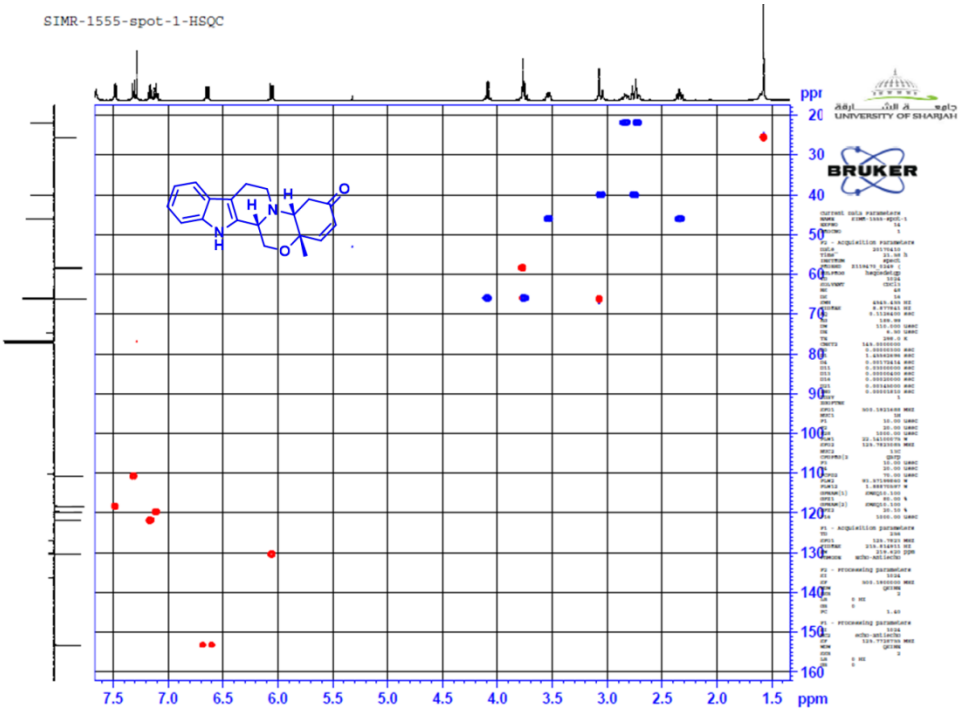

**Supplementary Figure 35** NOESY (500 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bR)-2a-methyl-6,6a,8,9,14,14b-hexahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (**5c**)



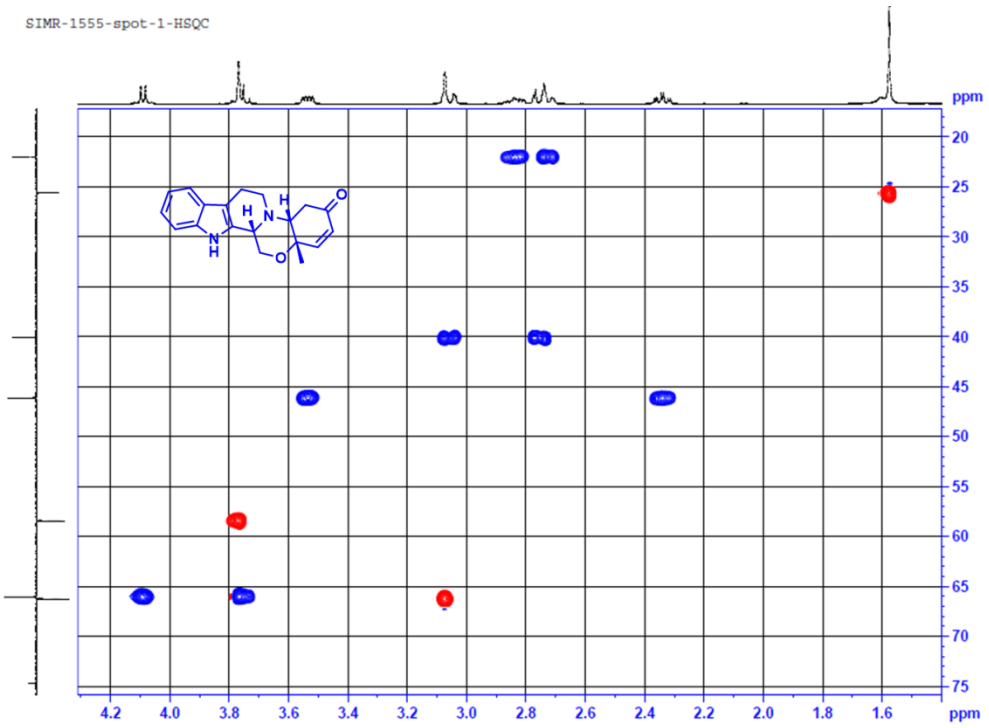
**Supplementary Figure 36** $^{1}$H NMR (500 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bS)-2a-methyl-6,6a,8,9,14,14b-hexahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (**6c**)



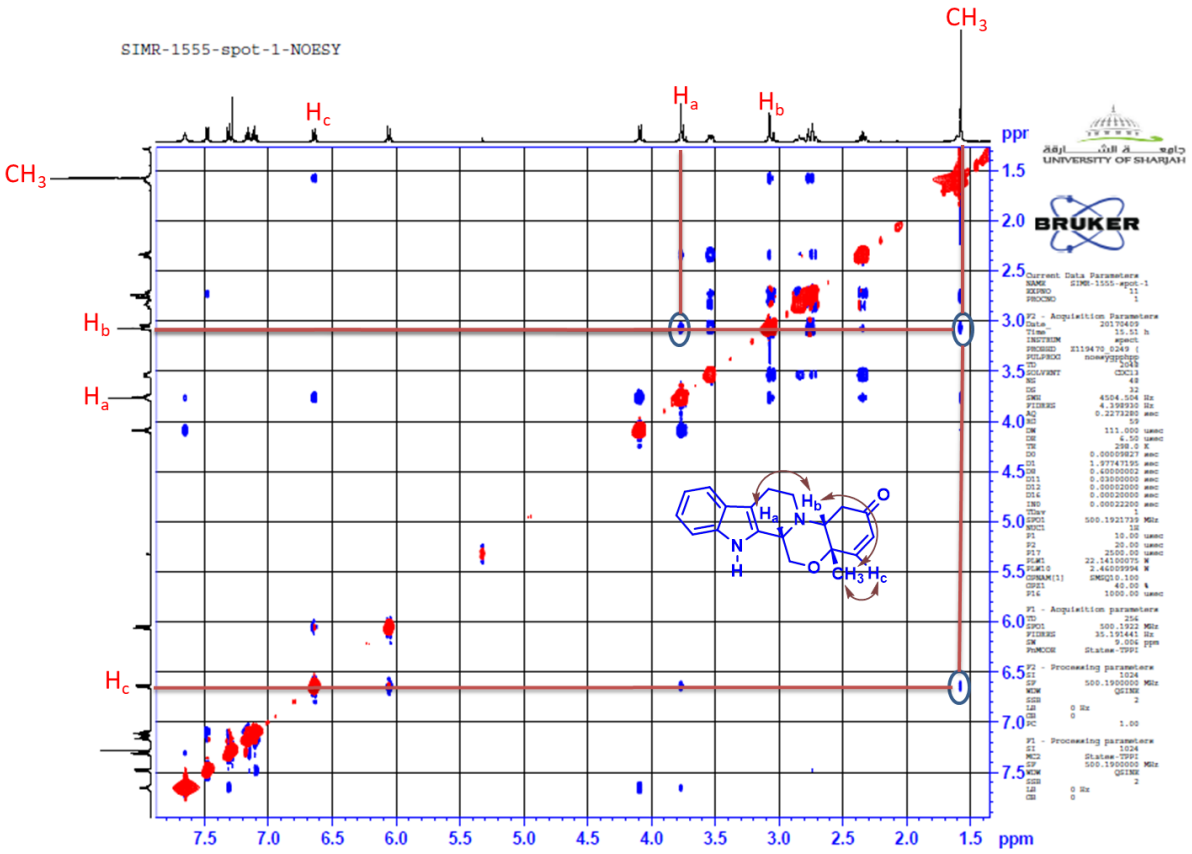
**Supplementary Figure 37** APT NMR (125 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bS)-2a-methyl-6,6a,8,9,14,14b-hexahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (**6c**)



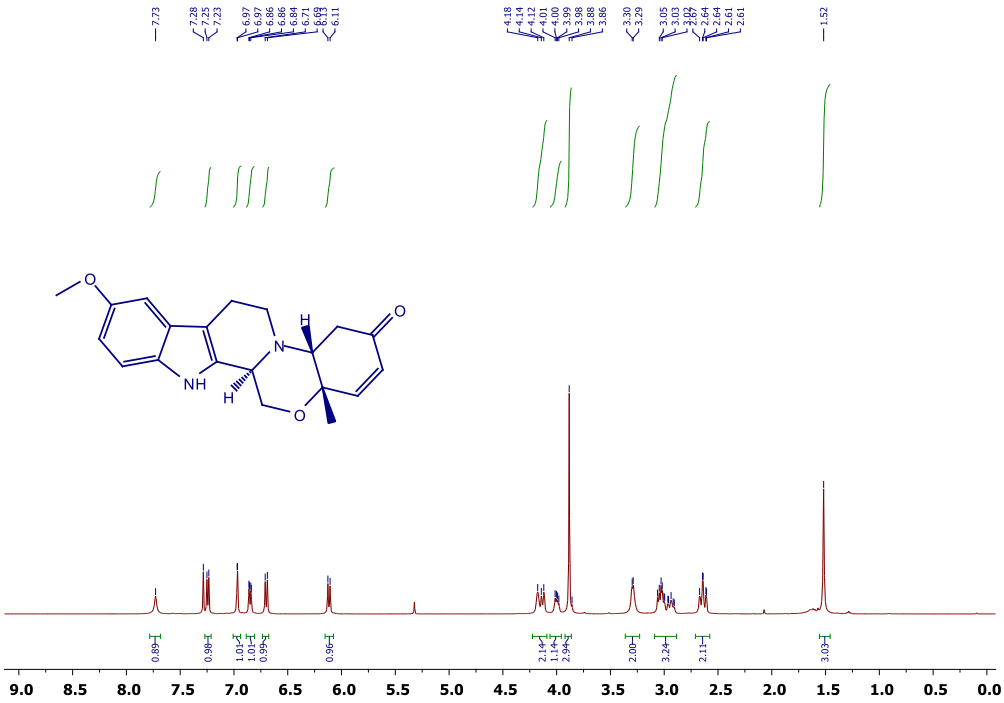

**Supplementary Figure 38** HSQC (500 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bS)-2a-methyl-6,6a,8,9,14,14b-hexahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (**6c**)



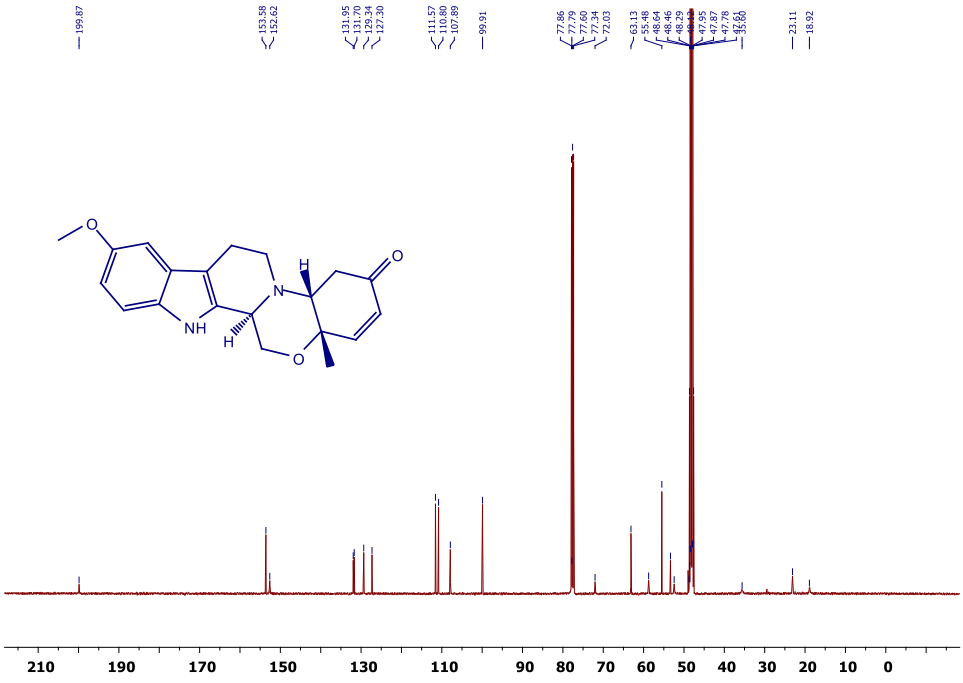

**Supplementary Figure 39** HSQC (Expansion) spectrum of (2aS,6aR,14bS)-2a-methyl-6,6a,8,9,14,14b-hexahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (**6c**)



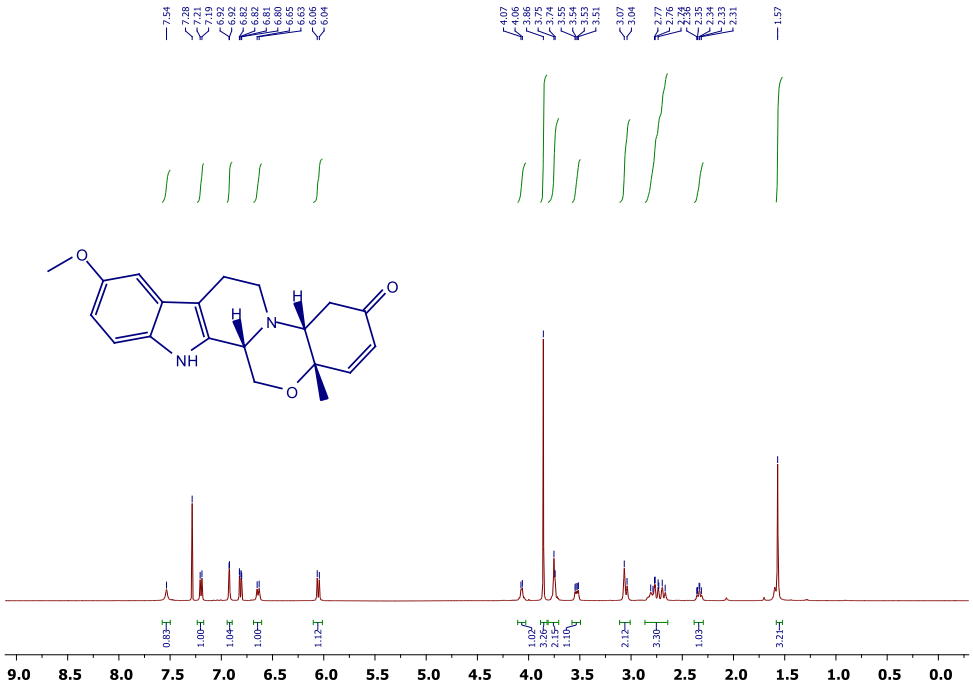

**Supplementary Figure 40** NOESY (500 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bS)-2a-methyl-6,6a,8,9,14,14b-hexahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (**6c**)



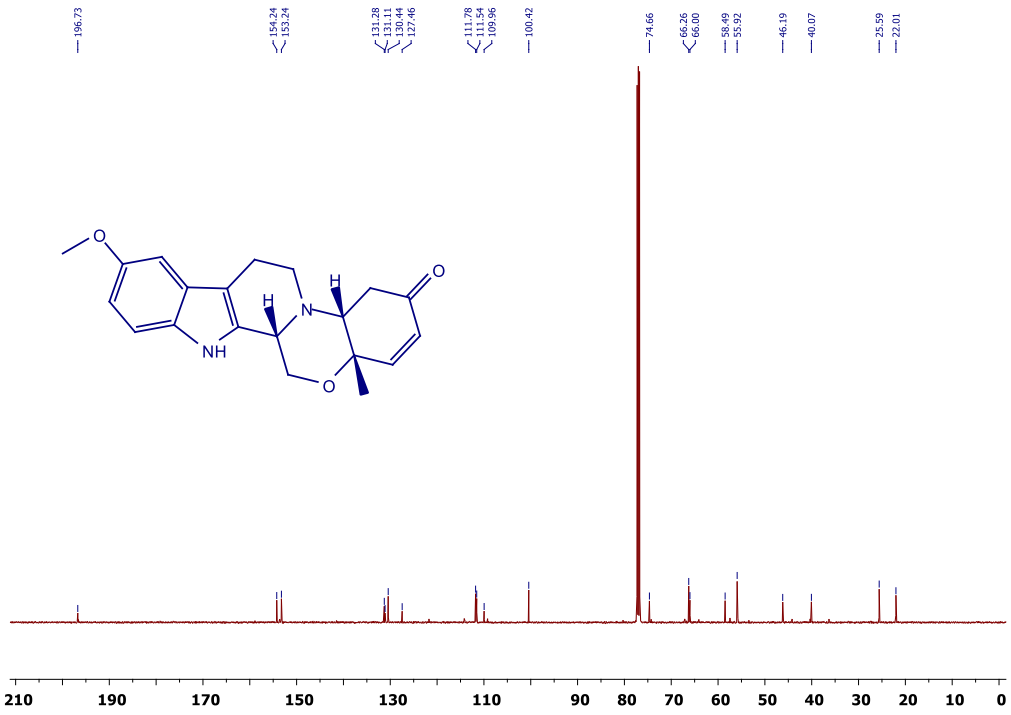
**Supplementary Figure 41** $^{1}H$ NMR (500 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bR)-11-methoxy-2a-methyl-6,6a,8,9,14,14b-hexahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (**5d**)



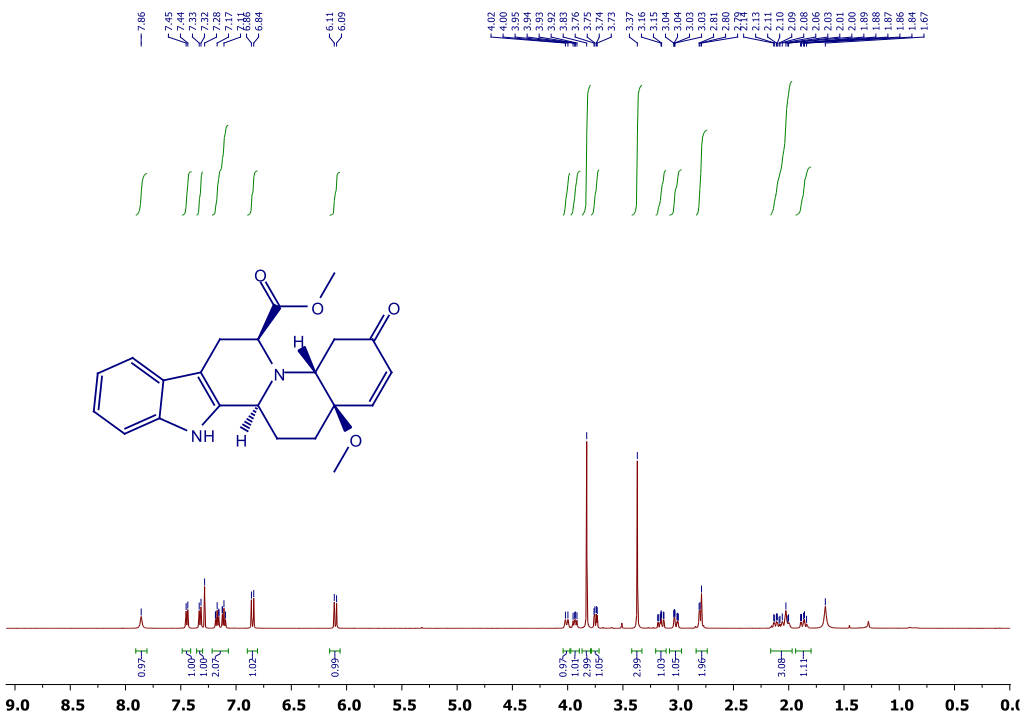
**Supplementary Figure 42** $^{13}C$ NMR (125 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bR)-11-methoxy-2a-methyl-6,6a,8,9,14,14b-hexahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (**5d**)



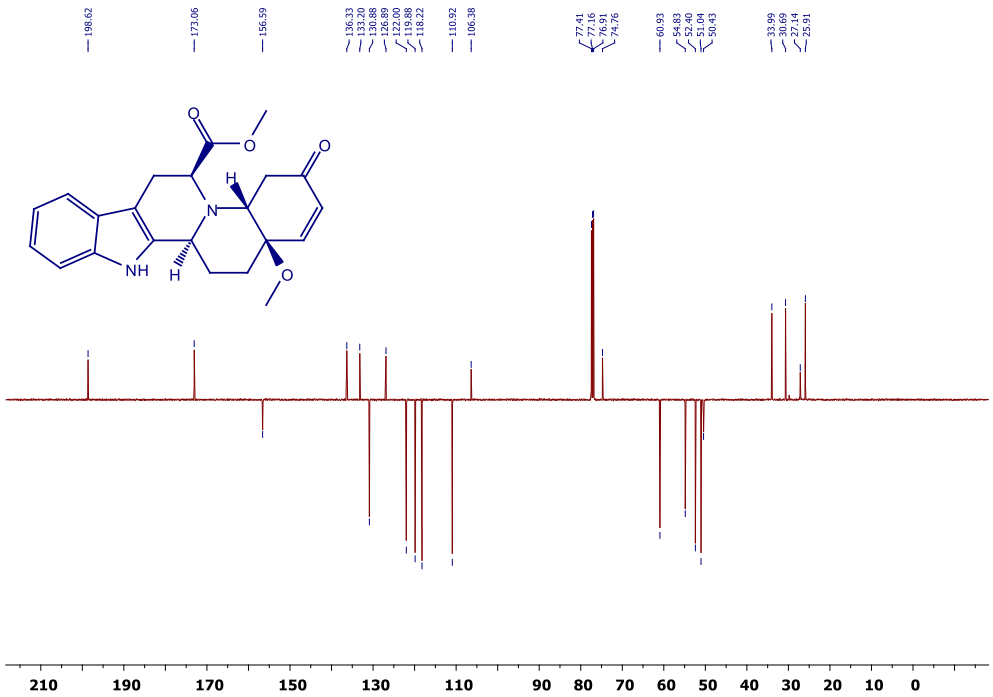
**Supplementary Figure 43** $^{1}H$ NMR (500 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bS)-11-methoxy-2a-methyl-6,6a,8,9,14,14b-hexahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (**6d**)



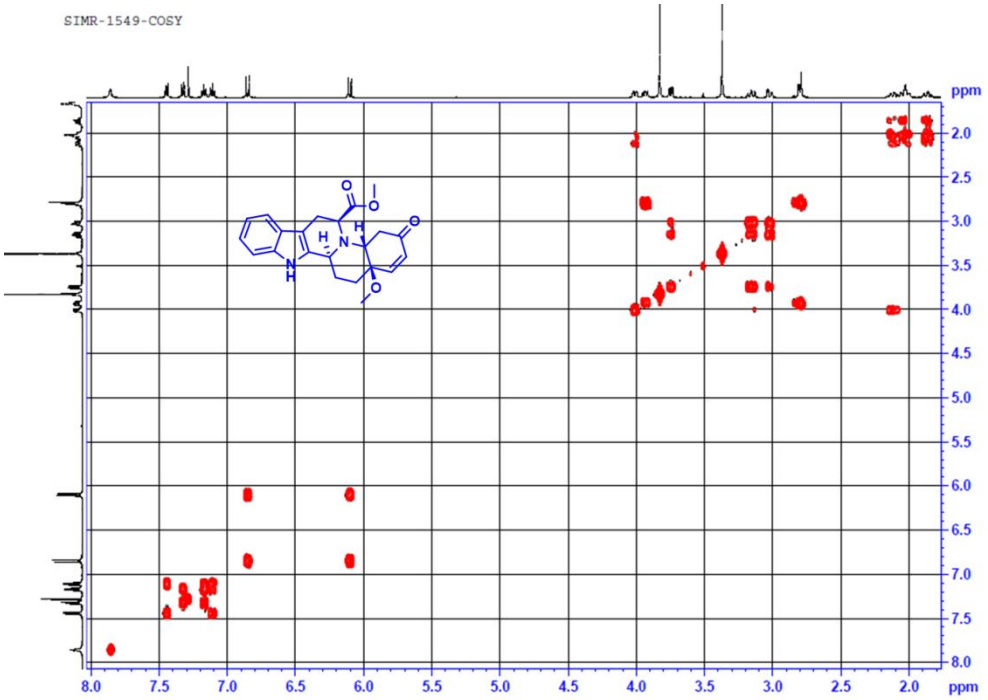
**Supplementary Figure 44** $^{13}C$ NMR (125 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bS)-11-methoxy-2a-methyl-6,6a,8,9,14,14b-hexahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (**6d**)



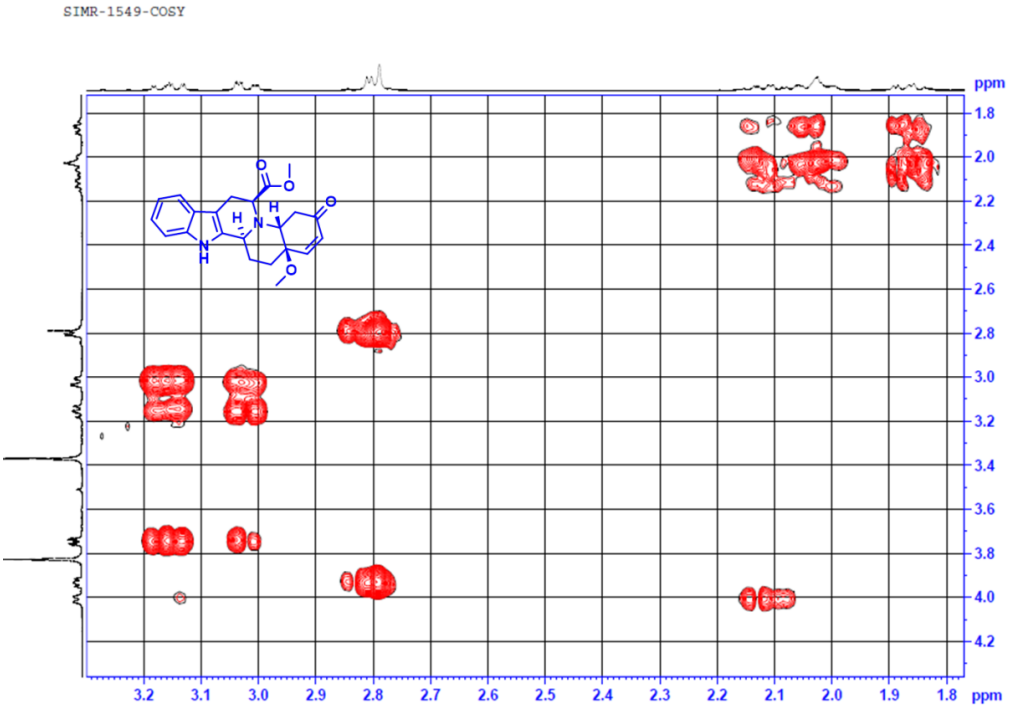
**Supplementary Figure 45** $^{1}$H NMR (500 MHz, $CDCl_3$) spectrum of methyl (2aR,6aR,8S,14bS)-2a-methoxy-5-oxo-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinoline-8-carboxylate (**8a**)



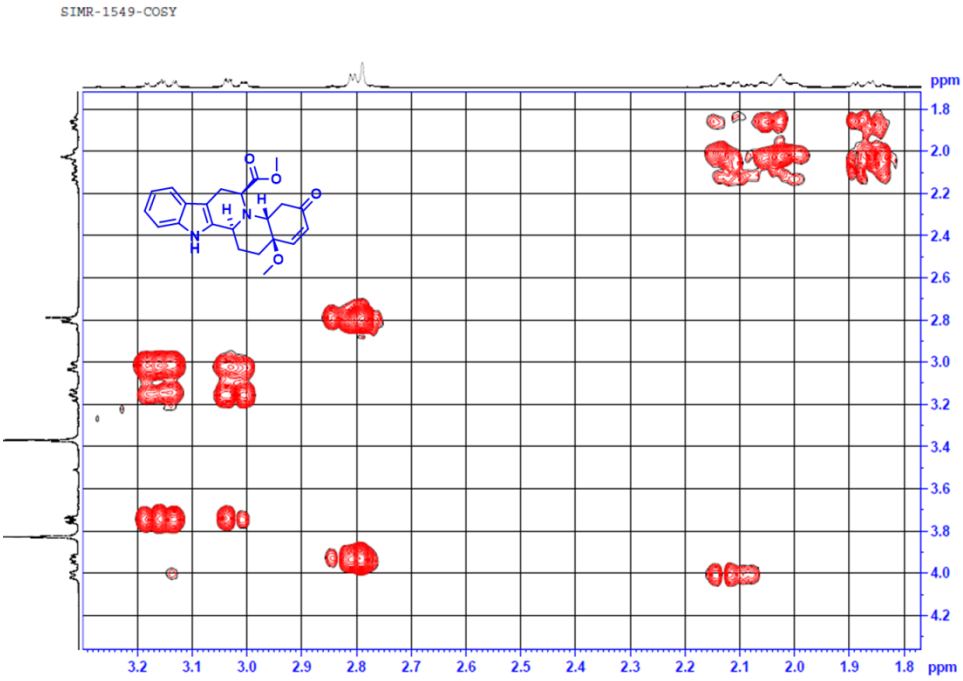
**Supplementary Figure 46** APT NMR (125 MHz, $CDCl_3$) spectrum of methyl (2aR,6aR,8S,14bS)-2a-methoxy-5-oxo-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinoline-8-carboxylate (**8a**)



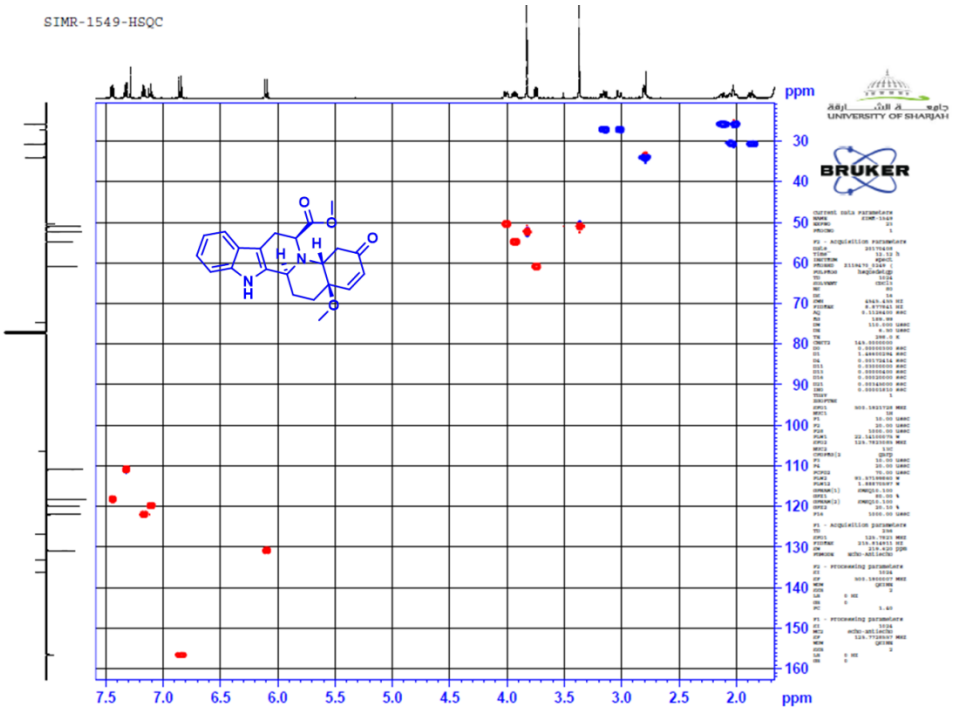

**Supplementary Figure 47** COSY (500 MHz, $CDCl_3$) spectrum of methyl (2aR,6aR,8S,14bS)-2a-methoxy-5-oxo-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinoline-8-carboxylate (**8a**)



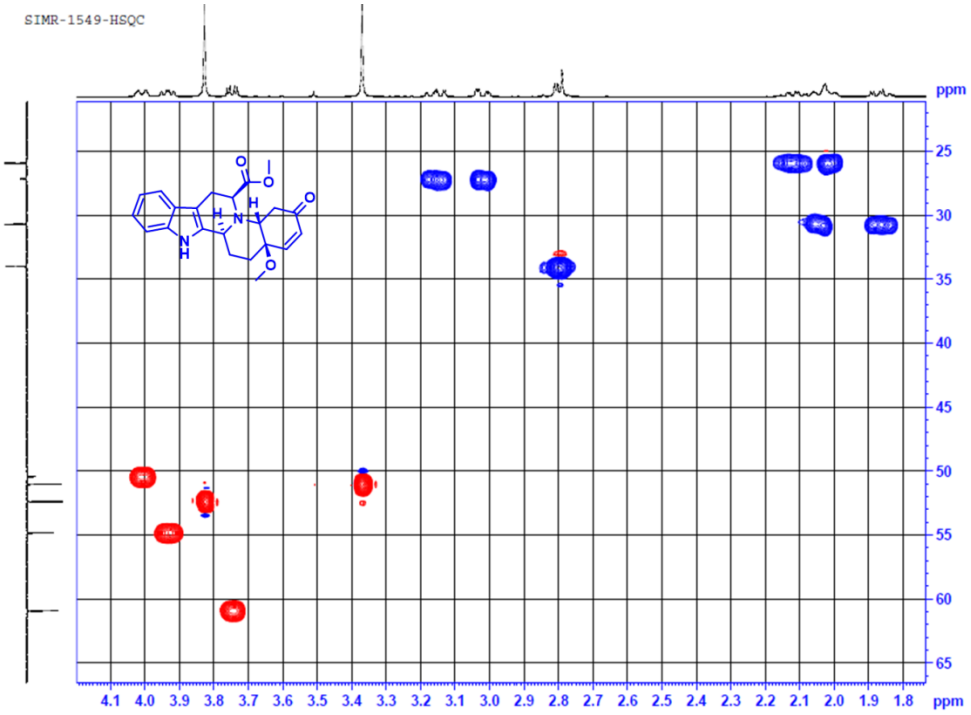

**Supplementary Figure 48** COSY (Expansion) spectrum of methyl (2aR,6aR,8S,14bS)-2a-methoxy-5-oxo-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinoline-8-carboxylate (**8a**)



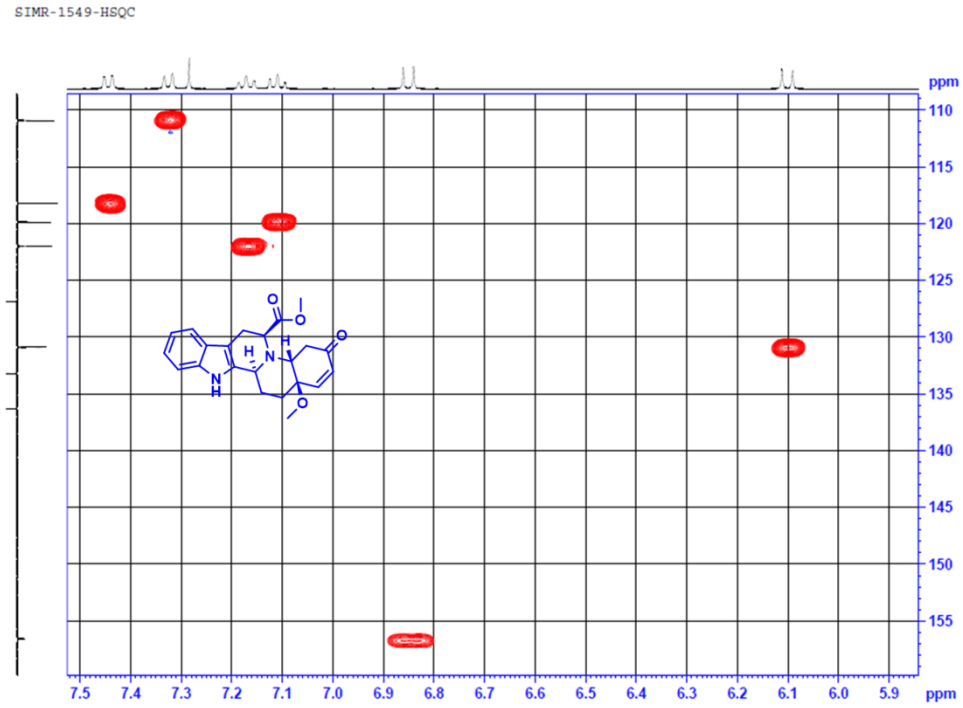

**Supplementary Figure 49** COSY (Expansion) spectrum of methyl (2aR,6aR,8S,14bS)-2a-methoxy-5-oxo-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinoline-8-carboxylate (**8a**)



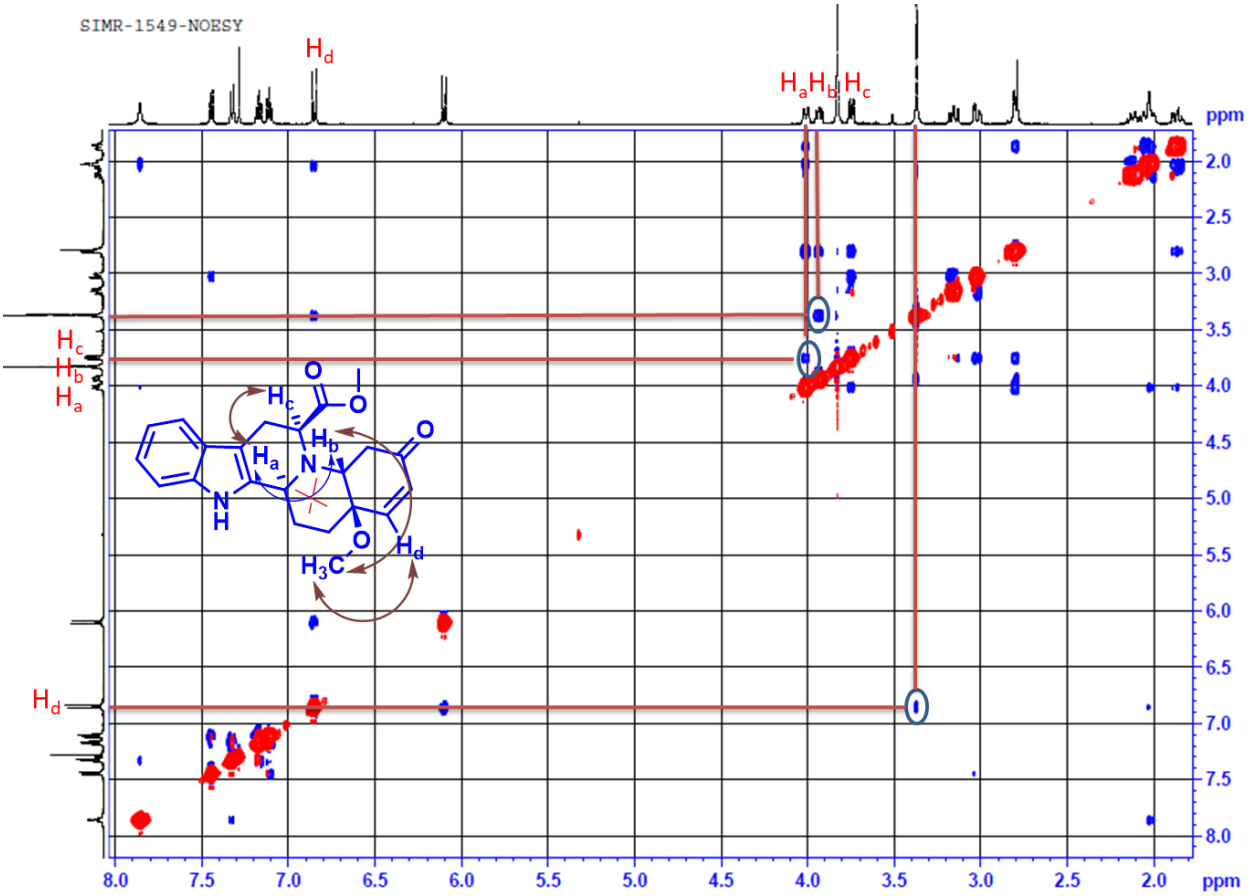

**Supplementary Figure 50** HSQC (500 MHz, $CDCl_3$) spectrum of methyl (2aR,6aR,8S,14bS)-2a-methoxy-5-oxo-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinoline-8-carboxylate (**8a**)



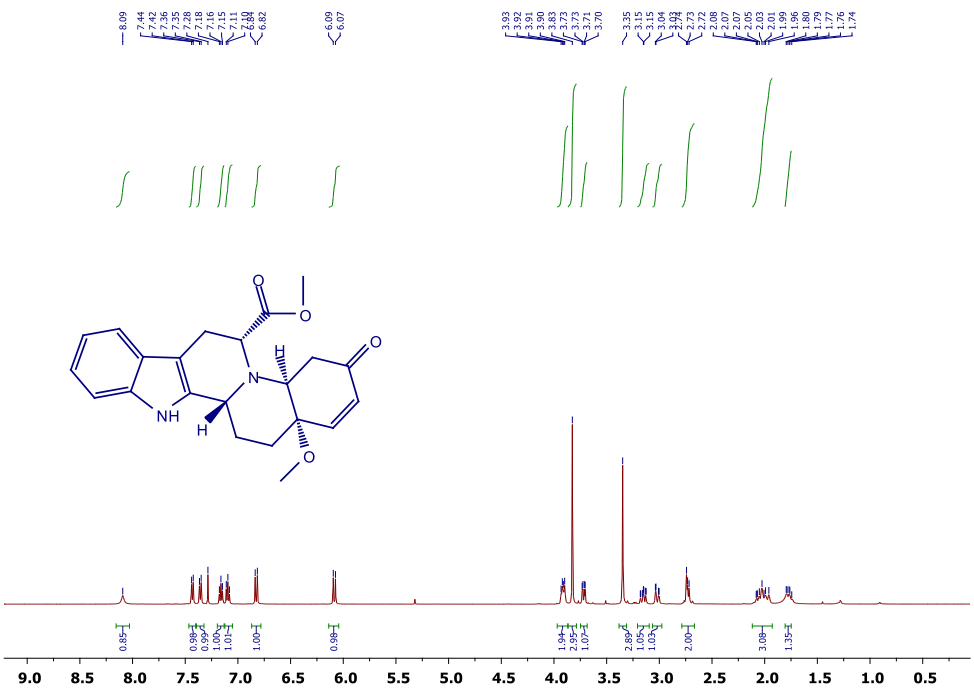

**Supplementary Figure 51** HSQC (Expansion) spectrum of methyl (2aR,6aR,8S,14bS)-2a-methoxy-5-oxo-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinoline-8-carboxylate (**8a**)



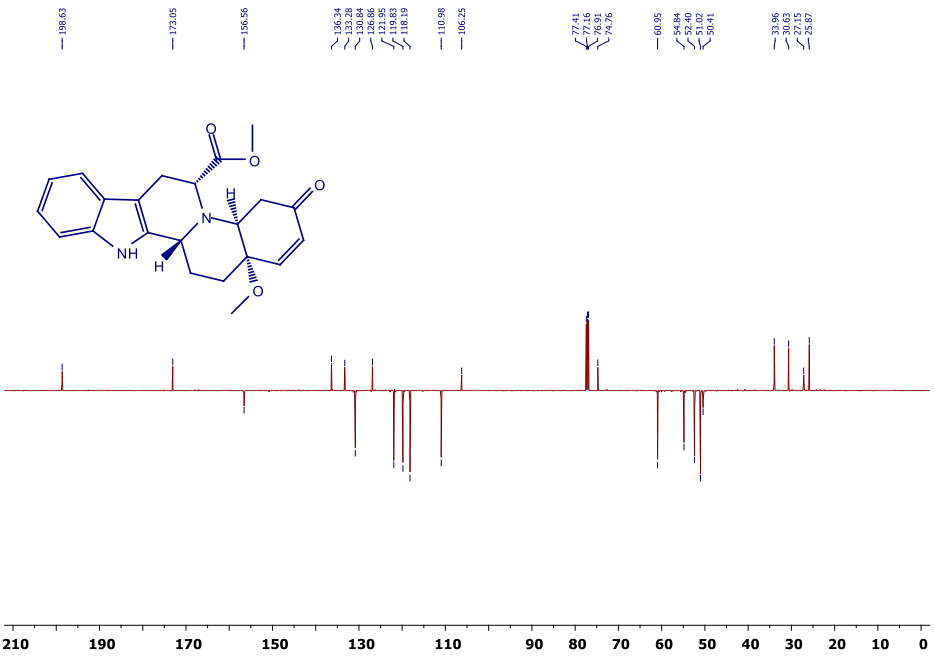

**Supplementary Figure 52** HSQC (Expansion) spectrum of methyl (2aR,6aR,8S,14bS)-2a-methoxy-5-oxo-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinoline-8-carboxylate (**8a**)



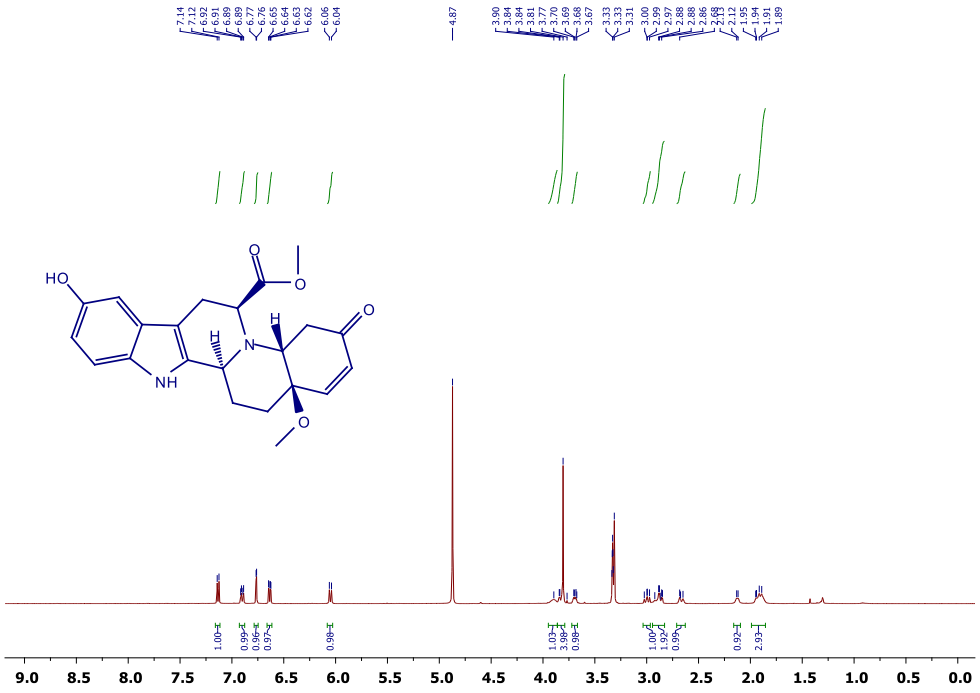

**Supplementary Figure 53** NOESY (500 MHz, $CDCl_3$) spectrum of methyl (2aR,6aR,8S,14bS)-2a-methoxy-5-oxo-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinoline-8-carboxylate (**8a**)



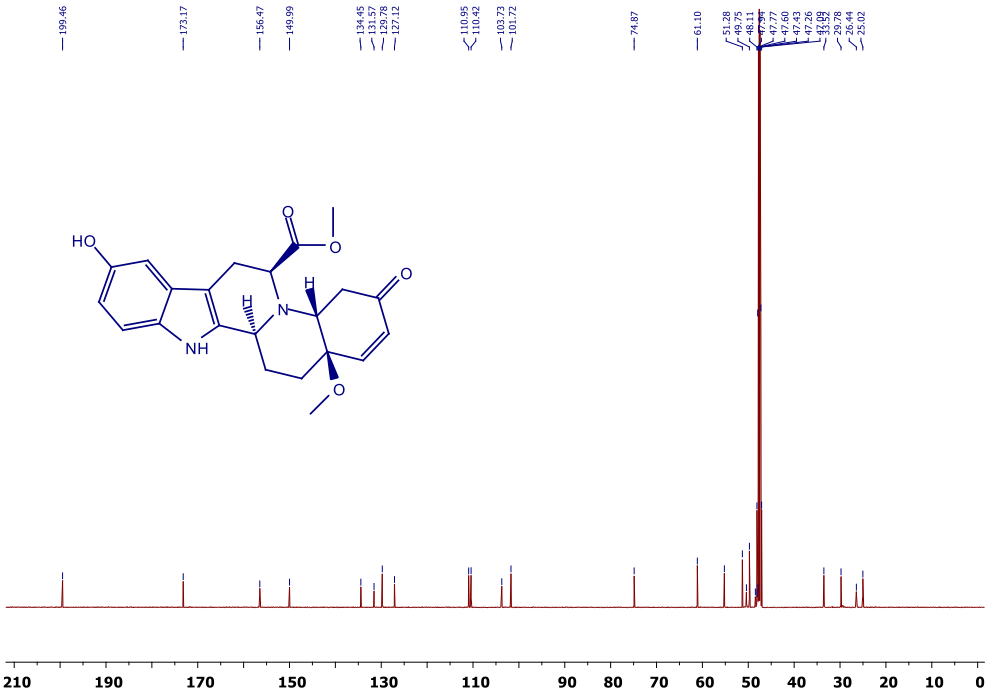
**Supplementary Figure 54** $^{1}$H NMR (500 MHz, $CDCl_3$) spectrum of methyl (2aS,6aS,8R,14bR)-2a-methoxy-5-oxo-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinoline-8-carboxylate (**8b**)



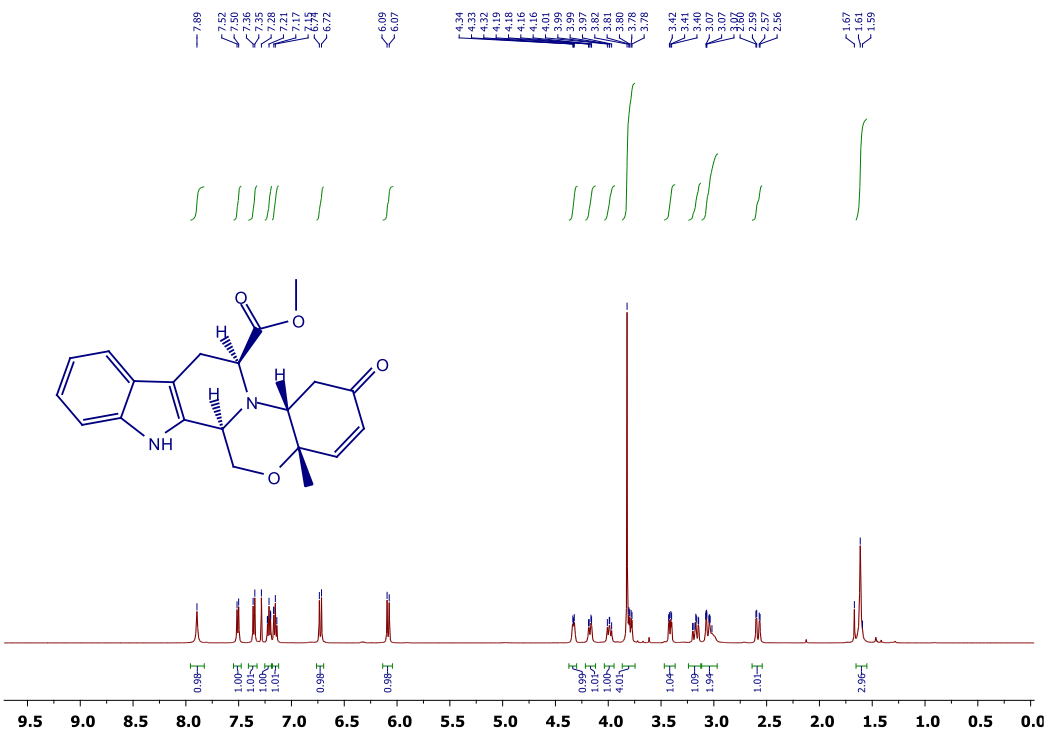
**Supplementary Figure 55** APT NMR (125 MHz, $CDCl_3$) spectrum of methyl (2aS,6aS,8R,14bR)-2a-methoxy-5-oxo-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinoline-8-carboxylate (**8b**)



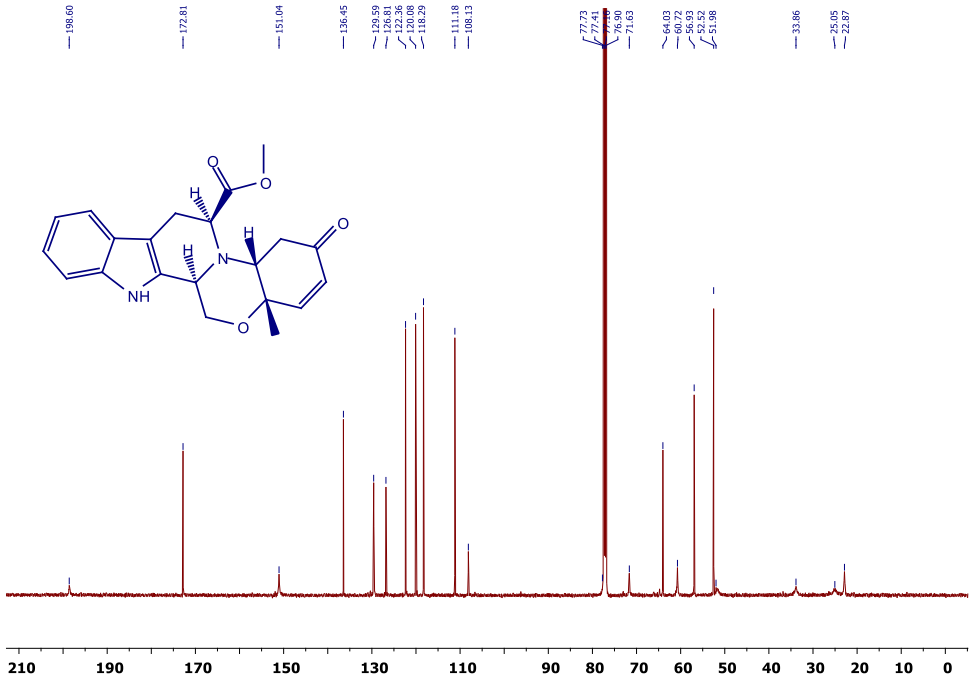
**Supplementary Figure 56** $^{1}$H NMR (500 MHz, $CD_3OD$) spectrum of Methyl (2aR,6aR,8S,14bS)-11-hydroxy-2a-methoxy-5-oxo-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinoline-8-carboxylate (**8c**)



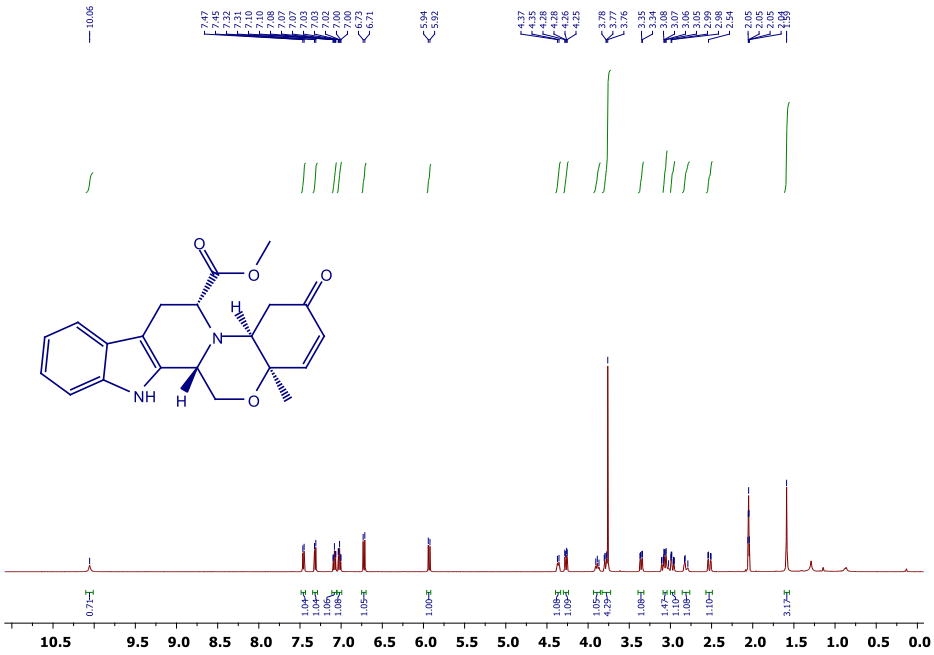
**Supplementary Figure 57** $^{13}$C NMR (125 MHz, $CD_3OD$) spectrum of Methyl (2aR,6aR,8S,14bS)-11-hydroxy-2a-methoxy-5-oxo-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinoline-8-carboxylate (**8c**)



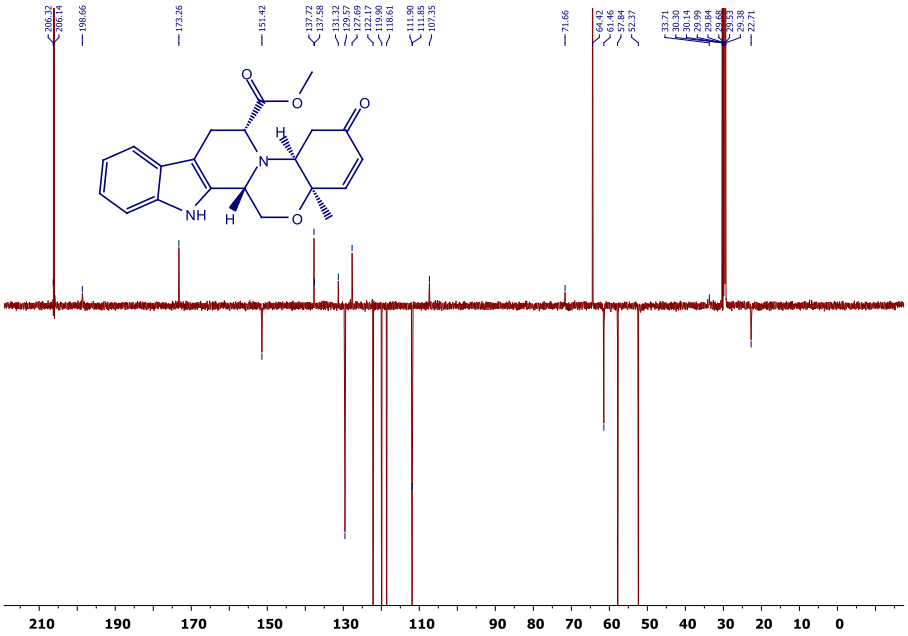
**Supplementary Figure 58** $^{1}$H NMR (500 MHz, $CDCl_3$) spectrum of methyl (2aS,6aR,8S,14bR)-2a-methyl-5-oxo-2a,5,6,6a,8,9,14,14b-octahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-8-carboxylate (**8d**)



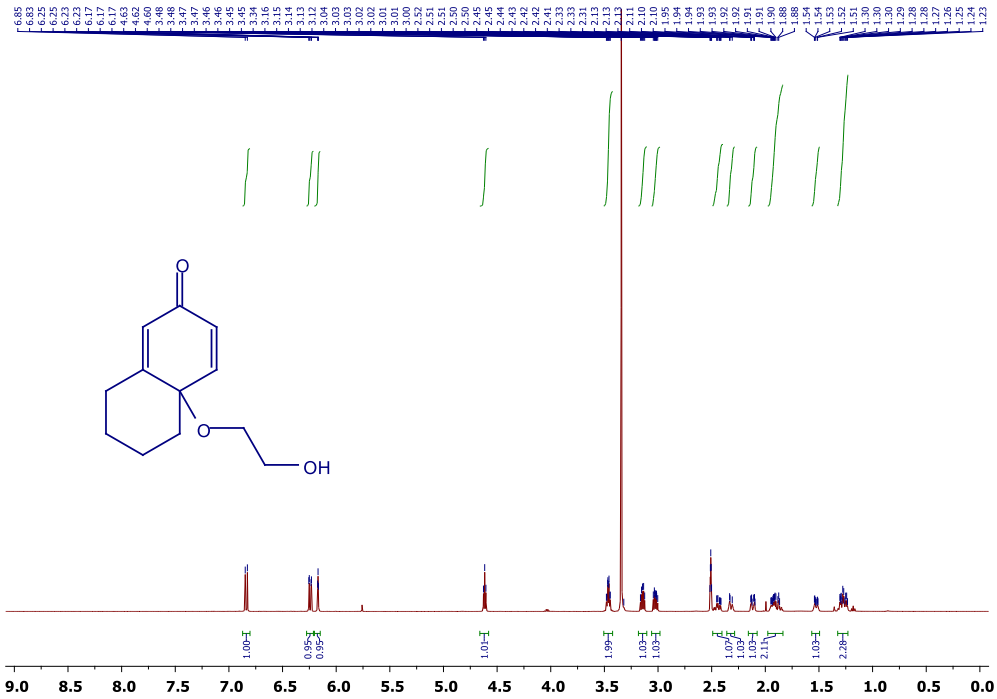
**Supplementary Figure 59** $^{13}$C NMR (125 MHz, $CDCl_3$) spectrum of methyl (2aS,6aR,8S,14bR)-2a-methyl-5-oxo-2a,5,6,6a,8,9,14,14b-octahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-8-carboxylate (**8d**)



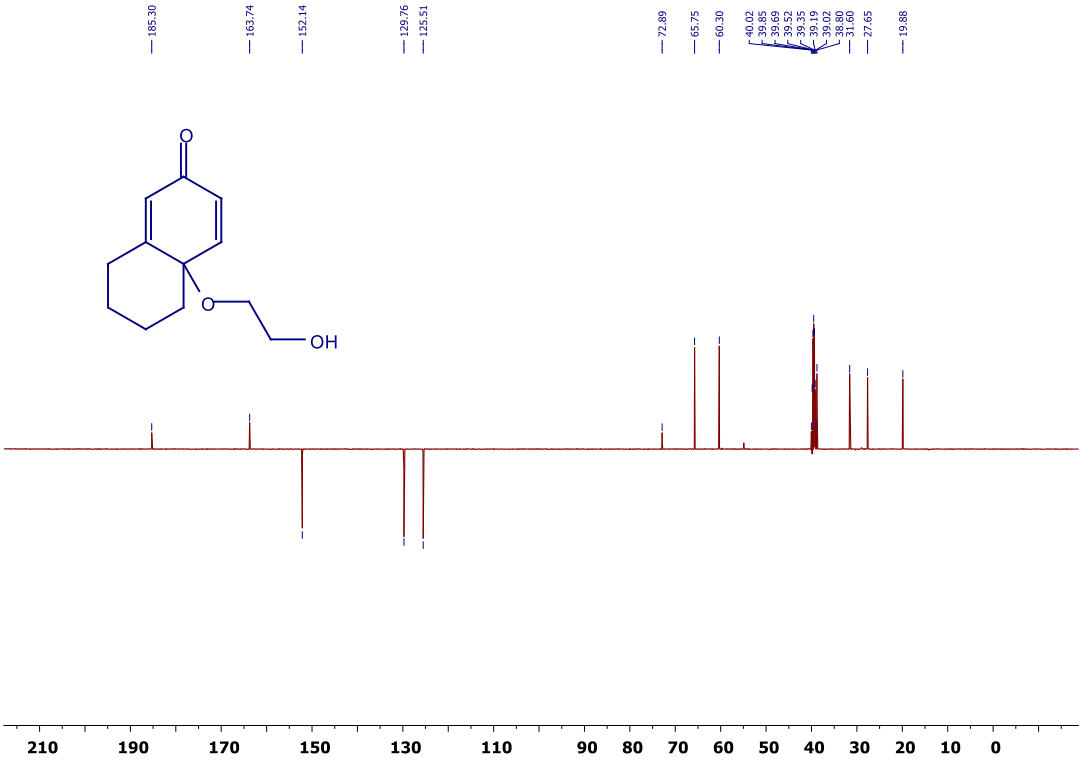
**Supplementary Figure 60** $^{1}$H NMR (500 MHz, Acetone-$d_6$) spectrum of methyl (2aR,6aS,8R,14bS)-2a-methyl-5-oxo-2a,5,6,6a,8,9,14,14b-octahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-8-carboxylate (**8e**)



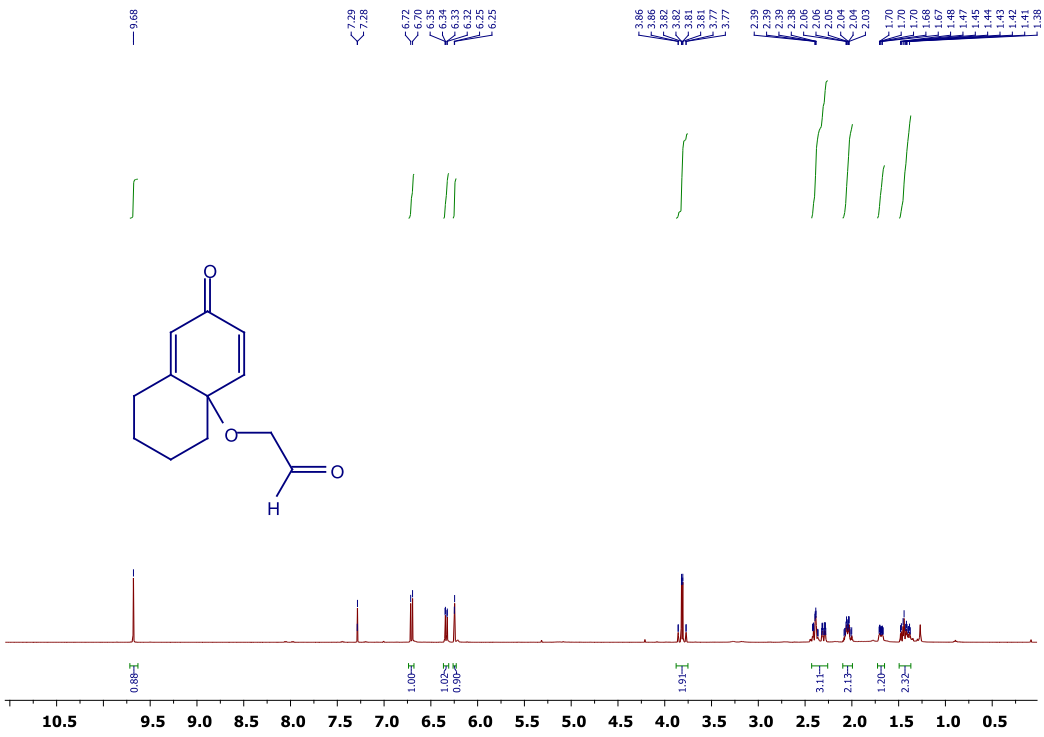
**Supplementary Figure 61** APT NMR (125 MHz, Acetone-$d_6$) spectrum of methyl (2aR,6aS,8R,14bS)-2a-methyl-5-oxo-2a,5,6,6a,8,9,14,14b-octahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-8-carboxylate (**8e**)



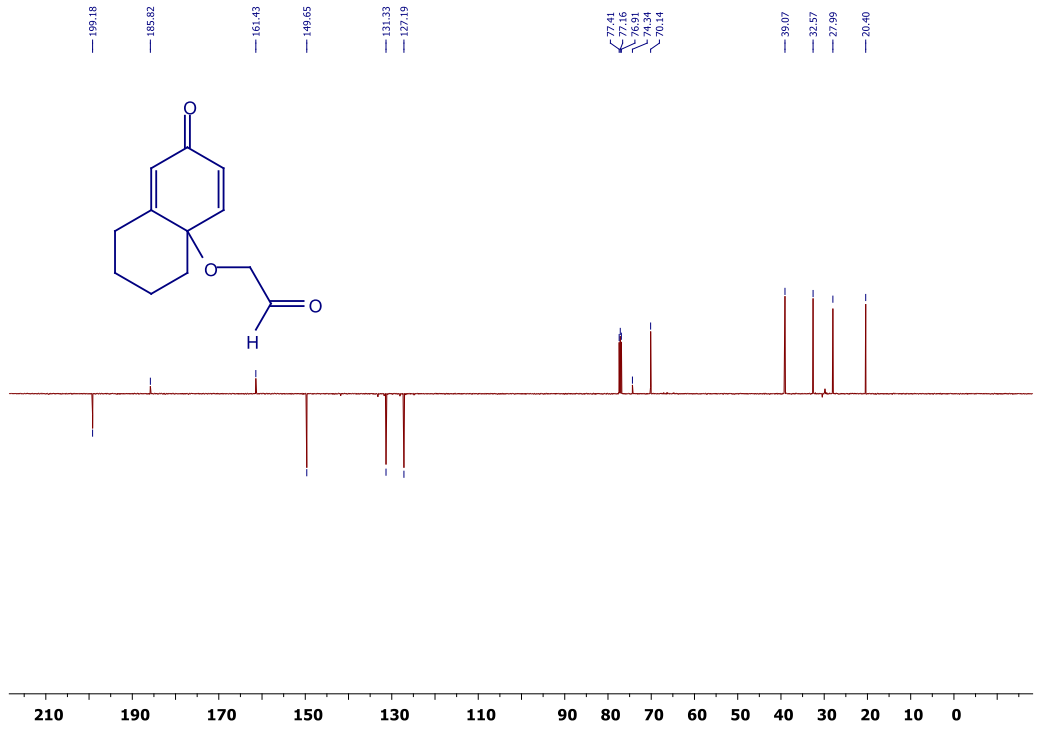

**Supplementary Figure 62** $^{1}$H NMR (500 MHz, DMSO-$d_6$) spectrum of 4a-(2-hydroxyethoxy)-5,6,7,8-tetrahydronaphthalen-2(4aH)-one (**9b**)



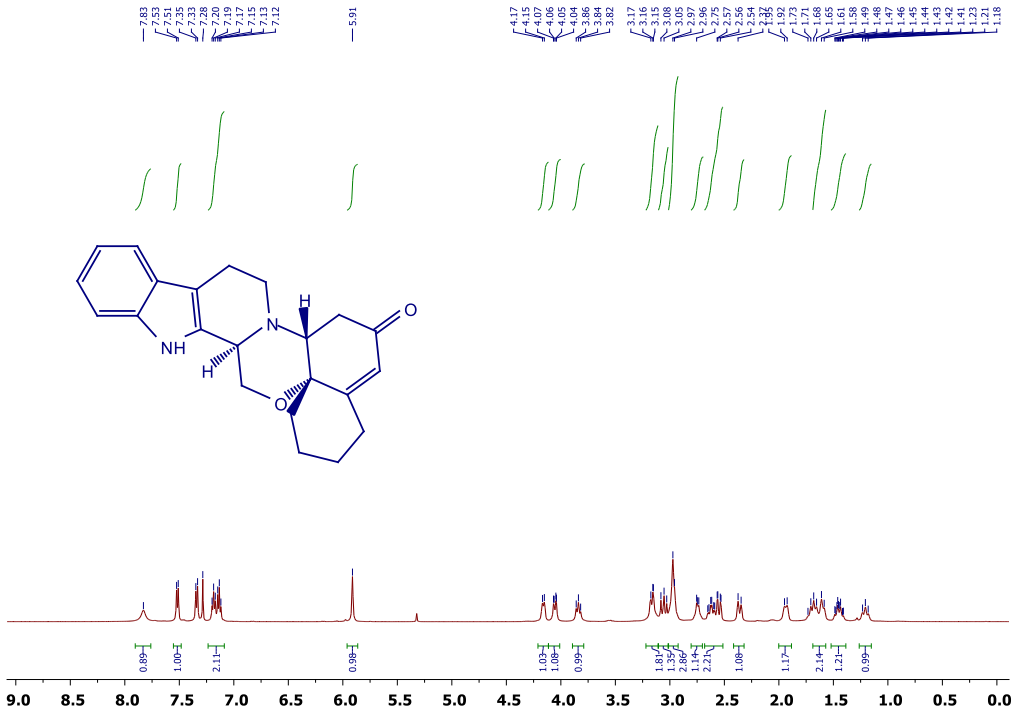

**Supplementary Figure 63** APT NMR (125 MHz, DMSO-$d_6$) spectrum of 4a-(2-hydroxyethoxy)-5,6,7,8-tetrahydronaphthalen-2(4aH)-one (**9b**)



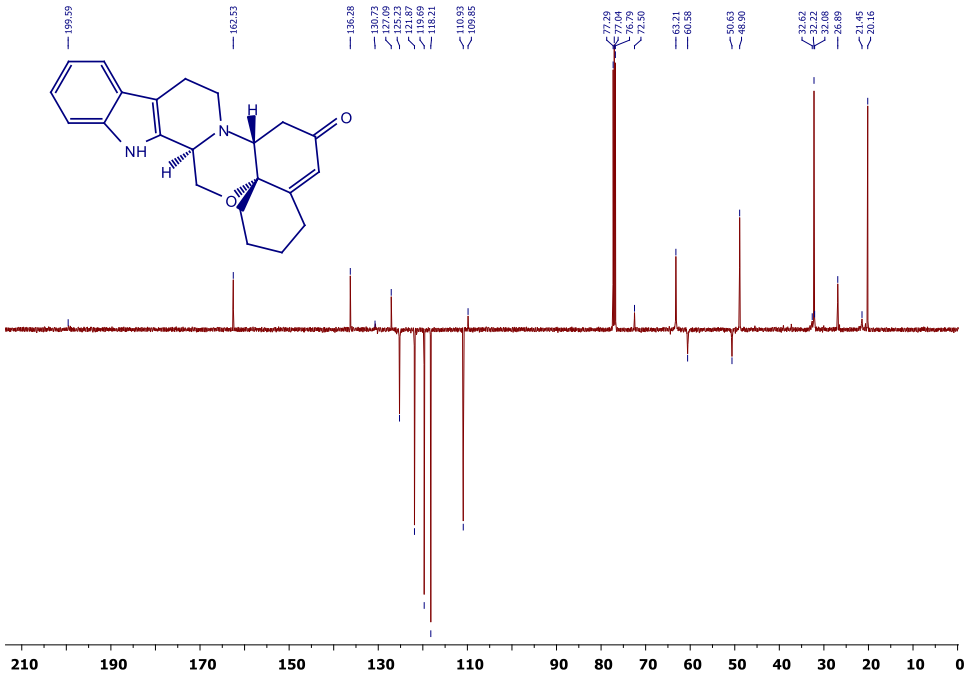
**Supplementary Figure 64** $^{1}$H NMR (500 MHz, $CDCl_3$) spectrum of 2-((7-oxo-1,3,4,7-tetrahydronaphthalen-4a(2H)-yl)oxy)acetaldehyde (**9**)



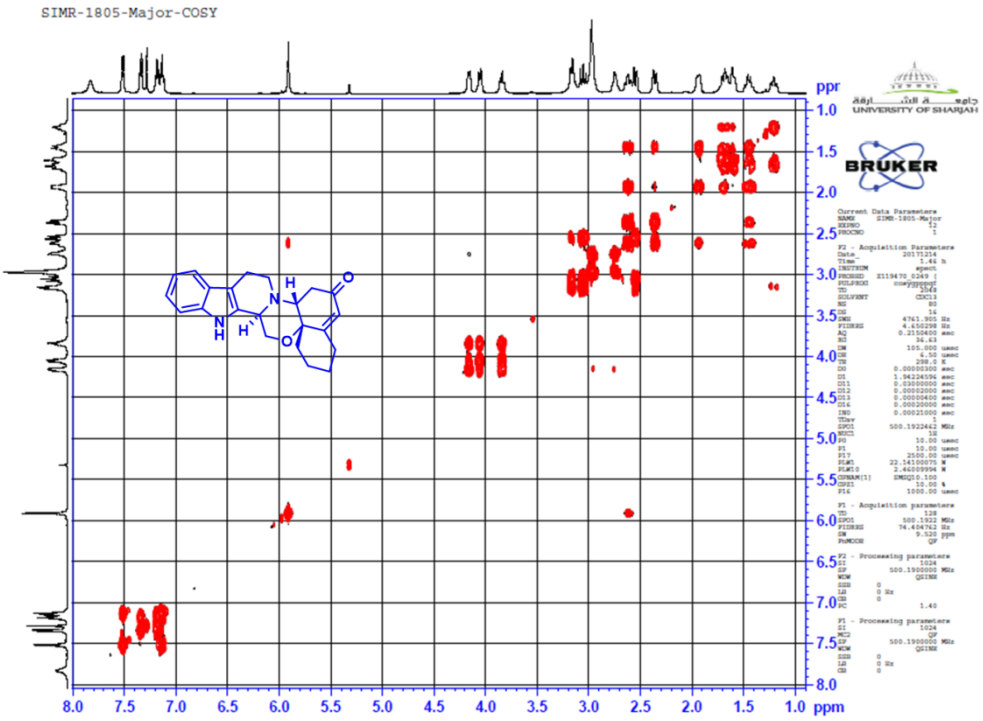
**Supplementary Figure 65** APT NMR (125 MHz, $CDCl_3$) spectrum of 4a-(2-hydroxyethoxy)-5,6,7,8-tetrahydronaphthalen-2(4aH)-one (**9**)



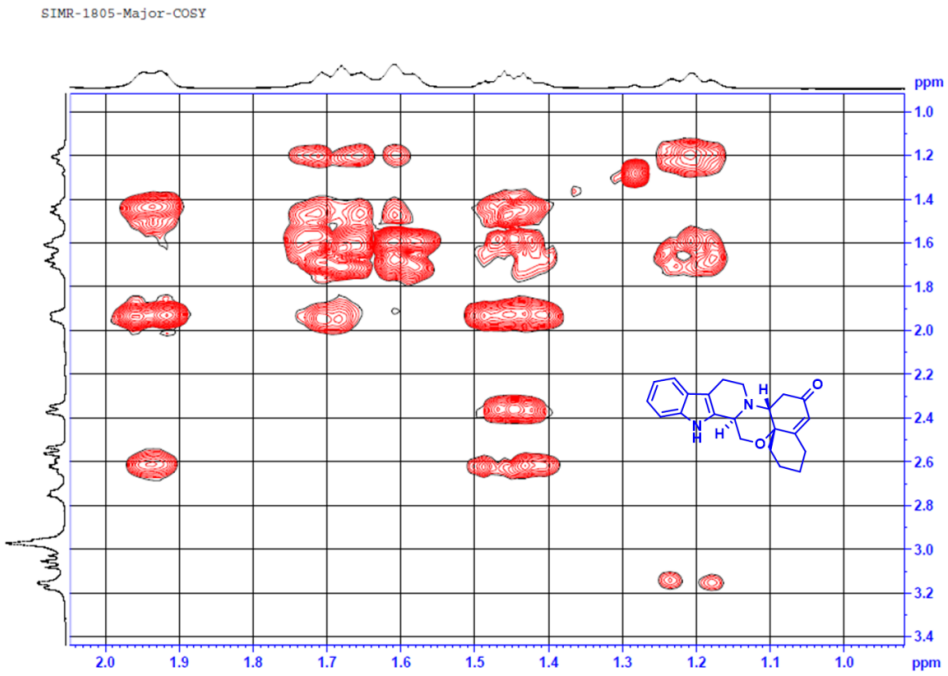

**Supplementary Figure 66** $^{1}$H NMR (500 MHz, $CDCl_3$) spectrum of (2aS,9aR,17bR)-3,4,5,6,9,9a,11,12,17,17b-decahydro-1H,8H-naphtho[1",8a":5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-8-one (**10**)



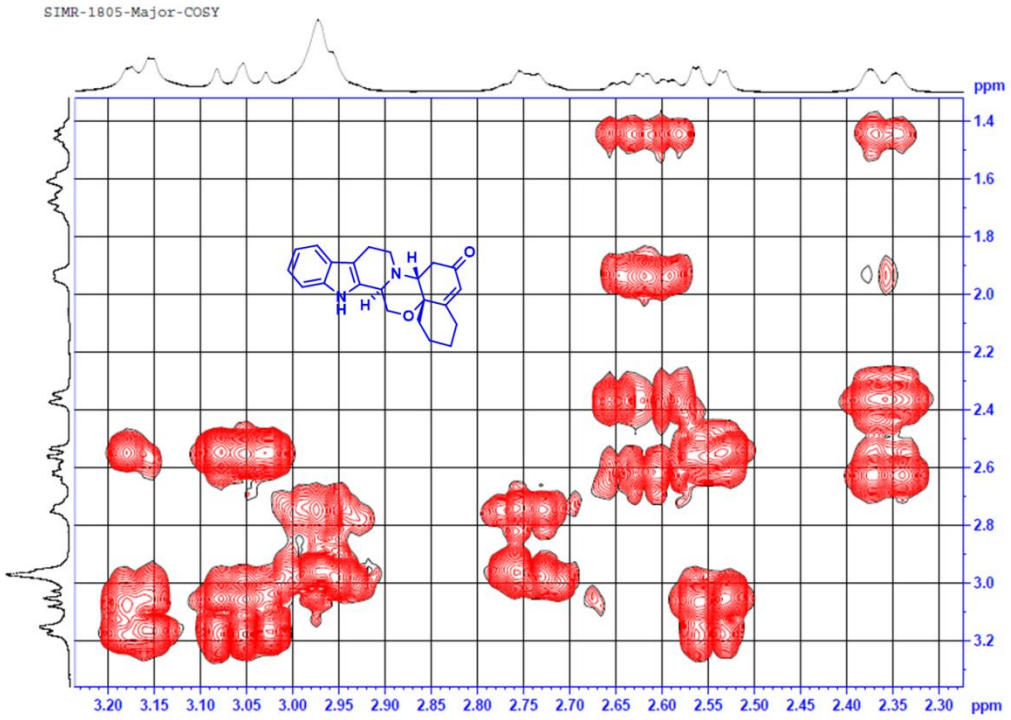

**Supplementary Figure 67** APT NMR (125 MHz, $CDCl_3$) spectrum of (2aS,9aR,17bR)-3,4,5,6,9,9a,11,12,17,17b-decahydro-1H,8H-naphtho[1",8a":5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-8-one (**10**)



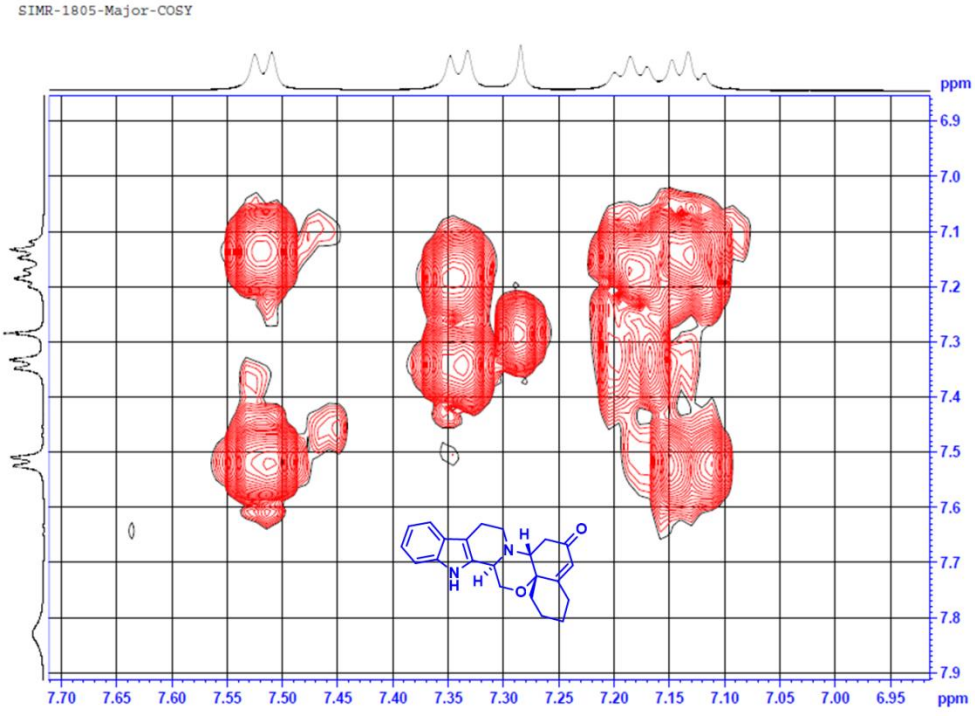

**Supplementary Figure 68** COSY (500 MHz, $CDCl_3$) spectrum of (2aS,9aR,17bR)-3,4,5,6,9,9a,11,12,17,17b-decahydro-1H,8H-naphtho[1",8a":5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-8-one (**10**)



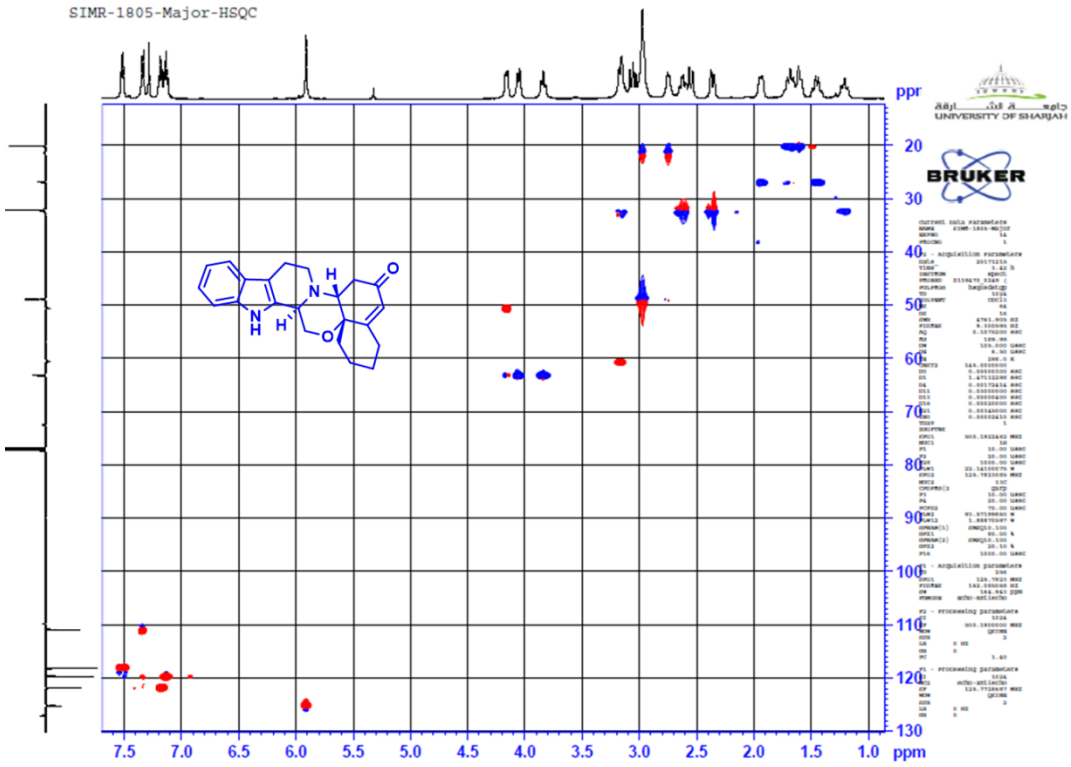

**Supplementary Figure 69** COSY (Expansion) spectrum of (2aS,9aR,17bR)-3,4,5,6,9,9a,11,12,17,17b-decahydro-1H,8H-naphtho[1",8a":5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-8-one (**10**)



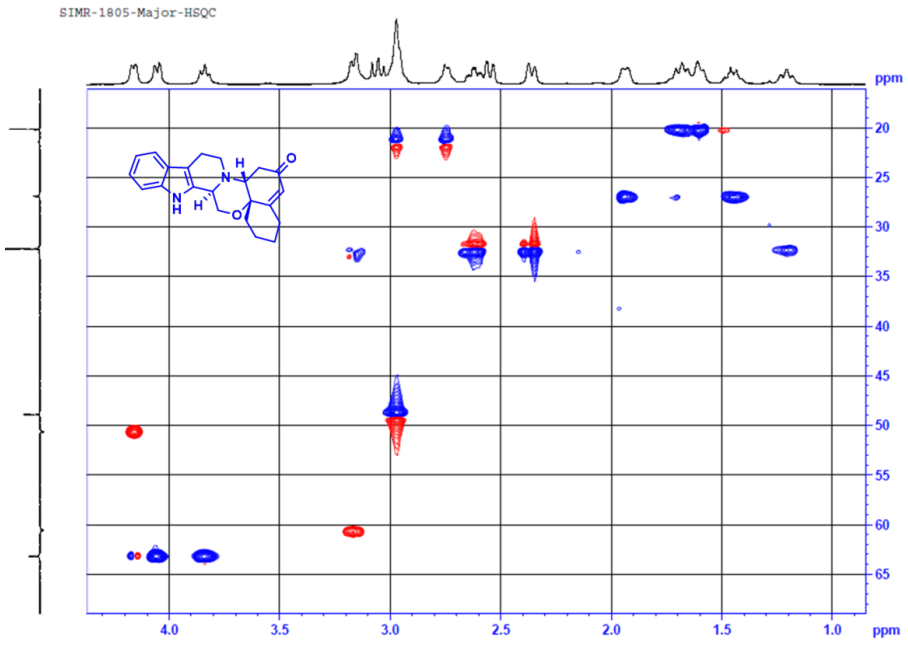

**Supplementary Figure 70** COSY (Expansion) spectrum of (2aS,9aR,17bR)-3,4,5,6,9,9a,11,12,17,17b-decahydro-1H,8H-naphtho[1",8a":5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-8-one (**10**)



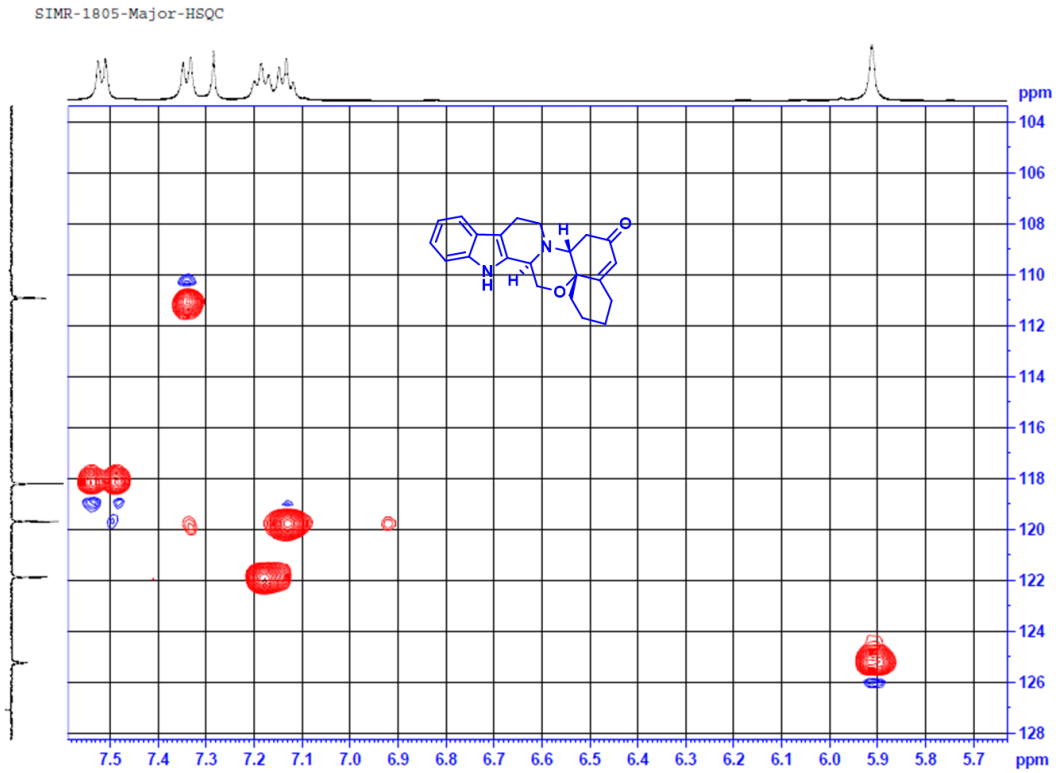

**Supplementary Figure 71** COSY (Expansion) spectrum of (2aS,9aR,17bR)-3,4,5,6,9,9a,11,12,17,17b-decahydro-1H,8H-naphtho[1",8a":5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-8-one (**10**)



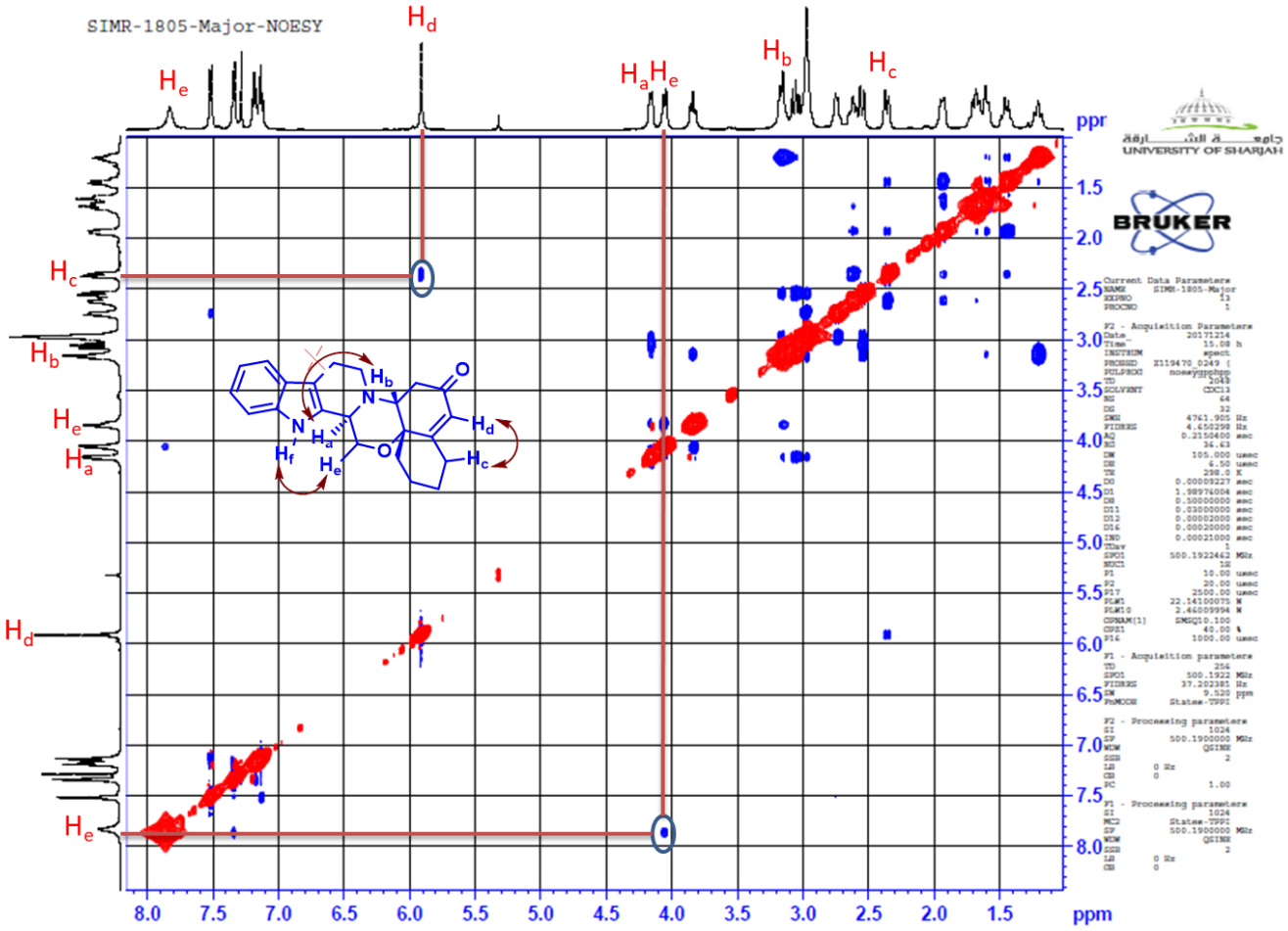

**Supplementary Figure 72** HSQC (500 MHz, $CDCl_3$) spectrum of (2aS,9aR,17bR)-3,4,5,6,9,9a,11,12,17,17b-decahydro-1H,8H-naphtho[1",8a":5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-8-one (**10**)



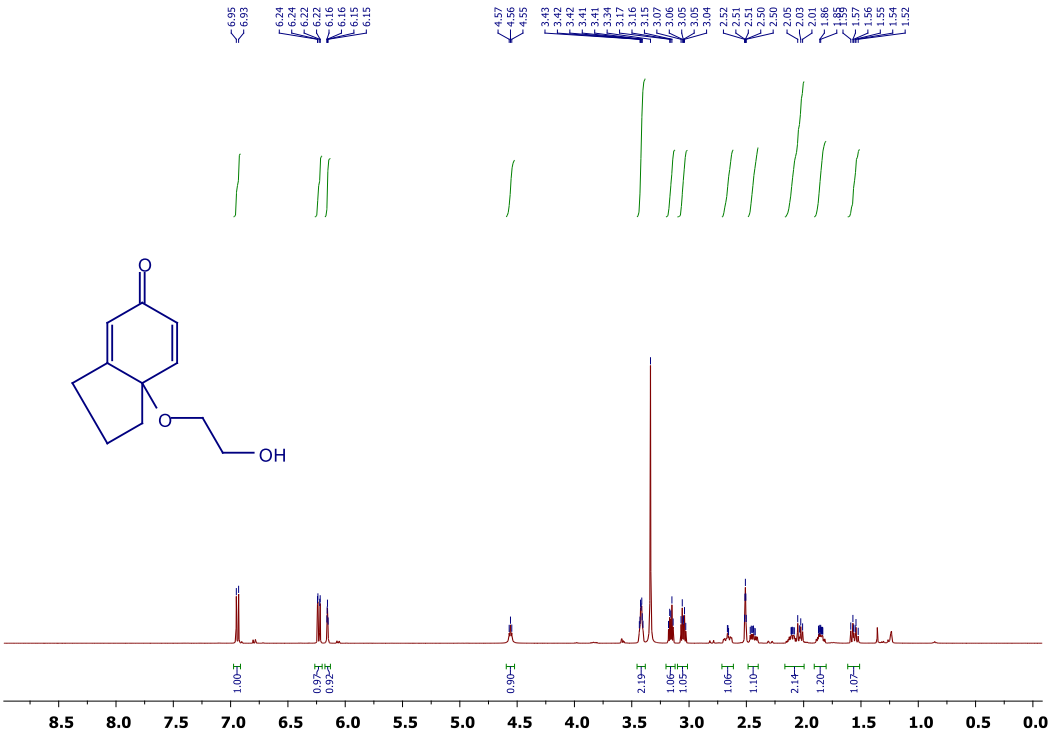

**Supplementary Figure 73** HSQC (Expansion) spectrum of (2aS,9aR,17bR)-3,4,5,6,9,9a,11,12,17,17b-decahydro-1H,8H-naphtho[1",8a":5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-8-one (**10**)



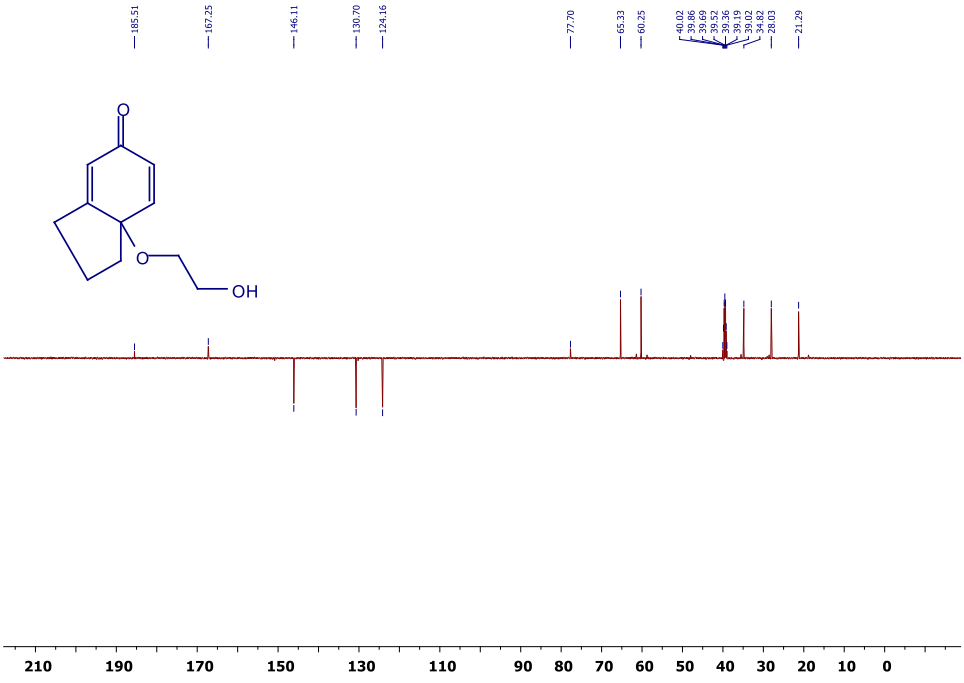

**Supplementary Figure 74** HSQC (Expansion) spectrum of (2aS,9aR,17bR)-3,4,5,6,9,9a,11,12,17,17b-decahydro-1H,8H-naphtho[1",8a":5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-8-one (**10**)



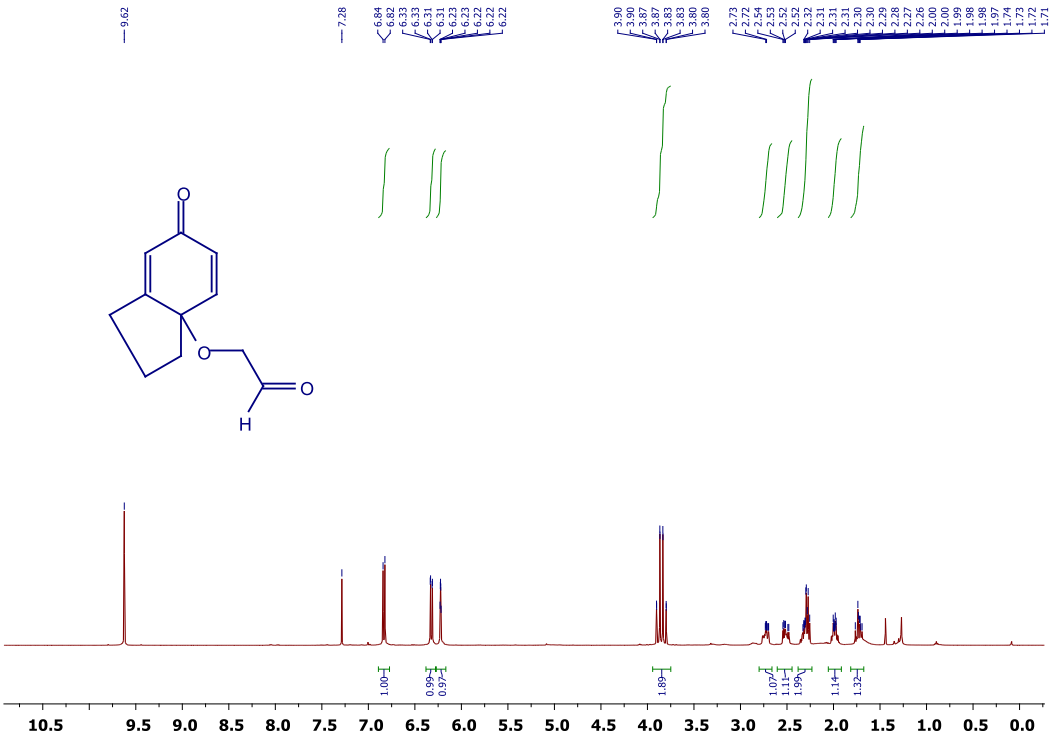

**Supplementary Figure 75** NOESY (500 MHz, $CDCl_3$) spectrum of (2aS,9aR,17bR)-3,4,5,6,9,9a,11,12,17,17b-decahydro-1H,8H-naphtho[1",8a":5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-8-one (**10**)



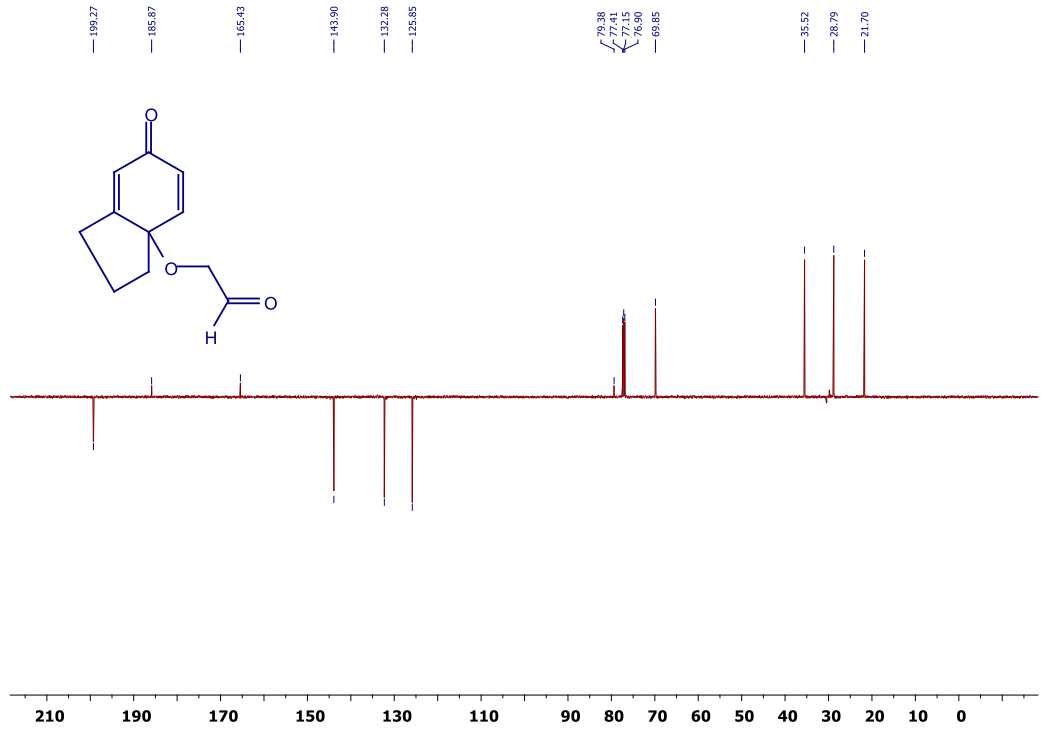

**Supplementary Figure 76** $^{1}$H NMR (500 MHz, DMSO-$d_6$) spectrum of 7a-(2-hydroxyethoxy)-1,2,3,7a-tetrahydro-5H-inden-5-one (**11b**)



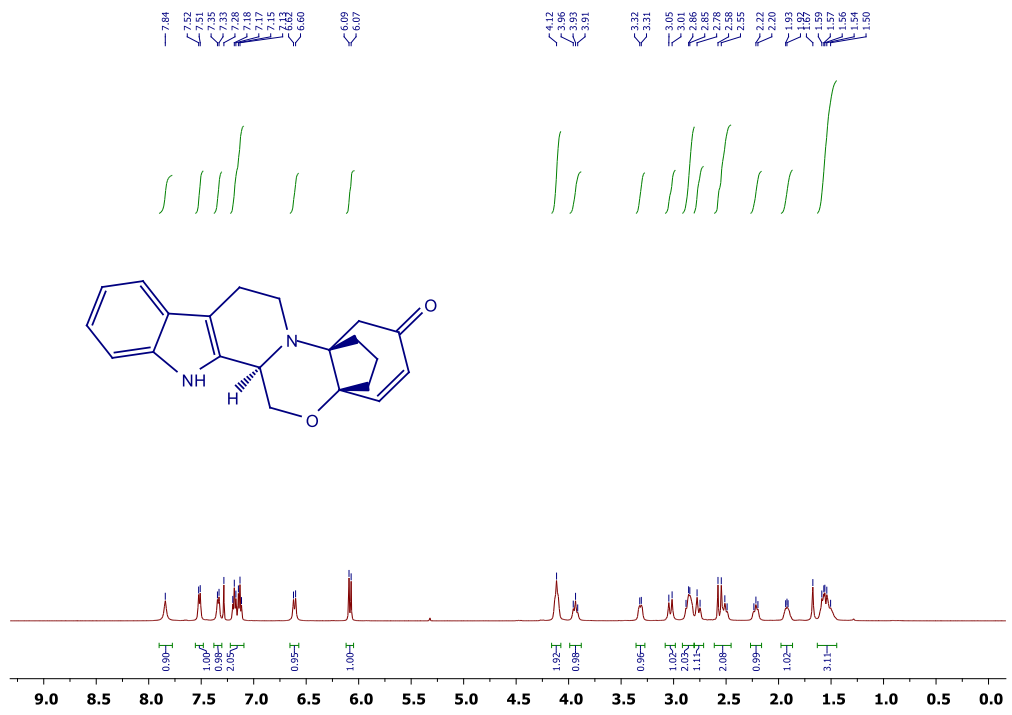

**Supplementary Figure 77** APT NMR (125 MHz, DMSO-$d_6$) spectrum of 7a-(2-hydroxyethoxy)-1,2,3,7a-tetrahydro-5H-inden-5-one (**11b**)



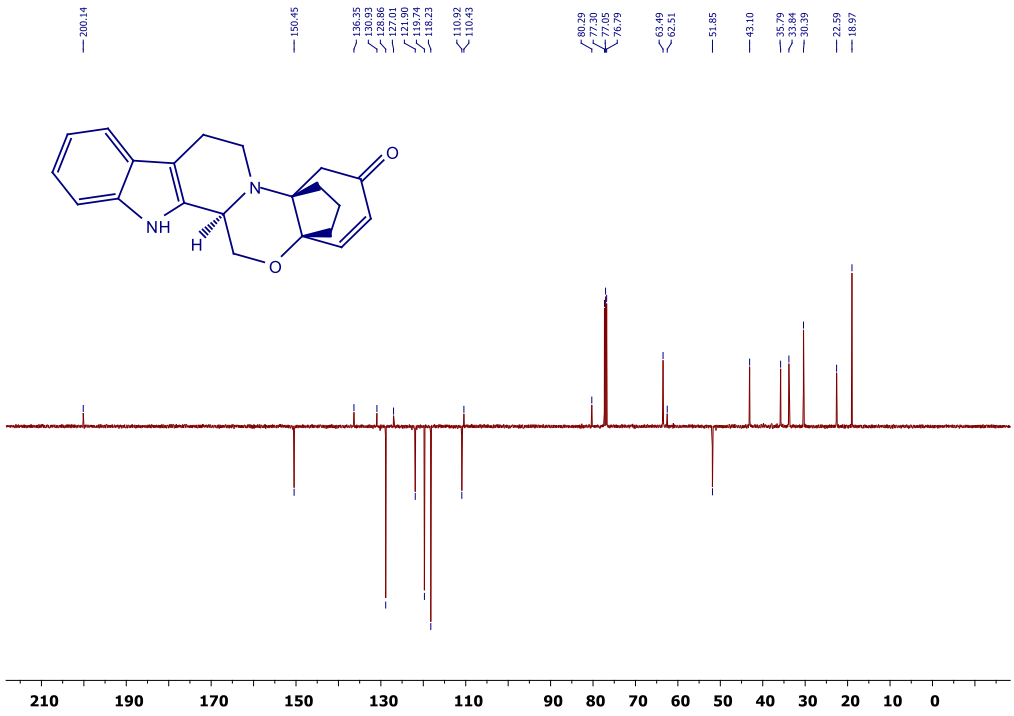
**Supplementary Figure 78** $^{1}$H NMR (500 MHz, $CDCl_3$) spectrum of 2-((6-oxo-1,2,3,6-tetrahydro-3aH-inden-3a-yl)oxy)acetaldehyde (**11**)



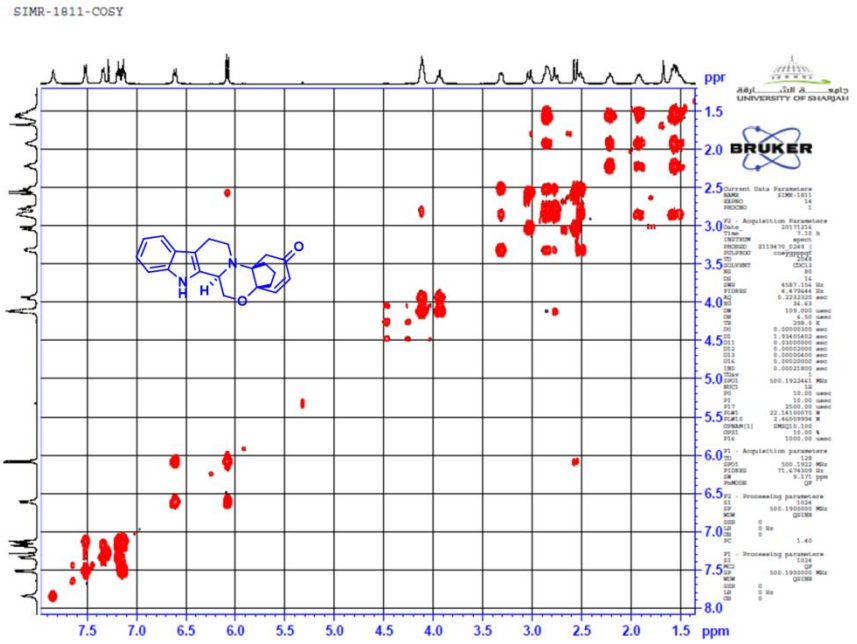
**Supplementary Figure 79** APT NMR (125 MHz, $CDCl_3$) spectrum of 2-((6-oxo-1,2,3,6-tetrahydro-3aH-inden-3a-yl)oxy)acetaldehyde (**11**)



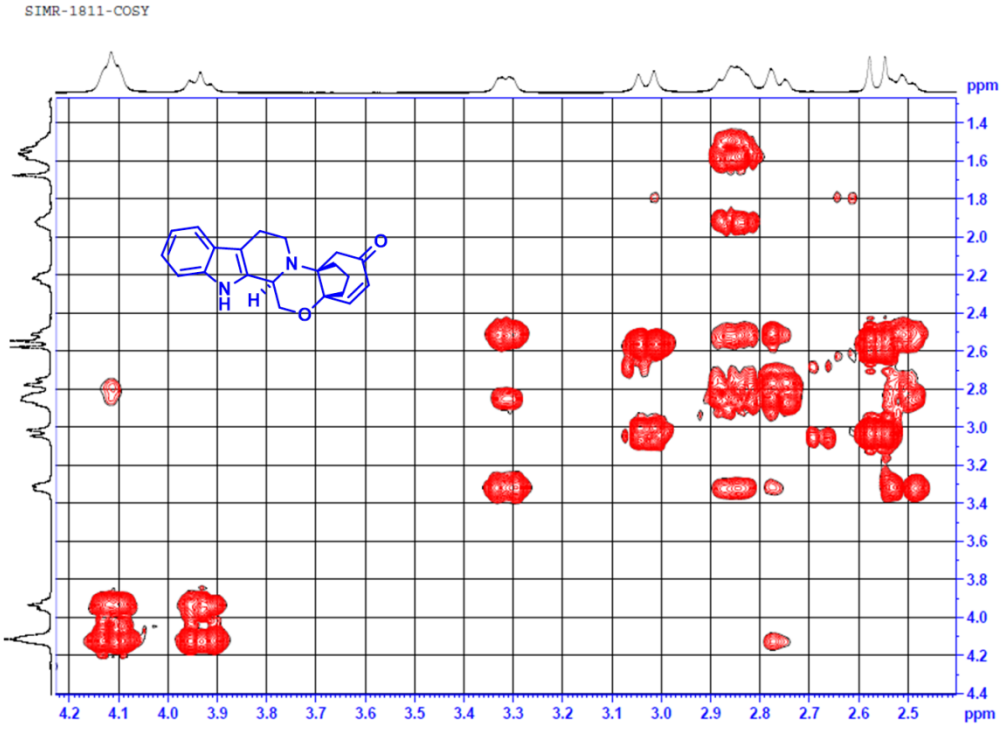
**Supplementary Figure 80** $^{1}$H NMR (500 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bR)-8,9,14,14b-tetrahydro-1H-2a,6a-propanobenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(6H)-one (**12**)



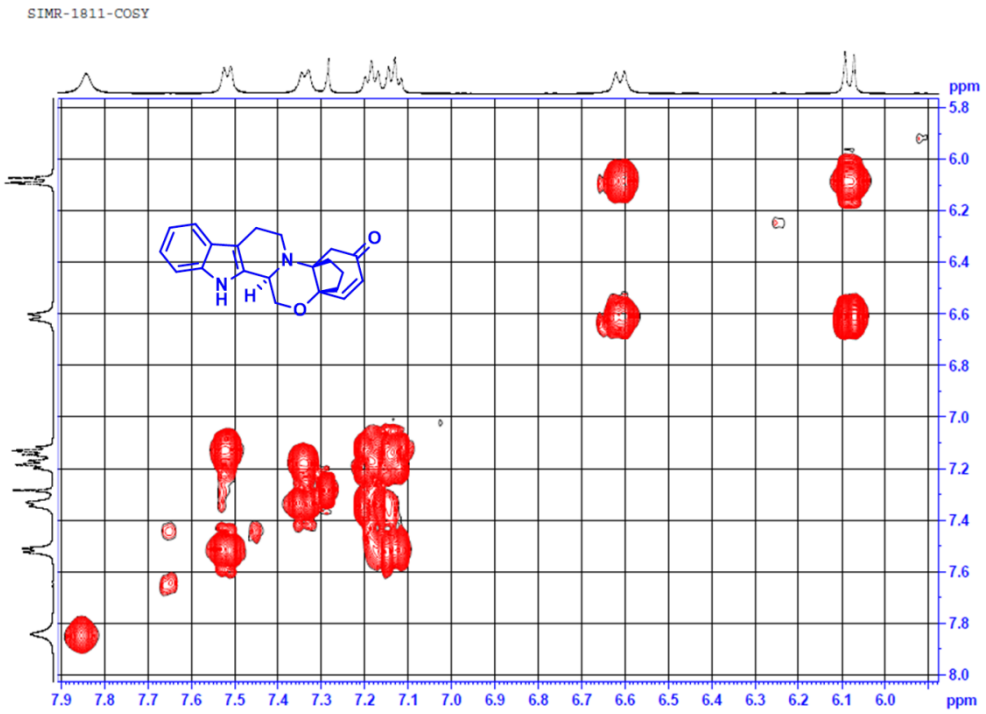
**Supplementary Figure 81** APT NMR (125 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bR)-8,9,14,14b-tetrahydro-1H-2a,6a-propanobenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(6H)-one (**12**)



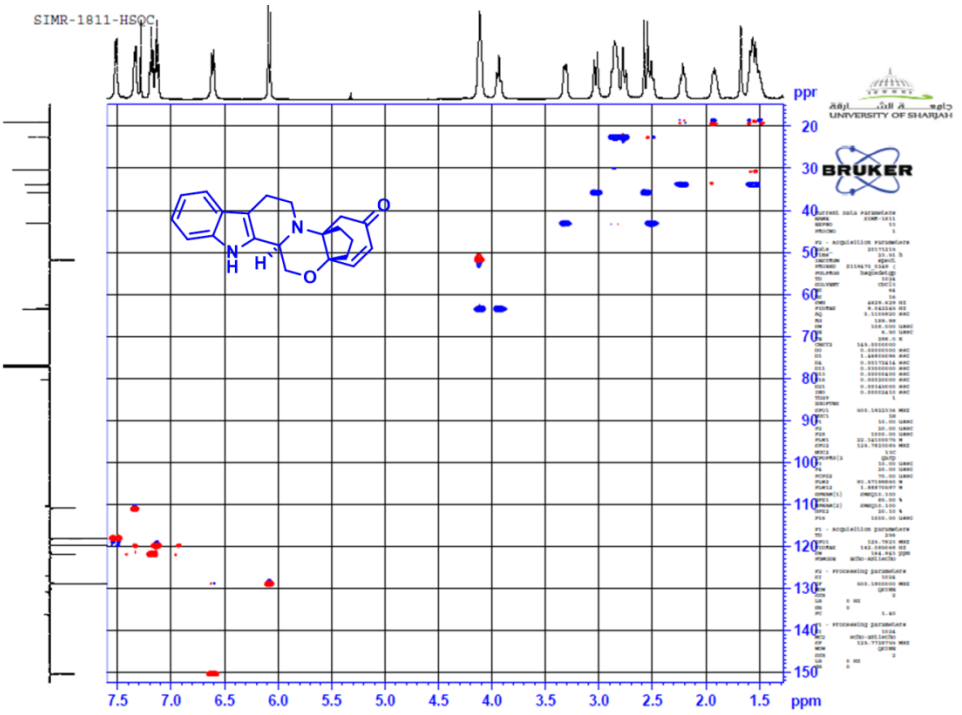

**Supplementary Figure 82** COSY (500 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bR)-8,9,14,14b-tetrahydro-1H-2a,6a-propanobenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(6H)-one (**12**)



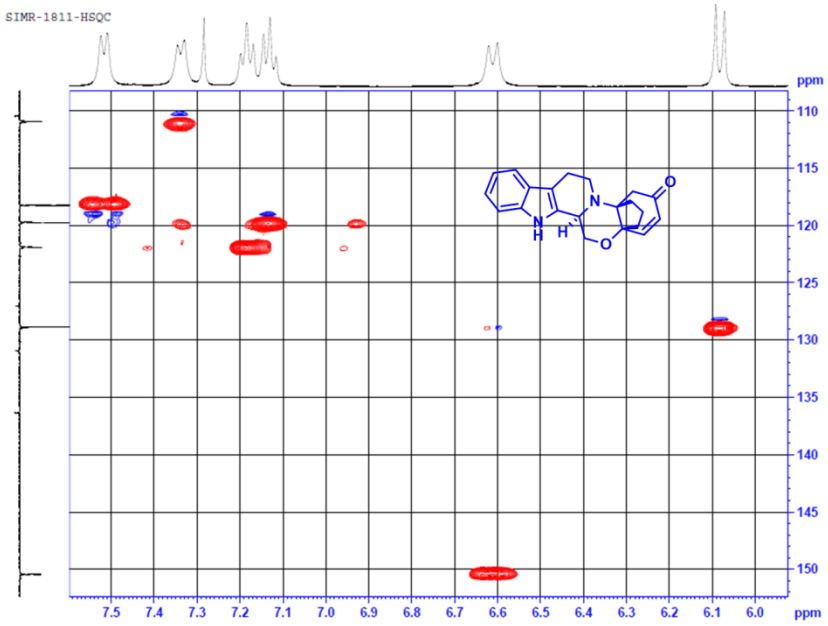

**Supplementary Figure 83** COSY (Expansion) spectrum of (2aS,6aR,14bR)-8,9,14,14b-tetrahydro-1H-2a,6a-propanobenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(6H)-one (**12**)



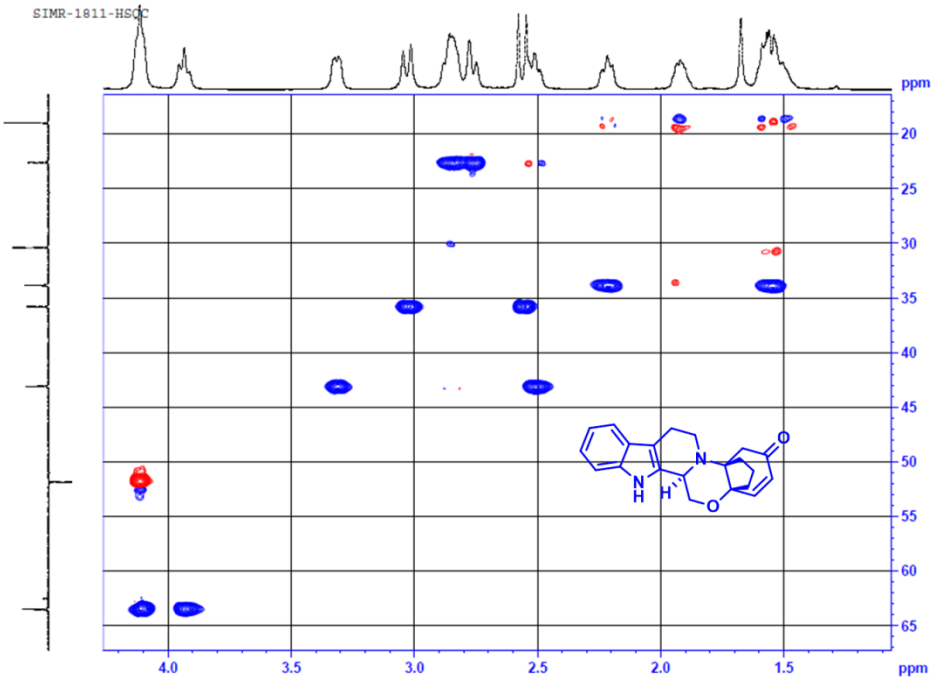

**Supplementary Figure 84** COSY (Expansion) spectrum of (2aS,6aR,14bR)-8,9,14,14b-tetrahydro-1H-2a,6a-propanobenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(6H)-one (**12**)



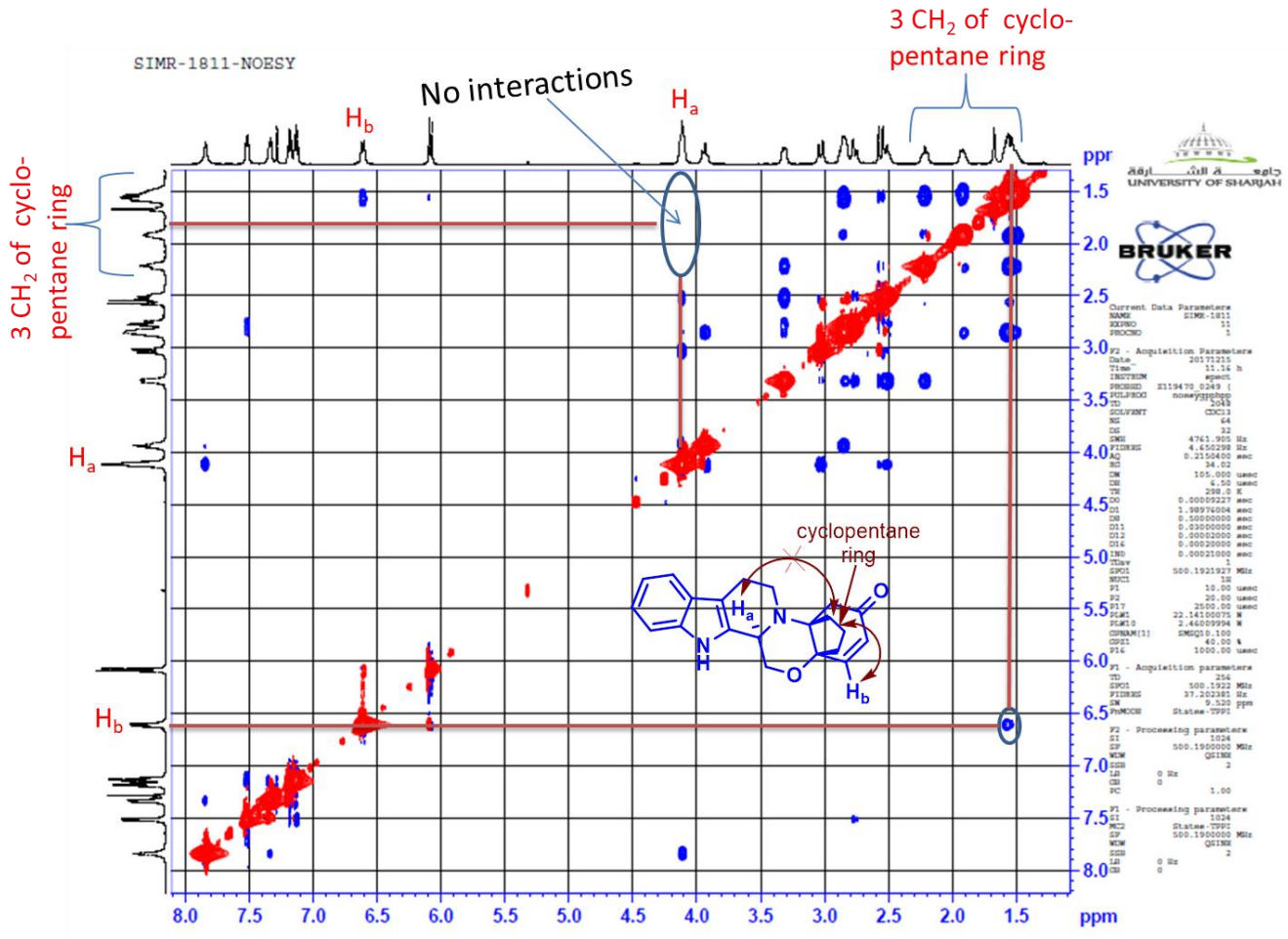

**Supplementary Figure 85** HSQC (500 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bR)-8,9,14,14b-tetrahydro-1H-2a,6a-propanobenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(6H)-one (**12**)



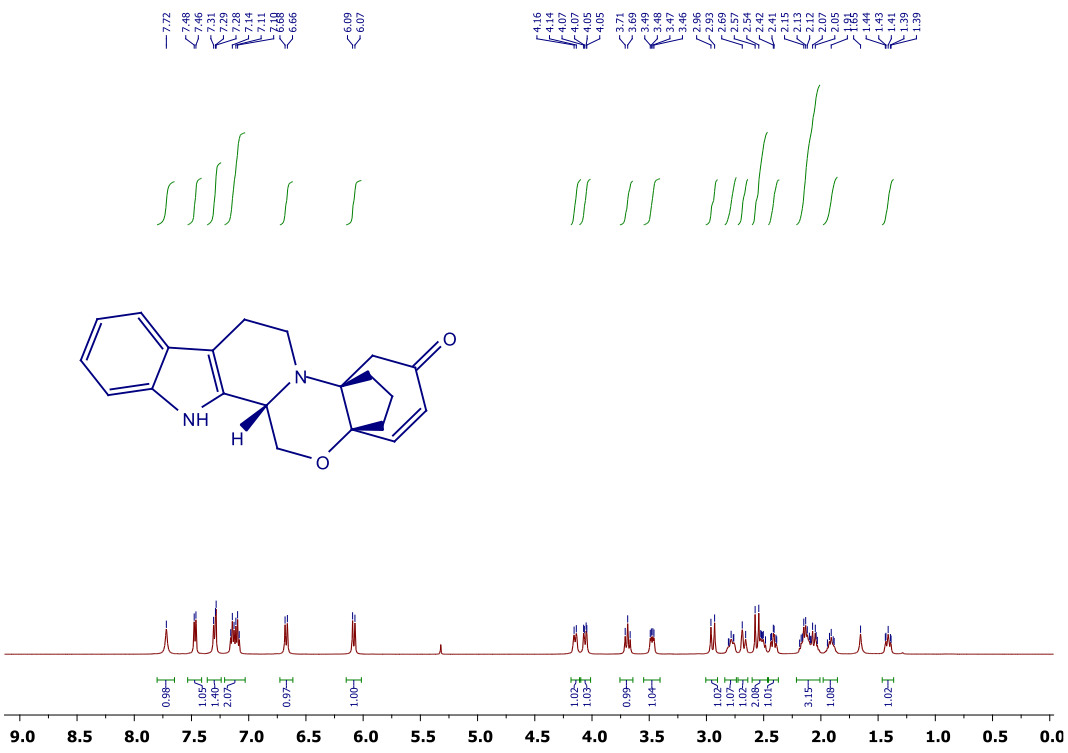

**Supplementary Figure 86** HSQC (Expansion) spectrum of (2aS,6aR,14bR)-8,9,14,14b-tetrahydro-1H-2a,6a-propanobenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(6H)-one (**12**)



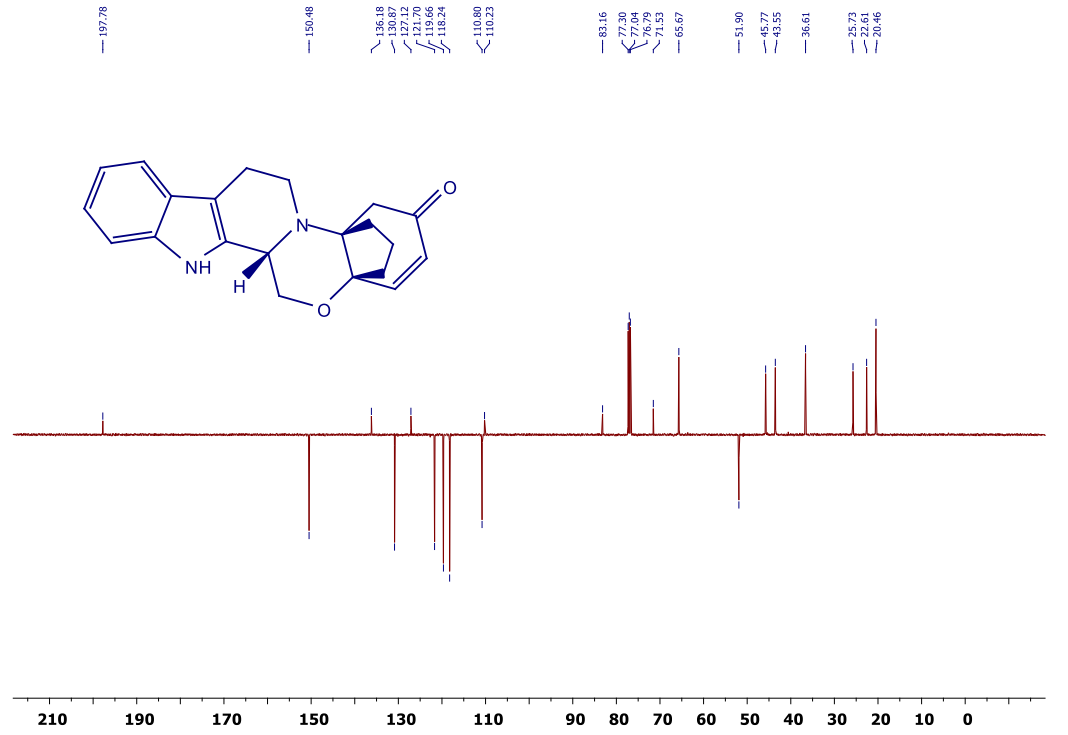

**Supplementary Figure 87** HSQC (Expansion) spectrum of (2aS,6aR,14bR)-8,9,14,14b-tetrahydro-1H-2a,6a-propanobenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(6H)-one (**12**)



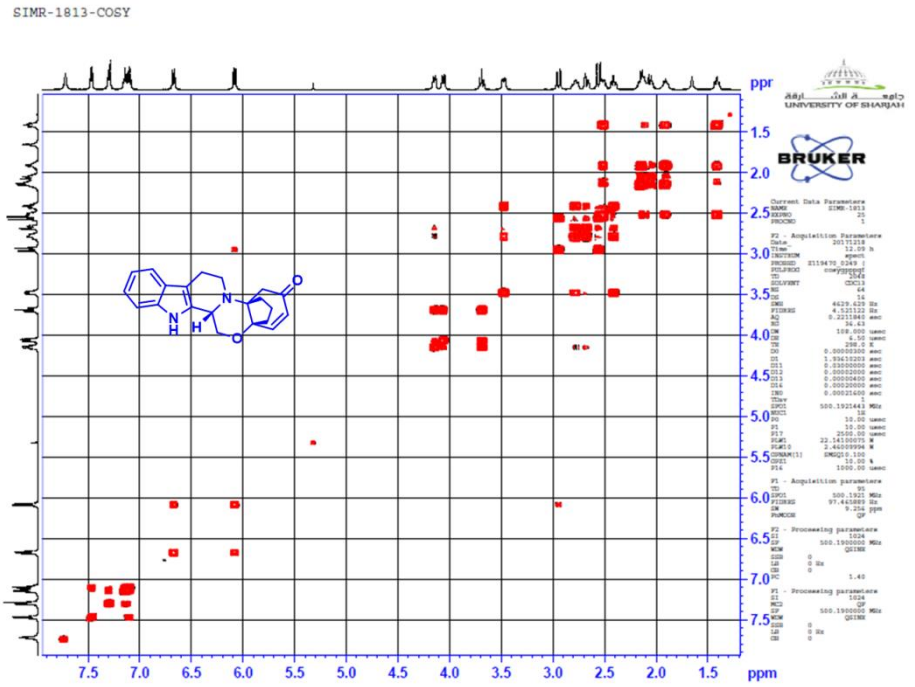

**Supplementary Figure 88** NOESY (500 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bR)-8,9,14,14b-tetrahydro-1H-2a,6a-propanobenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(6H)-one (**12**)



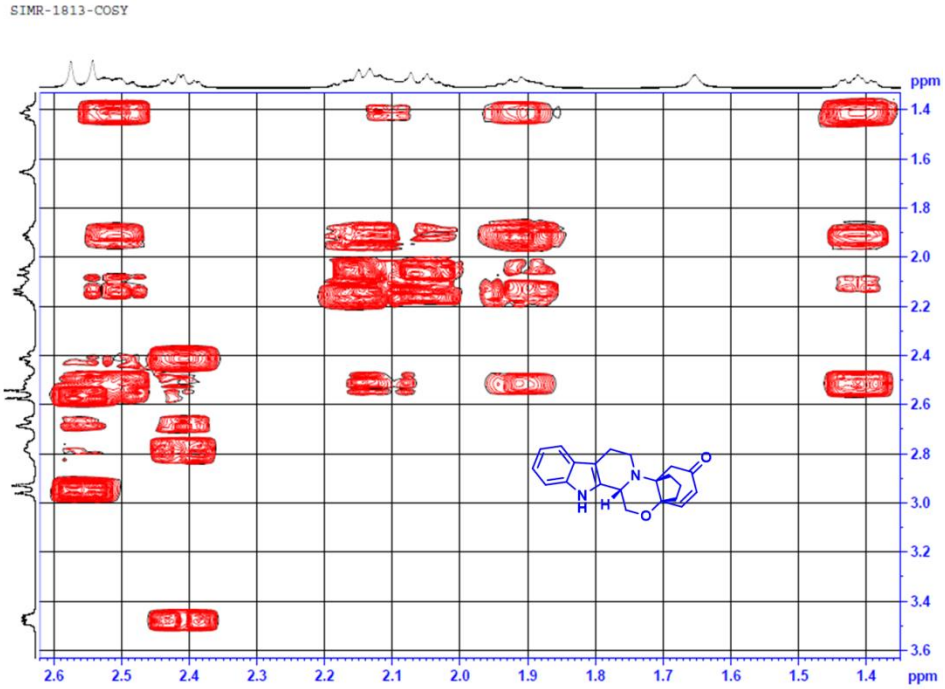
**Supplementary Figure 89** $^{1}$H NMR (500 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bS)-8,9,14,14b-tetrahydro-1H-2a,6a-propanobenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(6H)-one (**13**)



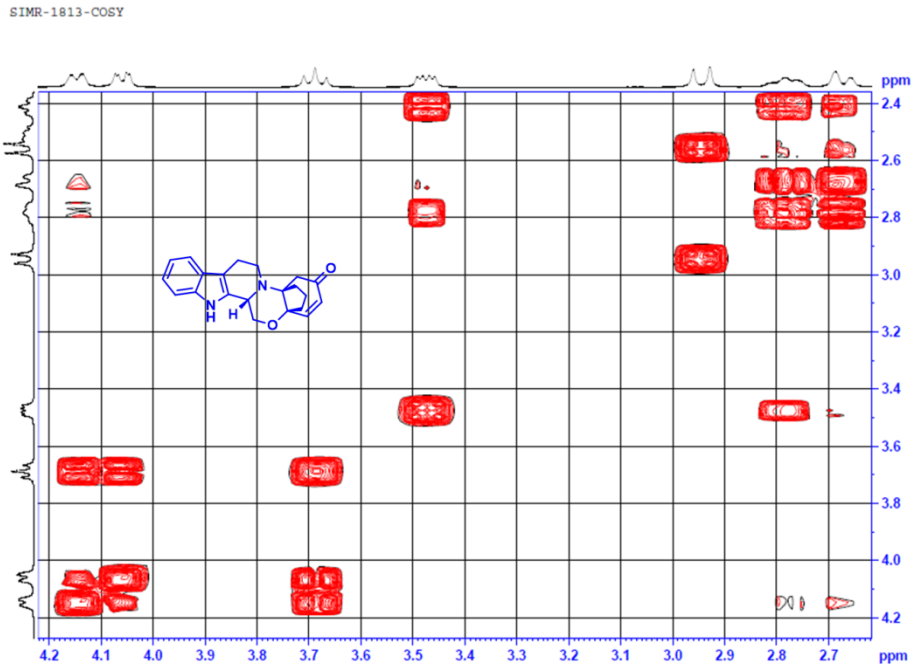
**Supplementary Figure 90** APT NMR (125 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bS)-8,9,14,14b-tetrahydro-1H-2a,6a-propanobenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(6H)-one (**13**)



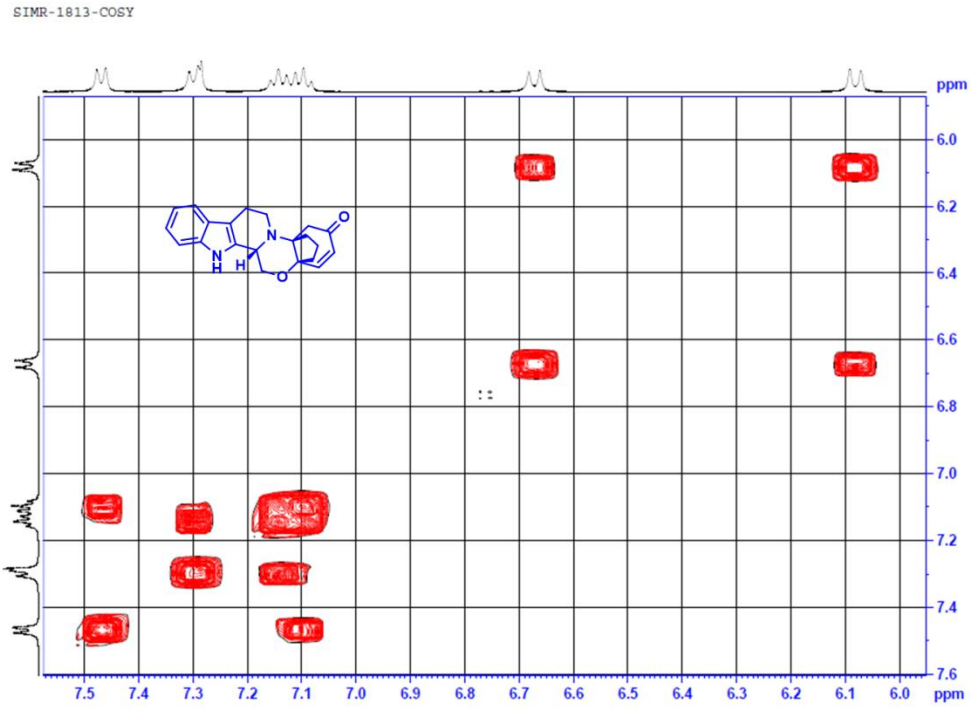

**Supplementary Figure 91** COSY (500 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bS)-8,9,14,14b-tetrahydro-1H-2a,6a-propanobenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(6H)-one (**13**)



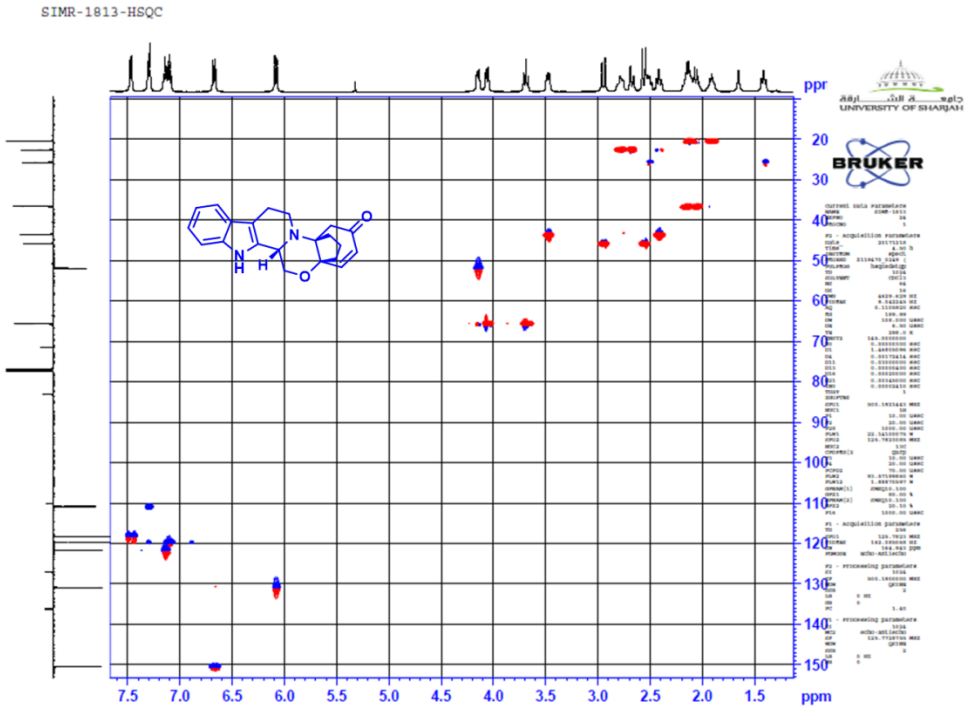

**Supplementary Figure 92** COSY (Expansion) spectrum of (2aS,6aR,14bS)-8,9,14,14b-tetrahydro-1H-2a,6a-propanobenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(6H)-one (**13**)



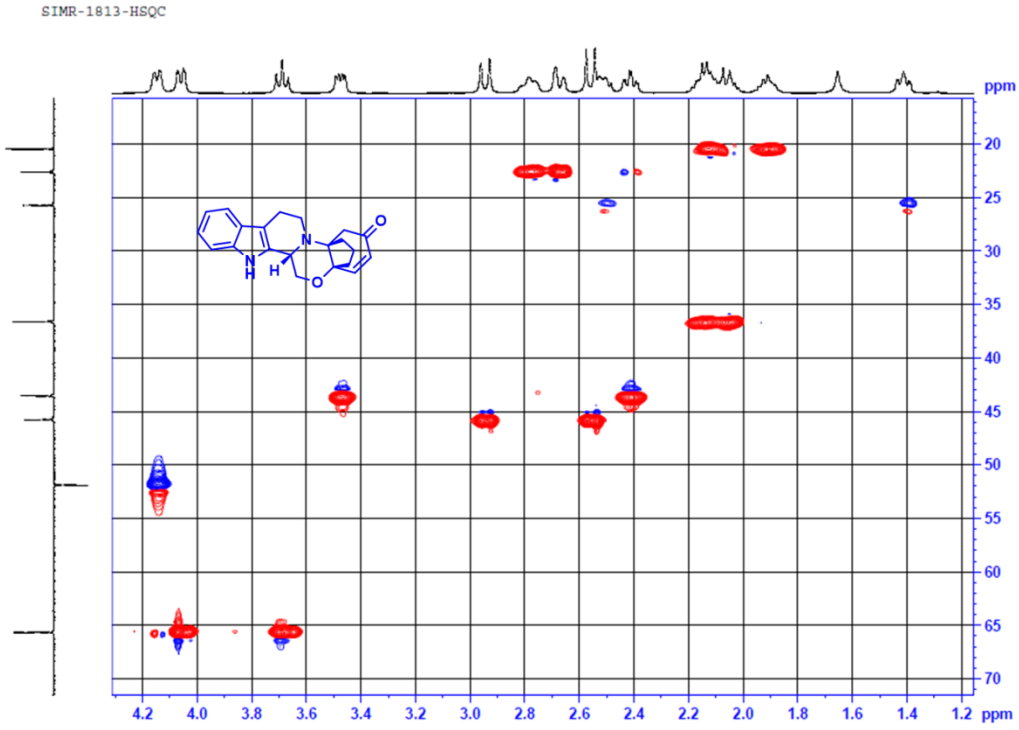

**Supplementary Figure 93** COSY (Expansion) spectrum of (2aS,6aR,14bS)-8,9,14,14b-tetrahydro-1H-2a,6a-propanobenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(6H)-one (**13**)



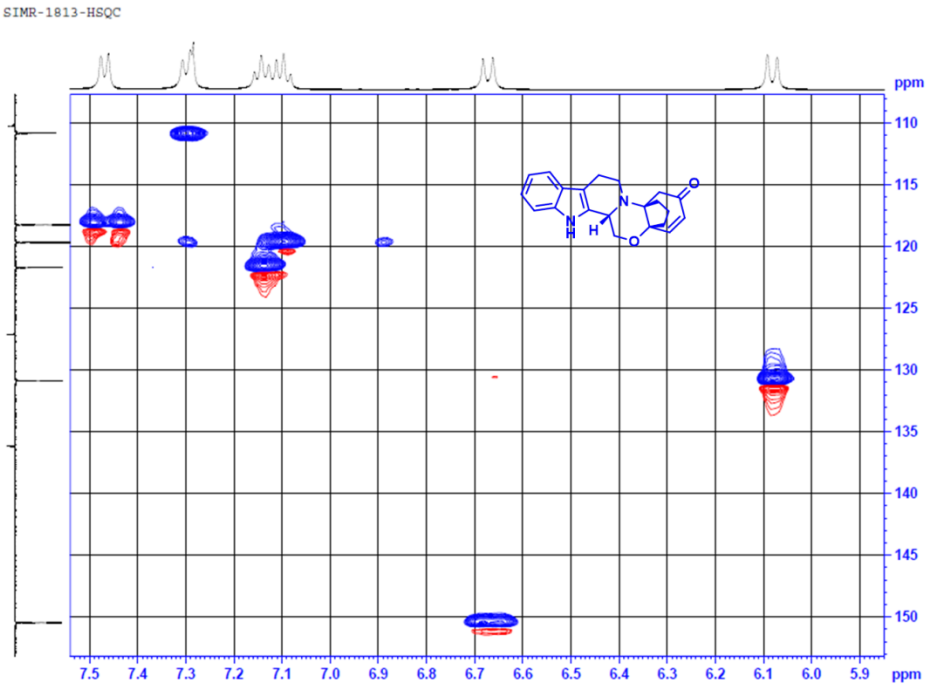

**Supplementary Figure 94** COSY (Expansion) spectrum of (2aS,6aR,14bS)-8,9,14,14b-tetrahydro-1H-2a,6a-propanobenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(6H)-one (**13**)



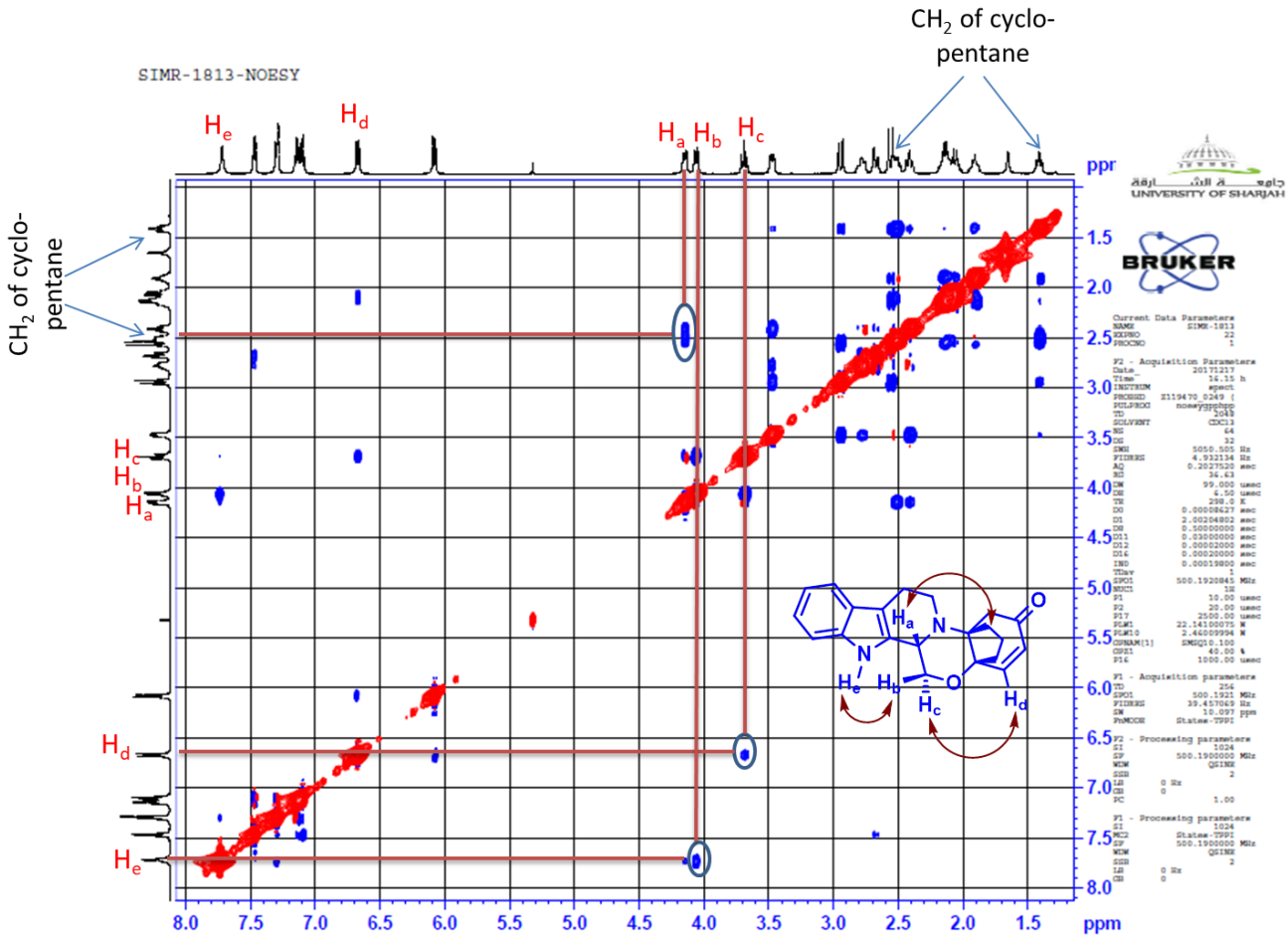

**Supplementary Figure 95** HSQC (500 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bS)-8,9,14,14b-tetrahydro-1H-2a,6a-propanobenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(6H)-one (**13**)



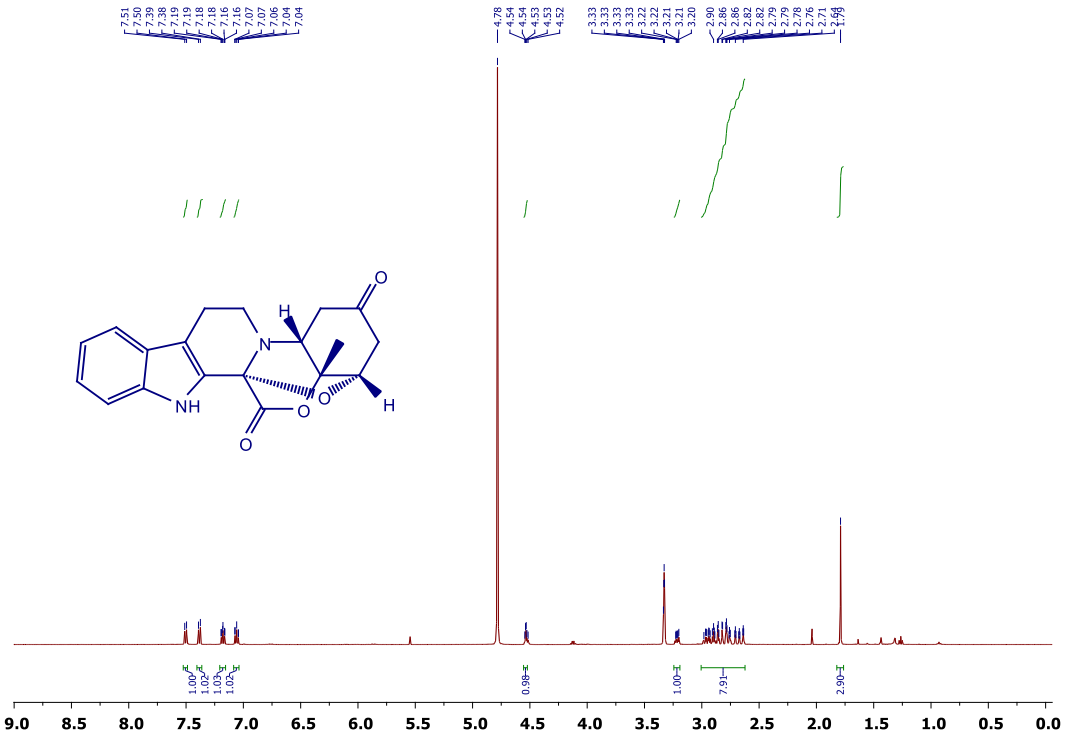

**Supplementary Figure 96** HSQC (Expansion) spectrum of (2aS,6aR,14bS)-8,9,14,14b-tetrahydro-1H-2a,6a-propanobenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(6H)-one (**13**)



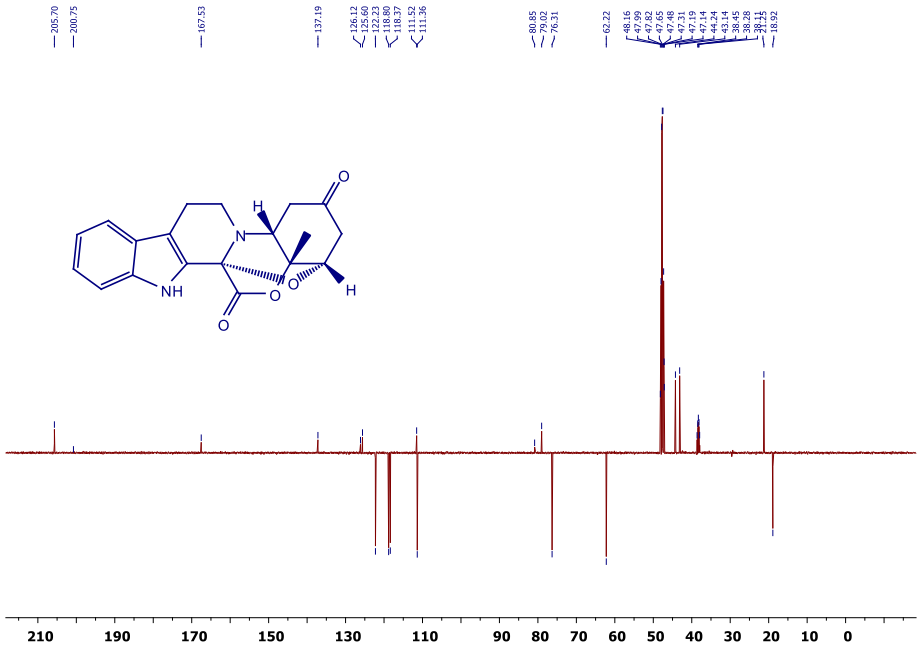

**Supplementary Figure 97** HSQC (Expansion) spectrum of (2aS,6aR,14bS)-8,9,14,14b-tetrahydro-1H-2a,6a-propanobenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(6H)-one (**13**)



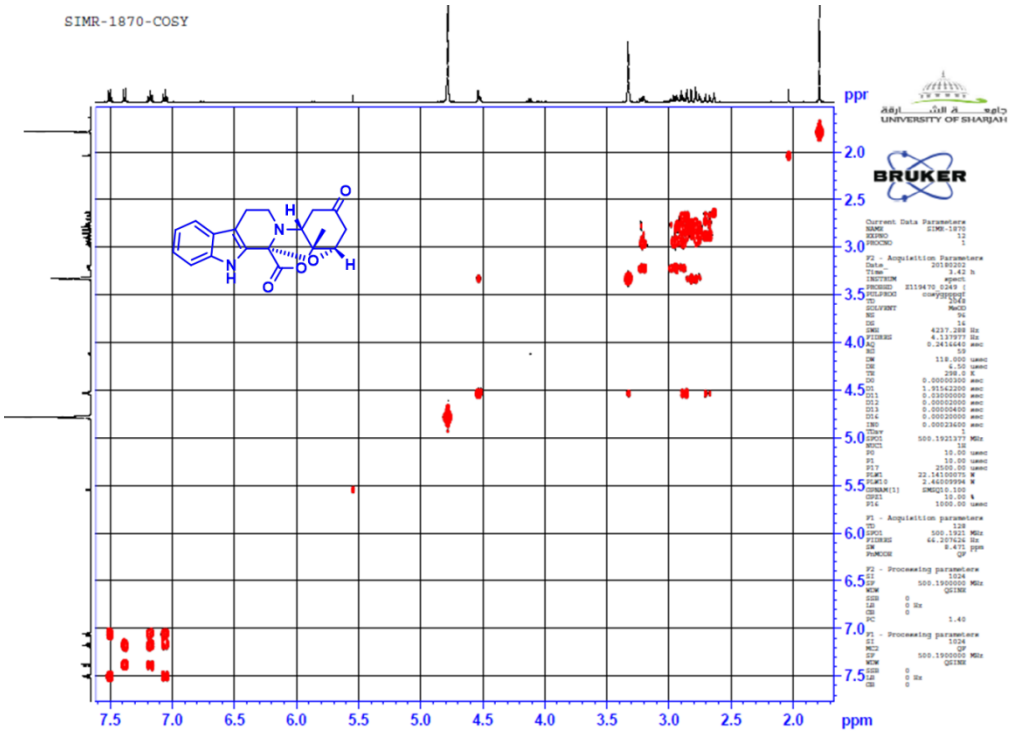

**Supplementary Figure 98** NOESY (500 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bS)-8,9,14,14b-tetrahydro-1H-2a,6a-propanobenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(6H)-one (**13**)



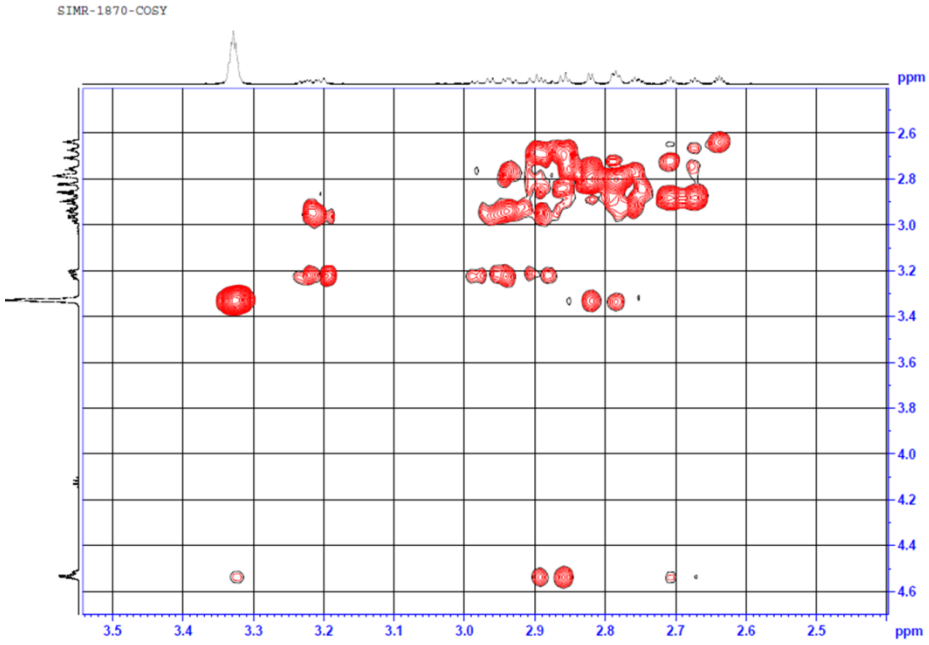
**Supplementary Figure 99** $^{1}$H NMR (500 MHz, $CD_3OD$) spectrum of (2aR,3S,6aR,14bS)-2a-methyl-3,4,6,6a,9,14-hexahydro-1H,8H-3,14b-epoxybenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-1,5(2aH)-dione (**14**)



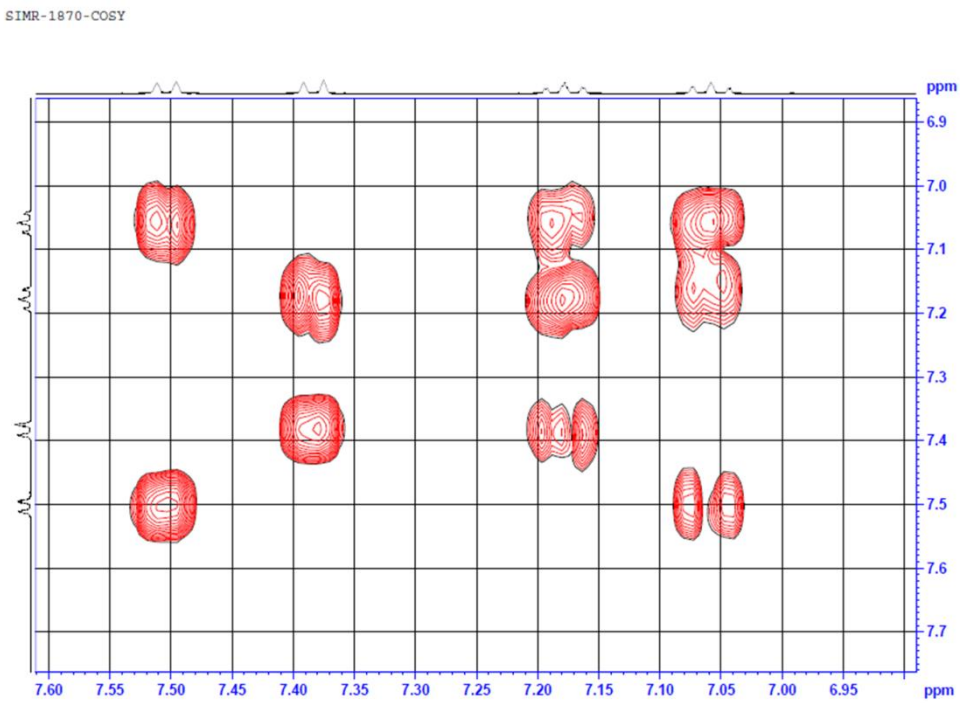
**Supplementary Figure 100** APT NMR (125 MHz, $CD_3OD$) spectrum of (2aR,3S,6aR,14bS)-2a-methyl-3,4,6,6a,9,14-hexahydro-1H,8H-3,14b-epoxybenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-1,5(2aH)-dione (**14**)



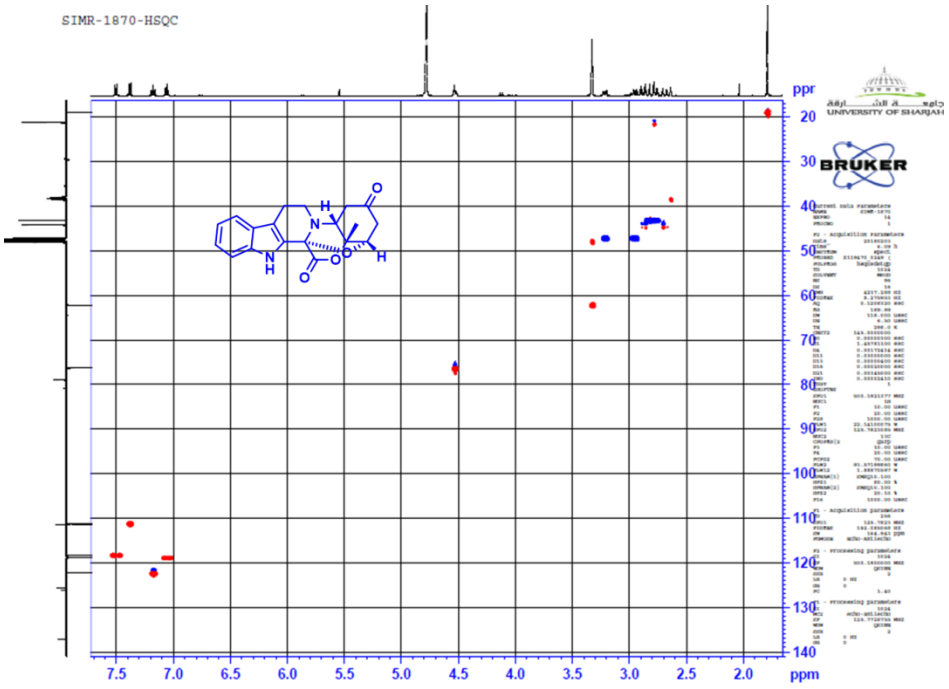

**Supplementary Figure 101** COSY (500 MHz, $CD_3OD$) spectrum of (2aR,3S,6aR,14bS)-2a-methyl-3,4,6,6a,9,14-hexahydro-1H,8H-3,14b-epoxybenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-1,5(2aH)-dione (**14**)



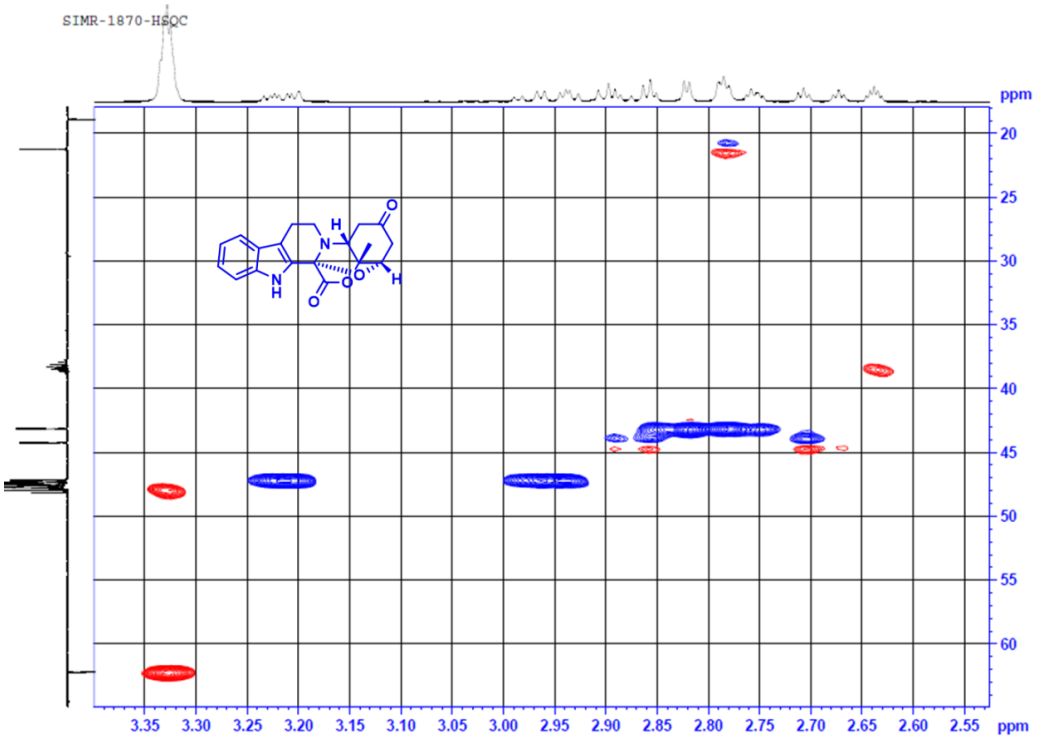

**Supplementary Figure 102** COSY (Expansion) spectrum of (2aR,3S,6aR,14bS)-2a-methyl-3,4,6,6a,9,14-hexahydro-1H,8H-3,14b-epoxybenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-1,5(2aH)-dione (**14**)



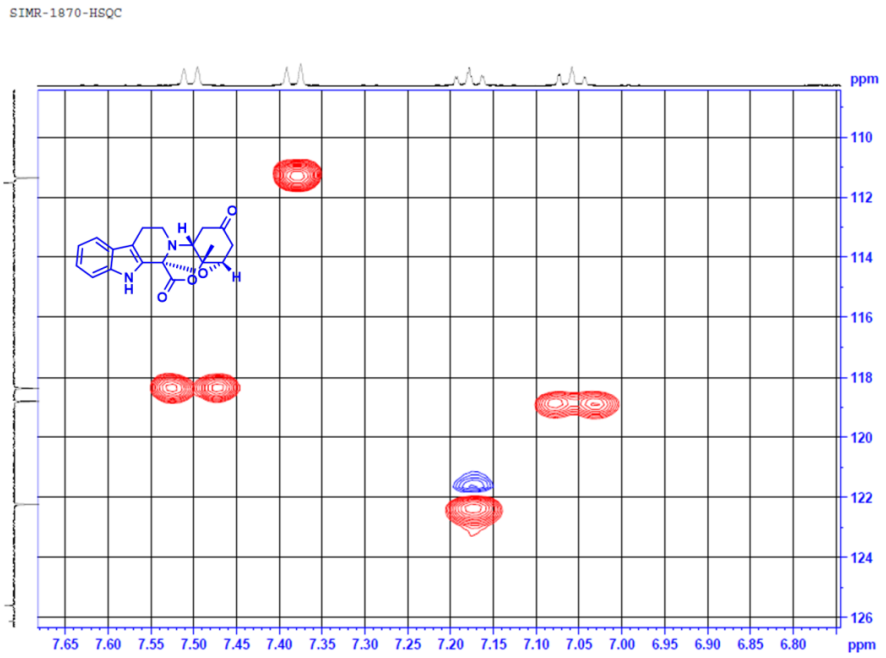

**Supplementary Figure 103** COSY (Expansion) spectrum of (2aR,3S,6aR,14bS)-2a-methyl-3,4,6,6a,9,14-hexahydro-1H,8H-3,14b-epoxybenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-1,5(2aH)-dione (**14**)



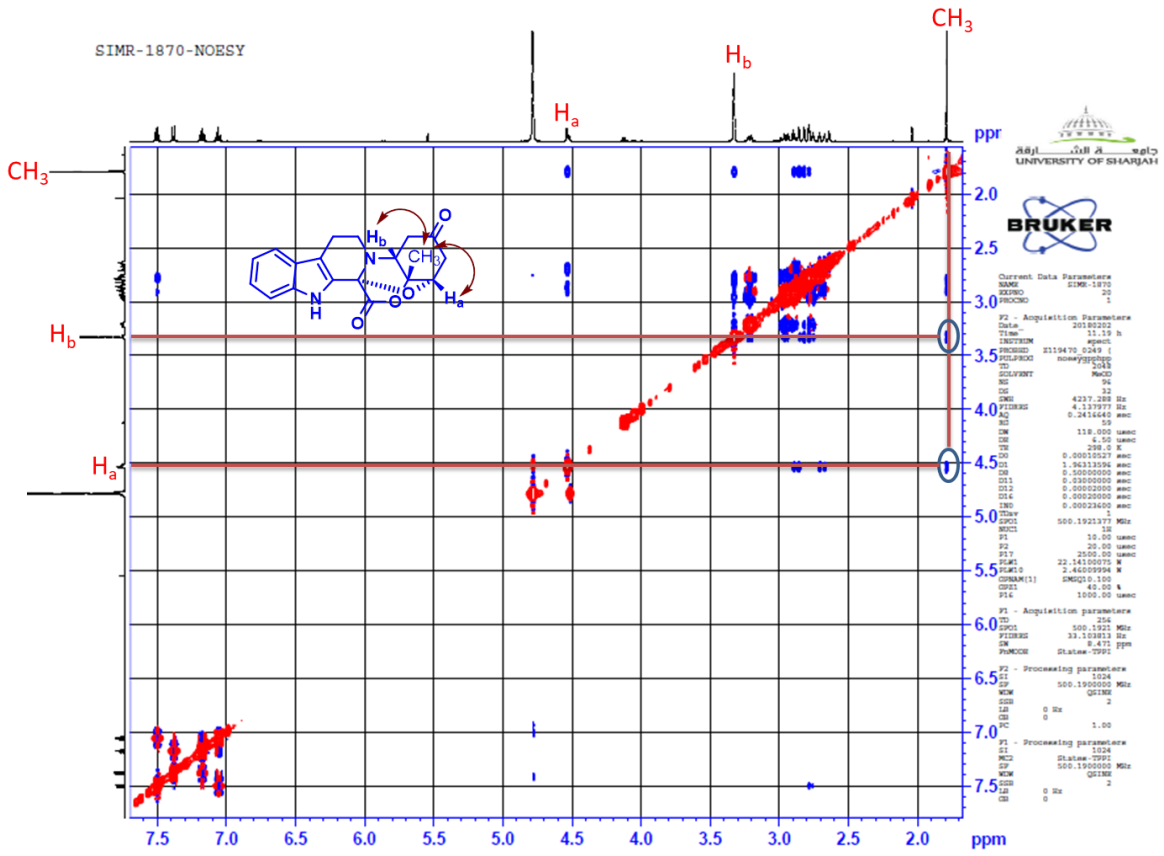

**Supplementary Figure 104** HSQC (500 MHz, $CD_3OD$) spectrum of (2aR,3S,6aR,14bS)-2a-methyl-3,4,6,6a,9,14-hexahydro-1H,8H-3,14b-epoxybenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-1,5(2aH)-dione (**14**)



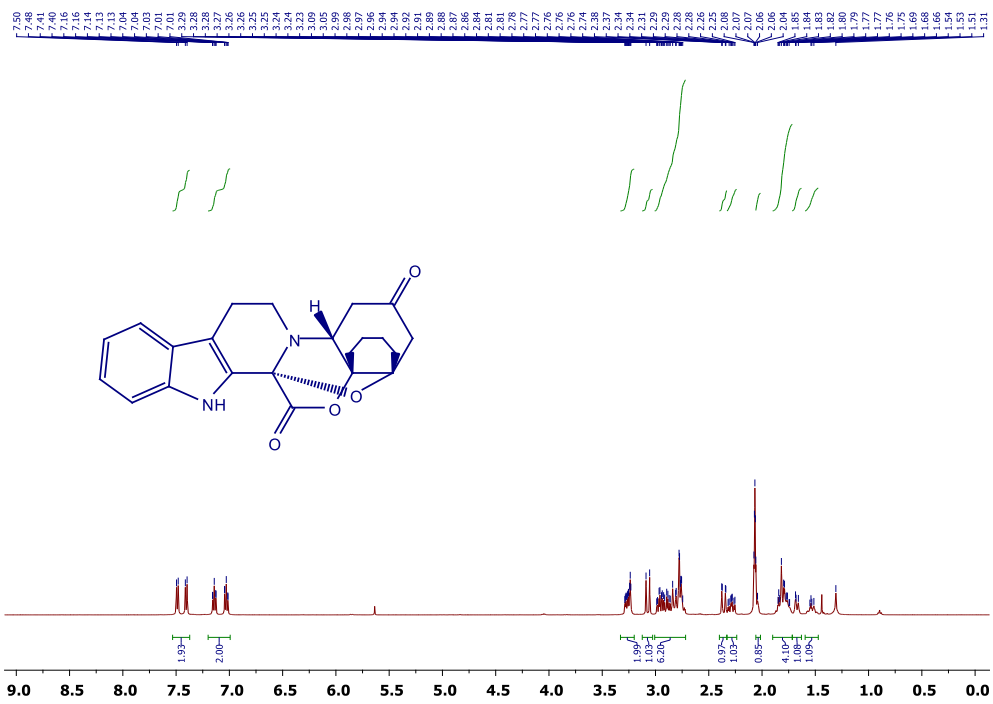

**Supplementary Figure 105** HSQC (Expansion) spectrum of (2aR,3S,6aR,14bS)-2a-methyl-3,4,6,6a,9,14-hexahydro-1H,8H-3,14b-epoxybenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-1,5(2aH)-dione (**14**)



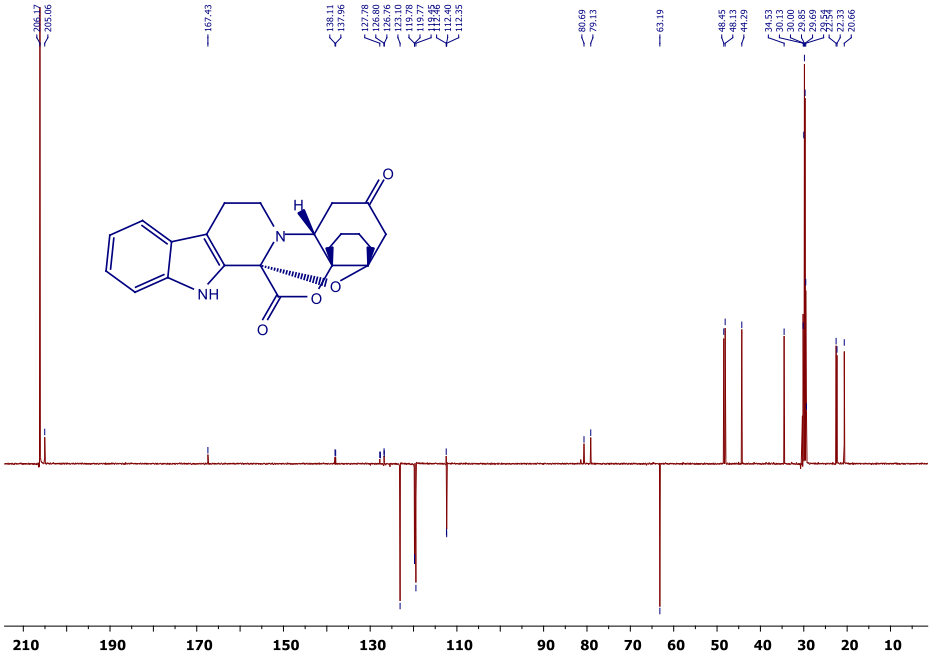

**Supplementary Figure 106** HSQC (Expansion) spectrum of (2aR,3S,6aR,14bS)-2a-methyl-3,4,6,6a,9,14-hexahydro-1H,8H-3,14b-epoxybenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-1,5(2aH)-dione (**14**)



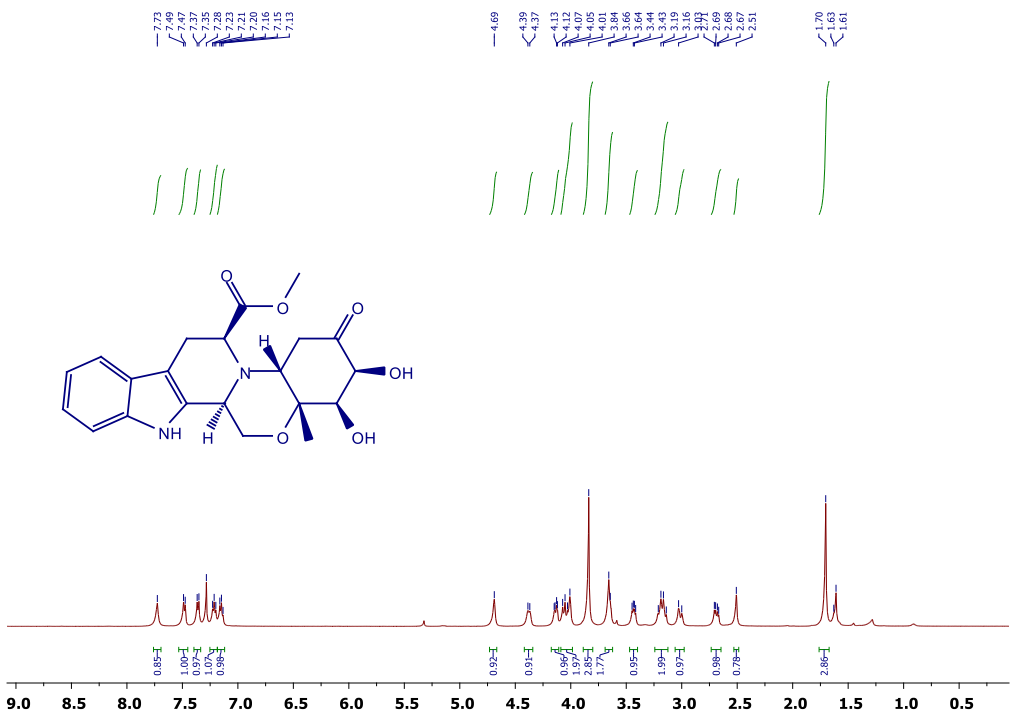

**Supplementary Figure 107** NOESY (500 MHz, $CD_3OD$) spectrum of (2aR,3S,6aR,14bS)-2a-methyl-3,4,6,6a,9,14-hexahydro-1H,8H-3,14b-epoxybenzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-1,5(2aH)-dione (**14**)



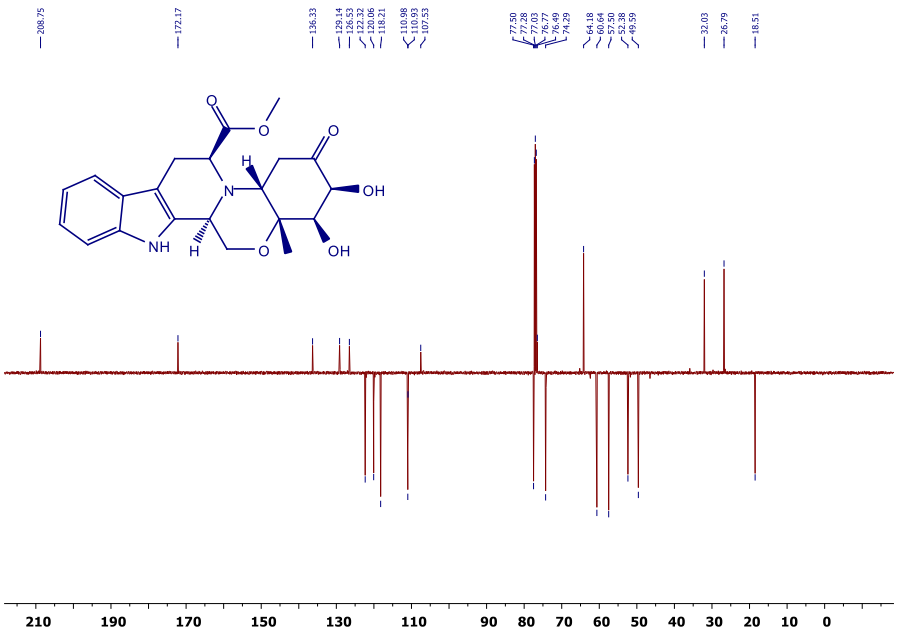
**Supplementary Figure 108** $^{1}$H NMR (500 MHz, Acetone-$d_6$) spectrum of (2aR,6aS,9aR,17bS)-3,4,5,6,9,9a,12,17-octahydro-1H,11H-6a,17b-epoxynaphtho[1",8a":5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-1,8(7H)-dione (**15**)



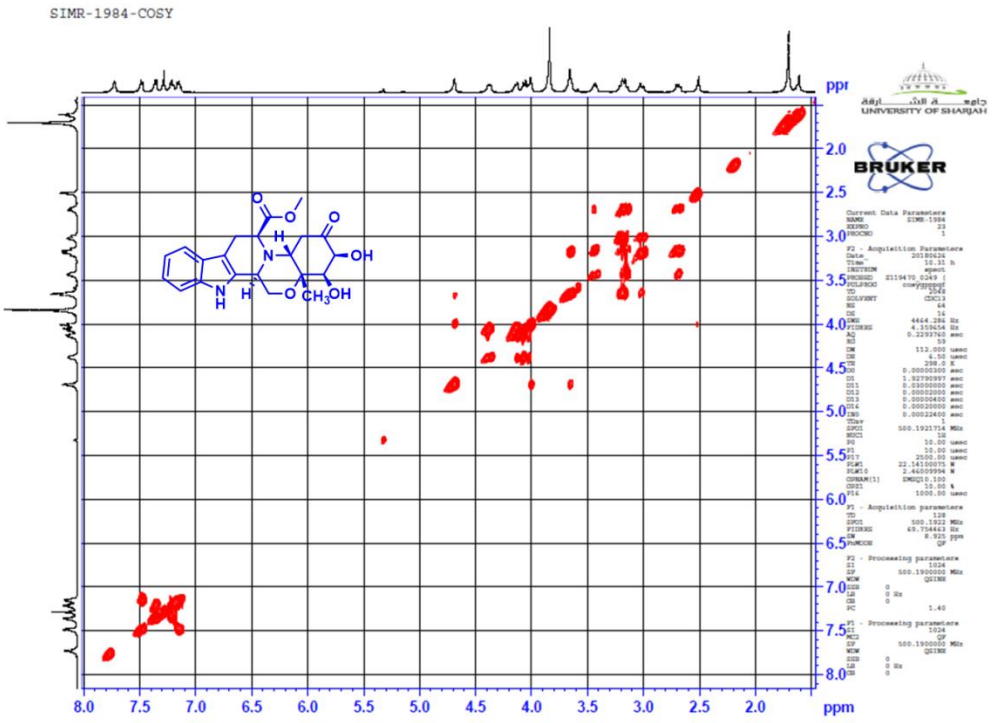
**Supplementary Figure 109** APT NMR (125 MHz, Acetone-$d_6$) spectrum of (2aR,6aS,9aR,17bS)-3,4,5,6,9,9a,12,17-octahydro-1H,11H-6a,17b-epoxynaphtho[1",8a":5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-1,8(7H)-dione (**15**)



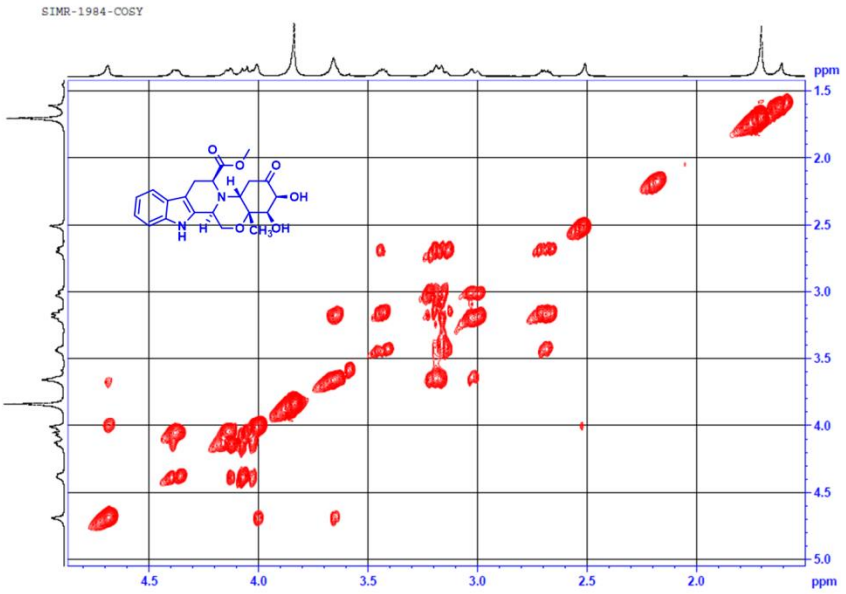
**Supplementary Figure 110** $^{1}$H (500 MHz, $CDCl_3$) spectrum of methyl (2aR,3R,4S,6aR,8S,14bR)-3,4-dihydroxy-2a-methyl-5-oxo-2a,3,4,5,6,6a,8,9,14,14b-decahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-8-carboxylate (**16**)



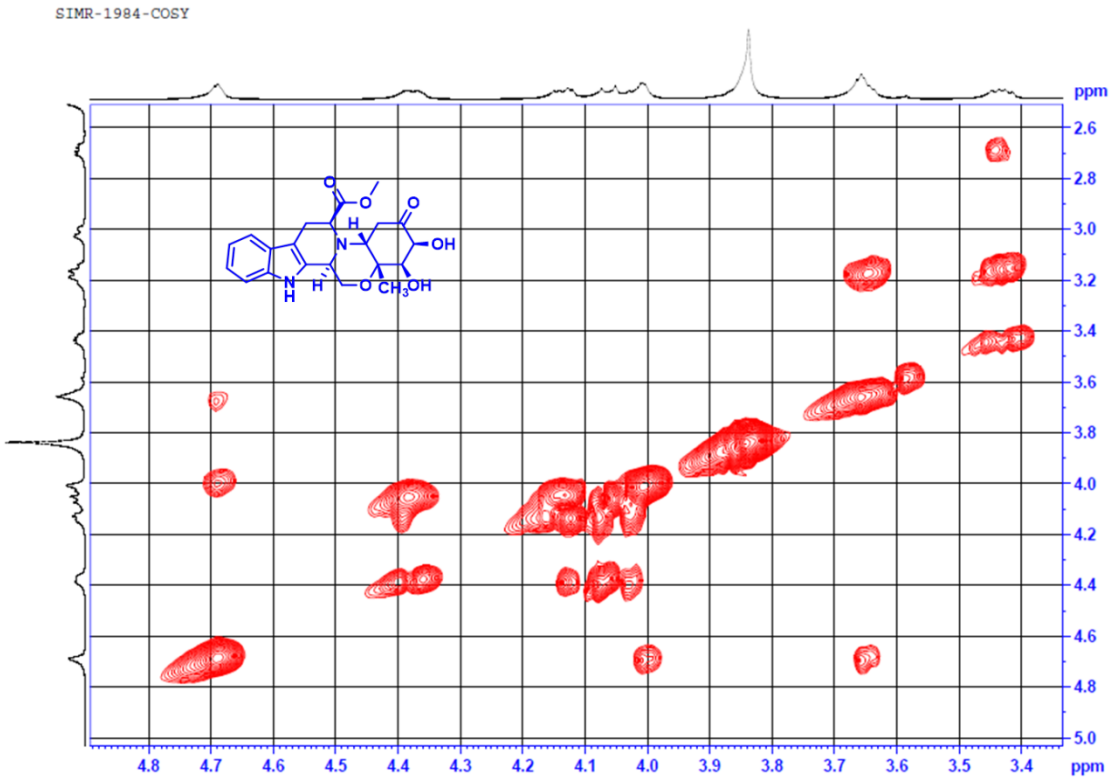
**Supplementary Figure 111** APT (125 MHz, $CDCl_3$) spectrum of methyl (2aR,3R,4S,6aR,8S,14bR)-3,4-dihydroxy-2a-methyl-5-oxo-2a,3,4,5,6,6a,8,9,14,14b-decahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-8-carboxylate (**16**)



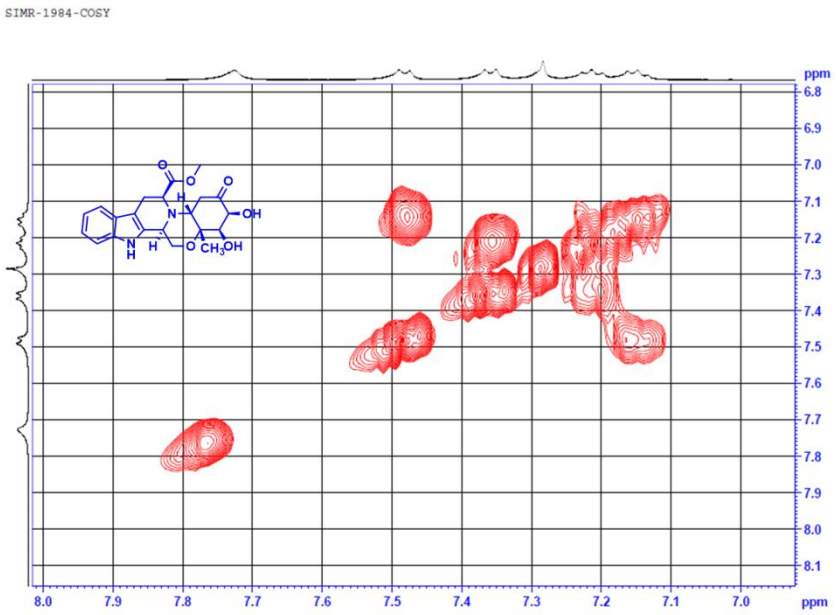

**Supplementary Figure 112** COSY (500 MHz, $CDCl_3$) spectrum of methyl (2aR,3R,4S,6aR,8S,14bR)-3,4-dihydroxy-2a-methyl-5-oxo-2a,3,4,5,6,6a,8,9,14,14b-decahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-8-carboxylate (**16**)



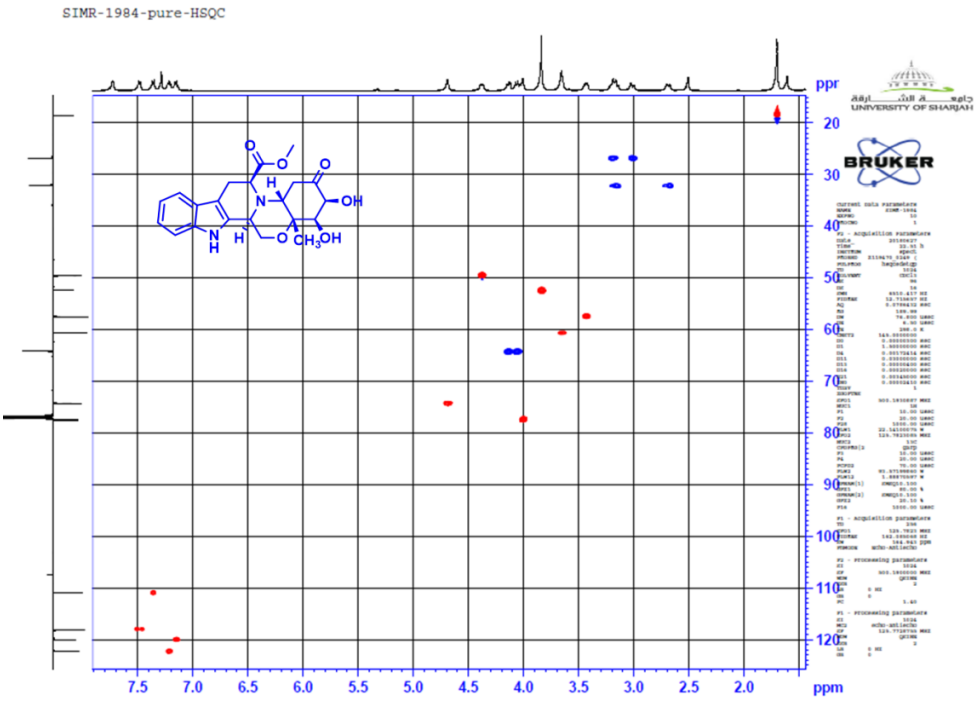

**Supplementary Figure 113** COSY (Expansion) spectrum of methyl (2aR,3R,4S,6aR,8S,14bR)-3,4-dihydroxy-2a-methyl-5-oxo-2a,3,4,5,6,6a,8,9,14,14b-decahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-8-carboxylate (**16**)



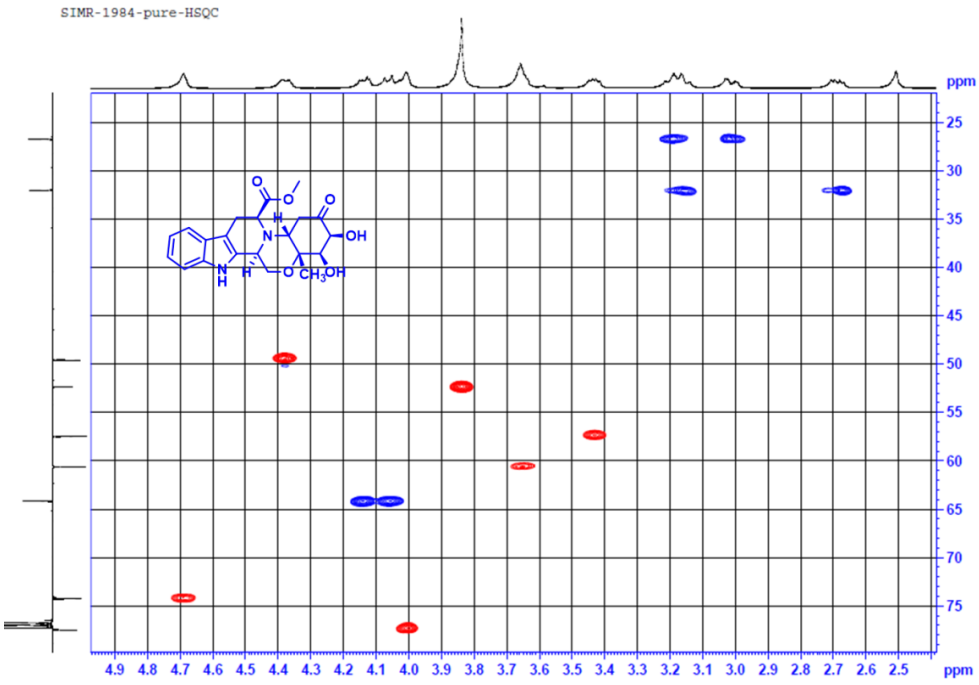

**Supplementary Figure 114** COSY (Expansion) spectrum of methyl (2aR,3R,4S,6aR,8S,14bR)-3,4-dihydroxy-2a-methyl-5-oxo-2a,3,4,5,6,6a,8,9,14,14b-decahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-8-carboxylate (**16**)



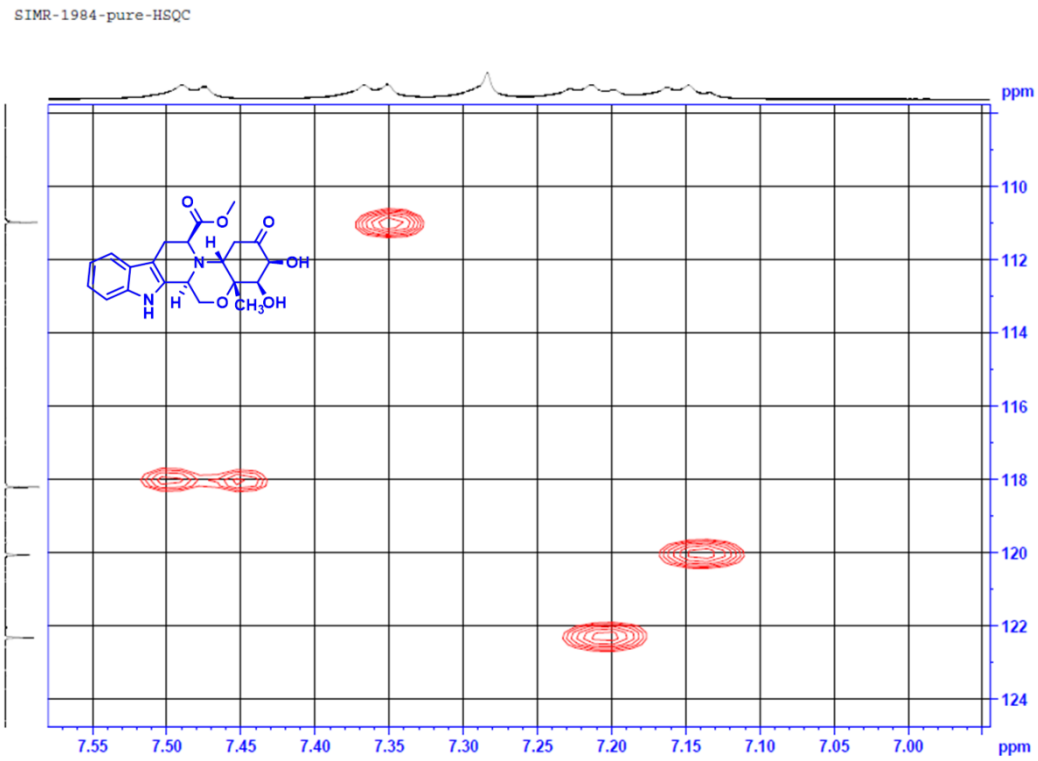

**Supplementary Figure 115** COSY (Expansion) spectrum of methyl (2aR,3R,4S,6aR,8S,14bR)-3,4-dihydroxy-2a-methyl-5-oxo-2a,3,4,5,6,6a,8,9,14,14b-decahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-8-carboxylate (**16**)



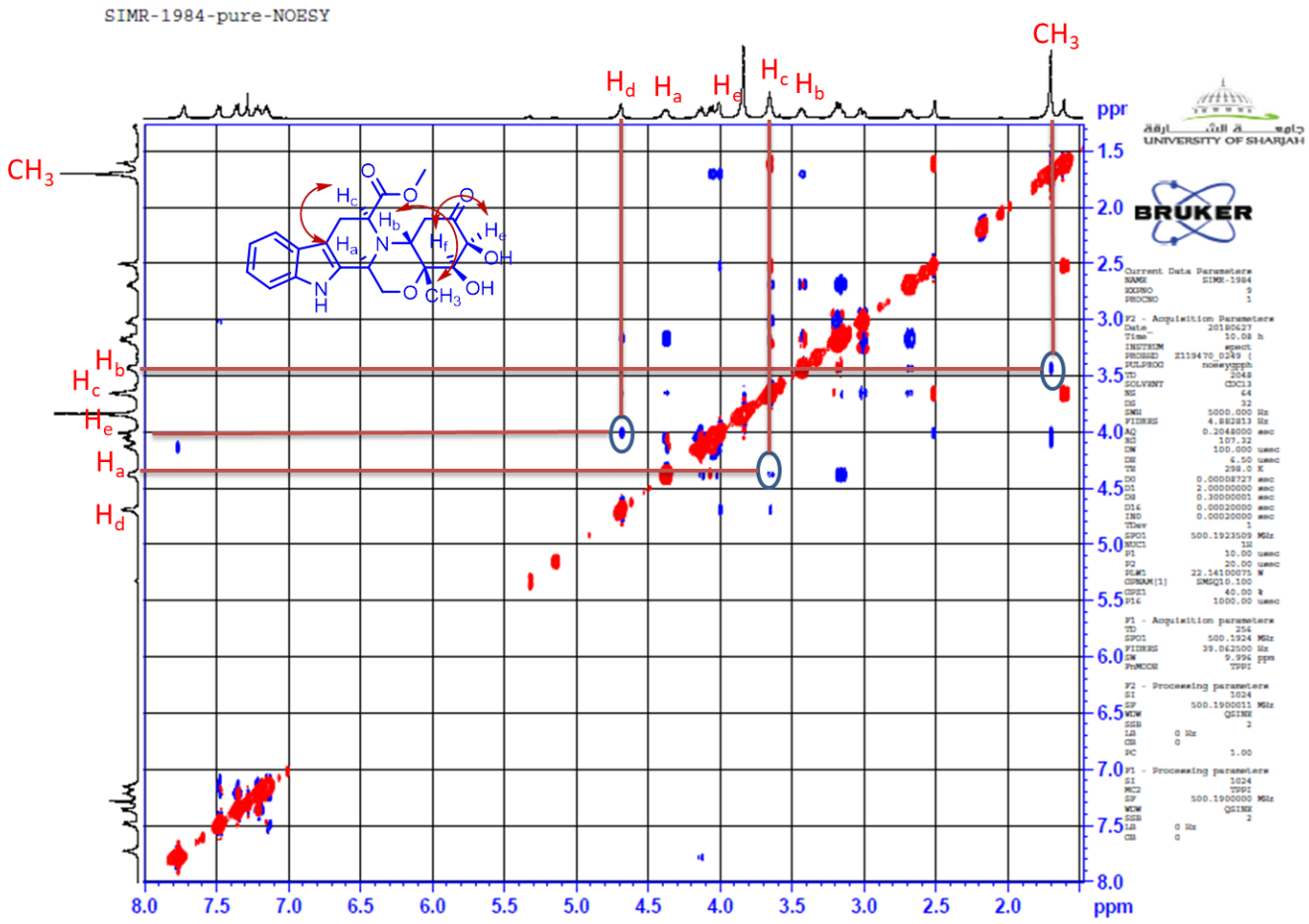

**Supplementary Figure 116** HSQC (500 MHz, $CDCl_3$) spectrum of methyl (2aR,3R,4S,6aR,8S,14bR)-3,4-dihydroxy-2a-methyl-5-oxo-2a,3,4,5,6,6a,8,9,14,14b-decahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-8-carboxylate (**16**)



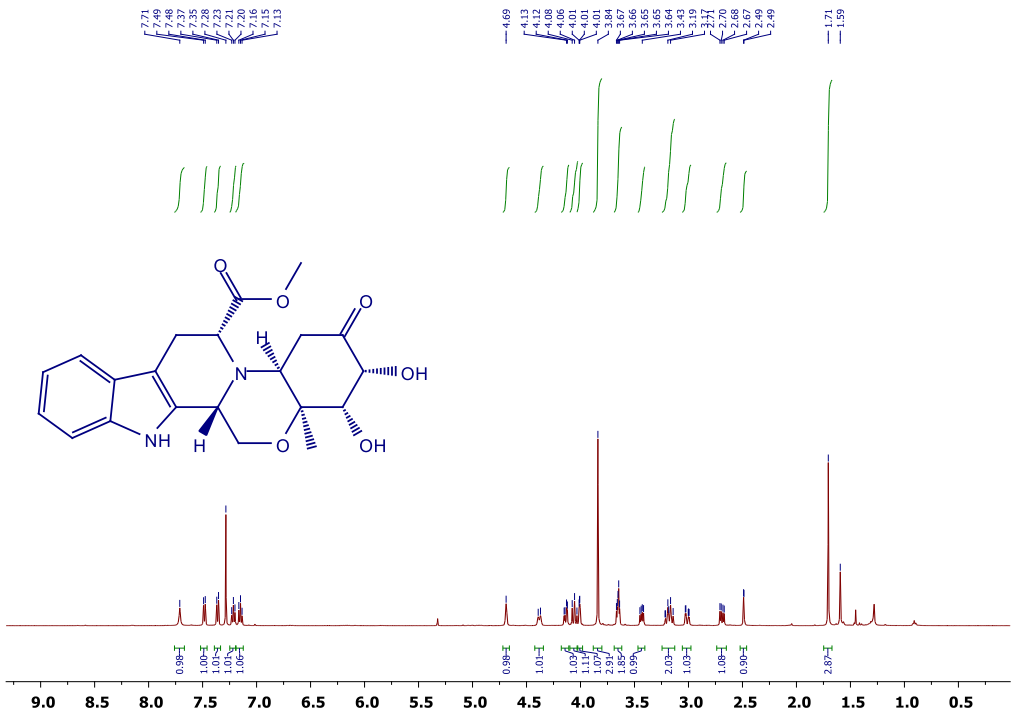

**Supplementary Figure 117** HSQC (Expansion) spectrum of methyl (2aR,3R,4S,6aR,8S,14bR)-3,4-dihydroxy-2a-methyl-5-oxo-2a,3,4,5,6,6a,8,9,14,14b-decahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-8-carboxylate (**16**)



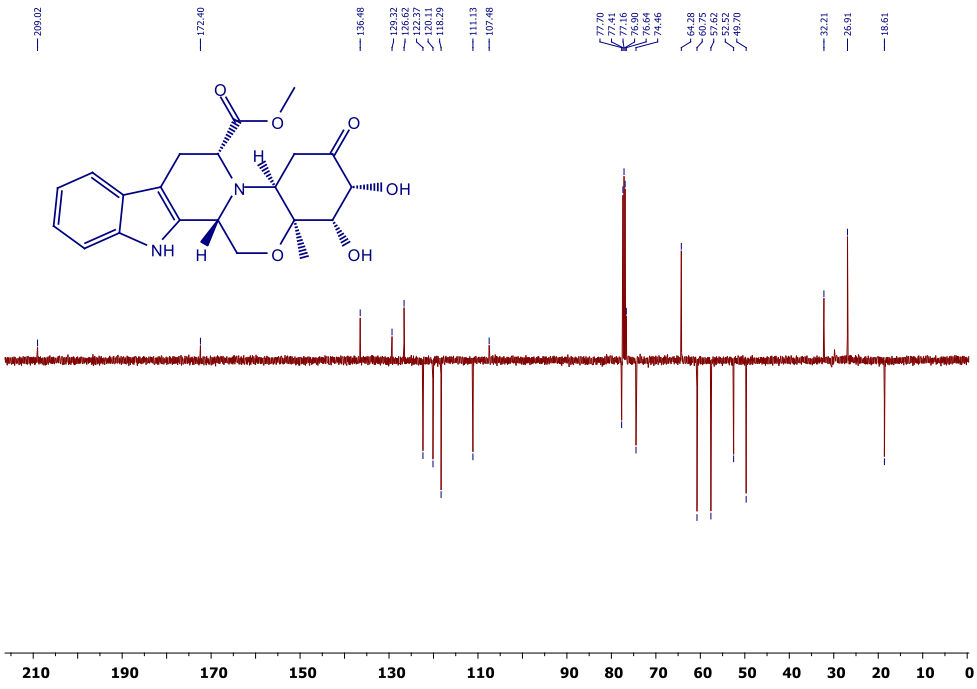

**Supplementary Figure 118** HSQC (Expansion) spectrum of methyl (2aR,3R,4S,6aR,8S,14bR)-3,4-dihydroxy-2a-methyl-5-oxo-2a,3,4,5,6,6a,8,9,14,14b-decahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-8-carboxylate (**16**)



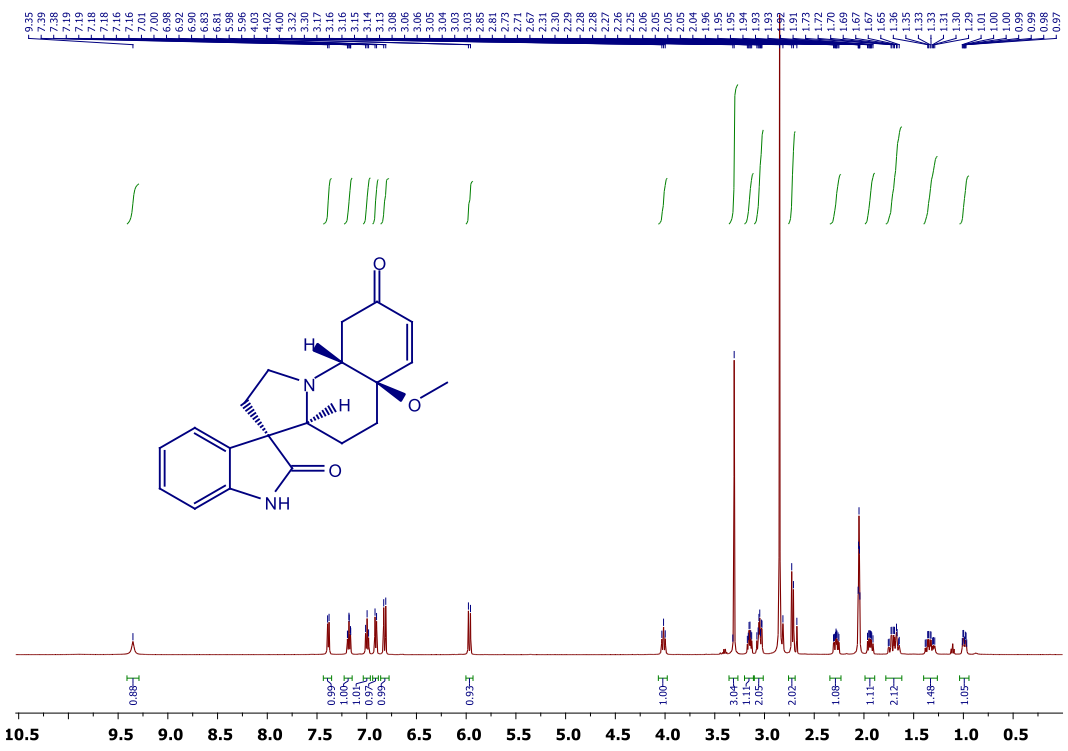

**Supplementary Figure 119** NOESY (500 MHz, $CDCl_3$) spectrum of methyl (2aR,3R,4S,6aR,8S,14bR)-3,4-dihydroxy-2a-methyl-5-oxo-2a,3,4,5,6,6a,8,9,14,14b-decahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-8-carboxylate (**16**)



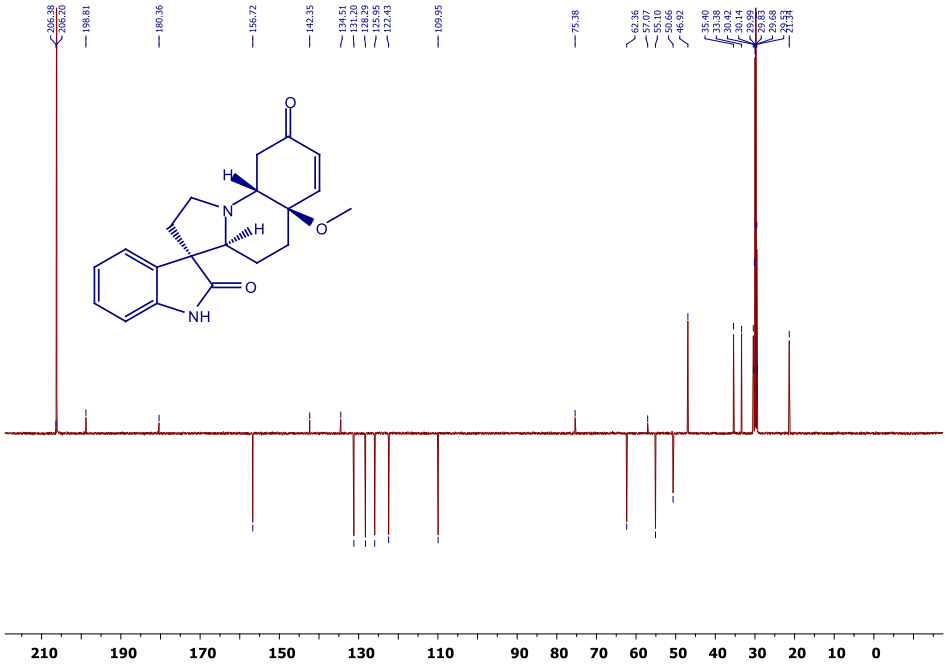
**Supplementary Figure 120** $^{1}H$ (500 MHz, $CDCl_3$) spectrum of methyl (2aS,3S,4R,6aS,8R,14bS)-3,4-dihydroxy-2a-methyl-5-oxo-2a,3,4,5,6,6a,8,9,14,14b-decahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-8-carboxylate (**17**)



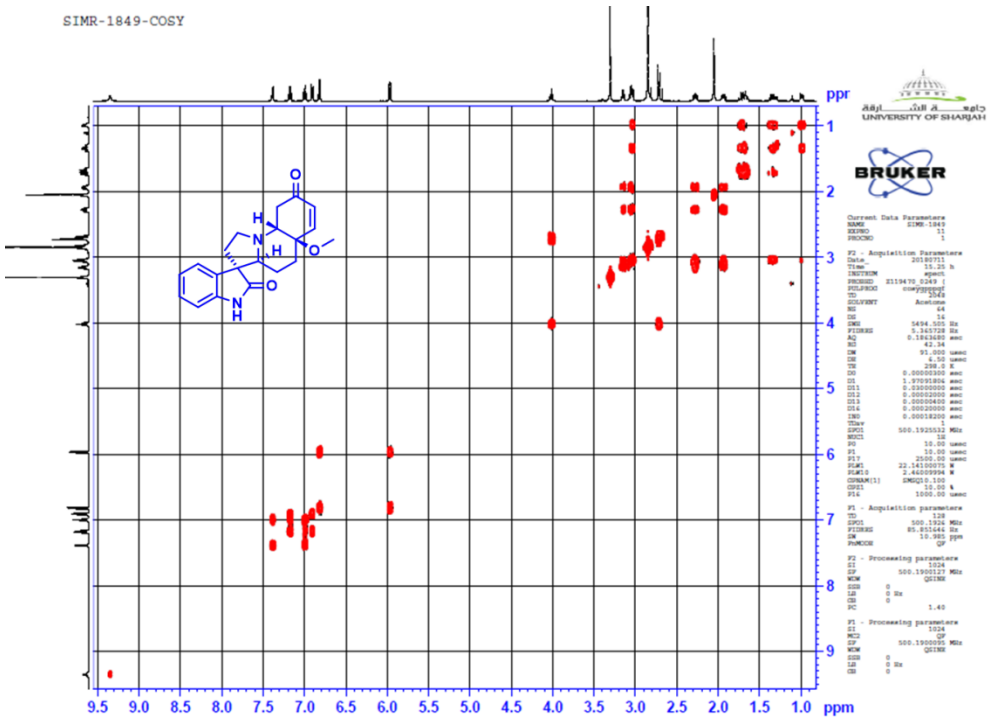
**Supplementary Figure 121** APT NMR (125 MHz, $CDCl_3$) spectrum of methyl (2aS,3S,4R,6aS,8R,14bS)-3,4-dihydroxy-2a-methyl-5-oxo-2a,3,4,5,6,6a,8,9,14,14b-decahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indole-8-carboxylate (**17**)



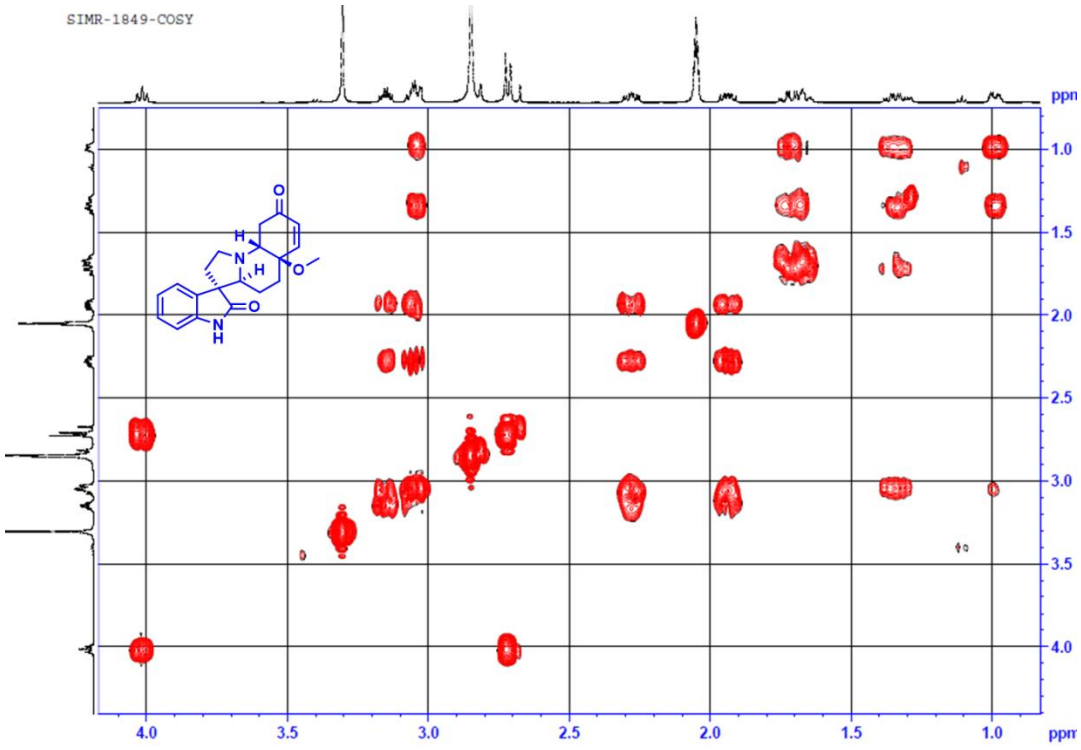
**Supplementary Figure 122** $^{1}$H (500 MHz, Acetone-$d_6$) spectrum of (3S,3a'S,5a'R,9a'R)-5a'-methoxy-1',2',3a',4',5',5a',9',9a'-octahydro-8'H-spiro[indoline-3,3'-pyrrolo[1,2-a]quinoline]-2,8'-dione (**18**)



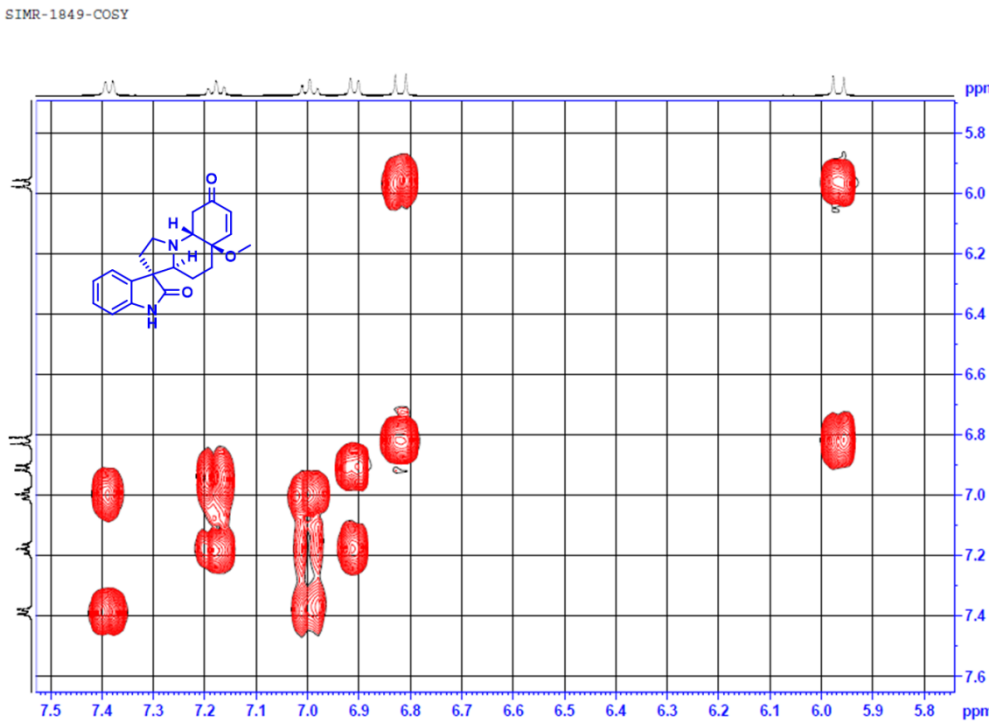
**Supplementary Figure 123** APT NMR (500 MHz, Acetone-$d_6$) spectrum of (3S,3a'S,5a'R,9a'R)-5a'-methoxy-1',2',3a',4',5',5a',9',9a'-octahydro-8'H-spiro[indoline-3,3'-pyrrolo[1,2-a]quinoline]-2,8'-dione (**18**)



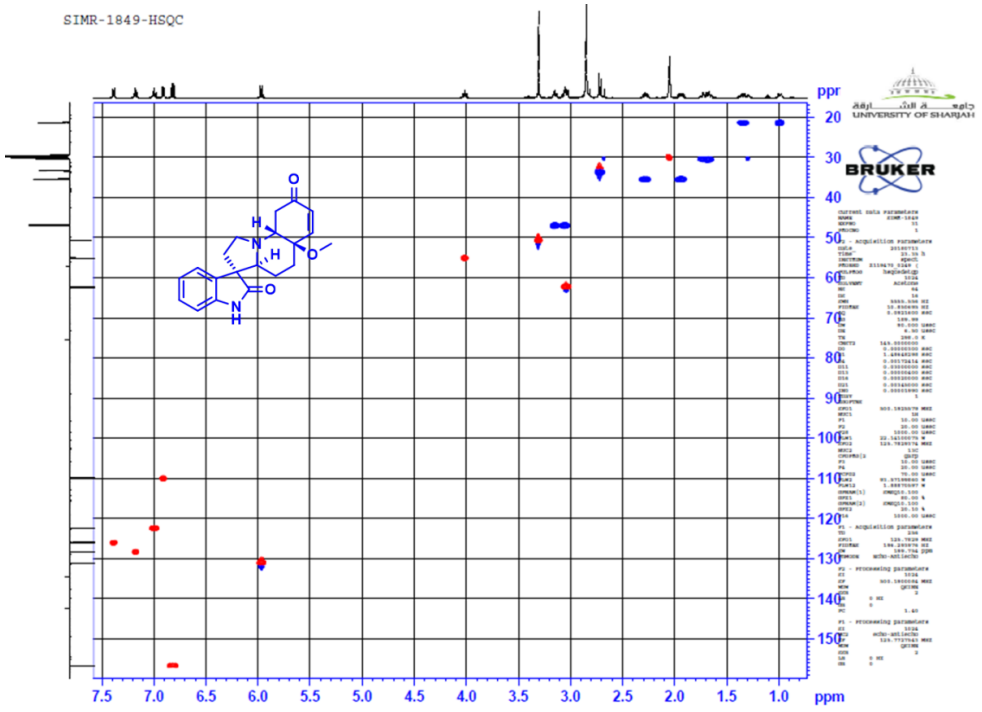

**Supplementary Figure 124** COSY (500 MHz, Acetone-$d_6$) spectrum of (3S,3a'S,5a'R,9a'R)-5a'-methoxy-1',2',3a',4',5',5a',9',9a'-octahydro-8'H-spiro[indoline-3,3'-pyrrolo[1,2-a]quinoline]-2,8'-dione (**18**)



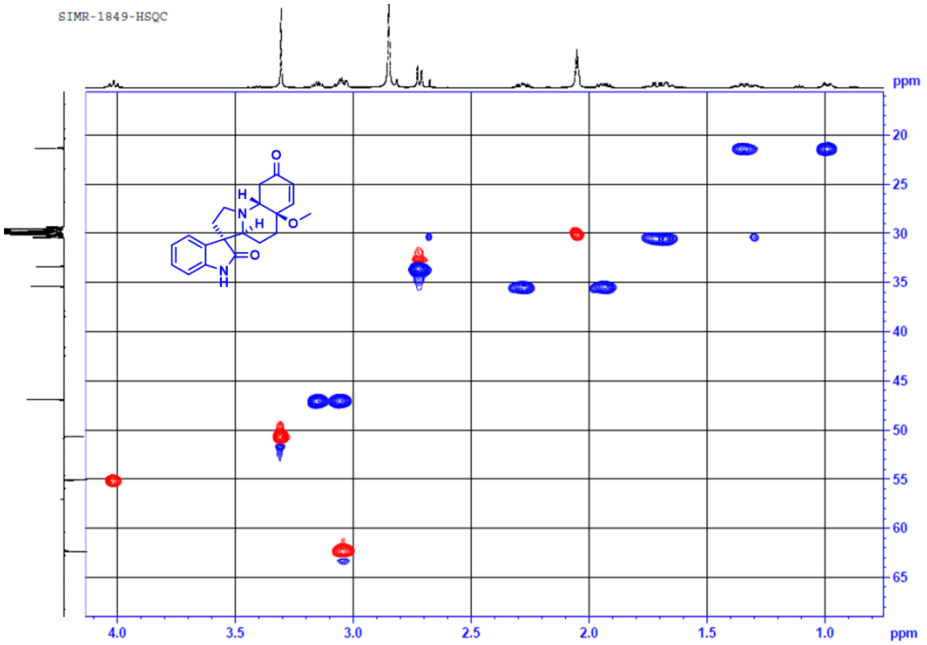

**Supplementary Figure 125** COSY (Expansion) spectrum of (3S,3a'S,5a'R,9a'R)-5a'-methoxy-1',2',3a',4',5',5a',9',9a'-octahydro-8'H-spiro[indoline-3,3'-pyrrolo[1,2-a]quinoline]-2,8'-dione (**18**)



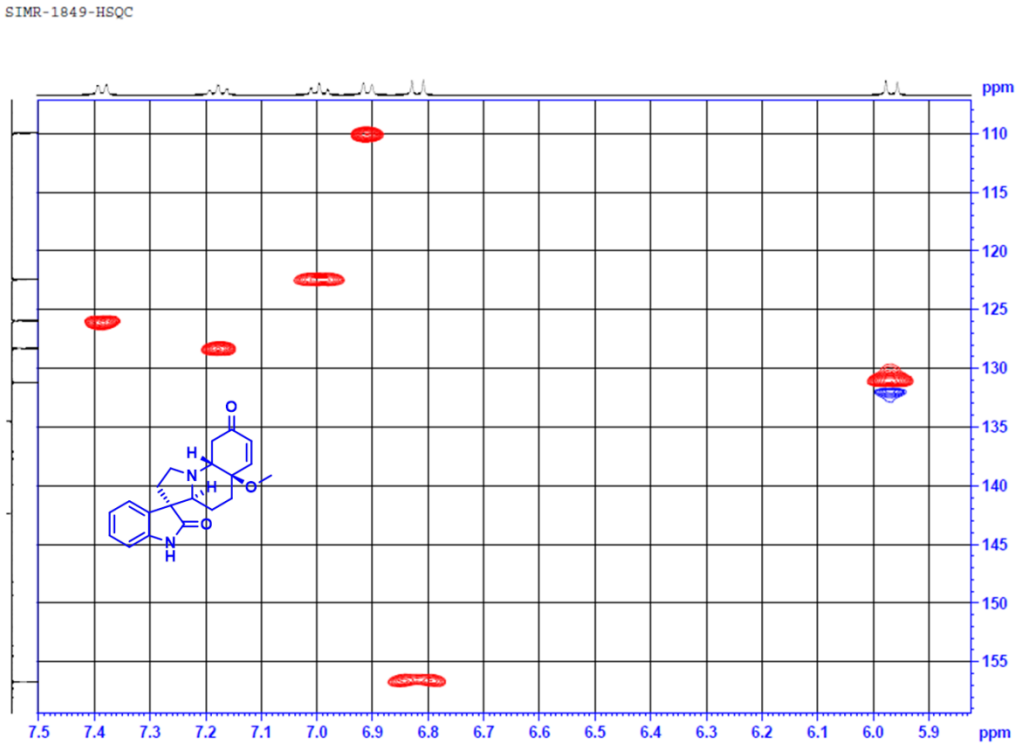

**Supplementary Figure 126** COSY (Expansion) spectrum of (3S,3a'S,5a'R,9a'R)-5a'-methoxy-1',2',3a',4',5',5a',9',9a'-octahydro-8'H-spiro[indoline-3,3'-pyrrolo[1,2-a]quinoline]-2,8'-dione (**18**)



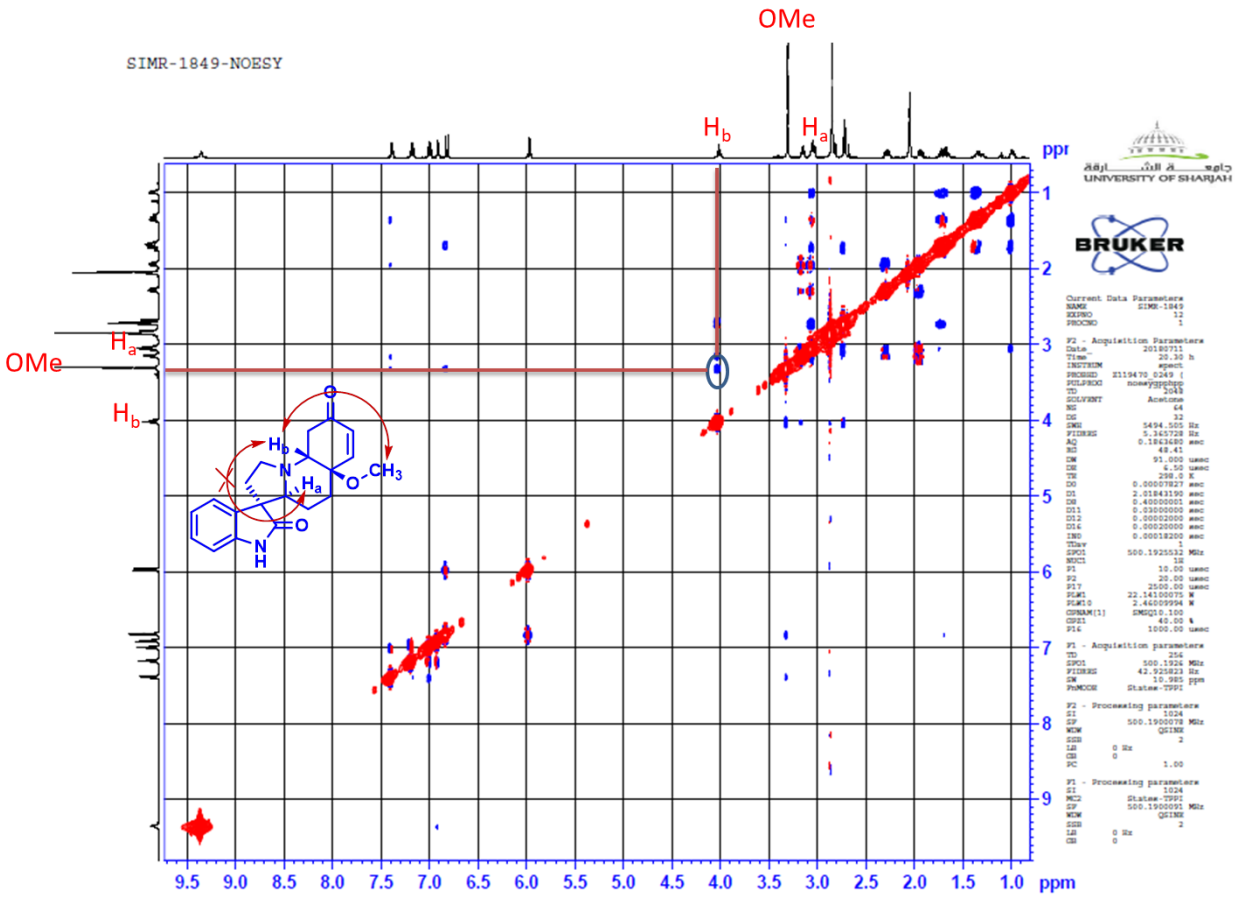

**Supplementary Figure 127** HSQC (500 MHz, Acetone-$d_6$) spectrum of (3S,3a'S,5a'R,9a'R)-5a'-methoxy-1',2',3a',4',5',5a',9',9a'-octahydro-8'H-spiro[indoline-3,3'-pyrrolo[1,2-a]quinoline]-2,8'-dione (**18**)



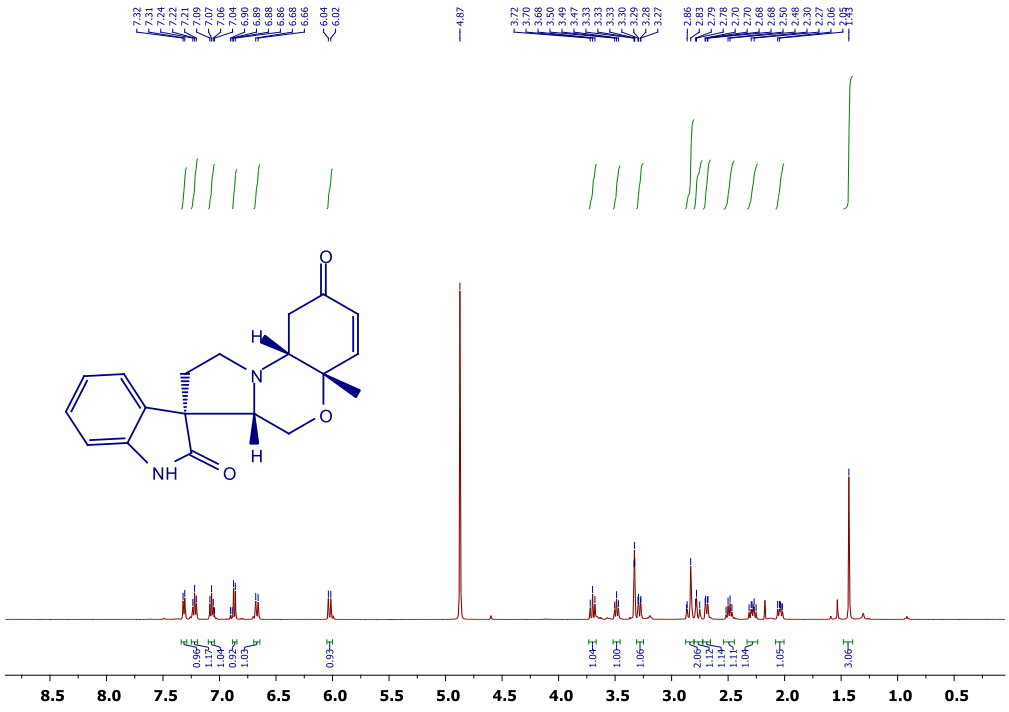

**Supplementary Figure 128** HSQC (Expansion) spectrum of (3S,3a'S,5a'R,9a'R)-5a'-methoxy-1',2',3a',4',5',5a',9',9a'-octahydro-8'H-spiro[indoline-3,3'-pyrrolo[1,2-a]quinoline]-2,8'-dione (**18**)



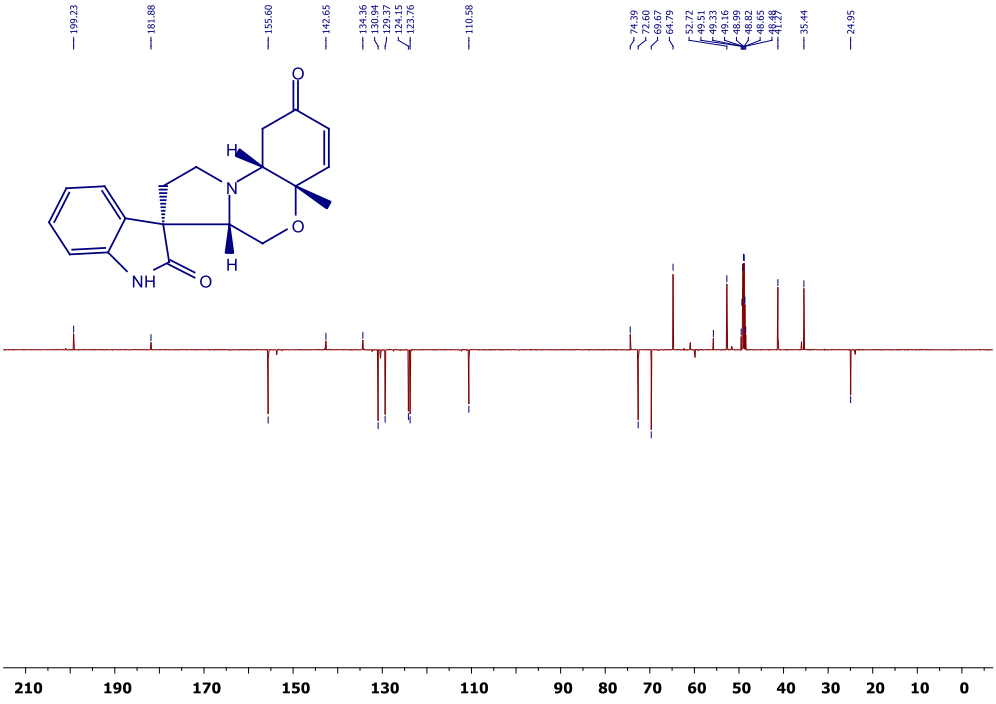

**Supplementary Figure 129** HSQC (Expansion) spectrum of (3S,3a'S,5a'R,9a'R)-5a'-methoxy-1',2',3a',4',5',5a',9',9a'-octahydro-8'H-spiro[indoline-3,3'-pyrrolo[1,2-a]quinoline]-2,8'-dione (**18**)



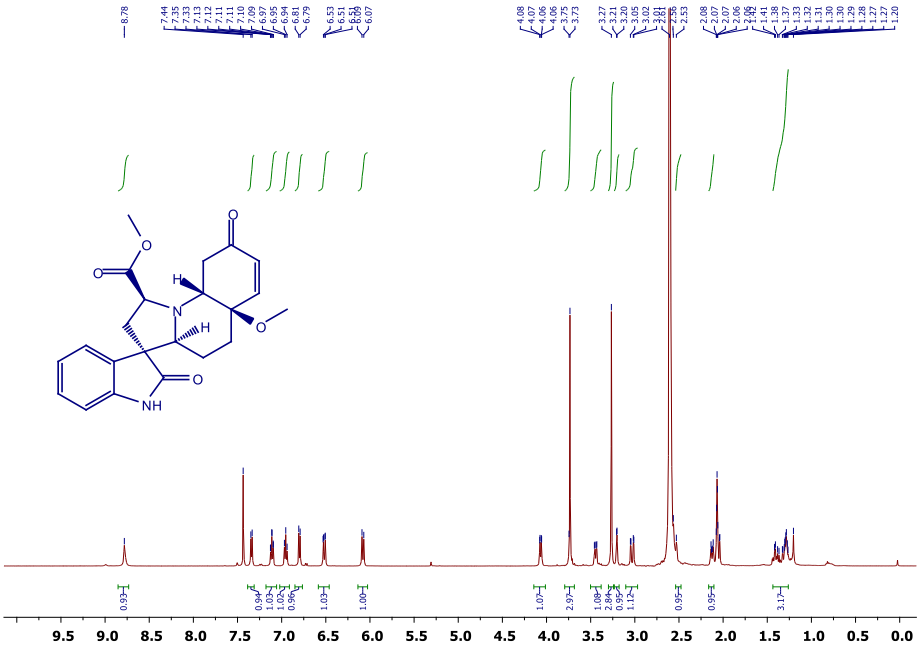

**Supplementary Figure 130** NOESY (500 MHz, Acetone-$d_6$) spectrum of (3S,3a'S,5a'R,9a'R)-5a'-methoxy-1',2',3a',4',5',5a',9',9a'-octahydro-8'H-spiro[indoline-3,3'-pyrrolo[1,2-a]quinoline]-2,8'-dione (**18**)



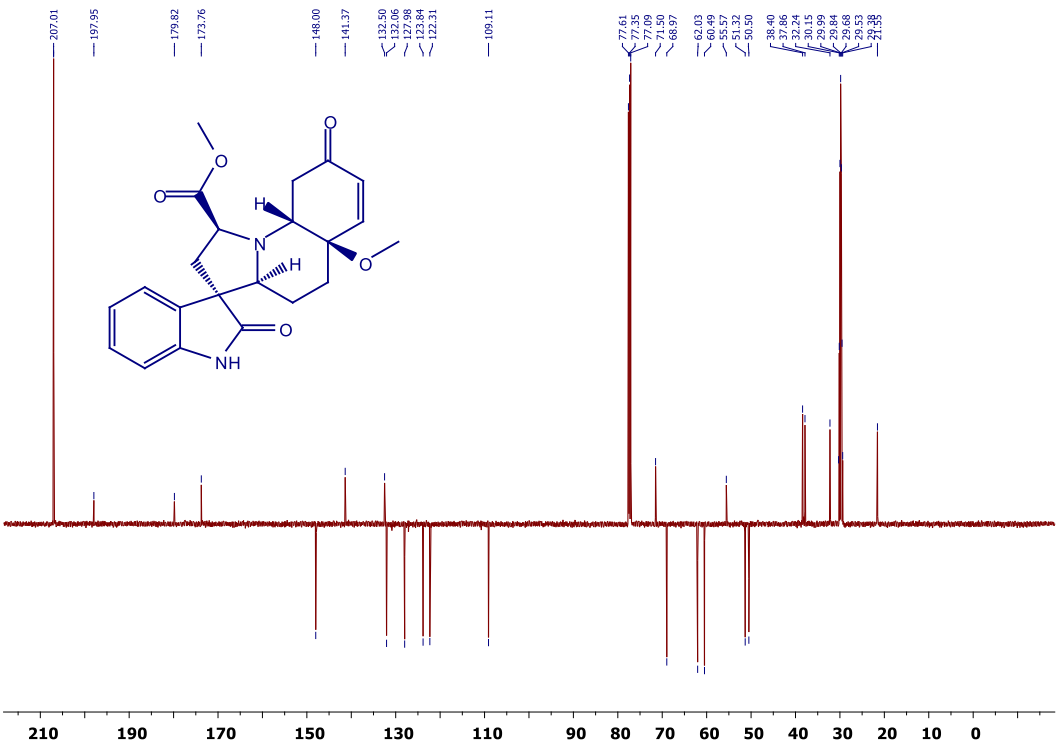
**Supplementary Figure 131** $^{1}$H NMR (500 MHz, $CD_3OD$) spectrum of (3S,3aS,5aS,9aR)-5a-methyl-1,2,3a,4,9,9a-hexahydrospiro[benzo[b]pyrrolo[1,2-d][1,4]oxazine-3,3'-indoline]-2',8(5aH)-dione (**19**)



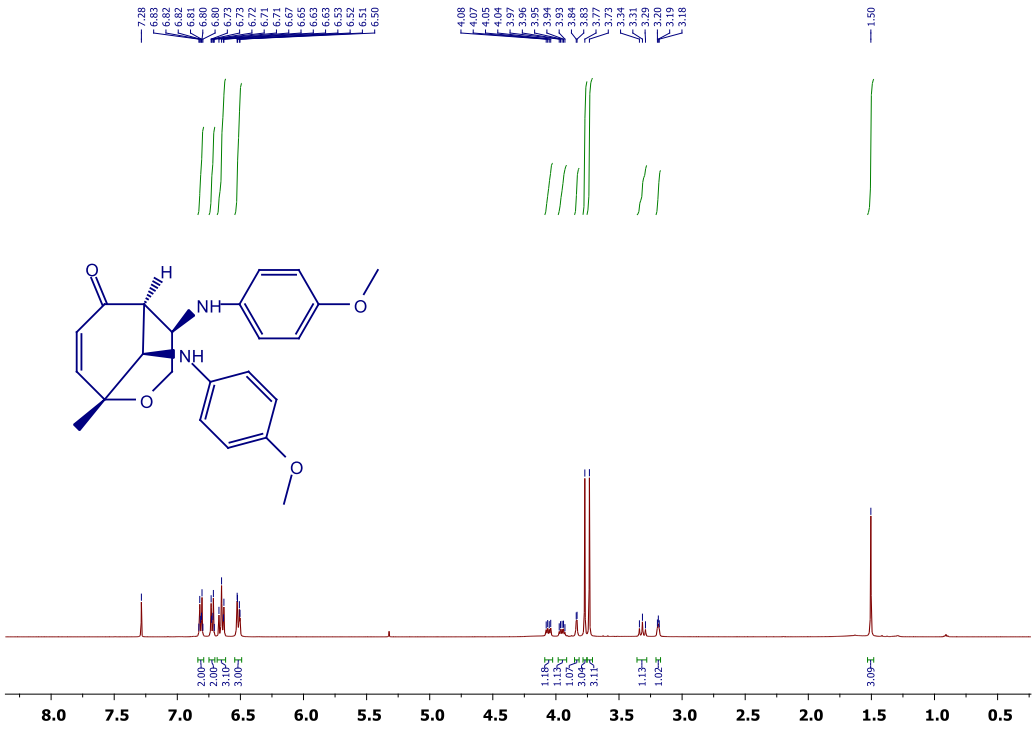
**Supplementary Figure 132** APT NMR (125 MHz, $CD_3OD$) spectrum of (3S,3aS,5aS,9aR)-5a-methyl-1,2,3a,4,9,9a-hexahydrospiro[benzo[b]pyrrolo[1,2-d][1,4]oxazine-3,3'-indoline]-2',8(5aH)-dione (**19**)



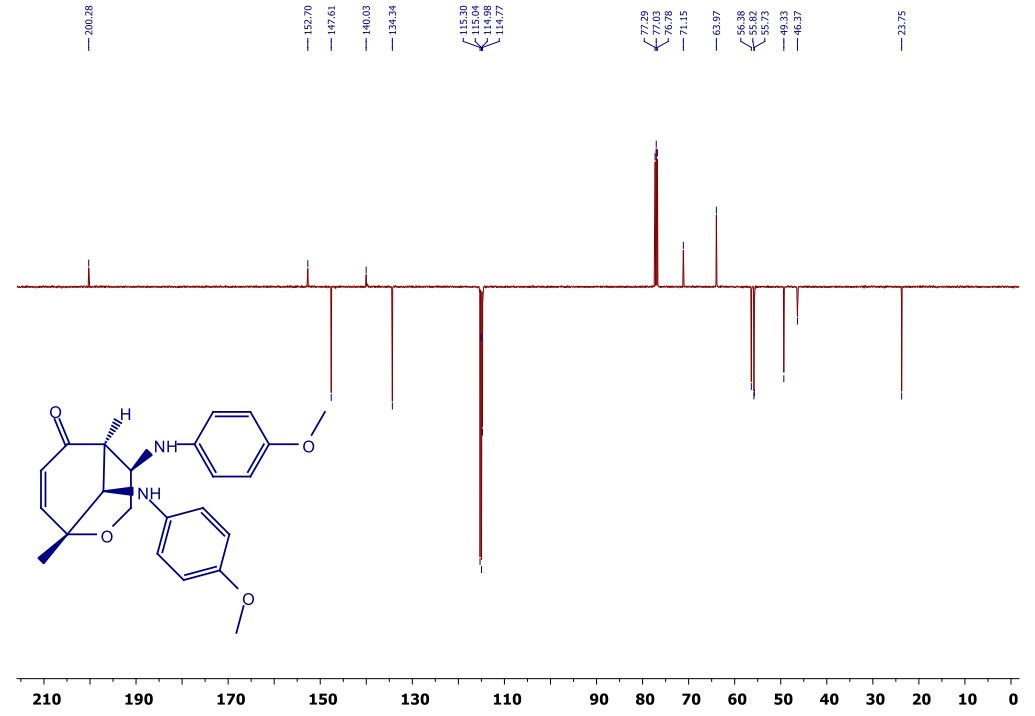
**Supplementary Figure 133** $^{1}$H NMR (500 MHz, $CDCl_3$+Acetone-$d_6$) spectrum of methyl (1'S,3S,3a'S,5a'R,9a'R)-5a'-methoxy-2,8'-dioxo-1',2',3a',4',5a',8',9',9a'-octahydro-5'H-spiro[indoline-3,3'-pyrrolo[1,2-a]quinoline]-1'-carboxylate (**20**)



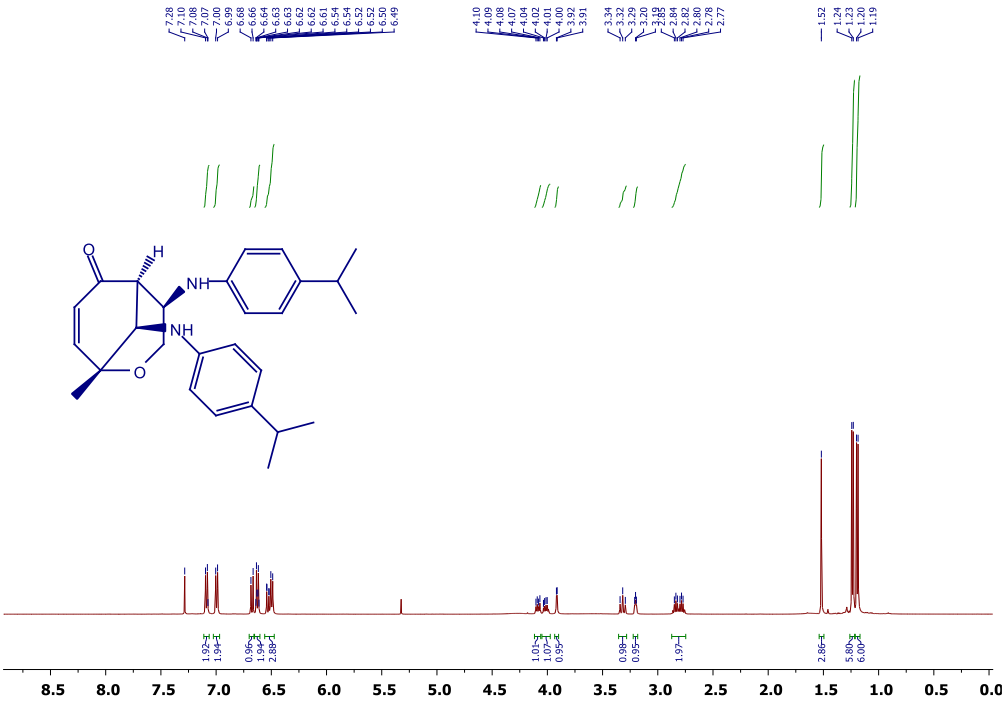
**Supplementary Figure 134** APT NMR (125 MHz, $CDCl_3$+Acetone-$d_6$) spectrum of methyl (1'S,3S,3a'S,5a'R,9a'R)-5a'-methoxy-2,8'-dioxo-1',2',3a',4',5a',8',9',9a'-octahydro-5'H-spiro[indoline-3,3'-pyrrolo[1,2-a]quinoline]-1'-carboxylate (**20**)



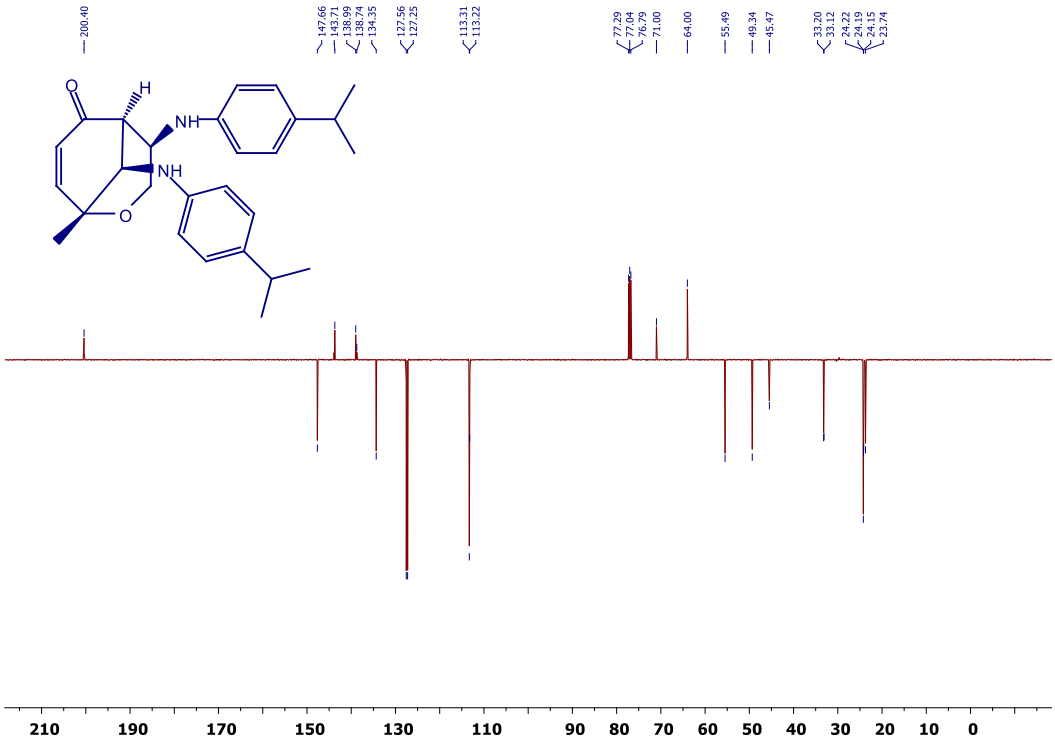
**Supplementary Figure 135** $^{1}H$ NMR (500 MHz, $CDCl_3$) spectrum of (1R,4R,5S,9R)-4,9-bis((4-methoxyphenyl)amino)-1-methyl-2-oxabicyclo[3.3.1]non-7-en-6-one (**22a**)



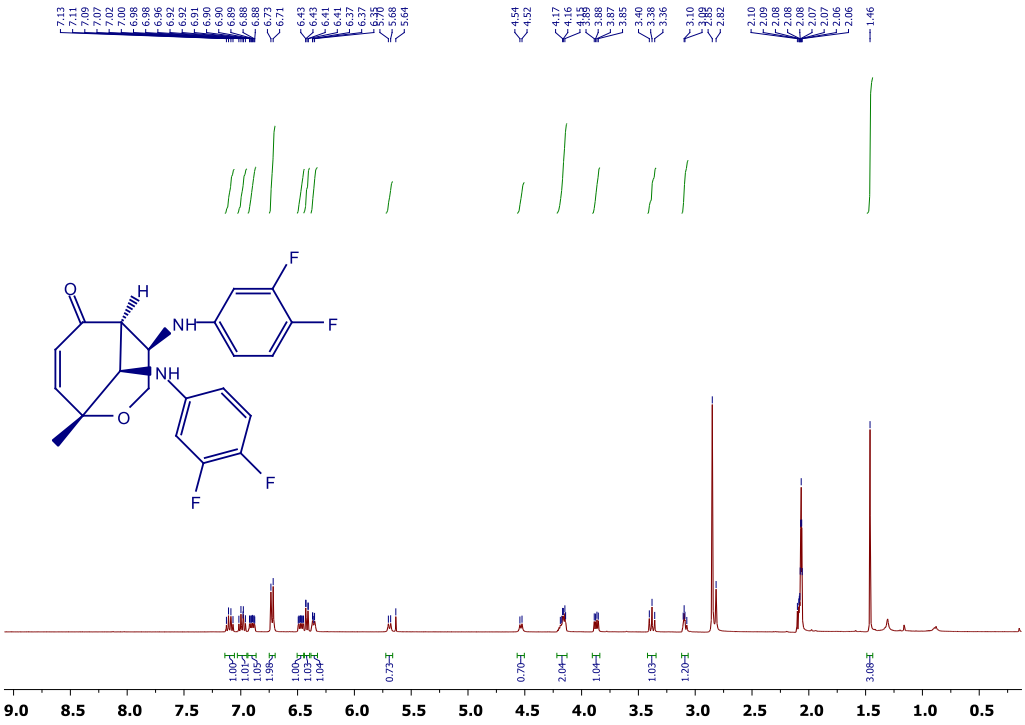
**Supplementary Figure 136** APT NMR (125 MHz, $CDCl_3$) spectrum of (1R,4R,5S,9R)-4,9-bis((4-methoxyphenyl)amino)-1-methyl-2-oxabicyclo[3.3.1]non-7-en-6-one (**22a**)



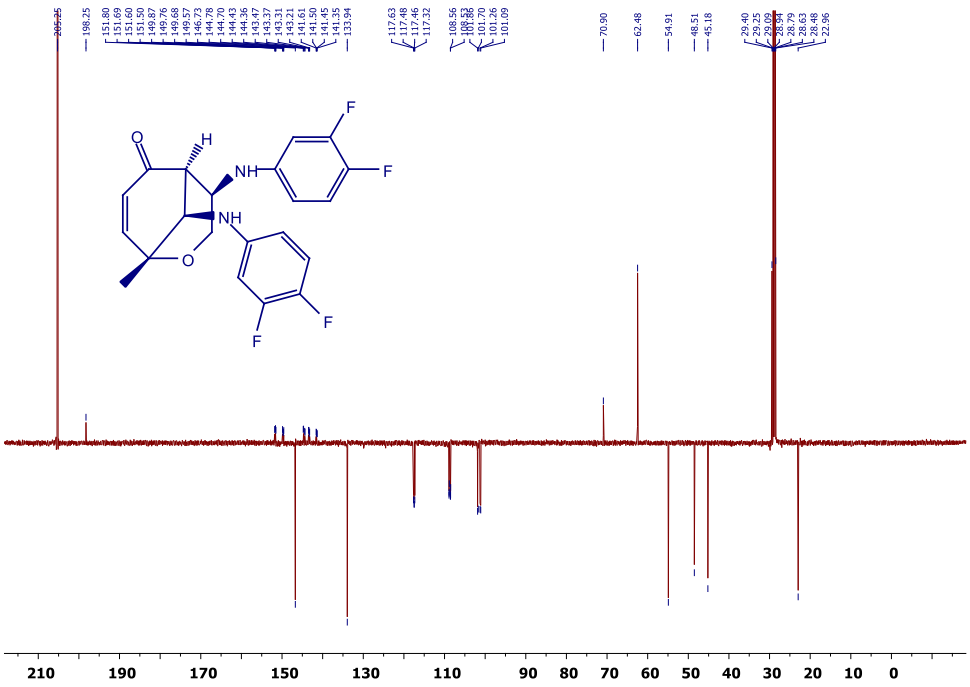
**Supplementary Figure 137** $^{1}$H NMR (500 MHz, $CDCl_3$) spectrum of (1R,4R,5S,9R)-4,9-bis((4-isopropylphenyl)amino)-1-methyl-2-oxabicyclo[3.3.1]non-7-en-6-one (**22b**)



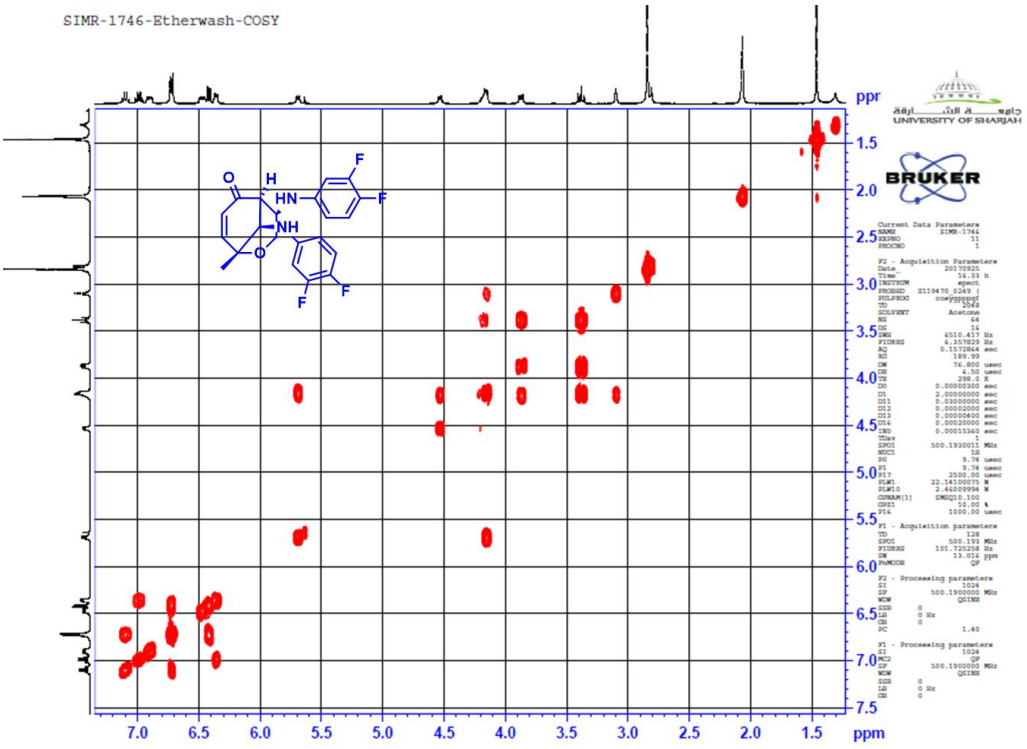
**Supplementary Figure 138** APT NMR (125 MHz, $CDCl_3$) spectrum of (1R,4R,5S,9R)-4,9-bis((4-isopropylphenyl)amino)-1-methyl-2-oxabicyclo[3.3.1]non-7-en-6-one (**22b**)



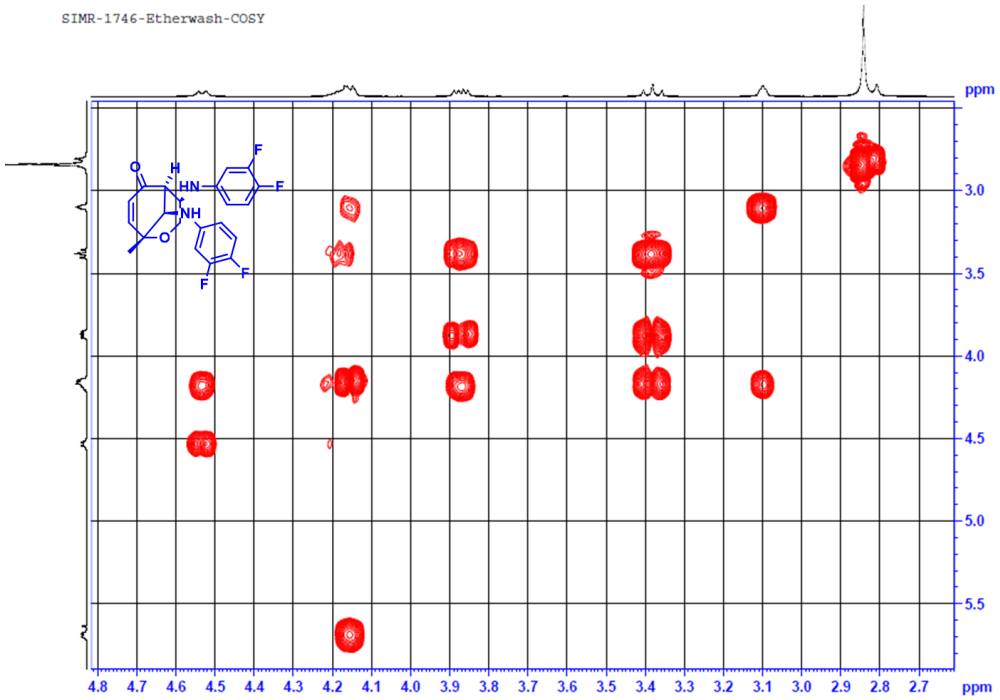

**Supplementary Figure 139** $^{1}$H NMR (500 MHz, Acetone-$d_6$) spectrum of (1R,4R,5S,9R)-4,9-bis((3,4-difluorophenyl)amino)-1-methyl-2-oxabicyclo[3.3.1]non-7-en-6-one (**22c**)



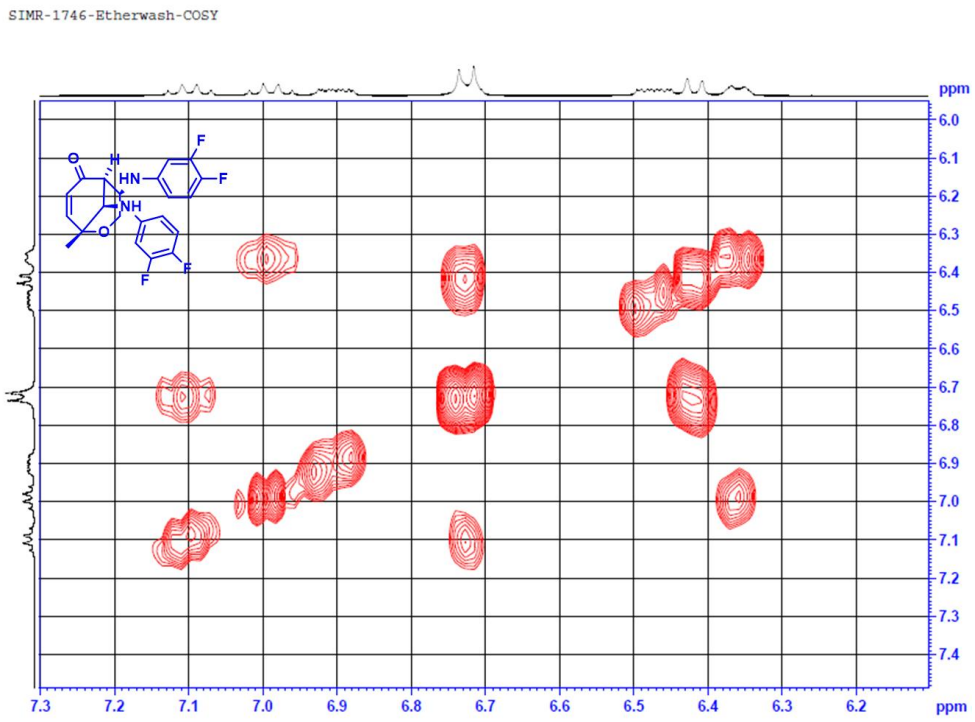

**Supplementary Figure 140** APT NMR (125 MHz, Acetone-$d_6$) spectrum of (1R,4R,5S,9R)-4,9-bis((3,4-difluorophenyl)amino)-1-methyl-2-oxabicyclo[3.3.1]non-7-en-6-one (**22c**)



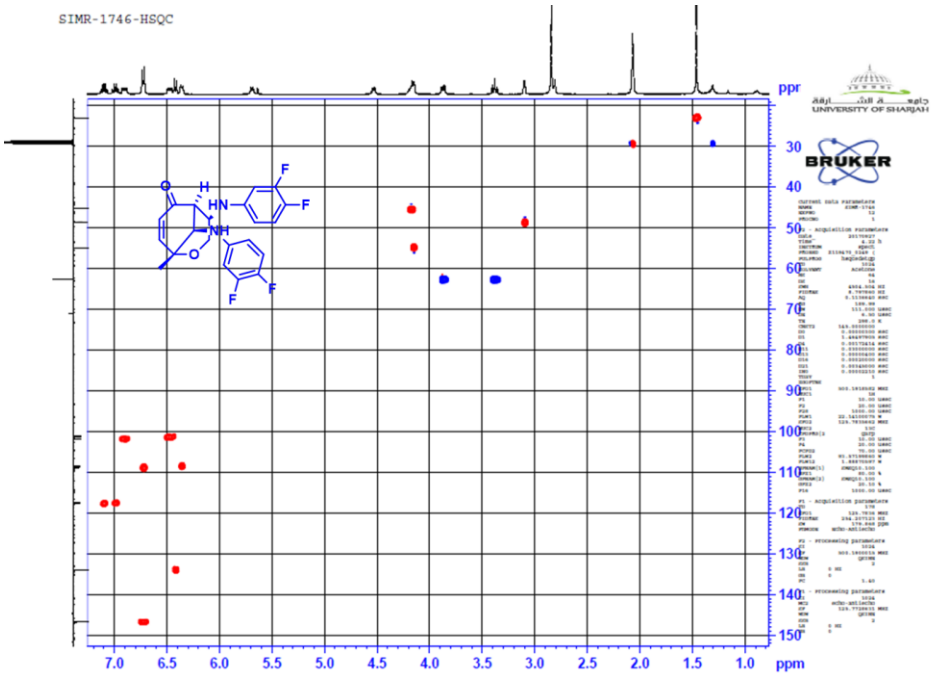

**Supplementary Figure 141** COSY (500 MHz, Acetone-$d_6$) spectrum of (1R,4R,5S,9R)-4,9-bis((3,4-difluorophenyl)amino)-1-methyl-2-oxabicyclo[3.3.1]non-7-en-6-one (**22c**)



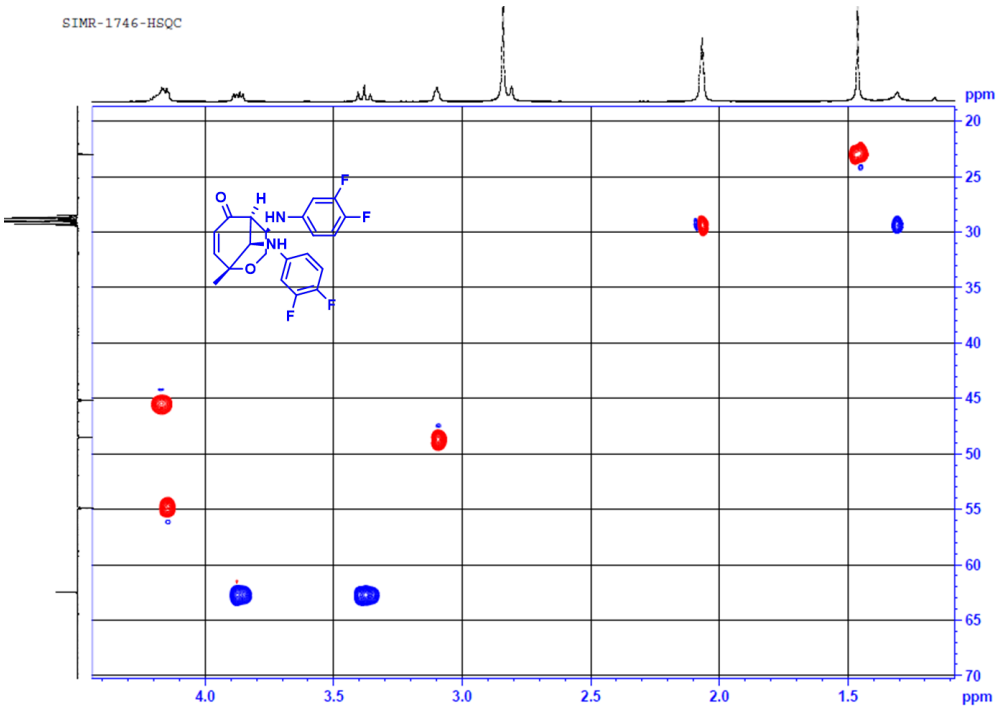

**Supplementary Figure 142** COSY (Expansion) spectrum of (1R,4R,5S,9R)-4,9-bis((3,4-difluorophenyl)amino)-1-methyl-2-oxabicyclo[3.3.1]non-7-en-6-one (**22c**)



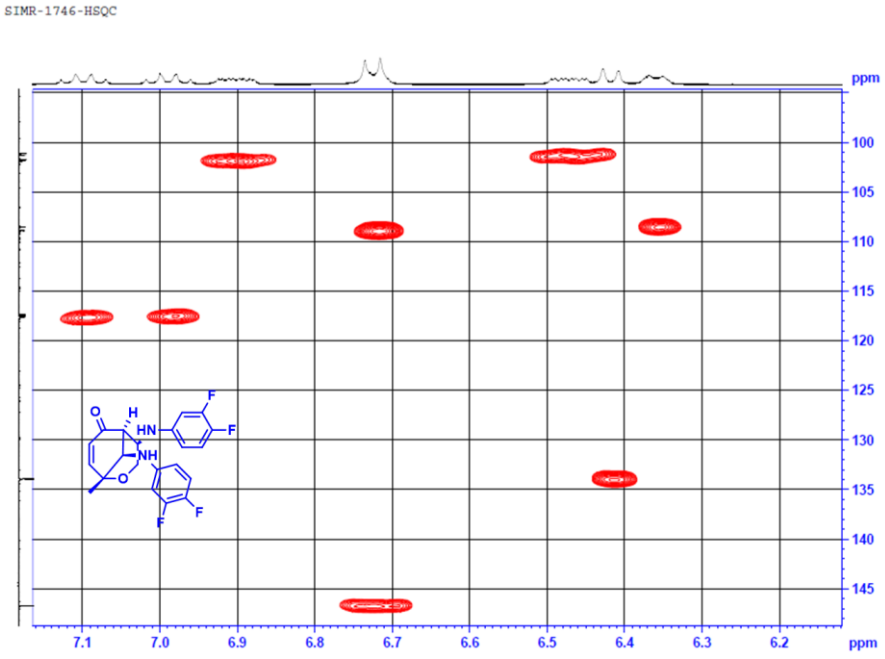

**Supplementary Figure 143** COSY (Expansion) spectrum of (1R,4R,5S,9R)-4,9-bis((3,4-difluorophenyl)amino)-1-methyl-2-oxabicyclo[3.3.1]non-7-en-6-one (**22c**)



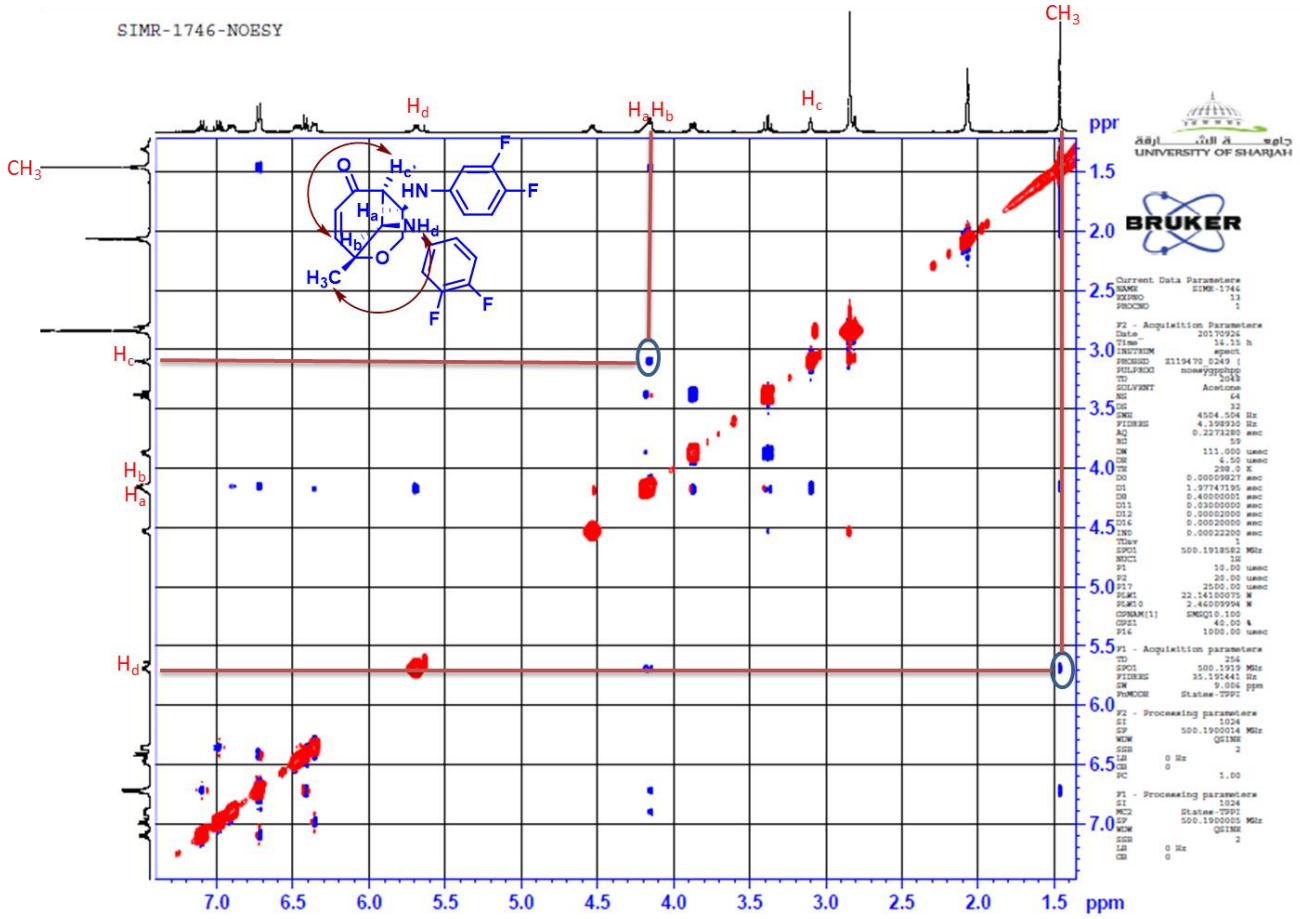

**Supplementary Figure 144** HSQC (500 MHz, Acetone) spectrum of (1R,4R,5S,9R)-4,9-bis((3,4-difluorophenyl)amino)-1-methyl-2-oxabicyclo[3.3.1]non-7-en-6-one (**22c**)



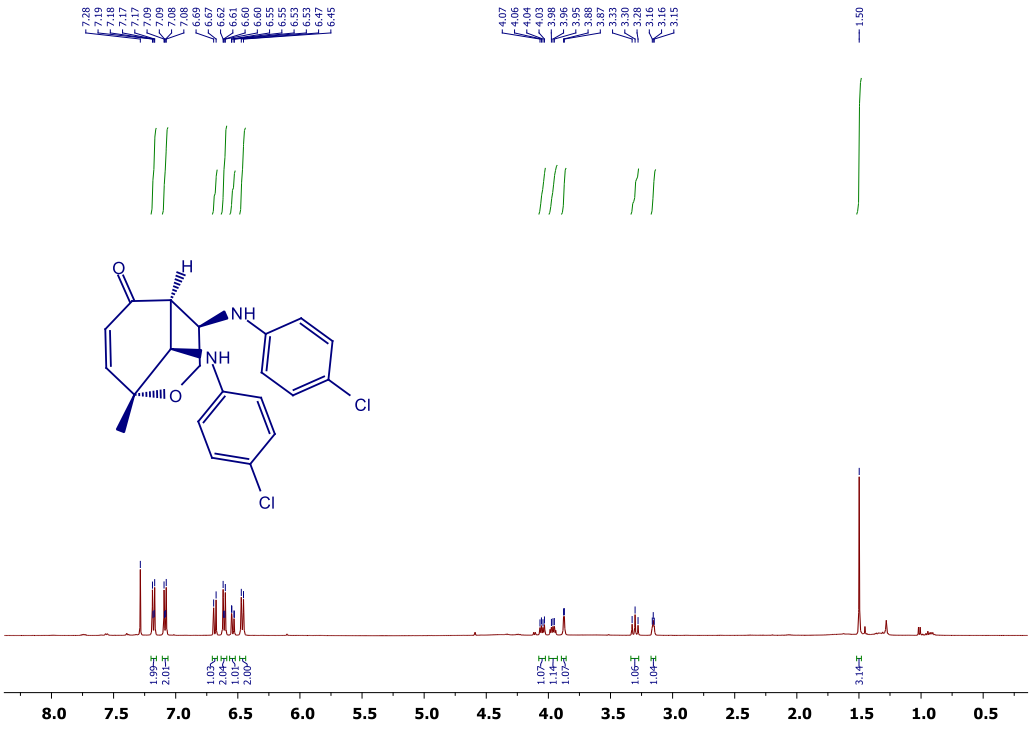

**Supplementary Figure 145** HSQC (Expansion) spectrum of (1R,4R,5S,9R)-4,9-bis((3,4-difluorophenyl)amino)-1-methyl-2-oxabicyclo[3.3.1]non-7-en-6-one (**22c**)



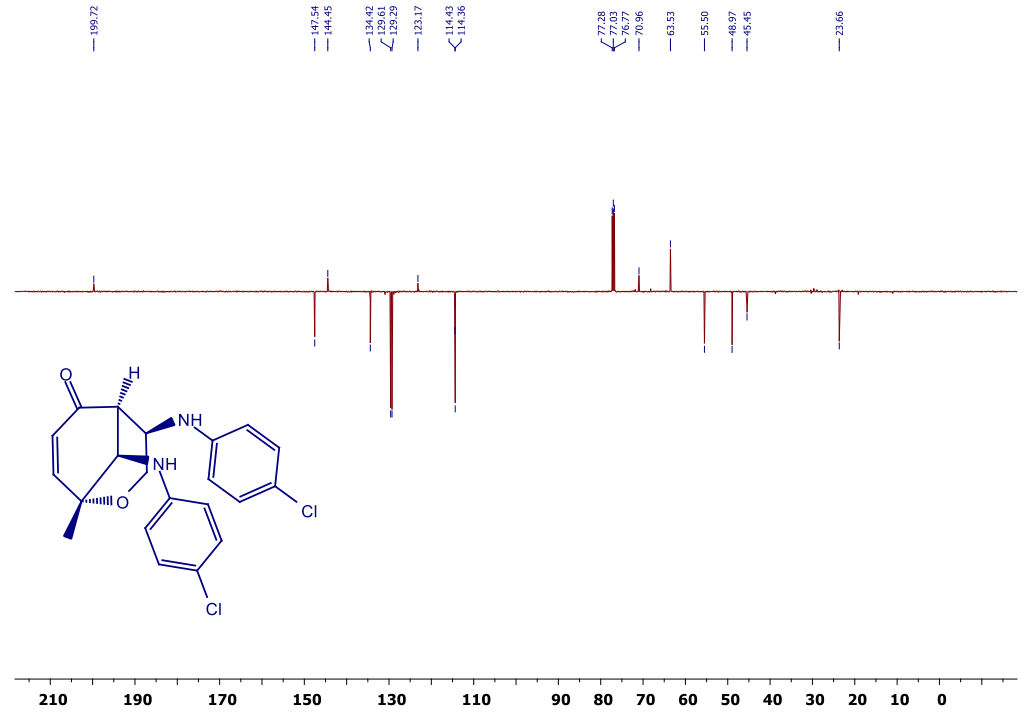

**Supplementary Figure 146** HSQC (Expansion) spectrum of (1R,4R,5S,9R)-4,9-bis((3,4-difluorophenyl)amino)-1-methyl-2-oxabicyclo[3.3.1]non-7-en-6-one (**22c**)



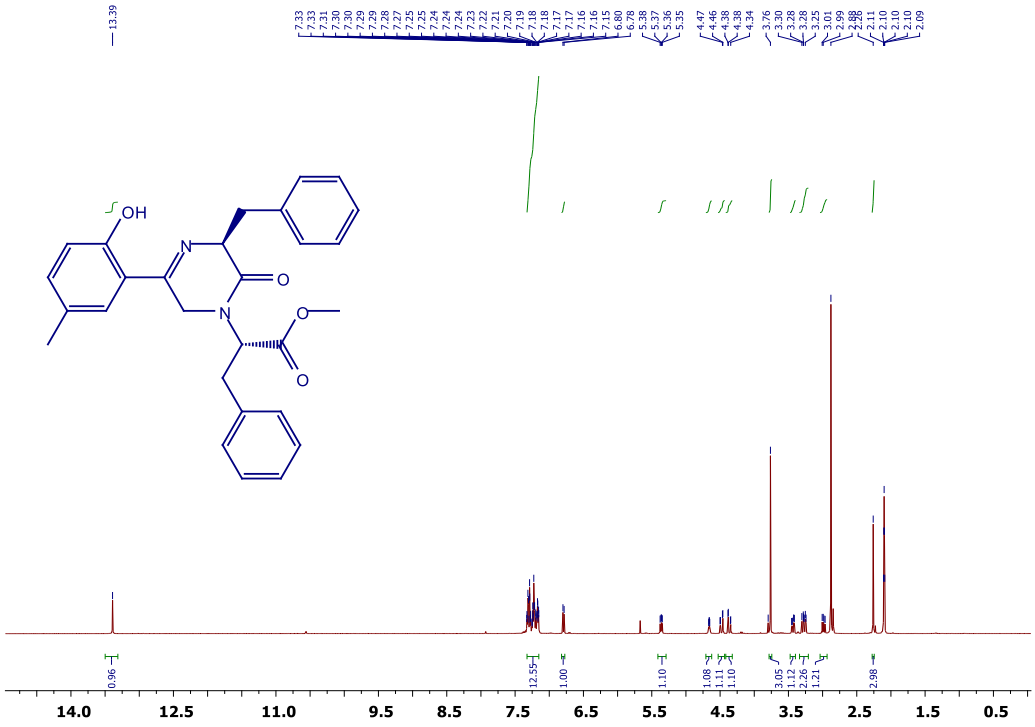

**Supplementary Figure 147** NOESY (500 MHz, Acetone-$d_6$) spectrum of (1R,4R,5S,9R)-4,9-bis((3,4-difluorophenyl)amino)-1-methyl-2-oxabicyclo[3.3.1]non-7-en-6-one (**22c**)



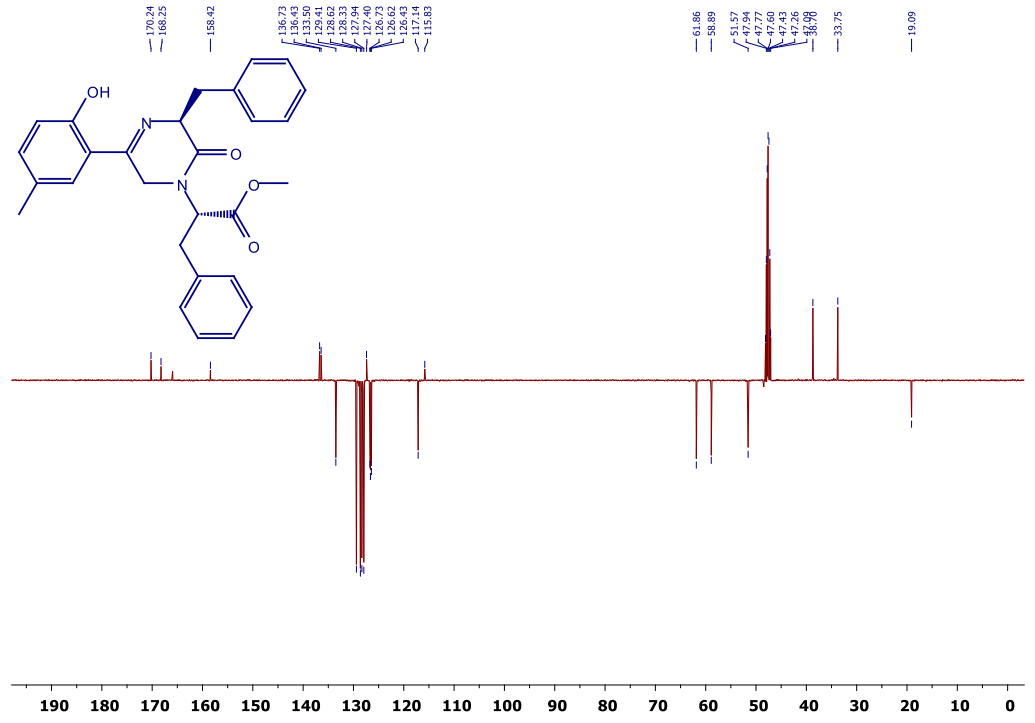

**Supplementary Figure 148** $^{1}H$ (500 MHz, $CDCl_3$) spectrum of (1R,4R,5S,9R)-4,9-bis((4-chlorophenyl)amino)-1-methyl-2-oxabicyclo[3.3.1]non-7-en-6-one (**22d**)



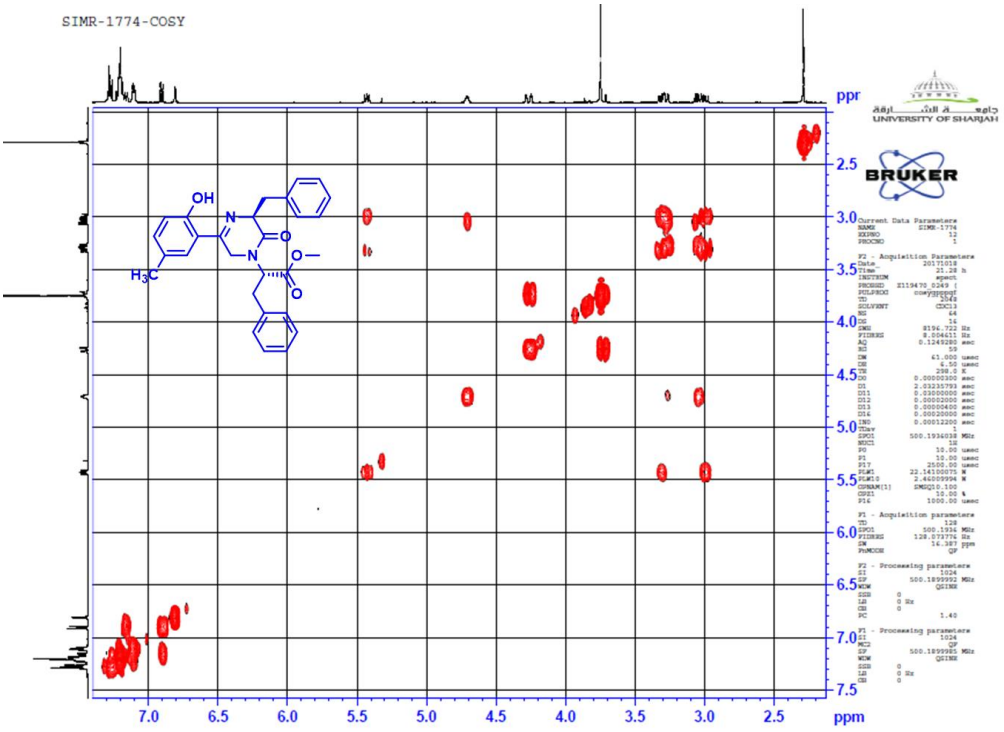

**Supplementary Figure 149** APT NMR (125 MHz, $CDCl_3$) spectrum of (1R,4R,5S,9R)-4,9-bis((4-chlorophenyl)amino)-1-methyl-2-oxabicyclo[3.3.1]non-7-en-6-one (**22d**)



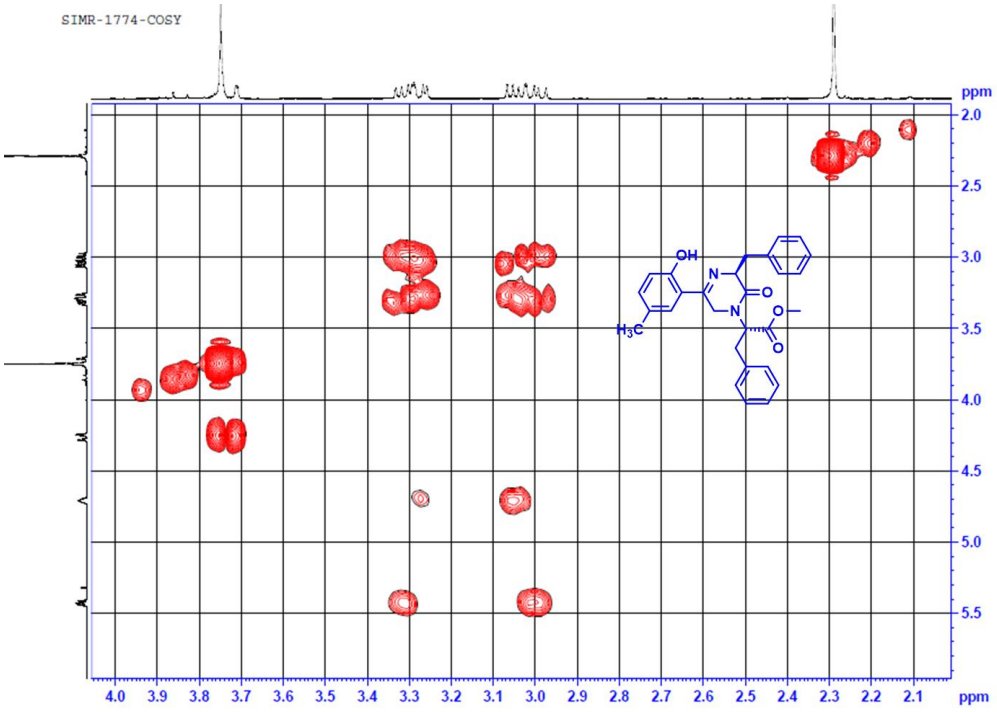
**Supplementary Figure 150** $^{1}$H (500 MHz, Acetone-$d_6$) spectrum of methyl (S)-2-((S)-3-benzyl-5-(2-hydroxy-5-methylphenyl)-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-phenylpropanoate (**24a**)



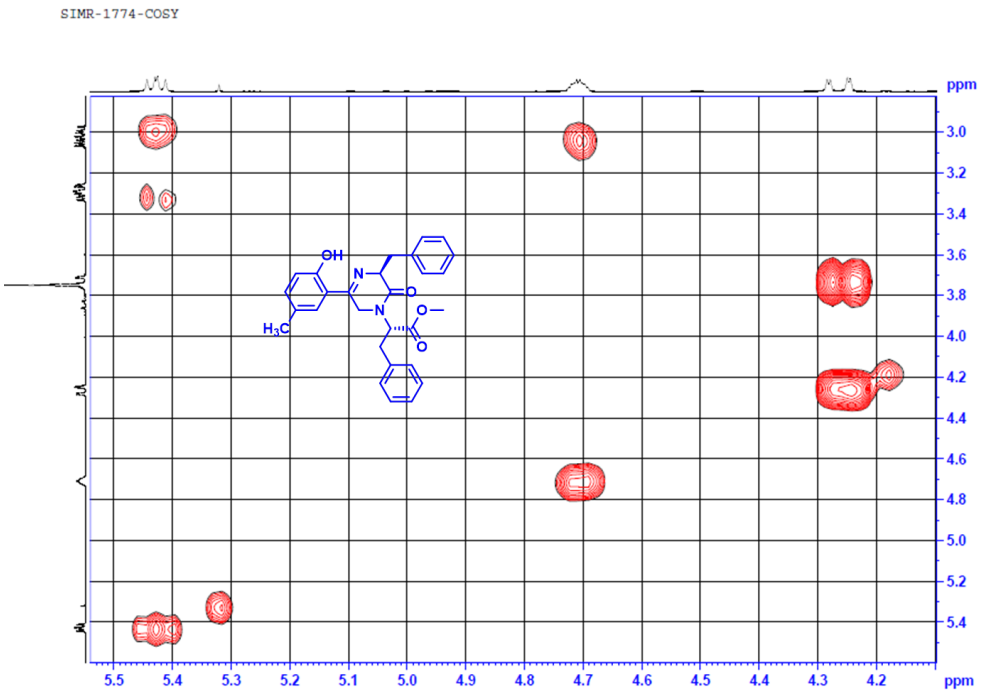
**Supplementary Figure 151** APT NMR (125 MHz, $CD_3OD$) spectrum of methyl (S)-2-((S)-3-benzyl-5-(2-hydroxy-5-methylphenyl)-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-phenylpropanoate (**24a**)



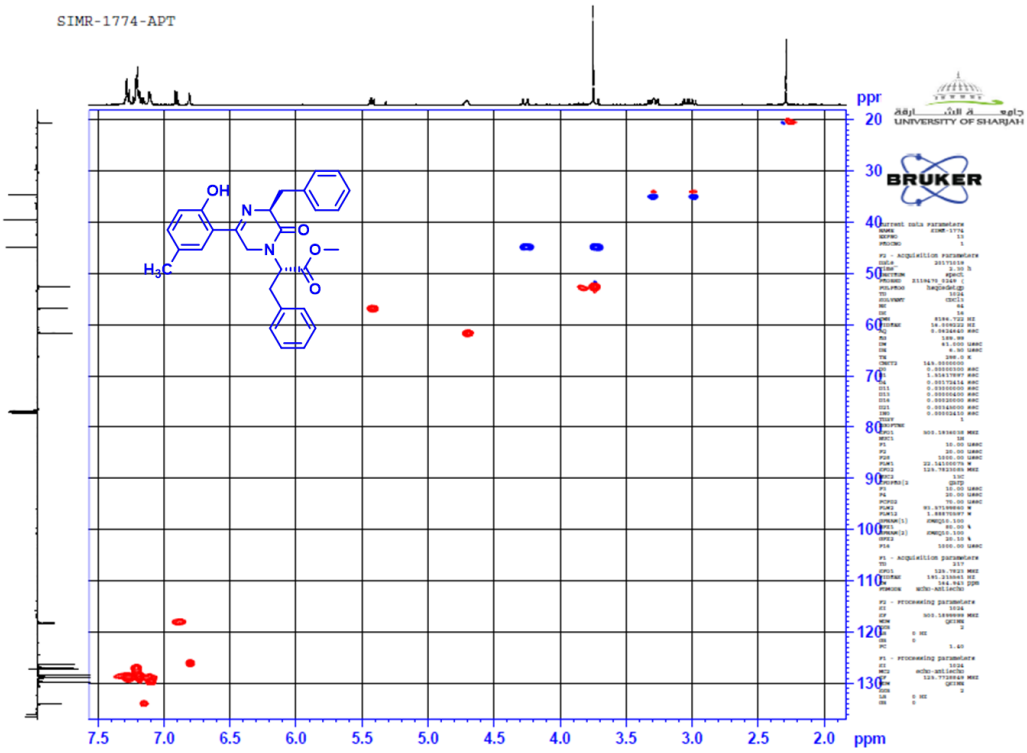

**Supplementary Figure 152** COSY (500 MHz, $CDCl_3$) spectrum of methyl (S)-2-((S)-3-benzyl-5-(2-hydroxy-5-methylphenyl)-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-phenylpropanoate (**24a**)



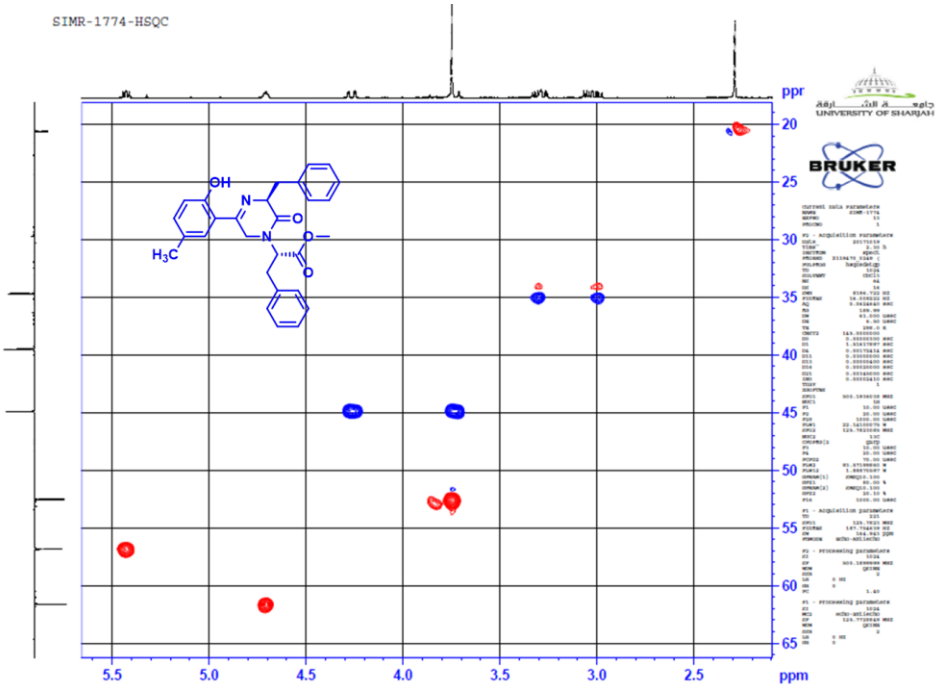

**Supplementary Figure 153** COSY (Expansion) spectrum of methyl (S)-2-((S)-3-benzyl-5-(2-hydroxy-5-methylphenyl)-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-phenylpropanoate (**24a**)



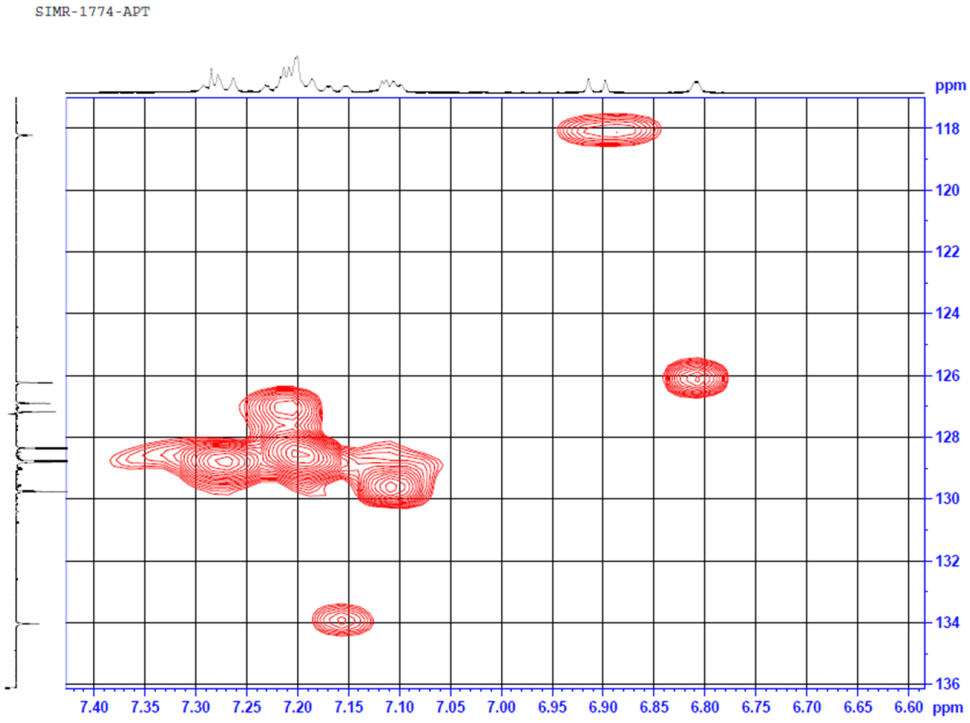

**Supplementary Figure 154** COSY (Expansion) spectrum of methyl (S)-2-((S)-3-benzyl-5-(2-hydroxy-5-methylphenyl)-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-phenylpropanoate (**24a**)



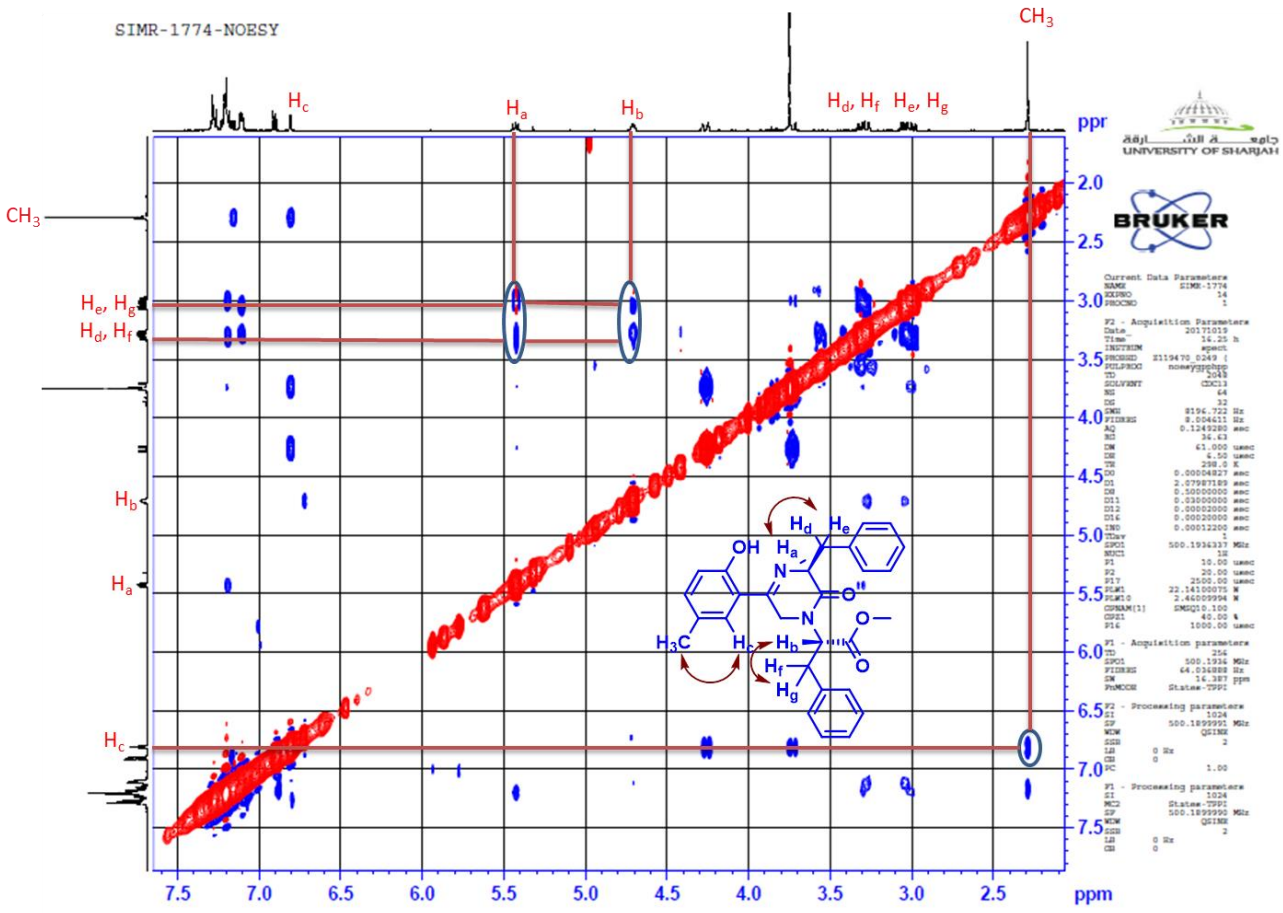

**Supplementary Figure 155** HSQC (500 MHz, $CDCl_3$) spectrum of methyl (S)-2-((S)-3-benzyl-5-(2-hydroxy-5-methylphenyl)-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-phenylpropanoate (**24a**)



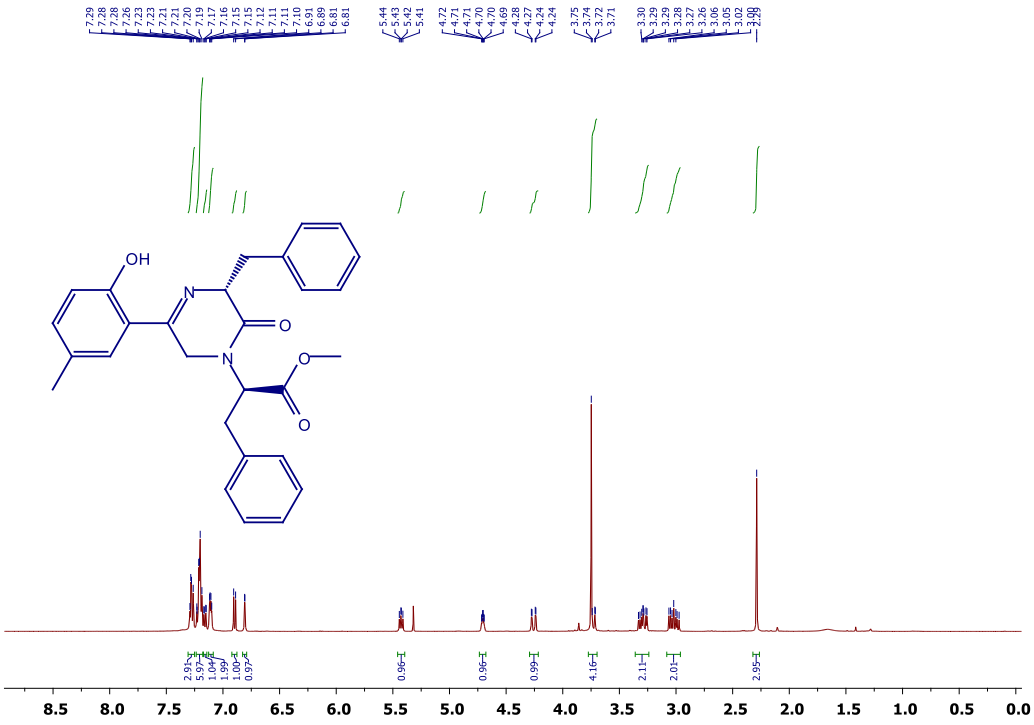

**Supplementary Figure 156** HSQC (Expansion) spectrum of methyl (S)-2-((S)-3-benzyl-5-(2-hydroxy-5-methylphenyl)-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-phenylpropanoate (**24a**)



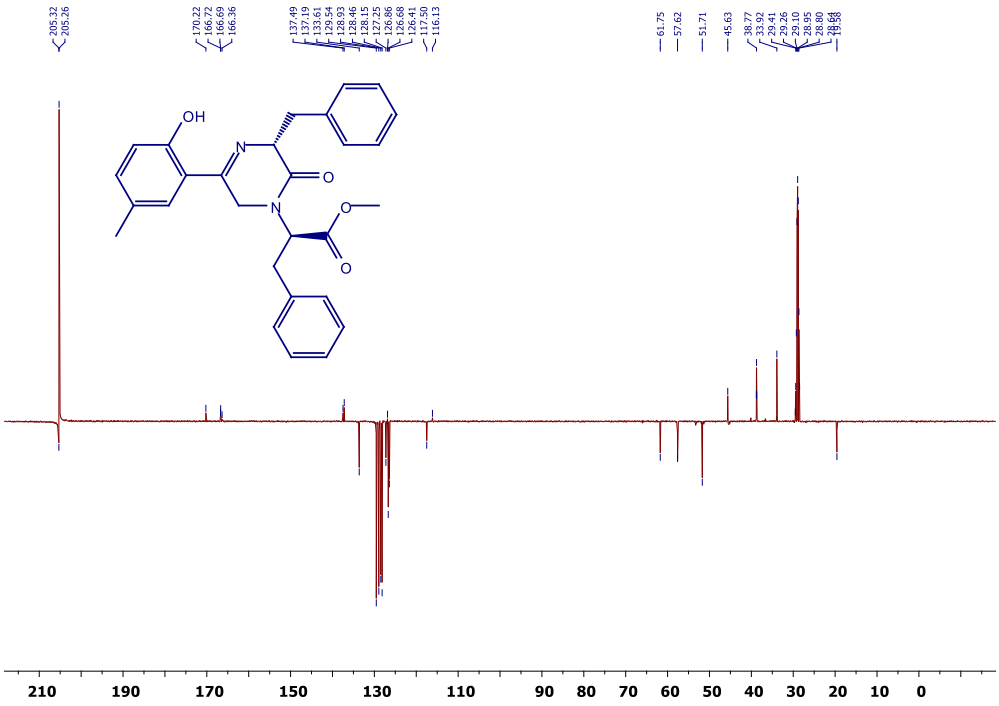

**Supplementary Figure 157** HSQC (Expansion) spectrum of methyl (S)-2-((S)-3-benzyl-5-(2-hydroxy-5-methylphenyl)-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-phenylpropanoate (**24a**)



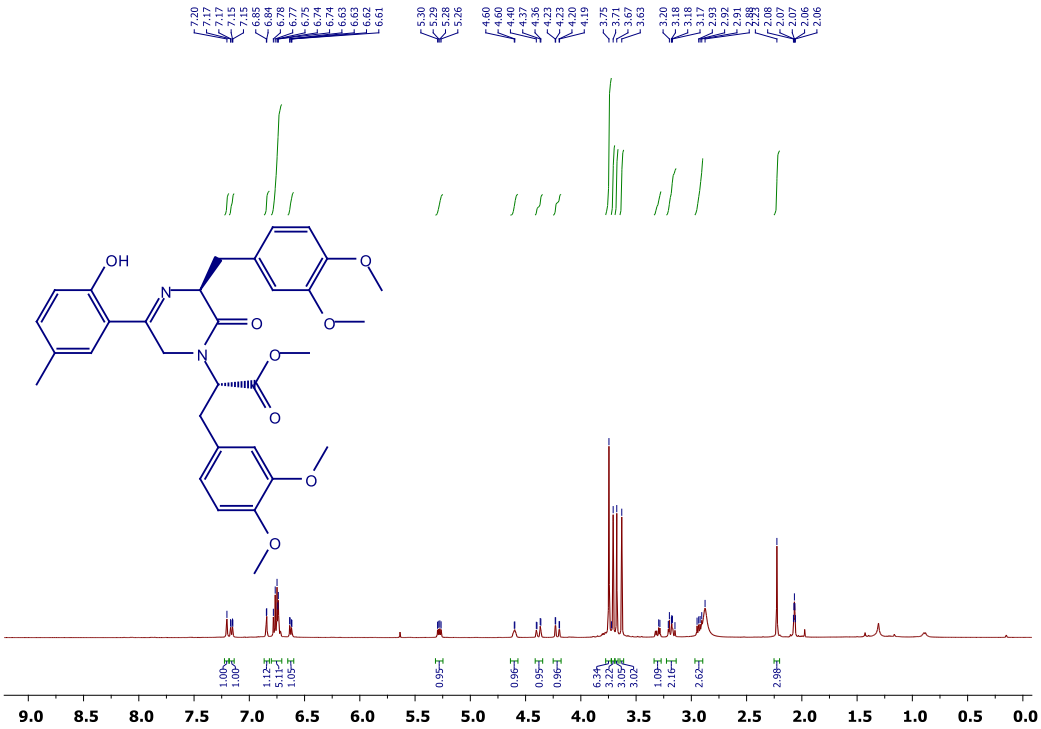

**Supplementary Figure 158** NOESY (500 MHz, $CDCl_3$) spectrum of methyl (S)-2-((S)-3-benzyl-5-(2-hydroxy-5-methylphenyl)-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-phenylpropanoate (**24a**)



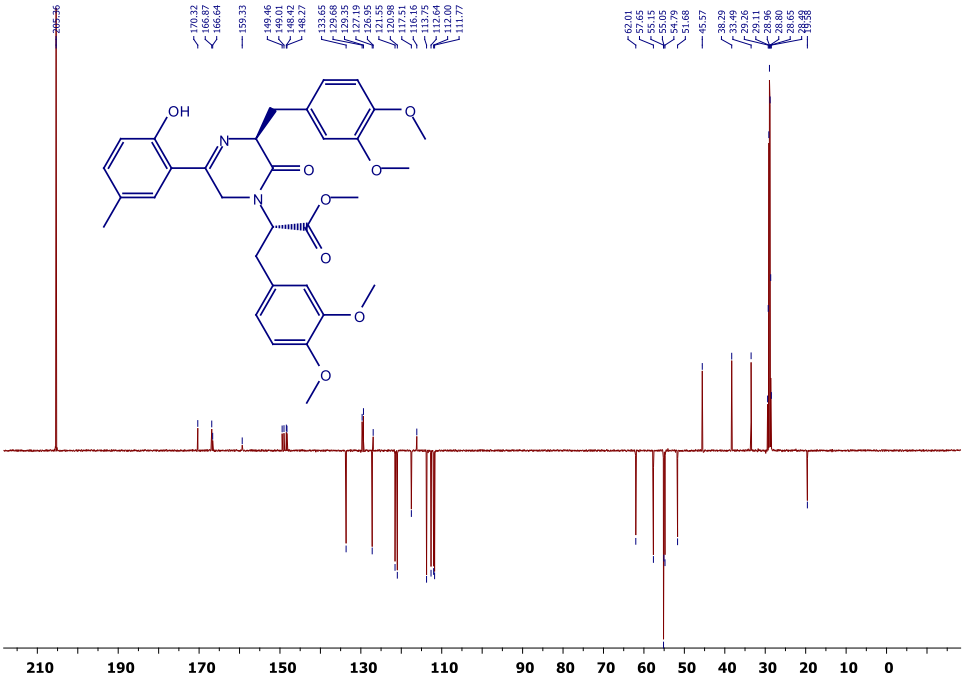
**Supplementary Figure 159** $^{1}H$ (500 MHz, $CDCl_3$) spectrum of methyl (R)-2-((R)-3-benzyl-5-(2-hydroxy-5-methylphenyl)-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-phenylpropanoate (**24b**)



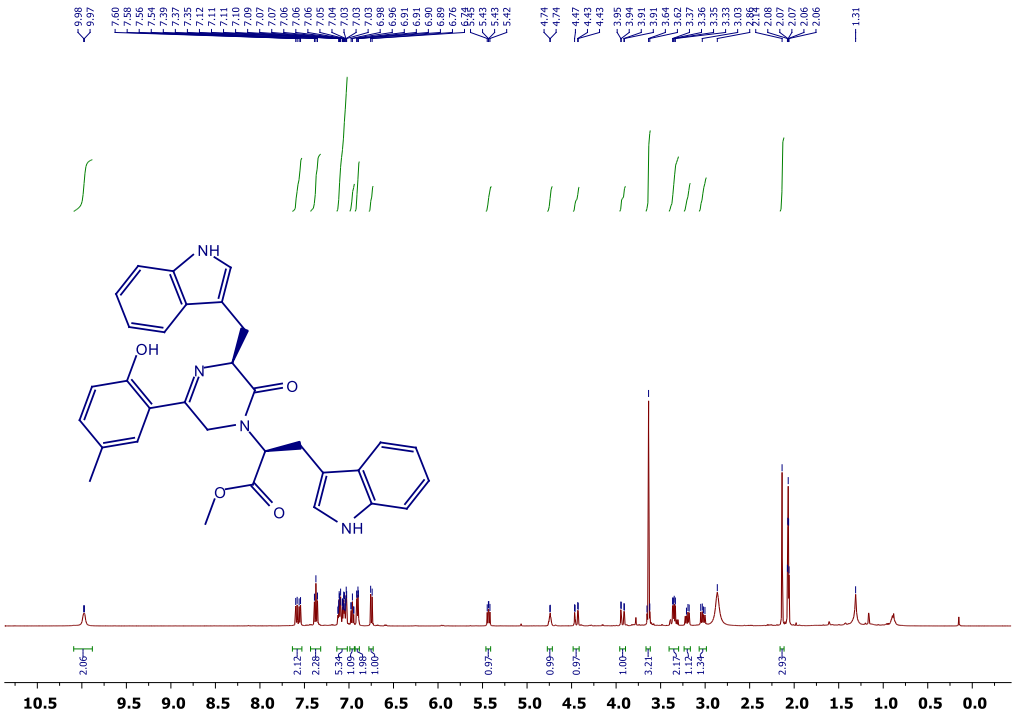
**Supplementary Figure 160** APT NMR (125 MHz, Acetone-$d_6$) spectrum of methyl (R)-2-((R)-3-benzyl-5-(2-hydroxy-5-methylphenyl)-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-phenylpropanoate (**24b**)



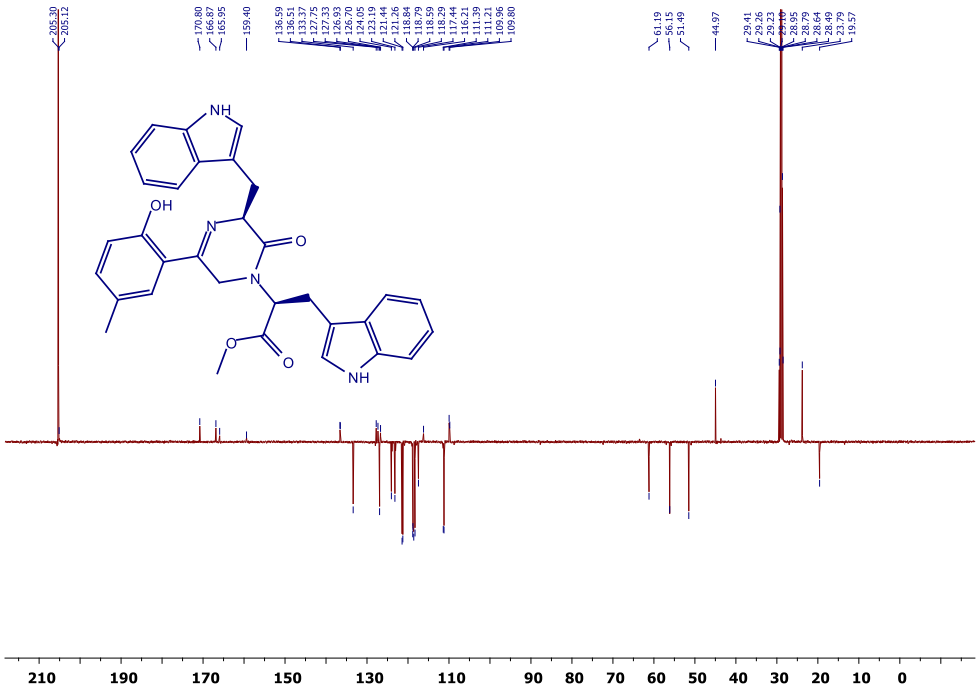
**Supplementary Figure 161** $^{1}$H (500 MHz, Acetone-$d_6$) spectrum methyl (S)-2-((S)-3-(3,4-dimethoxybenzyl)-5-(2-hydroxy-5-methylphenyl)-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-(3,4-dimethoxyphenyl)propanoate (**24c**)



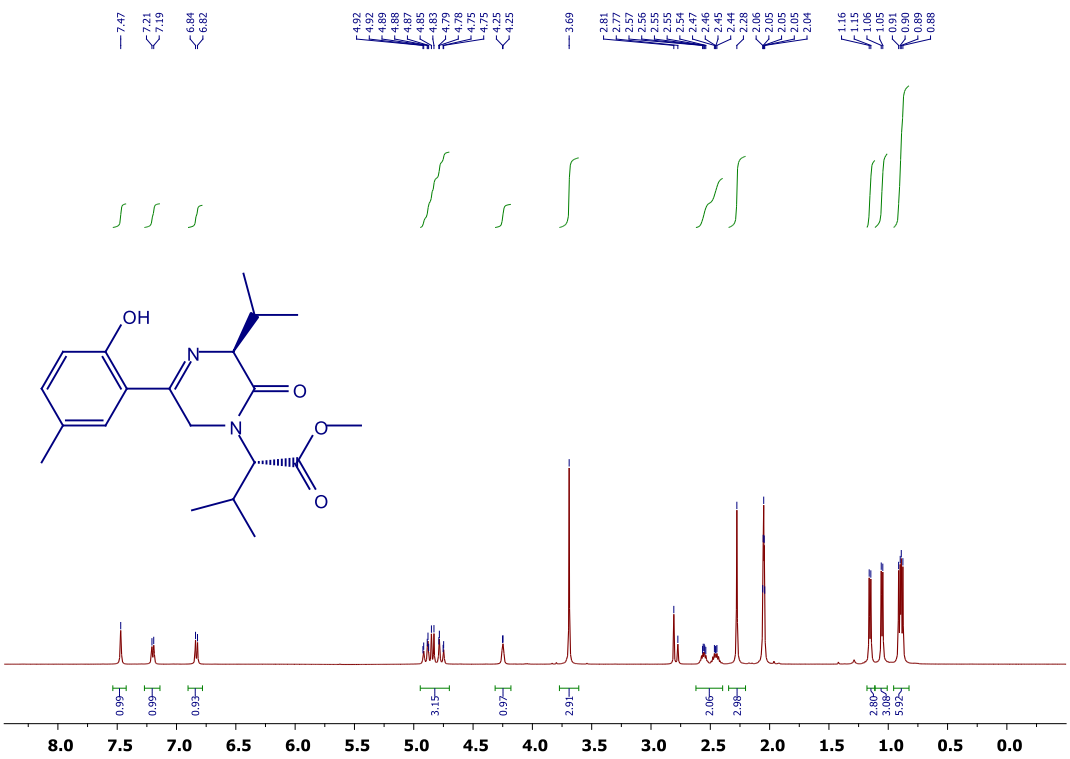
**Supplementary Figure 162** APT NMR (125 MHz, Acetone-$d_6$) spectrum methyl (S)-2-((S)-3-(3,4-dimethoxybenzyl)-5-(2-hydroxy-5-methylphenyl)-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-(3,4-dimethoxyphenyl)propanoate (**24c**)



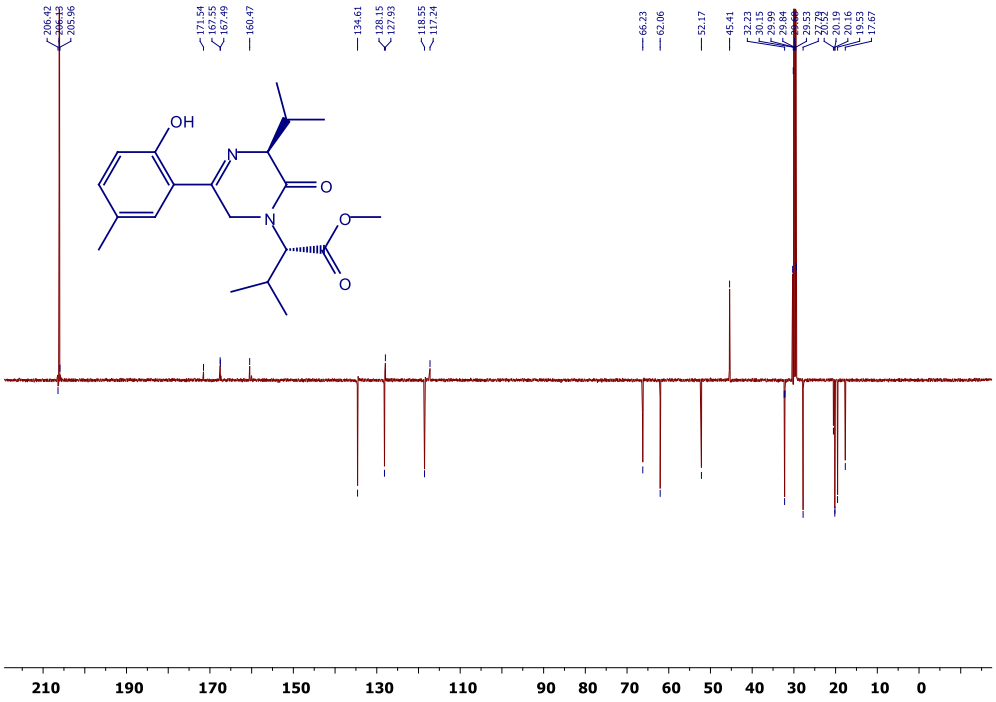
**Supplementary Figure 163** $^{1}$H (500 MHz, Acetone-$d_6$) spectrum methyl (S)-2-((S)-3-((1H-indol-3-yl)methyl)-5-(2-hydroxy-5-methylphenyl)-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-(1H-indol-3-yl)propanoate (**24d**)



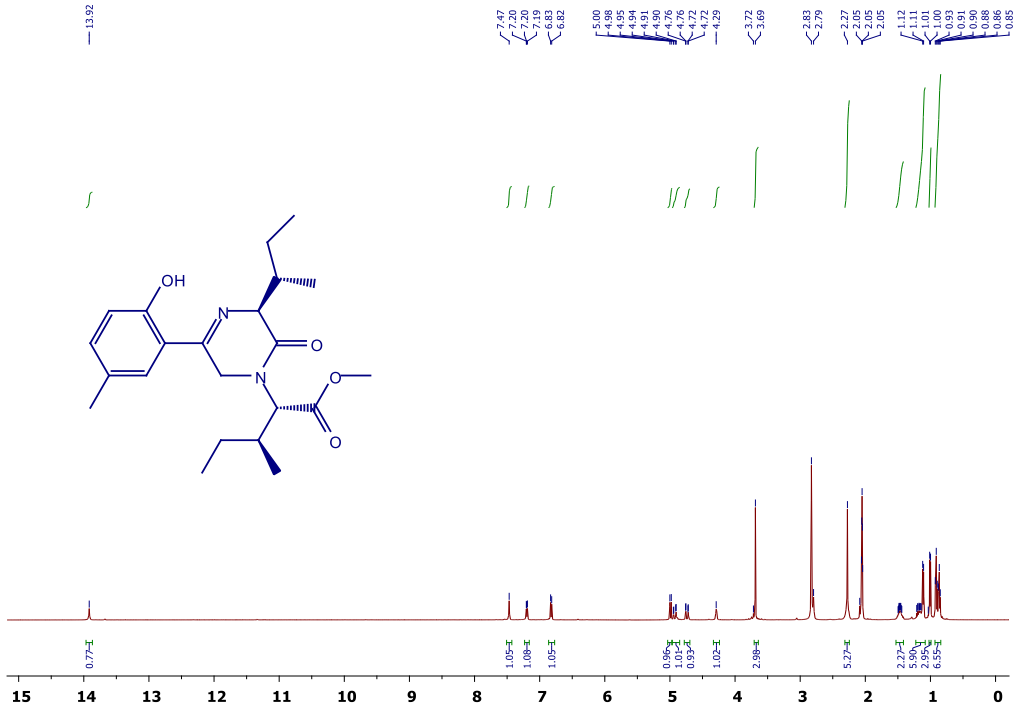
**Supplementary Figure 164** APT NMR (125 MHz, Acetone-$d_6$) spectrum methyl (S)-2-((S)-3-((1H-indol-3-yl)methyl)-5-(2-hydroxy-5-methylphenyl)-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-(1H-indol-3-yl)propanoate (**24d**)



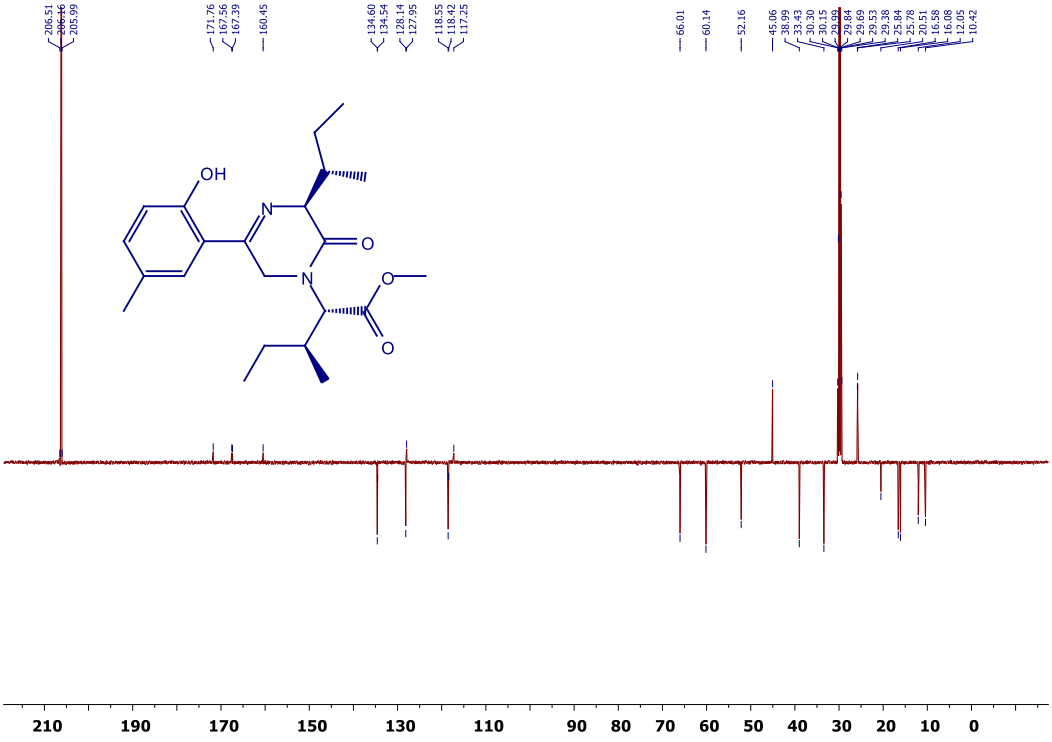

**Supplementary Figure 165** $^{1}$H (500 MHz, Acetone-$d_6$) spectrum methyl (S)-2-((S)-5-(2-hydroxy-5-methylphenyl)-3-isopropyl-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-methylbutanoate (**24e**)



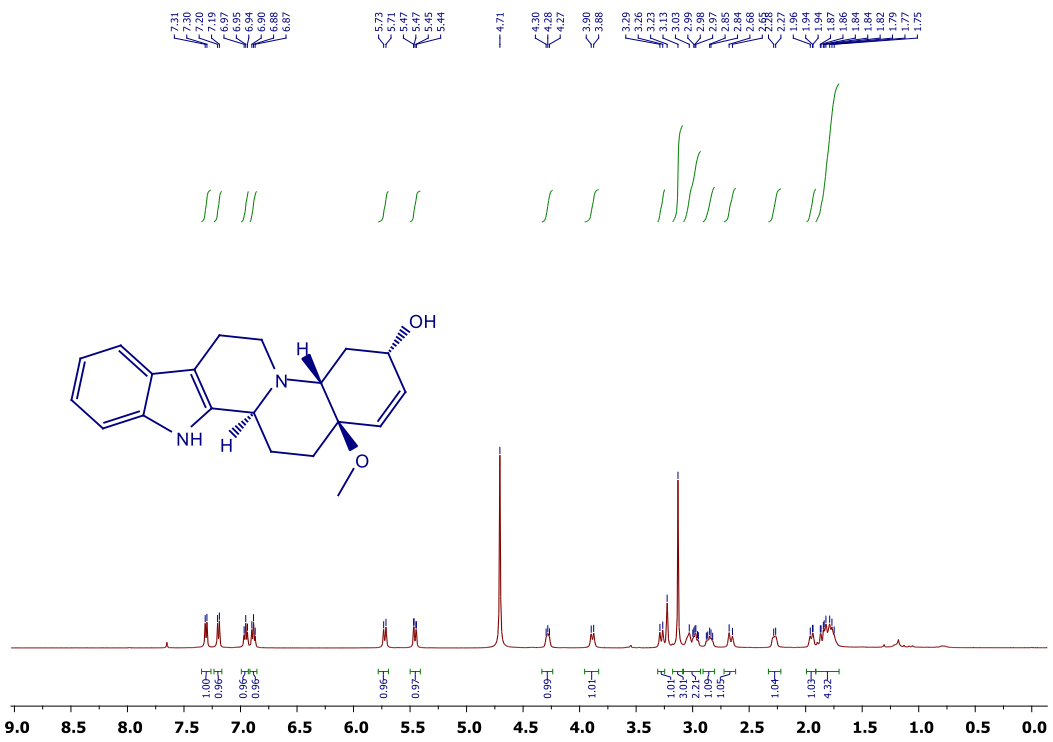

**Supplementary Figure 166** APT NMR (125 MHz, Acetone-$d_6$) spectrum methyl (S)-2-((S)-5-(2-hydroxy-5-methylphenyl)-3-isopropyl-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-methylbutanoate (**24e**)



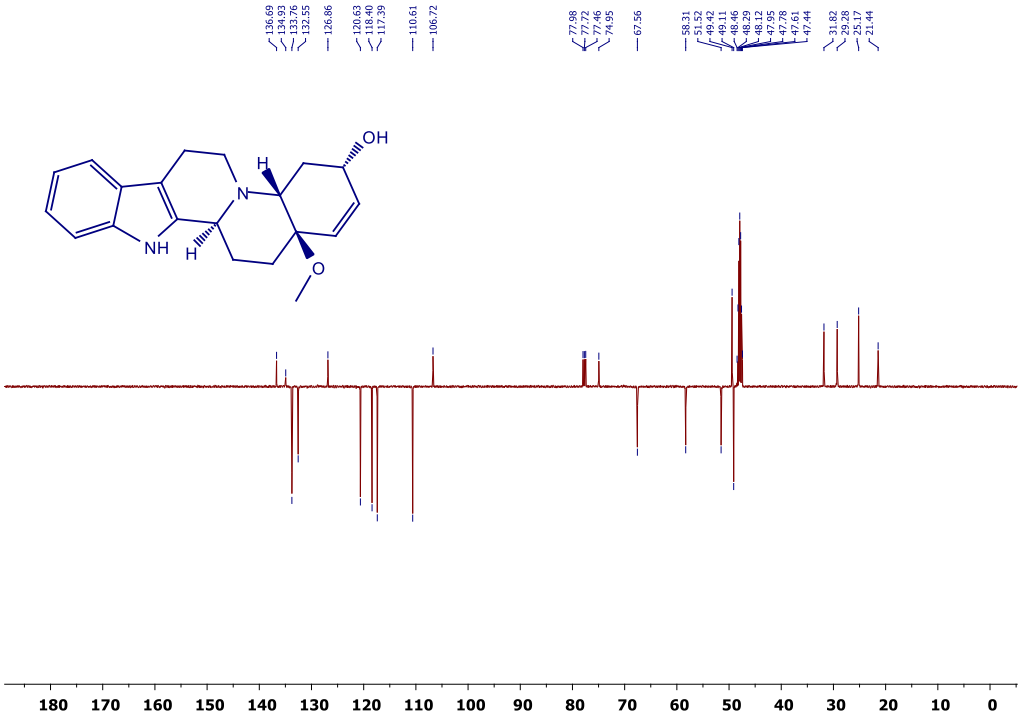

**Supplementary Figure 167** $^{1}H$ (500 MHz, $CDCl_3$) spectrum methyl (2S,3S)-2-((S)-3-((S)-sec-butyl)-5-(2-hydroxy-5-methylphenyl)-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-methylpentanoate (**24f**)



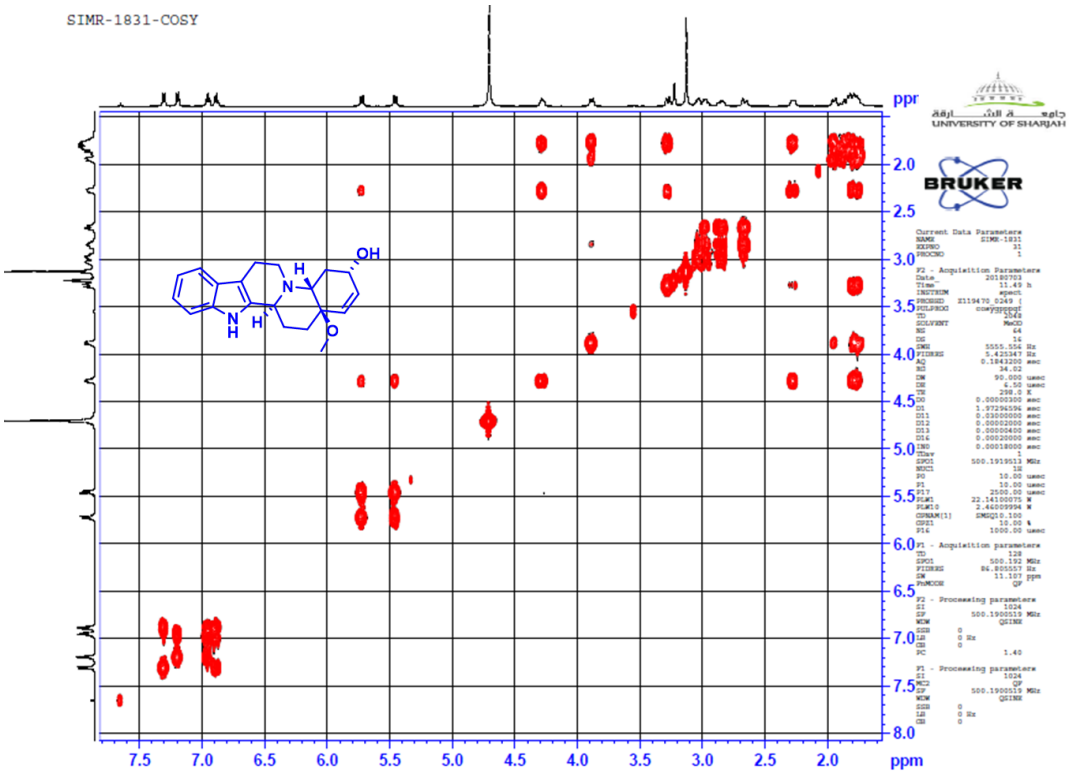

**Supplementary Figure 168** APT NMR (125 MHz, $CDCl_3$) spectrum methyl (2S,3S)-2-((S)-3-((S)-sec-butyl)-5-(2-hydroxy-5-methylphenyl)-2-oxo-3,6-dihydropyrazin-1(2H)-yl)-3-methylpentanoate (**24f**)



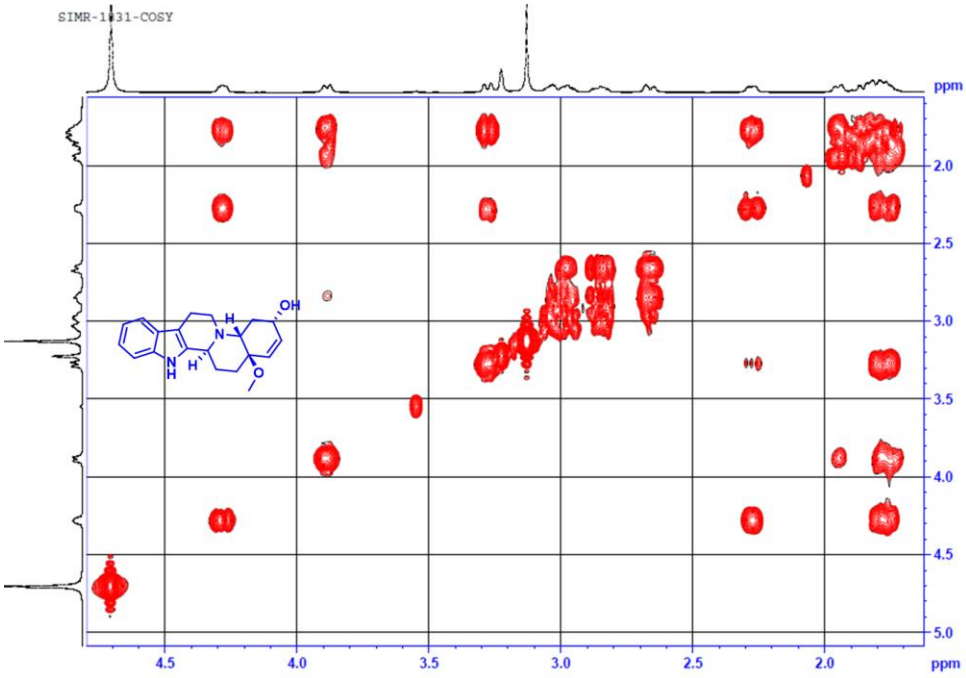

**Supplementary Figure 169** $^{1}H$ (500 MHz, $CD_3OD$) spectrum of (2aR,5S,6aR,14bS)-2a-methoxy-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5-ol (**25**)



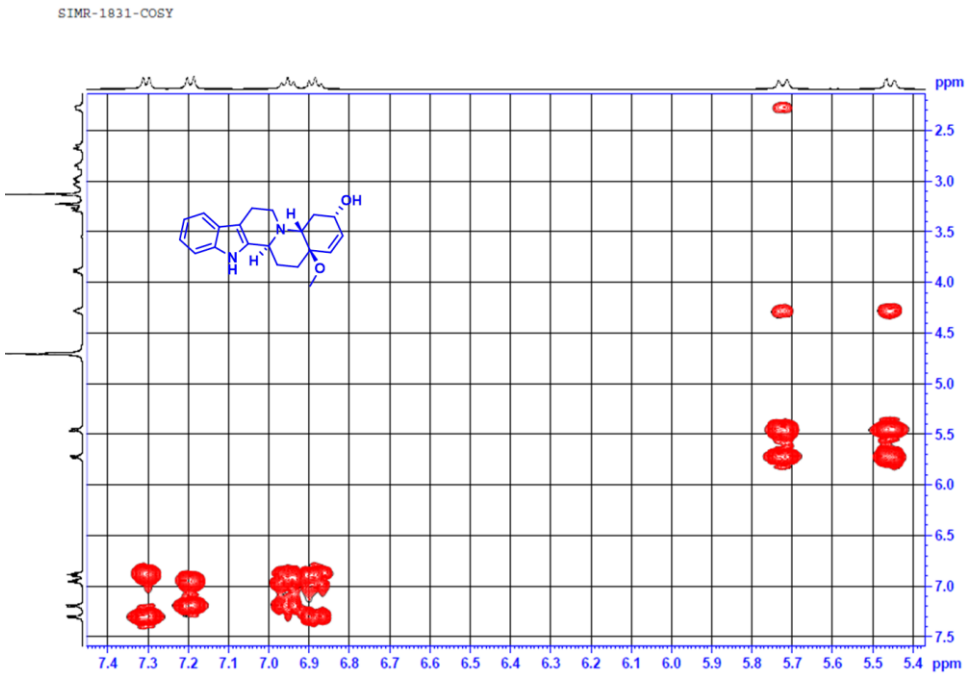

**Supplementary Figure 170** APT NMR (125 MHz, $CD_3OD$) spectrum of (2aR,5S,6aR,14bS)-2a-methoxy-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5-ol (**25**)



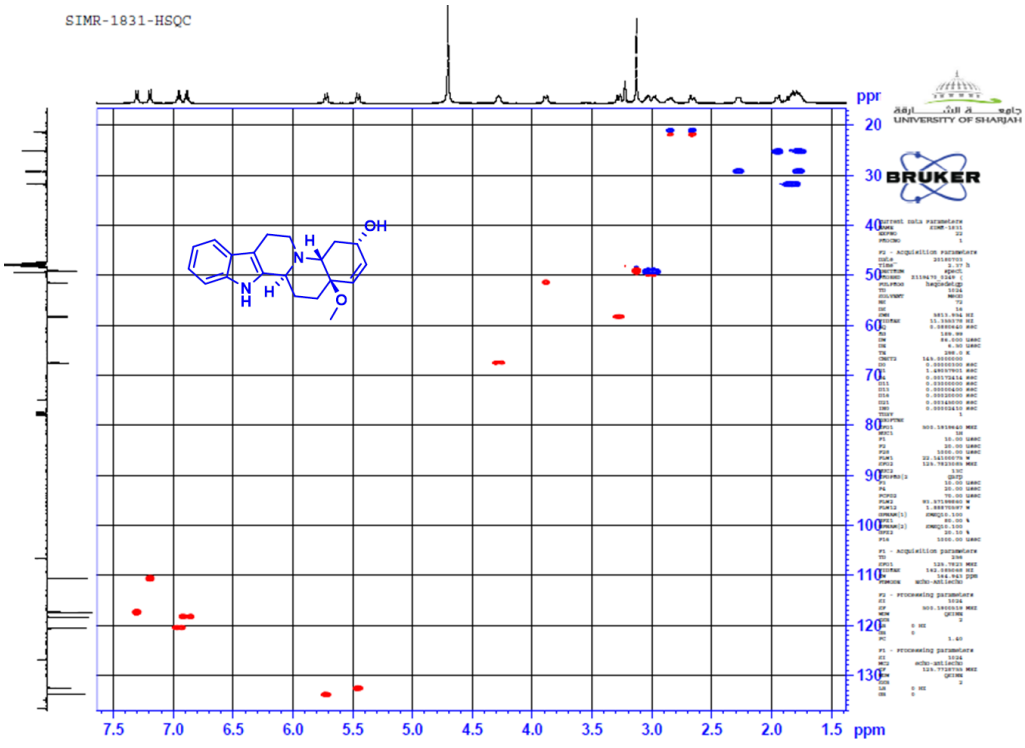

**Supplementary Figure 171** COSY (500 MHz, $CD_3OD$) spectrum of (2aR,5S,6aR,14bS)-2a-methoxy-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5-ol (**25**)



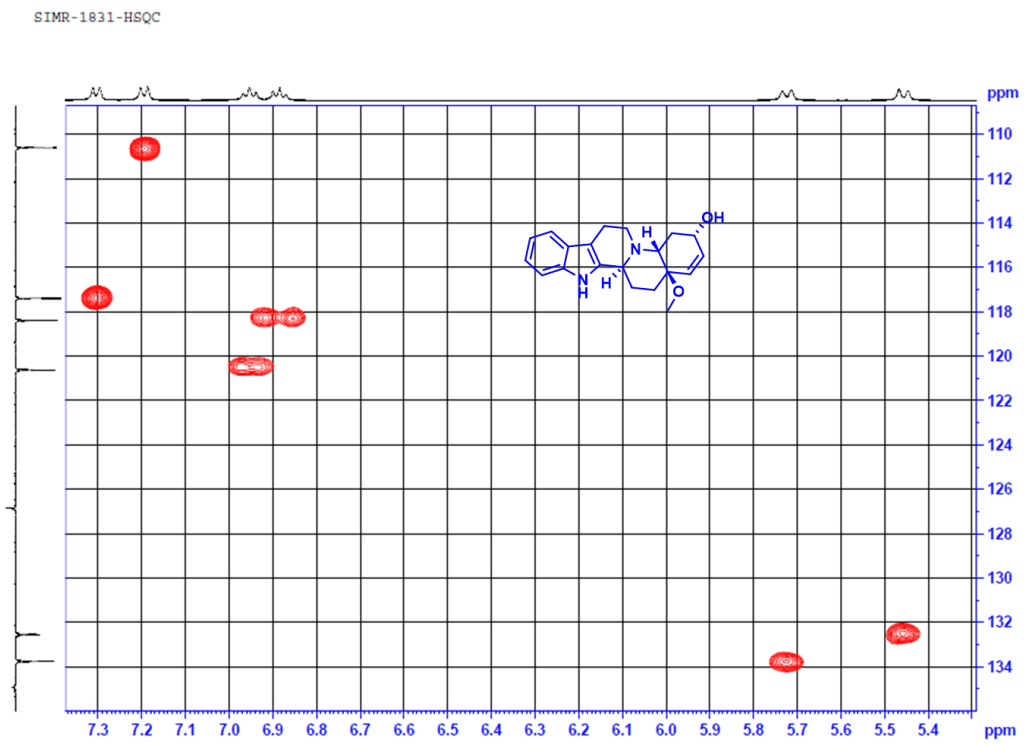

**Supplementary Figure 172** COSY (Expansion) spectrum of (2aR,5S,6aR,14bS)-2a-methoxy-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5-ol (**25**)



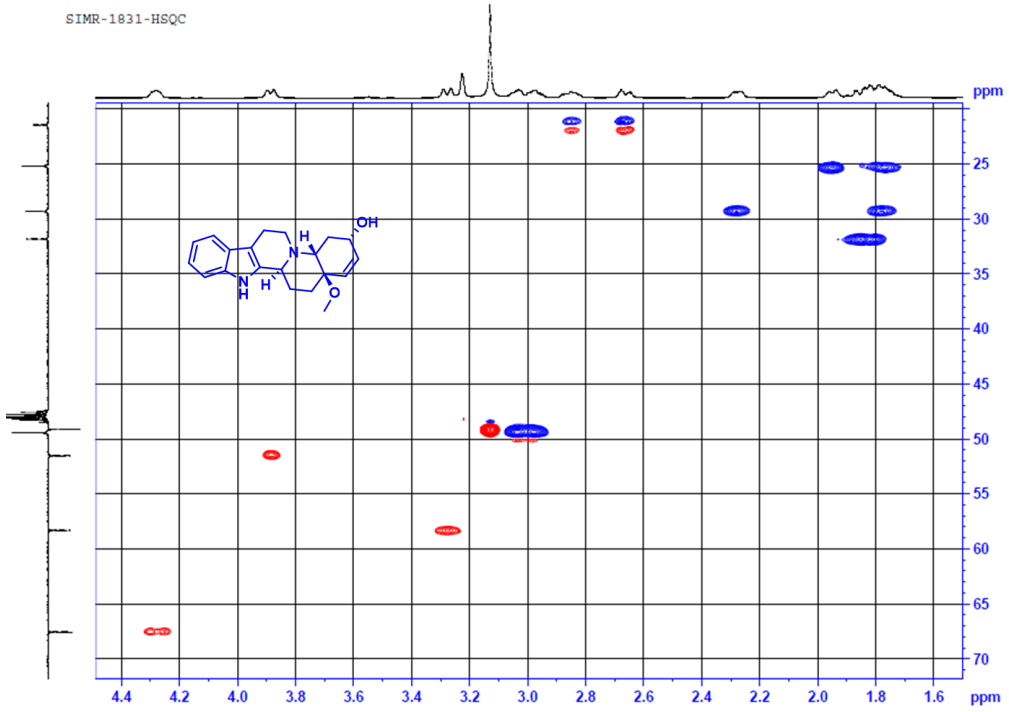

**Supplementary Figure 173** COSY (Expansion) spectrum of (2aR,5S,6aR,14bS)-2a-methoxy-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5-ol (**25**)



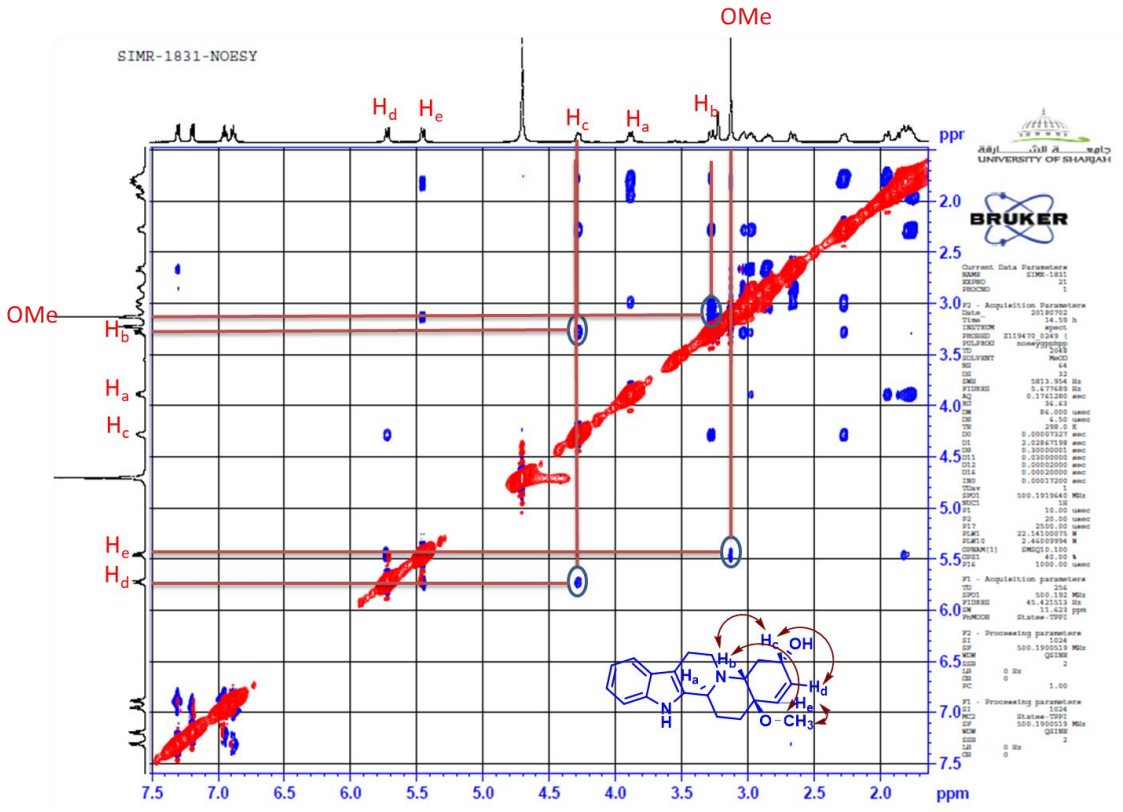

**Supplementary Figure 174** HSQC (500 MHz, $CD_3OD$) spectrum of (2aR,5S,6aR,14bS)-2a-methoxy-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5-ol (**25**)



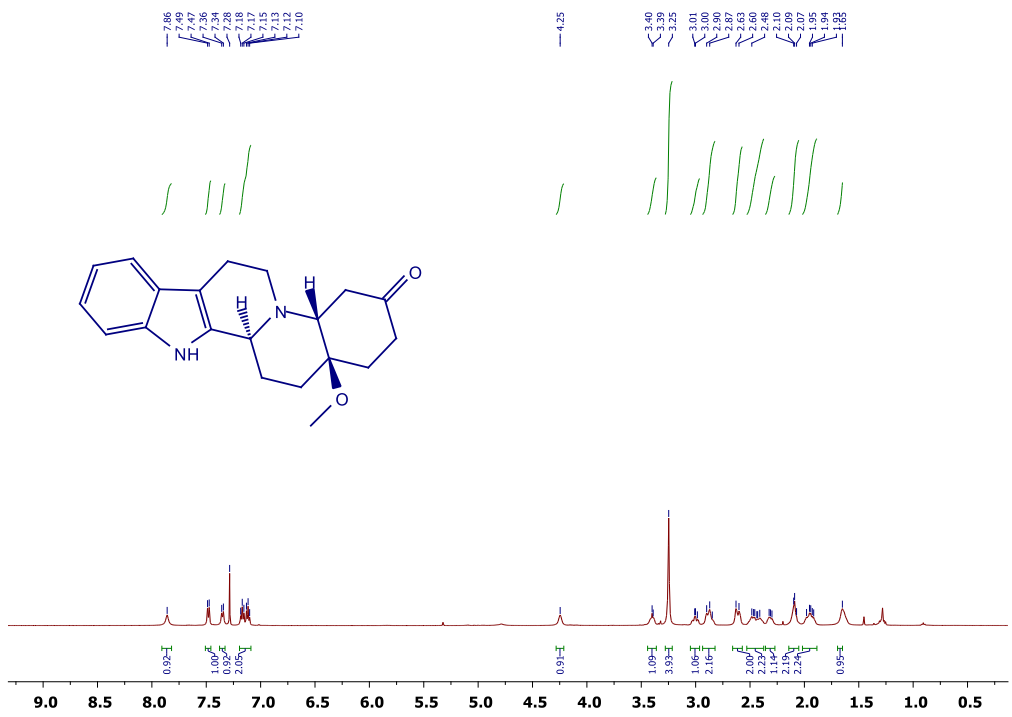

**Supplementary Figure 175** HSQC (Expansion) spectrum of (2aR,5S,6aR,14bS)-2a-methoxy-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5-ol (**25**)



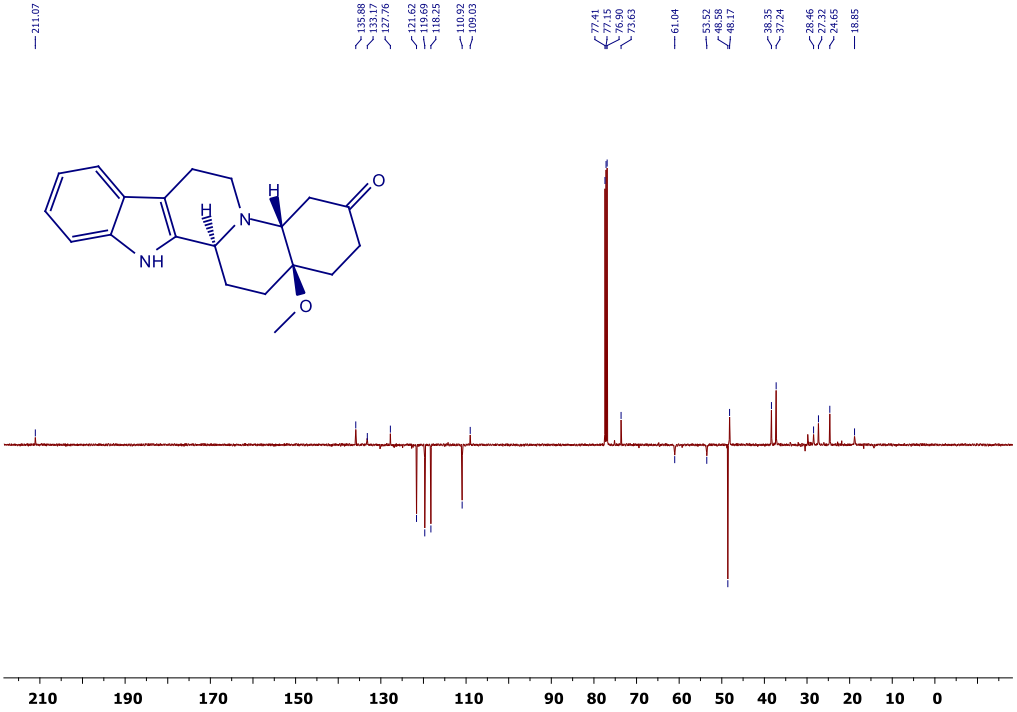

**Supplementary Figure 176** HSQC (Expansion) spectrum of (2aR,5S,6aR,14bS)-2a-methoxy-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5-ol (**25**)



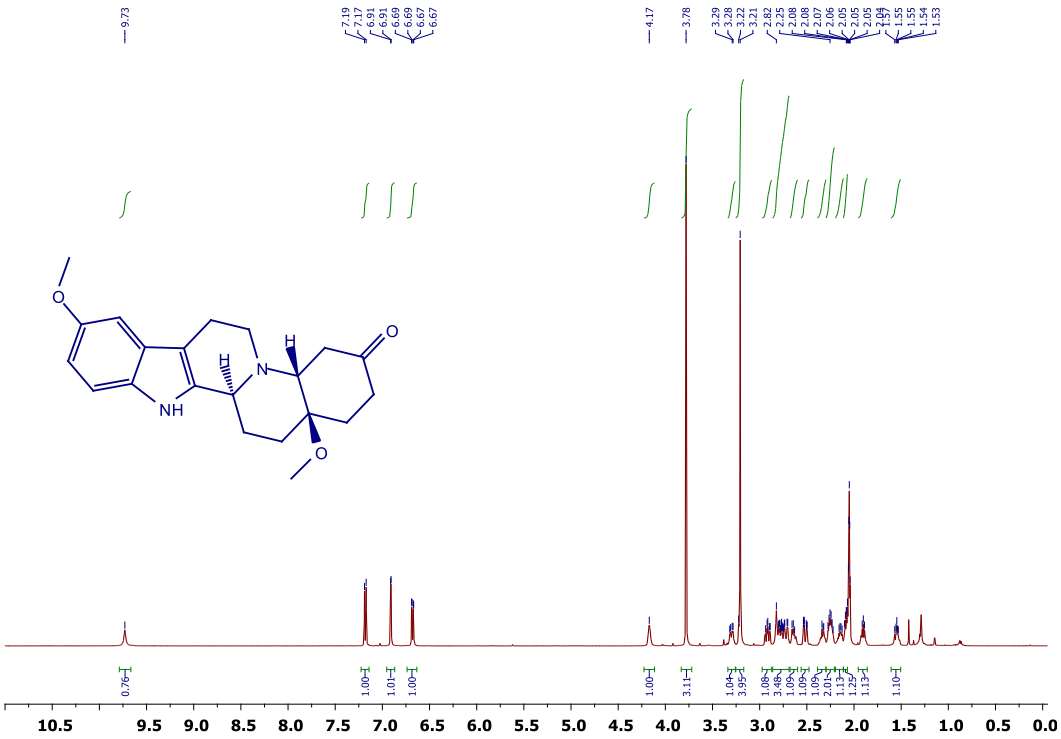

**Supplementary Figure 177** NOESY (500 MHz, $CD_3OD$) spectrum of (2aR,5S,6aR,14bS)-2a-methoxy-1,2,2a,5,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5-ol (**25**)



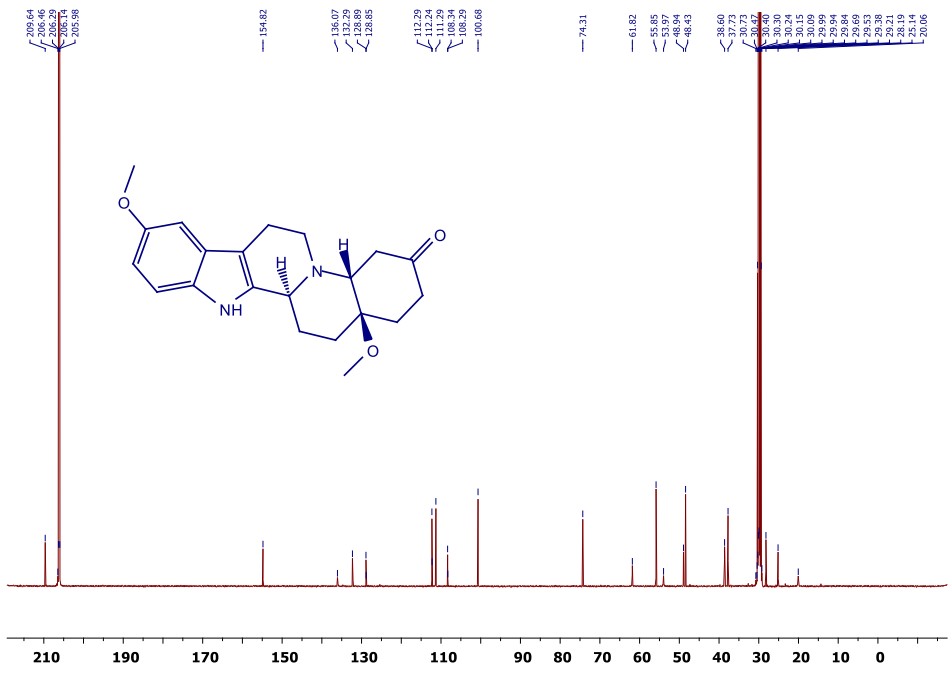
**Supplementary Figure 178** $^{1}$H NMR (500 MHz, $CDCl_3$) spectrum of (2aR,6aR,14bS)-2a-methoxy-2,2a,3,4,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5(1H)-one (**26a**)



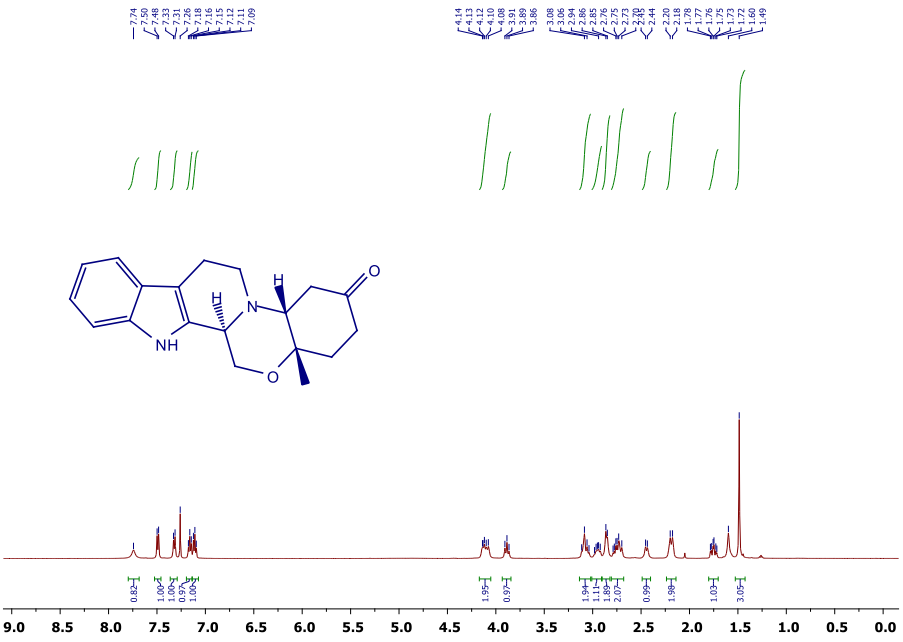
**Supplementary Figure 179** APT NMR (125 MHz, $CDCl_3$) spectrum of (2aR,6aR,14bS)-2a-methoxy-2,2a,3,4,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5(1H)-one (**26a**)



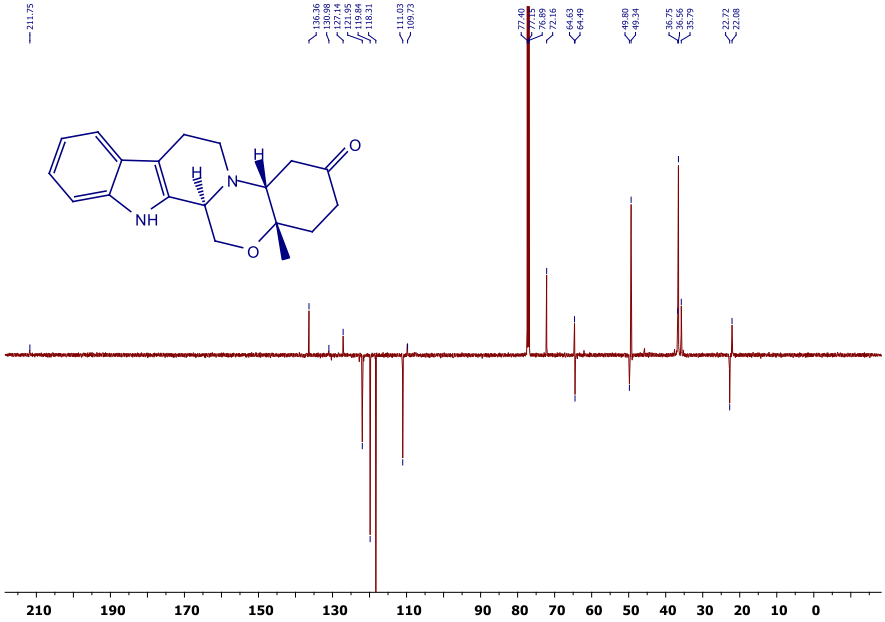
**Supplementary Figure 180** $^{1}$H NMR (500 MHz, Acetone-$d_6$) spectrum of (2aR,6aR,14bS)-2a,11-dimethoxy-2,2a,3,4,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5(1H)-one (**26b**)



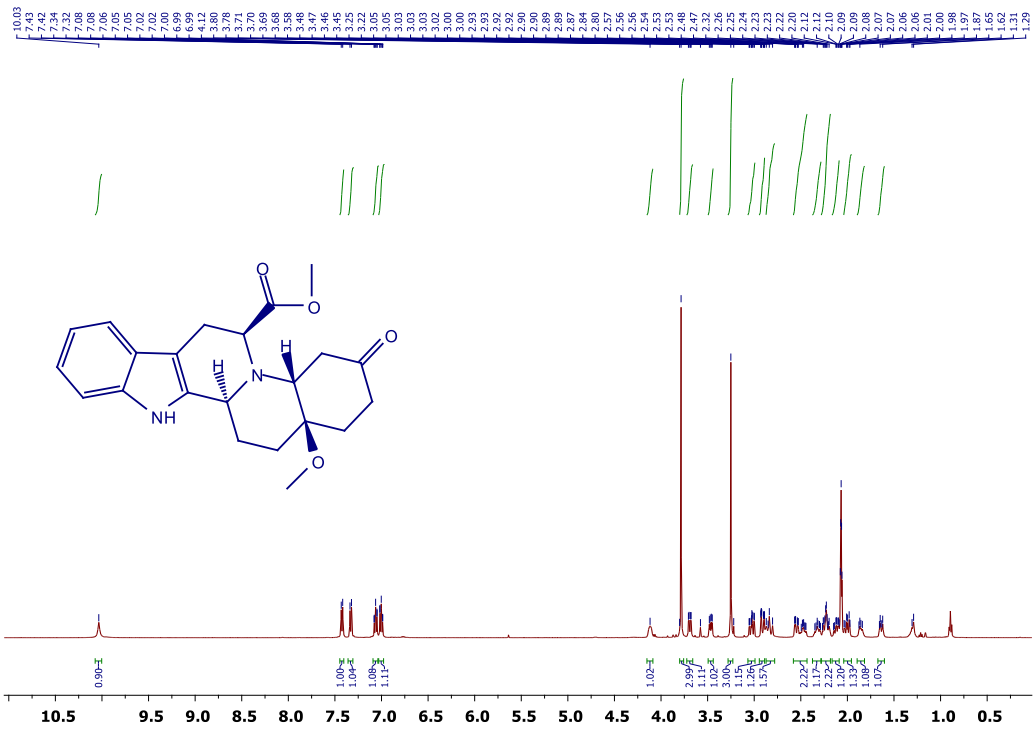
**Supplementary Figure 181** $^{13}$C NMR (125 MHz, Acetone-$d_6$) spectrum of (2aR,6aR,14bS)-2a,11-dimethoxy-2,2a,3,4,6,6a,8,9,14,14b-decahydroindolo[2',3':3,4]pyrido[1,2-a]quinolin-5(1H)-one (**26b**)



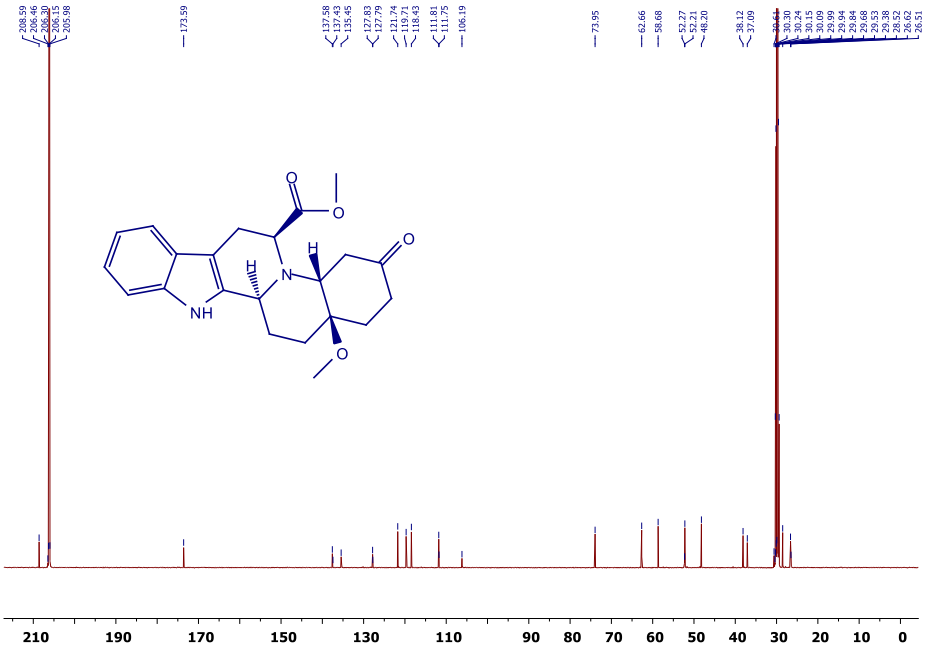

**Supplementary Figure 182** $^{1}$H NMR (500 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bR)-2a-methyl-3,4,6,6a,8,9,14,14b-octahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (**26c**)



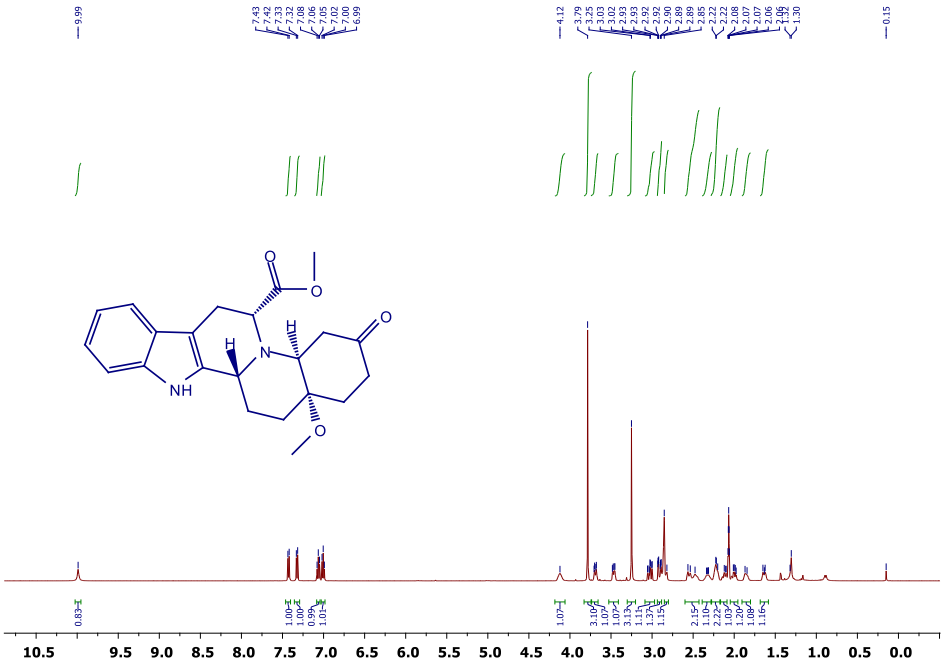

**Supplementary Figure 183** APT NMR (125 MHz, $CDCl_3$) spectrum of (2aS,6aR,14bR)-2a-methyl-3,4,6,6a,8,9,14,14b-octahydro-1H-benzo[5',6'][1,4]oxazino[4',3':1,2]pyrido[3,4-b]indol-5(2aH)-one (**26c**)



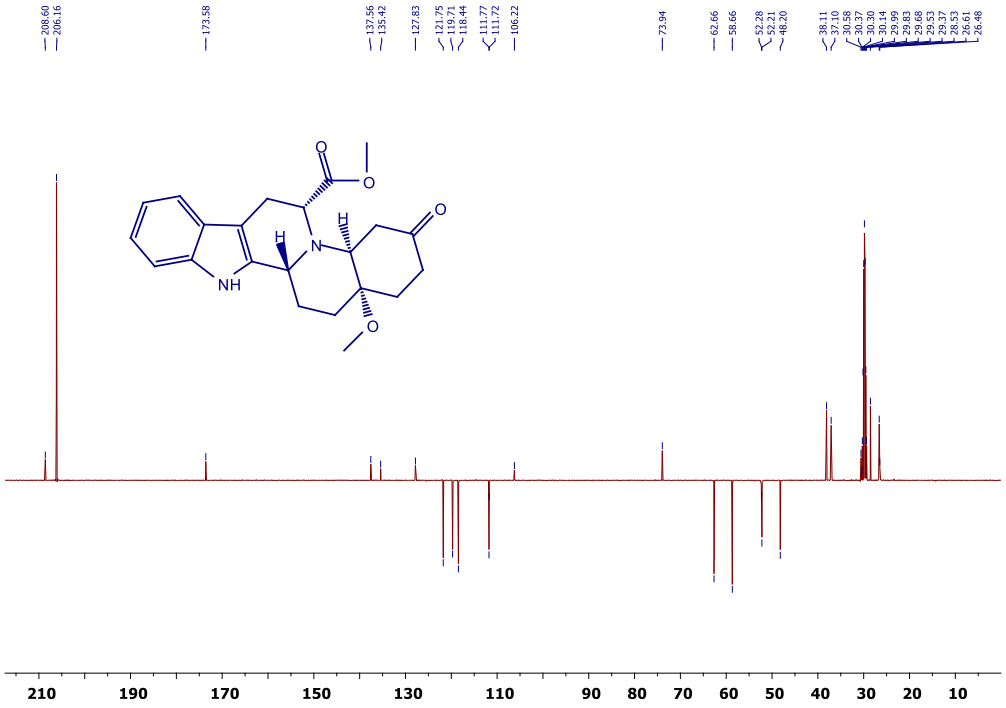
**Supplementary Figure 184** $^{1}$H NMR (500 MHz, Acetone-$d_6$) spectrum of methyl (2aR,6aR,8S,14bS)-2a-methoxy-5-oxo-1,2,2a,3,4,5,6,6a,8,9,14,14b-dodecahydroindolo[2',3':3,4]pyrido[1,2-a]quinoline-8-carboxylate (**26d**)



**Supplementary Figure 185** $^{13}$C NMR (125 MHz, Acetone-$d_6$) spectrum of methyl (2aR,6aR,8S,14bS)-2a-methoxy-5-oxo-1,2,2a,3,4,5,6,6a,8,9,14,14b-dodecahydroindolo[2',3':3,4]pyrido[1,2-a]quinoline-8-carboxylate (**26d**)



**Supplementary Figure 186** $^{1}$H NMR (500 MHz, Acetone-$d_6$) methyl (2aS,6aS,8R,14bR)-2a-methoxy-5-oxo-1,2,2a,3,4,5,6,6a,8,9,14,14b-dodecahydroindolo[2',3':3,4]pyrido[1,2-a]quinoline-8-carboxylate (**26e**)



**Supplementary Figure 187** APT NMR (125 MHz, Acetone-$d_6$) methyl (2aS,6aS,8R,14bR)-2a-methoxy-5-oxo-1,2,2a,3,4,5,6,6a,8,9,14,14b-dodecahydroindolo[2',3':3,4]pyrido[1,2-a]quinoline-8-carboxylate (**26e**)

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