Synthesis of Jacaranone-derived Nitrogenous Cyclohexadienones and Their Antiproliferative and Antiprotozoal Activities

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Supporting Information

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Table 1: Synthesis and compared overall yields of compounds 7, 11 and 12, final oxidation step to the dienones 13 – 15

| Entry | X | Method<sup>a</sup> | Product | Yield/%<sup>b</sup> |
|-------|---|------------------|---------|------------------|
| 1     | O | A                | 7a      | 71               |
| 2     | O | B                | 7a      | 73               |
| 3     | O | C                | 7a      | 23               |
| 4     | O | A                | 7b      | 58               |
| 5     | O | B                | 7b      | 55               |
| 6     | O | C                | 7b      | 51               |
| 7     | O | A                | 7c      | 62               |
| 8     | O | B                | 7c      | 58               |
| 9     | O | C                | 7c      | 98               |
| 10    | O | B                | 7d      | 89               |
| 11    | O | C                | 7d      | 67               |
| 12    | O | B                | 7e      | 90               |
| 13    | O | C                | 7e      | 67               |
| 14    | O | B                | 7f      | 0                |
|    |   |   |   |   |   |
|----|---|---|---|---|---|
| 15 | O | C | 7f | 86 |
| 16 | O | B | 7g | 0  |
| 17 | O | C | 7g | 71 |
| 18 | O | B | 7h | 86 |
| 19 | O | C | 7h | 79 |
| 20 | O | B | 7i | 92 |
| 21 | O | C | 7i | 98 |
| 22 | O | B | 7j | 79 |
| 23 | O | C | 7j | 98 |
| 24 | H, H | B→D | 11a | 53 |
| 25 | H, H | F | 11a | 48 |
| 27 | H, H | D | 11b | 0  |
| 28 | H, H | E | 11b | 42 |
| 29 | H, H | F | 11b | 64 |
| 30 | H, H | D | 11c | 0  |
| 31 | H, H | F | 11c | 69 |
| 32 | H, H | D | 11d | 0  |
| 33 | H, H | F | 11d | 61 |
| 34 | H, H | B→D | 11e | 53 |
| 35 | O, OH | B→D | 12 | 76 |

1 Reaction conditions: (i) 13a-j, 15: PhI(OAc)₂, CH₃CN/H₂O (12:5), 0 °C, 7 min (13a: 67%, 13b: 17%, 13c: 55%, 13d: 40%, 13e: 64%, 13f: 19%, 13g: 18%, 13h: 79%, 13i: 88%, 13j: 49%, 15: 65%); 14a-e: PhI(OAc)₂,
CH₃CN/H₂O/phosphate buffer (12:3:2), pH = 6.4, 0 °C, 7 min (14a: 16%, 14b: 0%, 14c: 28%, 14d: 0%, 14e: 0%).

**Method A:** preparation of imides via Mitsunobu reaction; method B: AcOH-assisted condensation of tyramine; method C: PEG 400-assisted condensation of tyramine; method D: preparation of amines from imides; method E: preparation of amines by catalytic amination; method F: preparation of amines via alkyl bromides

**Isolated yield.**
Table 2: Calculated physicochemical properties of the tested compounds.

| compd | MW    | logP | logS | HBD | HBA | tPSA (Å²) | ASA (Å²) | ASapho (Å²) | ASapol (Å²) |
|-------|-------|------|------|-----|-----|-----------|----------|-------------|-------------|
|       |       | pH 7.4 | pH 7.4 | pH 7.4 | pH 7.4 | pH 7.4 | pH 7.4 | pH 7.4 |
| 13a   | 283.28| 0.85  | -4.38| 1   | 4   | 74.68    | 398.81   | 297.48      | 101.33      |
| 13b   | 233.22| -0.18 | -3.11| 1   | 4   | 74.68    | 309.98   | 200.20      | 109.77      |
| 13c   | 235.24| -0.60 | -2.09| 1   | 4   | 74.68    | 347.12   | 241.44      | 105.68      |
| 13d   | 352.17| 1.89  | -5.79| 1   | 4   | 74.68    | 433.57   | 332.23      | 101.34      |
| 13e   | 302.11| -0.38 | -4.12| 1   | 4   | 74.68    | 348.25   | 231.55      | 116.70      |
| 13f   | 284.27| -0.06 | -1.76| 1   | 5   | 87.57    | 391.80   | 273.57      | 118.23      |
| 13g   | 251.24| -1.13 | -2.34| 1   | 5   | 83.91    | 361.20   | 242.04      | 119.16      |
| 13h   | 289.33| 0.81  | -3.86| 1   | 4   | 74.68    | 395.92   | 302.04      | 93.88       |
| 13i   | 287.32| 0.66  | -4.34| 1   | 4   | 74.68    | 400.77   | 305.51      | 95.26       |
| 13j   | 287.32| 0.55  | -3.15| 1   | 4   | 74.68    | 371.43   | 276.99      | 94.44       |
| 14a   | 255.32| 1.89  | 0.00 | 1   | 3   | 41.74    | 401.42   | 337.80      | 63.62       |
| 14c   | 223.27| 0.04  | 0.58 | 1   | 4   | 49.77    | 363.97   | 285.49      | 78.49       |
| 15    | 291.35| 0.58  | -3.83| 2   | 4   | 77.84    | 397.62   | 303.73      | 93.89       |
The molecular weight (MW), log\(P\), log\(S\), hydrogen bond donor (HBD), hydrogen bond acceptor (HBA), topological polar surface area (tPSA), accessible surface area (ASA), hydrophobic accessible surface area (ASAp\(ho\)) and polar accessible surface area (ASAp\(ol\)) were calculated using Marvin 18.10.0, ChemAxon (https://www.chemaxon.com).
### Table 3: Calculated ligand efficiency metrics of the tested compounds.

| compd | $P. falciparum$ | $T. brucei rhodesiense$ |
|-------|----------------|-----------------|
|       | LE  | LLE | LELP | LE  | LLE | LELP | LE  | LLE | LELP |
| 13a   | 0.35426 | 4.3071 | 3.1496 | 0.37897 | 4.6853 | 2.9443 |
| 13b   | 0.43214 | 5.9852 | -1.4583 | 0.4574 | 6.2982 | -1.3778 |
| 13c   | 0.40866 | 5.4188 | -0.86821 | 0.41635 | 5.5141 | -0.85216 |
| 13d   | 0.32745 | 3.1621 | 7.1088 | 0.31276 | 2.9158 | 7.4427 |
| 13e   | 0.2981 | 3.9202 | 0.6991 | 0.4076 | 5.4367 | 0.51128 |
| 13f   | 0.29739 | 4.3834 | 0.56794 | 0.28413 | 4.1803 | 0.59445 |
| 13g   | 0.37554 | 6.1041 | -3.1336 | 0.36695 | 5.9914 | -3.207 |
| 13h   | 0.36037 | 4.9418 | 1.5945 | 0.37696 | 5.1957 | 1.5243 |
| 13i   | 0.38487 | 5.2504 | 1.6655 | 0.3984 | 5.4575 | 1.6089 |
| 13j   | 0.35311 | 5.1061 | 0.84732 | 0.3928 | 5.7136 | 0.76171 |
| 14a   | 0.39973 | 4.7611 | 1.9388 | 0.45074 | 5.4676 | 1.7194 |
| 14c   | 0.42541 | 5.0059 | -0.10437 | 0.56335 | 6.6146 | -0.078814 |
| 15    | 0.3403 | 4.4189 | 2.3224 | 0.38014 | 5.0287 | 2.079 |
The ligand efficiency (LE), lipophilic ligand efficiency (LLE) and ligand efficiency lipophilic price (LELP) are based on IC$_{50}$ values in nmol/L and were calculated using the DataWarrior software, version 4.7.2 (http://www.openmolecules.org/datawarrior.html).
Fig. 1 BOILED-Egg analysis of all synthesized dienones. Substances within the white ellipse (egg white) are anticipated to have good intestinal absorption (passive absorption); the yellow region (yolk) is the physicochemical space of molecules with high probability to permeate the blood-brain barrier. The BOILED–Egg model also reflects the variability in IC$_{50}$ values of our evaluated compounds after altering the dienone skeleton.

The plot was prepared by using the free web tool SwissADME (www.swissadme.ch).
| compd | CCRF-CEM | MDA-MB-231 | HCT 116 | U251 | MRC-5 |
|-------|----------|------------|---------|------|-------|
|       | 5 µg/mL  | 50 µg/mL   | 5 µg/mL | 50 µg/mL | 5 µg/mL | 50 µg/mL | 5 µg/mL | 50 µg/mL | 5 µg/mL | 50 µg/mL |
| **13a** | 4.42 ± 1.95 | 1.15 ± 0.57 | 37.76 ± 3.13 | 17.38 ± 1.50 | 55.36 ± 4.79 | 1.76 ± 0.15 | 90.65 ± 4.53 | 3.21 ± 0.65 | 43.74 ± 4.17 | 1.93 ± 0.27 |
| **13b** | -1.08 ± 0.41 | 3.46 ± 0.46 | 1.71 ± 0.23 | 6.61 ± 0.28 | 0.13 ± 0.22 | -0.32 ± 0.14 | 95.21 ± 2.89 | -0.41 ± 0.13 | 14.61 ± 3.58 | 0.62 ± 0.05 |
| **13c** | 79.06 ± 7.04 | 2.15 ± 0.08 | 79.79 ± 4.02 | 5.72 ± 0.95 | 99.04 ± 2.69 | 1.10 ± 0.14 | 93.33 ± 4.65 | 0.59 ± 0.06 | 139.35 ± 3.57 | 3.55 ± 0.63 |
| **13d** | 13.80 ± 3.18 | 3.33 ± 0.82 | 28.59 ± 1.24 | 24.84 ± 2.30 | 41.24 ± 4.07 | 0.44 ± 0.13 | 72.11 ± 9.10 | 1.79 ± 0.51 | 46.44 ± 5.26 | 1.01 ± 0.14 |
| **13e** | -2.60 ± 0.50 | 0.59 ± 0.16 | 81.32 ± 1.60 | 9.53 ± 0.37 | 45.33 ± 5.40 | -0.43 ± 0.12 | 95.64 ± 2.66 | 1.95 ± 0.25 | 97.01 ± 5.81 | 0.38 ± 0.05 |
| **13f** | 99.83 ± 2.36 | 21.74 ± 6.20 | 112.14 ± 5.31 | 23.02 ± 1.33 | 90.99 ± 5.01 | 23.81 ± 7.25 | 91.76 ± 3.22 | 93.66 ± 2.82 | 108.57 ± 2.95 | 111.87 ± 2.68 |
| **13g** | 86.92 ± 6.14 | 8.05 ± 0.88 | 104.42 ± 2.43 | 7.63 ± 0.24 | 96.00 ± 3.74 | 68.10 ± 5.16 | 94.70 ± 1.74 | 65.60 ± 2.29 | 115.85 ± 3.68 | 89.59 ± 1.80 |
|     | 13h    | 13i    | 13j    | 14a    | 14c    | 15     |
|-----|--------|--------|--------|--------|--------|--------|
|     | 15.70  | 0.69   | 70.84  | 16.36  | 44.30  | 0.49   |
|     | ± 3.62 | ± 0.47 | ± 2.20 | ± 0.39 | ± 1.15 | ± 0.19 |
|     | 2.26   | 1.23   | 32.44  | 16.56  | 1.04   | 0.15   |
|     | ± 0.96 | ± 0.31 | ± 2.46 | ± 1.75 | ± 0.50 | ± 0.16 |
|     | 89.92  | 15.39  | 87.73  | 89.02  | 98.62  | 63.27  |
|     | ± 6.44 | ± 1.27 | ± 2.33 | ± 2.76 | ± 1.23 | ± 1.00 |
|     | 94.58  | 57.97  | 95.02  | 92.47  | 97.28  | 62.12  |
|     | ± 7.31 | ± 6.28 | ± 4.23 | ± 4.39 | ± 2.36 | ± 1.80 |
|     | 22.81  | -0.18  | 56.75  | 4.33   | 87.72  | 1.58   |
|     | ± 2.79 | ± 0.21 | ± 2.79 | ± 0.17 | ± 3.25 | ± 0.21 |
|     | 42.39  | 0.57   | 105.06 | 6.05   | 111.43 | 1.44   |
|     | ± 2.45 | ± 0.14 | ± 7.90 | ± 0.29 | ± 6.45 | ± 0.31 |

| VBN (0.01 µg/mL) | CCRF-CEM | MDA-MB-231 | HCT 116 | U251 | MRC-5 |
|------------------|-----------|-------------|---------|------|-------|
|                  | 23.60 ± 7.62 | 42.05 ± 7.97 | 38.99 ± 5.10 | 45.31 ± 3.81 | 63.82 ± 5.29 |

The XTT viability assay included leukemia (CCRF-CEM), breast cancer (MDA-MB-231), colon cancer (HCT-116) and glioblastoma cells (U251) as well as non-tumorigenic lung fibroblasts (MRC-5), the results are expressed as metabolic active cells in % of control, vinblastine (VBN) was used as reference compound.
2-[4-(Thexyldimethylsilyloxy)phenyl]ethanol (5): Colourless oil, 98%, $R_f$

$= 0.27$ (CH:EtOAC = 2:1); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.08$ (d, $J = 8.5$ Hz, 2H, H-2/6), 6.78 (d, $J = 8.5$ Hz, 2H, H-3/5), 3.82 (t, $J = 6.5$ Hz, 2H, H-8), 2.80 (t, $J = 6.5$ Hz, 2H, H-7), 1.73 (hept, $J = 6.9$ Hz, 1H, CH-(CH$_3$)$_2$), 0.94 (d, $J = 6.9$ Hz, 6H, (CH$_3$)$_2$-CH), 0.94 (s, 6H, (CH$_3$)$_2$-C), 0.21 (s, 6H, (CH$_3$)$_2$-Si) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 154.1$ (C-4), 130.8 (C-1), 129.9 (C-2/6), 120.2 (C-3/5), 63.8 (C-8), 38.4 (C-7), 34.1 (CH-(CH$_3$)$_2$), 25.0 (C-(CH$_3$)$_2$), 20.1 ((CH$_3$)$_2$-C), 18.6 ((CH$_3$)$_2$-CH), -2.5 ((CH$_3$)$_2$-Si) ppm; HRMS (ESI) calcd. for C$_{16}$H$_{29}$O$_2$Si ([M+H]$^+$): 281.1937; Found: 281.1931.
1. \( N-[4-(\text{Thexyldimethylsilyloxy})\text{phenethyl}]\text{phthalimide (6a)} \)

2. Yellowish solid; Yield 90\%; \( R_f = 0.26 \) (CH:EtOAC = 7:1).
1. \(N-[4-(\text{Thexyldimethylsilyloxy})\text{phenethyl}]\text{maleimide} \ (6b)\)

2. Yellowish solid; Yield 70\%; \(R_f = 0.64 \) (CHCl\(_3\):EtOAC = 9:1).
1. \( N\-[4\-(\text{Thyldimethylsilyloxy})\text{phenethyl}]\text{succinimide} \ (6c) \)

2. White solid; Yield 77\%; \( R_f = 0.43 \) (CHCl\(_3\):EtOAC = 9:1).
1  *N-(4-Hydroxyphenethyl)phthalimide (7a)*

2  White solid; Yield 73% (AcOH), 23% (PEG 400); $R_f = 0.44$ (CH:EtOAC = 1:1).
1. *N-(4-Hydroxyphenethyl)maleimide (7b)*

2. Slightly yellow solid; Yield 55% (AcOH), 51% (PEG 400); $R_f = 0.38$ (CH:EtOAC = 1:1).
1. \textit{N-(4-Hydroxyphenethyl)succinimide (7c)}

2. White solid; Yield 58\% (AcOH), 98\% (PEG 400); \(R_f = 0.17\) (CH:EtOAC = 1:1).
4,5-Dichloro-N-(4-hydroxyphenethyl)phthalimide (7d)

White solid; Yield 89% (AcOH), 67% (PEG 400); R<sub>f</sub> = 0.52 (CH:EtOAC = 1:1).
3,4-Dichloro-N-(4-hydroxyphenethyl)maleimide (7e)

White solid; Yield 90% (AcOH), 67% (PEG 400); $R_f = 0.47$ (CH:EtOAC = 1:1).
**N-(4-Hydroxyphenethyl)pyridine-2,3-dicarboximide (7f)**

White solid; Yield 0% (AcOH), 86% (PEG 400); $R_f = 0.40$ (CH:EtOAC = 1:1).

[Diagram of the compound]
\textit{N-(4-Hydroxyphenethyl)morpholine-3,5-dione (7g)}

White solid; Yield 0\% (AcOH), 71\% (PEG 400); \(R_f = 0.36\) (CH:EtOAC = 1:1).
**N-(4-Hydroxyphenethyl)hexahydropthalimide (7h)**

White solid; Yield 86% (AcOH), 79% (PEG 400); $R_f = 0.50$ (CH:EtOAC = 1:1).
1 *N-(4-Hydroxyphenethyl)-3,4,5,6-tetrahydrophthalimide (7i)*

White solid; Yield 92% (AcOH), 98% (PEG 400); R_f = 0.41 (CH:EtOAC = 3:1).
1. *N-(4-Hydroxyphenethyl)-1,2,3,6-tetrahydrophthalimide (7j)*

White solid; Yield 79% (AcOH), 98% (PEG 400); $R_f = 0.32$ (CH:EtOAC = 3:1).
4-(Thexyldimethylsilyloxy)phenethyl bromide (9)

Yellow oil, 81%, \( R_f = 0.70 \) (CH:EtOAC = 1:1); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.05 \) (d, \( J = 8.4 \) Hz, 2H, H-2/6), 6.77 (d, \( J = 8.5 \) Hz, 2H, H-3/5), 3.52 (t, \( J = 7.8 \) Hz, 2H, H-8), 3.08 (t, \( J = 7.8 \) Hz, 2H, H-7), 1.72 (hept, \( J = 6.9 \) Hz, 1H, CH-(CH\(_3\))\(_2\)), 0.94 (d, \( J = 6.9 \) Hz, 6H, (CH\(_3\))\(_2\)-CH), 0.94 (s, 6H, (CH\(_3\))\(_2\)-C), 0.21 (s, 6H, (CH\(_3\))\(_2\)-Si) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 154.4 \) (C-4), 131.5 (C-1), 129.6 (C-2/6), 120.2 (C-3/5), 38.8 (C-7), 34.1 (CH-(CH\(_3\))\(_2\)), 33.3 (C-8), 25.0 (C-(CH\(_3\))\(_2\)), 20.1 ((CH\(_3\))\(_2\)-C), 18.6 ((CH\(_3\))\(_2\)-CH), -2.5 ((CH\(_3\))\(_2\)-Si) ppm; HRMS (EI) Calcd. for C\(_{16}\)H\(_{27}\)SiOBr [M]\(^+\) = 342.1014; Found: 342.1017.
**N-(4-Hydroxyphenethyl)isoindoline (11a)**

White solid; Yield 60% (proton-sponge<sup>®</sup>), 0% (conventional); \( R_f = 0.30 \) (CH:EtOAC = 1:3). \(^1\)H NMR (400 MHz, DMSO-d<sub>6</sub>): \( \delta = 9.15 \) (s, 1H, 4-OH), 7.24 – 7.16 (m, 4H, ArH), 7.05 (d, \( J = 8.4 \) Hz, 2H, H-2/6), 6.67 (d, \( J = 8.3 \) Hz, 2H, H-3/5), 3.87 (s, 4H, CH<sub>2</sub>-N), 2.86 – 2.81 (m, 2H, H-8), 2.69 (t, \( J = 7.7 \) Hz, 2H, H-7) ppm; \(^13\)C NMR (100 MHz, DMSO-d<sub>6</sub>): \( \delta = 155.9 \) (C-4), 140.5 (ArC), 130.7 (C-1), 129.9 (C-2/6), 127.0 (ArC), 122.6 (ArC), 115.4 (C-3/5), 58.9 (CH<sub>2</sub>-N), 57.9 (C-8), 34.3 (C-7) ppm; HRMS (EI) calcd. for C<sub>16</sub>H<sub>17</sub>NO [M]<sup>+</sup> = 239.1310; Found: 239.1303.
1. *N-(4-Hydroxyphenethyl)pyrrolidine (11b)*

White solid; Yield 81% (proton-sponge\textsuperscript{®}), 86% (conventional); $R_f = 0.22$

(CHCl\textsubscript{3}:MeOH = 1:1); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): $\delta = 6.99$ (d, $J = 8.3$ Hz, 2H, H-2/6), 6.63 (d, $J = 8.3$ Hz, 2H, H-3/5), 2.75 (s, 4H, H-7/8), 2.69 – 2.62 (m, 4H, CH\textsubscript{2}-N), 1.88 – 1.79 (m, 4H, CH\textsubscript{2}-CH\textsubscript{2}-N) ppm; \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): $\delta = 155.2$ (C-4), 130.6 (C-1), 129.5 (C-2/6), 115.7 (C-3/5), 58.6 (C-8), 54.0 (CH\textsubscript{2}-N), 34.2 (C-7), 23.3 (CH\textsubscript{2}-CH\textsubscript{2}-N) ppm; HRMS (El) calcd. for C\textsubscript{12}H\textsubscript{17}NO [M]\textsuperscript{+} = 191.1310; Found: 191.1304.
**N-(4-Hydroxyphenethyl)morpholine (11c)**

White solid; Yield 87% (proton-sponge\textsuperscript{®}), 87% (conventional); $R_f = 0.27$

CHCl\textsubscript{3}:MeOH (15:1); $^1$H NMR (400 MHz, DMSO-d\textsubscript{6}): $\delta = 9.14$ (s, 1H, 4-OH), 6.99 (d, $J = 8.5$ Hz, 2H, H-2/6), 6.65 (d, $J = 8.5$ Hz, 2H, H-3/5), 3.56 (t, $J = 4.6$ Hz, 4H, CH\textsubscript{2}-O), 2.62 – 2.57 (m, 2H, H-7), 2.44 – 2.39 (m, 2H, H-8), 2.41 – 2.35 (m, 4H, CH\textsubscript{2}-N) ppm; $^{13}$C NMR (100 MHz, DMSO-d\textsubscript{6}): $\delta = 155.9$ (C-4), 130.7 (C-1), 129.9 (C-2/6), 115.5 (C-3/5), 66.6 (CH\textsubscript{2}-O), 61.1 (C-8), 53.8 (CH\textsubscript{2}-N), 32.1 (C-7) ppm; HRMS (El) calcd. for C\textsubscript{12}H\textsubscript{17}NO\textsubscript{2} [M\textsuperscript{+}] = 207.1259; Found: 207.1255.
N-(4-Hydroxyphenethyl)octahydroisoindole (11d)

White solid; Yield 77% (proton-sponge®), 79% (conventional); $R_f = 0.19$

(CHCl$_3$:EtOH = 5:2$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 6.93$ (d, $J = 8.3$ Hz, 2H, H-2/6), 6.77 (d, $J = 8.3$ Hz, 2H, C-3/5), 3.18 (dd, $J = 10.7$, 6.3 Hz, 2H, CH$_2$(a)-N), 3.06 – 3.00 (m, 2H, H-8), 2.93 – 2.87 (m, 2H, CH$_2$(b)-N), 2.86 – 2.80 (m, 2H, H-7), 2.34 – 2.24 (m, 2H, CH-CH$_2$), 1.67 – 1.58 (m, 2H, CH$_2$(a)-CH), 1.54 – 1.45 (m, 2H, CH$_2$(a)-CH$_2$-CH), 1.52 – 1.43 (m, 2H, CH$_2$(b)-CH), 1.39 – 1.31 (m, 2H, CH$_2$(b)-CH$_2$-CH) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 156.4$ (C-4), 129.5 (C-2/6), 128.1 (C-1), 115.9 (C-3/5), 59.0 (C-8), 57.1 (CH$_2$-N), 36.7 (CH-CH$_2$), 32.3 (C-7), 25.9 (CH$_2$-CH), 22.5 (CH$_2$-CH$_2$-CH) ppm; HRMS (El) calcd. for C$_{16}$H$_{23}$NO [M]$^+ = 245.1780$; Found: 245.1772.
N-(4-Hydroxyphenethyl)-4,5,6,7-tetrahydroisoindole (11e)

Slightly yellow oil; Yield 100%; $R_f = 0.69$ (EtOAc); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.00$ (d, $J = 8.2$ Hz, 2H, H-2/6), 6.75 (d, $J = 8.2$ Hz, 2H, H-3/5), 6.31 (s, 2H, CH-N), 3.97 – 3.91 (m, 2H, H-8), 3.01 – 2.90 (m, 2H, H-7), 2.59 – 2.52 (m, 4H, CH$_2$-C=), 1.76 – 1.68 (m, 4H, CH$_2$-CH$_2$-C=) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 154.3$ (C-4), 130.7 (C-1), 129.8 (C-2/6), 119.4 (C=C(H)-N), 115.9 (CH-N), 115.4 (C-3/5), 51.3 (C-8), 37.6 (C-7), 24.2 (CH$_2$-CH$_2$-C=), 22.0 (CH$_2$-C=) ppm; HRMS (El) calcd. for C$_{16}$H$_{19}$NO $[M]^+ = 241.1467$; Found: 241.1465.
1. **3-Hydroxy-N-(4-hydroxyphenethyl)octahydroisoindole-1-one (12)**

2. White solid; Yield 88%; $R_f = 0.28$ (CH:EtOAc = 1:3).
N-[2-(1-Hydroxy-4-oxocyclohexa-2,5-dien-1-yl)ethyl]phthalimide) (13a)

White crystals; Yield 67%; $R_f = 0.42$ (CH:EtOAc = 1:3); mp: 161-162°C;

$^1$H NMR (300 MHz, DMSO-d$_6$): $\delta = 7.88 - 7.80$ (m, 4H, ArH), 6.97 (d, $J = 10.2$ Hz, 2H, H-2/6), 6.10 (d, $J = 10.2$ Hz, 2H, H-3/5), 5.88 (s, 1H, 1-OH), 3.68 – 3.50 (m, 2H, H-8), 2.08 – 1.88 (m, 2H, H-7) ppm; $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta = 185.0$ (C-4), 167.7 ((CO)N), 152.2 (C-2/6), 134.4 (ArC), 131.7 (ArC), 127.1 (C-3/5), 123.0 (ArC), 67.5 (C-1), 37.8 (C-7), 33.1 (C-8) ppm; HRMS (EI) calcd. for C$_{16}$H$_{13}$NO$_4$ [M]$^+$ = 283.0845; Found: 283.0845.
**N-[2-(1-Hydroxy-4-oxocyclohexa-2,5-dien-1-yl)ethyl]maleimide (13b)**

Yellow crystals; Yield 17%; $R_f = 0.40$ (CH:EtOAc = 1:5); mp: 151-152°C;

$^1$H NMR (300 MHz, DMSO-d$_6$): $\delta = 6.99$ (s, 2H, CH-(CO)N), 6.91 (d, $J = 10.1$ Hz, 2H, H-2/6), 6.08 (d, $J = 10.1$ Hz, 2H, H-3/5), 5.85 (s, 1H, 1-OH), 3.45 - 3.38 (m, 2H, H-8), 1.93 - 1.85 (m, 2H, H-7) ppm; $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta = 185.0$ (C-4), 170.8 ((CO)N), 152.1 (C-2/6), 134.6 (CH-(CO)N), 127.1 (C-3/5), 67.4 (C-1), 37.9 (C-7), 32.8 (C-8) ppm;

HRMS (EI) calcd. for C$_{12}$H$_{11}$NO$_4$ [M]$^+$ = 233.0688; Found: 233.0686.
N-[2-(1-Hydroxy-4-oxocyclohexa-2,5-dien-1-yl)ethyl]succinimide (13c)

White solid; Yield 55%; $R_f = 0.51$ (CHCl$_3$:CH$_3$CN = 1:3); mp: 128-129°C;

$^1$H NMR (400 MHz, DMSO-d$_6$): $\delta = 6.93$ (d, $J = 10.2$ Hz, 2H, H-2/6), 6.10 (d, $J = 10.2$ Hz, 2H, H-3/5), 5.86 (s, 1H, 1-OH), 2.57 (s br, 4H, CH$_2$-(CO)N), 3.38-3.31 (m, 2H, H-8), 1.89 – 1.77 (m, 2H, H-7) ppm; $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta = 185.5$ (C-4), 178.0 ((CO)N), 152.6 (C-2/6), 127.5 (C-3/5), 67.9 (C-1), 37.5 (C-7), 33.9 (C-8), 28.4 (CH$_2$-(CO)N) ppm;

HRMS (EI) calcd. for C$_{12}$H$_{13}$NO$_4$ [M]$^+$ = 235.0845; Found: 235.0826.
4,5-Dichloro-N-[2-(1-hydroxy-4-oxocyclohexa-2,5-dien-1-yl)ethyl]phthalimide (13d)

White crystals; Yield 40%; \( R_f = 0.22 \) (CH:EtOAc = 1:1); mp: 213-214°C;

\(^1\)H NMR (400 MHz, DMSO-\( d_6 \)): \( \delta = 8.17 \) (s, 2H, ArH), 6.96 (d, \( J = 10.1 \) Hz, 2H, H-2/6), 6.10 (d, \( J = 10.1 \) Hz, 2H, H-3/5), 5.89 (s, 1H, 1-OH), 3.62 – 3.56 (m, 2H, H-8), 2.02 – 1.95 (m, 2H, H-7) ppm; \(^{13}\)C NMR (100 MHz, DMSO-\( d_6 \)): \( \delta = 185.5 \) (C-4), 166.4 ((CO)N), 152.6 (C-2/6), 137.7 (C(Cl)=), 132.1 (C=C(CO)N), 127.6 (C-3/5), 125.6 (ArC), 67.9 (C-1), 38.0 (C-7), 34.0 (C-8) ppm; HRMS (EI) calcd. for \( C_{16}H_{11}Cl_2NO_4 \) [M]\(^+\) = 351.0065; Found: 351.0090.
3,4-Dichloro-N-[2-(1-hydroxy-4-oxocyclohexa-2,5-dien-1-yl)ethyl]maleimide (13e)

Yellowish crystals; Yield 64%; $R_f = 0.30$ (CH:EtOAc = 1:1); mp: 168-169°C; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta = 6.95$ (d, $J = 10.1$ Hz, 2H, H-2/6), 6.11 (d, $J = 10.1$ Hz, 2H, H-3/5), 5.91 (s br, 1H, 1-OH), 3.53 – 3.46 (m, 2H, H-8), 1.95 – 1.90 (m, 2H, H-7) ppm; $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta = 185.4$ (C-4), 163.3 ((CO)N), 152.5 (C-2/6), 132.9 (C(Cl)=), 127.6 (C-3/5), 67.8 (C-1), 37.9 (C-7), 34.8 (C-8) ppm; HRMS (EI) calcd. for C$_{12}$H$_6$Cl$_2$NO$_4$ [M]$^+$ = 300.9909; Found: 300.9914.
N-[2-(1-Hydroxy-4-oxocyclohexa-2,5-dien-1-yl)ethyl]pyridine-2,3-dicarboximide (13f)

White crystals; Yield 19%; Rf = 0.37 (CHCl₃:CH₃CN = 1:1); mp: 167-168°C; ¹H NMR (400 MHz, DMSO-d₆): δ = 8.95 (dd, J = 5.0, 1.5 Hz, 1H, ArH), 8.27 (dd, J = 7.7, 1.5 Hz, 1H, ArH), 7.77 (dd, J = 7.7, 5.0 Hz, 1H, ArH), 6.98 (d, J = 10.1 Hz, 2H, C-2/6), 6.11 (d, J = 10.1, 2H, H-3/5), 5.88 (s, 1H, 1OH), 3.69 – 3.57 (m, 2H, C-8), 2.05 – 1.94 (m, 2H, H-7) ppm; ¹³C NMR (100 MHz, DMSO-d₆): δ = 185.5 (C-4), 166.6 ((CO)N), 155.2 (ArC), 152.6 (C-2/6), 152.0 (ArC), 131.6 (ArC), 128.3 (ArC), 127.7 (ArC), 127.6 (C-3/5), 68.0 (C-1), 38.1 (C-7), 33.7 (C-8) ppm; HRMS (EI) calcd. for C₁₅H₁₂N₂O₄ [M]⁺ = 284.0797; Found: 284.0792.
N-[2-(1-Hydroxy-4-oxocyclohexa-2,5-dien-1-yl)ethyl]morpholine-3,5-dione (13g)

Yellowish solid; Yield 18%; $R_f = 0.33$ (CHCl₃:EtOAc = 1:5); mp: 142-143°C; $^1$H NMR (400 MHz, DMSO-d₆): $\delta = 6.94$ (d, $J = 10.1$ Hz, 2H, H-2/6), 6.12 (d, $J = 10.0$ Hz, 2H, H-3/5), 4.36 (s, 4H, CH₂-(CO)N), 3.70–3.56 (m, 2H, H-8), 1.89–1.78 (m, 2H, H-7) ppm; $^{13}$C NMR (100 MHz, DMSO-d₆): $\delta = 185.5$ (C-4), 170.1 ((CO)N), 152.7 (C-2/6), 127.5 (C-3/5), 68.0 (C-1), 67.4 (CH₂-(CO)N), 37.8 (C-7), 33.8 (C-8) ppm; HRMS (EI) calcd. for C₁₂H₁₃NO₅ [M]$^+$ = 251.0794; Found: 251.0794.
N-[2-(1-Hydroxy-4-oxocyclohexa-2,5-dien-1-yl)ethyl]hexahydropthalimide (13h)

Yellow crystals; Yield 79%; $R_f = 0.29$ (CH:EtOAc = 1:3); mp: 135-136°C;

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta = 6.94$ (d, $J = 10.1$ Hz, 2H, H-2/6), 6.10 (d, $J = 10.1$ Hz, 2H, H-3/5), 5.84 (s, 1H, 1-OH), 3.40 – 3.35 (m, 2H, H-8), 2.93 – 2.82 (m, 2H, CH-(CO)N), 1.85 – 1.80 (m, 2H, H-7), 1.71 (s, 2H, CH$_2$(a)-CH), 1.60 – 1.51 (m, 2H, CH$_2$(b)-CH), 1.42 – 1.32 (m, 2H, CH$_2$(a)-CH$_2$-CH), 1.31 – 1.21 (m, 2H, CH$_2$(b)-CH$_2$-CH) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta = 185.4$ (C-4), 179.7 ((CO)N), 152.7 (C-2/6), 127.5 (C-3/5), 67.9 (C-1), 39.3 (CH-(CO)N), 37.6 (C-7), 33.8 (C-8), 23.5 (CH$_2$-CH), 21.6 (CH$_2$-CH$_2$-CH) ppm; HRMS (EI) calcd. for C$_{16}$H$_{19}$NO$_4$ [M]$^+$ = 289.1314; Found: 289.1310.
Orange solid; Yield 88%; $R_f = 0.18$ (CH:EtOAc = 1:1); mp: 93-94°C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta = 6.92$ (d, $J = 10.1$ Hz, 2H, H-2/6), 6.08 (d, $J = 10.1$ Hz, 2H, H-3/5), 5.85 (s, 1H, 1-OH), 3.42 – 3.36 (m, 2H, H-8), 2.24 – 2.17 (m, 4H, CH$_2$-C=), 1.86 (dd, $J = 8.5$, 6.8 Hz, 2H, H-7), 1.69 – 1.62 (m, 4H, CH$_2$-CH$_2$-C=) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta = 185.5$ (C-4), 170.9 ((CO)N), 152.6 (C-2/6), 141.5 (C=C(CO)), 127.5 (C-3/5), 67.9 (C-1), 38.6 (C-7), 33.0 (C-8), 21.3 (CH$_2$-CH$_2$-C=), 19.9 (CH$_2$-C=) ppm; HRMS (EI) calcd. for C$_{16}$H$_{17}$NO$_4$ [M]$^+$ = 287.1158; Found: 287.1160.
"N-[2-(1-Hydroxy-4-oxocyclohexa-2,5-dien-1-yl)ethyl]-1,2,3,6-
tetrahydrophthalimide (13j)"

White crystals; Yield 49%; \( R_f = 0.28 \) (CH:EtOAc = 1:1); mp: 145-146°C;

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta = 6.90 \) (d, \( J = 10.1 \) Hz, 2H, H-2/6), 6.09

(d, \( J = 10.1 \) Hz, 2H, H-3/5), 5.87 (s, 1H, 1-OH), 5.85 – 5.82 (m, 2H, CH=CH), 3.31 - 3.36 (m, 2H, H-8), 3.11 – 3.06 (m, 2H, CH-(CO)N), 2.39

– 2.32 (m, 2H, CH\(_2\)(a)-CH), 2.21 – 2.13 (m, 2H, CH\(_2\)(b)-CH), 1.79 (td, \( J = 7.5, 1.5 \) Hz, 2H, H-7) ppm; \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \( \delta = 185.5 \) (C-4), 180.3 ((CO)N), 152.5 (C-2/6), 128.1 (CH=CH), 127.6 (C-3/5), 67.8 (C-1), 38.9 (CH-(CO)N), 37.8 (C-7), 34.1 (C-8), 23.5 (CH\(_2\)-CH) ppm; HRMS

(EI) calcd. for C\(_{16}\)H\(_{17}\)NO\(_4\) [M]\(^+\) = 287.1158; Found: 287.1154.
**N-[2-(1-Hydroxy-4-oxocyclohexa-2,5-dien-1-yl)ethyl]isoindoline (14a)**

Brownish solid; Yield 16%; $R_f = 0.50$ (CHCl$_3$:EtOH = 1:5); mp: 103-104°C; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta =$ 7.24 – 7.12 (m, 4H, ArH), 6.99 (d, $J = 10.1$ Hz, 2H, H-2/6), 6.06 (d, $J = 10.1$ Hz, 2H, H-3/5), 3.81 – 3.77 (m, 4H, CH$_2$-N), 2.70 – 2.62 (m, 2H, H-8), 1.93 – 1.85 (m, 2H, H-7) ppm; $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta =$ 185.3 (C-4), 153.2 (C-2/6), 139.8 (ArC), 126.5 (ArC), 126.3 (C-3/5) 122.0 (ArC), 68.0 (C-1), 58.3 (CH$_2$-N), 50.0 (C-8), 38.6 (C-7) ppm; HRMS (EI) calcd. for C$_{16}$H$_{17}$NO$_2$ [M$^+$] = 255.1259; Found: 255.1251.
Brownish solid; Yield 28%; \( R_f = 0.37 \) (EtOAc:EtOH = 1:1); mp: 98-99°C;

\(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \( \delta = 6.95 \) (d, \( J = 10.0 \) Hz, 2H, H-2/6), 6.04 (d, \( J = 10.0 \) Hz, 2H, H-3/5), 3.56 - 3.46 (m, 4H, CH\(_2\)-O), 2.32 - 2.26 (m, 4H, CH\(_2\)-N), 2.25 - 2.20 (m, 2H, H-8), 1.79 (t, \( J = 7.6 \) Hz, 2H, H-7) ppm;

\(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)): \( \delta = 185.8 \) (C-4), 153.8 (C-2/6), 126.8 (C-3/5), 68.5 (C-1), 66.6 (CH\(_2\)-O), 53.7 (CH\(_2\)-N), 53.4 (C-8), 37.0 (C-7) ppm;

HRMS (EI) calcd. for C\(_{12}\)H\(_{17}\)NO\(_3\) [M]\(^+\) = 223.1208; Found: 223.1201.
3-Hydroxy-N-[2-(1-hydroxy-4-oxocyclohexa-2,5-dien-1-yl)ethyl]octahydroisoindole-1-one (15)

Beige solid; Yield 65%; $R_f = 0.14$ (EtOAc); mp: 127-128°C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta = 6.97 - 6.91$ (m, 2H, H-2/6), 6.08 (d, $J = 11.0$ Hz, 2H, H-3/5), 5.90 (d, $J = 6.6$ Hz, 1H, 9'-OH), 5.82 (s, 1H, 1-OH), 4.55 (d, $J = 6.6$ Hz, 1H, H-9'), 3.39 – 3.31 (m, 1H, H-8(a)), 3.05 – 2.96 (m, 1H, H-8(b)), 2.63 – 2.56 (m, 1H, H-3'), 2.06 – 1.98 (m, 1H, H-8'), 1.89 – 1.82 (m, 1H, H-7(a)), 1.83 – 1.77 (m, 1H, H-4'(a)), 1.80 – 1.72 (m, 1H, H-7(b)), 1.72 – 1.66 (m, 1H, H-7'(a)), 1.49 – 1.35 (m, 3H, H-4'(/b)/5'/a/6'/a), 1.19 – 1.06 (m, 1H, H-6'(b)), 0.95 – 0.89 (m, 1H, H-5'(b)), 0.91 – 0.83 (m, 1H, H-7'(b)) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta = 185.6$ (C-4), 175.2 (C-2'), 153.2 (C-2/6), 127.3 (C-3/5), 85.6 (C-9'), 68.1 (C-1), 40.8 (C-8'), 38.5 (C-3'), 38.1 (C-7), 35.2 (C-8), 26.3 (C-7'), 23.3 (C-6'), 23.2 (C-4'), 23.1 (C-5') ppm; HRMS (EI) calcd. for C$_{16}$H$_{21}$NO$_4$ [M]$^+ = 291.1471$; Found: 291.1469.