SUPPLEMENTARY MATERIAL

Design, synthesis, and antimicrobial activities of new tanshinone IIA esters

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Sixteen new ester derivatives with various ClogP values of tanshinone IIA (TSIIA), a major lipophilic component of Salvia miltiorrhiza, were designed and synthesised, including 6 aliphatic esters (3a-e, 5a), one phosphate ester (4c), and 9 aromatic esters (5b-j). Their antimicrobial activities against three Gram-positive bacteria strains, Staphylococcus aureus, Bacillus subtilis, and Bacillus amyloliquefaciens, and two Gram-negative bacteria strains, Pseudomonas aeruginosa and Escherichia coli, as well as two fungi species, Candida albicans and Saccharomyces cerevisiae, were evaluated in vitro by broth microdilution susceptibility tests. The results showed that keeping ClogP values in a certain range is necessary for their antimicrobial activities. For those compounds with ClogP values between 5 and 10, their MIC values showed positive correlations with ClogP values. In particular, compound 3e exhibited fourfold and twofold higher potency than the standard drug amphotericin B against fungi C. albicans and S. cerevisiae with MIC values of 1.95 and 7.81 µg/mL, respectively.

Keywords: tanshinone IIA; ester derivatives; ClogP; synthesis; antimicrobial

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Contents

**Part 1.** Spectroscopic data of compounds 3a-e,4a-c, and 5a-j.

**Part 2.** $^1$H NMR, $^{13}$C NMR, and MS spectra of compounds 3a-e,4a-c, and 5a-j, as well as NOESY spectrum of 3e.
Part 1. Spectroscopic data of compounds 3a-e, 4a-c, and 5a-j.

1,6,6-trimethyl-6,7,8,9-tetrahydrophenanthro[1,2-b]furan-10,11-diyldiacetate (3a): White amorphous solid; yield 84%; mp. 168 – 171 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.08 (d, $J = 8.8$ Hz, 1H), 7.56 (d, $J = 8.8$ Hz, 1H), 7.46 (q, $J = 1.2$ Hz, 1H), 3.40 – 3.09 (m, 2H), 2.40 (s, 3H), 2.39 (s, 3H), 2.26 (d, $J = 1.2$ Hz, 3H), 1.92 – 1.76 (m, 2H), 1.73 – 1.64 (m, 2H), 1.34 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.27, 168.78, 150.30, 144.26, 141.65, 134.86 (possibly overlapped signal), 131.43, 126.50, 124.24, 119.36, 118.39, 117.50, 115.50, 38.29, 34.90, 31.97 (possibly overlapped signal), 29.74, 21.11, 20.48, 20.15, 8.88. ESI MS (positive) m/z 783.0 [2M + Na]$^+$. 

1,6,6-trimethyl-6,7,8,9-tetrahydrophenanthro[1,2-b]furan-10,11-dipropionate (3b): White amorphous solid; yield 82%; mp. 96 – 98 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.08 (d, $J = 8.8$ Hz, 1H), 7.55 (d, $J = 8.8$ Hz, 1H), 7.45 (q, $J = 1.2$ Hz, 1H), 3.34 – 2.98 (m, 2H), 2.69 (q, $J = 7.6$ Hz, 2H), 2.67 (q, $J = 7.6$ Hz, 2H), 2.24 (d, $J = 1.2$ Hz, 3H), 1.86 – 1.77 (m, 2H), 1.72 – 1.65 (m, 2H), 1.36 – 1.31 (m, 12H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.61, 172.19, 150.26, 144.11, 141.58, 134.94 (possibly overlapped signal), 131.49, 126.38, 124.35, 119.32, 118.37, 117.59, 115.53, 38.30, 34.89, 31.98 (possibly overlapped signal), 29.89, 27.97, 27.42, 20.12, 9.20, 9.16, 9.00. ESI MS (positive) m/z 839.2 [2M + Na]$^+$. 

1,6,6-trimethyl-6,7,8,9-tetrahydrophenanthro[1,2-b]furan-10,11-diyldibutyrate (3c): White amorphous solid; yield 85%; mp. 101 – 102 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.08 (d, $J = 8.8$ Hz, 1H), 7.55 (d, $J = 8.8$ Hz, 1H), 7.45 (q, $J = 1.2$ Hz, 1H), 3.47 – 2.80 (m, 2H), 2.64 (t, $J = 7.4$ Hz, 2H), 2.62 (t, $J = 7.4$ Hz, 2H), 2.24 (d, $J = 1.2$ Hz, 3H), 1.90 – 1.77 (m, 6H), 1.71 – 1.65 (m, 2H), 1.35 (s, 6H), 1.10 (t, $J = 7.4$ Hz, 3H), 1.08 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 171.81, 171.41, 150.26, 144.07, 141.56, 134.97, 134.93, 131.49, 126.36, 124.38, 119.32, 118.37, 117.60, 115.53, 38.33, 36.37, 35.80, 34.90, 31.99 (possibly overlapped signal), 29.97, 20.11, 18.30, 18.21, 13.95, 13.88, 9.06. ESI MS (positive) m/z 895.3 [2M + Na]$^+$. 

1,6,6-trimethyl-6,7,8,9-tetrahydrophenanthro[1,2-b]furan-10,11-diyl-dipentanoate (3d): White amorphous solid; yield 81%; mp. 101 – 103 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.09 (d, \(J = 8.8\) Hz, 1H), 7.55 (d, \(J = 8.8\) Hz, 1H), 7.45 (s, 1H), 3.49 – 2.89 (m, 2H), 2.66 (t, \(J = 7.4\) Hz, 2H), 2.65 (t, \(J = 7.4\) Hz, 2H), 2.25 (s, 3H), 1.86 – 1.75 (m, 6H), 1.72 – 1.65 (m, 2H), 1.54 – 1.44 (m, 4H), 1.35 (s, 6H), 1.01 (t, \(J = 7.4\) Hz, 3H), 0.99 (t, \(J = 7.4\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 171.97, 171.57, 150.26, 144.07, 141.55, 134.98, 134.94, 131.49, 126.35, 124.38, 119.31, 118.36, 117.60, 115.53, 38.32, 34.90, 34.22, 33.69, 31.98 (possibly overlapped signal), 29.97, 26.86, 26.81, 22.46, 22.43, 20.11, 13.81, 13.75, 9.06. ESI MS (positive) \(m/z\) 951.4 [2M + Na]⁺.

4-((11-hydroxy-1,6,6-trimethyl-6,7,8,9-tetrahydrophenanthro[1,2-b]furan-10-yl)oxy)-4-oxo butanoic acid (3e): Light pink amorphous solid; yield 81%; mp. 140 – 143 °C; \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta\) 8.00 (d, \(J = 8.7\) Hz, 1H), 7.56 (q, \(J = 1.2\) Hz, 1H), 7.47 (d, \(J = 8.7\) Hz, 1H), 3.24 (t, \(J = 6.0\) Hz, 2H), 3.07 (d, \(J = 6.5\) Hz, 2H), 2.82 (d, \(J = 6.5\) Hz, 2H), 2.45 (d, \(J = 1.2\) Hz, 3H), 1.91 – 1.84 (m, 2H), 1.77 – 1.72 (m, 2H), 1.39 (s, 6H); \(^1\)H NMR (600 MHz, DMSO) \(\delta\) 12.26 (s, 1H), 9.35 (s, 1H), 7.92 (d, \(J = 8.7\) Hz, 1H), 7.77 (q, \(J = 1.2\) Hz, 1H), 7.46 (d, \(J = 8.7\) Hz, 1H), 3.14 (t, \(J = 5.4\) Hz, 2H), 3.02 (t, \(J = 6.6\) Hz, 2H), 2.61 (t, \(J = 6.6\) Hz, 2H), 2.38 (d, \(J = 1.2\) Hz, 3H), 1.78 – 1.74 (m, 2H), 1.65 – 1.62 (m, 2H), 1.30 (s, 6H); \(^{13}\)C NMR (150 MHz, DMSO) \(\delta\) 174.04, 172.25, 149.82, 143.75, 143.05, 141.82, 130.21, 128.66, 125.27, 124.19, 118.05, 116.86, 116.31, 115.24, 38.52, 35.05, 32.28, 29.97, 29.66, 29.23, 29.06, 20.22, 9.88. ESI MS (positive) \(m/z\) 397.3 [M + H]⁺, 815.3 [2M + Na]⁺.

Tetraethyl (1,6,6-trimethyl-6,7,8,9-tetrahydrophenanthro[1,2-b]furan-10,11-diyl) bis (phosphate) (4a): Light yellow oil; yield 65%; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.01 (d, \(J = 8.8\) Hz, 1H), 7.53 (d, \(J = 8.8\) Hz, 1H), 7.44 (q, \(J = 1.2\) Hz, 1H), 4.32 – 4.24 (m, 4H), 4.14 – 4.06 (m, 4H), 3.41 (t, \(J = 5.6\) Hz, 2H), 2.47 (d, \(J = 1.2\) Hz, 3H), 1.79 – 1.72 (m, 4H), 1.36 (s, 6H), 1.34 (t, \(J = 7.0\) Hz, 6H), 1.34 (t, \(J = 7.0\) Hz, 6H), 1.18 (t, \(J = 7.0\) Hz, 6H), 1.18 (t, \(J = 7.0\) Hz, 6H); \(^{31}\)P NMR (202 MHz, CDCl\(_3\)): \(\delta\) 3.26, 2.34. ESI MS (positive) \(m/z\) 569.2 [M + H]⁺.
Tetrabenyl (1,6,6-trimethyl-6,7,8,9-tetrahydroanthra[1,2-b]furan-10,11-diyl) bis(phosphate) (4b): Light yellow oil; yield 68%; \( ^1 \)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.00 (d, \( J = 8.8 \) Hz, 1H), 7.53 (d, \( J = 8.8 \) Hz, 1H), 7.42 (q, \( J = 1.2 \) Hz, 1H), 7.37 – 7.27 (m, 3H), 7.24 – 7.16 (m, 14H), 7.09 – 7.06 (m, 3H), 5.17 – 5.06 (m, 4H), 4.98 (s, 2H), 4.96 (s, 2H), 3.30 (t, \( J = 6.4 \) Hz, 2H), 2.39 (d, \( J = 1.2 \) Hz, 3H), 1.94 – 1.70 (m, 2H), 1.70 – 1.64 (m, 2H), 1.31 (s, 6H); \( ^{31} \)P NMR (202 MHz, CDCl\(_3\)) \( \delta \) 6.90, 6.19. ESI MS (positive) \( m/z \) 817.3 [M + H]

Sodium 1,6,6-trimethyl-6,7,8,9-tetrahydroanthra[1,2-b]furan-10,11-diyl-bis(phosphate) (4c): White amorphous solid; yield 26%; mp. 181 – 183 °C; \( ^1 \)H NMR (500 MHz, CD\(_3\)OD) \( \delta \) 7.84 (d, \( J = 8.7 \) Hz, 1H), 7.39 (s, 1H), 7.38 (d, \( J = 8.4 \) Hz, 1H), 3.77 (t, \( J = 5.4 \) Hz, 2H), 2.56 (s, 3H), 1.82 – 1.75 (m, 2H), 1.76 – 1.67 (m, 2H), 1.31 (s, 6H); \( ^{13} \)C NMR (125 MHz, CD\(_3\)OD) \( \delta \) 148.35, 142.05, 140.09, 137.87, 133.87 (possibly overlapped signal), 126.09, 124.39, 119.10, 117.72, 117.56, 116.71, 38.76, 34.47, 31.27 (possibly overlapped signal), 30.59, 19.46, 8.71; \( ^{31} \)P NMR (202 MHz, CD\(_3\)OD) \( \delta \) 11.80, 10.43. ESI MS (positive) \( m/z \) 522.9 [M – Na + 2H]

1,6,6-trimethyl-6,7,8,9-tetrahydroanthra[1,2-b]furan-10,11-diyl bis(2-methylacrylate) (5a): White amorphous solid; yield 82%; mp. 154 – 156 °C; \( ^1 \)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.11 (d, \( J = 8.8 \) Hz, 1H), 7.58 (d, \( J = 8.8 \) Hz, 1H), 7.47 (s, 1H), 6.40 (d, \( J = 0.8 \) Hz, 1H), 6.38 (d, \( J = 0.8 \) Hz, 1H), 5.81 (d, \( J = 0.9 \) Hz, 1H), 5.79 (d, \( J = 0.9 \) Hz, 1H), 3.59 – 3.47 (m, 1H), 2.97 – 2.79 (m, 1H), 2.22 (s, 3H), 2.09 (d, \( J = 0.6 \) Hz, 3H), 2.07 (d, \( J = 0.7 \) Hz, 3H), 1.85 – 1.74 (m, 2H), 1.72 – 1.63 (m, 2H), 1.36 (s, 6H); \( ^{13} \)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 165.71, 165.32, 150.27, 144.04, 141.55, 135.73, 135.15 (possibly overlapped signal), 134.89, 131.67, 127.98 (possibly overlapped signal), 126.35, 124.52, 119.28, 118.33, 117.73, 115.65, 38.27, 34.89, 31.99, 31.98, 29.86, 20.11, 18.58, 18.45, 8.93. ESI MS (positive) \( m/z \) 887.3 [2M + Na]

1,6,6-trimethyl-6,7,8,9-tetrahydroanthra[1,2-b]furan-10,11-diyl dibenzoate (5b): White amorphous solid; yield 78%; mp. 234 – 236 °C; \( ^1 \)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.16 (d, \( J = 8.8 \) Hz, 1H), 8.13 (dd, \( J = 8.4 \), 1.2 Hz, 1H), 8.05 (dd, \( J = 8.4 \), 1.2 Hz, 1H),
7.60 (d, J = 8.8 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.49 (q, J = 1.2 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H), 3.65 – 3.53 (m, 1H), 2.97 – 2.81 (m, 1H), 2.18 (d, J = 1.2 Hz, 3H), 1.74 – 1.66 (m, 2H), 1.65 – 1.57 (m, 2H), 1.36 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 165.41, 164.96, 150.41, 144.18, 141.64, 135.38, 135.09, 133.68, 133.60, 131.84, 130.30 (possibly overlapped signal), 130.16 (possibly overlapped signal), 129.10, 128.54 (possibly overlapped signal), 128.47 (possibly overlapped signal), 128.41, 126.48, 124.67, 119.41, 118.38, 117.91, 115.80, 38.22, 34.90, 32.01, 31.96, 30.00, 20.02, 9.06. ESI MS (positive) m/z 505.5 [M + H]+.

1,6,6-trimethyl-6,7,8,9-tetrahydrophenanthro[1,2-b]furan-10,11-diyl bis(4-methoxybenzoate) (5e): White amorphous solid; yield 79%; mp. 189 – 190 °C; 1H NMR (500 MHz, CDCl3) δ 8.14 (d, J = 8.6 Hz, 1H), 8.09 (d, J = 8.8 Hz, 2H), 8.02 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 8.8 Hz, 1H), 7.48 (s, 1H), 6.86 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.63 – 3.49 (m, 1H), 2.98 – 2.83 (m, 1H), 2.18 (s, 3H), 1.74 – 1.67 (m, 2H), 1.66 – 1.60 (m, 2H), 1.35 (s, 6H); 13C NMR (125 MHz, CDCl3) δ 165.11, 164.66, 163.88, 163.82, 150.31, 144.01, 141.51, 135.53, 135.28, 132.47 (possibly overlapped signal), 132.36 (possibly overlapped signal), 131.89, 126.30, 124.82, 121.59, 120.84, 119.33, 118.32, 118.05, 115.85, 113.81 (possibly overlapped signal), 113.75 (possibly overlapped signal), 55.44, 38.27, 34.88, 32.01, 31.95, 29.96, 20.05, 9.02. ESI MS (positive) m/z 587.8 [M + Na]+.

1,6,6-trimethyl-6,7,8,9-tetrahydrophenanthro[1,2-b]furan-10,11-diyl bis(benzo[d][1,3]dioxole-5-carboxylate) (5d): White amorphous solid; yield 45%; mp. 141 – 143 °C; 1H NMR (500 MHz, CDCl3) δ 8.13 (d, J = 8.8 Hz, 1H), 7.78 (dd, J = 8.2, 1.7 Hz, 1H), 7.72 (dd, J = 8.2, 1.7 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 1.7 Hz, 1H), 7.50 (d, J = 1.7 Hz, 1H), 7.48 (q, J = 1.2 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 6.06 – 5.98 (m, 4H), 3.65 – 3.38 (m, 1H), 3.01 – 2.76 (m, 1H), 2.18 (d, J = 1.2 Hz, 3H), 1.76 – 1.68 (m, 2H), 1.67 – 1.58 (m, 2H), 1.35 (s, 6H); 13C NMR (125 MHz, CDCl3) δ 164.63, 164.19, 152.25, 152.17, 150.30, 147.81, 147.78, 144.07, 141.55, 135.37, 135.10, 131.77, 126.51, 126.41, 126.37, 124.64, 123.05, 122.32, 119.31, 118.30, 117.87, 115.73, 109.99, 109.87, 108.16, 108.09, 101.94 (possibly
overlapped signal), 38.19, 34.86, 31.98, 31.90, 29.94, 20.01, 9.02. ESI MS (positive) m/z 615.7 [M + Na]+.

1,6,6-trimethyl-6,7,8,9-tetrahydrophenanthro[1,2-b]furan-10,11-diyl-bis(2-chlorobenzoate) (5e): White amorphous solid; yield 73%; mp. 186 – 187 °C; 1H NMR (500 MHz, CDCl3) δ 8.15 (d, J = 8.8 Hz, 1H), 8.13 (dd, J = 8.0, 1.5 Hz, 1H), 8.10 (dd, J = 8.0, 1.5 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.51 (q, J = 1.2 Hz, 1H), 7.49 – 7.40 (m, 4H), 7.30 (td, J = 7.8, 1.5 Hz, 1H), 7.24 (td, J = 7.8, 1.5 Hz, 1H), 3.74 – 3.39 (m, 1H), 3.19 – 2.71 (m, 1H), 2.25 (d, J = 1.2 Hz, 3H), 1.81 – 1.69 (m, 2H), 1.67 – 1.59 (m, 2H), 1.36 (s, 6H); 13C NMR (125 MHz, DMSO) δ 163.44, 162.93, 150.54, 144.31, 141.76, 135.29, 135.28, 135.04, 134.77, 133.74, 133.63, 132.63, 132.53, 131.69 (possibly overlapped signal), 131.64, 128.02, 127.36, 126.82, 126.74, 126.63, 124.51, 119.51, 118.42, 117.68, 115.69, 38.21, 34.93, 31.98 (possibly overlapped signal), 30.07, 20.00, 9.14. ESI MS (positive) m/z = 573.6 [M + H]+.

1,6,6-trimethyl-6,7,8,9-tetrahydrophenanthro[1,2-b]furan-10,11-diyl-bis(3-chlorobenzoate) (5f): White amorphous solid; yield 76%; mp. 150 – 153 °C; 1H NMR (500 MHz, CDCl3) δ 8.15 (d, J = 8.8 Hz, 1H), 8.09 (t, J = 1.7 Hz, 1H), 8.04 – 8.00 (m, 2H), 7.94 (dt, J = 7.8, 1.2 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.32 – 7.47 (m, 3H), 7.33 (t, J = 8.0 Hz, 1H), 7.29 (t, J = 8.0 Hz, 1H), 3.61 – 3.46 (m, 1H), 2.93 – 2.80 (m, 1H), 2.18 (d, J = 1.2 Hz, 3H), 1.79 – 1.68 (m, 2H), 1.69 – 1.60 (m, 2H), 1.35 (s, 6H); 13C NMR (125 MHz, CDCl3) δ 164.16, 163.68, 150.45, 144.40, 141.79, 135.11, 134.83, 134.78, 134.74, 133.86, 133.78, 131.60 (possibly overlapped signal), 130.65, 130.17, 130.03, 129.96, 129.88, 128.27, 128.14, 126.66, 124.40, 119.42, 118.41, 117.67, 115.61, 38.12, 34.87, 31.92 (possibly overlapped signal), 29.93, 19.95, 9.00. ESI MS (negative) m/z 571.2 [M – H]−, ESI MS (positive) m/z 595.5 [M + H]+.

1,6,6-trimethyl-6,7,8,9-tetrahydrophenanthro[1,2-b]furan-10,11-diyl-bis(4-chlorobenzoate) (5g): White amorphous solid; yield 79%; mp. 145 – 146 °C; 1H NMR (500 MHz, CDCl3) δ 8.15 (d, J = 8.8 Hz, 1H), 8.07 (d, J = 8.6 Hz, 2H), 7.99 (d, J = 8.6 Hz, 2H), 7.60 (d, J = 8.8 Hz, 1H), 7.49 (q, J = 1.2 Hz, 1H), 7.38 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 3.60 – 3.46 (m, 1H), 2.93 – 2.79 (m, 1H), 2.16 (d, J
= 1.2 Hz, 3H), 1.76 – 1.67 (m, 2H), 1.66 – 1.59 (m, 2H), 1.35 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 164.42, 163.98, 150.49, 144.40, 141.79, 140.55, 140.44, 135.12, 134.87, 131.64, 131.60 (possibly overlapped signal), 131.47 (possibly overlapped signal), 129.10 (possibly overlapped signal), 129.05 (possibly overlapped signal), 127.42, 126.75, 126.66, 124.49, 119.47, 118.45, 117.71, 115.63, 38.17, 34.92, 31.98 (possibly overlapped signal), 30.06, 20.01, 9.05. ESI MS (negative) m/z 571.3 [M – H$^-$].

1,6,6-trimethyl-6,7,8,9-tetrahydrophenanthro[1,2-b]furan-10,11-diyl-bis(4-fluorobenzoate) (5h): White amorphous solid; yield 74%; mp. 216 – 218 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.19 – 8.13 (m, 3H), 8.11 – 8.05 (m, 2H), 7.61 (d, J = 8.8 Hz, 1H), 7.50 (q, J = 1.2 Hz, 1H), 7.07 (t, J = 8.6 Hz, 2H), 7.03 (t, J = 8.6 Hz, 2H), 3.61 – 3.49 (m, 1H), 2.97 – 2.82 (m, 1H), 2.18 (d, J = 1.2 Hz, 3H), 1.75 – 1.69 (m, 2H), 1.66 – 1.57 (m, 2H), 1.36 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 166.22 (d, J = 255.8 Hz), 166.18 (d, J = 255.8 Hz), 164.31, 163.84, 150.46, 144.33, 141.74, 135.21, 134.92, 132.87 (d, J = 14.8 Hz) (possibly overlapped signal), 132.79 (d, J = 14.8 Hz) (possibly overlapped signal), 131.68, 126.60, 125.29 (d, J = 2.4 Hz) (possibly overlapped signal), 124.58 (d, J = 2.4 Hz) (possibly overlapped signal), 124.55, 119.44, 118.43, 117.78, 115.90 (d, J = 22.0 Hz), 115.85 (d, J = 22.0 Hz), 115.67, 38.18, 34.91, 31.98, 31.93, 29.99, 20.01, 9.03. ESI MS (positive) m/z 541.0 [M + H$^+$].

1,6,6-trimethyl-6,7,8,9-tetrahydrophenanthro[1,2-b]furan-10,11-diyl-bis(4-trifluoromethyl)benzoate) (5i): White amorphous solid; yield 71%; mp. 192 – 195 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.25 (d, J = 8.2 Hz, 2H), 8.19 (d, J = 8.7 Hz, 1H), 8.17 (d, J = 8.2 Hz, 2H), 7.66 (d, J = 8.2 Hz, 2H), 7.64 (d, J = 8.7 Hz, 1H), 7.62 (d, J = 8.2 Hz, 2H), 7.52 (q, J = 1.2 Hz, 1H), 3.63 – 3.49 (m, 1H), 2.95 – 2.82 (m, 1H), 2.19 (d, J = 1.2 Hz, 3H), 1.79 – 1.68 (m, 2H), 1.68 – 1.59 (m, 2H), 1.37 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 164.01, 163.58, 150.59, 144.61, 141.95, 135.36 (q, J = 32.8 Hz), 135.26 (q, J = 32.8 Hz), 135.05, 134.75, 132.12, 131.56, 131.47, 130.62 (possibly overlapped signal), 130.48 (possibly overlapped signal), 126.84, 125.72 (q,
1,6,6-trimethyl-6,7,8,9-tetrahydrophenanthro[1,2-b]furan-10,11-diyl-dipicolinate (5j):
White amorphous solid; yield 85%; mp. 193 – 194 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.68 (d, $J = 4.6$ Hz, 1H), 8.61 (d, $J = 4.6$ Hz, 1H), 8.20 (d, $J = 7.8$ Hz, 1H), 8.14 (d, $J = 8.8$ Hz, 1H), 8.13 (d, $J = 7.8$ Hz, 1H), 7.74 (td, $J = 7.8$, 1.5 Hz, 1H), 7.69 (td, $J = 7.8$, 1.5 Hz, 1H), 7.60 (d, $J = 8.8$ Hz, 1H), 7.48 (q, $J = 1.2$ Hz, 1H), 7.42 – 7.34 (m, 2H), 3.80 – 3.46 (m, 1H), 3.02 – 2.74 (m, 1H), 2.20 (d, $J = 1.2$ Hz, 3H), 1.74 – 1.65 (m, 2H), 1.64 – 1.57 (m, 2H), 1.33 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 163.51, 163.06, 150.51, 150.17, 150.15, 147.10, 146.49, 144.33, 141.75, 137.05, 137.01, 135.26, 134.95, 131.81, 127.29, 127.19, 126.65, 125.93, 125.78, 124.46, 119.51, 118.38, 117.74, 115.77, 38.20, 34.90, 31.96 (possibly overlapped signal), 29.89, 19.99, 8.99. ESI MS (positive) $m/z$ 507.5 [M + H]$^+$. 

Part 2. $^1$H NMR, $^{13}$C NMR, and MS spectra of compounds 3a-e, 4a-c, and 5a-j, as well as NOESY spectrum of 3e.

Figure S1. $^1$H NMR, $^{13}$C NMR, MS spectra of compound 3a
TACE #8-18 RT: 0.29-0.54 AV: 5 NL: 1.36E8
F: + c ESI Full ms [50.00-1000.00]
Figure S2. $^1$H NMR, $^{13}$C NMR, MS spectra of compound 3b
Figure S3. $^1$H NMR, $^{13}$C NMR, MS spectra of compound 3c
TBU #28-43 RT: 0.92-1.36 AV: 8 NL: 1.16E9
F: + c ESI Full ms [ 50.00-1000.00]
Figure S4. $^1$H NMR, $^{13}$C NMR, MS spectra of compound 3d
Figure S5. $^1$H NMR (CD$_3$OD), NOESY (CD$_3$OD), $^1$H NMR (DMSO), $^{13}$C NMR (DMSO), MS spectra of compound 3e
Figure S6. $^1$H NMR, $^{31}$P NMR, MS spectra of compound 4a
Figure S7. $^1$H NMR, $^{13}$C NMR, MS spectra of compound 4b
Sample directory: sample
Format: C6D30
Ambient temperature: 298K
Sample delay: 1.000 sec
Pulse width: 10.0 degrees
Acq. time: 3.599 sec
NMRD (pH): 1.00
150 repetitions
Resonance FID: 151.690709 MHz
Resonance FID: 150.590219 MHz
Power: 41.0 W
On during acquisition: off
During delay: on
Data processed
FT size: 27768
Total time: 8 min, 24 sec

$^1$H NMR (9.612 分钟) 1H NMR 300 MHz ZCR-2012-8-7-4,4
Figure S8. $^1$H NMR, $^{13}$C NMR, MS spectra of compound 4c
Figure S9. $^1$H NMR, $^{13}$C NMR, MS spectra of compound 5a
Figure S10. $^1$H NMR, $^{13}$C NMR, MS spectra of compound 5b
Figure S11. $^1$H NMR, $^{13}$C NMR, MS spectra of compound 5c
Figure S12. $^1$H NMR, $^{13}$C NMR, MS spectra of compound 5d
T15 #9-13 RT: 0.28-0.41 AV: 3 NL: 6.09E7
F: + c ESI Full ms [50.00-1000.00]

50 100 150 200 250 300 350 400 450 500 ...

714.57 715.58 610.52 279.42 716.44 318.71 615.68 666.54 123.22 658.45 512.97 280.47 638.59 274.68 717.34 319.75 540.99 105.12 362.77 762.27 311.36 569.61 866.53 102.17 822.59 427.74 374.71 718.36 251.50 917.33 964.32 149.21 763.17 485.38 838.81 218.45 101.22
Figure S13. $^1$H NMR, $^{13}$C NMR, MS spectra of compound 5e
Figure S14. $^1$H NMR, $^{13}$C NMR, MS spectra of compound 5f
Figure S15. $^1$H NMR, $^{13}$C NMR, MS spectra of compound 5g
Figure S16. $^1$H NMR, $^{13}$C NMR, MS spectra of compound 5h.
Figure S17. $^1$H NMR, $^{13}$C NMR, MS spectra of compound 5i
T13 #9-14 RT: 0.28-0.41 AV: 3 NL: 3.78E7
F: + c ESI Full ms [50.00-1000.00]

**Diagram Description:**
- The diagram shows a mass spectrum with several peaks indicated.
- Peaks are labeled with their corresponding m/z values.
- The y-axis represents relative abundance, ranging from 0 to 110.
- The x-axis represents mass, with values ranging from 120 to 1110.

**Chemical Structure:**
- The structure of T13 #9-14 is shown, indicating its molecular composition.
- The structure includes a ring system with attached functional groups.

**Notes:**
- The spectrum is annotated with high-abundance peaks, suggesting the presence of significant molecules.
- The F+ c ESI Full ms indicates the analysis method used for the spectrum.
Figure S18. $^1$H NMR, $^{13}$C NMR, MS spectra of compound 5j
