

Supplementary Information

Synthesis, Crystal Structure and Biological Activity of Novel Diester Cyclophanes

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Experimental

General method of preparation of diacid chlorides **1**

O-phthalic acid (0.83 g, 5 mmol) was treated with SOCl₂ (12 mL) and catalytic DMF under refluxing condition for 8 h. Solvent was evaporated under vacuum. The residue was dissolved in dry PhMe and evaporated to obtain diacid chlorides **1** as pale yellow solid at high yield of 98%.

General method of preparation of **3a-3f**

Epoxyethane (5 mL) was added dropwise to a stirred mixture of substituted aniline **2** (0.02 mol), H₂O (10 mL) and propanoic acid (1 mL) at 0 °C over a period 30 min. The reaction mixture was stirred for 24 h at room temperature. After, 50 mL of dichloromethane was added to the mixture and the organic phase was separated. Then the organic layer was washed with 20 mL of saturated sodium carbonate and 5 mL water prior to anhydrous MgSO₄. The solvent was removed to leave the crude product, which was purified by chromatography on silica gel (petroleum ether/ethyl acetate = 1:1→1:3).

Compound 3a. White solid, Yield 85%, m.p. 52-53 °C (lit.¹ 53-54 °C); ¹H NMR (400 MHz, CDCl₃): δ 7.01 (d, 2H, *J* 8.8 Hz, ArH), 6.56 (d, 2H, *J* 8.4 Hz, ArH), 4.40 [s, 2H, 2 (-OH)], 3.71 [t, 4H, *J* 4.8 Hz, 2 (-O-CH₂-)], 3.43 [t, 4H, *J* 5.0 Hz, 2 (-N-CH₂-)], 2.23 (s, 3H, -CH₃).

Compound 3b. White solid, yield 90%, m.p. 68-69 °C (lit.² 73 °C); ¹H NMR (400 MHz, CDCl₃): δ 6.83 (d, 2H, *J* 8.8 Hz, ArH), 6.74 (t, 2H, *J* 9.2 Hz, ArH), 3.76 [t, 4H, 2 (-O-CH₂-)], 3.75 (s, 3H, -OCH₃), 3.45 [t, 4H, *J* 4.0 Hz, 2 (-N-CH₂-)], 2.24 [s, 2H, (-OH)].

Compound 3c. White solid, yield 92%, m.p. 95-96 °C (lit.¹ 95-96 °C); ¹H NMR (400 MHz, CDCl₃): δ 7.16 (d, 2H, *J* 9.2 Hz, ArH), 6.60 (d, 2H, *J* 9.2 Hz, ArH), 3.82 [t, 4H, *J* 4.6 Hz, 2 (-O-CH₂-)], 3.60 [s, 2H, 2 (-OH)], 3.54 [t, 4H, *J* 4.8 Hz, 2 (-N-CH₂-)].

Compound 3d. White solid, yield 80%, m.p. 65-66 °C (lit.³ 65-67 °C); ¹H NMR (400 MHz, CDCl₃): δ 7.11 (t, 1H, *J* 8.4 Hz, ArH), 6.56 (d, 1H, *J* 7.6 Hz, ArH), δ 6.47 (d, 2H, *J* 7.2 Hz, ArH), 4.22 [s, 2H, 2 (-OH)], 3.78 [t, 4H, *J* 4.6 Hz, 2 (-O-CH₂-)], 3.51 [t, 4H, *J* 4.8 Hz, 2 (-N-CH₂-)], 2.30 (s, 3H, -CH₃).

Compound 3e. White solid, yield 95%, m.p. 86-87 °C (lit.⁴ 90-92 °C); ¹H NMR (400 MHz, CDCl₃): δ 7.12 (t, 1H, *J* 8.0 Hz, ArH), 6.69 (t, 1H, *J* 4.8 Hz, ArH), 6.62 (t, 1H, *J* 2.0 Hz, ArH), 6.52-6.54 (m, 1H, ArH), 3.93 [s, 2H, 2 (-OH)], 3.81 [t, 4H, *J* 4.8 Hz, 2 (-O-CH₂-)], 3.54 [t, 4H, *J* 4.8 Hz, 2 (-N-CH₂-)].

Compound 3f. White solid, yield 90%, m.p. 102-103 °C (lit.³ 103-104 °C); ¹H NMR (400 MHz, CDCl₃): δ 6.42 (s, 1H, ArH), 6.31 (s, 2H, ArH), 3.81 [t, 4H, *J* 4.8 Hz, 2 (-O-CH₂-)], 3.53 [t, 4H, *J* 4.4 Hz, 2 (-N-CH₂-)], 2.26 [s, 6H, 2(-CH₃)].

General Method of Preparation of **3g-3h**

A mixture of substituted aniline (10 mmol), 2-chloroethanol (2 mL), CaCO₃ (2.00 g, 20 mmol) and KI (10% mmol) were added to 14 mL water and refluxed for 8 h. Filtered, the filtrate was extracted with EtOAc (14 mL×3), and the combined organic layers were washed with saturated NaCl (14 mL×2), dried over anhydrous MgSO₄, filtered, concentrated and purified by chromatography on silica gel (petroleum ether/ethyl acetate = 1:1→1:3).

Compound 3g. Yellow solid, yield 52%, m.p. 99-100 °C (lit.⁵ 100-102 °C); ¹H NMR (400 MHz,

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CDCl₃): δ 7.48-7.55 (m, 2H, ArH), 7.34 (t, 1H, *J* 8.4 Hz, ArH), 6.98 (t, 1H, *J* 4.2 Hz, ArH), 3.91 [t, 4H, *J* 5.0 Hz, 2 (-O-CH₂-)], 3.67 [t, 4H, *J* 4.8 Hz, 2 (-N-CH₂-)], 3.48 [s, 2H, 2 (-OH)].

Compound 3h. White solid, yield 62%, m.p. 81-82 °C (lit.⁶ 75-78 °C); ¹H NMR (400 MHz, CDCl₃): δ 7.28 (d, 2H, *J* 8.4 Hz, ArH), 6.54 (d, 2H, *J* 8.8 Hz, ArH), 3.92 [s, 2H, 2 (-OH)], 3.79 [t, 4H, *J* 4.4 Hz, 2 (-O-CH₂-)], 3.52 [t, 4H, *J* 4.8 Hz, 2 (-N-CH₂-)].

General procedure for the synthesis of medium-sized cyclophanes **4a-4h**

A dry, 1000-mL, three-necked flask was charged with 2 mmol of compound **3**, 0.32 mL of pyridine, 30 mg of DMAP and 600 mL of CH₂Cl₂. To the above vigorously stirred system, 1,2-benzenedicarbonyl chloride **1** (0.61 g, 3 mmol) in CH₂Cl₂ (200 mL) was added dropwise over a period of 10 h. The reaction solution was stirred for 24 h at room temperature and then refluxed for another 10 h (reaction monitored by TLC). When the reaction was complete, the solvent was evaporated under reduced pressure, and the residual solution was washed with water (20 mL \times 3) and dried over anhydrous MgSO₄. Then the solvent was removed to leave crude product, which was purified by chromatography on silica gel (petroleum ether/ethyl acetate = 10:1).

Compound 4a. C₁₉H₁₉NO₄. White solid (56%), m.p. 135-136 °C; IR (KBr): 3066, 2957, 2919, 1712, 1611, 1519, 1453, 1294, 1130, 798, 736, 698 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.79-7.82 (m, 2H, ArH), 7.57-7.59 (m, 2H, ArH), 7.10 (d, 2H, *J* 8.8 Hz, ArH), 6.54 (d, 2H, *J* 8.4 Hz, ArH), 4.55 [t, 4H, *J* 4.0 Hz, 2 (-O-CH₂-)], 3.80 [t, 4H, *J* 4.0 Hz, 2 (-N-CH₂-)], 2.27 (s, 3H, -CH₃); Anal. Calcd. for C₁₉H₁₉NO₄: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.35; H, 5.33; N, 4.36. MALDI-TOF HRMS: *m/z* 348.1196 [M+Na]⁺.

Compound 4b. C₁₉H₁₉NO₅. White solid (22%), m.p. 138-139 °C; IR (KBr): 2993, 2958, 2922, 1714, 1608, 1514, 1453, 1296, 1129, 811, 735, 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.80-7.82 (m, 2H, ArH), δ 7.57-7.60 (m, 2H, ArH), 6.89 (d, 2H, *J* 8.8 Hz, ArH), 6.58 (d, 2H, *J* 9.2 Hz, ArH), 4.54 [t, 4H, *J* 4.2 Hz, 2 (-O-CH₂-)], 3.78 [t, 4H, *J* 4.2 Hz, 2 (-N-CH₂-)], 3.77 [s, 3H, -OCH₃]; Anal. Calcd. for C₁₉H₁₉NO₅: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.81; H, 5.65; N, 4.22. MALDI-TOF HRMS: *m/z* 342.1315 [M+H]⁺.

Compound 4c. C₁₈H₁₆ClNO₄. White solid (38%), m.p. 155-156 °C; IR (KBr): 3072, 2929, 1713, 1592, 1502, 1375, 1285, 1111, 1008, 796, 737, 693 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.80-7.82 (m, 2H, ArH), δ 7.58-7.60 (m, 2H, ArH), 7.22 (d, 2H, *J* 9.6 Hz ArH), 6.54 (d, 2H, *J* 9.6 Hz ArH), 4.53 [t, 4H, *J* 4.4 Hz, 2 (-O-CH₂-)], 3.80 [t, 4H, *J* 4.2 Hz, 2 (-N-CH₂-)]; Anal. Calcd. for C₁₈H₁₆ClNO₄: C, 62.52; H, 4.66; N, 4.05. Found: C, 62.49; H, 5.69; N, 4.16. MALDI-TOF HRMS: *m/z* 368.0664 [M+Na]⁺.

Compound 4d. C₁₉H₁₉NO₄. White solid (42%), m.p. 144-145 °C; IR (KBr): 3035, 2937, 2857, 1715, 1601, 1497, 1444, 1293, 1130, 772, 745, 695 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.80-7.82 (m, 2H, ArH), 7.57-7.59 (m, 2H, ArH), 7.16-7.20 (m, 1H, ArH), 6.62 (d, *J* 7.6 Hz, 1H, ArH), 6.45 (t, *J* 4.6 Hz, 2H, ArH), 4.56 [t, 4H, *J* 4.2 Hz, 2 (-O-CH₂-)], 3.82 [t, 4H, *J* 4.4 Hz, 2 (-N-CH₂-)], 2.35 (s, 3H, -CH₃); Anal. Calcd. for C₁₉H₁₉NO₄: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.20; H, 5.83; N, 4.38. MALDI-TOF HRMS: *m/z* 348.1209 [M+Na]⁺.

Compound 4e. C₁₈H₁₆ClNO₄. White solid (30%), m.p. 198-199 °C; IR (KBr): 2924, 2860, 1716, 1594, 1492, 1388, 1293, 1132, 830, 745, 694 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.80-7.82 (m, 2H, ArH), 7.58-7.61 (m, 2H, ArH), 7.19 (t, 1H, *J* 8.2 Hz, ArH), 6.75-6.77 (m, 1H, ArH), 6.58 (t, 1H, *J* 2.2 Hz, ArH), 6.48-6.51 (m, 1H, ArH), 4.55 [t, 4H, *J* 4.2 Hz, 2 (-O-CH₂-)], 3.81 [t, 4H, *J* 2.2 Hz, 2 (-N-CH₂-)]; Anal. Calcd. for C₁₈H₁₆ClNO₄: C, 62.52; H, 4.66; N, 4.05. Found: C, 62.58; H, 4.62; N, 4.12. MALDI-TOF HRMS: *m/z* 368.0661 [M+Na]⁺.

Compound 4f. C₂₀H₂₁NO₄. White solid (36%), m.p. 151-152 °C; IR (KBr): 2923, 2856, 1713, 1596, 1476, 1361, 1283, 1129, 818, 741, 695 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.80-7.82 (m, 2H, ArH), 7.57-7.59 (m, 2H, ArH), 6.47 (s, 1H, ArH), 6.24 (s, 2H, ArH), 4.56 [t, 4H, *J* 4.0 Hz, 2 (-O-CH₂-)], 3.80 [t, 4H, *J* 4.0 Hz, 2 (-N-CH₂-)], 2.31 [s, 6H, 2 (-CH₃)]; Anal. Calcd. for C₂₀H₂₁NO₄: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.83; H, 6.18; N, 4.20. MALDI-TOF HRMS: *m/z* 362.1355 [M+Na]⁺.

Compound 4g. C₁₈H₁₆N₂O₆. Yellow solid (45%), m.p. 165-166 °C; IR (KBr): 2998, 2928, 2856, 1716, 1613, 1524, 1441, 1352, 1293, 1131, 789, 742 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.81-7.83 (m, 2H, ArH), 7.60-7.64 (m, 3H, ArH), 7.40-7.46 (m, 2H, ArH), 6.90-6.93 (m, 1H, ArH), 4.59 [t, 4H, *J* 4.4 Hz, 2 (-O-CH₂-)],

3.90 [t, 4H, J 4.2 Hz, 2 (-N-CH₂-)]; Anal. Calcd. for C₁₈H₁₆N₂O₆: C, 60.67; H, 4.53; N, 7.86. Found: C, 60.79; H, 4.02; N, 7.86. MALDI-TOF HRMS: m/z 357.1075 [M+H]⁺.

Compound 4h. C₁₈H₁₆BrNO₄. White solid (45%), m.p. 163-164 °C; IR (KBr): 2991, 2956, 2848, 1707, 1590, 1499, 1445, 1356, 1293, 1131, 1005, 804, 740, 694 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.80-7.82 (m, 2H, ArH), δ 7.58-7.60 (m, 2H, ArH), 7.36 (d, 2H, J 8.8 Hz, ArH), 6.50 (d, 2H, J 9.2 Hz, ArH), 4.53 [t, 4H, J 4.2 Hz, 2 (-O-CH₂-)], 3.80 [t, 4H, J 4.0 Hz, 2 (-N-CH₂-)]; Anal. Calcd. for C₁₈H₁₆BrNO₄: C, 55.40; H, 4.13; N, 3.59. Found: C, 55.36; H, 4.19; N, 3.66. MALDI-TOF HRMS: m/z 412.0127 [M+Na]⁺.

Reference

1. Ross, W. C. J.; *J. Chem. Soc.* **1949**, 183.
2. Anker, R. M.; Cook, A. H.; Heilbron, I. M.; *J. Chem. Soc.* **1945**, 917.
3. Tong, L. K. J.; Glesmann, M. C.; Bent, R. L.; *J. Am. Chem. Soc.* **1960**, 82, 1988.
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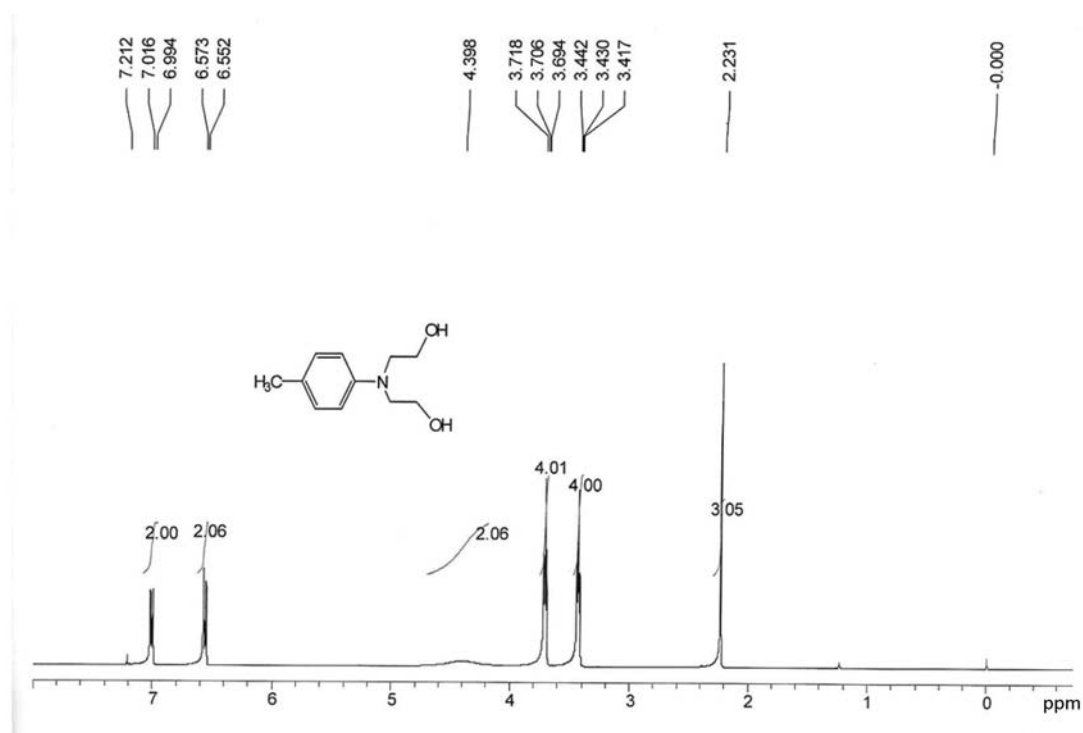


Figure S1. ¹H NMR spectrum (400 MHz, CDCl₃) of compound 3a.

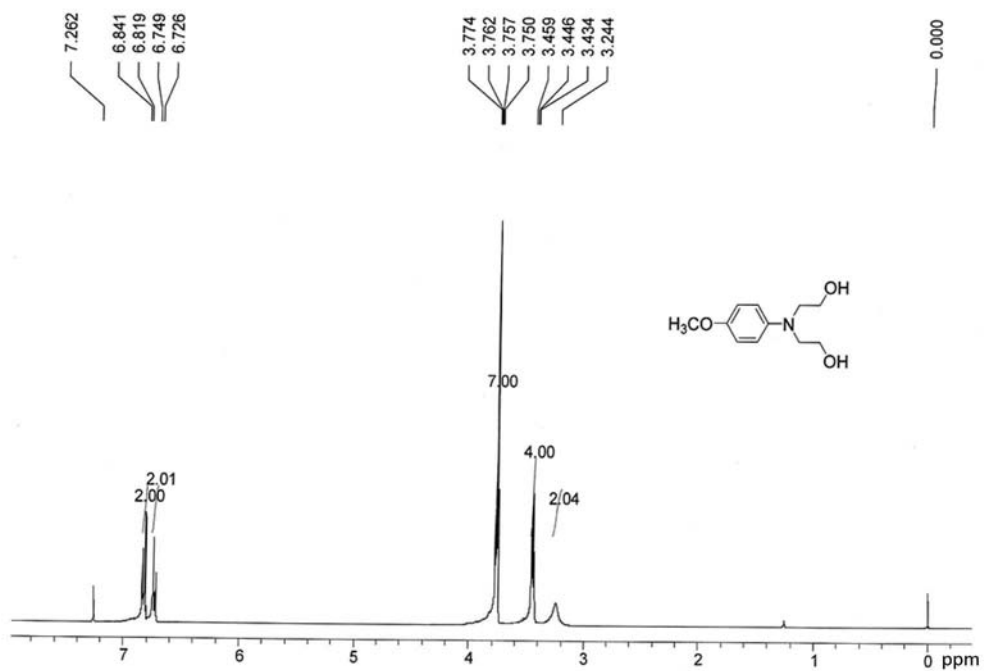


Figure S2. ¹H NMR spectrum (400 MHz, CDCl₃) of compound 3b.

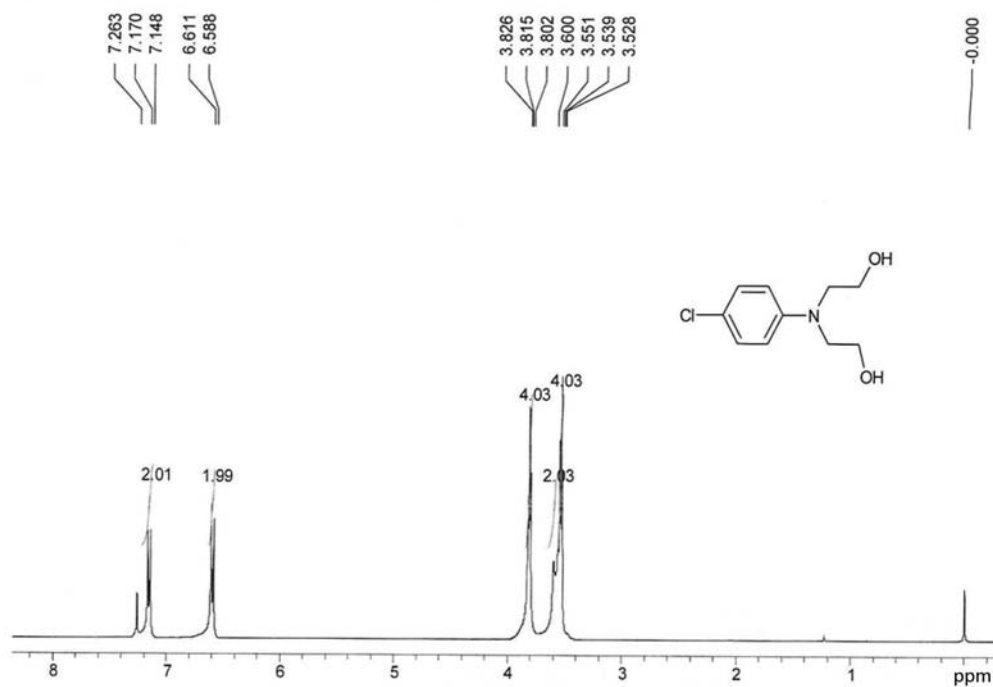


Figure S3. ¹H NMR spectrum (400 MHz, CDCl₃) of compound 3c.

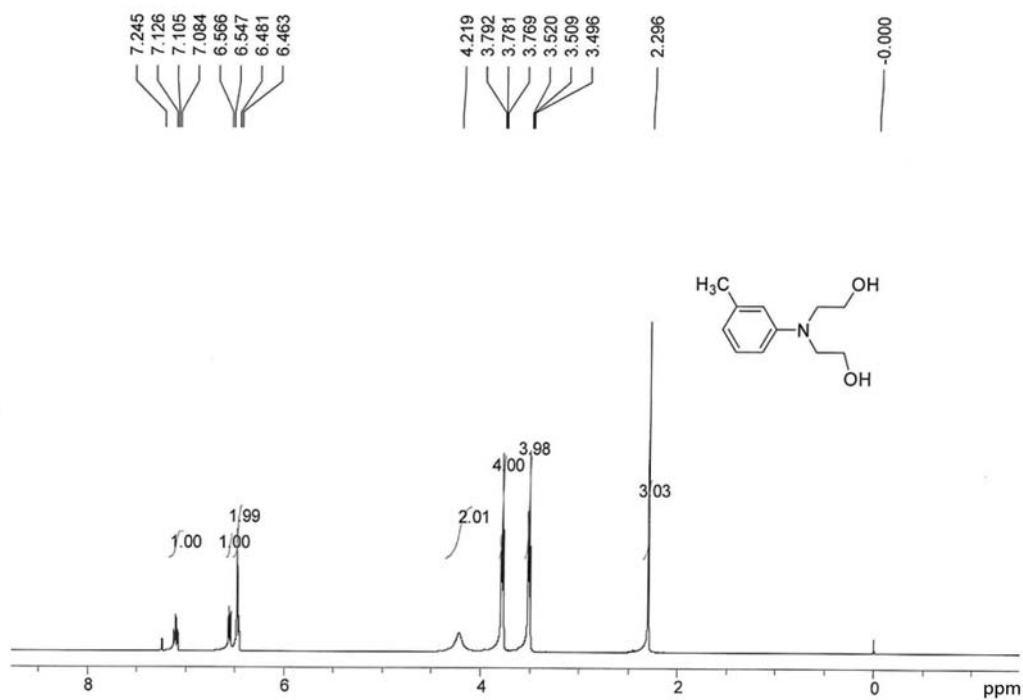


Figure S4. ¹H NMR spectrum (400 MHz, CDCl₃) of compound 3d.

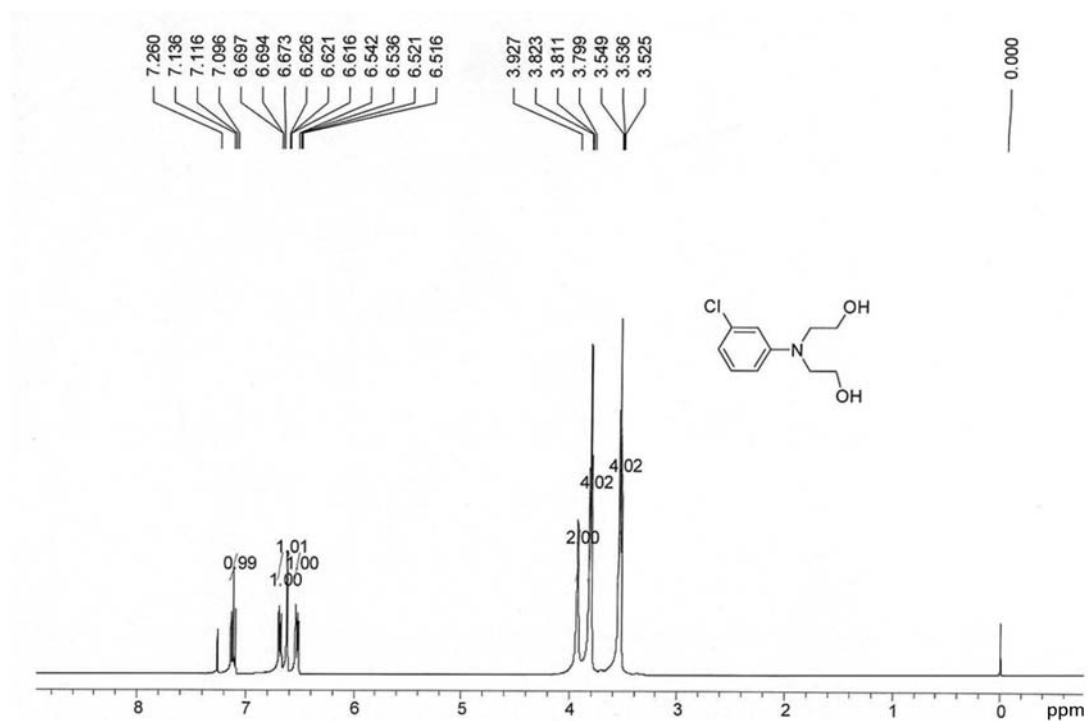


Figure S5. ¹H NMR spectrum (400 MHz, CDCl₃) of compound 3e.

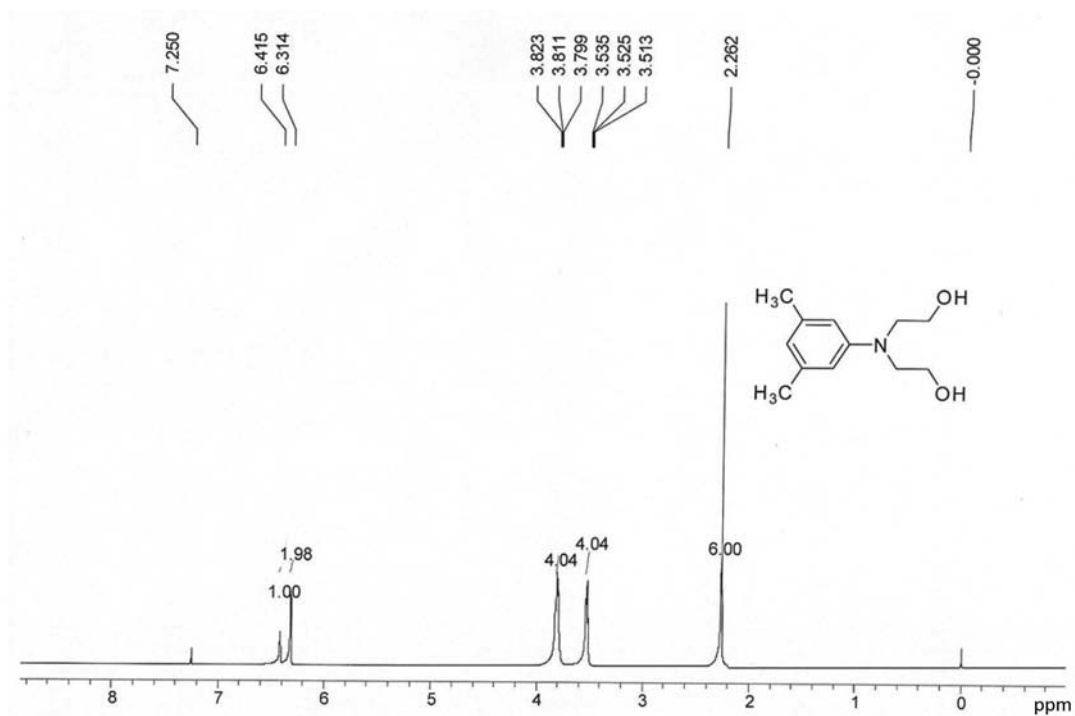


Figure S6. ^1H NMR spectrum (400 MHz, CDCl_3) of compound **3f**.

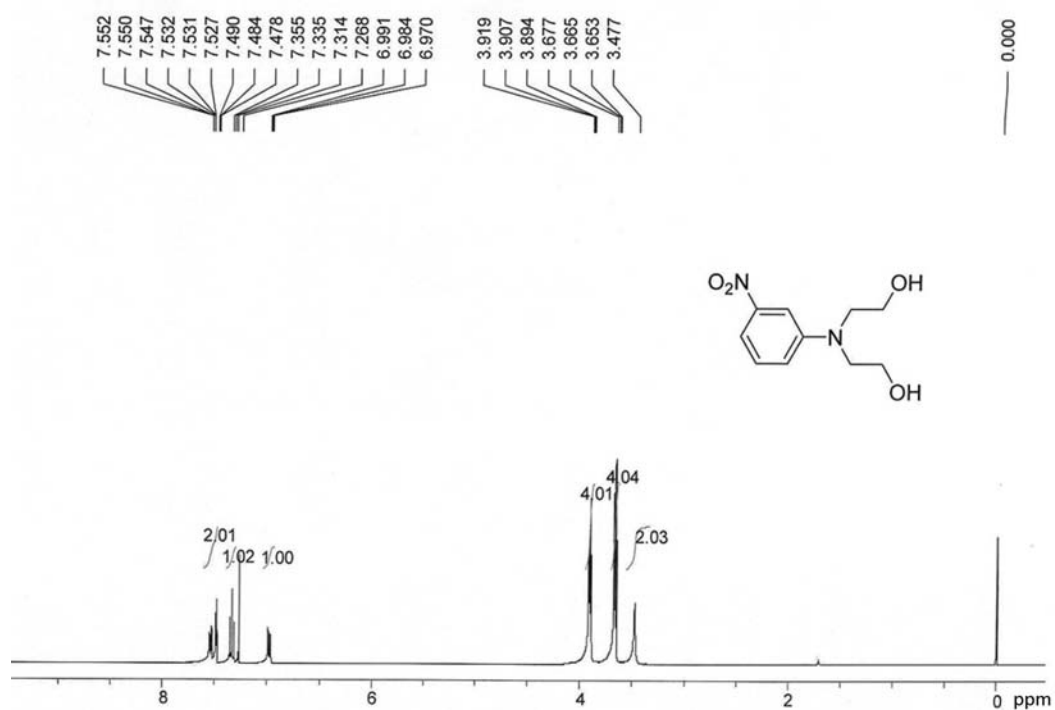


Figure S7. ^1H NMR spectrum (400 MHz, CDCl_3) of compound **3g**.

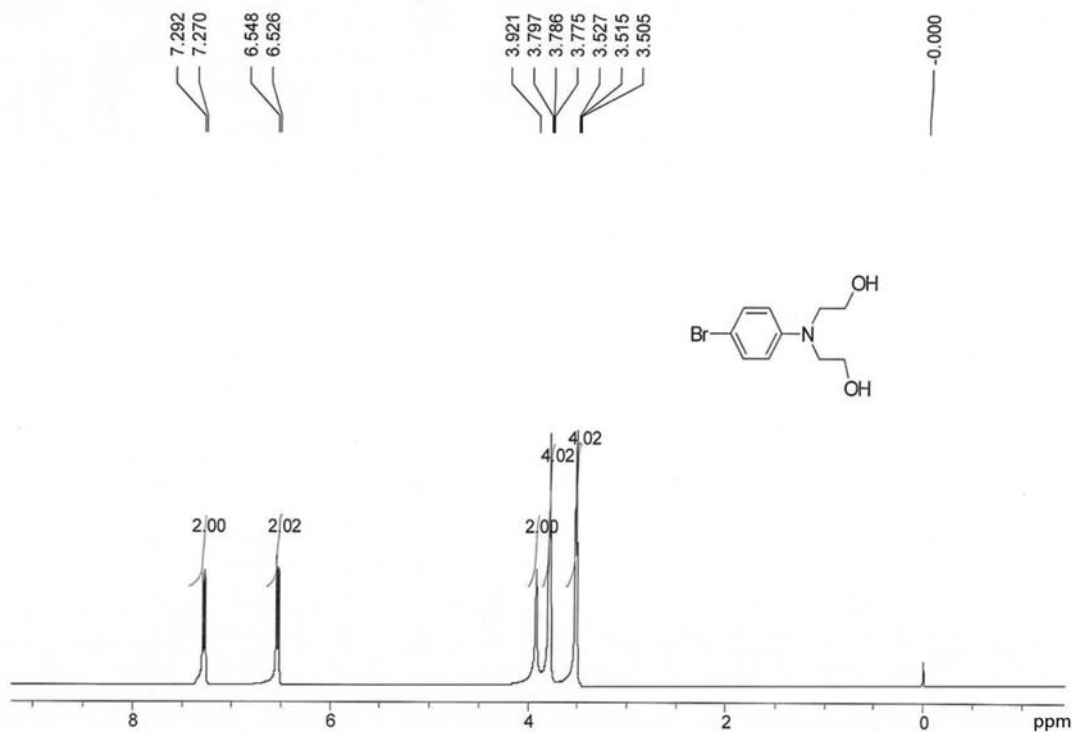
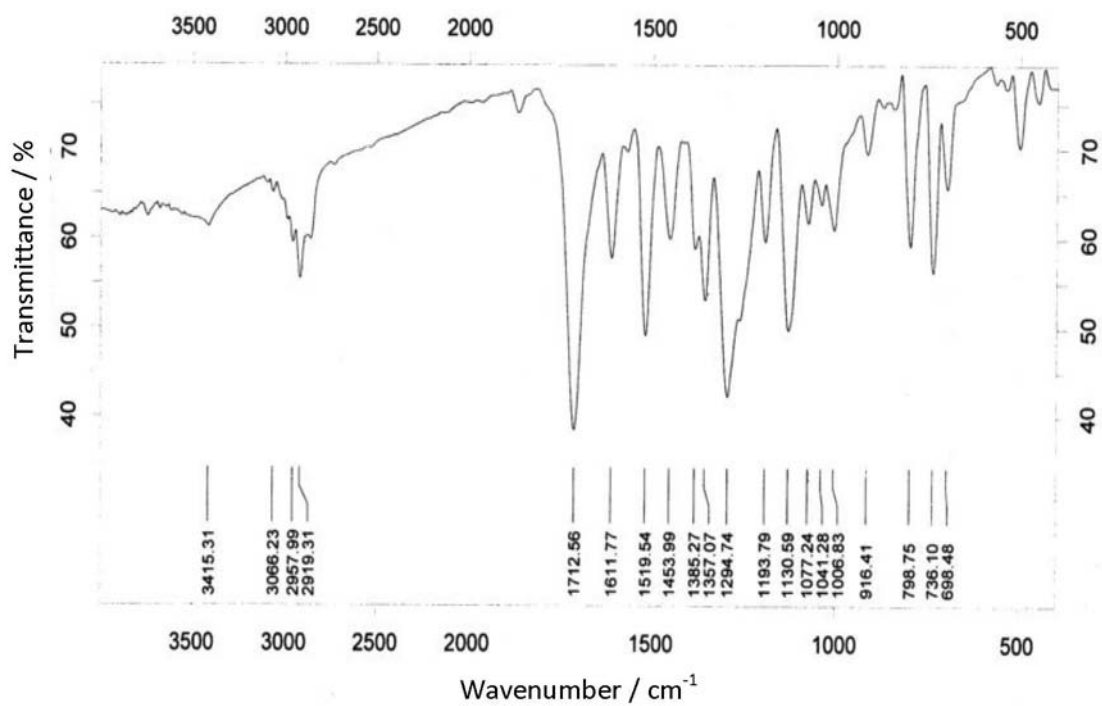
Figure S8. ¹H NMR spectrum (400 MHz, CDCl₃) of compound 3h.

Figure S9. IR of compound 4a.

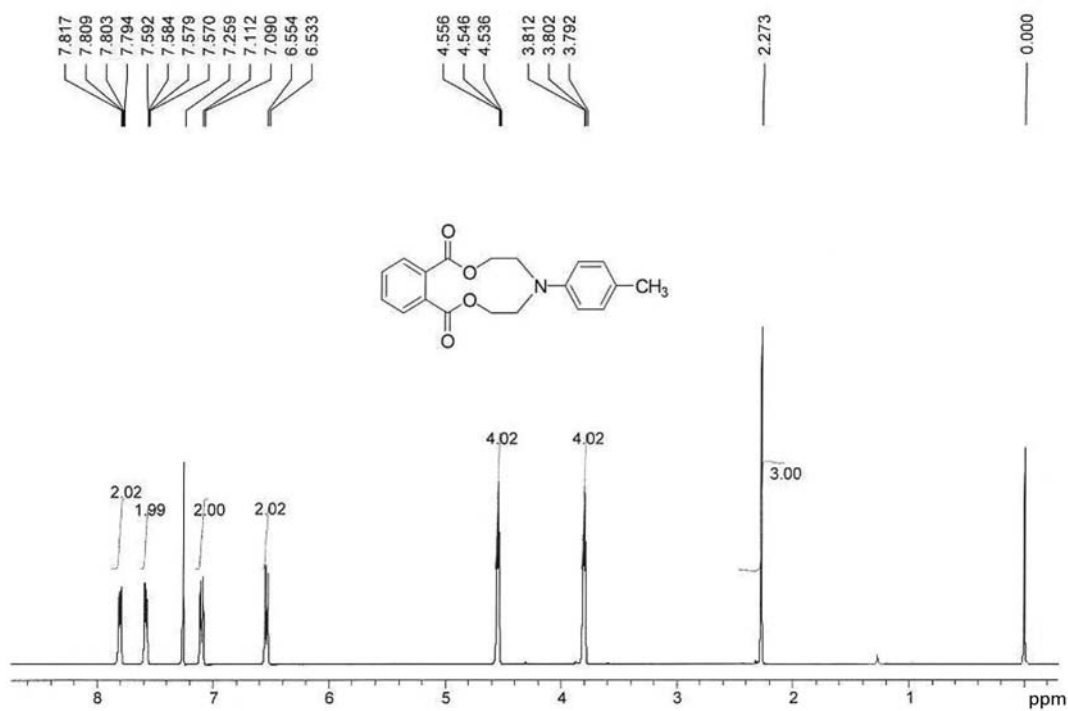


Figure S10. ¹H NMR spectrum (400 MHz, CDCl₃) of compound 4a.

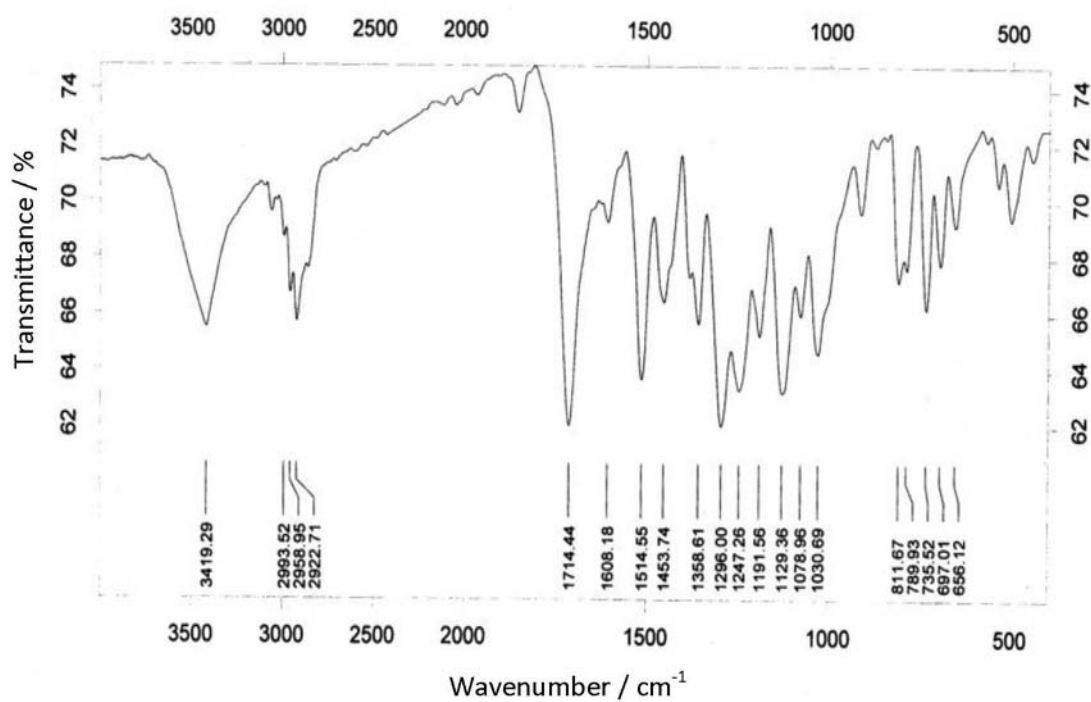


Figure S11. IR of compound 4b.

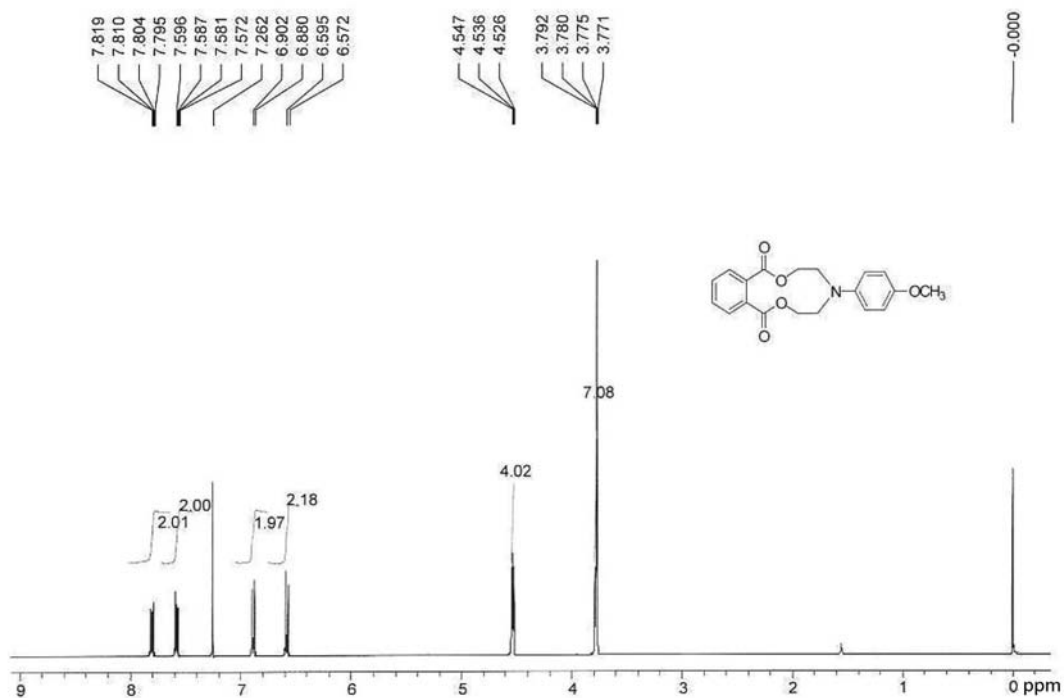


Figure S12. ^1H NMR spectrum (400 MHz, CDCl_3) of compound 4b.

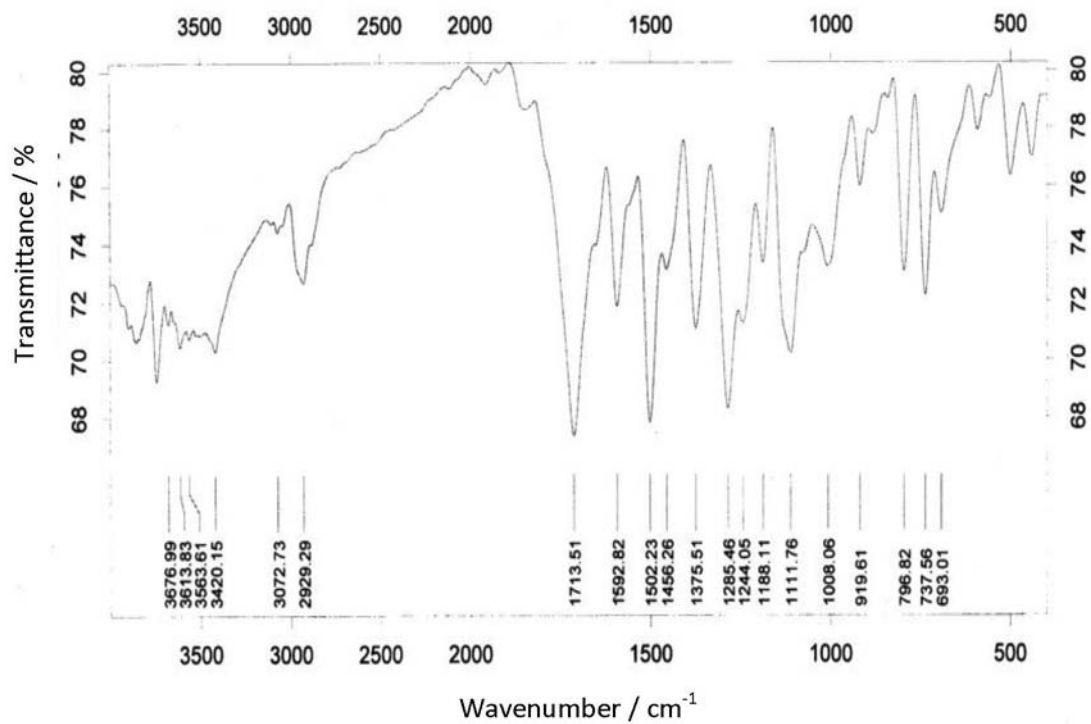


Figure S13. IR of compound 4c.

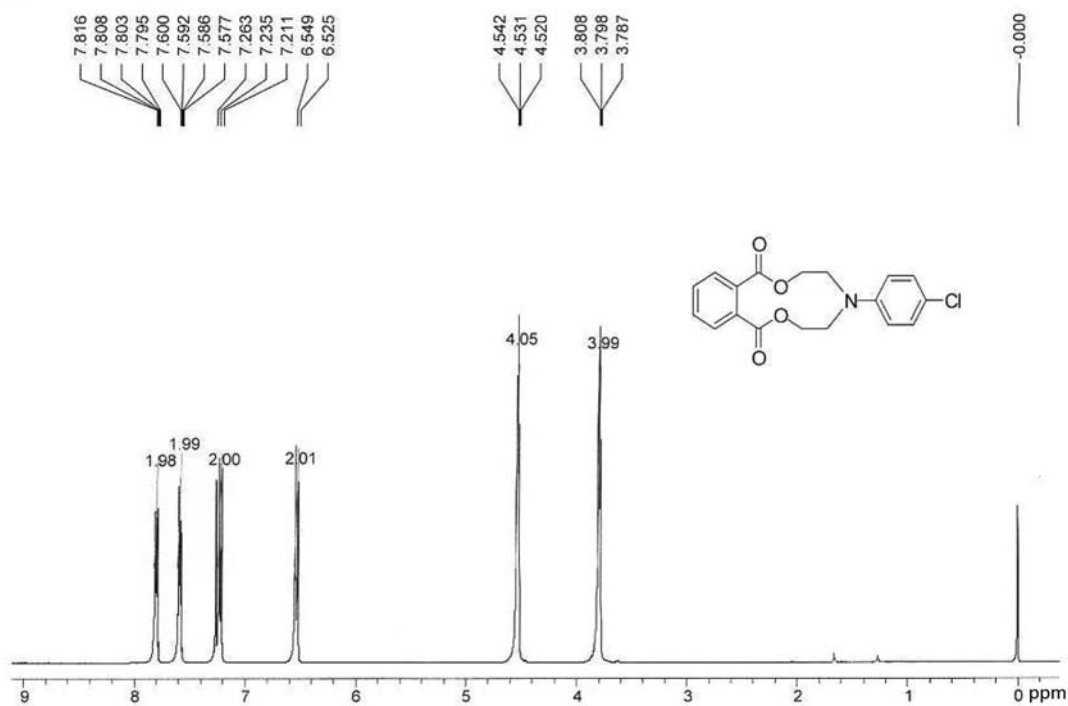


Figure S14. ^1H NMR spectrum (400 MHz, CDCl_3) of compound 4c.

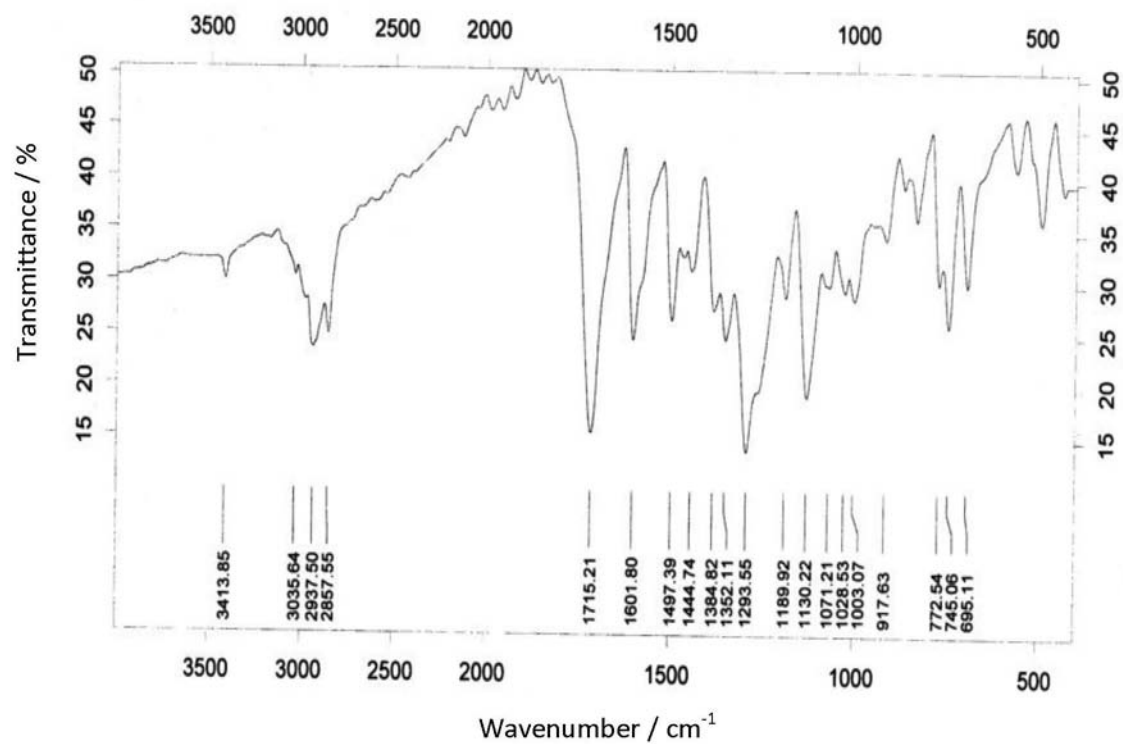


Figure S15. IR of compound 4d.

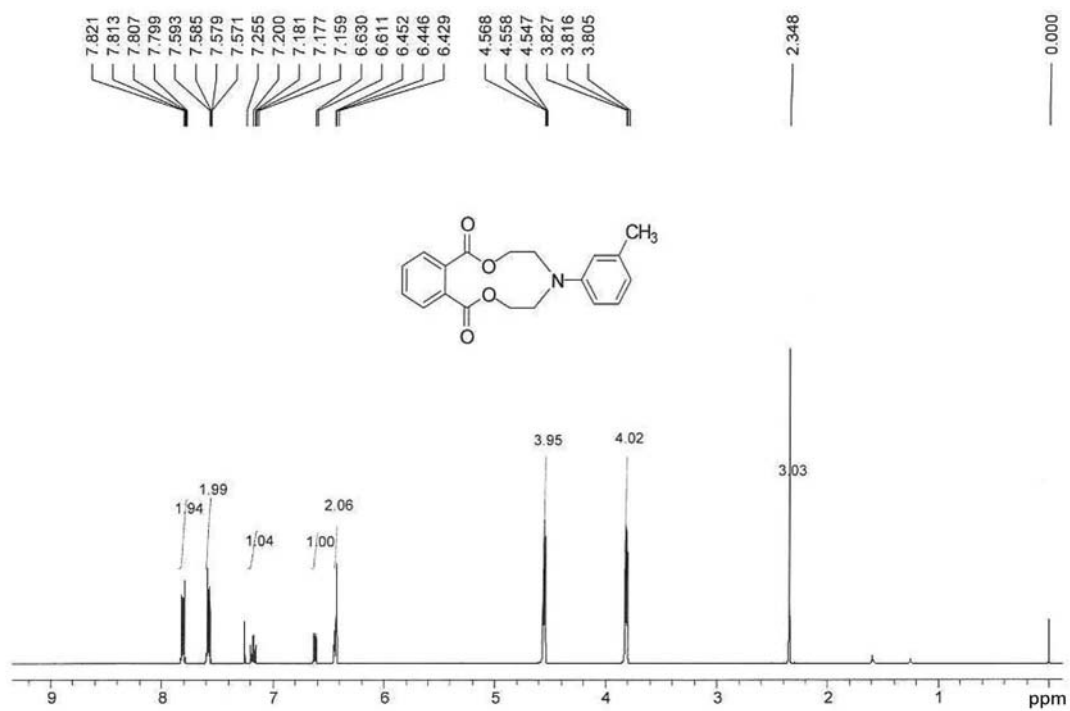


Figure S16. ¹H NMR spectrum (400 MHz, CDCl₃) of compound 4d.

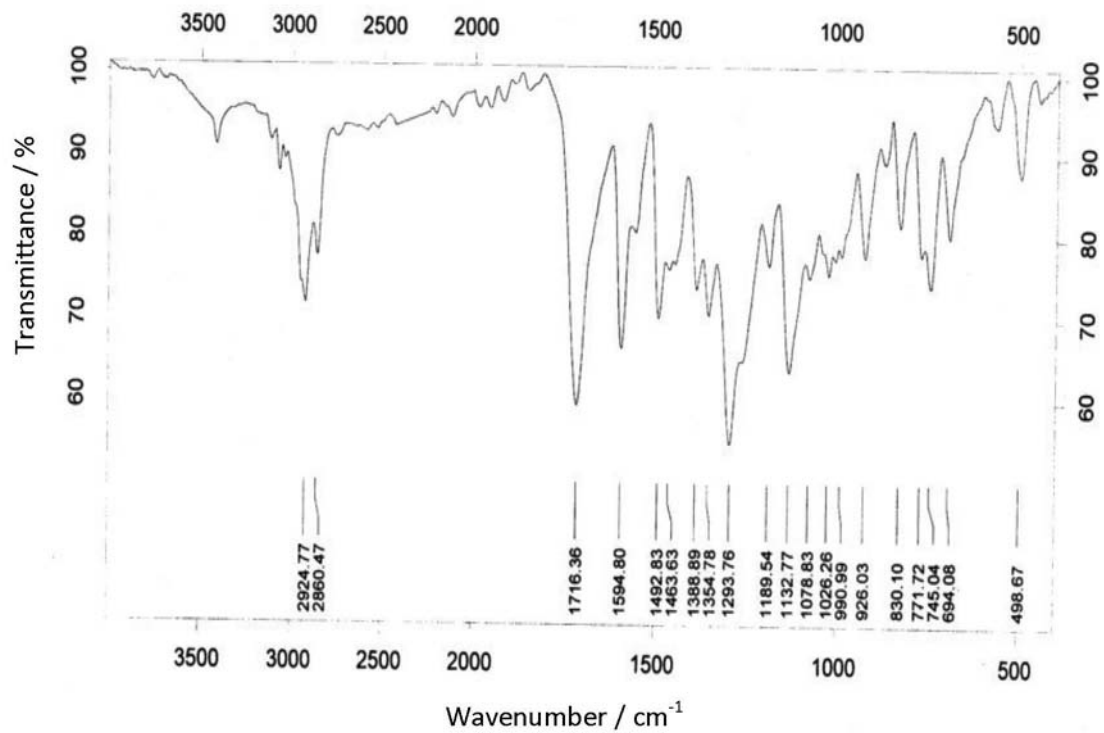


Figure S17. IR of compound 4e.

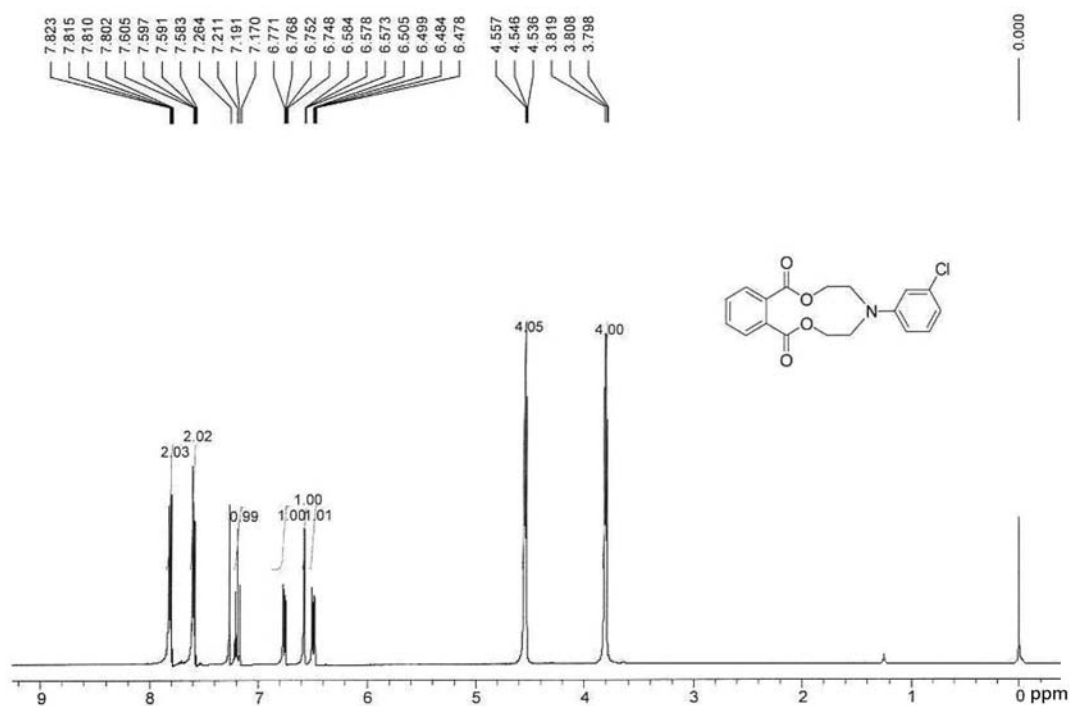


Figure S18. ¹H NMR spectrum (400 MHz, CDCl₃) of compound 4e.

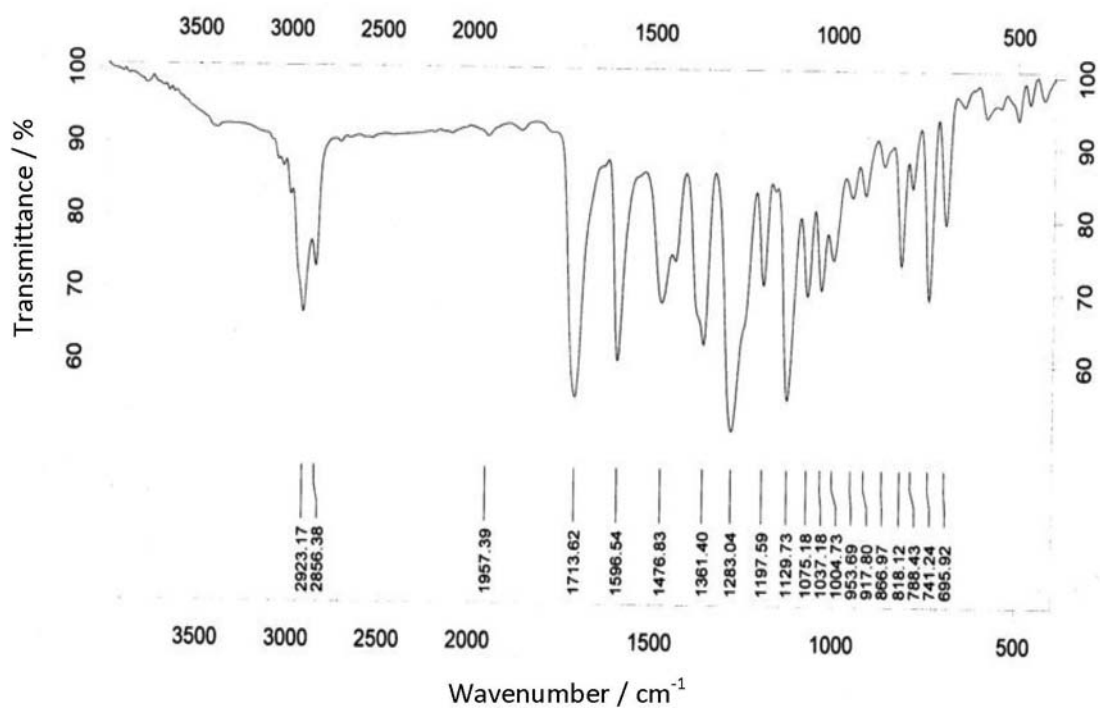


Figure S19. IR of compound 4f.

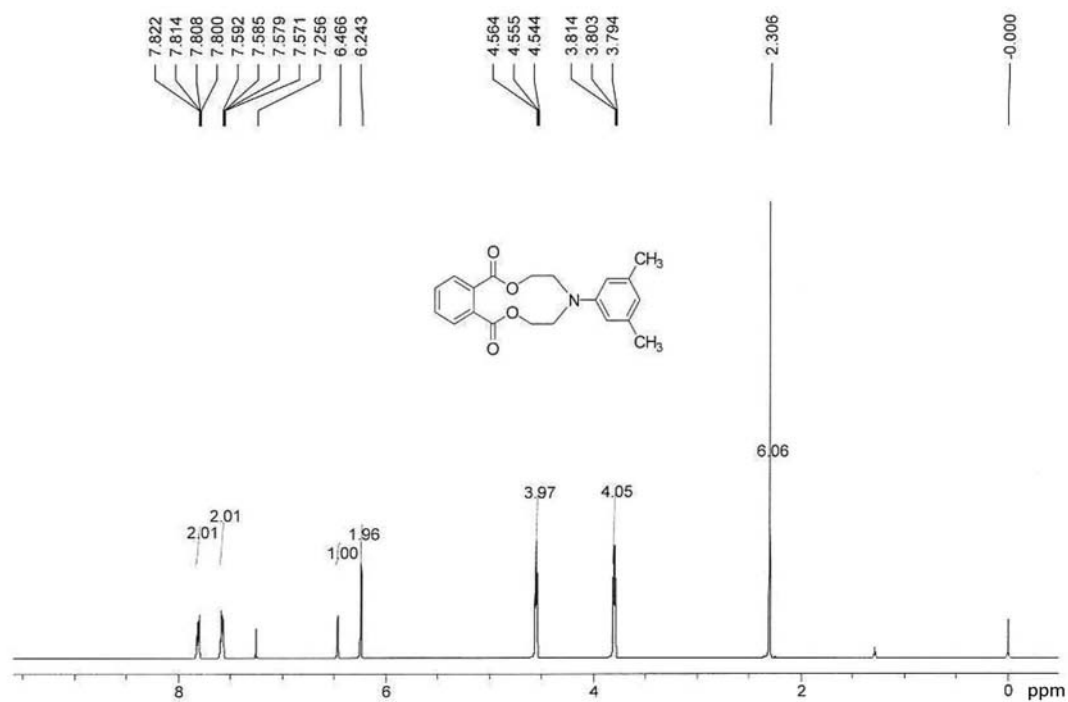


Figure S20. ^1H NMR spectrum (400 MHz, CDCl_3) of compound 4f.

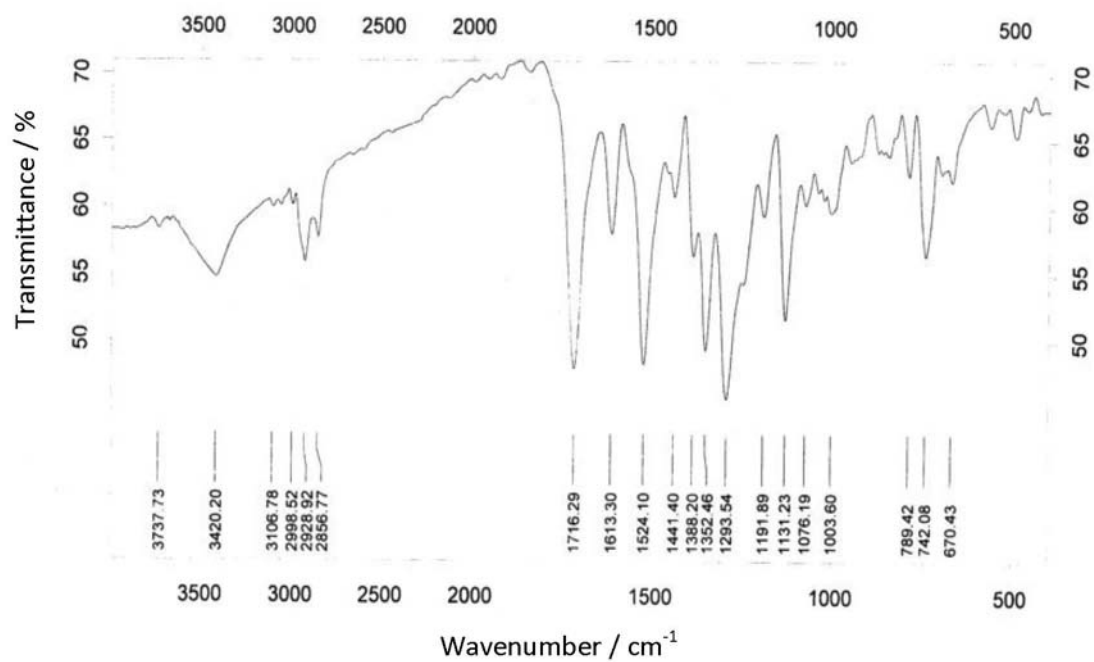


Figure S21. IR of compound 4g.

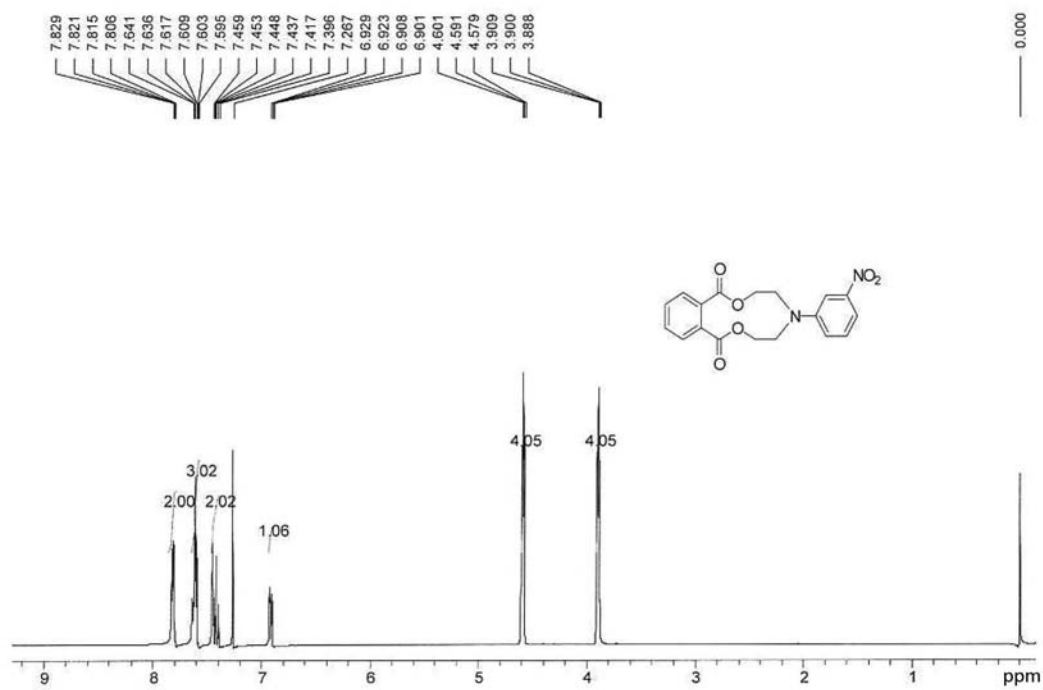


Figure S22. ¹H NMR spectrum (400 MHz, CDCl₃) of compound 4g.

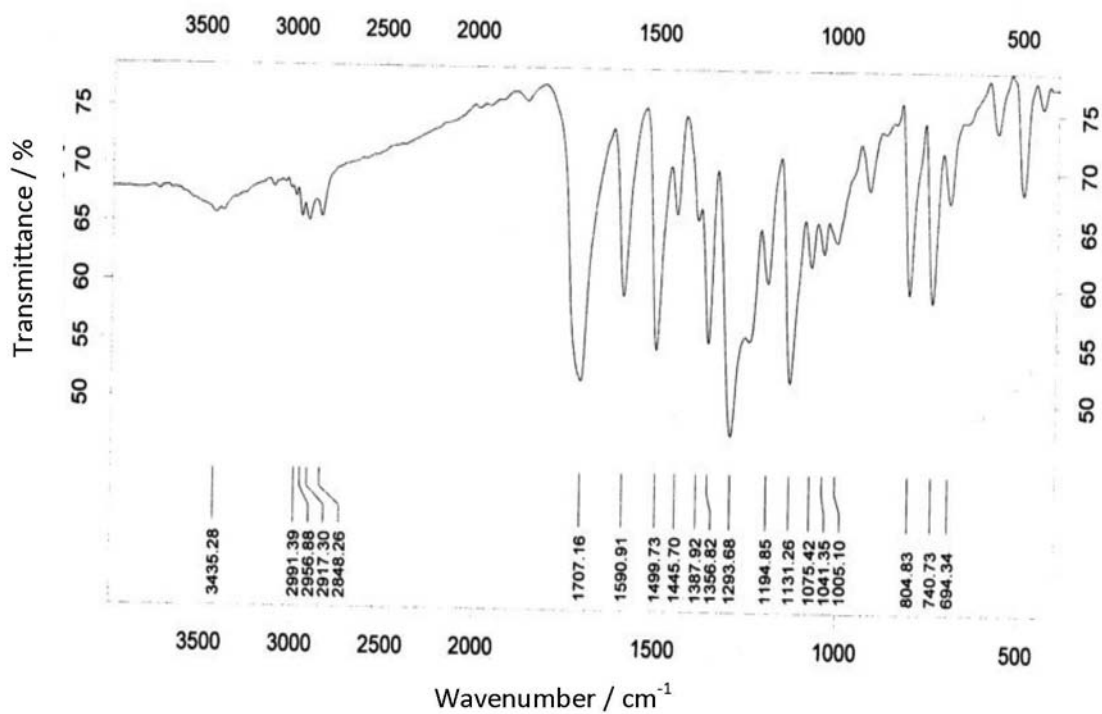


Figure S23. IR of compound 4h.

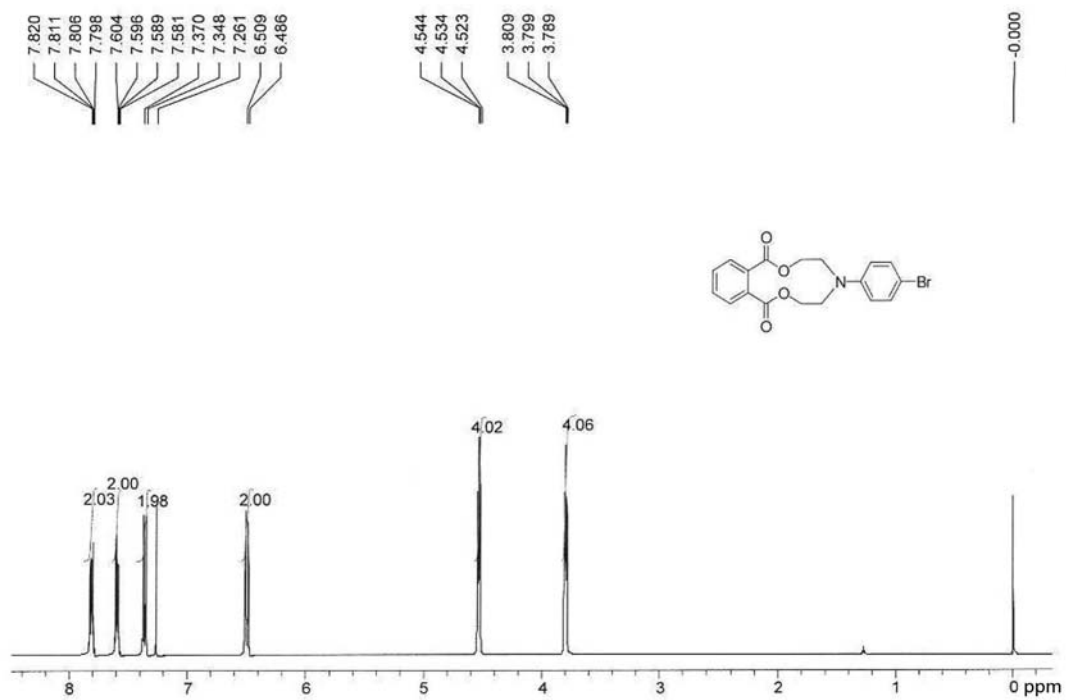


Figure S24. ¹H NMR spectrum (400 MHz, CDCl₃) of compound 4h.