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Supplementary Information

Synthesis, Crystal Structure and Biological Activity of Novel Diester Cyclophanes

Pengfei Zhang, Bingqin Yang,* Xianwen Fang, Zhao Cheng and Meipan Yang

Department of Chemistry, Key Laboratory of Synthetic and Natural Functional Molecule Chemistry, Northwest University, Xi'an 710069, Shaanxi, P. R. China

Experimental

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

O-phthalic acid (0.83 g, 5 mmol) was treated with $SOCl_2$ (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), H_2O (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 5mL water prior to anhydrous $MgSO_4$. 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); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (d, 2H, *J* 8.8 Hz, ArH), 6.56 (d, 2H, *J* 8.4Hz, ArH), 4.40 [s, 2H, 2 (-OH)], 3.71 [t, 4H, *J* 4.8 Hz, 2 (-O-CH_2-)], 3.43 [t, 4H, *J* 5.0 Hz, 2 (-N-CH_2-)], 2.23 (s, 3H, -CH_3).

Compound 3b. White solid, yield 90%, m.p. 68-69 °C (lit.[2] 73 °C); ^{1}H NMR (400 MHz, $CDCl_3$): 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-CH_2-)], 3.75 (s, 3H, -OCH_3), 3.45 [t, 4H, *J* 4.0 Hz, 2 (-N-CH_2-)], 2.24 [s, 2H, 2 (-OH)].

*e-mail: yangbq@nwu.edu.cn

Compound 3c. White solid, yield 92%, m.p. 95-96 °C (lit.[1] 95-96 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (d, 2H, *J* 9.2 Hz, ArH), 6.60 (d, 2H, *J* 9.2Hz, ArH), 3.82 [t, 4H, *J* 4.6 Hz, 2 (-O-CH_2-)], 3.60 [s, 2H, 2 (-OH)], 3.54 [t, 4H, *J* 4.8 Hz, 2 (-N-CH_2-)].

Compound 3d. White solid, yield 80%, m.p. 65-66 °C (lit.[3] 65-67 °C); ^{1}H NMR (400 MHz, $CDCl_3$): 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-CH_2-)], 3.51 [t, 4H, *J* 4.8 Hz, 2 (-N-CH_2-)], 2.30 (s, 3H, -CH_3).

Compound 3e. White solid, yield 95%, m.p. 86-87 °C (lit.[4] 90-92 °C); ^{1}H NMR (400 MHz, $CDCl_3$): 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-CH_2-)], 3.54 [t, 4H, *J* 4.8 Hz, 2 (-N-CH_2-)].

Compound 3f. White solid, yield 90%, m.p. 102-103 °C (lit.[3] 103-104 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.42 (s, 1H, ArH), 6.31 (s, 2H, ArH), 3.81 [t, 4H, *J* 4.8 Hz, 2 (-O-CH_2-)], 3.53 [t, 4H, *J* 4.4 Hz, 2 (-N-CH_2-)], 2.26 [s, 6H, 2(-CH_3)].

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

A mixture of substituted aniline (10 mmol), 2-chloroethanol (2 mL), $CaCO_3$ (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 $MgSO_4$, 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); ^{1}H NMR (400 MHz,

$CDCl_3$): δ 7.48-7.55 (m, 2H, ArH), 7.34 (t, 1H, *J* 8.4Hz, ArH), 6.98 (t, 1H, *J* 4.2 Hz ,ArH), 3.91 [t, 4H, *J* 5.0Hz, 2 (-O-CH_2-)], 3.67 [t, 4H, *J* 4.8 Hz, 2 (-N-CH_2-)], 3.48 [s, 2H, 2 (-OH)].

Compound 3h. White solid, yield 62%, m.p. 81-82 °C (lit.[6] 75-78°C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, 2H, *J* 8.4 Hz, ArH), 6.54 (d, 2H, *J* 8.8Hz, ArH), 3.92 [s, 2H, 2 (-OH)], 3.79 [t, 4H, *J* 4.4Hz, 2 (-O-CH_2-)], 3.52 [t, 4H, *J* 4.8 Hz, 2 (-N-CH_2-)].

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 CH_2Cl_2. To the above vigorously stirred system, 1,2-benzenedicarbonyl chloride **1** (0.61 g, 3 mmol) in CH_2Cl_2 (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 × 3) and dried over anhydrous $MgSO_4$. 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. $C_{19}H_{19}NO_4$. White solid (56%), m.p. 135-136 °C; IR (KBr): 3066, 2957, 2919, 1712, 1611, 1519, 1453, 1294, 1130, 798, 736, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 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-CH_2-)], 3.80 [t, 4H, *J* 4.0 Hz, 2 (-N-CH_2-)], 2.27 (s, 3H, -CH_3); Anal. Calcd. for $C_{19}H_{19}NO_4$: 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. $C_{19}H_{19}NO_5$. White solid (22%), m.p. 138-139 °C; IR (KBr): 2993, 2958, 2922, 1714, 1608, 1514, 1453, 1296, 1129, 811, 735, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 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-CH_2-)], 3.78 [t, 4H, J 4.2 Hz, 2 (-N-CH_2-), 3.77 [s, 3H, -OCH_3]; Anal. Calcd. for $C_{19}H_{19}NO_5$: 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. $C_{18}H_{16}ClNO_4$. White solid (38%), m.p. 155-156 °C; IR (KBr): 3072, 2929, 1713, 1592, 1502, 1375, 1285, 1111, 1008, 796, 737, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 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-CH_2-)], 3.80 [t, 4H, *J* 4.2 Hz, 2 (-N-CH_2-)]; Anal. Calcd. for $C_{18}H_{16}ClNO_4$: 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. $C_{19}H_{19}NO_4$. White solid (42%), m.p. 144-145 °C; IR (KBr): 3035, 2937, 2857, 1715, 1601, 1497, 1444, 1293, 1130, 772, 745, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 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-CH_2-)], 3.82 [t, 4H, *J* 4.4 Hz, 2 (-N-CH_2-)], 2.35 (s, 3H, -CH_3); Anal. Calcd. for $C_{19}H_{19}NO_4$: 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. $C_{18}H_{16}ClNO_4$. White solid (30%), m.p. 198-199 °C; IR (KBr): 2924, 2860, 1716, 1594, 1492, 1388, 1293, 1132, 830, 745, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 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-CH_2-)], 3.81 [t, 4H, *J* 2.2 Hz, 2 (-N-CH_2-)]; Anal. Calcd. for $C_{18}H_{16}ClNO_4$: 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. $C_{20}H_{21}NO_4$. White solid (36%), m.p. 151-152 °C; IR (KBr): 2923, 2856, 1713, 1596, 1476, 1361, 1283, 1129, 818, 741, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 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-CH_2-)], 3.80 [t, 4H, *J* 4.0 Hz, 2 (-N-CH_2-)], 2.31 [s, 6H, 2 (-CH_3); Anal. Calcd. for $C_{20}H_{21}NO_4$: 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. $C_{18}H_{16}N_2O_6$. Yellow solid (45%), m.p. 165-166 °C; IR (KBr): 2998, 2928, 2856, 1716, 1613, 1524, 1441, 1352, 1293, 1131, 789, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 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-CH_2-)],

3.90 [t, 4H, *J* 4.2 Hz, 2 (-N-CH_2-)]; Anal. Calcd. for $C_{18}H_{16}N_2O_6$: 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. $C_{18}H_{16}BrNO_4$. 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, $CDCl_3$): 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-CH_2-)], 3.80 [t, 4H, *J* 4.0 Hz, 2 (-N-CH_2-)]; Anal. Calcd. for $C_{18}H_{16}BrNO_4$: 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 $[M+Na]^+$.

Rerference

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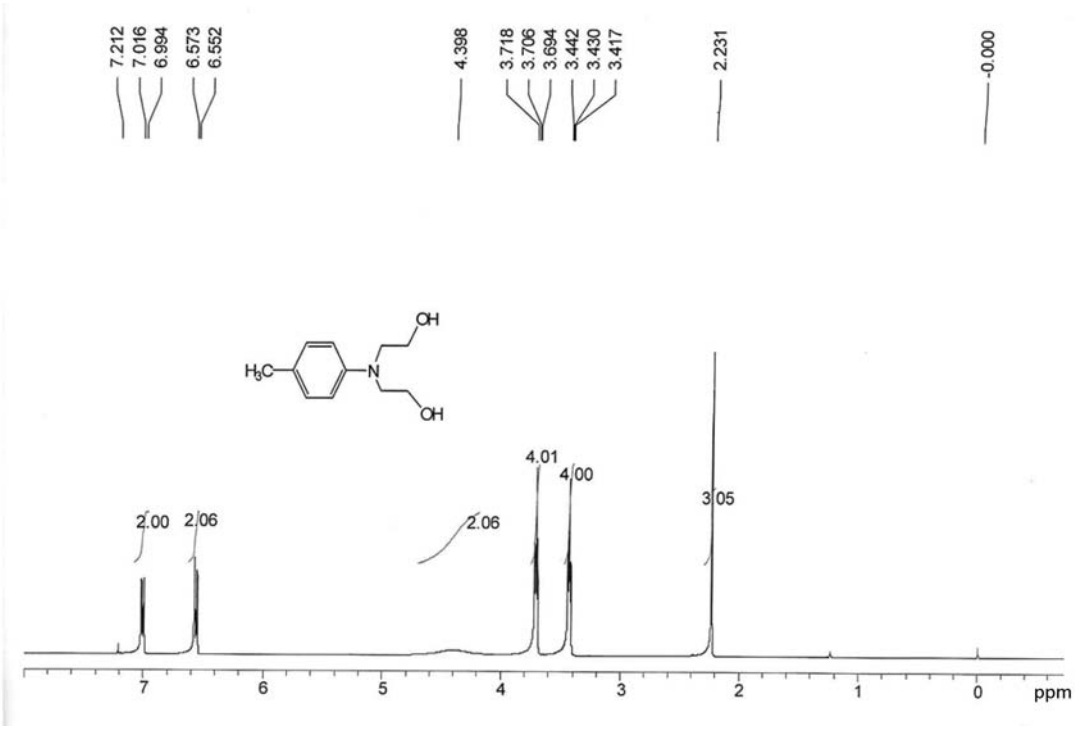

Figure S1. ^1H NMR spectrum (400 MHz, $CDCl_3$) of compound **3a**.

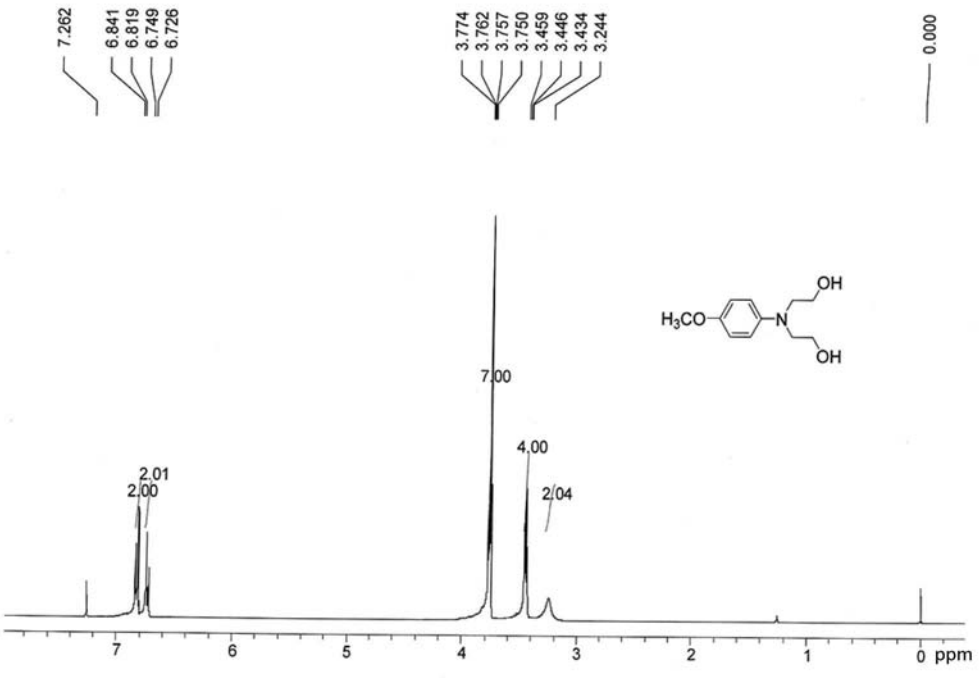

Figure S2. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **3b**.

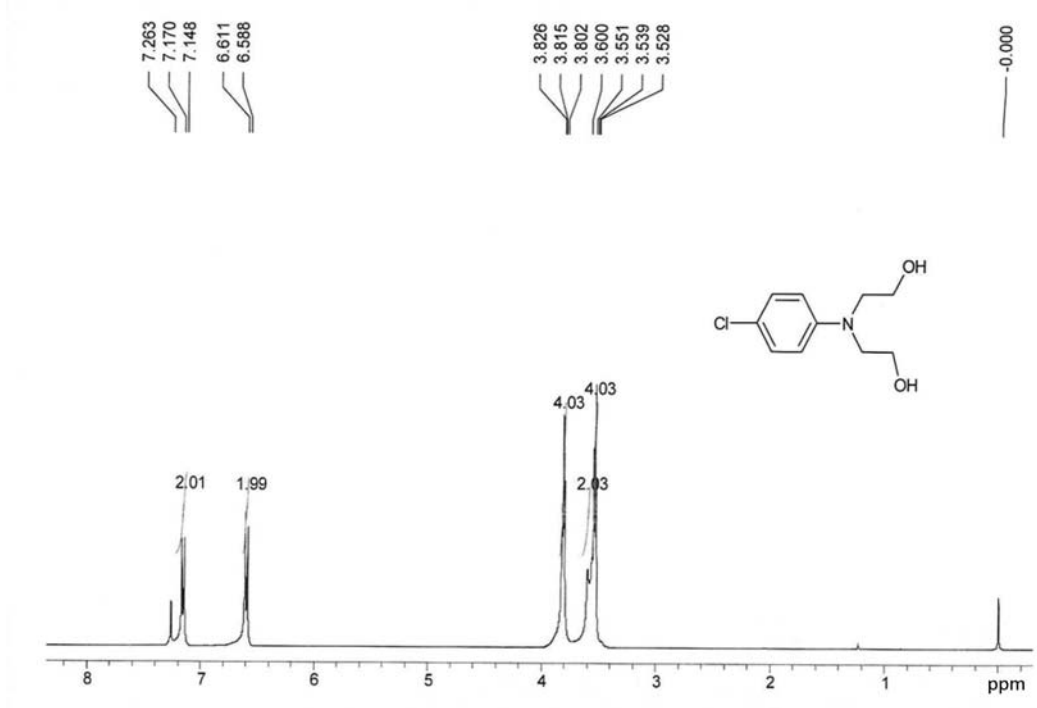

Figure S3. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **3c**.

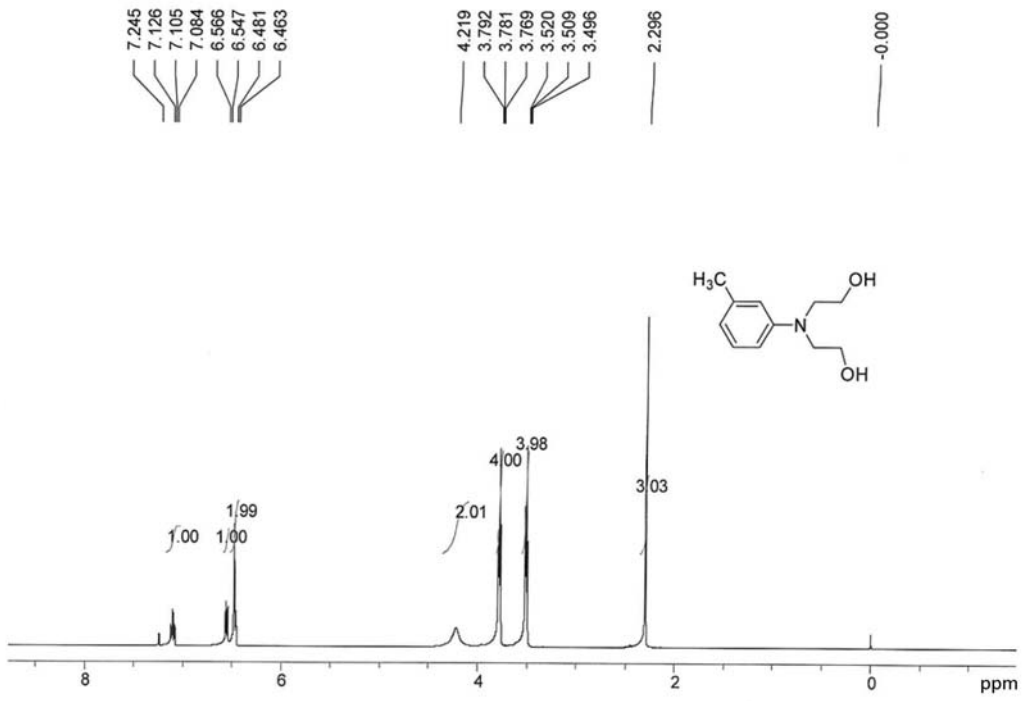

Figure S4. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **3d**.

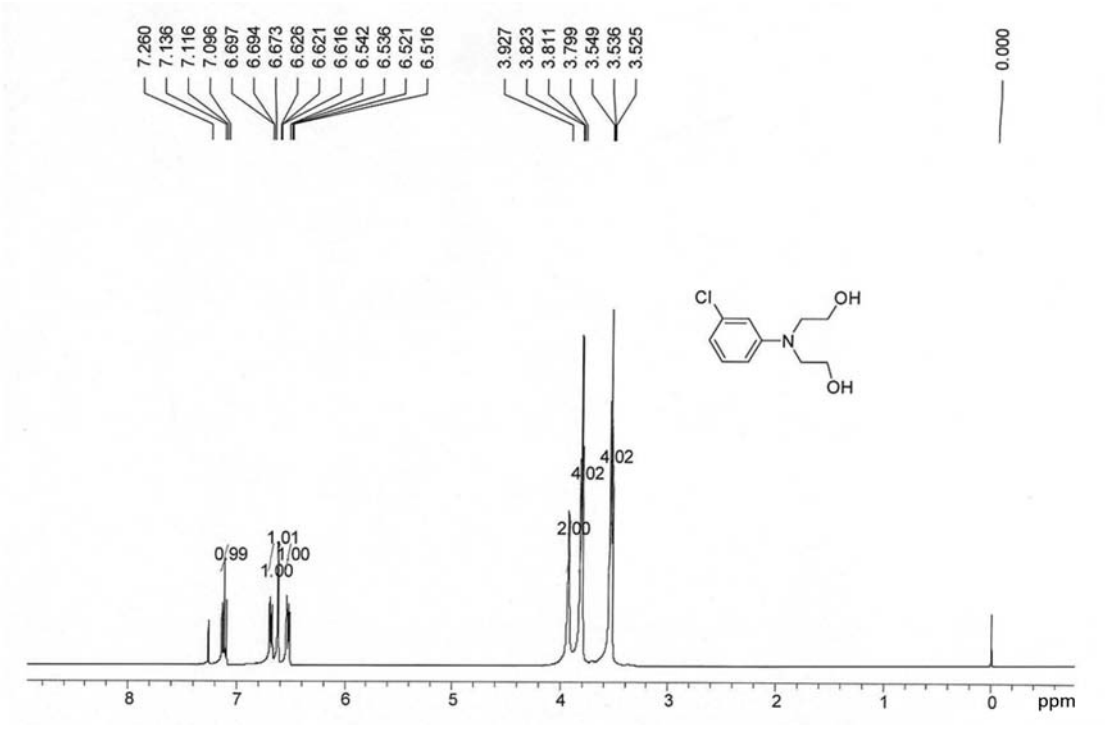

Figure S5. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **3e**.

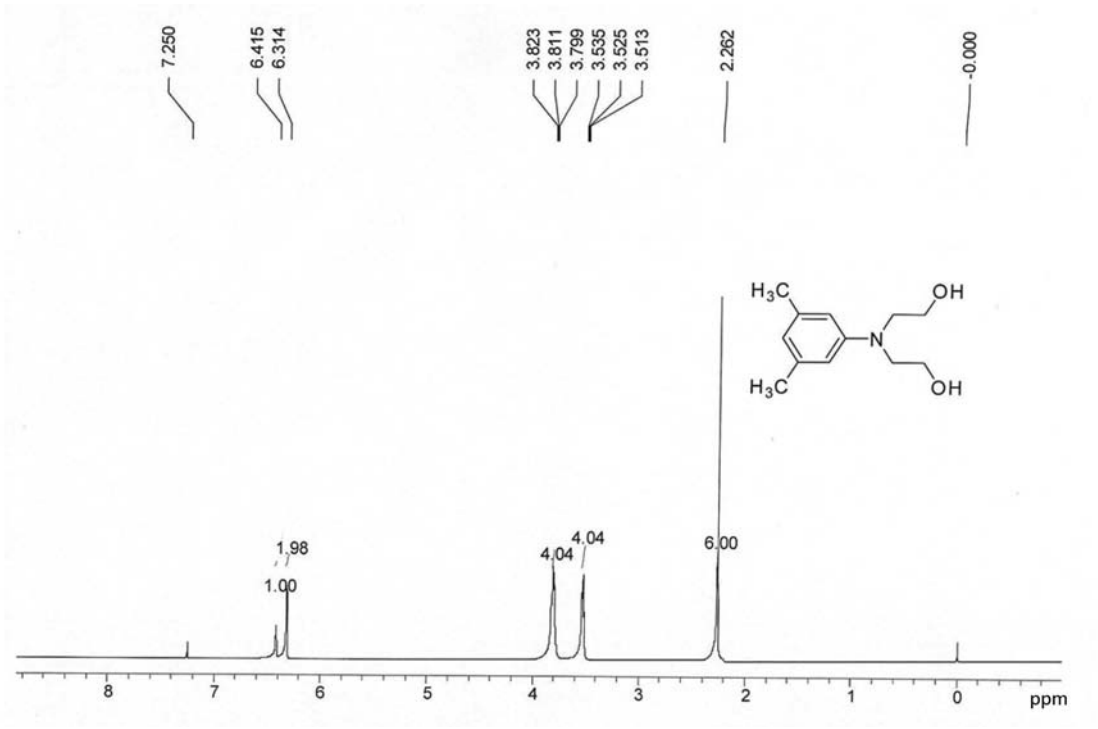

Figure S6. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **3f**.

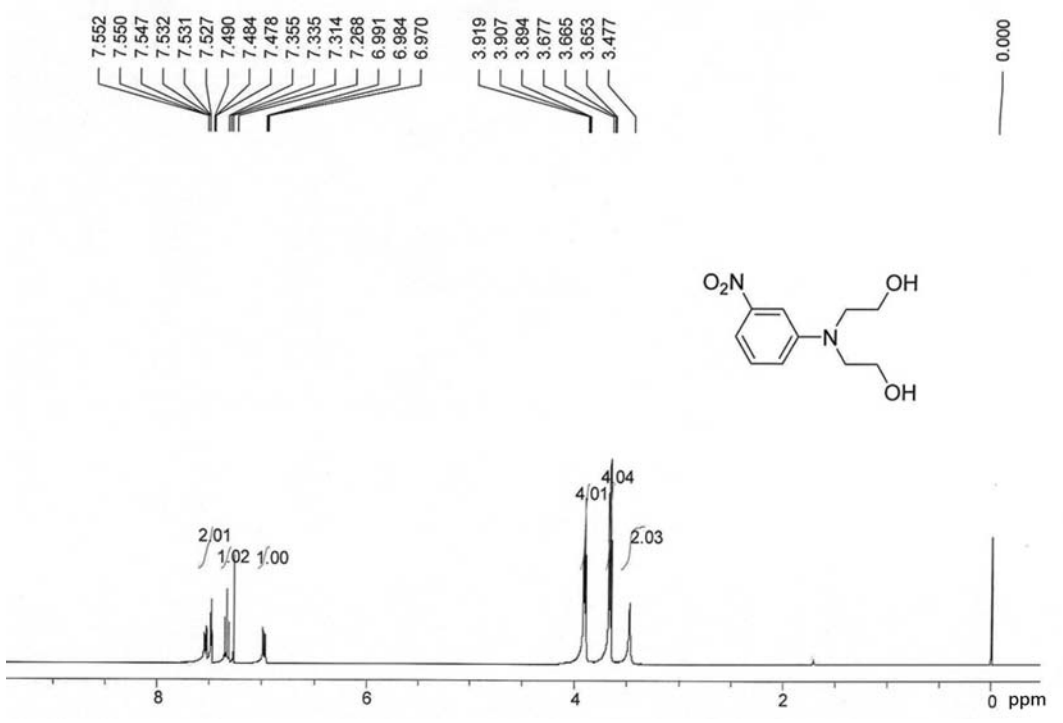

Figure S7. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **3g**.

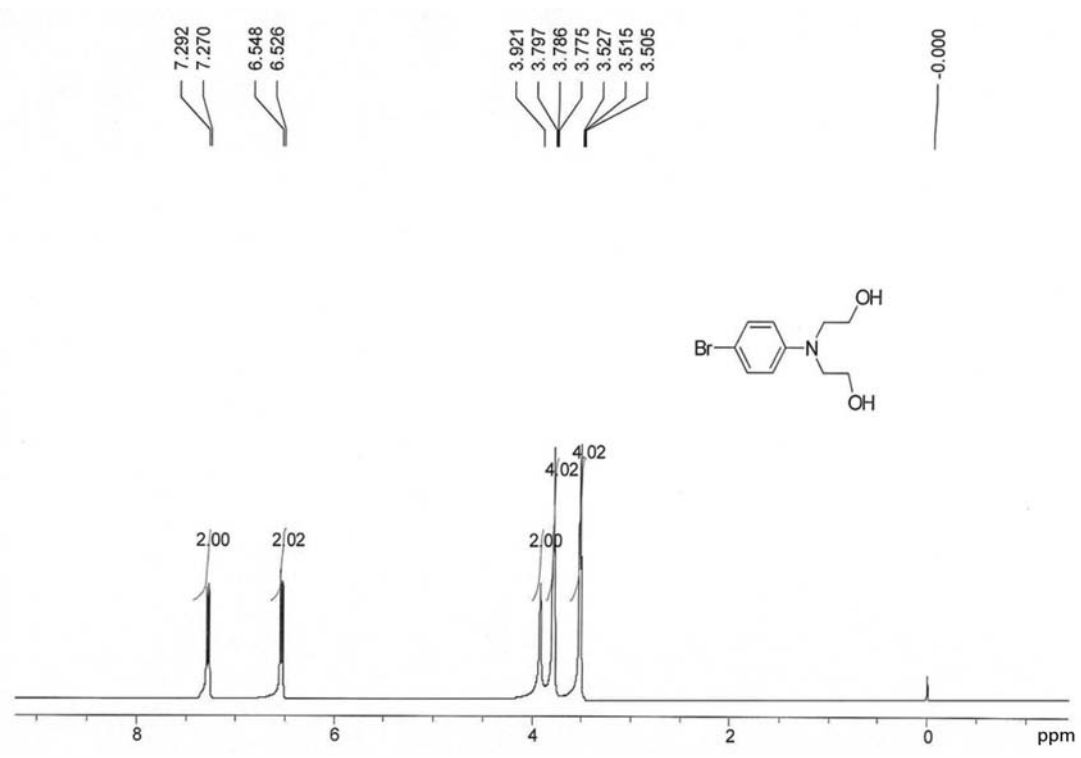

Figure S8. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **3h**.

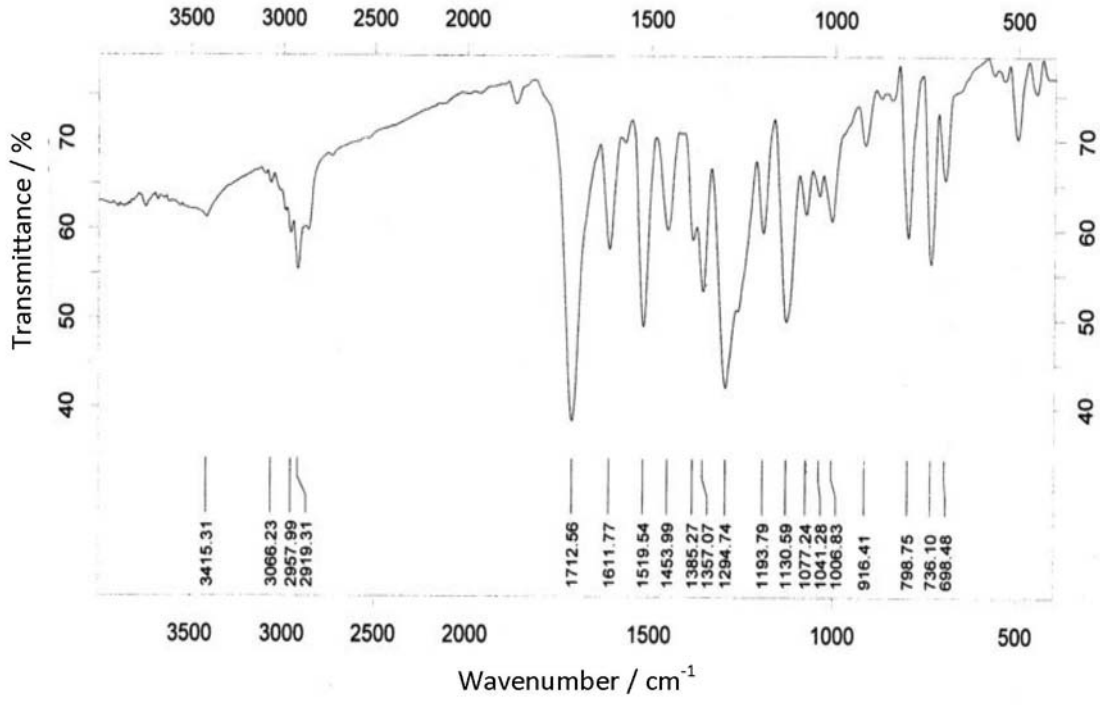

Figure S9. IR of compound **4a**.

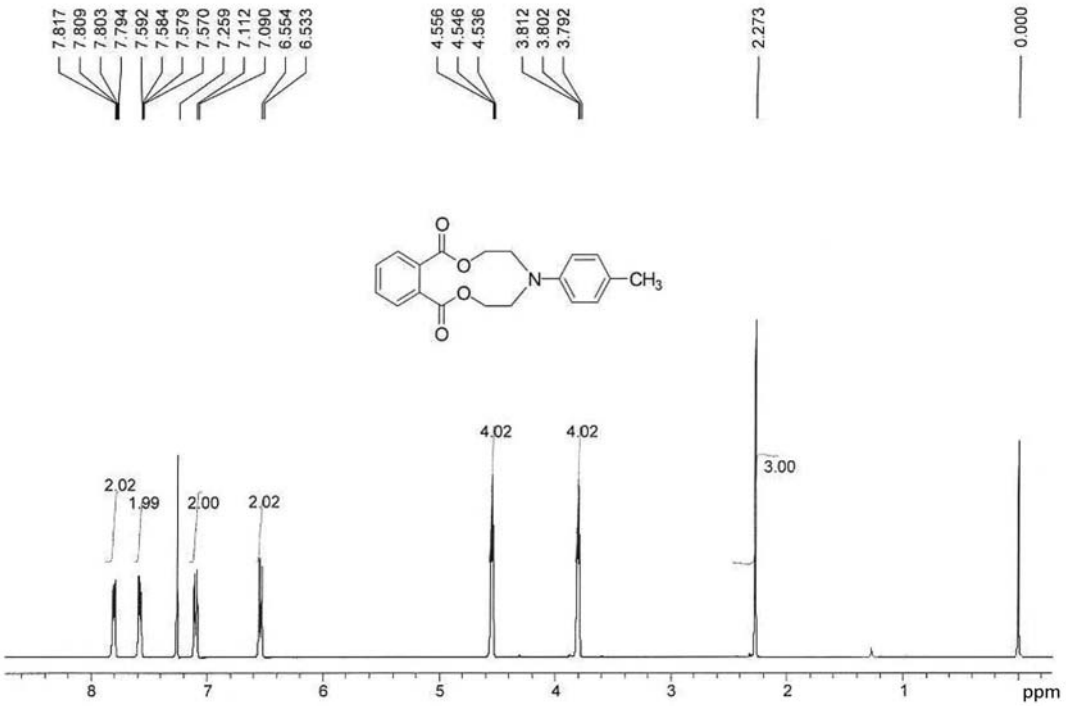

Figure S10. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **4a**.

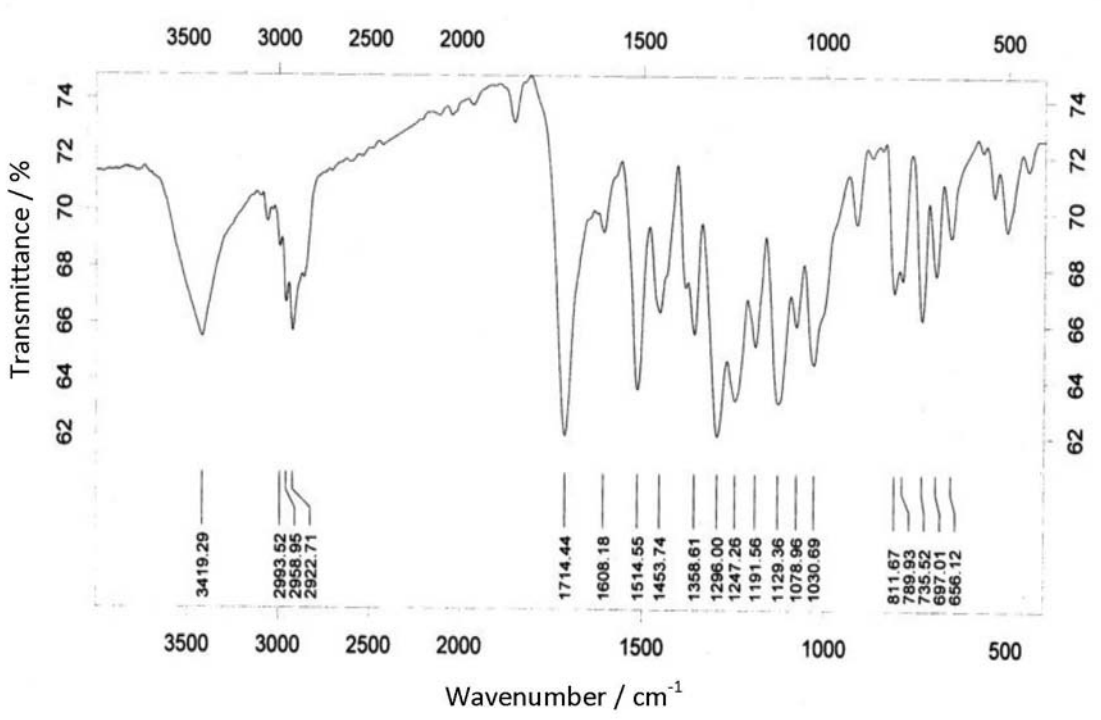

Figure S11. IR of compound **4b**.

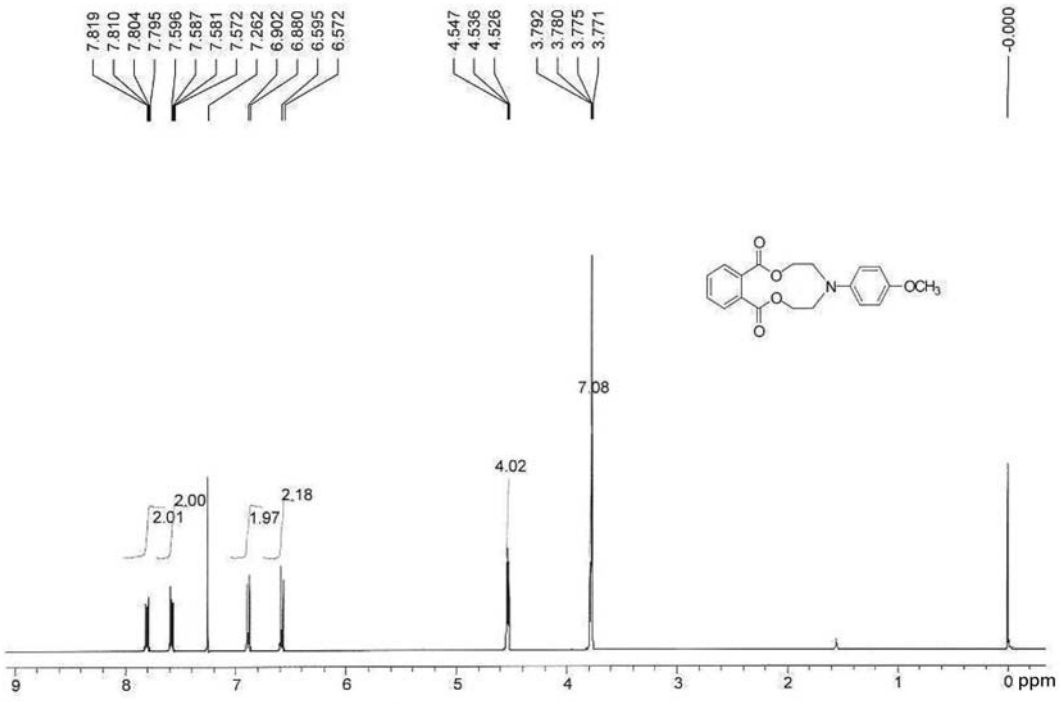

Figure S12. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **4b**.

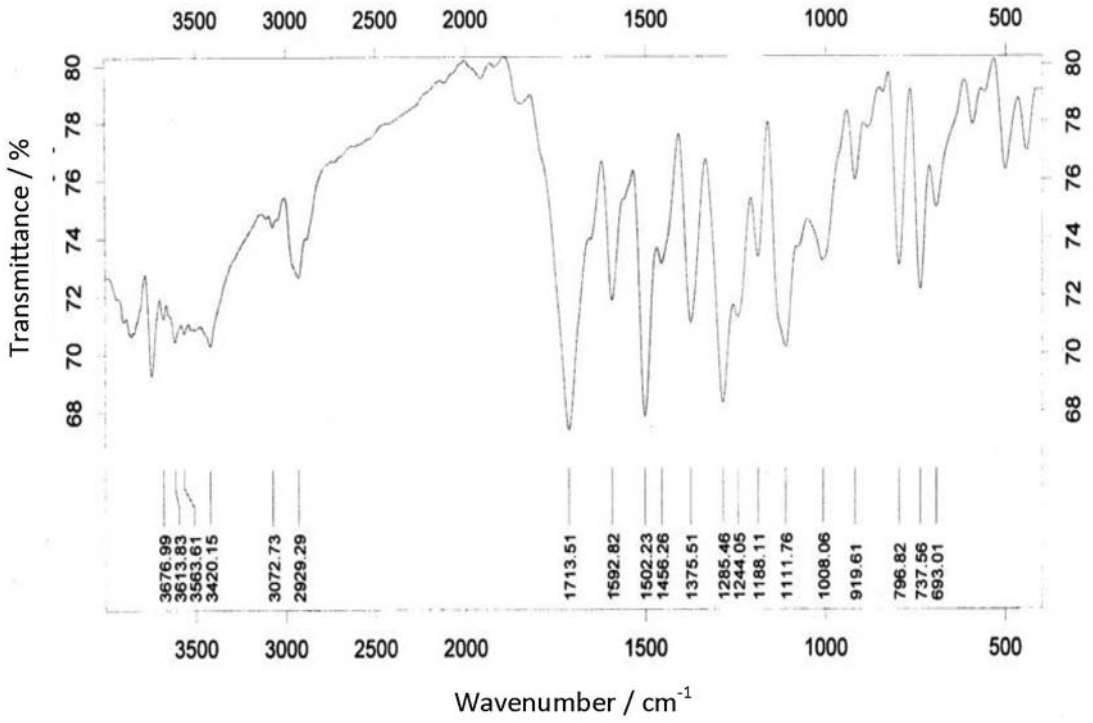

Figure S13. IR of compound **4c**.

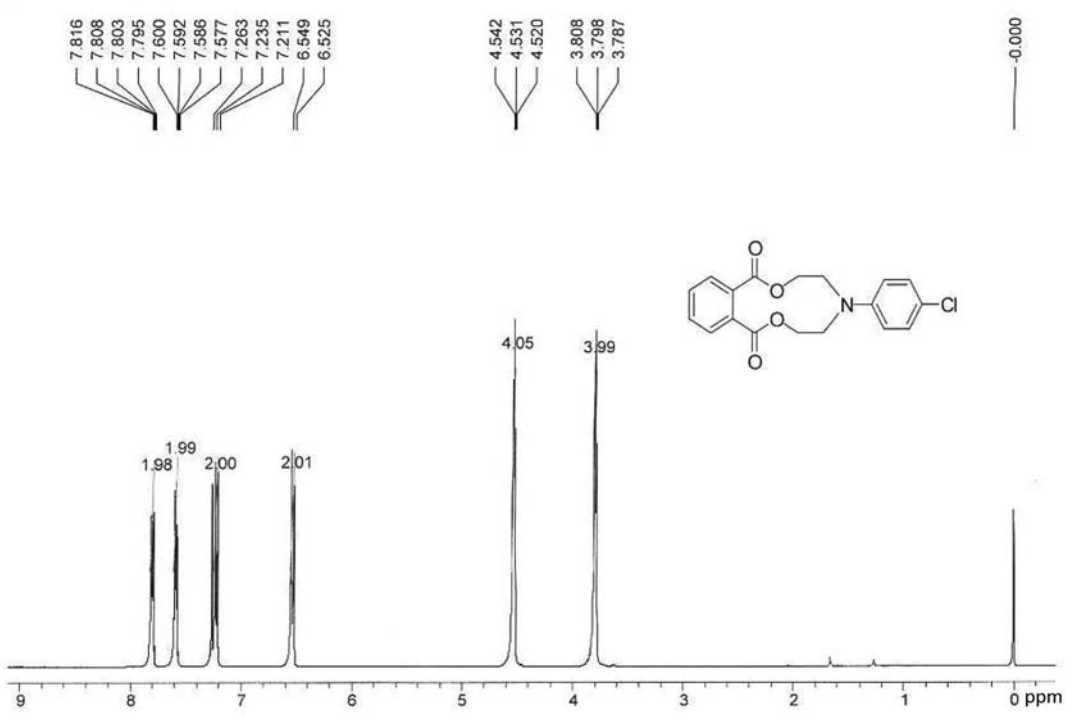

Figure S14. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **4c**.

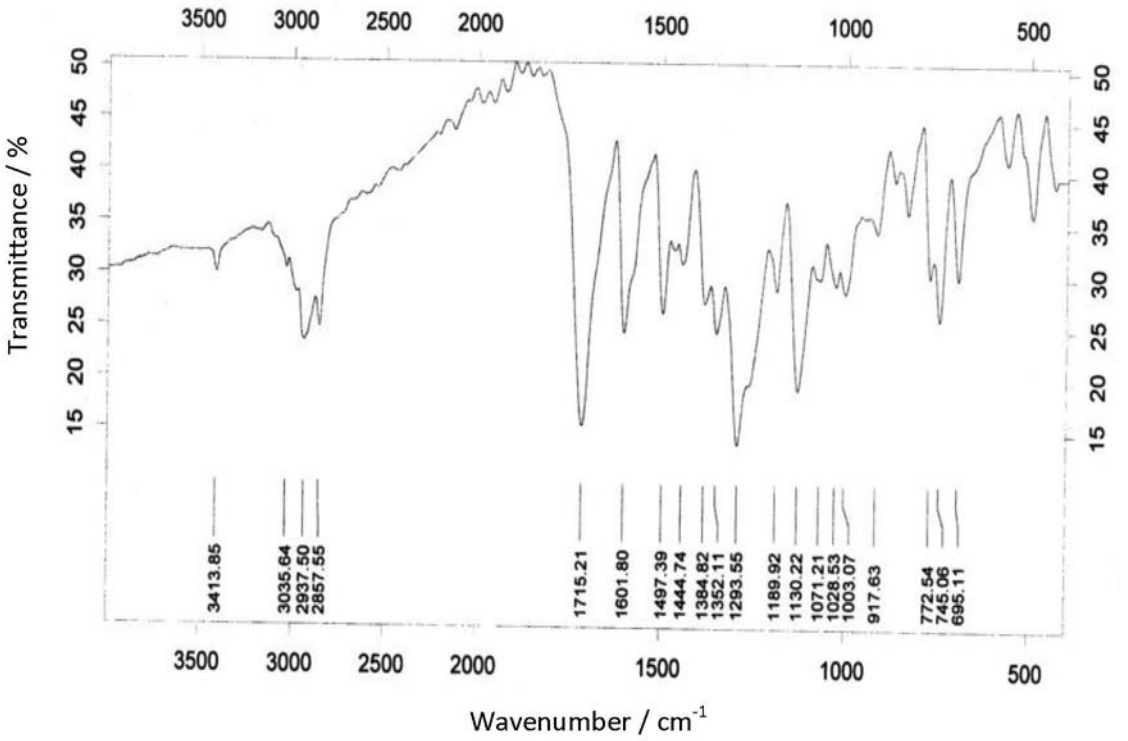

Figure S15. IR of compound **4d**.

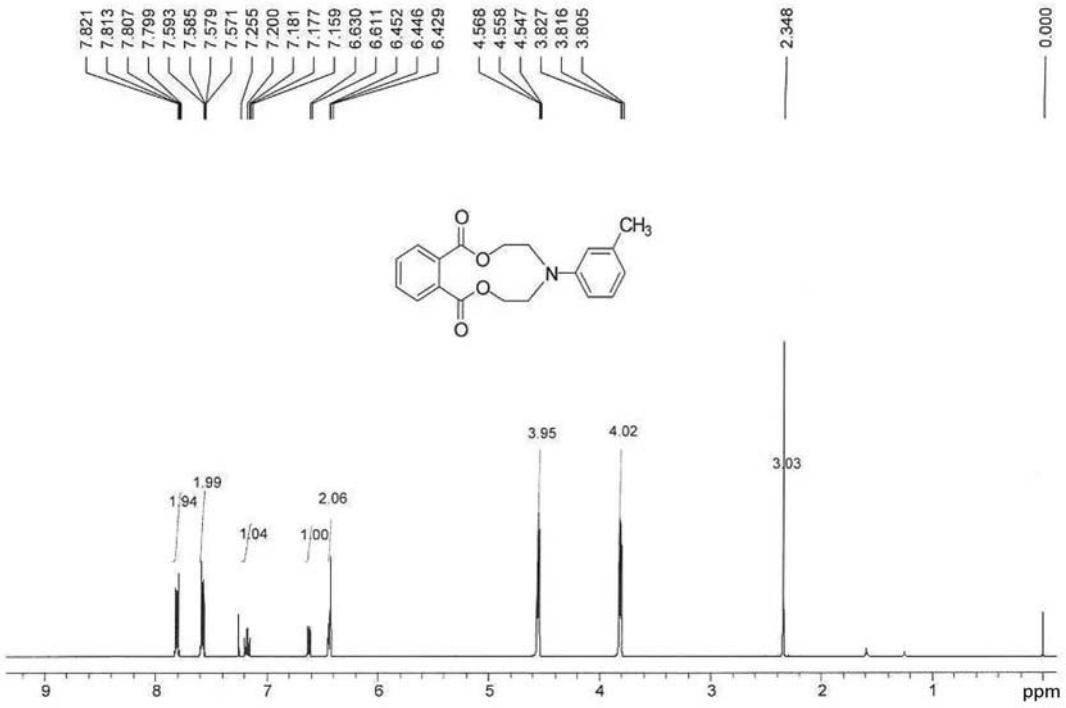

Figure S16. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **4d**.

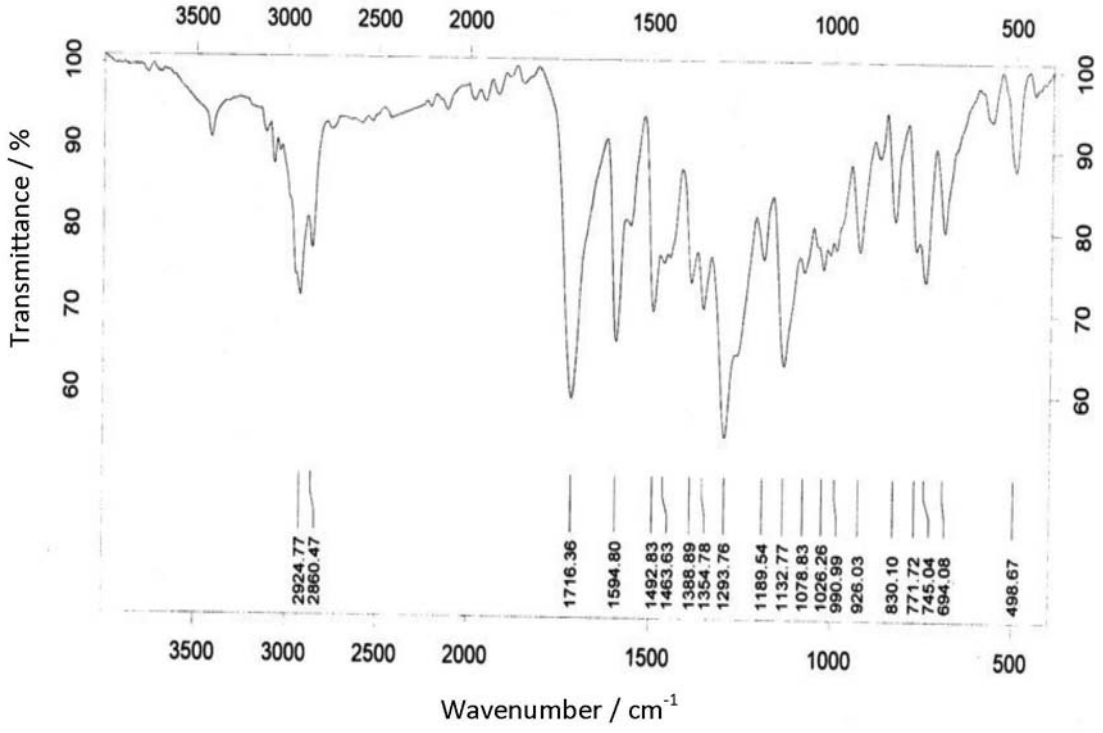

Figure S17. IR of compound **4e**.

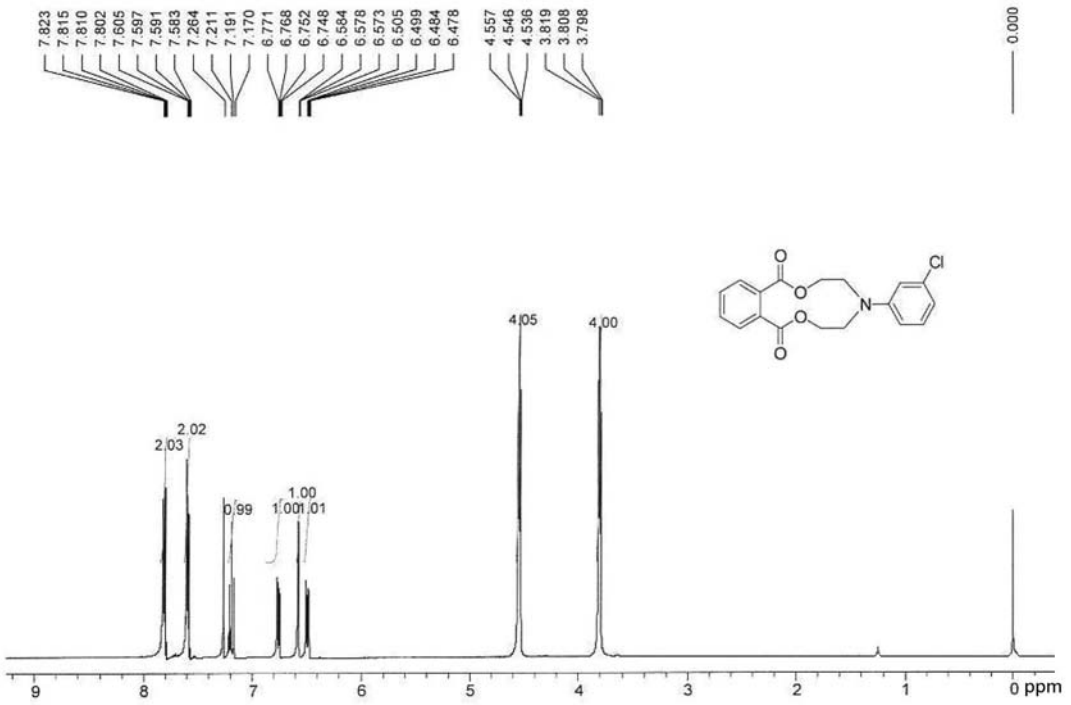

Figure S18. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **4e**.

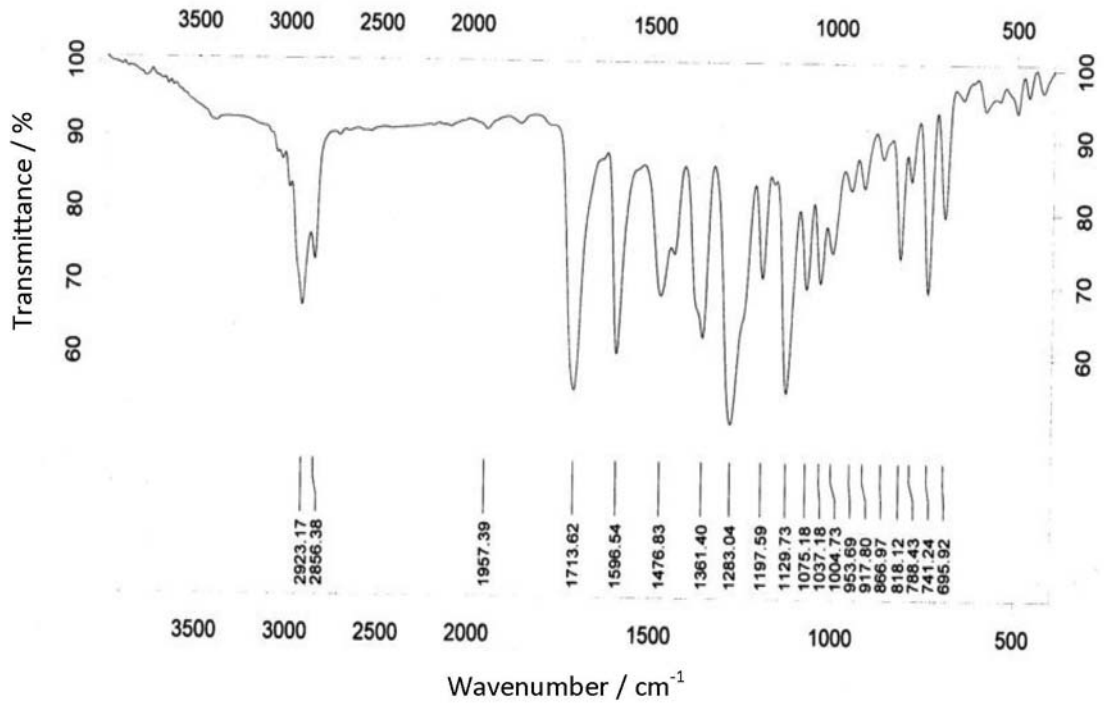

Figure S19. IR of compound **4f**.

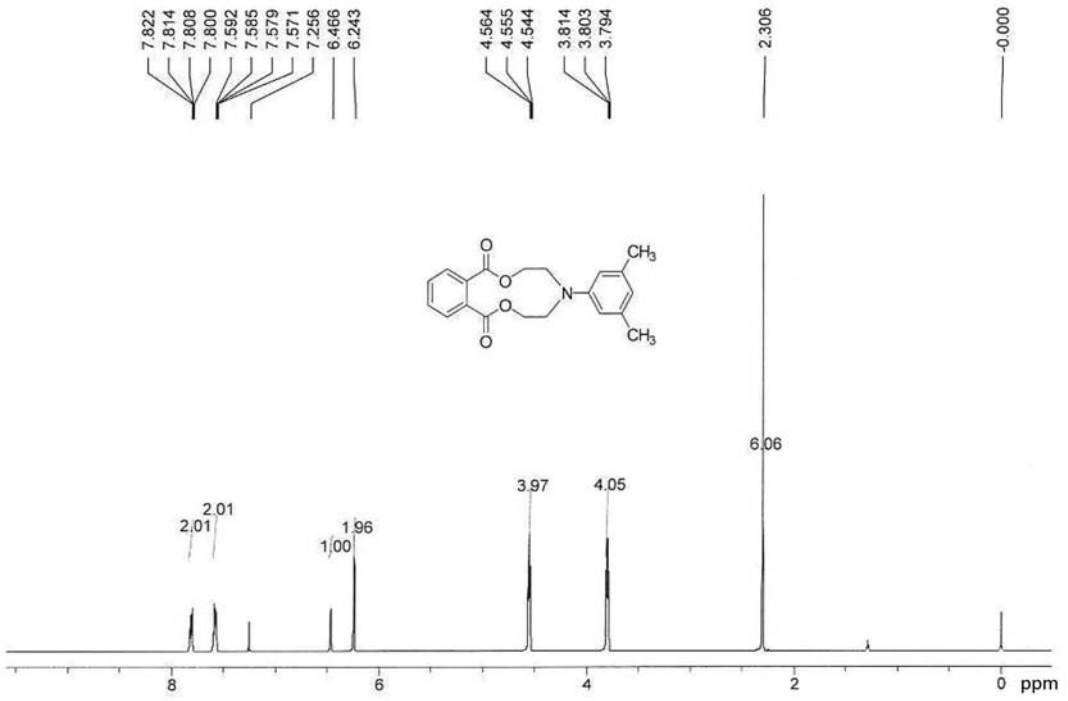

Figure S20. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **4f**.

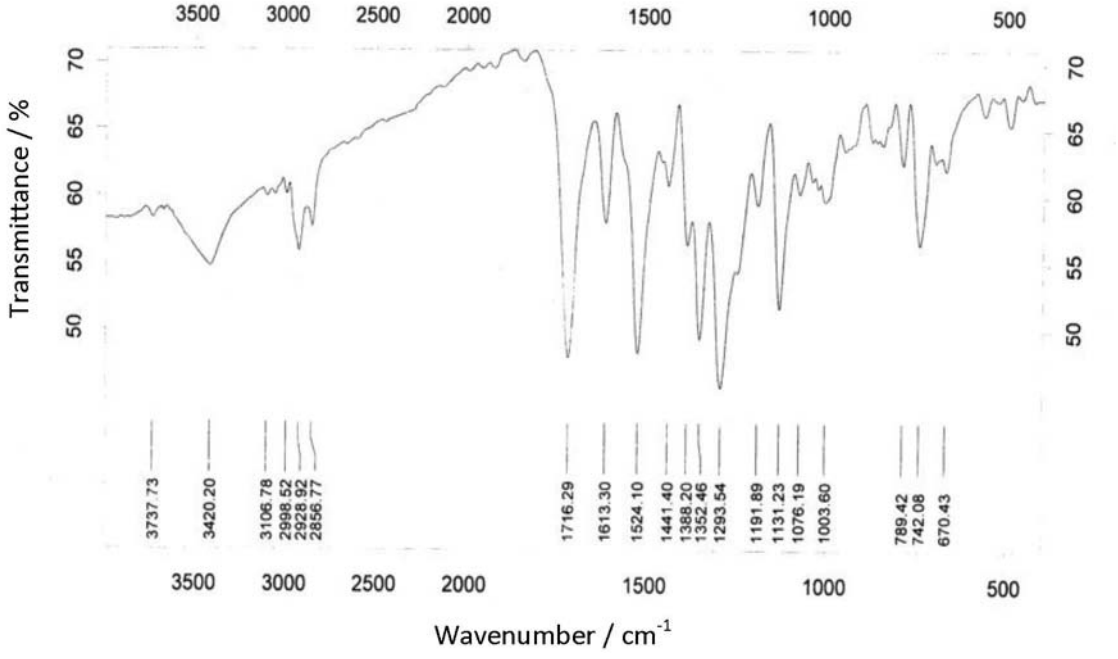

Figure S21. IR of compound **4g**.

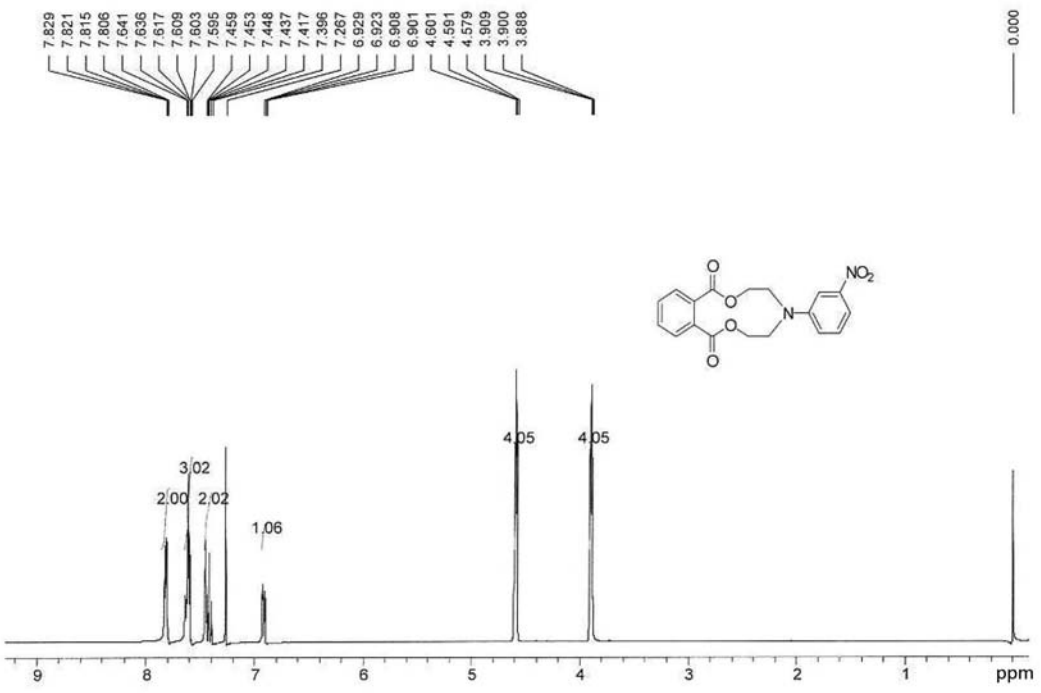

Figure S22. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **4g**.

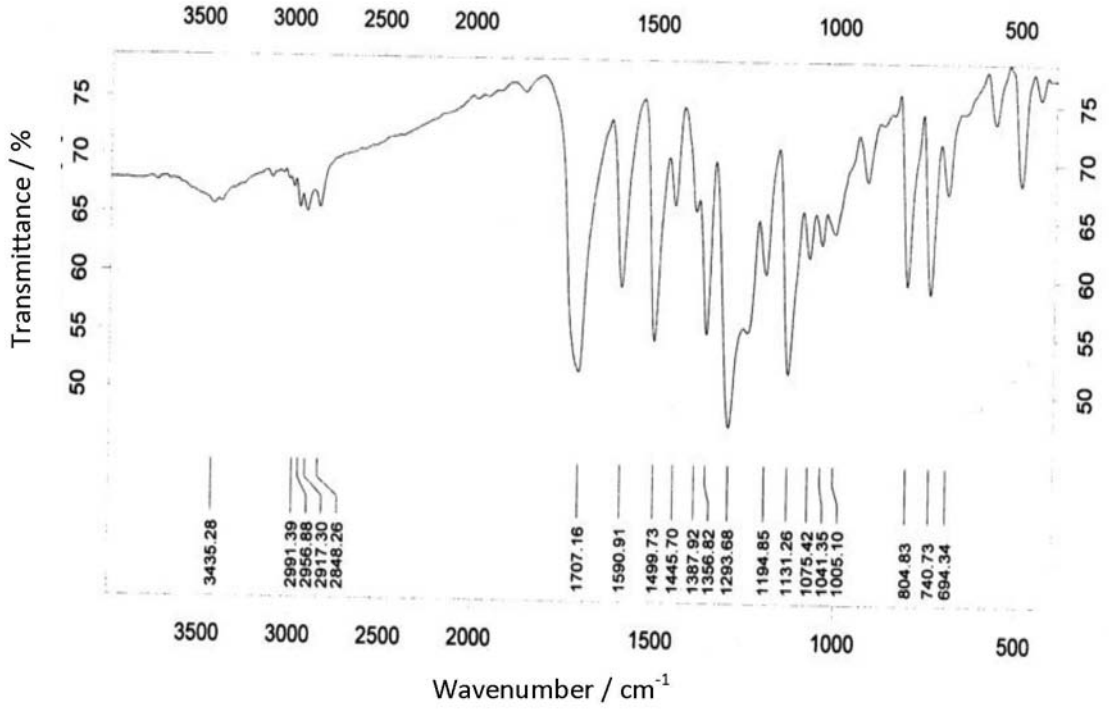

Figure S23. IR of compound **4h**.

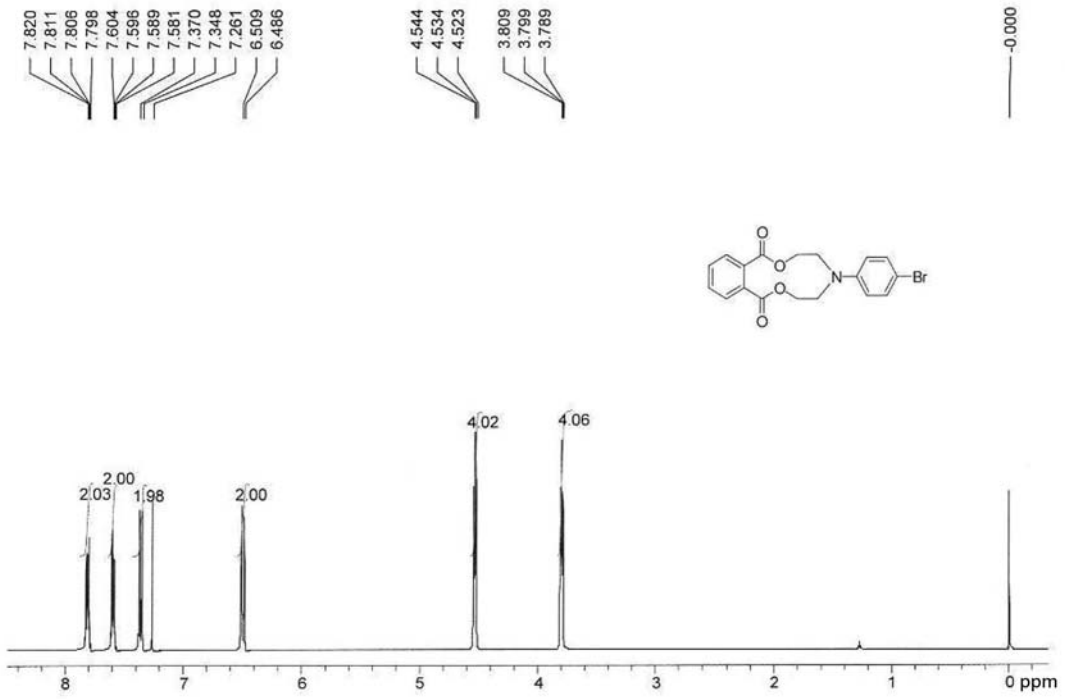

Figure S24. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **4h**.