Supporting Information

Synthesis, structure–activity relationship studies and evaluation of a TLR 3/8/9 agonist and its analogues

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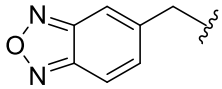
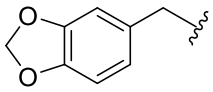
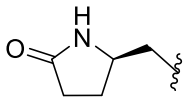
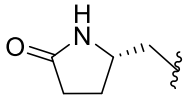
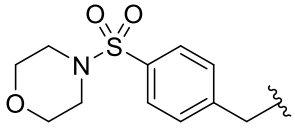
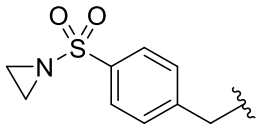
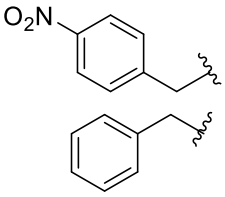
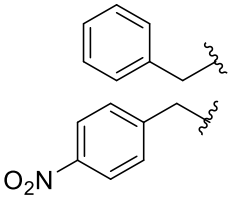
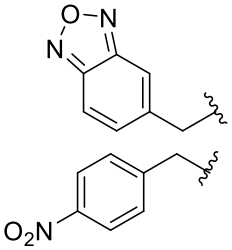
Table 1. NF-κB activation of compounds **1**, **9**-**67** in hTLR3, hTLR8, hTLR9 and hTLR7 HEK-blue reporter cells

Compound	R	TLR NF-κB activation (μM)			
		TLR3	TLR8	TLR9	TLR7
1	4-NO_2PhCH_2	22 4.80 (ref 19)	27 13.5 (ref 19)	58 5.7 (ref 19)	>50 >100 (ref 19)
9	2-naphthylCH_2	ND[a]	>5	>5	>5
10	4-PhPhCH_2	ND[a]	>5	>5	>5
11	4-pyridylCH_2	ND[a]	>5	>5	>5
12	4-CNPhCH_2	ND[a]	>5	>5	>5
13		ND[a]	>100	>100	>100
14	3,4-F_2PhCH_2	ND[a]	>5	>5	>5
15		ND[a]	>5	>5	>5
16	5-benzthienylCH_2	ND[a]	>5	>5	>5
17	NBoc-5-indoylCH_2	ND[a]	>5	>5	>5
18	6-benzthiazolylCH_2	ND[a]	>100	>100	>100
19	4-(1,2,3-thiadiazol-4-yl)PhCH_2	ND[a]	>5	>5	>5

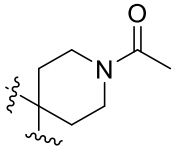
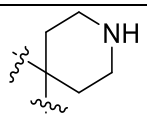
20	3-(4-CF_3)pyridylCH_2	ND[a]	>5	>5	>5
21	3-(4-NO_2)pyridylCH_2	ND[a]	>5	>5	>5
22	3,4-Cl_2PhCH_2	ND[a]	>5	>5	>5
23	3-Me,4-NO_2PhCH_2	ND[a]	>5	>5	>5
24	3-MeO,4-NO_2PhCH_2	ND[a]	>100	>100	>100
25	2-F,4-NO_2PhCH_2	ND[a]	>5	>5	>5
26	4-MeO_2CPhCH_2	ND[a]	>5	>5	>5
27	4-HO_2CPhCH_2	ND[a]	>5	>5	>5
28	4-MeC(O)PhCH_2	ND[a]	>5	>5	>5
29	3-NO_2PhCH_2	ND[a]	>5	>5	>5
30	2-NO_2PhCH_2	ND[a]	>5	>5	>5
31	4-CF_3PhCH_2	ND[a]	>5	>5	>5
32	4-NO_2PhC(O)	ND[a]	>5	>5	>5
33	3-CF_3PhCH_2	ND[a]	>5	>5	>5
34	2-CF_3PhCH_2	ND[a]	>5	>5	>5
35	4-CF_3OPhCH_2	ND[a]	>5	>5	>5
36	3-CNPhCH_2	ND[a]	>5	>5	>5
37	2-CNPhCH_2	ND[a]	>5	>5	>5
38	2-pyridylCH_2	ND[a]	>5	>5	>5
39	3-pyridylCH_2	ND[a]	>5	>5	>5
40	4-ClPhCH_2	ND[a]	>5	>5	>5
41	3-ClPhCH_2	ND[a]	>5	>5	>5
42	2-ClPhCH_2	ND[a]	>5	>5	>5
43	3-MeOPhCH_2	ND[a]	>5	>5	>5

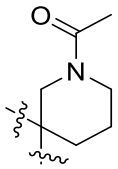
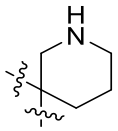
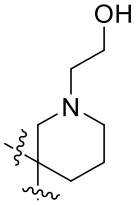
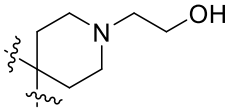
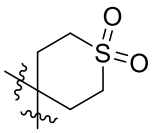
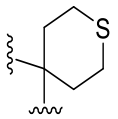
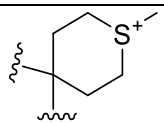
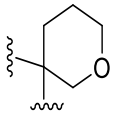
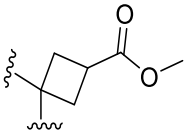
44	2-MeOPhCH$_2$	ND[a]	>5	>5	>5
45	3-CF$_3$OPhCH$_2$	ND[a]	>5	>5	>5
46	4-FPhCH$_2$	ND[a]	>5	>5	>5
47	3-FPhCH$_2$	ND[a]	>5	>5	>5
48	2-FPhCH$_2$	ND[a]	>5	>5	>5
49	4-MePhCH$_2$	ND[a]	>5	>5	>5
50	3-MePhCH$_2$	ND[a]	>5	>5	>5
51	2-MePhCH$_2$	ND[a]	>5	>5	>5
52	4-*t*BuPhCH$_2$	ND[a]	>5	>5	>5
53	PhCH$_2$	ND[a]	>5	>5	>5
54	7-quinolylCH$_2$	ND[a]	>5	>5	>5
55	5-nitrofuran-2-yl-CH$_2$	ND[a]	>100	>100	>100
56	5-nitrothiophen-2-yl-CH$_2$	ND[a]	>100	>100	>100
57		ND[a]	>5	>5	>5
58		ND[a]	>5	>5	>5
59	4-MeSO$_2$PhCH$_2$	ND[a]	>5	>5	>5
60	4-FSO$_2$PhCH$_2$	ND[a]	>5	>5	>5
61	4-MeOSO$_2$PhCH$_2$	ND[a]	>5	>5	>5
62		ND[a]	>5	>5	>5
63	Me$_2$NSO$_2$PhCH$_2$	ND[a]	>5	>5	>5

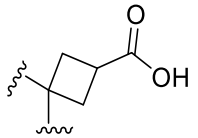
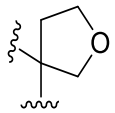
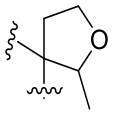
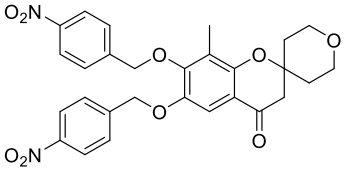
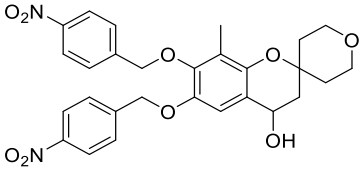
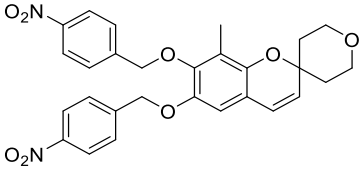
64		ND[a]	>5	>5	>5
65		ND[a]	>5	>5	>5
66		ND[a]	>5	>5	>5
67		ND[a]	>5	>5	>5

[a]ND: Not determined.

Table 2. NF-κB activation of compounds **68-88** in hTLR3, hTLR8, hTLR9 and hTLR7 HEK-blue reporter cells

Compound No.	Substituent	TLR NF-κB activation (μM)		
		TLR8	TLR9	hTLR7
68		>5	>5	>5
69		>125	111	>125

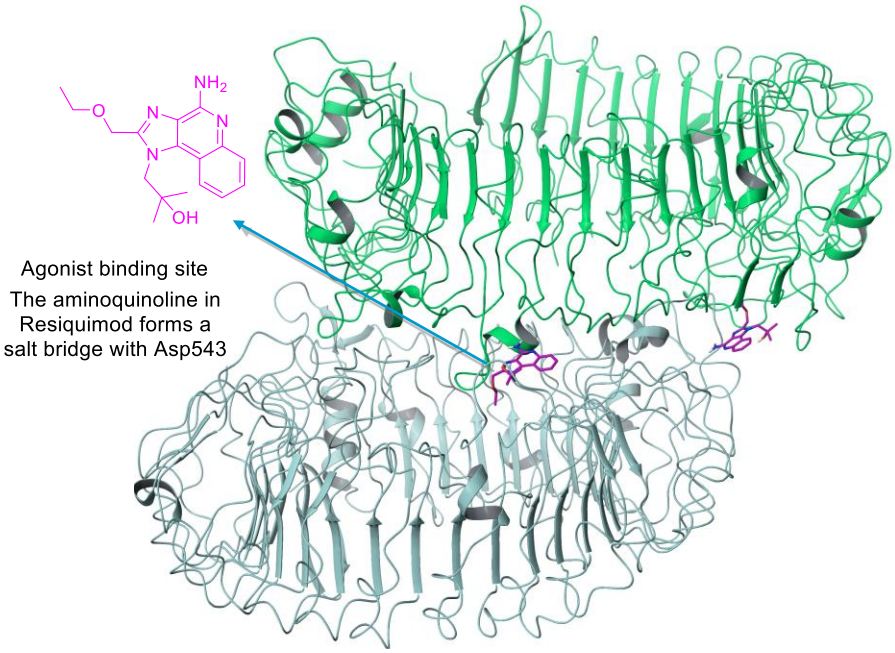
70		>5	>5	>5
71		>5	>5	>5
72		>5	>5	>5
73		>5	>5	>5
74		>5	>5	>5
75		>5	>5	>5
76		>5	>5	>5
77		>5	>5	>5
78		>5	>5	>5
79		>5	>5	>5

80		>5	>5	>5
81		>5	>5	>5
82		>5	>5	>5
86		>5	>5	>5
87		>5	>5	>5
88		>5	>5	>5

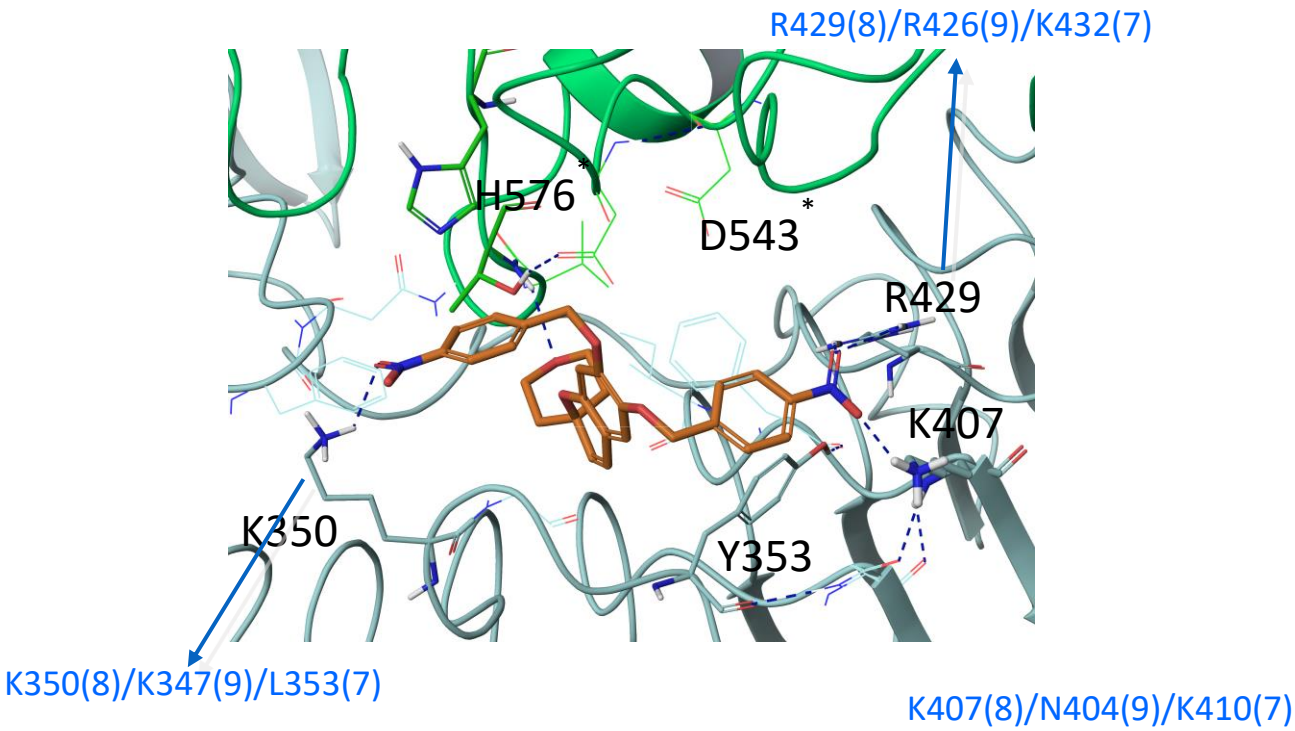
Molecular Modeling. Maestro from the Schrödinger suite of programs[S1,S2] was used for ligand building, geometry optimization, conformational analyses and overlays. hTLR8 and horse TLR9 crystal structures were downloaded from the RCSB PDB[S3] and processed using the protein preparation wizard in Maestro from the Schrödinger suite of programs.[S4,S5] Human TLR9 homology model was built using the horse TLR9 crystal structure[S6] as the template using the Prime from the Schrödinger suite of programs.[S7-S9] Compound **1** was docked in hTLR8 crystal structure and in hTLR9 homology model using the Glide program from the Schrödinger suite of programs.[S10-S13] Best docked poses of **1** were compared with the co-crystallized resiquimod- and DNA 5'-xCx agonist fragment-bound structures using the protein structure alignment tool available in Maestro from the Schrödinger suite of programs.

S1. Schrödinger Release 2016-3: Maestro, Schrödinger, LLC, New York, NY, 2016.
S2. Schrödinger Release 2018-1: Maestro, Schrödinger, LLC, New York, NY, 2018.
S3. www.rcsb.org; Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, Shindyalov IN, Bourne PE. The Protein Data Bank, Nucl Acids Res. 2000;28:235–242.

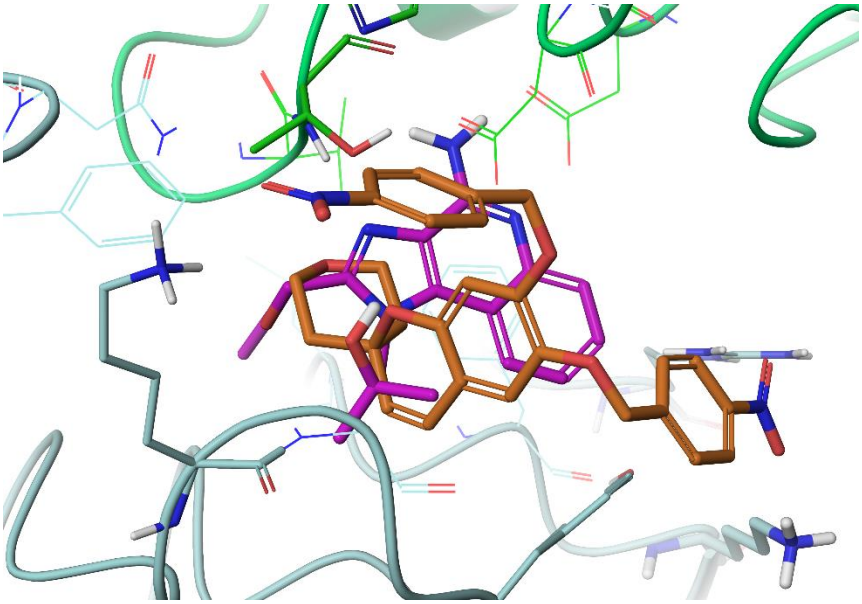
S4. Schrödinger: Protein Preparation Wizard; Epik, Schrödinger, LLC, New York, NY; Impact, Schrödinger, LLC, New York, NY; Prime, Schrödinger, LLC, New York, NY.
S5. Sastry GM, Adzhigirey M, Day T, Annabhimoju R, Sherman W. Protein and ligand preparation: Parameters, protocols, and influence on virtual screening enrichments. J Comput. Aid Mol Des. 2013;27:221–234.
S6. Ohto U, Shibata T, Tanji H, Ishida H, Krayukhina E, Uchiyama S, Miyake K, Shimizu T. Structural basis of CpG and inhibitory DNA recognition by Toll-like receptor 9. *Nature*. 2015;520:702–705.
S7. Schrödinger: Prime, Schrödinger, LLC, New York, NY.
S8. Jacobson MP, Pincus DL. Rapp CS, Day TJF, Honig B, Shaw DE, Friesner RA. A hierarchical approach to all-atom protein loop prediction. Proteins: Structure, Function and Bioinformatics. 2004;55:351–367.
S9. Jacobson MP, Friesner RA, Xiang Z, Honig B. On the role of crystal packing forces in determining protein sidechain conformations. J Mol Biol. 2002;320:597–608.
S10. Schrödinger: Glide, Schrödinger, LLC, New York, NY.
S11. Friesner RA, Murphy RB, Repasky MP, Frye LL, Greenwood JR, Halgren TA, Sanschagrin PC, Mainz DT. Extra precision Glide: Docking and scoring incorporating a model of hydrophobic enclosure for protein-ligand complexes. J Med Chem. 2006;49:6177–6196.
S12. Halgren TA, Murphy RB, Friesner RA, Beard HS, Frye LL, Pollard WT, Banks JL. Glide: A new approach for rapid, accurate docking and scoring. 2. Enrichment factors in database screening, J Med Chem. 2004;47:1750–1759.
S13. Friesner RA, Banks JL, Murphy RB, Halgren TA, Klicic JJ, Mainz DT, Repasky MP, Knoll EH, Shaw DE, Shelley M, Perry JK, Francis P, Shenkin PS. Glide: A new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. J Med Chem. 2004;47:1739–1749.



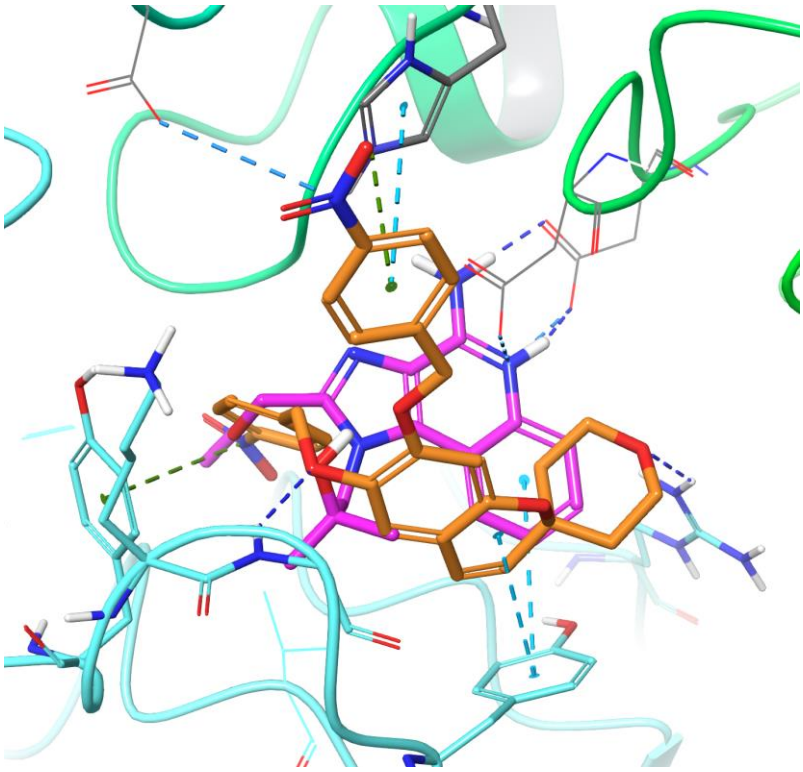
Supplementary Figure 1. hTLR8 crystal structure with Resiquimod (R848) (magenta sticks) [PDB code 3W3L]. Each protomer of dimer is colored distinctly.



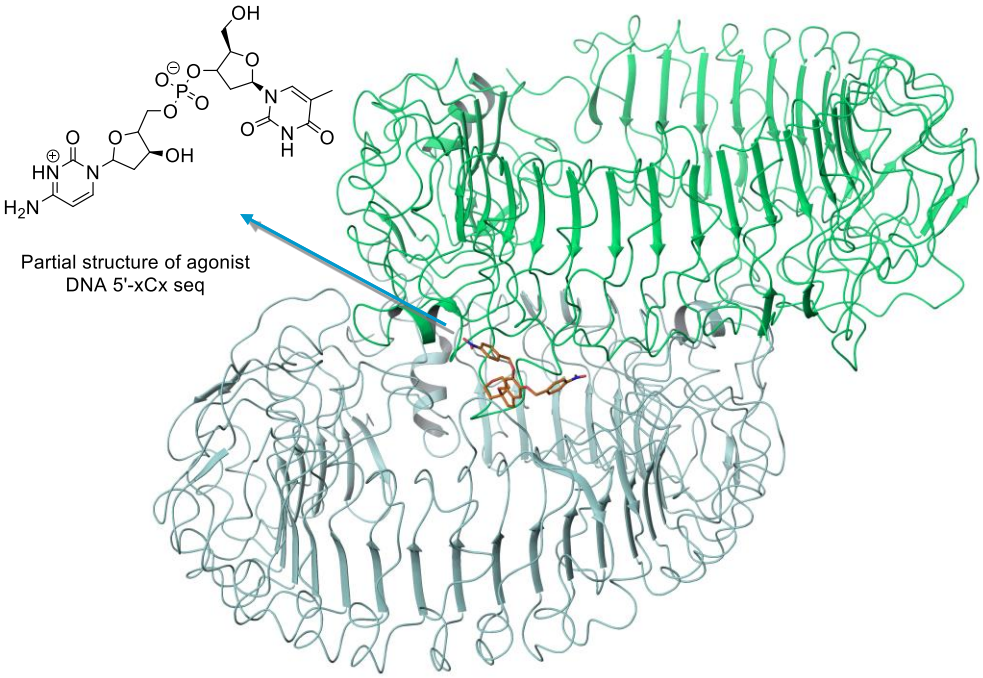
Supplementary Figure 2(a). Docked model of **1** in hTLR8 – Pose 1. The THP O atom can be seen H-bonding to T574 backbone NH, and the two Nitro groups are involved in polar interactions with arginine and lysines.



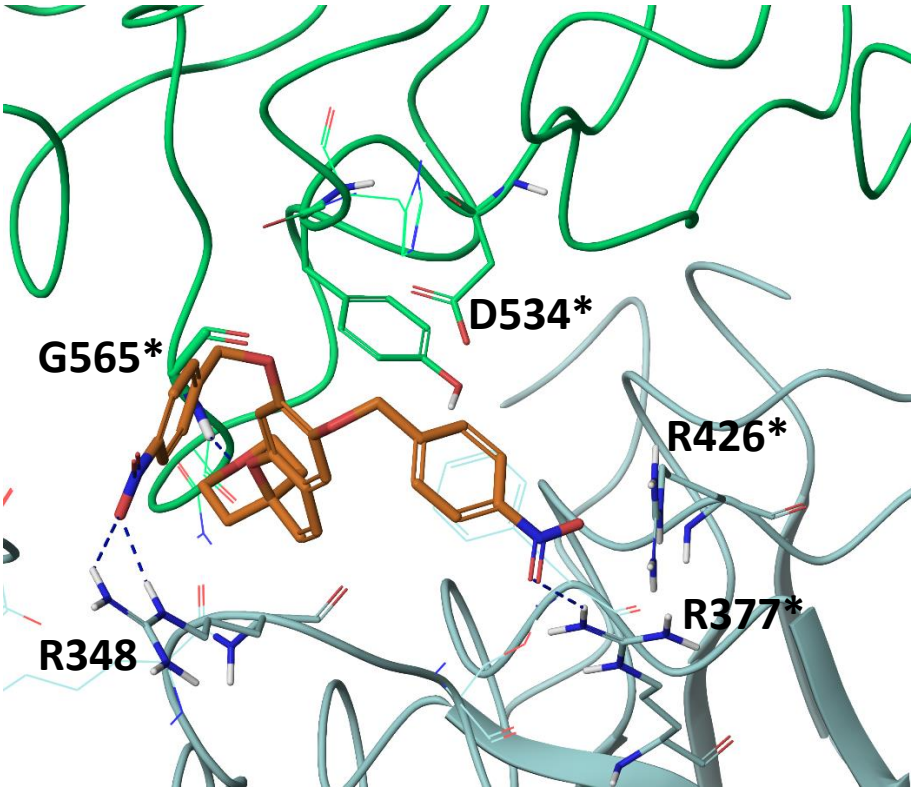
Supplementary Figure 2(b). Docked model of **1** (orange) overlaid with Resiquimod co-crystal (magenta) in hTLR8 – Pose 1



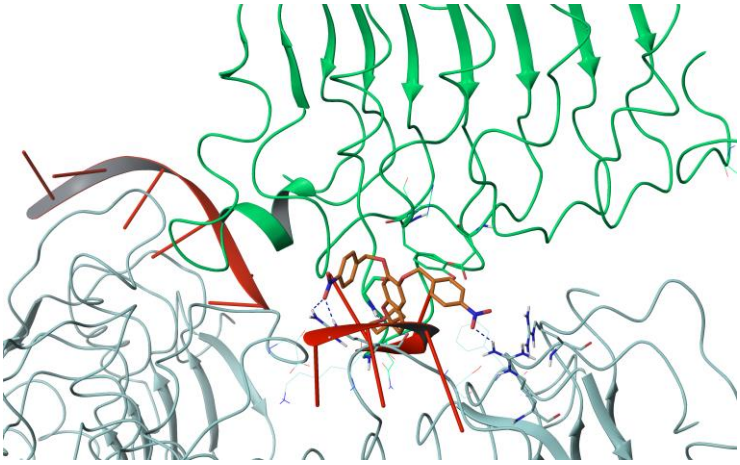
Supplementary Figure 2(c). Docked model of **1** (orange) overlaid with Resiquimod co-crystal (magenta) in hTLR8 (Pose 2) – showing one of the nitrobenzenes interacting with Y348 and pointing to a hydrophobic pocket.

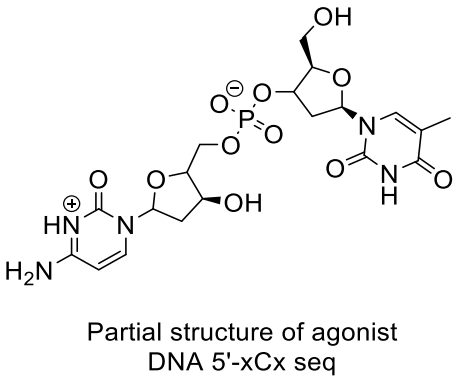


Supplementary Figure 3. hTLR9 homology model based on horse TLR9 dimer crystal structure [PDB Code:3WPC]



Supplementary Figure 4(a). Docked model of **1** in hTLR9 homology model. The THP O atom H-bonds to G565 backbone NH, and the two Nitro groups are heavily involved in polar interactions with arginines.





Supplementary Figure 4(b). Docked model of **1** (orange) in hTLR9 homology model overlaid with 5'-xCx DNA co-crystal (red). R377 H-bonds with G3 base N in native crystal structure.

Adaptations of the general procedure:

Synthesis of compounds 65-67, General procedure. A solution of **5** (50 mg, 0.2 mmol) and potassium carbonate (30 mg, 0.22 mmol) in acetone (5 mL) was treated with R^1Br (0.2 mmol). The reaction mixture was stirred at 80 °C for 12 h. When the reaction was complete, the mixture was cooled to room temperature, and R^2Br (0.2 mmol) and potassium carbonate (30 mg, 0.22 mmol) were added. The resultant mixture was stirred at 80 °C for 12 h, after which the solution was poured into water and extracted with ethyl acetate. The organic layer was dried with Na_2SO_4, filtered, concentrated, and purified by flash column chromatography to afford the corresponding chromanone. A mixture of the chromanone (0.1 mmol) and 2 M $LiBH_4$ in THF (0.1 mL, 0.2 mmol) in THF (0.5 mL) was stirred at 23 ˚C for 12 h. The reaction was quenched with the addition of methanol, and the reaction mixture was adjusted to pH 1-2 with the addition of aqueous 2 N HCl prior to removal of solvents under reduced pressure. The residue was dissolved in EtOAc (5 mL) and washed sequentially with water and saturated aqueous NaCl. The organic phase was dried with Na_2SO_4, filtered, concentrated, and the residue was purified by flash column chromatography to afford the chromanol. The chromanol (0.08 mmol) was dissolved in ethyl acetate (1 mL), and aqueous 4 N HCl (0.4 mL,1.58 mmol) was added. The reaction mixture was stirred at 23 ˚C for 12 h, and then basified with addition of a saturated aqueous $NaHCO_3$ solution (3 mL) followed by extraction with EtOAc (10 mL). The combined organic layers were dried with Na_2SO_4, filtered, concentrated, and purified by flash column chromatography to afford compounds **65-67**.

Synthesis of compounds 68-73, General procedure. A solution of **3** (2 g, 10.2 mmol) in methanol was treated sequentially with pyrrolidine (0.84 mL, 10.2 mmol) and the corresponding *N*-Boc-oxopiperidine (6.1 g, 30.6 mmol), and the reaction mixture was stirred for 12 h. Concentration and purification by flash column chromatography over silica gel furnished the chromanone. The chromanone was dissolved in CH_2Cl_2 (5 mL) and slowly treated with boron tribromide (1 M in CH_2Cl_2, 30.6 mL, 30.6 mmol) at 0 ˚C under nitrogen. The reaction mixture was stirred at 23 ˚C for 12 h, after which it was concentrated in vacuo to furnish the corresponding catechol bearing the free amine. This crude amine was treated with triethylamine (10 equiv), acetic anhydride (3.3 equiv) and DMAP (0.6 equiv) in a mixture of THF-CH_2Cl_2 (1:1) and stirred for 12 h at 23 ˚C. The mixture was neutralized with the addition of a saturated ammonium chloride solution, followed by extraction with ethyl acetate. The organic layer was dried with Na_2SO_4, filtered, concentrated, and the resulting triacetate was dissolved a mixture of methanol and saturated aqueous sodium bicarbonate. After stirring for 45 min at 23 ˚C, the mixture extracted with ethyl acetate, and the organic layer was dried with Na_2SO_4, filtered, concentrated. The residue was purified by flash column chromatography over silica gel to afford the corresponding catechols. A solution of the resulting catechol and potassium carbonate (2.2 equiv) in acetone was treated with *p*-nitrobenzylbromide (2.2 equiv). The reaction mixture was stirred at 60 °C for 12 h. When the reaction was complete, the mixture was cooled to room temperature, and the solution was poured into water and extracted with ethyl acetate. The organic layer was dried with Na_2SO_4, filtered, concentrated, and purified by flash column chromatography to afford the corresponding bis 4-nitrobenzyl derivatives. A mixture of the above compounds and $NaBH_4$ (2 equiv) in THF was stirred at 60 ˚C for 18 h, after which the solution was poured into water and extracted with ethyl acetate. The organic phase was dried with Na_2SO_4, filtered, concentrated, and purified by flash column chromatography to afford the corresponding chromanol. The chromanol was dissolved in ethyl acetate, and aqueous 4 N HCl in dioxane (8 equiv) was added. The reaction mixture was stirred at 23 ˚C for 12 h, and then basified with the addition of a saturated aqueous $NaHCO_3$

solution (3 mL) followed by extraction with EtOAc (10 mL). The combined organic layers were dried with Na_2SO_4, filtered, concentrated, and purified by flash column chromatography to afford compounds **68** and **70**. Aqueous 3 N HCl as added to the acetates **68** and **70**, and the mixture was warmed at reflux for 24 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified using PTLC (10% methanol/CH_2Cl_2) to yield compounds **69** and **71**, respectively. Amines **69** and **71** were dissolved in CH_2Cl_2, and bromoethanol (2 equiv) was added, followed by the addition of *i*Pr_2NEt (3 equiv). The resulting mixture was stirred for 12 h at 40 ˚C. Ethyl acetate was added and the solution was poured into water and extracted with ethyl acetate. The organic phase was dried with Na_2SO_4, filtered, concentrated, and purified by flash column chromatography to afford compounds **72** and **73**.

Synthesis of compounds 74-82, General procedure. A solution of **3** (2 g, 10.2 mmol) in methanol was treated sequentially with pyrrolidine (0.84 mL, 10.2 mmol) and the corresponding ketone (30.6 mmol), and the reaction mixture was warmed at reflux for 12 h. Concentration and purification by flash column chromatography over silica gel afforded the corresponding chromanone. The chromanones were then converted to compounds **74-82** following the same sequence of steps as outlined for compounds **1**, **9**-**67**.

Synthesis of compounds 86-88. A solution of **84** (2.0 g, 9.5 mmol) in methanol was treated sequentially with pyrrolidine (0.78 mL, 9.5 mmol) and tetrahydro-4*H*-pyran-4-one (2.85 g, 28.5 mmol), and the reaction mixture was warmed at reflux for 12 h. Purification by flash column chromatography (SiO_2, EtOAc/hexane 1:4) gave the chromanone as a yellow solid, which was dissolved in CH_2Cl_2 (5 mL) and slowly treated with boron tribromide (1 M in CH_2Cl_2, 28.5 mL, 28.5 mmol) at 0 ˚C under nitrogen, and the reaction mixture was stirred at 23 ˚C for 12 h. The reaction mixture was poured into ice water and extracted with EtOAc (3x). The combined organic layers were dried with Na_2SO_4, filtered, concentrated, and the residue was purified by flash column chromatography (SiO_2, EtOAc/hexane 4:1) to give **85** as an off-white solid. A solution of **85** and potassium carbonate (2.2 equiv) in acetone was treated with *p*-nitrobenzylbromide (2.2 equiv). The reaction mixture was stirred at 60 °C for 12 h. When the reaction was complete, the mixture was cooled to room temperature, and the solution was poured into water and extracted with ethyl acetate. The organic layer was dried with Na_2SO_4, filtered, concentrated, and purified by flash column chromatography to afford **86** (121 mg, 72%) as a yellow solid. A mixture of **86** and $NaBH_4$ (2 equiv) in THF was stirred at 60 ˚C for 18 h, after which the solution was poured into water and extracted with ethyl acetate. The organic phase was dried with Na_2SO_4, filtered, concentrated, and purified by flash column chromatography to afford **87** (43 mg, 59%) as an off-white solid. **87** was dissolved in ethyl acetate, and aqueous 4 N HCl in dioxane (8 equiv) was added. The reaction mixture was stirred at 23 ˚C for 12 h, and then basified with the addition of a saturated aqueous $NaHCO_3$ solution followed by extraction with EtOAc. The combined organic layers were dried with Na_2SO_4, filtered, concentrated, and purified by flash column chromatography to afford **88** (11 mg, 54%) as a yellow solid.

Characterization data:

6,7-bis((4-nitrobenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(1)**. 76% (16.5 mg), mp 177–178 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (t, *J* = 8.6 Hz, 4H), 7.60 (t, *J* = 9.0 Hz, 4H), 6.62 (s, 1H), 6.52 (s, 1H), 6.26 (d, *J* = 9.7 Hz, 1H), 5.51 (d, *J* = 9.8 Hz, 1H), 5.22 (s, 2H), 5.16 (s, 2H), 3.87 (td, *J* = 11.1, 2.6 Hz, 2H), 3.74 (dt, *J* = 11.6, 3.9 Hz, 2H), 1.96–1.89 (m, 2H), 1.75 (td, *J* = 10.3, 5.3 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.5, 148.0, 147.8, 147.7, 144.9, 144.2, 142.5, 127.7, 127.6, 124.0, 123.9, 122.9, 115.3, 114.6, 103.9, 71.5, 70.0, 63.4, 35.8. HRMS

(ESI) calcd for $C_{27}H_{25}N_2O_8$ $[M+H]^+$, 505.1611; found, 505.1612. Identical in all respects with data published.[19]

6,7-bis(naphthalen-2-ylmethoxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(9)**. 81% (18 mg), mp 72–73 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88–7.83 (m, 5H), 7.80–7.74 (m, 3H), 7.59 (ddd, *J* = 8.4, 6.7, 1.7 Hz, 2H), 7.49 (dddt, *J* = 13.5, 7.2, 5.5, 3.4 Hz, 4H), 6.72 (s, 1H), 6.64 (d, *J* = 0.6 Hz, 1H), 6.29 (d, *J* = 9.8 Hz, 1H), 5.49 (d, *J* = 9.7 Hz, 1H), 5.32 (d, *J* = 0.8 Hz, 2H), 5.26 (d, *J* = 0.9 Hz, 3H), 3.93–3.87 (m, 2H), 3.75 (dt, *J* = 11.6, 4.2 Hz, 2H), 1.98–1.93 (m, 2H), 1.78–1.74 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.9, 150.6, 146.0, 135.6, 133.7, 133.6, 135.5, 133.3, 133.2,131.2, 128.9, 128.8, 128.7, 128.6, 128.0, 127.9, 127.5, 126.4, 126.3,126.3, 126.2, 126.12, 126.1, 125.5, 124.4, 116.2, 112.2, 103.0, 76.8, 71.0, 70.9, 65.5, 65.4, 34.6, 34.5. HRMS (ESI) calcd for $C_{35}H_{31}O_4$ $[M+H]^+$, 515.2222; found, 515.2221.

6,7-bis([1,1'-biphenyl]-4-ylmethoxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(10)**. 71% (17.3 mg), mp 67–68 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64–7.59 (m, 8H), 7.55 (d, *J* = 7.9 Hz, 2H), 7.52 (d, *J* = 7.9 Hz, 2H), 7.46 (td, *J* = 7.5, 5.0 Hz, 4H), 7.38 (td, *J* = 7.4, 4.4 Hz, 2H), 6.71 (s, 1H), 6.63 (s, 1H), 6.32 (d, *J* = 9.7 Hz, 1H), 5.51 (d, *J* = 9.7 Hz, 1H), 5.21 (s, 2H), 5.14 (s, 2H), 3.93 (td, *J* = 11.1, 2.5 Hz, 2H), 3.77 (dt, *J* = 11.7, 4.0 Hz, 2H), 1.98 (d, *J* = 14.0 Hz, 2H), 1.78 (ddd, *J* = 14.5, 10.6, 4.7 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.9, 150.6, 146.0, 140.8, 140.7, 139.0, 138.9, 135.6, 135.5, 131.2, 129.1, 129.0, 128.9, 128.9, 128.2, 128.2, 128.2, 128.2, 128.1, 128.1, 128.0, 128.0, 127.8, 127.7, 127.2, 127.0, 127.0, 125.6, 127.2, 112.2, 116.3, 103.0, 76.8, 71.4, 71.3, 65.4, 65.4, 34.7, 34.6. HRMS (ESI) calcd for $C_{39}H_{35}O_4$ $[M+H]^+$, 567.2535; found, 567.2538.

4,4'-(((2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl)bis(oxy))bis (methylene))dipyridine **(11).** 57% (10.2 mg), mp 171–172 ˚C; ^{1}H NMR (600 MHz, methanol-d_4) δ 8.54–8.50 (m, 4H), 7.56–7.51 (m, 4H), 6.81 (s, 1H), 6.65 (s, 1H), 6.36 (d, *J* = 9.7 Hz, 1H), 5.59 (d, *J* = 9.8 Hz, 1H), 5.22 (s, 2H), 5.15 (s, 2H), 3.89 (ddd, *J* = 11.1, 10.4, 2.6 Hz, 2H), 3.73 (dt, *J* = 11.5, 4.1 Hz, 2H), 1.93–1.86 (m, 2H), 1.77 (ddd, *J* = 14.5, 10.8, 4.7 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.9, 150.6, 150.6, 150.6, 150.5, 150.4, 148.0, 147.9, 146.0, 131.2, 125.6, 122.9, 122.6, 122.9, 122.8, 116.3, 112.2,103.0, 76.8, 71.2, 71.1, 65.4, 65.2, 34.8, 34.6. HRMS (ESI) calcd for $C_{25}H_{25}N_2O_4$ $[M+H]^+$, 417.1814; found, 417.1809.

4,4'-(((2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl)bis(oxy))bis (methylene))dibenzonitrile **(12)**. 56% (11 mg), mp 165 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71–7.67 (m, 4H), 7.58–7.54 (m, 4H), 6.62 (s, 1H), 6.53 (s, 1H), 6.28 (d, *J* = 9.8 Hz, 1H), 5.53 (d, *J* = 9.8 Hz, 1H), 5.19 (s, 2H), 5.13 (s, 2H), 3.89 (ddd, *J* = 11.6, 10.3, 2.6 Hz, 2H), 3.76 (dt, *J* = 11.5, 4.2 Hz, 2H), 1.95 (dt, *J* = 12.0, 2.6 Hz, 2H), 1.78 (ddd, *J* = 14.5, 10.6, 4.7 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.9, 150.6, 146.0, 138.6, 138.5, 132.7, 132.6, 132.5, 132.5, 131.2, 128.7, 128.5, 128.4, 128.4, 125.6, 119.4, 119.3, 116.3, 112.2, 111.8, 111.2, 103.0, 76.8, 71.4, 71.3, 65.4, 65.2, 34.7, 34.6. HRMS (ESI) calcd for $C_{29}H_{25}N_2O_4$ $[M+H]^+$, 465.1814; found, 465.1819.

5,5'-(((2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl)bis(oxy))bis (methylene))bis(benzo[c][1,2,5]oxadiazole) **(13)** 61% (13 mg), mp 163 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90–7.87 (m, 2H), 7.87–7.84 (m, 2H), 7.50 (dq, *J* = 2.7, 1.5 Hz, 2H), 6.70 (s, 1H), 6.59 (s, 1H), 6.30 (d, *J* = 9.7 Hz, 1H), 5.55 (d, *J* = 9.7 Hz, 1H), 5.22 (s, 2H), 5.17 (s, 2H), 3.93–3.87 (m, 2H), 3.76 (dt, *J* = 11.6, 4.2 Hz, 2H), 1.98–1.93 (m, 2H), 1.78 (ddd, *J* = 14.7, 10.7, 4.7 Hz, 2H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 151.9, 150.7, 149.8, 149.7, 146.6, 146.4, 146.0, 143.1, 143.0, 131.2, 126.1, 125.9, 119.8, 119.7, 125.5, 119.8, 119.6, 116.2, 112.2, 103.0, 76.8, 71.0, 70.9, 65.4, 65.2, 34.6, 34.6. HRMS (ESI) calcd for $C_{27}H_{23}N_4O_6$ $[M+H]^+$, 499.1618; found, 499.1621.

6,7-bis((3,4-difluorocyclohexa-1,5-dien-1-yl)methoxy)-2',3',5',6'-tetrahydrospiro [chromene-2,4'-pyran] **(14).** 38% (7.9 mg), mp 158 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28–7.25 (m, 2H), 7.20–7.11 (m, 4H), 6.63 (s, 1H), 6.53 (s, 1H), 6.29 (d, *J* = 9.6 Hz, 1H), 5.53 (d, *J* = 9.7 Hz, 1H), 5.21 (s, 2H), 5.17 (s, 2H), 3.93 – 3.88 (m, 2H), 3.76 (dt, *J* = 11.6, 4.2 Hz, 2H), 1.96 (dq, *J* = 14.1, 2.3 Hz, 2H), 1.77 (ddd, *J* = 14.5, 10.7, 4.7 Hz, 2H). HRMS (ESI) calcd for $C_{27}H_{27}F_4O_4$ $[M+H]^+$, 487.1532; found, 487.1537.

6,7-bis(benzo[d][1,3]dioxol-5-ylmethoxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(15).** 69% (15 mg), mp 143 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.93 (s, 1H), 6.91 (d, *J* = 7.8, 1H), 6.88 (d, *J* = 7.6, 1H), 6.83 (d, *J* = 7.8, 1H), 6.79 (d, *J* = 7.9, 1H), 6.63 (s, 1H), 6.55 (s, 1H), 6.29 (d, *J* = 9.7 Hz, 1H), 5.99 (s, 2H), 5.97 (s, 2H), 5.49 (d, *J* = 9.7 Hz, 1H), 5.02 (s, 2H), 4.95 (d, *J* = 3.6 Hz, 3H), 3.90 (qd, *J* = 11.5, 2.7 Hz, 2H), 3.76 (dt, *J* = 11.6, 4.1 Hz, 2H), 1.96 (dq, *J* = 14.1, 2.3 Hz, 2H), 1.77 (ddd, *J* = 14.5, 10.7, 4.7 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.8, 147.4, 147.3, 147.0, 146.9, 146.8, 142.5, 131.0, 130.2, 126.4, 122.7, 120.8, 120.7, 114.7, 114.1, 107.9, 107.7, 107.6, 103.5, 100.6, 100.5, 73.4, 72.4, 70.7, 62.8, 35.2. HRMS (ESI) calcd for $C_{29}H_{27}O_8$ $[M+H]^+$, 507.2019; found, 507.2021.

6,7-bis(benzo[b]thiophen-5-ylmethoxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(16).** 43% (9.7 mg), mp 147–148 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (d, *J* = 9.0 Hz, 2H), 7.48 (d, *J* = 5.1 Hz, 2H), 7.45 (m, 4H), 7.30 (d, 7.0 Hz, 2H), 6.71 (s, 1H), 6.63 (s, 1H), 6.29 (d, *J* = 9.7 Hz, 1H), 5.50 (d, *J* = 9.7 Hz, 1H), 5.27 (s, 2H), 5.20 (s, 2H), 3.92 (t, *J* = 10.7 Hz, 2H), 3.77 (dd, *J* = 10.0, 5.4 Hz, 2H), 1.96 (d, *J* = 13.8 Hz, 2H), 1.77 (ddd, *J* = 14.8, 10.8, 4.9 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.5, 147.7, 143.3, 139.8, 133.2, 127.0, 126.9, 124.2, 124.0, 124.0, 123.3, 122.8, 122.8, 122.7, 122.7, 122.6, 122.6, 115.3, 104.1, 73.2, 71.5, 67.9, 63.4, 35.8. HRMS (ESI) calcd for $C_{31}H_{27}O_4S_2$ $[M+H]^+$, 527.1351; found, 527.1349.

di-tert-butyl 5,5'-(((2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl)bis (oxy))bis(methylene))bis(1H-indole-1-carboxylate) **(17).** 45% (13.4 mg), mp 97–98 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (d, *J* = 20.4 Hz, 2H), 7.66 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.62–7.51 (m, 3H), 7.38 (ddd, *J* = 23.0, 8.5, 1.7 Hz, 2H), 6.64 (s, 1H), 6.58 (s, 1H), 6.53 (dd, *J* = 3.7, 0.7 Hz, 1H), 6.48 (dd, *J* = 3.7, 0.8 Hz, 1H), 6.25 (d, *J* = 9.7 Hz, 1H), 5.45 (d, *J* = 9.7 Hz, 1H), 5.21 (s, 2H), 5.14 (s, 2H), 3.88 (td, *J* = 11.2, 2.6 Hz, 2H), 3.73 (dt, *J* = 11.5, 4.2 Hz, 2H), 1.93 (dt, *J* = 11.7, 2.6 Hz, 2H), 1.76–1.71 (m, 2H), 1.68 (s, 9H), 1.67 (s, 9H). HRMS (ESI) calcd for $C_{41}H_{45}N_2O_8$ $[M+H]^+$, 693.3176; found, 693.3188.

6,6'-(((2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl)bis(oxy))bis (methylene))bis(benzo[d]thiazole) **(18).** 51% (11.6 mg), mp 154–155 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (s, 1H), 9.00 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 9.0 Hz, 2H), 7.58 (ddd, *J* = 15.2, 8.4, 1.7 Hz, 2H), 6.71 (s, 1H), 6.62 (s, 1H), 6.30 (d, *J* = 9.7 Hz, 1H), 5.51 (d, *J* = 9.7 Hz, 1H), 5.28 (s, 2H), 5.22 (s, 2H), 3.91 (td, *J* = 11.1, 2.6 Hz, 2H), 3.75 (dt, *J* = 11.6, 4.2 Hz, 2H), 1.96 (dq, *J* = 14.1, 2.3 Hz, 2H), 1.77 (ddd, *J* = 14.5, 10.7, 4.7 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.8, 149.6, 147.3, 142.4, 126.7, 125.3, 125.2, 123.1, 122.9, 122.6, 120.4, 120.2 (2), 114.6, 114.4, 103.4, 73.6, 72.2, 70.4, 62.8, 35.2. HRMS (ESI) calcd for $C_{29}H_{25}N_2O_4S_2$ $[M+H]^+$, 529.1256; found, 529.1250.

4,4'-((((2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl)bis(oxy))bis (methylene))bis(4,1-phenylene))bis(1,2,3-thiadiazole) **(19).** 39% (9.8 mg), mp 116–117 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.67 (s, 1H), 8.09 (dd, *J* = 9.6, 7.3 Hz, 4H), 7.63 (dd, *J* = 9.2, 6.9 Hz, 4H), 6.71 (s, 1H), 6.61 (s, 1H), 6.33 (d, *J* = 9.6 Hz, 1H), 5.52 (d, *J* = 9.7 Hz, 1H), 5.22 (s, 2H), 5.16 (s, 2H), 3.95–3.88 (m, 2H), 3.76 (dt, *J* = 11.6, 4.2 Hz, 2H), 1.97 (dq, *J* = 14.2, 2.5 Hz, 2H), 1.77 (ddd, *J* = 14.6, 10.7, 4.7 Hz, 2H). HRMS (ESI) calcd for $C_{31}H_{26}N_4O_4S_2$ $[M+H]^+$, 583.1474; found, 583.1481.

5,5'-(((2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl)bis(oxy))bis (methylene))bis(2-(trifluoromethyl)pyridine) **(20).** 86% (19.2 mg), mp 162–163 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.79 (s, 1H), 7.97–7.92 (m, 2H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 6.67 (s, 1H), 6.58 (s, 1H), 6.30 (d, *J* = 9.8 Hz, 1H), 5.56 (d, *J* = 9.8 Hz, 1H), 5.21 (s, 2H), 5.15 (s, 2H), 3.90 (td, *J* = 11.2, 2.6 Hz, 2H), 3.77 (dt, *J* = 11.6, 4.2 Hz, 2H), 1.96 (d, *J* = 13.9 Hz, 2H), 1.79 (ddd, *J* = 14.5, 10.7, 4.7 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.4, 148.9, 148.9, 148.2, 142.4, 136.3, 136.3, 135.6, 127.8, 122.8, 120.5 (3), 120.4 (2), 115.5, 114.9, 103.9, 74.4, 69.7, 68.2, 63.3, 35.8. HRMS (ESI) calcd for $C_{27}H_{23}F_6N_2O_4$ $[M+H]^+$, 553.1562; found, 553.1561.

5,5'-(((2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl)bis(oxy))bis (methylene))bis(2-nitropyridine) **(21).** 67% (14.6 mg), mp 173–174 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.70 (s, 1H), 8.34 (d, *J* = 8.2 Hz, 1H), 8.30 (d, *J* = 8.6 Hz, 1H), 8.15 – 8.09 (m, 2H), 6.67 (s, 1H), 6.58 (s, 1H), 6.30 (d, *J* = 9.8 Hz, 1H), 5.57 (d, *J* = 9.7 Hz, 1H), 5.29 (s, 2H), 5.22 (s, 2H), 3.89 (td, *J* = 11.1, 2.5 Hz, 2H), 3.77 (dt, *J* = 11.6, 4.1 Hz, 2H), 1.97 (dg, *J* = 14.1, 2.5 Hz, 2H), 1.78 (ddd, *J* = 14.2, 10.7, 4.5 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.6, 155.4, 151.9, 150.6, 149.2, 149.1, 146.0, 137.4, 137.3, 132.4, 132.4, 131.5, 125.4, 116.2, 115.3, 115.2, 112.2, 103.0, 76.8, 69.7, 69.6, 65.3, 65.2, 34.7, 34.6. HRMS (ESI) calcd for $C_{25}H_{23}N_2O_8$ $[M+H]^+$, 507.1516; found, 507.1519.

6,7-bis((3,4-dichlorobenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(22).** 53% (12.6 mg), mp 143–144 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (t, *J* = 2.1 Hz, 2H), 7.45 (s, 1H), 7.44 (s, 1H), 7.27 (ddd, *J* = 4.5, 2.7, 1.4 Hz, 2H), 6.64 (s, 1H), 6.53 (s, 1H), 6.30 (d, *J* = 9.7 Hz, 1H), 5.53 (d, *J* = 9.7 Hz, 1H), 5.06 (s, 2H), 5.00 (s, 2H), 3.91 (td, *J* = 11.1, 2.6 Hz, 2H), 3.77 (dt, *J* = 11.6, 4.2 Hz, 2H), 1.96 (dq, *J* = 14.1, 2.4 Hz, 2H), 1.79 (ddd, *J* = 13.9, 10.7, 4.6 Hz, 2H). HRMS (ESI) calcd for $C_{27}H_{23}Cl_4O_4$ $[M+H]^+$, 551.0350; found, 551.0344.

6,7-bis((3-methyl-4-nitrobenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(23).** 51% (11.7 mg), mp 139–141 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.8 Hz, 2H), 7.44–7.42 (m, 4H), 6.65 (s, 1H), 6.55 (s, 1H), 6.30 (d, *J* = 9.8 Hz, 1H), 5.54 (d, *J* = 9.8 Hz, 1H), 5.17 (s, 2H), 5.12 (s, 2H), 3.90 (ddd, *J* = 13.3, 9.0, 2.6 Hz, 2H), 3.77 (dt, *J* = 11.6, 4.2 Hz, 2H), 2.63 (s, 3H), 2.62 (s, 3H), 1.96 (dt, *J* = 12.1, 2.6 Hz, 2H), 1.79 (ddd, *J* = 14.6, 10.6, 4.7 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.9, 150.6, 148.1, 148.1, 146.1, 139.3, 139.2, 133.8, 134.0, 131.3, 130.0, 129.9, 125.5, 125.1, 125.1, 124.7, 124.6, 112.2, 116.2, 103.1, 76.8, 71.1, 71.0, 65.4, 65.3, 34.6, 34.6, 20.6, 20.6. HRMS (ESI) calcd for $C_{29}H_{29}N_2O_8$ $[M+H]^+$, 533.1924; found, 533.1928.

6,7-bis((3-methoxy-4-nitrobenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(24).** 31% (7.5 mg), mp 170 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 10.1, 8.2 Hz, 2H), 7.23–7.20 (m, 2H), 7.11–7.05 (m, 2H), 6.65 (s, 1H), 6.56 (s, 1H), 6.30 (d, *J* = 9.7 Hz, 1H), 5.55 (d, *J* = 9.7 Hz, 1H), 5.17 (s, 2H), 5.12 (s, 2H), 3.92 (s, 6H), 3.89 (dd, *J* = 10.8, 2.4 Hz, 2H), 3.77 (dt, *J* =

11.6, 4.0 Hz, 2H), 1.96 (d, *J* = 13.8 Hz, 2H), 1.79 (ddd, *J* = 14.4, 10.6, 4.7 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.3, 153.2, 151.9, 150.6, 146.1, 138.6, 138.4, 138.2, 138.1, 131.2, 127.1, 127.1, 125.5, 124.0, 124.2, 116.3, 113.3, 113.2, 112.1, 103.0, 76.8, 71.4, 71.3, 65.3, 65.2, 56.8, 56.7, 34.7, 34.6. HRMS (ESI) calcd for $C_{29}H_{29}N_2O_{10}$ $[M+H]^+$, 565.1822; found, 565.1826.

6,7-bis((2-fluoro-4-nitrobenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(25).** 56% (13 mg), mp 167–168 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.0, 2H), 8.02–7.96 (m, 2H), 7.82–7.76 (m, 2H), 6.69 (s, 1H), 6.59 (s, 1H), 6.31 (d, *J* = 9.8 Hz, 1H), 5.56 (d, *J* = 9.7 Hz, 1H), 5.27 (s, 2H), 5.22 (s, 2H), 3.88 (td, *J* = 11.6, 4.1 Hz, 2H), 3.76 (dt, *J* = 12.2, 4.4 Hz, 2H), 1.96 (dq, *J* = 14.1, 2.4 Hz, 2H), 1.79 (ddd, *J* = 13.9, 10.7, 4.6 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.2, 152.2, 141.8, 131.6, 129.4, 122.7, 119.6, 119.4, 117.1, 114.8, 112.4, 111.2, 111.2, 111.1, 103.8, 101.6, 67.2, 63.2, 57.6, 45.0, 29.7. HRMS (ESI) calcd for $C_{27}H_{23}F_2N_2O_8$ $[M+H]^+$, 541.1422; found, 541.1425.

dimethyl 4,4'-(((2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl)bis(oxy)) bis(methylene))dibenzoate **(26).** 42% (9.6 mg), mp 78–79 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$ δ 8.10–8.03 (m, 4H), 7.55–7.50 (m, 4H), 6.64 (s, 1H), 6.54 (s, 1H), 6.28 (d, *J* = 9.7 Hz, 1H), 5.51 (d, *J* = 9.7 Hz, 1H), 5.19 (s, 2H), 5.13 (s, *2*H), 3.95 (s, 3H), 3.94 (s, 3H), 3.90 (td, *J* = 11.2, 2.6 Hz, 2H), 3.76 (dt, *J* = 11.6, 4.1 Hz, 2H), 1.95 (dt, *J* = 14.8, 2.5 Hz, 2H), 1.77 (ddd, *J* = 14.5, 10.7, 4.8 Hz, 2H). HRMS (ESI) calcd for $C_{31}H_{31}O_8$ $[M+H]^+$, 531.2019; found, 531.2016.

4,4'-(((2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl)bis(oxy))bis (methylene))dibenzoic acid **(27).** 89% (19.2 mg), mp 139–141 ˚C; ^{1}H NMR (600 MHz, methanol-d_4) δ 8.05–8.01 (m, 4H), 7.58–7.53 (m, 4H), 6.77 (s, 1H), 6.64 (s, 1H), 6.36 (d, *J* = 9.8 Hz, 1H), 5.57 (d, *J* = 9.7 Hz, 1H), 5.21 (s, 2H), 5.15 (s, 2H), 3.91 (td, *J* = 11.2, 2.7 Hz, 2H), 3.73 (dt, *J* = 11.6, 4.2 Hz, 2H), 1.92 (dt, *J* = 11.8, 2.7 Hz, 2H), 1.77 (ddd, *J* = 14.5, 10.8, 4.7 Hz, 2H). HRMS (ESI) calcd for $C_{29}H_{27}O_8$ $[M+H]^+$, 503.1706; found, 503.1701.

1,1'-((((2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl)bis(oxy))bis (methylene))bis(4,1-phenylene))bis(ethan-1-one) **(28).** 79% (15.7 mg), mp 67–69 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00–7.96 (m, 4H), 7.57–7.51 (m, 4H), 6.64 (s, 1H), 6.55 (s, 1H), 6.28 (d, *J* = 9.8 Hz, 1H), 5.51 (d, *J* = 9.7 Hz, 1H), 5.20 (s, 2H), 5.14 (s, 2H), 3.90 (td, *J* = 11.1, 2.6 Hz, 2H), 3.76 (dt, *J* = 11.5, 4.1 Hz, 2H), 2.64 (s, 3H), 2.63 (s, 3H), 1.95 (dt, *J* = 11.8, 2.6 Hz, 2H), 1.77 (ddd, *J* = 14.5, 10.7, 4.7 Hz, 2H). HRMS (ESI) calcd for $C_{31}H_{31}O_6$ $[M+H]^+$, 499.2121; found, 499.2122.

6,7-bis((3-nitrobenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran **(29).** 61% (13.2 mg), mp 111–113 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.38 (d, *J* = 7.8 Hz, 2H), 8.22–8.17 (m, 2H), 7.81 (ddt, *J* = 6.6, 2.9, 1.5 Hz, 2H), 7.63–7.56 (m, 2H), 6.70 (s, 1H), 6.59 (s, 1H), 6.32 (d, *J* = 9.7 Hz, 1H), 5.55 (d, *J* = 9.8 Hz, 1H), 5.22 (s, 2H), 5.17 (s, 2H), 3.90 (td, *J* = 11.7, 4.2 Hz, 2H), 3.78 (dt, *J* = 11.6, 4.1 Hz, 2H), 1.95 (dq, *J* = 13.9, 2.4 Hz, 2H), 1.80 (ddd, *J* = 14.1, 10.6, 4.6 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.5, 148.0, 142.6, 139.6, 133.2, 133.1, 129.8, 129.7, 127.6, 123.2, 123.0 (2), 122.2, 115.3, 114.6, 103.8, 74.3 71.4, 69.9, 63.4, 35.8, 29.8. HRMS (ESI) calcd for $C_{27}H_{25}N_2O_8$ $[M+H]^+$, 505.1611; found, 505.1612.

6,7-bis((2-nitrobenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(30).** 47% (10.2 mg), mp 87–88 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20–8.15 (m, 2H), 8.04 (d, *J* = 7.9 Hz, 1H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.68 (dtd, *J* = 15.4, 7.6, 1.3 Hz, 2H), 7.51 (tdd, *J* = 7.7, 3.4, 1.5 Hz, 2H),

6.71 (s, 1H), 6.60 (s, 1H), 6.32 (d, *J* = 9.7 Hz, 1H), 5.55 (s, 2H), 5.53 (d, *J* = 9.4 Hz, 1H), 5.49 (s, 2H), 3.92 (td, *J* = 11.1, 2.6 Hz, 2H), 3.78 (dt, *J* = 11.6, 4.1 Hz, 2H), 1.97 (dt, *J* = 11.9, 2.7 Hz, 2H), 1.78 (ddd, *J* = 14.5, 10.7, 4.7 Hz, 2H).HRMS (ESI) calcd for $C_{27}H_{25}N_2O_8$ $[M+H]^+$, 505.1611; found, 505.1612.

6,7-bis((4-(trifluoromethyl)benzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(31).** 63% (14.9 mg), mp 138–139 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 13.4, 8.1 Hz, 4H), 7.55 (t, *J* = 9.1 Hz, 4H), 6.65 (s, 1H), 6.56 (s, 1H), 6.29 (d, *J* = 9.7 Hz, 1H), 5.52 (d, *J* = 9.7 Hz, 1H), 5.19 (s, 2H), 5.13 (s, 2H), 3.90 (td, *J* = 11.1, 2.6 Hz, 2H), 3.76 (dt, *J* = 11.6, 4.2 Hz, 2H), 1.98 (dt, *J* = 12.1, 2.6 Hz, 2H), 1.78 (ddd, *J* = 14.4, 10.7, 4.7 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.9, 150.6, 146.1, 137.2, 137.1, 131.2, 130.4, 130.4, 128.7, 128.6, 128.5, 128.4, 126.1, 126.0, 125.9, 125.9, 125.5, 124.4, 124.3, 116.3, 112.1, 103.1, 76.8, 71.3, 71.2, 65.3, 65.2, 34.6, 34.6. HRMS (ESI) calcd for $C_{29}H_{25}F_6O_4$ $[M+H]^+$, 551.1657; found, 551.1651.

2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl bis(4-nitrobenzoate) **(32).** 28% (6.4 mg), mp 58-59 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 – 8.23 (m, 10H), 7.05 (s, 1H), 6.94 (s, 1H), 6.41 (d, *J* = 9.9 Hz, 1H), 5.71 (d, *J* = 9.9 Hz, 1H), 3.91 (td, *J* = 11.3, 2.5 Hz, 3H), 3.80 (ddd, *J* = 11.7, 4.6, 3.1 Hz, 3H), 1.97 (dt, *J* = 12.0, 2.6 Hz, 2H), 1.81 (ddd, *J* = 14.5, 10.7, 4.8 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.7, 162.2, 151.2 (2), 151.0, 141.8, 135.6, 134.1, 133.9, 131.3 (2), 130.3, 124.0, 123.9, 122.3, 120.7, 120.6, 111.7, 75.1, 63.2, 36.1. HRMS (ESI) calcd for $C_{27}H_{21}N_2O_{10}$ $[M+H]^+$, 533.1196; found, 533.1198.

6,7-bis((3-(trifluoromethyl)benzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(33).** 42% (9.9 mg), mp 113–115 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.73 (s, 1H), 7.67–7.58 (m, 4H), 7.50 (dt, *J* = 18.8, 7.7 Hz, 2H), 6.69 (s, 1H), 6.59 (s, 1H), 6.32 (d, *J* = 9.7 Hz, 1H), 5.53 (d, *J* = 9.7 Hz, 1H), 5.17 (s, 2H), 5.10 (s, 2H), 3.95–3.90 (m, 2H), 3.77 (dt, *J* = 11.6, 4.2 Hz, 2H), 1.97 (dt, *J* = 11.7, 2.6 Hz, 2H), 1.79 (ddd, *J* = 14.3, 10.6, 5.1 Hz, 2H). HRMS (ESI) calcd for $C_{29}H_{25}F_6O_4$ $[M+H]^+$, 551.1657; found, 551.1653.

6,7-bis((2-(trifluoromethyl)benzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(34).** 44% (10.4 mg), mp 97–98 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88–7.82 (m, 2H), 7.70 (dd, *J* = 12.6, 7.8 Hz, 2H), 7.56 (td, *J* = 7.9, 2.3 Hz, 2H), 7.43 (q, *J* = 8.3 Hz, 2H), 6.66 (s, 1H), 6.56 (s, 1H), 6.30 (d, *J* = 9.7 Hz, 1H), 5.52 (d, *J* = 9.7 Hz, 1H), 5.34 (s, 2H), 5.29 (s, 2H), 3.92 (td, *J* = 11.1, 2.6 Hz, 2H), 3.76 (dt, *J* = 11.6, 4.1 Hz, 2H), 1.97 (dq, *J* = 14.1, 2.4 Hz, 2H), 1.79 (ddd, *J* = 13.9, 10.7, 4.6 Hz, 2H). HRMS (ESI) calcd for $C_{29}H_{25}F_6O_4$ $[M+H]^+$, 551.1657; found, 551.1651.

6,7-bis((4-(trifluoromethoxy)benzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(35).** 53% (13.2 mg), mp 161–162 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50–7.47 (m, 2H), 7.46–7.43 (m, 3H), 7.25–7.23 (m, 2H), 7.22–7.19 (m, 3H), 6.66 (s, 1H), 6.57 (s, 1H), 6.30 (d, *J* = 9.7 Hz, 1H), 5.52 (d, *J* = 9.7 Hz, 1H), 5.12 (s, 2H), 5.05 (s, 2H), 3.91 (td, *J* = 11.1, 2.6 Hz, 2H), 3.77 (dt, *J* = 11.6, 4.1 Hz, 2H), 1.96 (dt, *J* = 11.9, 2.6 Hz, 2H), 1.78 (ddd, *J* = 14.5, 10.7, 4.8 Hz, 2H). HRMS (ESI) calcd for $C_{29}H_{25}F_6O_6$ $[M+H]^+$, 583.1555; found, 583.1559.

3,3'-(((2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl)bis(oxy))bis (methylene))dibenzonitrile **(36).** 54% (10.8 mg), mp 131–132 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71–7.67 (m, 2H), 7.63–7.61 (m, 2H), 7.59 (dt, *J* = 7.7, 1.5 Hz, 2H), 7.49 (q, *J* = 7.8 Hz, 2H), 6.65 (s, 1H), 6.55 (s, 1H), 6.30 (d, *J* = 9.8 Hz, 1H), 5.54 (d, *J* = 9.7 Hz, 1H), 5.14 (s, 2H), 5.08 (s, 2H), 3.90 (td, *J* = 11.2, 2.6 Hz, 2H), 3.76 (dt, *J* = 11.6, 4.2 Hz, 2H), 1.95 (dt, *J* = 11.8, 2.5 Hz, 2H),

1.80 (ddd, *J* = 14.3, 10.6, 5.1 Hz, 2H). HRMS (ESI) calcd for $C_{29}H_{25}N_2O_4$ $[M+H]^+$, 465.1814; found, 465.1821.

***2,2'-(((2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl)bis(oxy))bis (methylene))dibenzonitrile* (37).** 41% (8.2 mg), mp 116–117 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77–7.73 (m, 2H), 7.68 (dt, *J* = 7.7, 1.6 Hz, 2H), 7.64–7.59 (m, 2H), 7.48–7.44 (m, 2H), 6.74 (s, 1H), 6.62 (s, 1H), 6.32 (d, *J* = 9.8 Hz, 1H), 5.54 (d, *J* = 9.8 Hz, 1H), 5.31 (s, 2H), 5.27 (s, 2H), 3.95–3.89 (m, 2H), 3.77 (dt, *J* = 11.6, 4.1 Hz, 2H), 1.97 (dq, *J* = 14.2, 2.5 Hz, 2H), 1.79 (ddd, *J* = 14.3, 10.8, 4.7 Hz, 3H). HRMS (ESI) calcd for $C_{29}H_{25}N_2O_4$ $[M+H]^+$, 465.1814; found, 465.1819.

***2,2'-(((2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl)bis(oxy))bis (methylene))dipyridine* (38).** 68% (12.2 mg), mp 155–156 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.61 (dt, *J* = 11.2, 4.6 Hz, 2H), 7.72 (tdq, *J* = 7.6, 3.9, 1.8 Hz, 2H), 7.66–7.58 (m, 2H), 7.26–7.22 (m, 2H), 6.66 (s, 1H), 6.57 (s, 1H), 6.28 (d, *J* = 9.7 Hz, 1H), 5.49 (d, *J* = 9.7 Hz, 1H), 5.29 (s, 2H), 5.25 (s, 2H), 3.92 (td, *J* = 11.1, 2.6 Hz, 2H), 3.74 (dt, *J* = 11.6, 4.1 Hz, 2H), 1.99 (dq, *J* = 14.2, 2.6 Hz, 2H), 1.75 (ddd, *J* = 14.1, 10.7, 4.5 Hz, 2H). HRMS (ESI) calcd for $C_{25}H_{25}N_2O_4$ $[M+H]^+$, 417.1814; found, 417.1809.

***3,3'-(((2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl)bis(oxy))bis (methylene))dipyridine* (39).** 55% (9.8 mg), mp 161–162 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.65 (s, 1H), 8.60 (d, *J* = 18.6 Hz, 2H), 7.82–7.75 (m, 2H), 7.35 (dd, *J* = 8.0, 4.5 Hz, 1H), 7.30 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.67 (s, 1H), 6.58 (s, 1H), 6.30 (d, *J* = 9.8 Hz, 1H), 5.53 (d, *J* = 9.7 Hz, 1H), 5.13 (s, 2H), 5.07 (s, 2H), 3.91 (td, *J* = 11.1, 2.6 Hz, 2H), 3.77 (dt, *J* = 11.7, 4.2 Hz, 2H), 1.98 (dq, *J* = 13.9, 2.4 Hz, 2H), 1.80 (ddd, *J* = 14.1, 10.6, 4.6 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.9, 150.6, 148.4, 148.2, 147.6, 147.5, 146.1, 135.7, 135.6, 134.5, 134.1, 131.2, 125.6, 124.5, 124.4, 116.2, 112.2, 103.0, 76.8, 69.6, 69.7, 65.3, 65.2, 34.7, 34.6. HRMS (ESI) calcd for $C_{25}H_{25}N_2O_4$ $[M+H]^+$, 417.1814; found, 417.1809.

***6,7-bis((4-chlorobenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran* (40).** 62% (12.9 mg), mp 168–169 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38–7.37 (m, 4H), 7.35–7.33 (m, 4H), 6.63 (s, 1H), 6.54 (s, 1H), 6.28 (d, *J* = 9.6 Hz, 1H), 5.51 (d, *J* = 9.8 Hz, 1H), 5.08 (s, 2H), 5.02 (s, 2H), 3.90 (td, *J* = 11.2, 2.7 Hz, 2H), 3.76 (dt, *J* = 11.6, 4.2 Hz, 2H), 1.95 (dq, *J* = 14.1, 2.4 Hz, 2H), 1.78 (ddd, *J* = 14.1, 10.7, 4.5 Hz, 2H). HRMS (ESI) calcd for $C_{27}H_{25}Cl_2O_4$ $[M+H]^+$, 483.1130; found, 483.1138.

***6,7-bis((3-chlorobenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]* (41).** 52% (10.8 mg), mp 121–122 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.46 (dd, *J* = 2.1, 1.1 Hz, 1H), 7.35–7.32 (m, 4H), 7.31–7.30 (m, 2H), 6.65 (s, 1H), 6.55 (s, 1H), 6.30 (d, *J* = 9.7 Hz, 1H), 5.52 (d, *J* = 9.7 Hz, 1H), 5.10 (s, 2H), 5.04 (s, 2H), 3.91 (td, *J* = 11.3, 2.6 Hz, 2H), 3.76 (dt, *J* = 11.6, 4.2 Hz, 2H), 1.98 (dq, *J* = 14.2, 2.6 Hz, 2H), 1.78 (ddd, *J* = 14.2, 10.7, 4.8 Hz, 2H). HRMS (ESI) calcd for $C_{27}H_{25}Cl_2O_4$ $[M+H]^+$, 483.1130; found, 483.1135.

***6,7-bis((2-chlorobenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]* (42).** 39% (8.1 mg), mp 108 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$ δ 7.69–7.63 (m, 4H), 7.41 (ddt, *J* = 13.4, 7.4, 2.0 Hz, 4H), 6.65 (s, 1H), 6.54 (s, 2H), 6.39 (d, *J* = 9.9 Hz, 1H), 5.41 (d, *J* = 9.9 Hz, 1H), 5.23 (s, 2H), 5.19 (s, 2H), 3.89 (td, *J* = 11.1, 2.3 Hz, 2H), 3.77 (dt, *J* = 11.6, 4.1 Hz, 2H), 1.96 (dq, *J* = 13.9, 2.6 Hz, 2H), 1.78 (ddd, *J* = 14.5, 10.7, 4.8 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.0, 147.8, 143.0, 135.4, 134.8, 132.6, 129.4, 129.3, 129.1, 128.9, 128.9, 127.2, 127.1, 127.0, 123.2, 114.9,

114.7, 103.9, 74.1, 69.9, 68.4, 63.5, 35.8. HRMS (ESI) calcd for $C_{27}H_{25}Cl_2O_4$ $[M+H]^+$, 483.1130; found, 483.1135.

6,7-bis((3-methoxybenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(43).** 76% (15.5 mg), mp 131–132 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 12.4, 7.7 Hz, 2H), 7.07–7.00 (m, 4H), 6.89–6.84 (m, 2H), 6.66 (s, 1H), 6.57 (s, 1H), 6.29 (d, *J* = 9.7 Hz, 1H), 5.50 (d, *J* = 9.7 Hz, 1H), 5.12 (s, 2H), 5.06 (s, 2H), 3.91 (td, *J* = 11.2, 2.6 Hz, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.78 (dt, *J* = 11.8, 4.2 Hz, 8H), 1.99 (dg, *J* = 14.1, 2.6 Hz, 2H), 1.77 (ddd, *J* = 14.4, 10.7, 4.7 Hz, 2H). HRMS (ESI) calcd for $C_{29}H_{31}O_6$ $[M+H]^+$, 475.2121; found, 475.2118.

6,7-bis((2-methoxybenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(44).** 61% (12.4 mg), mp 98–99 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69–7.64 (m, 2H), 7.37 (dtd, *J* = 12.6, 7.8, 1.8 Hz, 2H), 7.34–7.26 (m, 2H), 6.67 (s, 1H), 6.57 (s, 1H), 6.31 (d, *J* = 9.7 Hz, 1H), 5.52 (d, *J* = 9.7 Hz, 1H), 5.22 (s, 2H), 5.16 (s, 2H), 3.92 (td, *J* = 11.2, 2.6 Hz, 2H), 3.76 (dt, *J* = 11.6, 4.1 Hz, 2H), 1.97 (dt, *J* = 11.8, 2.6 Hz, 2H), 1.78 (ddd, *J* = 14.6, 10.7, 4.7 Hz, 2H). HRMS (ESI) calcd for $C_{29}H_{31}O_6$ $[M+H]^+$, 475.2121; found, 475.2117.

6,7-bis((3-(trifluoromethoxy)benzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(45).** 41% (10.3 mg), mp 151–152 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44–7.31 (m, 6H), 7.19 (dddd, *J* = 13.1, 6.7, 2.5, 1.2 Hz, 2H), 6.66 (s, 1H), 6.56 (s, 1H), 6.30 (d, *J* = 9.8 Hz, 1H), 5.52 (d, *J* = 9.7 Hz, 1H), 5.14 (s, 2H), 5.07 (s, 2H), 3.91 (td, *J* = 11.2, 2.6 Hz, 2H), 3.77 (dt, *J* = 11.6, 4.2 Hz, 2H), 1.96 (dq, *J* = 14.1, 2.4 Hz, 2H), 1.78 (ddd, *J* = 14.5, 10.8, 4.7 Hz, 2H). HRMS (ESI) calcd for $C_{29}H_{25}F_6O_6$ $[M+H]^+$, 583.1555; found, 583.1551.

6,7-bis((4-fluorobenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(46).** 38% (7.4 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44–7.36 (m, 4H), 7.10–7.02 (m, 4H), 6.64 (s, 1H), 6.56 (s, 1H), 6.29 (d, *J* = 9.7 Hz, 1H), 5.51 (d, *J* = 9.7 Hz, 1H), 5.08 (s, 2H), 5.01 (s, 2H), 3.91 (td, *J* = 11.2, 2.6 Hz, 2H), 3.76 (dt, *J* = 11.6, 4.2 Hz, 2H), 1.98 (dt, *J* = 11.8, 2.6 Hz, 2H), 1.78 (ddd, *J* = 14.5, 10.7, 4.7 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.6, 162.6, 151.9, 150.6, 146.1, 132.4, 132.3, 131.2, 130.1, 129.9, 129.8, 129.9, 125.6, 116.2, 115.4, 115.3, 115.5, 115.3, 112.2, 103.0, 76.8, 71.5, 71.3, 65.4, 65.3, 34.9, 34.6. HRMS (ESI) calcd for $C_{27}H_{25}F_2O_4$ $[M+H]^+$, 451.1721; found, 451.1720.

6,7-bis((3-fluorobenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(47).** 46% (8.9 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38–7.32 (m, 2H), 7.24–7.17 (m, 4H), 7.03 (dtt, *J* = 11.8, 5.4, 2.9 Hz, 2H), 6.60 (s, 1H), 6.43 (s, 1H), 6.36 (d, *J* = 9.9 Hz, 1H), 5.40 (d, *J* = 9.9 Hz, 1H), 5.11 (s, 2H), 5.06 (s, 2H), 3.96 (td, *J* = 11.4, 2.6 Hz, 2H), 3.79 (dt, *J* = 11.6, 4.2 Hz, 2H), 1.96 (dq, *J* = 13.9, 2.6 Hz, 2H), 1.76 (ddd, *J* = 14.3, 10.6, 4.6 Hz, 2H). HRMS (ESI) calcd for $C_{27}H_{25}F_2O_4$ $[M+H]^+$, 451.1721; found, 451.1718.

6,7-bis((2-fluorobenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(48).** 53% (10.3 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (ddd, *J* = 10.0, 6.0, 1.9 Hz, 2H), 7.36–7.29 (m, 2H), 7.19–7.05 (m, 4H), 6.69 (s, 1H), 6.60 (s, 1H), 6.30 (d, *J* = 9.7 Hz, 1H), 5.51 (d, *J* = 9.7 Hz, 1H), 5.20 (s, 2H), 5.14 (s, 2H), 3.92 (td, *J* = 11.2, 2.6 Hz, 2H), 3.76 (dt, *J* = 11.6, 4.1 Hz, 2H), 1.96 (dq, *J* = 14.0, 2.5 Hz, 2H), 1.77 (ddd, *J* = 14.4, 10.7, 4.7 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.3, 159.7, 150.2, 147.8, 143.0, 130.0, 129.8, 129.7, 129.6, 129.6, 127.2, 124.9, 124.7, 124.3, 123.2, 115.4, 115.4, 115.3, 115.2, 115.0, 104.0, 74.1, 66.6, 65.1, 63.4, 35.8. HRMS (ESI) calcd for $C_{27}H_{25}F_2O_4$ $[M+H]^+$, 451.1721; found, 451.1714.

***6,7-bis((4-methylbenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]* (49).** 68% (12.9 mg), mp 67–68 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 17.9, 7.8 Hz, 4H), 7.19 (dd, *J* = 15.7, 7.7 Hz, 4H), 6.64 (s, 1H), 6.57 (s, 1H), 6.28 (d, *J* = 9.7 Hz, 1H), 5.48 (d, *J* = 9.7 Hz, 1H), 5.10 (s, 2H), 5.03 (s, 2H), 3.91 (td, *J* = 11.1, 2.6 Hz, 2H), 3.76 (dt, *J* = 11.6, 4.1 Hz, 2H), 2.39 (s, 3H), 2.38 (s, 3H), 1.96 (dt, *J* = 11.8, 2.6 Hz, 2H), 1.76 (ddd, *J* = 14.5, 10.7, 4.7 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.5, 147.6, 143.3, 137.7, 137.6, 134.7, 134.1, 129.4, 129.3, 129.3, 129.2, 127.8, 127.8, 127.6, 127.5, 126.9, 123.4, 115.1, 114.6, 104.0, 72.9, 71.2, 63.5, 35.8, 21.4. HRMS (ESI) calcd for $C_{29}H_{31}O_4$ $[M+H]^+$, 443.2222; found, 443.2226.

***6,7-bis((3-methylbenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]* (50).** 56% (10.6 mg), mp 62–63 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (d, *J* = 5.9 Hz, 4H), 7.26–7.24 (m, 2H), 7.17–7.12 (m, 2H), 6.67 (s, 1H), 6.59 (s, 1H), 6.30 (d, *J* = 9.7 Hz, 1H), 5.50 (d, *J* = 9.7 Hz, 1H), 5.11 (s, 2H), 5.04 (s, 2H), 3.92 (td, *J* = 11.1, 2.6 Hz, 2H), 3.76 (dt, *J* = 11.6, 4.1 Hz, 2H), 2.38 (s, 3H), 2.36 (s, 3H), 1.97 (dt, *J* = 11.6, 2.6 Hz, 2H), 1.78 (ddd, *J* = 14.5, 10.7, 4.8 Hz, 2H). HRMS (ESI) calcd for $C_{29}H_{31}O_4$ $[M+H]^+$, 443.2222; found, 443.2218.

***6,7-bis((2-methylbenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]* (51).** 51% (9.7 mg), mp 60–61 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.42–7.39 (m, 1H), 7.26 (ddd, *J* = 7.1, 3.3, 1.4 Hz, 1H), 7.22 (ddd, *J* = 8.0, 5.2, 2.8 Hz, 3H), 7.19 (dd, *J* = 8.6, 2.7 Hz, 2H), 6.69 (s, 1H), 6.61 (s, 1H), 6.32 (d, *J* = 9.7 Hz, 1H), 5.51 (d, *J* = 9.7 Hz, 1H), 5.09 (s, 2H), 5.03 (s, 2H), 3.94 (td, *J* = 11.1, 2.6 Hz, 2H), 3.77 (dt, *J* = 11.6, 4.1 Hz, 2H), 2.40 (s, 3H), 2.35 (s, *3*H), 1.98 (dt, *J* = 12.0, 2.6 Hz, 2H), 1.79 (ddd, *J* = 14.5, 10.7, 4.8 Hz, 2H). HRMS (ESI) calcd for $C_{29}H_{31}O_4$ $[M+H]^+$, 443.2222; found, 443.2227.

***6,7-bis((4-(tert-butyl)benzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]* (52).** 57% (12.9 mg), mp 51–52 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, *J* = 2.0 Hz, 4H), 7.38 (d, *J* = 3.1 Hz, 4H), 6.67 (s, 1H), 6.58 (s, 1H), 6.30 (d, *J* = 9.7 Hz, 1H), 5.49 (d, *J* = 9.7 Hz, 1H), 5.11 (s, 2H), 5.04 (s, 2H), 3.91 (td, *J* = 11.2, 2.6 Hz, 2H), 3.76 (dt, *J* = 11.6, 4.1 Hz, 2H), 1.96 (dq, *J* = 14.0, 2.3 Hz, 2H), 1.77 (ddd, *J* = 14.5, 10.7, 4.7 Hz, 2H), 1.36 (s, 9H), 1.35 (s, 9H). HRMS (ESI) calcd for $C_{35}H_{43}O_4$ $[M+H]^+$, 527.3161; found, 527.3159.

***6,7-bis(benzyloxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]* (53).** 80% (14.2 mg), mp 79 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.43 (m, 4H), 7.42–7.32 (m, 6H), 6.66 (s, 1H), 6.57 (s, 1H), 6.29 (d, *J* = 9.7 Hz, 1H), 5.49 (d, *J* = 9.7 Hz, 1H), 5.15 (s, 2H), 5.08 (s, 2H), 3.91 (td, *J* = 11.1, 2.6 Hz, 2H), 3.74 (dt, *J* = 11.5, 4.2 Hz, 2H), 1.96 (dt, *J* = 14.6, 2.5 Hz, 2H), 1.77 (ddd, *J* = 14.4, 10.7, 4.7 Hz, 2H). HRMS (ESI) calcd for $C_{27}H_{27}O_4$ $[M+H]^+$, 415.1909; found, 415.1912.

***7,7'-(((2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl)bis(oxy))bis (methylene))diquinoline* (54).** 63% (14 mg), mp 111 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.96 (dddd, *J* = 10.0, 5.8, 4.1, 1.7 Hz, 2H), 8.21 (dt, *J* = 8.2, 2.0 Hz, 2H), 8.12 (dq, *J* = 7.1, 1.3 Hz, 1H), 8.08 (dq, *J* = 7.1, 1.3 Hz, 1H), 7.79 (dt, *J* = 8.1, 1.5 Hz, 2H), 7.60–7.53 (m, 2H), 7.49–7.44 (m, 2H), 6.84 (s, 1H), 6.80 (s, 1H), 6.29 (d, *J* = 9.7 Hz, 1H), 5.95 (s, 2H), 5.92 (s, 2H), 5.46 (d, *J* = 9.7 Hz, 1H), 3.89 (td, *J* = 11.2, 2.5 Hz, 2H), 3.74 (dt, *J* = 11.5, 4.1 Hz, 2H), 1.96 (dq, *J* = 14.0, 2.7 Hz, 2H), 1.75 (ddd, *J* = 14.5, 10.9, 4.8 Hz, 2H). HRMS (ESI) calcd for $C_{33}H_{29}N_2O_4$ $[M+H]^+$, 517.2127; found, 517.2124.

***6,7-bis((5-nitrofuran-2-yl)methoxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]* (55).** 39% (8.1 mg), mp 151–152 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (d, *J* = 3.7 Hz, 2H), 6.57 (d,

J = 3.7 Hz, 2H), 6.54 (s, 1H), 6.44 (s, 1H), 6.27 (d, *J* = 9.7 Hz, 1H), 5.48 (d, *J* = 9.7 Hz, 1H), 5.15 (s, 2H), 5.08 (s, 2H), 3.92 (td, *J* = 11.2, 2.5 Hz, 2H), 3.77 (dt, *J* = 11.6, 4.0 Hz, 2H), 1.96 (dt, *J* = 14.2, 2.7 Hz, 2H), 1.76 (ddd, *J* = 14.5, 10.8, 4.8 Hz, 2H). HRMS (ESI) calcd for $C_{23}H_{21}N_2O_{10}$ $[M+H]^+$, 485.1196; found, 485.1189.

6,7-bis((5-nitrothiophen-2-yl)methoxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(56).** 77% (17.1 mg), mp 158–159 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, *J* = 4.1 Hz, 1H), 7.84 (d, *J* = 4.1 Hz, 1H), 7.07 (dt, *J* = 4.2, 0.9 Hz, 1H), 7.01 (dt, *J* = 4.1, 1.0 Hz, 1H), 6.69 (s, 1H), 6.58 (s, 1H), 6.31 (d, *J* = 9.8 Hz, 1H), 5.57 (d, *J* = 9.8 Hz, 1H), 5.28 (s, 2H), 5.21 (s, 2H), 3.90 (td, *J* = 11.2, 2.6 Hz, 2H), 3.78 (dt, *J* = 11.6, 4.2 Hz, 2H), 1.96 (dt, *J* = 13.7, 3.3 Hz, 2H), 1.81 (ddd, *J* = 14.5, 10.7, 4.7 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.7, 142.0, 128.5, 128.2, 125.2, 125.1, 122.7, 118.1, 116.2, 104.5, 74.5, 68.3, 63.4, 35.8, 29.8. HRMS (ESI) calcd for $C_{23}H_{21}N_2O_8S_2$ $[M+H]^+$, 517.0739; found, 517.0726.

(5R,5'R)-5,5'-(((2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl)bis(oxy)) bis(methylene))bis(pyrrolidin-2-one) **(57).** 23% (4.2 mg), mp 58–59 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.32 (s, 1H), 6.50 (s, 1H), 6.41 (s, 1H), 6.31 (d, *J* = 9.8 Hz, 1H), 5.51 (d, *J* = 9.7 Hz, 1H), 4.12–4.03 (m, 4H), 3.99 (tdd, *J* = 12.3, 6.3, 3.5 Hz, 4H), 3.93–3.70 (m, 4H), 3.44 (dd, *J* = 10.2, 4.9 Hz, 1H), 3.37 (dd, *J* = 10.4, 6.9 Hz, 1H), 2.54–2.42 (m, 2H), 2.36 (dddd, *J* = 20.1, 12.2, 10.1, 5.6 Hz, 2H), 2.08–1.98 (m, 2H), 1.96–1.84 (m, 2H). HRMS (ESI) calcd for $C_{23}H_{29}N_2O_6$ $[M+H]^+$, 429.2026; found, 429.2031.

(5S,5'S)-5,5'-(((2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl)bis(oxy)) bis(methylene))bis(pyrrolidin-2-one) **(58).** 31% (5.7 mg), mp 57 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.52 (s, 1H), 6.57 (s, 1H), 6.41 (s, 1H), 6.30 (d, *J* = 9.8, 1H), 5.51 (d, *J* = 9.7, 1H), 3.95–3.87 (m, 4H), 3.60 (dd, *J* = 9.9, 7.9 Hz, 4H), 3.50 (dd, *J* = 10.2, 5.9 Hz, 4H), 3.45 (dd, *J* = 10.2, 7.7 Hz, 1H), 3.26 (dd, *J* = 10.0, 6.0 Hz, 1H), 2.54 (dd, *J* = 17.2, 9.0 Hz, 2H), 2.23 (dd, *J* = 17.1, 7.2 Hz, 2H), 1.95 (dd, *J* = 35.2, 21.5 Hz, 4H). HRMS (ESI) calcd for $C_{23}H_{29}N_2O_6$ $[M+H]^+$, 429.2026; found, 429.2029.

6,7-bis((4-(methylsulfonyl)benzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(59).** 56% (13.7 mg), mp 160–161 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00–7.92 (m, 4H), 7.65 (dd, *J* = 8.2, 6.0 Hz, 4H), 6.65 (s, 1H), 6.55 (s, 1H), 6.29 (d, *J* = 9.7 Hz, 1H), 5.54 (d, *J* = 9.7 Hz, 1H), 5.22 (s, 2H), 5.17 (s, 2H), 3.94 (td, *J* = 11.2, 2.6 Hz, 2H), 3.76 (dt, *J* = 11.5, 4.2 Hz, 2H), 3.10 (s, 3H), 3.09 (s, 3H), 1.99 (dt, *J* = 12.0, 2.6 Hz, 2H), 1.78 (ddd, *J* = 14.5, 10.6, 4.7 Hz, 2H). HRMS (ESI) calcd for $C_{29}H_{31}O_8S_2$ $[M+H]^+$, 571.1460; found, 571.1467.

4,4'-(((2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl)bis(oxy))bis (methylene))dibenzenesulfonyl fluoride **(60).** 51% (12.7 mg), mp 165–166 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (ddd, *J* = 11.5, 7.5, 1.8 Hz, 4H), 7.71 (t, *J* = 7.6 Hz, 4H), 6.64 (s, 1H), 6.54 (s, 1H), 6.29 (dd, *J* = 9.8, 2.0 Hz, 1H), 5.55 (d, *J* = 9.8 Hz, 1H), 5.26 (s, 2H), 5.20 (s, 2H), 3.89 (tdd, *J* = 11.1, 8.3, 2.6 Hz, 2H), 3.77 (dp, *J* = 11.5, 4.0 Hz, 2H), 1.95 (dd, *J* = 13.7, 3.8 Hz, 2H), 1.79 (tdd, *J* = 14.1, 10.6, 4.7 Hz, 2H). HRMS (ESI) calcd for $C_{27}H_{25}F_2O_8S_2$ $[M+H]^+$, 579.0959; found, 579.0953.

dimethyl 4,4'-(((2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl)bis(oxy)) bis(methylene))dibenzenesulfonate **(61).** 59% (15.3 mg), mp 151 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97–7.90 (m, 4H), 7.65 (t, *J* = 8.0 Hz, 4H), 6.65 (s, 1H), 6.55 (s, 1H), 6.29 (d, *J* = 9.7 Hz, 1H),

5.54 (d, *J* = 9.7 Hz, 1H), 5.22 (s, 2H), 5.17 (s, 2H), 3.90 (td, *J* = 11.1, 2.6 Hz, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.76 (dt, *J* = 11.6, 4.1 Hz, 2H), 1.95 (dt, *J* = 11.9, 2.7 Hz, 2H), 1.78 (ddd, *J* = 14.5, 10.6, 4.7 Hz, 2H). HRMS (ESI) calcd for $C_{29}H_{31}O_{10}S_2$ $[M+H]^+$, 603.1359; found, 603.1360.

4,4'-((((2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl)bis(oxy))bis (methylene))bis(4,1-phenylenesulfonyl))dimorpholine **(62).** 61% (18.7 mg), mp 168–169 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 14.2, 8.1 Hz, 4H), 7.64 (dd, *J* = 11.0, 8.1 Hz, 4H), 6.66 (s, 1H), 6.57 (s, 1H), 6.30 (d, *J* = 9.7 Hz, 1H), 5.54 (d, *J* = 9.7 Hz, 1H), 5.22 (s, 2H), 5.16 (s, 2H), 3.90 (td, *J* = 11.2, 2.5 Hz, 2H), 3.77 (dq, *J* = 7.7, 5.2, 3.7 Hz, 10H), 3.03 (q, *J* = 5.0 Hz, 8H), 1.96 (dt, *J* = 11.8, 2.6 Hz, 2H), 1.79 (ddd, *J* = 14.4, 10.6, 4.7 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.6, 148.0, 143.2, 142.6, 142.5, 134.9, 134.7, 128.3, 128.2, 127.8, 127.6, 123.0, 115.2, 114.8, 103.9, 71.8, 70.2, 66.2, 63.4, 46.1, 35.8. HRMS (ESI) calcd for $C_{35}H_{40}N_2O_{10}S_2$ $[M+H]^+$, 713.2203; found, 713.2209.

4,4'-(((2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl)bis(oxy))bis (methylene))bis(N,N-dimethylbenzenesulfonamide) **(63).** 31% (8.4 mg), mp 179–180 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82–7.77 (m, 4H), 7.66–7.61 (m, 4H), 6.66 (s, 1H), 6.56 (s, 1H), 6.29 (d, *J* = 9.7 Hz, 1H), 5.54 (d, *J* = 9.7 Hz, 1H), 5.21 (s, 3H), 5.15 (s, 2H), 3.93 (td, *J* = 11.3, 2.4 Hz, 2H), 3.76 (dt, *J* = 11.6, 4.2 Hz, 2H), 2.74 (s, 6H), 2.73 (s, 6H), 1.97 (dt, *J* = 11.6, 2.7 Hz, 2H), 1.78 (ddd, *J* = 14.5, 10.6, 4.8 Hz, 2H). HRMS (ESI) calcd for $C_{31}H_{37}N_2O_8S_2$ $[M+H]^+$, 629.1991; found, 629.1986.

1,1'-((((2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-6,7-diyl)bis(oxy))bis (methylene))bis(4,1-phenylenesulfonyl))bis(aziridine) **(64).** 21% (5.64 mg), mp 173–174 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82–7.77 (m, 4H), 7.66–7.61 (m, 4H), 6.66 (s, 1H), 6.56 (s, 1H), 6.29 (d, *J* = 9.7 Hz, 1H), 5.54 (d, *J* = 9.7 Hz, 1H), 5.21 (s, 3H), 5.15 (s, 2H), 3.93 (td, *J* = 11.3, 2.4 Hz, 2H), 3.76 (dt, *J* = 11.6, 4.2 Hz, 2H), 1.97 (dt, *J* = 11.6, 2.7 Hz, 2H), 1.78 (ddd, *J* = 14.5, 10.6, 4.8 Hz, 2H), 0.86–1.04 (m, 2H), 0.81–0.85 (m, 2H). HRMS (ESI) calcd for $C_{31}H_{33}N_2O_8S_2$ $[M+H]^+$, 625.1678; found, 625.1672.

6-(benzyloxy)-7-((4-nitrobenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(65).** 18% (3.5 mg), mp 123 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.46–7.43 (m, 2H), 7.41–7.34 (m, 3H), 6.69 (s, 1H), 6.53 (s, 1H), 6.31 (d, *J* = 9.8 Hz, 1H), 5.53 (d, *J* = 9.7 Hz, 1H), 5.22 (s, 2H), 5.09 (s, 2H), 3.90 (td, *J* = 11.2, 2.6 Hz, 2H), 3.76 (dt, *J* = 11.6, 4.2 Hz, 2H), 1.98 (dt, *J* = 11.6, 2.7 Hz,, 2H), 1.78 (ddd, *J* = 14.4, 10.6, 4.7 Hz, 2H). HRMS (ESI) calcd for $C_{27}H_{26}NO_6$ $[M+H]^+$, 460.1760; found, 460.1755.

7-(benzyloxy)-6-((4-nitrobenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(66).** 21% (4.1 mg), mp 126 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 6.7 Hz, 2H), 7.43–7.36 (m, 3H), 6.64 (s, 1H), 6.61 (s, 1H), 6.29 (d, *J* = 9.7 Hz, 1H), 5.51 (d, *J* = 9.7 Hz, 1H), 5.14 (s, 2H), 5.13 (s, 2H), 3.91 (td, *J* = 11.1, 2.6 Hz, 2H), 3.76 (dt, *J* = 11.6, 4.2 Hz, 2H), 1.96 (dt, *J* = 11.4, 2.6 Hz, 2H), 1.78 (ddd, *J* = 14.2, 10.6, 4.7 Hz, 2H). HRMS (ESI) calcd for $C_{27}H_{26}NO_6$ $[M+H]^+$, 460.1760; found, 460.1762.

5-(((6-((4-nitrobenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-7-yl) oxy)methyl)benzo[c][1,2,5]oxadiazole **(67).** 31% (6.7 mg), mp 137–138 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.4 Hz, 2H), 7.90 (s, 1H), 7.85 (dd, *J* = 9.3, 1.0 Hz, 1H), 7.66 (d, *J* = 8.6 Hz,, 2H), 7.47 (dd, *J* = 9.2, 1.4 Hz, 1H), 6.69 (s, 1H), 6.55 (s, 1H), 6.30 (d, *J* = 9.7 Hz, 1H), 5.54 (d, *J*

= 9.7 Hz, 1H), 5.25 (s, 2H), 5.17 – 5.14 (m, 2H), 3.89 (td, *J* = 11.0, 2.6 Hz, 2H), 3.76 (dt, *J* = 11.6, 4.2 Hz, 2H), 1.95 (dt, *J* = 11.9, 2.6 Hz, 2H), 1.79 (td, *J* = 10.2, 9.7, 5.3 Hz, 2H). HRMS (ESI) calcd for $C_{27}H_{24}N_3O_7$ $[M+H]^+$, 502.1614; found, 502.1618.

1-(6,7-bis((4-nitrobenzyl)oxy)spiro[chromene-2,4'-piperidin]-1'-yl)ethan-1-one **(68).** 68% (13 mg), mp > 200 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.28–8.20 (m, 4H), 7.60 (dd, *J* = 8.6, 6.6 Hz, 4H), 6.63 (s, 1H), 6.50 (s, 1H), 6.28 (d, *J* = 9.7 Hz, 1H), 5.43 (d, *J* = 9.7 Hz, 1H), 5.21 (d, *J* = 2.9 Hz, 2H), 5.16 (s, 2H), 4.32 (d, *J* = 13.3 Hz, 1H), 3.62–3.51 (m, 2H), 3.15 (td, *J* = 13.8, 13.0, 3.1 Hz, 1H), 2.13–2.02 (m, 3H), 2.02–1.99 (m, 2H), 1.59 (dddd, *J* = 19.1, 13.9, 11.8, 4.9 Hz, 2H). HRMS (ESI) calcd for $C_{29}H_{28}N_3O_8$ $[M+H]^+$, 546.1876; found, 546.1880.

6,7-bis((4-nitrobenzyl)oxy)spiro[chromene-2,4'-piperidine] **(69).** 77% (8.9 mg), mp > 200 ˚C; ^{1}H NMR (600 MHz, CD_3OD) δ 8.27–8.19 (m, 4H), 7.71–7.65 (m, 4H), 6.86 (s, 1H), 6.70 (s, 1H), 6.46 (d, *J* = 9.7 Hz, 1H), 5.56 (d, *J* = 9.7 Hz, 1H), 5.26 (s, 2H), 5.20 (s, 2H), 3.37 (td, *J* = 12.9, 3.1 Hz, 2H), 3.27 (d, *J* = 12.7 Hz, 2H), 2.20 (dt, *J* = 14.8, 3.1 Hz, 3H), 2.03 (s, 1H), 1.87 (ddd, *J* = 14.6, 12.8, 4.6 Hz, 3H), 1.60 (s, 1H). HRMS (ESI) calcd for $C_{27}H_{26}N_3O_7$ $[M+H]^+$, 504.1766; found, 504.1764.

1-(6,7-bis((4-nitrobenzyl)oxy)spiro[chromene-2,3'-piperidin]-1'-yl)ethan-1-one **(70).** 64% (18.1 mg), mp > 200 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27–8.19 (m, 4H), 7.60 (td, *J* = 7.7, 6.8, 4.1 Hz, 4H), 6.63 (s, 1H), 6.51 (s, 1H), 6.33 (dd, *J* = 20.1, 9.8 Hz, 1H), 5.43 (dd, *J* = 9.8, 2.0 Hz, 1H), 5.24–5.12 (m, 4H), 4.45–4.39 (m, 1H), 3.80 (d, *J* = 13.9 Hz, 1H), 3.10 (dd, *J* = 28.3, 13.8 Hz, 1H), 2.85 – 2.75 (m, 1H), 2.14 (d, *J* = 14.5 Hz, 2H), 1.93 (s, 2H), 1.90 (s, 1H), 1.63 (td, *J* = 13.6, 12.8, 4.4 Hz, 1H), 1.55 (dt, *J* = 13.5, 3.9 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.2, 149.4, 149.0, 147.4, 147.3, 147.1, 145.0, 144.9, 144.3, 144.1, 142.4, 127.9, 127.5, 127.4, 127.3, 123.7, 123.6, 116.3, 103.1, 74.3, 74.0, 73.6, 72.9, 71.6, 70.8, 70.8, 70.6, 69.5, 69.4, 65.7, 62.0, 61.4, 53.6, 41.9, 39.1, 34.3, 31.8, 27.6, 24.2, 21.4, 21.2, 21.1, 20.6. HRMS (ESI) calcd for $C_{29}H_{28}N_3O_8$ $[M+H]^+$, 546.1876; found, 546.1883.

6,7-bis((4-nitrobenzyl)oxy)spiro[chromene-2,3'-piperidine] **(71).** 71% (11.5 mg), mp > 200 ˚C; ^{1}H NMR (600 MHz, CD_3OD) δ 8.28–8.19 (m, 4H), 7.71–7.65 (m, 4H), 6.87 (s, 1H), 6.71 (s, 1H), 6.52 (d, *J* = 9.8 Hz, 1H), 5.49 (d, *J* = 9.8 Hz, 1H), 5.29–5.25 (m, 2H), 5.21 (s, 2H), 3.48 (dt, *J* = 13.3, 1.9 Hz, 1H), 3.37 (ddd, *J* = 12.8, 4.2, 2.3 Hz, 1H), 3.10 (d, *J* = 13.2 Hz, 1H), 3.05–2.98 (m, 1H), 2.21–2.12 (m, 2H), 1.81 (d, *J* = 14.4 Hz, 1H), 1.75–1.68 (m, 1H). HRMS (ESI) calcd for $C_{27}H_{26}N_3O_7$ $[M+H]^+$, 504.1766; found, 504.1761.

2-(6,7-bis((4-nitrobenzyl)oxy)spiro[chromene-2,4'-piperidin]-1'-yl)ethan-1-ol **(72).** 53% (4.1 mg) mp > 200 ˚C; ^{1}H NMR (600 MHz, CD_3OD) δ 8.27–8.19 (m, 4H), 7.71–7.65 (m, 4H), 6.86 (s, 1H), 6.70 (s, 1H), 6.47 (d, *J* = 9.7 Hz, 1H), 5.58 (d, *J* = 9.7 Hz, 1H), 5.27 (s, 2H), 5.21 (s, 2H), 3.90 (tdd, *J* = 12.1, 8.5, 3.3 Hz, 1H), 3.84–3.81 (m, 1H), 3.39–3.34 (m, 2H), 3.22–3.17 (m, 1H), 3.29 (d, *J* = 12.7 Hz, 2H), 2.22 (dt, *J* = 14.8, 3.1 Hz, 3H), 2.04 (s, 1H), 1.87 (ddd, *J* = 14.6, 12.8, 4.6 Hz, 3H), 1.63 (s, 1H). HRMS (ESI) calcd for $C_{29}H_{30}N_3O_8$ $[M+H]^+$, 548.2028; found, 548.2031.

2-(6,7-bis((4-nitrobenzyl)oxy)spiro[chromene-2,3'-piperidin]-1'-yl)ethan-1-ol **(73).** 61% (5.2 mg), mp > 200 ˚C; ^{1}H NMR (600 MHz, CD_3OD) δ 8.27–8.22 (m, 4H), 7.69 (dd, *J* = 8.8, 3.3 Hz, 4H), 6.89 (s, 1H), 6.72 (s, 1H), 6.55 (d, *J* = 9.8 Hz, 1H), 5.50 (d, *J* = 9.8 Hz, 1H), 5.28 (d, *J* = 2.2 Hz, 2H), 5.22 (s, 2H), 3.89 (ddd, *J* = 12.1, 8.5, 3.3 Hz, 1H), 3.86–3.79 (m, 2H), 3.57–3.53 (m, 1H), 3.38–3.34 (m, 1H), 3.24–3.19 (m, 1H), 3.12 (dd, *J* = 15.6, 11.6 Hz, 2H), 2.28 (qt, *J* = 13.5, 4.0 Hz,

1H), 2.23–2.18 (m, 1H), 2.04 (d, *J* = 6.0 Hz, 1H), 1.91–1.84 (m, 1H), 1.70 (td, *J* = 13.9, 4.5 Hz, 1H). HRMS (ESI) calcd for $C_{29}H_{30}N_3O_8$ $[M+H]^+$, 548.2028; found, 548.2033.

***6,7-bis((4-nitrobenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-thiopyran] 1',1'-dioxide* (74).** 66% (12.9 mg), mp 145–146 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31–8.24 (m, 4H), 7.68–7.60 (m, 4H), 6.67 (s, 1H), 6.54 (s, 1H), 6.36 (d, *J* = 9.7 Hz, 1H), 5.50 (d, *J* = 9.7 Hz, 1H), 5.26 (s, 2H), 5.20 (s, 2H), 3.49 (td, *J* = 13.8, 3.6 Hz, 2H), 2.95 (dt, *J* = 11.2, 2.4 Hz, 2H), 2.51 (dt, *J* = 11.8, 2.6 Hz, 2H), 2.29 (td, *J* = 14.2, 3.4 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.8, 147.9, 147.8, 146.7, 144.6, 143.1, 127.7, 127.6, 125.6, 124.1, 124.1, 124.0, 114.6, 114.6, 103.5, 73.3, 71.3, 70.0, 46.6, 33.4. HRMS (ESI) calcd for $C_{27}H_{25}N_2O_9S$ $[M+H]^+$, 553.1281; found, 553.1273.

***6,7-bis((4-nitrobenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-thiopyran]* (75).** 63% (13.1 mg), mp 145–147 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.28–8.24 (m, 4H), 7.65–7.61 (m, 4H), 6.63 (s, 1H), 6.54 (s, 1H), 6.26 (d, *J* = 9.7 Hz, 1H), 5.48 (d, *J* = 9.8 Hz, 1H), 5.24 (s, 2H), 5.18 (s, 2H), 3.09 (ddd, *J* = 14.1, 11.8, 2.6 Hz, 2H), 2.46–2.41 (m, 2H), 2.28 (dt, *J* = 14.2, 3.8 Hz, 2H), 1.81 (ddd, *J* = 14.0, 11.8, 3.7 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.9, 147.2, 147.1, 144.4, 143.6, 142.0, 130.4, 130.2, 127.6, 127.1, 127.0, 125.9, 123.8, 123.6, 123.6, 123.4, 123.3, 122.0, 114.6, 114.0, 103.2, 74.6, 70.9, 69.4, 61.6, 35.6, 22.8. HRMS (ESI) calcd for $C_{27}H_{25}N_2O_7S$ $[M+H]^+$, 521.1382; found, 521.1376.

***1'-methyl-6,7-bis((4-nitrobenzyl)oxy)-2',3',5',6'-tetrahydro-1'H-spiro[chromene-2,4'-thiopyran]-1'-ium* (76).** 78% (8 mg), mp >200 ˚C; ^{1}H NMR (600 MHz, CD_3CN) δ 8.28–8.22 (m, 4H), 7.69–7.66 (m, 4H), 6.96 (s, 1H), 6.87 (s, 1H), 6.47 (d, *J* = 9.7 Hz, 1H), 5.57 (dd, *J* = 9.8, 2.2 Hz, 1H), 5.31 (s, 2H), 5.20 (s, 2H), 3.57 (td, *J* = 12.9, 2.7 Hz, 2H), 3.48 (td, *J* = 13.6, 3.8 Hz, 2H), 3.01 (s, 3H), 2.52–2.46 (m, 2H), 2.17 (td, *J* = 14.2, 3.4 Hz, 2H). HRMS (ESI) calcd for $C_{28}H_{27}N_2O_7S^+$ $[M]^+$, 535.1533; found, 535.1543.

***2,2-dimethyl-6,7-bis((4-nitrobenzyl)oxy)-2H-chromene* (77).** 83% (20 mg), mp 172–173 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.27–8.24 (m, 4H), 7.64–7.60 (m, 4H), 6.63 (s, 1H), 6.45 (s, 1H), 6.21 (d, *J* = 9.9 Hz, 1H), 5.53 (d, *J* = 9.8 Hz, 1H), 5.22 (s, 2H), 5.18 (s, 2H), 1.42 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.7, 148.0, 147.2, 147.1, 144.5, 143.8, 141.6, 128.8, 128.7, 128.5, 127.1, 127.0, 123.4, 123.3, 123.3, 123. 2, 121.0, 114.2, 113.9, 103.1, 75.9, 71.0, 69.3, 27.3, 27.3. HRMS (ESI) calcd for $C_{25}H_{23}N_2O_7$ $[M+H]^+$, 463.1505; found, 463.1509. Identical in all respects with published data.[19]

***6,7-bis((4-nitrobenzyl)oxy)-5',6'-dihydro-2'H,4'H-spiro[chromene-2,3'-pyran]* (78).** 57% (12.3 mg), mp 168 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28–8.23 (m, 4H), 7.64–7.60 (m, 4H), 6.61 (s, 1H), 6.46 (s, 1H), 6.42 (d, *J* = 10.0 Hz, 1H), 5.42 (d, *J* = 9.9 Hz, 1H), 5.22 (s, 2H), 5.18 (s, 2H), 3.69 (d, *J* = 11.7 Hz, 1H), 3.59 (d, *J* = 11.7 Hz, 1H), 3.47–3.36 (m, 2H), 2.04–1.97 (m, 2H), 1.79 – 1.69 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.7, 148.6, 147.8, 147.7, 144.9, 144.2, 142.4, 127.7, 127.7, 127.7, 127.6, 127.6, 127.5, 125.5, 124.0, 123.9, 123.9, 123.2, 114.8, 113.7, 103.2, 71.5, 70.0, 67.9, 35.3, 33.9, 27.3. HRMS (ESI) calcd for $C_{27}H_{25}N_2O_8$ $[M+H]^+$, 505.1611; found, 505.1613.

***methyl 6,7-bis((4-nitrobenzyl)oxy)spiro[chromene-2,1'-cyclobutane]-3'-carboxylate* (79).** 32% (6.5 mg), mp 138 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28–8.24 (m, 4H), 7.64–7.59 (m, 4H), 6.61 (s, 1H), 6.49 (s, 1H), 6.29 (d, *J* = 9.7 Hz, 1H), 5.82 (d, *J* = 9.8 Hz, 2H), 5.22 (s, 2H), 5.18 (s, 2H),

3.73 (d, *J* = 2.4 Hz, 3H), 3.27 (tt, *J* = 9.5, 7.1 Hz, 1H), 2.75–2.67 (m, 2H), 2.55–2.45 (m, 2H). HRMS (ESI) calcd for $C_{28}H_{25}N_2O_9$ $[M+H]^+$, 533.1560; found, 533.1554.

6,7-bis((4-nitrobenzyl)oxy)spiro[chromene-2,1'-cyclobutane]-3'-carboxylic acid **(80).** 37% (7.7 mg), mp 149–151 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29–8.23 (m, 4H), 7.62 (dd, *J* = 8.8, 2.1 Hz, 4H), 6.62 (s, 1H), 6.50 (s, 1H), 6.20 (d, *J* = 9.8 Hz, 1H), 5.84 (d, *J* = 9.7 Hz, 1H), 5.24 (s, 2H), 5.18 (s, 2H), 3.39 (t, *J* = 6.8 Hz, 1H), 2.58–2.53 (m, 2H), 2.01–1.94 (m, 2H). HRMS (ESI) calcd for $C_{27}H_{23}N_2O_9$ $[M+H]^+$, 519.1404; found, 519.1411.

6,7-bis((4-nitrobenzyl)oxy)-4',5'-dihydro-2'H-spiro[chromene-2,3'-furan] **(81).** 57% (12.7 mg), mp 163 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.28–8.23 (m, 4H), 7.66–7.60 (m, 4H), 6.64 (s, 1H), 6.51 (s, 1H), 6.36 (d, *J* = 9.8 Hz, 1H), 5.56 (d, *J* = 9.8 Hz, 1H), 5.23 (s, 2H), 5.19 (s, 2H), 4.15 – 4.09 (m, 2H), 4.00 (td, *J* = 8.6, 3.4 Hz, 1H), 3.60 (d, *J* = 10.0 Hz, 1H), 2.43 (dddd, *J* = 13.4, 6.7, 3.4, 1.2 Hz, 1H), 1.97 (dt, *J* = 13.4, 9.0 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.0, 147.4, 147.2, 147.1, 144.3, 143.6, 142.0, 127.1, 127.0 (2C), 124.1, 123.4 (4C), 122.8, 114.0, 114.0, 103.2, 103.2, 87.7, 85.3, 70.9, 69.3, 67.2, 39.4. HRMS (ESI) calcd for $C_{26}H_{23}N_2O_8$ $[M+H]^+$, 491.1454; found, 491.1460.

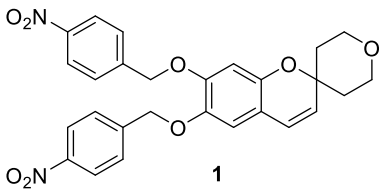
2'-methyl-6,7-bis((4-nitrobenzyl)oxy)-4',5'-dihydro-2'H-spiro[chromene-2,3'-furan] **(82).** 64% (13.8 mg), mp 167–168 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.28–8.23 (m, 4H), 7.65–7.60 (m, 4H), 6.60 (s, 1H), 6.51 (s, 1H), 6.36 (d, *J* = 9.9 Hz, 1H), 5.42 (d, *J* = 9.8 Hz, 1H), 5.22 (s, 2H), 5.18 (s, 2H), 4.14 (q, *J* = 8.0 Hz, 1H), 3.90 (ddd, *J* = 9.4, 8.4, 4.3 Hz, 1H), 3.66 (q, *J* = 6.3 Hz, 1H), 2.46 (ddd, *J* = 13.6, 7.7, 4.3 Hz, 1H), 2.08 – 2.00 (m, 1H), 1.25 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.1, 148.4, 147.2, 147.1, 144.4, 143.6, 141.5, 141.4, 127.3, 127.1, 127.0, 126.8, 124.2, 123.4, 123.3, 121.9, 114.2, 113.3, 102.4 (2C), 85.5, 82.8, 71.0, 69.2, 65.3, 40.4, 13.2. HRMS (ESI) calcd for $C_{27}H_{25}N_2O_8$ $[M+H]^+$, 505.1611; found, 505.1605.

1'-acetyl-8-methyl-6,7-bis((4-nitrobenzyl)oxy)spiro[chromane-2,4'-piperidin]-4-one **(86).** 72% **(**121 mg), mp >200 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23–8.18 (m, 4H), 7.60–7.53 (m, 4H), 7.31 (s, 1H), 7.26 (s, 1H), 5.19 (d, *J* = 6.2 Hz, 4H), 3.83–3.78 (m, 4H), 2.70 (s, 2H), 2.20 (s, 3H), 1.98 (dd, *J* = 14.2, 2.3 Hz, 2H), 1.81–1.74 (m, 2H). HRMS (ESI) calcd for $C_{28}H_{27}N_2O_9$ $[M+H]^+$, 535.1717; found, 535.1714.

8-methyl-6,7-bis((4-nitrobenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromane-2,4'-pyran]-4-ol **(87).** 59% (43 mg), mp >200 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.22–8.17 (m, 4H), 7.62–7.57 (m, 2H), 7.57–7.52 (m, 2H), 6.94 (s, 1H), 5.15 (d, *J* = 3.3 Hz, 2H), 5.09 (s, 2H), 4.82 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.86 (d, *J* = 2.8 Hz, 1H), 3.81 (dd, *J* = 5.0, 2.4 Hz, 1H), 3.77 (dd, *J* = 6.5, 4.4 Hz, 3H), 2.17 (s, 3H), 2.16 – 2.13 (m, 1H), 1.89–1.84 (m, 2H), 1.74–1.70 (m, 2H). HRMS (ESI) calcd for $C_{28}H_{29}N_2O_9$ $[M+H]^+$, 537.1873; found, 537.1868.

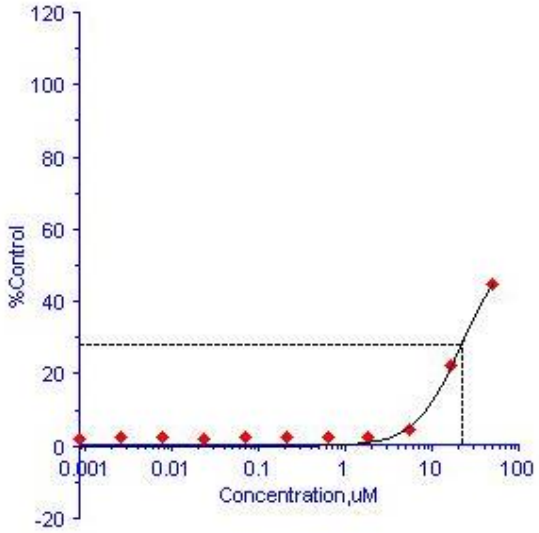
8-methyl-6,7-bis((4-nitrobenzyl)oxy)-2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran] **(88).** 54% (11 mg), mp 186–187 ˚C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23–8.17 (m, 4H), 7.61–7.57 (m, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.26 (s, 1H), 6.49 (s, 1H), 6.28 (d, *J* = 9.7 Hz, 1H), 5.54 (d, *J* = 9.7 Hz, 1H), 5.11 (d, *J* = 17.8 Hz, 4H), 3.89 (td, *J* = 11.5, 2.3 Hz, 2H), 3.78 (ddd, *J* = 11.6, 4.8, 2.6 Hz, 2H), 2.18 (s, 3H), 1.93 (dq, *J* = 14.3, 2.5 Hz, 2H), 1.76 (ddd, *J* = 13.8, 11.4, 4.9 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 147.7 (2), 147.3, 145.7, 145.5, 145.1, 144.6, 128.9, 128.2, 127.7, 124.0, 123.9, 123.9, 123.8, 123.8, 123.8, 123.3, 121.1, 117.6, 110.7, 74.1, 73.5, 70.9, 63.6, 35.7. HRMS (ESI) calcd for $C_{28}H_{27}N_2O_8$ $[M+H]^+$, 519.1767; found, 519.1769.

Dose-response curves of compounds 1, 13, 18, 24 and 69 on NF-κB activation in hTLR3, hTLR8, hTLR9 and hTLR7 HEK-blue reporter cells (representative of all generated):

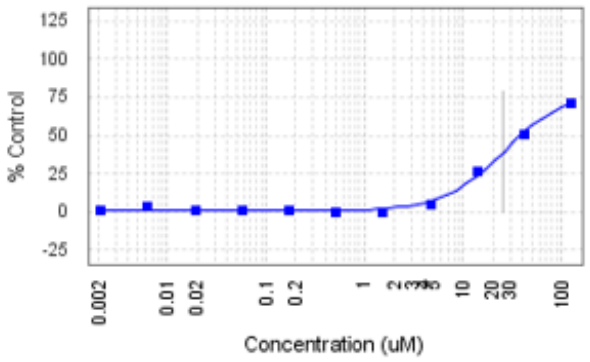


1

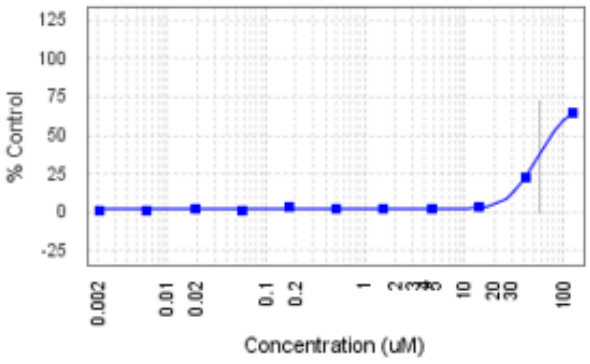
hTLR3

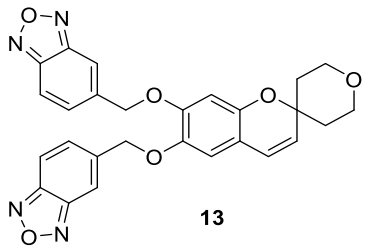


hTLR8



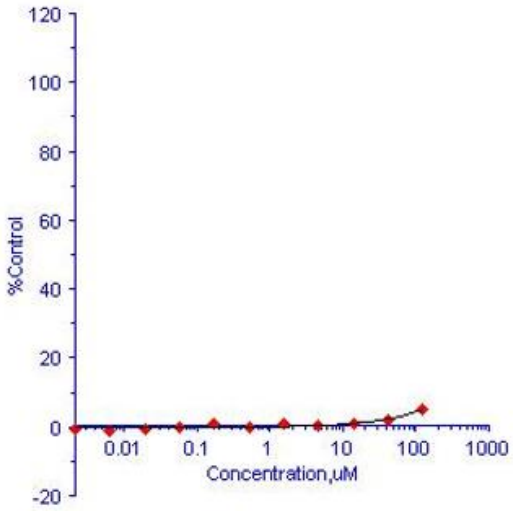
hTLR9



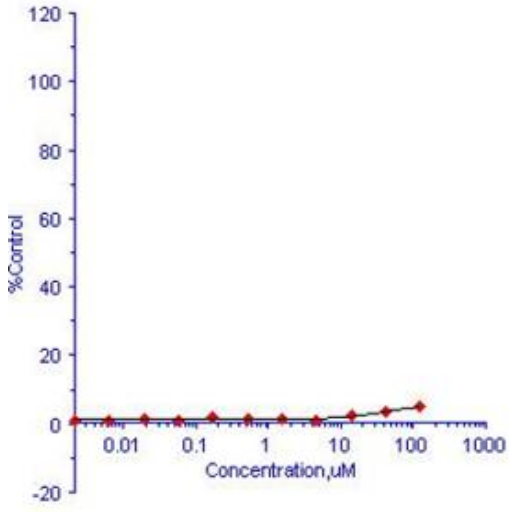


13

hTLR7



hTLR8



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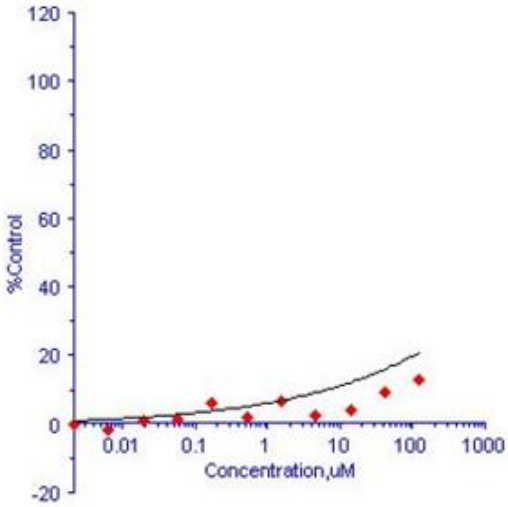
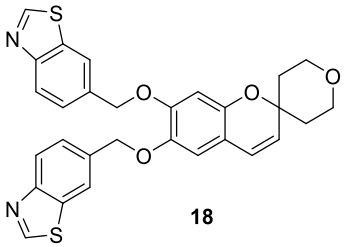
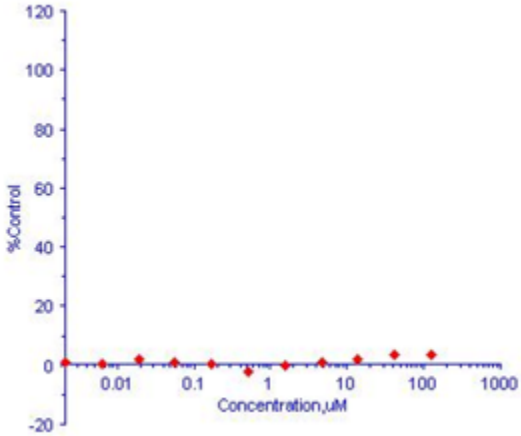




18

hTLR7



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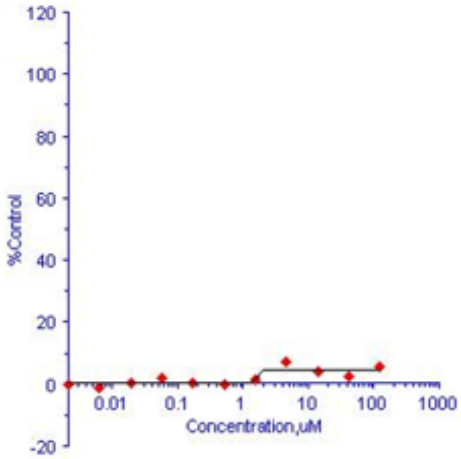

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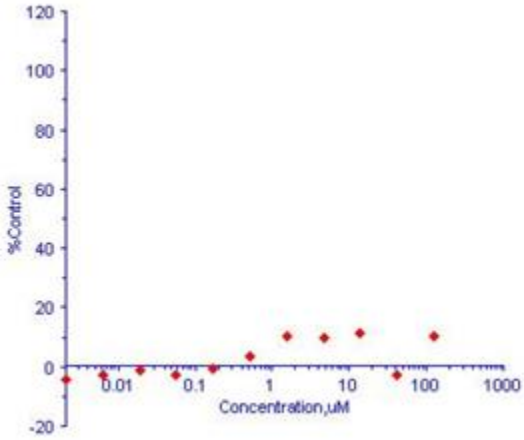
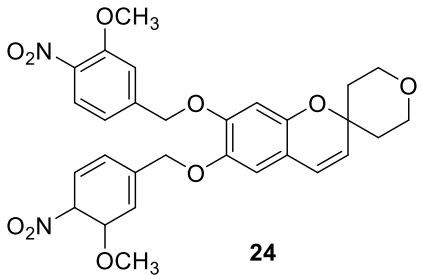
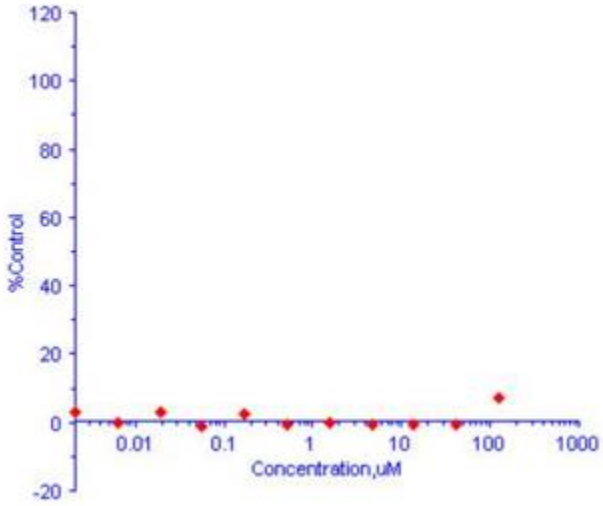




24

hTLR7



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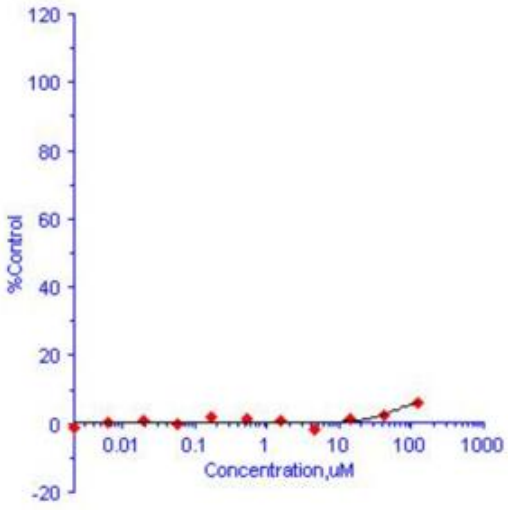

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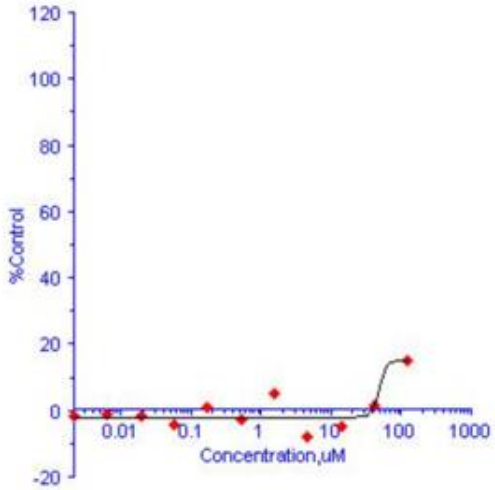
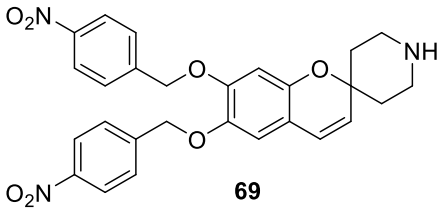
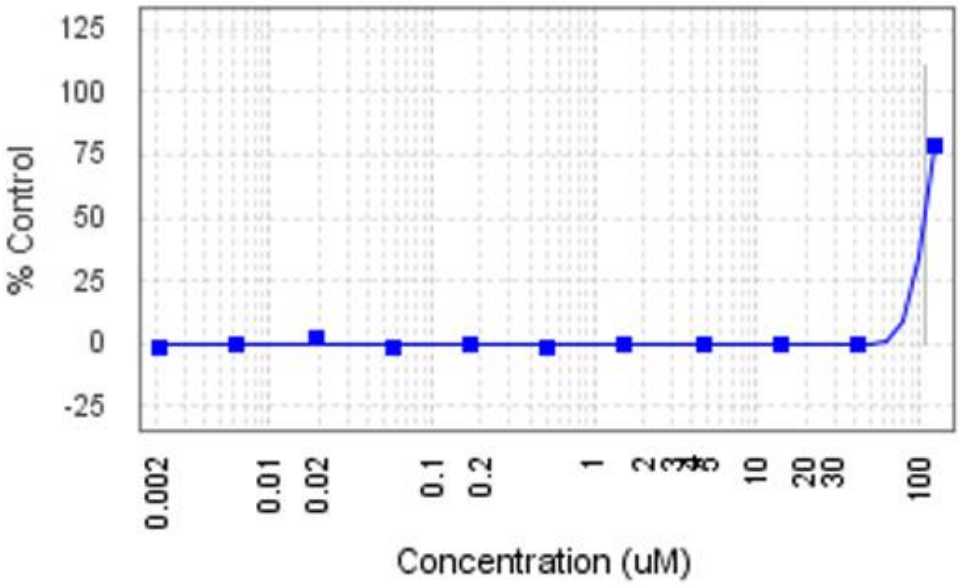
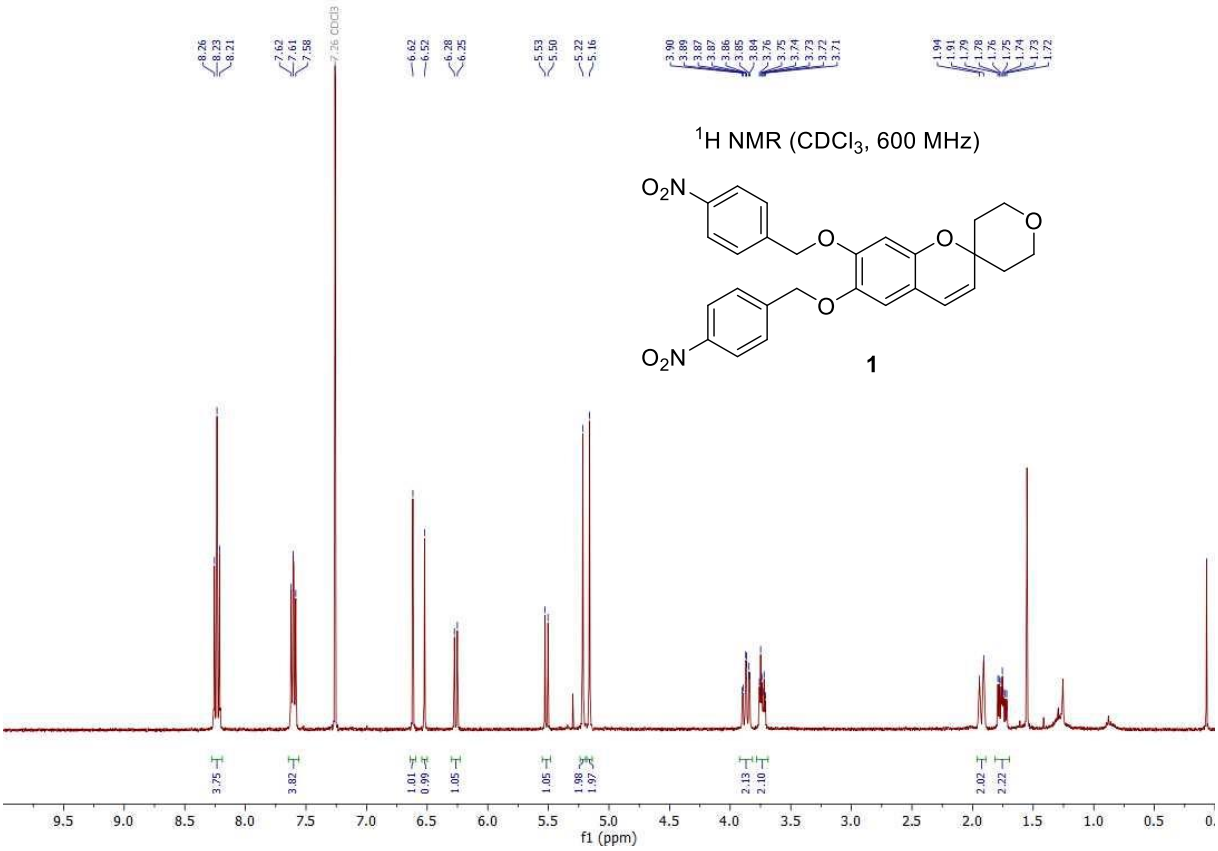


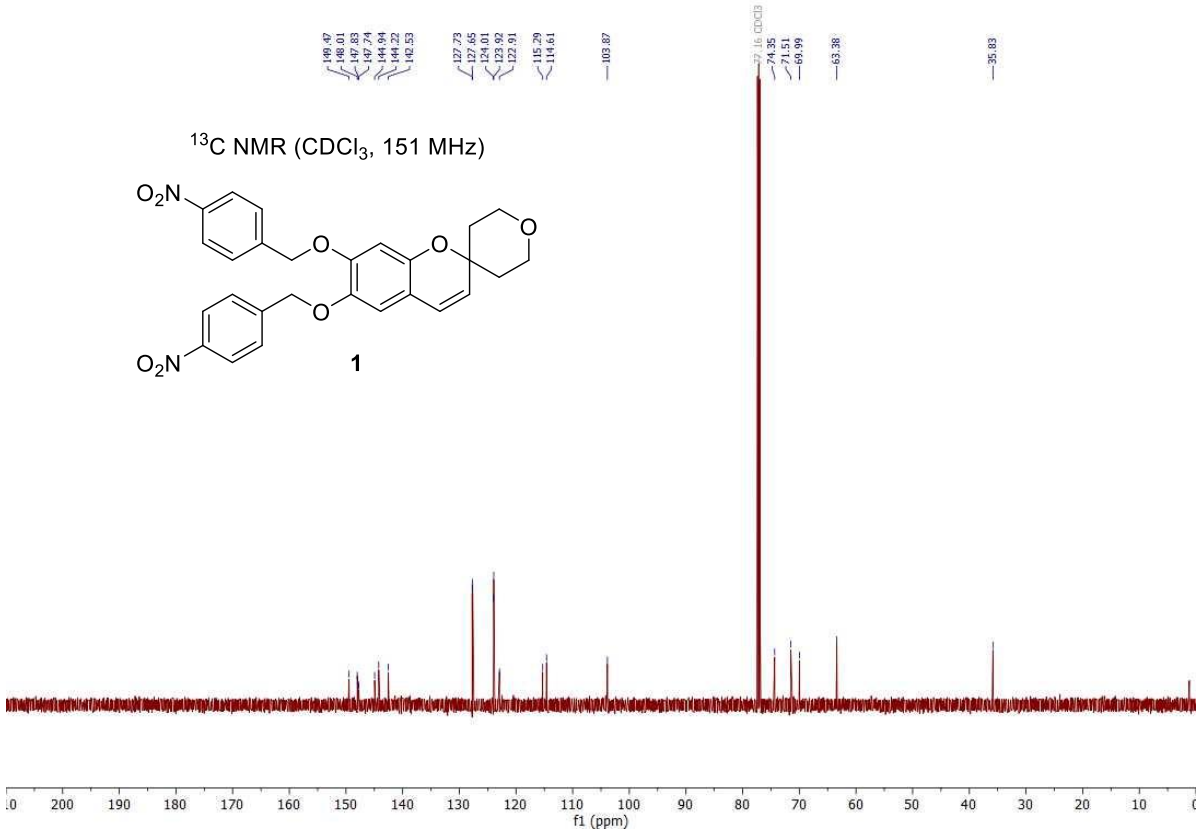

O2N
O
O
NH
O
O2N

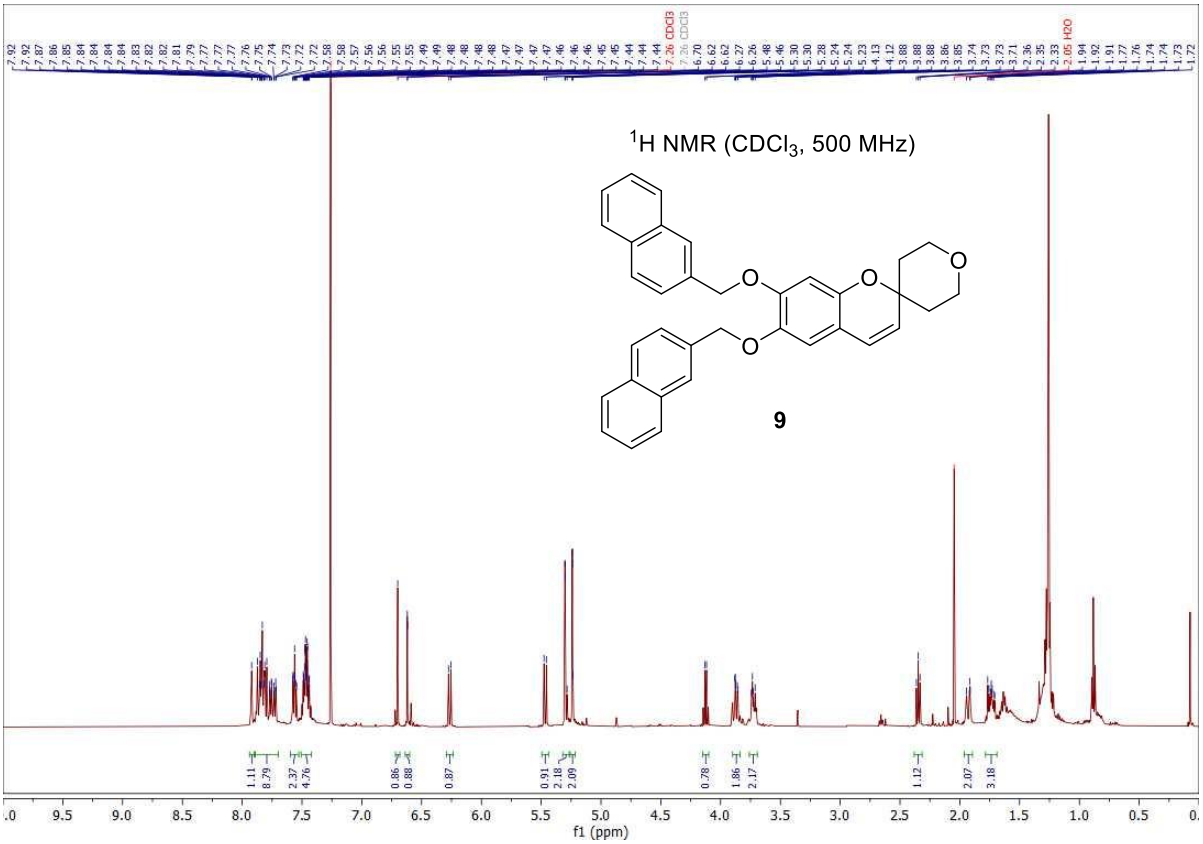
69

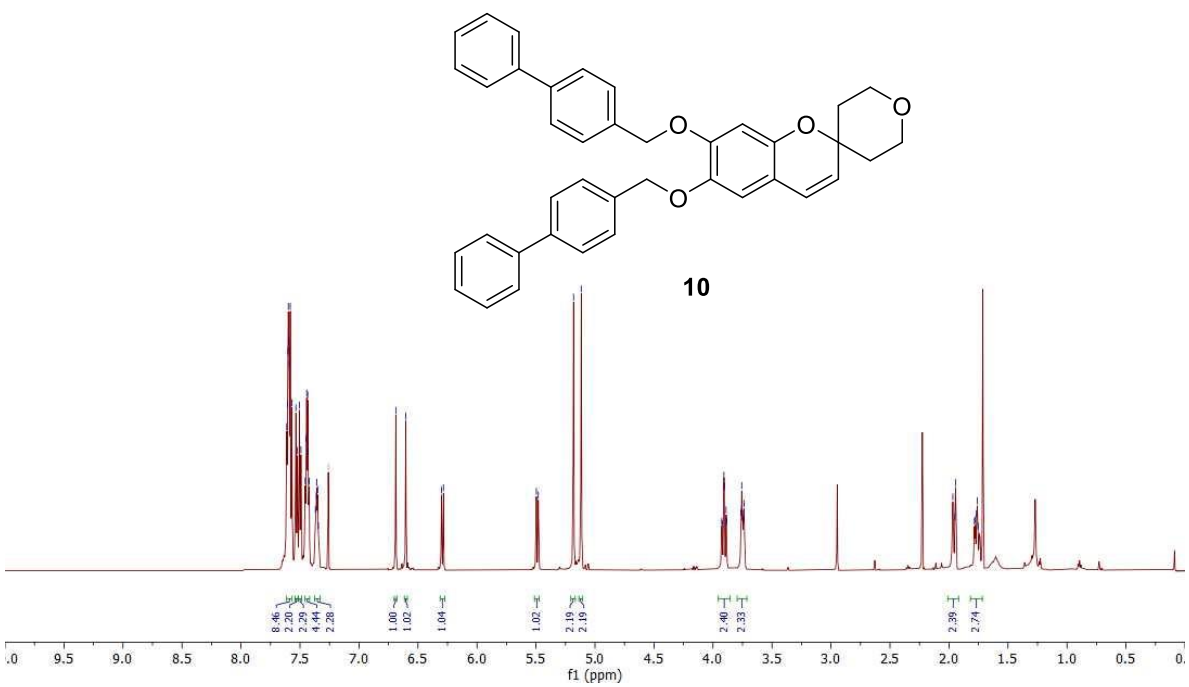
hTLR9


125
100
75
50
25
0
-25
% Control
0.002
0.01
0.02
0.1
0.2
1
10
20
30
100
Concentration (uM)

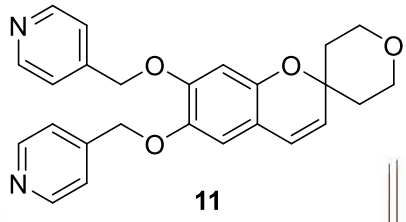

^{1}H NMR ($CDCl_3$, 600 MHz)
O_2N
O
O_2N
1
f1 (ppm)


^{13}C NMR ($CDCl_3$, 151 MHz)
O_2N
O
O_2N
1
f1 (ppm)


^{1}H NMR ($CDCl_3$, 500 MHz)
9
f1 (ppm)

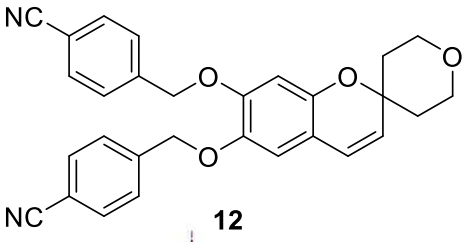

^{1}H NMR ($CDCl_3$, 600 MHz)
10
f1 (ppm)

^{1}H NMR (CD_3OD, 600 MHz)

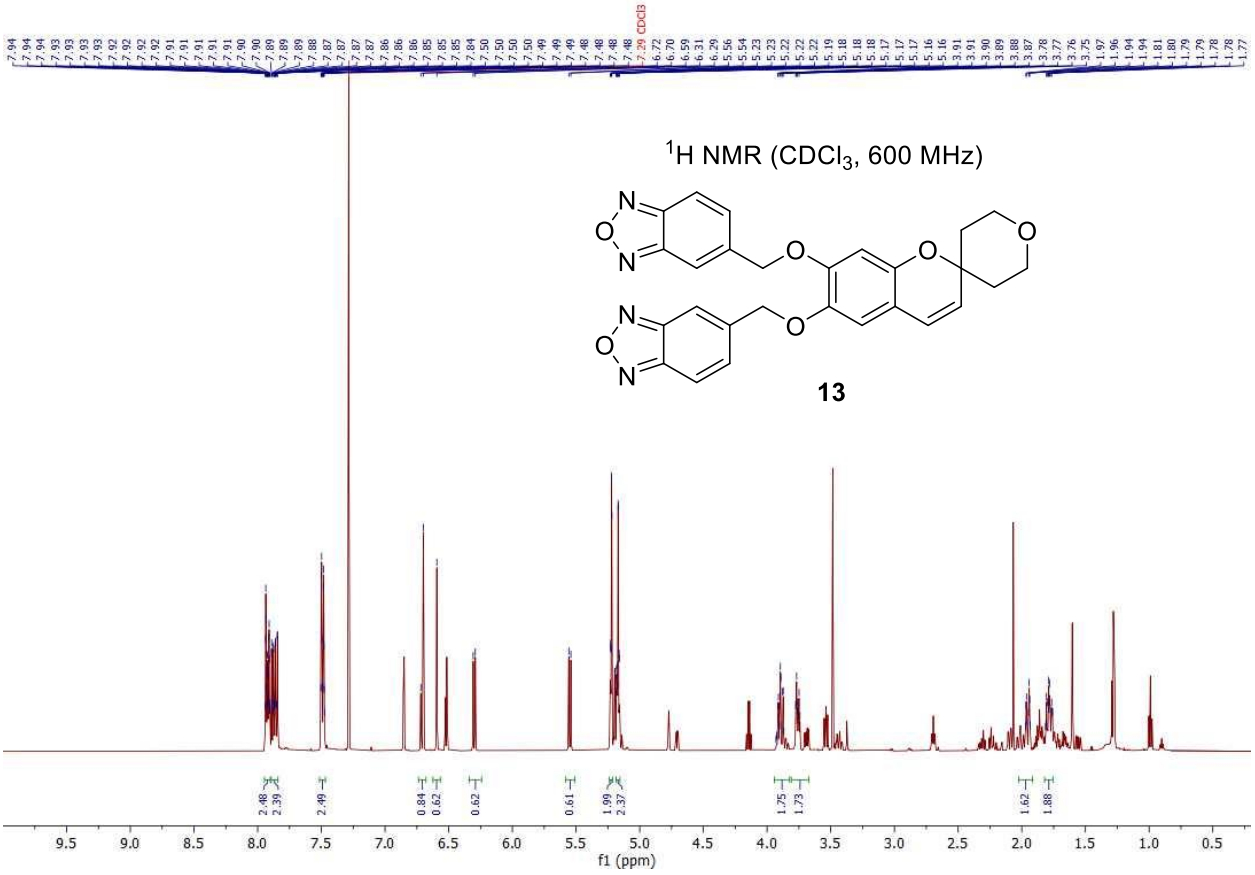


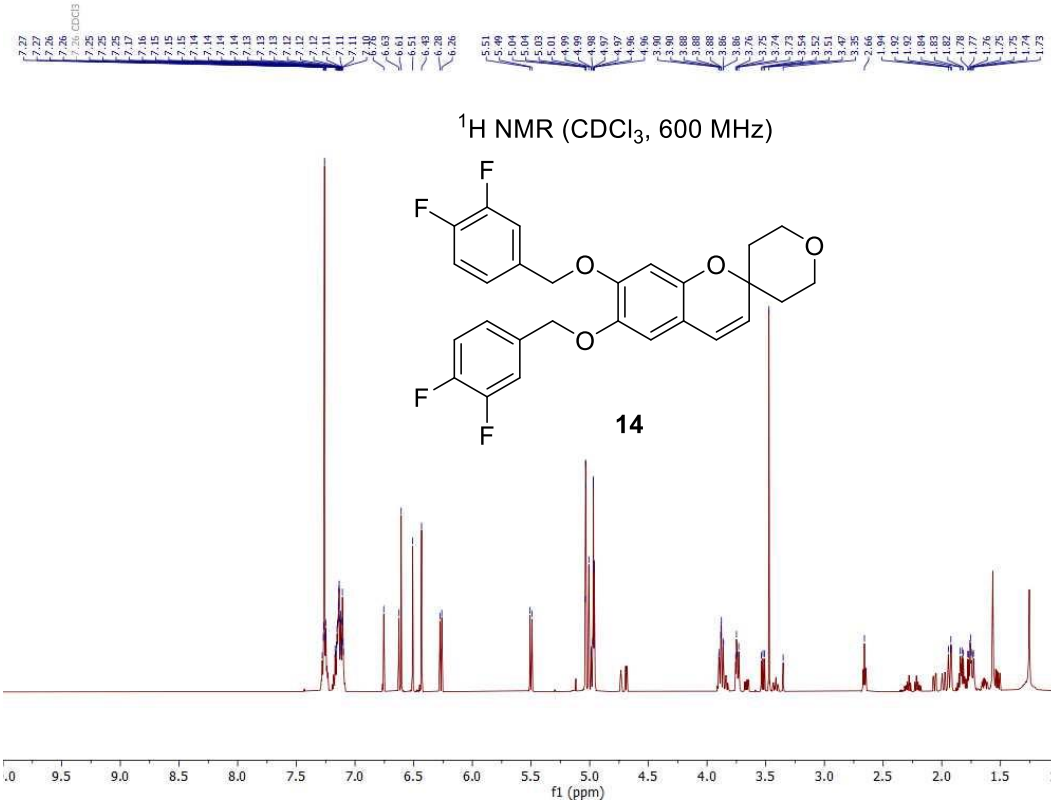
11

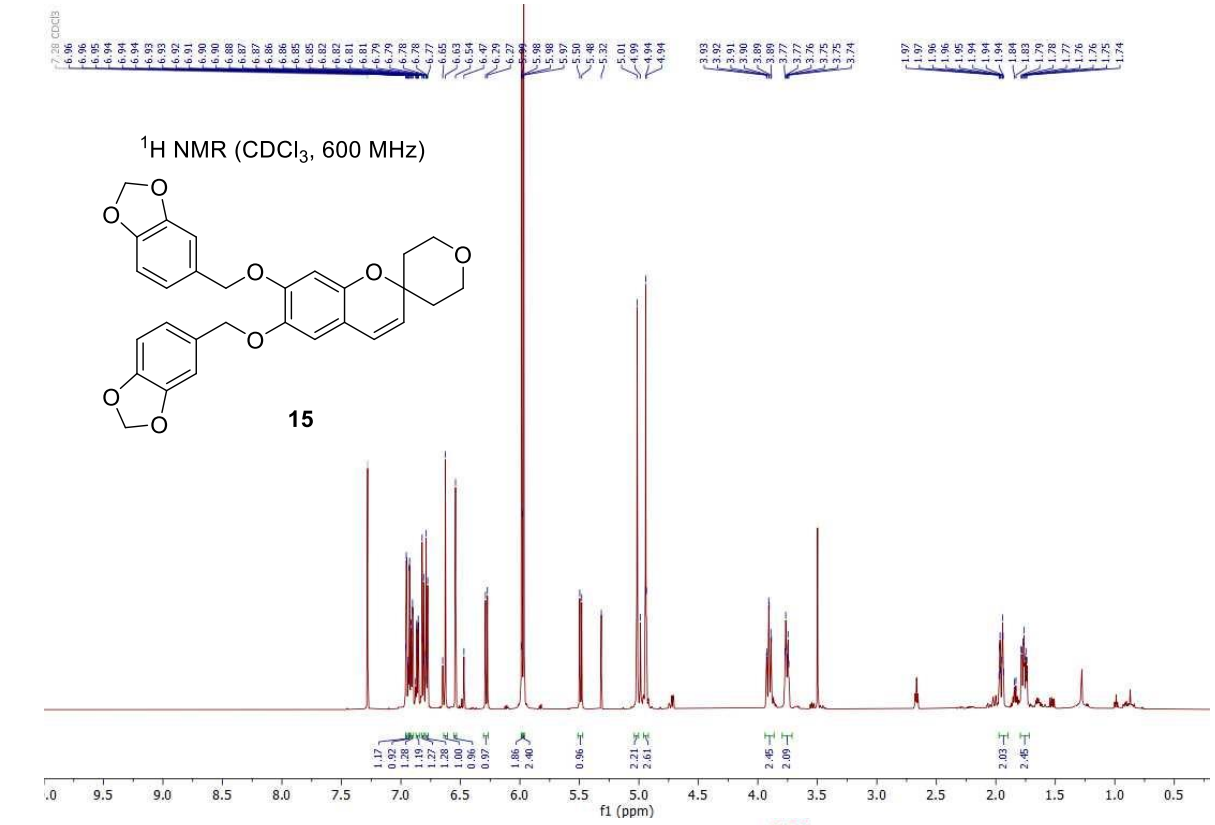
^{1}H NMR ($CDCl_3$, 600 MHz)

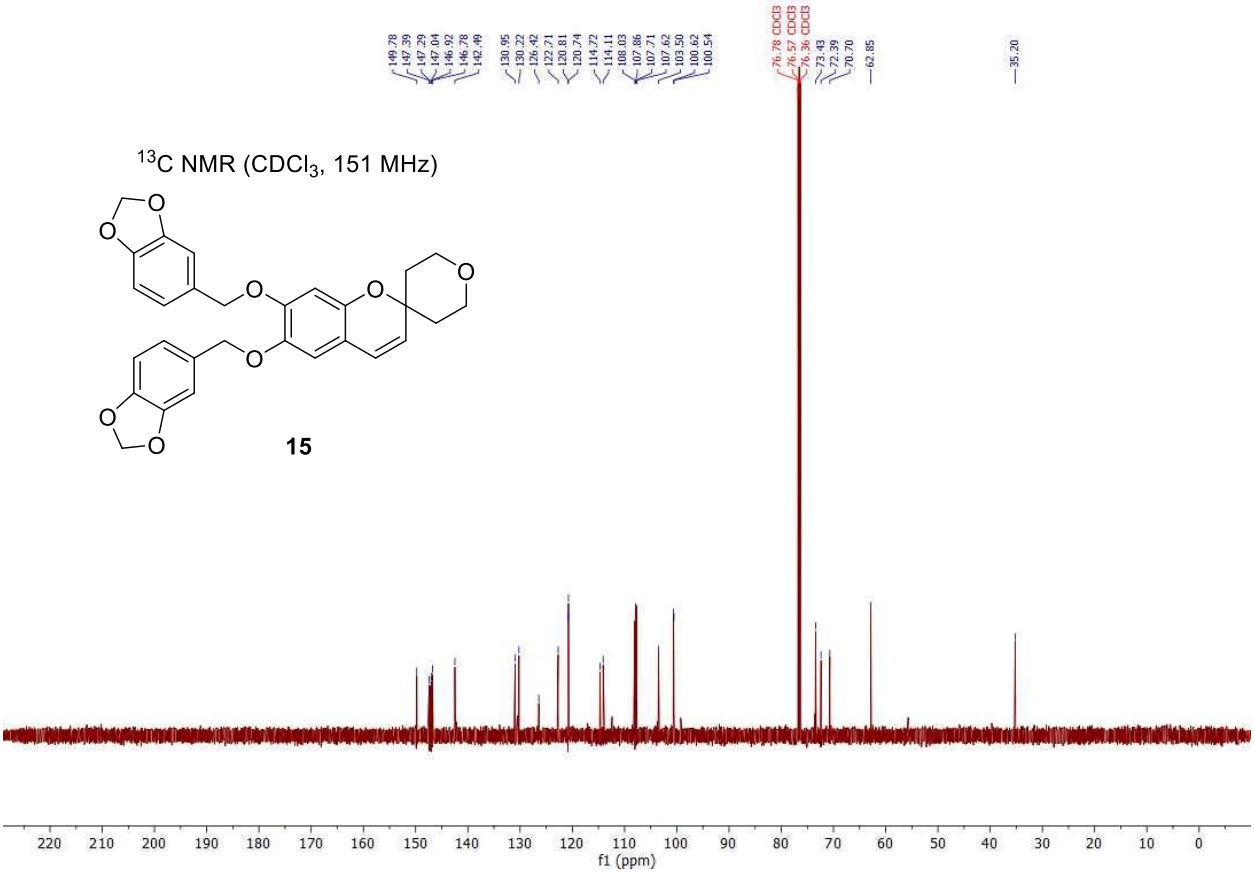


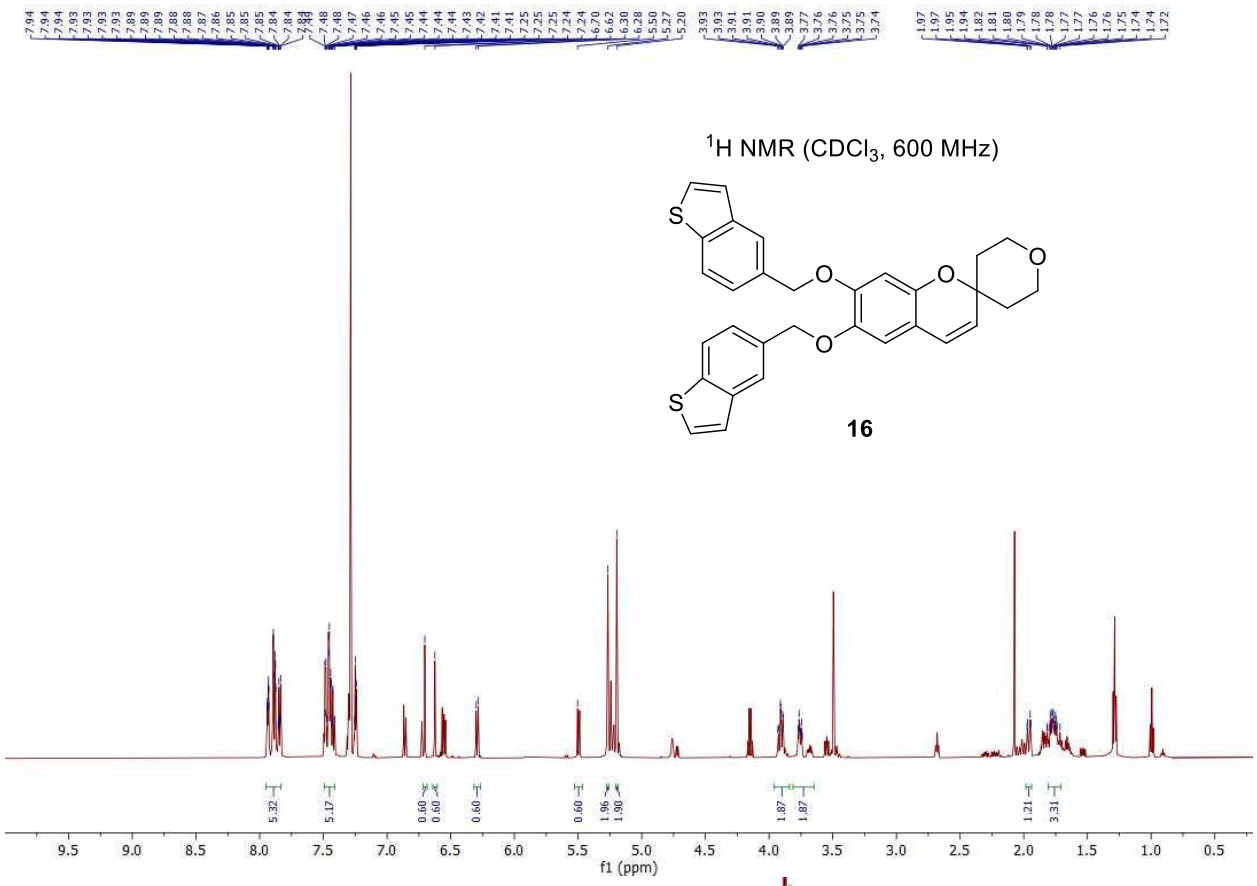
12

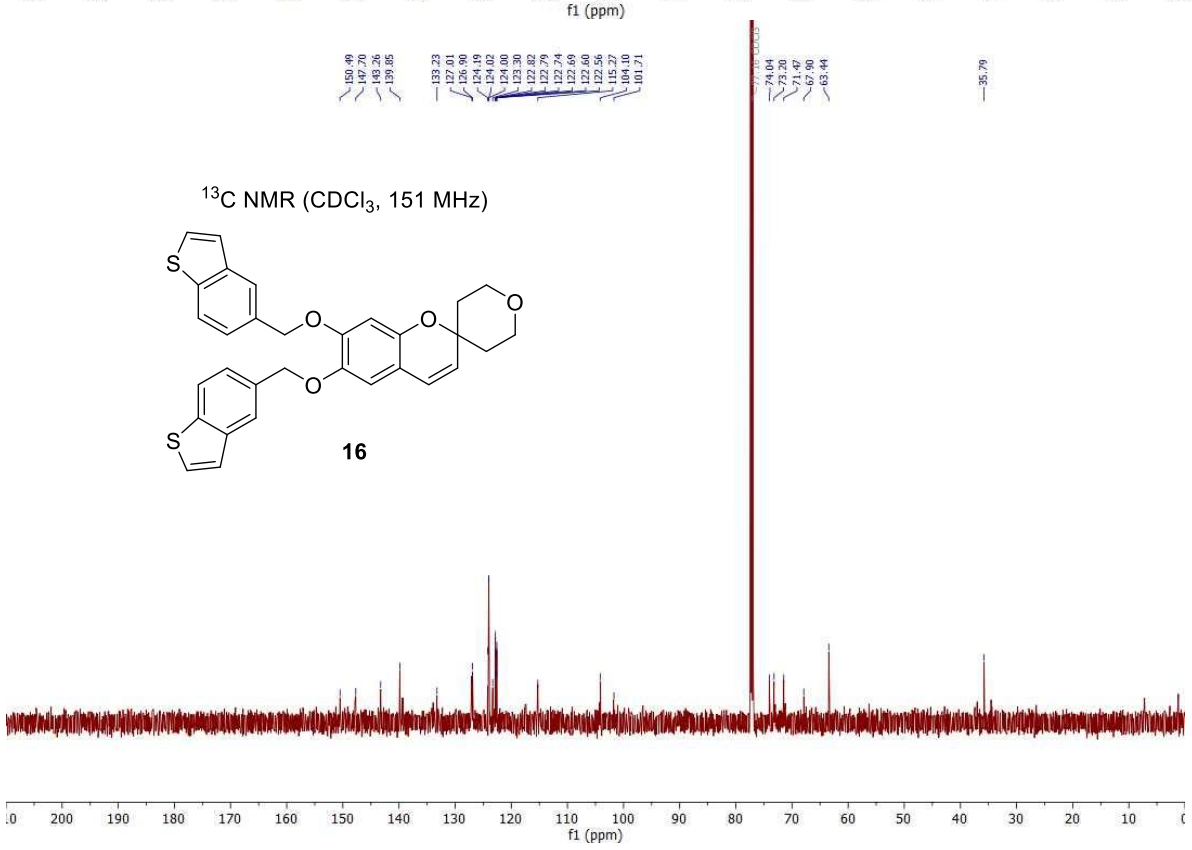

^{1}H NMR ($CDCl_3$, 600 MHz)
13
f1 (ppm)

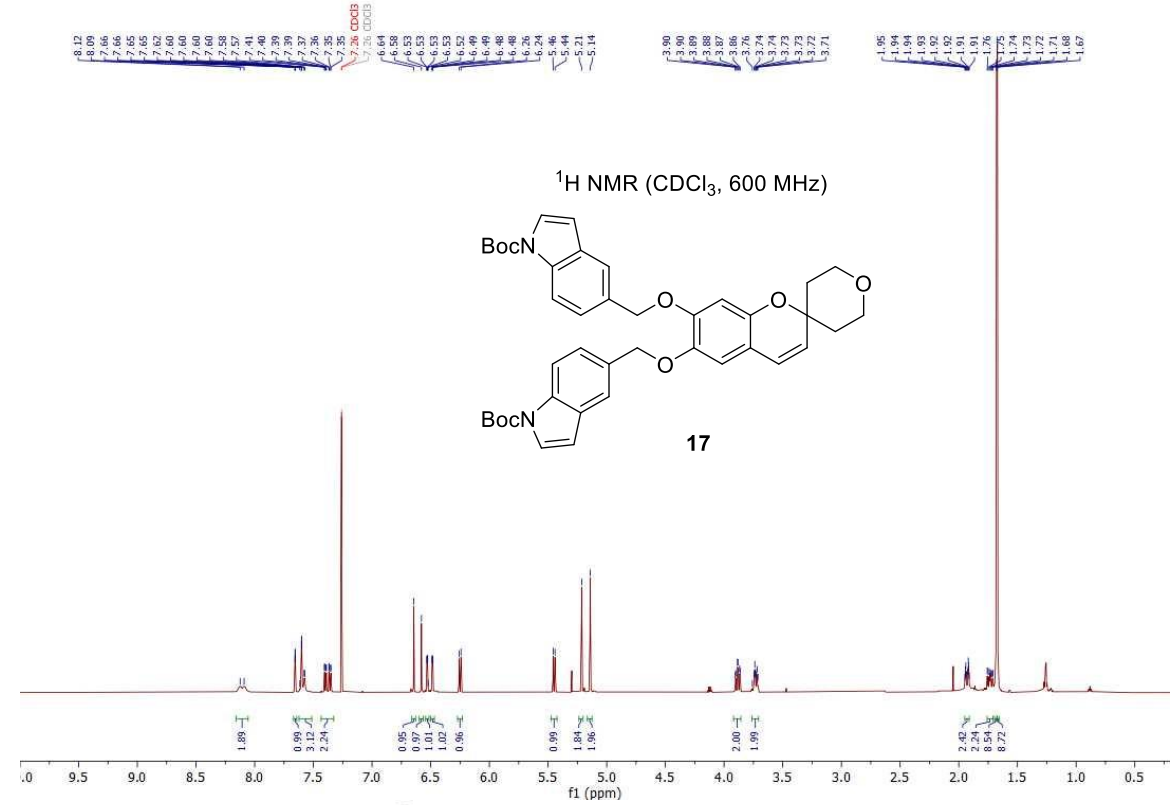

^{1}H NMR ($CDCl_3$, 600 MHz)
14
f1 (ppm)

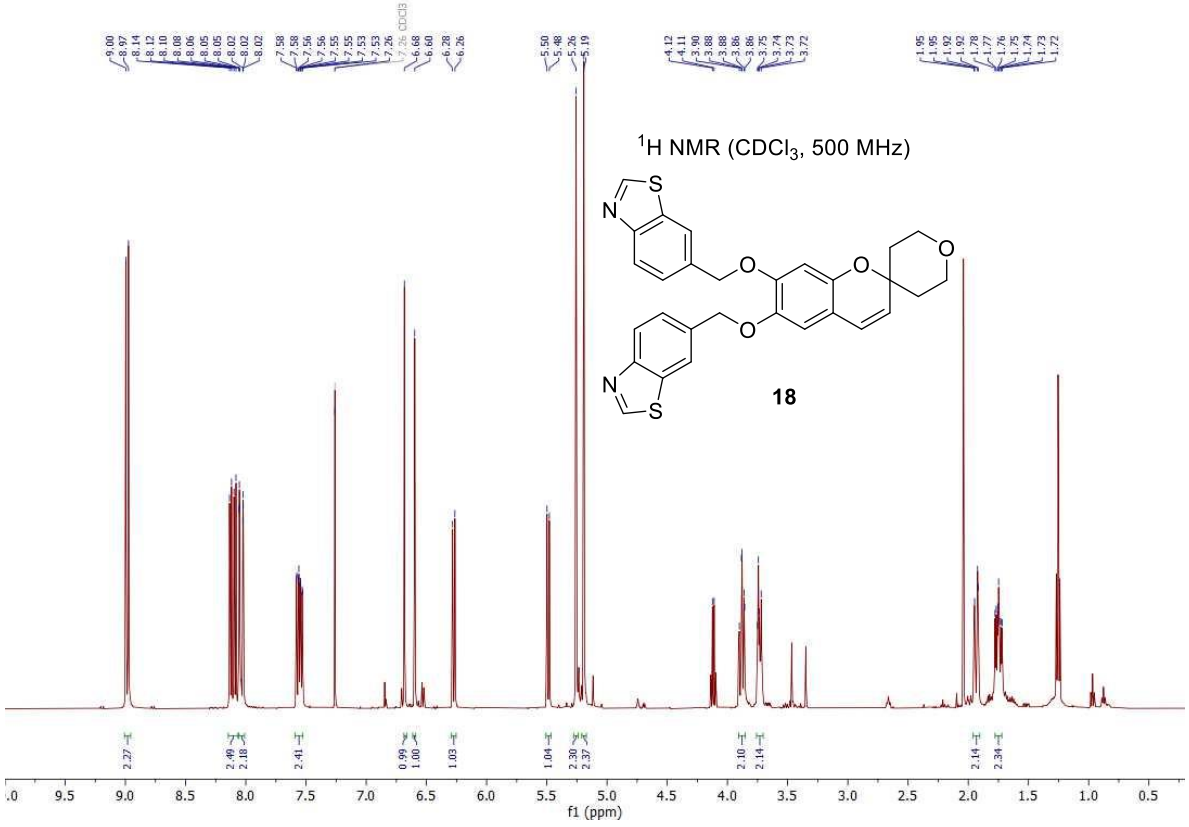

^{1}H NMR ($CDCl_3$, 600 MHz)
15
f1 (ppm)

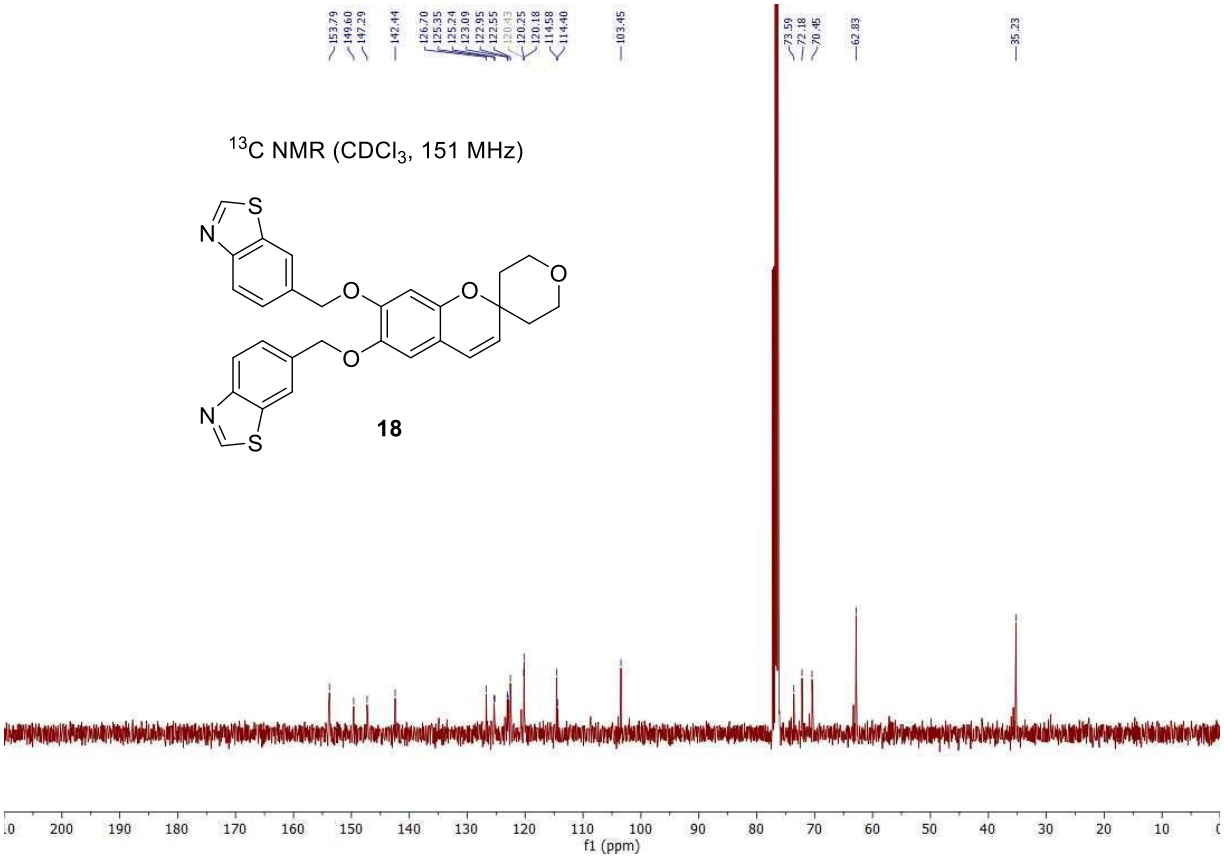

^{13}C NMR ($CDCl_3$, 151 MHz)
15
f1 (ppm)


^{1}H NMR ($CDCl_3$, 600 MHz)
16
f1 (ppm)


^{13}C NMR ($CDCl_3$, 151 MHz)
16
f1 (ppm)

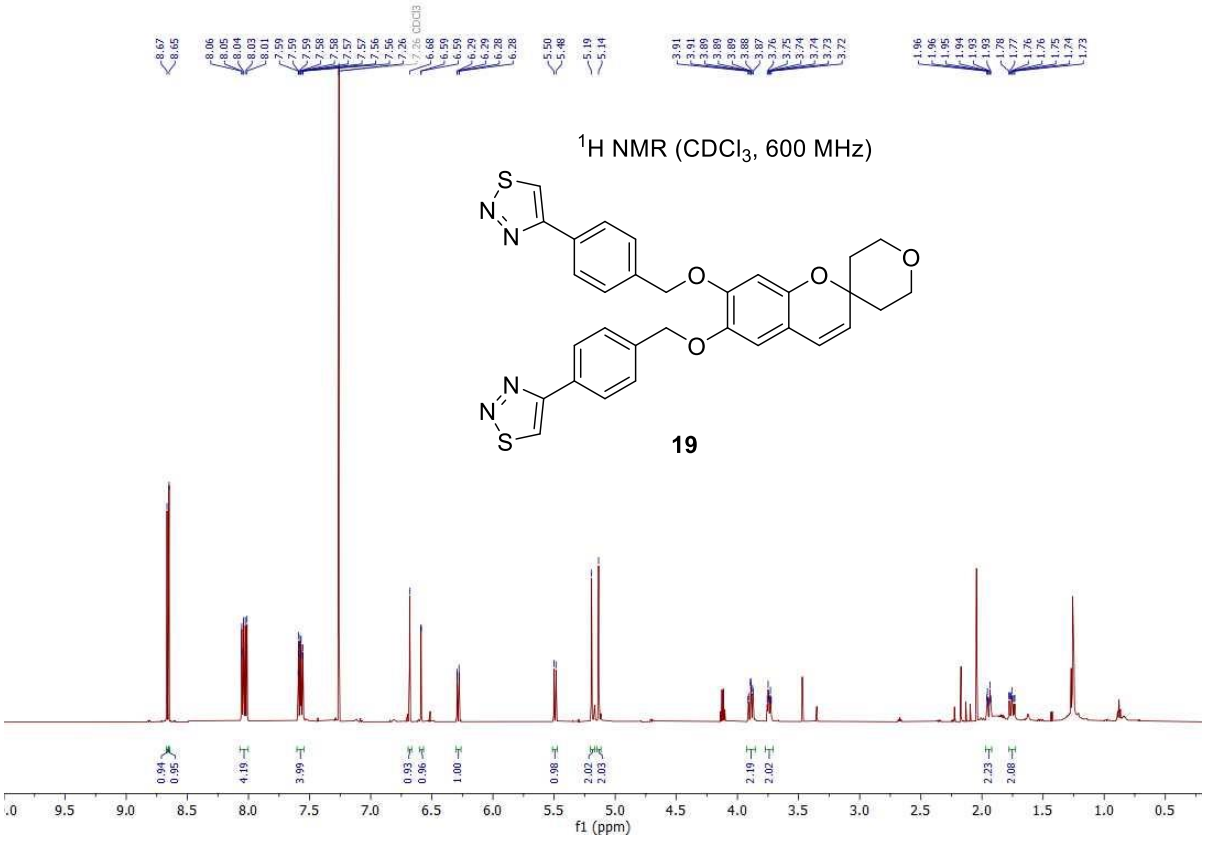

^{1}H NMR ($CDCl_3$, 600 MHz)
BocN
BocN
O
O
O
O
O
17
f1 (ppm)


^{1}H NMR ($CDCl_3$, 500 MHz)
S
N
N
S
O
O
O
O
18
f1 (ppm)



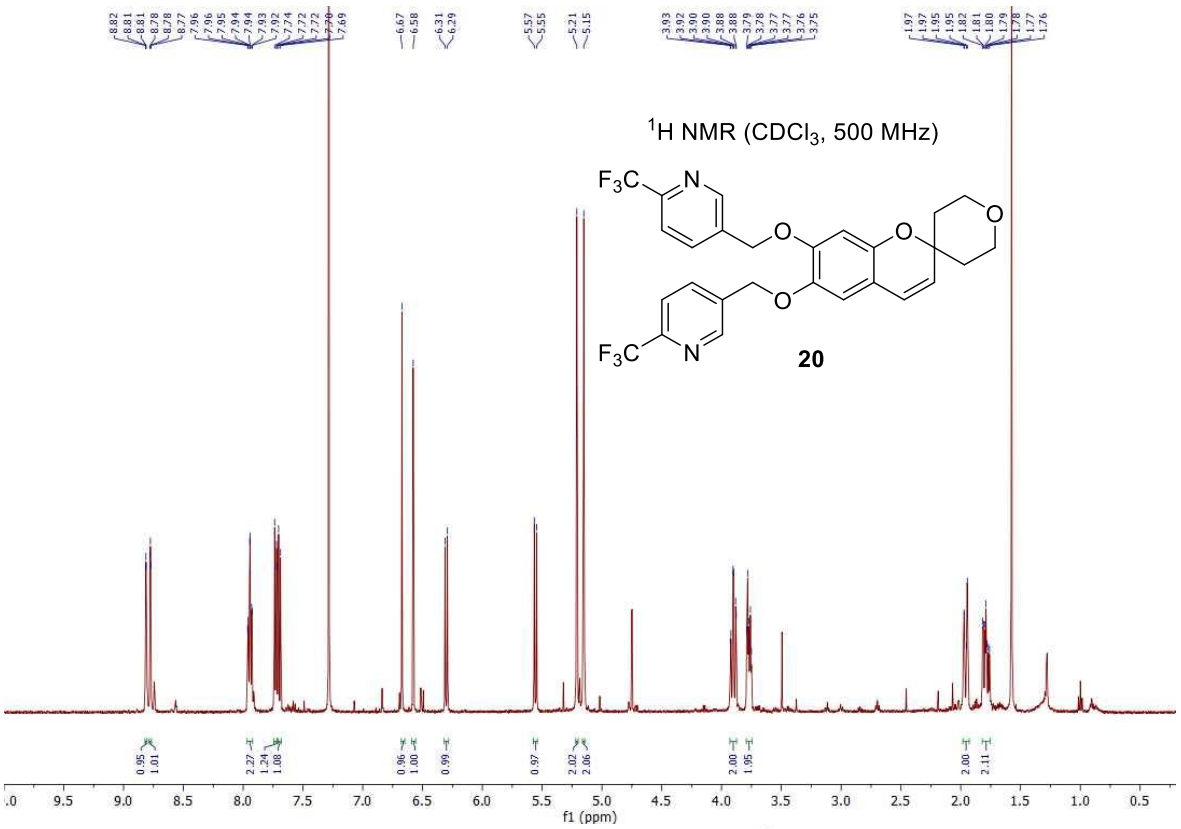
^{13}C NMR ($CDCl_3$, 151 MHz)

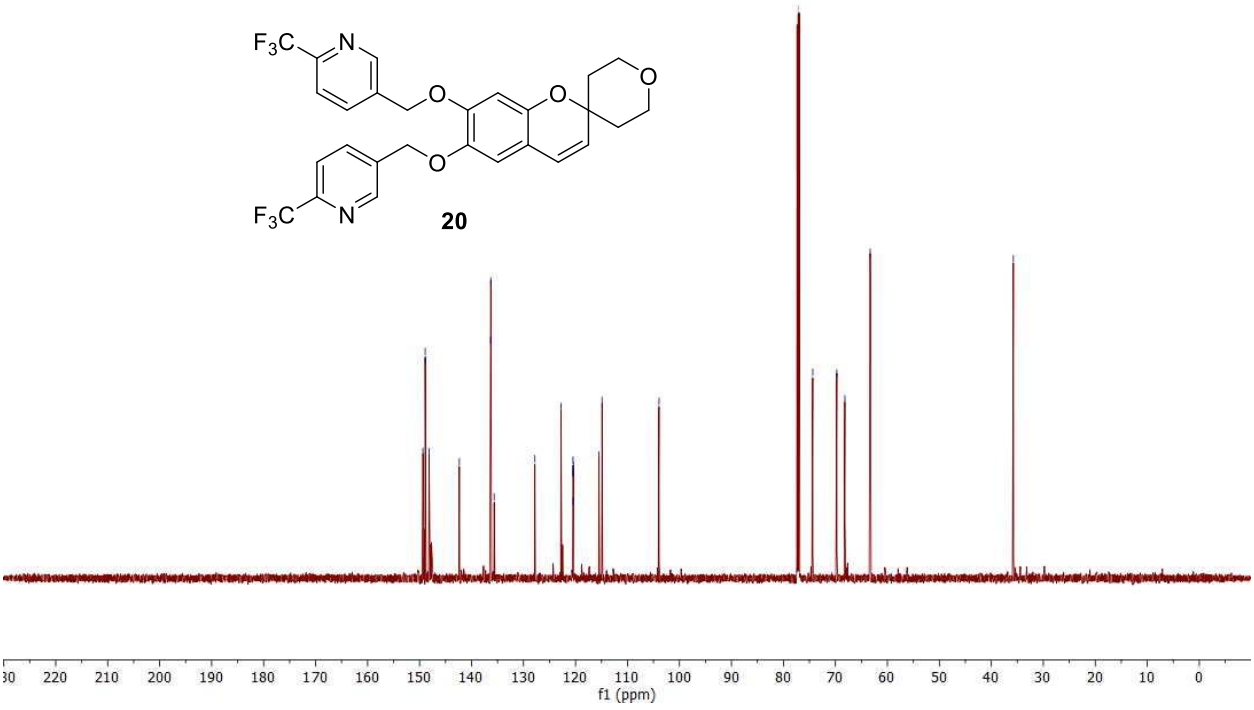
18

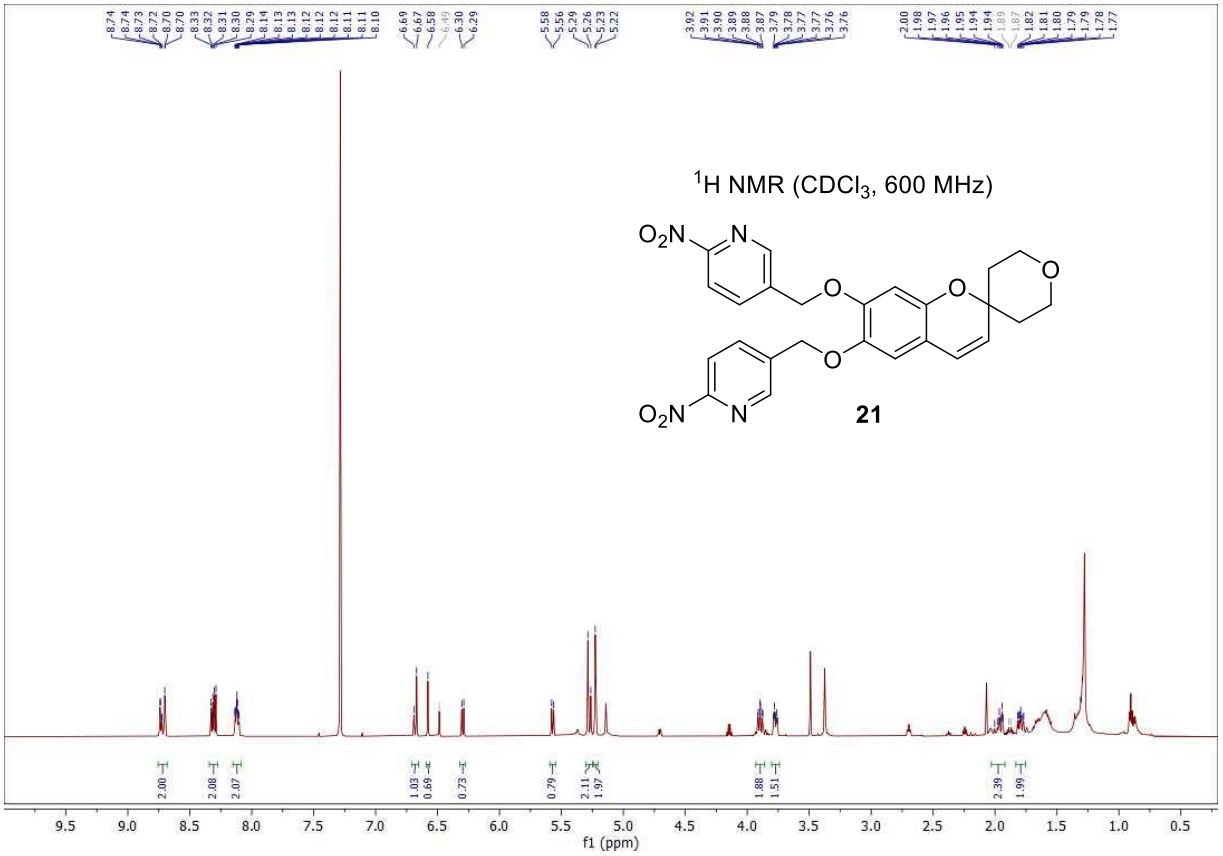


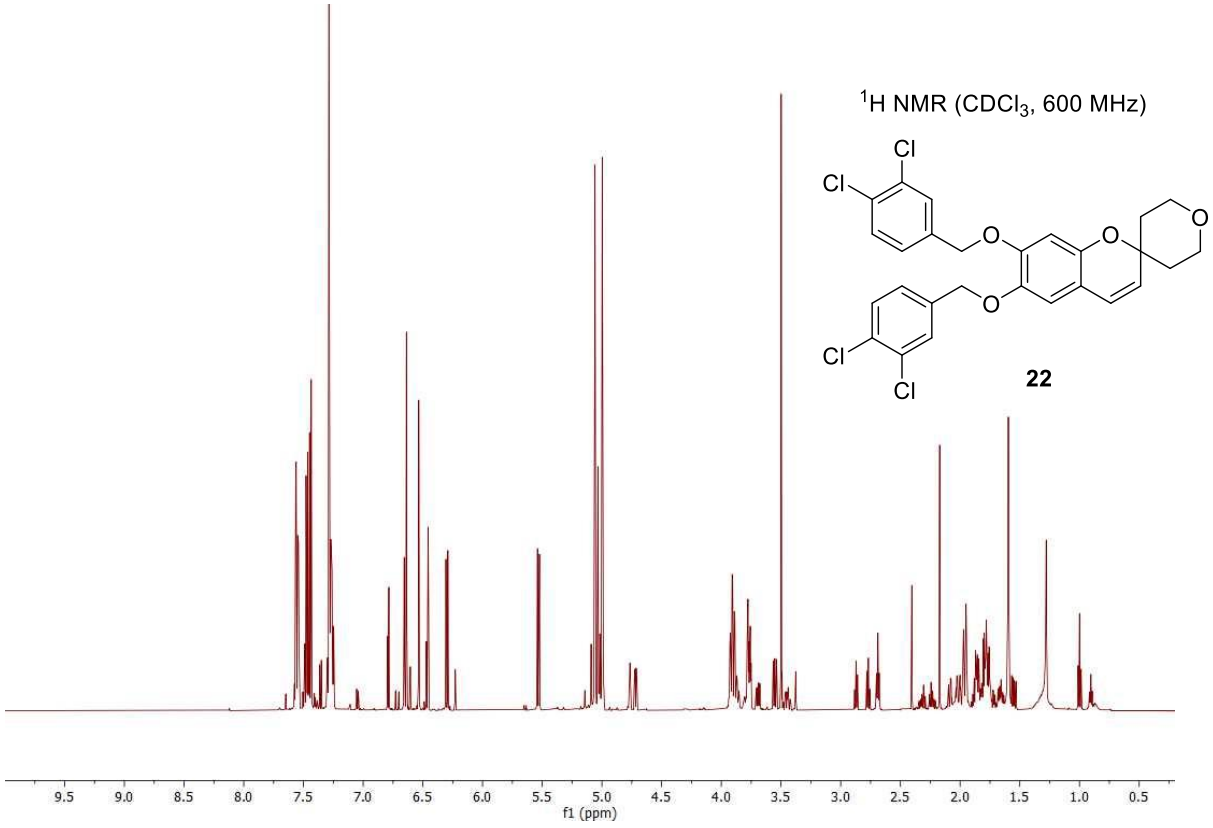
^{1}H NMR ($CDCl_3$, 600 MHz)

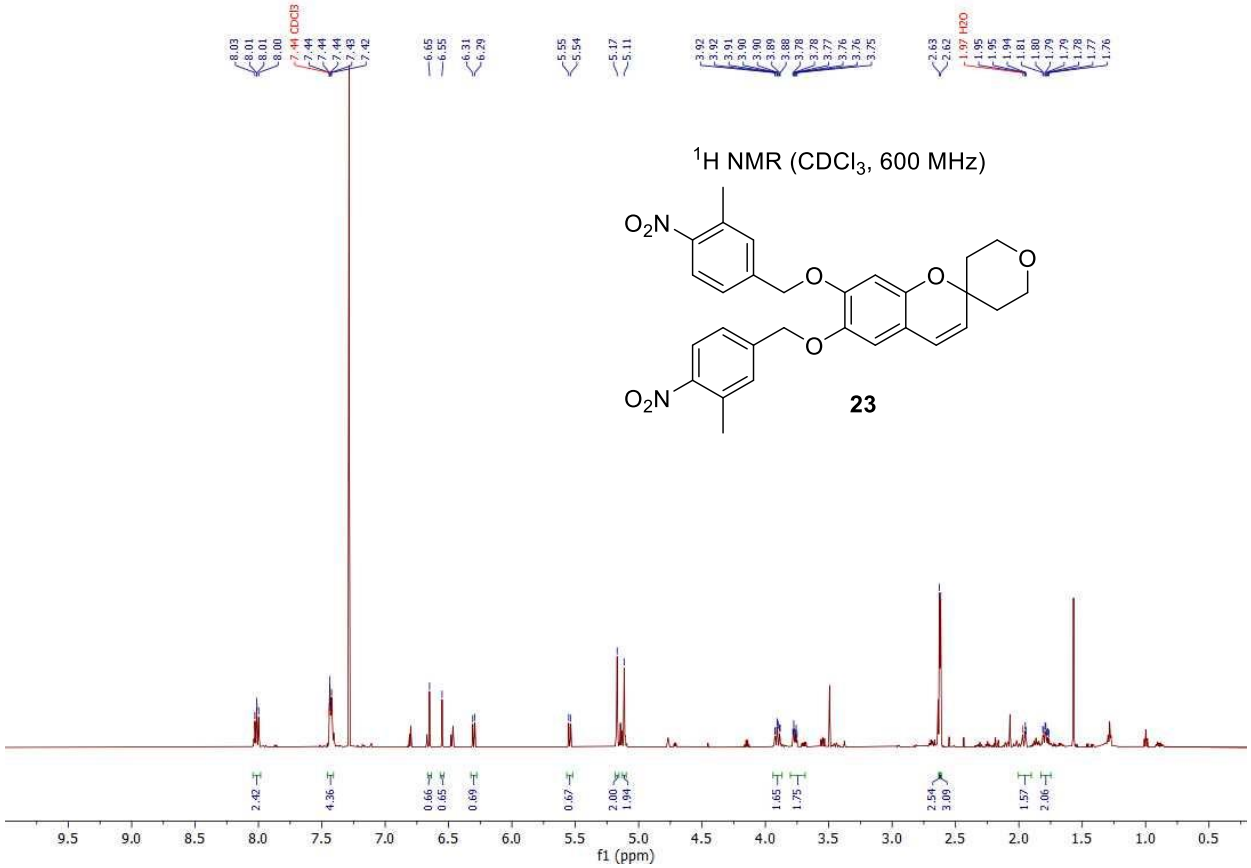
19

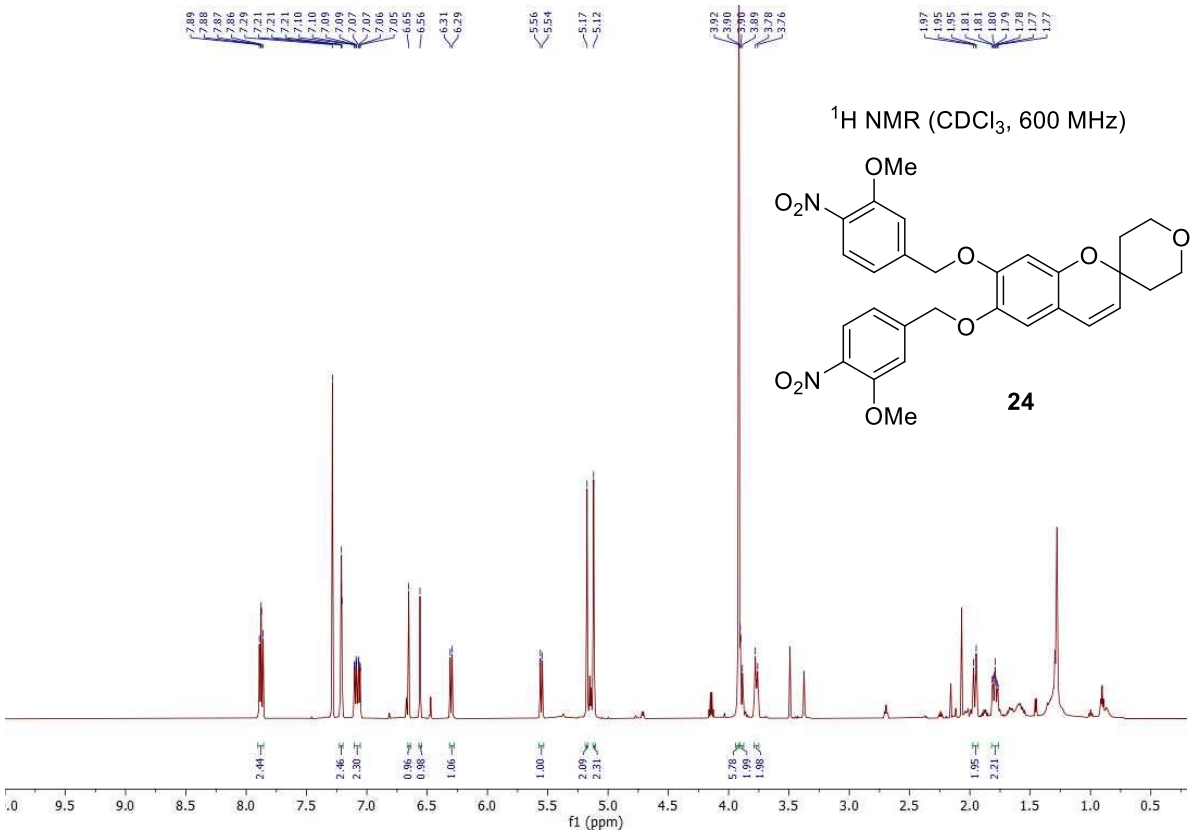

^{1}H NMR ($CDCl_3$, 500 MHz)
F_3C
N
O
O
O
O
F_3C
N
20
f1 (ppm)

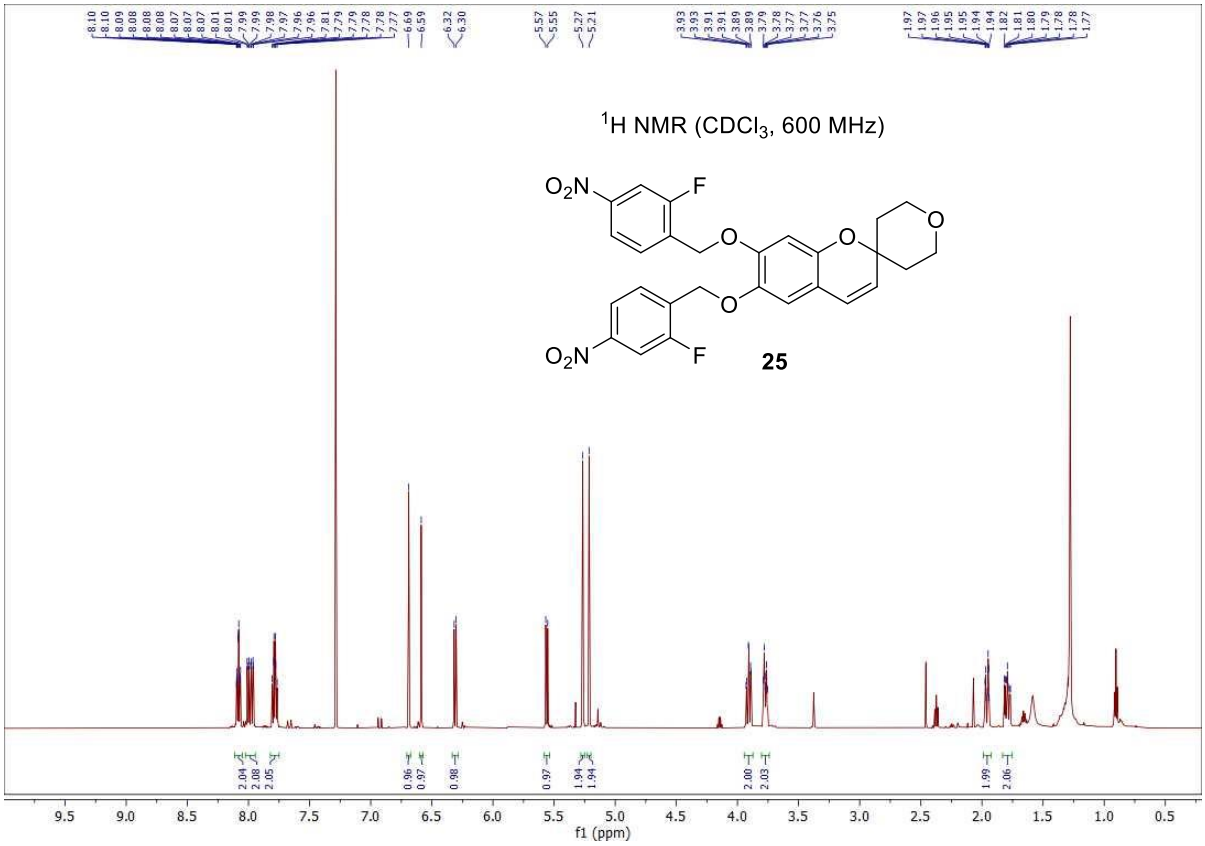

^{13}C NMR ($CDCl_3$, 151 MHz)
F_3C
N
O
O
O
O
F_3C
N
20
f1 (ppm)

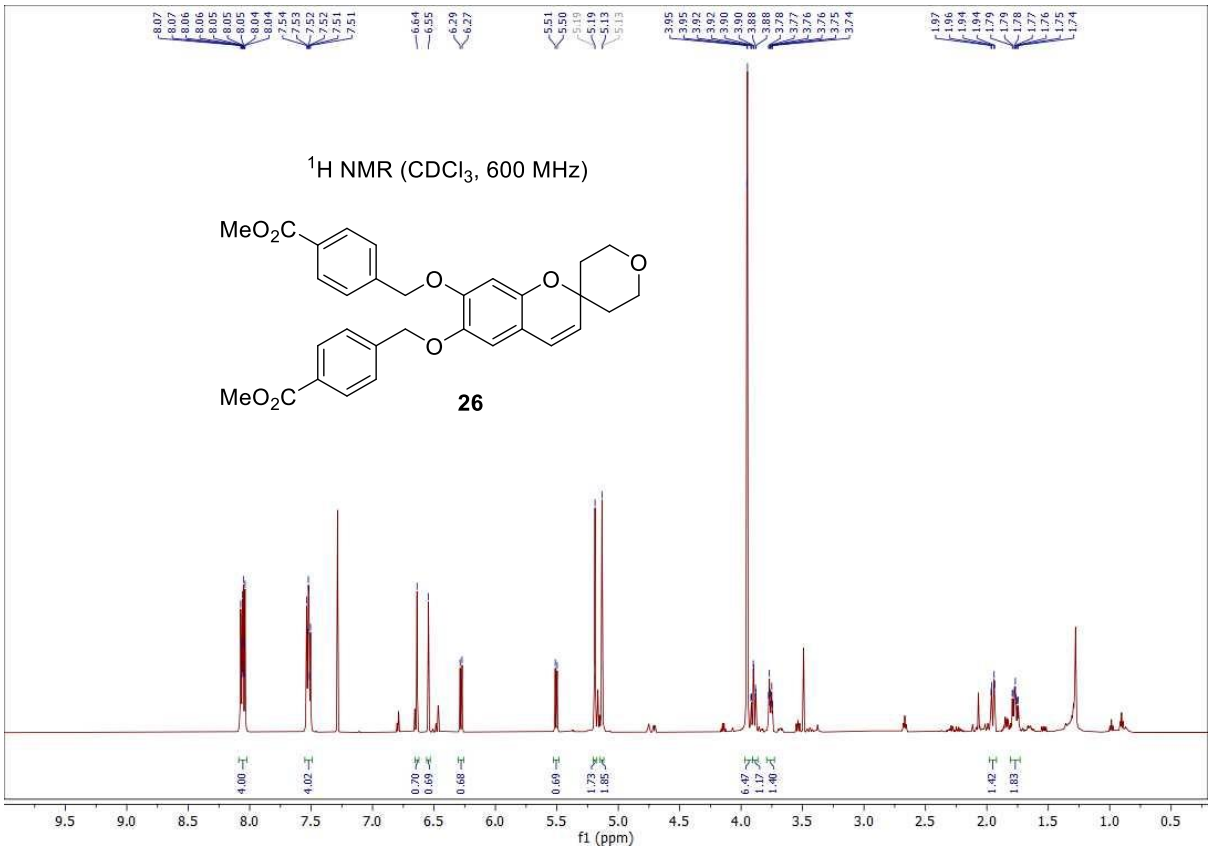

^{1}H NMR ($CDCl_3$, 600 MHz)
O_2N
N
O
O
O
O
O_2N
N
21
f1 (ppm)

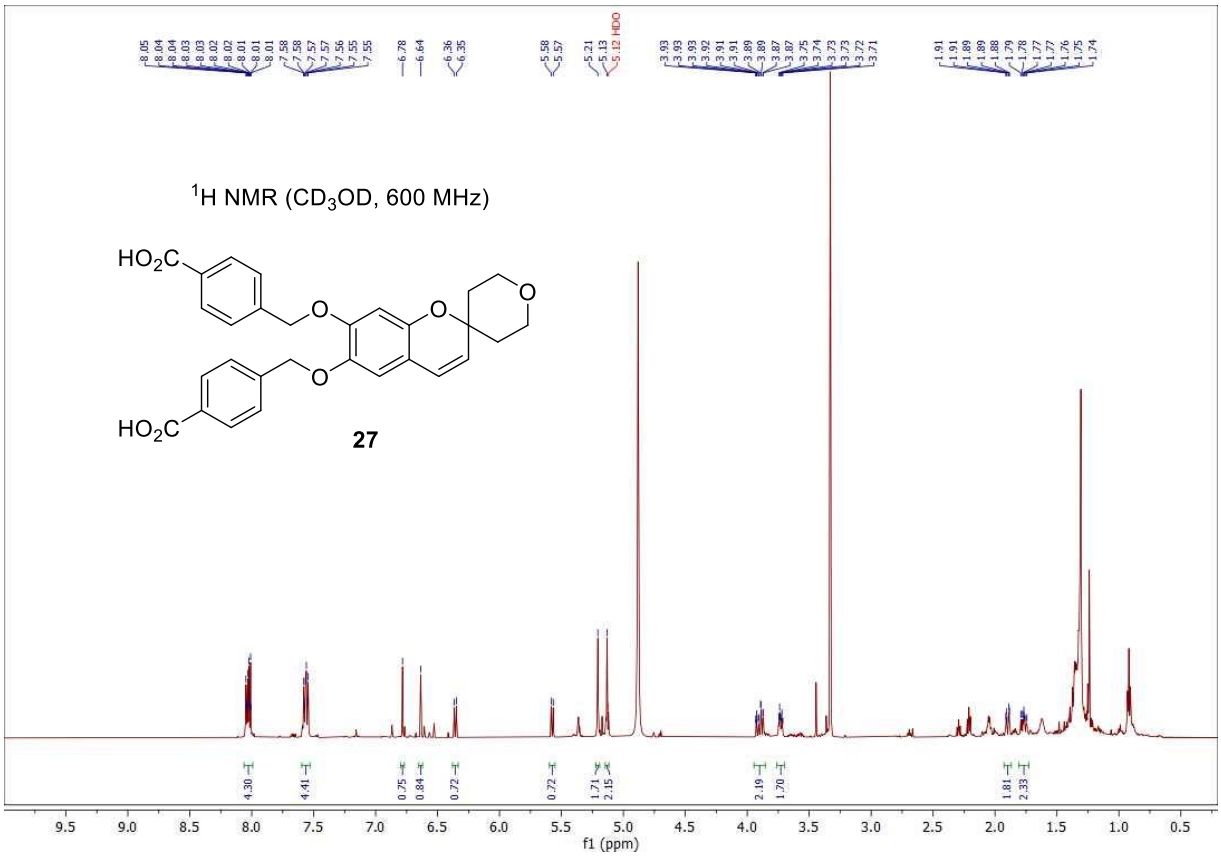

^{1}H NMR ($CDCl_3$, 600 MHz)
Cl
Cl
O
O
O
O
Cl
Cl
22
f1 (ppm)

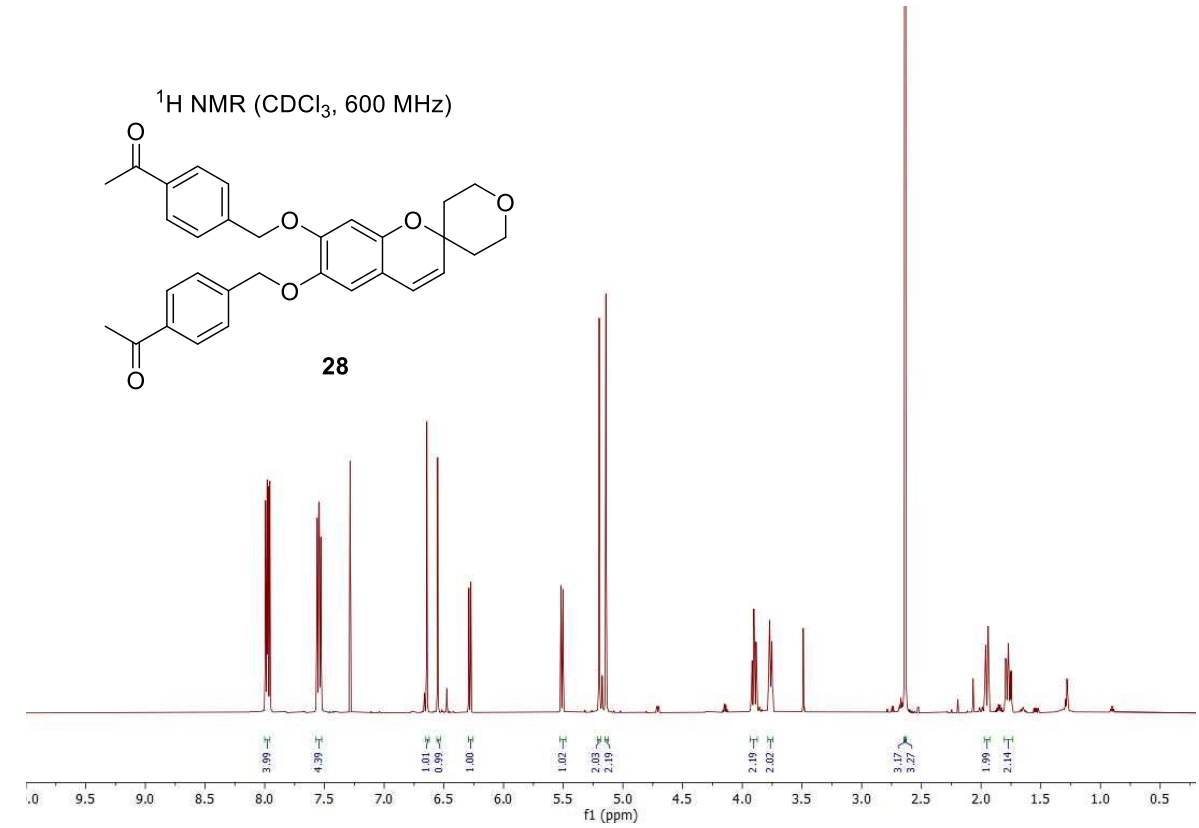

^{1}H NMR ($CDCl_3$, 600 MHz)
O_2N
O
O_2N
23
f1 (ppm)

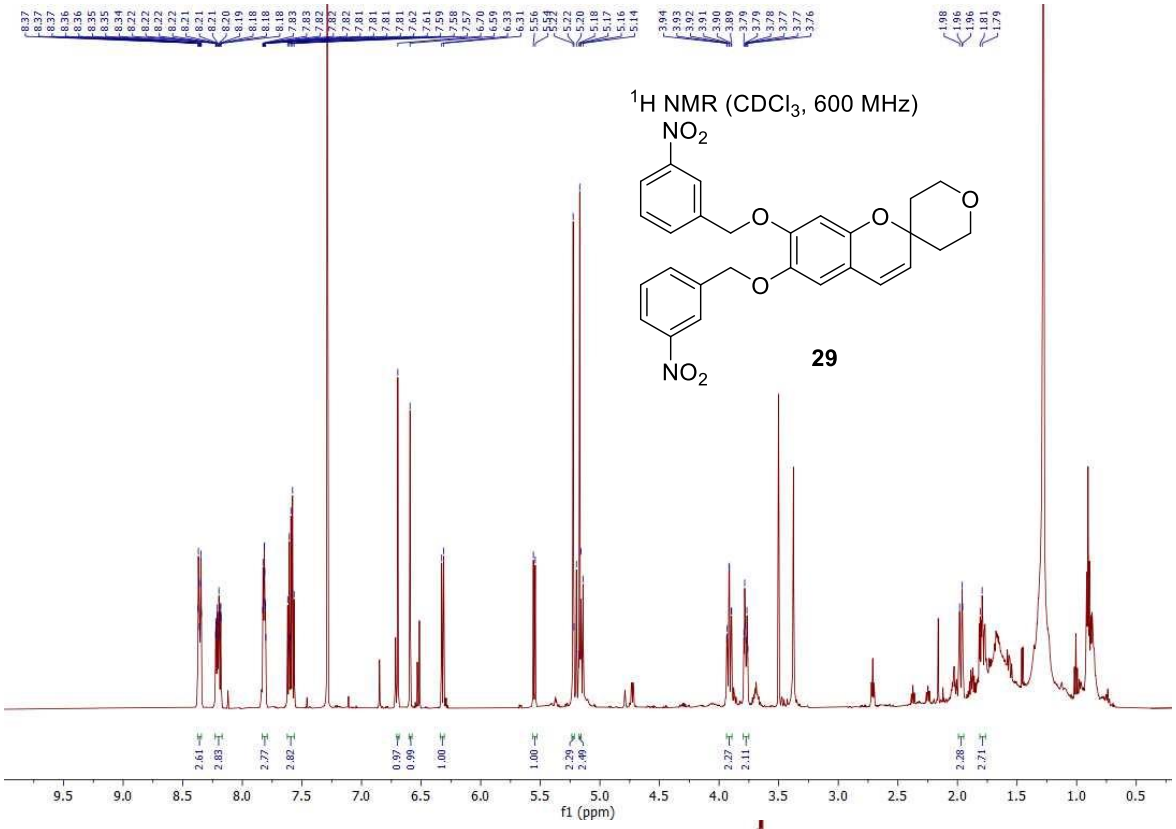

^{1}H NMR ($CDCl_3$, 600 MHz)
OMe
O_2N
O
O_2N
OMe
24
f1 (ppm)

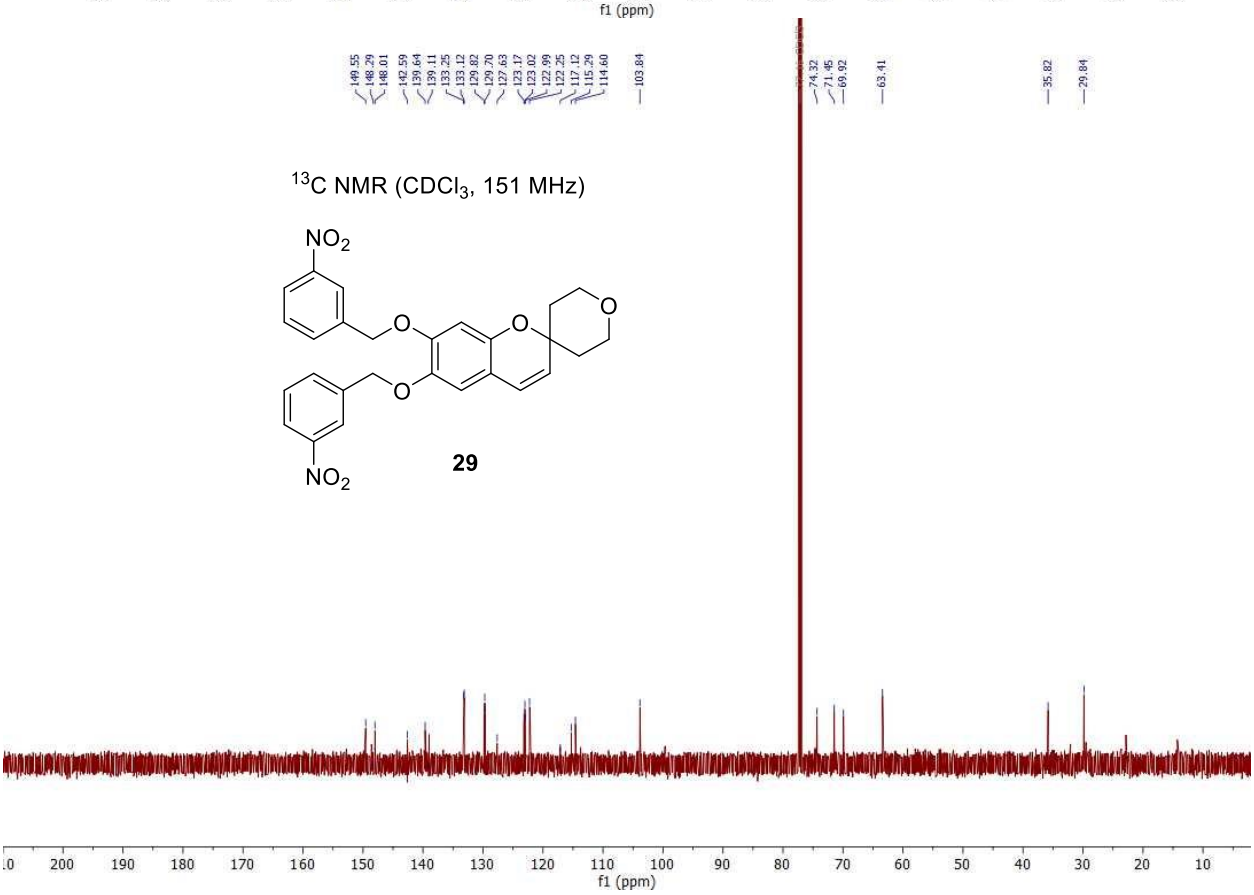

^{1}H NMR ($CDCl_3$, 600 MHz)
O_2N
F
O
O
O
O
O_2N
F
25
f1 (ppm)


^{1}H NMR ($CDCl_3$, 600 MHz)
MeO_2C
O
O
O
O
MeO_2C
26
f1 (ppm)

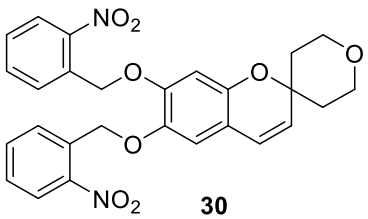

^{1}H NMR (CD_3OD, 600 MHz)
HO_2C
HO_2C
O
O
O
O
27
f1 (ppm)


^{1}H NMR ($CDCl_3$, 600 MHz)
O
O
O
O
O
O
28
f1 (ppm)


^{1}H NMR ($CDCl_3$, 600 MHz)
NO_2
O
O
O
O
NO_2
29
f1 (ppm)

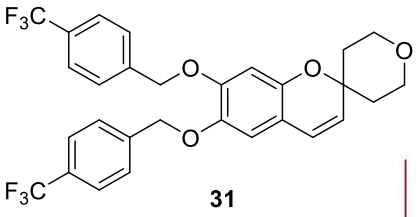

^{13}C NMR ($CDCl_3$, 151 MHz)
NO_2
O
O
O
O
NO_2
29
f1 (ppm)

^{1}H NMR ($CDCl_3$, 600 MHz)

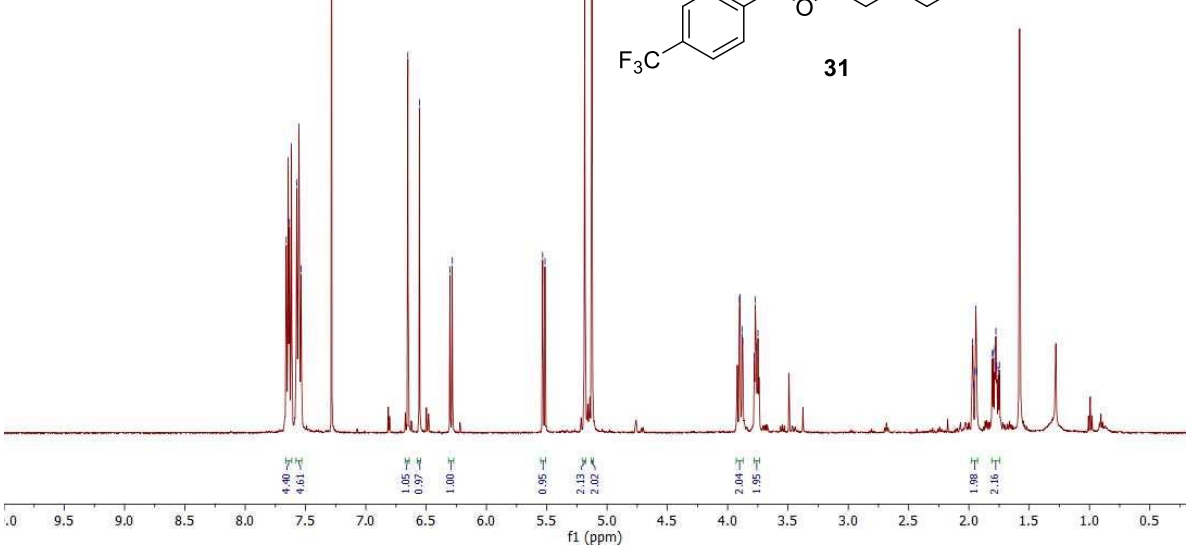


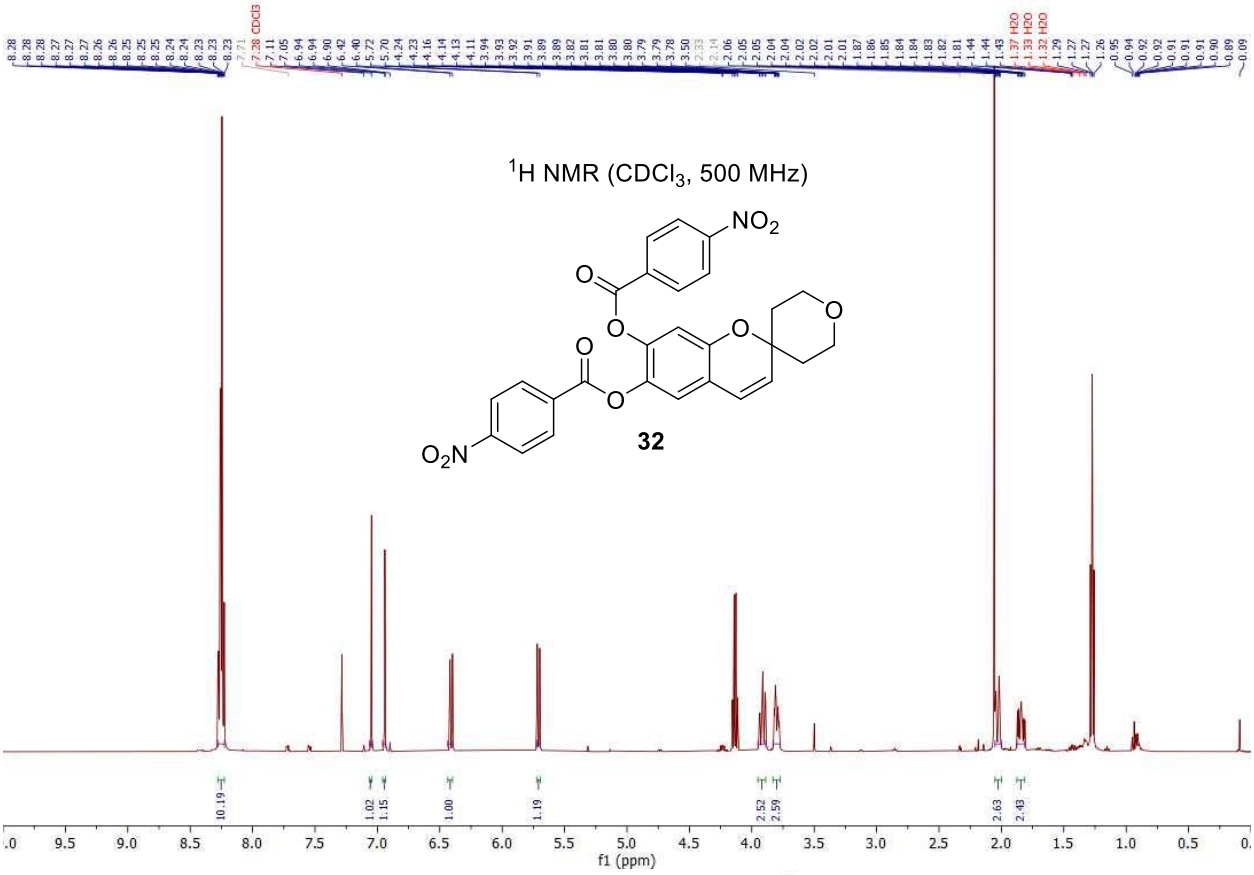
30

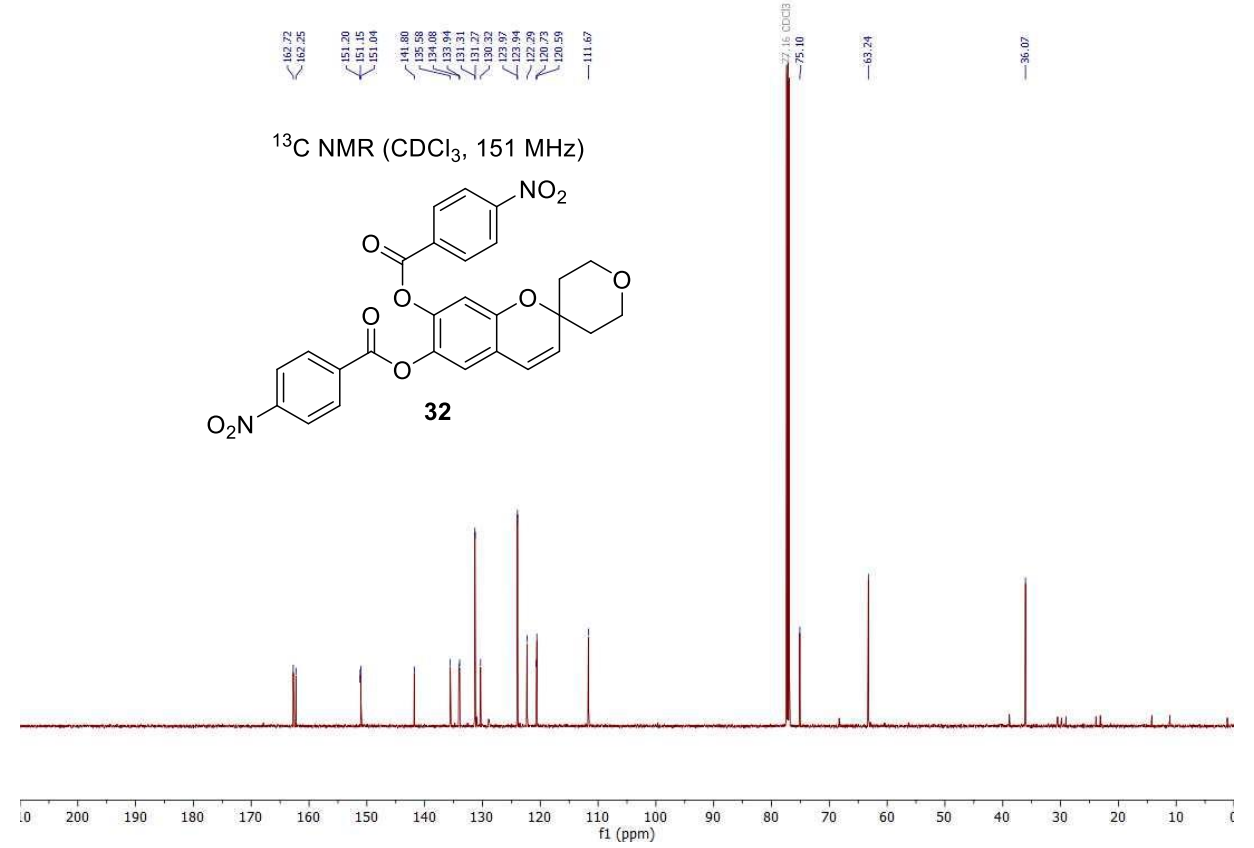
^{1}H NMR ($CDCl_3$, 500 MHz)

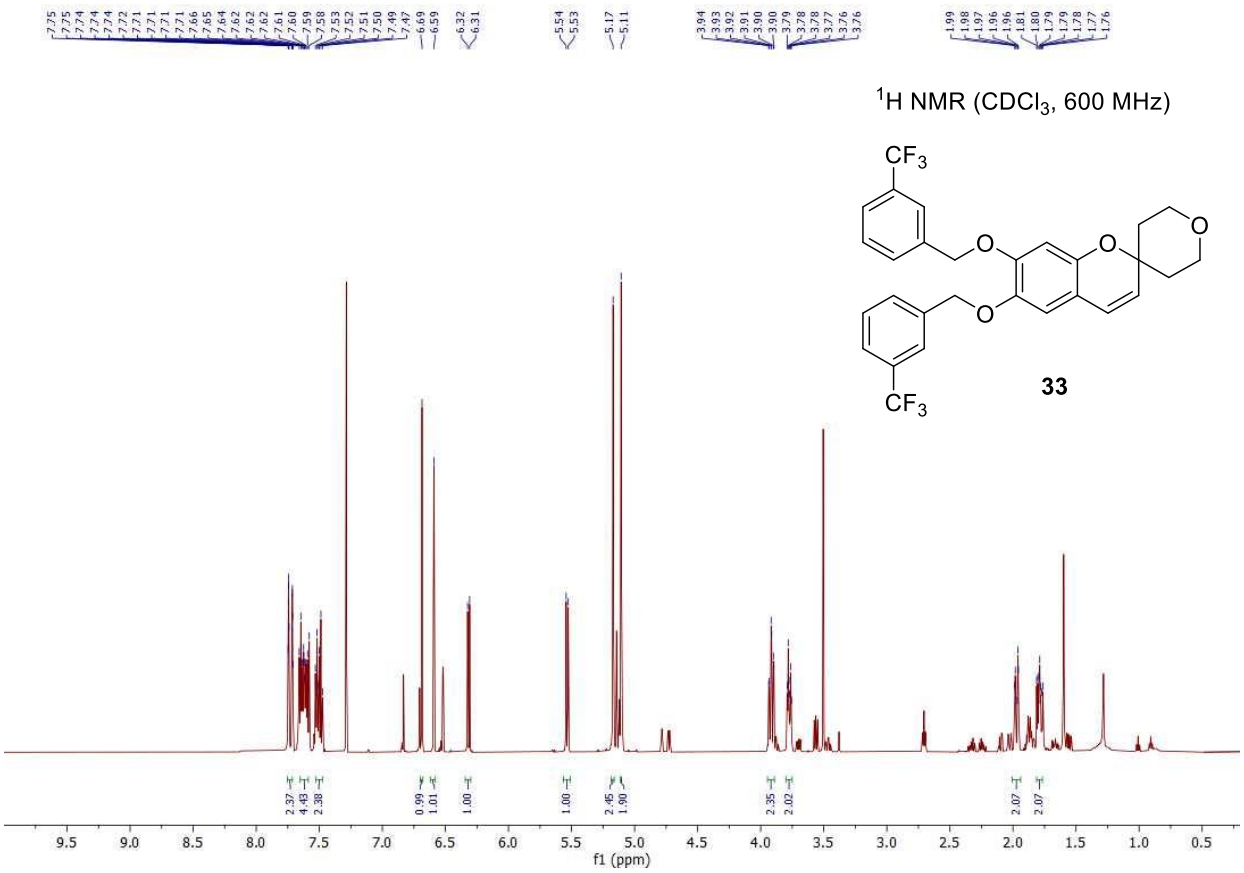


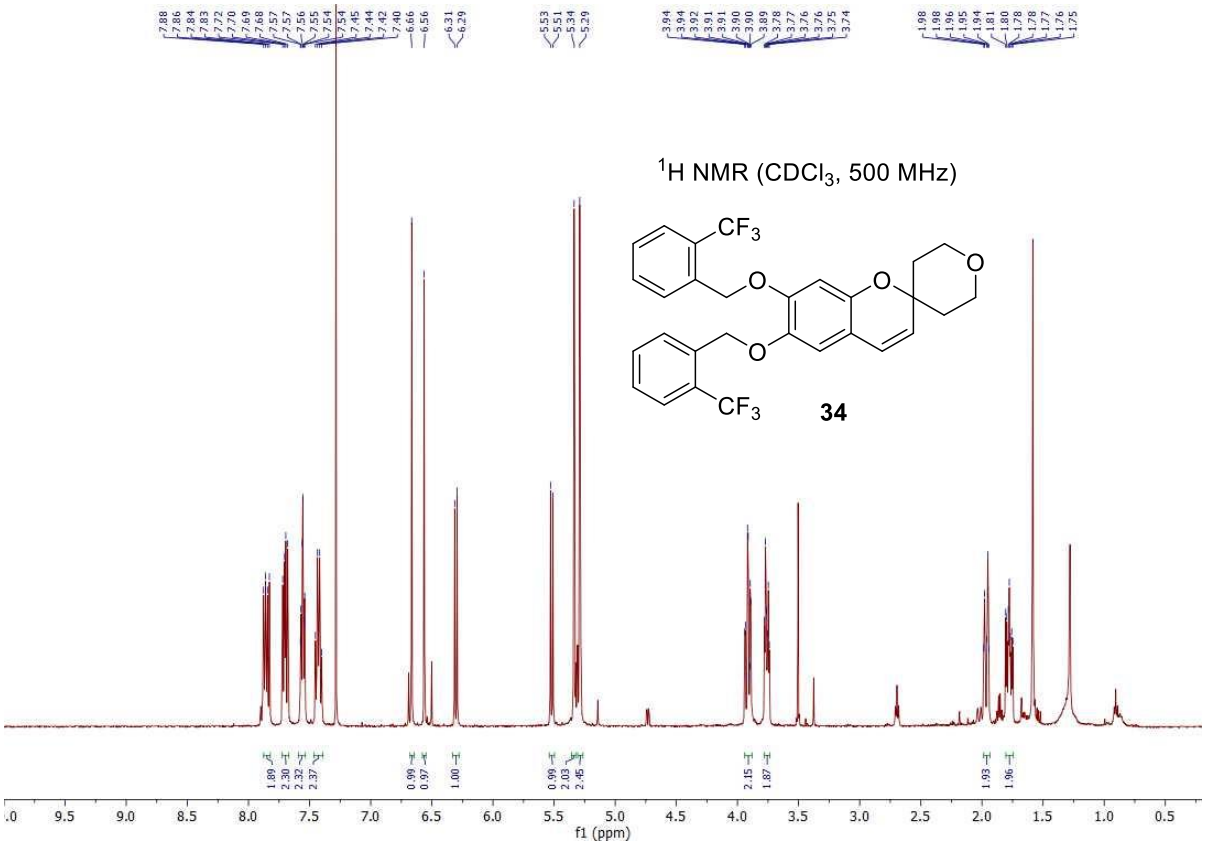
31

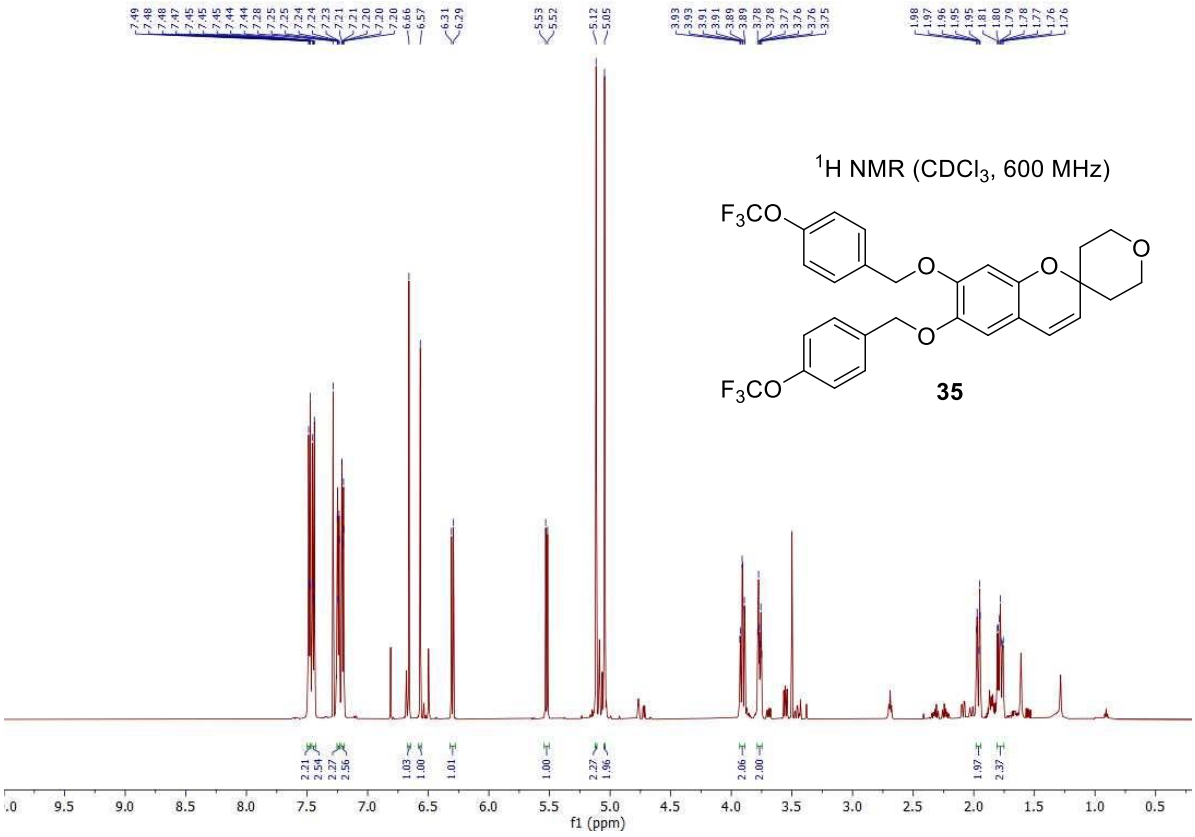


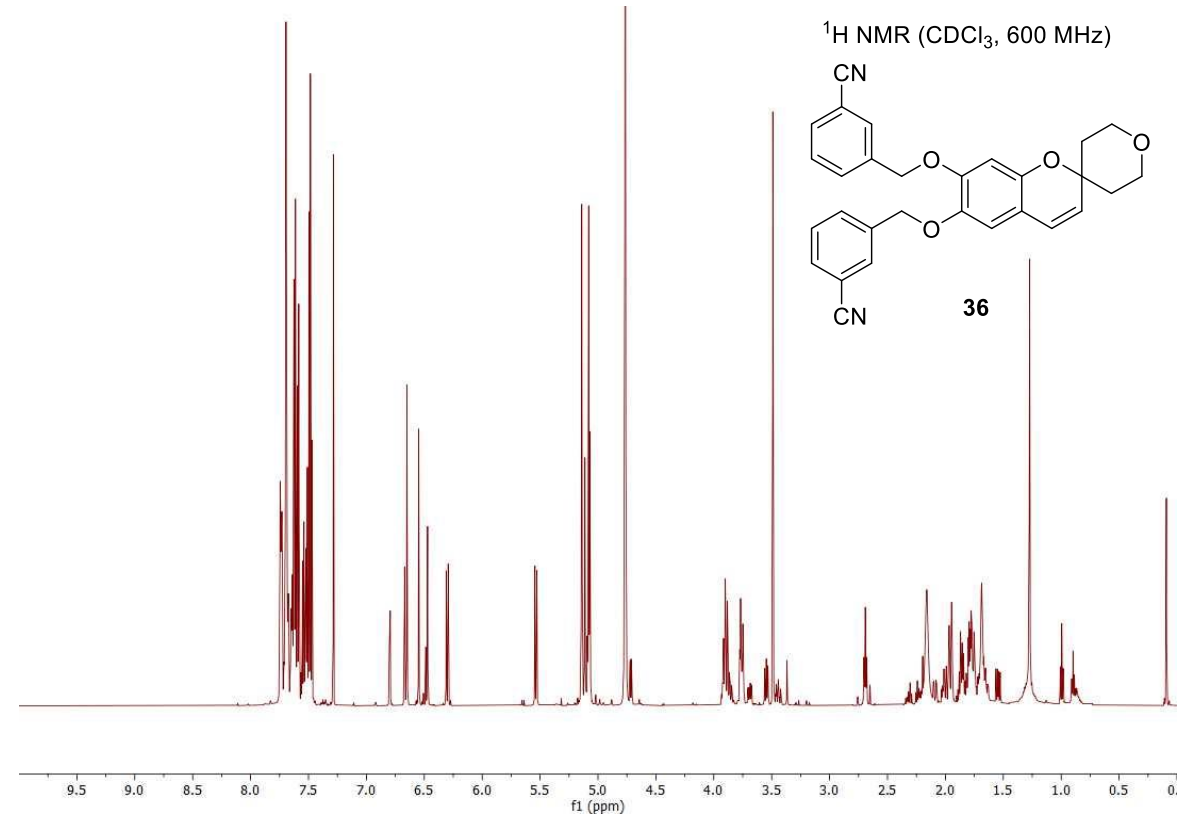

^{1}H NMR ($CDCl_3$, 500 MHz)
NO_2
O_2N
32
f1 (ppm)

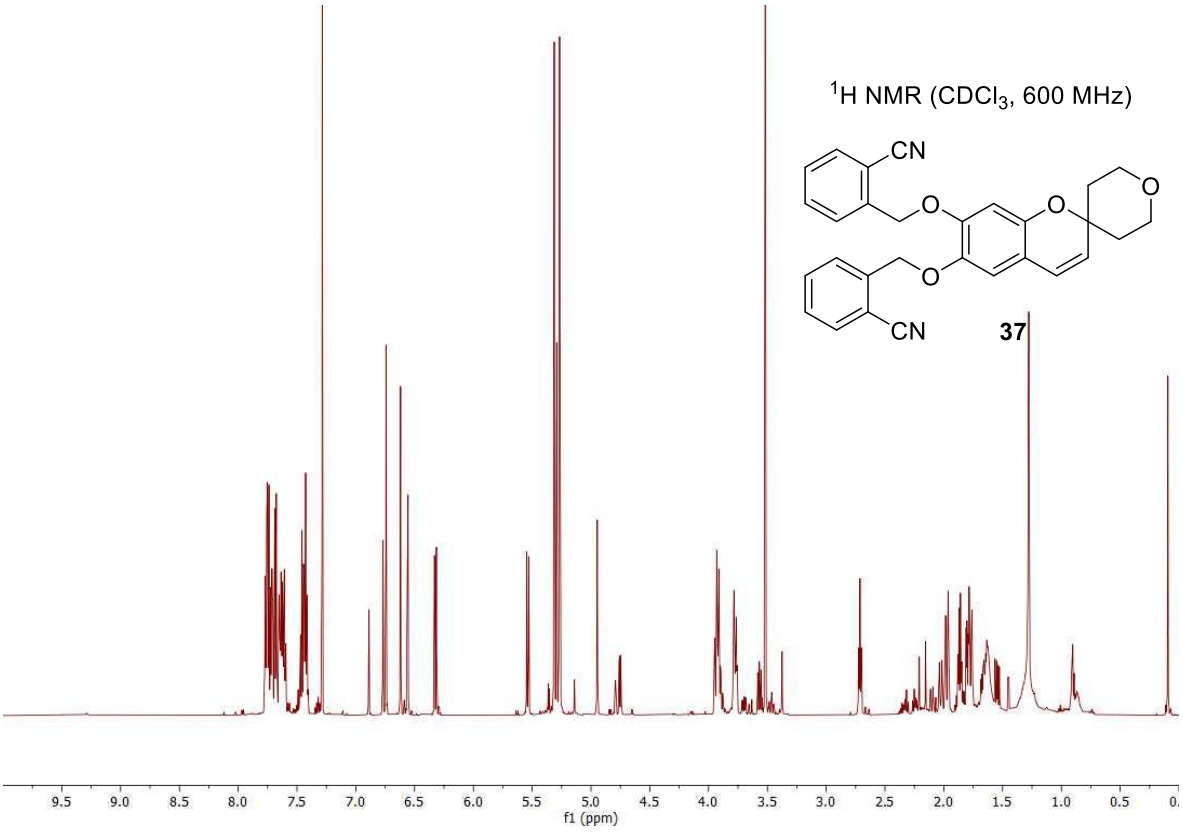

^{13}C NMR ($CDCl_3$, 151 MHz)
NO_2
O_2N
32
f1 (ppm)

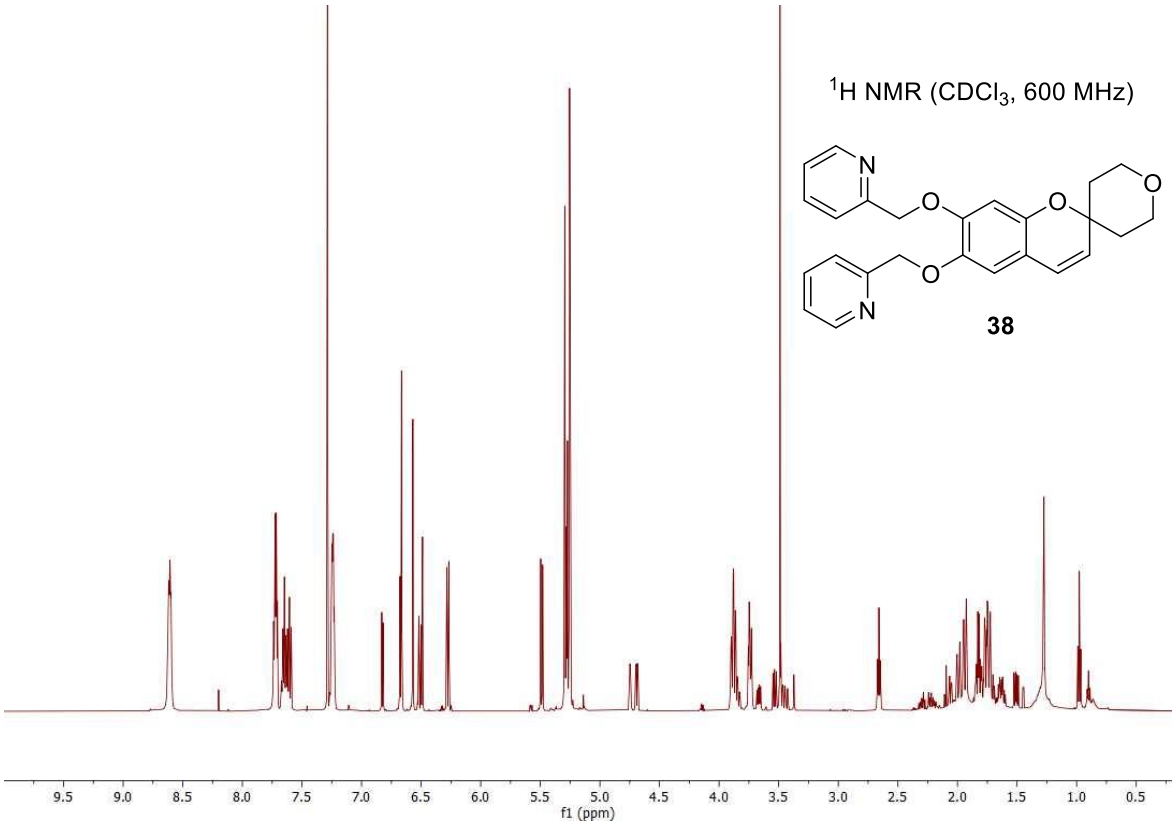

^{1}H NMR ($CDCl_3$, 600 MHz)
CF_3
O
O
O
O
CF_3
33
f1 (ppm)

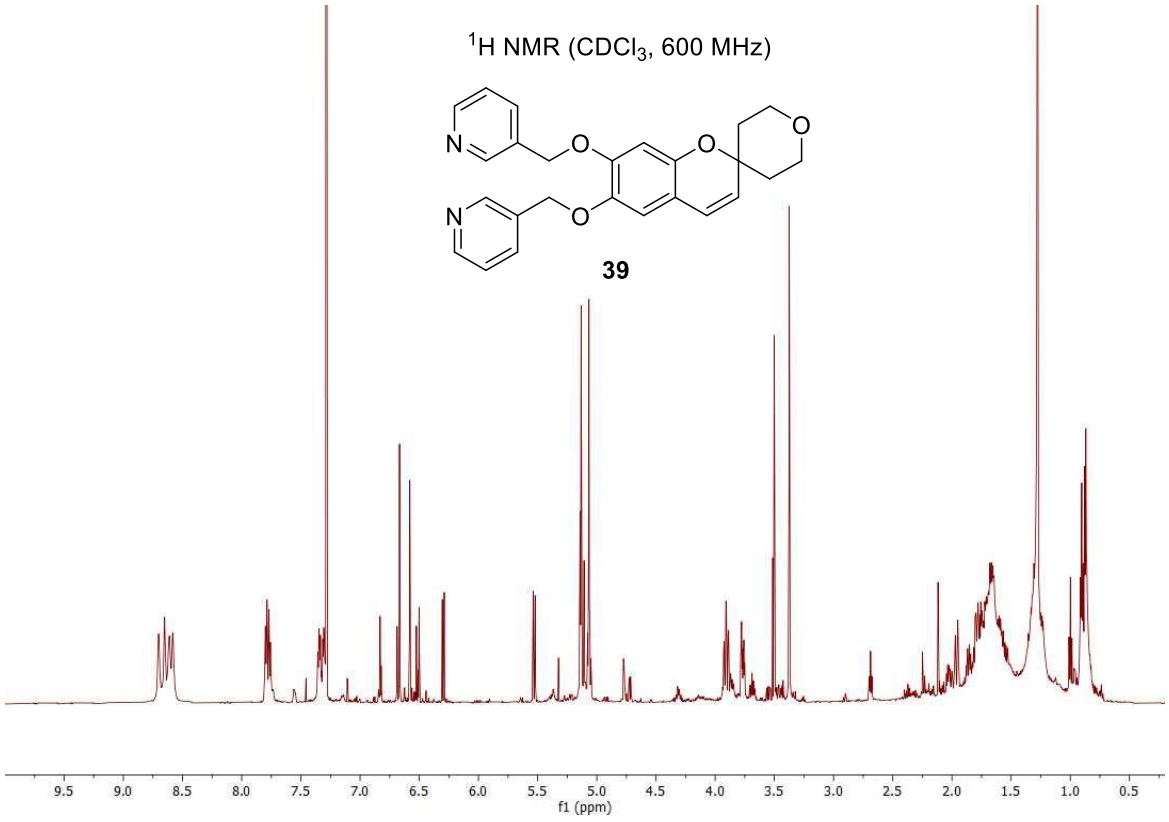

^{1}H NMR ($CDCl_3$, 500 MHz)
CF_3
O
O
O
O
CF_3
34
f1 (ppm)

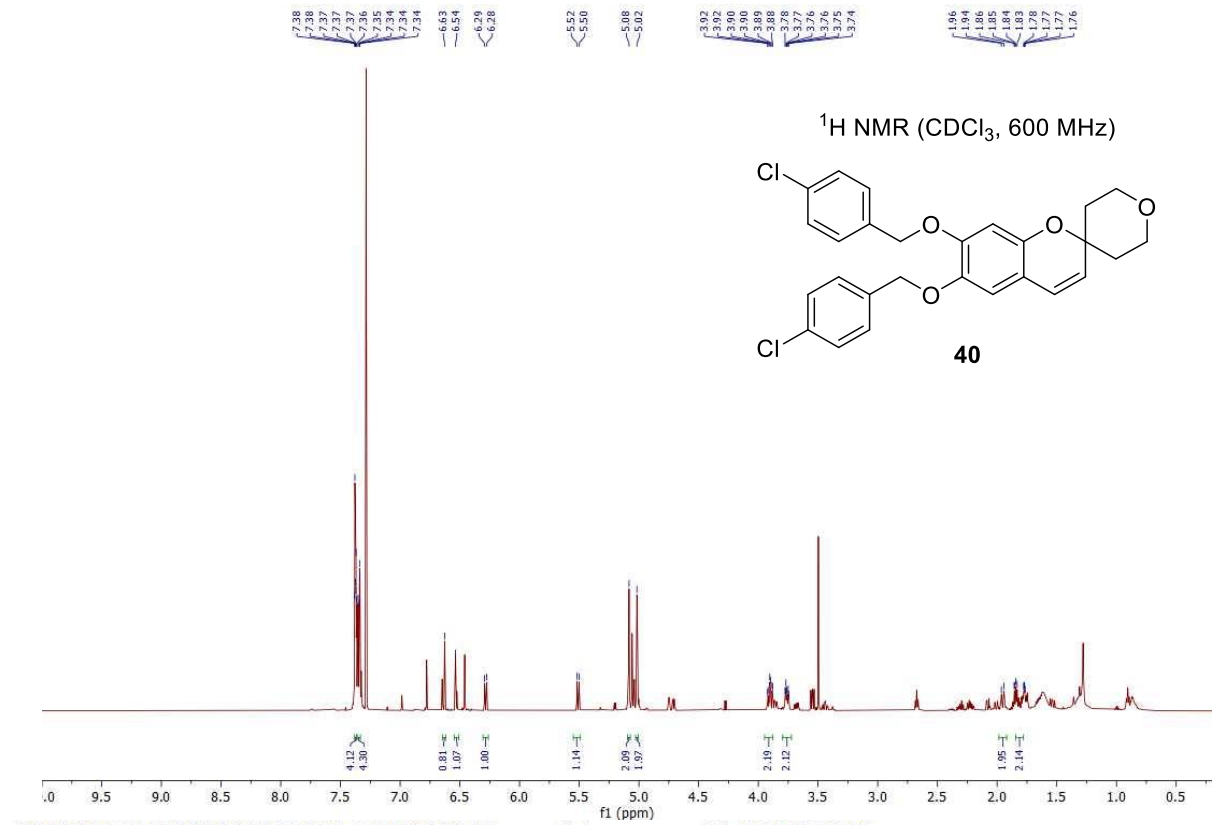

^{1}H NMR ($CDCl_3$, 600 MHz)
F_3CO
F_3CO
O
O
O
O
O
35
f1 (ppm)

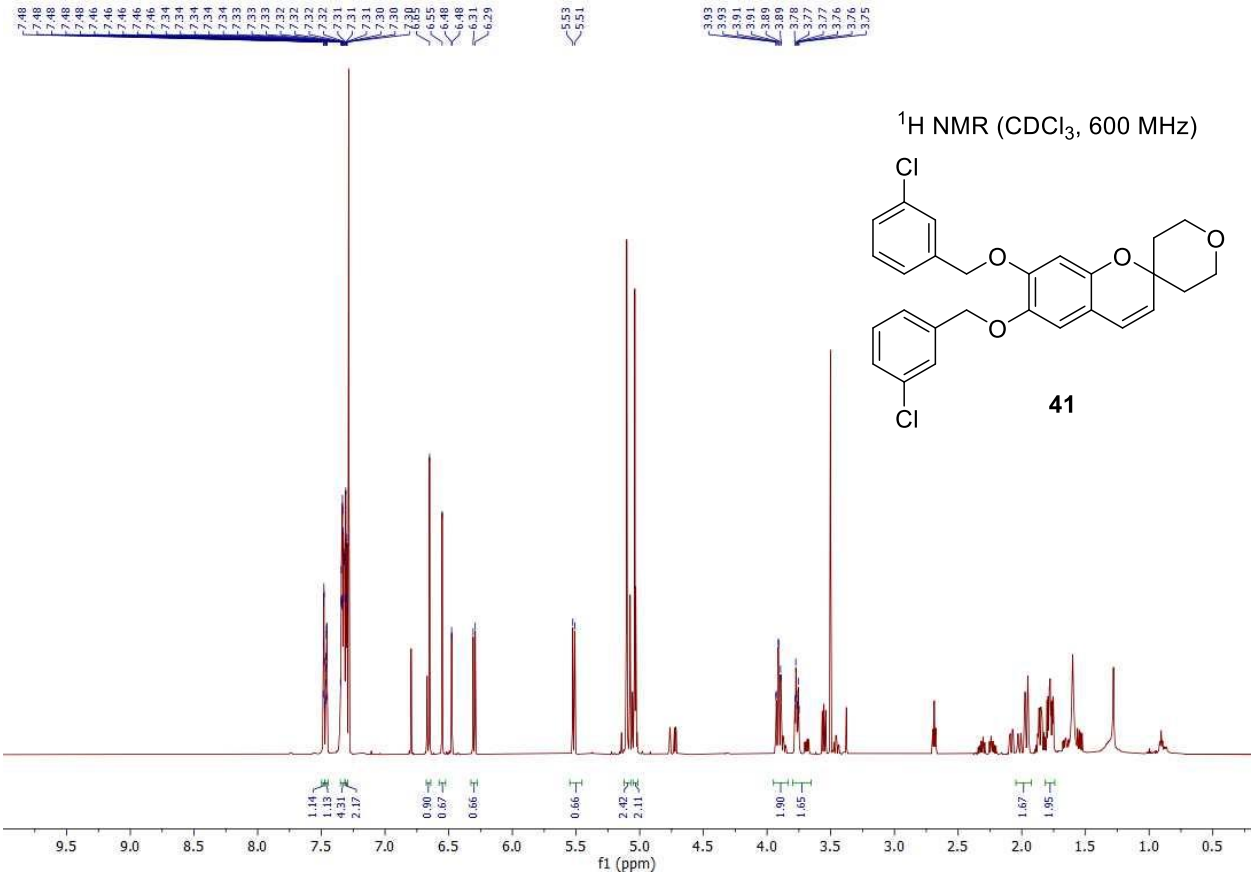

^{1}H NMR ($CDCl_3$, 600 MHz)
CN
CN
O
O
O
O
36
f1 (ppm)

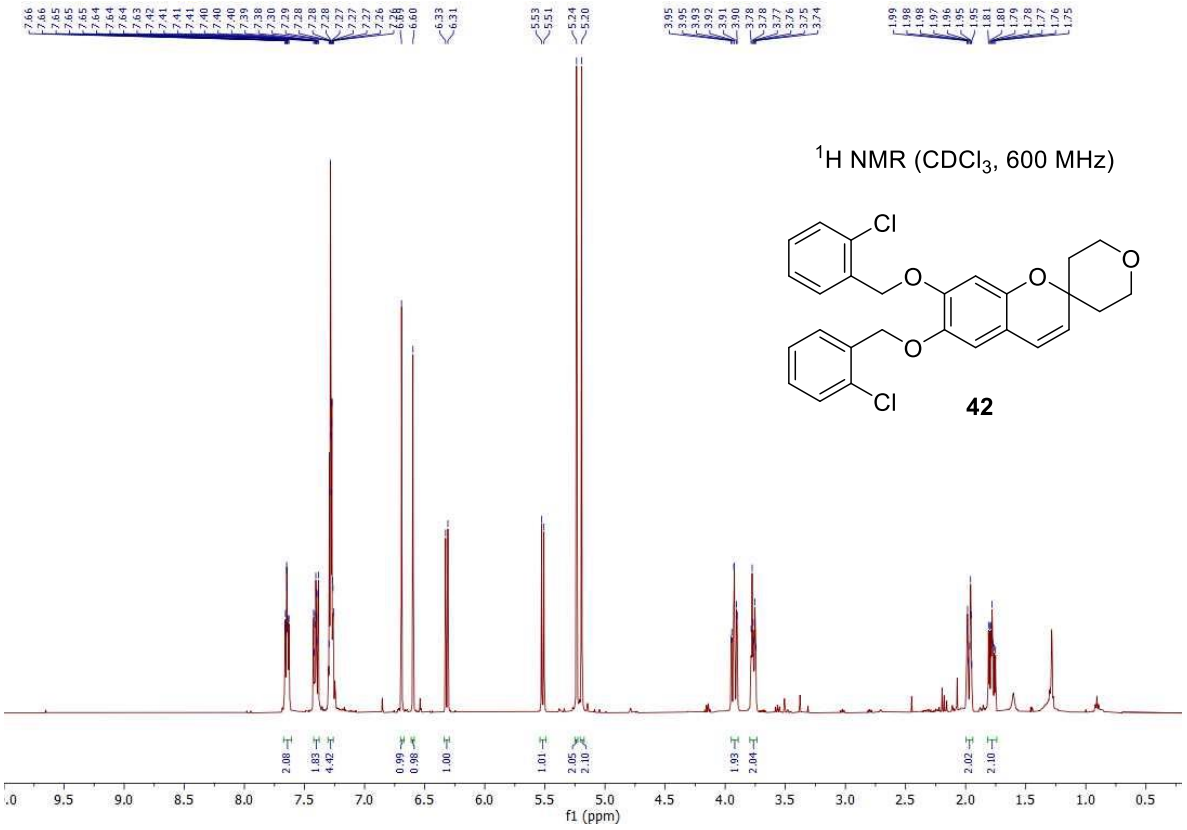

^{1}H NMR ($CDCl_3$, 600 MHz)
CN
O
O
O
O
CN
37
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

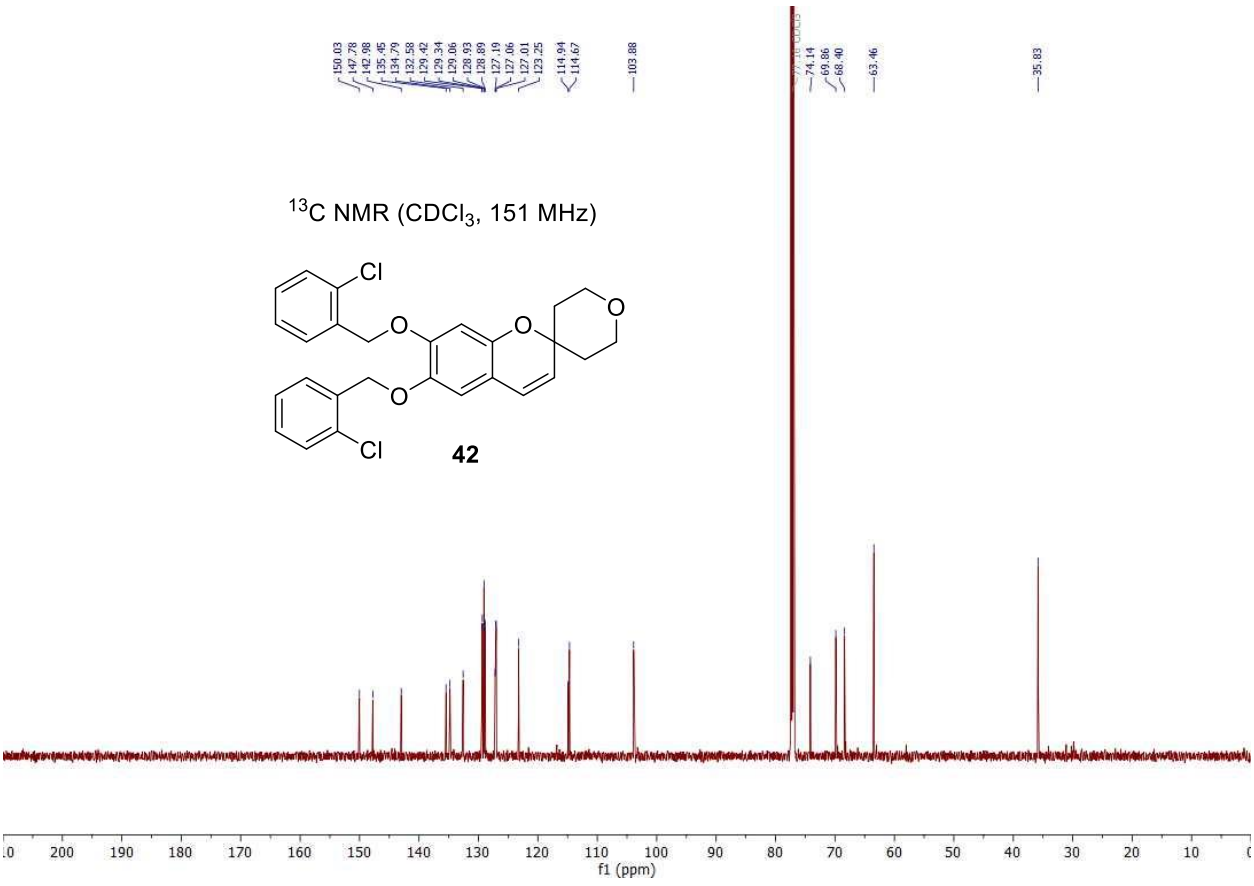

^{1}H NMR ($CDCl_3$, 600 MHz)
N
O
O
O
O
N
38
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

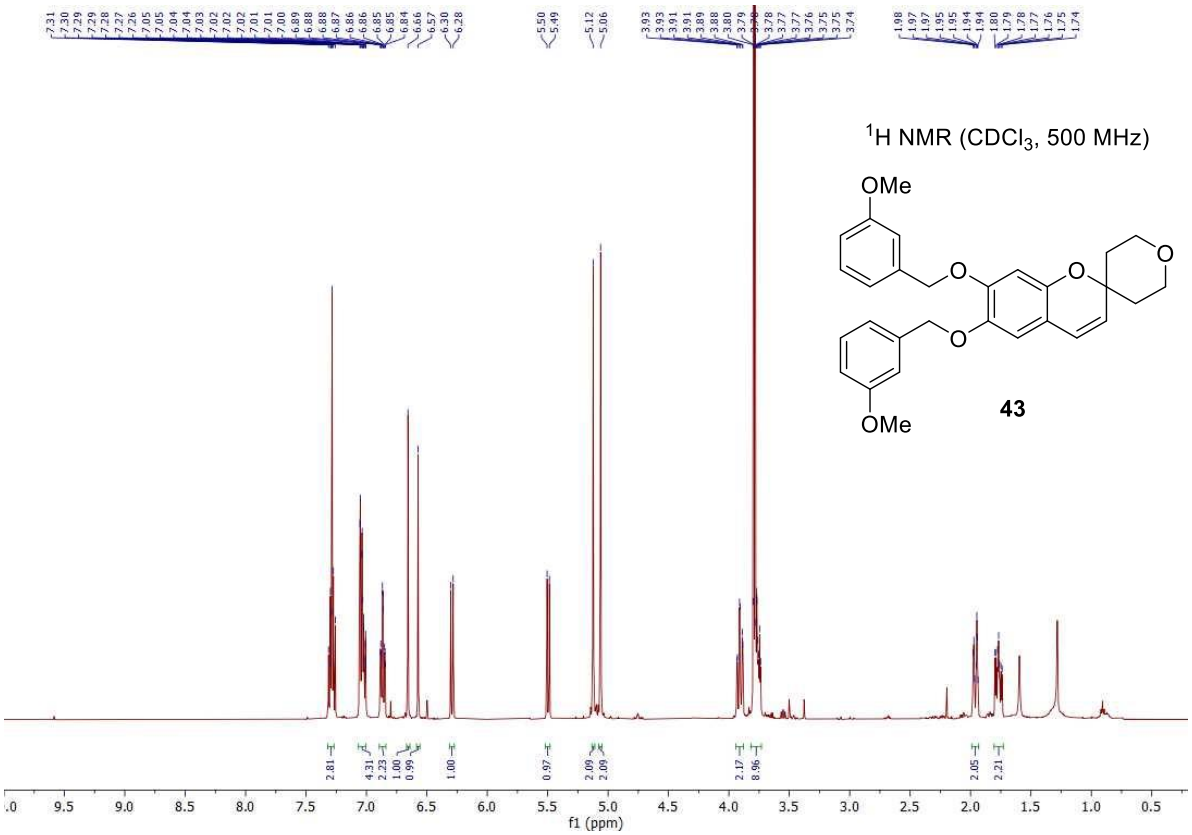

^{1}H NMR ($CDCl_3$, 600 MHz)
N
O
O
O
N
O
39
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

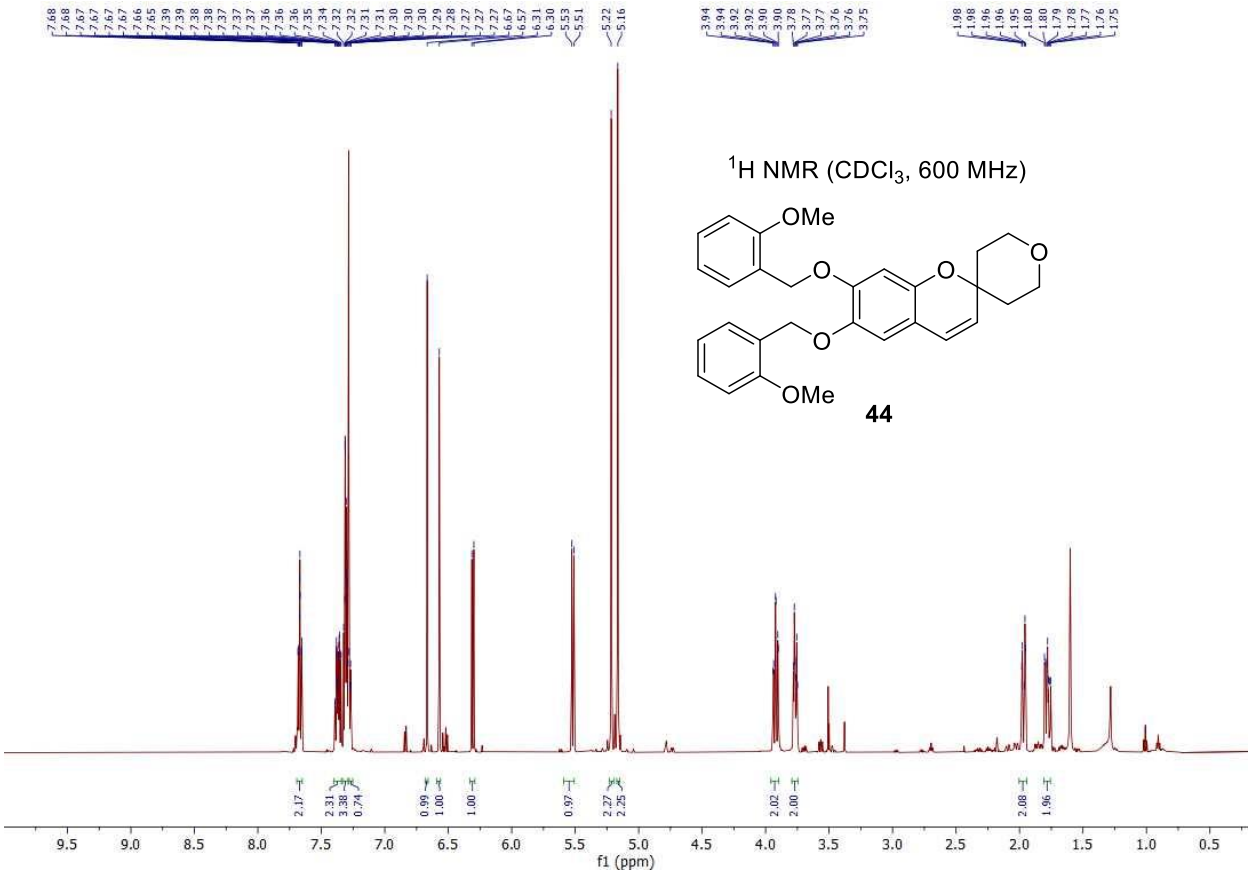

^{1}H NMR ($CDCl_3$, 600 MHz)
Cl
O
O
O
O
Cl
40
f1 (ppm)

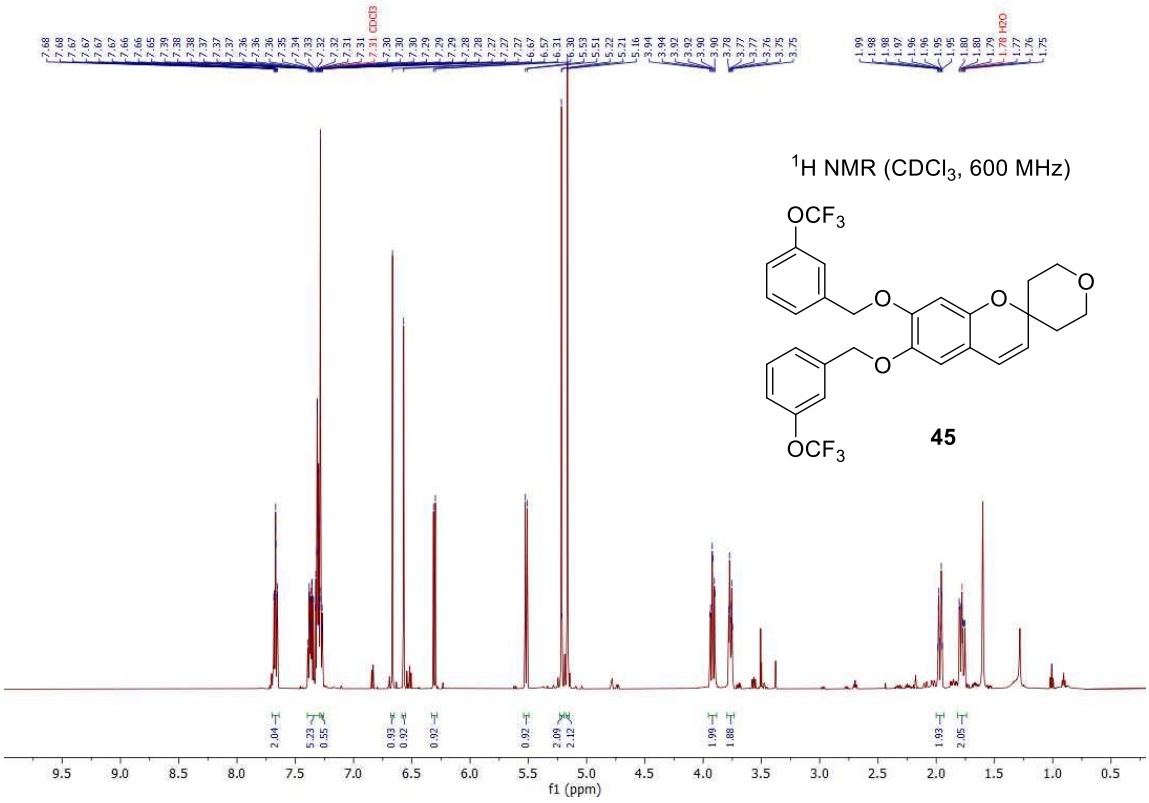

^{1}H NMR ($CDCl_3$, 600 MHz)
Cl
O
O
O
O
Cl
41
f1 (ppm)

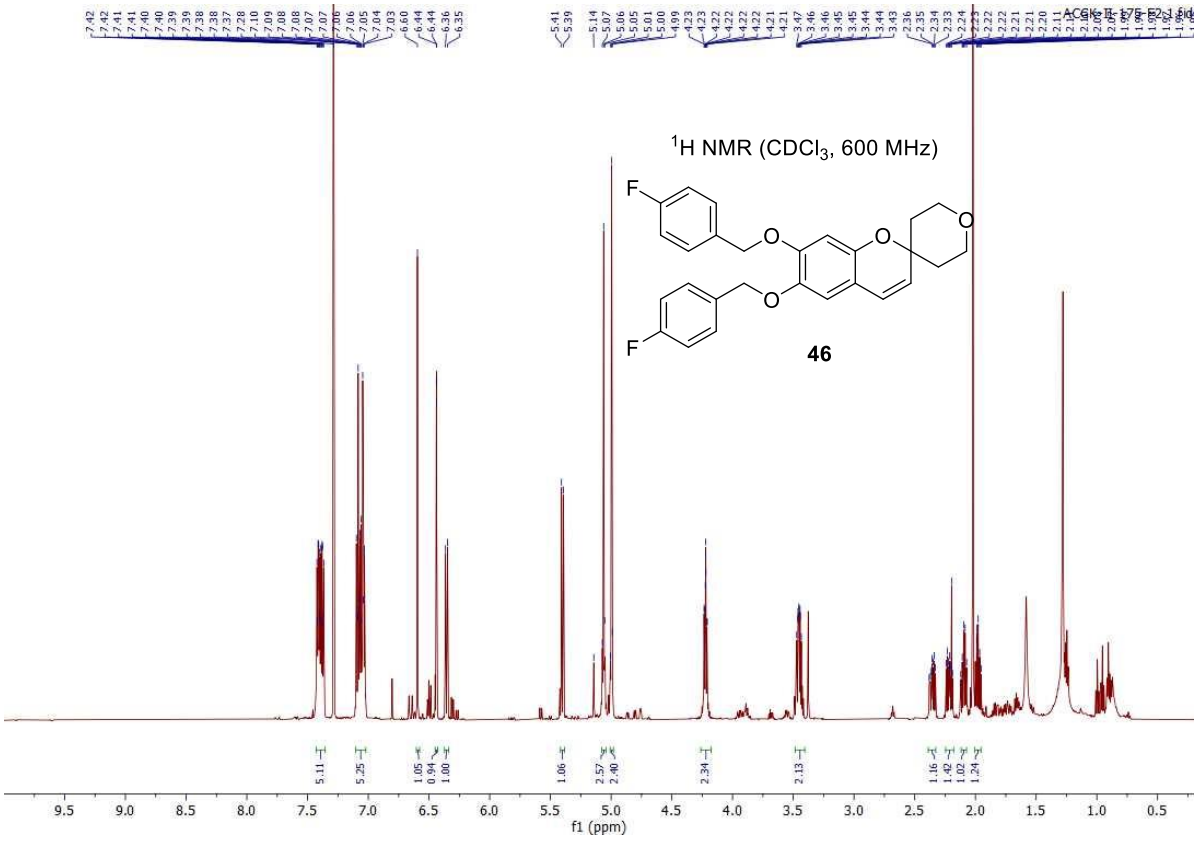

^{1}H NMR ($CDCl_3$, 600 MHz)
Cl
O
O
O
O
Cl
42
f1 (ppm)

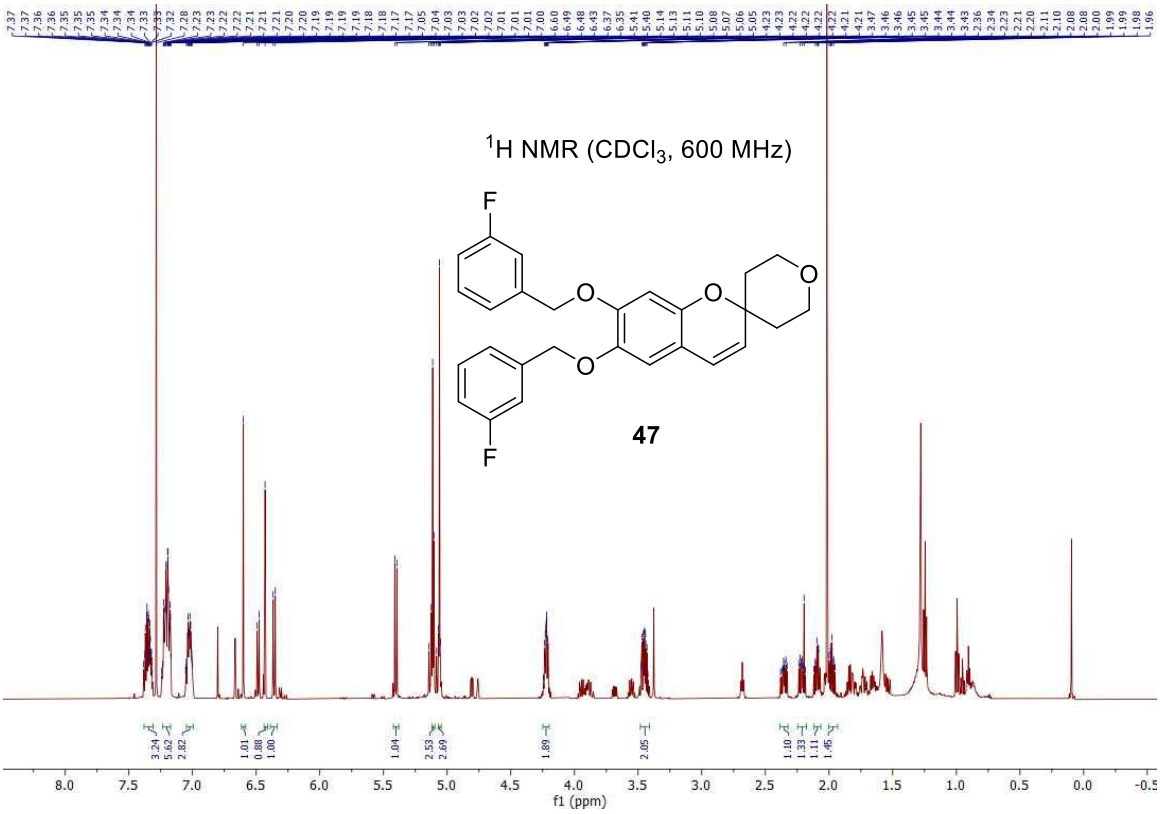

^{13}C NMR ($CDCl_3$, 151 MHz)
Cl
O
O
O
O
Cl
42
f1 (ppm)


^{1}H NMR ($CDCl_3$, 500 MHz)
OMe
O
O
O
O
OMe
43
f1 (ppm)

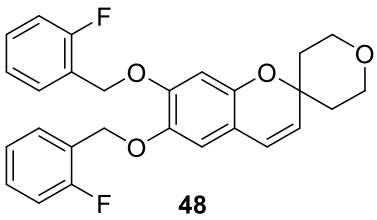

^{1}H NMR ($CDCl_3$, 600 MHz)
OMe
O
O
O
O
OMe
44
f1 (ppm)


^{1}H NMR ($CDCl_3$, 600 MHz)
OCF_3
O
O
O
O
OCF_3
45
f1 (ppm)

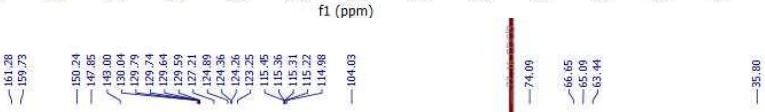

^{1}H NMR ($CDCl_3$, 600 MHz)
F
O
O
O
O
F
46
f1 (ppm)


^{1}H NMR ($CDCl_3$, 600 MHz)
F
O
O
O
O
F
47
3.24
5.62
2.82
1.01
0.88
1.00
1.04
2.53
2.69
1.89
2.05
1.10
1.33
1.11
1.45
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

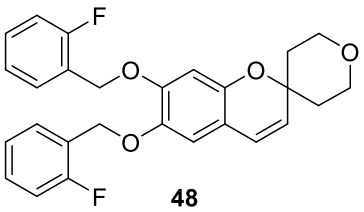
^{1}H NMR ($CDCl_3$, 500 MHz)



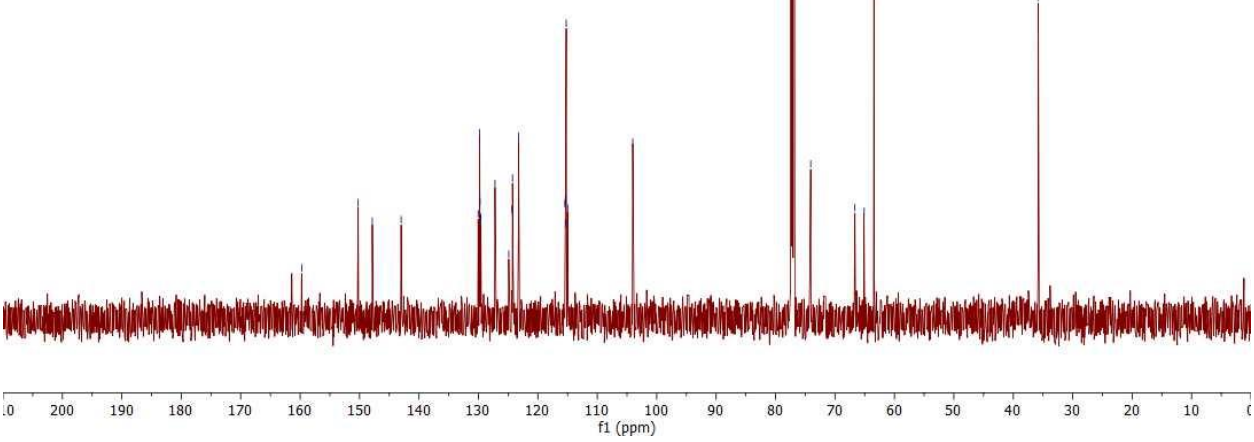
48

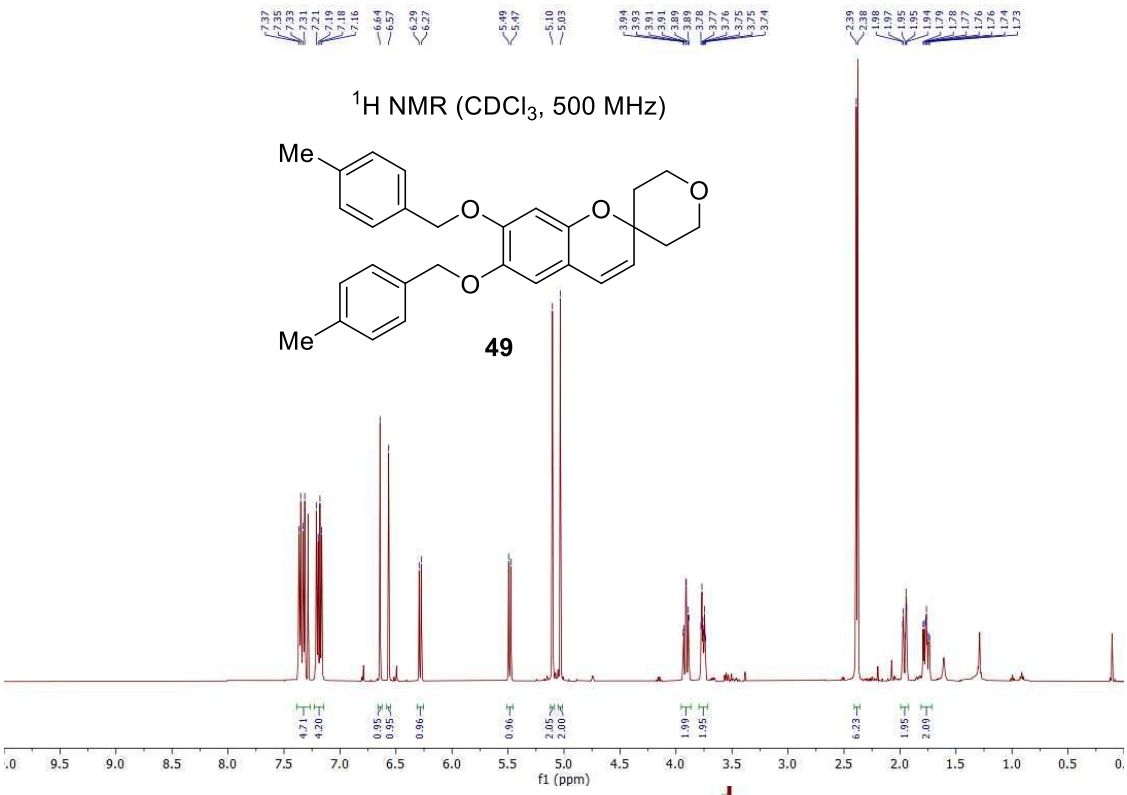


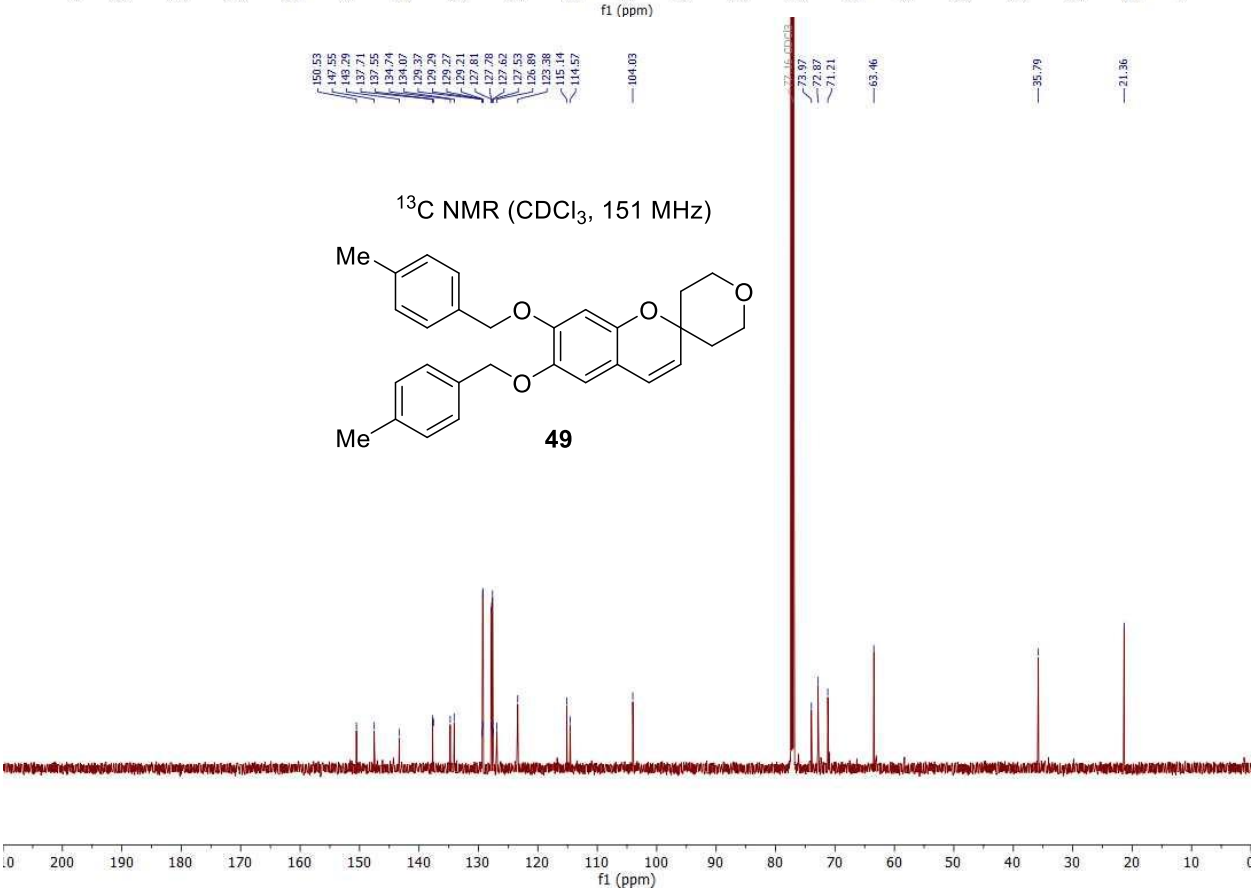
^{13}C NMR ($CDCl_3$, 151 MHz)

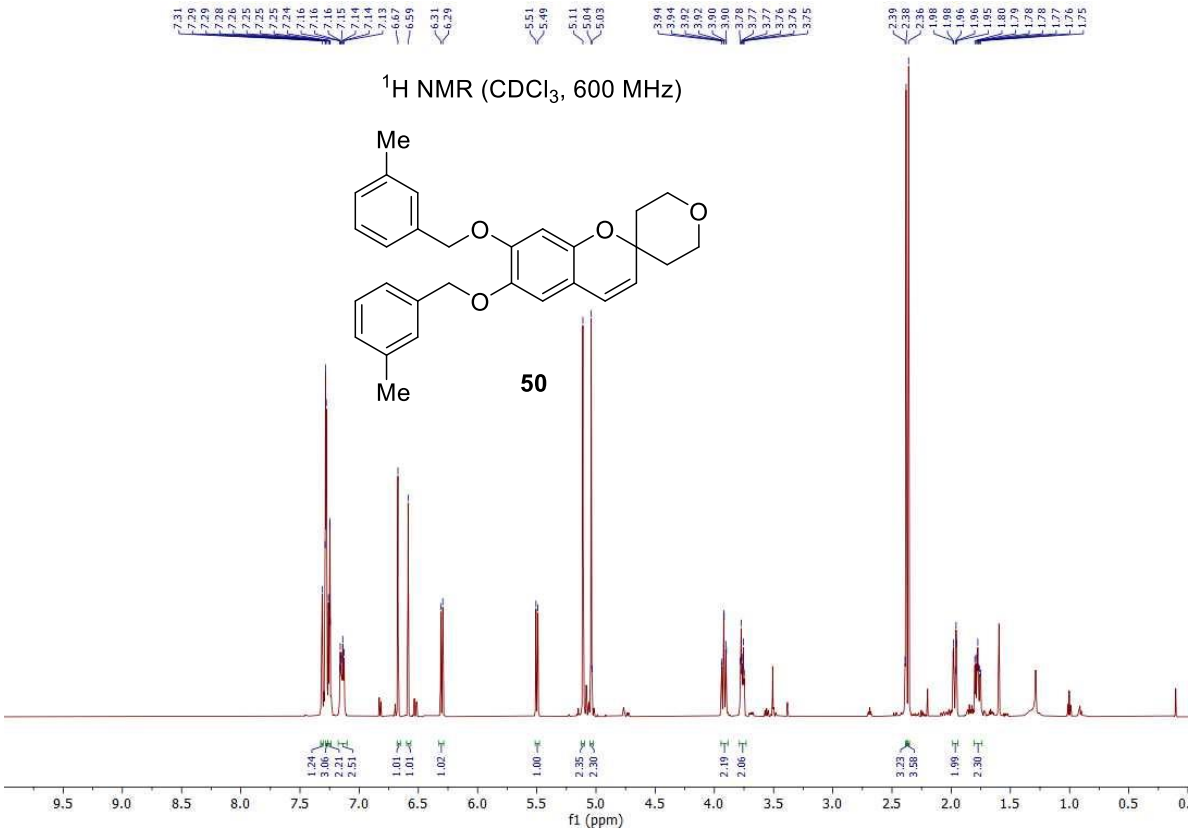


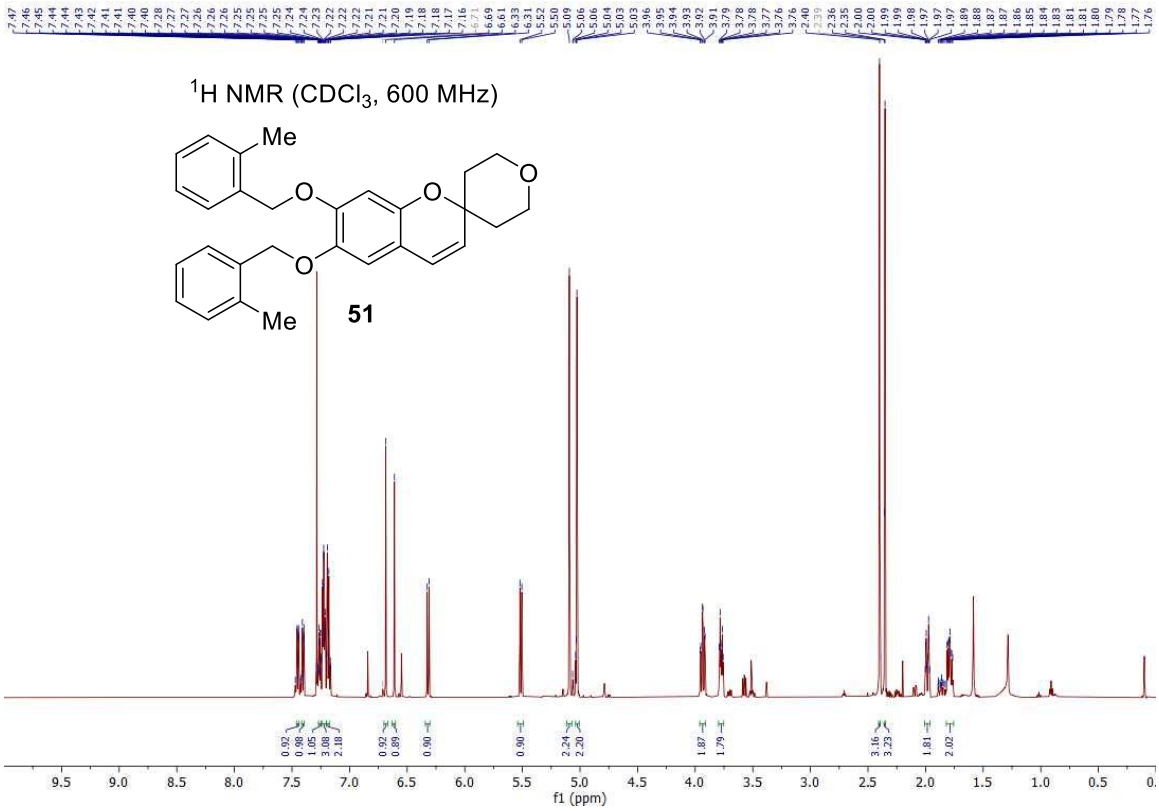
48



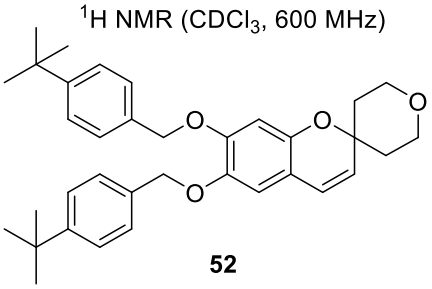

^{1}H NMR ($CDCl_3$, 500 MHz)
Me
O
O
O
O
Me
49
f1 (ppm)


^{13}C NMR ($CDCl_3$, 151 MHz)
Me
O
O
O
O
Me
49
f1 (ppm)


1H NMR (CDCl3, 600 MHz)
Me
O
O
O
O
Me
50
f1 (ppm)

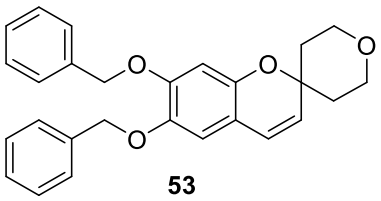

1H NMR (CDCl3, 600 MHz)
Me
O
O
O
O
Me
51
f1 (ppm)

^{1}H NMR ($CDCl_3$, 600 MHz)

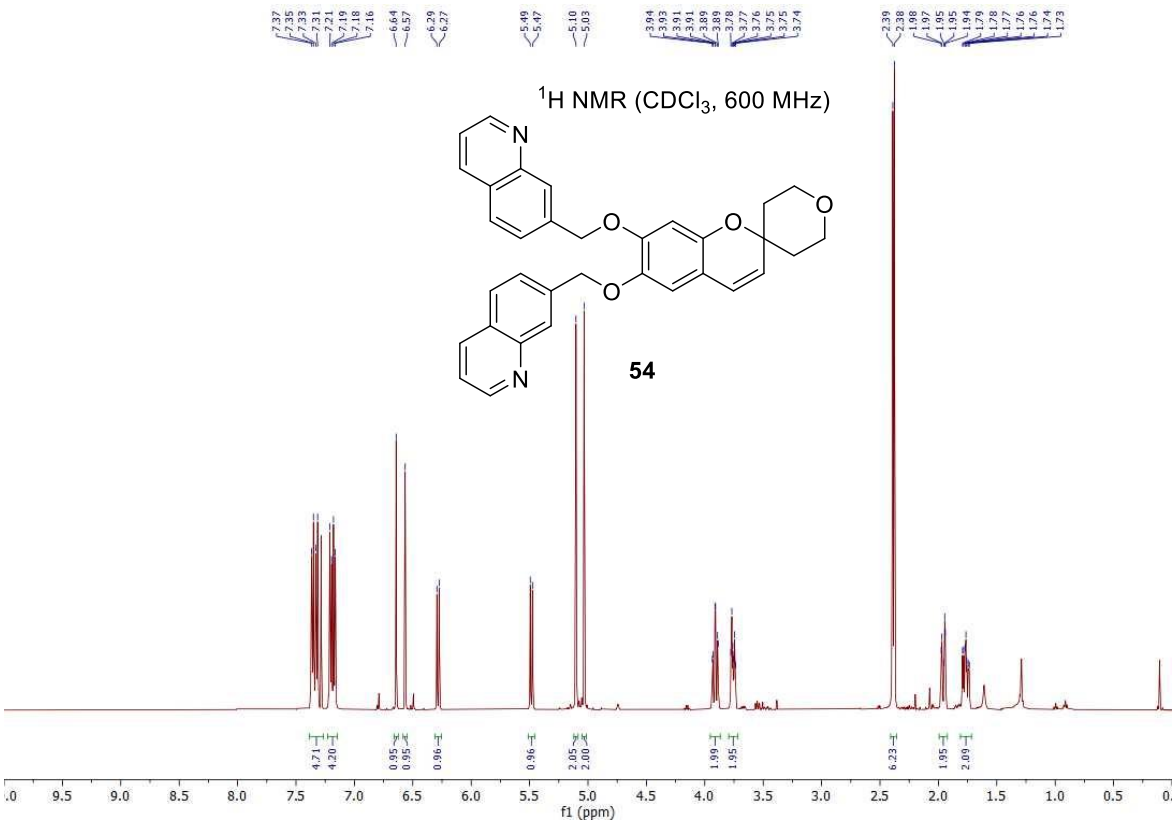


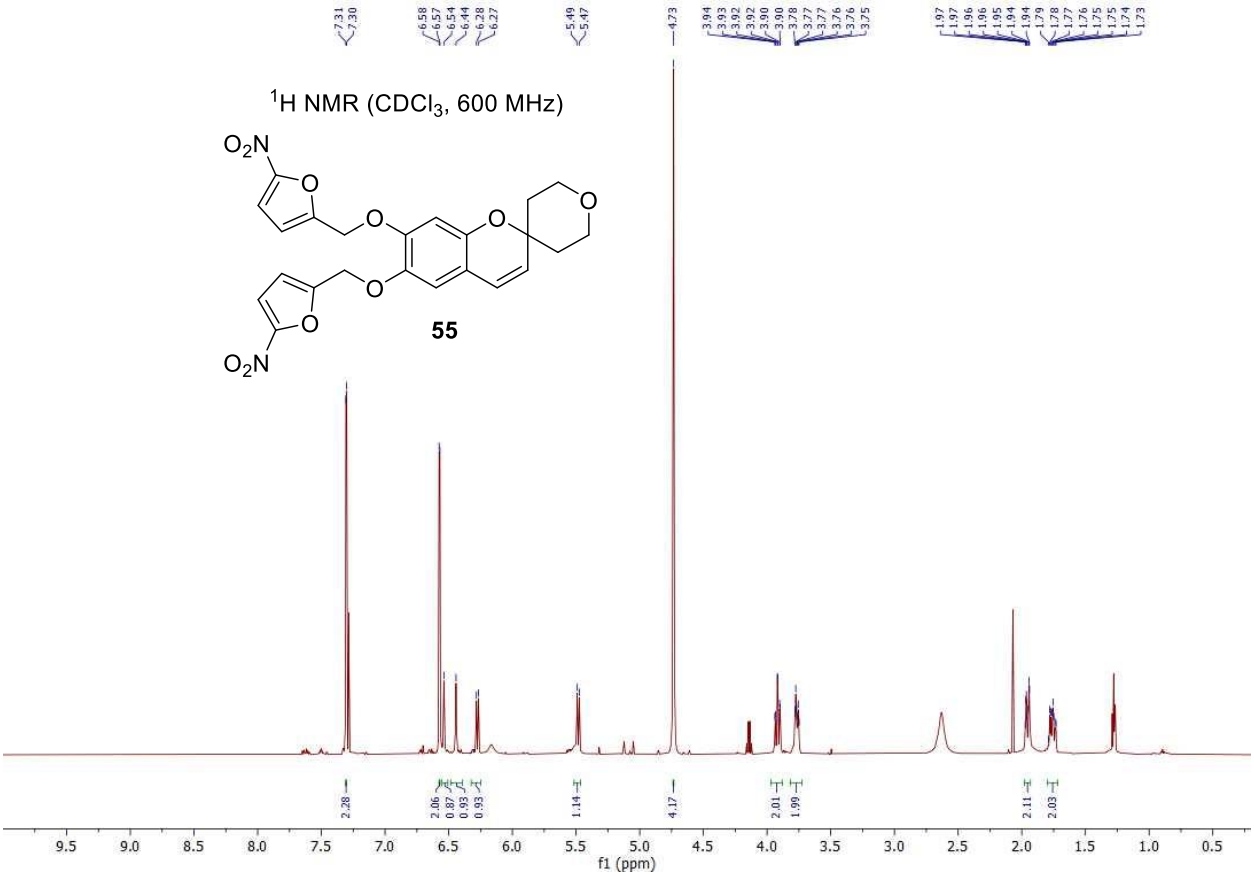
52

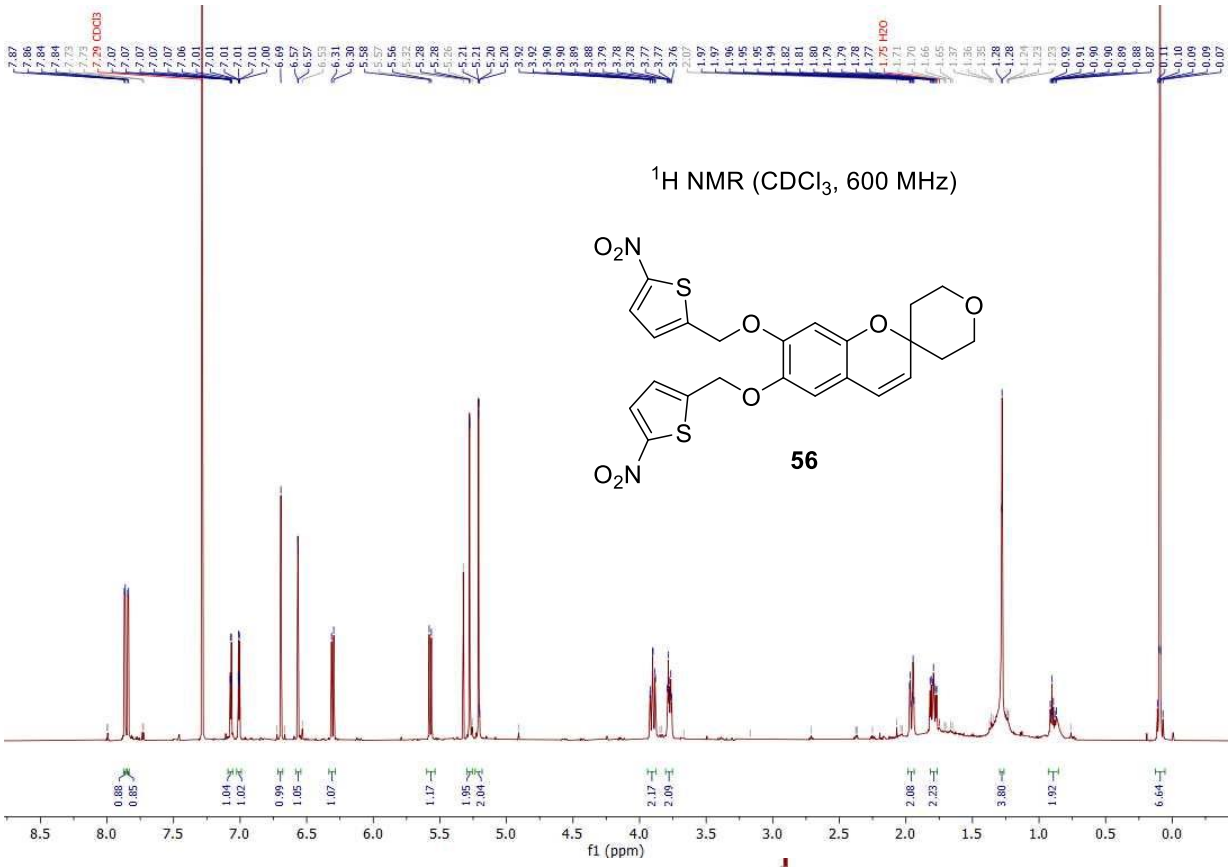
^{1}H NMR ($CDCl_3$, 500 MHz)

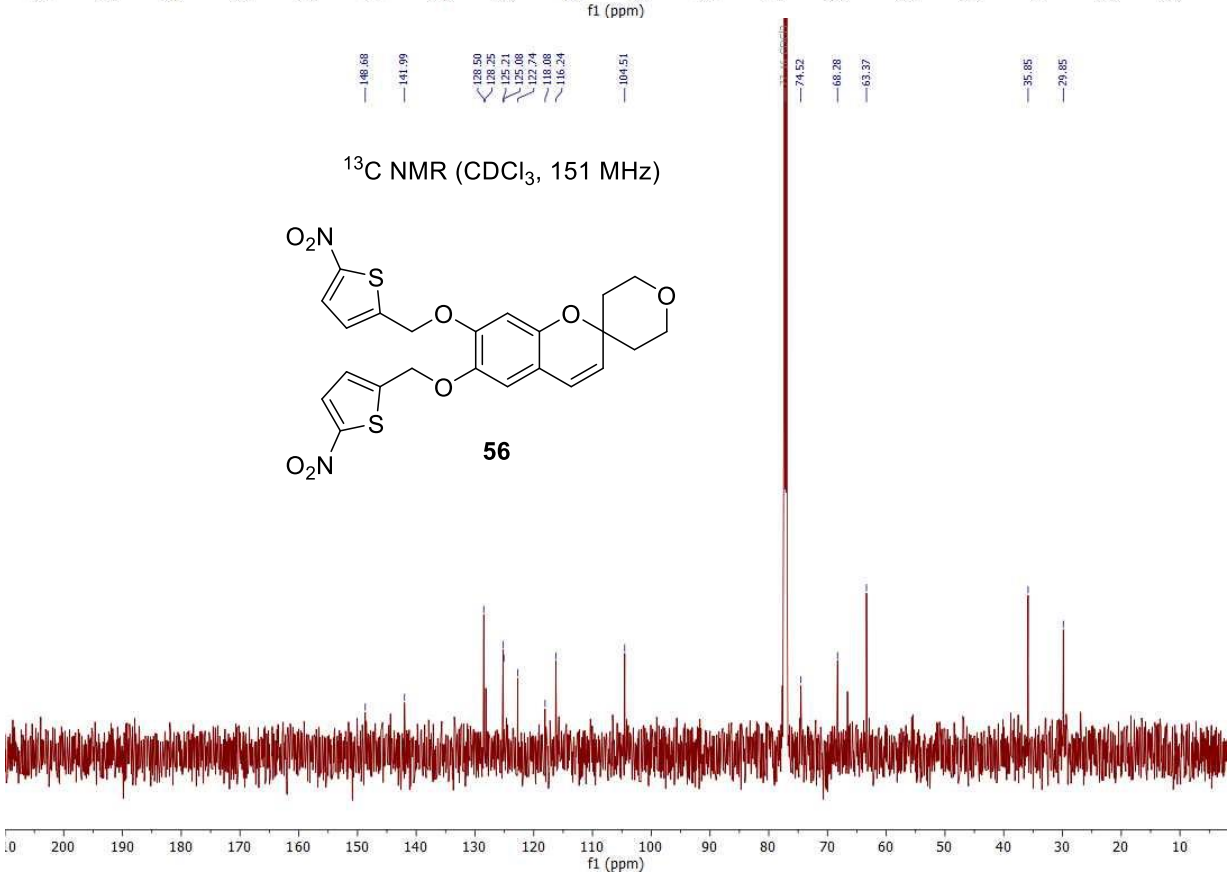


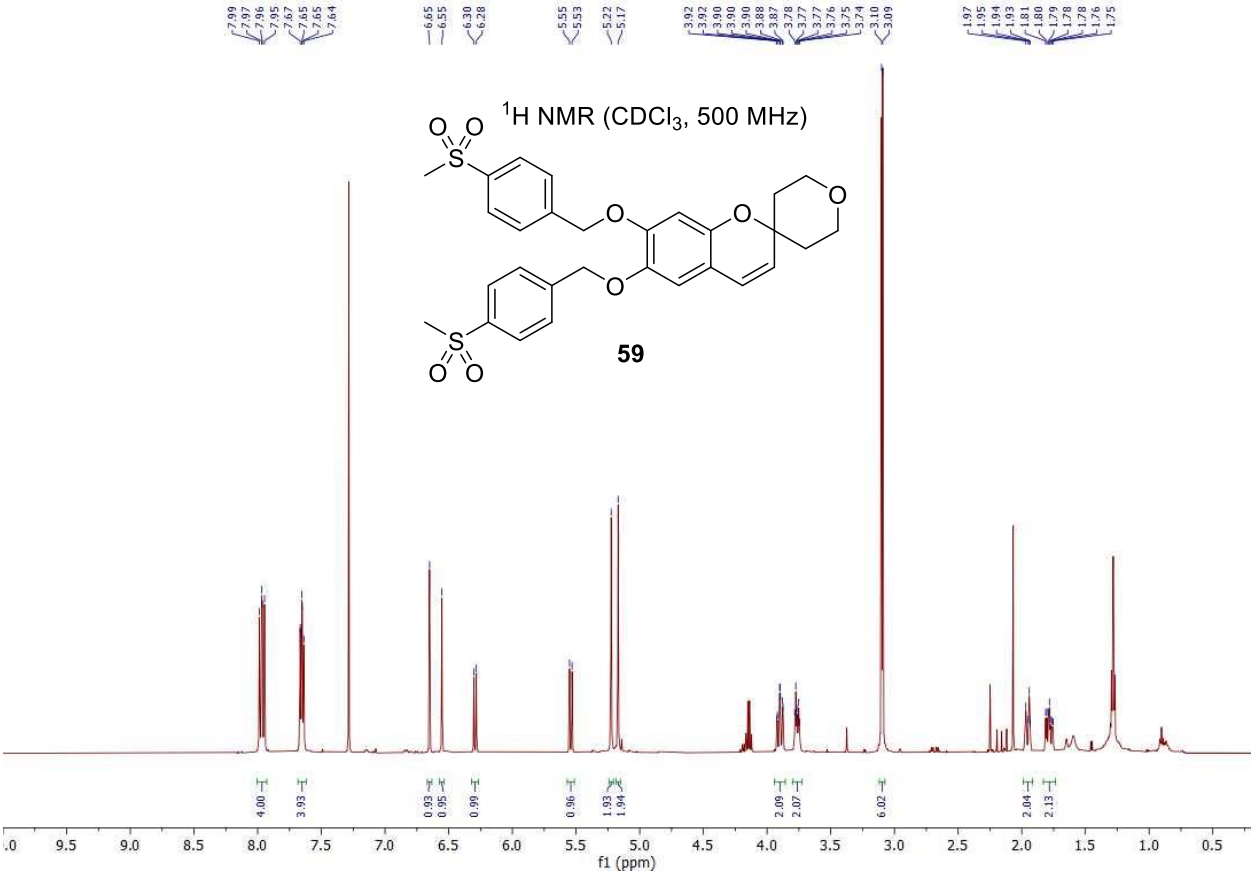
53

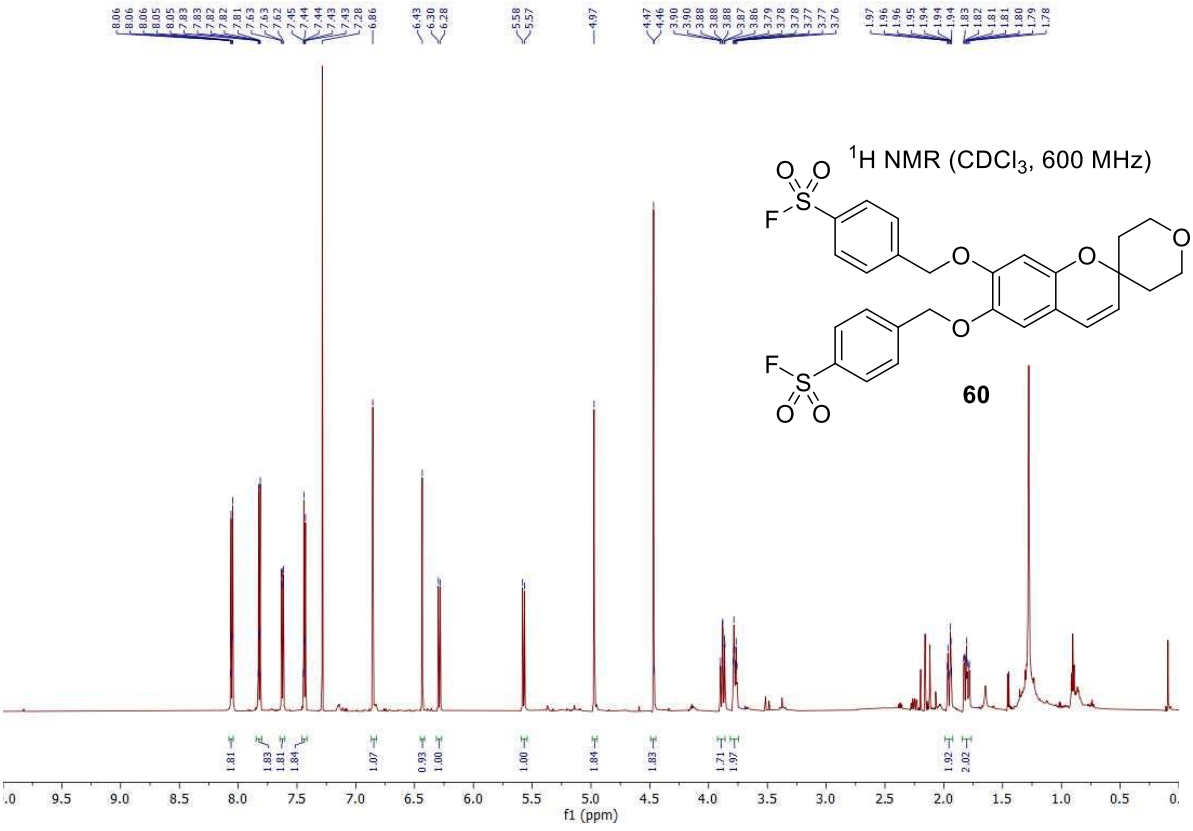

^{1}H NMR ($CDCl_3$, 600 MHz)
54
f1 (ppm)

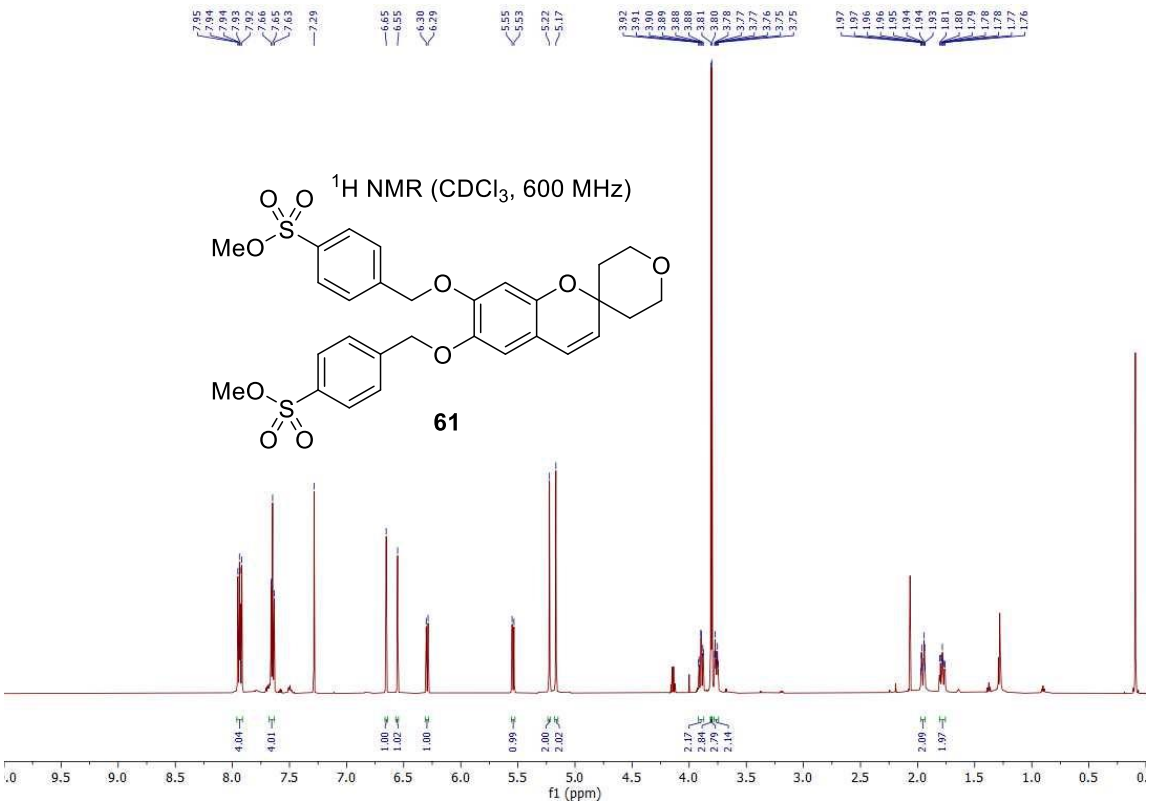

^{1}H NMR ($CDCl_3$, 600 MHz)
55
f1 (ppm)

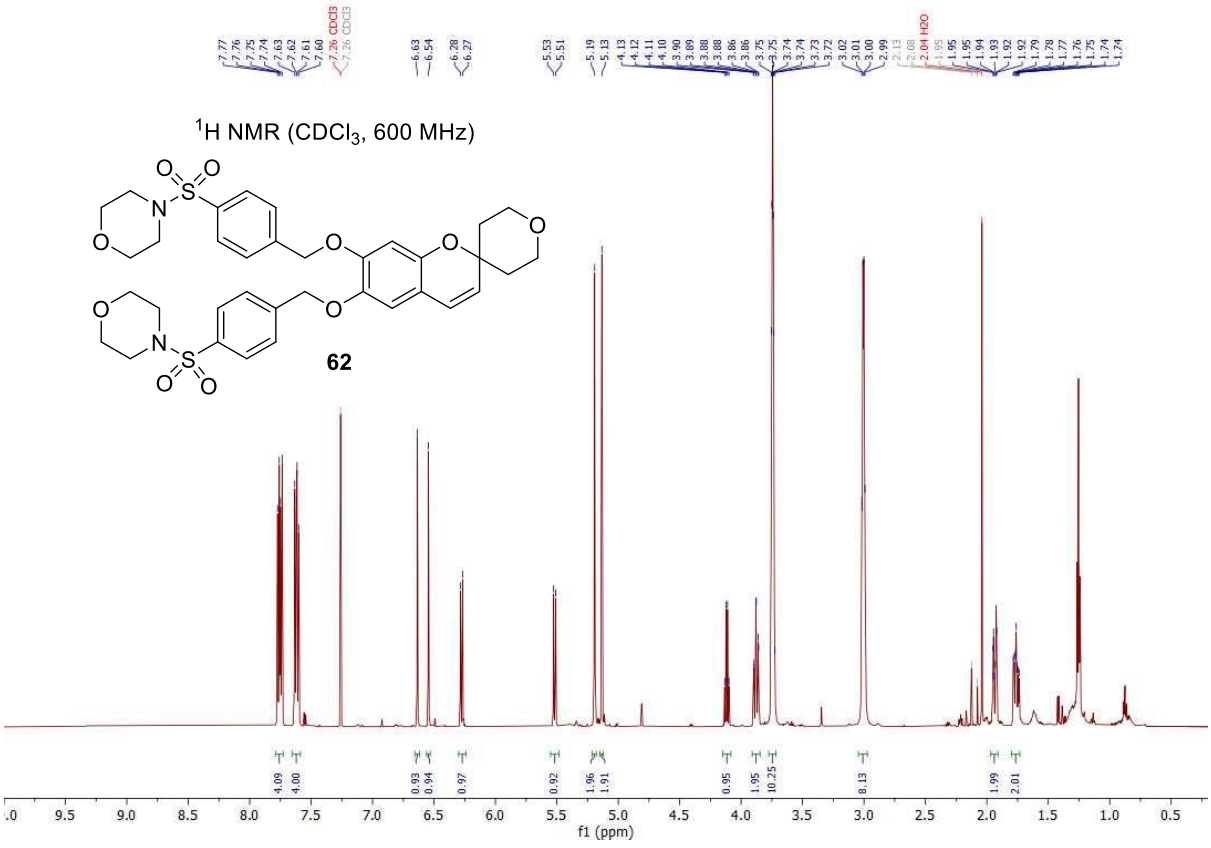

^{1}H NMR ($CDCl_3$, 600 MHz)
O_2N
S
O
O
O
O
S
O_2N
56
f1 (ppm)

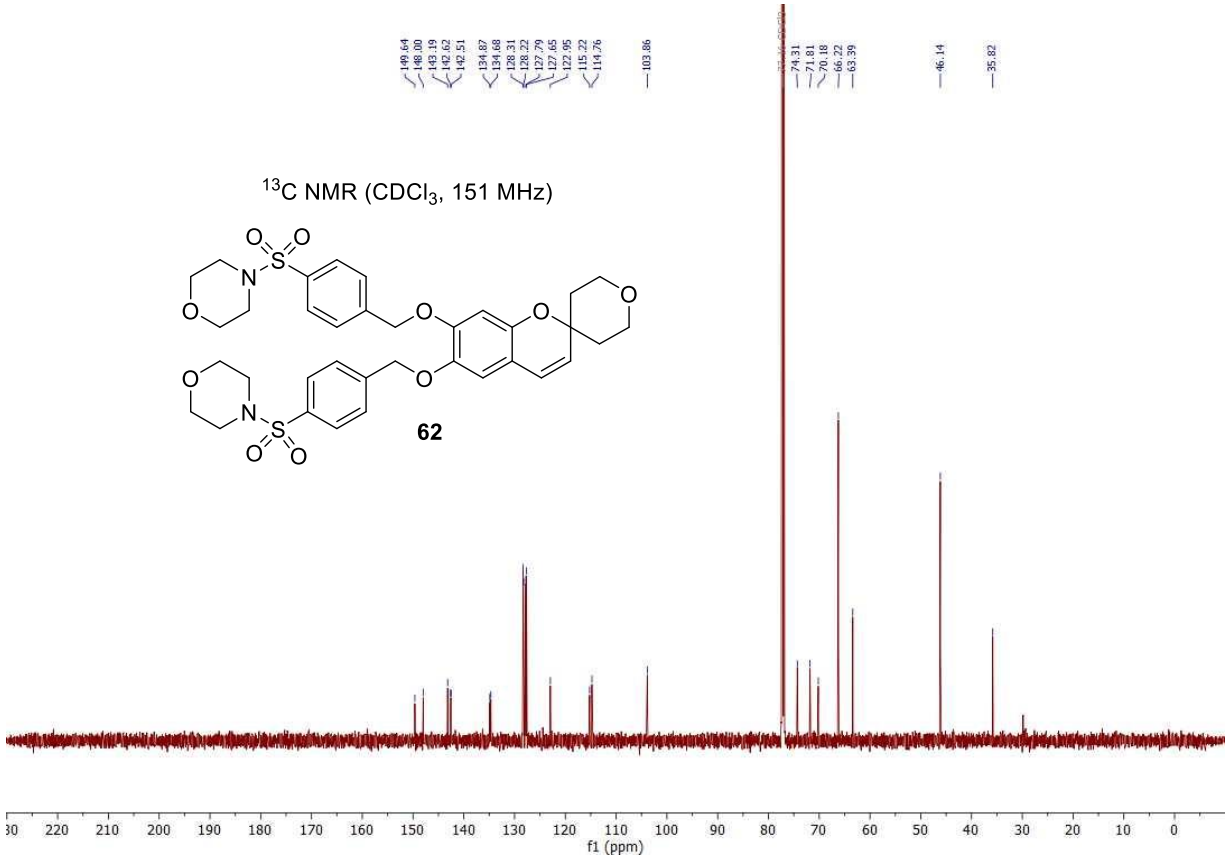

^{13}C NMR ($CDCl_3$, 151 MHz)
O_2N
S
O
O
O
O
S
O_2N
56
f1 (ppm)

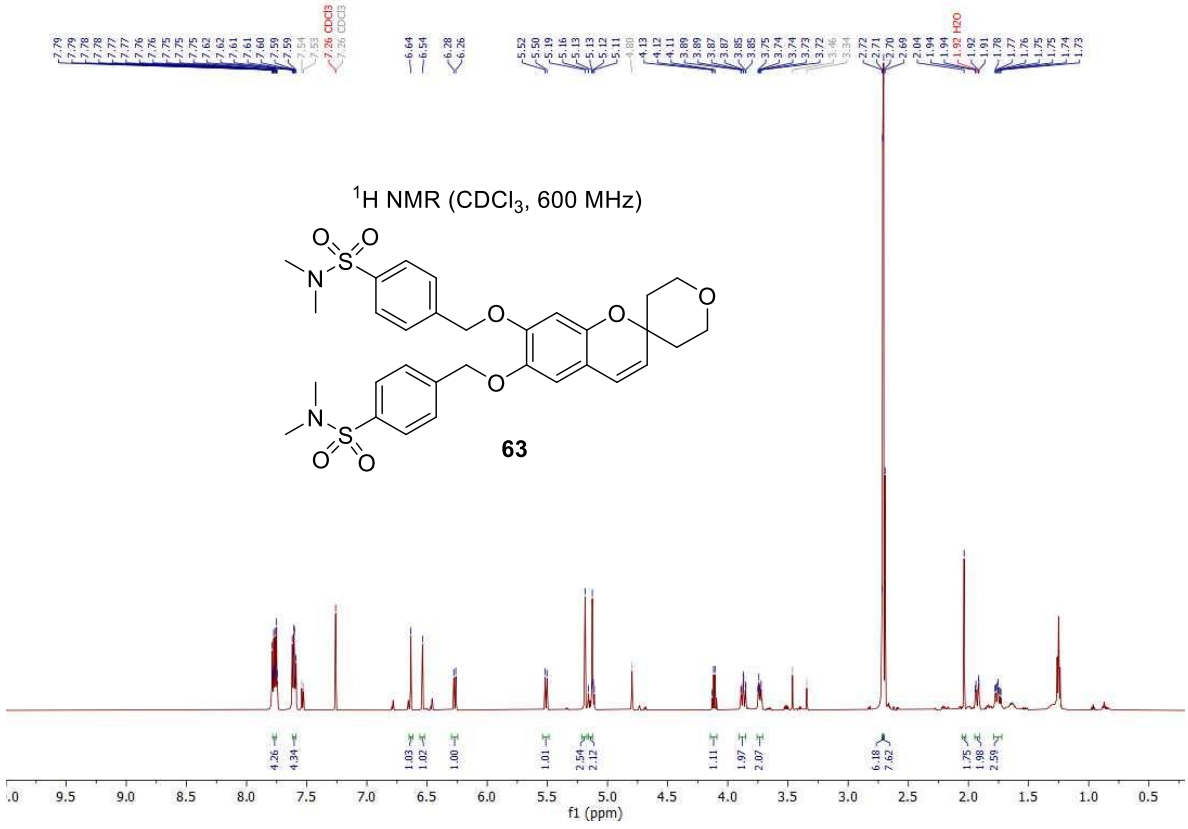

^{1}H NMR ($CDCl_3$, 500 MHz)
59
f1 (ppm)

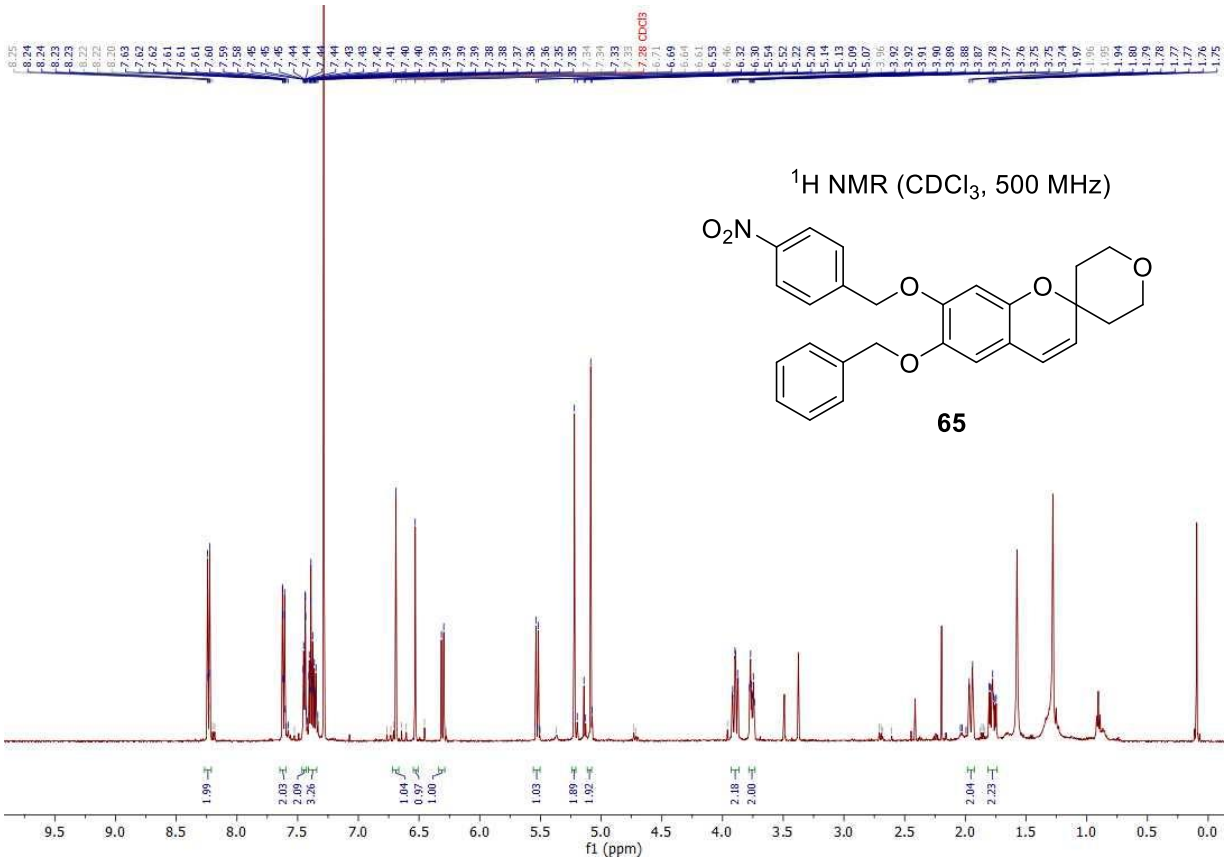

^{1}H NMR ($CDCl_3$, 600 MHz)
60
f1 (ppm)

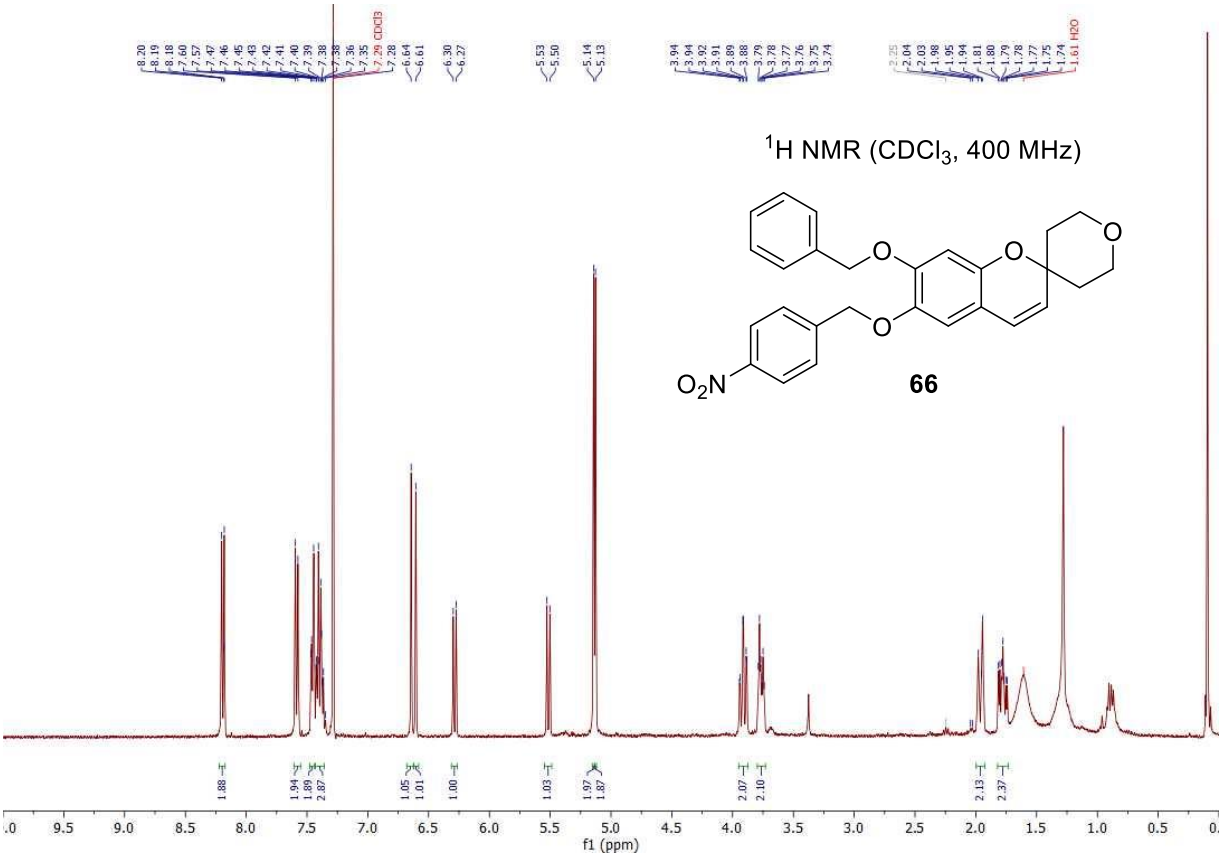

^{1}H NMR ($CDCl_3$, 600 MHz)
MeO
MeO
61
f1 (ppm)

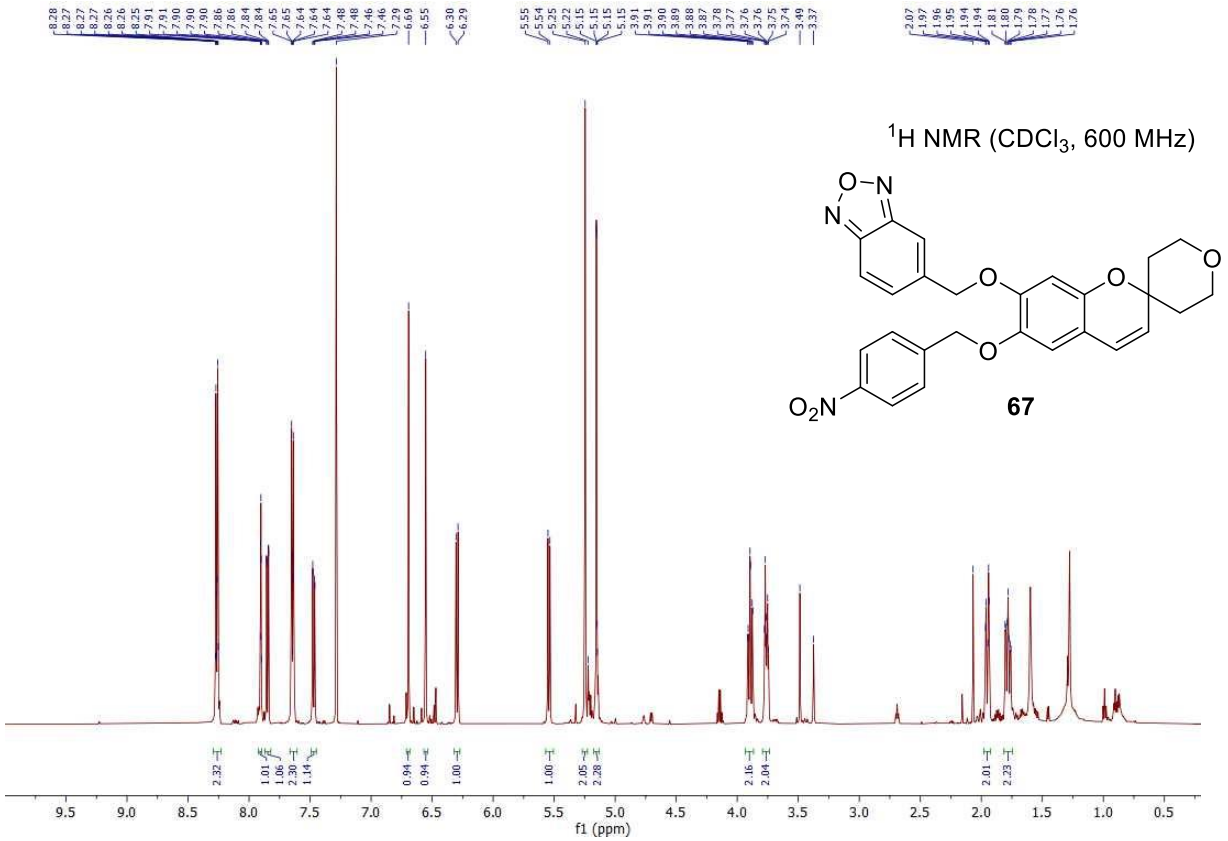

^{1}H NMR ($CDCl_3$, 600 MHz)
62
f1 (ppm)

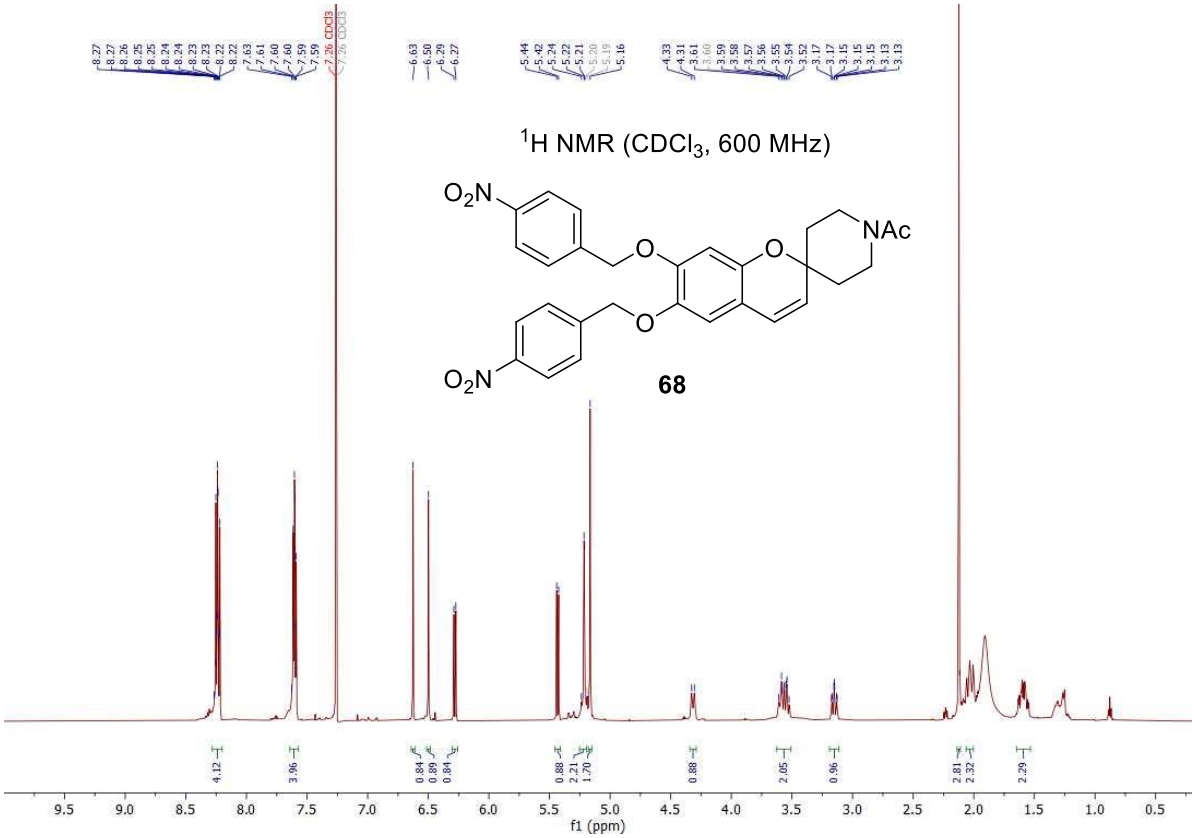

149.64
148.00
143.19
142.62
142.51
134.87
134.68
128.31
128.22
127.79
127.65
122.95
115.22
114.76
103.86
74.31
71.81
70.18
66.22
63.39
46.14
35.82
^{13}C NMR ($CDCl_3$, 151 MHz)
62
f1 (ppm)

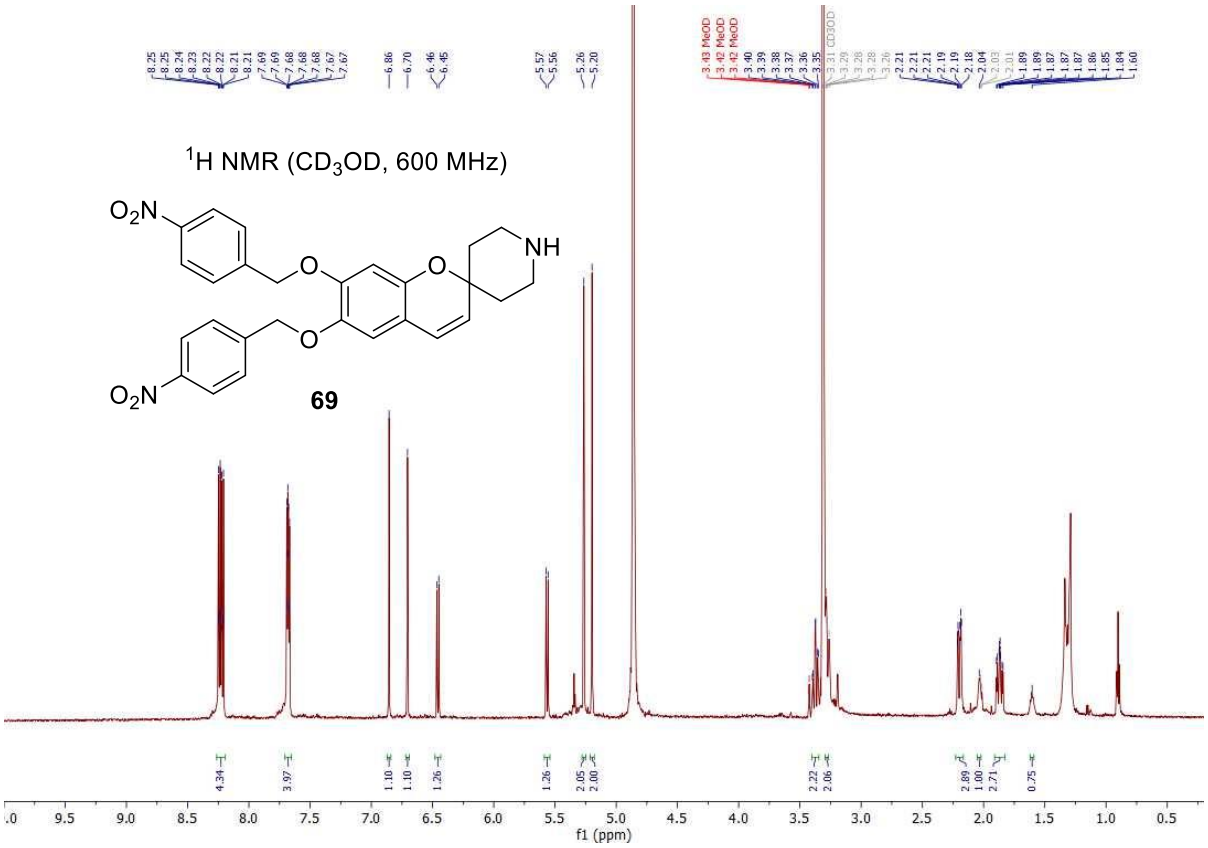

CDCl3
6.64
6.54
6.28
6.26
5.52
5.50
5.19
5.16
5.13
5.13
5.12
5.11
4.13
4.12
4.11
3.89
3.89
3.87
3.87
3.85
3.85
3.75
3.74
3.74
3.73
3.72
2.72
2.71
2.70
2.69
2.04
1.94
1.92
H2O
1.92
1.91
1.78
1.77
1.76
1.75
1.75
1.74
1.73
^{1}H NMR ($CDCl_3$, 600 MHz)
63
4.26
4.34
1.03
1.02
1.00
1.01
2.54
2.12
1.11
1.97
2.07
6.18
7.62
1.75
1.98
2.59
f1 (ppm)

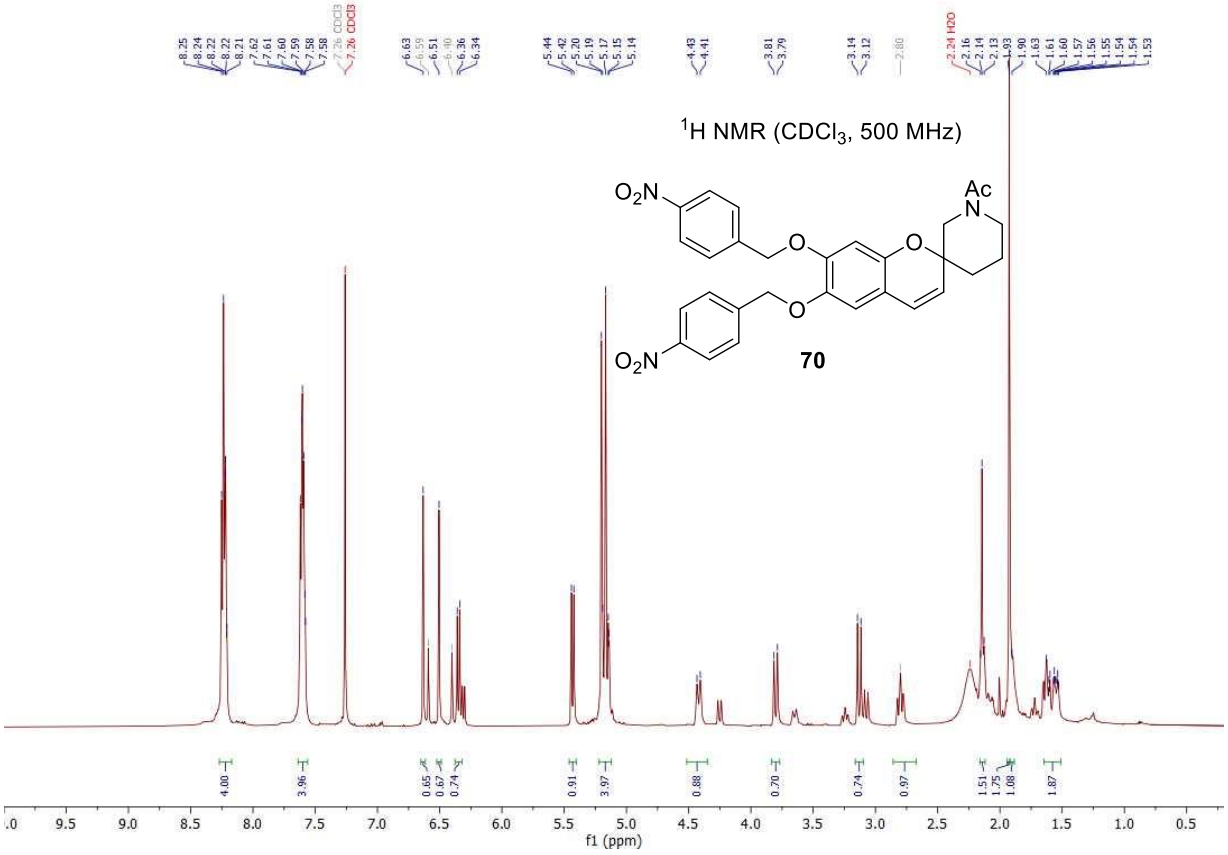

^{1}H NMR ($CDCl_3$, 500 MHz)
O_2N
O
O
O
O
65
f1 (ppm)

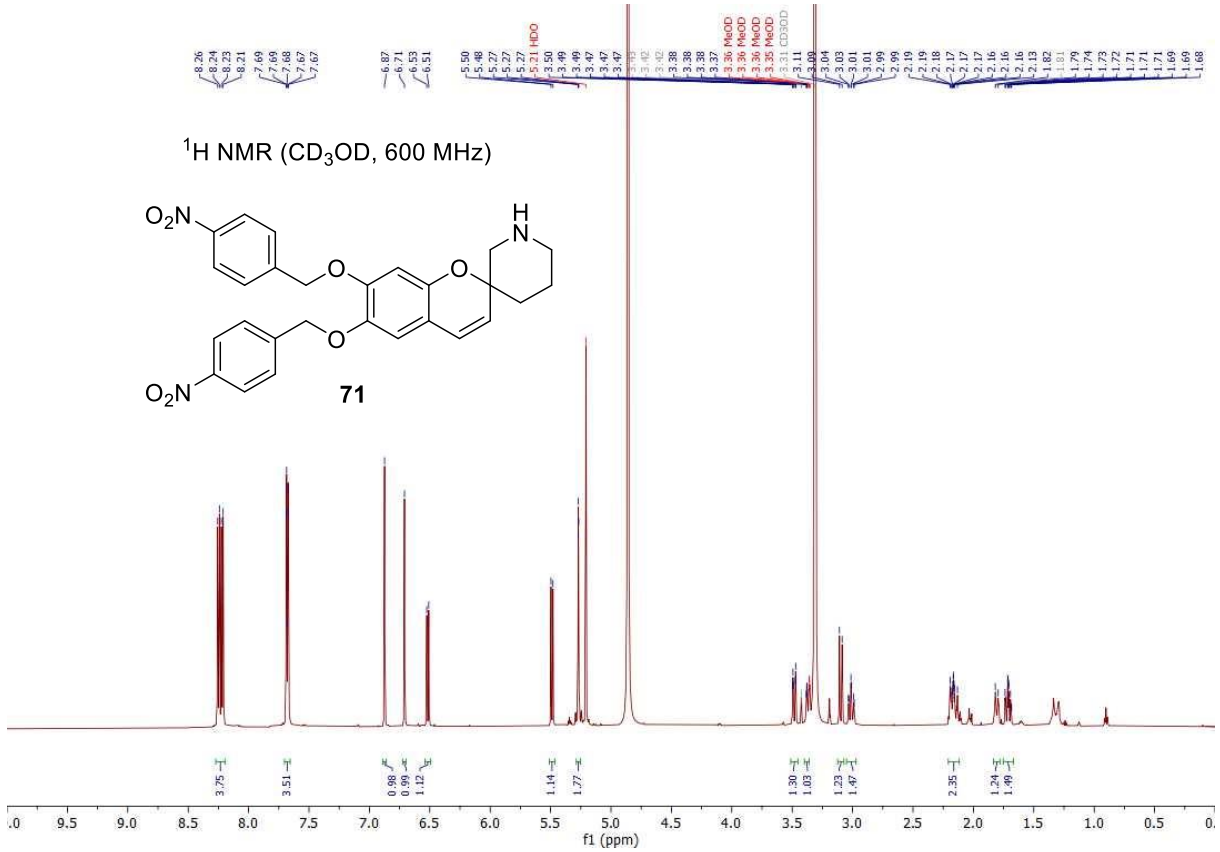

^{1}H NMR ($CDCl_3$, 400 MHz)
O
O
O
O
O_2N
66
f1 (ppm)

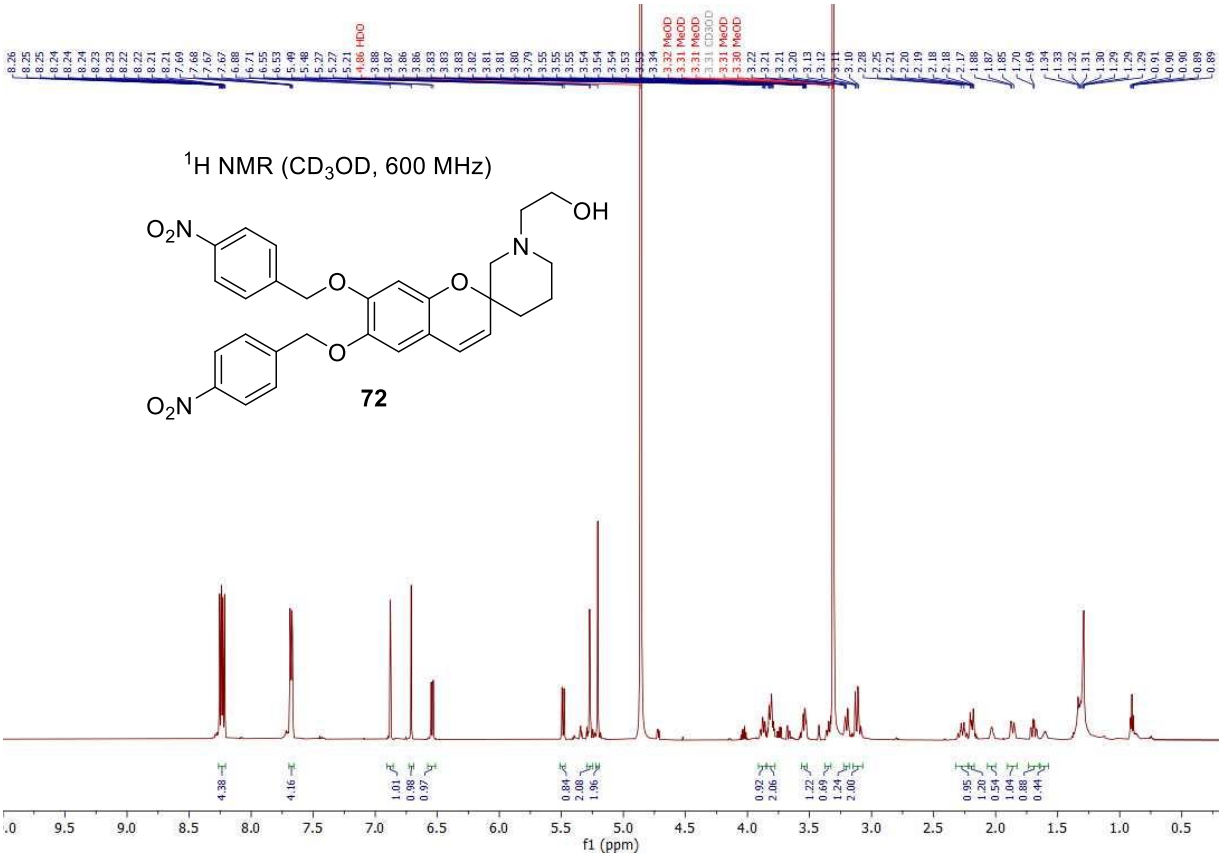

^{1}H NMR ($CDCl_3$, 600 MHz)
67
f1 (ppm)

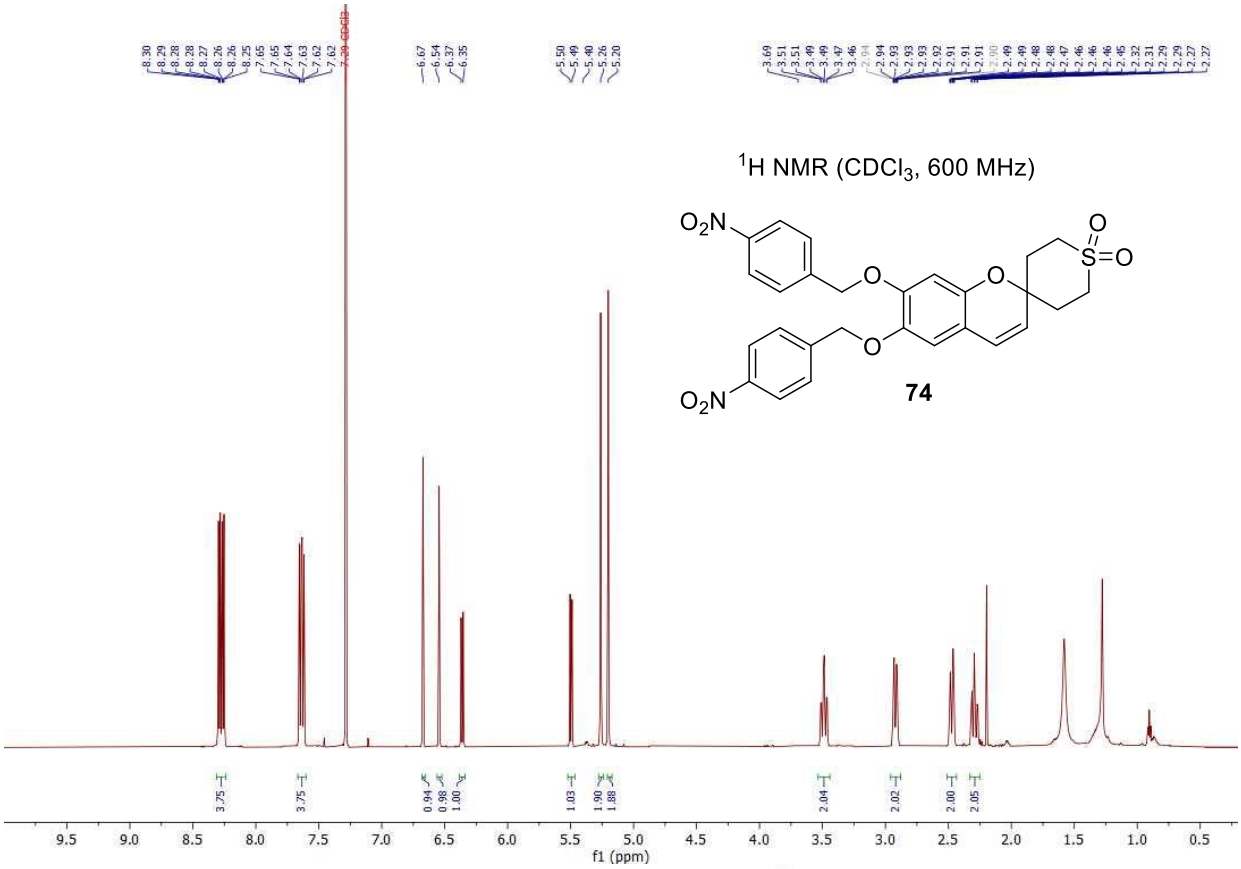

^{1}H NMR ($CDCl_3$, 600 MHz)
68
f1 (ppm)


^{1}H NMR (CD_3OD, 600 MHz)
O_2N
NH
O
O_2N
69
f1 (ppm)


^{1}H NMR ($CDCl_3$, 500 MHz)
O_2N
Ac
N
O
O_2N
70
f1 (ppm)

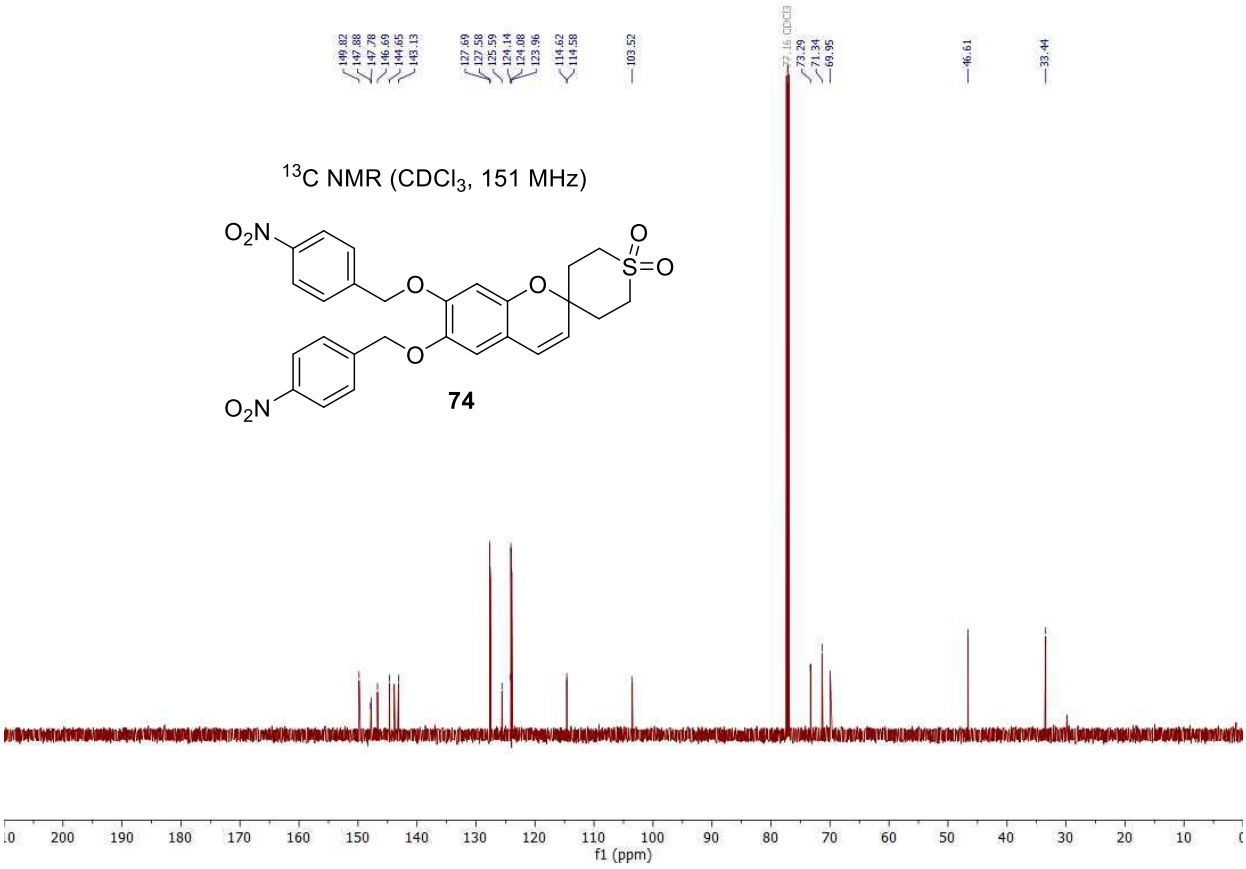

^{1}H NMR (CD_3OD, 600 MHz)
O_2N
O_2N
H
N
O
O
O
71
f1 (ppm)


^{1}H NMR (CD_3OD, 600 MHz)
O_2N
O_2N
OH
N
O
O
O
72
f1 (ppm)



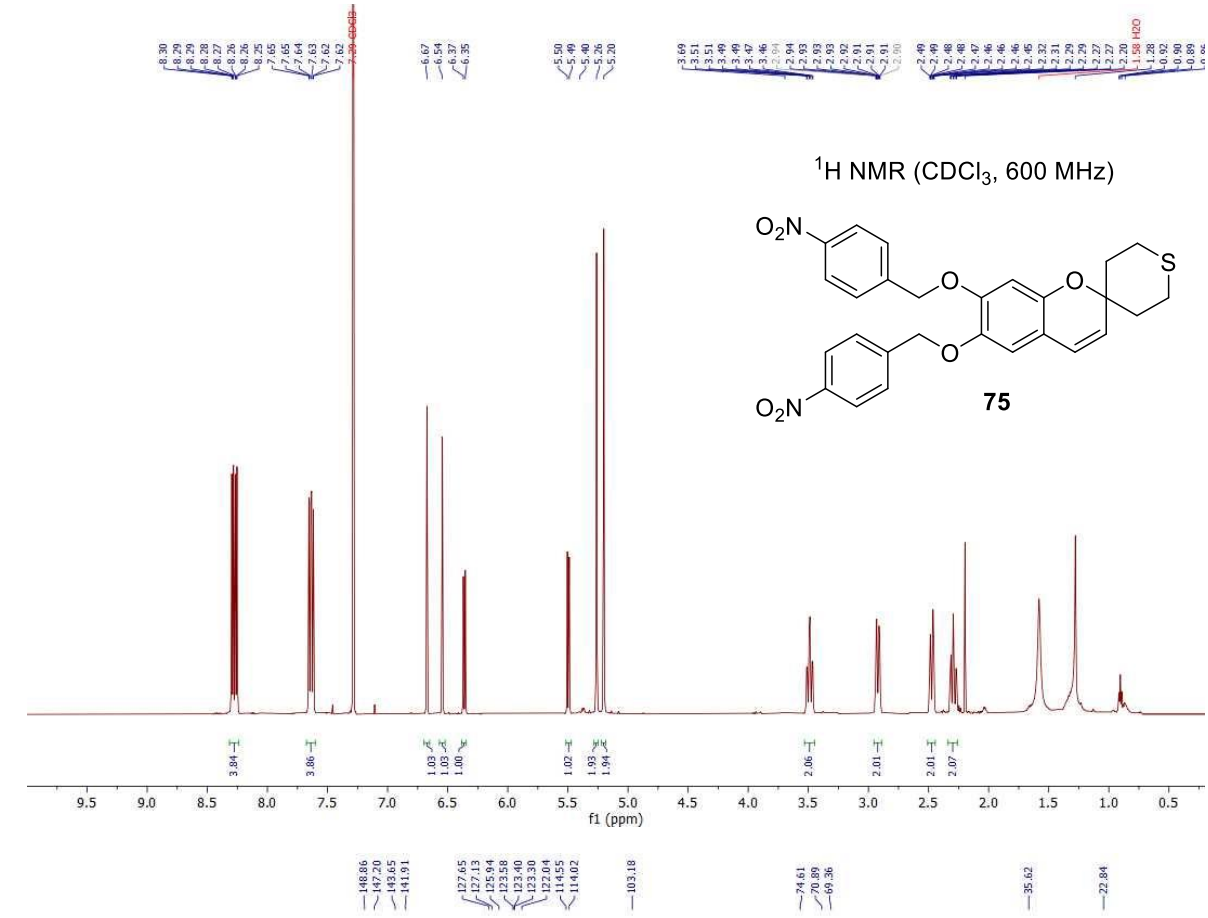
^{1}H NMR ($CDCl_3$, 600 MHz)

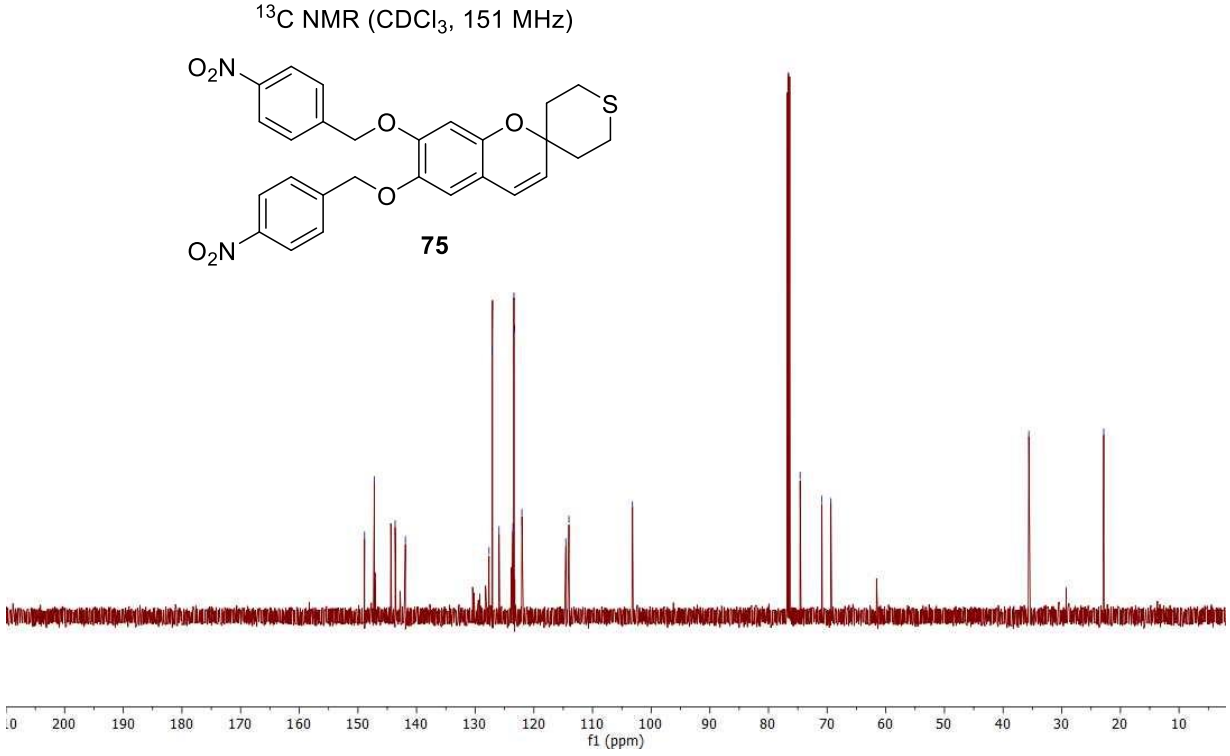
74



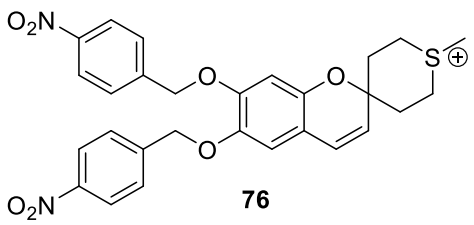
^{13}C NMR ($CDCl_3$, 151 MHz)

74


^{1}H NMR ($CDCl_3$, 600 MHz)
O_2N
O
O
S
O
O_2N
75
f1 (ppm)

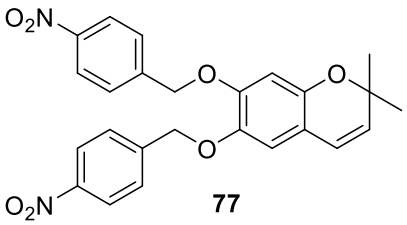

^{13}C NMR ($CDCl_3$, 151 MHz)
O_2N
O
O
S
O
O_2N
75
f1 (ppm)

^{1}H NMR (CD_3CN, 600 MHz)

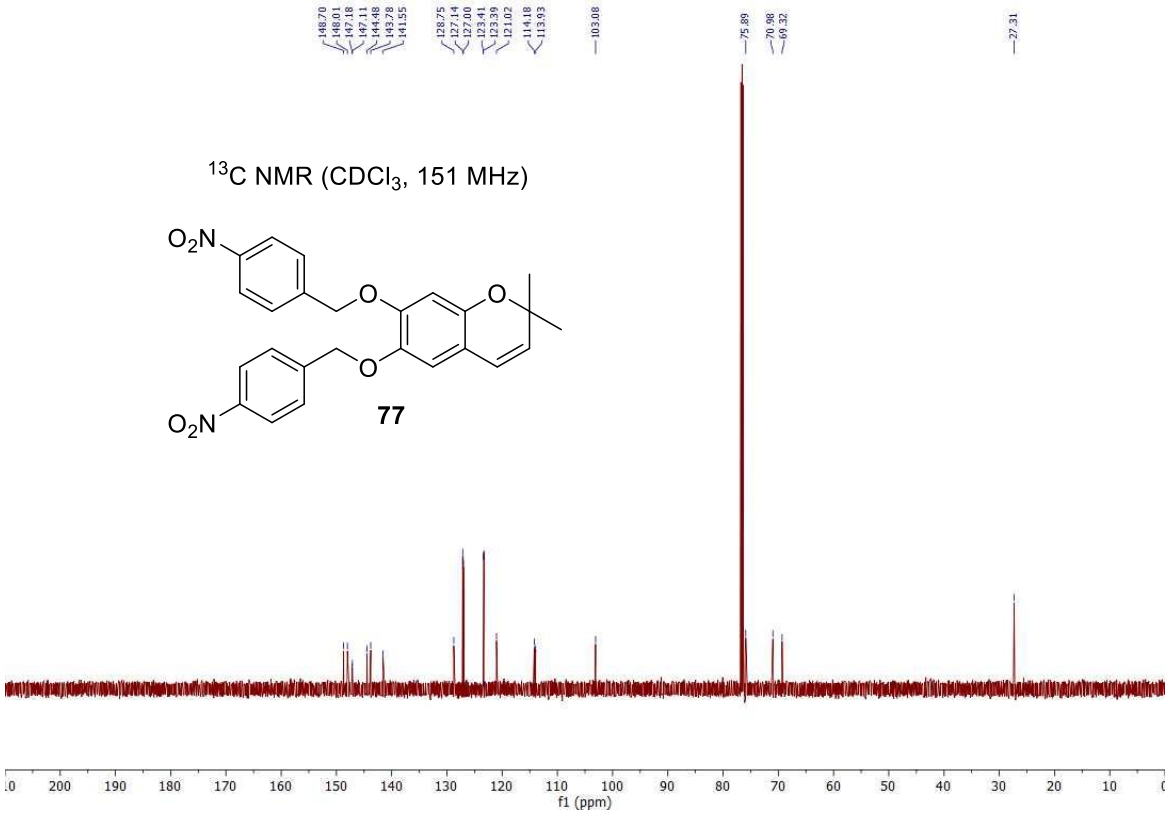


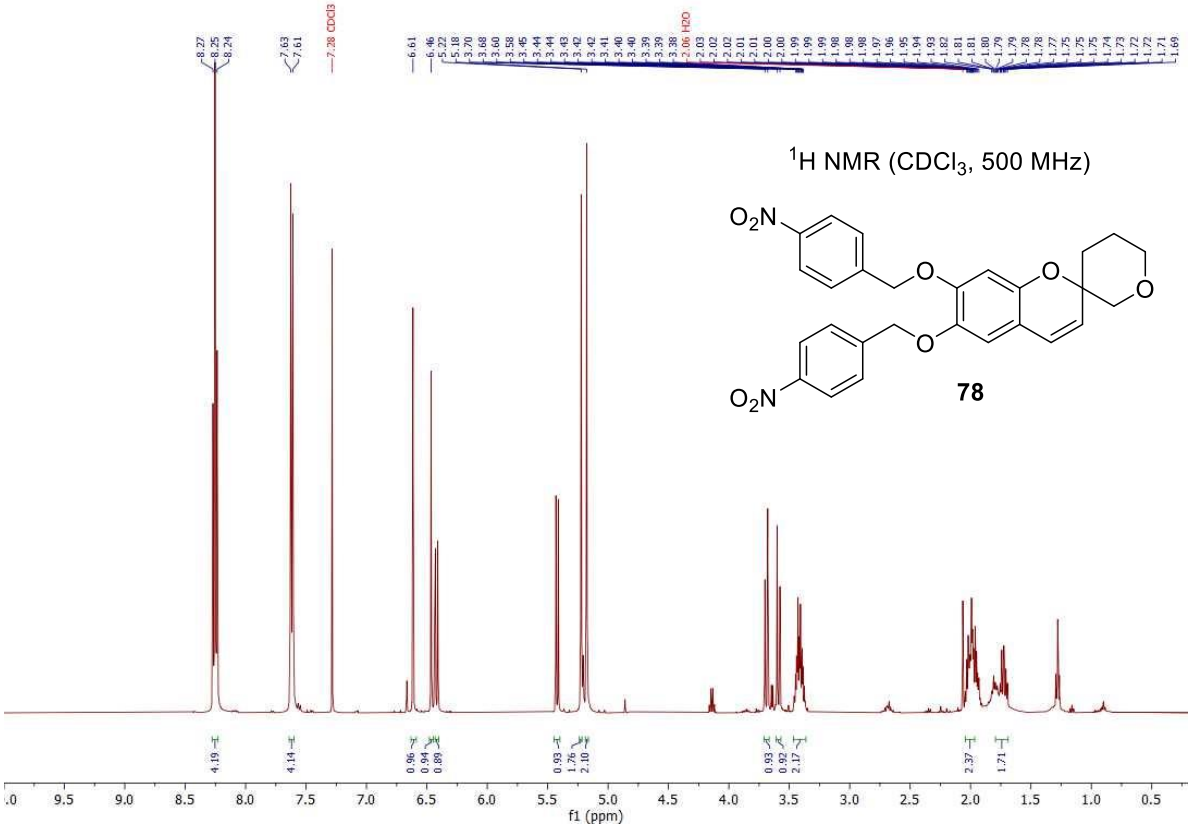
76

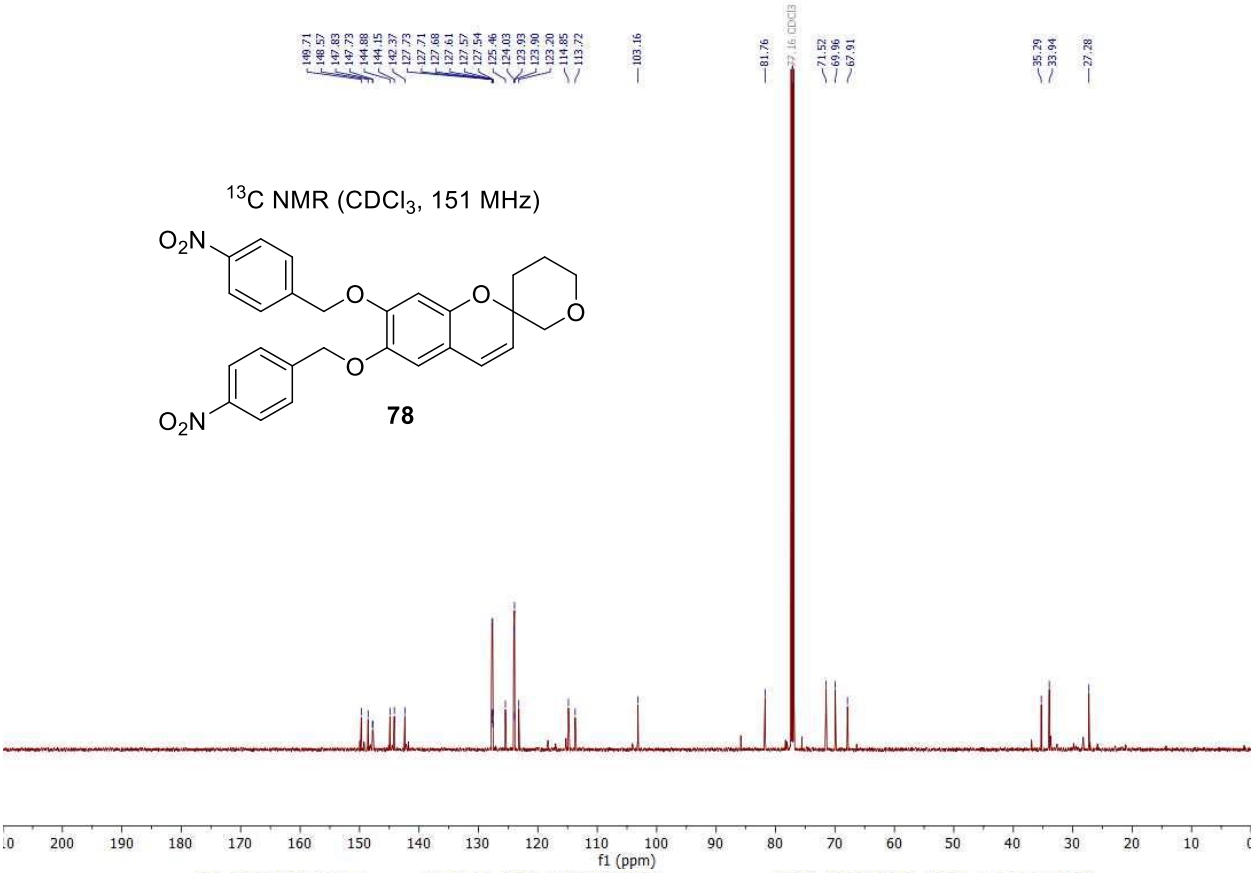
^{1}H NMR ($CDCl_3$, 600 MHz)

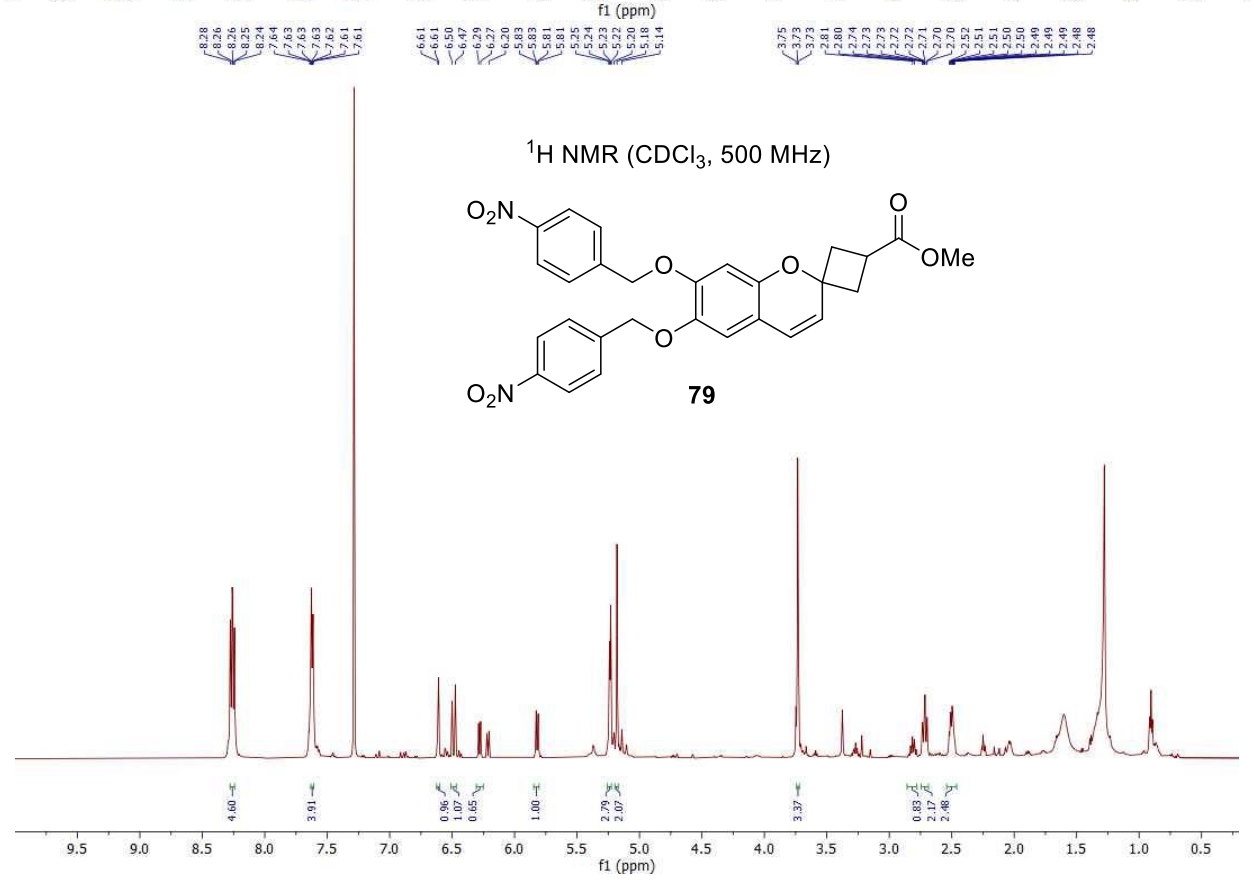


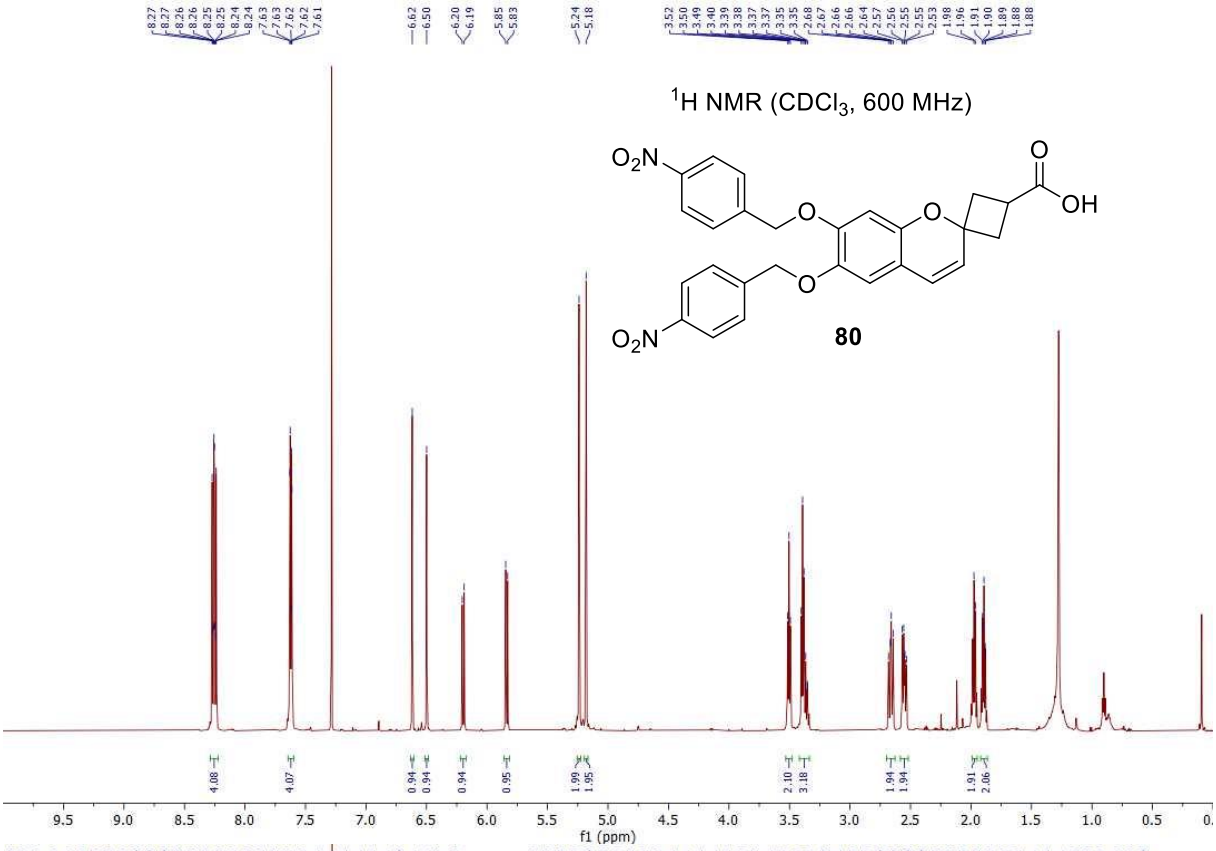
77

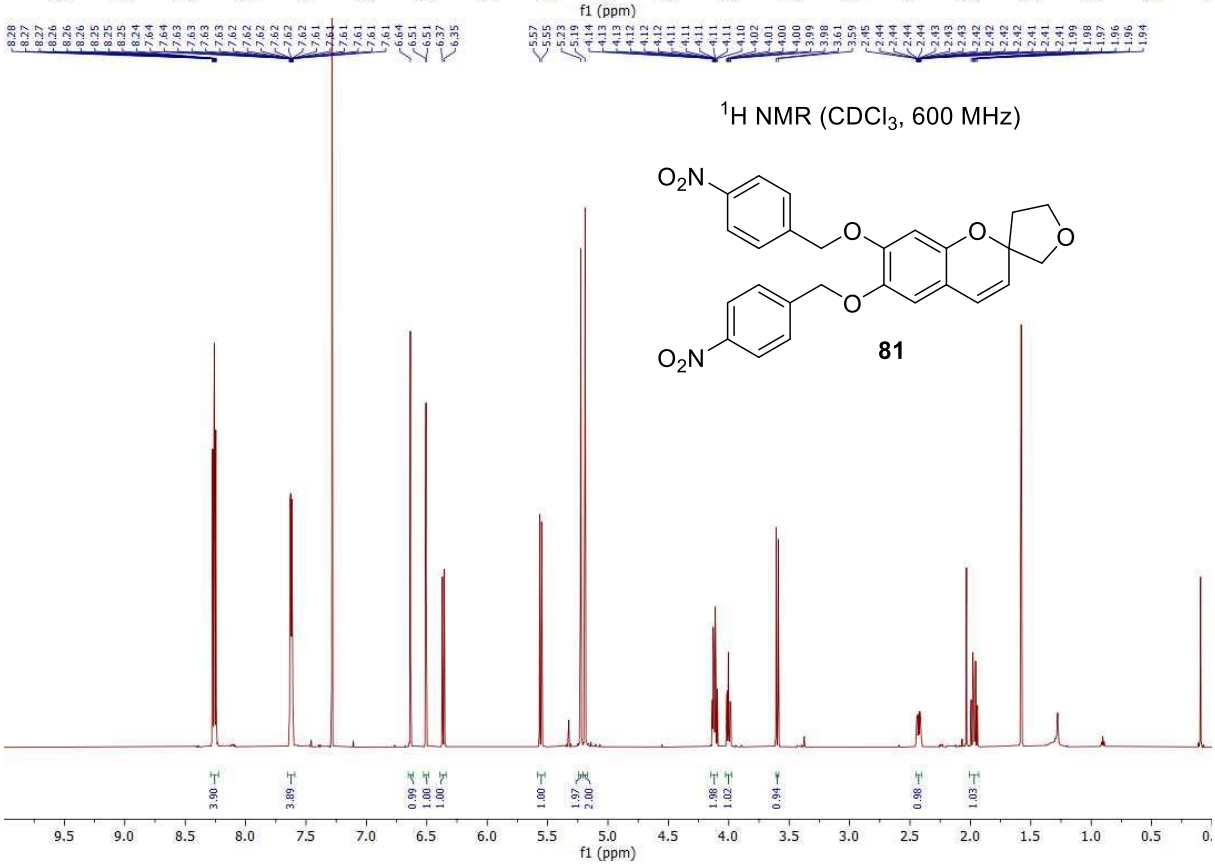

148.70
148.01
147.18
147.11
144.48
143.78
141.55
128.75
127.14
127.00
123.41
123.39
121.02
114.18
113.93
103.08
75.89
70.98
69.32
27.31
13C NMR (CDCl3, 151 MHz)
O2N
O
O
O
O2N
77
f1 (ppm)


8.27
8.25
8.24
7.63
7.61
7.26 CDCl3
6.61
6.46
5.22
5.18
3.70
3.68
3.60
3.58
3.45
3.44
3.44
3.43
3.42
3.41
3.40
3.39
3.38
2.06 H2O
1H NMR (CDCl3, 500 MHz)
O2N
O
O
O
O
O2N
78
4.19
4.14
0.96
0.94
0.89
0.93
1.76
2.10
0.93
0.92
2.17
2.37
1.71
f1 (ppm)

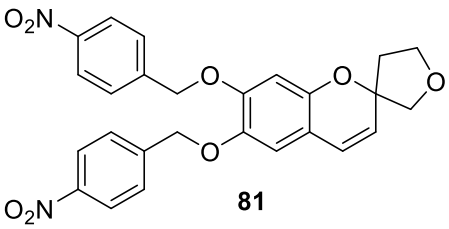

149.71
148.57
147.83
147.73
144.88
144.15
142.37
127.73
127.71
127.68
127.61
127.57
127.54
125.46
124.03
123.93
123.90
123.20
114.85
113.72
103.16
81.76
77.16 CDCl3
71.52
69.96
67.91
35.29
33.94
27.28
13C NMR (CDCl3, 151 MHz)
O2N
O
O
O
O
O2N
78
f1 (ppm)


8.28
8.26
8.26
8.25
8.24
7.64
7.63
7.63
7.63
7.62
7.61
7.61
6.61
6.61
6.50
6.47
6.29
6.27
6.20
5.83
5.83
5.81
5.81
5.25
5.24
5.23
5.22
5.20
5.18
5.14
3.75
3.73
3.73
2.81
2.80
2.74
2.73
2.73
2.72
2.72
2.71
2.70
2.70
2.52
2.51
2.51
2.50
2.50
2.49
2.49
2.49
2.48
2.48
1H NMR (CDCl3, 500 MHz)
O2N
O
O
O
OMe
O
O2N
79
4.60
3.91
0.96
1.07
0.65
1.00
2.79
2.07
3.37
0.83
2.17
2.48
f1 (ppm)

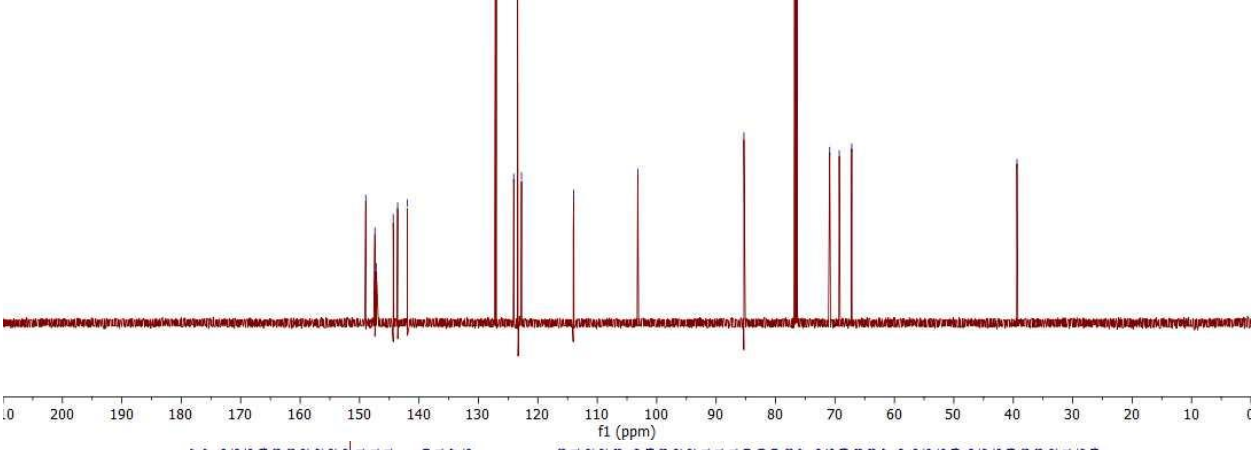

^{1}H NMR ($CDCl_3$, 600 MHz)
O_2N
O
OH
80
f1 (ppm)

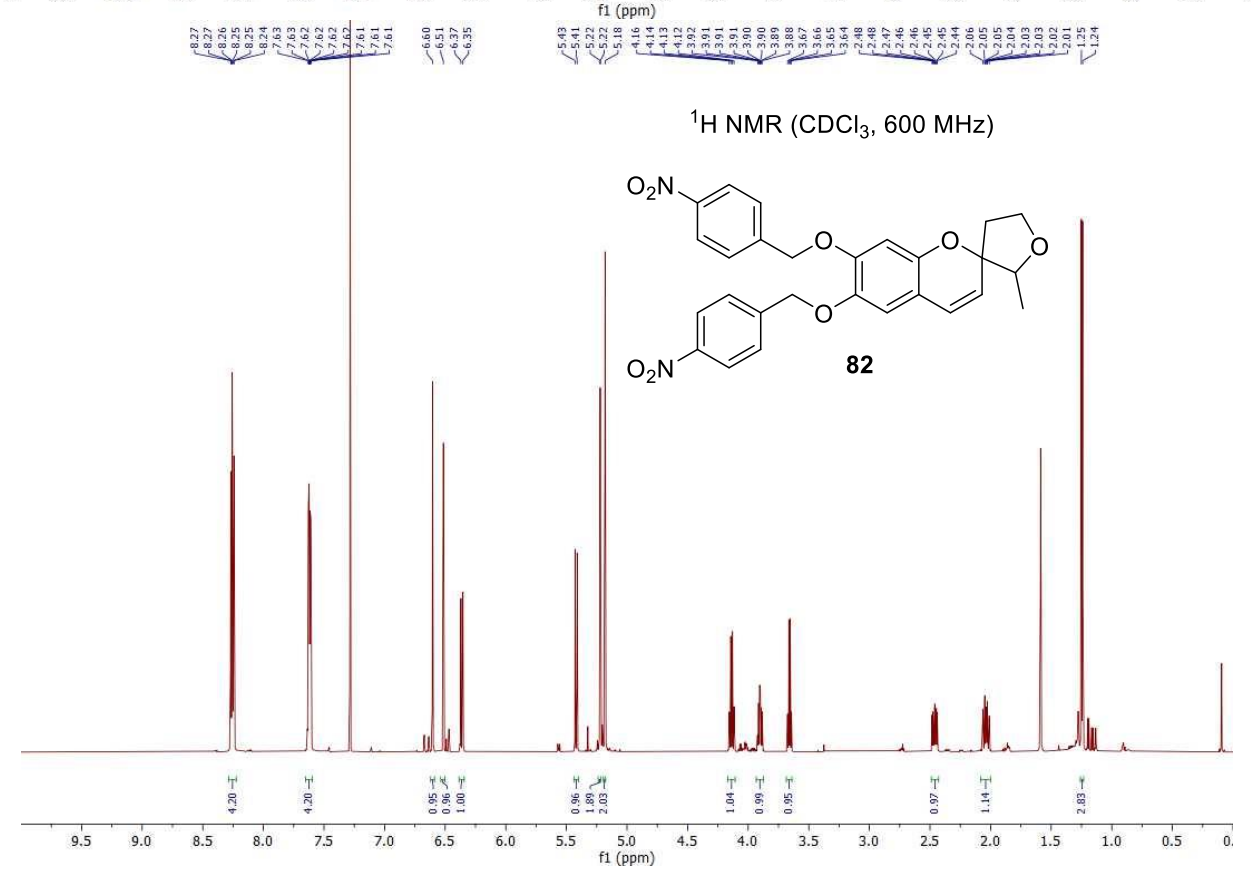

^{1}H NMR ($CDCl_3$, 600 MHz)
O_2N
81
f1 (ppm)

^{13}C NMR ($CDCl_3$, 151 MHz)



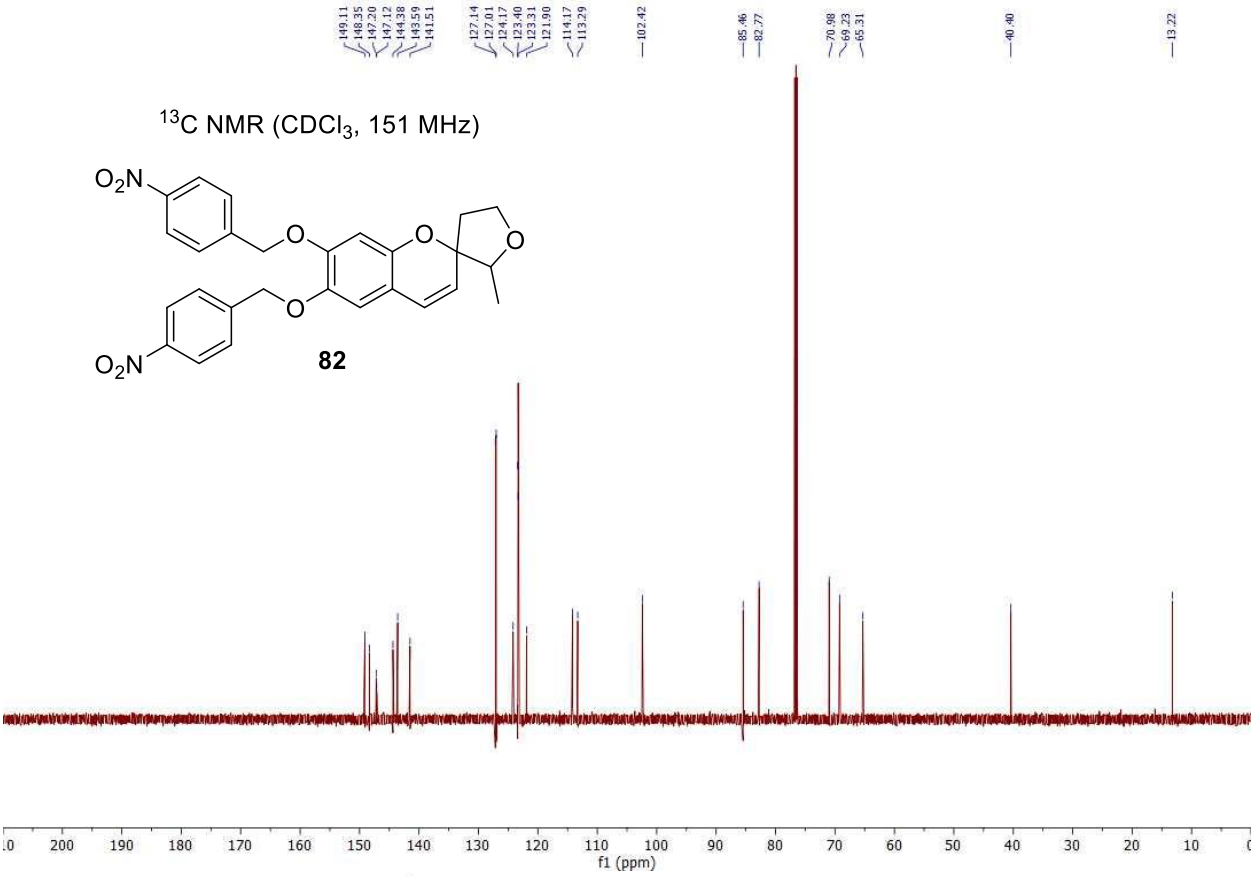
81

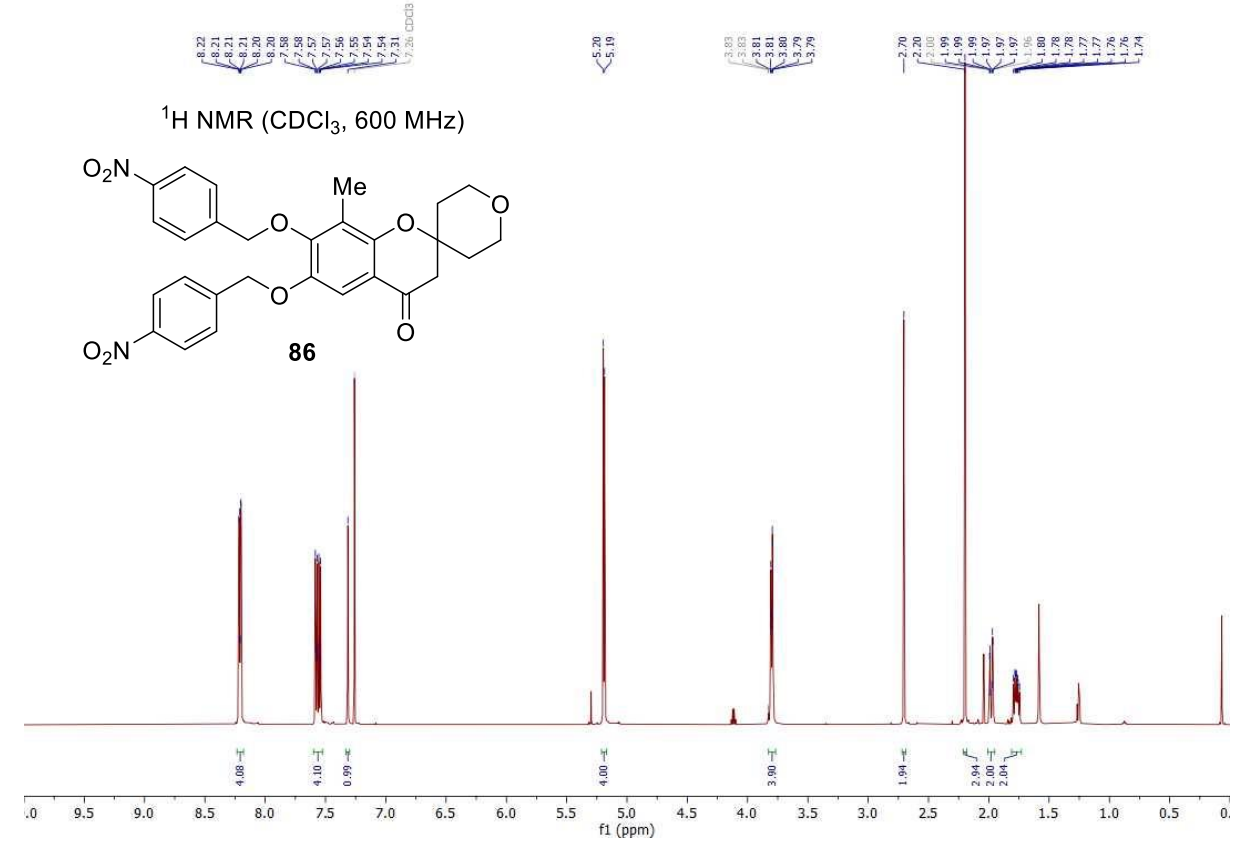




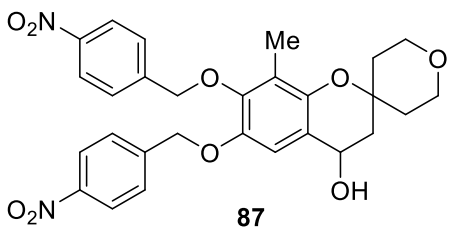
^{1}H NMR ($CDCl_3$, 600 MHz)

82

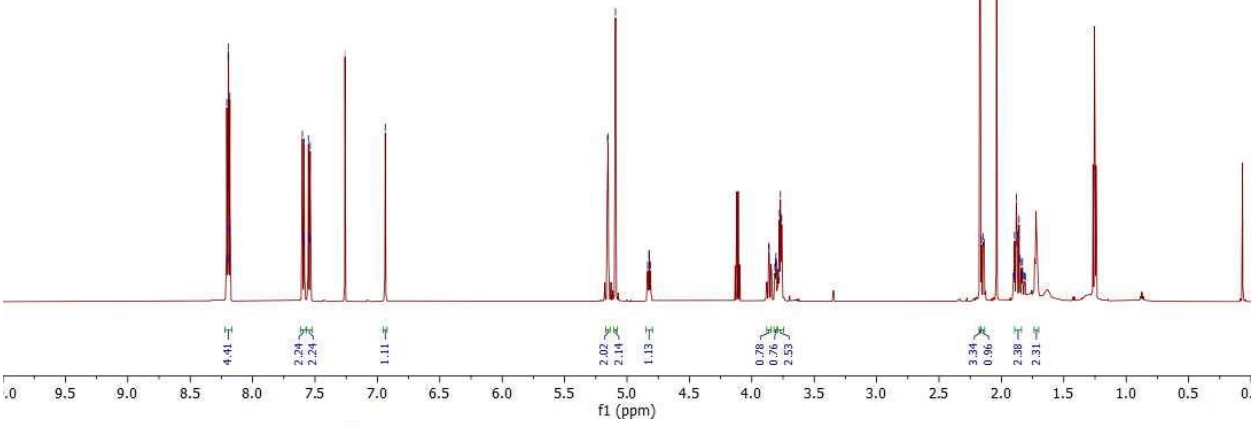

149.11
148.35
147.20
147.12
144.38
143.59
141.51
127.14
127.01
124.17
123.40
123.31
121.90
114.17
113.29
102.42
85.46
82.77
70.98
69.23
65.31
40.40
13.22
^{13}C NMR ($CDCl_3$, 151 MHz)
O_2N
O_2N
O
O
O
O
82
f1 (ppm)


8.22
8.21
8.21
8.20
8.20
7.58
7.58
7.57
7.57
7.56
7.55
7.54
7.54
7.31
7.26 CDCl3
5.20
5.19
3.83
3.83
3.81
3.81
3.80
3.79
3.79
2.70
2.00
1.99
1.99
1.97
1.97
1.97
1.86
1.80
1.78
1.78
1.77
1.77
1.76
1.76
1.74
^{1}H NMR ($CDCl_3$, 600 MHz)
O_2N
O_2N
Me
O
O
O
O
O
86
4.08
4.10
0.99
4.00
3.90
1.94
2.94
2.00
2.04
f1 (ppm)

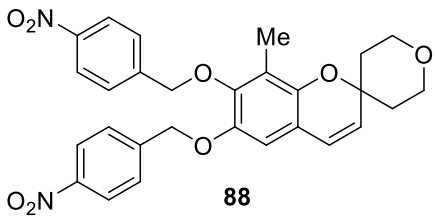
^{1}H NMR ($CDCl_3$, 600 MHz)



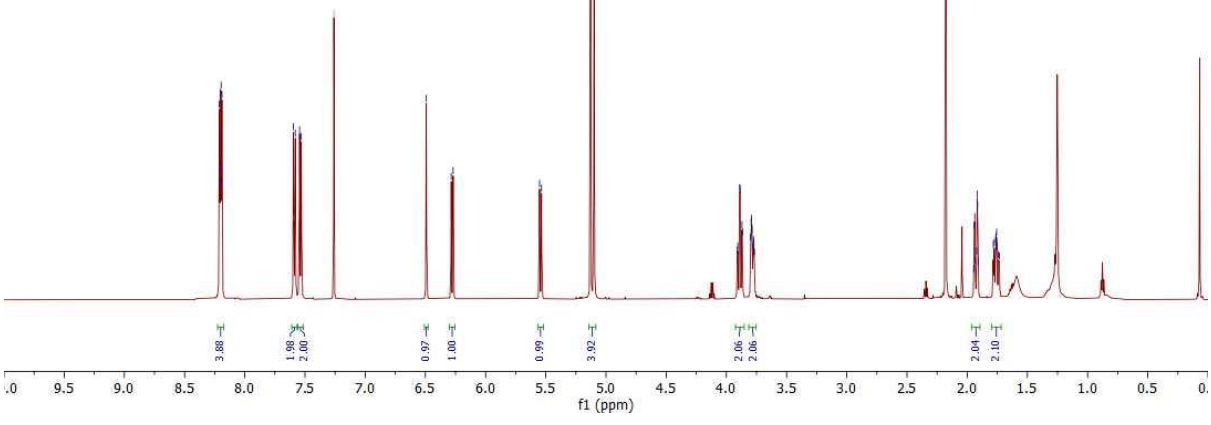
87

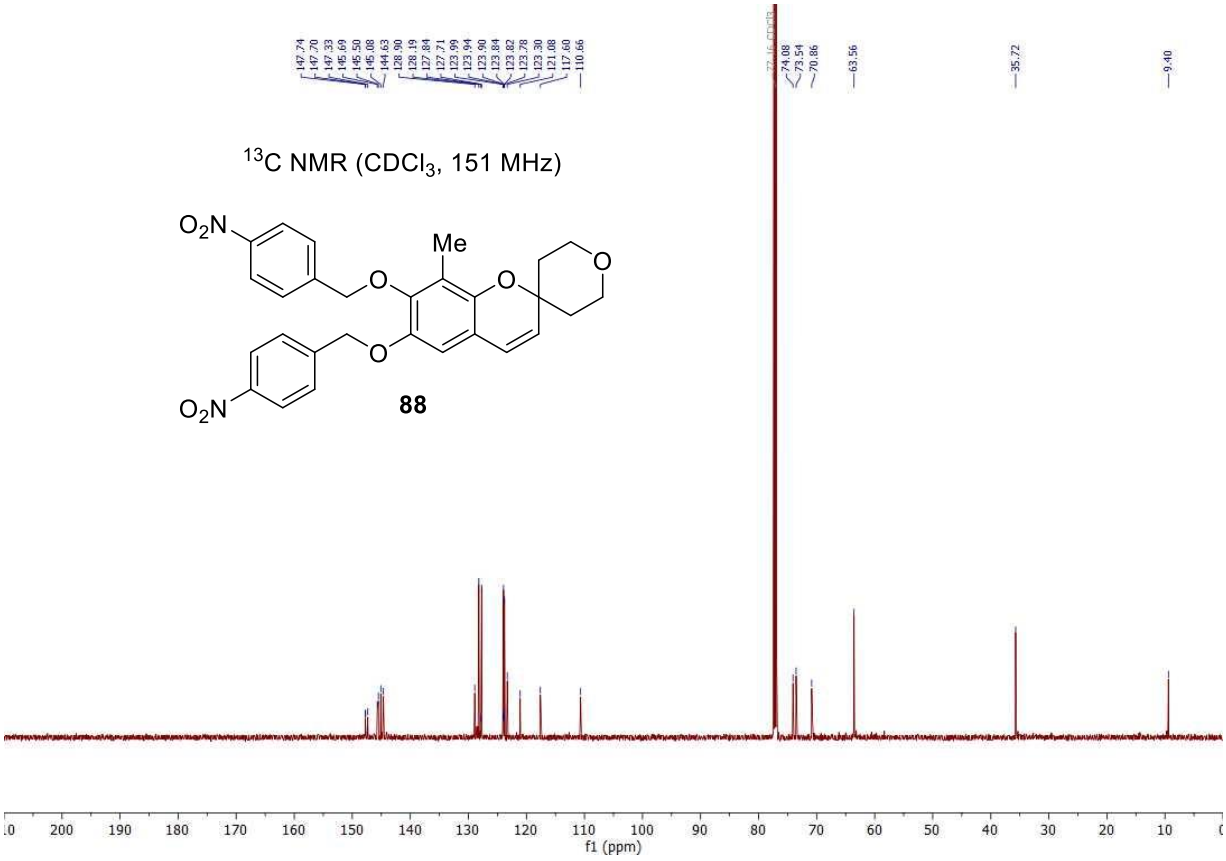


^{1}H NMR ($CDCl_3$, 600 MHz)



88




147.74
147.70
147.33
145.69
145.50
145.08
144.63
128.90
128.19
127.84
127.71
123.99
123.94
123.90
123.84
123.82
123.78
123.30
121.08
117.60
110.66
77.16
74.08
73.54
70.86
63.56
35.72
9.40
13C NMR (CDCl3, 151 MHz)
O2N
Me
O
O
O
O
O2N
88
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)