Synthesis of Tetrazines from *gem*-Difluoroalkenes under aerobic condition at room temperatue

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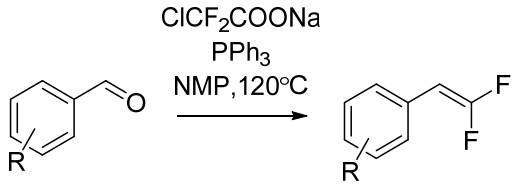
SUPPORTING INFORMATION

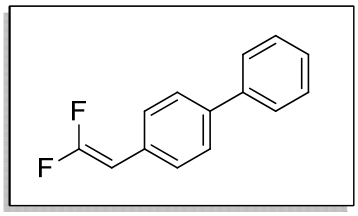
1. Reagents and instrumentation

All reagents were used as received from commercial sources without further purification or prepared as described in the literature. All solvents were dried over 4Å molecular sieves before use unless otherwise stated. Reactions were stirred using Teflon-coated magnetic stirring bars. Analytical TLC was performed with 0.20 mm silica gel 60F plates with 254 nm fluorescent indicator. TLC plates were visualized by ultraviolet light or by treatment with a spray of Pancaldi reagent {$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O} or a solution 0.5% ninhydrin in n-butanol. Chromatographic purification of products was carried out by flash column chromatography on silica gel (230-400 mesh). Melting points were determined using a WRX-4 visual melting point apparatus. Both melting points and boiling points are uncorrected. Infrared spectra were recorded on a IR Affinity-1. NMR spectra were measured in $CDCl_3$ (with TMS as internal standard) or D_2O or MeOD on a Bruker AV400 (^1H at 400 MHz, ^{13}C at 100 MHz, ^{19}F at 376 MHz) magnetic resonance spectrometer. High-resolution mass spectra (HRMS) were recorded on a SYNAPT G2Si High Definition MS System. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The HRMS were measured under ESI model (specified in the section of characterization data).

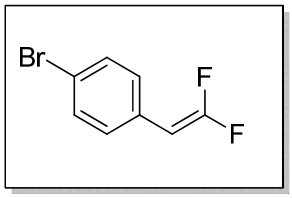


2. Preparation of 1,1−difluoroalkenes by decarboxylation of sodium chlorodifluroacetate.

The reactions were performed using a procedure similar to the ones described by Fuqua et al[1]. A solution of a carbonyl compound (10 mmol) and triphenylphosphine (12 mmol, 3.15 g) in dry N−methylpyrrolidone (5 mL) was prepared in a Schlenk flask under Argon atmosphere. At 120 °C, solid $ClCF_2CO_2Na$ (15 mmol, 2.29 g) was added portion wise over 30 min. After evolution of carbon dioxide ceased (c.a. 15 – 20 min after the addition of $ClCF_2CO_2Na$ was complete), the reaction mixture was cooled down and transferred into a separation funnel containing diethyl ether (150 ml). The organic phase was washed with water (150 mL), 30% H_2O_2 (30 mL) and brine (3 x 100 mL), dried (Na_2SO_4) and evaporated. The product was purified by column chromatography on silica gel using hexanes or hexanes–AcOEt 50:1 as eluent.



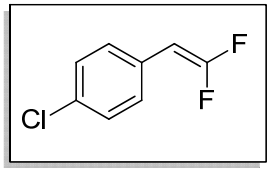
4−(2,2−difluorovinyl)−1,1'−biphenyl(1a). 65% yield. **^{1}H NMR (**400 MHz, $CDCl_3$**)** δ 7.61−7.33 (m, 9H), 5.32 (dd, 1H, J = 3.8, 26.4 Hz); **^{13}C NMR (**100 MHz, $CDCl_3$**):** δ 156.4 (dd, J = 288.0, 299.0 Hz), 140.5, 139.8(t, J = 2.0, 2.0 Hz), 129.4(t, J = 6.3, 6.3 Hz), 128.8, 128.0(dd, J = 3.6, 6.5 Hz), 127.4(2), 127.0, 82.0(dd, J = 13.4, 29.4 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ −81.86 (dd, J = 26.7, 30.6 Hz, 1F), −83.80(dd, J = 3.6, 30.7 Hz, 1F); **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$): δ −81.83 (d, J = 30.6 Hz, 1F), −83.59(d, J = 30.6 Hz, 1F).



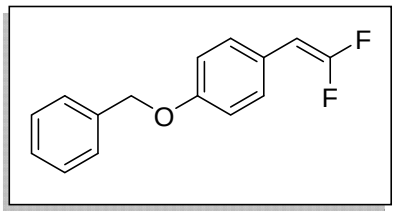
1−bromo−4−(2,2−difluorovinyl)benzene(1b). 73% yield. **^{1}H NMR (**400 MHz, $CDCl_3$**)** δ 7.45−7.17 (m, 4H), 5.22(dd, 1H, J = 3.6, 26.0 Hz); **^{13}C NMR (**100 MHz, $CDCl_3$**):** δ 156.4 (dd, J = 289.7, 300.0 Hz), 131.8, 129.3(dd, J = 6.0, 7.2 Hz), 129.1(dd, J = 3.6, 6.6 Hz), 120.8(dd, J = 2.4, 3.2 Hz), 81.6(dd, J = 13.4, 29.7 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ −81.20 (dd, J = 26.0, 29.0 Hz, 1F),

[1] S. A. Fuqua, W. G. Duncan and R. M. Silverstein, Organic Syntheses, 1967, 47, 19.

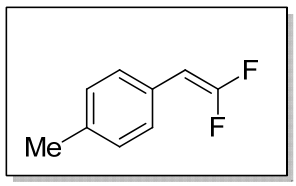
−83.04(dd, *J* = 3.6, 29.2 Hz, 1F); **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$): *δ* −81.20 (d, *J* = 29.6 Hz, 1F), −83.59(d, *J* = 30.9 Hz, 1F).



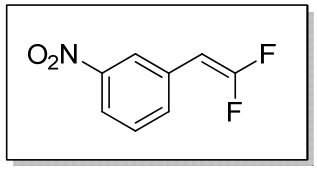
1−chloro−4−(2,2−difluorovinyl)benzene(1c). 55% yield. **^{1}H NMR (**400 MHz, $CDCl_3$**)** *δ* 7.29−7.21 (m, 4H), 5.21 (dd, 1H, *J* = 3.6, 26.0 Hz); **^{13}C NMR (**100 MHz, $CDCl_3$**):** *δ* 156.4 (dd, *J* = 288.5, 298.5 Hz), 132.8(t, *J* = 2.7, 2.7 Hz), 129.4(t, *J* = 6.3, 6.3 Hz), 128.9, 128.8(dd, *J* = 3.6, 6.6 Hz), 81.5(dd, *J* = 13.8, 30.4 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): *δ* −81.53 (dd, *J* = 26.6, 30.0 Hz, 1F), −83.84(dd, *J* = 3.3, 30.0 Hz, 1F); **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$): *δ* −81.51 (d, *J* = 30.0 Hz, 1F), −83.34(d, *J* = 30.1 Hz, 1F).



4−(2,2−difluorovinyl)−1,1'−biphenyl(1d). 65% yield. **^{1}H NMR (**400 MHz, $CDCl_3$**)** *δ* 7.61−7.33 (m, 9H), 5.32 (dd, 1H, *J* = 3.8, 26.4 Hz); **^{13}C NMR (**100 MHz, $CDCl_3$**):** *δ* 156.4 (dd, *J* = 288.0, 299.0 Hz), 140.5, 139.8(t, *J* = 2.0, 2.0 Hz), 129.4(t, *J* = 6.3, 6.3 Hz), 128.8, 128.0(dd, *J* = 3.6, 6.5 Hz), 127.4(2), 127.0, 82.0(dd, *J* = 13.4, 29.4 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): *δ* −81.86 (dd, *J* = 26.7, 30.6 Hz, 1F), −83.80 (dd, *J* = 3.6, 30.7 Hz, 1F); **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$): *δ* −81.83 (d, *J* = 30.6 Hz, 1F), −83.59(d, *J* = 30.6 Hz, 1F).

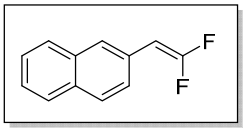


1−(2,2−difluorovinyl)−4−methylbenzene(1e). 55% yield. **^{1}H NMR (**400 MHz, $CDCl_3$**)** *δ* 7.22−7.12 (m, 4H), 5.22 (dd, 1H, *J* = 4.0, 28.0 Hz), 2.33(s, 3H); **^{13}C NMR (**100 MHz, $CDCl_3$**):** *δ* 156.1 (dd, *J* = 288.4, 298.4 Hz), 136.8, 129.4, 127.5 (dd, *J* = 3.6, 6.2 Hz), 81.9 (dd, *J* = 14.0, 29.0 Hz), 21.1. **^{19}F NMR** (376 MHz, $CDCl_3$): *δ* −83.22 (dd, *J* = 26.6, 34.0 Hz, 1F), −85.32 (dd, *J* = 3.4, 34.0 Hz, 1F); **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$): *δ* −83.20 (d, *J* = 34.0 Hz, 1F), −85.32(d, *J* = 34.0 Hz, 1F).

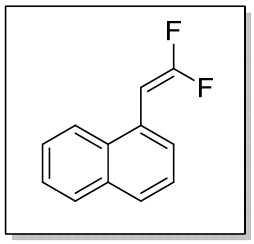


1−(2,2−difluorovinyl)−4−methylbenzene(1f). 43% yield. **^{1}H NMR (**400 MHz, $CDCl_3$**)** *δ* 8.20−7.50 (m, 4H), 5.40 (dd, 1H, *J* = 3.1, 25.1 Hz); **^{13}C NMR (**100 MHz, $CDCl_3$**):** *δ* 156.9 (dd, *J* = 289.4, 298.3 Hz), 148.6, 133.2(dd, *J* = 3.6, 6.6 Hz), 132.2(dd, *J* = 6.2, 7.8 Hz), 129.6, 122.3(dd, *J* = 3.8, 6.9 Hz),121.8(t, *J* = 1.8, 1.8 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): *δ* −79.03 (dd, *J* =

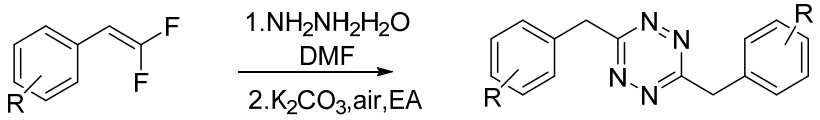
24.6, 24.6 Hz, 1F), −80.74 (dd, *J* = 3.2, 24.1 Hz, 1F); **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$): *δ* −79.01 (d, *J* = 24.0 Hz, 1F), −80.73(d, *J* = 24.1 Hz, 1F).



2−(2,2−difluorovinyl)naphthalene(1g). 61% yield. **^{1}H NMR (**400 MHz, $CDCl_3$**)** *δ* 7.82−7.76 (m, 4H), 7.50−7.47 (3H, m), 5.44(dd, 1H, *J* = 3.8, 26.3 Hz), **^{13}C NMR (**100 MHz, $CDCl_3$**)** *δ* 156.4 (dd, *J* = 288.7, 298.6 Hz), 133.4, 132.3, 128.3, 127.8, 127.6, 126.6(dd, *J* = 4.8, 6.2 Hz), 126.4, 126.0, 125.4(dd, *J* = 2.5, 6.4 Hz), 82.5(dd, *J* = 13.3, 29.1 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): *δ* −81.88 (dd, *J* = 26.3, 30.9 Hz, 1F), −83.61(dd, *J* = 3.8, 30.9 Hz, 1F); **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$): *δ* −81.85 (d, *J* = 30.9 Hz, 1F), −83.59(d, *J* = 30.9 Hz).



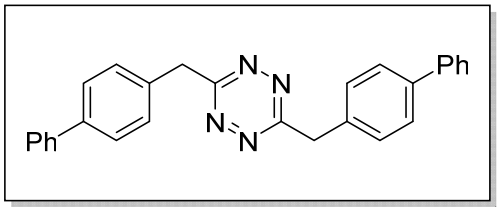
1,1−Difluoro−2−(1−naphthyl)ethane(1h). 73% yield. **^{1}H NMR (**400 MHz, $CDCl_3$**)** *δ*, 7.86−7.37 (7H, m), 5.79 (dd, 1H, *J* = 3.0, 24.6 Hz). **^{13}C NMR (**100 MHz, $CDCl_3$**)** *δ* 156.8 (dd, *J* = 288.8, 296.5 Hz), 131.6, 131.5, 128.8, 128.1, 126.7, 126.6 (dd, *J* = 1.8, 6.5 Hz), 126.5, 126.1, 125.6, 123.8, 78.8 (dd, *J* = 15.4, 29.1 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): *δ* −82.99 (dd, *J* = 3.3, 29.5 Hz, 1F), −84.94(dd, *J* = 24.7, 29.1 Hz, 1F); **^{19}F {^{1}H} NMR** (376 MHz, $CDCl_3$): *δ* −82.98 (d, *J* = 29.3 Hz, 1F), −84.94(d, *J* = 28.8 Hz).



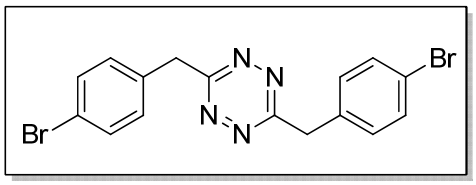
3. Synthesis of symmetric 3,6-dialkyl-1,2,4,5−tetrazine(3a−3h)

To a solution of 1,1−difluoroalkenes (**1a**, 50 mg, 0.27 mmol) in N,N-dimethylformide (DMF,5 mL) was added hydrazine (80%, 35 mg, 1.35 mmol). After stirring at room temperature for 4−6 hours, saturated ammonium chloride (20 mL) was added and the reaction mixture was extracted with dichloromethane (10 mL×3). The organic layer was combined, dried with anhydrous sodium sulfate. The solvent was concentrated and the crude product was dissolved in a suspension of Ethyl Acetate(5 mL) and 10% potassium carbonate solution(wt%, 5 mL) and stirred at room temperature for 24h under air atomerspere until the organic layer turned into amaranth obviously. The organic layer was collected, dried with anhydrous sodium sulfate. The crude product was purified by flash column

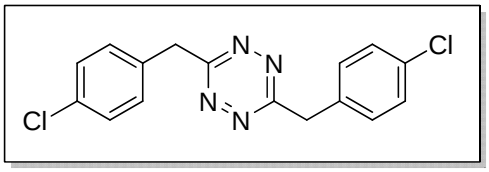
chromatography[silica gel(#100–200), toluene] to afford the pure 1,2,4,5−tetrazines(**3a−3h**).



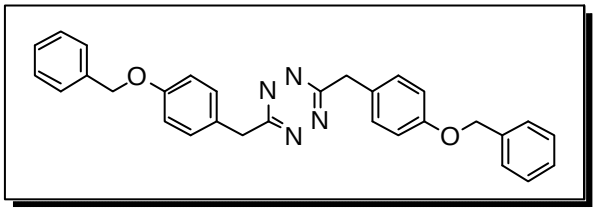
3,6−bis([1,1'−biphenyl]−4−ylmethyl)−1,2,4,5−tetrazine (3a). (41 mg, 83%). purple solid; **m.p.** 200−202°C; **IR(KBr)** nmax/cm^{-1} 2924, 2850, 1488, 1451, 1432, 1388, 851, 750; **^{1}H NMR (**400 MHz, $CDCl_3$**)** 7.55−7.33 (m, 18H), 4.65 (s, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.2, 140.6, 140.4, 134.8, 129.7, 128.8, 127.6, 127.4, 127.1, 40.9; **HRMS (ESI)**: calcd. for $C_{28}H_{22}N_4$ $[M+H]^+$ 415.19172, found 415.19124.



3,6−bis(4−bromobenzyl)−1,2,4,5−tetrazine (3b). (124 mg, 77%). purple solid. **^{1}H NMR (**400 MHz, $CDCl_3$**)** 7.45−7.28 (m, 8H), 4.59 (s, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.9, 134.6, 132.0, 131.0, 121.6, 40.6 {**lit.^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44 (d, J = 8.4, 4H), 7.29 (d, J = 8.3, 4H), 4.55 (s, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.9 (u), 134.6 (u), 132.1 (dn), 131.0 (dn),121.6 (u), 40.6 (u)}[2].



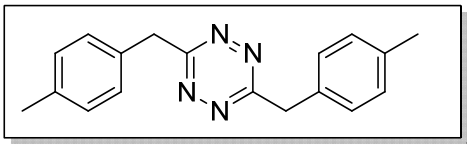
3,6−bis(4−chlorobenzyl)−1,2,4,5−tetrazine (3c). (62 mg, 91%). purple solid. **^{1}H NMR (**400 MHz, $CDCl_3$**)** δ 7.38−7.30 (m, 8H), 4.59 (s, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.0, 134.1, 133.5,130.6, 129.1, 40.6. {**lit.: ^{1}H NMR** (400 MHz, $CDCl_3$) δ:3.48 (s, 4H, CH2), 6.13 (br, 2H, NH), 7.17–7.32 (m, 8H, Ph)}[3].



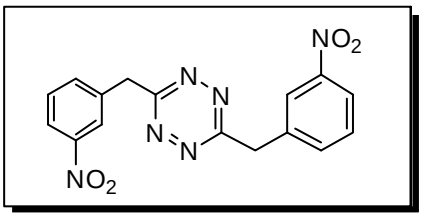
3,6−bis(4−(benzyloxy)benzyl)−1,2,4,5−tetrazine (3d). (39 mg, 61%). purple solid. **m.p.** 164 °C; **IR(KBr)** nmax/cm^{-1} 2926, 2905, 1614, 1513, 1470, 1454, 1432, 1383, 1298, 1178, 1013, 840, 697; **^{1}H NMR (**400 MHz, $CDCl_3$**)** 7.41−6.90 (m, 18H), 5.02 (s, 4H)，4.52（s, 4H）. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.3, 158.1, 136.9, 130.4, 128.6, 128.2, 128.0, 127.4, 115.3, 70.0, 40.4;

[2] R. Selvaraj and J. M. Fox, *Tetrahedron Lett.*, 2014, 55, 4795-4797.
[3] G. W. Rao and W. X. Hu, *Bioorg. Med. Chem. Lett.*, 2006, 16, 3702-3705.

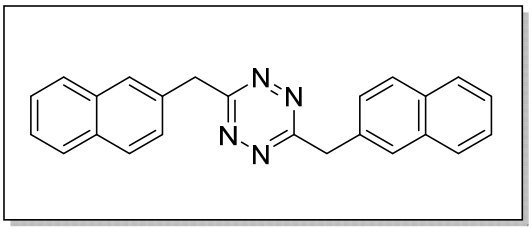
HRMS (ESI): calcd. for $C_{30}H_{26}N_4O_2$ $[M+H]^+$ 475.21285, found 475.21242.



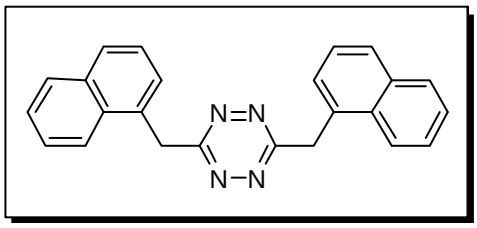
3,6−bis(4−methylbenzyl)−1,2,4,5−tetrazine (3e). **m.p**. 95−97 °C; (152 mg, 82%). purple solid. **^{1}H NMR (**400 MHz, $CDCl_3$**)** 7.30−7.10 (m, 8H), 4.54 (s, 4H), 2.30 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.3, 137.0, 132.8, 129.3, 129.6, 129.1, 40.8 , 21.0; **HRMS (ESI)**: calcd. for $C_{18}H_{18}N_4$ $[M+H]^+$ 291.16042, found 291.16007.{**lit1^{1}H NMR** (500 MHz, $CDCl_3$): δ=2.50 (s, 6H), 7.43 (d, *J*=8.0Hz, 4H), 8.54 (d, *J*=8.0Hz, 4H).}[4]



3,6−bis(3−nitrobenzyl)−1,2,4,5−tetrazine (3f). (26 mg, 66%). purple solid. **m.p.** 167-169°C; **IR(KBr)** nmax/cm^{-1} 2922, 2851, 1525, 1470, 1381, 1346, 726; **^{1}H NMR (**400 MHz, $CDCl_3$**)** 8.30−7.51 (m, 8H), 4.75 (s, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.6, 148.6，137.2, 135.5, 129.9, 124.4, 127.7, 40.4; **HRMS (ESI)**: calcd. for $C_{16}H_{12}N_6O_4$ $[M+H]^+$, 355.11493, found 355.11458.



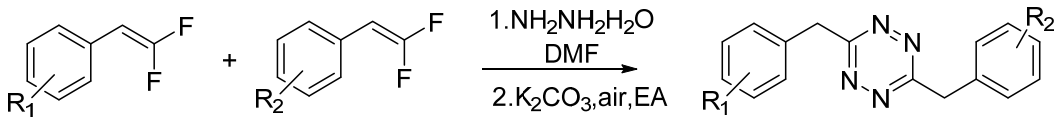
3,6−bis(naphthalen−2−ylmethyl)−1,2,4,5−tetrazine (3g). (101 mg, 61%). purple solid. **m.p.** 191-193 °C; **IR(KBr)** nmax/cm^{-1} 2924, 2853, 1599, 1508, 1430, 1380, 836, 747; **^{1}H NMR (**400 MHz, $CDCl_3$**)** 7.87−7.43 (m, 14H), 4.74 (s, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.2, 133.5, 133.2, 132.5, 128.7, 128.1, 127.7, 127.7, 127.1, 126.3, 126.0, 41.4; **HRMS (ESI)**: calcd. for $C_{24}H_{18}N_4$ $[M+H]^+$ 363.16024, found 363.15997.



3,6−bis(naphthalen−1−ylmethyl)−1,2,4,5−tetrazine (3h). (88 mg, 71%). purple solid. **m.p.** 151-153 °C; **IR(KBr)** nmax/cm^{-1} 2924, 2853, 1596, 1511, 1397, 1377, 784, 766;. **^{1}H NMR (**400 MHz, $CDCl_3$**)**

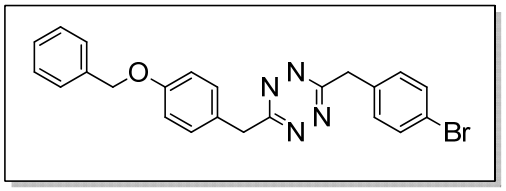
[4] H. X. Liu and Y. Y. Wei, *Tetrahedron Lett.*, 2013, 54, 4645-4648.

8.20−7.37 (m, 14H), 4.94 (s, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.2, 134.0, 132.2, 131.8, 128.8, 128.4, 128.4, 126.6, 125.9, 125.6, 124.0, 38.7; **HRMS (ESI)**: calcd. for $C_{24}H_{18}N_4$ $[M+H]^+$ 363.16003, found 363.16042.

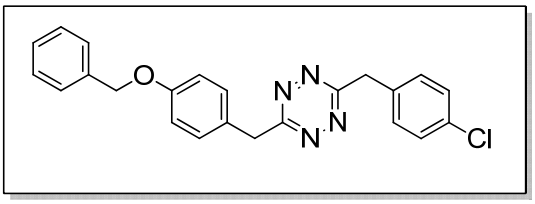


4. S**ynthesis of asymmetric 3,6-dialkyl-1,2,4,5−tetrazines (5a−5l)**

In one flask, 1,1−difluoroalkenes (**1a** or **1c**, 0.11 mmol) and hydrazine (35 mg, 80%, 0.55 mmol) were stirred in DMF (3 mL) at room temperature. In another flask, another 1,1−difluoroalkene (1.1 mmol) and hydrazine (350 mg, 80%, 5.50 mmol) were stirred in DMF (3 mL) at room temperature. After 4−6 hours, the two reaction mixtures were mixed and saturated ammonium chloride (20 mL) was added. The reaction mixture was extracted with DCM (10mL×3). The solvent was evaporated and the crude product was dissolved in a suspension of Ethyl Acetate(5 mL) and 10% potassium carbonate solution(wt%, 5 mL) and then stirred at room temperature for 24h under air until the organic layer turned into amaranth obviously. Finally the organic layer was collected, dried with sodium sulfate and evaporated un vacuu. The crude product was purified by flash column chromatography [silica gel(#100–200), toluene] to afford the pure 1,2,4,5−tetrazines(**5a-5l**).

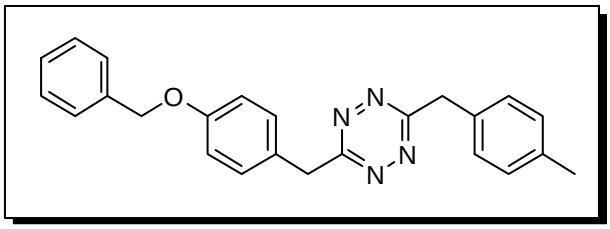


3−(4−(benzyloxy)benzyl)−6−(4−bromobenzyl)−1,2,4,5−tetrazine (5a). (29 mg, 85%). purple solid. **m.p**. 103-105 °C; **IR(KBr)** nmax/cm^{-1} 2927, 2855, 1512, 1379, 1295, 1251,787; **^{1}H NMR (**400 MHz, $CDCl_3$**)** 7.45−6.91 (m, 13H), 5.02(s, 2H), 4.54 (s, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.5, 168.7, 158.1, 136.9, 134.7, 132.0, 131.0, 130.4, 128.6, 128.0, 128.0, 127.4, 127.4, 121.5, 115.3, 70.0, 40.6, 40.4; **HRMS (ESI)**: calcd. for $C_{23}H_{19}BrN_4O$ $[M+H]^+$, 447.08150, found 447.08101.

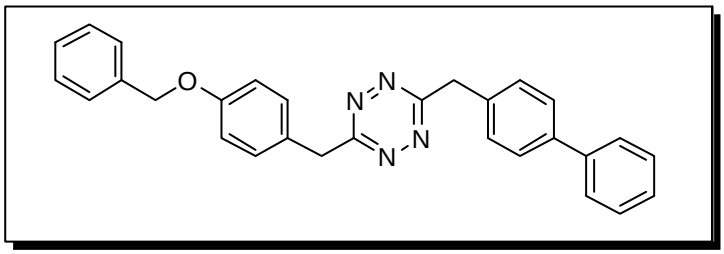


3−(4−(benzyloxy)benzyl)−6−(4−chlorobenzyl)−1,2,4,5−tetrazine (5b). (26 mg, 84%). purple

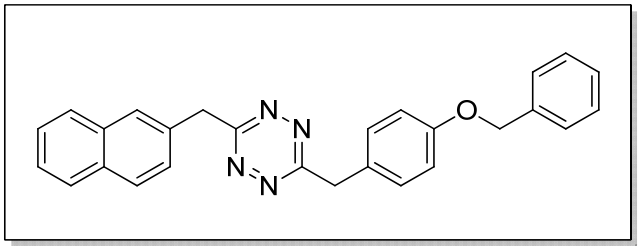
solid.**m.p**. 98-100 °C; **IR(KBr)** nmax/cm^{-1} 2924, 2852, 1514, 1492, 1382, 1253,743; **^{1}H NMR (**400 MHz, $CDCl_3$**)** 7.39−6.91 (m, 13H), 5.02(s, 2H), 4.56 (s, 2H), 4.54(s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.5, 168.8, 158.1, 136.9, 134.2, 133.4, 130.6, 130.4, 129.0, 128.6, 128.0, 127.4, 115.3, 70.0, 40.5, 40.4; **HRMS (ESI)**: calcd. for $C_{23}H_{19}ClN_4O$ $[M+H]^+$, 403.13202, found 403.13133.



3−(4−(benzyloxy)benzyl)−6−(4−methylbenzyl)−1,2,4,5−tetrazine (5c). (35 mg, 87%) yield. purple solid. **m.p**. 94-96 °C; **IR(KBr)** nmax/cm^{-1} 2922, 2854, 1529, 1383, 1248, 1012, 740; **^{1}H NMR (**400 MHz, $CDCl_3$**)** 7.38−6.90 (m, 13H), 5.02(s, 2H), 4.54(s, 2H), 4.52(s, 2H), 2.30(s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.3, 169.3, 158.1, 137.0, 136.9, 132.8, 130.3, 129.5, 129.1, 128.6, 128.2, 127.9, 127.4, 115.3, 70.0, 40.8, 40.4, 21.0; **HRMS (ESI)**: calcd. for $C_{24}H_{22}N_4O$ $[M+H]^+$, 383.18664, found 383.18637.

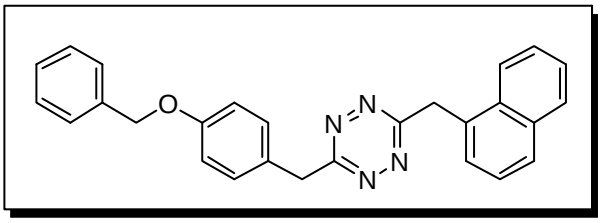


3−([1,1'−biphenyl]−4−ylmethyl)−6−(4−(benzyloxy)benzyl)−1,2,4,5−tetrazine (5d). (17 mg, 79%). purple solid. **m.p**. 131-133 °C; **IR(KBr)** nmax/cm^{-1} 2925, 2853, 1514, 1383, 1245, 1013, 755; **^{1}H NMR (**400 MHz, $CDCl_3$**)** 7.55−6.90 (m, 18H), 5.02 (s, 2H), 4.63(s, 2H), 4.54(s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.4, 169.1, 130.4, 129.7, 128.8, 128.6, 128.0., 127.6, 127.4, 127.4, 127.1, 115.3, 70.1, 40.9, 40.4; **HRMS (ESI)**: calcd. for $C_{29}H_{24}N_4O$ $[M+H]^+$, 445.20229, found 445.20164.

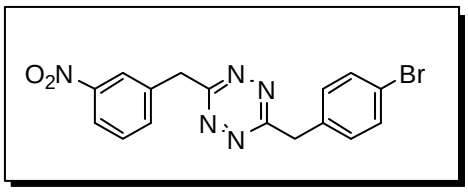


3−([1,1'−biphenyl]−4−ylmethyl)−6−(4−(benzyloxy)benzyl)−1,2,4,5−tetrazine (5e). (124 mg, 83%). purple solid. **m.p**. 146-148 °C; **IR(KBr)** nmax/cm^{-1} 2921, 2849, 1513, 1383, 1248, 1014, 836; **^{1}H NMR (**400 MHz, $CDCl_3$**)** 7.86−6.89 (m, 17H), 5.01 (s, 2H), 4.75(s, 2H), 4.53(s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.4, 169.1, 158.5,136.9, 133.3, 132.5, 130.3, 128.6., 128.6, 128.1, 128.0, 127.7,

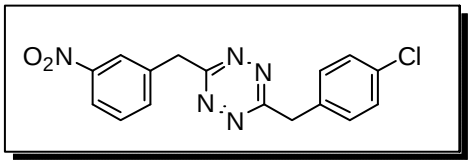
127.7, 127.4, 127.1, 126.3, 126.0, 115.3, 70.0, 41.4, 40.4; **HRMS (ESI)**: calcd. for $C_{27}H_{22}N_4O$ $[M+H]^+$, 419.18644, found 419.18634.



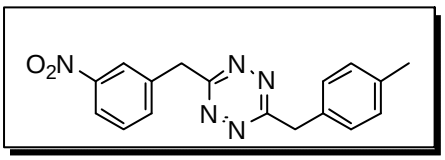
3−(4−(benzyloxy)benzyl)−6−(naphthalen−1−ylmethyl)−1,2,4,5−tetrazine (5f). (18 mg, 80%). purple solid. **m.p**. 106-108 °C; **IR(KBr)** nmax/cm^{-1} 2923, 2855, 1513, 1415, 1377, 1245, 1046, 786; **^{1}H NMR (**400 MHz, $CDCl_3$**)** 8.27−8.24 (m, 1H), 7.38−7.25 (m, 14H); 6.90−6.88 (d, *J* = 8Hz, 2H); 5.03 (s, 2H), 5.00(s, 2H), 4.49(s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.3, 169.2, 158.1, 136.9, 134.0, 132.2, 130.4., 128.8, 128.6, 128.4, 128.1, 128.0, 127.4, 126.6, 125.9, 125.6, 124.0, 70.0, 40.4, 38.7; **HRMS (ESI)**: calcd. for $C_{27}H_{22}N_4O$ $[M+H]^+$, 419.18644, found 419.18634.



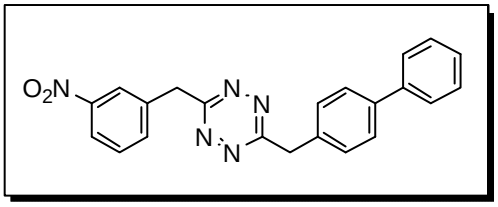
3−(4−bromobenzyl)−6−(3−nitrobenzyl)−1,2,4,5−tetrazine (5g). (13 mg, 77%). purple solid. **m.p**. 80-82 °C; **IR(KBr)** nmax/cm^{-1} 2920, 2849, 1529, 1491, 1380, 1351 733; **^{1}H NMR (**400 MHz, $CDCl_3$**)** 8.29−7.29 (m, 8H), 4.72 (s, 2H), 4.58(s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.2, 168.4, 148.5，137.4, 135.5, 134.4, 132.1, 131.0, 129.9, 122.6, 121.7, 40.7, 40.7; **HRMS (ESI)**: calcd. for $C_{16}H_{12}BrN_5O_2$ $[M+H]^+$, 386.02471, found 386.02430.



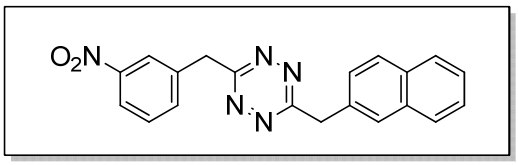
3−(4−chlorobenzyl)−6−(3−nitrobenzyl)−1,2,4,5−tetrazine (5h). (31 mg, 76%). purple solid. **m.p**. 75-77 °C; **IR(KBr)** nmax/cm^{-1} 2920, 2849, 1529, 1491, 1380, 1351,733; **^{1}H NMR (**400 MHz, $CDCl_3$**)** 8.30−7.28 (m, 8H), 4.72 (s, 2H), 4.59(s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.2, 168.4, 137.4, 135.5, 133.9, 133.6, 130.6, 129.9, 129.1, 124.4, 122.6, 40.7, 40.6; **HRMS (ESI)**: calcd. for $C_{16}H_{12}ClN_5O_2$ $[M+H]^+$, 342.07523, found 342.07474.



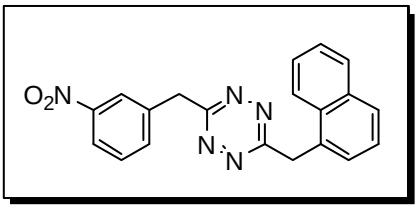
3−(4−methylbenzyl)−6−(3−nitrobenzyl)−1,2,4,5−tetrazine (5i). (22 mg, 81%). purple solid. **m.p**. 73-75 °C; **IR(KBr)** nmax/cm^{-1} 2922, 2851, 1522, 1426, 1382, 1345, 730; **^{1}H NMR (**400 MHz, $CDCl_3$**)** 8.30−7.28 (m, 8H), 4.72 (s, 2H), 4.59(s, 2H), 2.17(s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.2, 168.4, 148.5，137.4, 135.5, 133.9, 130.6, 129.9, 129.1, 124.4, 122.6, 40.9, 40.7, 21.0; **HRMS (ESI)**: calcd. for $C_{17}H_{15}N_5O_2$ $[M+H]^+$, 322.12985, found 322.12946.



3−([1,1'−biphenyl]−4−ylmethyl)−6−(3−nitrobenzyl)−1,2,4,5−tetrazine (5j). (24 mg, 78%). purple solid. **m.p**. 92-94°C; **IR(KBr)** nmax/cm^{-1} 2925, 2853, 1529, 1488, 1380, 1350,759; **^{1}H NMR (**400 MHz, $CDCl_3$**)** 8.31−7.26 (m, 13H), 5.02(s, 2H), 4.72(s, 2H), 4.67(s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.6, 168.3, 140.5, 137.5, 135.5, 134.5, 129.7, 128.8, 127.7, 127.4, 127.0, 124.4, 122.6, 40.9, 40.7; **HRMS (ESI)**: calcd. for $C_{22}H_{17}N_5O_2$ $[M+H]^+$, 384.14550, found 384.14503.



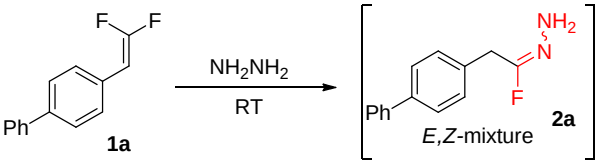
3−(naphthalen−2−ylmethyl)−6−(3−nitrobenzyl)−1,2,4,5−tetrazine (5k). (19 mg, 83%). purple solid. **m.p**. 113-115 °C; **IR(KBr)** nmax/cm^{-1} 2922, 2851, 1529, 1464, 1380, 1353,734; **^{1}H NMR (**400 MHz, $CDCl_3$**)** 8.29−7.44 (m, 13H), 4.78(s, 2H), 4.70(s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.6, 167.3, 146.1, 134.5, 132.5, 131.9, 131.5, 128.8, 127.9, 127.7, 127.1, 126.7, 126.6, 126.0, 125.4, 125.1, 123.4, 121.6, 40.4, 39.7; **HRMS (ESI)**: calcd. for $C_{20}H_{15}N_5O_2$ $[M+H]^+$, 358.12985, found 358.12924.



3−(naphthalen−1−ylmethyl)−6−(3−nitrobenzyl)−1,2,4,5−tetrazine (5l). (18 mg, 78%). **m.p**. 100-102 °C; **IR(KBr)** nmax/cm^{-1} 2922, 2850, 1529, 1463, 1379, 1351, 790; **^{1}H NMR (**400 MHz, $CDCl_3$**)** purple solid. 8.28−7.48 (m, 11H), 5.07 (s, 2H), 4.68(s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.8, 168.0, 137.4, 135.5, 134.0, 131.9,

131.7, 129. 8, 128.9, 128.5, 128.4, 126.7, 126.0, 125.7, 124.4, 123.8, 122.6, 40.7, 38.8; **HRMS (ESI)**: calcd. for $C_{20}H_{15}N_5O_2$ $[M+H]^+$, 358.12985, found 358.12971.

5. Screen of the solvent effect in the conversion of gem-difluoroalkene 1a to fluorohydrazone 2a[a]

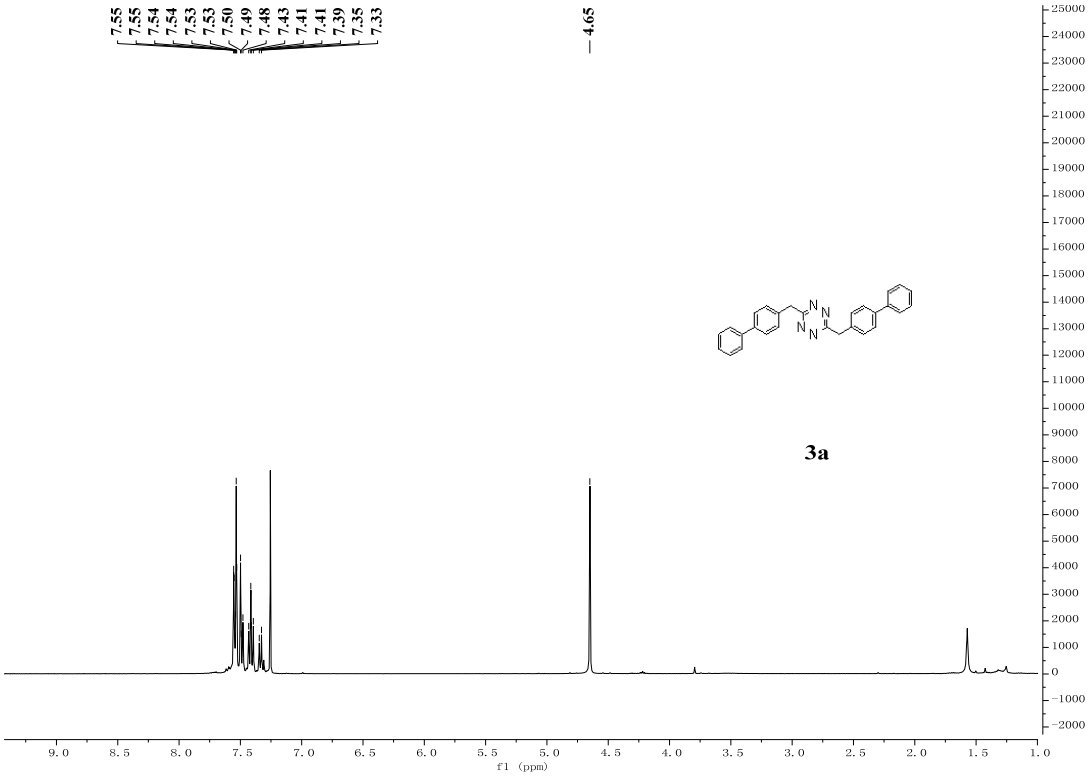


Solvent	Temperature（° C）	Conversion（%）
Toluene	**RT**	**3**
CH_2Cl_2	**RT**	**0**
$CHCl_3$	**RT**	**0**
THF	**RT**	**52**
THF	**40**	**61**
THF	**60**	**65**
THF	**80**	**67**
DMF	**RT**	**99**

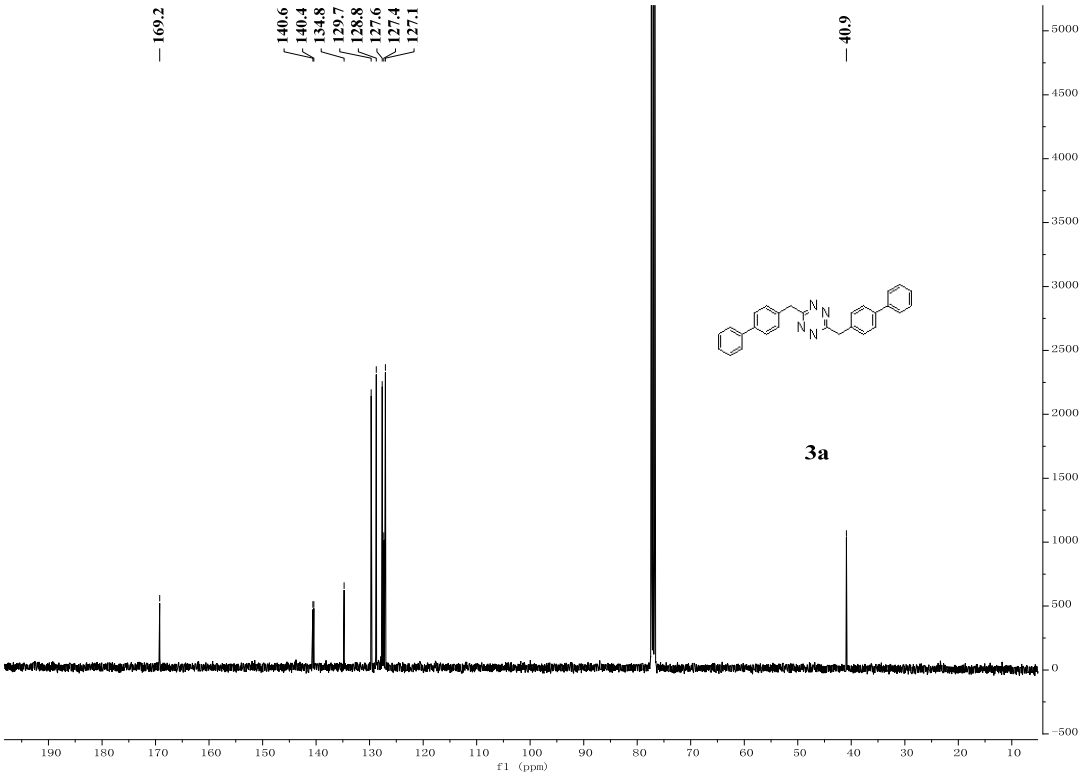
[a] The conversion was calculated based on the recovery of the starting material.

6. NMR spectra of novel compounds and intermediate

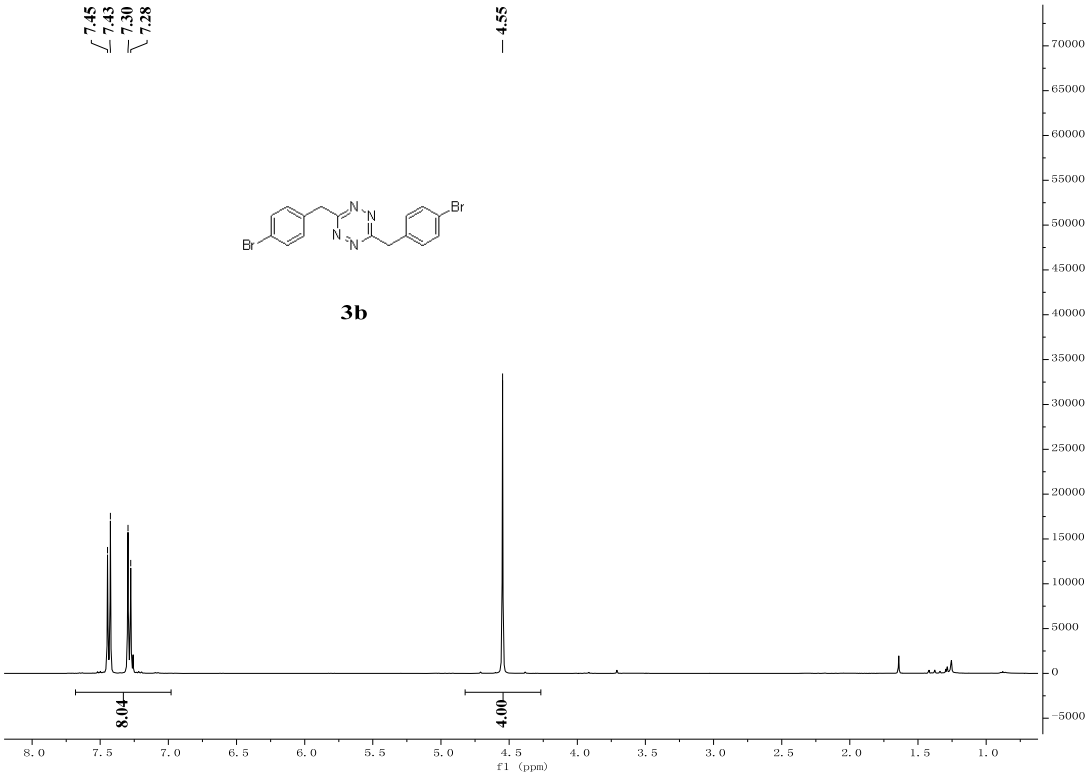
^{1}H NMR ($CDCl_3$, 400 MHz, 25 ºC) of **3a**



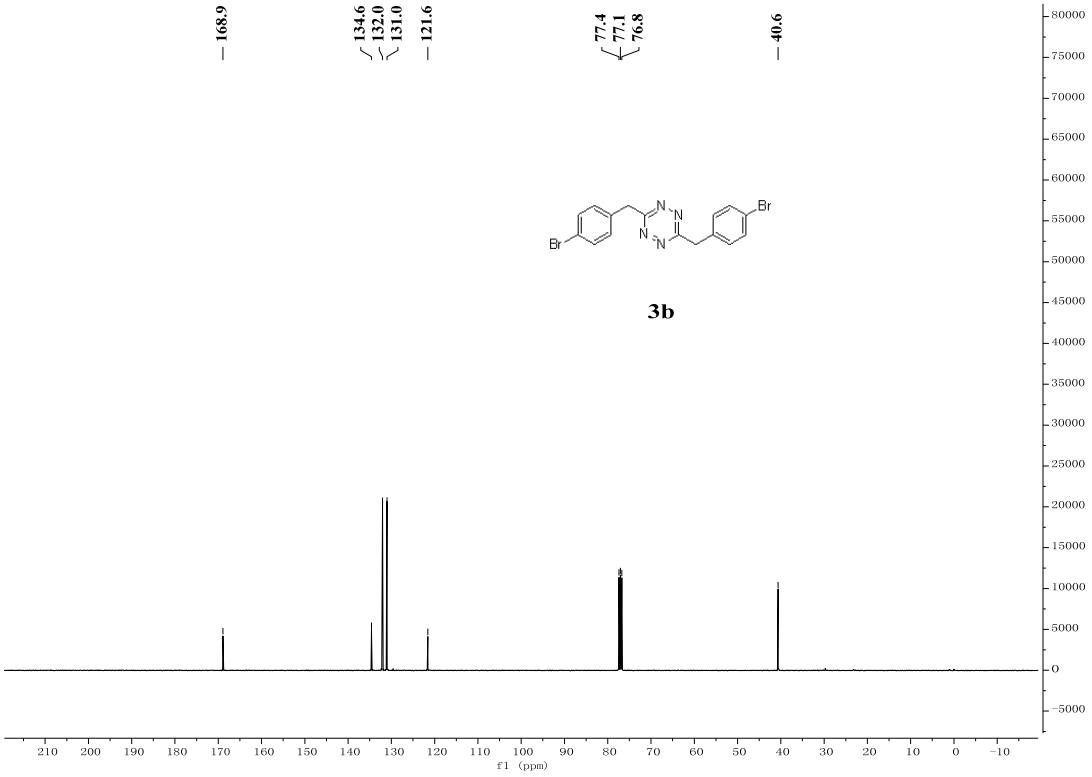
^{13}C NMR ($CDCl_3$, 100 MHz, 25 ºC) of **3a**



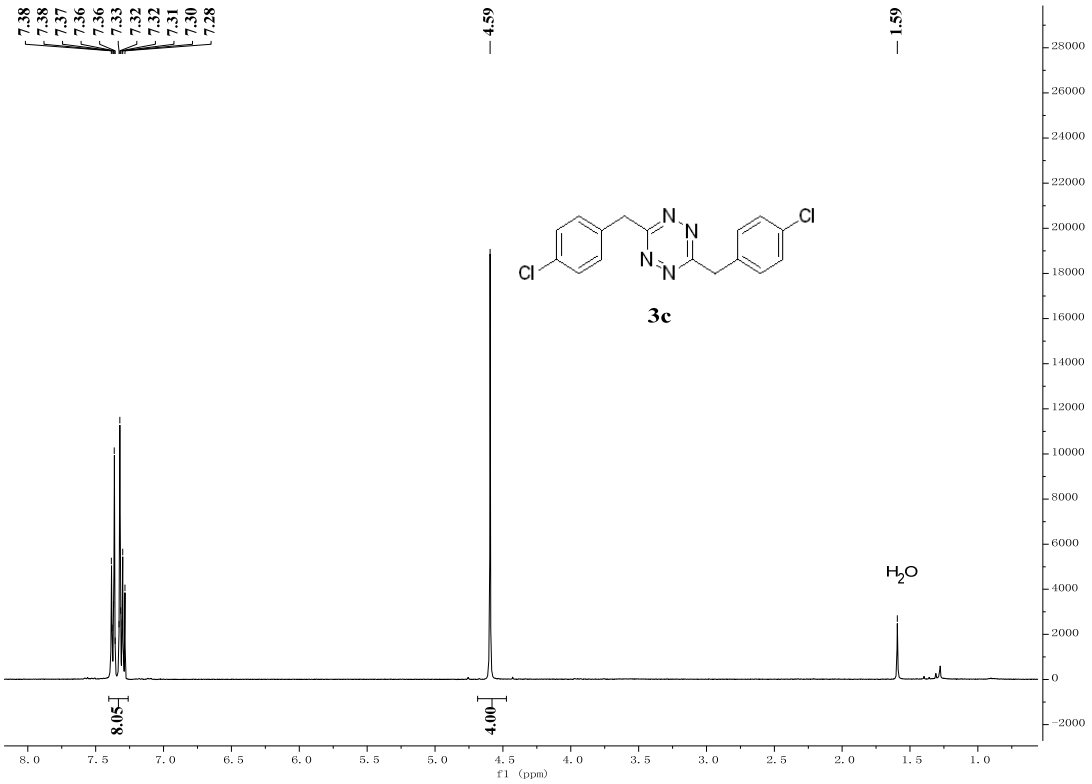
^{1}H NMR ($CDCl_3$, 400 MHz, 25 ºC) of **3b**



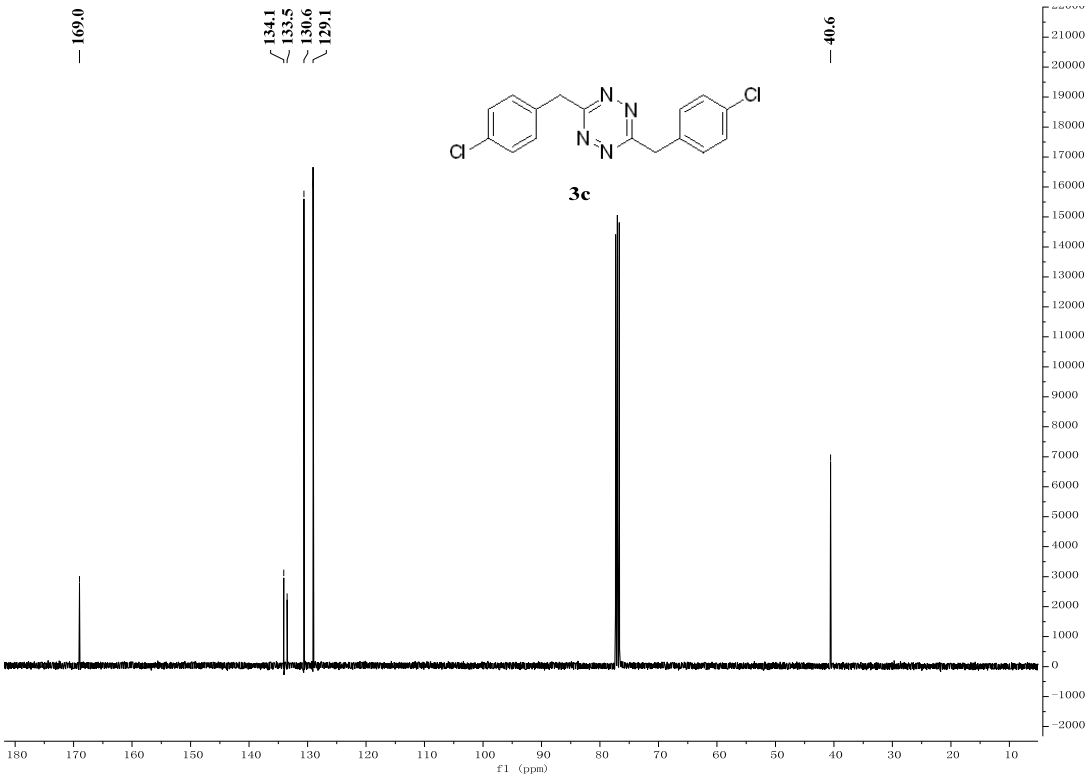
^{13}C NMR ($CDCl_3$, 100 MHz, 25 ºC) of **3b**



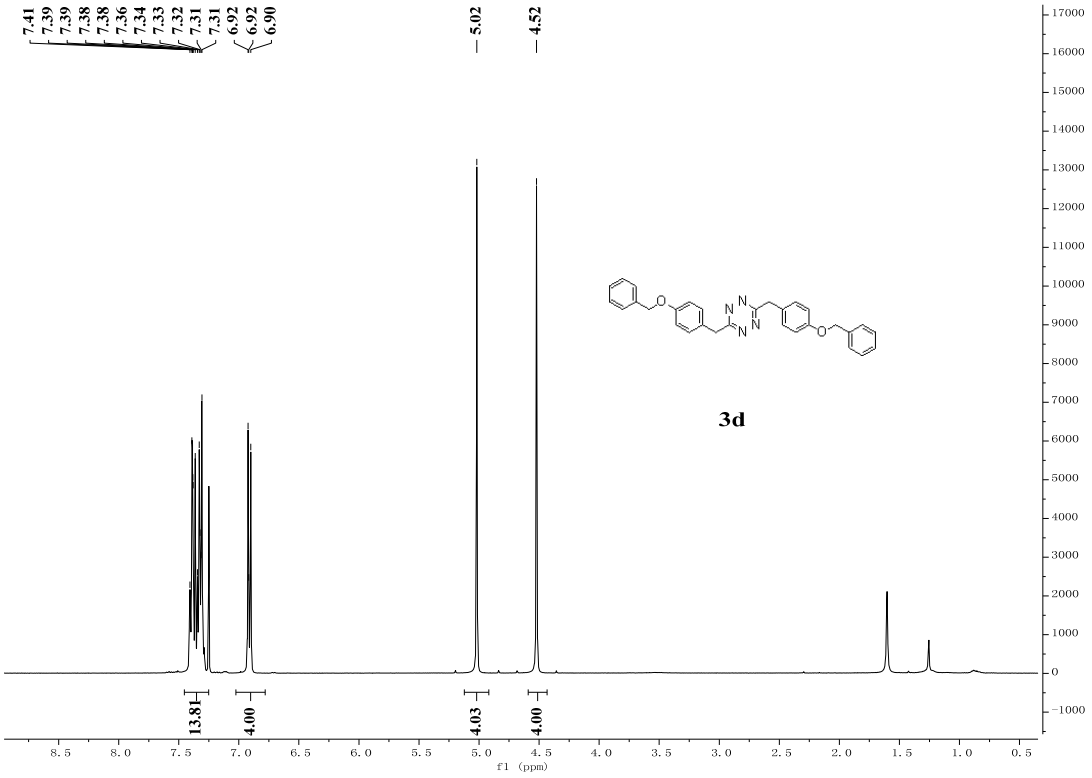
^{1}H NMR ($CDCl_3$, 400 MHz, 25 ºC) of **3c**



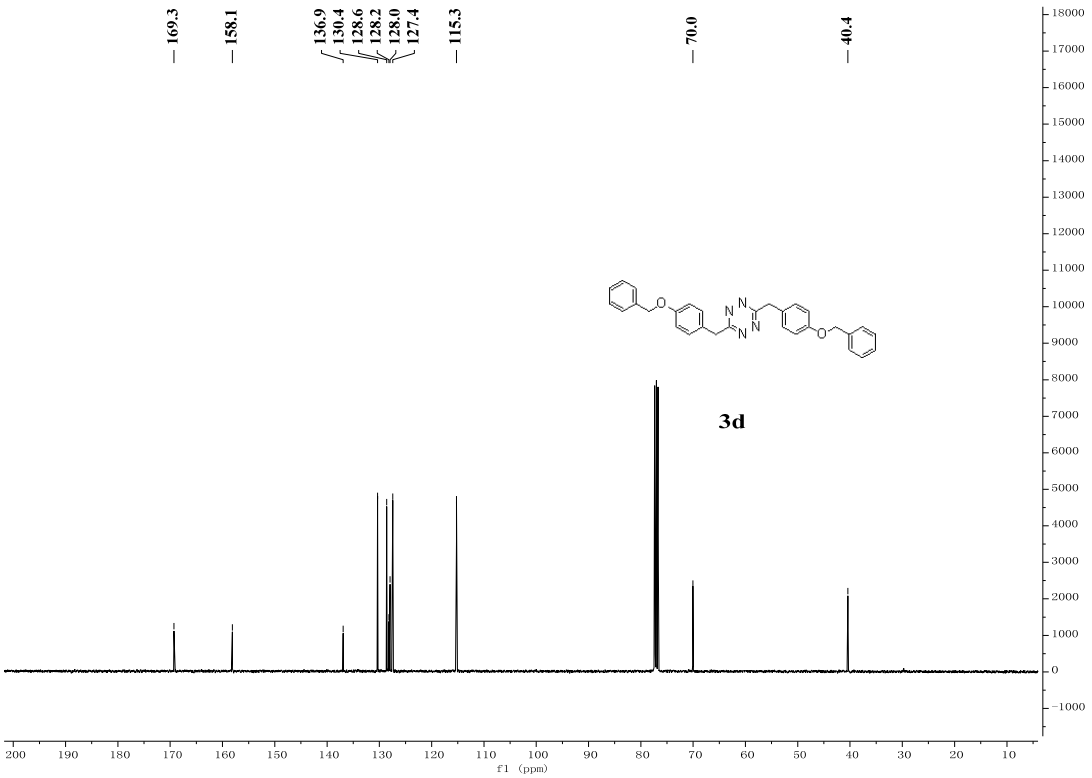
^{13}C NMR ($CDCl_3$, 100 MHz, 25 ºC) of **3c**



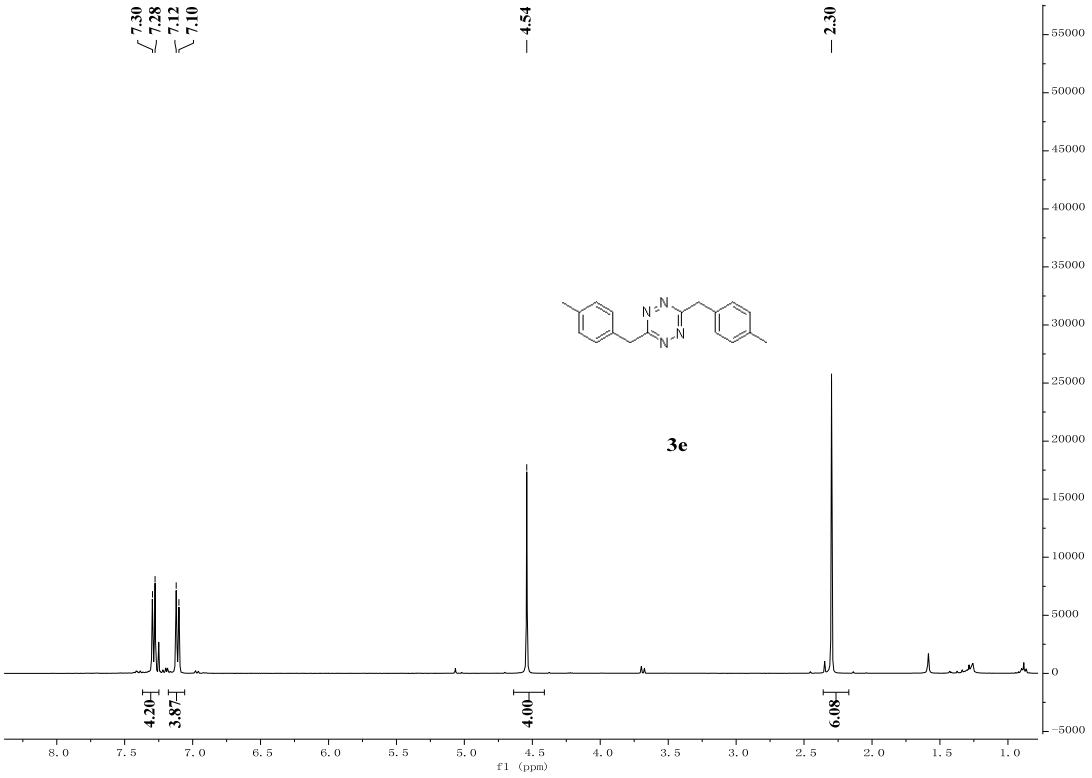
^{1}H NMR ($CDCl_3$, 400 MHz, 25 ºC) of **3d**



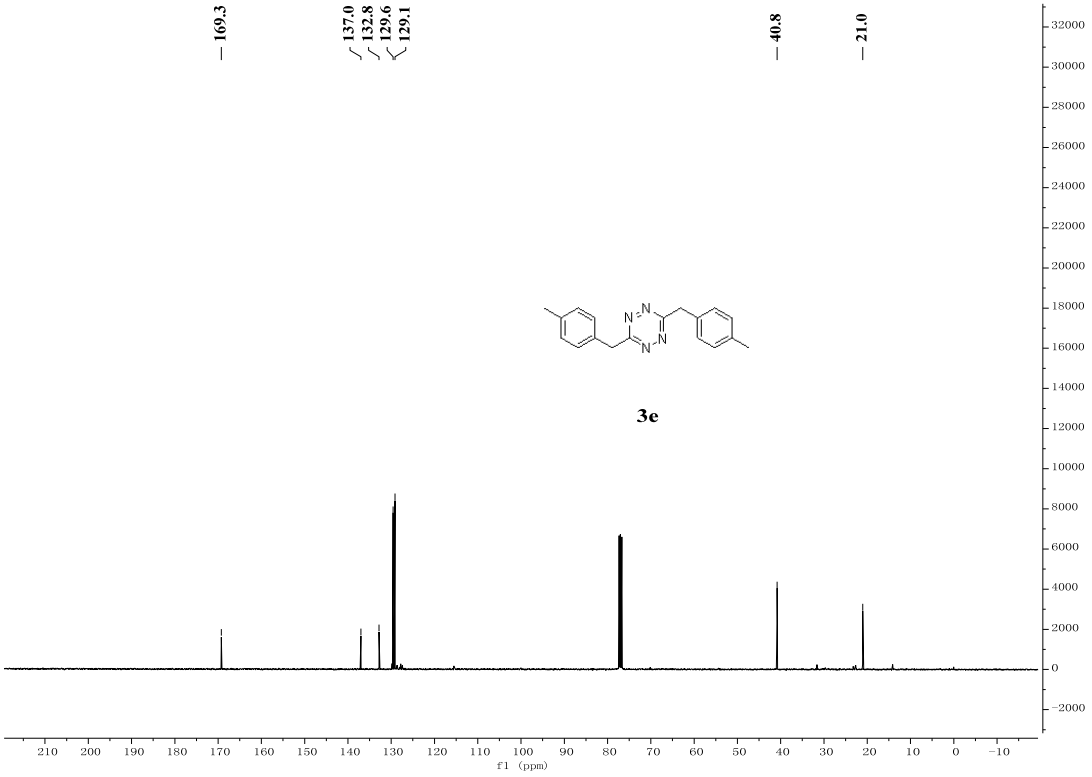
^{13}C NMR ($CDCl_3$, 100 MHz, 25 ºC) of **3d**



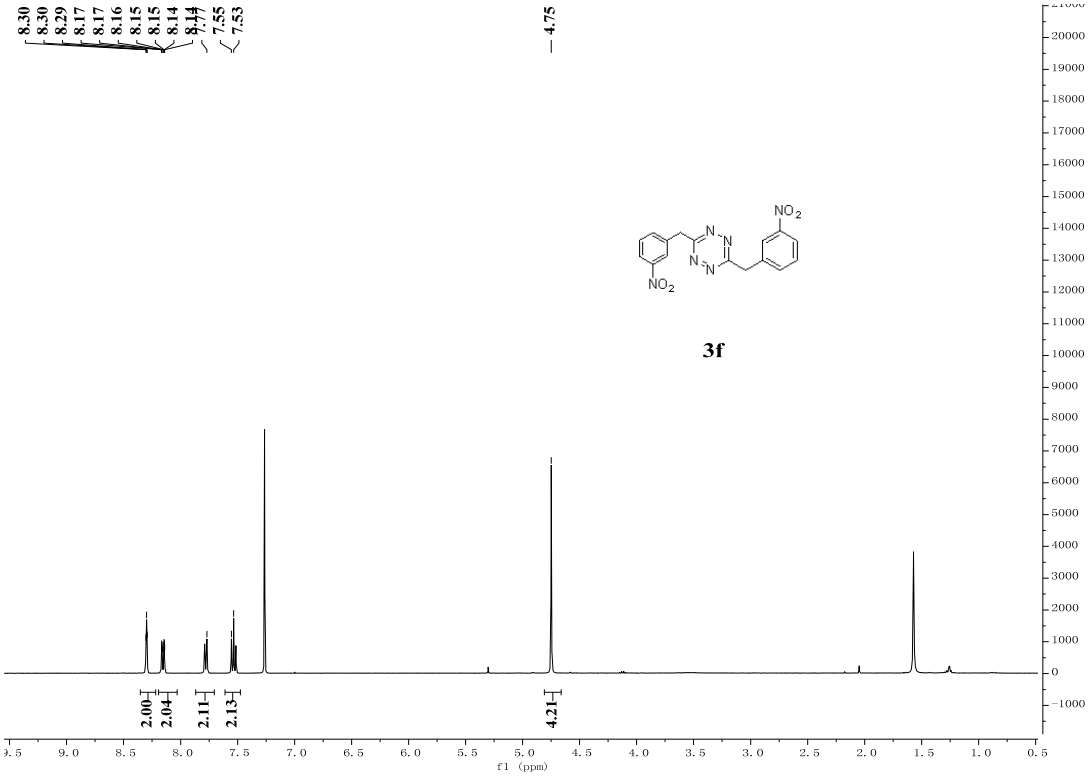
^{1}H NMR ($CDCl_3$, 400 MHz, 25 ºC) of **3e**



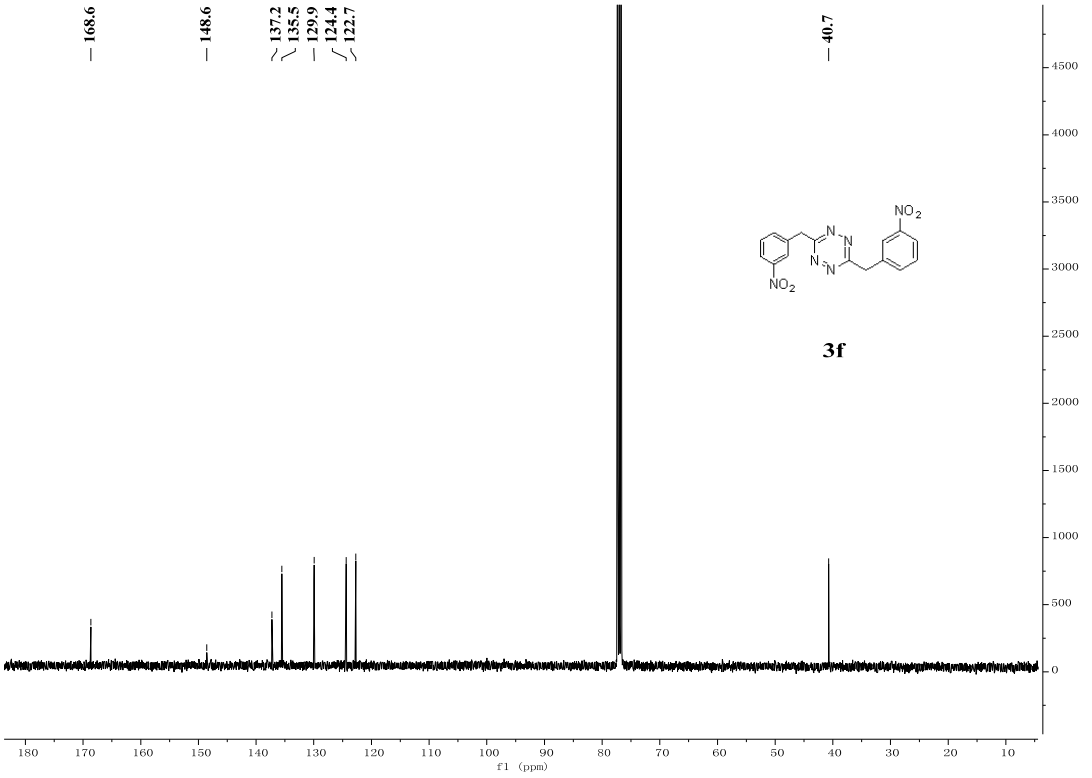
^{13}C NMR ($CDCl_3$, 100 MHz, 25 ºC) of **3e**



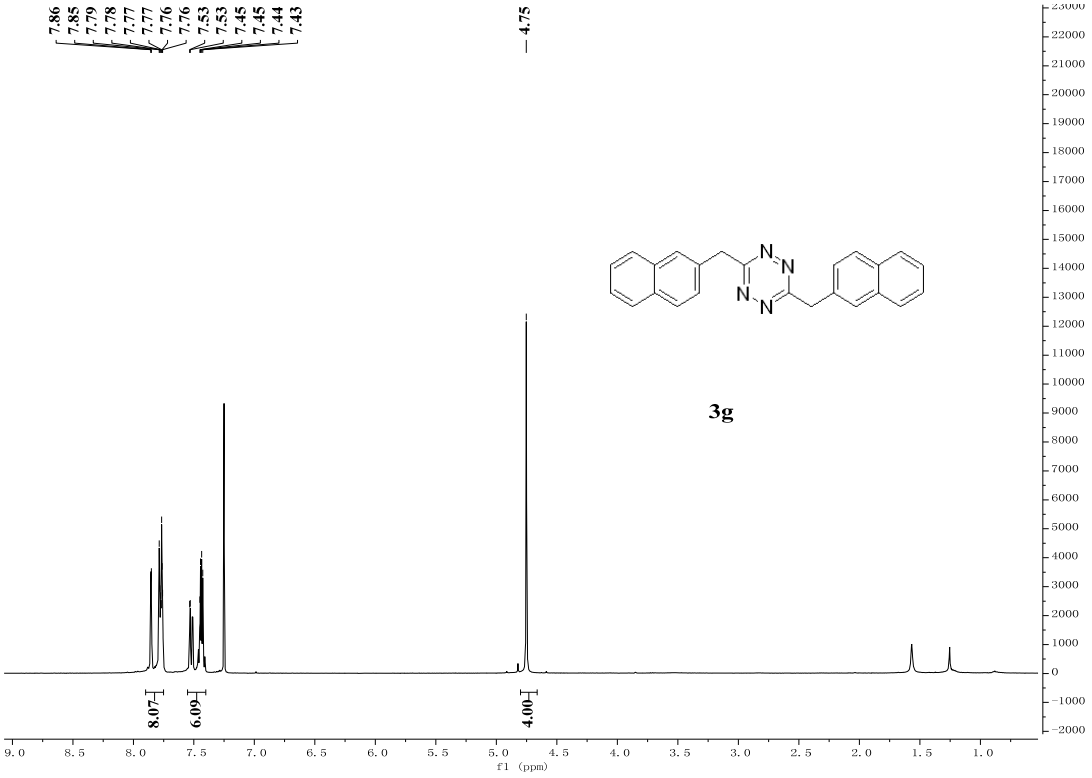
^{1}H NMR ($CDCl_3$, 400 MHz, 25 ºC) of **3f**



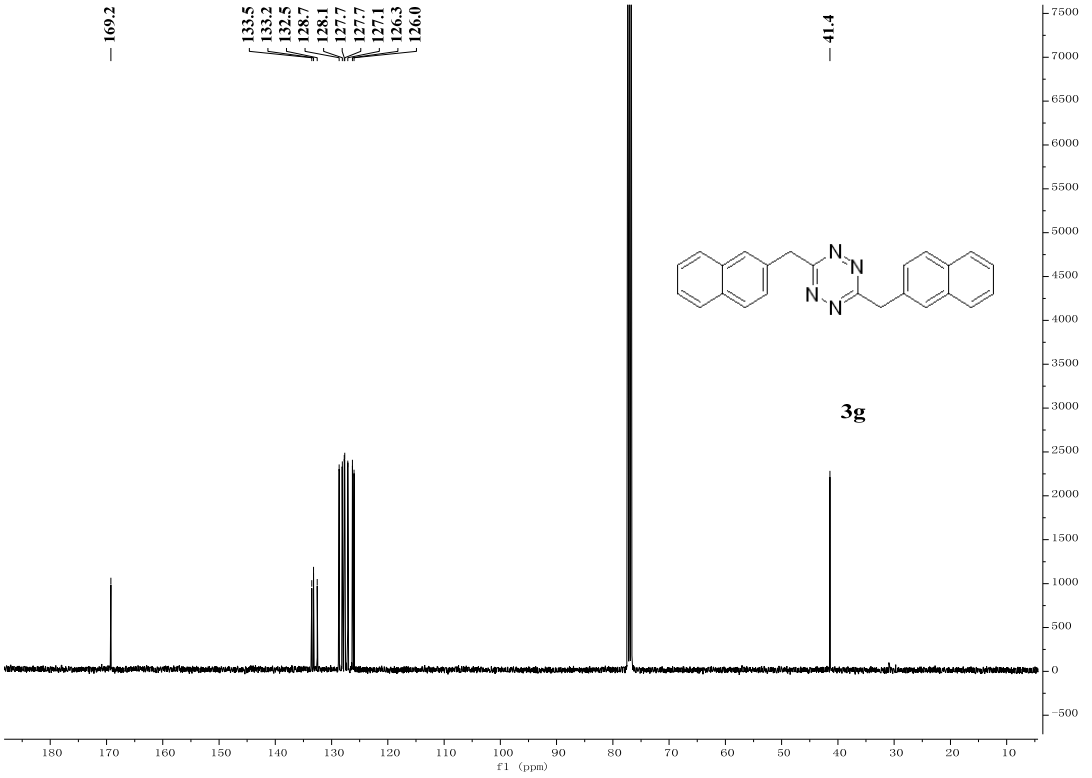
^{13}C NMR ($CDCl_3$, 100 MHz, 25 ºC) of **3f**



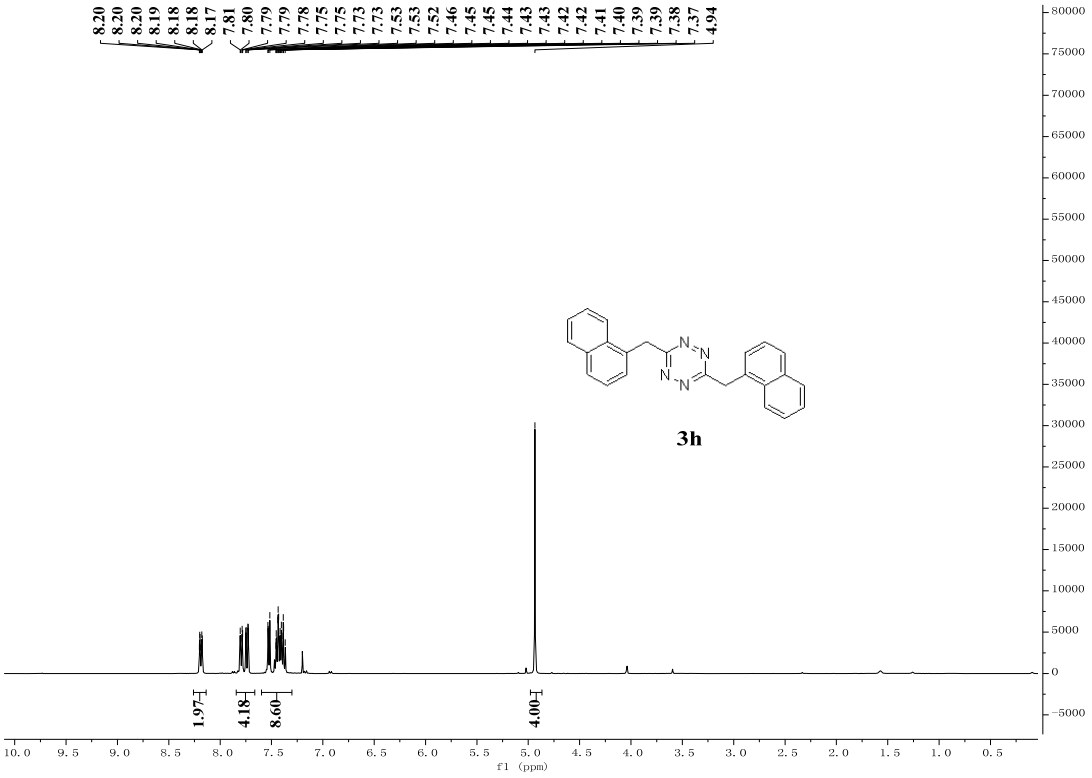
^{1}H NMR ($CDCl_3$, 400 MHz, 25 ºC) of **3g**



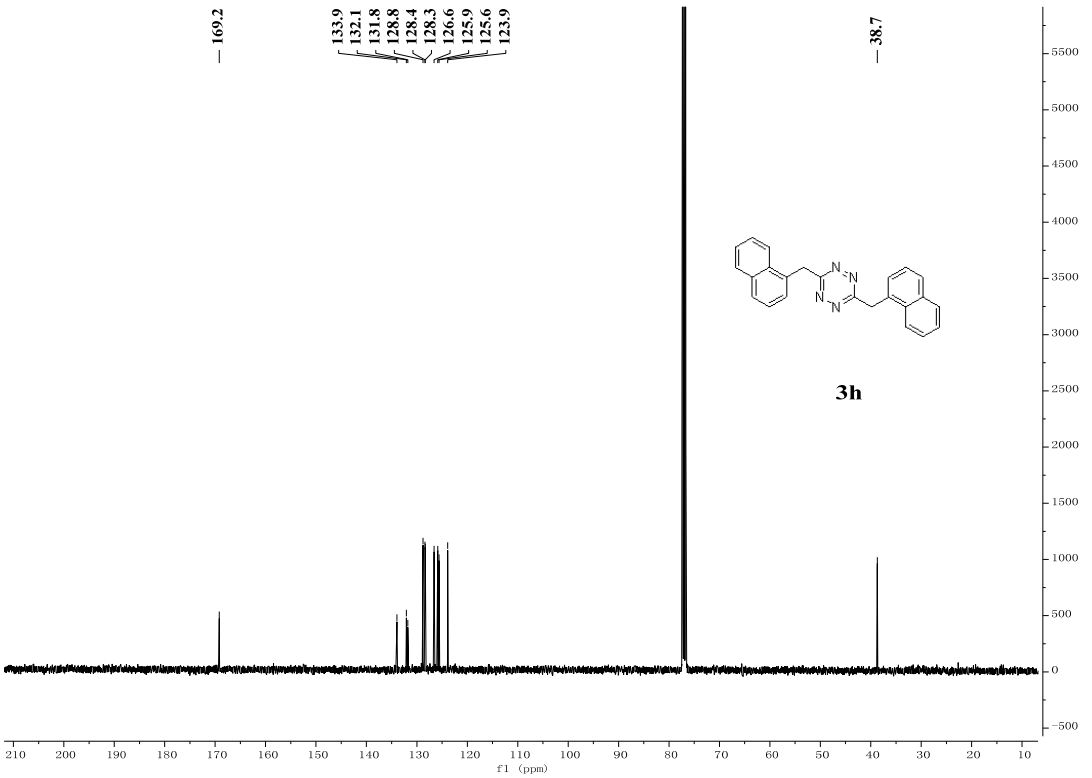
^{13}C NMR ($CDCl_3$, 100 MHz, 25 ºC) of **3g**



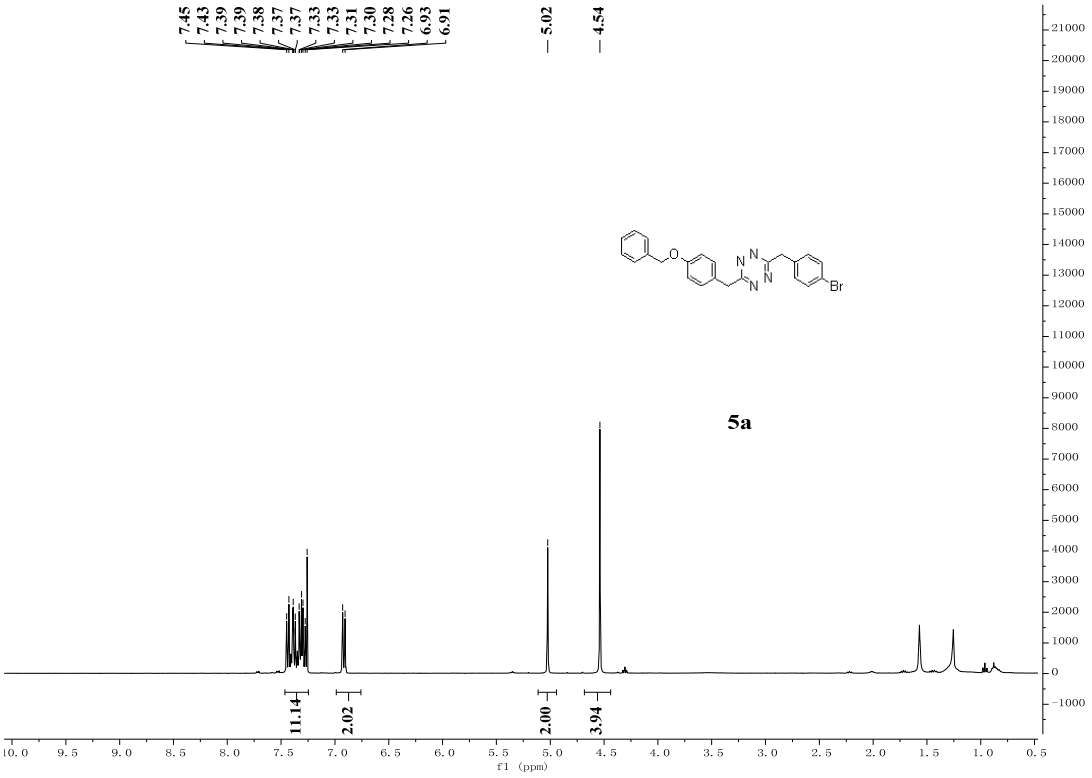
^{1}H NMR ($CDCl_3$, 400 MHz, 25 ºC) of **3h**



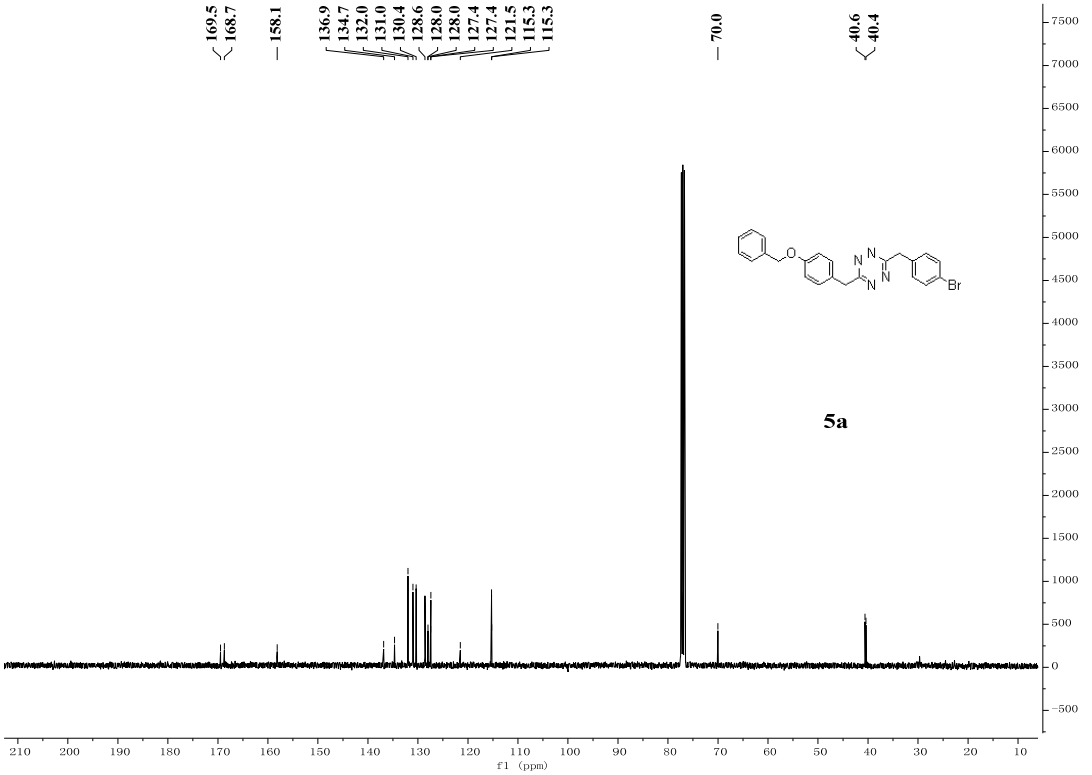
^{13}C NMR ($CDCl_3$, 100 MHz, 25 ºC) of **3h**



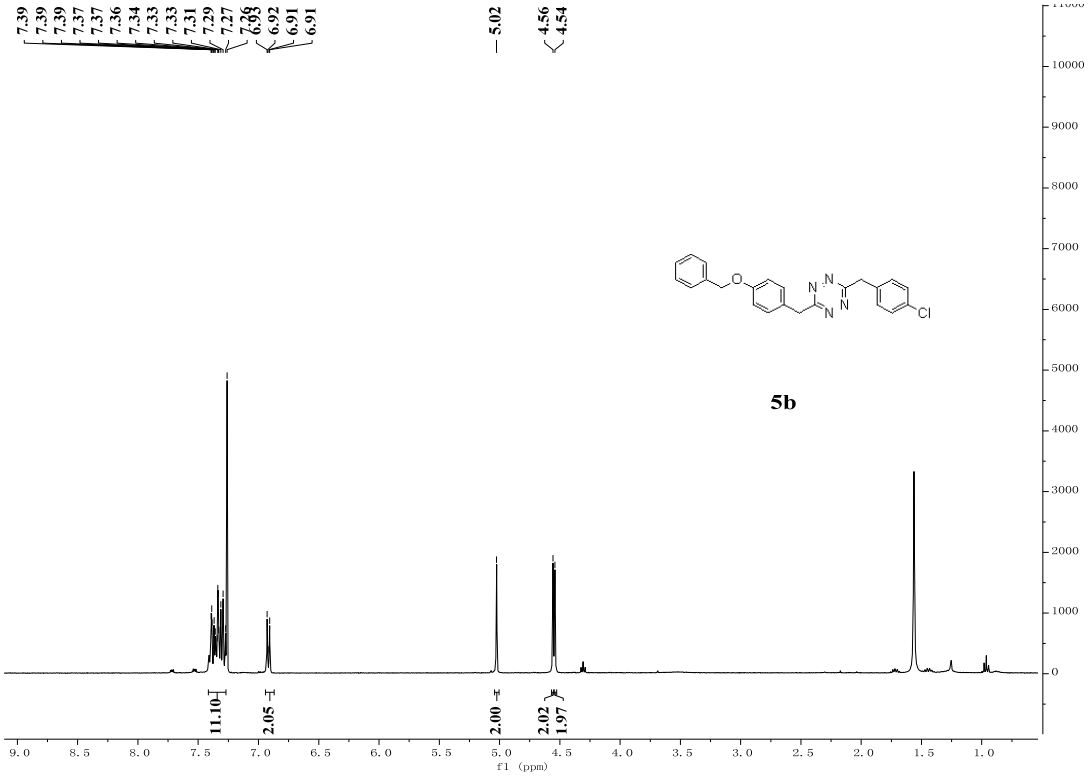
^{1}H NMR ($CDCl_3$, 400 MHz, 25 ºC) of **5a**



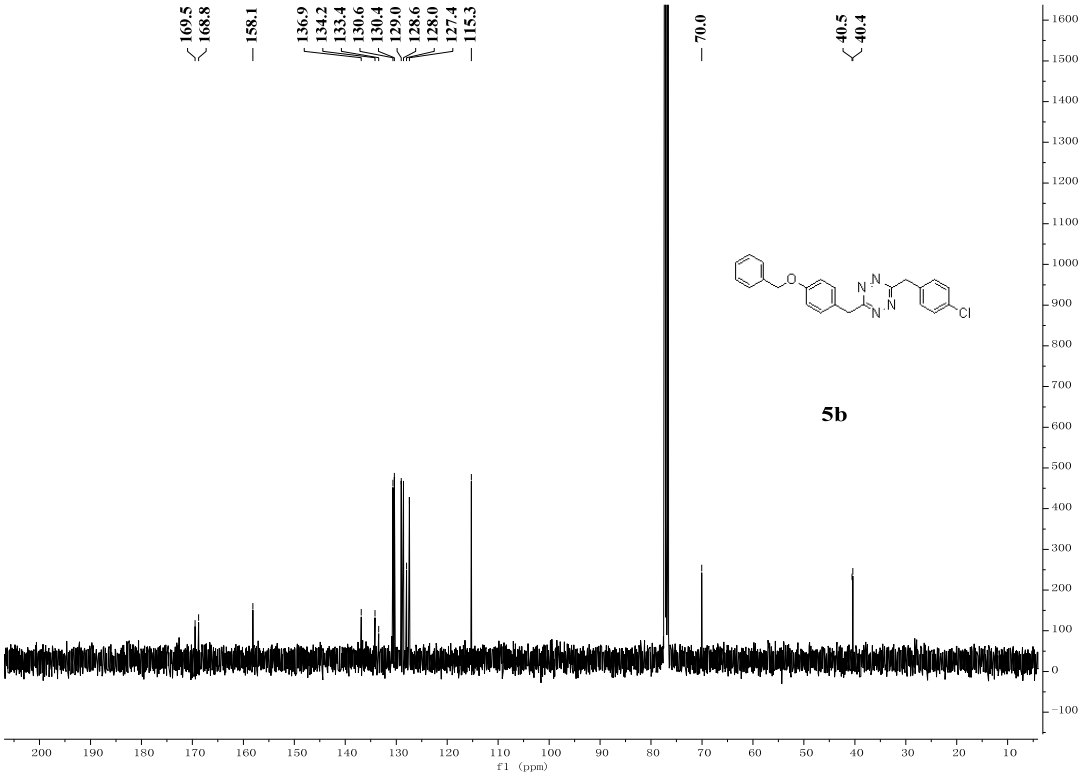
^{13}C NMR ($CDCl_3$, 100 MHz, 25 ºC) of **5a**



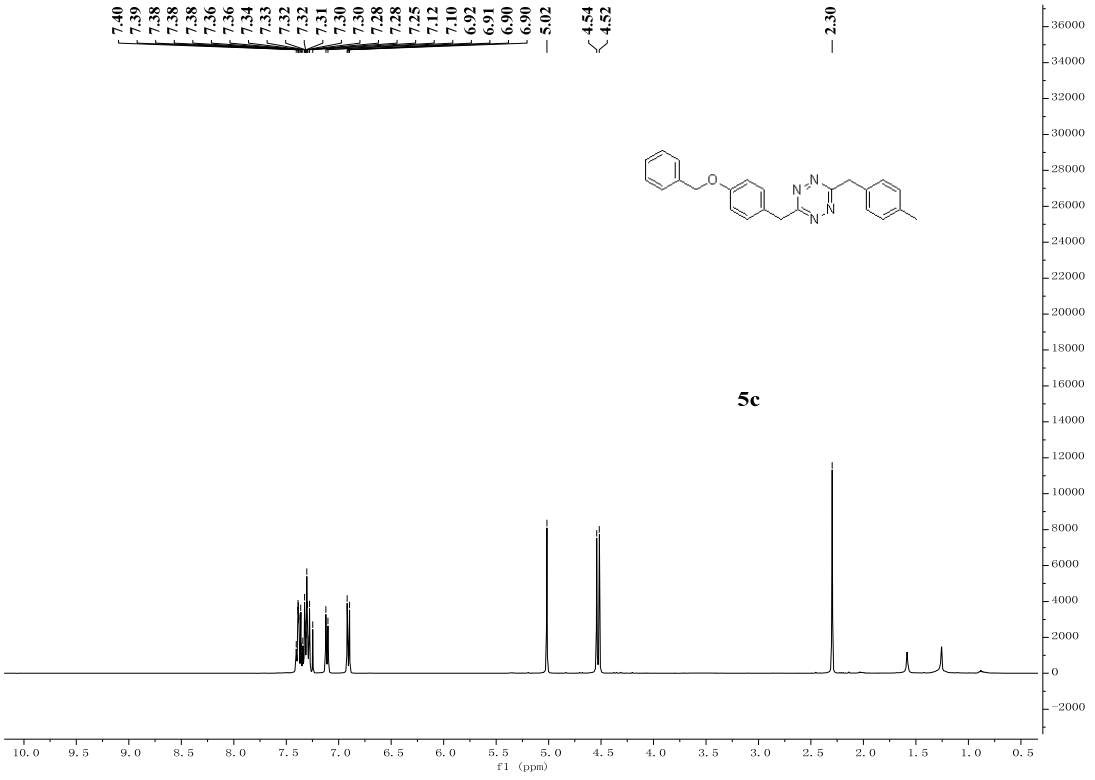
^{1}H NMR ($CDCl_3$, 400 MHz, 25 ºC) of **5b**



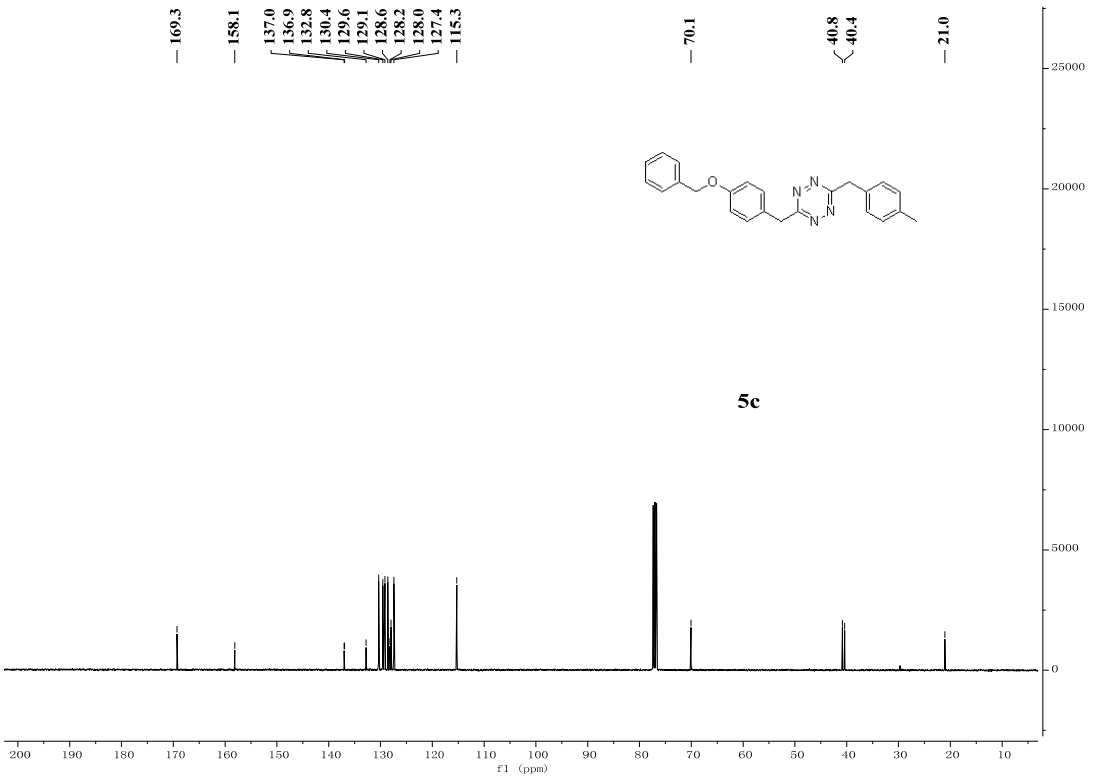
^{13}C NMR ($CDCl_3$, 100 MHz, 25 ºC) of **5b**



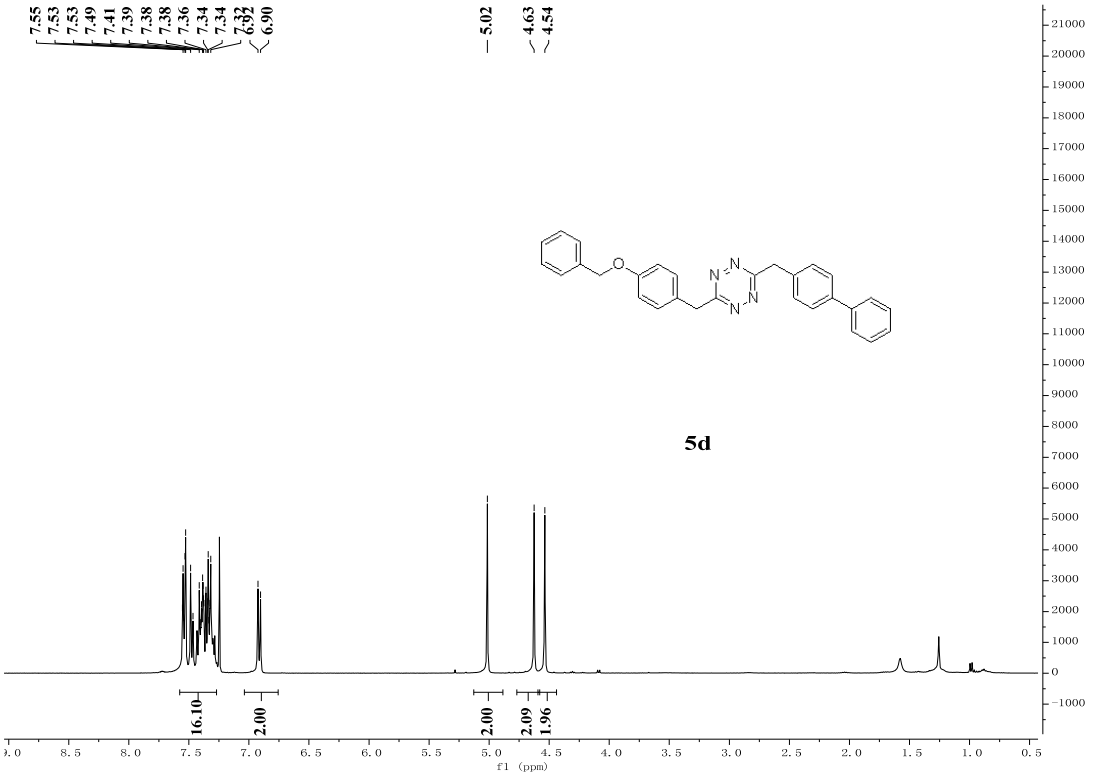
^{1}H NMR ($CDCl_3$, 400 MHz, 25 ºC) of **5c**



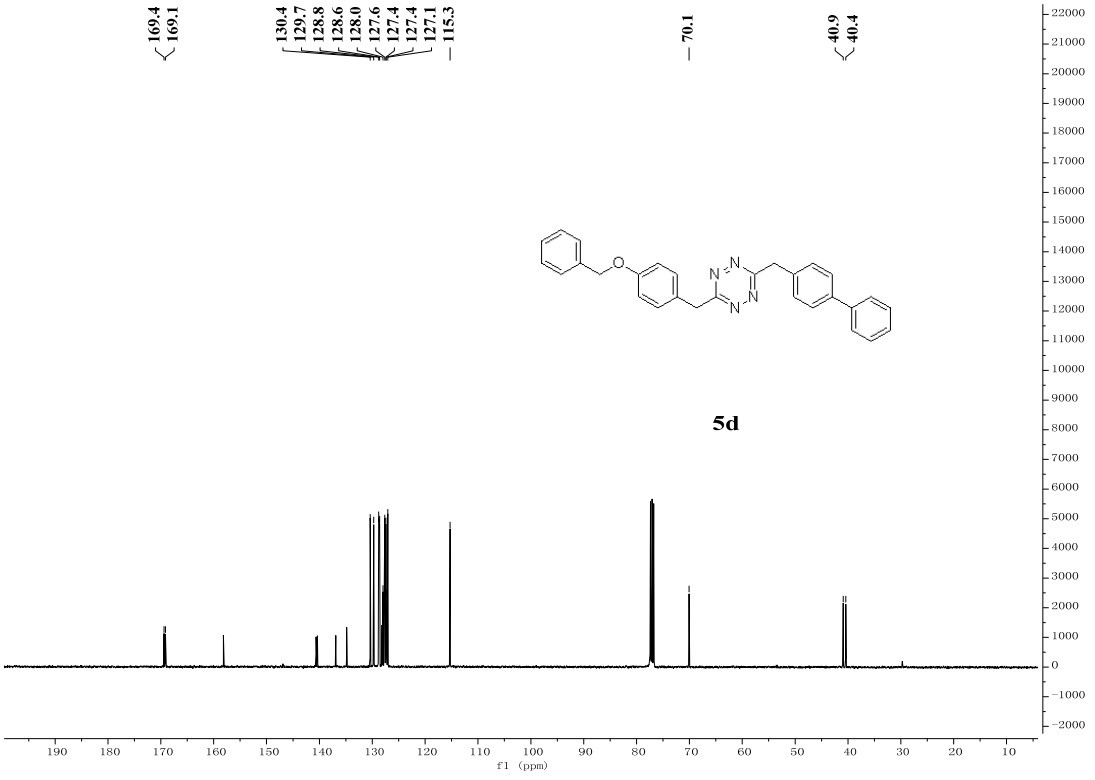
^{13}C NMR ($CDCl_3$, 100 MHz, 25 ºC) of **5c**



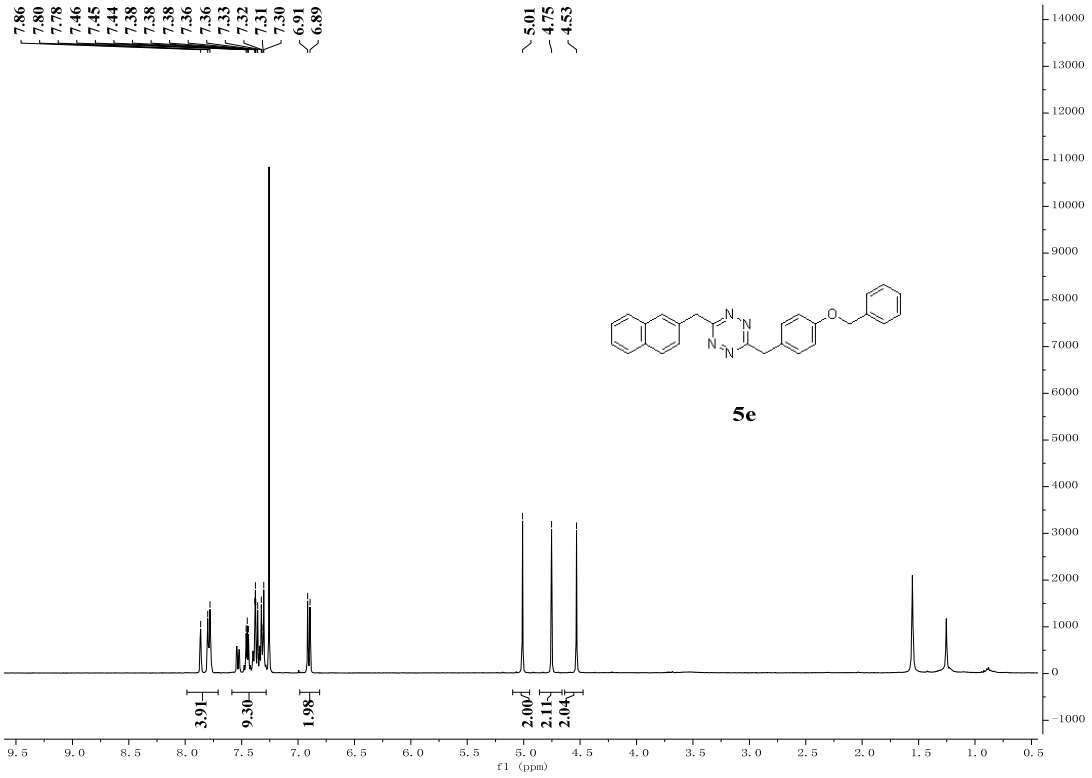
^{1}H NMR ($CDCl_3$, 400 MHz, 25 ºC) of **5d**



^{13}C NMR ($CDCl_3$, 100 MHz, 25 ºC) of **5d**

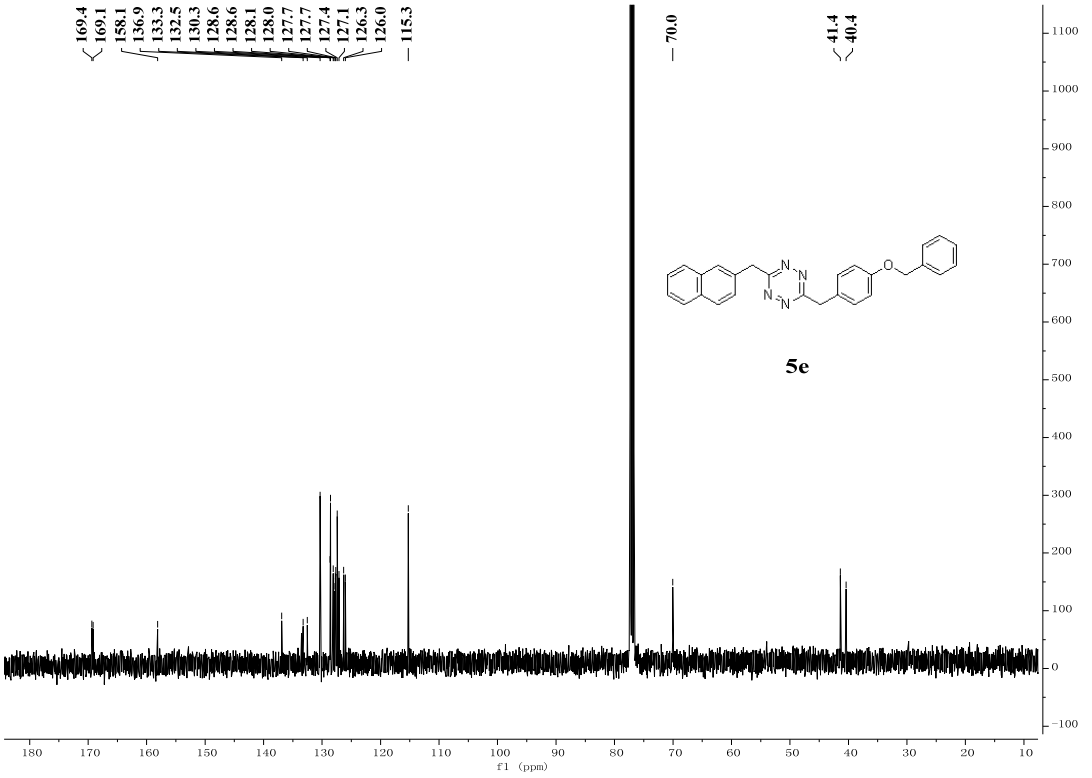


^{1}H NMR ($CDCl_3$, 400 MHz, 25 ºC) of **5e**



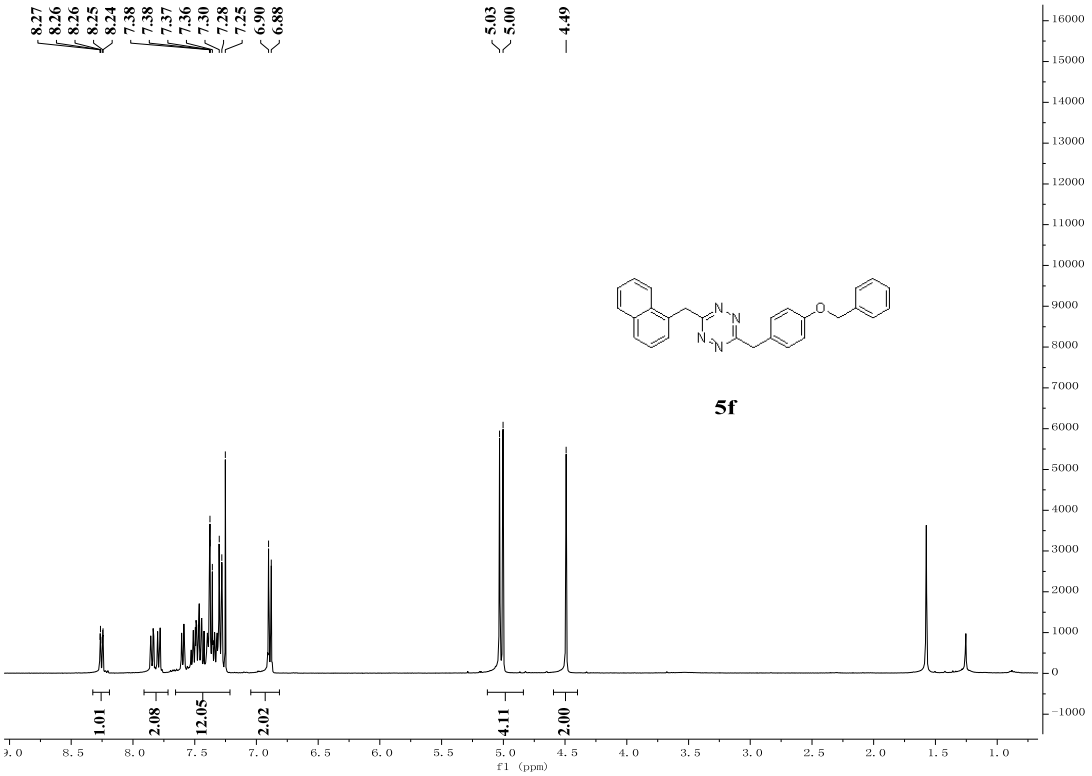
5e

^{13}C NMR ($CDCl_3$, 100 MHz, 25 ºC) of **5e**



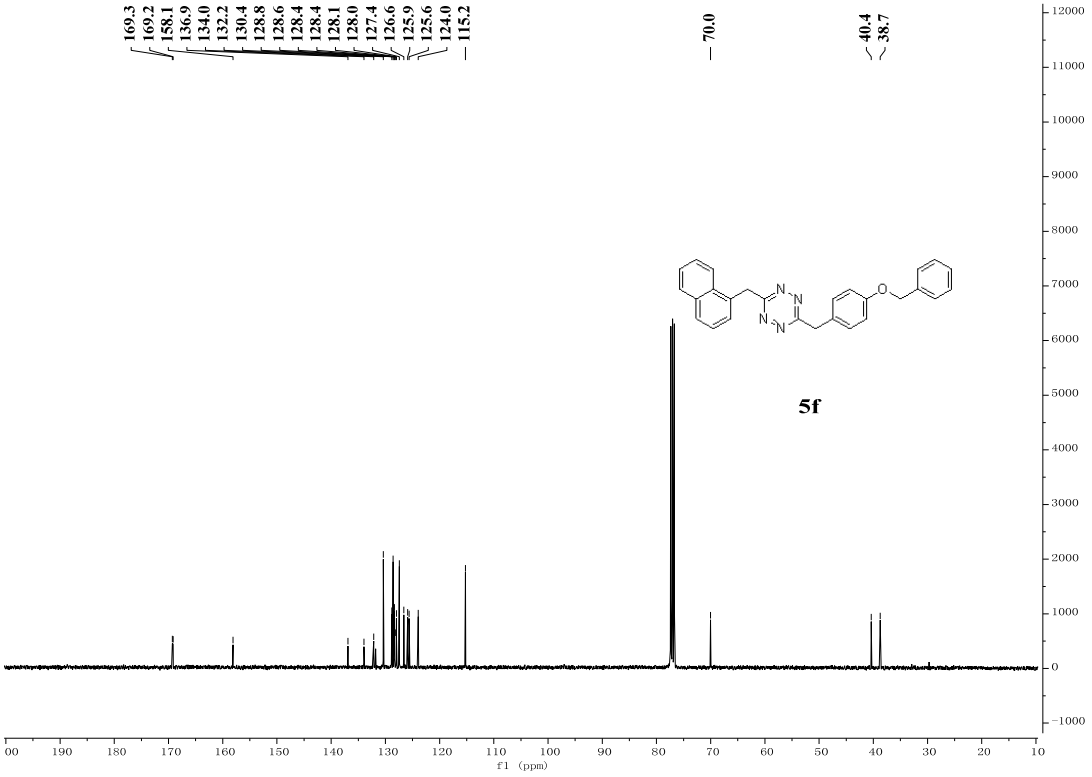
5e

^{1}H NMR ($CDCl_3$, 400 MHz, 25 ºC) of **5f**



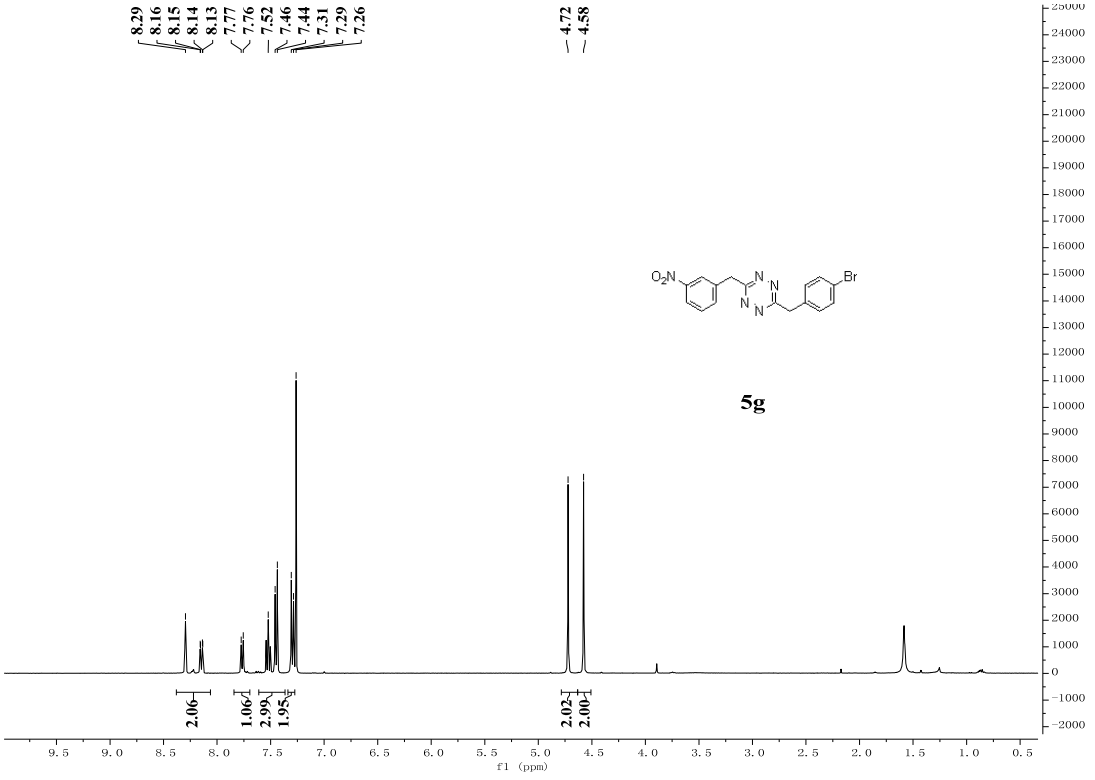
5f

^{13}C NMR ($CDCl_3$, 100 MHz, 25 ºC) of **5f**

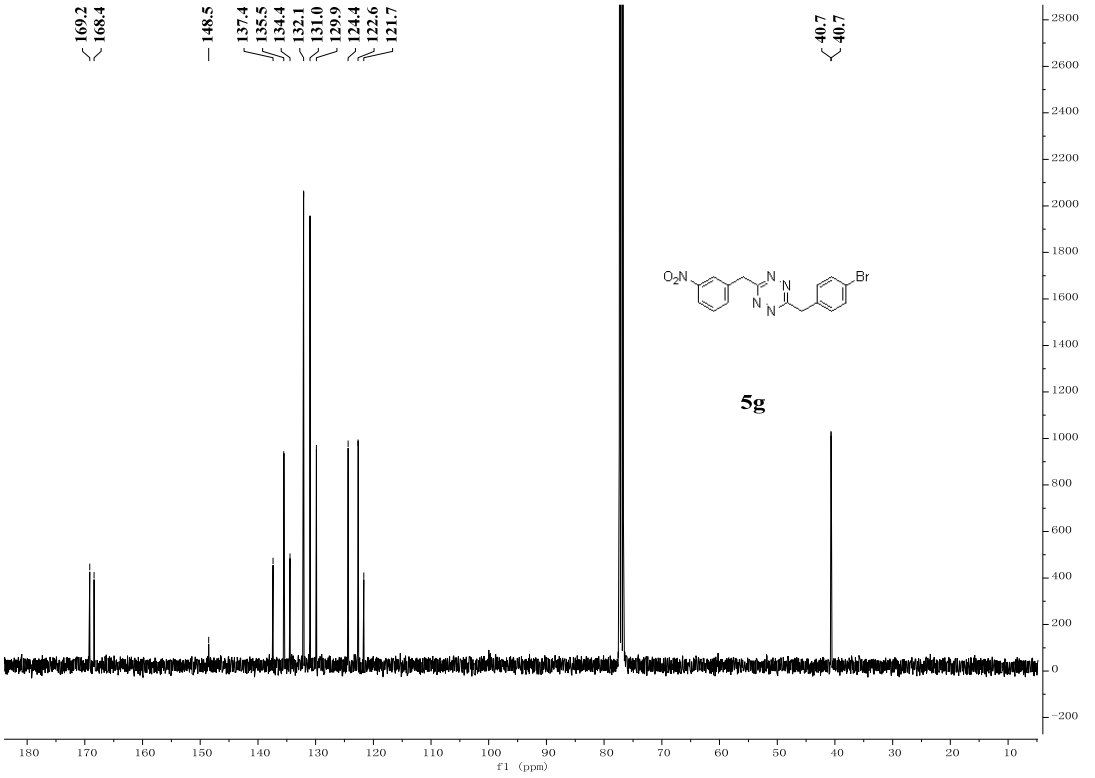


5f

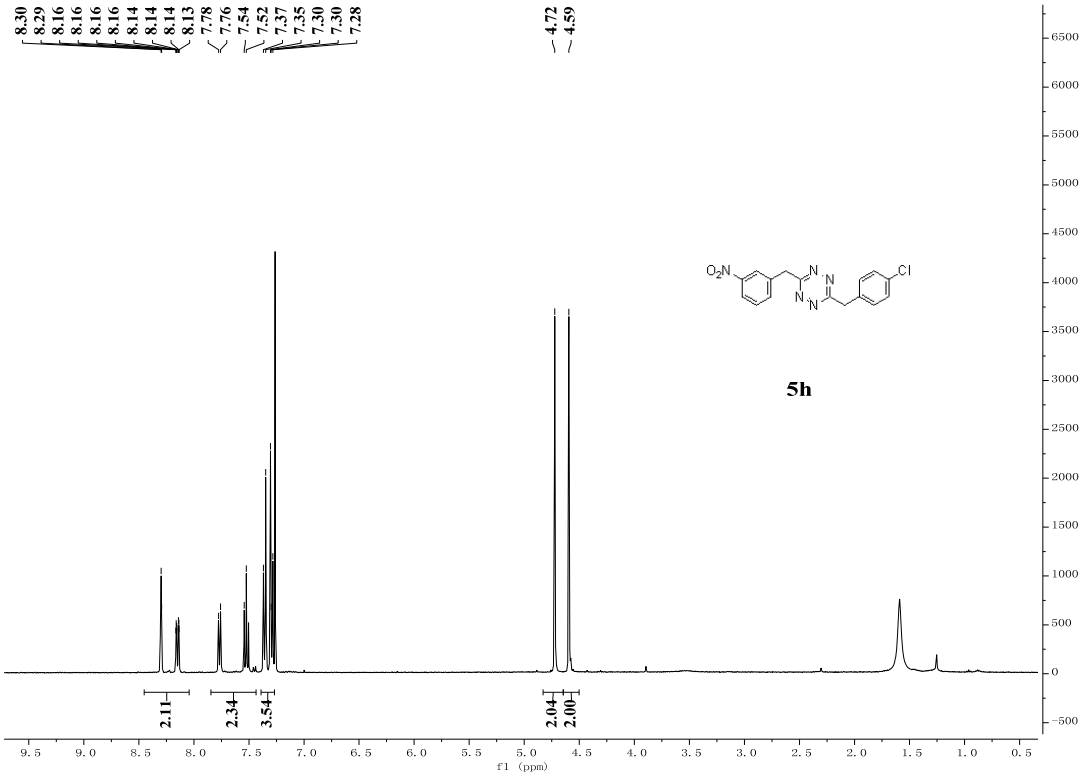
^{1}H NMR ($CDCl_3$, 400 MHz, 25 ºC) of **5g**



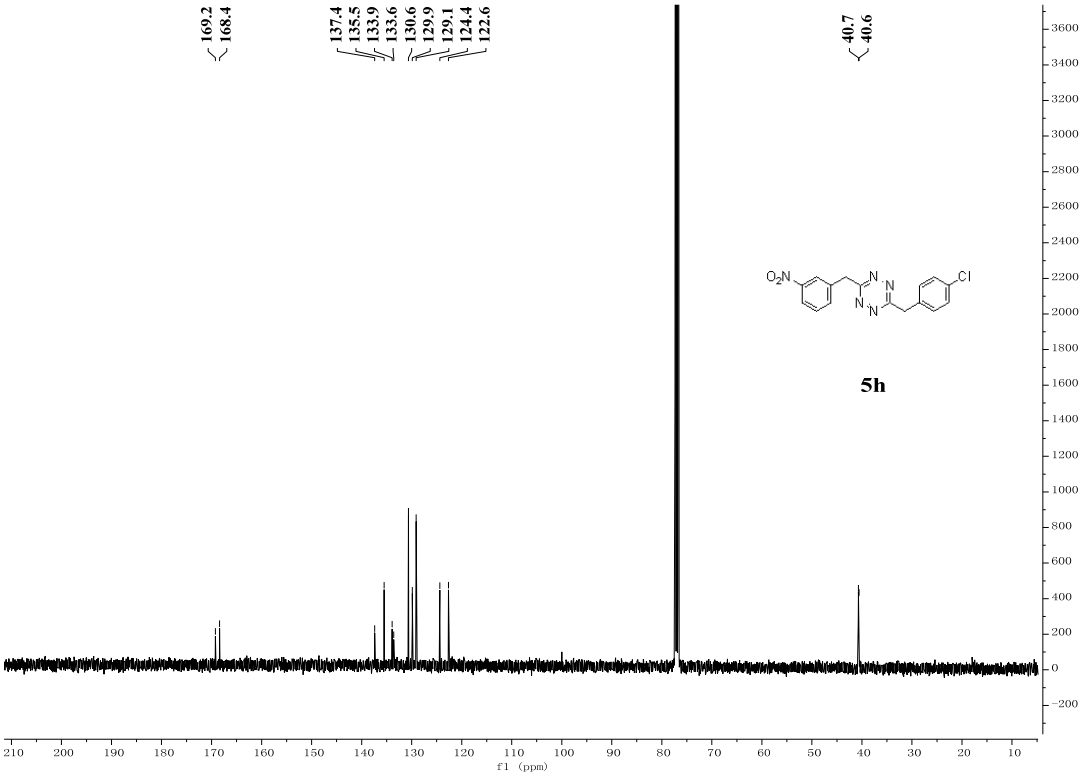
^{13}C NMR ($CDCl_3$, 100 MHz, 25 ºC) of **5g**



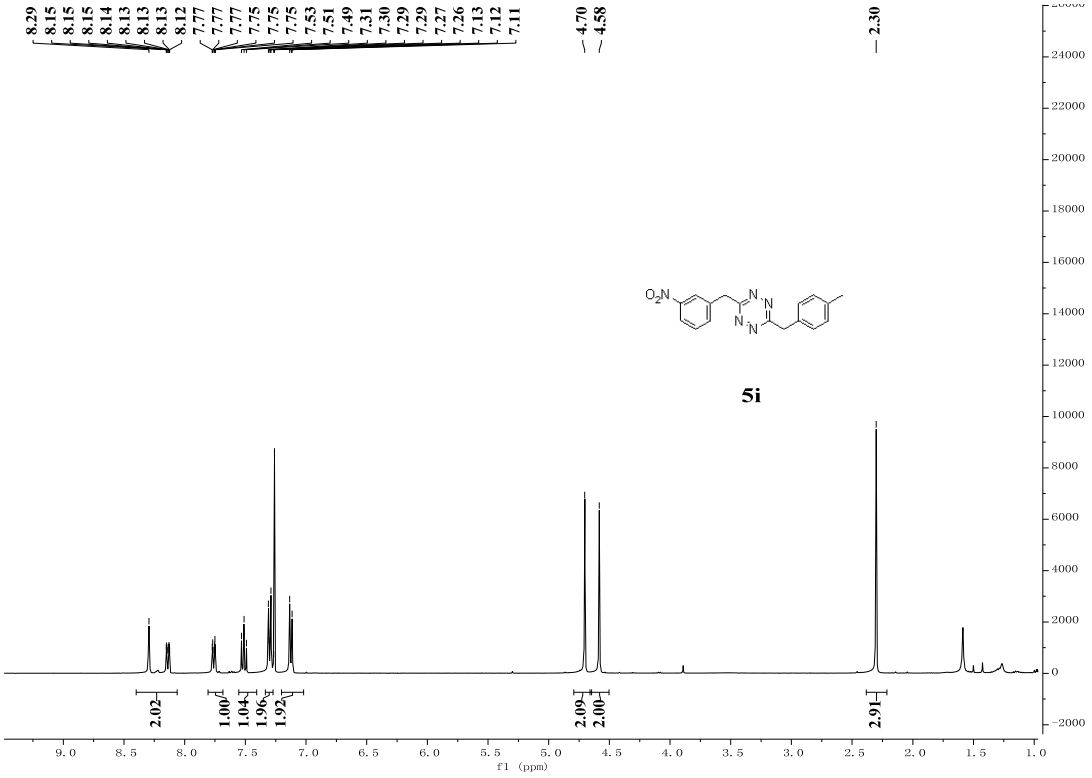
^{1}H NMR ($CDCl_3$, 400 MHz, 25 ºC) of **5h**



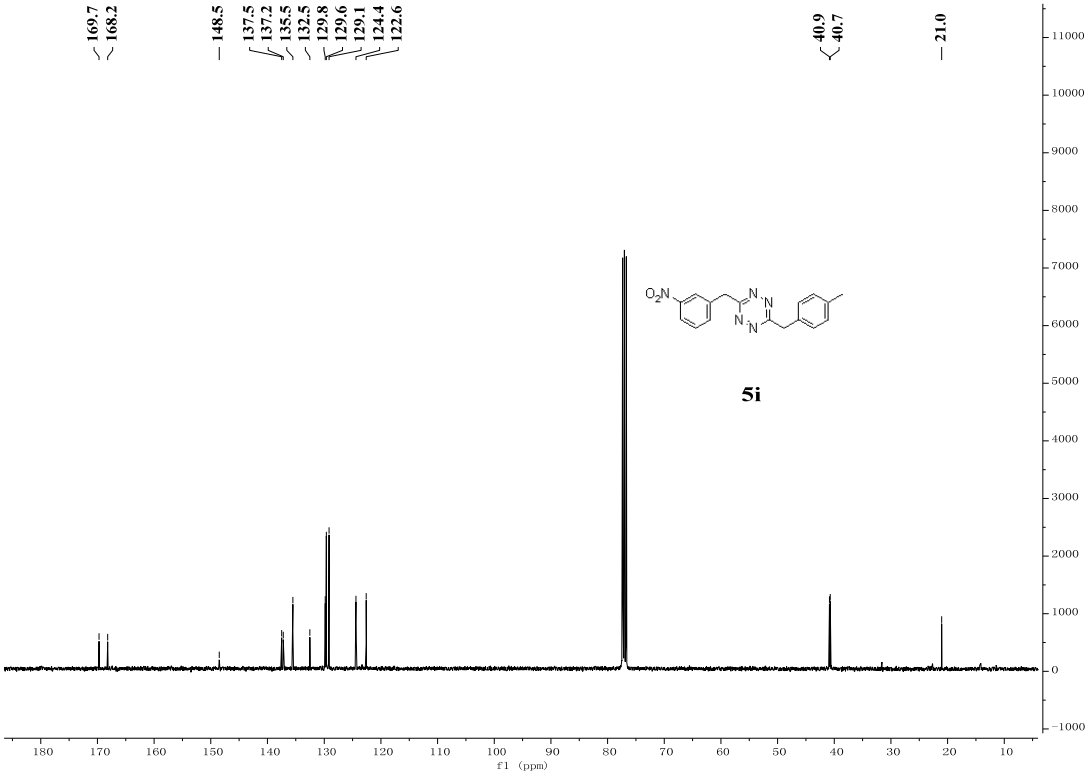
^{13}C NMR ($CDCl_3$, 100 MHz, 25 ºC) of **5h**



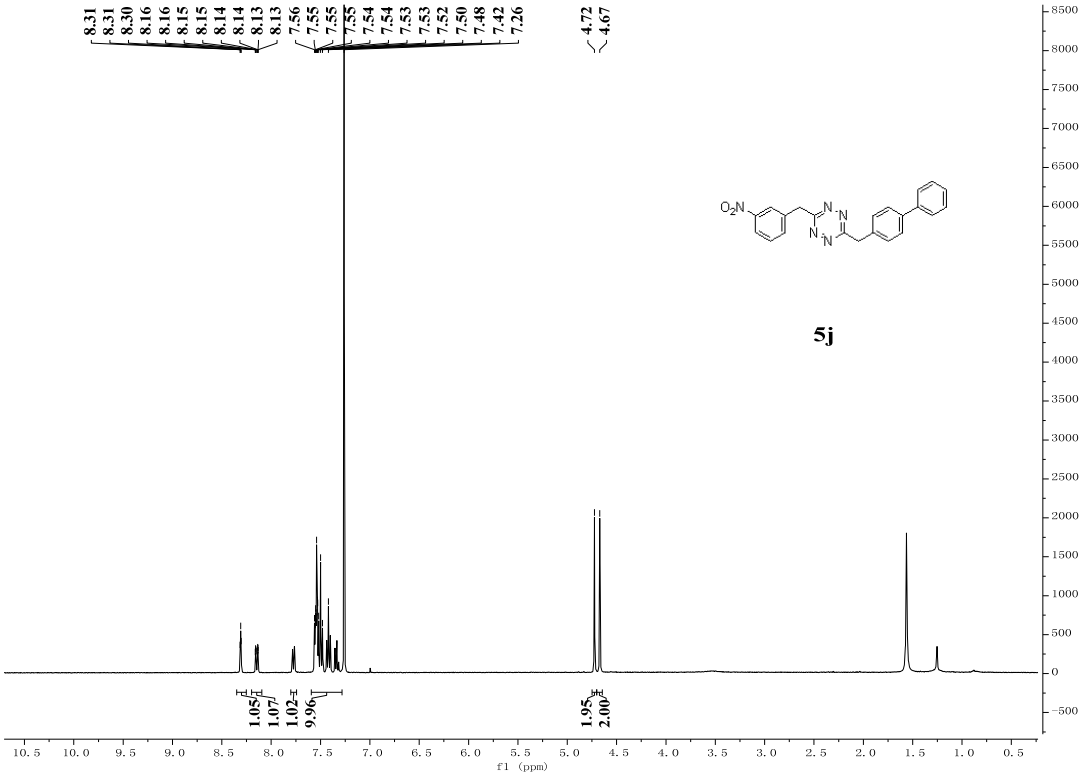
^{1}H NMR ($CDCl_3$, 400 MHz, 25 ºC) of **5i**



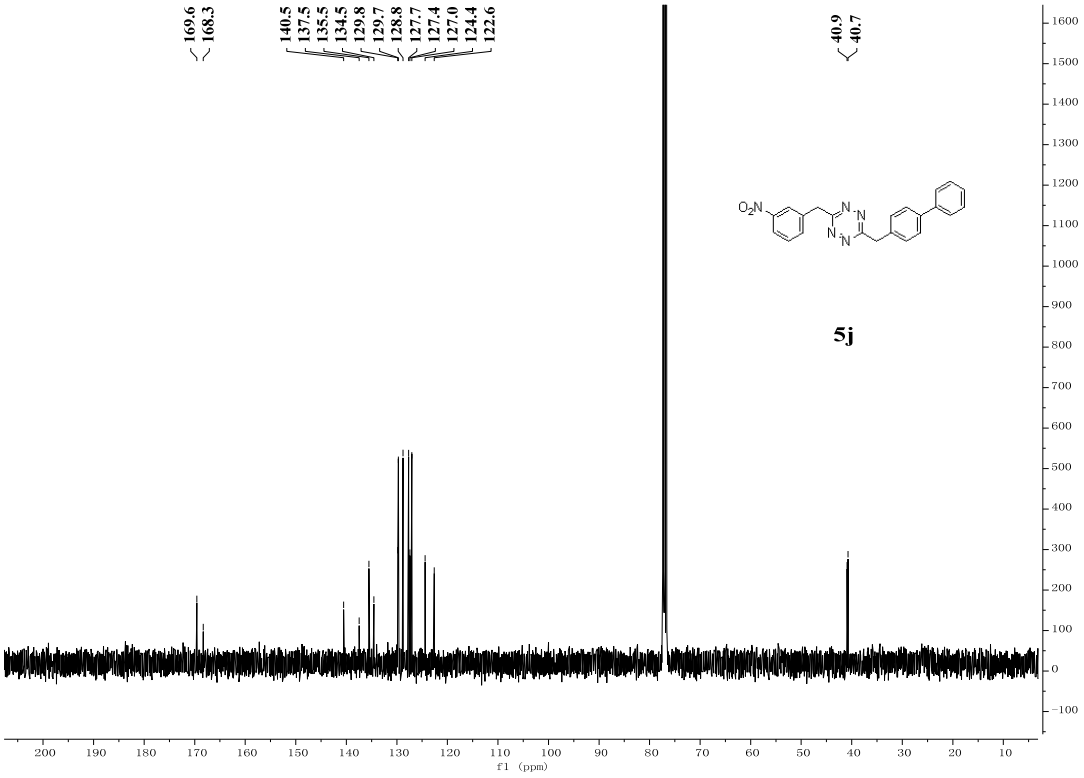
^{13}C NMR ($CDCl_3$, 100 MHz, 25 ºC) of **5i**



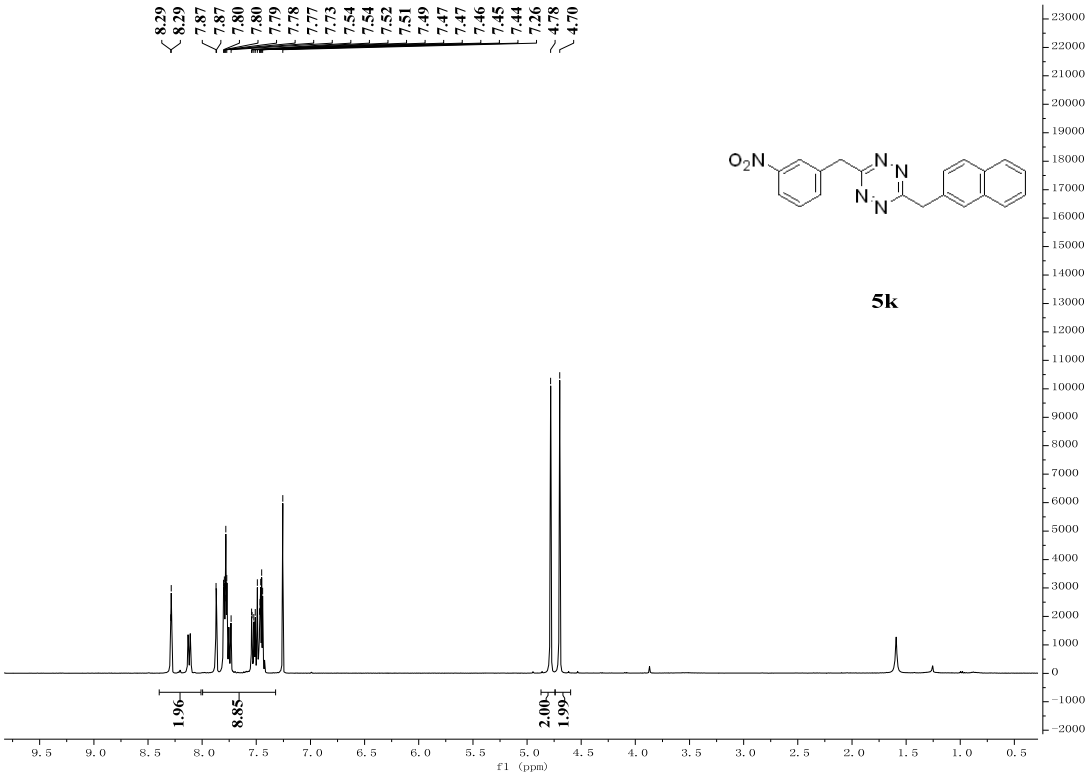
^{1}H NMR ($CDCl_3$, 400 MHz, 25 ºC) of **5j**



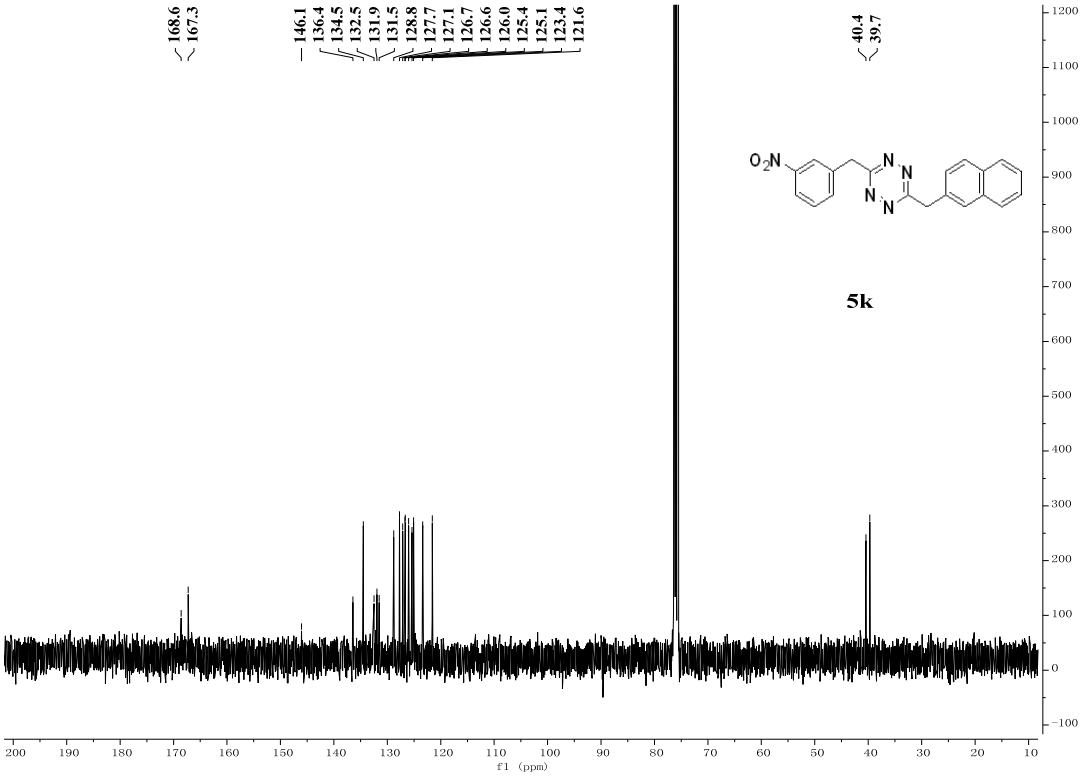
^{13}C NMR ($CDCl_3$, 100 MHz, 25 ºC) of **5j**



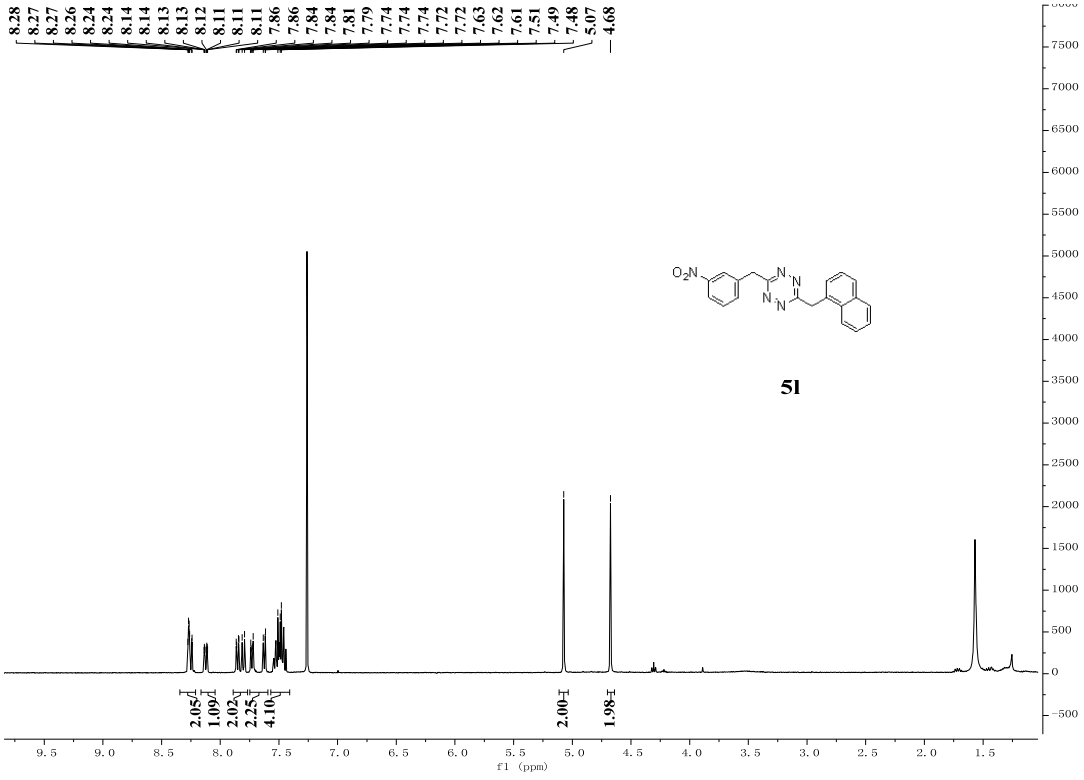
^{1}H NMR ($CDCl_3$, 400 MHz, 25 ºC) of **5k**



^{13}C NMR ($CDCl_3$, 100 MHz, 25 ºC) of **5k**

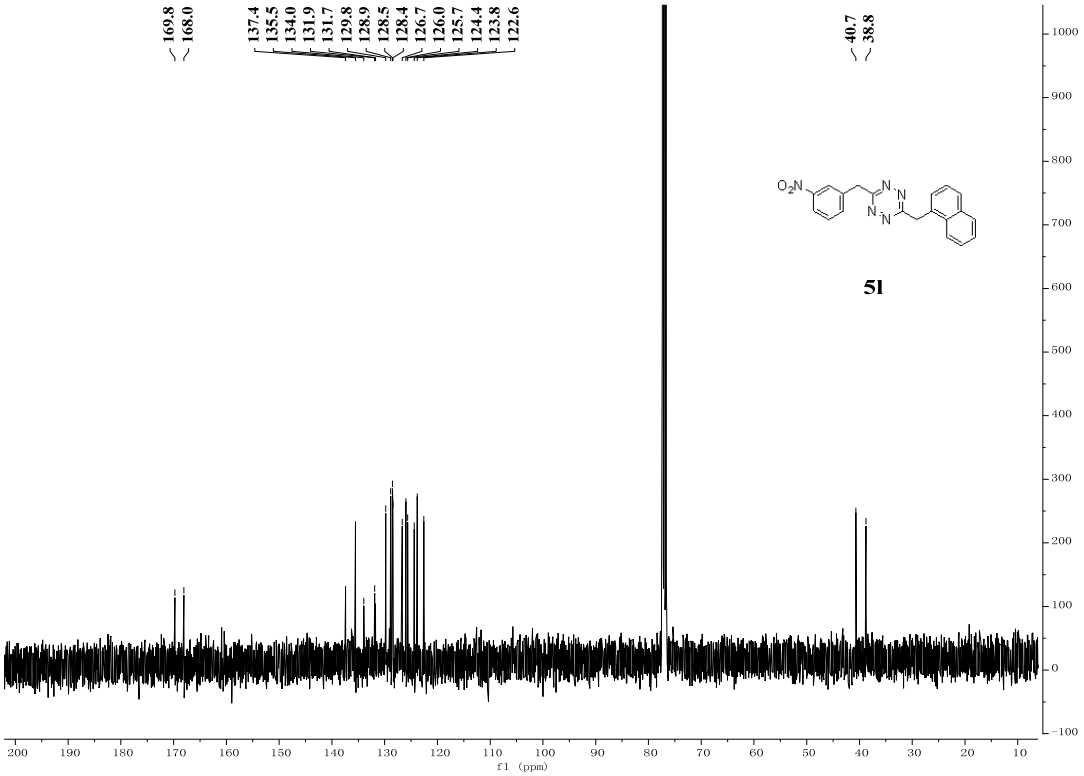


^{1}H NMR ($CDCl_3$, 400 MHz, 25 ºC) of **5l**



5l

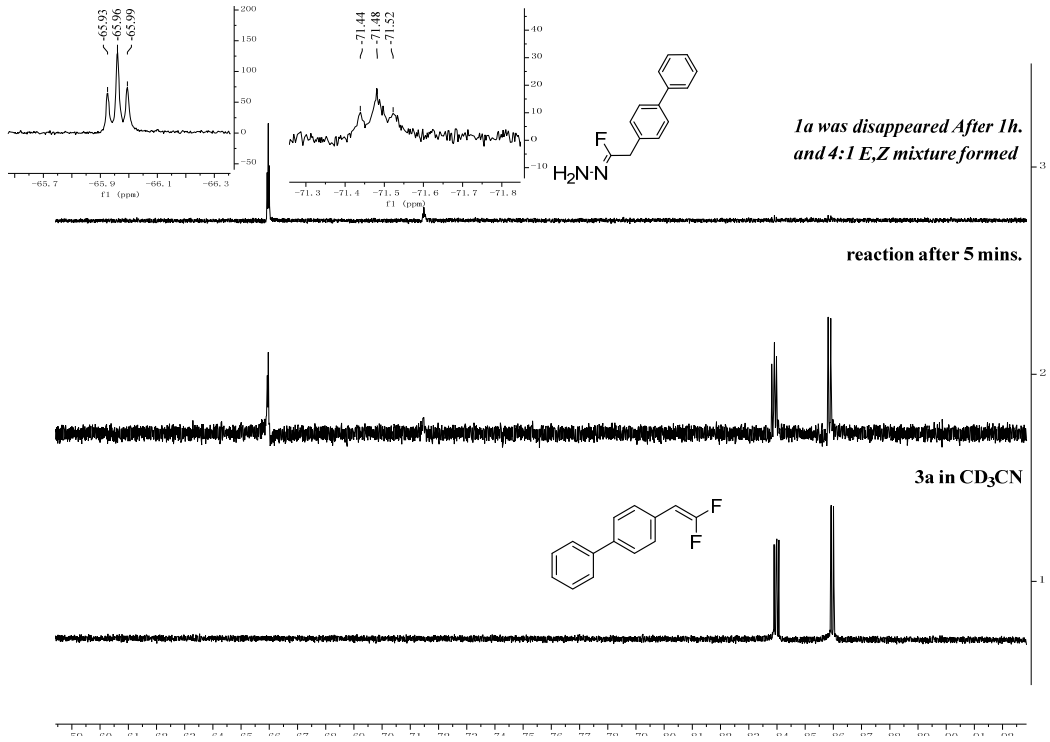
^{13}C NMR ($CDCl_3$, 100 MHz, 25 ºC) of **5l**



5l

7. NMR comparison of 1a and fluorohydrazone 2a in CD_3CN

^{19} FNMR (**CD_3CN**, 376MHz, 25 ºC)



^{1}H NMR (**CD_3CN**, 400MHz, 25 ºC)