PYRAZOLES: 'ONE-POT' SYNTHESES FROM ARENES AND CARBOXYLIC ACIDS

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Supporting Information

Contents:

1. General information.

^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance 400 spectrometer at room temperature with solvent signals as internal reference. To assign the chemical shifts in the ^{1}H and ^{13}C NMR spectra the following symbols were used: H^{R} and C^{R} for hydrogen and carbon atoms of the aryl (R = Ar), adamantyl (R = Ad) and pyrazole (R = Pyr) fragments. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; m, multiplet. Coupling constants (*J*) are given in hertz. Melting points (mp) are uncorrected. X-Ray analysis was performed on a Stoe STADIVARI Pilatus-100 K diffractometer, purchased through MSU Development Program, and corrected for absorption using the SADABS program;[1] calculations were carried out using the SHELXTL program.[2] Analytical thin layer chromatography (TLC) was carried out with silica gel plates (silica gel 60, F254, supported on aluminium); the revelation was carried out by using a UV lamp (365 nm). Column chromatography was performed on silica gel 60 (230–400 mesh, Merck). Chemicals were commercial grade and used without further purification. Solvents were purified and dried according to standard procedures. TFAA was freshly distilled from P_2O_5. Diketones **4h-i** were prepared as reported.[3] Diketone **4j** was obtained similar to literature procedure.[3]

2. Synthetic procedures and characterization data.

Synthesis of arylmethyl ketones 3. Tipical procedure.

A solution of arene **1** (1 mmol), acetic acid **2a** (60 mg, 1 mmol) and TFAA (0.85 mL, 6 mmol) in dichlorometane (1 mL) was stirred for 15 minutes at room temperature. The required quantity of triflic acid (usually 44 μL, 0.5 mmol) was then added, and the resulting solution was stirred at room temperature for 0.25 – 4 hours (TLC monitoring). The reaction mixture was evaporated under reduced pressure, and after quenching with water, the residue was redissolved in dichloromethane (10 mL), washed with 5% $NaHCO_3$ (2x3 mL), water (2x3 mL), and dried over $MgSO_4$. The solvent was removed in vacuum, and the crude reaction mixture was purified by silica gel chromatography (*n*-hexane/CH_2Cl_2). In the case of benzene and *o*-xylene the structure and yield of the obtained compounds were determined on the basis of ^{1}H NMR spectra of selected mixtures of the crude products. Ketones **3c-g** were individually isolated by chromatographic separation.

2,4-Dimethylacetophenone (**3c**): Obtained from *m*-xylene **1c** (106 mg, 1 mmol), acetic acid **2a** (60 mg, 1 mmol), TFAA (0.85 mL, 6 mmol) and TfOH (44 μL, 0.5 mmol). Yield 88% (130 mg), oil (lit.[4], oil), R_f = 0.58 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 7.64 (d, 1H, *J* = 8.1 Hz, H^{Ar}), 7.10-7.02 (m, 2H, H^{Ar}), 2.56 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 2.36 (s, 3H, CH_3).

4-Acetylanisole (**3d**): Obtained from anisole **1d** (108 mg, 1 mmol), acetic acid **2a** (60 mg, 1 mmol), TFAA (0.85 mL, 6 mmol) and TfOH (44 μL, 0.5 mmol). Yield 100% (150 mg), mp 39 °C (lit.[5], mp 38.5-39 °C), R_f = 0.59

(CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ =7.94 (d, 2H, *J* = 8.9 Hz, H^{Ar}), 6.94 (d, 2H, *J* = 8.9 Hz, H^{Ar}), 3.87 (s, 3H, OCH_3), 2.56 (s, 3H, CH_3).

2-Acetyl-dibenzofurane (**3e**): Obtained from dibenzofurane **1e** (168 mg, 1 mmol), acetic acid **2a** (60 mg, 1 mmol), TFAA (0.85 mL, 6 mmol) and TfOH (44 μL, 0.5 mmol). Yield 83% (175 mg), yellow solid, mp 83-85 °C (lit.[6], 84-85.5 °C), R_f = 0.58 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 8.61-8.60 (m, 1H, H^{Ar}), 8.13-8.11 (m, 1H, H^{Ar}), 8.03-8.01 (m, 1H, H^{Ar}), 7.62-7.60 (m, 2H, H^{Ar}), 7.53-7.51 (m, 1H, H^{Ar}), 7.43-7.39 (m, 1H, H^{Ar}), 2.73 (s, 3H, CH_3).

2-Acetylthiophene (**3f**): Obtained from thiophene **1f** (84 mg, 1 mmol), acetic acid **2a** (60 mg, 1 mmol), TFAA (0.85 mL, 6 mmol) and TfOH (44 μL, 0.5 mmol). Yield 100% (126 mg), oil (lit.[7], oil), R_f = 0.57 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 7.72-7.69 (m, 1H, H^{Ar}), 7.65-7.63 (m, 1H, H^{Ar}), 7.14-7.12 (m, 1H, H^{Ar}), 2.57 (s, 3H, CH_3).

2-Acetyl-5-bromothiophene (**3g**): Obtained from 2-bromothiophene **1g** (162 mg, 1 mmol), acetic acid **2a** (60 mg, 1 mmol), TFAA (0.85 mL, 6 mmol) and TfOH (44 μL, 0.5 mmol). Yield 100% (205 mg), red solid, mp 93-95 °C (lit.[8], 95-96 °C), R_f = 0.64 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 7.44 (d, 1H, *J* = 3.9 Hz, H^{Ar}), 7.11 (d, 1H, *J* = 3.9 Hz, H^{Ar}), 2.52 (s, 3H, CH_3).

4-(1-Adamantyl)-1-(2,4-dichlorophenyl)butane-1,3-dione (4j): Obtained from 1-(2,4-dichlorophenyl)ethanone (189 mg, 1 mmol), adamantylacetic acid **2c** (194 mg, 1 mmol), TFAA (0.85 mL, 6 mmol) and TfOH (88 μL, 1 mmol) at room temperature, according to the literature.[3] Yield 69% (254 mg), yellow solid, mp 81-82 °C, R_f = 0.85 (CH_2Cl_2). $C_{20}H_{22}Cl_2O_2$ (365.29): calcd. C 65.76, H 6.07; found C 66.02, H 6.71. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58-7.56 (m, 1H, H^{Ar}), 7.46 (bs, 1H, H^{Ar}), 7.34-7.1 (m, 1H, H^{Ar}), 5.97 (s, 1H, C<u>H</u>=C(OH)), 2.14 (s, 2H, CH_2Ad), 1.99 (bs, 3H, CH^{Ad}), 1.73-1.65 (m, 12H, CH_2^{Ad}). ^{13}C NMR (100 MHz, $CDCl_3$):δ= 192.1 (CO), 184.5 (CH=<u>C</u>(OH)), 136.6 (C^{Ar}), 134.2 (C^{Ar}), 132.2 (C^{Ar}), 130.6 (CH^{Ar}), 130.1 (CH^{Ar}), 126.9 (CH^{Ar}), 103.0 (<u>C</u>H=C(OH)), 52.6 (CH_2^{Ad}), 42.4 (CH_2^{Ad}), 36.3 (CH_2^{Ad}), 34.0 (C^{Ad}), 28.3 (CH^{Ad}).

'One-pot' synthesis of β-diketones 4. Typical procedure: A solution of arene **1** (1 mmol), acetic acid **2a** (60 mg, 1 mmol) and TFAA (0.85 mL, 6 mmol) in dichlorometane (1 mL) was stirred for 15 minutes at room temperature. The required quantity of triflic acid (usually 44 μL, 0.5 mmol) was then added, and the resulting solution was stirred at room temperature for 0.5 – 2 hours (TLC monitoring). Subsequently without isolation of thereaction product, 1 mmol of *tert*-butylacetic acid (**2b**) or 1-adamantylacetic acid (**2c**) was added, and kept for 2-6 hours (TLC monitoring). Reaction mixture was evaporated under reduced pressure, and after quenching with water, the residue was redissolved in dichloromethane (10 mL), washed with 5% $NaHCO_3$ (2x3 mL), water (2x3 mL), and dried over $MgSO_4$. The solvent was removed in vacuum, and the crude reaction mixture was purified by silica gel chromatography (*n*-hexane/CH_2Cl_2). The structure and yield of the obtained compounds were determined on the basis of ^{1}H NMR spectra of selected mixtures of the crude products. Diketones **4f** and **4g** were individually isolated by chromatographic separation.

1-(Dibenzofuran-2-yl)-5,5-dimethylhexane-1,3-dione (**4f**): Obtained from dibenzofuran **1e** (168 mg, 1 mmol), acetic acid **2a** (60 mg, 1 mmol), dichlorometane (1 mL), TFAA (0.85 mL, 6 mmol) and TfOH (44 μL, 0.5 mmol) for 2 hours and the subsequent addition of **2b** (116 mg, 1.0 mmol) and TfOH (22 μL, 0.25 mmol) for 3 hours. Yield 62% (190 mg), orange oil, R_f = 0.85 (CH_2Cl_2). $C_{16}H_{22}O_2$ (308.37): calcd, % C 77.90, H 6.54; found, % C 78.18, H 6.76. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) keto-enol (2:98), enol tautomer: δ = 8.54-8.53 (m, 1H, H^{Ar}), 8.03-8.01 (m, 2H, $2H^{Ar}$), 7.61-7.58 (m, 2H, $2H^{Ar}$), 7.52-7.48 (m, 1H, H^{Ar}), 7.43-7.39 (m, 1H, H^{Ar}), 6.23 (s, 1H, C<u>H</u>=C(OH)), 2.33 (s, 2H, CH_2), 1.11 (s, 9H, CH_3). ^{13}CNMR (100 MHz, $CDCl_3$, 298 K): δ = 191.9 (CO), 185.7 (C=<u>C</u>(OH)), 158.2 (C^{Ar}), 156.4 (C^{Ar}), 130.3 (C^{Ar}), 127.5 (CH^{Ar}), 126.2 (CH^{Ar}), 124.3 (C^{Ar}), 123.3 (C^{Ar}), 122.9 (CH^{Ar}), 120.5 (CH^{Ar}), 119.9 (CH^{Ar}), 111.5 (CH^{Ar}), 111.3 (CH^{Ar}), 97.6 (<u>C</u>=C(OH)), 51.6 (CH_2), 31.6 (<u>C</u>$(CH_3)_3$), 29.6 (C(<u>C</u>H_3)).

4-(1-Adamantyl)-1-(thienyl-2)butane-1,3-dione (**4g**): Obtained from thiophene **1f** (84 mg, 1 mmol), acetic acid **2a** (60 mg, 1 mmol), dichlorometane (1 mL), TFAA (0.85 mL, 6 mmol) and TfOH (44 μL, 0.5 mmol) for 1 hour and the subsequent addition of 1-adamantylacetic acid **2c** (194 mg, 1.0 mmol) for 2 hours. Yield 60% (180 mg), brown powder, mp 110-115 °C, R_f = 0.66 (CH_2Cl_2). $C_{18}H_{22}O_2S$ (302.13): calcd, % C71.48, H7.33; found, % C71.12, H7.07. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 7.70-7.69 (m, 1H, H^{Ar}), 7.60-7.59 (m, 1H, H^{Ar}), 7.14-7.12 (m, 1H, H^{Ar}), 5.94 (s, 1H, C<u>H</u>=C(OH)), 2.09 (s, 2H, CH_2), 1.98 (bs, 3H, CH^{Ad}), 1.75-1.59 (m, 12H, CH_2^{Ad}). ^{13}C NMR (100 MHz, $CDCl_3$, 298 K):δ= 186.9 (CO), 182.2 (C=<u>C</u>(OH)), 142.0 (C^{Ar}), 132.0 (CH^{Ar}), 129.7 (CH^{Ar}), 127.8 (CH^{Ar}), 97.8 (<u>C</u>=C(OH)), 51.5 (CH_2^{Ad}), 42.4 (CH_2Ad), 36.3 (CH_2^{Ad}), 33.7 (C^{Ad}), 28.3 (CH_2^{Ad}).

3. ^{1}H and ^{13}C NMR spectra.

4f

Fig. S-3-1 ^{1}H NMR spectrum of 1-(dibenzofuran-2-yl)-5,5-dimethylhexane-1,3-dione **4f.**

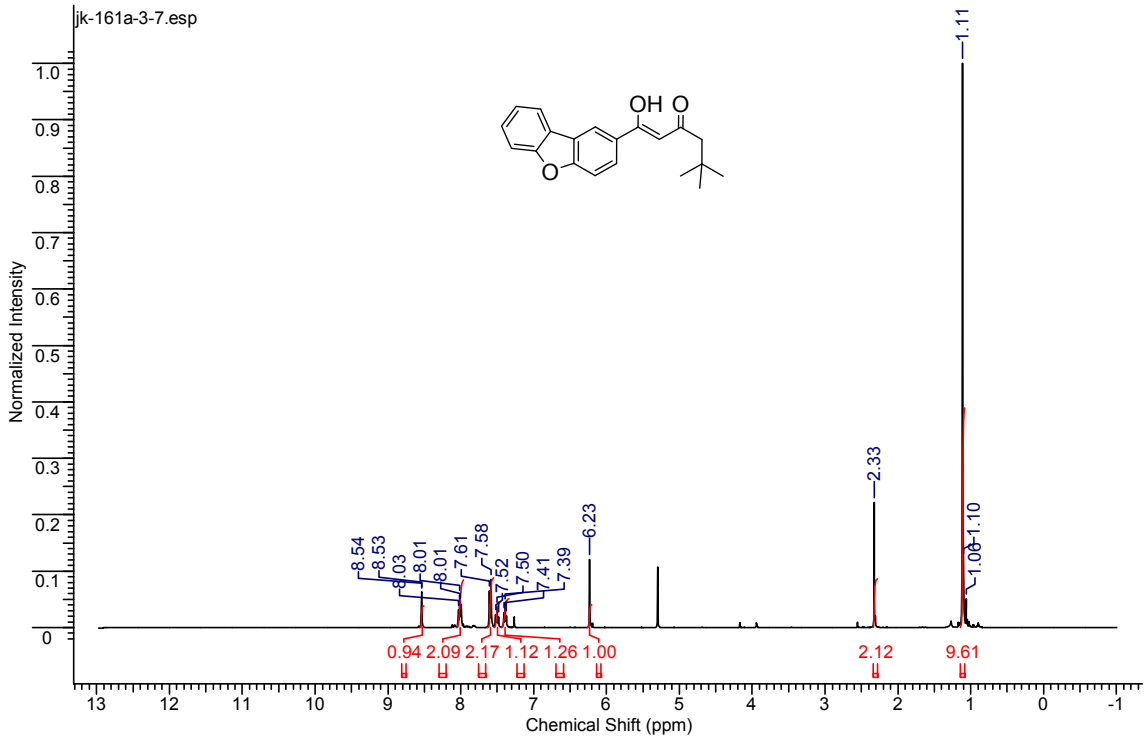
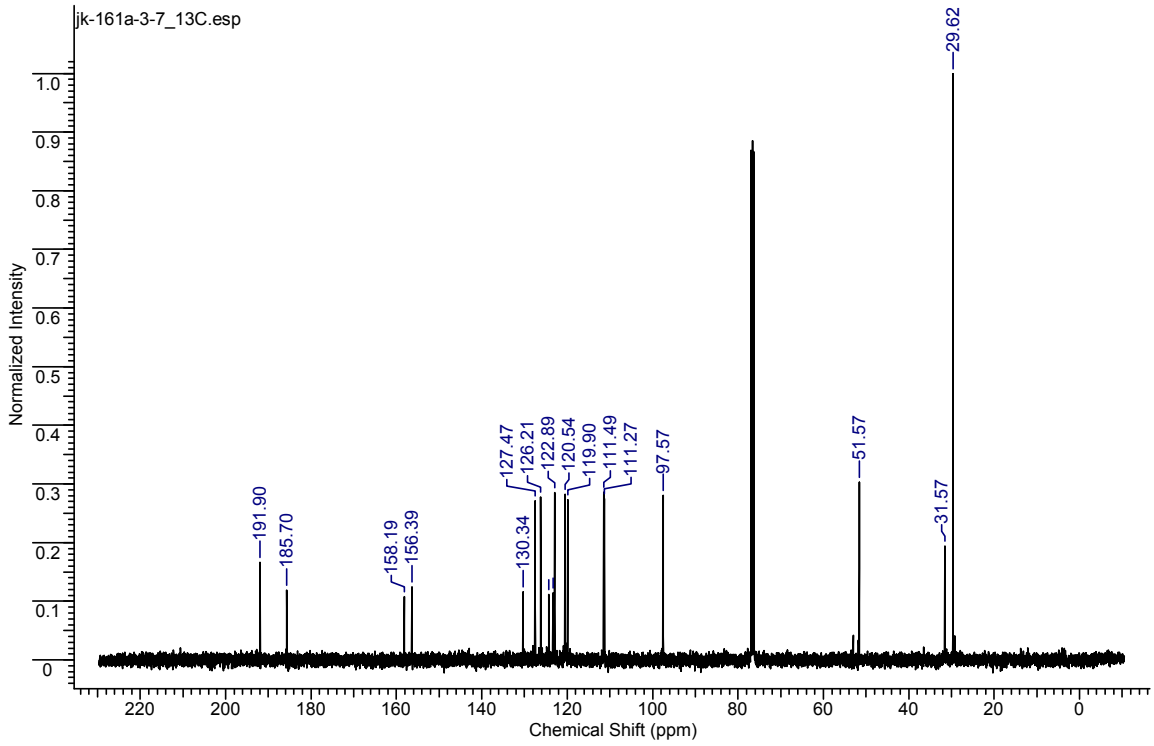


Fig. S-3-2 ^{13}C NMR spectrum of 1-(dibenzofuran-2-yl)-5,5-dimethylhexane-1,3-dione **4f.**



4g

Fig. S-3-3 ^{1}H NMR spectrum of 4-(1-adamantyl)-1-(thienyl-2)butane-1,3-dione **4g.**

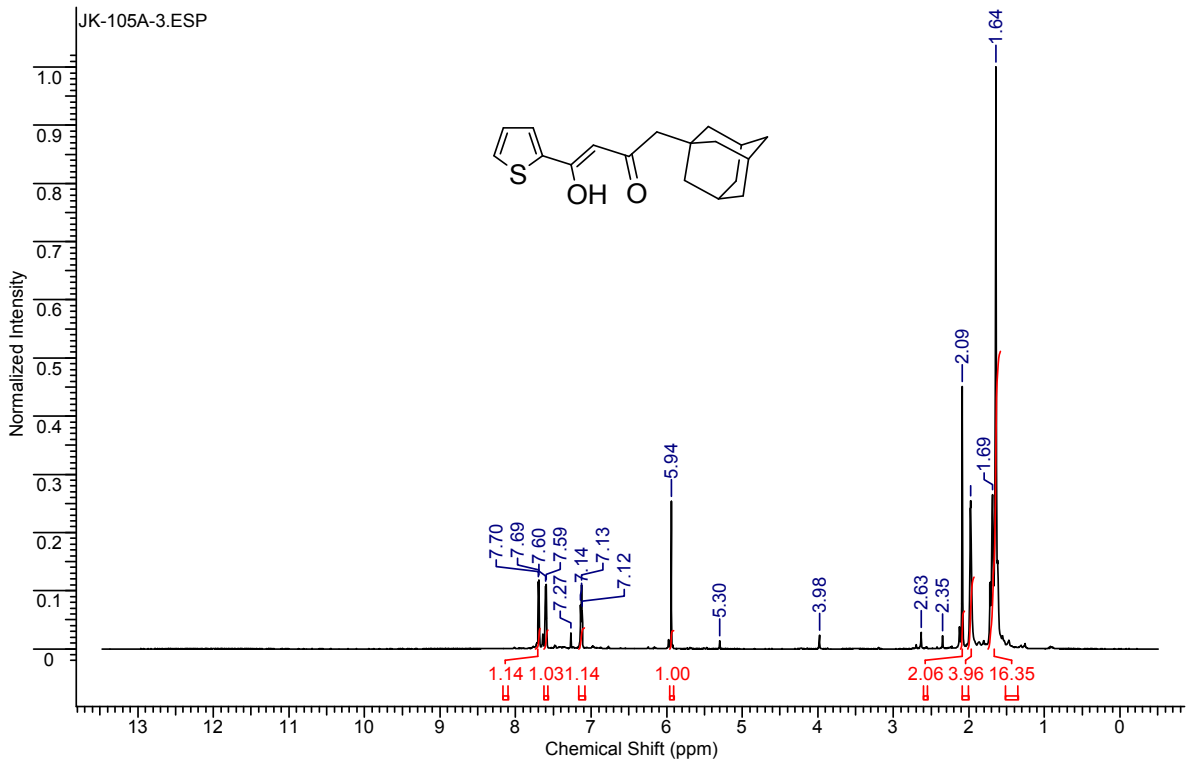
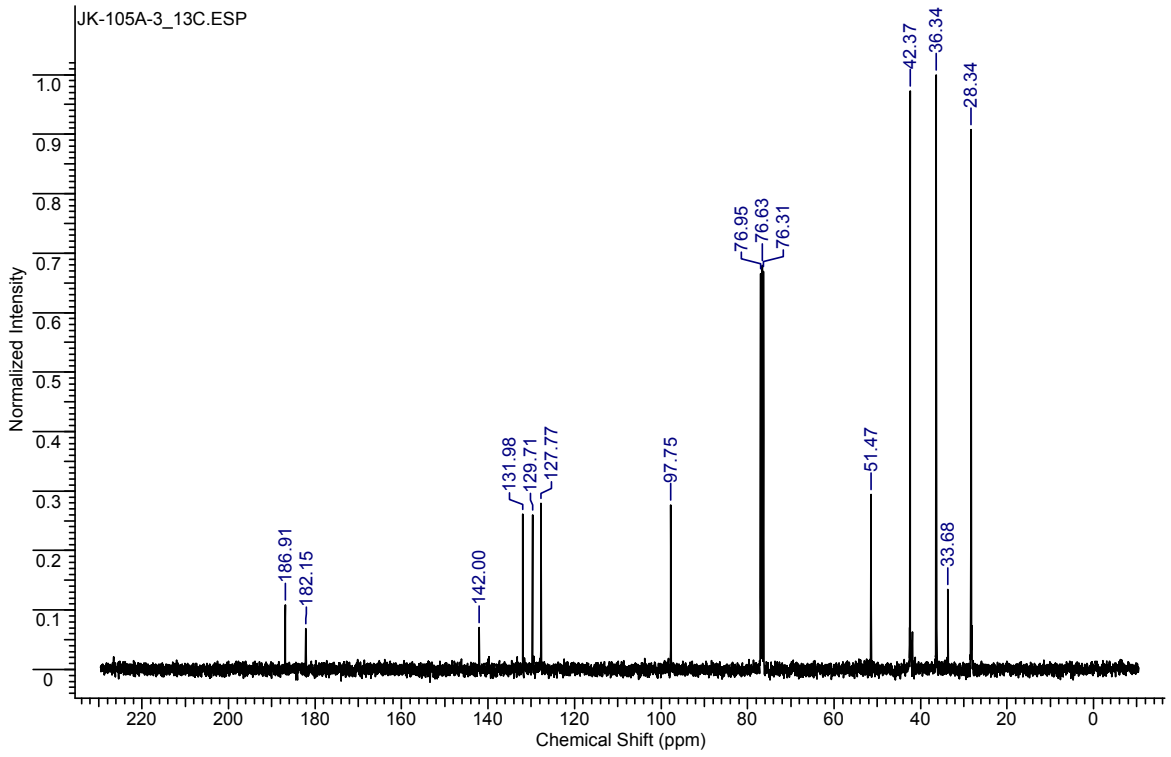


Fig. S-3-4 ^{13}C NMR spectrum of 4-(1-adamantyl)-1-(thienyl-2)butane-1,3-dione **4g.**



4j

Fig. S-3-5 ^{1}H NMR spectrum of 4-(1-adamantyl)-1-(2,4-dichlorophenyl)butane-1,3-dione **4j.**

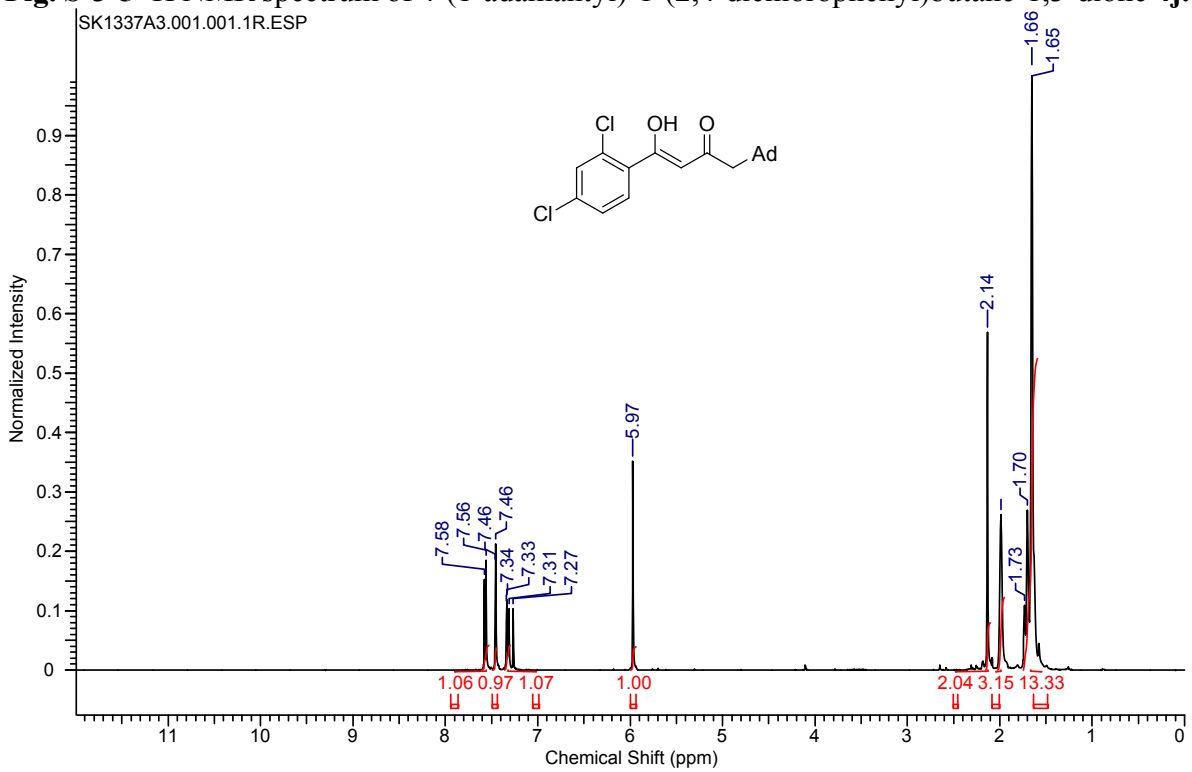
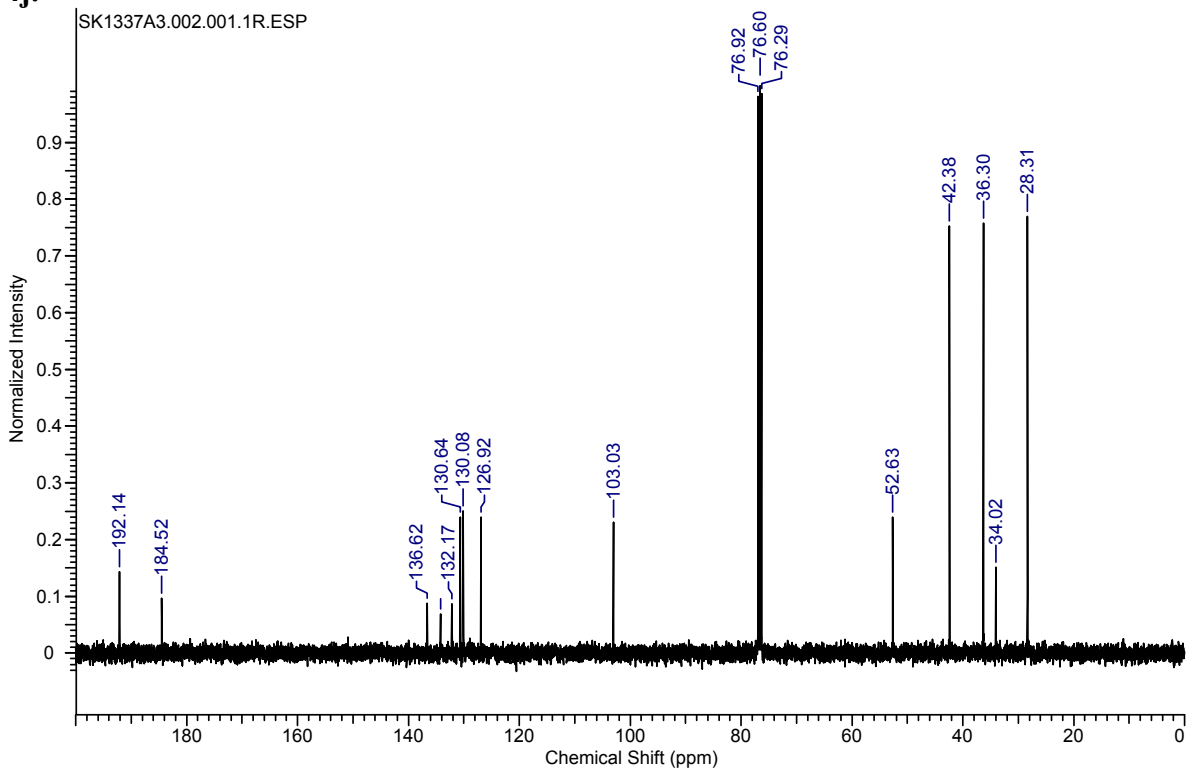


Fig. S-3-6 ^{13}C NMR spectrum of 4-(1-adamantyl)-1-(2,4-dichlorophenyl)butane-1,3-dione **4j.**



5a

Fig. S-3-7 ^{1}H NMR spectrum of 3-(3,4-dimethylphenyl)-5-neopentyl-1*H*-pyrazole **5a.**

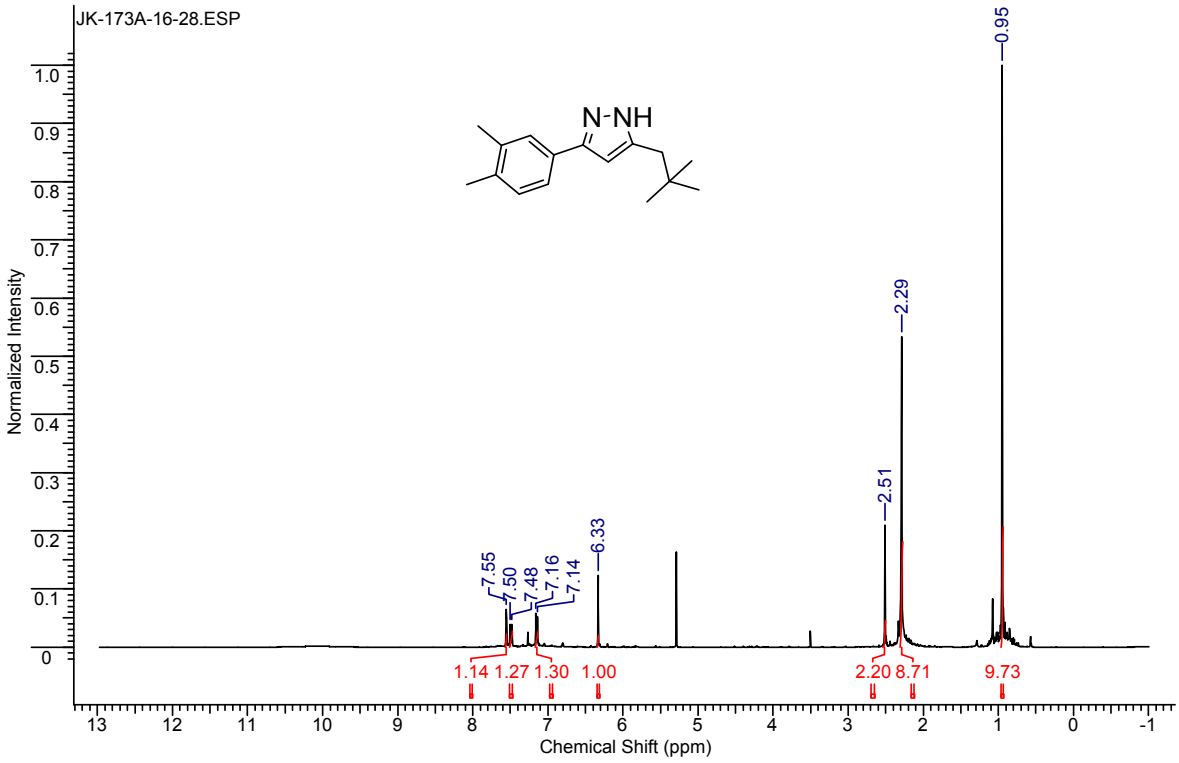
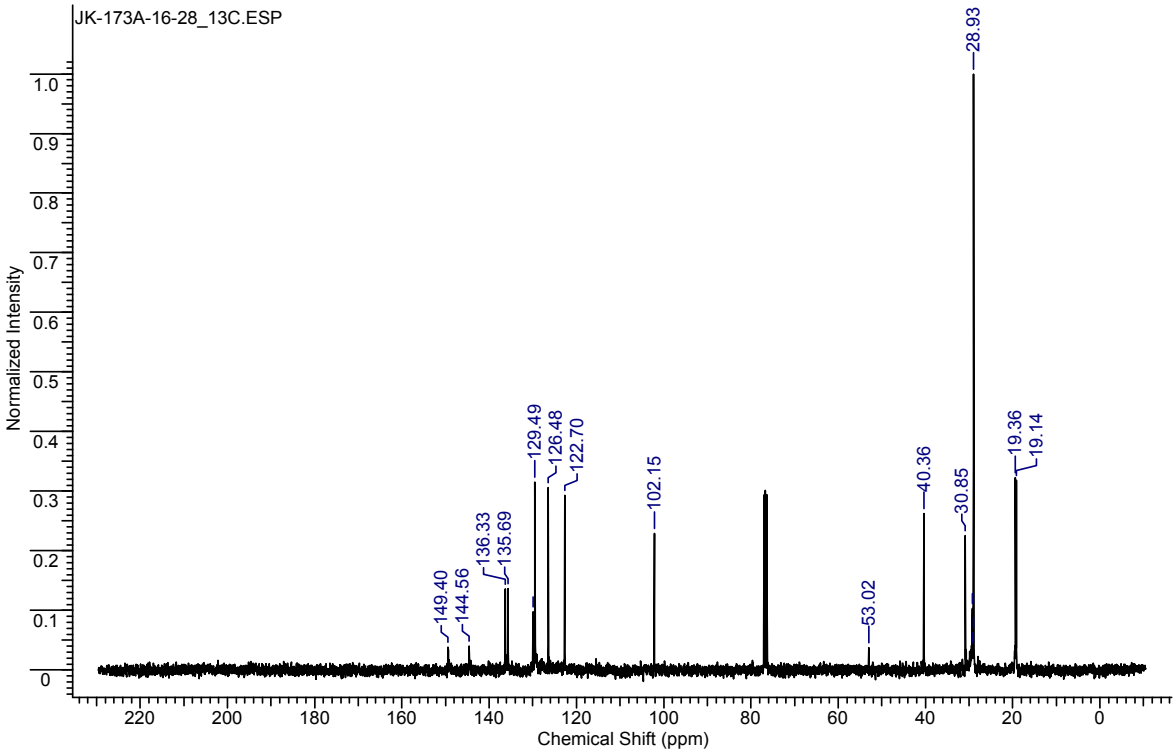


Fig. S-3-8 ^{13}C NMR spectrum of 3-(3,4-dimethylphenyl)-5-neopentyl-1*H*-pyrazole **5a.**



5b

Fig. S-3-9 ^{1}H NMR spectrum of 5-(1-adamantylmethyl)-3-phenyl-*1H*-pyrazole **5b.**

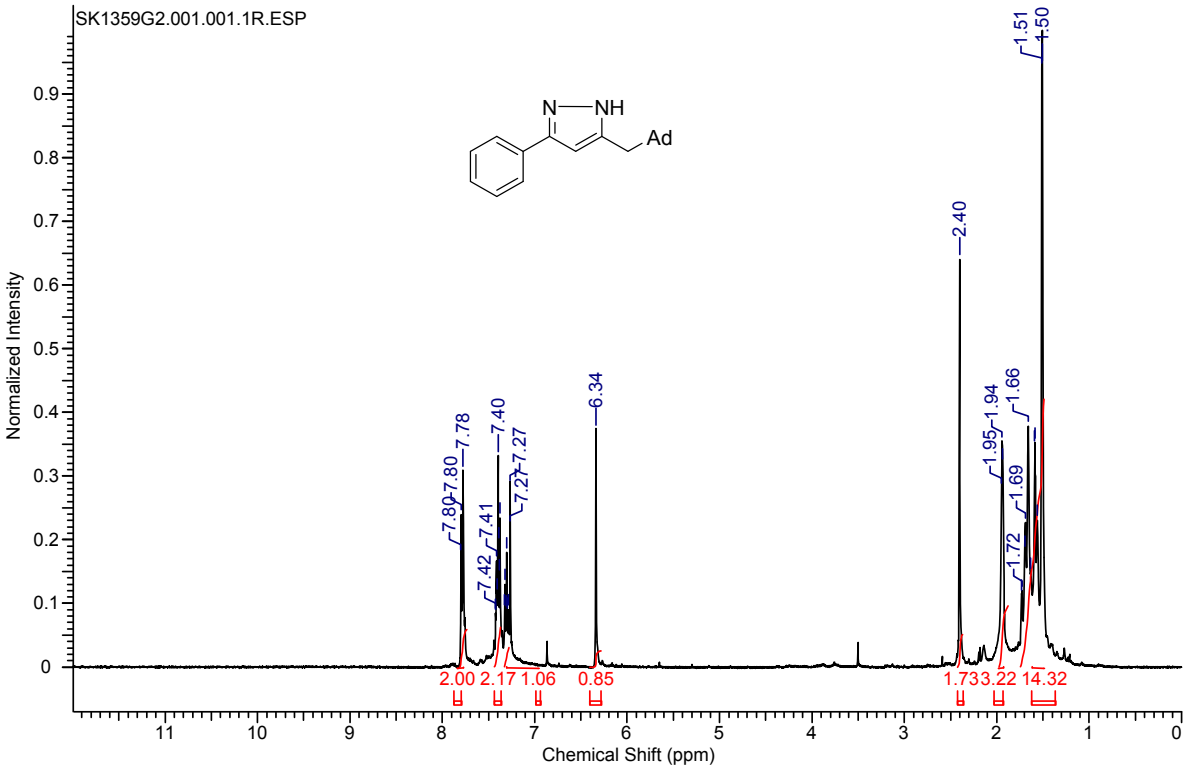
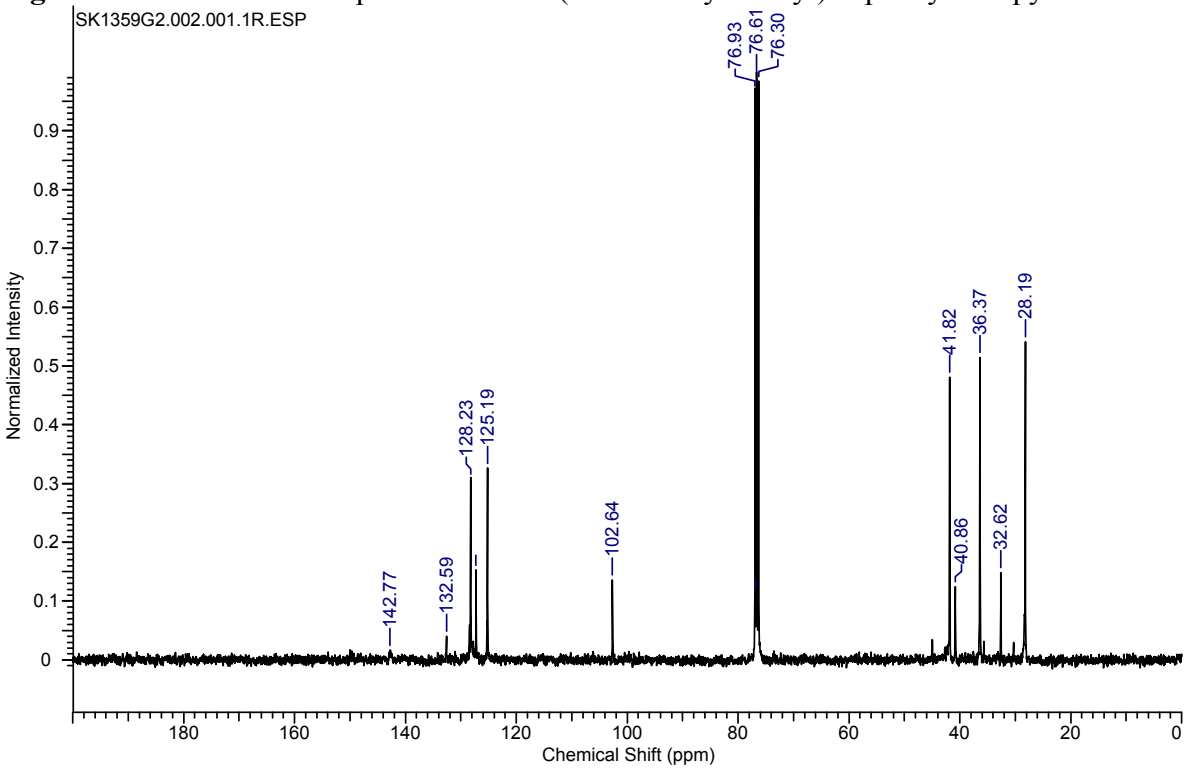


Fig. S-3-10 ^{13}C NMR spectrum of 5-(1-adamantylmethyl)-3-phenyl-*1H*-pyrazole **5b.**



5c

Fig. S-3-11 ^{1}H NMR spectrum of 3-(4-methoxyphenyl)-5-neopentyl-1*H*-pyrazole **5c.**

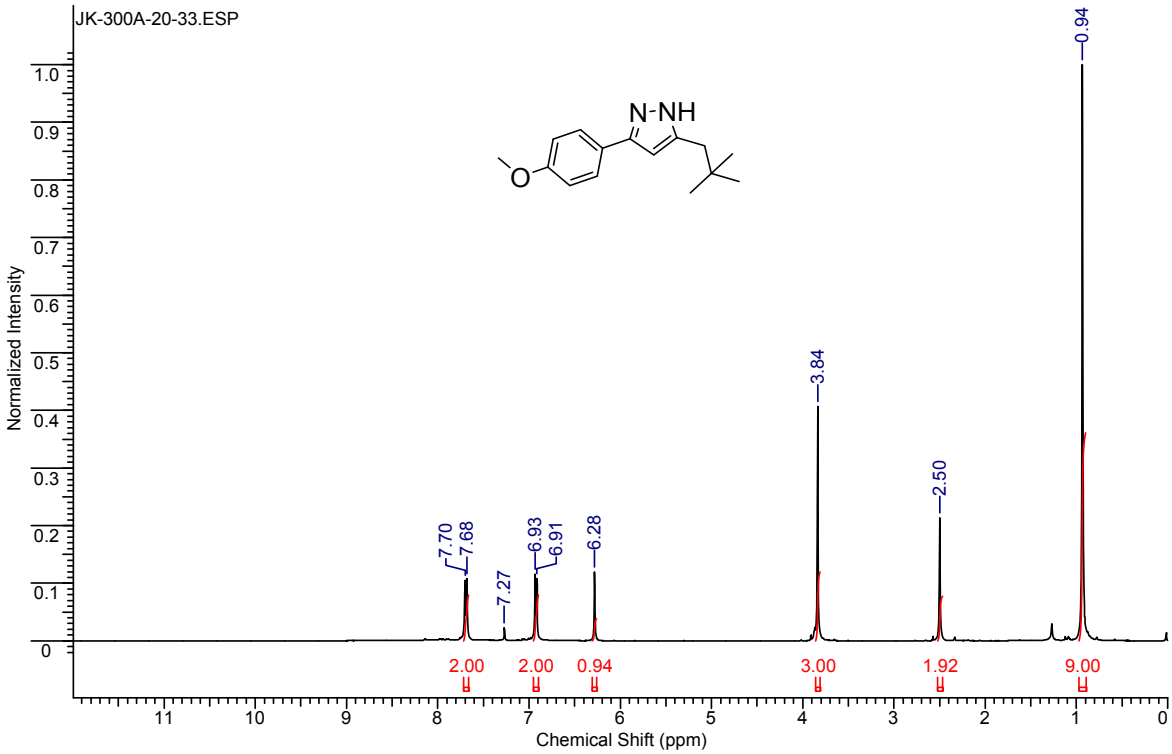
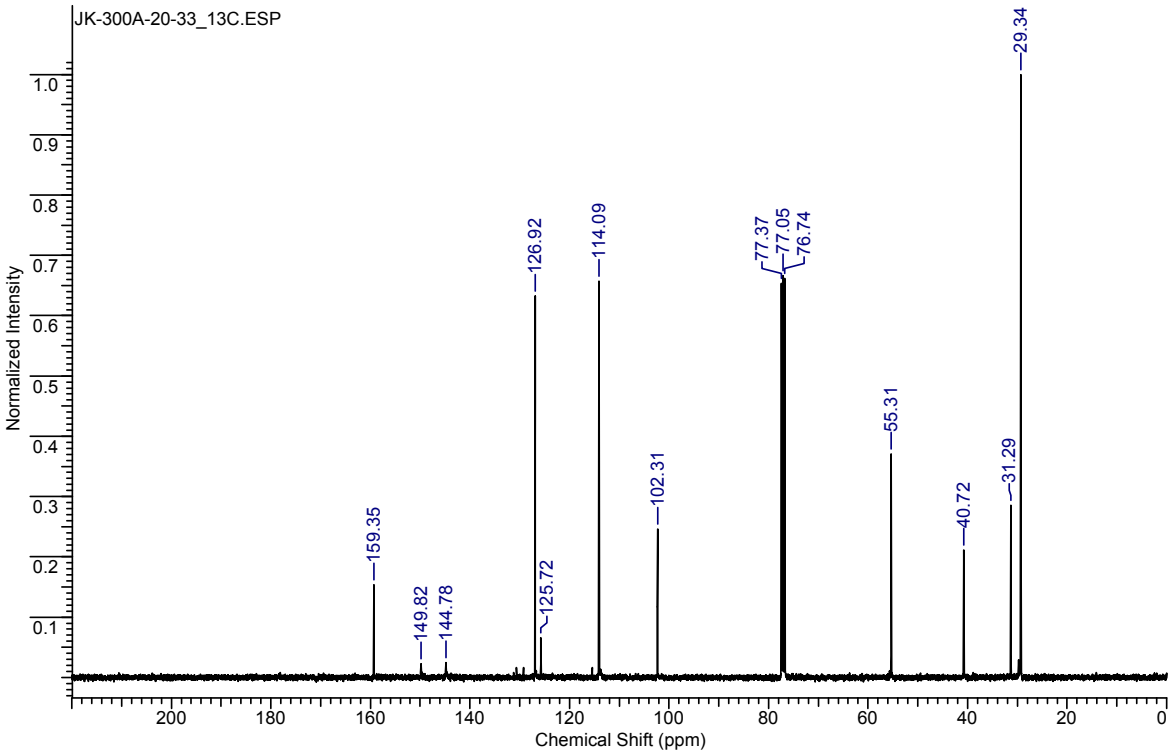


Fig. S-3-12 ^{13}C NMR spectrum of 3-(4-methoxyphenyl)-5-neopentyl-1*H*-pyrazole **5c.**



5d

Fig. S-3-13 ^{1}H NMR spectrum of 5-(1-adamantylmethyl)-3-(4-methoxyphenyl)-1*H*-pyrazole **5d**.

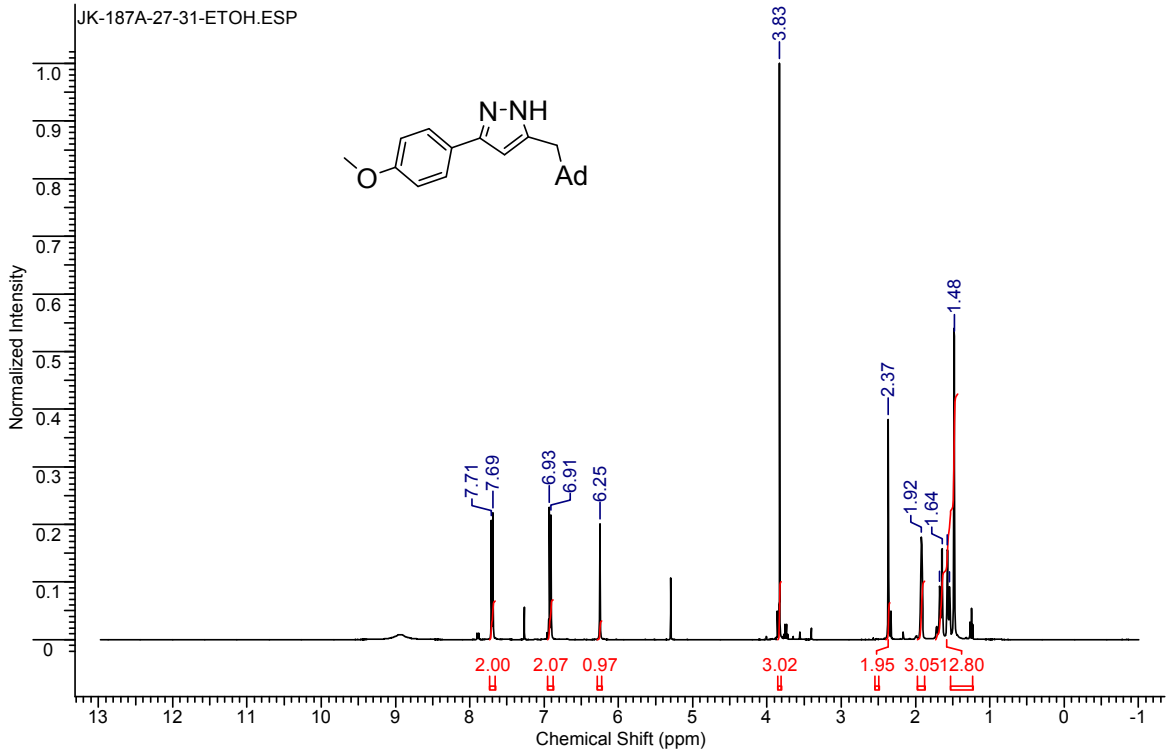
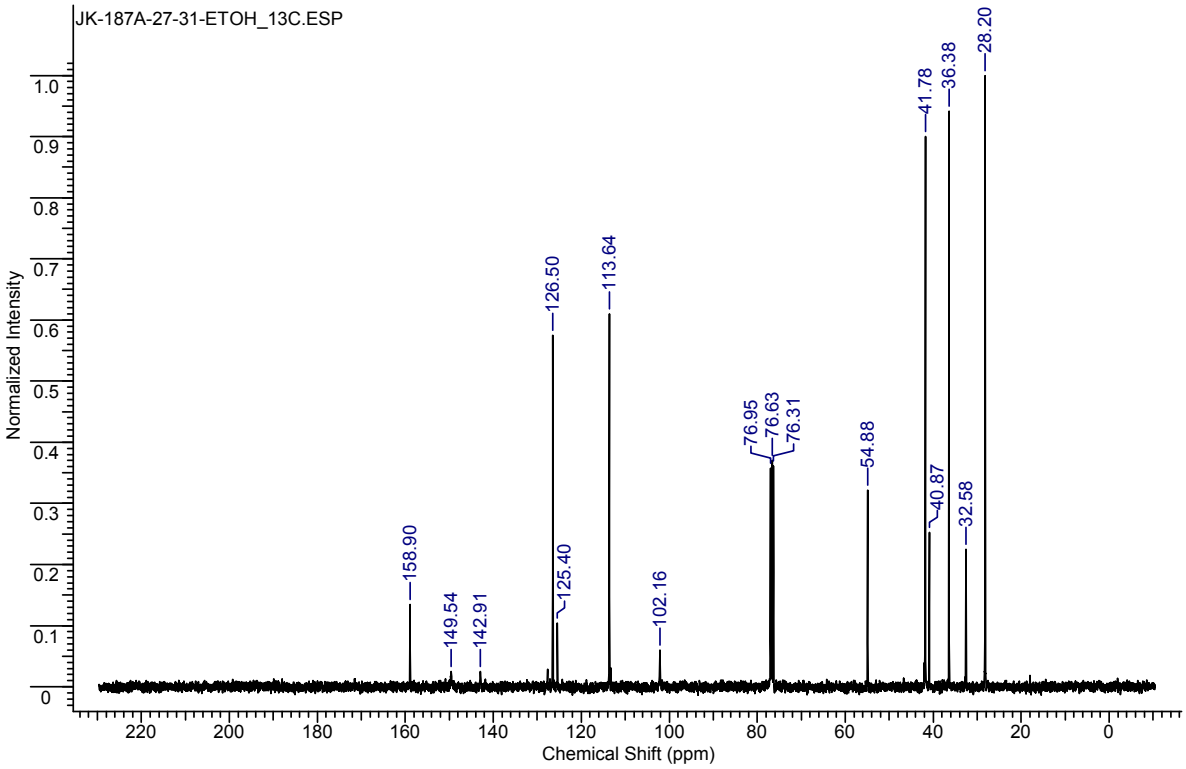


Fig. S-3-14 ^{13}C NMR spectrum of 5-(1-adamantylmethyl)-3-(4-methoxyphenyl)-1*H*-pyrazole **5d**.



5e

Fig. S-3-15 ^{1}H NMR spectrum of 5-neopentyl-3-(thienyl-2)-1*H*-pyrazole **5e.**

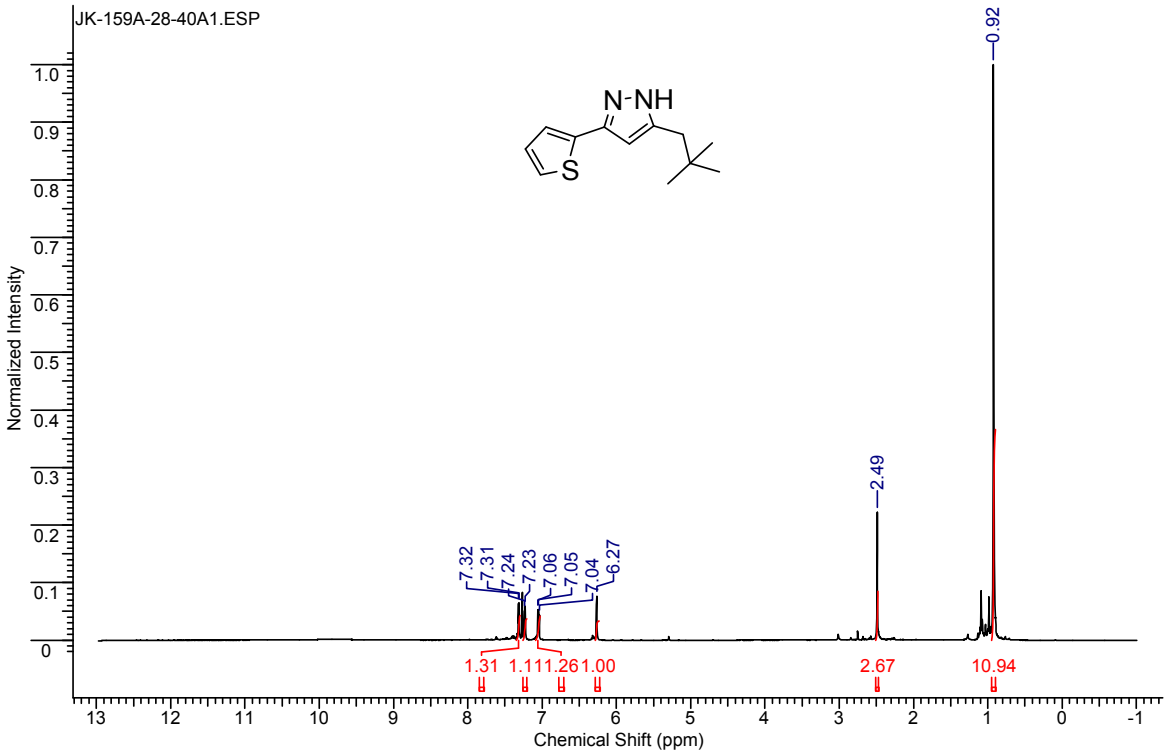
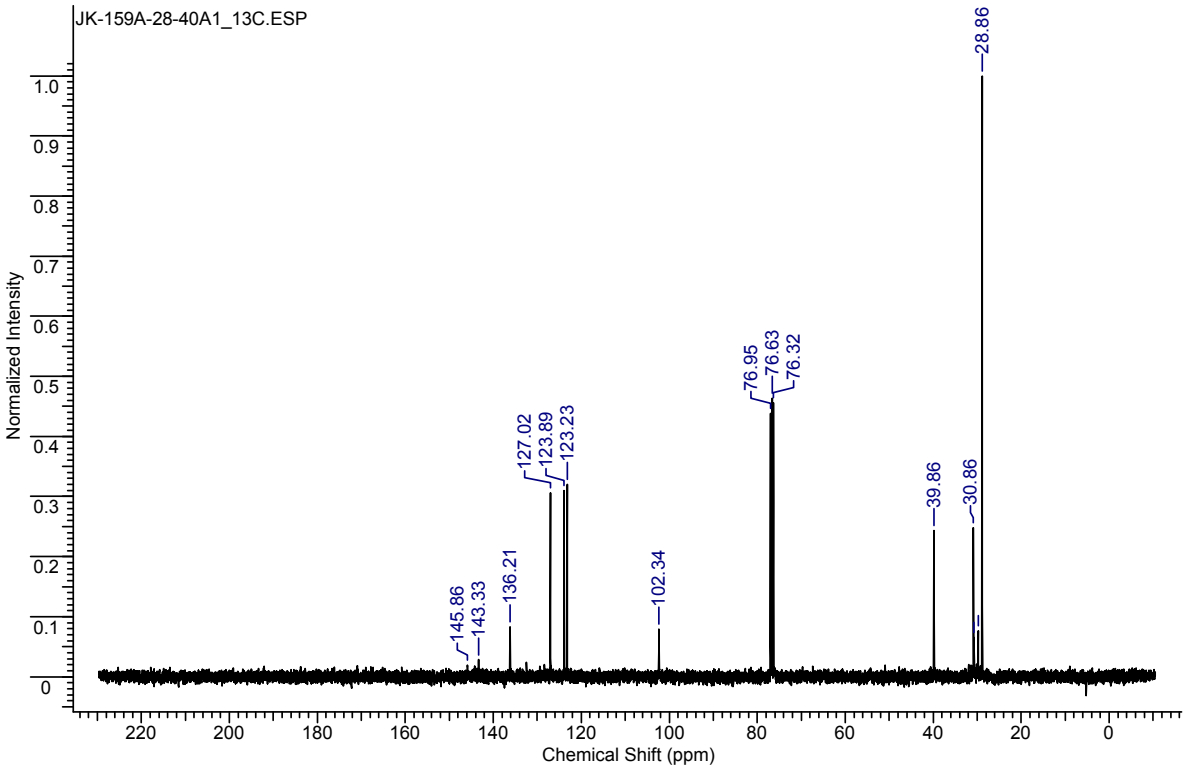


Fig. S-3-16 ^{13}C NMR spectrum of 5-neopentyl-3-(thienyl-2)-1*H*-pyrazole **5e.**



5f

Fig. S-3-17 ^{1}H NMR spectrum of 5-(1-adamantylmethyl)-3-(thienyl-2)-1*H*-pyrazole **5f.**

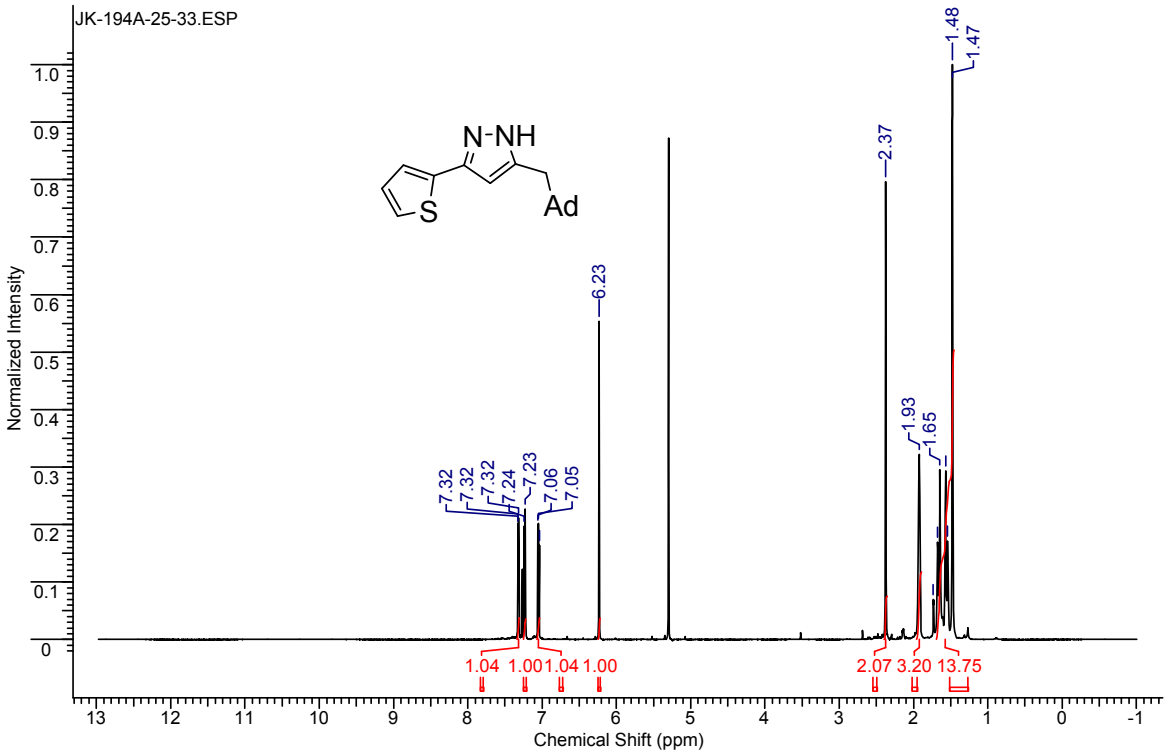
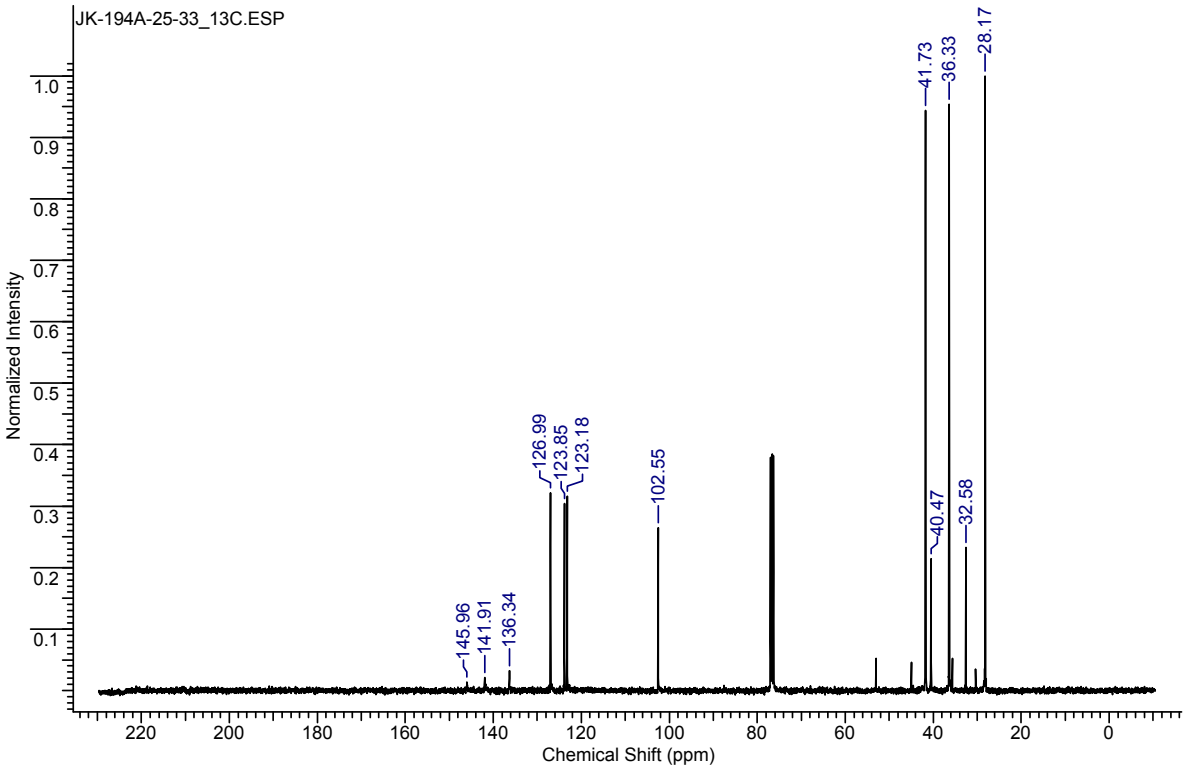


Fig. S-3-18 ^{13}C NMR spectrum of 5-(1-adamantylmethyl)-3-(thienyl-2)-1*H*-pyrazole **5f.**



5g

Fig. S-3-19 ^{1}H NMR spectrum of 5-(3-hydroxy-1-adamantylmethyl)-3-(thienyl-2)-1*H*-pyrazole **5g**.

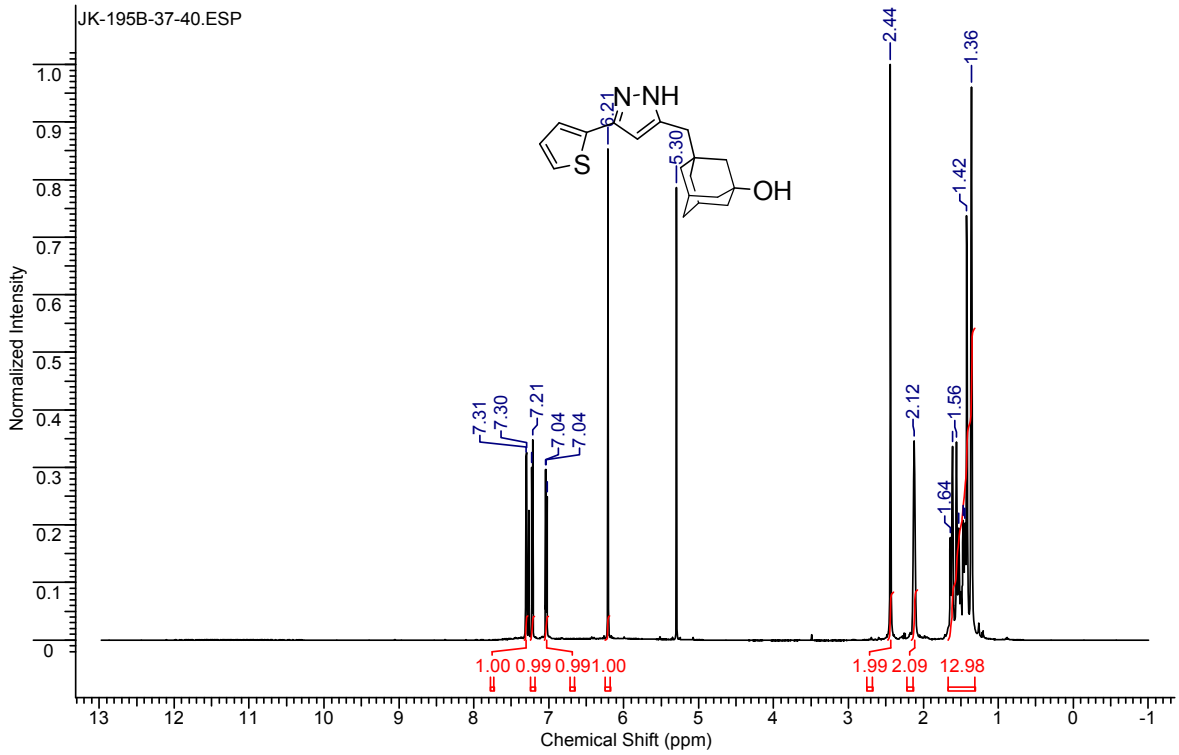
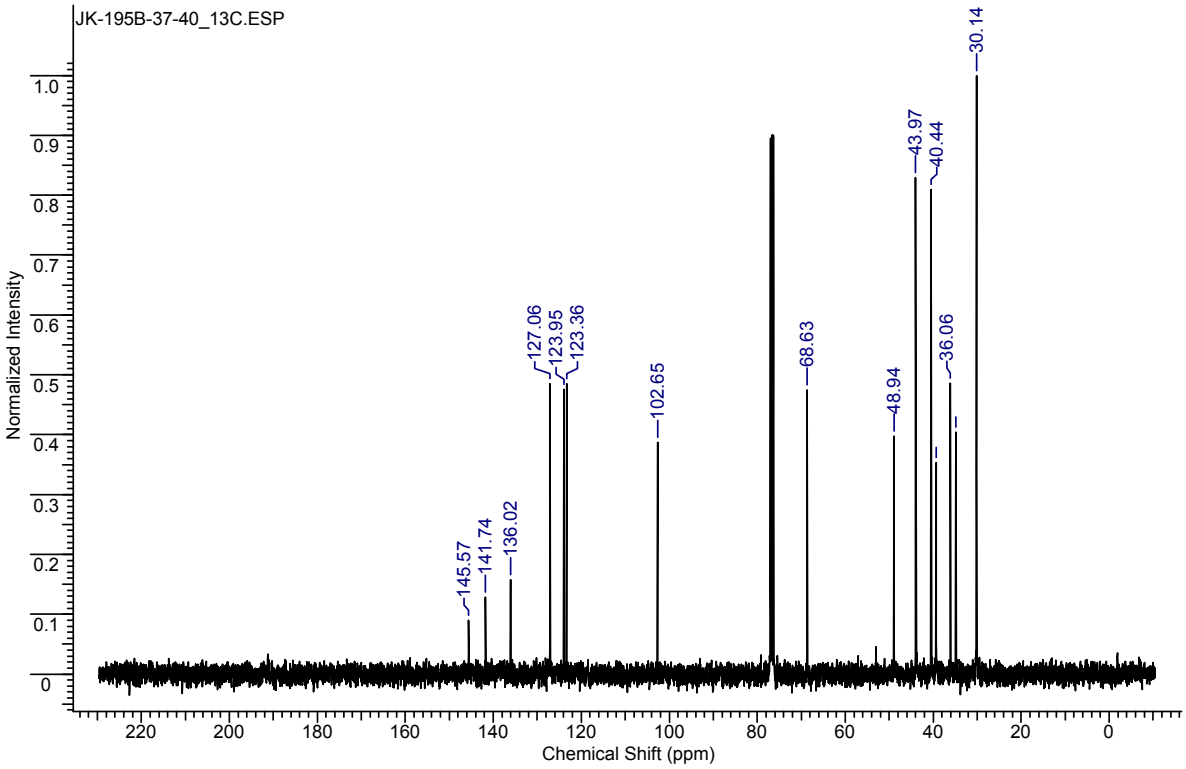


Fig. S-3-20 ^{13}C NMR spectrum of 5-(3-hydroxy-1-adamantylmethyl)-3-(thienyl-2)-1*H*-pyrazole **5g**.



5h

Fig. S-3-21 ^{1}H NMR spectrum of 3-(5-bromothienyl-2)-5-neopentyl-1*H*-pyrazole **5h**.

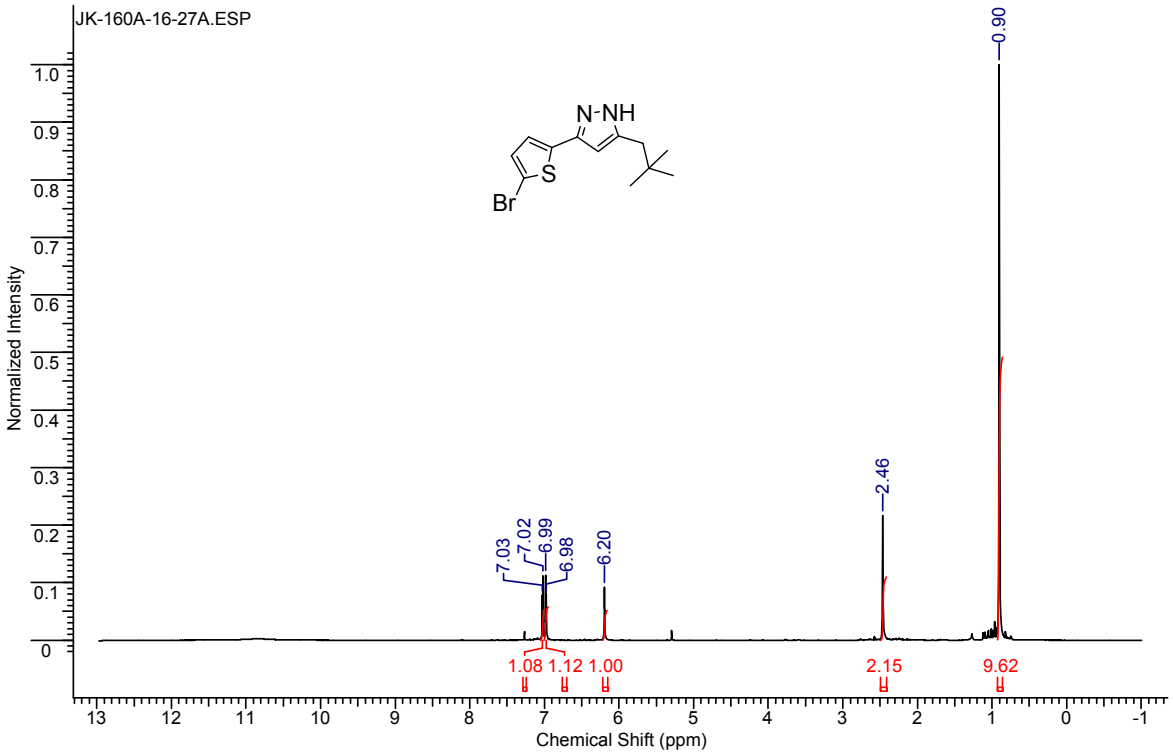
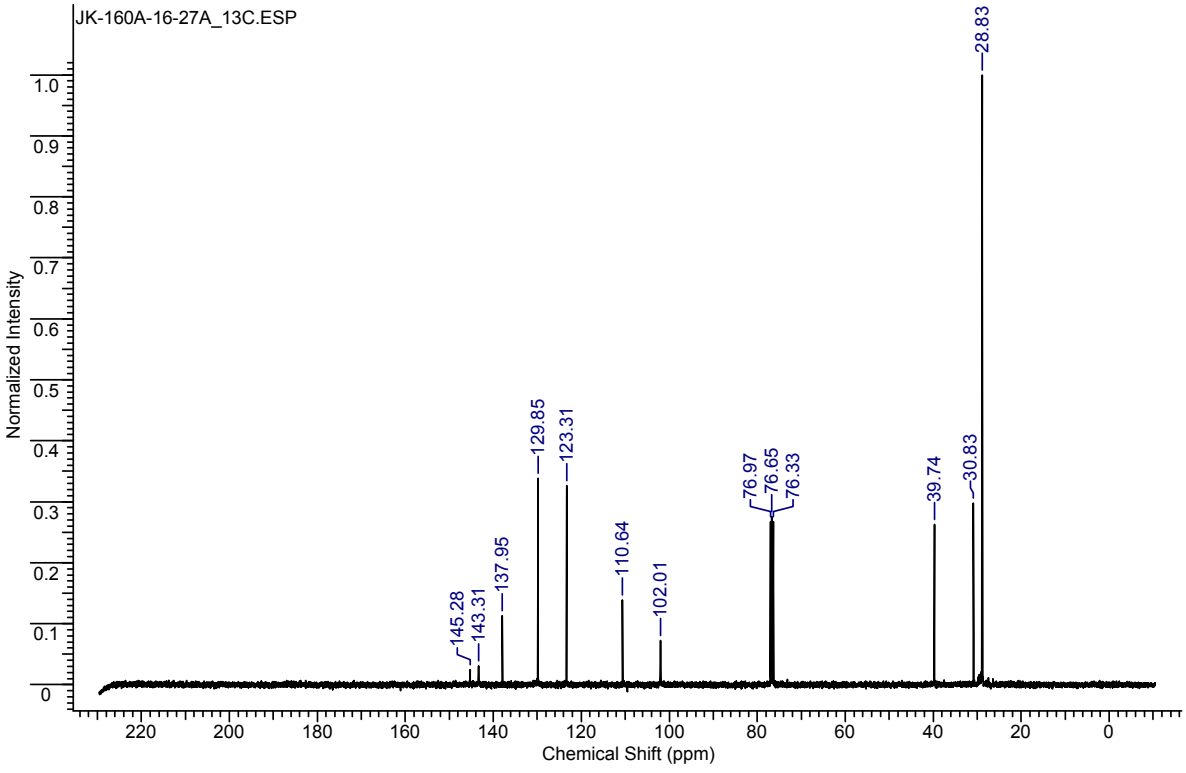


Fig. S-3-22 ^{13}C NMR spectrum of 3-(5-bromothienyl-2)-5-neopentyl-1*H*-pyrazole **5h**.



5i

Fig. S-3-23 ^{1}H NMR spectrum of 3-(dibenzofuran-2-yl)-5-neopentyl-1*H*-pyrazole **5i**.

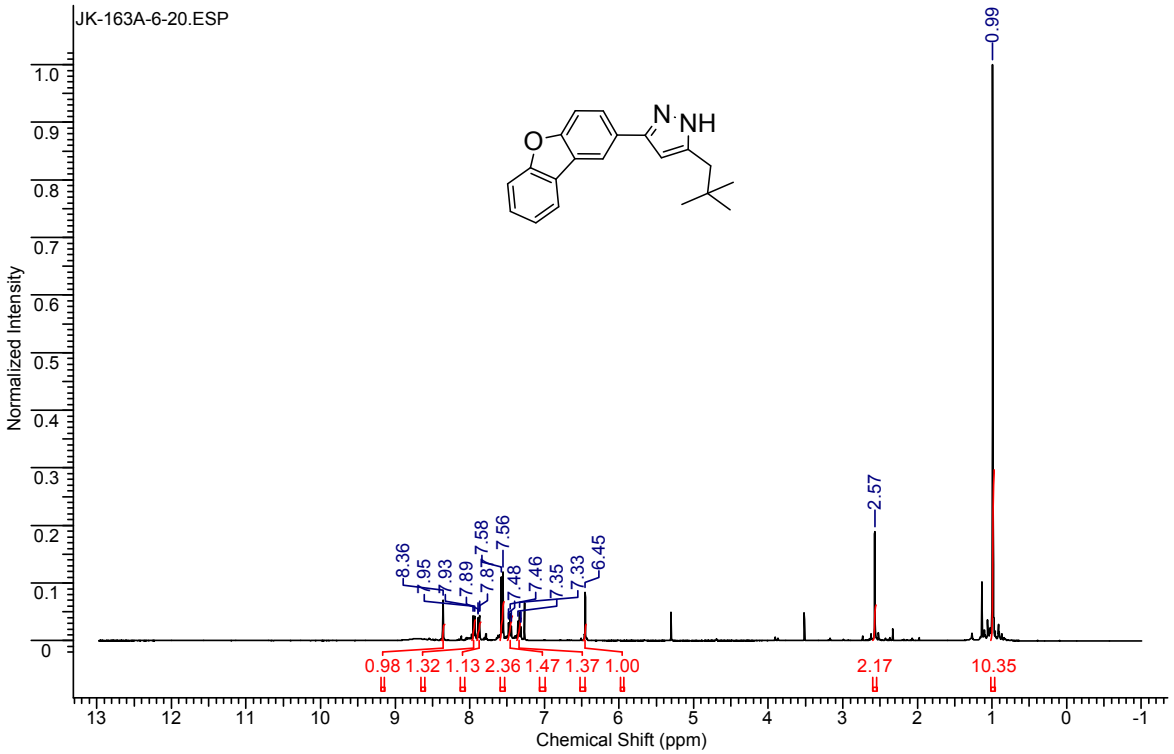
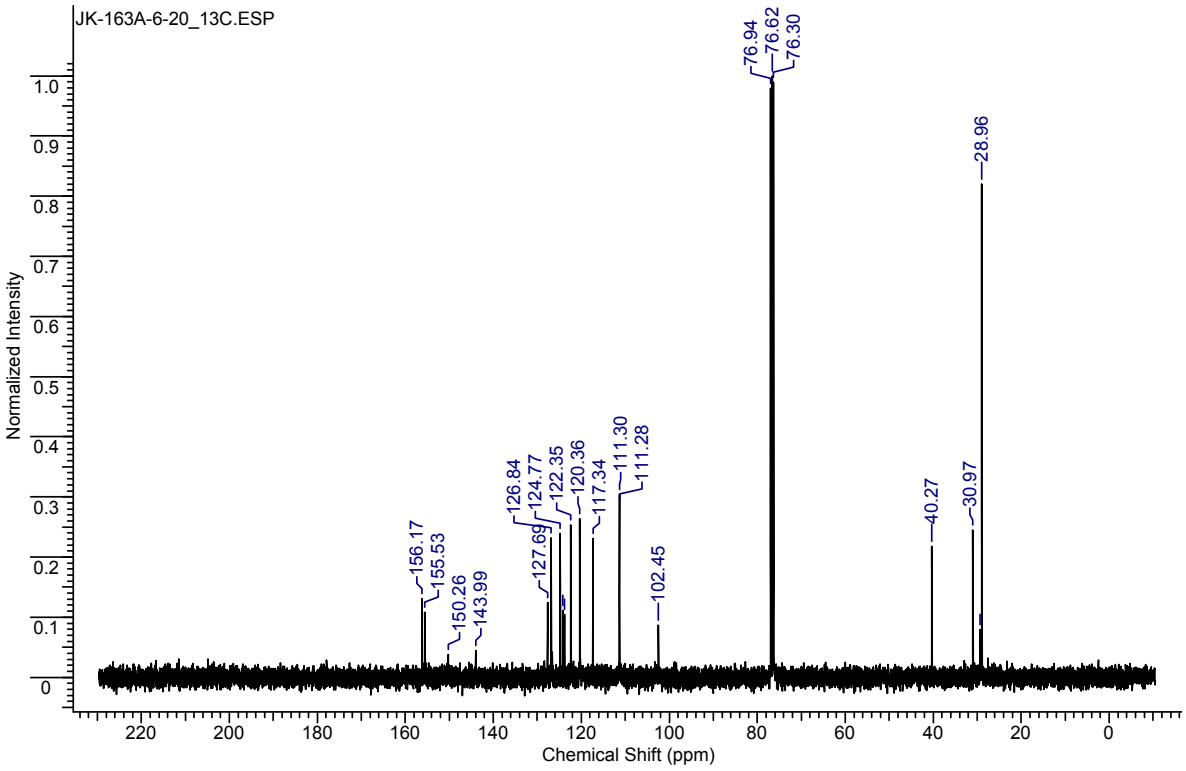


Fig. S-3-24 ^{13}C NMR spectrum of 3-(dibenzofuran-2-yl)-5-neopentyl-1*H*-pyrazole **5i**.



5j

Fig. S-3-25 ^{1}H NMR spectrum of 5-(1-adamantylmethyl)-3-(dibenzofuran-2-yl)-1*H*-pyrazole **5j**.

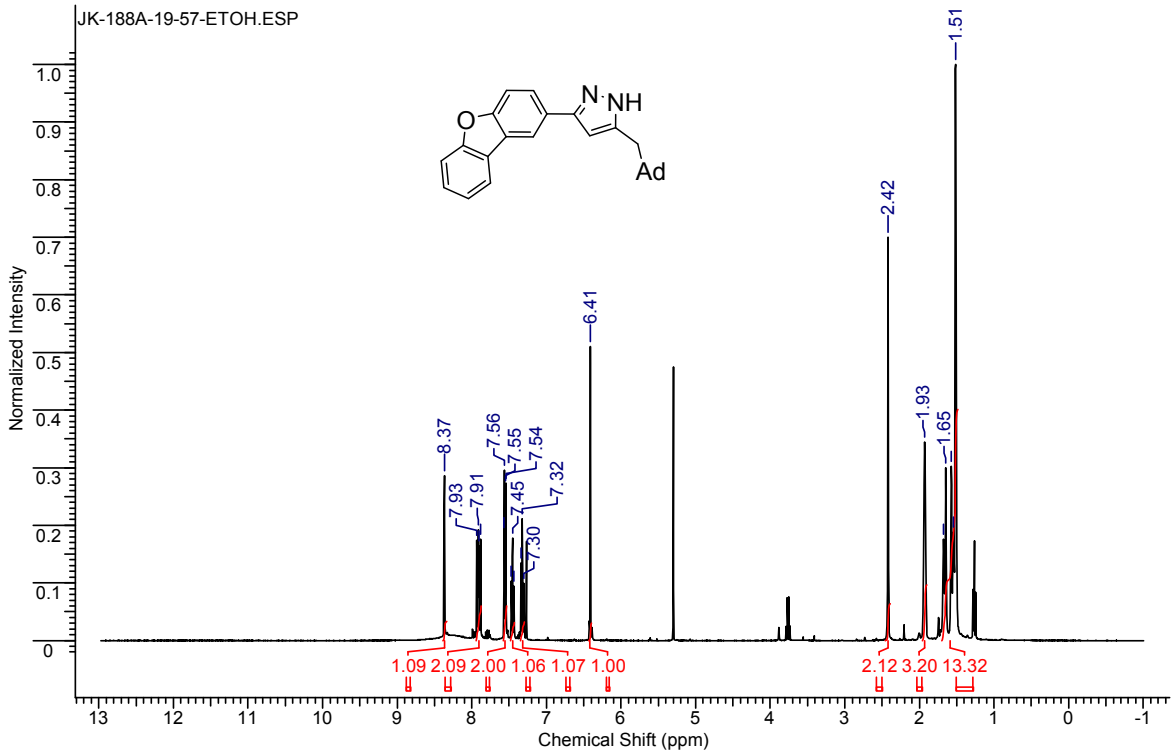
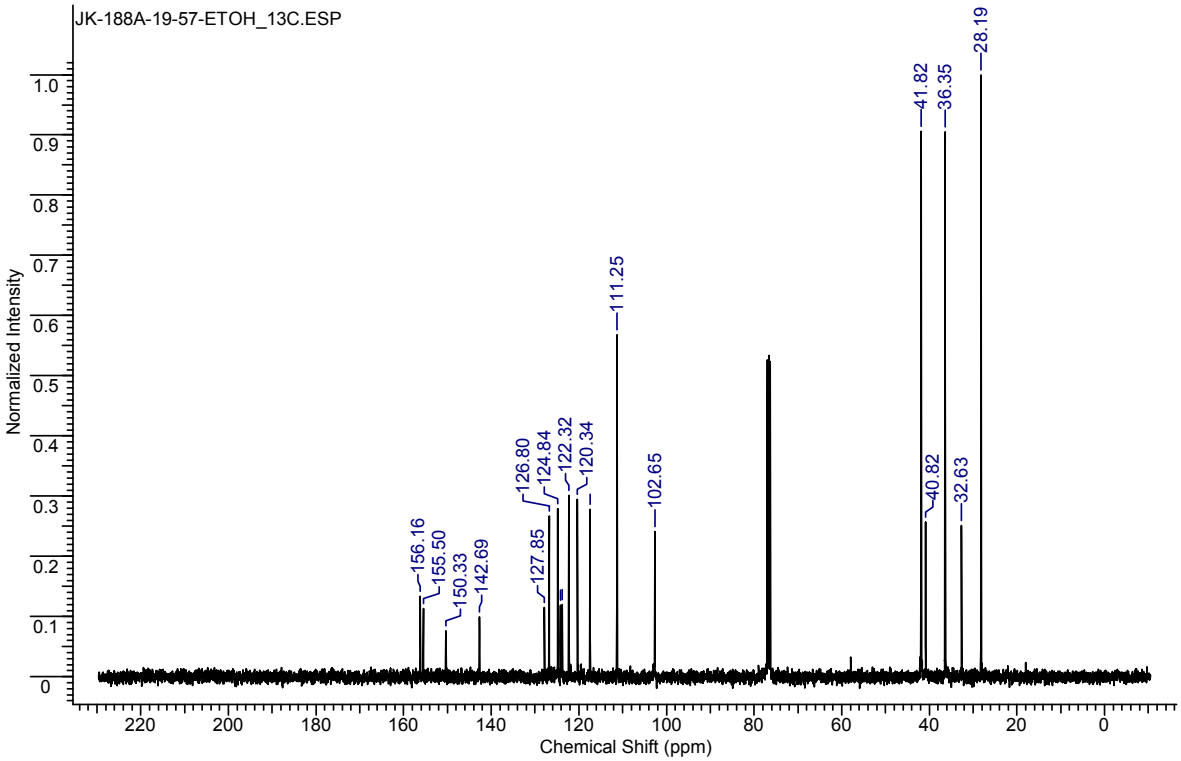


Fig. S-3-26 ^{13}C NMR spectrum of 5-(1-adamantylmethyl)-3-(dibenzofuran-2-yl)-1*H*-pyrazole **5j**.



5k

Fig. S-3-27 ^{1}H NMR spectrum of 5-(1-adamantylmethyl)-3-(2,4-dichlorophenyl)-*1H*-pyrazole **5k**.

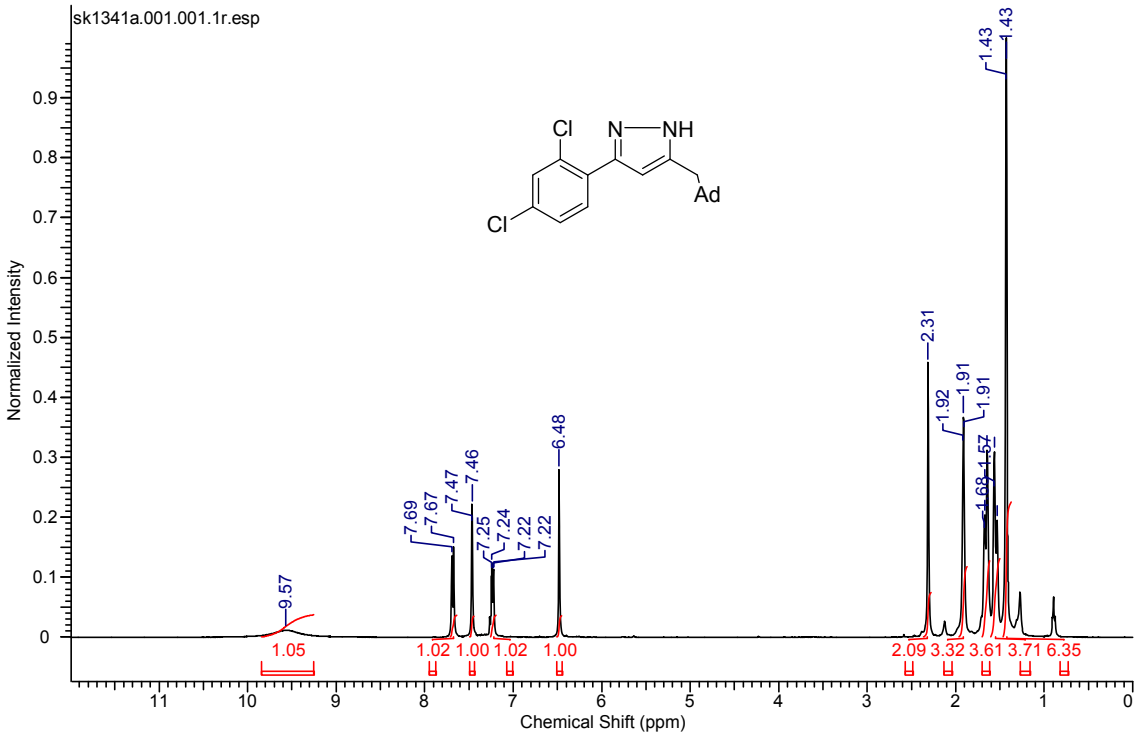
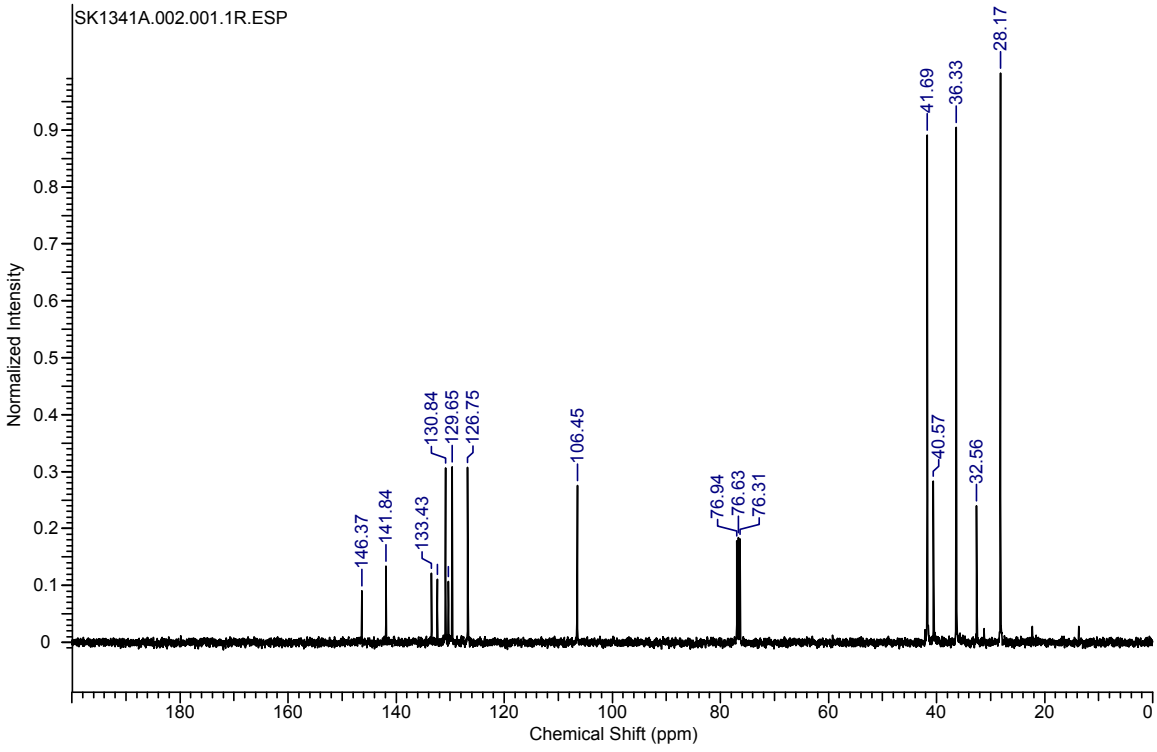


Fig. S-3-28 ^{13}C NMR spectrum of 5-(1- adamantylmethyl)-3-(2,4-dichlorophenyl)-*1H*-pyrazole **5k**.



5l

Fig. S-3-29 ^{1}H NMR spectrum of 5-(3-hydroxy-1-adamantylmethyl)-3-phenyl-1*H*-pyrazole **5l**. (Used CD_3Cl/CF_3COOD mixture)

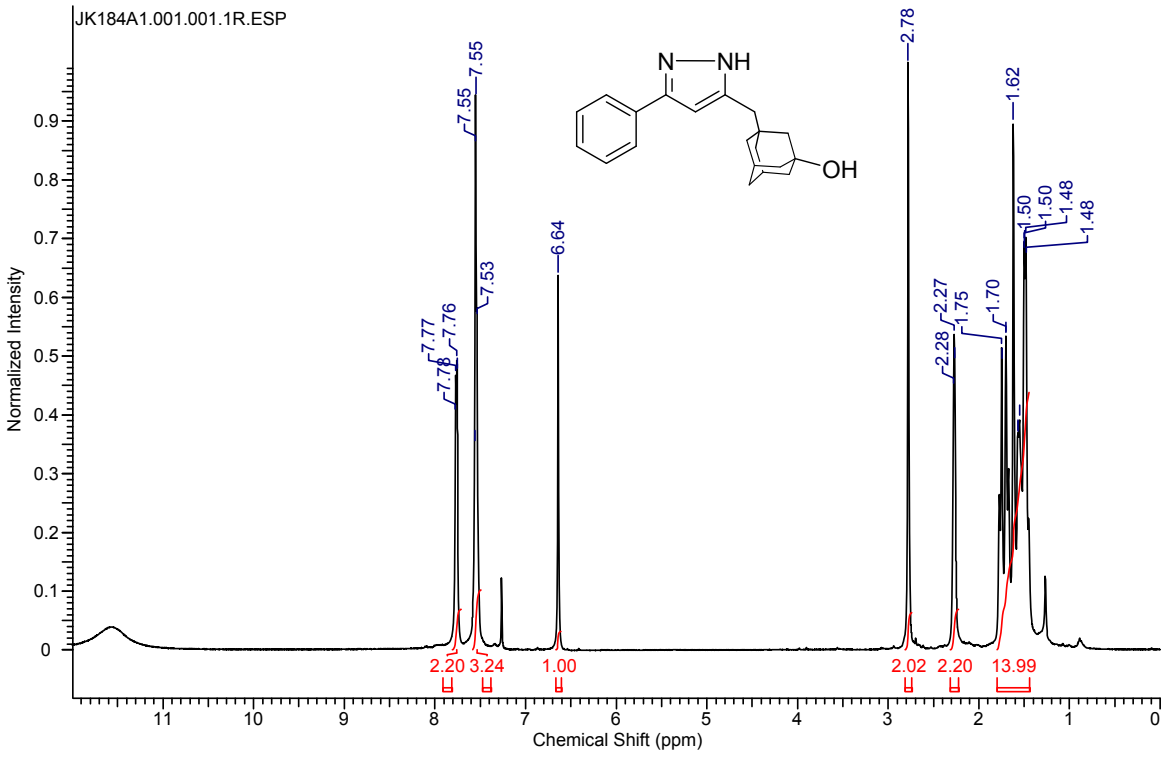
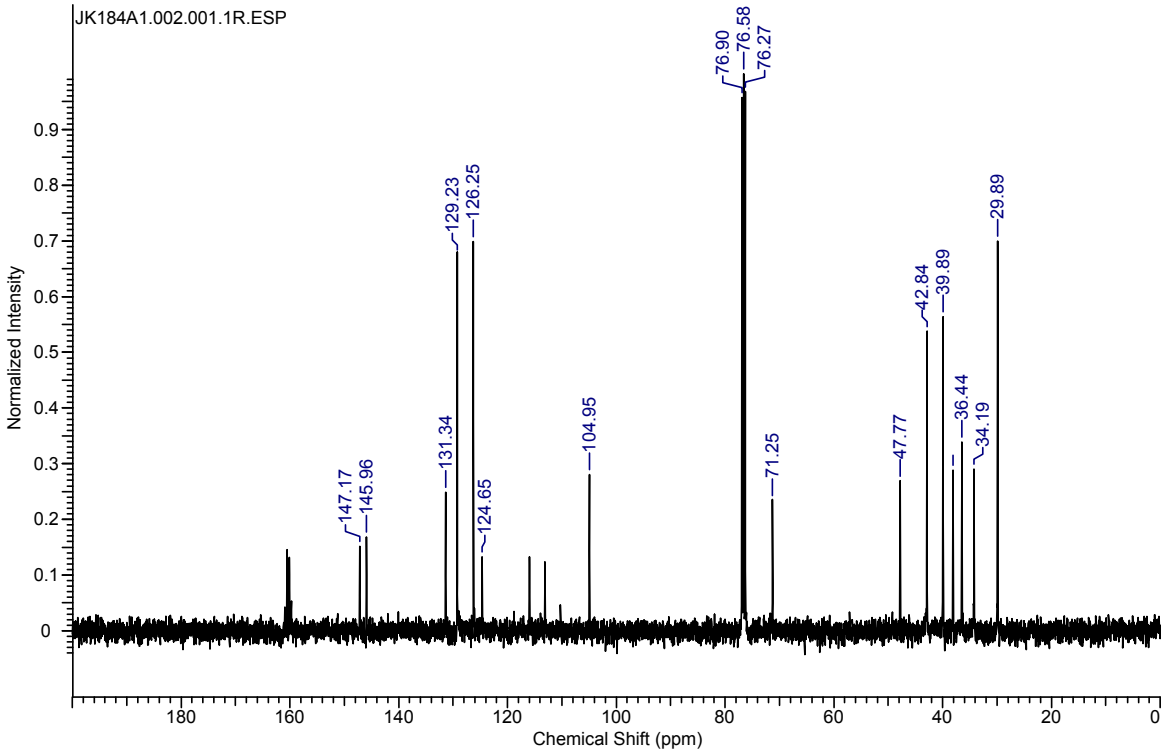


Fig. S-3-30 ^{13}C NMR spectrum of 5-(3-hydroxy-1-adamantylmethyl)-3-phenyl-1*H*-pyrazole **5l**. (Used CD_3Cl/CF_3COOD mixture)



6

Fig. S-3-31 ^{1}H NMR spectrum of dehydroacetic acid **6**.

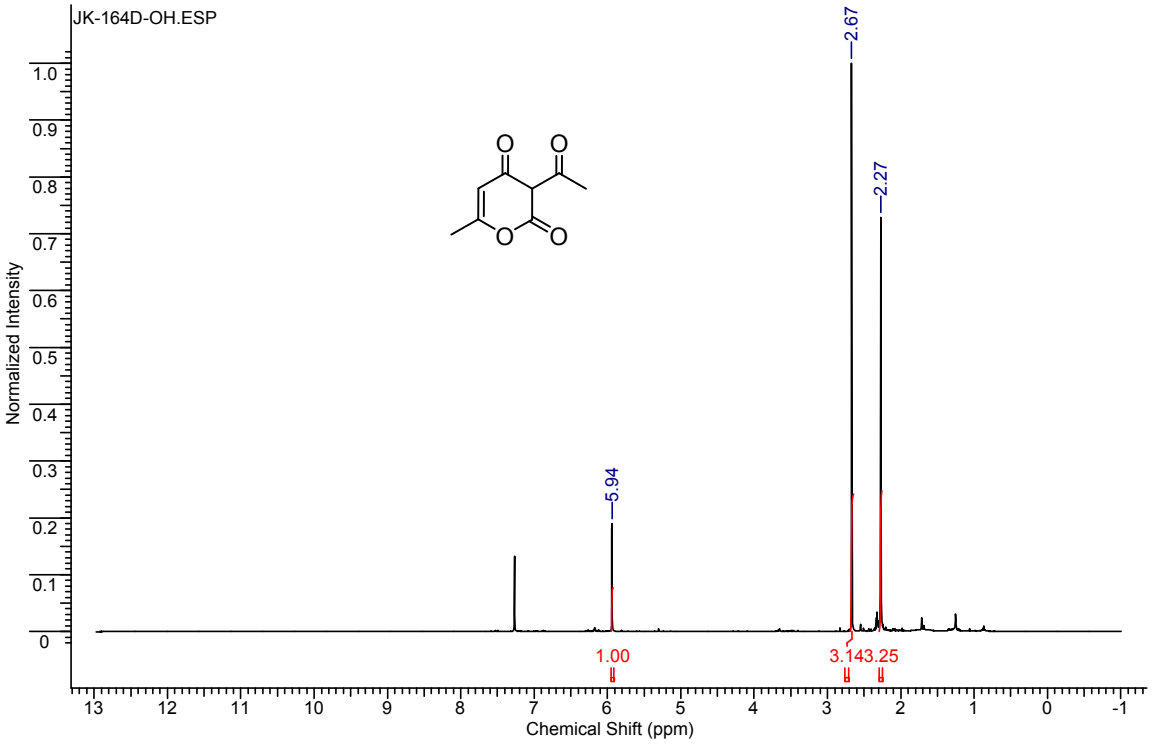
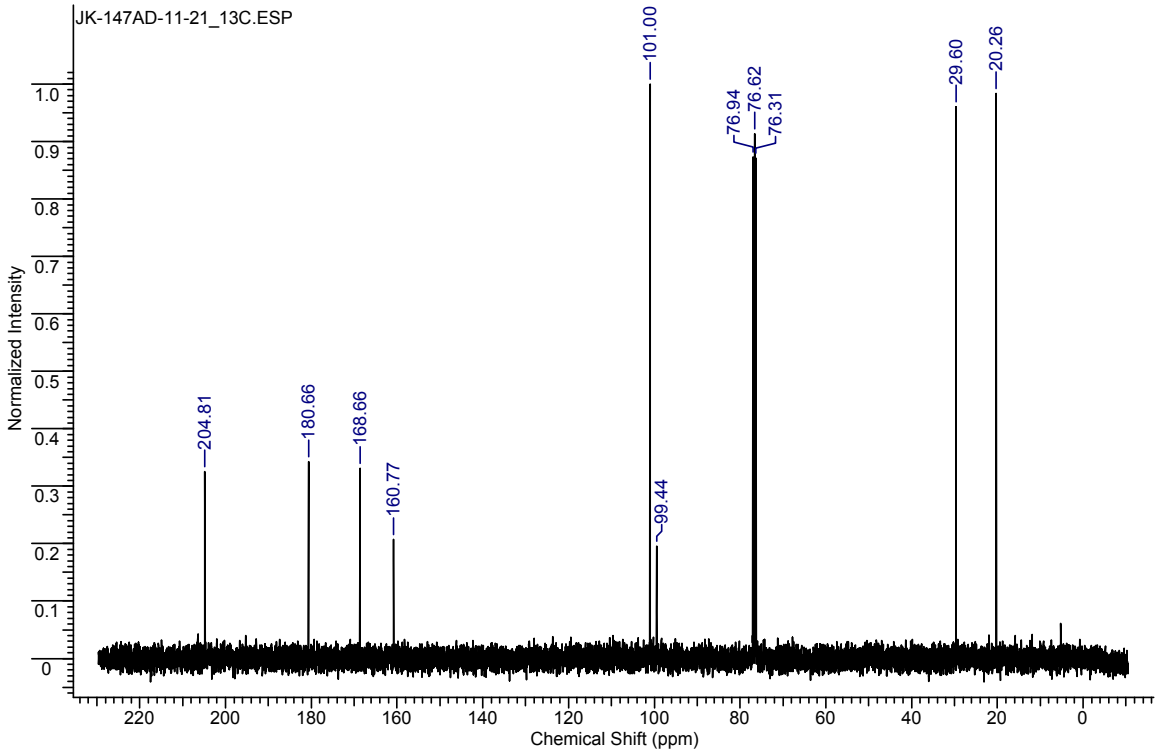


Fig. S-3-32 ^{13}C NMR spectrum of dehydroacetic acid **6**.



8a

Fig. S-3-33 ^{1}H NMR spectrum of 2-(bis(4-fluorophenyl)methyl)-5,5-dimethyl-1-phenylhexane-1,3-dione **8a**.

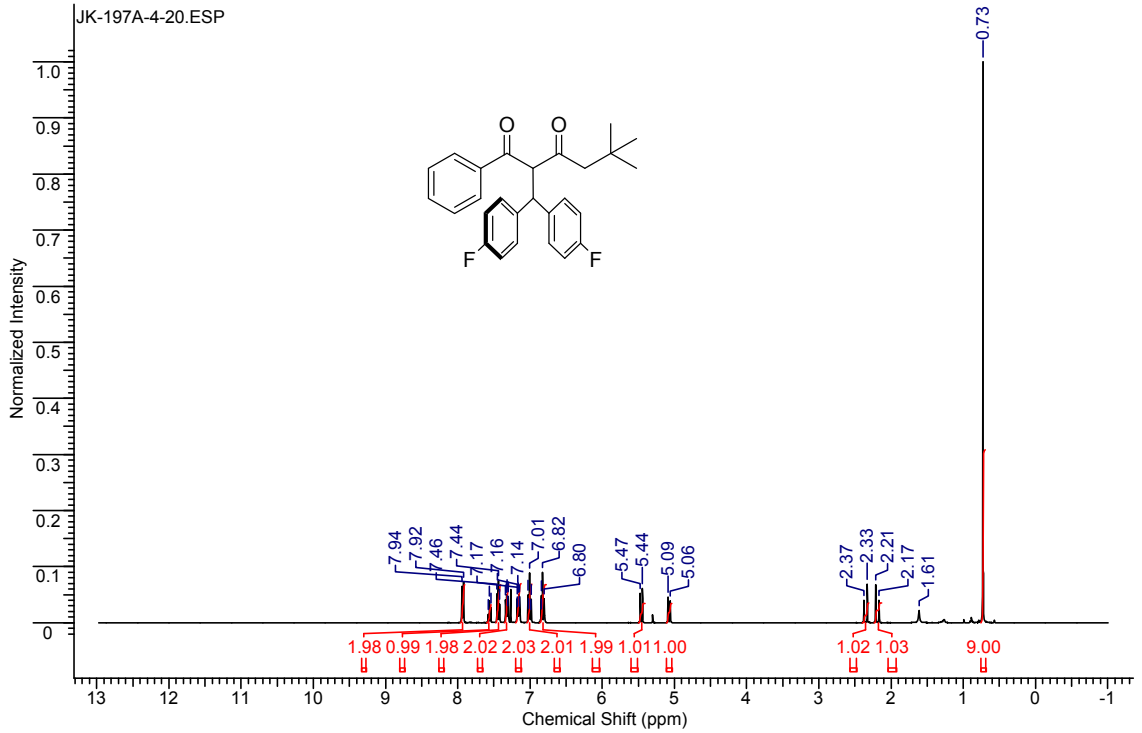
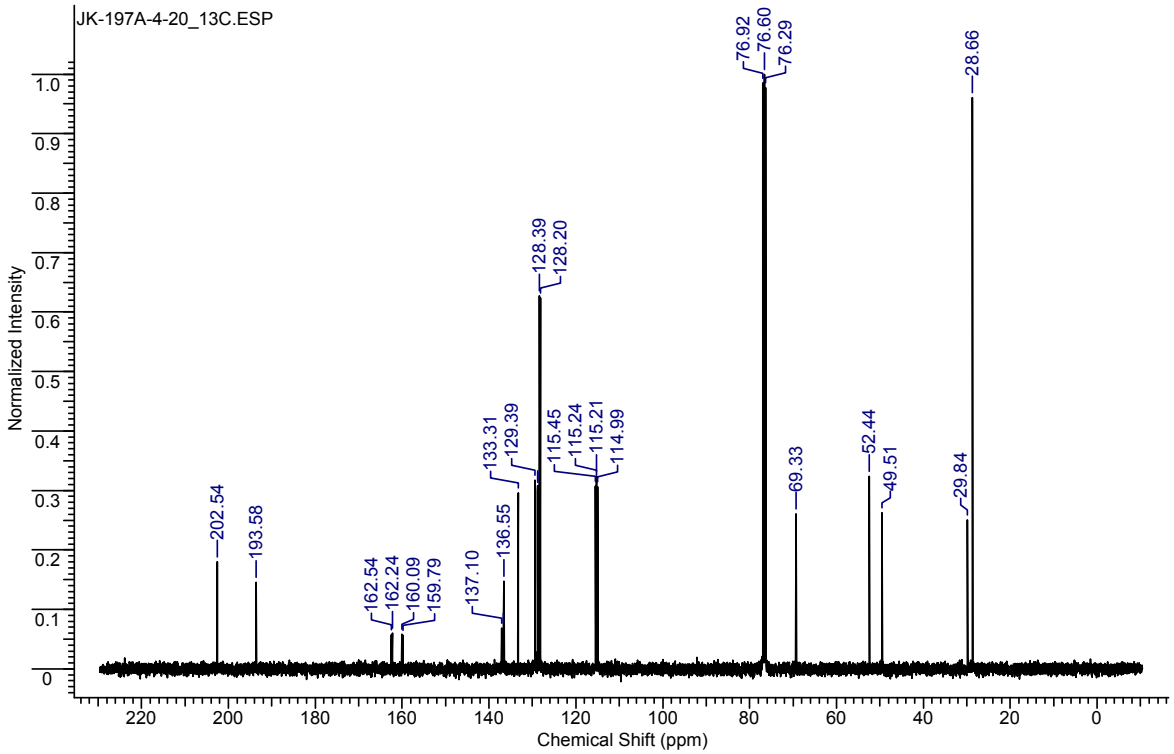


Fig. S-3-34 ^{13}C NMR spectrum of 2-(bis(4-fluorophenyl)methyl)-5,5-dimethyl-1-phenylhexane-1,3-dione **8a**.



8b

Fig. S-3-35 ^{1}H NMR spectrum of 2-(bis(4-fluorophenyl)methyl)-4-(1-adamantyl)-1-phenylbutane-1,3-dione **8b**.

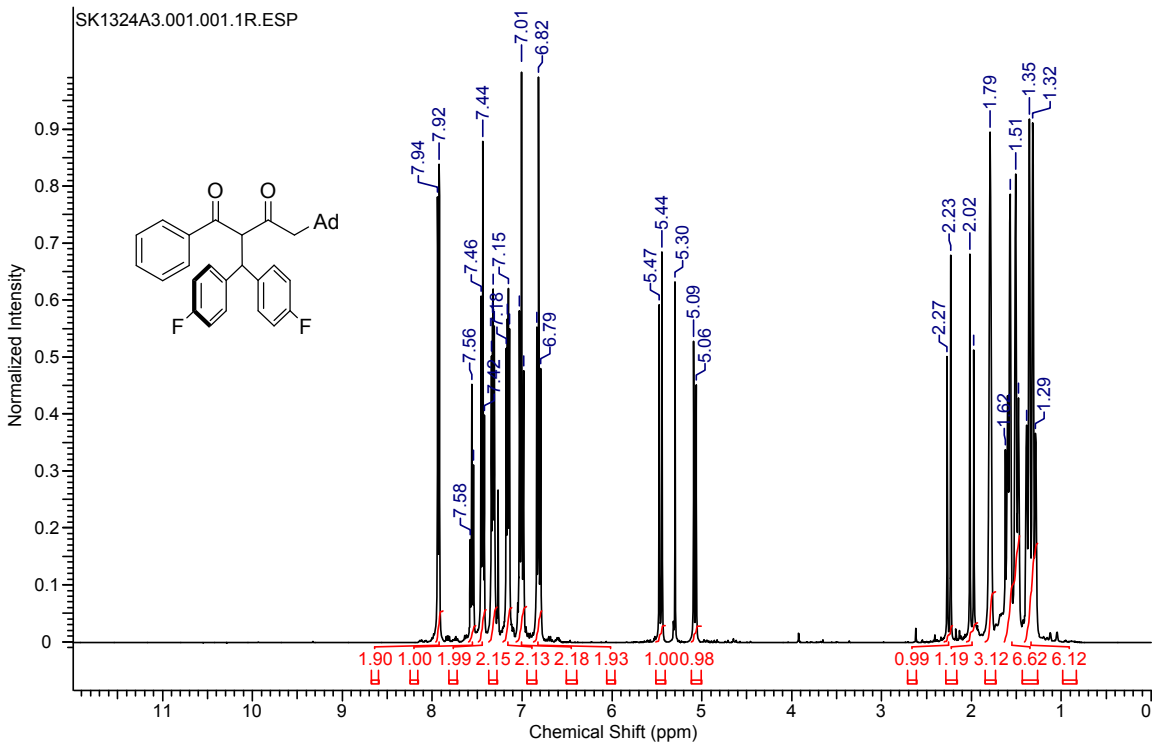
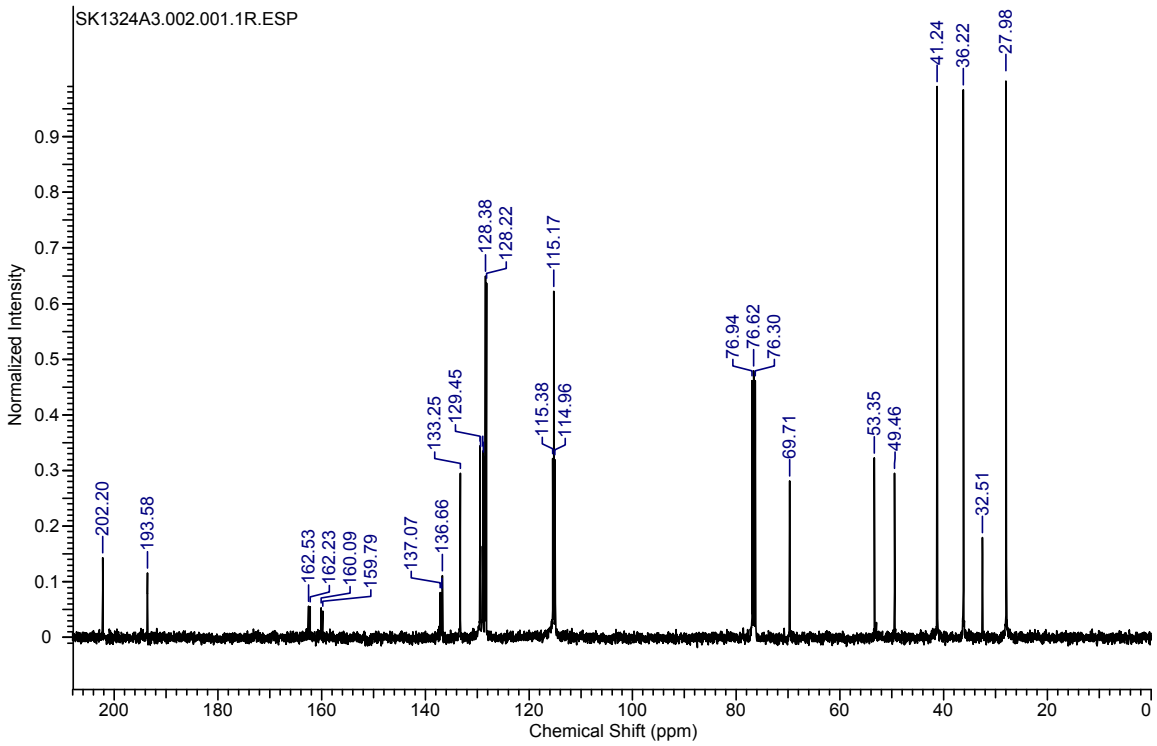


Fig. S-3-36 ^{13}C NMR spectrum of 2-(bis(4-fluorophenyl)methyl)-4-(1-adamantyl)-1-phenylbutane-1,3-dione **8b**.



8c

Fig. S-3-37 ^{1}H NMR spectrum of 2-(bis(4-fluorophenyl)methyl)-4-(1-adamantyl)-1-(2,4-dichlorophenyl)butane-1,3-dione **8c**.

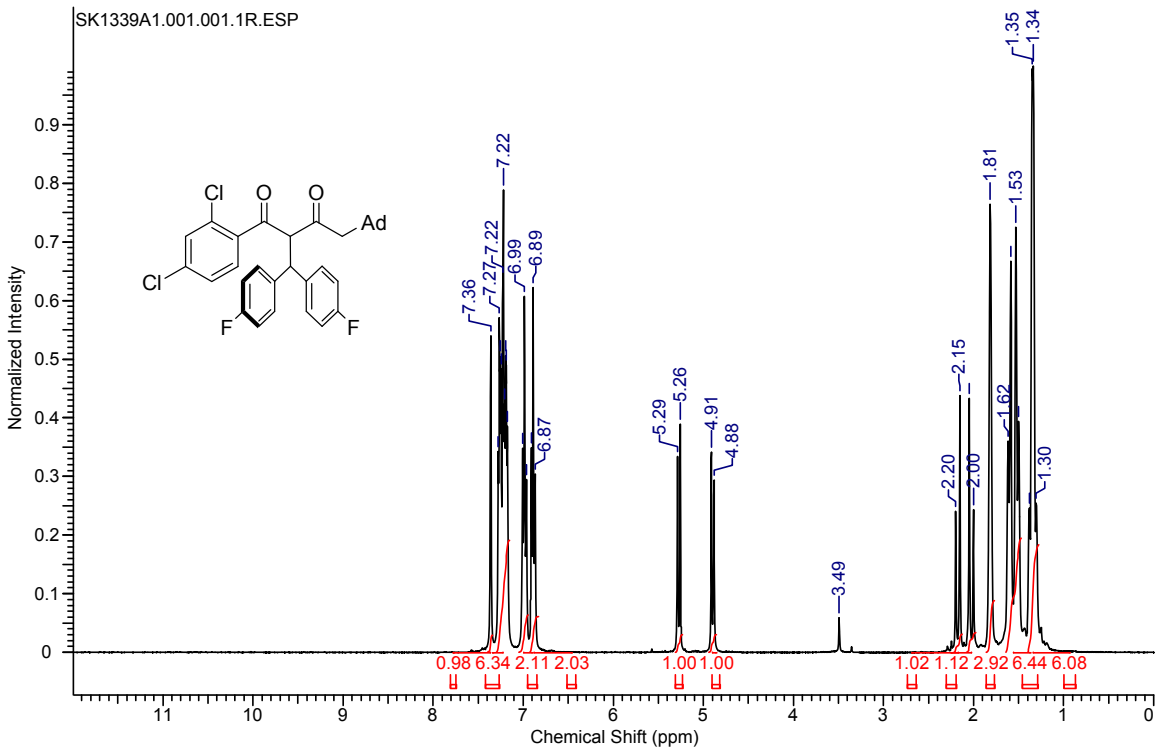
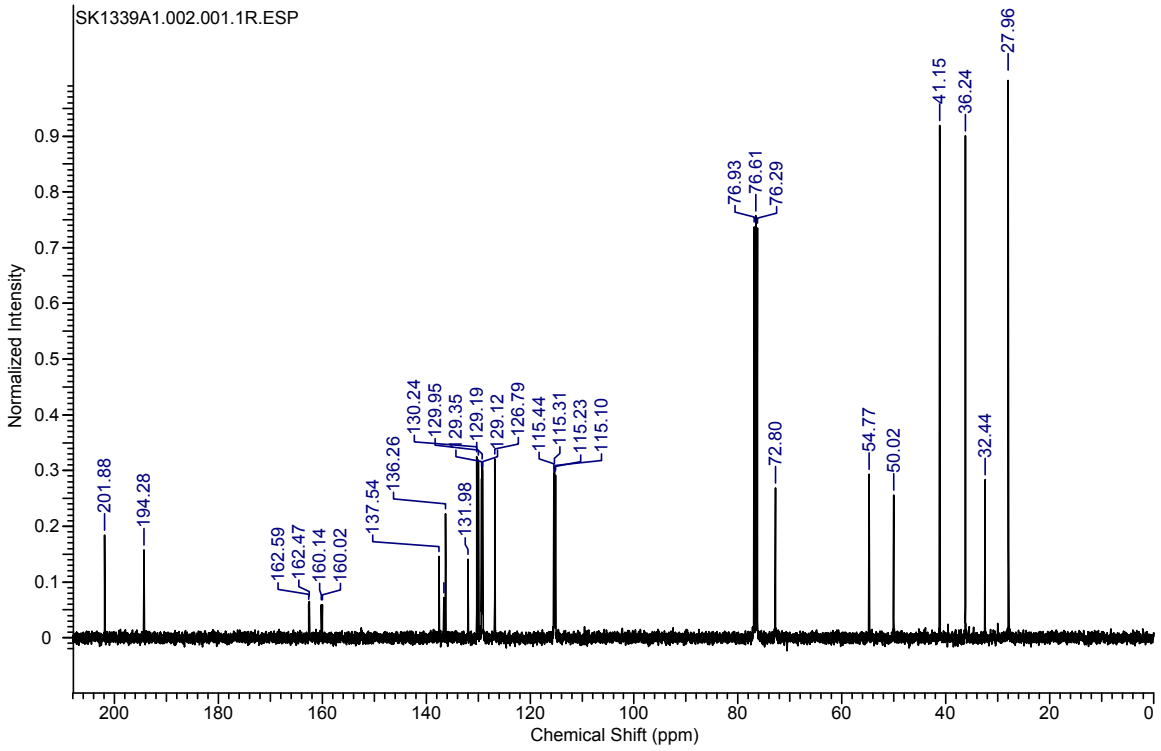


Fig. S-3-38 ^{13}C NMR spectrum of 2-(bis(4-fluorophenyl)methyl)-4-(1-adamantyl)-1-(2,4-dichlorophenyl)butane-1,3-dione **8c**.



8d

Fig. S-3-39 ^{1}H NMR spectrum of 2-(Bis(4-fluorophenyl)methyl)-5,5-dimethyl-1-(4-methylphenyl)butane-1,3-dione **8d**.

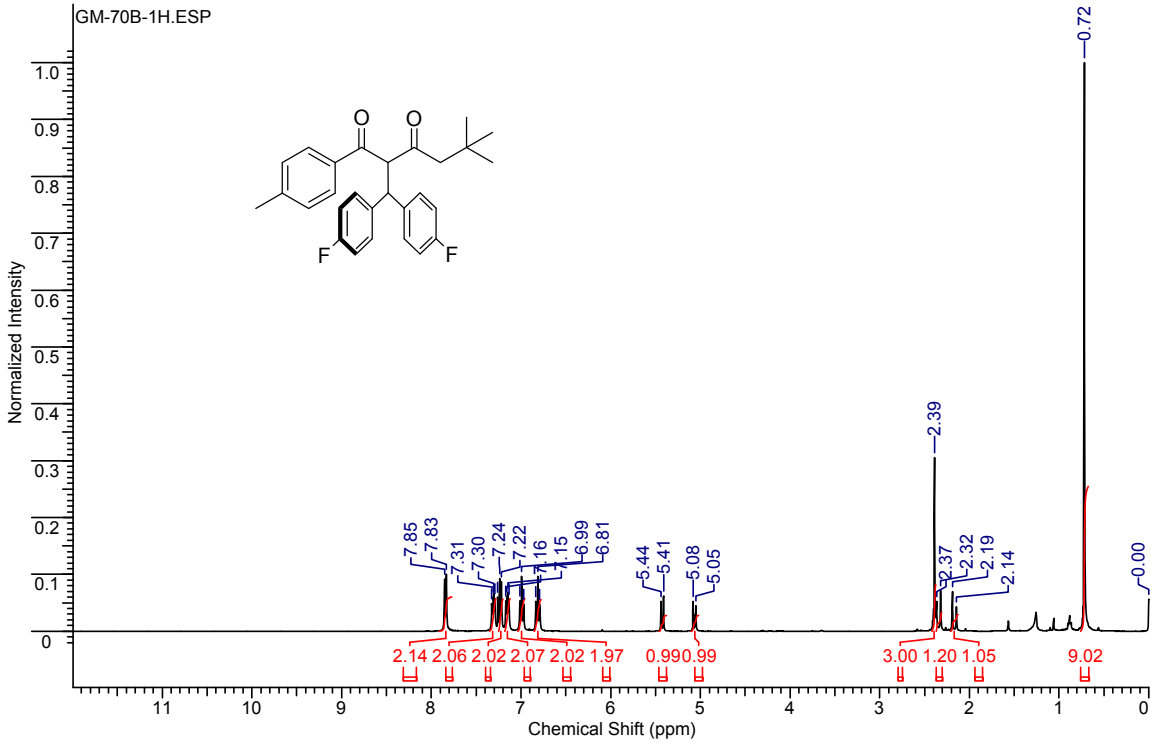
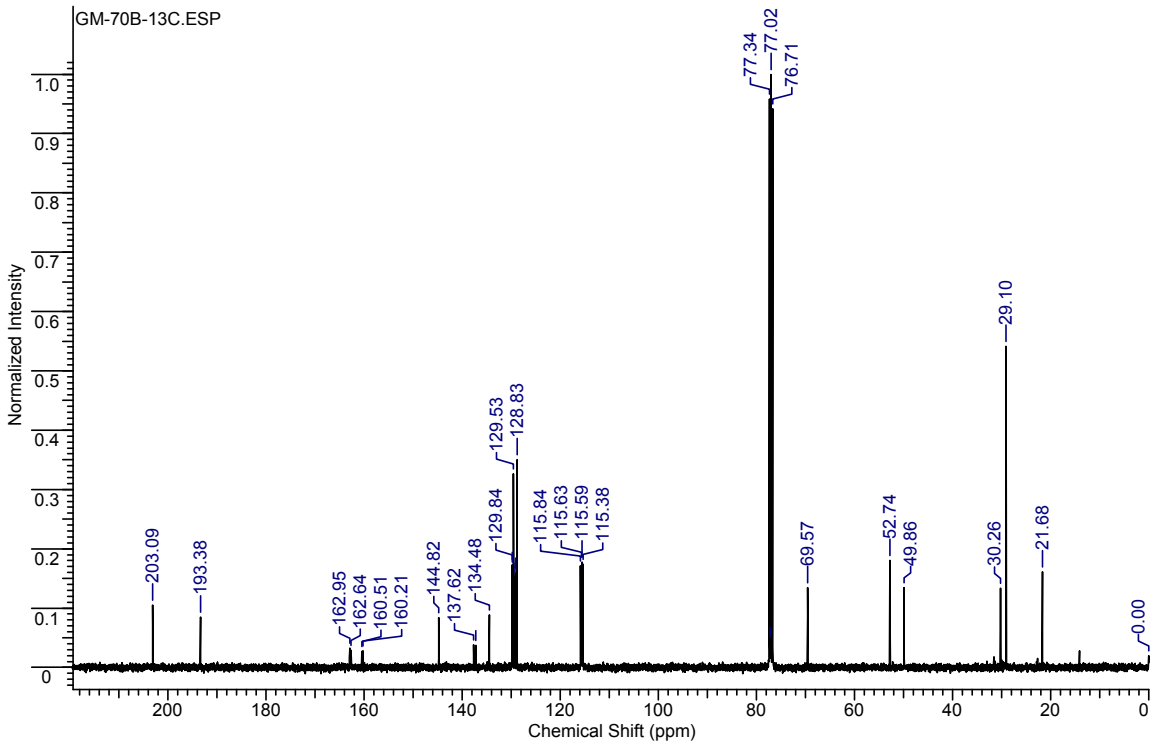


Fig. S-3-40 ^{13}C NMR spectrum of 2-(Bis(4-fluorophenyl)methyl)-5,5-dimethyl-1-(4-methylphenyl)butane-1,3-dione **8d**.



8e

Fig. S-3-41 ^{1}H NMR spectrum of 2-(Bis(4-fluorophenyl)methyl)-5,5-dimethyl-1-(4-methoxyphenyl)butane-1,3-dione **8e**.

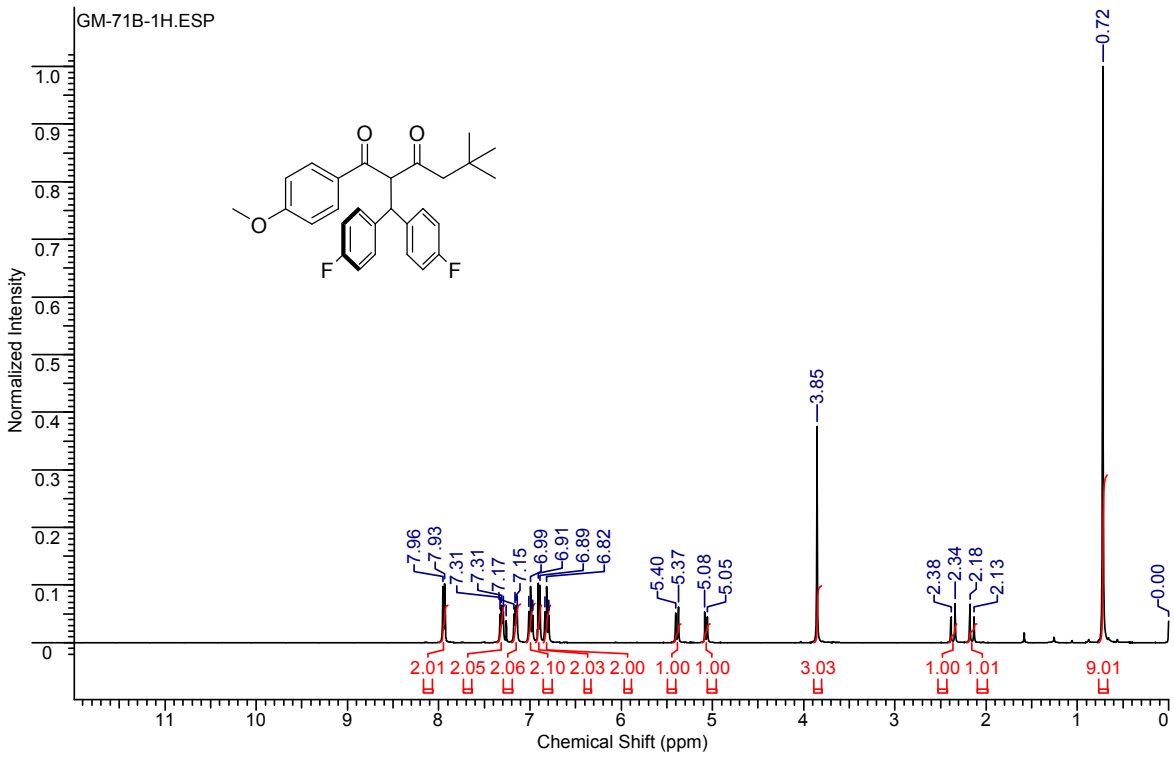
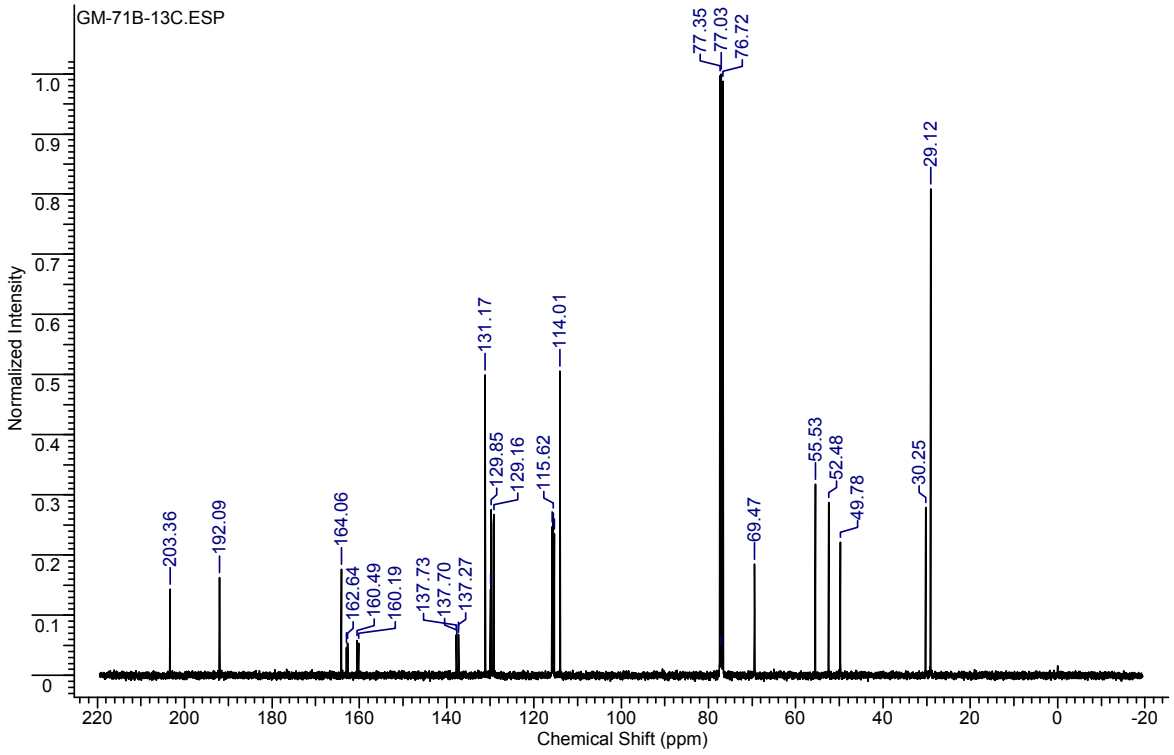


Fig. S-3-42 ^{13}C NMR spectrum of 2-(Bis(4-fluorophenyl)methyl)-5,5-dimethyl-1-(4-methoxyphenyl)butane-1,3-dione **8e**.



8f

Fig. S-3-43 ^{1}H NMR spectrum of 2-(Bis(4-fluorophenyl)methyl)-5,5-dimethyl-1-(4-chlorophenyl)butane-1,3-dione **8f**.

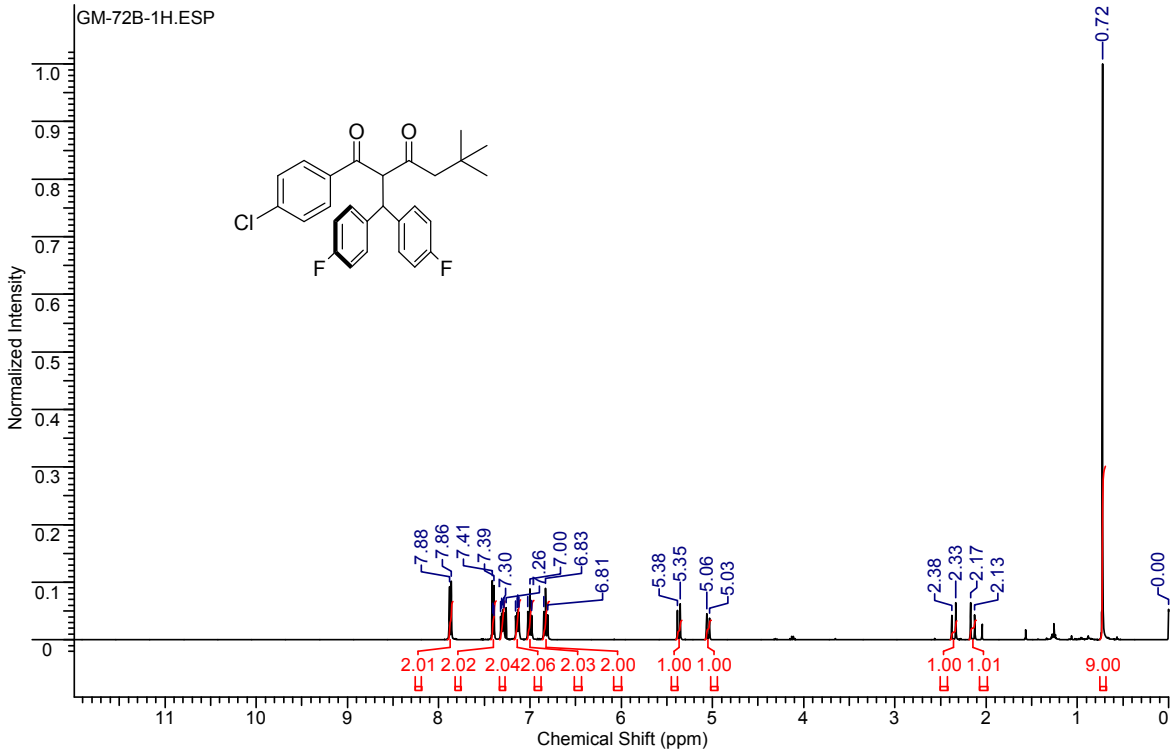
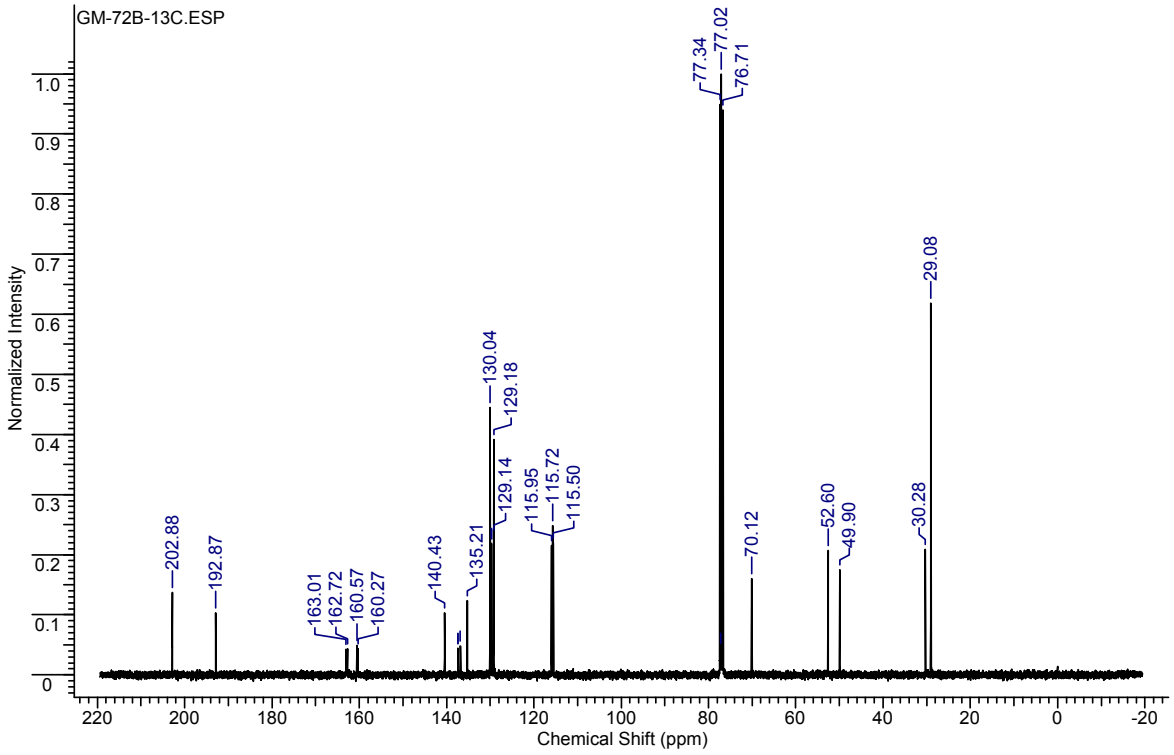


Fig. S-3-44 ^{13}C NMR spectrum of 2-(Bis(4-fluorophenyl)methyl)-5,5-dimethyl-1-(4-chlorophenyl)butane-1,3-dione **8f**.



8g

Fig. S-3-45 ^{1}H NMR spectrum of 2-(Bis(4-fluorophenyl)methyl)-5,5-dimethyl-1-(3-chlorophenyl)butane-1,3-dione **8g**.

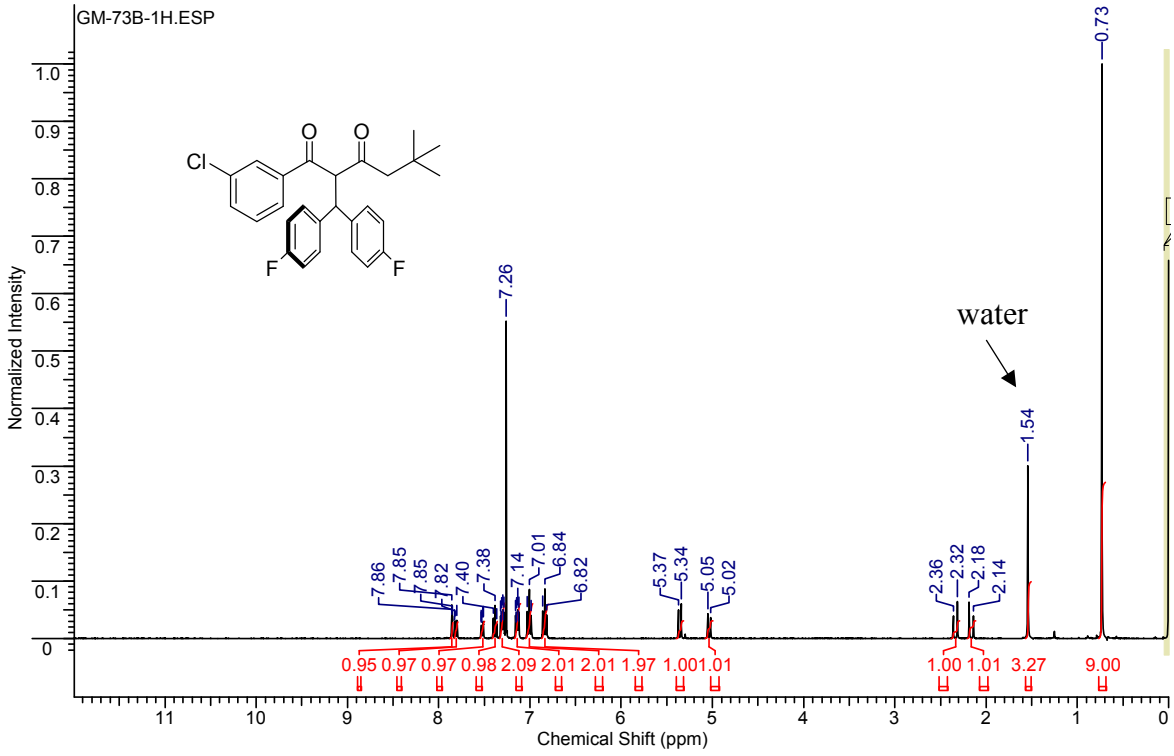
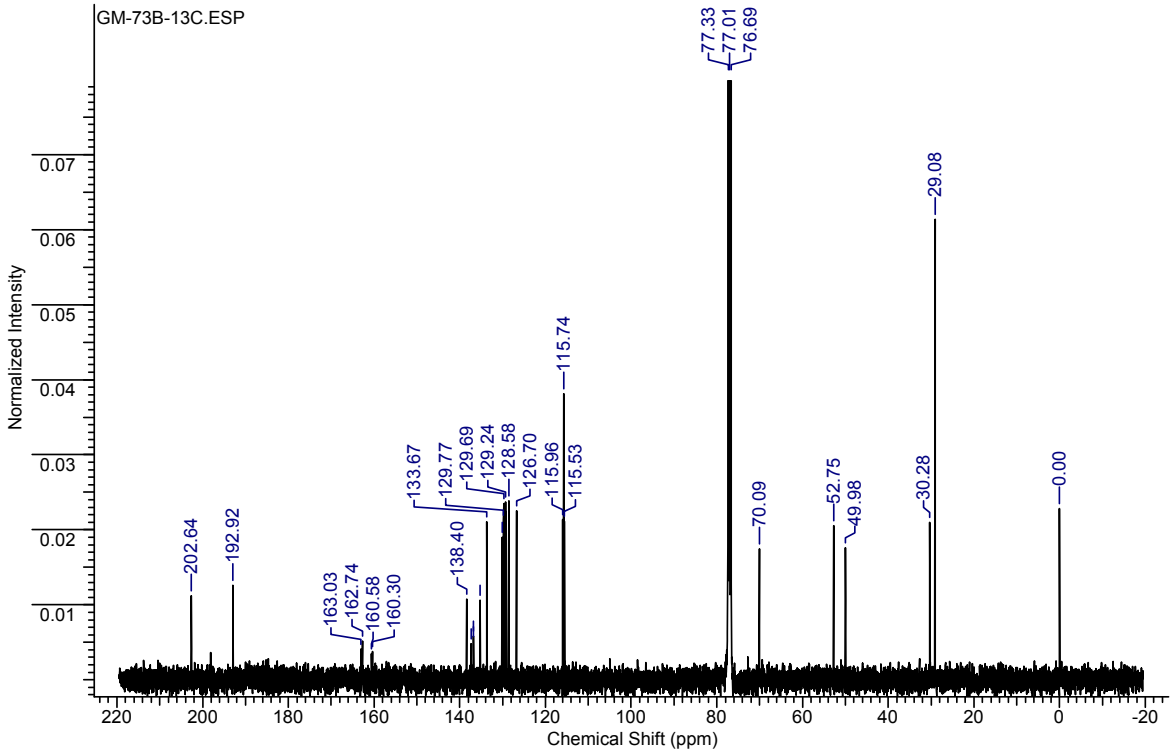


Fig. S-3-46 ^{13}C NMR spectrum of 2-(Bis(4-fluorophenyl)methyl)-5,5-dimethyl-1-(3-

chlorophenyl)butane-1,3-dione **8g**.



8h

Fig. S-3-47 ^{1}H NMR spectrum of 2-(Bis(4-fluorophenyl)methyl)-5,5-dimethyl-1-(2-chlorophenyl)butane-1,3-dione **8h**.

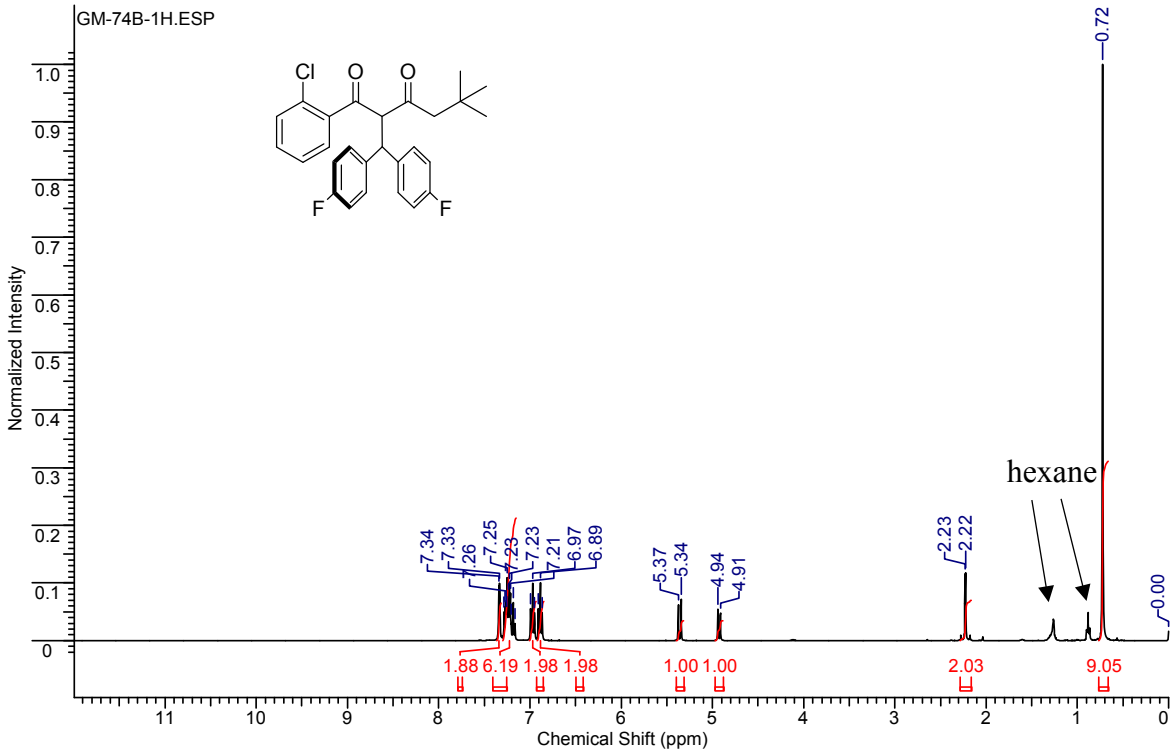
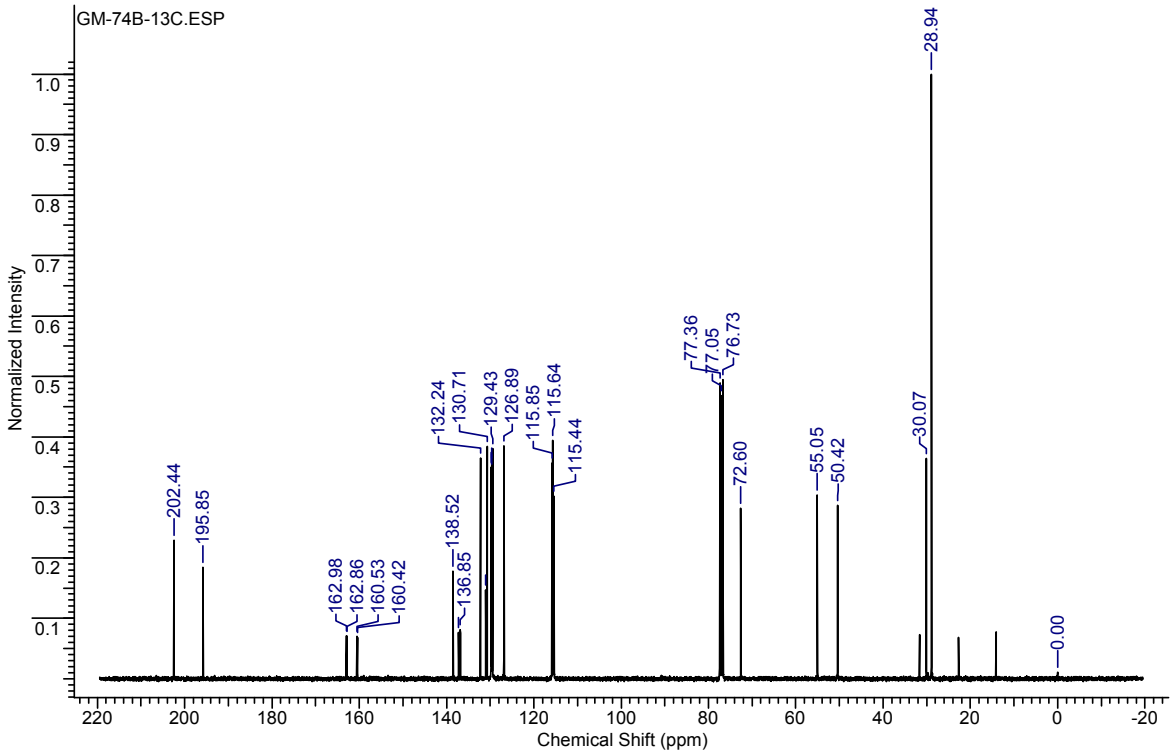


Fig. S-3-48 ^{13}C NMR spectrum of 2-(Bis(4-fluorophenyl)methyl)-5,5-dimethyl-1-(2-chlorophenyl)butane-1,3-dione **8h**.



8i

Fig. S-3-49 ^{1}H NMR spectrum of 2-(bis(4-fluorophenyl)methyl)-5,5-dimethyl-1-(thiophen-2-yl)hexane-1,3-dione **8i**.

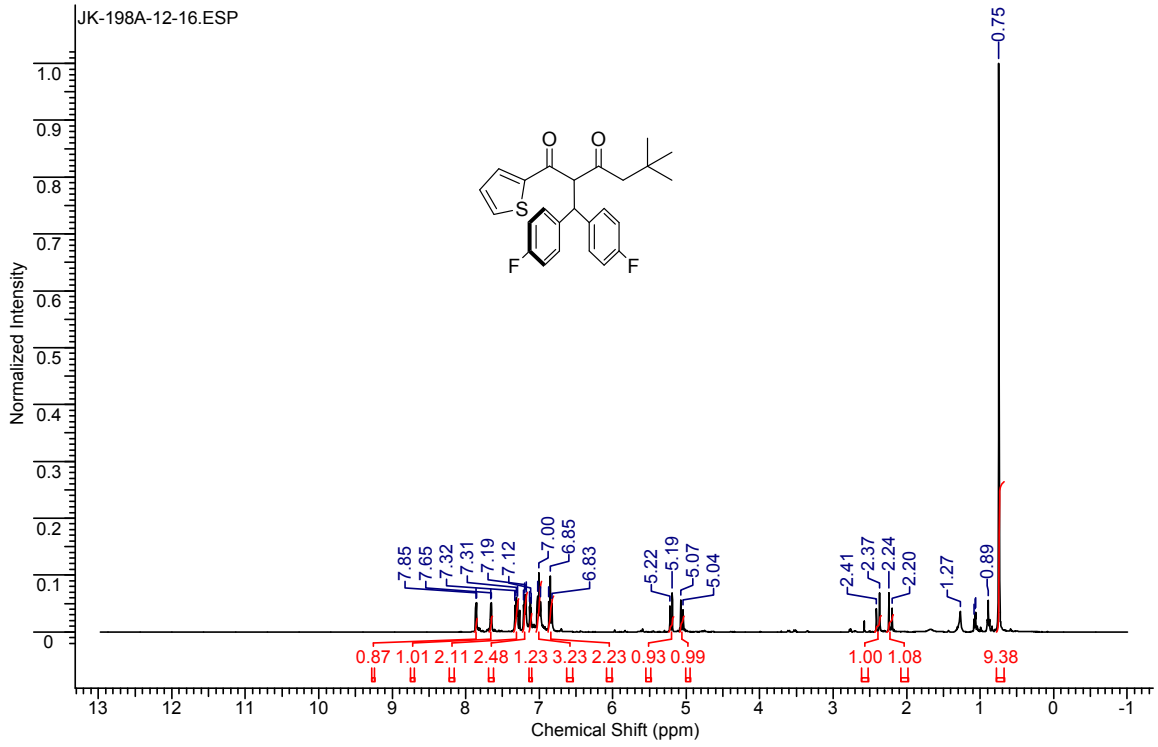
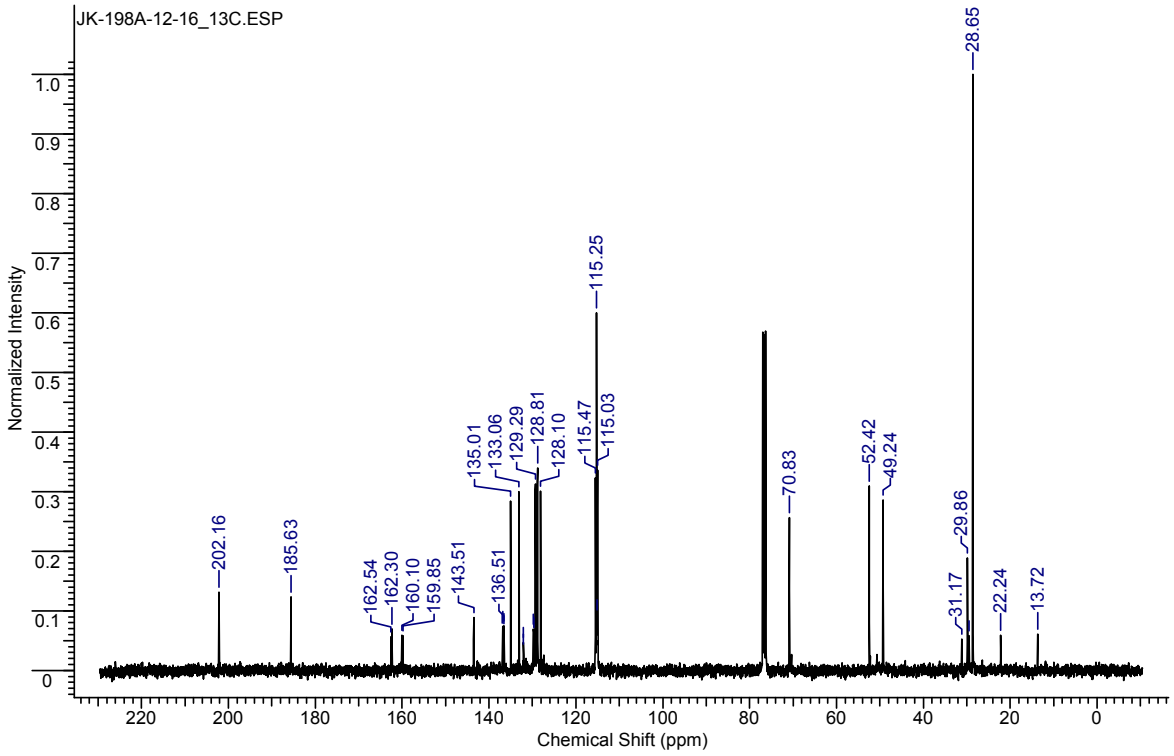


Fig. S-3-50 ^{13}C NMR spectrum of 2-(bis(4-fluorophenyl)methyl)-5,5-dimethyl-1-(thiophen-2-yl)hexane-1,3-dione **8i**.



8j

Fig. S-3-51 ^{1}H NMR spectrum of 2-(bis(4-fluorophenyl)methyl)-5,5-dimethyl-1-(5-bromothiophen-2-yl)hexane-1,3-dione **8j**.

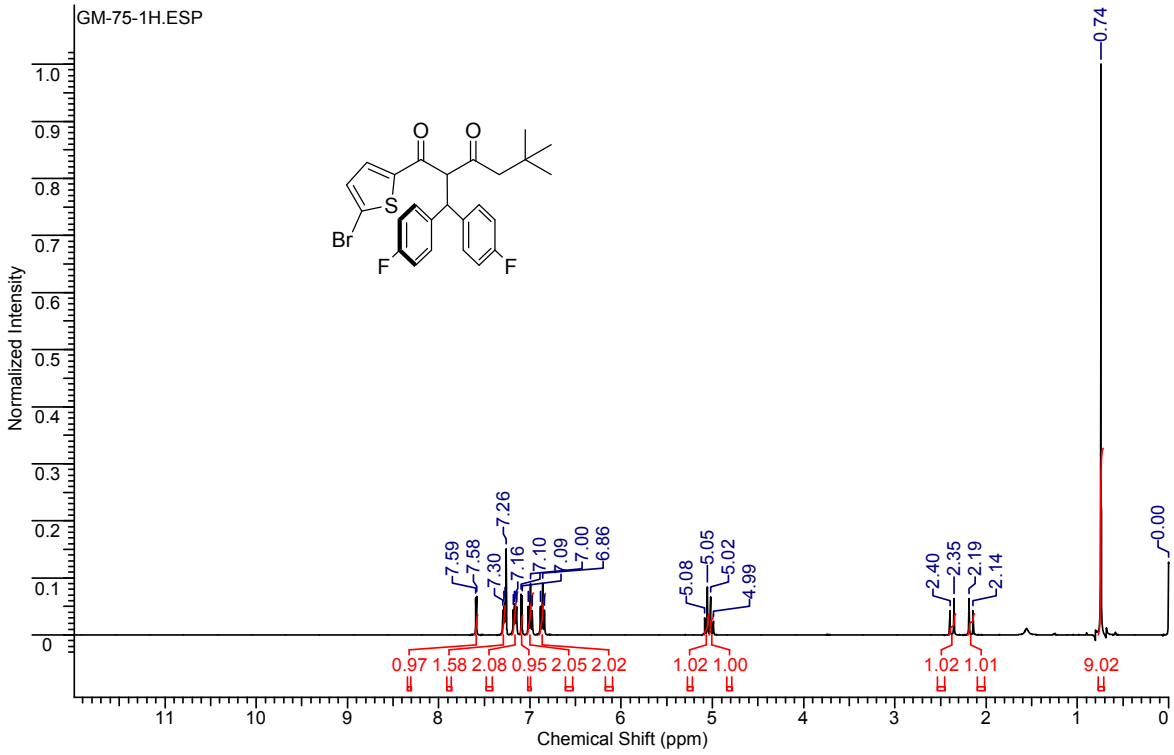
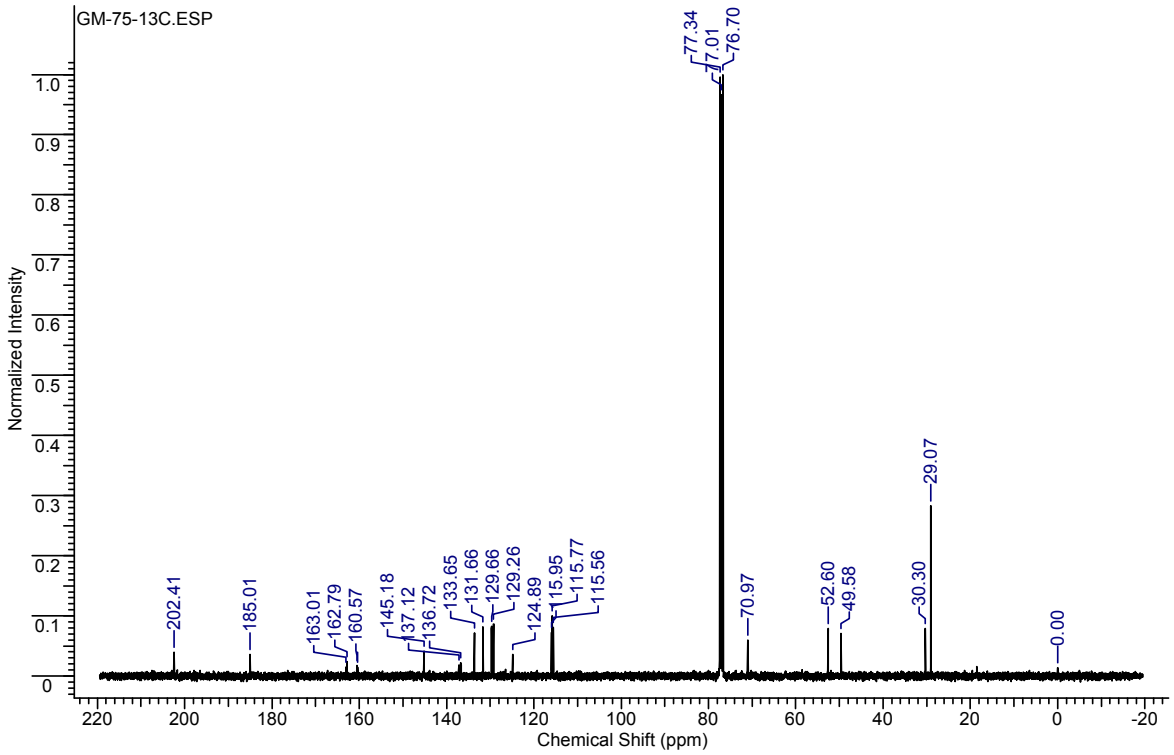


Fig. S-3-52 ^{13}C NMR spectrum of 2-(bis(4-fluorophenyl)methyl)-5,5-dimethyl-1-(5-bromothiophen-2-yl)hexane-1,3-dione **8j**.



8k

Fig. S-3-53 ^{1}H NMR spectrum of 2-(bis(4-fluorophenyl)methyl)-5,5-dimethyl-1-(4,5-dibromothiophen-2-yl)hexane-1,3-dione **8k**.

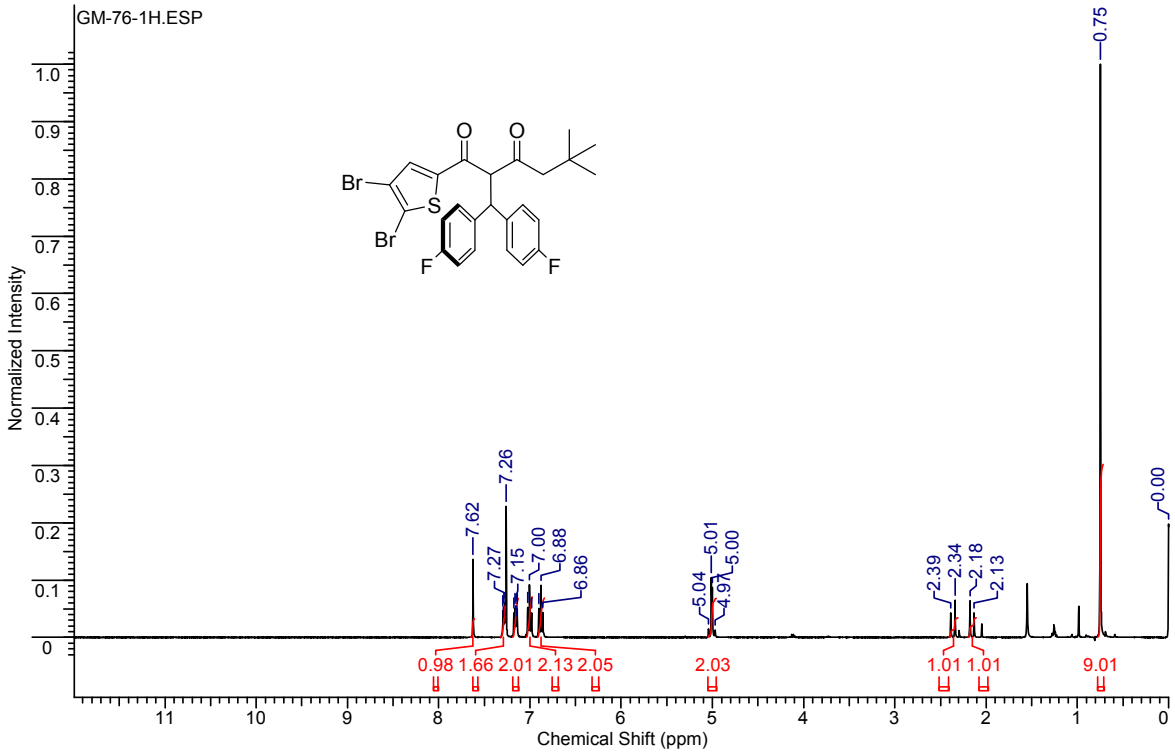
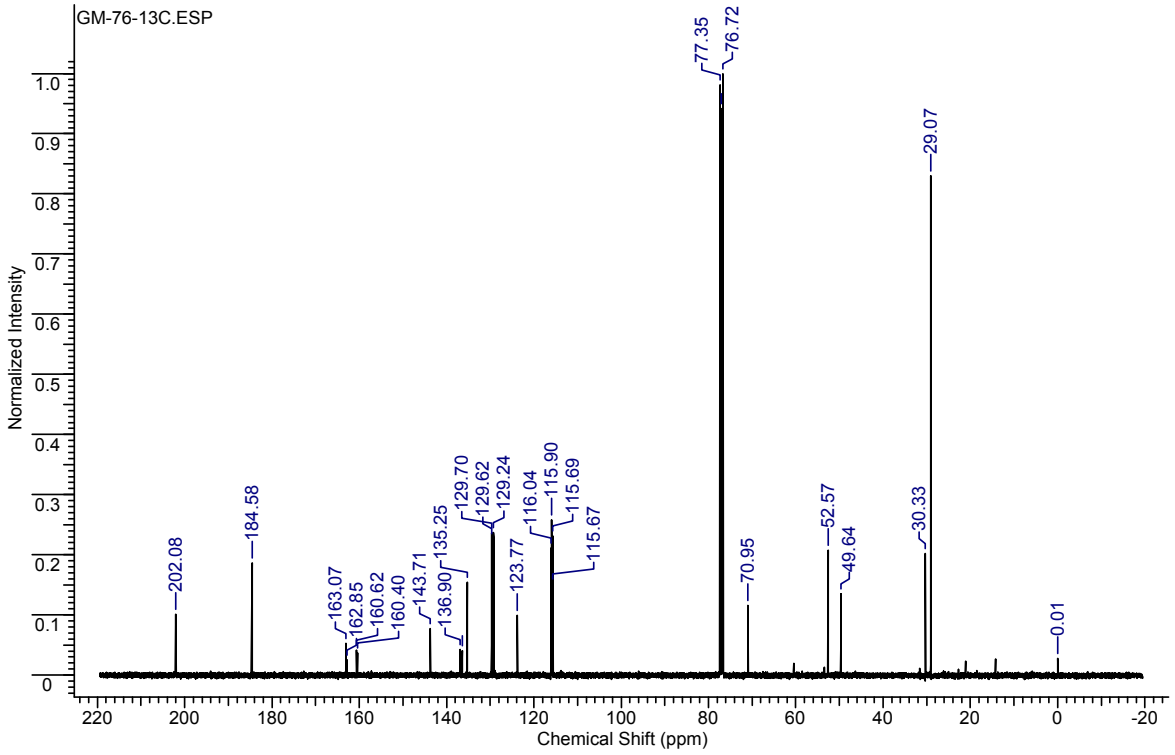


Fig. S-3-54 ^{13}C NMR spectrum of 2-(bis(4-fluorophenyl)methyl)-5,5-dimethyl-1-(4,5-dibromothiophen-2-yl)hexane-1,3-dione **8k**.



8l

Fig. S-3-55 ^{1}H NMR spectrum of 2-(bis(4-fluorophenyl)methyl)-5,5-dimethyl-1-(3,4-dibromothiophen-2-yl)hexane-1,3-dione **8l**.

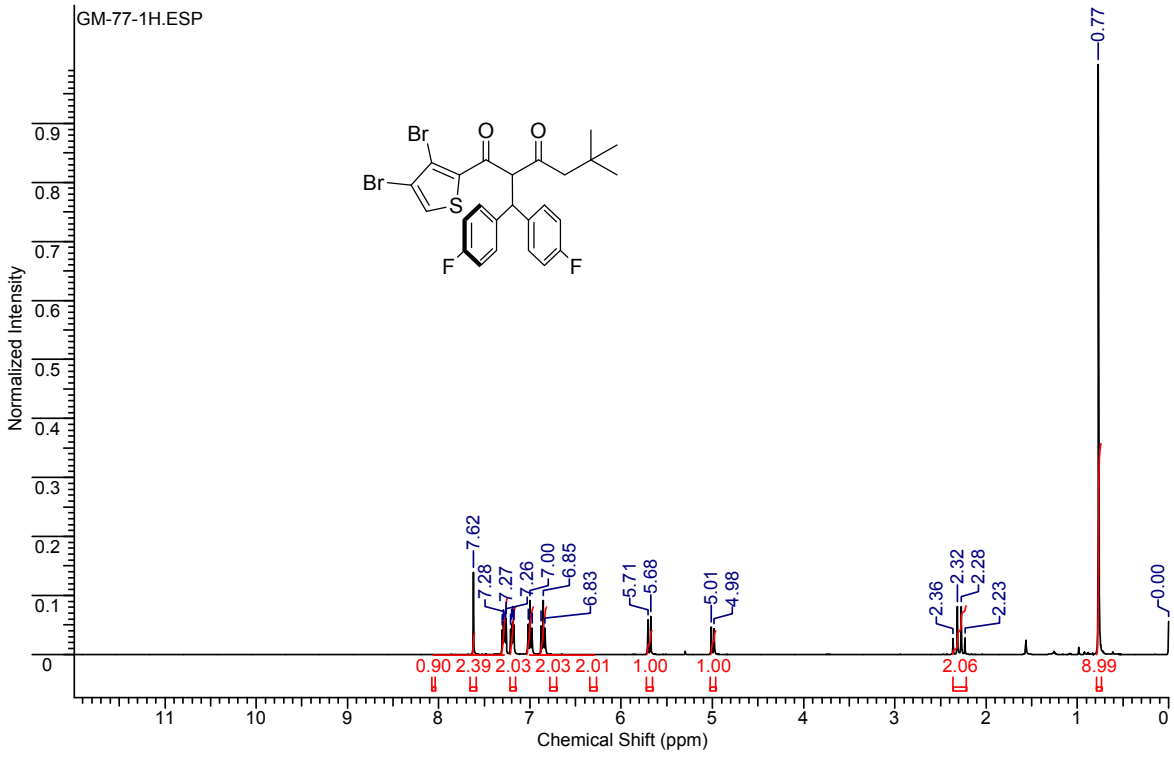
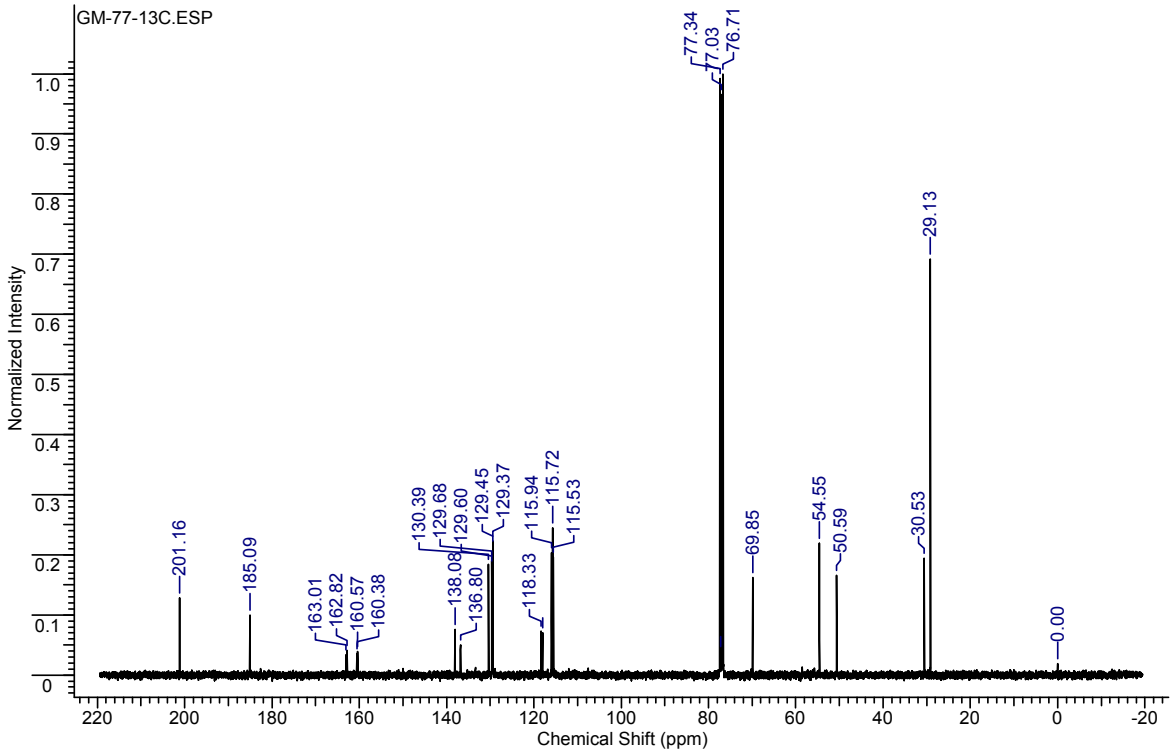


Fig. S-3-56 ^{13}C NMR spectrum of 2-(bis(4-fluorophenyl)methyl)-5,5-dimethyl-1-(3,4-dibromothiophen-2-yl)hexane-1,3-dione **8l**.



9 **Fig. S-3-57** ^{1}H NMR spectrum of 2-benzhydryl-1-phenyl-5,5-dimethylhexane-1,3-dione **9**.

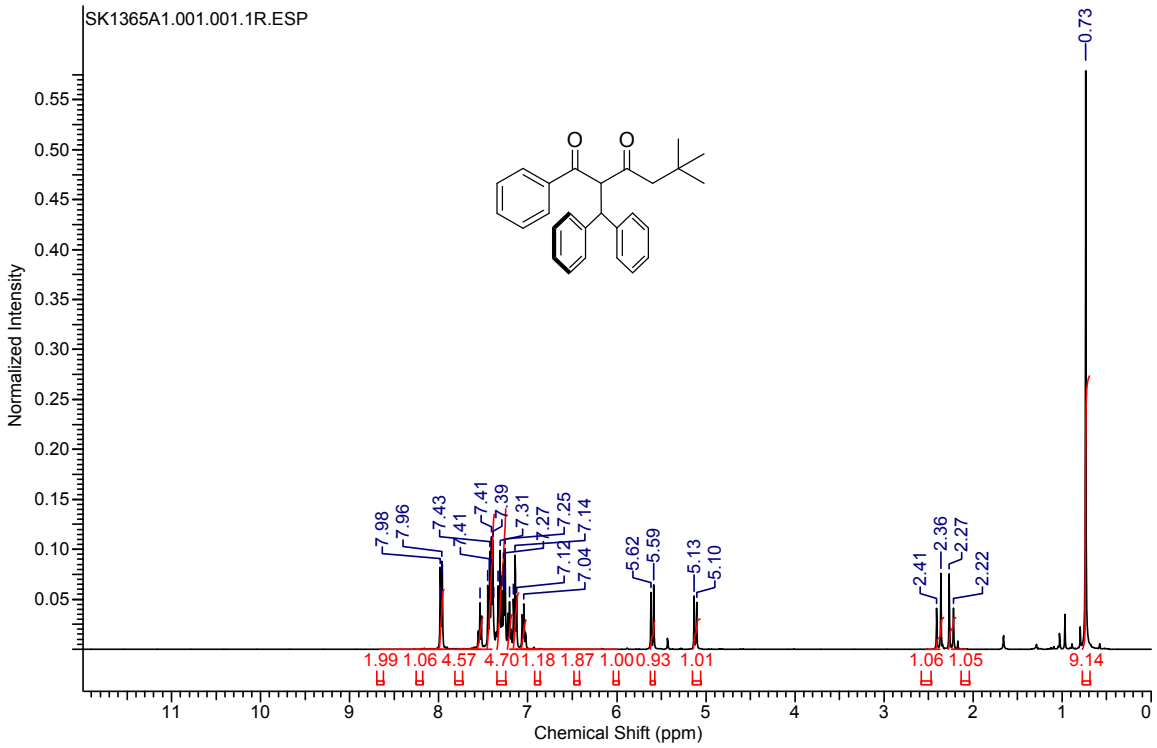
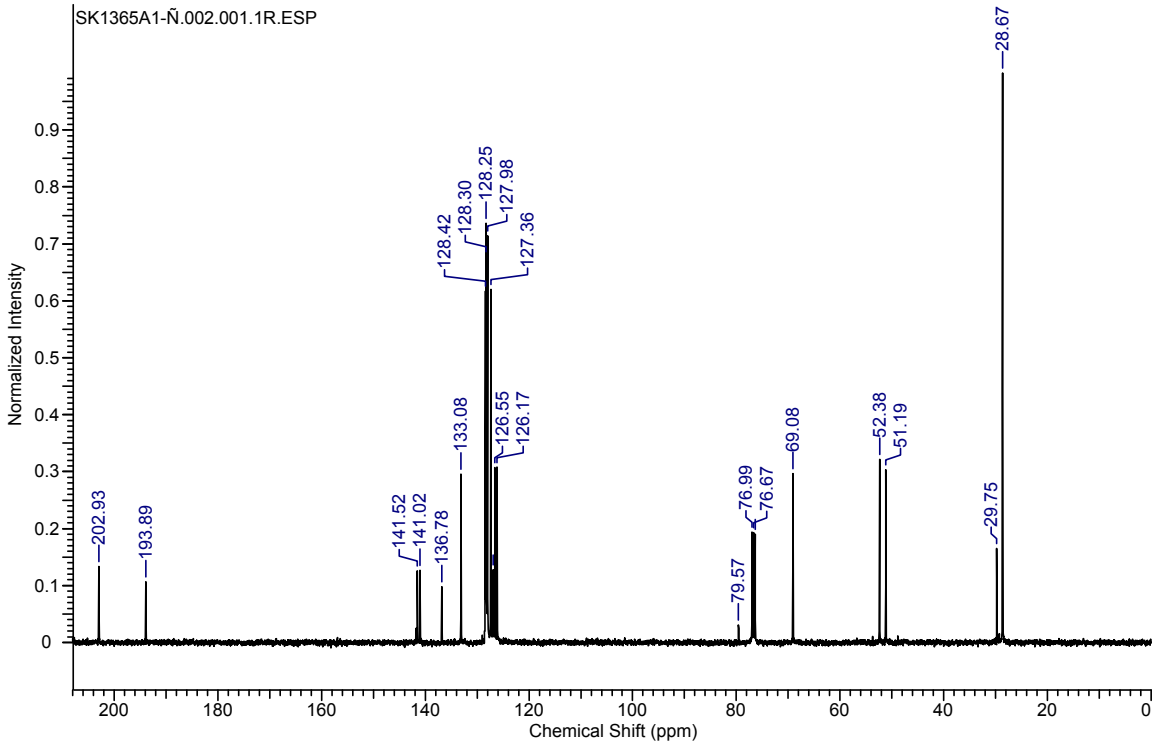


Fig. S-3-58 ^{13}C NMR spectrum of 2-benzhydryl-1-phenyl-5,5-dimethylhexane-1,3-dione **9**.



10a

Fig. S-3-59 ^{1}H NMR spectrum of 2-(bis(4-fluorophenyl)methyl)-4-(3-hydroxy-1-adamantyl)-1-phenylbutane-1,3-dione **10a**.

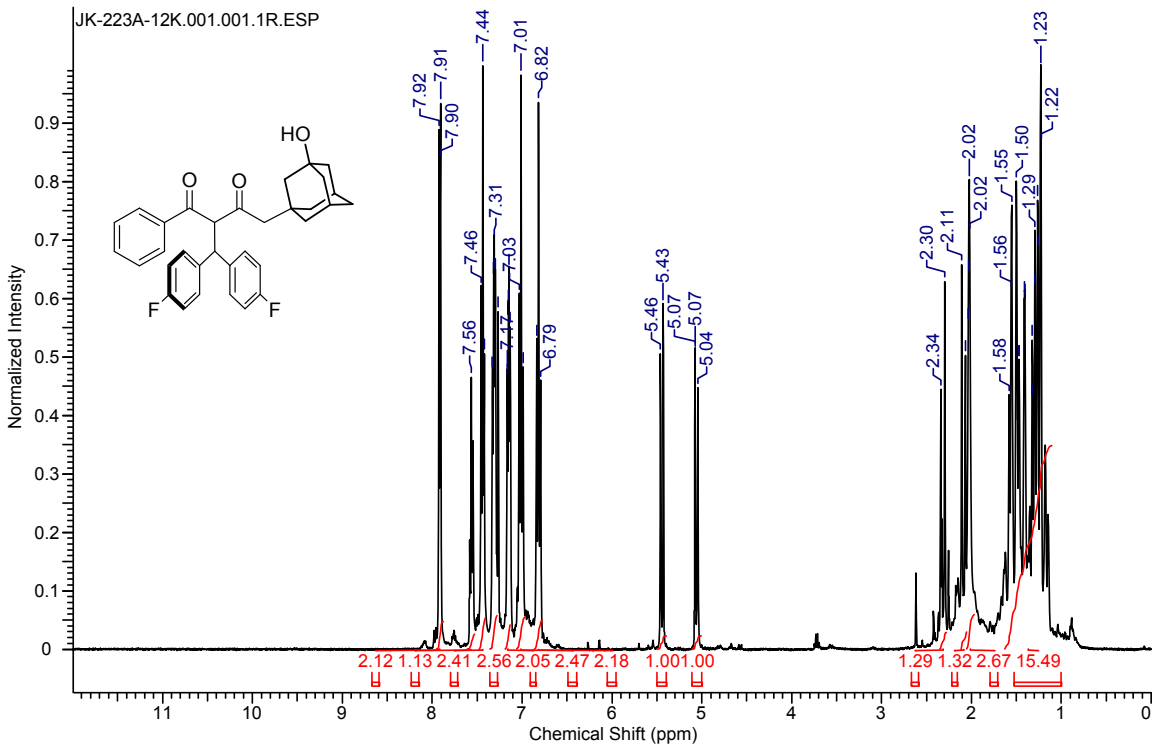
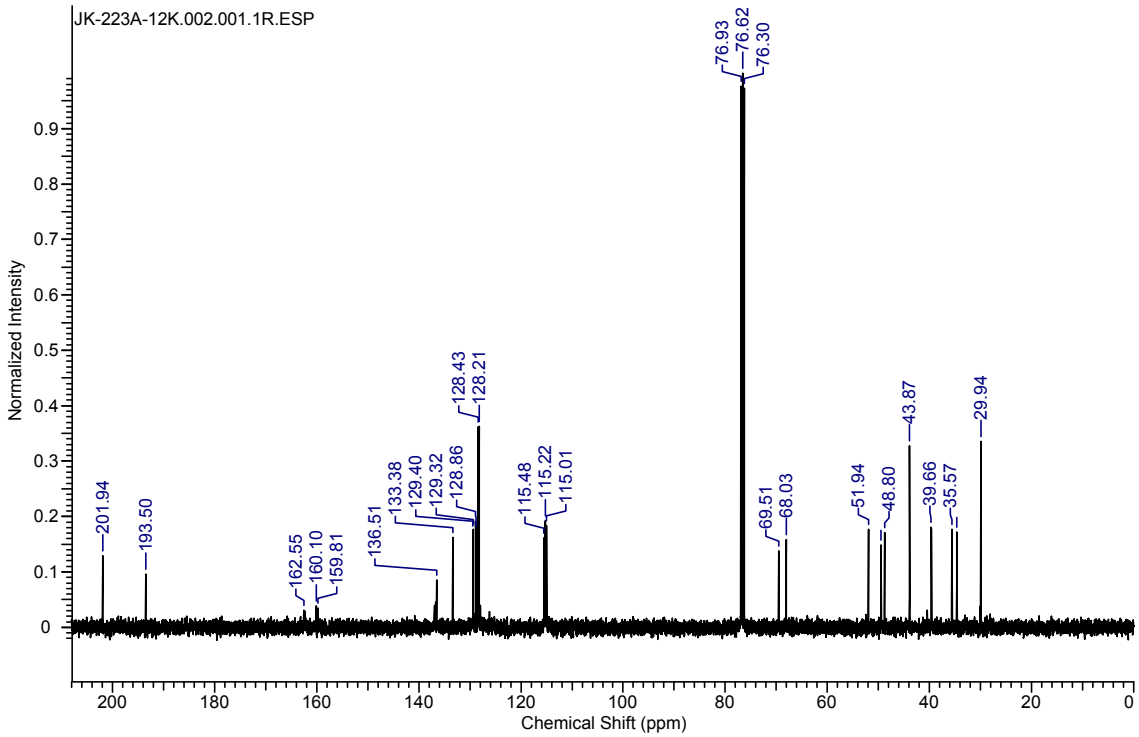


Fig. S-3-60 ^{13}C NMR spectrum of 2-(bis(4-fluorophenyl)methyl)-4-(3-hydroxy-1-adamantyl)-1-phenylbutane-1,3-dione **10a**.



10b

Fig. S-3-61 ^{1}H NMR spectrum of 2-(bis(4-fluorophenyl)methyl)-4-(3-hydroxy-1-adamantyl)-1-(2,4-dichlorophenyl)butane-1,3-dione **10b**.

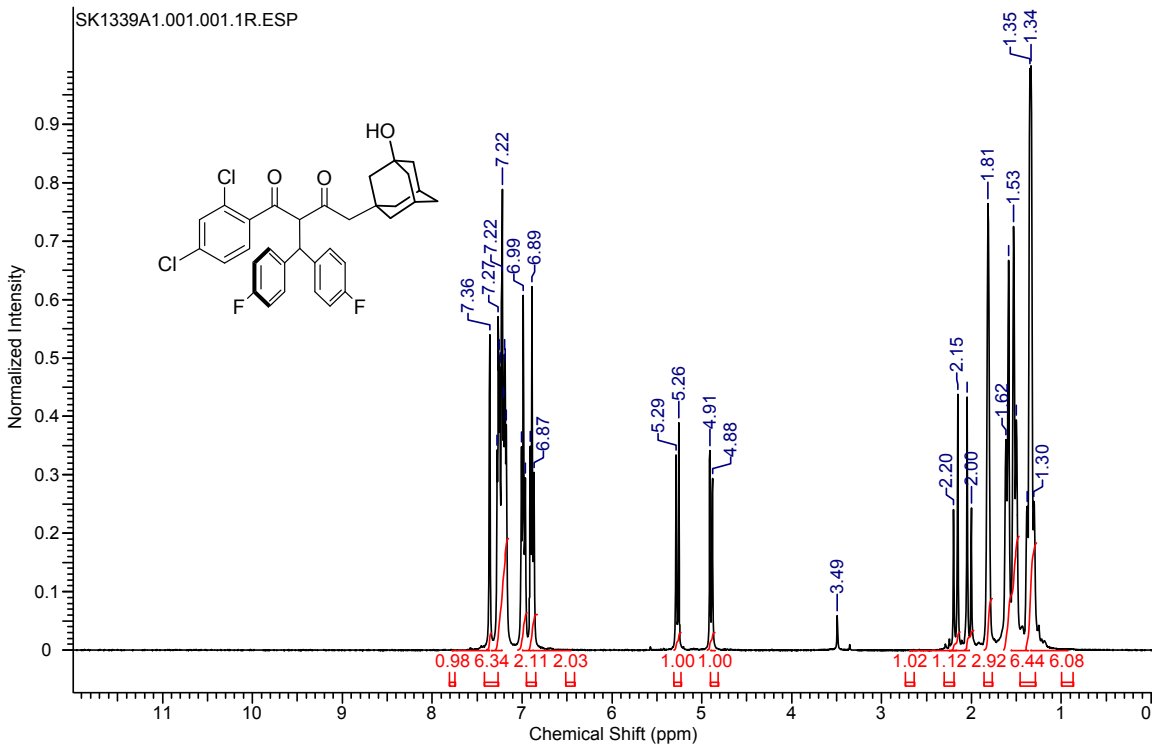
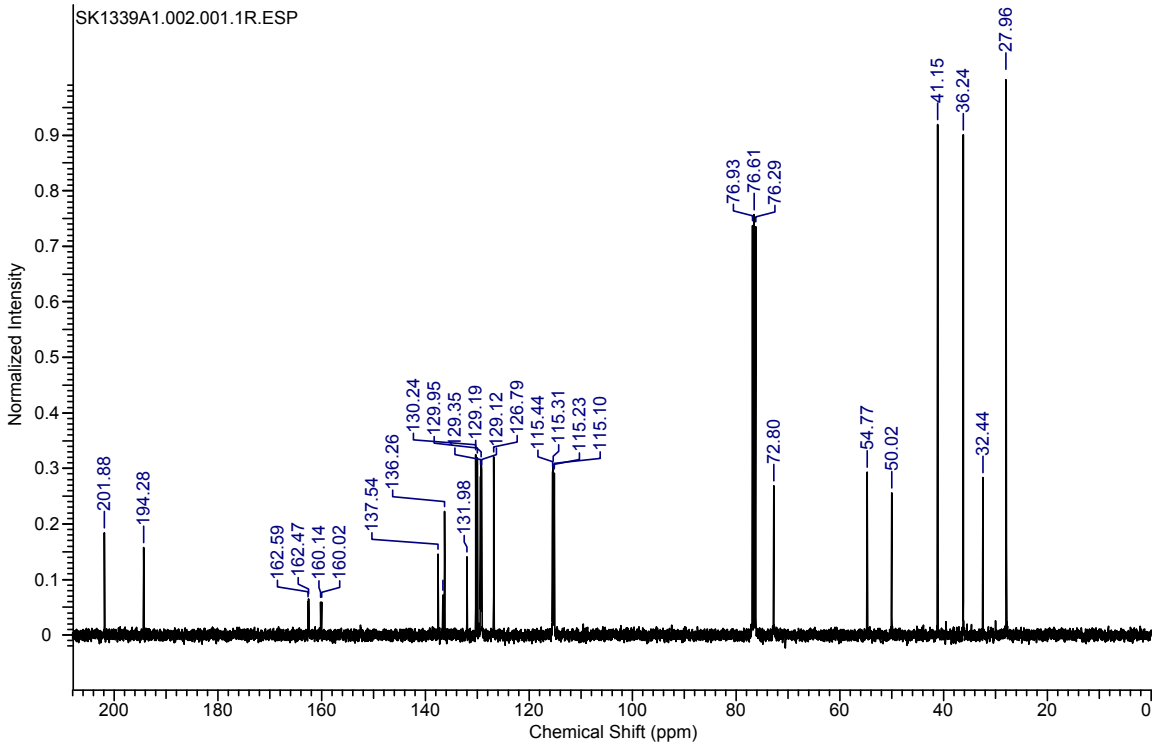


Fig. S-3-62 ^{13}C NMR spectrum of 2-(bis(4-fluorophenyl)methyl)-4-(3-hydroxy-1-adamantyl)-1-(2,4-dichlorophenyl)butane-1,3-dione **10b**.



11a

Fig. S-3-63 ^{1}H NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-5-neopentyl-3-phenyl-1*H*-pyrazole **11a**.

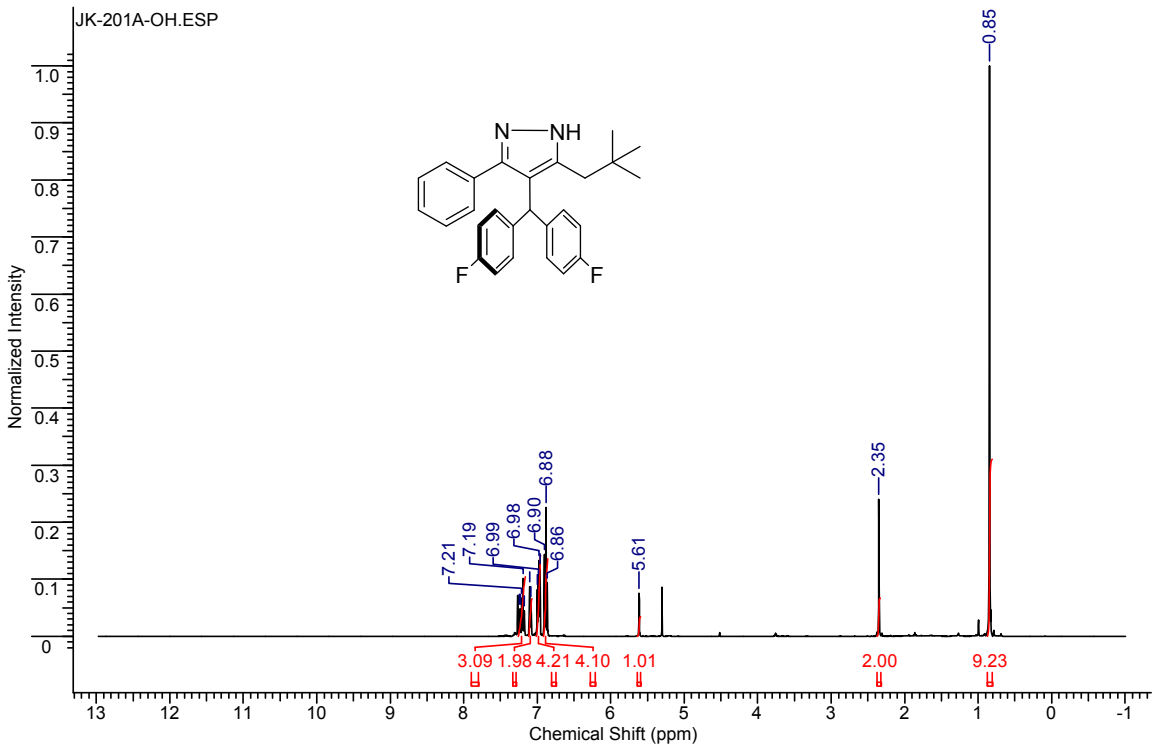
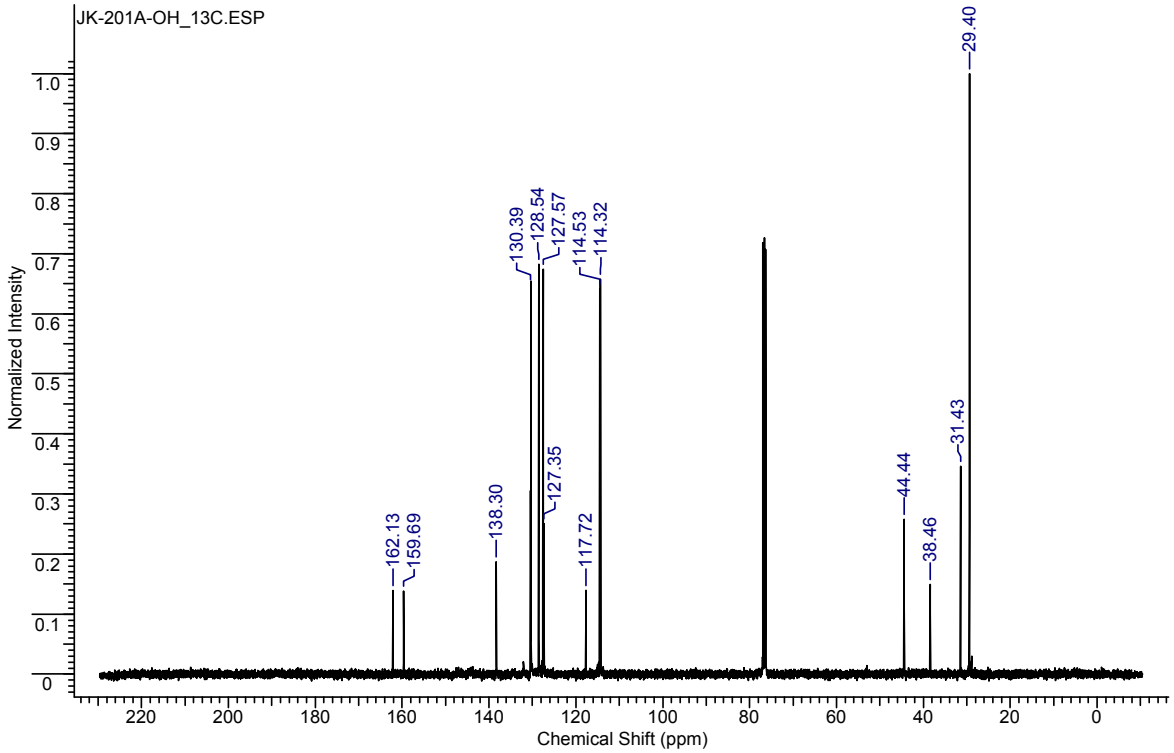


Fig. S-3-64 ^{13}C NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-5-neopentyl-3-phenyl-1*H*-pyrazole **11a**.



11b

Fig. S-3-65 ^{1}H NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-5-(1-adamantylmethyl)-3-phenyl-1*H* -pyrazole **11b**.

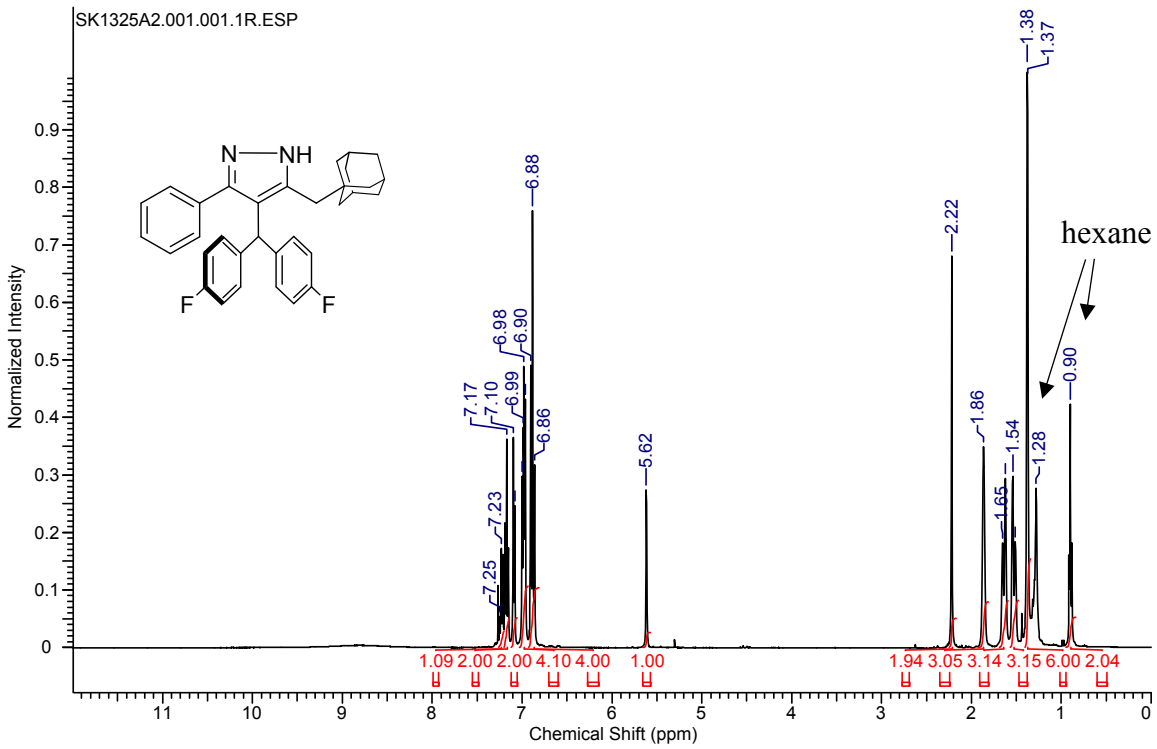
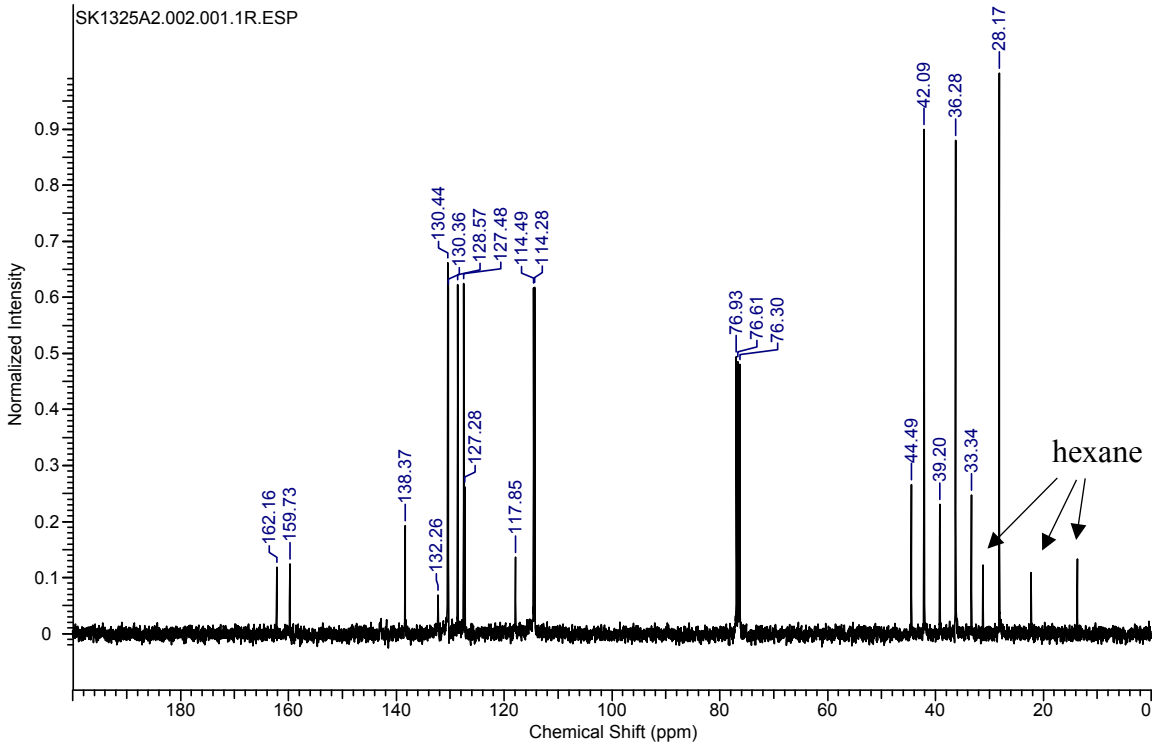


Fig. S-3-66 ^{13}C NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-5-(1-adamantylmethyl)-3-phenyl -1*H* -pyrazole **11b**.



11c

Fig. S-3-67 ^{1}H NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-5-(1-adamantylmethyl)-3-(2,4-dichlorophenyl)-1*H*-pyrazole **11c**.

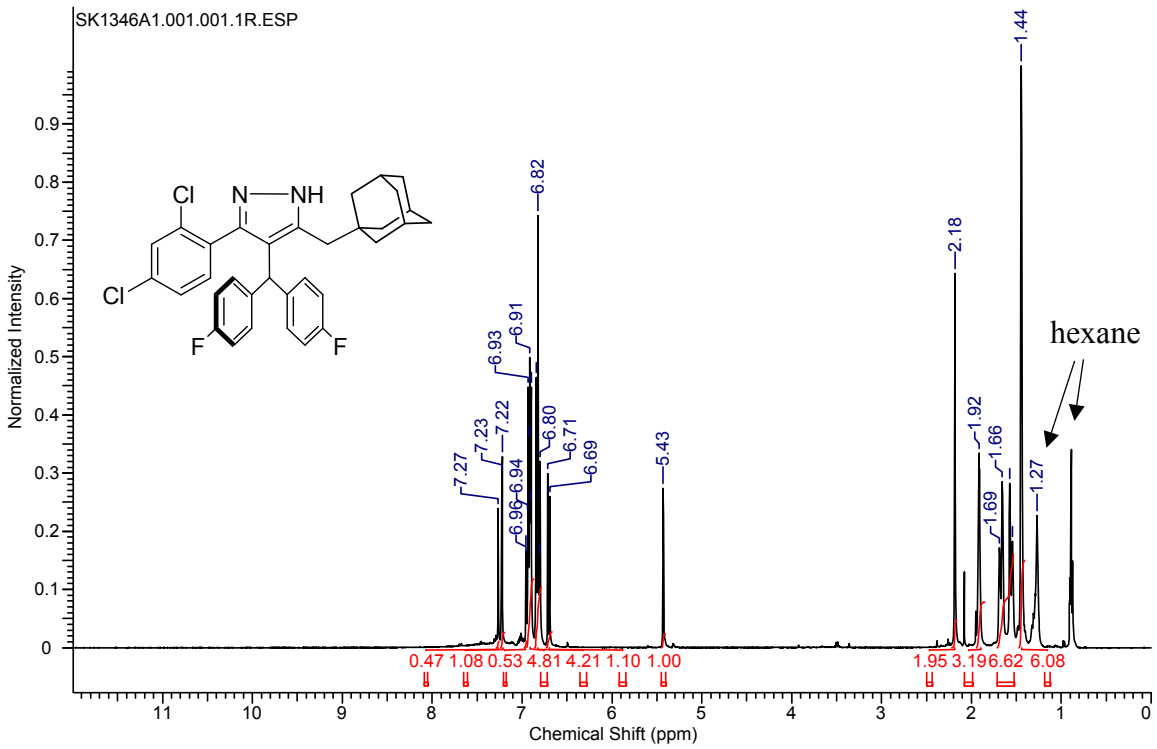
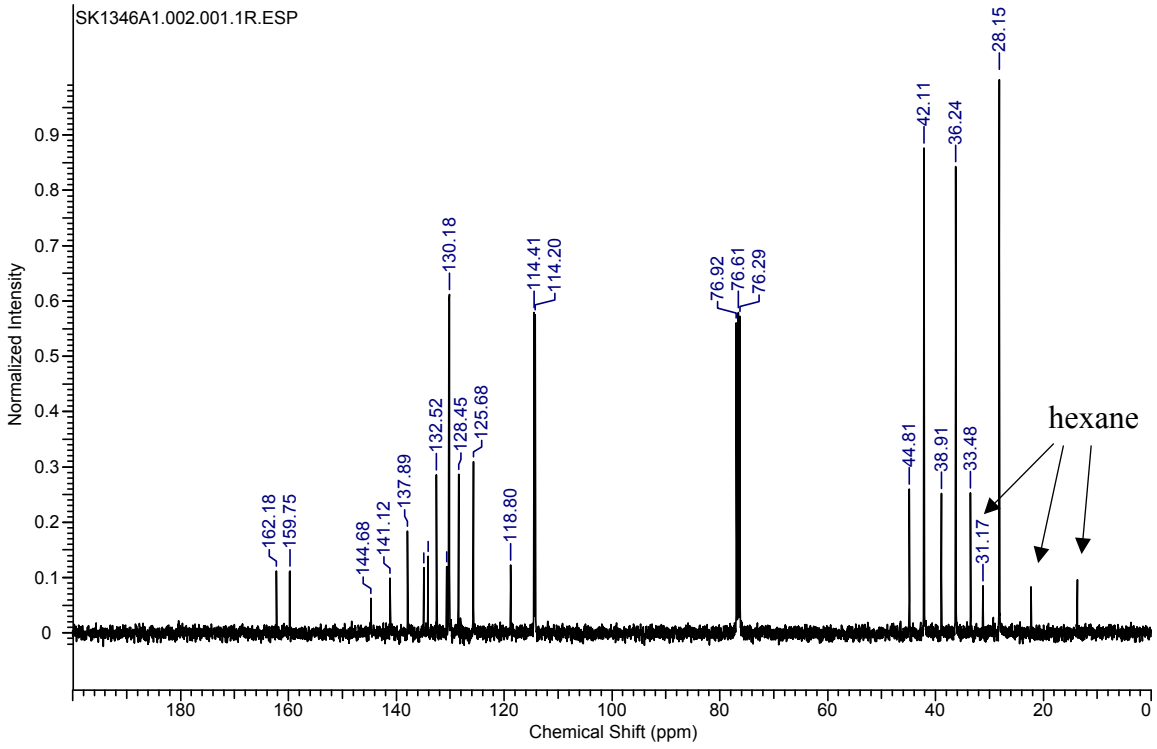


Fig. S-3-68 ^{13}C NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-5-(1-adamantylmethyl)-3-(2,4-dichlorophenyl)- 1*H* -pyrazole **11c**.



11d

Fig. S-3-69 ^{1}H NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-5-(3-hydroxy-1-adamantylmethyl)-3-phenyl-1*H*-4-pyrazole **11d**.

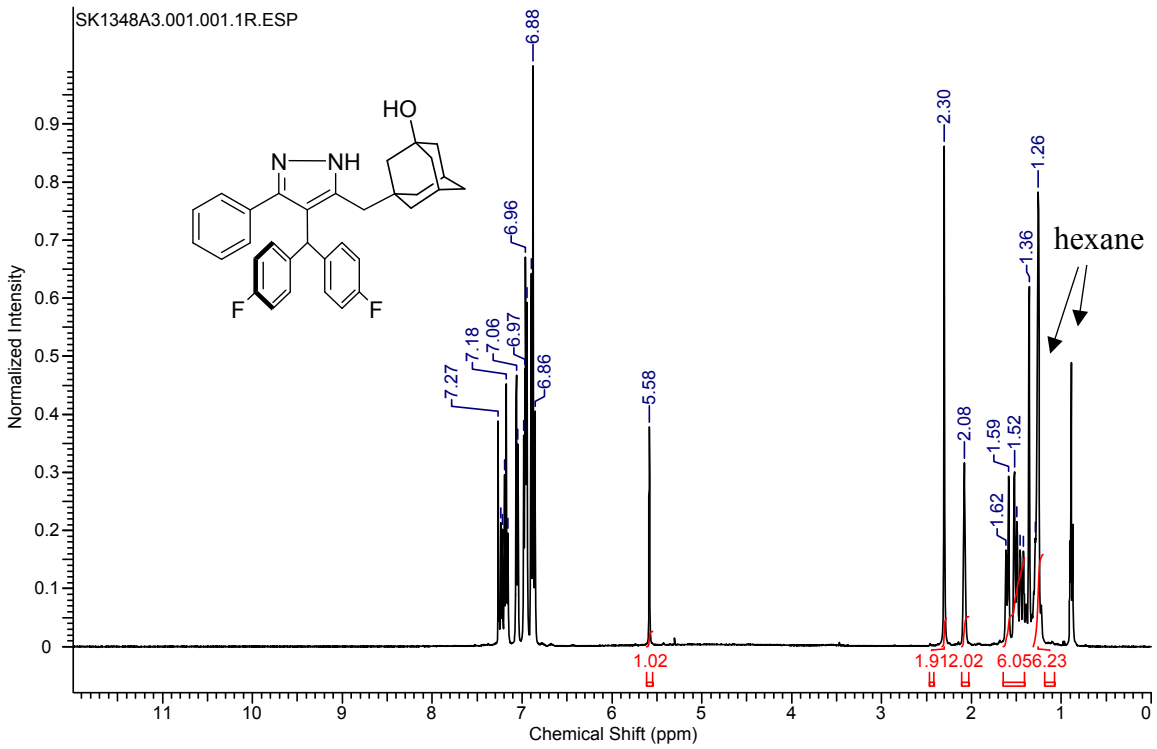
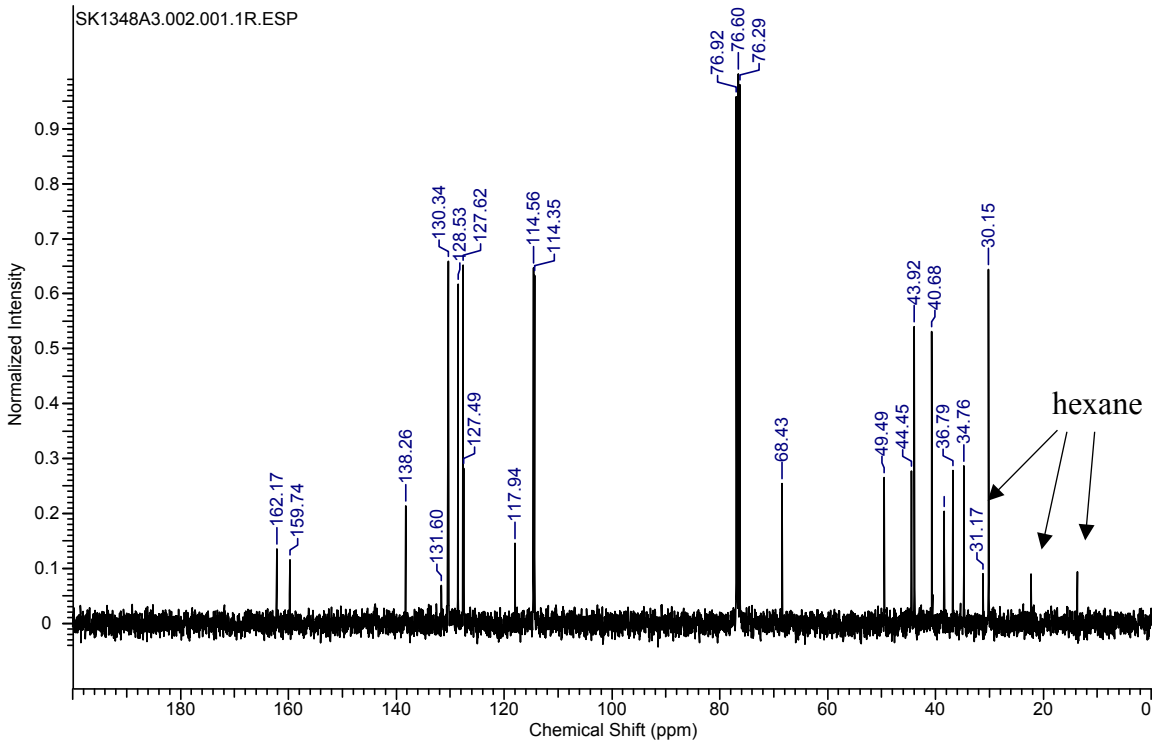


Fig. S-3-70 ^{13}C NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-5-(3-hydroxy-1-adamantylmethyl)-3-phenyl-1*H*-4-pyrazole **11d**.



11e

Fig. S-3-71 ^{1}H NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-3-(2,4-dichlorophenyl)-5-(3-hydroxy-1-adamantylmethyl)-1*H*-4-pyrazole **11e**.

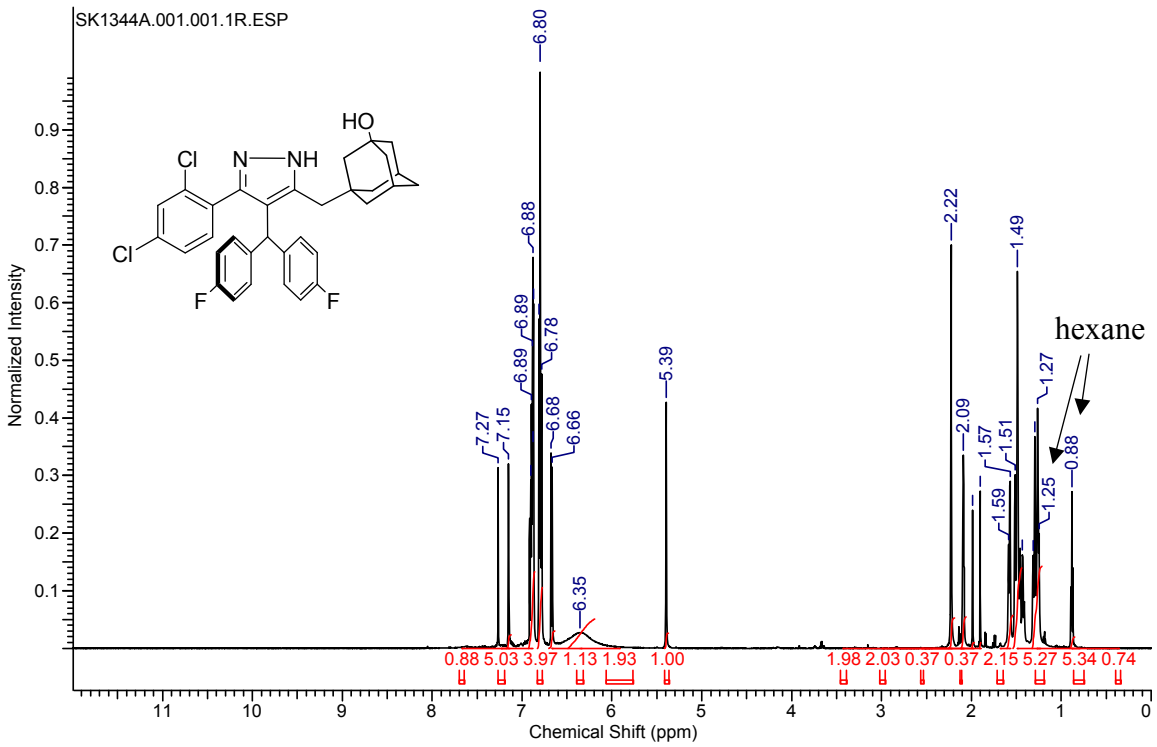
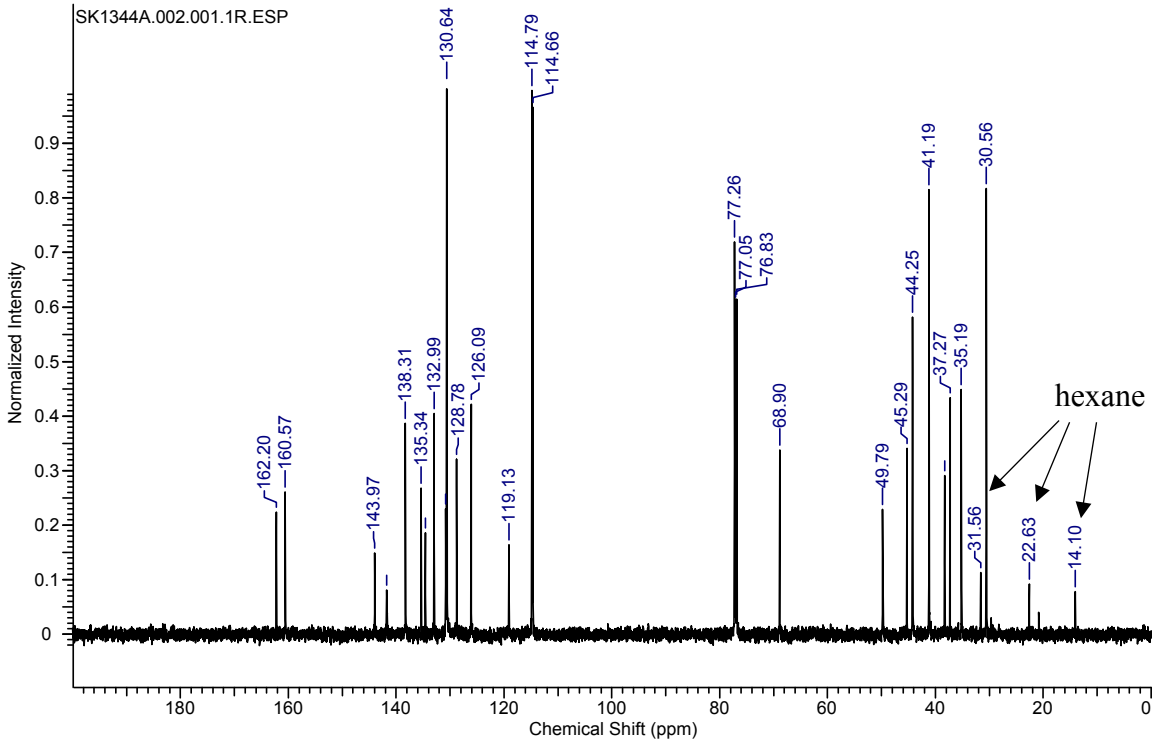


Fig. S-3-72 ^{13}C NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-3-(2,4-dichlorophenyl)-5-(3-hydroxy-1-adamantylmethyl)-1*H*-4-pyrazole **11e**.



11f

Fig. S-3-73 ^{1}H NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-3-(4-chlorophenyl)-5-neopentyl-*1H*-pyrazole **11f**.

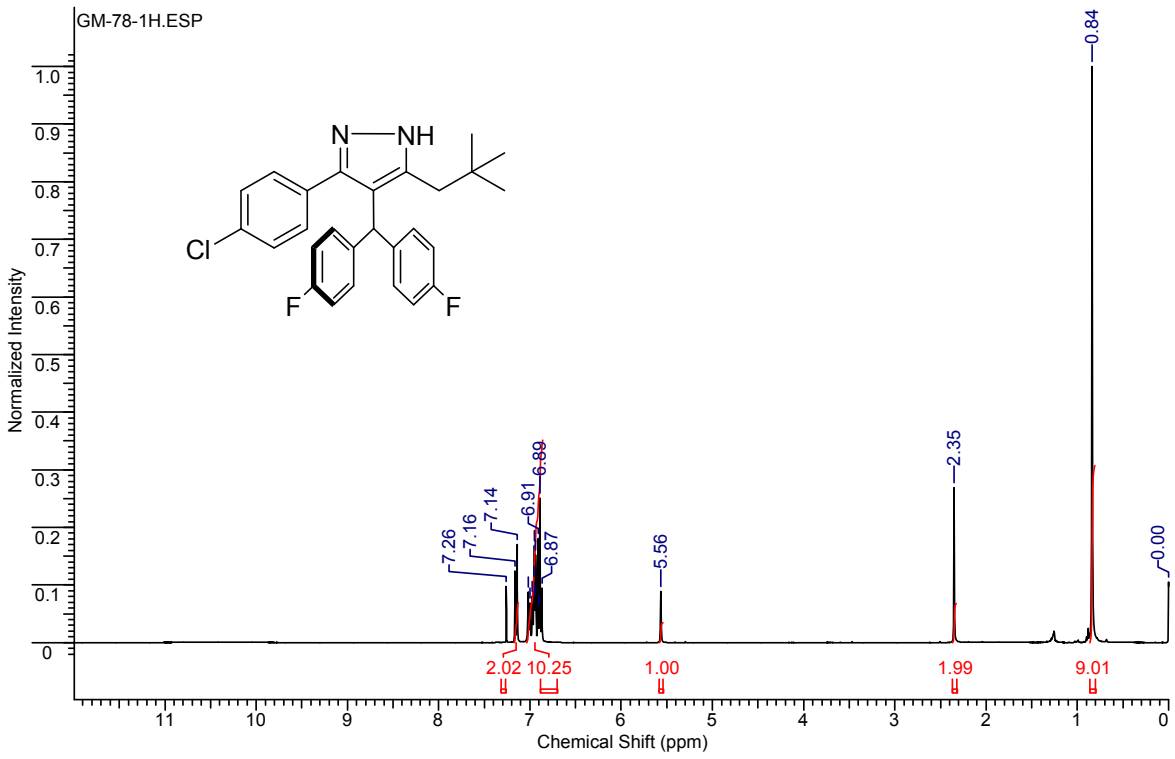
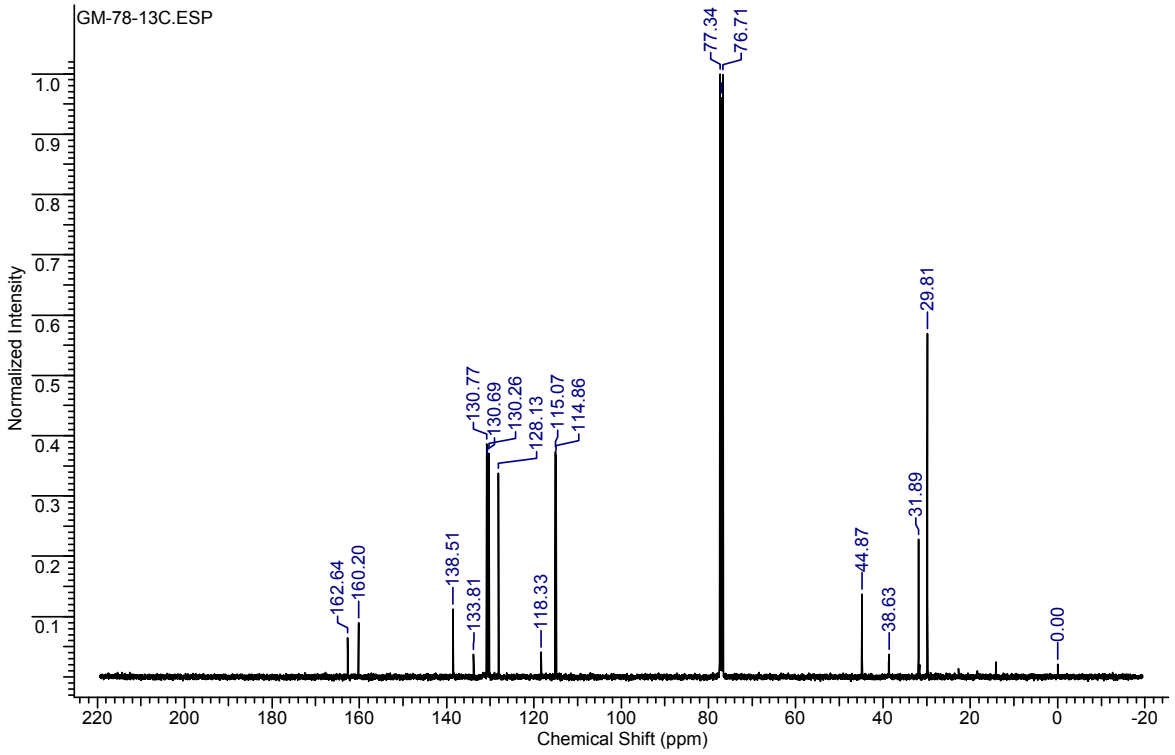


Fig. S-3-74 ^{13}C NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-3-(4-chlorophenyl)-5-neopentyl-*1H*-pyrazole **11f**.



11g

Fig. S-3-75 ^{1}H NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-3-(3-chlorophenyl)-5-neopentyl-1*H*-pyrazole **11g**.

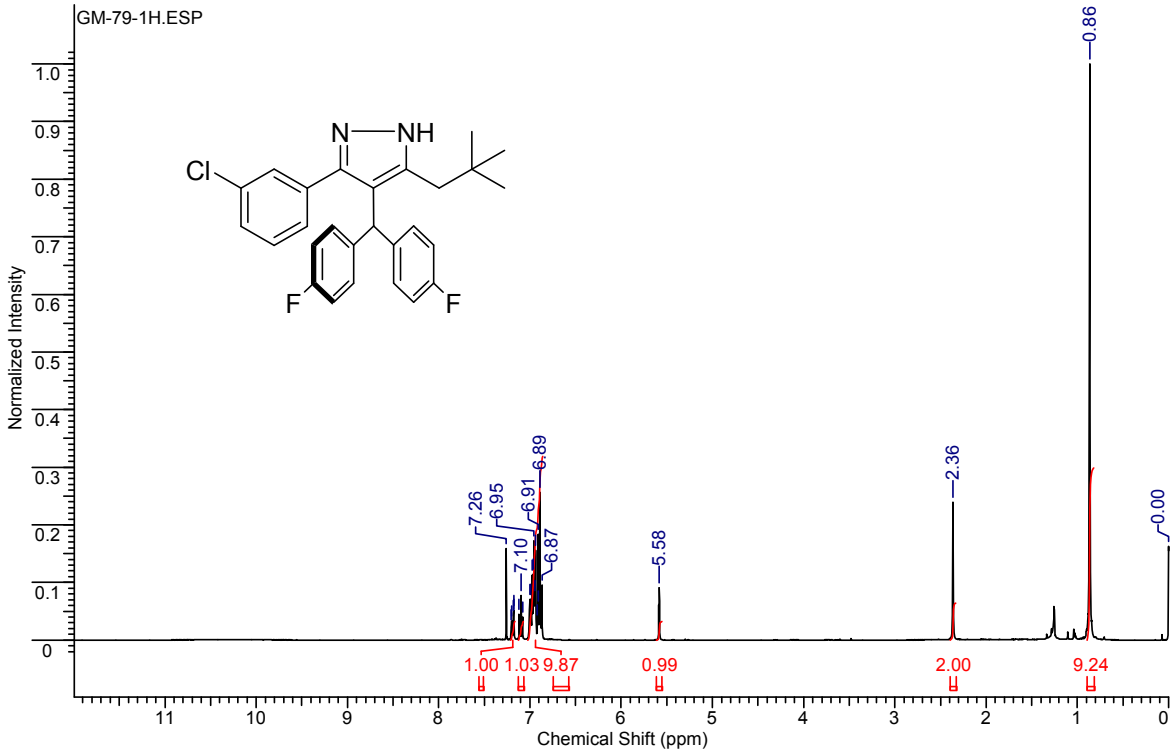
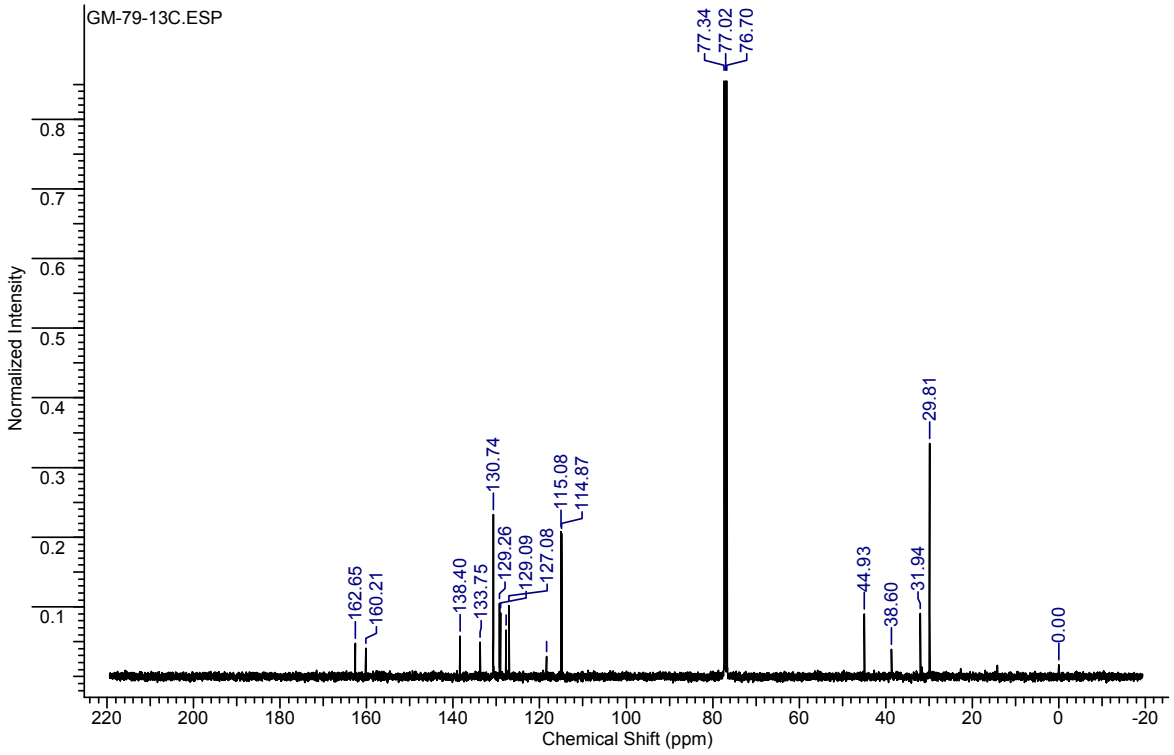


Fig. S-3-76 ^{13}C NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-3-(3-chlorophenyl)-5-neopentyl-1*H*-pyrazole **11g**.



11h

Fig. S-3-77 ^{1}H NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-3-(2-chlorophenyl)-5-neopentyl-*1H*-pyrazole **11h**.

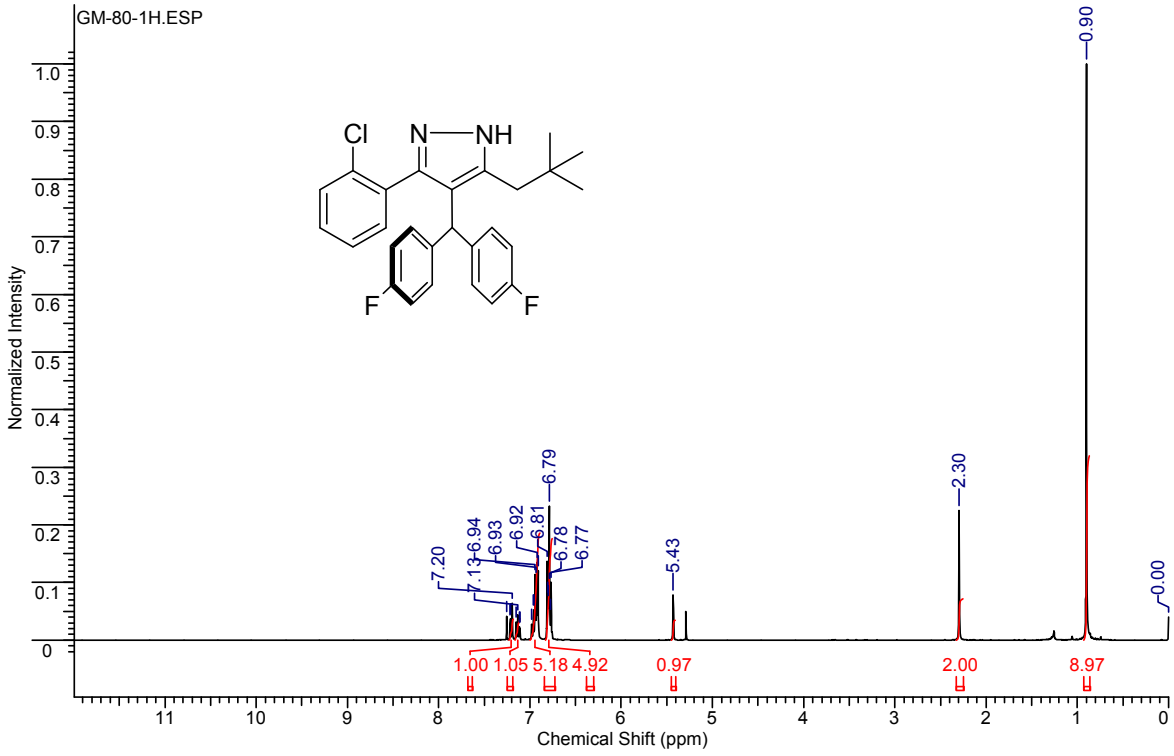
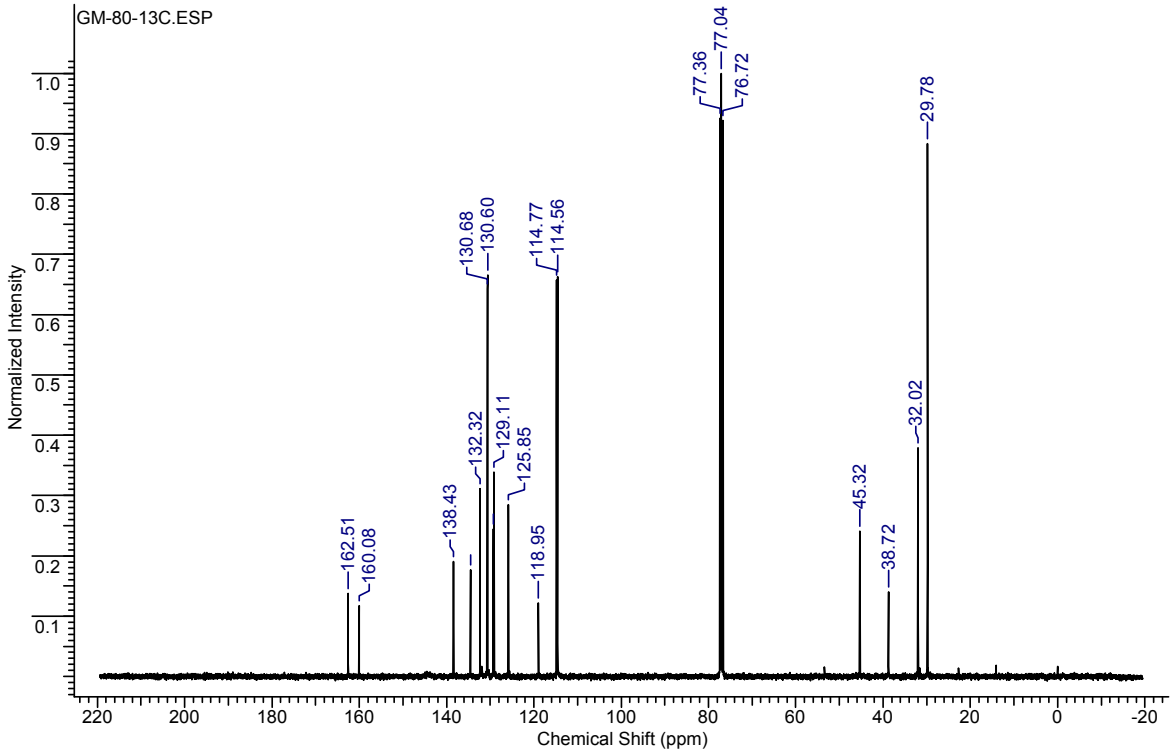


Fig. S-3-78 ^{13}C NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-3-(2-chlorophenyl)-5-

neopentyl-*1H*-pyrazole **11h**.



11i **Fig. S-3-79** ^{1}H NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-5-neopentyl-3-(thienyl-2)-1*H*-pyrazole **11i**.

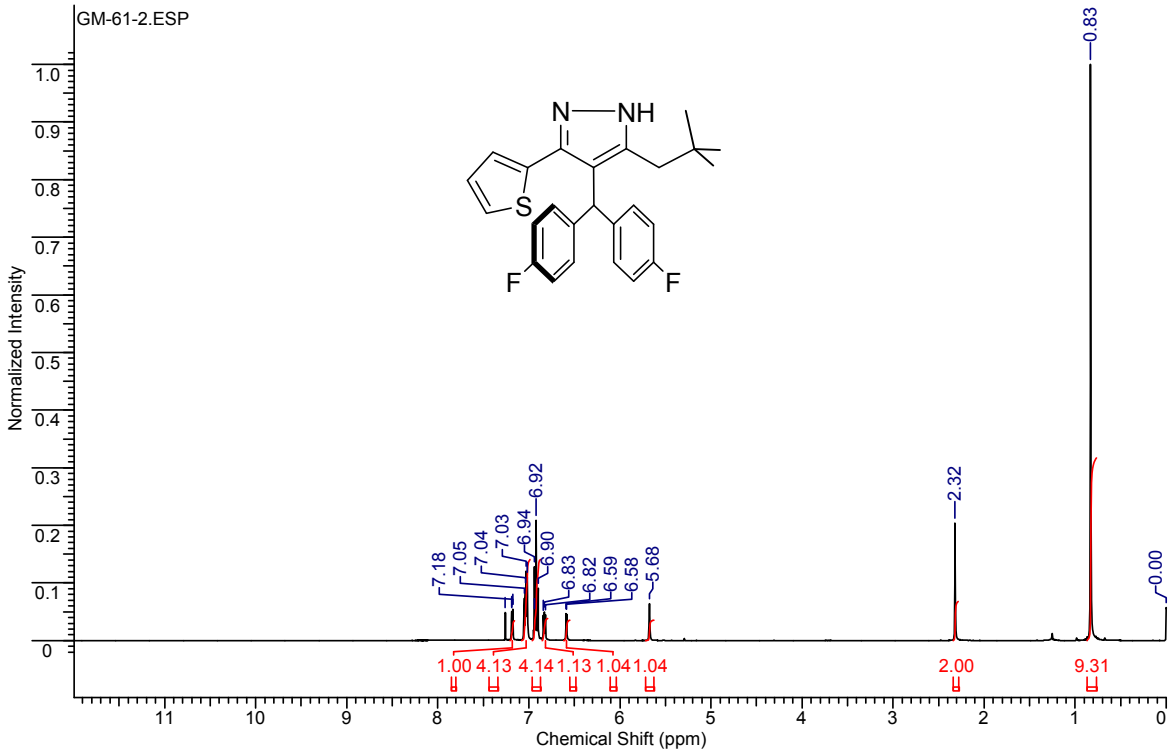
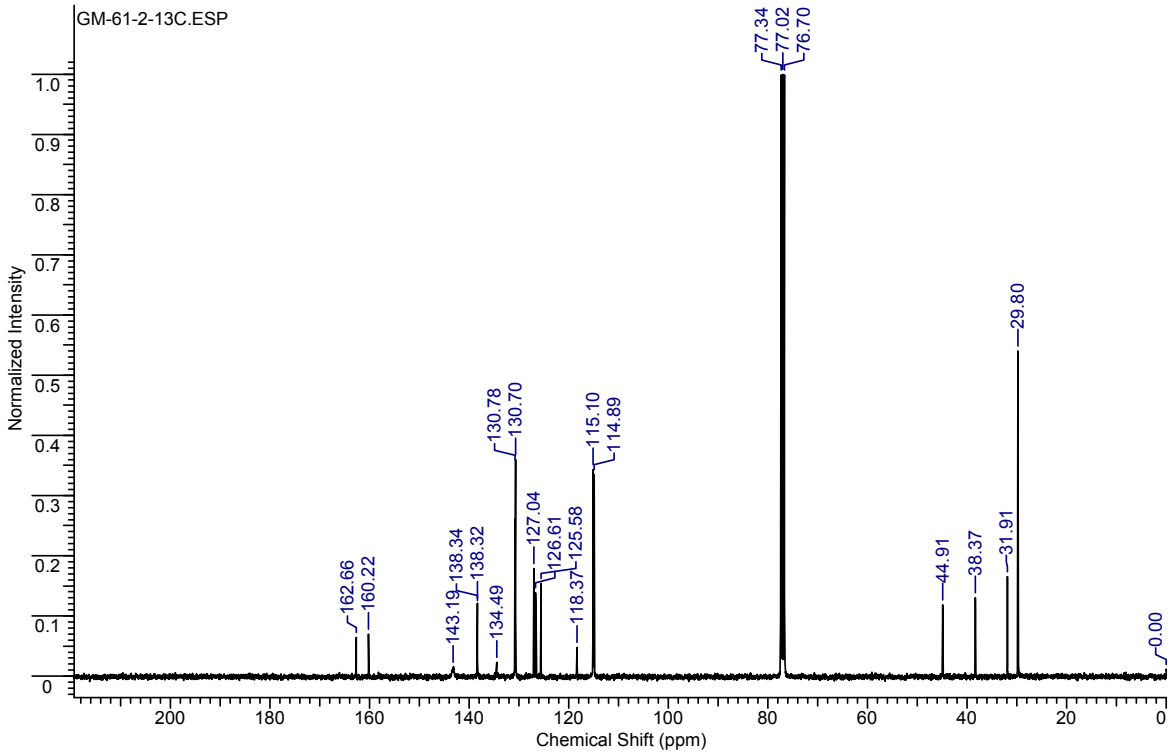


Fig. S-3-80 ^{13}C NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-5-neopentyl-3-(thienyl-2)-1*H*-pyrazole **11i**.



11j

Fig. S-3-81 ^{1}H NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-3-(5-bromothiophen-2-yl)-5-neopentyl-1*H*-pyrazole **11j**.

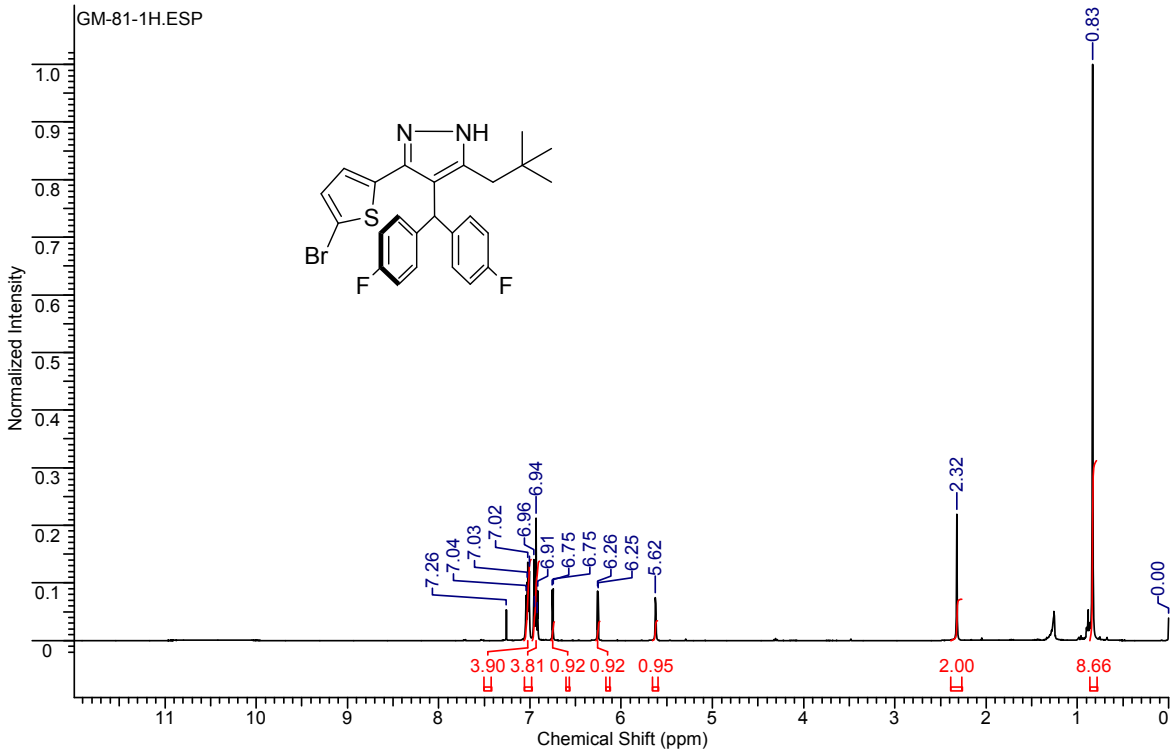
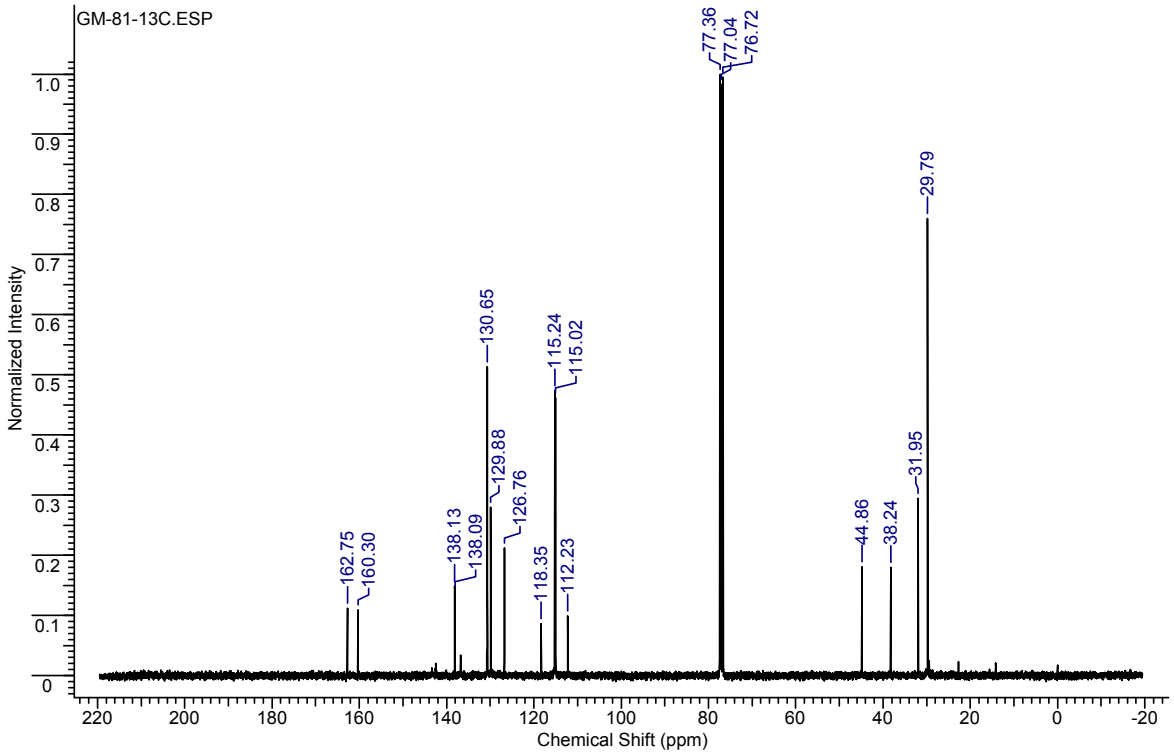


Fig. S-3-82 ^{13}C NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-3-(5-bromothiophen-2-yl)-5-neopentyl-1*H*-pyrazole **11j**.



11k

Fig. S-3-83 ^{1}H NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-3-(4,5-dibromothiophen-2-yl)-5-neopentyl-1*H*-pyrazole **11k**.

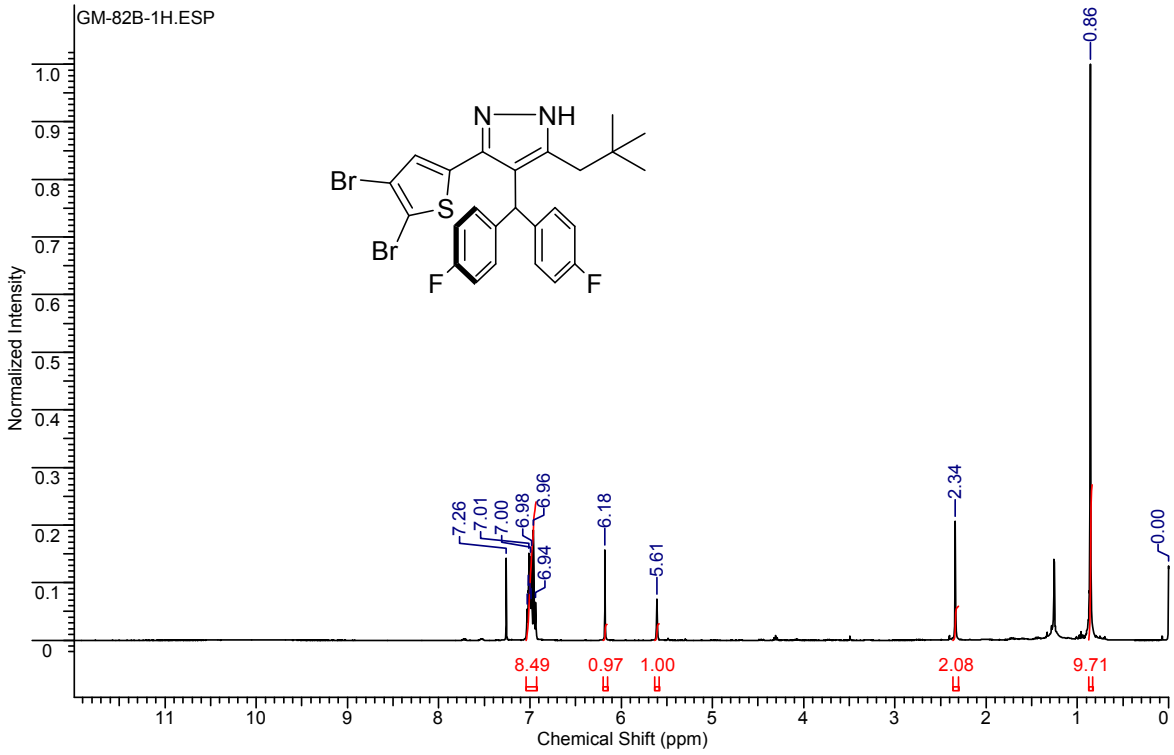
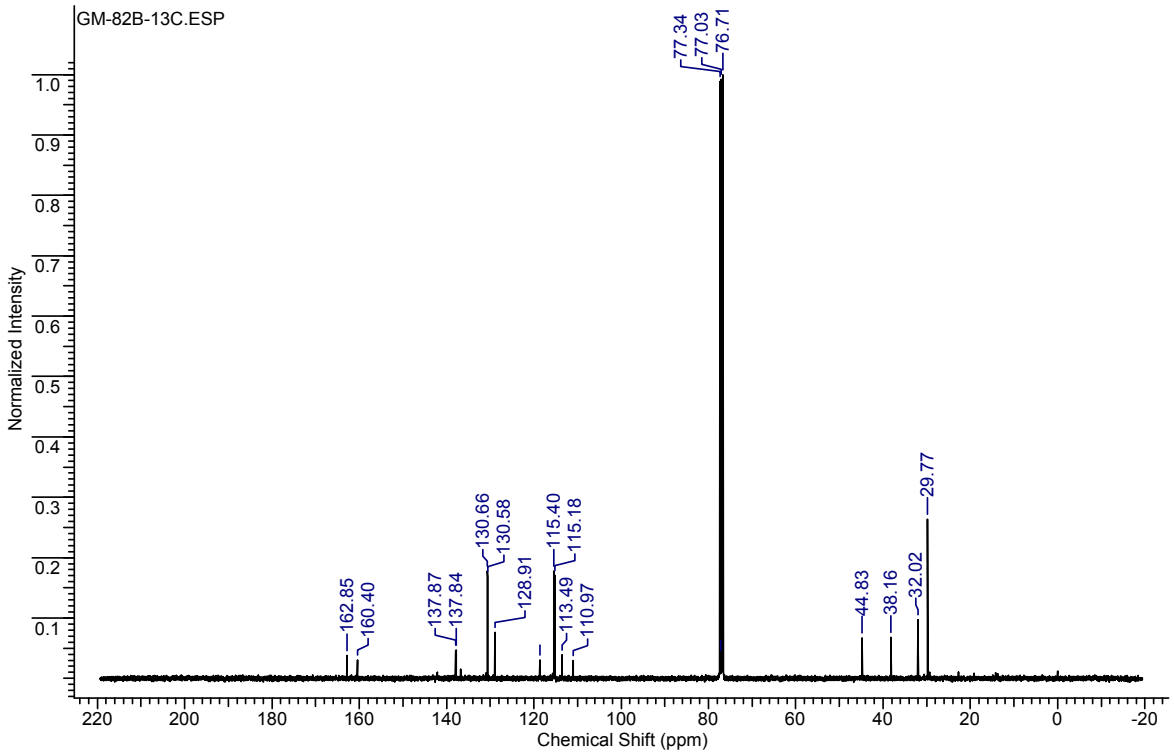


Fig. S-3-84 ^{13}C NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-3-(4,5-dibromothiophen-2-yl)-5-neopentyl-1*H*-pyrazole **11k**..



11l

Fig. S-3-85 ^{1}H NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-3-(3,4-dibromothiophen-2-yl)-5-neopentyl-1*H*-pyrazole **11l**.

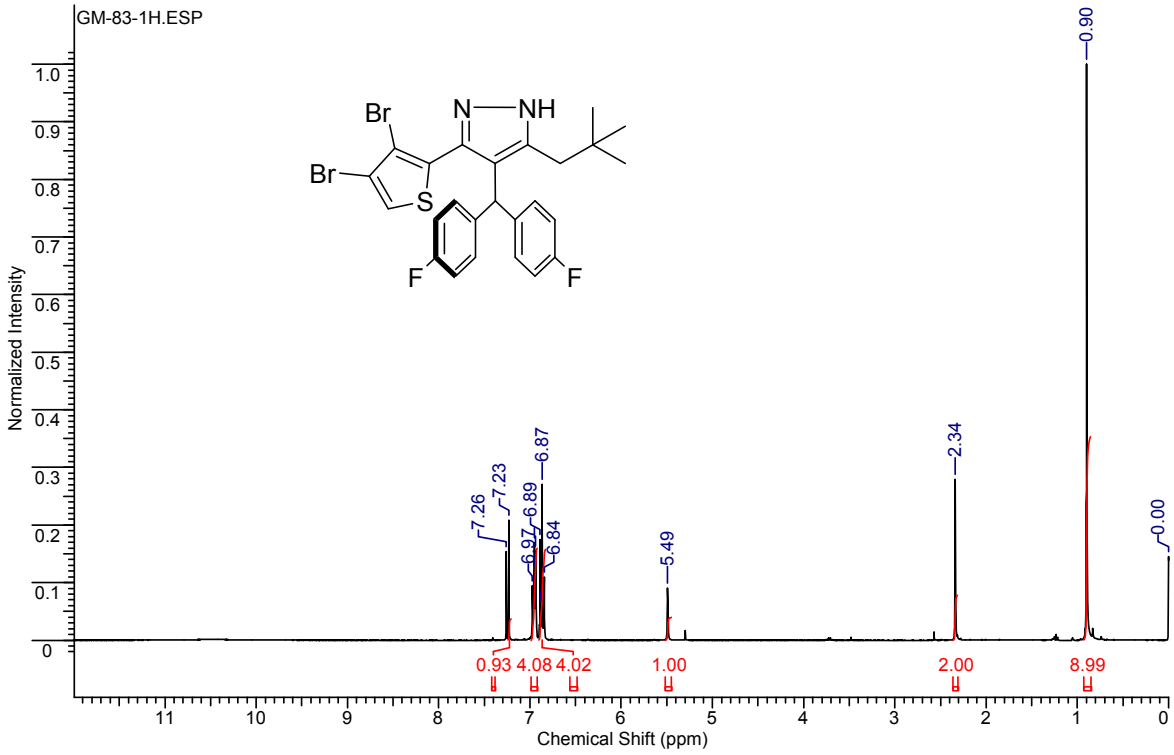
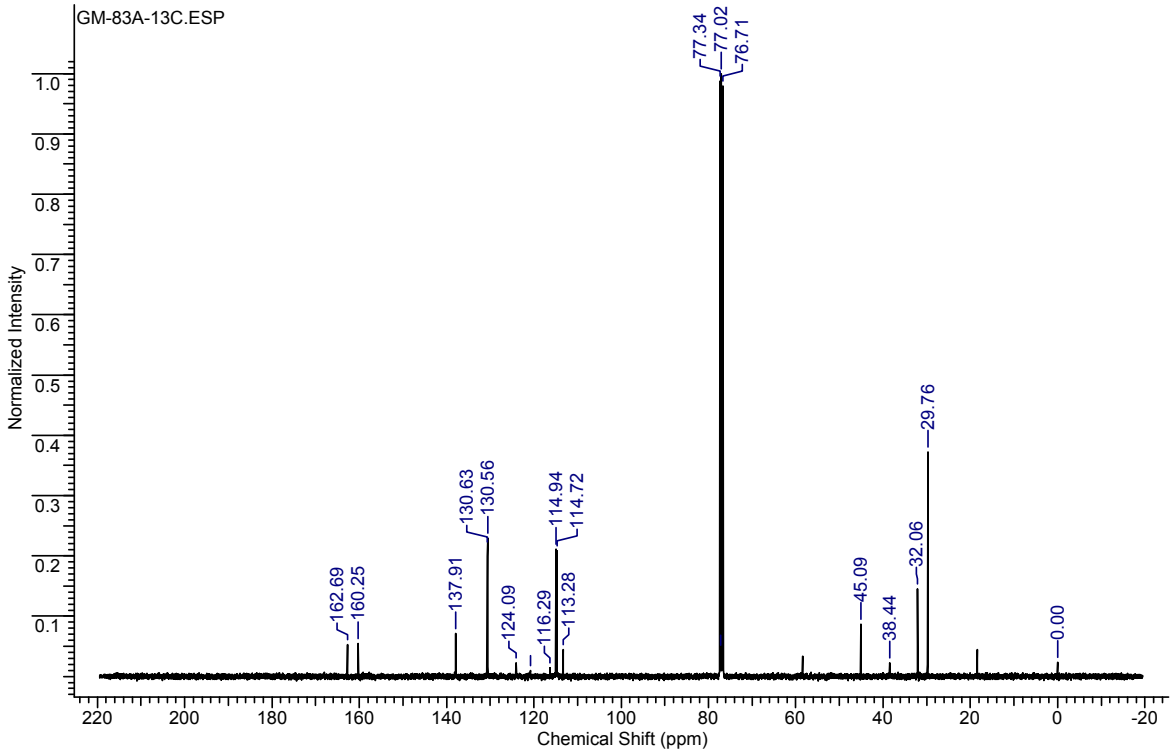


Fig. S-3-86 ^{13}C NMR spectrum of 4-(bis(4-fluorophenyl)methyl)-3-(3,4-dibromothiophen-2-yl)-5-neopentyl-1*H*-pyrazole **11l**.



12

Fig. S-3-87 ^{1}H NMR spectrum of 4-benzhydryl-5-neopentyl-3-phenyl-1*H*-pyrazole **12**.

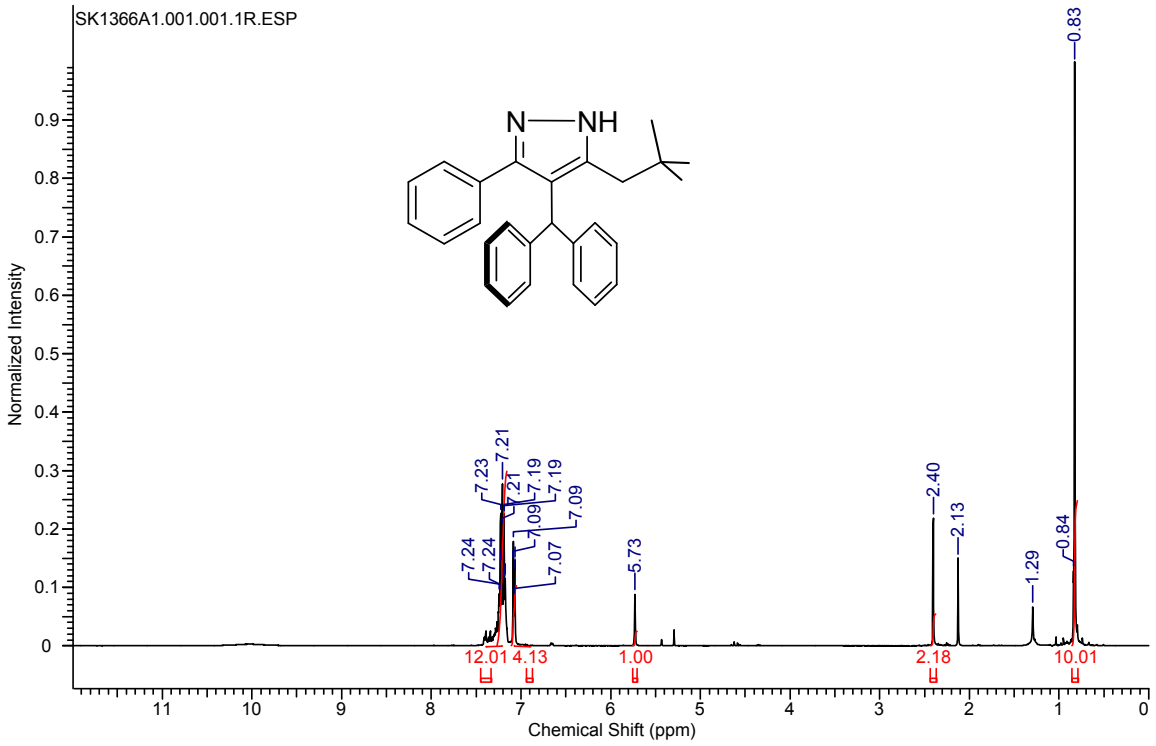
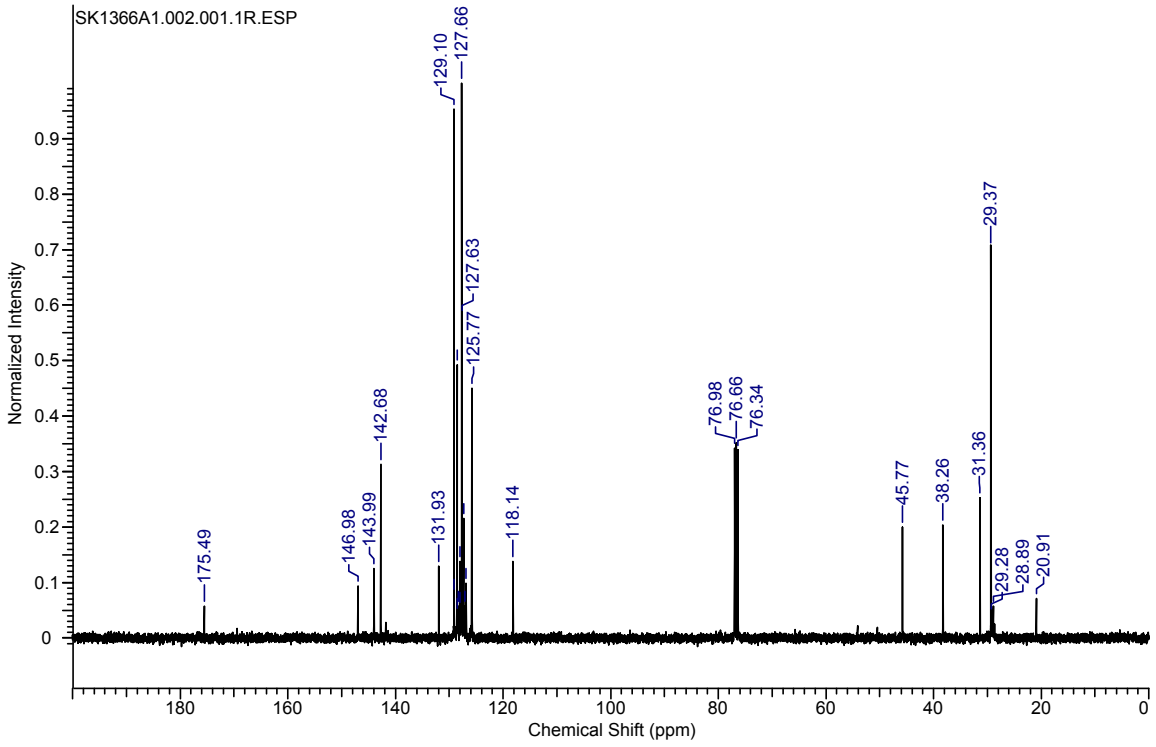


Fig. S-3-88 ^{13}C NMR spectrum of 4-benzhydryl-5-neopentyl-3-phenyl-1*H*-pyrazole **12**.



14a

Fig. S-3-89 ^{1}H NMR spectrum of 3-methyl-1,4-dihydroindeno[1,2-*c*]pyrazole **14a**.

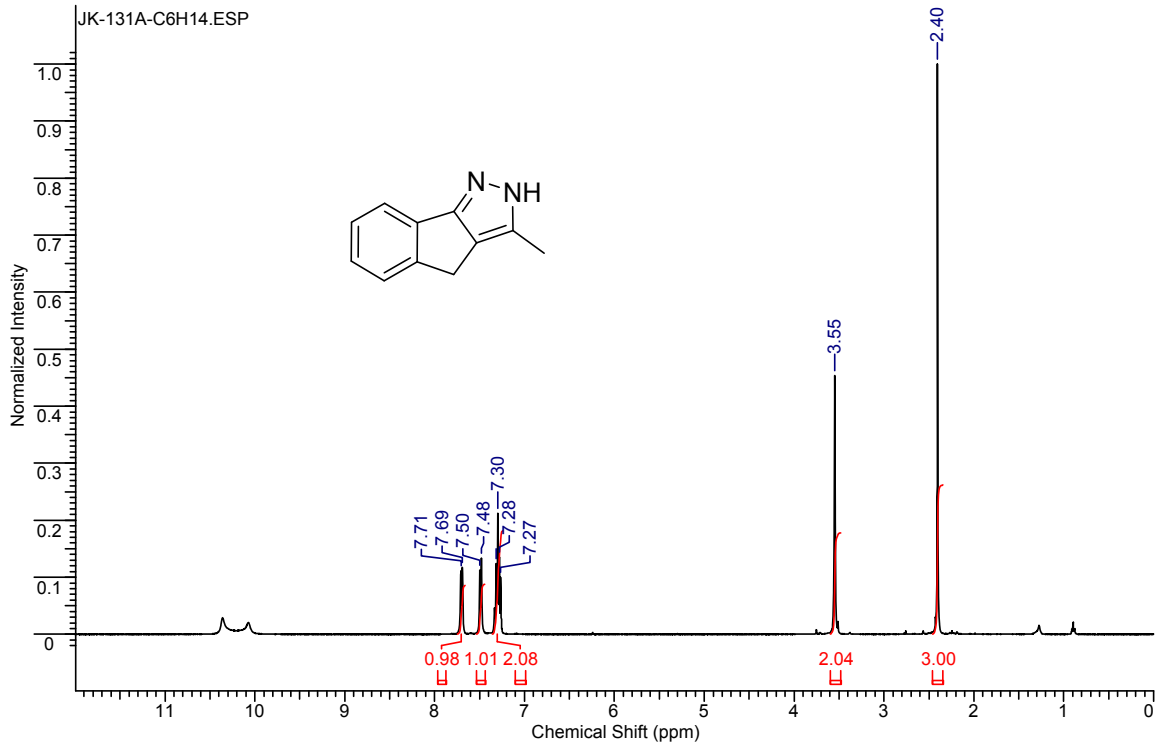
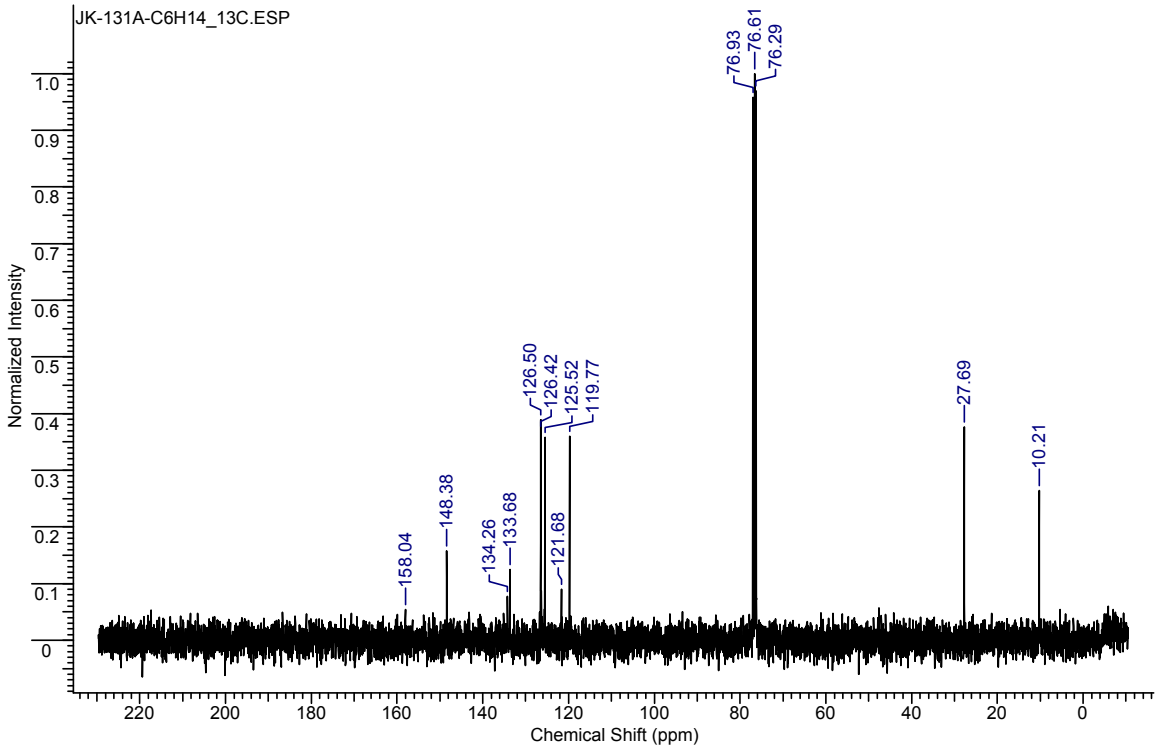


Fig. S-3-90 ^{13}C NMR spectrum of 3-methyl-1,4-dihydroindeno[1,2-*c*]pyrazole **14a**.



14b

Fig. S-3-91 ^{1}H NMR spectrum of 3-(1-adamantylmethyl)-1,4-dihydroindeno[1,2-*c*]pyrazole **14b**.

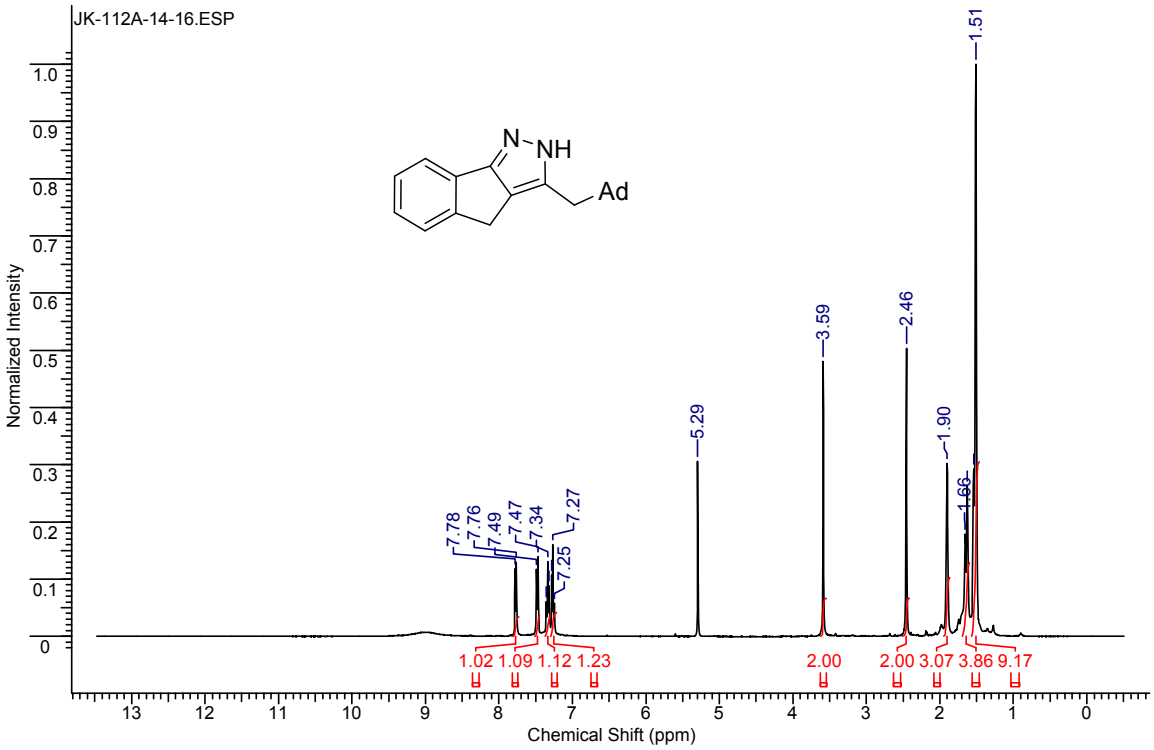
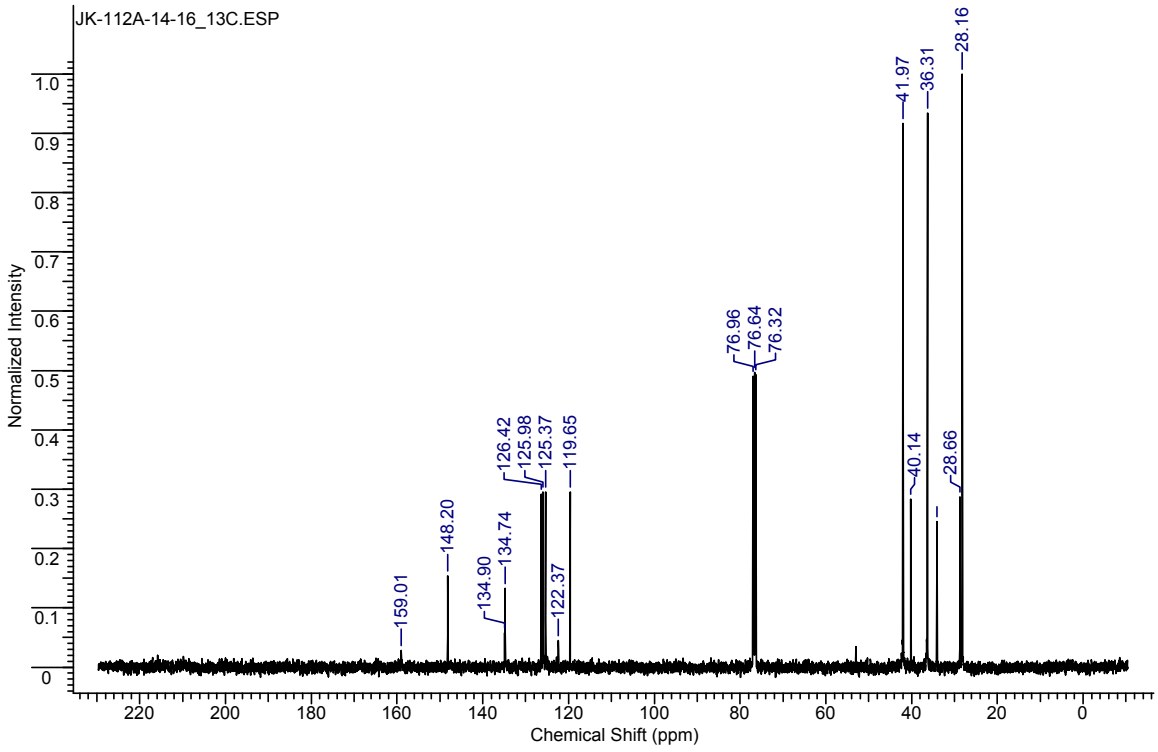


Fig. S-3-92 ^{13}C NMR spectrum of 3-(1-adamantylmethyl)-1,4-dihydroindeno[1,2-*c*]pyrazole **14b**.



14c

Fig. S-3-93 ^{1}H NMR spectrum of 3-(3-Hydroxy-1-adamantylmethyl)-2,4-dihydroindeno[1,2-c]pyrazole **14c**.

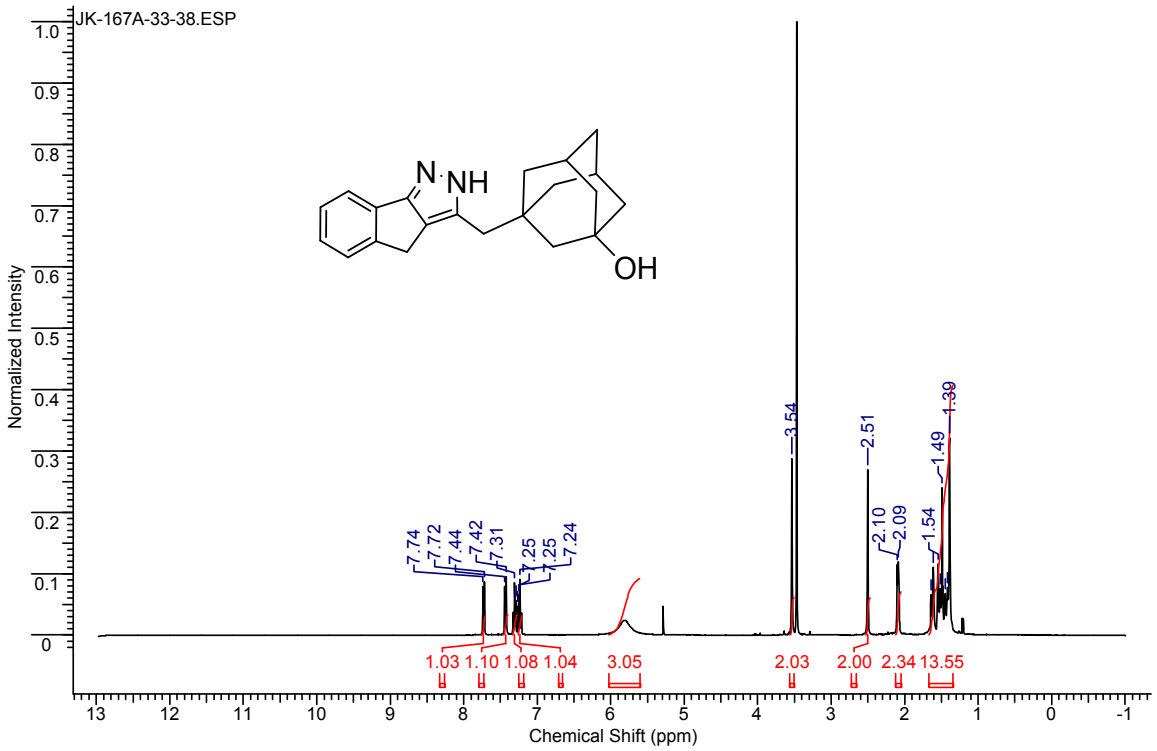
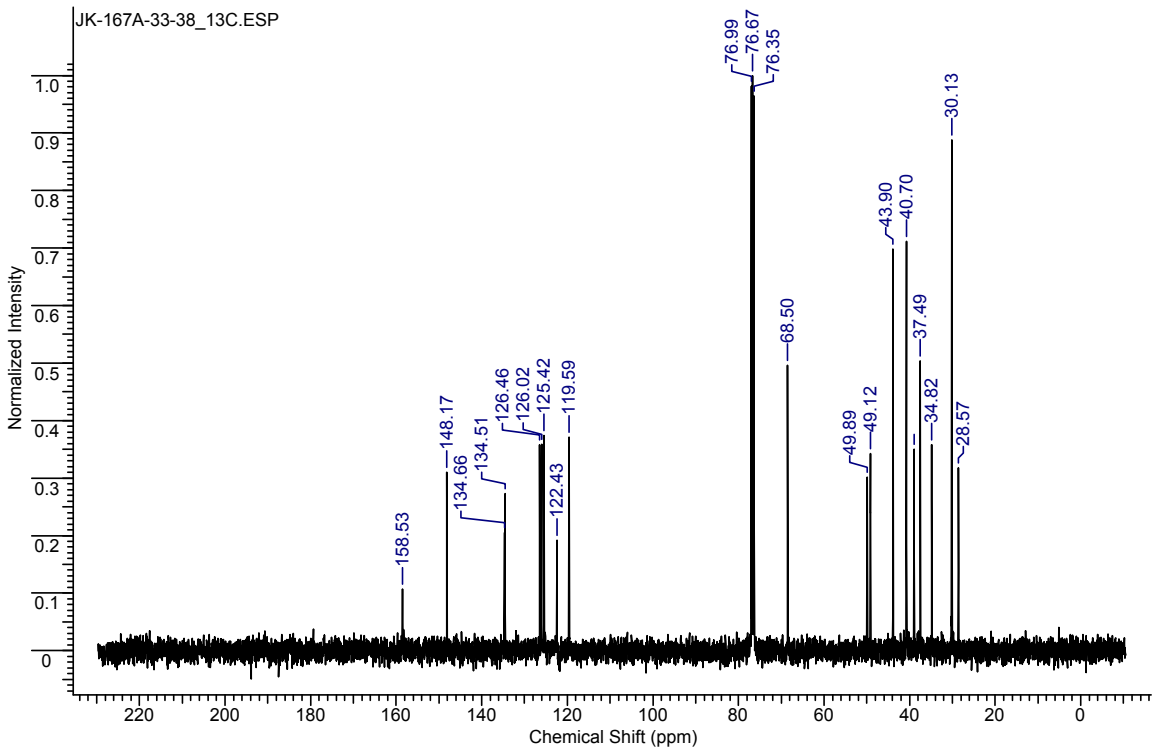


Fig. S-3-94 ^{13}C NMR spectrum of 3-(3-Hydroxy-1-adamantylmethyl)-2,4-dihydroindeno[1,2-c]pyrazole **14c**.



14d

Fig. S-3-95 ^{1}H NMR spectrum of 3-neopentyl-2,4-dihydroindeno[1,2-c]pyrazole **14d**.

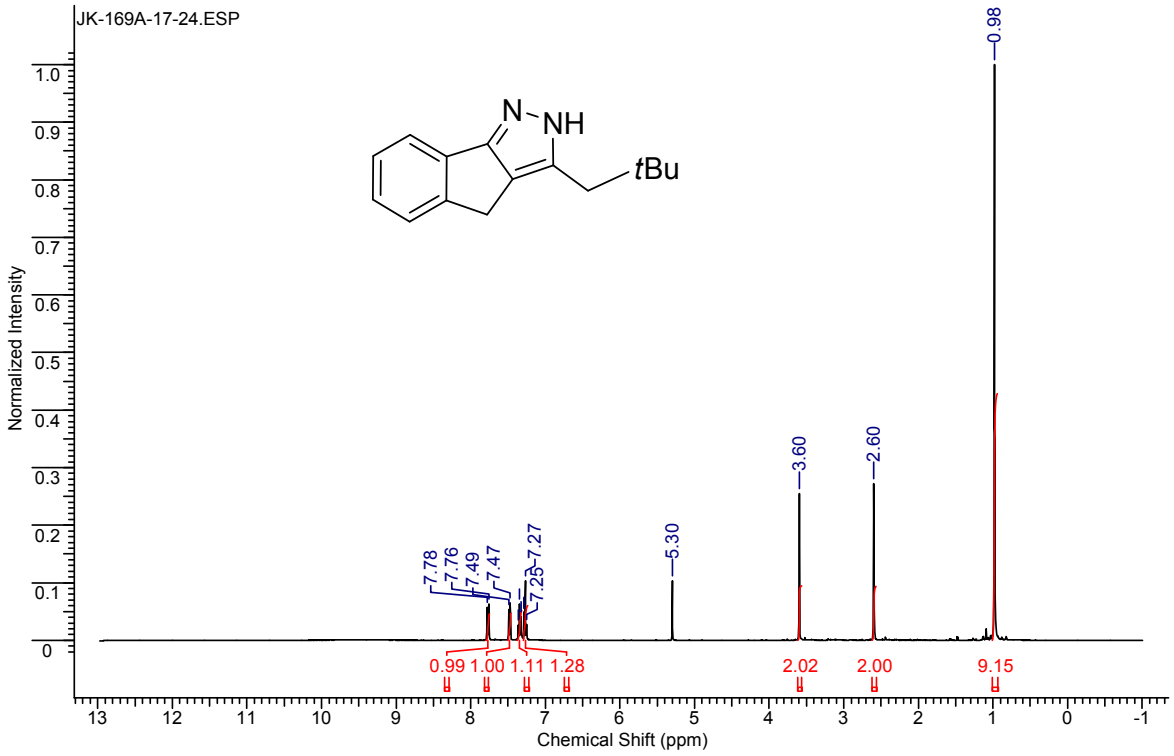
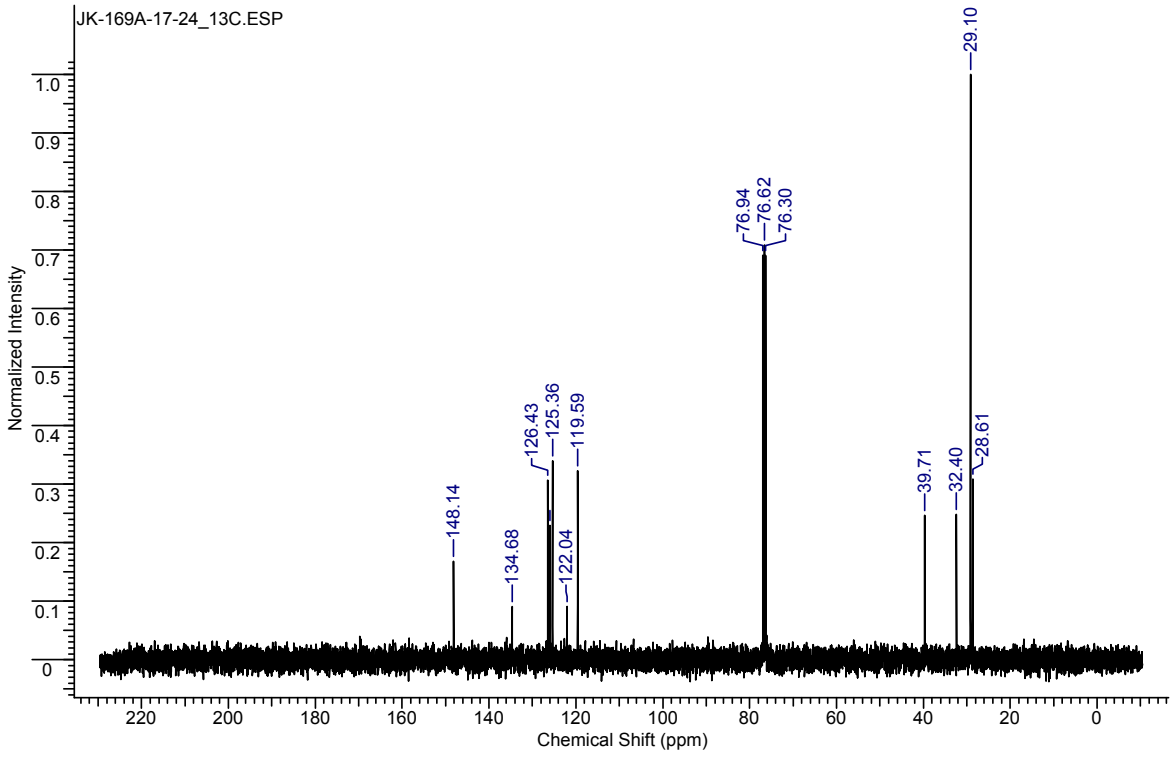


Fig. S-3-96 ^{13}C NMR spectrum of 3-neopentyl-2,4-dihydroindeno[1,2-c]pyrazole **14d**.



14e

Fig. S-3-97 ^{1}H NMR spectrum of 3-(1-adamantylmethyl)-4,5-dihydro-*2H*-benzo[*g*]indazole **14e**.

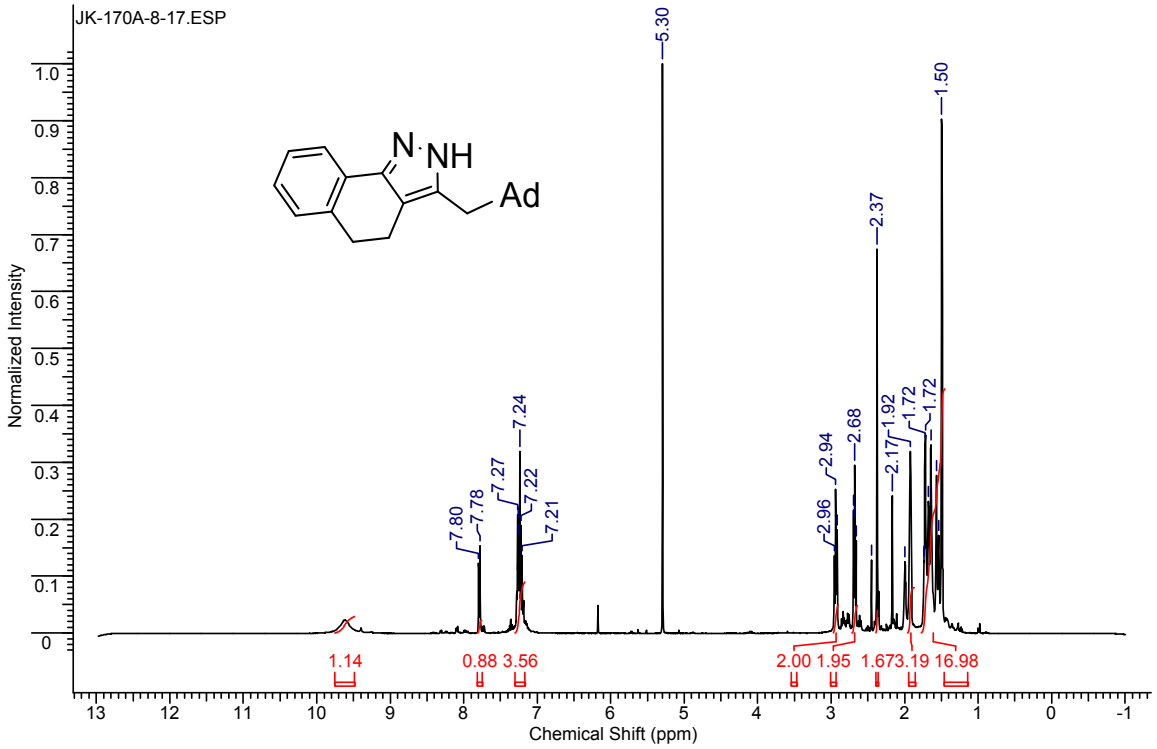
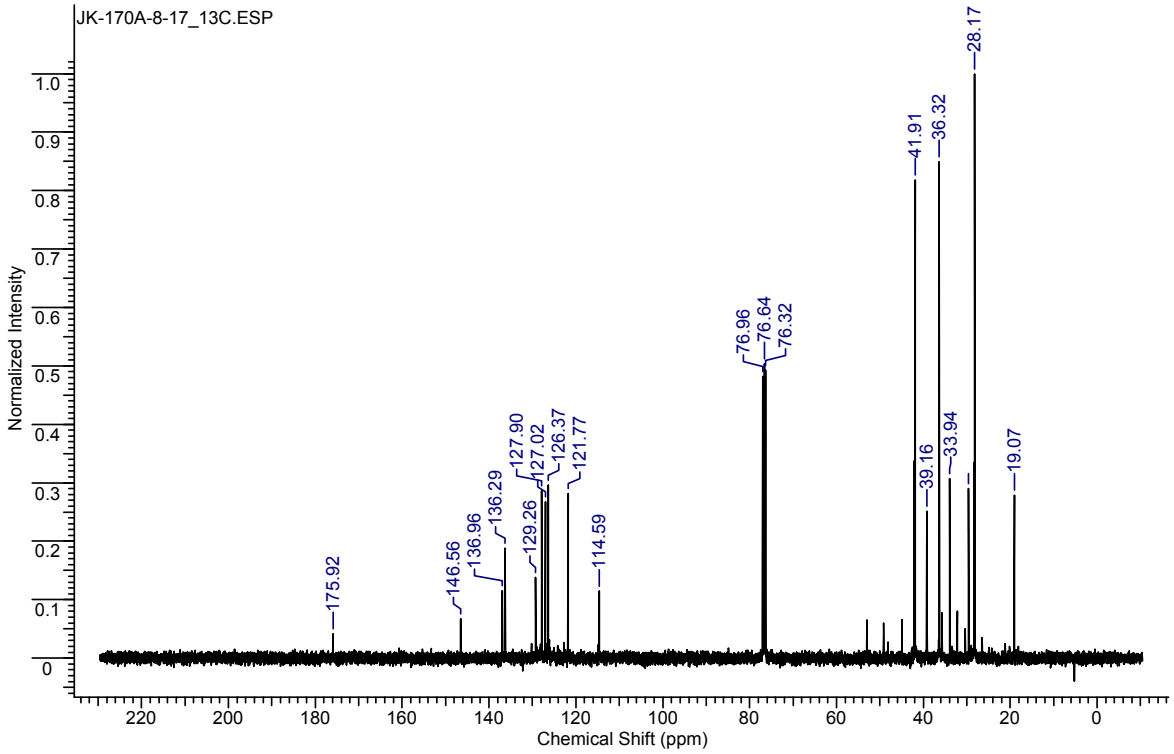


Fig. S-3-98 ^{13}C NMR spectrum of 3-(1-adamantylmethyl)-4,5-dihydro-*2H*-benzo[*g*]indazole **14e**.



14f

Fig. S-3-99 ^{1}H NMR spectrum of 3-(3-hydroxy-1-adamantylmethyl)-4,5-dihydro-*2H*-benzo[*g*]indazole **14f**.

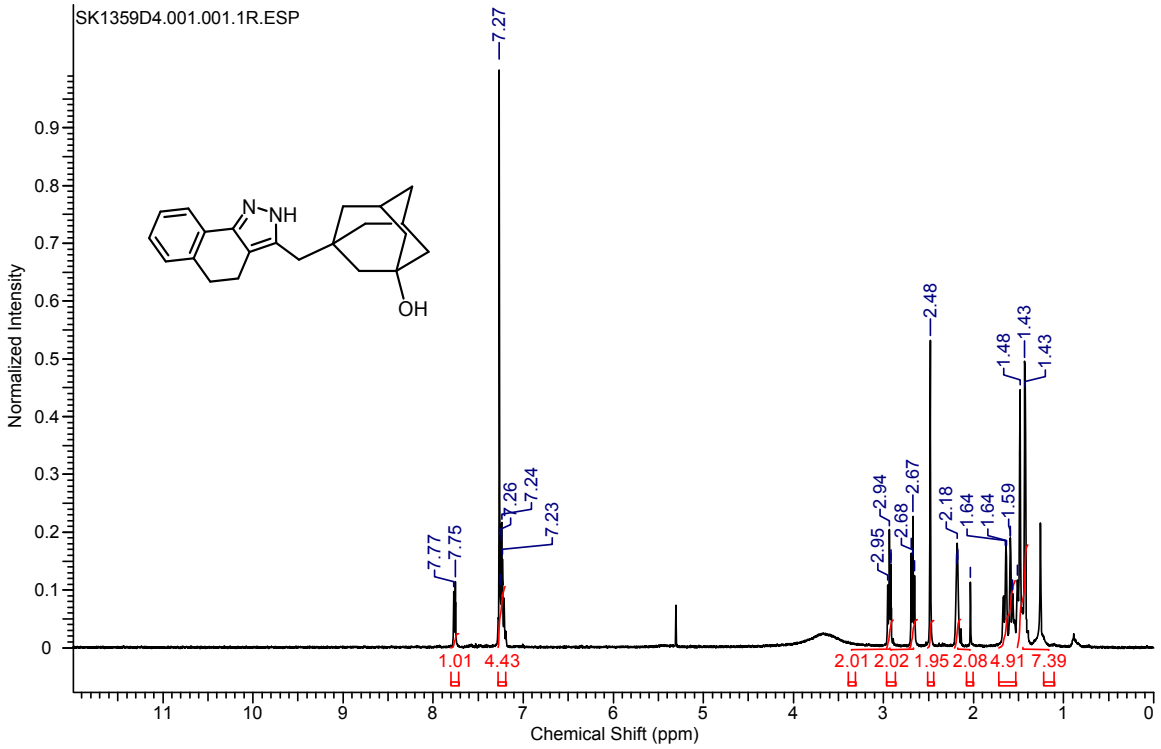
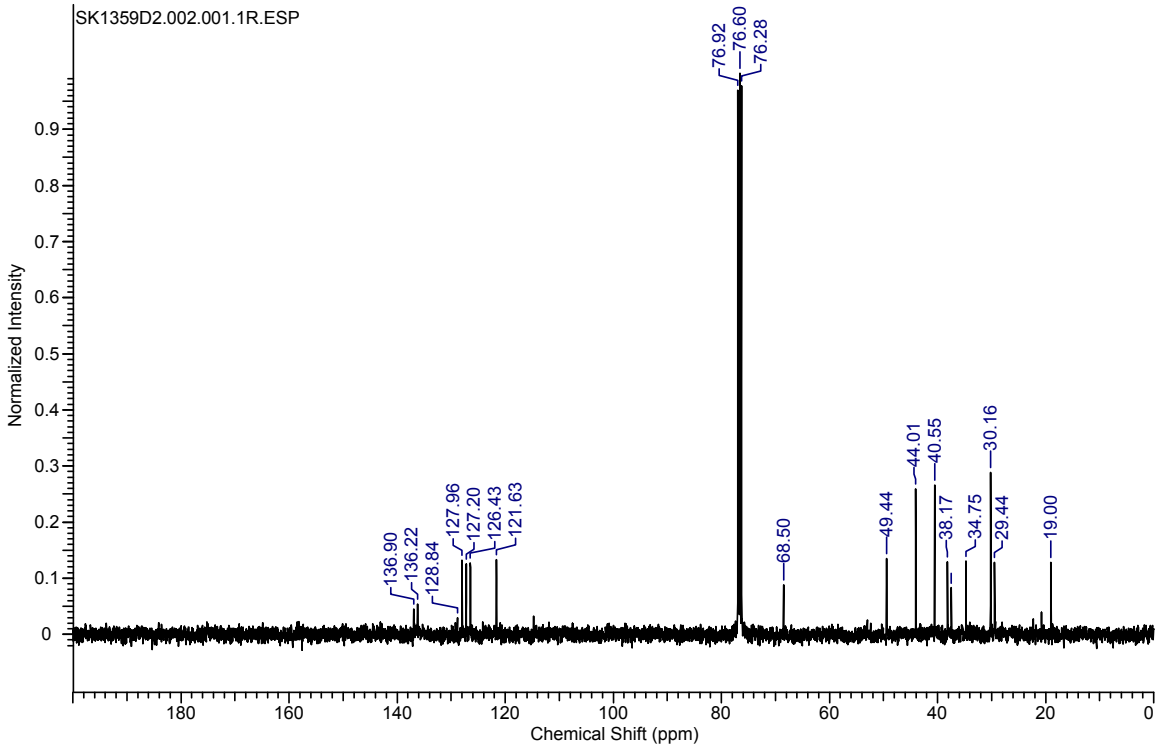


Fig. S-3-100 ^{13}C NMR spectrum of 3-(3-hydroxy-1-adamantylmethyl)-4,5-dihydro-*2H*-benzo[*g*]indazole **14f**.



4. Molecular structures (X-ray diffraction).

Fig. S-4-1 Molecular structures of diketone **8b**; thermal ellipsoids are shown with 50% probability. (CCDC 1520160)

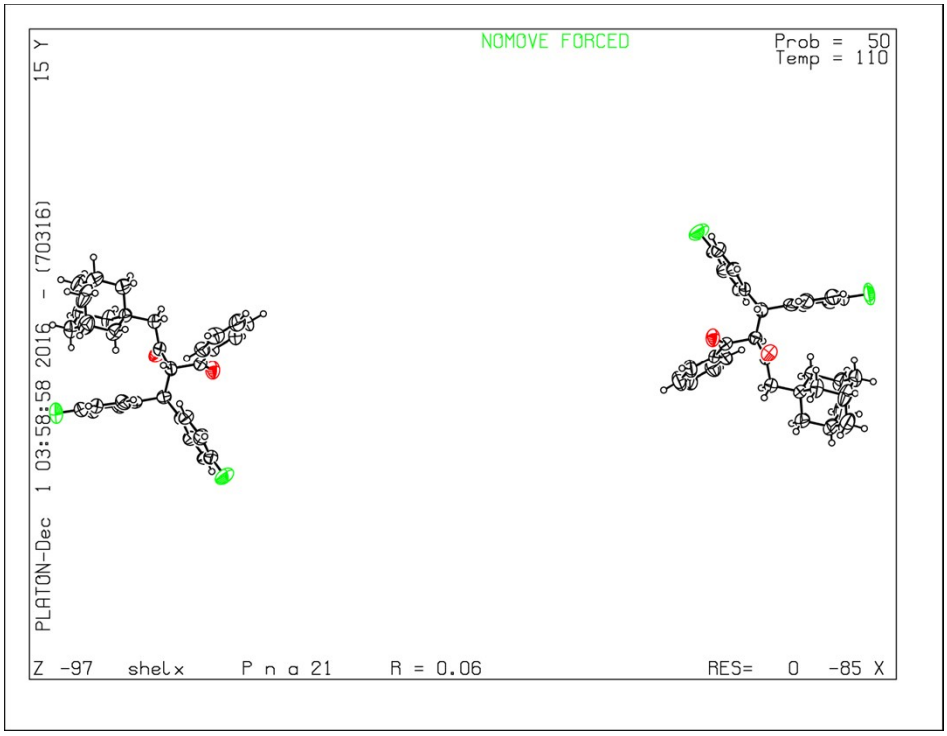


Fig. S-4-2 Molecular structures of pyrazole **11a**; thermal ellipsoids are shown with 50% probability. (CCDC 1520161)

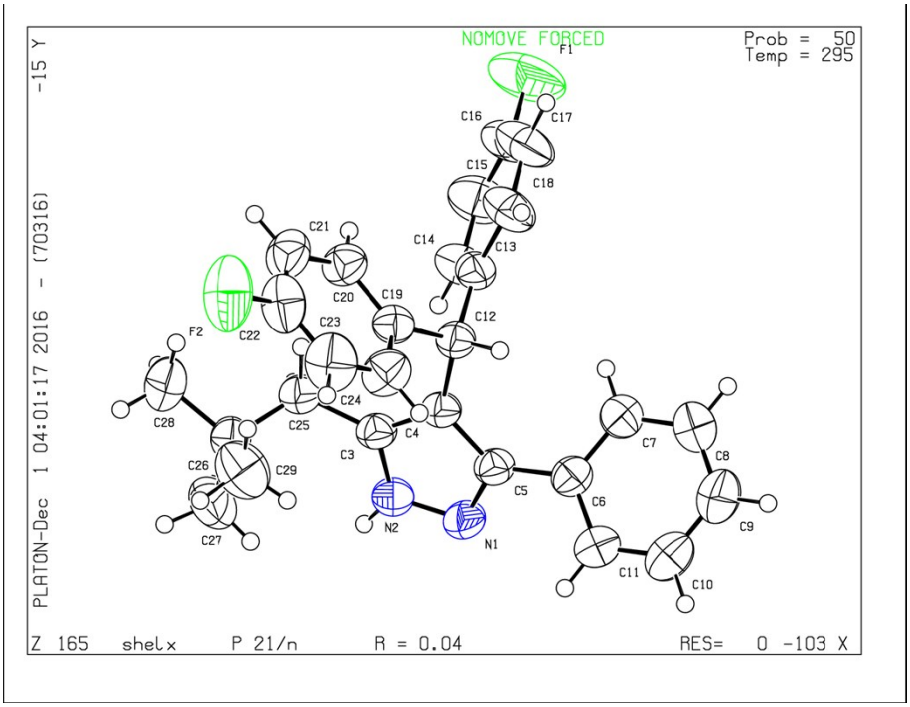
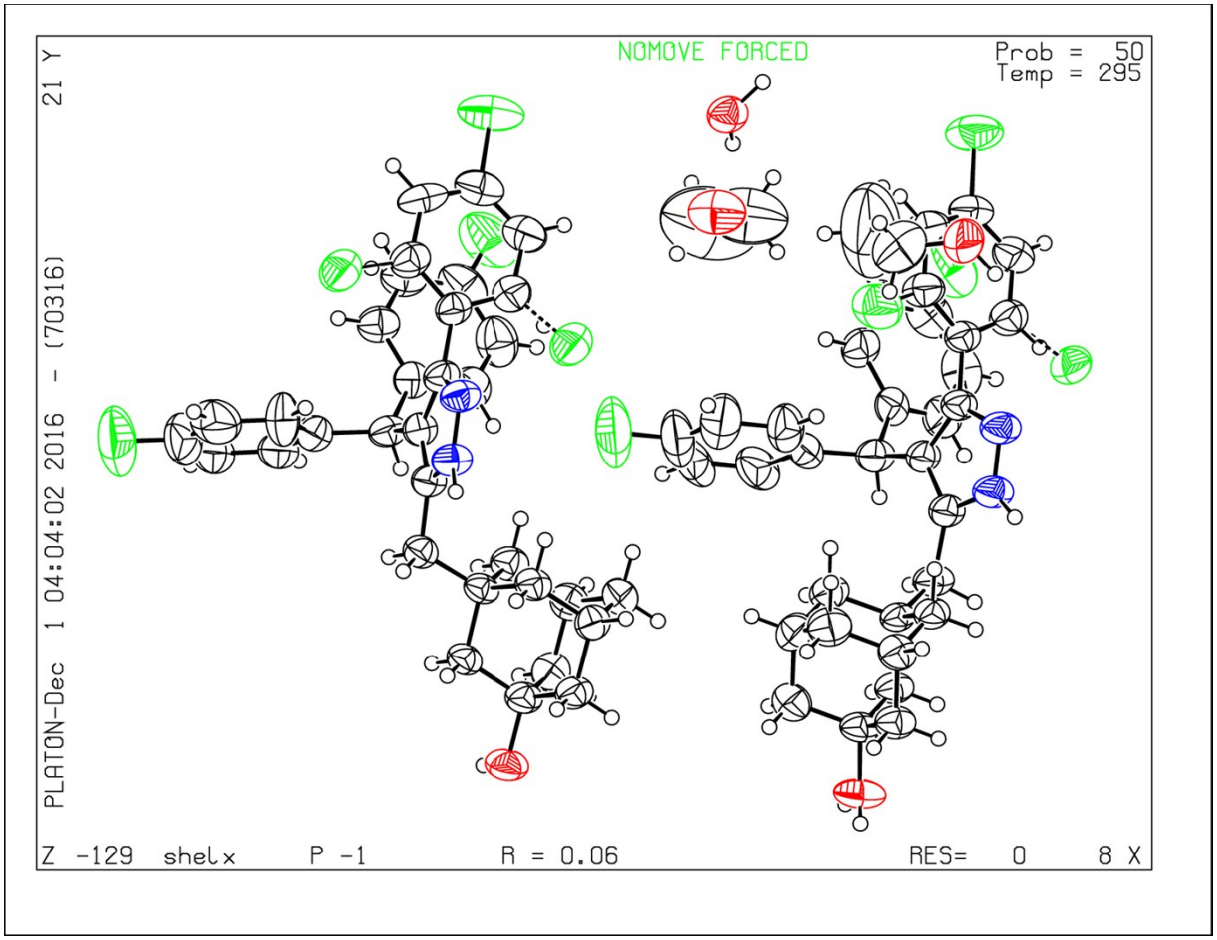


Fig. S-4-3 Molecular structures of pyrazole **11d**; thermal ellipsoids are shown with 50% probability. (CCDC 1520162)



5. Determination *in vitro* growth inhibitory activity

Cell culture. The human cancer cell lines were obtained from the American Type Culture Collection (ATCC, Manassas, VA). Human H1975 (NSCLC), MDM-MB-231 (breast), HCT116 (colon) and A549 (NSCLC) were maintained in RPMI medium, contained 10% fetal bovine serum (FBS). Cells were grown in a 37 ºC incubator with 5% CO_2.

Cell viability assay The effect of the compounds on the cell viability of different cancer cell lines was determined by performing colorimetric MTT assay, in which the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyletetrazolium bromide) is reduced to its insoluble crystal form formazan. Briefly different cancer cells (HCT116, MDA-MB-231, H1975 and A549) cells were harvested from exponential-phase maintenance cultures, counted by trypan blue exclusion, and dispensed at concentration of 5,000 cells per well within three replicate in 96-well culture platesfor overnight. Further, the cells were treated with increasing concentration of the drugs (0, 4, 20, 100 and 500 μM in 0.5% DMSO) in triplicates for 48 h. MTT (M2128, Sigma) reagent (5 mg/mL) was added to each well 3 h prior to the termination time point and plates were placed back in the incubator at 37 ºC. After 3 h, the formazan crystals were dissolved in 100 mL DMSO. Optical density was measured at 570 nm by using a microplate reader.

Statistical analysis. The experiments were performed in triplicate for three independent experiments. Graph data represent the mean- standard error calculated from indicated number of independent experiments. Results were analyzed and graphs built using GraphPad Prizm ver. 5.02 by GraphPad Software.

Table S-5-1. *In vitro* growth inhibitory concentrations (IC50 / μM) of synthesized pyrazoles in the lung cancer cell line H1975 (48 h treatment)

entry	compounds	series[a]	clogP[b]	IC50 mean±SEM[c]
1	**5b**	**B**	6.93	62.58±12.2
2	**5c**	**A**	4.50	52.67±9.5
3	**5d**	**B**	6.96	27.31±3.2
4	**5e**	**A**	4.60	80.85±10.9
5	**5f**	**B**	7.07	25.85±4.6
6	**5g**	**C**	3.94	160.9±30.3
7	**5i**	**A**	6.40	28.79±1.53
8	**5j**	**B**	8.87	39.65±7.5
9	**5k**	**B**	8.16	42.77±8.26
10	**5l**	**C**	3.80	109.0±17.89
11	**11a**	**A**	7.68	**6.64±0.7**[d]

entry	compounds	series[a]	clogP[b]	IC50 mean±SEM[c]
12	**11b**	**B**	10.37	20.31±3.4
13	**11c**	**B**	11.60	37.76±6.8
14	**11d**	**C**	7.01	**8.97±0.9**
15	**11e**	**C**	8.25	**6.95±0.5**
16	**11f**	**A**	8.05	**8.58±1.5**
17	**12**	**A**	7.39	20.56±0.3
18	**14b**	B	6.74	41.62±3.8
29	**14c**	C	3.61	88.31±6.3
20	**14d**	A	4.29	95.33±18.18
21	**14e**	B	7.15	28.33±2.80
22	**14f**	C	4.02	32.86±6.08
	Etoposide			**3.3±0.2**

a **A** -neopentyl series; **B** - 1-adamantylmethyl series; **C** - 3-hydroxy-1-adamantylmethyl series.

b ClogP values of the synthesized compounds were calculated using ChemBioDraw Ultra v.12.

cThe experimentswere performed in triplicate for three independent experiments. Results were analyzed and graphs built using GraphPad Prizm ver. 5.02 by GraphPad Software.

dThe product in bold represent 4 products displayed an IC50 < 10 μm.

6. Reference

1 G. M. Sheldrick, SADABS, v. 2.03, Bruker/Siemens Area Detector Absorption Correction Program, *Bruker AXS*, Madison, Wisconsin, 2003.

2 G. M. Sheldrick, *Acta Crystallogr. Sect. A: Fundam. Crystallogr.*, 2008, **A64**, 112.

3 J. K. Kim,E. A. Shokova,V. A. Tafeenko and V. V. Kovalev. *Beilstein J. Org. Chem*.,2014**, 10***,* 2270.

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