SUPPORTING INFORMATION

The First Synthesis of a Novel 5:7:5-Fused Diimidazodiazepine Ring System and Some of its Chemical Properties

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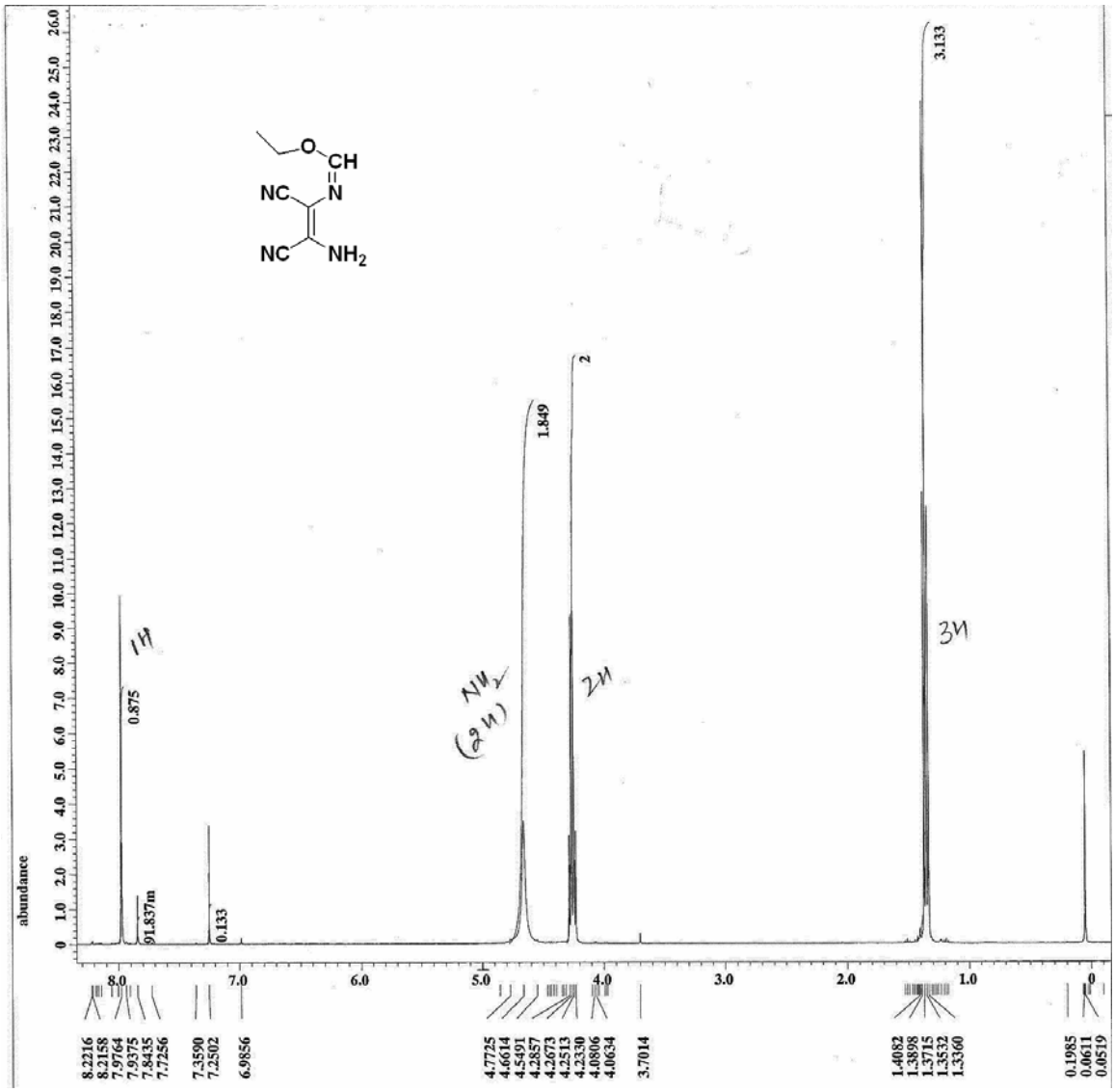

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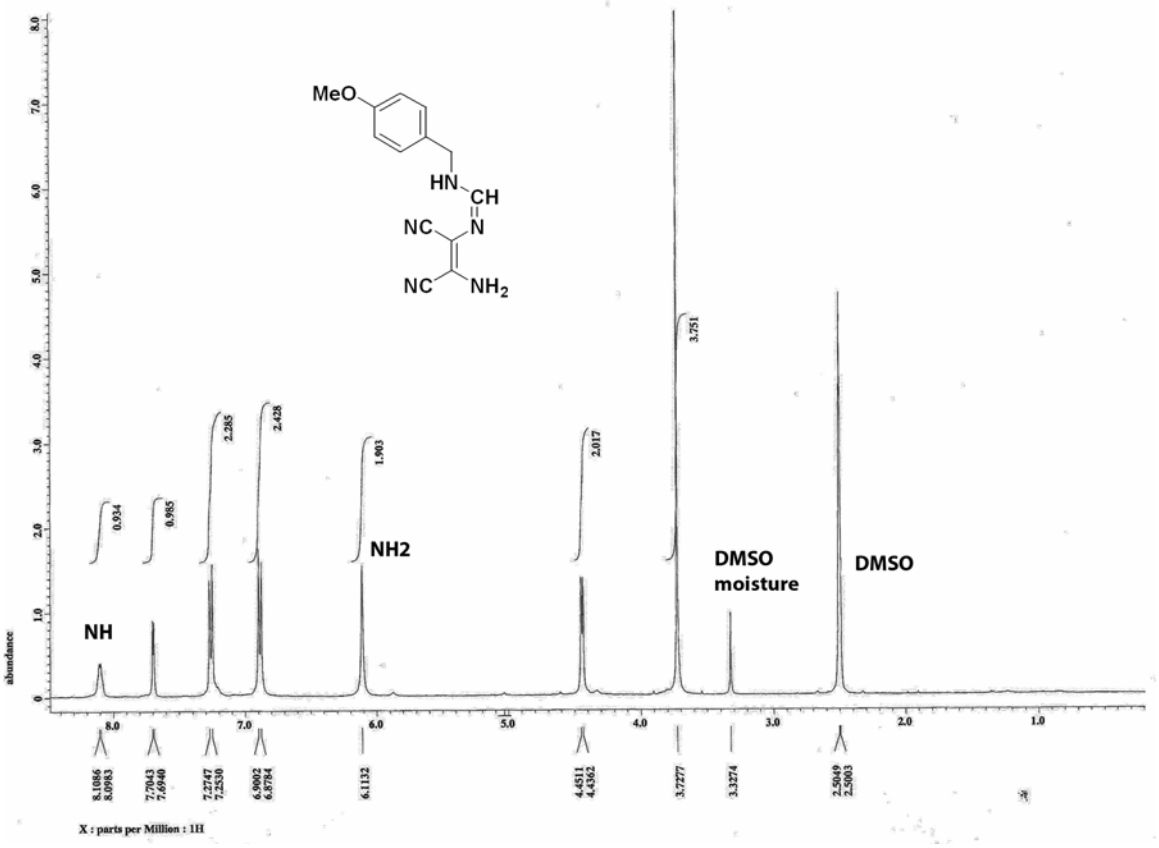

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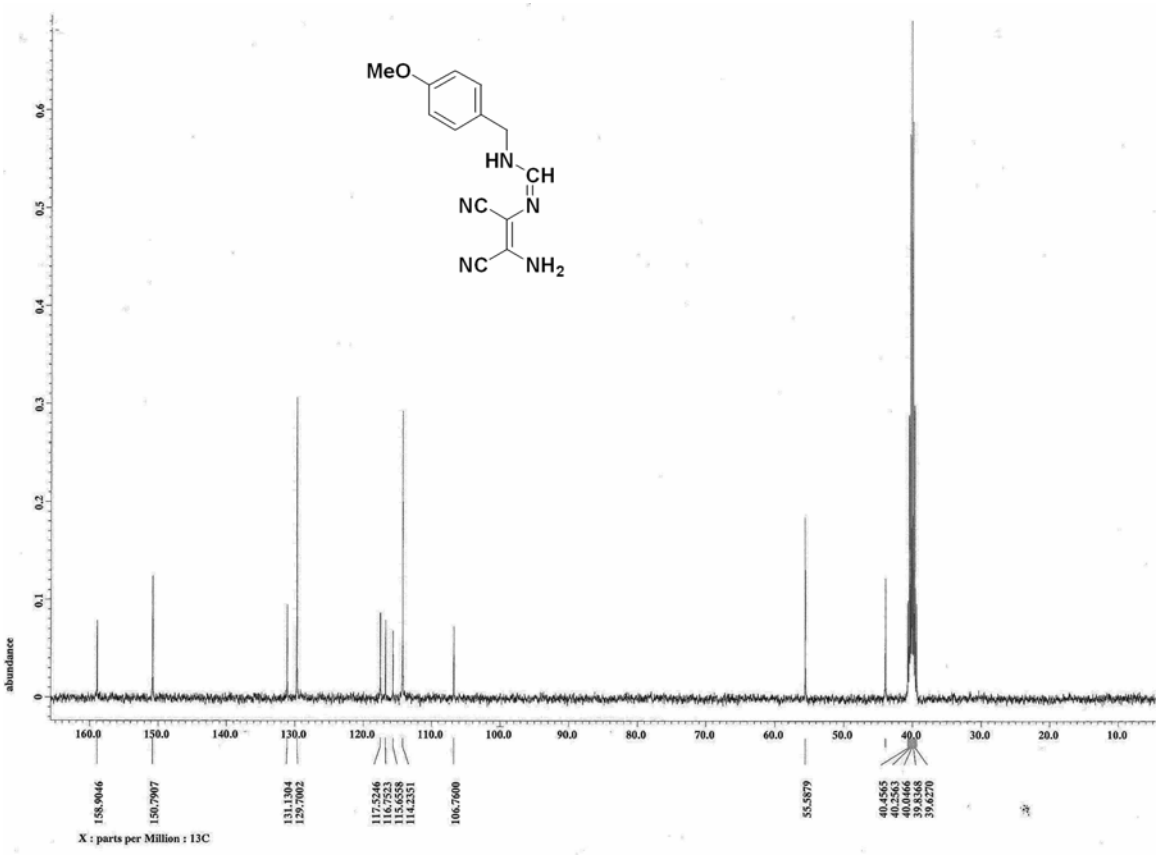

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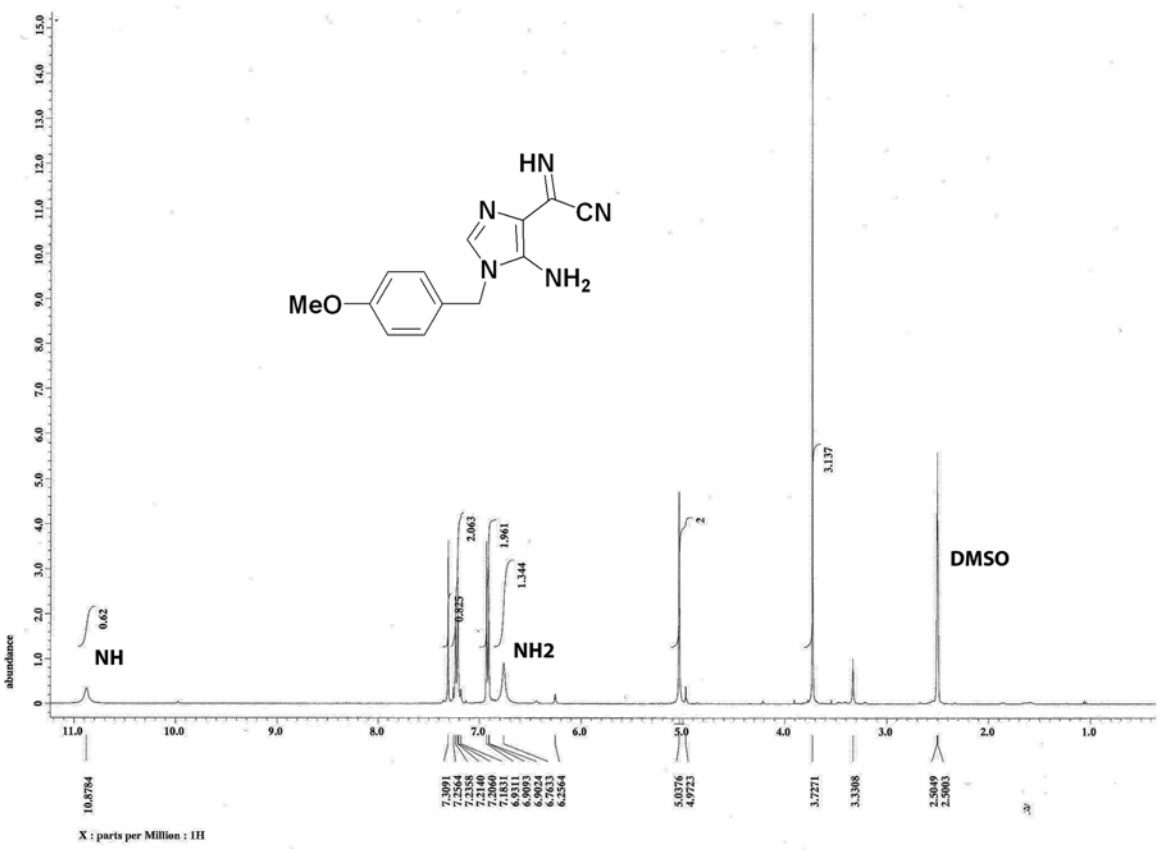

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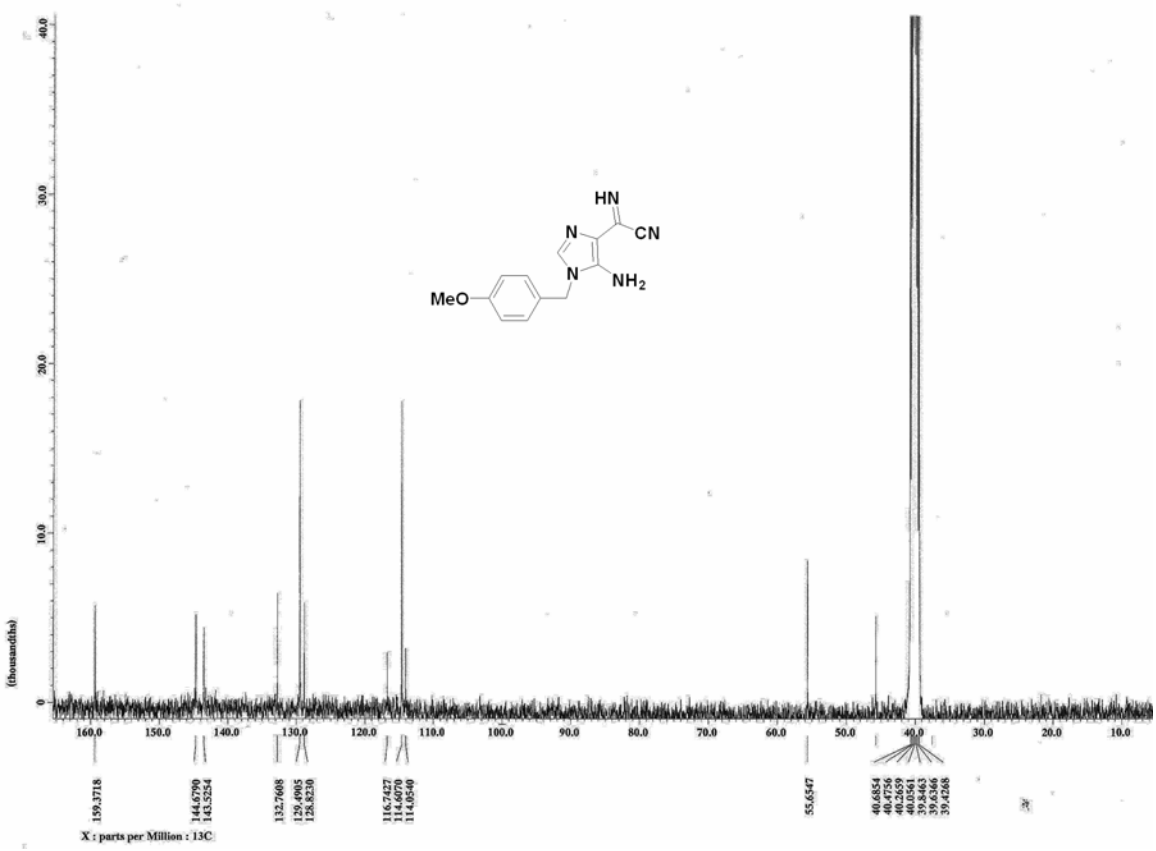

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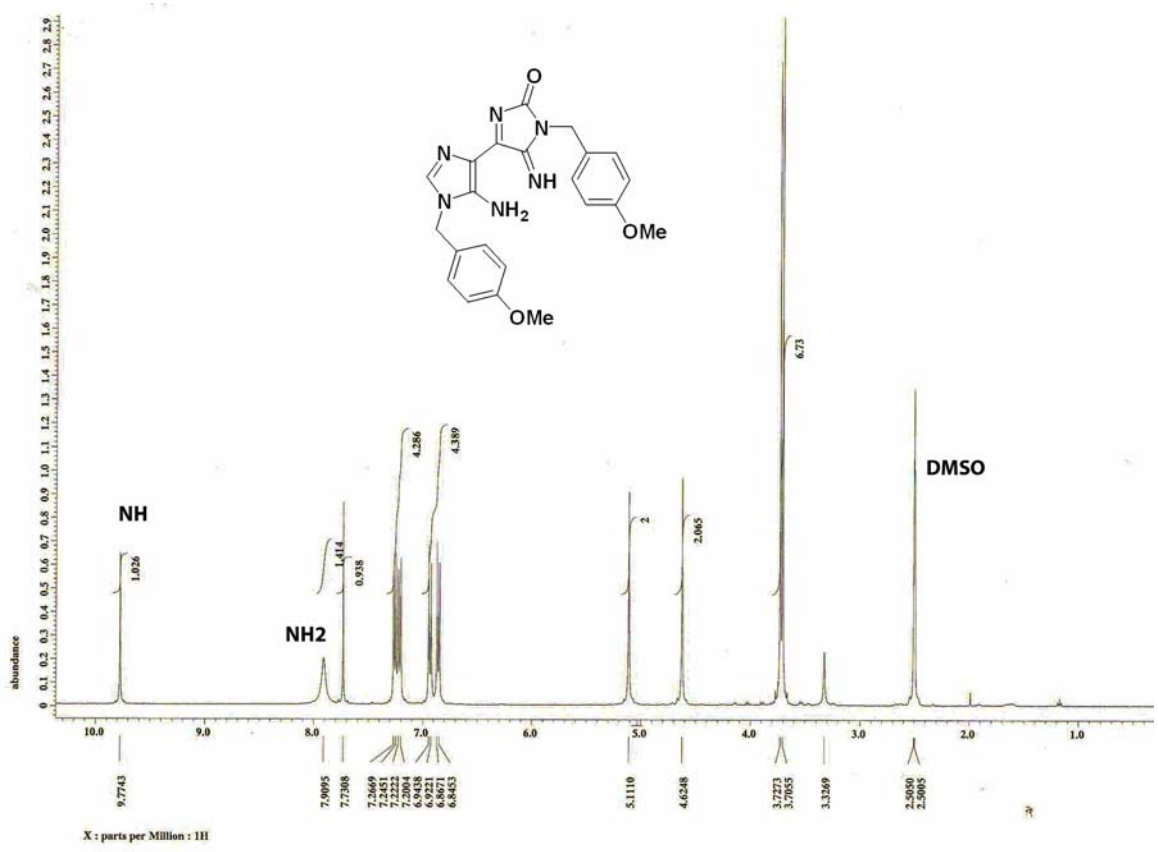
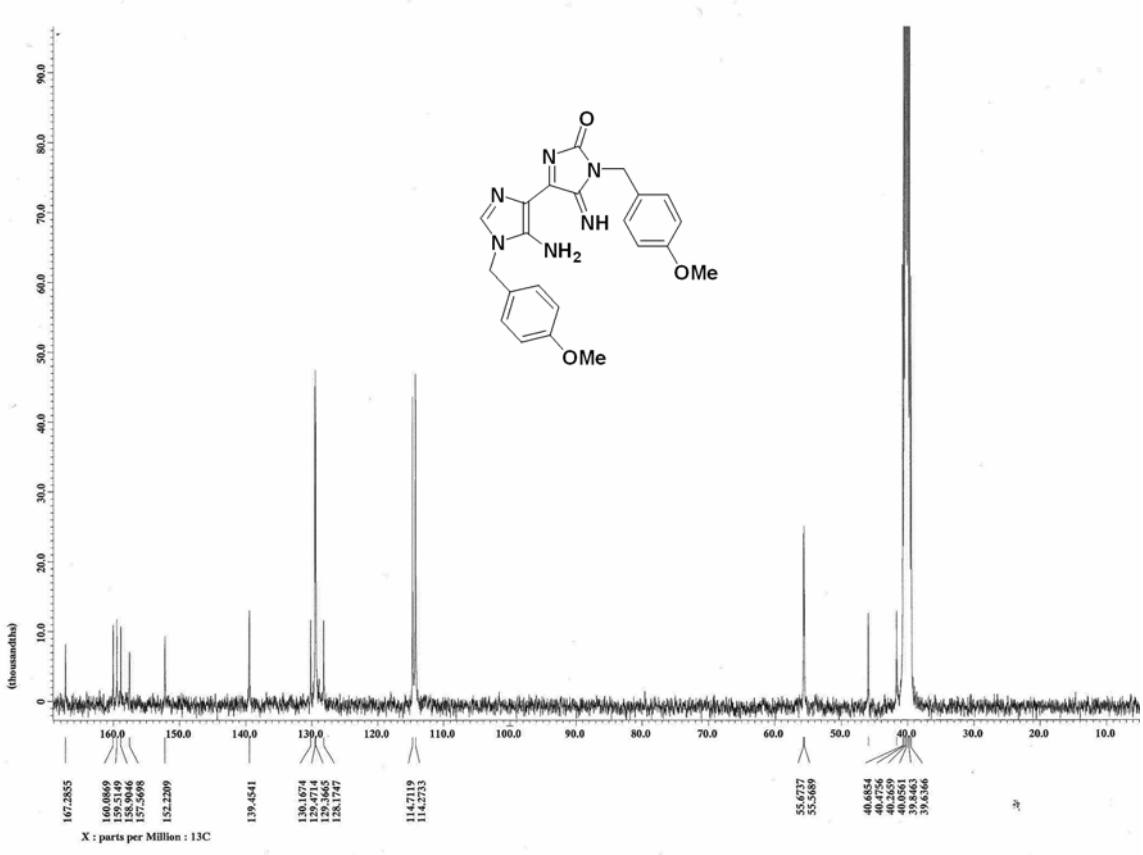


Compound 9: ^{13}C NMR



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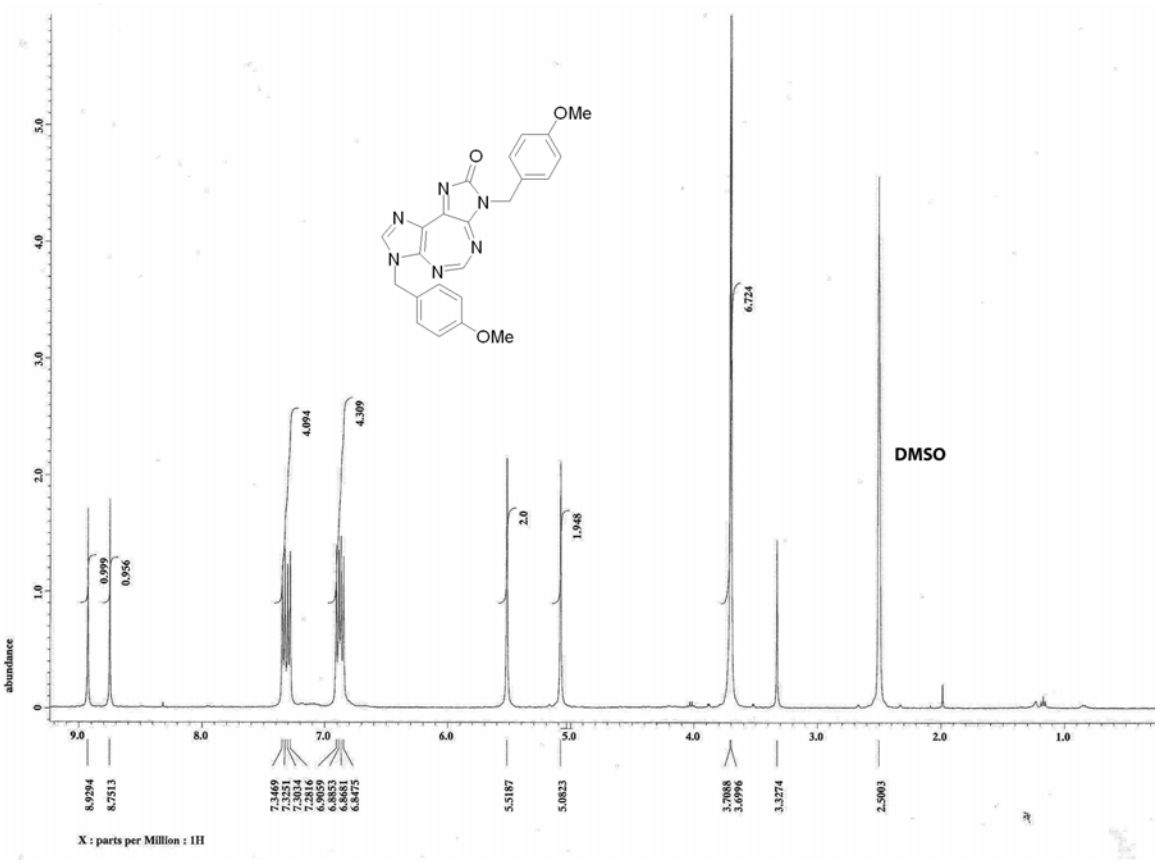

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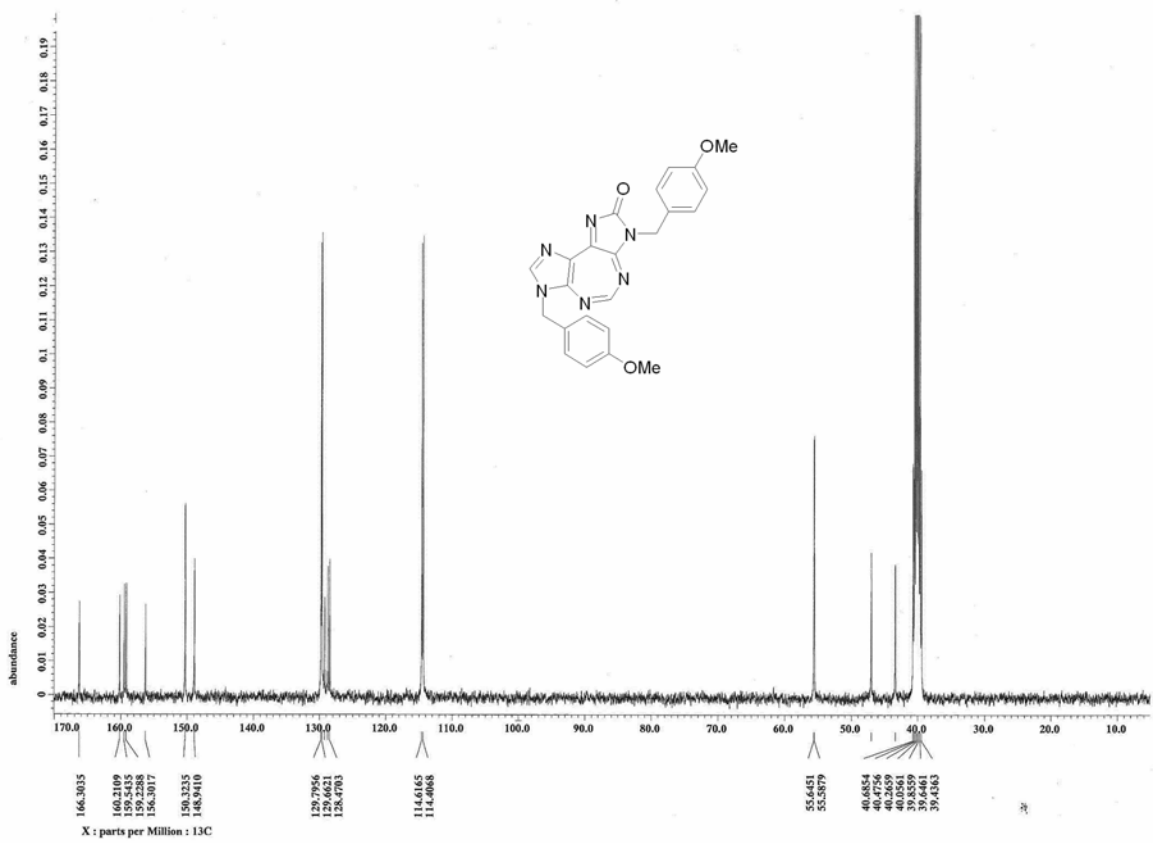

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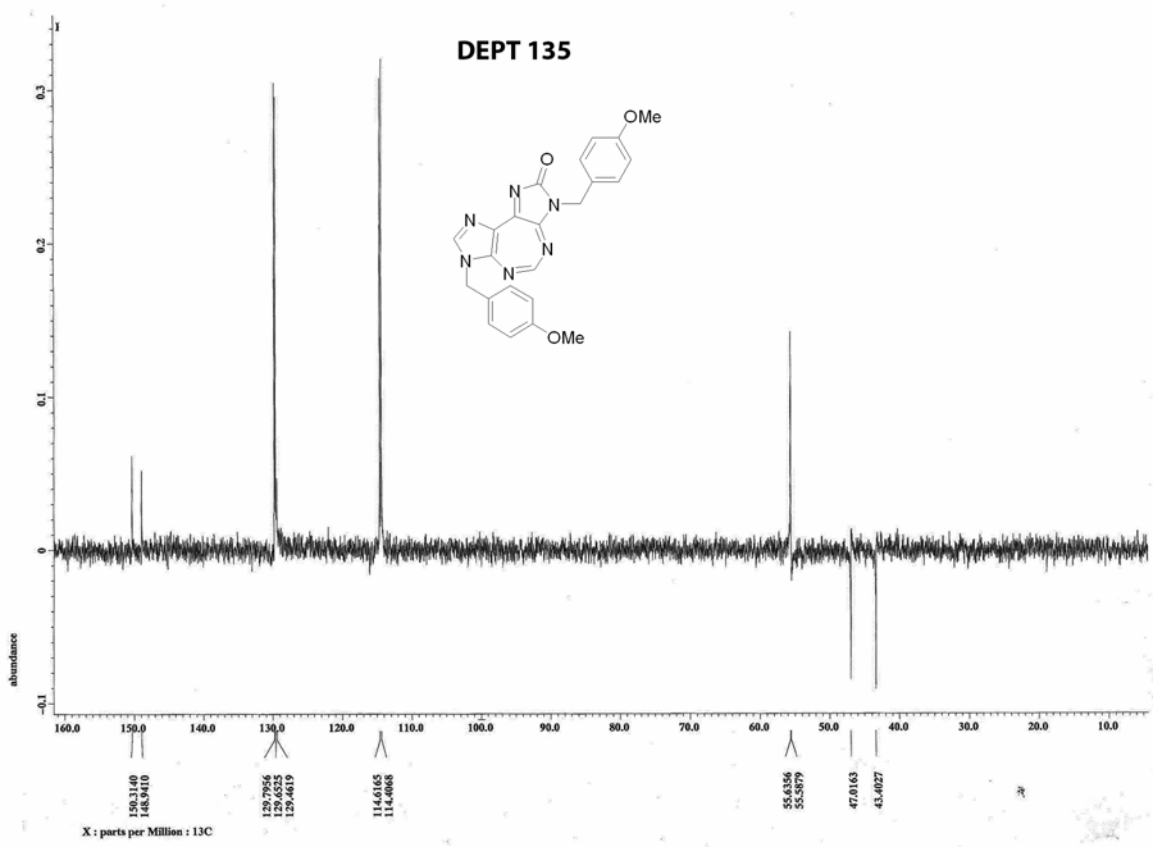

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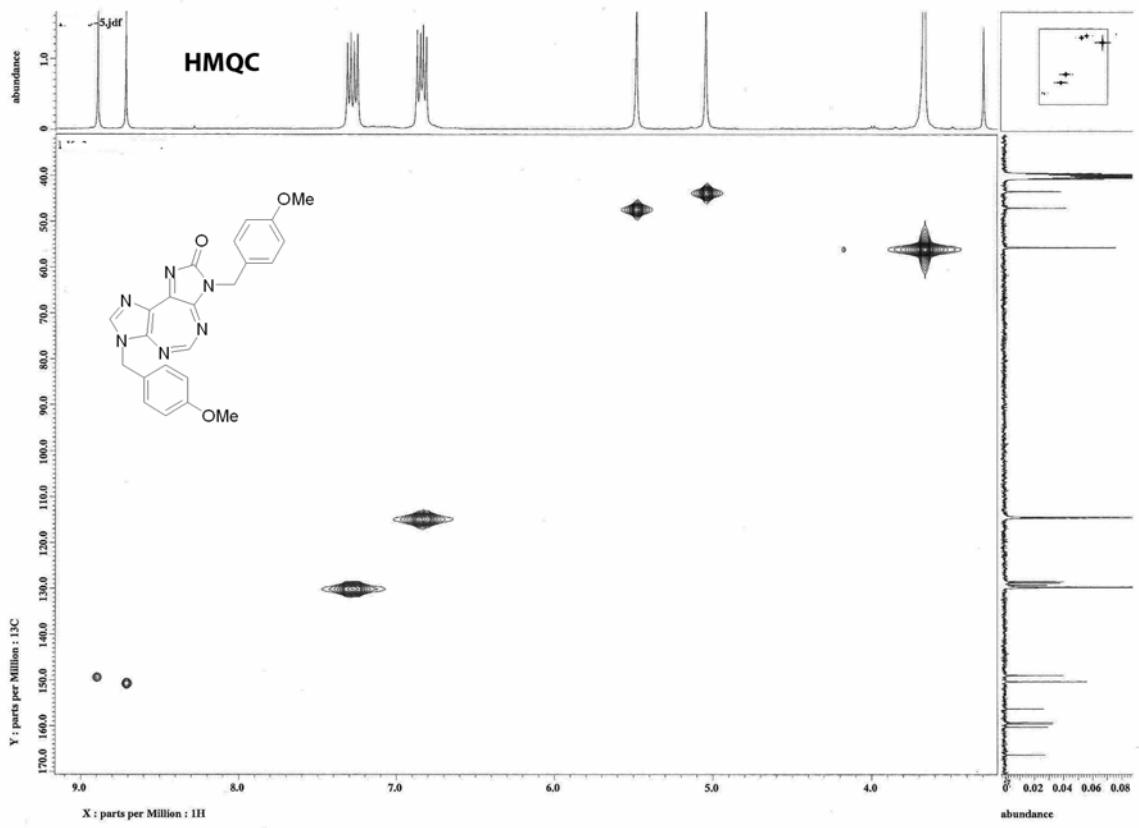

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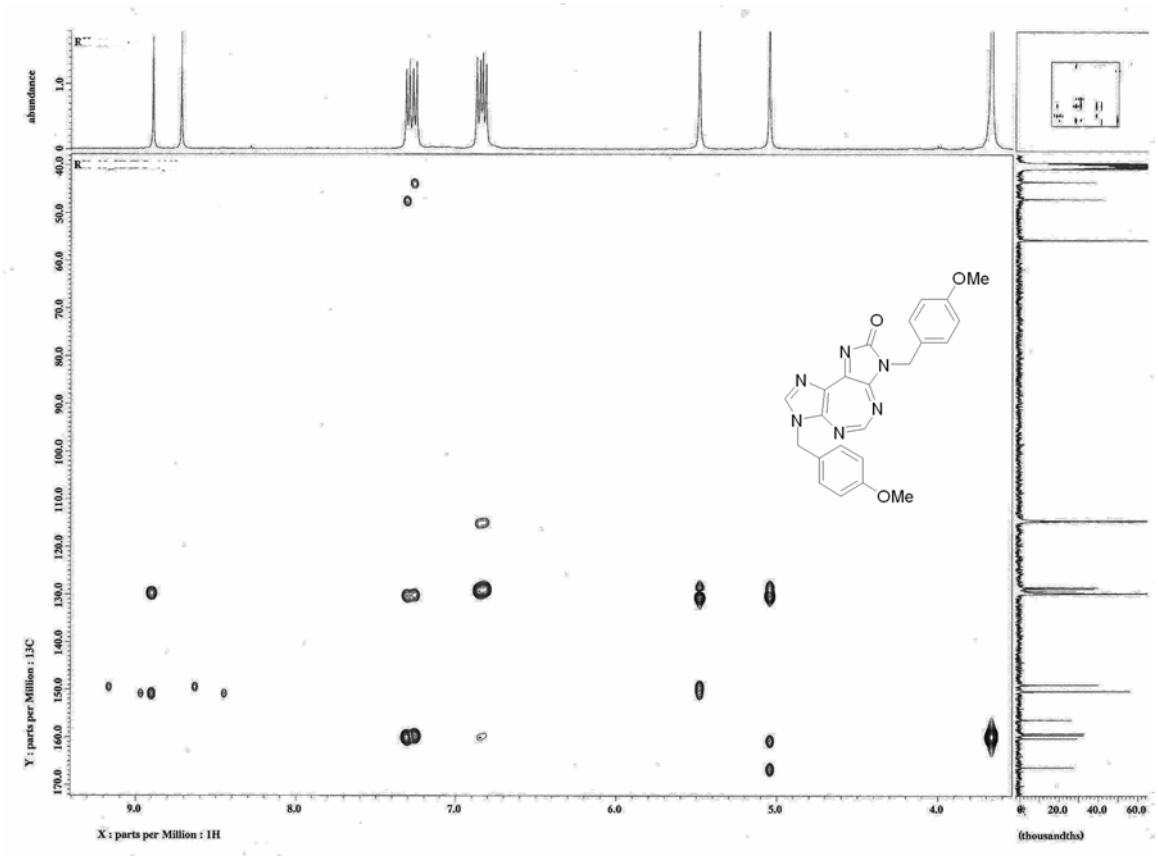

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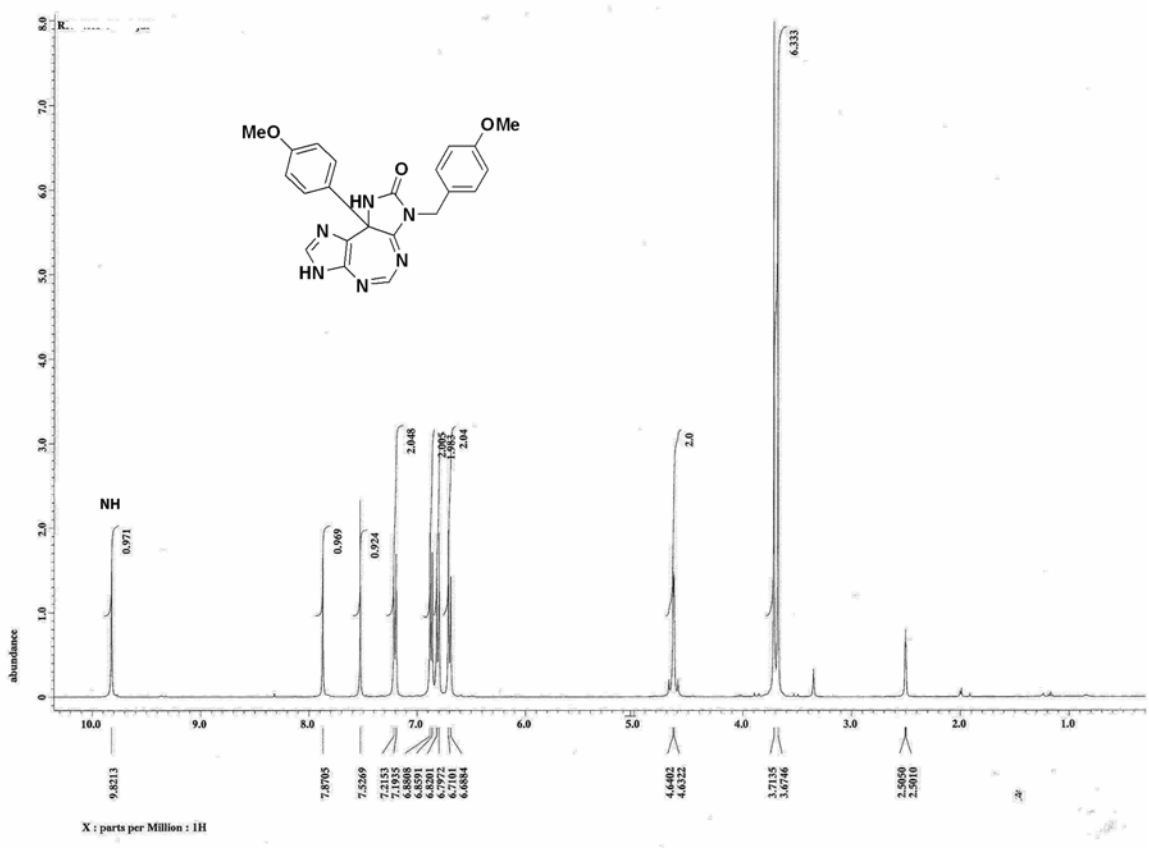
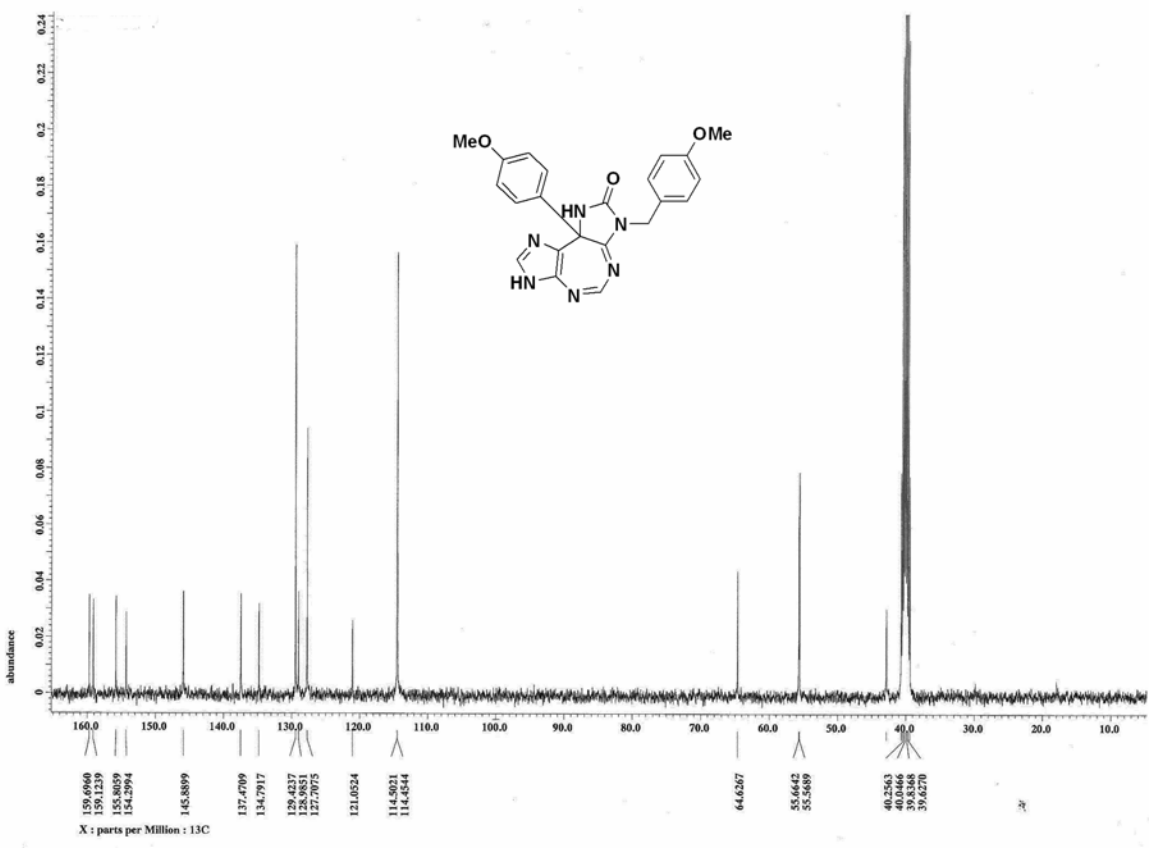


Compound 11: ^{13}C NMR



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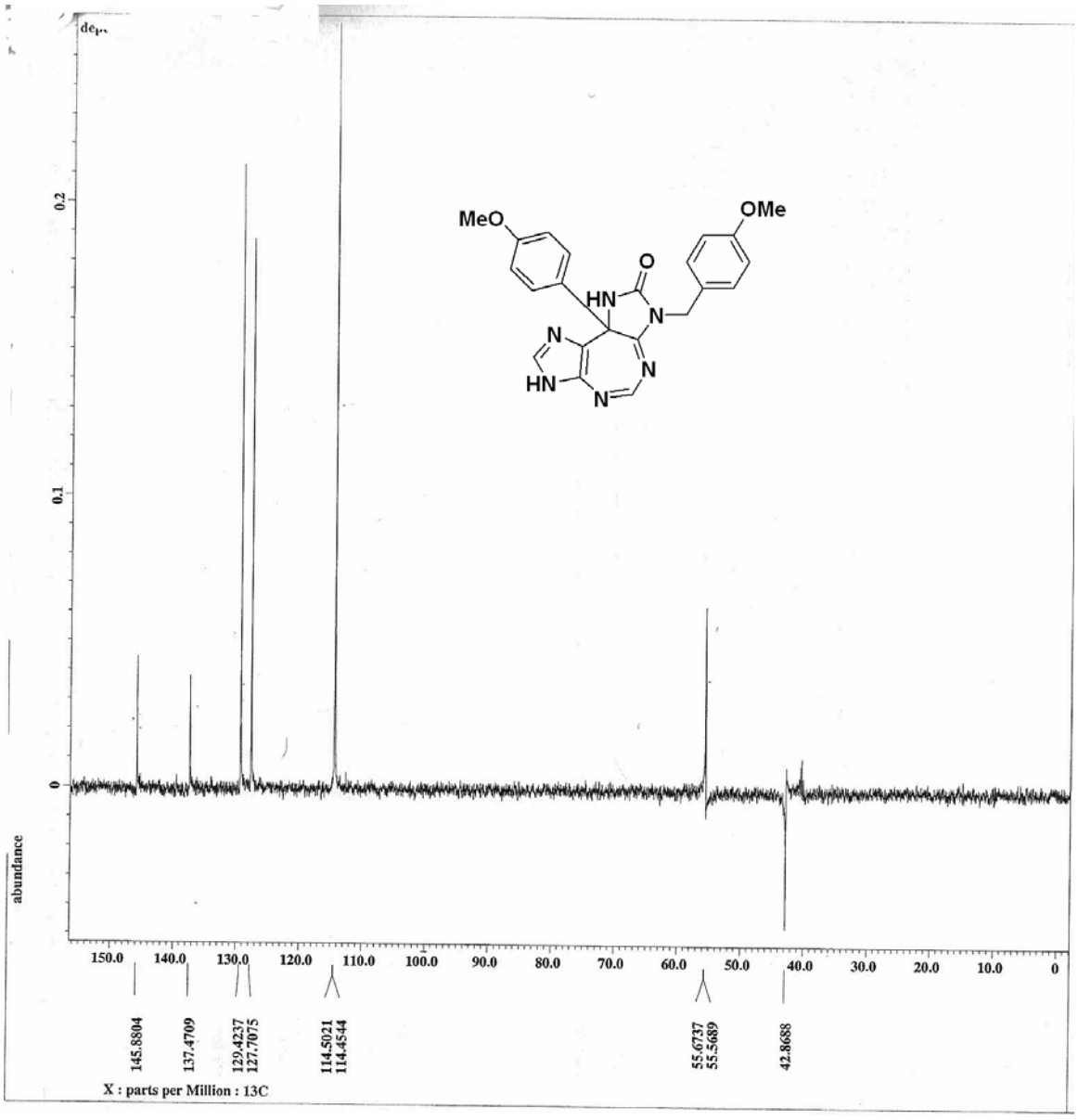

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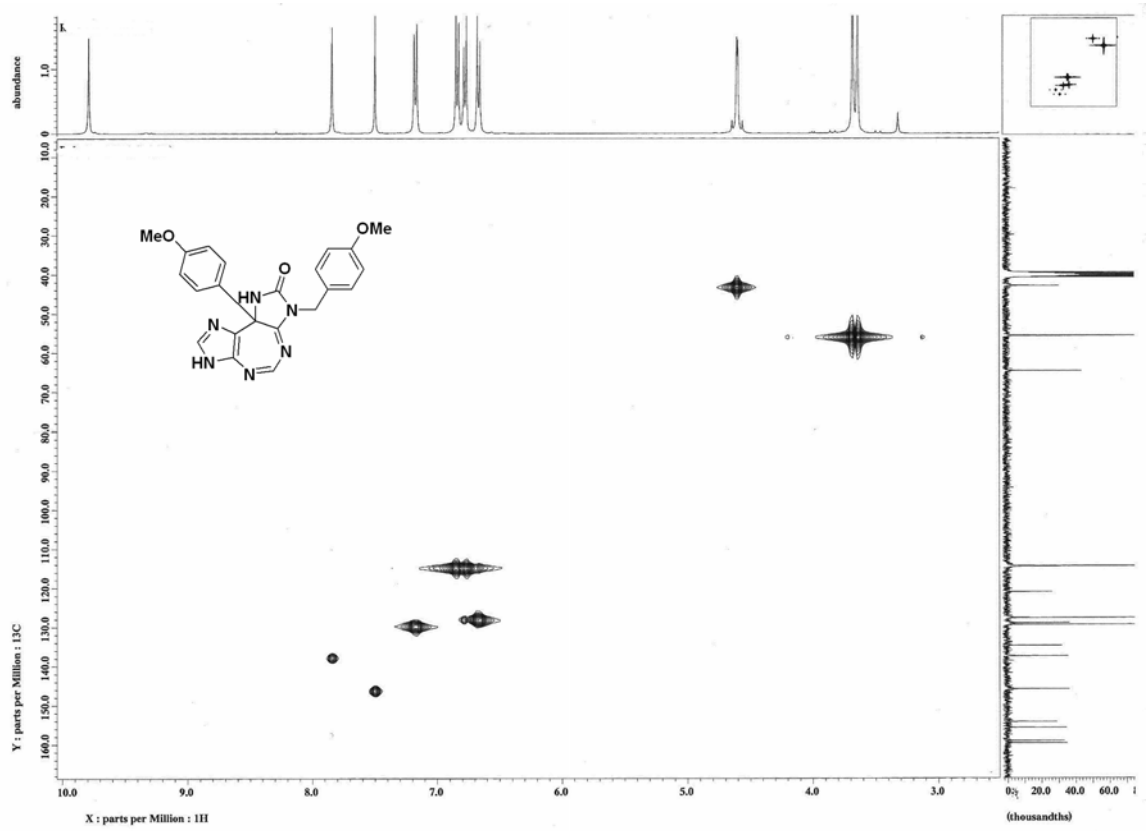

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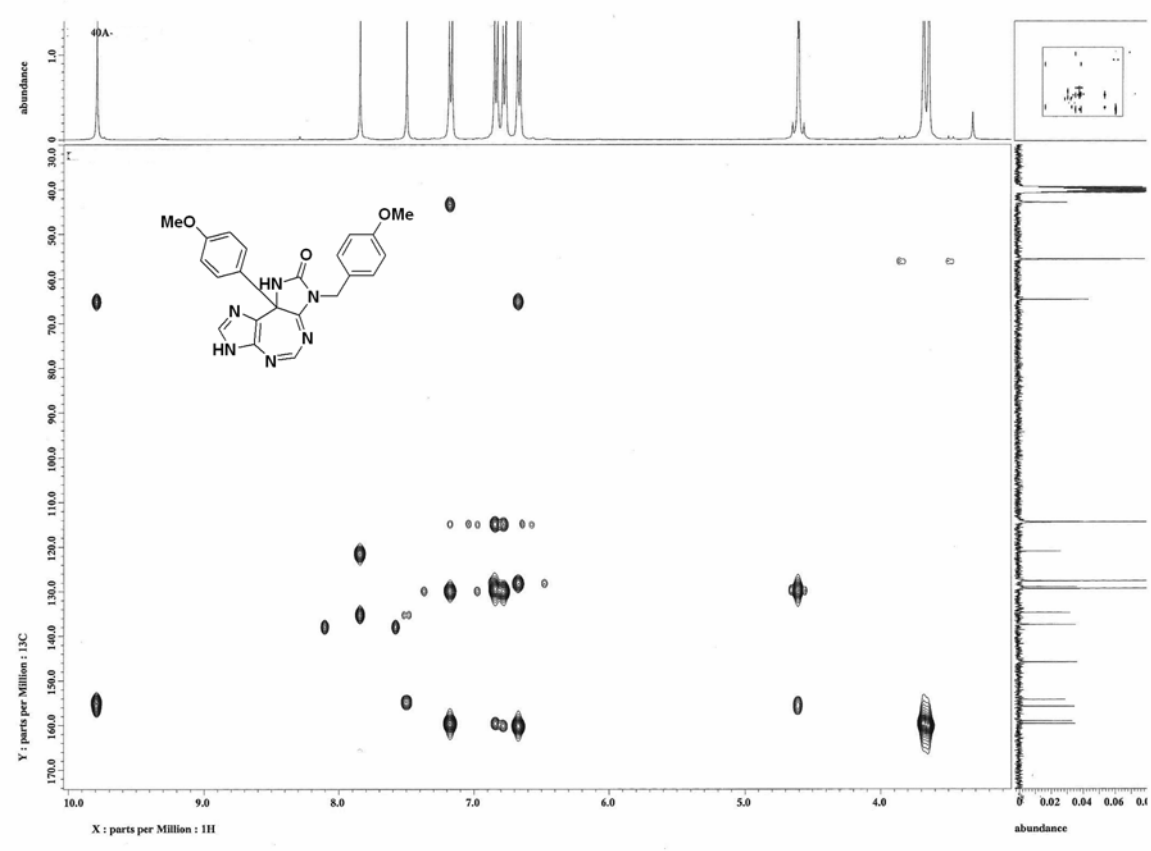

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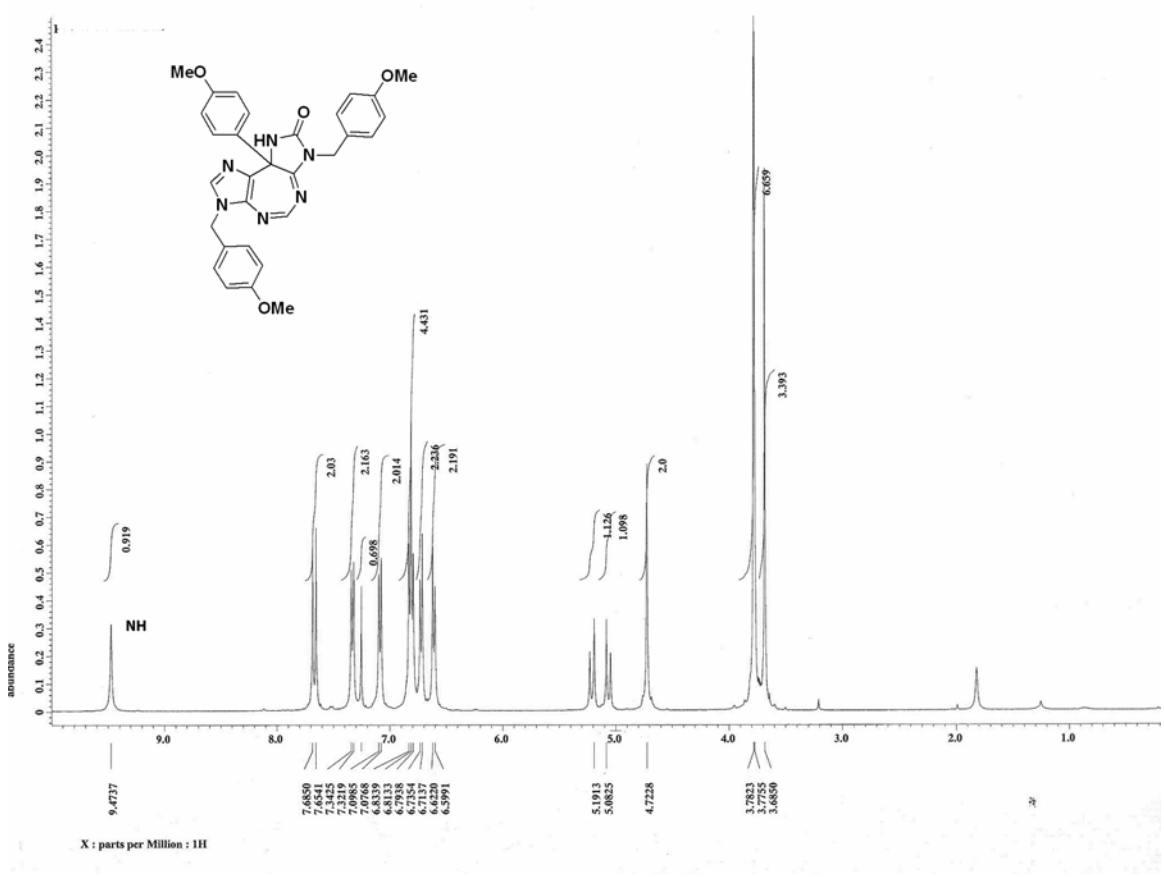

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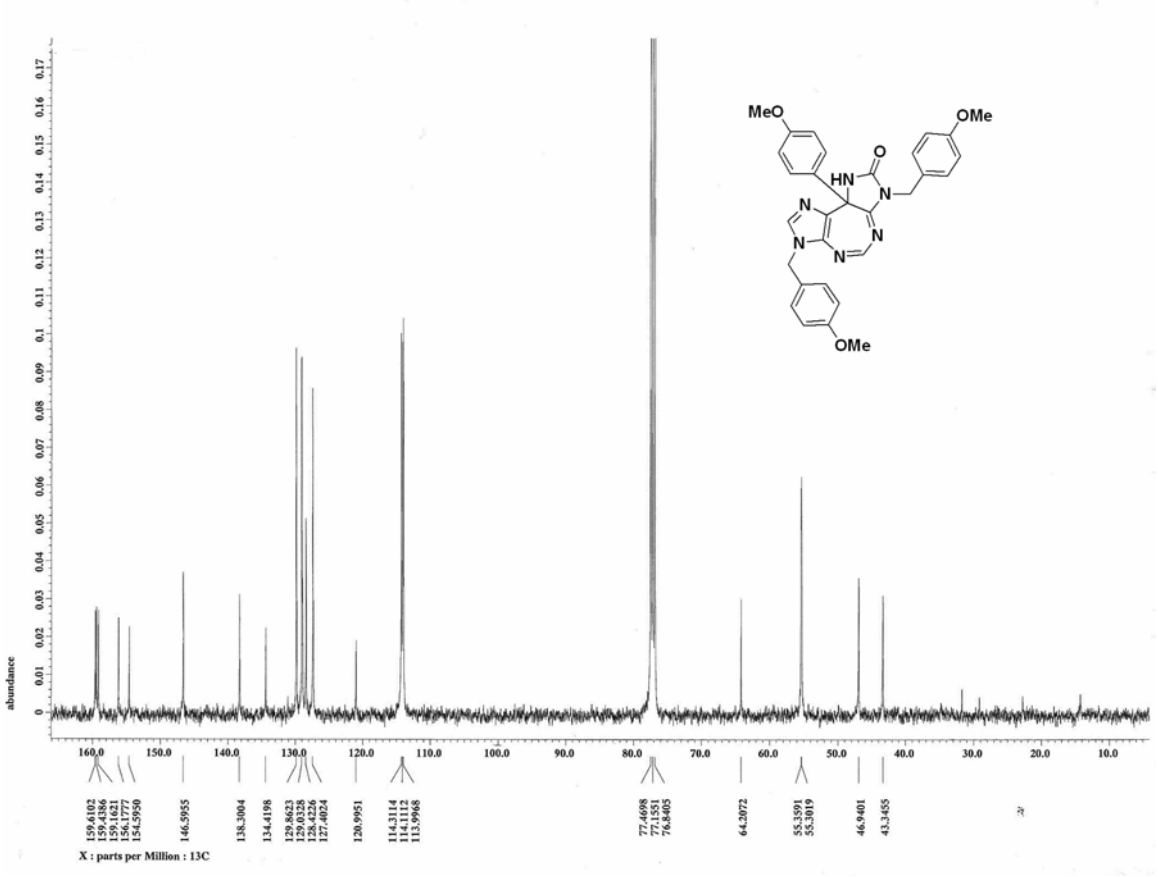

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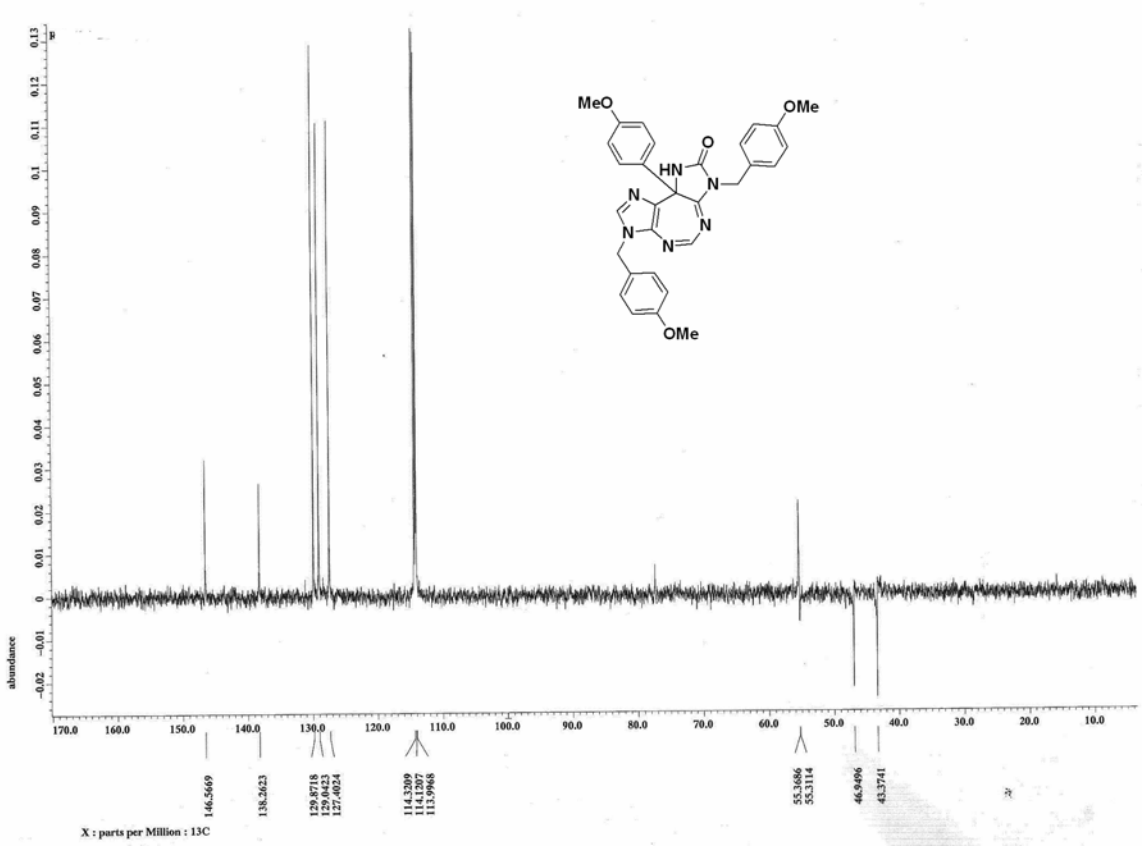

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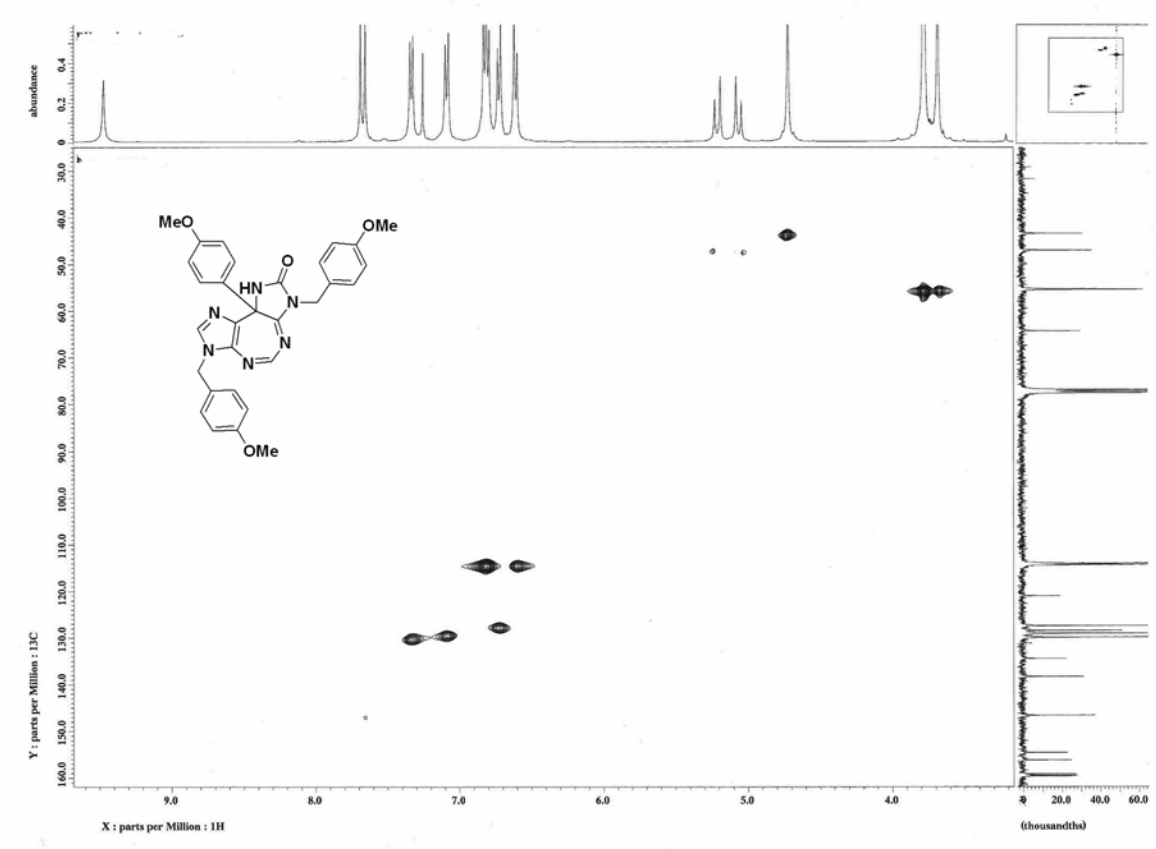

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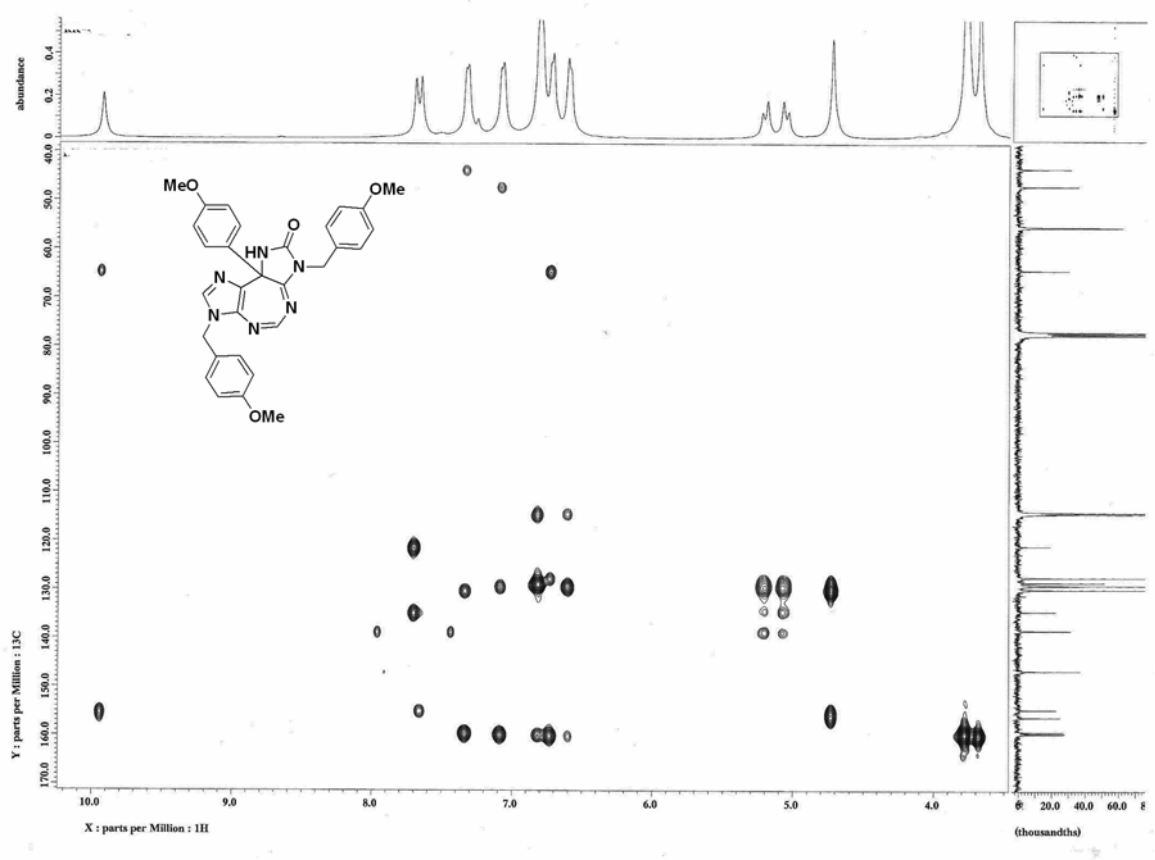

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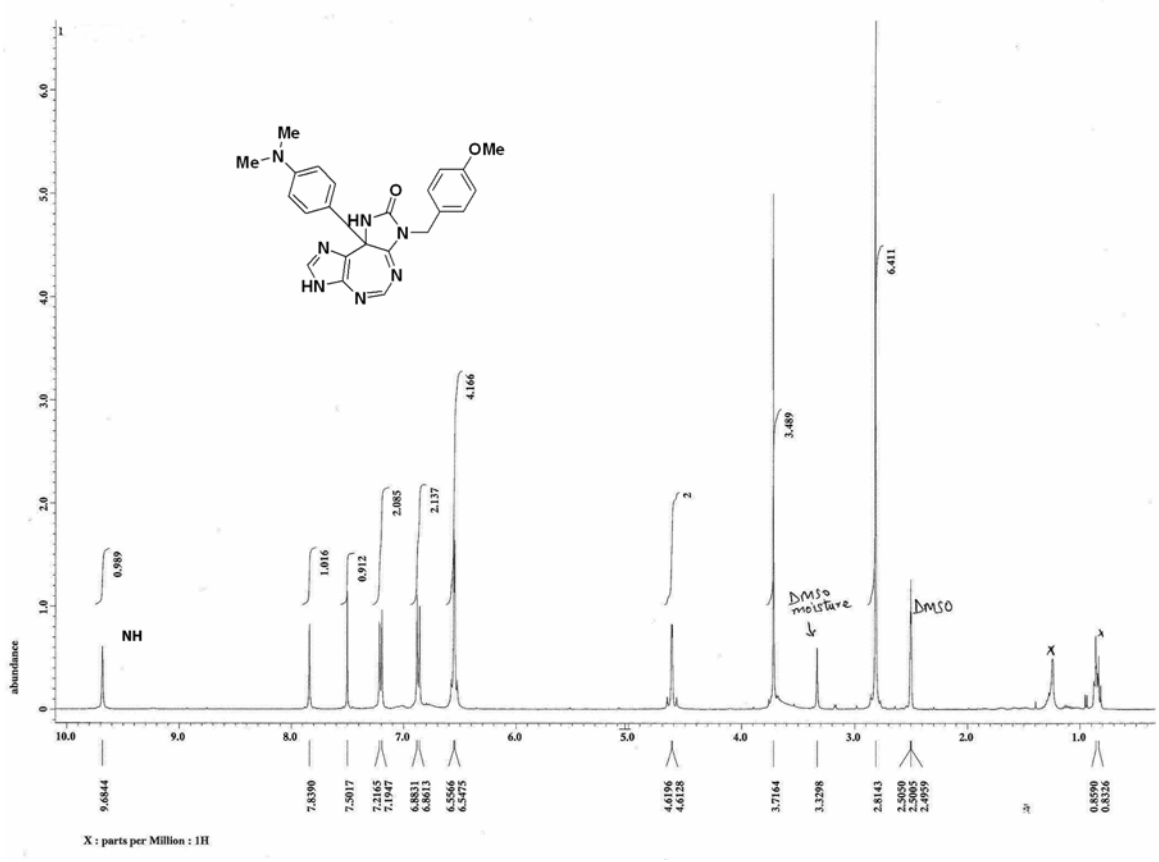

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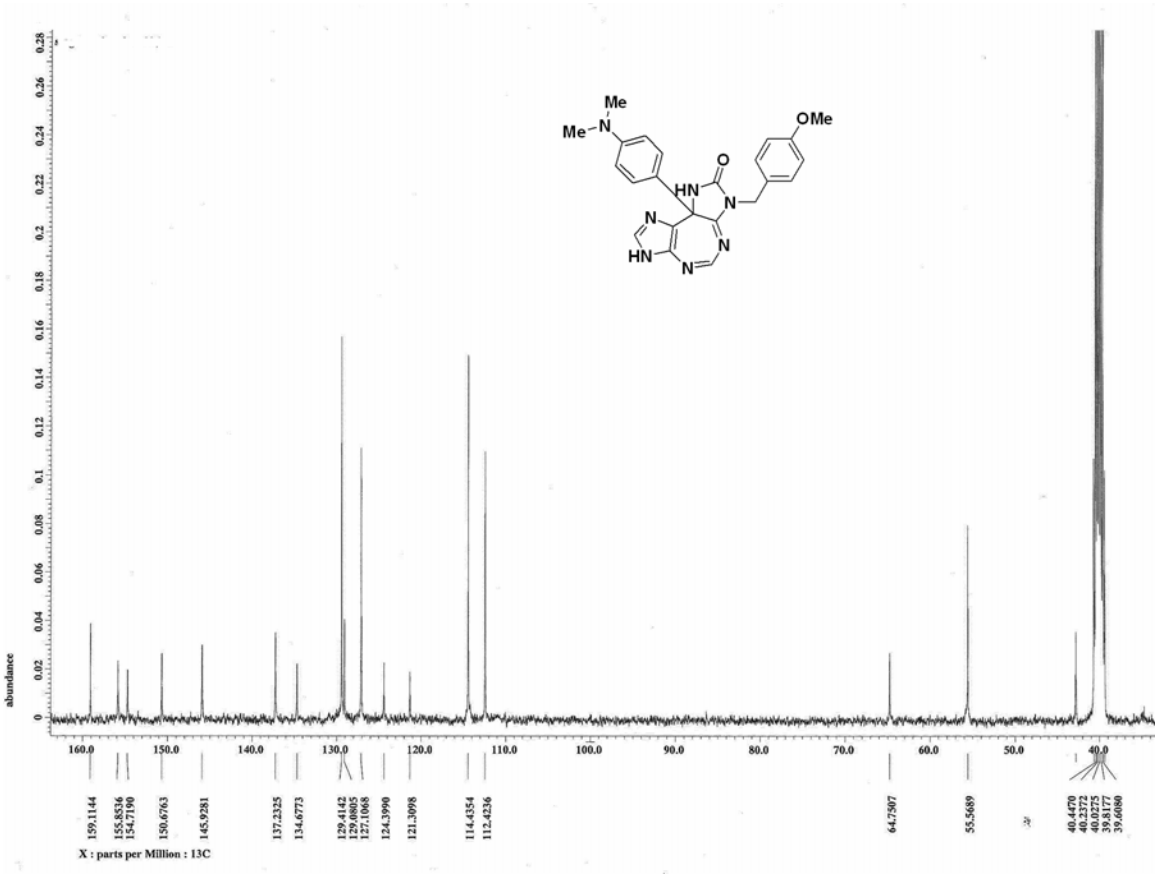

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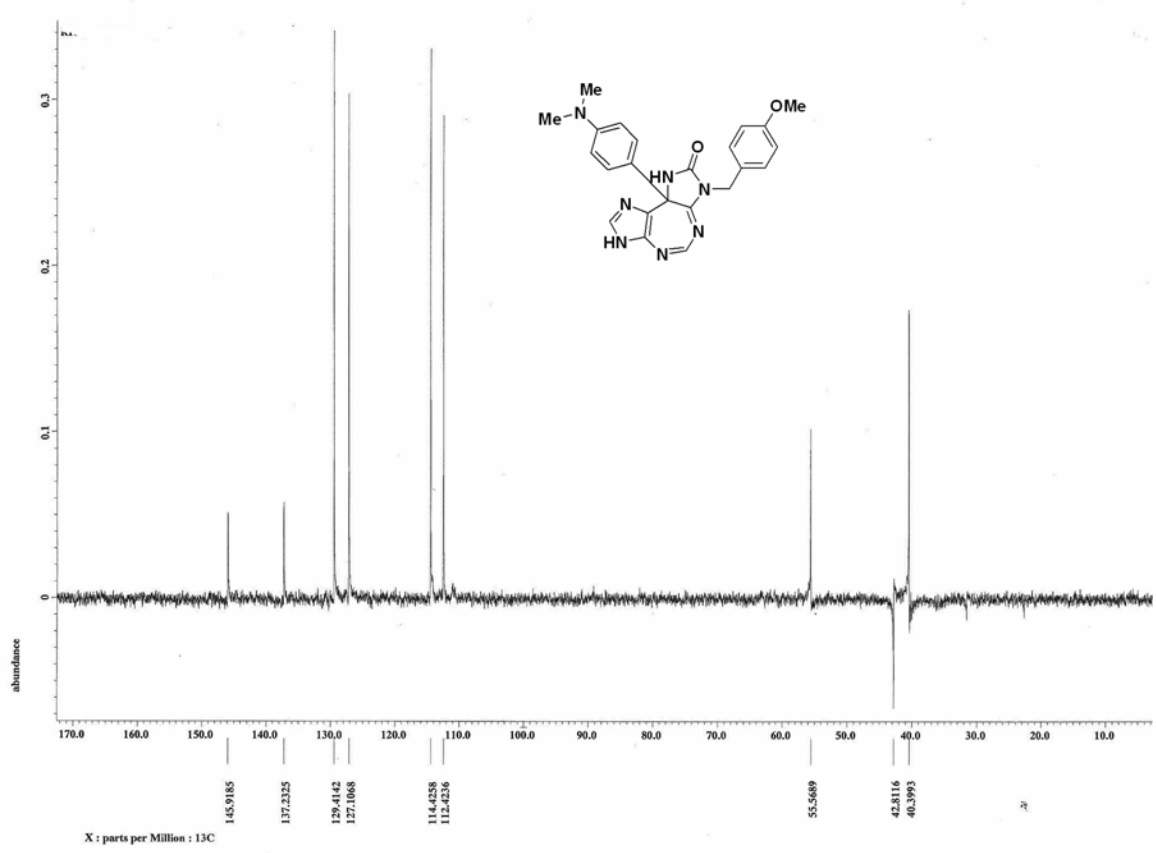

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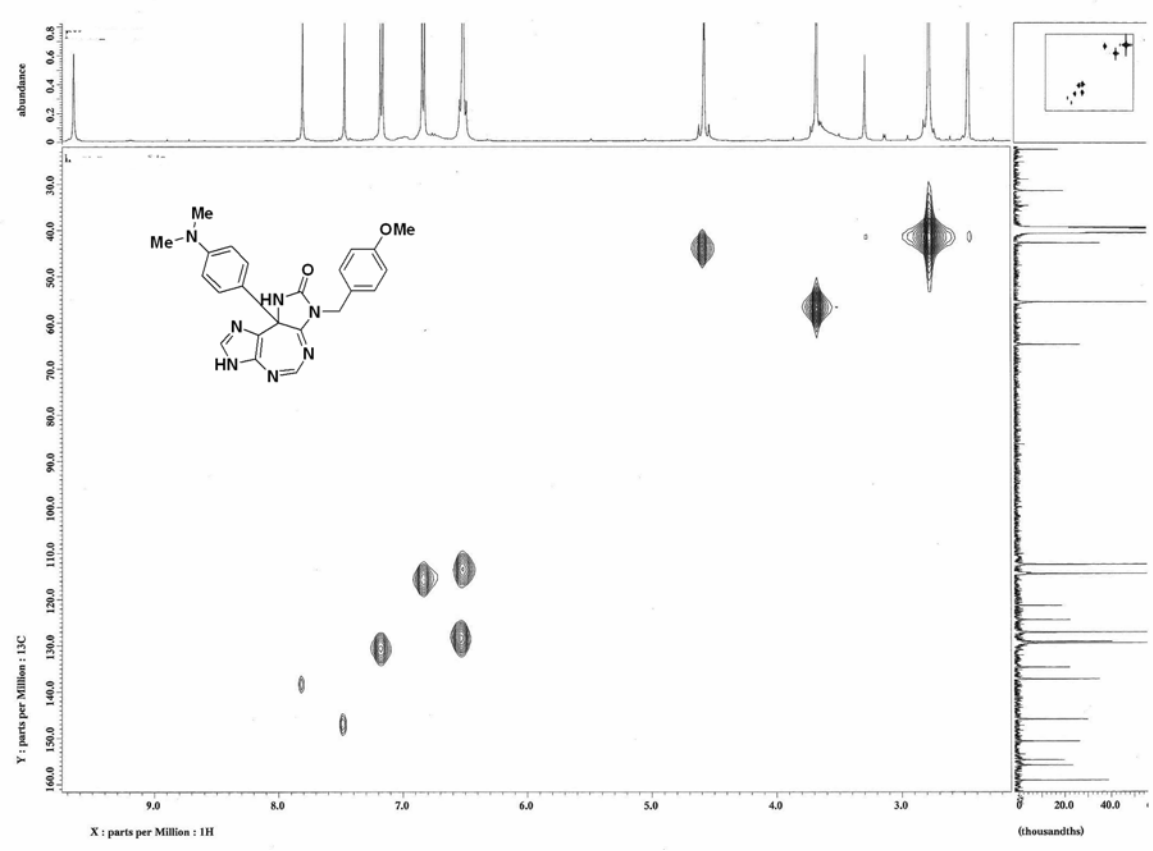

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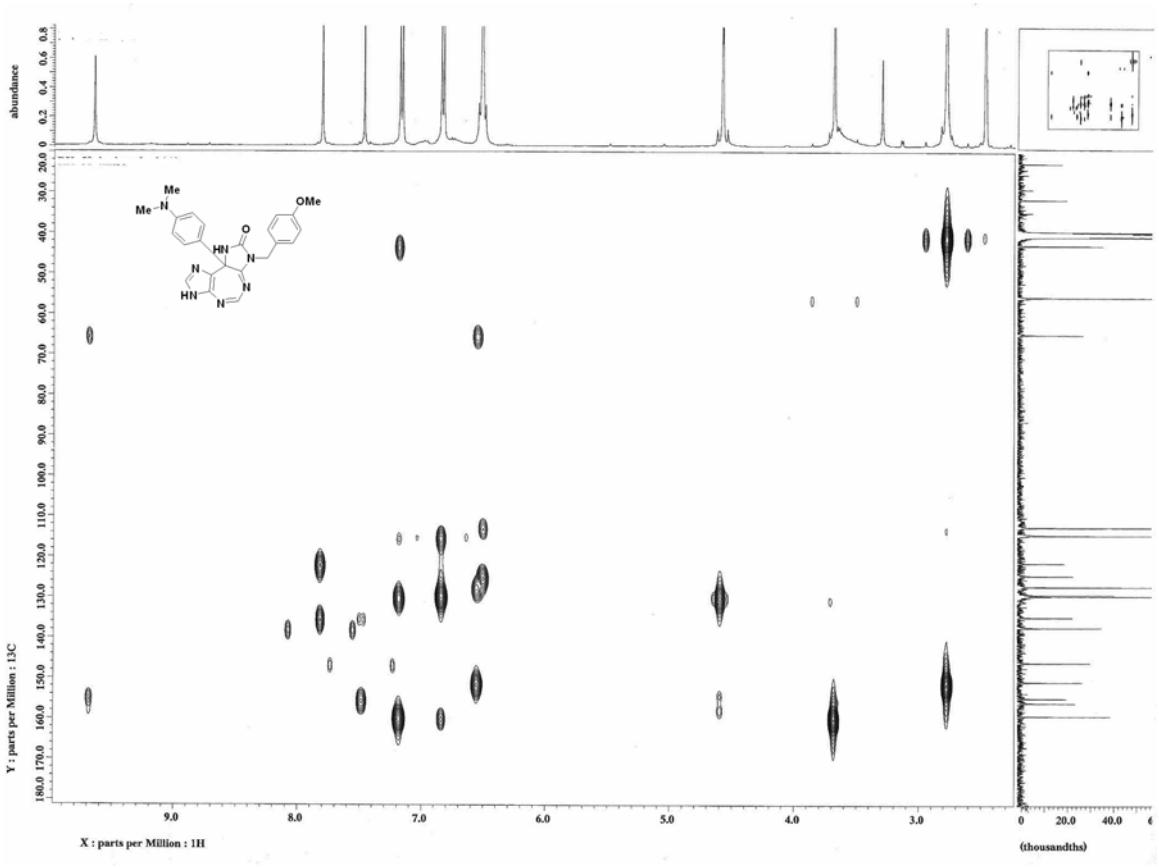

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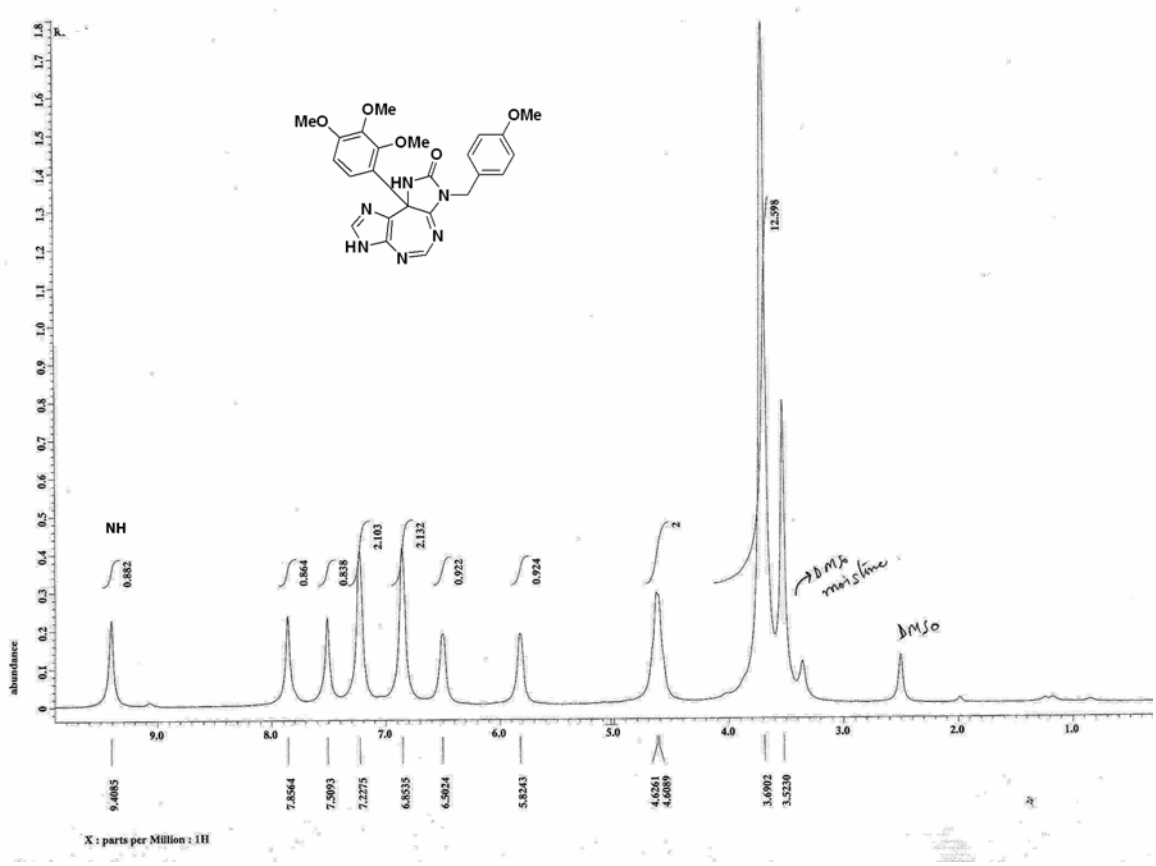

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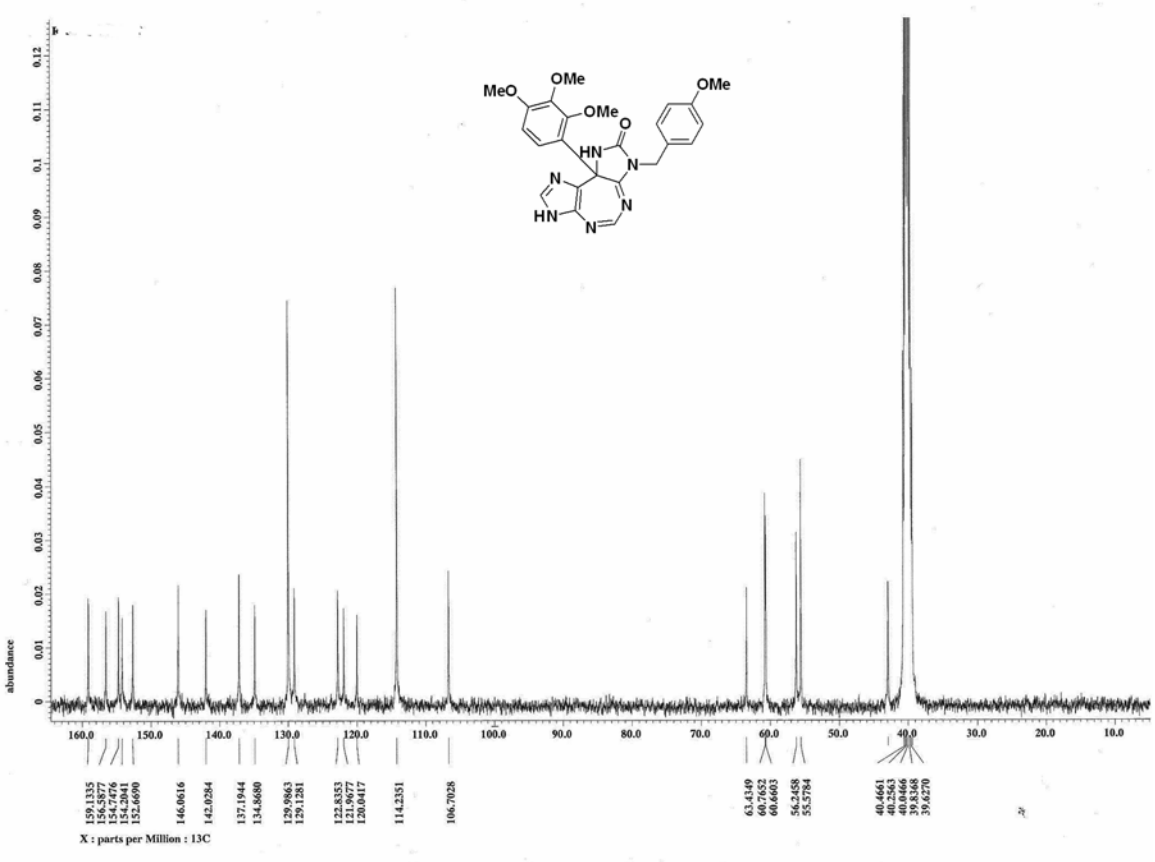
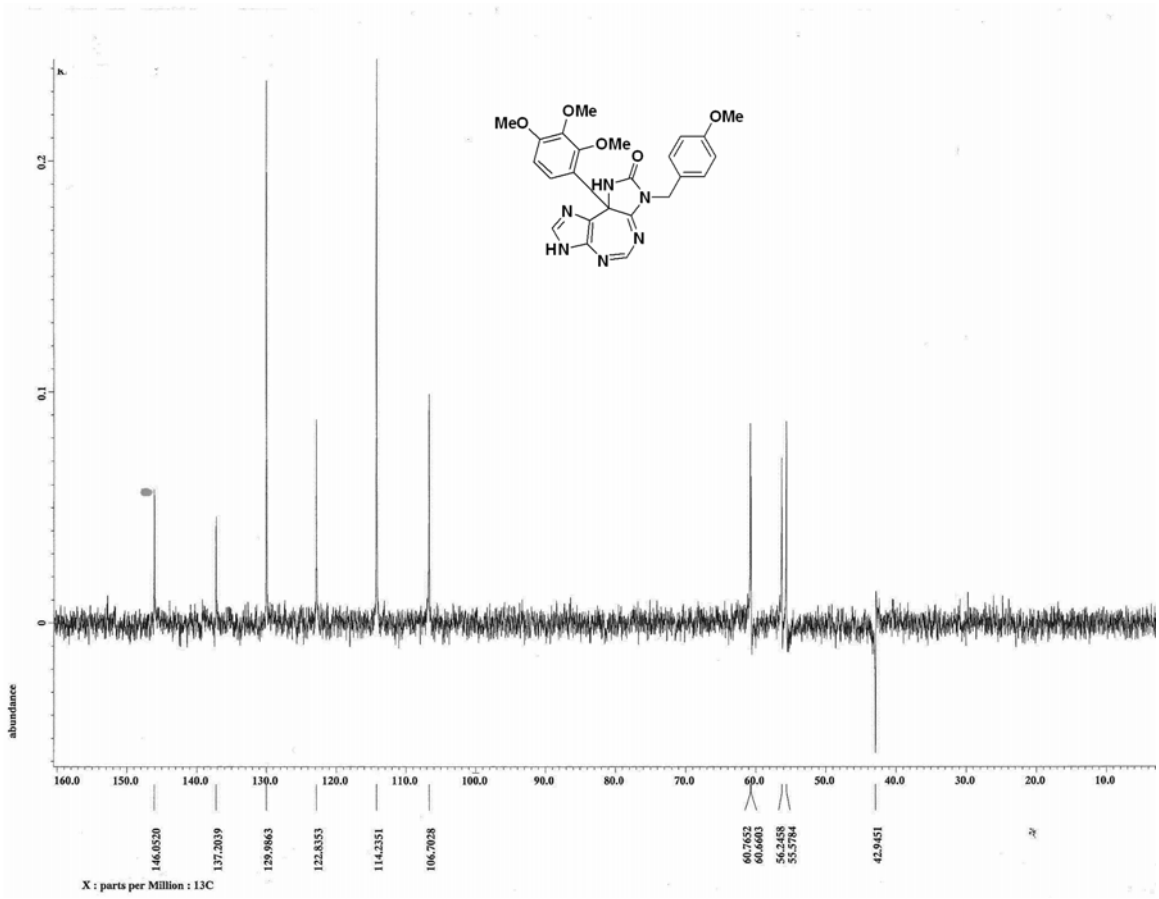


Compound 14: ^{13}C DEPT 135



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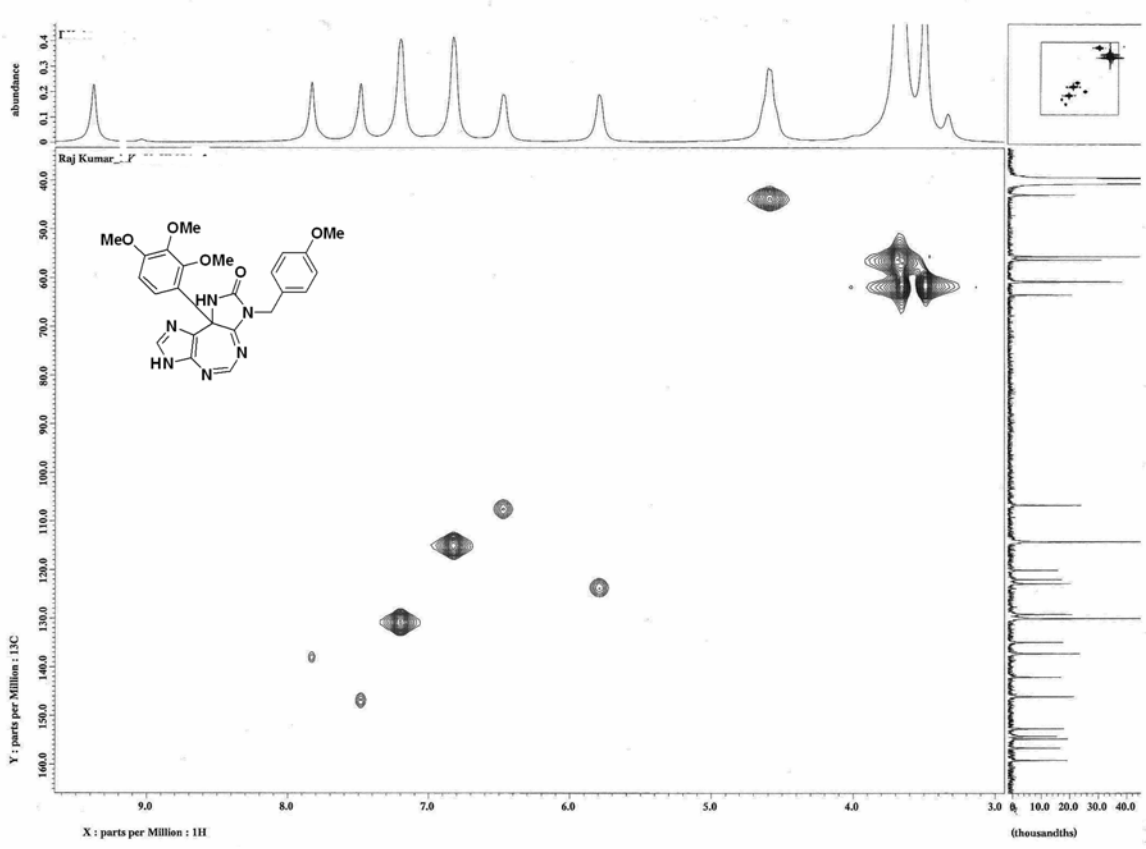
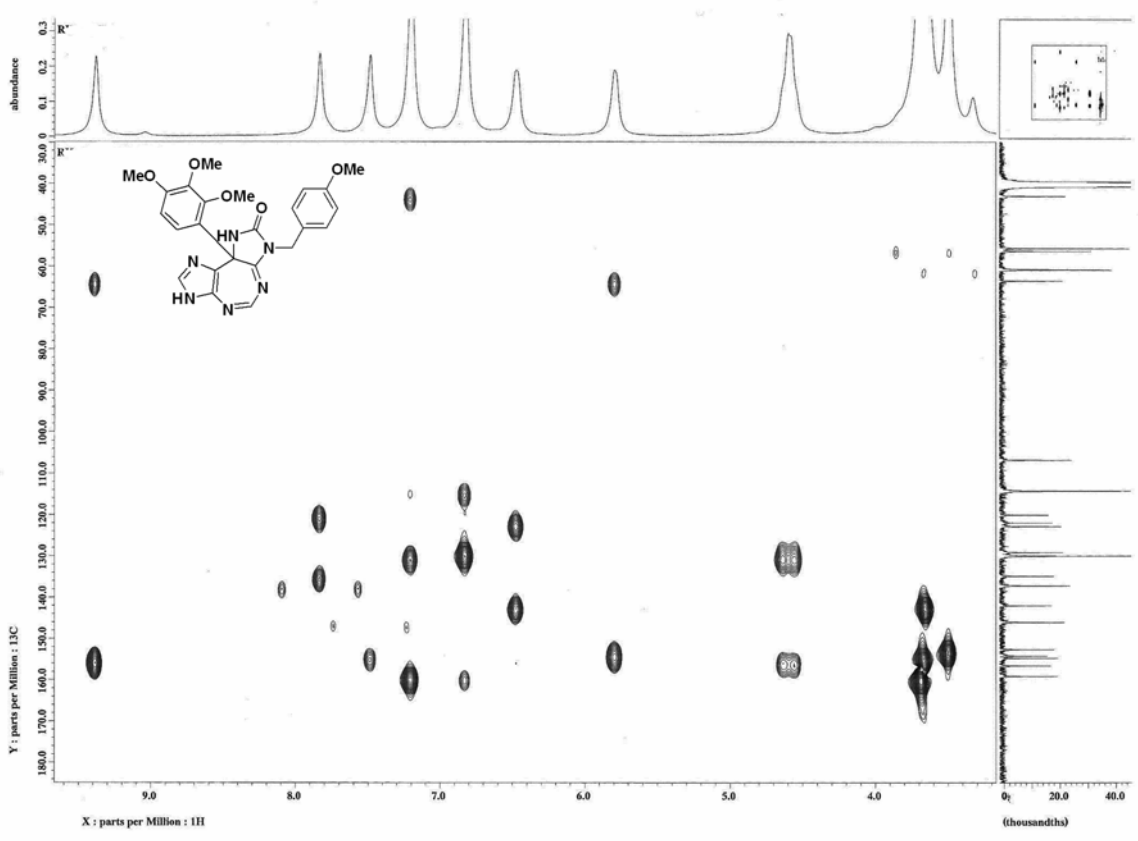


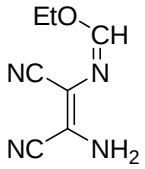
Compound 14: HMBC



Experimental

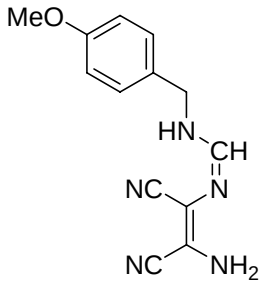
General. The ^{1}H and ^{13}C NMR spectra were recorded on a JEOL-400 NMR spectrometer, operating at 400 MHZ for ^{1}H, and 100 MHz for ^{13}C NMR. Thin layer chromatography was performed on Merck Kieselgel 60 F_{254} (0.2 mm thickness). Flash column chromatography was performed using 32-63 mesh silica gel. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. The high resolution mass spectra were recorded either at the Mass Spectral Analysis Service, Department of Chemistry, The Johns Hopkins University, Baltimore, MD. Anhydrous solvents were purchased and used without further drying and alcohols were dried over sodium metal, distilled, and stored over molecular sieves.

Synthesis of ethyl (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formimidate[1] (5):



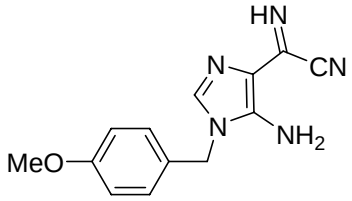
A mixture of diaminomaleonitrile (**4**, 6.0 g, 55.5 mmol, 1 equiv) and triethyl orthoformate (9.2 mL, 55.5 mmol, 1 equiv) in dioxane (80 mL) was heated at reflux in a flask fitted with a short Vigreux column, a distillation head, a condenser, and a receiver. Ethanol mixed with 1,4-dioxane was collected continuously until the temperature in the distillation head reached 99-100 °C (approximately 20 min). The clear brown liquid in the distillation pot was allowed to cool overnight. The reaction mixture was diluted with hot diethyl ether, filtered to remove the dark brown solid impurity, and left to cool overnight to give **5** as colorless needles (6 g, 65%). IR (KBr): 3309 (N-H str.), 2247 (CN str.), 2207 (CN str.), 1636 (C=N str.), 1608, 1256 (C-O str.), 810 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 7.3 Hz, 3 H, CH_3), 4.25 (q, *J* = 7.3 Hz, 2 H, CH_2), 4.66 (brs, 2 H, D_2O-exchangable NH_2), 7.97 (s, 1 H, CH).

Synthesis of (4-methoxybenzyl)-(*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formimidine (6):



4-methoxybenzyl amine (0.92 mL, 6.70 mmol, 1.1 equiv) was added to a suspension of **5** (1 g, 6.09 mmol, 1 equiv) in dry EtOH which contained aniline hydrochloride (0.02 g). The mixture was stirred at room temperature until TLC showed that all the formimidate had disappeared (~3 h) and the pale yellow solid was obtained by filtration, washed with diethyl ether and dried to give **6** (1.2 g, 65%). mp: 96-98 °C, IR (KBr): 3309 (N-H str.), 2225 (CN str.), 2206 (CN str.), 1632 (C=N str.), 1591, 1511, 1247 (C-O str.) cm^{-1}. ^{1}H NMR (400 MHz, d_6-DMSO): δ = 3.72 (s, 3 H, OCH_3), 4.44 (d, J = 4.5 Hz, 2 H, CH_2), 6.11 (s, 2 H, D_2O-exchangable NH_2), 6.89 (d, J = 8.2 Hz, 2 H, Ar-H), 7.26 (d, J = 8.2 Hz, 2 H, Ar-H), 7.70 (d, J = 2.3 Hz, 1 H, CH), 8.10 (brs, 1 H, D_2O-exchangable NH). ^{13}C NMR (100 MHz, d_6-DMSO): δ = 43.4, 55.6, 106.8, 114.2, 115.7, 116.8, 117.6, 129.7, 131.1, 150.8, 158.9. HRMS (FAB) Calcd for $C_{14}H_{14}N_4O$, 254.1168 (M^+); observed m/z 255.1115 $(M+H)^+$.

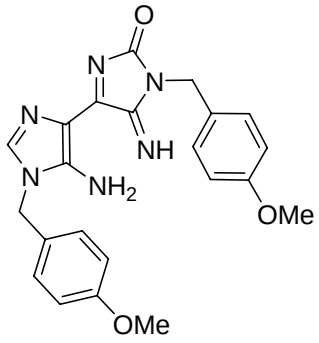
Synthesis of 5-amino-1-(4-methoxybenzyl)-4-cyanoformimidoylimidazole (7):



To a suspension of **6** (2.0 g) in dry EtOH (10 mL), DBU was added (1 drop). The reaction mixture was stirred 2 h at room temperature under nitrogen atmosphere until starting material was disappeared (TLC). The precipitated product was filtered, washed with diethyl ether and dried under vacuum to afford **7** as off-white solid (1.35 g, 67%). mp: 92-94 °C, IR (KBr): 3290 (N-H str.), 3122 (N-H str.), 2218 (CN str.), 1629 (C=N str.), 1549, 1515 (C-O str.), 1254, 810 cm^{-1}. ^{1}H NMR (400 MHz, d_6-DMSO): δ = 3.72 (s, 3 H, OCH_3), 5.03 (s, 2 H, CH_2), 6.76 (brs, 2 H, D_2O-exchangable NH_2), 6.91 (d, J = 8.2 Hz, 2 H, Ar-H), 7.22 (d, J = 8.2 Hz, 2 H, Ar-H), 7.30 (s, 1 H, Imid-H), 10.87 (s, 1 H,

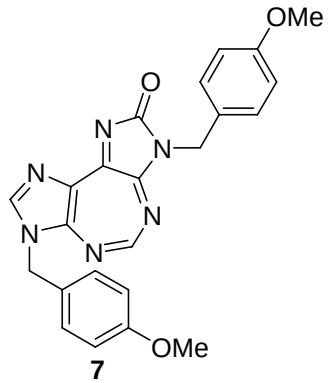
D_2O-exchangable NH). ^{13}C NMR (100 MHz, d_6-DMSO): δ = 45.7, 55.7, 114.1, 114.6, 116.7, 128.8, 129.5, 132.8, 143.5, 144.7, 159.4. HRMS (FAB) Calcd for $C_{13}H_{13}N_5O$, 255.1120 (M^+); observed m/z 256.1113 $(M+H)^+$.

Synthesis of 4-(1-(4-methoxybenzyl)-5-amino-1*H*-imidazol-4-yl)-1-(4-methoxybenzyl)-5-imino-1*H*-imidazol-2(5*H*)-one (9):



To a suspension of **7** (1.35 g, 5.29 mmol, 1 equiv) in dry MeCN (10 mL), 4-methoxybenzyl isocyanate was added (2.16 mL, 15.87 mmol, 3 equiv) under nitrogen atmosphere at 0 °C. The reaction mixture was stirred at rt for 6 h until starting material was disappeared (TLC). The yellow precipitate was filtered, washed with diethyl ether and dried under vacuum to afford the mixture of (*Z*)-1-(4-methoxybenzyl)-3-((1-(4-methoxybenzyl)-5-amino-1*H*-imidazol-4-yl)(cyano)methylene) urea (**8**) and **9** as yellow solid. Further, 2-5 drops of DBU were added to a suspension of **8** and **9** and the reaction mixture was stirred for 1 h. The deep yellow precipitate was filtered, washed with diethyl ether and dried under vacuum to afford **9** as yellow solid (1.6 g, 75%). mp: decomposed > 215-217 °C, IR: 3195 (N-H str.), 3131 (N-H str.), 1702 (C=O), 1643, 1513, 1249, 773 cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO): δ = 3.70 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 4.62 (s, 2 H, CH_2), 5.11 (s, 2 H, CH_2), 6.85 (d, *J* = 8.2 Hz, 2 H, Ar-H), 6.93 (d, *J* = 8.2 Hz, 2 H, Ar-H), 7.21 (d, *J* = 8.2 Hz, 2 H, Ar-H), 7.25 (d, *J* = 8.2 Hz, 2 H, Ar-H), 7.73 (s, 1 H, Imid-H), 7.90 (brs, 2 H, D_2O-exchangable NH_2), 9.77 (s, 1 H, D_2O-exchangable NH). ^{13}C NMR (100 MHz, d_6-DMSO): δ = 41.7, 45.9, 55.6, 55.7, 114.3, 114.7, 128.2, 129.4, 129.5, 130.2, 139.5, 152.2, 157.6, 158.9, 159.5, 160.1, 167.3. HRMS (FAB) Calcd for $C_{22}H_{22}N_6O_3$, 418.1753 (M^+); observed m/z 419.1824 $(M+H)^+$.

Synthesis of 3:



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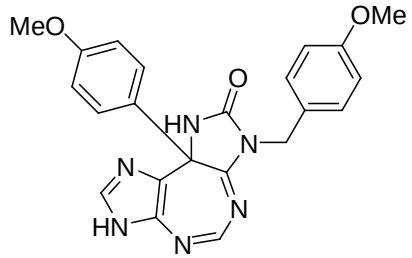
To a suspension of **9** (1.0 g, 2.39 mmol, 1 equiv) in MeCN (10 mL), triethyl orthoformate (2.8 g, 19.13 mmol, 8 equiv) was added followed by 2 drops of sulfuric acid. The reaction mixture was heated at reflux for 1.5 h until starting material was disappeared (TLC). The precipitated product was filtered, washed with diethyl ether and dried under vacuum to afford **3** as pale yellow solid (0.77 g, 76%). mp: 175-177 °C, IR : 1737 (C=O), 1610, 1589, 1251, 1176 cm^{-1}. ^{1}H NMR (400 MHz, d_6-DMSO): δ = 3.69 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 5.08 (s, 2 H, CH_2), 5.51 (s, 2 H, CH_2), 6.85 (d, J = 8.2 Hz, 2 H, Ar-H), 6.89 (d, J = 8.2 Hz, 2 H, Ar-H), 7.29 (d, J = 8.2 Hz, 2 H, Ar-H), 7.33 (d, J = 8.2 Hz, 2 H, Ar-H), 8.75 (s, 1 H, Ar-C=N-H), 8.92 (s, 1 H, Imid-H). ^{13}C NMR (100 MHz, d_6-DMSO): δ = 43.4, 47.0, 55.6, 55.7, 114.4, 114.6, 128.5, 128.8, 129.2, 129.7, 129.8, 148.9, 150.3, 156.3, 159.2, 159.5, 160.2, 166.3. HRMS (FAB) Calcd for $C_{23}H_{20}N_6O_3$, 428.1597 (M^+); observed m/z 429.1667 $(M+H)^+$.

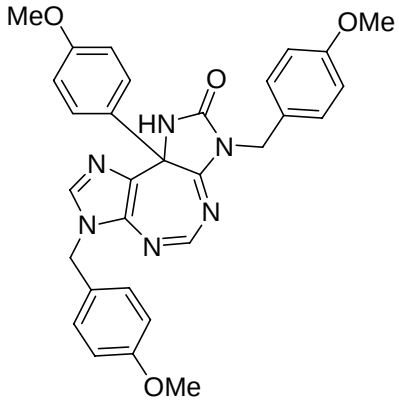
Synthesis of 11:



To a stirred suspension of **3** (0.43 g, 1 mmol) in anisole (5 mL), TFA (10 mL, dropwsie) was added. The reaction mixture was heated at 60 °C for 3 h. TFA was evaporated on rotary evaporator after the disappearance of starting material (TLC) and excess of sodium bicarbonate was added. The reaction mixture was extracted with EtOAc (30 × 3 mL), washed with brine, dried (anhyd. Na_2SO_4) and adsorbed over silica and purified through

column chromatography to afford **11** as yellowish white solid (0.34 g, 81%). mp: 223-225 °C, IR : 1743 (C=O str.), 1619, 1513, 1249 (C-O str.) cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO): δ = 3.67 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 4.63 (dd, *J* = 15.1, 18.3 Hz , 2 H, CH_2), 6.68 (d, *J* = 8.6 Hz, 2 H, Ar-H), 6.80 (d, *J* = 9.16 Hz, 2 H, Ar-H), 6.86 (d, *J* = 8.7 Hz, 2 H, Ar-H), 7.19 (d, *J* = 8.6 Hz, 2 H, Ar-H), 7.53 (s, 1 H, Ar-CH=N-), 7.87 (s, 1 H, Imid-H), 9.82 (brs, 1 H, D_2O-exchangable NH), ^{13}C NMR (100 MHz, d_6-DMSO): δ = 42.9, 55.6, 55.7, 64.6, 114.4, 114.5, 121.1, 127.7, 129.0, 129.4, 134.8, 137.5, 145.9, 154.3, 155.8, 159.1, 159.7. HRMS (FAB) Calcd for $C_{22}H_{20}N_6O_3$, 416.1597 (M^+); observed m/z 417.1669 $(M+H)^+$.

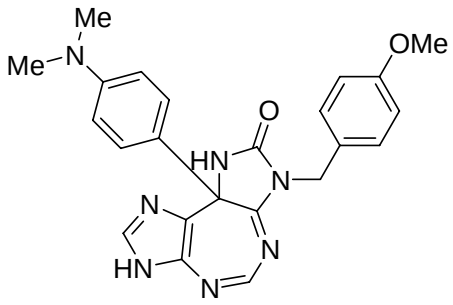
Synthesis of 12:



To a stirred suspension of **3** (0.43 g, 1 mmol) in anisole (5 mL), TFA (10 mL, dropwsie) was added and the reaction mixture was stirred at rt for 12 h. TFA was evaporated on rotary evaporator after the disappearance of starting material (TLC) and excess of sodium bicarbonate was added. The reaction mixture was extracted with EtOAc (30 × 3 mL), washed with brine, dried (anhyd. Na_2SO_4) and adsorbed over silica and purified through column chromatography to afford **12** (0.32 g, 60%, yellowish solid) and **11** (0.042 g, 10%). mp: 95-97 °C, IR : 1754 (C=O str.), 1612, 1512, 1250 (C-O str.) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.68 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 4.72 (s, 2 H, CH_2), 5.13 (q, *J* = 14.2 Hz , 2 H, CH_2), 6.61 (d, *J* = 8.6 Hz, 2 H, Ar-H), 6.72 (d, *J* = 8.6 Hz, 2 H, Ar-H), 6.79-6.83 (m, 4H, Ar-H), 7.08 (d, *J* = 8.6 Hz, 2 H, Ar-H), 7.33 (d, *J* = 8.6 Hz, 2 H, Ar-H), 7.65 (s, 1 H, Ar-CH=N-), 7.69 (s, 1 H, Imid-H), 9.47 (brs, 1 H, D_2O-exchangable NH), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.4, 46.9, 55.3, 55.4, 64.2,

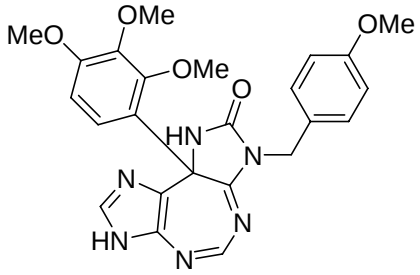
114.0, 114.1, 114.3, 121.0, 127.4, 128.4, 129.0, 129.9, 134.4, 138.3, 146.6, 154.6, 156.2, 159.2, 159.4, 159.6. HRMS (FAB) Calcd for $C_{30}H_{28}N_6O_4$, 536.2172 (M^+); observed m/z 537.2235 $(M+H)^+$.

Synthesis of 13:



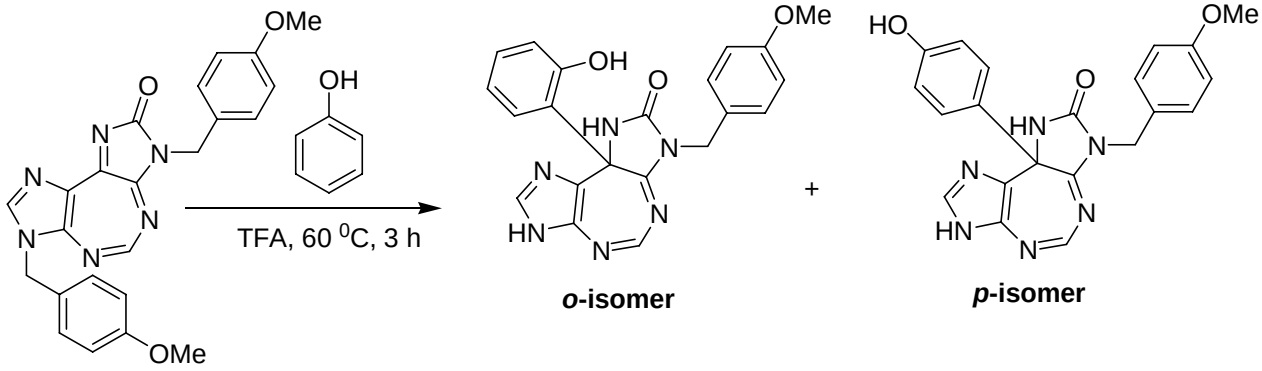
To a stirred suspension of **3** (0.43 g, 1 mmol) in *N*,*N*-dimethylaniline (5 mL), TFA (10 mL, dropwsie) was added. The reaction mixture was heated at 60 °C for 6 h. TFA was evaporated on rotary evaporator after the disappearance of starting material (TLC) and excess of sodium bicarbonate was added. The reaction mixture was extracted with EtOAc (30 × 3 mL), washed with brine, dried (anhyd. Na_2SO_4) and adsorbed over silica and purified through column chromatography to afford **13** as yellowish white solid (0.33 g, 78%); mp: decomposed > 225 °C, IR : 1730 (C=O str.), 1610, 1525, 1248 (C-O str.) cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO): δ = 2.81 (s, 6 H, $N(CH_3)_2$), 3.71 (s, 3 H, OCH_3), 4.62 (dd, *J* = 15.1, 18.3 Hz, 2 H, CH_2), 6.52 (d, *J* = 9.2 Hz, 2 H, Ar-H), 6.56 (d, *J* = 9.2 Hz, 2 H, Ar-H), 6.85 (d, *J* = 8.72 Hz, 2 H, Ar-H), 7.20 (d, *J* = 8.72 Hz, 2 H, Ar-H), 7.50 (s, 1 H, Ar-CH=N-), 7.83 (s, 1 H, Imid-H), 9.68 (brs, 1 H, D_2O-exchangable NH), ^{13}C NMR (100 MHz, d_6-DMSO): δ = 40.4 (visible in DEPT 135), 42.8, 55.6, 64.8, 112.4, 114.4, 121.3, 124.4, 127.1, 129.1, 129.4, 134.7, 137.2, 145.9, 150.7, 154.7, 155.8, 159.1. HRMS (FAB) Calcd for $C_{23}H_{23}N_7O_2$, 429.1913 (M^+); observed m/z 430.1980 $(M+H)^+$.

Synthesis of 14:

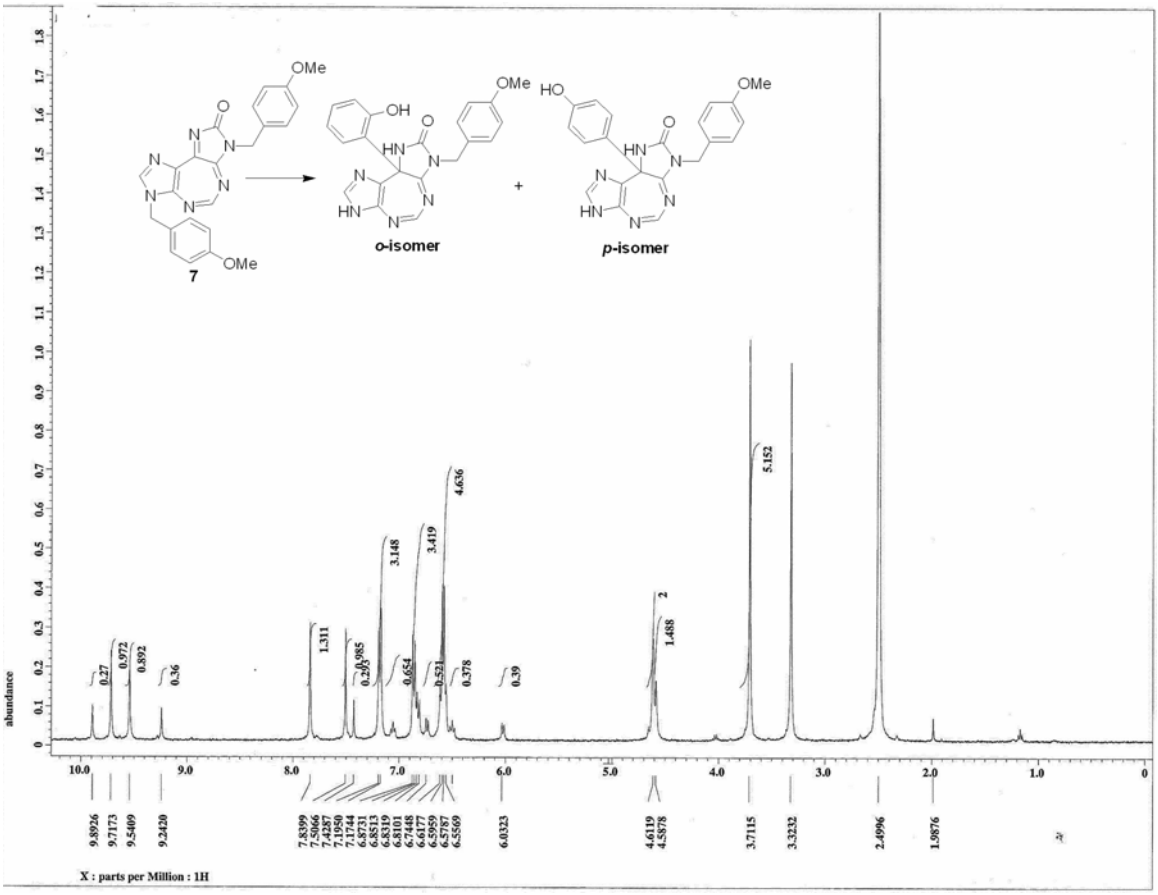


To a stirred suspension of **3** (0.43 g, 1 mmol) in 1,2,3-trimethoxybenzene (5 mL), TFA (10 mL, dropwsie) was added. The reaction mixture was heated at 60 °C for 3 h. TFA was evaporated on rotary evaporator after the disappearance of starting material (TLC) and excess of sodium bicarbonate was added. The reaction mixture was extracted with EtOAc (30 × 3 mL), washed with brine, dried (anhyd. Na_2SO_4) and adsorbed over silica and purified through column chromatography to afford **14** as yellowish white solid (0.38 g, 80%); mp: decomposed > 225 °C. IR : 1734 (C=O str.), 1620, 1514, 1247 (C-O str.) cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO): δ = 3.52 (s, 3 H, OCH_3), 3.69 (s, 6 H, OCH_3), 4.60 (dd, *J* = 15.1, 18.3 Hz, 2 H, CH_2), 5.80 (*J* = 8.7 Hz, 1 H, Ar-H), 6.50 (*J* = 8.7 Hz, 1 H, Ar-H), 6.85 (d, *J* = 8.7 Hz, 2 H, Ar-H), 7.22 (d, *J* = 8.7 Hz, 2 H, Ar-H), 7.50 (s, 1 H, Ar-CH=N-), 7.85 (s, 1 H, Imid-H), 9.40 (brs, 1 H, D_2O-exchangable NH). ^{13}C NMR (100 MHz, d_6-DMSO): δ = 42.9, 55.6, 56.3, 60.7, 60.8, 63.4, 106.7, 114.2, 120.0, 122.0, 122.8, 129.1, 129.9, 134.9, 137.2, 142.0, 146.0, 152.6, 154.2, 154.7, 156.6, 159.1. HRMS (FAB) Calcd for $C_{24}H_{24}N_6O_5$, 476.1808 (M^+); observed m/z 477.1875 $(M+H)^+$.

Reaction of 3 with phenol in TFA:



To a stirred suspension of **3** (0.43 g, 1 mmol) in phenol (5 mL), TFA (10 mL, dropwsie) was added. The reaction mixture was heated at 60 °C for 3 h. TFA was evaporated on rotary evaporator after the disappearance of starting material (TLC) and excess of sodium bicarbonate was added. The reaction mixture was extracted with EtOAc (30 × 3 mL), washed with brine, dried (anhyd. Na_2SO_4) afford mixture of *o* and *p* isomers (0.37 g, 79%) and were not separated.



Reaction of 3 with aniline in TFA:

To a stirred suspension of **3** (0.43 g, 1 mmol) in aniline (5 mL), TFA (10 mL, dropwsie) was added. The reaction mixture was heated at 60 °C for 2 h. The multiple spots (more than 8) appeared on TLC and were not separated.

Reaction of 3 with nitrobenzene in TFA:

To a stirred suspension of **3** (0.43 g, 1 mmol) in nitobenzene (5 mL), TFA (10 mL, dropwsie) was added. The reaction mixture was heated at 60 °C for 12 h. The starting material remained unchanged.

References

1. Sun, Z.; Hosmane, R. S. *Synth. Commun.* **2001**, *31*, 549-554.