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SUPPORTING INFORMATION

Synthesis and Complementary Self-association of Novel Lipophilic π-Conjugated Nucleoside Oligomers

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SUPPORTING INFORMATION

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1. Synthesis and Characterization.

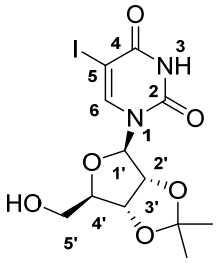
General Methods.

LSI-MS and **HR-MS** spectra were determined on a *VG AutoSpec* apparatus (FAB) or an *Applied Biosystems QSTAR* equipment (ESI) in the positive mode. **NMR** spectra were recorded with a *BRUKER AC-300* (300 MHz) instrument. The temperature was actively controlled at 298 K. Chemical shifts are measured in ppm using the signals of the deuterated solvent as the internal standard [$CHCl_3$, calibrated at 7.26 ppm (^1H) and 77.0 ppm (^{13}C); DMSO calibrated at 2.50 ppm (^1H) and 39.5 ppm (^{13}C)]. **UV-Visible** experiments were conducted using a *Jasco V-660* apparatus, taking data every 1 nm at a speed of 200 nm/min.

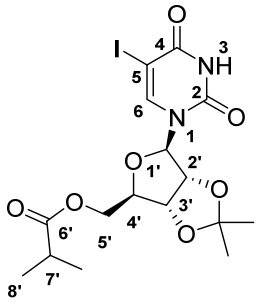
Starting materials.

Chemicals were purchased from commercial suppliers and used without further purification. Solid, hygroscopic reagents were dried in a vacuum oven before use. Reaction solvents were thoroughly dried before use using standard methods. Column chromatography was carried out on silica gel *Merck-60* (230-400 mesh, 60 Å), and TLC on aluminium sheets precoated with silica gel 60 F254 (Merck). The synthesis and characterization of compounds: **U4**[1], ***i*C3**[2] **C4**[3], **G5**[4]**, G4**[5], **A4**[3] and **1**[6] have been reported elsewhere.

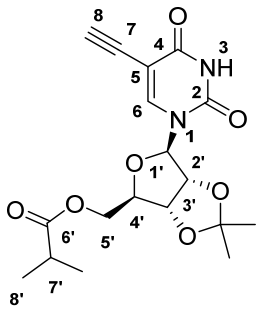
Uridine



U3. U3 was synthesized according to a literature procedure[7] adapted to our molecule. Iodouridine **U4**[1] (67.55 mmol, 25.0 g) was made to react with $HClO_4$ (70%) (1.88 eq, 101.32 mmol, 8.76 mL) in acetone (1000 mL). After stirring for 30 min, the reaction was completed. Then, dry $CaCO_3$ was added and the resulting mixture was stirred overnight. The reaction mixture was then filtered through a short silica plug (acetone/$CHCl_3$; (3:1)) and the product was collected after evaporation of the solvent. The product was purified by recrystallization in AcOEt to give a white solid. (24,06 g, 87%). **^{1}H-NMR** (300 MHz, DMSO-d_6) δ(ppm)= 11.73 (s (broad), 1H, CON*H*), 8.33 (s, 1H, H^6); 5.82 (d, J = 2.1 Hz, 1H, $H^{1'}$), 5.17 (t, J = 5.2 Hz, 1H, CH_2-O*H*), 4.92 (dd, J = 6.5 Hz, J' = 2.6 Hz, 1H, $H^{2'}$), 4.75 (dd, J = 6.5 Hz, J' = 3.5 Hz, 1H, $H^{3'}$), 4.15–4.05 (m, 1H, $H^{4'}$), 3.68–3.52 (m, 2H, $H^{5'}$), 1.48 (s, 3H,-OC-CH'_3), 1.29 (s, 3H, -OC-CH_3).



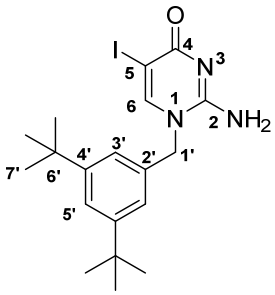
U2. To a solution of **U3** (12.19 mmol, 5.0 g) and catalitic DMAP (0.2 eq, 2.44 mmol, 298 mg) in dry MeCN (120 mL), NEt_3 (1.5 eq, 18.29 mmol, 2.54 mL) and isobutyric anhydride (1.1 eq, 13.41 mmol, 2.23 mL) were added. The reaction mixture was stirred at room temperature overnight. MeOH (2 mL) was then added the mixture further stirred for 30 min. The solvent was evaporated under reduced pressure. Then, the mixture was dissolved in $CHCl_3$ and washed with $NaHCO_3$ (sat) (2 x 100 mL) and NaCl (2 x 100 mL). The organic phase was dried with $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography in $CHCl_3$/MeOH (60:1). 5.04 g of compound **U2** were obtained (86% yield). **^{1}H-NMR** (300 MHz, DMSO-d_6) δ(ppm) = 11.81 (s (broad), 1H, CON*H*), 8.14 (s, 1H, H^6), 5.78 (s, 1H, $H^{1'}$), 5.06 (dd, J = 6.4 J' = 1.8 Hz , 1H, $H^{2'}$), 4.78 (d, J = 6.2 Hz, 1H, $H^{3'}$), 4.27–4.17 (m, 3H, $H^{4'}$, $H^{5'}$), 1.48 (s, 3H, -CH_3), 1.29 (s, 3H, -CH_3), 1.11 (s, 3H, -COCH-(CH_3)$_2$), 1.08 (s, 3H, -COCH-(CH_3)$_2$). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ(ppm) = 176.5, 160.2, 149.8, 146.0, 114.8, 94.1, 85.1, 84.7, 80.8, 68.7, 63.8, 33.9, 27.1, 25.3, 19.1, 19.0. ., **HRMS (ESI+):** Calculated for $C_{16}H_{22}IN_2O_7$: 481.0393 $[M+H]^+$. Found: 481.0479 $[M+H]^+$



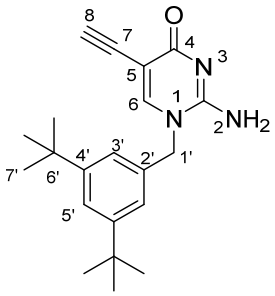
U1. Following *Standard Procedure A*, to a solution of compound **U2** (16.65 mmol, 8 g), $Pd(PPh_3)_2Cl_2$ (0.33 mmol, 0.234 g) and CuI (0.17 mmol, 32 mg) in NEt_3/THF (4:1) (80 mL) TMSA (1.5 eq, 24.98 mmol, 3.83 mL) was added and the mixture was stirred at 40 ºC for 18 h. After reaction completion, the deprotection reaction is carried out without further purification following the *Standard Procedure* B. The crude product obtained after solvent evaporation was suspended in dry THF (100 mL) and TBAF·3H_2O (1.2 eq, 19.98 mmol, 6.30 g) was added. After reaction completion the solvent was evaporated and the resulting residue was purified by column chromatography using $CHCl_3$/ AcOEt (5:1) as eluent. 4.85 g of compound **U1** were obtained as a white solid (77% yield). **^{1}H-NMR** (300 MHz, DMSO-d_6) δ(ppm) = 11.76 (s, 1H, CON*H*), 8.05 (s, 1H, H^4), 5.81 (d, J = 1.9 Hz, 1H, $H^{1'}$), 5.06 (dd, J = 6.5, J' = 1.9 Hz, 1H, $H^{2'}$), 4.81 – 4.77 (m, 1H, $H^{3'}$), 4.27 – 4.19 (m, 3H,

H$^{4'}$ y C*H*$_2$), 4.14 (s, 1H, -C*H*), 2.62 – 2.53 (m, 1H, -COC*H*), 1.49 (s, 3H, -C*H*$_3$), 1.29 (s, 3H, C*H*$_3$), 1.09 (dd, *J* = 7.0, *J'* = 1.7 Hz, 6H, -COCH-(C*H*$_3$)$_2$). **^{13}C-NMR** (75 MHz, $CDCl_3$) *δ*(ppm) = 176.5, 161.2, 148.9, 144.7, 114.8, 99.4, 93.9, 85.0, 84.8, 82.4, 80.6, 74.1, 63.7, 33.8, 27.1, 25.3, 19.1, 18.9. **HRMS (ESI+):** Calculated for $C_{18}H_{22}N_2O_7Na$: 401.0393 $[M+Na]^+$. Found: 401.1337 $[M+Na]^+$.

Isocitidine

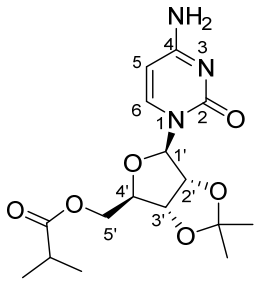


iC2. The synthesis of **iC2** was performed according to a published procedure[8] that was adapted to our molecule. To a solution of **iC3**[2] (13.15 mmol, 3.05 g) in DMF (50 mL) 3,5-di-*tert*-butylbenzyl bromide (14.47 mmol, 4.09 g) and TBAF·$3H_2O$ (15.78 mmol, 4.09 g) were added. The mixture was heated to 40 ºC. After 2 hours, the solvent was evaporated under vacuum and the mixture was redissolved in $CHCl_3$ and washed with water (2 x 50 mL). The organic phase was dried over $MgSO_4$, the solvent evaporated and the residue purified by column chromatography using $CHCl_3$/MeOH (30:1) as eluent. 4.16 g of compound **iC2** were obtained (72% yield) as a yellow oil. **^{1}H-NMR** (300 MHz, $CDCl_3$) *δ*(ppm) = 7.45 (s, 1H, *H*^{6}), 7.43 (s, 1H, *H*$^{5'}$), 7.01 (s, 2H, *H*$^{3'}$), 6.62 (s(broad), 2H, N*H*$_2$), 4.89 (s, 2H, H$^{1'}$), 1.30 (s, 18H, -C(C*H*$_3$)$_3$). **^{13}C-NMR** (75.0 MHz, DMSO-*d*$_6$) *δ*(ppm) = 151.2, 146.8, 132.5, 121.9, 120.6, 77.4, 68.7, 53.8, 34.3, 30.8. **HRMS (ESI+):** Calculated for $C_{19}H_{27}IN_3O$: 440.1121 $[M+H]^+$. Found: 440.1197 $[M+H]^+$.

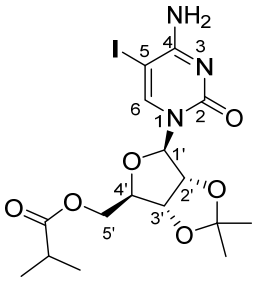


iC1. Following *Standard Procedure A*, over a solution of **iC2** (6.12 mmol, 2.69 g), $Pd(PPh_3)_2Cl_2$ (0.122 mmol, 85.9 mg) and CuI (0.061 mmol, 11.66 mg) in NEt_3/THF 4:1 (120 mL) were added. Then, TMSA (9.18 mmol, 0.902 g) was added. The crude was directly deprotected with TBAF $3H_2O$ (7.34 mmol, 2.31 g) using *Standard Procedure B*. The compound was purified by column chromatography in $CHCl_3$/MeOH (30:1). Recrystallization in MeCN finally yielded **iC1** (1.04 g, 68%) as a pale solid. **^{1}H-NMR** (300 MHz, $CDCl_3$) *δ*(ppm) = 7.43 (s, 1H, *H*$^{5'}$), 7.40 (s, 1H, *H*^{6}), 7.01 (s, 2H, *H*$^{3'}$), 6.39 (s(broad), 2H, N*H*$_2$), 4.89 (s, 2H, *H*$^{1'}$), 3.49 (s, 1H, *H*^{8}), 1.30 (s, 18H, -C(C*H*$_3$)$_3$). **^{13}C-NMR** (75 MHz, DMSO-*d*$_6$) δ(ppm) = 150.7, 147.3, 134.6, 121.4, 121.1, 82.6, 78.4, 53.1, 34.5, 31.1, 23.0, 19.2, 13.4. **HRMS (ESI+):** Calculated for $C_{21}H_{28}N_3O$: 338.2154 $[M+H]^+$. Found: 338.2235 $[M+H]^+$.

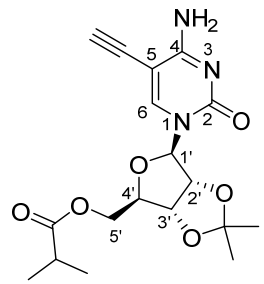
Cytidine



C3. The protected **C4**[3] (20.33 mmol, 5.76 g) and a catalytic amount of 4-dimethylaminopyridine (0.2 eq, 4.07 mmol, 497 mg) were dissolved in 106 mL of dry MeCN. Then NEt_3 (1.5 eq, 30.50 mmol, 4.24 mL) and isobutyric anhydride (1.1 eq, 22.37 mmol, 3.71 mL) were added. The mixture is stirred at room temperature overnight. The reaction is followed by TLC and, once finished, 2 mL MeOH were added and the mixture is further stirred for 30 min in order to react with the remaining anhydride. The solvent was removed and the solid was extracted with water (3 x 100 mL). The organic layer was dried over $MgSO_4$ and the solvent is evaporated. The product was then purified by chromatography on silica gel eluted with $CHCl_3$/MeOH (20:1), obtaining a yellow solid (5.91 g, 82%). **^{1}H-NMR** (300 MHz, DMSO-d_6): δ(ppm) = 11.81 (s (broad), 1H, CON*H*), 8.14 (s, 1H, H$^{1'}$); 5.78 (s, 1H, H$^{5'}$), 5.06 (dd, *J* = 6.4, *J'* = 1.8 Hz , 1H, *H*^{6}), 4.78 (d, *J* = 6.2 Hz, 1H, *H*^{5}), 4.35–4.10 (m, 3H, *H*$^{2'}$, *H*$^{3'}$, *H*$^{4'}$), 2.55–2.49 (m, 1H, -COC*H*), 1.48 (s, 3H, -OC-C*H*$_3$), 1.29 (s, 3H, -OC-C*H*$_3$), 1.11 (s, 3H, -COCH-C*H*$_3$), 1.09 (s, 3H, -COCH-C*H*$_3$).



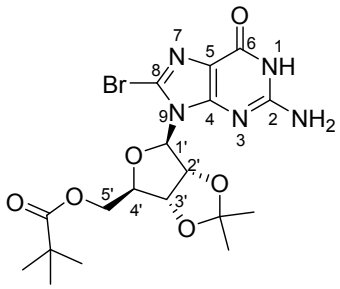
C2. A suspension of **C3** (16.72 mmol, 5.91 g), I_2 (15.0 mmol, 3.78 g) and HIO_3 (27.9 mmol, 4.92 g) in 148 mL acetic acid was stirred overnight at 40 ºC. Once the reaction was completed, the insoluble HIO_3 was filtered and discarded. A 1:1 AcOEt/Et_2O mixture (250 mL) was added to the reaction mixture and this was washed with 3 x 150 mL water, 3 x 150 mL $NaHCO_3$ (sat), 1 x 150 mL $Na_2S_2O_3$ (sat) and finally 1 x 150 mL water. The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The product was collected after recrystallization in a mixture Et_2O/*i*Pr_2O as a yellow solid (3.72 g, 46%). **^{1}H-NMR** (300 MHz, DMSO-d_6): δ(ppm) = 8.31 (s, 1H, N*H*), 8.06 (s, 1H, H$^{1'}$); 5.71 (s, 1H, H$^{5'}$), 5.00 (dd, *J* = 6.4, *J'* = 1.8 Hz , 1H, *H*^{6}), 4.28–4.16 (m, 3H, *H*$^{2'}$, *H*$^{3'}$, *H*$^{4'}$), 2.60–2.53 (m, 1H, -COC*H*), 1.47 (s, 3H, -OC-C*H*$_3$), 1.28 (s, 3H, -OC-C*H*$_3$), 1.10 (s, 3H, -COCH-C*H*$_3$), 1.07 (s, 3H, -COCH-C*H*$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ(ppm) = 176.6, 164.3, 154.6, 148.3, 114.2, 95.8, 85.9, 85.6, 81.2, 64.3, 56.9, 34.0, 27.2, 25.4, 19.2, 19.1., **HRMS (ESI+):** Calculated for $C_{16}H_{22}IN_3O_6$: 480.0553 $[M+H]^+$. Found: 480.0625 $[M+H]^+$.



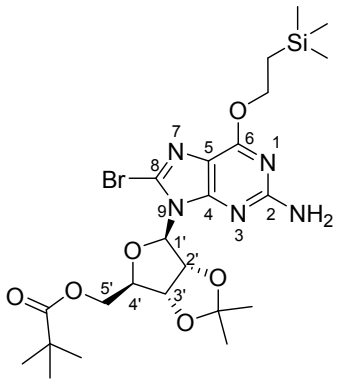
C1. **C1** was prepared following the *Standard Procedure A* for a Sonogashira coupling. **C2** (2.08 mmol, 1.00 g), $Pd(PPh_3)_2Cl_2$ (0.042 mmol, 29.0 mg) and CuI (0.03 mmol, 4.0 mg) were dissolved in the THF/NEt_3 mixture (20 mL). Then TMSA (6 mmol, 0.79 g) was added and the mixture was stirred at 40 ºC during 24 h. The product was used in the next reaction without purification. Following *Standard Procedure B*, TBAF·$3H_2O$ (3.2 mmol, 1.0 g) was added over a THF (20 mL) solution of the previous crude product. **C1** was purified by chromatography on silica gel eluted by $CHCl_3$/MeOH; (20:1). A final recrystallization using CH_2Cl_2/hexane yielded **C1** as a brown solid

(0.61 g, 80%). **1H-NMR** (300 MHz, DMSO-d^6) δ(ppm) = 8.04 (s, 1H, $H^{1'}$); 7.86 (s (broad), 1H, N*H*); 6.96 (s (broad), 1H, N*H*) 5.76 (s, 1H, $H^{5'}$), 4.99 (dd, *J* = 6.4, *J'* = 1.8 Hz , 1H, H^6), 4.80 (dd, *J* = 6.4, *J'* = 3.1 Hz, 1H, $H^{4'}$), 4.36 (s, 1H, -CC*H*), 1.47 (s, 3H, -OC-CH_3), 1.28 (s, 3H, -OC-CH_3), 1.07 (d, *J* = 7.0 Hz, 6H, -COCH-(CH_3)$_2$). **^{13}C-NMR** (75 MHz, DMSO-d_6) δ(ppm) = 175.8, 164.5, 153.1, 147.6, 112.9, 93.8, 89.3, 86.1, 84.8, 84.3, 80.9, 75.2, 63.9, 33.1, 26.9, 25.1, 18.7, 18.7, 13.4. **HRMS (ESI+):** Calculated for $C_{18}H_{24}N_3O_6$: 378.1587 $[M+H]^+$. Found: 378.1654 $[M+H]^+$.

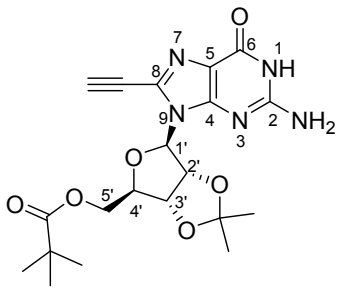
Guanosine



G3. In a 500-mL round-bottomed flask, equipped with a magnetic stirrer, **G4**[5] (12.0 mmol, 4.83 g) and DMAP (2.4 mmol, 290 mg) were placed. Dry DMF (400 mL) was added and the mixture was stirred at room temperature under argon until the solid was dissolved. Then, NEt_3 (18 mmol, 2.5 mL) and trimethylacetic anhydride (36.0 mmol, 7.30 mL) were added. The resulting mixture was stirred at 130 ºC until **G5** was consumed. Afterwards, MeOH (7 mL) was added and the mixture was stirred during 15 minutes. The solvent was then eliminated under reduced pressure and the solid was directly purified by chromatography on silica gel eluted with $CHCl_3$/MeOH (30:1) and then by recrystallization (CH_2Cl_2/hexane). We obtained a white solid (4.32 g, 63%). **^{1}H-NMR** (300 MHz, DMSO-*d*$_6$): *δ*(ppm) = 10.89 (s, 1H, N*H*), 6.68 (s (broad), 2H, N*H*$_2$), 5.91 (d, *J* = 1.2 Hz, 1H, *H*$^{1'}$), 5.45 (d, *J* = 6.0 Hz, 1H, *H*$^{2'}$), 5.28 (dd, *J* = 3.6, *J'* = 6.0 Hz, 1H, *H*$^{3'}$), 4.22 (m, 2H, *H*$^{5'}$, *H*$^{5''}$), 4.11 (m, 1H, *H*$^{4'}$), 1.51 (s, 3H, C*H*$_3$), 1.32 (s, 3H, C*H*$_3$), 1.09 (s, 9H, -COC-C*H*$_3$)$_3$). **^{13}C-NMR**, (75 MHz, DMSO-*d*$_6$) *δ*(ppm) = 177.1, 155.6, 153.8, 151.4, 120.2, 117.0, 113.2, 89.8, 85.6, 83.2, 81.4, 64.0, 38.2, 26.9, 26.8, 25.3. **HRMS (ESI+):** Calculated for $C_{18}H_{25}BrN_5O_6$: 486.0910 $[M+H]^+$. Found: 486.0979 $[M+H]^+$.



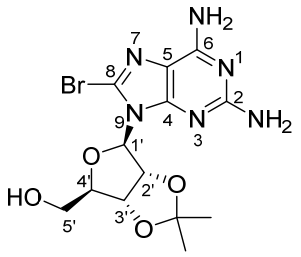
G2. In a 50-mL round-bottomed flask, equipped with a magnetic stirrer, **G3** (1.70 mmol, 1.17 g), PPh_3 (2.55 mmol, 668.8 mg) and DIAD (2.38 mmol, 0.47 mL) were placed. Dry dioxane (15 mL) was added and the mixture was stirred at room temperature under argon atmosphere until the solid was dissolved. Then 2-trimethylsilylethanol was added dropwise (2.72 mmol, 0.39 mL) and the mixture was stirred at room temperature during 12 h. Finally, the solvent was eliminated under reduced pressure and the oil obtained was purified by chromatography on silica gel eluted with Hexane/AcOEt (6:1) to yield a brown solid (1.50 g, 99%). **^{1}H-NMR** (300 MHz, DMSO-d_6): *δ*(ppm) = 10.92 (s, 1H, N*H*), 6.70 (s (broad), 2H, N*H*$_2$), 5.91 (d, *J* = 1.2 Hz, 1H, *H*$^{1'}$), 5.45 (d, *J* = 6.0 Hz, 1H, *H*$^{2'}$), 5.27 (dd, *J* = 3.6, *J'* = 6.0 Hz, 1H, *H*$^{3'}$), 4.50 (t, *J* = 8.2 Hz, 2H, CO-C*H*$_2$-), 4.22 (m, 2H, *H*$^{5'}$, *H*$^{5''}$), 4.11 (m, 1H, *H*$^{4'}$), 1.51 (s, 3H, C*H*$_3$), 1.32 (s, 3H, C*H*$_3$), 1.09 (s, 9H, -COC-(C*H*$_3$)$_3$), 0.06 (s, 9H, Si(C*H*$_3$)$_3$.



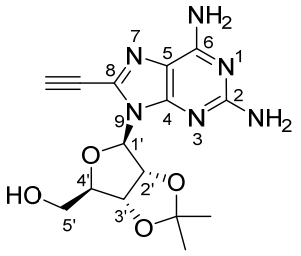
G1 was directly from **G2** via Sonogashira reaction and fluoride-mediated deprotection. The first step was carried out following *Standard Procedure A*. **G2** (1.65 mmol, 0.97 g), $Pd(PPh_3)_2Cl_2$ (0.03 mmol, 23.0 mg), CuI (0.01 mmol, 4.0 mg), TMSA (5 mmol, 0.62 g) and THF/ NEt_3 (20 mL) were mixed. The mixture was then stirred at 40 ºC during 24 h. After removal of the solvent under

vacuum, the resulting crude oil was reacted in the presence of TBAF $3H_2O$ (1 mmol, 0.31 g) in THF (5 mL) following *Standard Procedure B*. After solvent evaporation the brown oil was purified by chromatography on silica gel eluted with $CHCl_3$/MeOH (20:1). **G1** was obtained as a pale solid (0.563 g 44%). **^{1}H-NMR** (300 MHz, DMSO-d_6): δ(ppm) = 6.77 (s (broad), 2H, NH_2), 6.02 (d, J = 1.3 Hz, 1H, $H^{1'}$), 5.37 (d, J = 6.4 Hz, 1H, $H^{2'}$), 5.26 (m, 1H, $H^{3'}$), 4.84 (s, 1H, CC-H); 4.29 (t, J = 8.2 Hz, 2H, -CO_2CH_2-), 4.24-4.09(m, 3H, CH $H^{1'}$, $H^{4'}$), 1.51 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.09 (s, 9H, -COC-(CH_3)$_3$). **^{13}C-NMR**, (75 MHz, DMSO-d_6) δ(ppm) = 177.2, 156.2, 154.3, 150.1, 128.4, 116.7, 113.3, 88.6, 86.0, 85.4, 83.4, 81.4, 72.9, 64.2, 38.2, 27.0, 26.8, 25.3. **HRMS (ESI+):** Calculated for $C_{20}H_{26}N_5O_6$: 432,1805 $[M+H]^+$. Found: 432.1889 $[M+H]^+$.

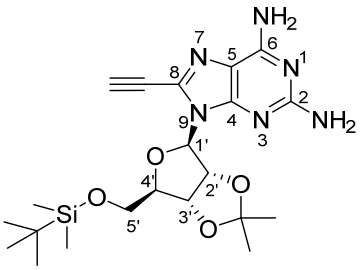
2-AminoAdenosine



DAP3. DAP4[3] (62.1 mmol, 20.0 g) was dissolved in a MeCN/H_2O (4:1) (500 mL) solvent mixture and N-bromosuccinimide (NBS; 84.3 mmol, 15.0 g) was added in three portions, the mixture was stirred for 2 h at room temperature. Once the reaction was completed, MeCN was removed under vacuum pressure, and $NaHCO_3$ (sat) was added until a yellow precipitate appeared. This solid was then filtered, washed with cold MeCN and purified by chromatography on silica gel eluted with $CHCl_3$/MeOH (20:1). Product **A3** was obtained as a white solid (12.4 g, 50%). **^{1}H-NMR** (300 MHz, DMSO-*d*^{6}) *δ*(ppm) = 11.05 (s, 2H, N*H*$_2$), 6.96 (s, 2H, N*H*$_2$), 5.89 (d, *J* = 2.1 Hz, 1H, *H*$^{1'}$), 5.51 (dd, *J* = 6.2, *J'* = 2.1 Hz, 1H, *H*$^{2'}$), 5.13 (dd, *J* = 6.3, *J'* = 3.3 Hz, 1H, *H*$^{3'}$), 5.10 (t, *J* = 5.8 Hz, 1H, OH), 4.11 - 4.09 (m, *J* = 6.1, 1H, H$^{4'}$), 3.47 – 3.32 (m, 2H, -C*H*$_2$-OH), 1.53 (s, 3H, -OC-C*H*$_3$), 1.33 (s, 3H, -OC-C*H*$_3$). **^{13}C-NMR** (75 MHz, $CDCl_3$) *δ*(ppm) = 159.2, 155.4, 151.3, 122.6, 115.1, 114.0, 93.4, 85.6, 82.2, 81.7, 63.4, 27.8, 25.6. **HRMS (ESI+):** Calculated for $C_{13}H_{18}BrN_6O_4$: 401.0495 $[M+H]^+$. Found: 401.0582 $[M+H]^+$.



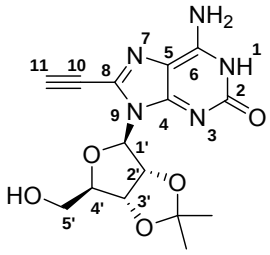
DAP2. DAP2 was prepared following *Standard Procedure A*. **DAP3** (21.0 mmol, 8.42 g), $Pd(PPh_3)_2Cl_2$ (0.4 mmol, 281 mg), CuI (0.2 mmol, 38.0 mg), TMSA (63.0 mmol, 8.1 g) were mixed in the THF/NEt_3 solvent (20 mL). The mixture was then stirred at 40 ºC during 24 h. After removal of the solvent, a brown oil was obtained that was used in the following reaction step without previous purification. Then, following *Standard Procedure B*, the brown oil was dissolved in THF (15 mL) and TBAF·3H_2O (0.021 mol, 6.7 mg) was added. After reaction and solvent removal, the brown solid obtained was purified by chromatography on silica gel using $CHCl_3$/MeOH (20:1) as eluent. **A2** was obtained as a white solid (7.95 g, 98%). **1H-NMR** (300 MHz, DMSO-d_6) δ(ppm): 7.04 (s (broad), 2H, N*H*$_2$), 6.06 (s (broad), 2H, N*H*$_2$), 6.00 (d, *J* = 2.4 Hz, 1H, *H*$^{1'}$), 5.42 (dd, *J* = 6.2, *J'* = 2.4 Hz, 1H, *H*$^{2'}$), 5.09 (dd, *J* = 6.2, *J'* = 3.4 Hz, 2H, *H*$^{3'}$), 4.83 (s, 1H, -CC*H*), 4.11 (dt, *J* = 5.8, *J'* = 3.3 Hz, 1H, *H*$^{4'}$), 3.64 – 3.45 (m, 2H, C*H*$_2$-OH), 1.53 (s, 3H, -OC-C*H*$_3$), 1.32 (s, 3H, -OC-C*H*$_3$).



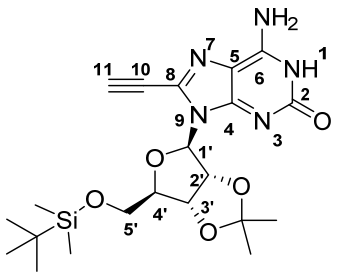
DAP1. DAP2 (0.86 mmol, 300 mg) and imidazole (1.72 mmol, 117 mg) were placed into a dried bottomed flask. Then DMF (11 mL) and TMSA (1.72 mmol, 258 mg) were added. The mixture was stirred for 12 hours at room temperature. The solvent was evaporated under reduced pressure, leaving a brown oil that was purified by chromatography on silica gel eluted with $CHCl_3$/MeOH (20:1). **DAP1** was obtained as a white solid (5.31 g, 43%). **^{1}H-NMR** (300 MHz, DMSO-*d*^{6}) *δ* (ppm) = 6.98 (s (broad), 2H, N*H*$_2$), 6.10 (s (broad), 2H, N*H*$_2$), 6.02 (s, 1H, *H*$^{1'}$), 5.50 (dd, *J* = 6.2, *J'* = 1.5 Hz, 1H, *H*$^{2'}$), 5.12 (dd, *J* = 6.3, *J'* = 3.5 Hz, 1H, *H*$^{3'}$), 4.80 (s, 1H, -CC*H*), 4.08

(ddd, J = 7.3, J' = 5.7, J'' = 3.4 Hz, 1H, $H^{4'}$), 3.72 – 3.69 (m, 2H, $H^{5'}$), 1.51 (s, 3H, OC-CH_3), 1.33 (s, 3H, -OC-CH_3), 0.77 (s, 9H, SiC(CH_3)$_3$), 0.16 (d, J = 4.8 Hz, 6H, Si(CH_3)$_2$). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ(ppm) = 160.5, 156.2, 150.9, 130.9, 114.4, 114.0, 90.1, 87.8, 83.4, 83.1, 82.5, 73.1, 63.5, 27.4, 26.0, 25.7, 18.5, -5.2, -5.3. **HRMS (ESI+):** Calculated for $C_{21}H_{33}N_6O_4Si$: 461.2254 $[M+H]^+$. Found: 461.2333 $[M+H]^+$.

Isoguanosine

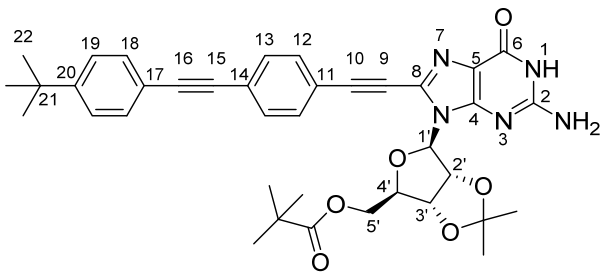


iG2. iG2 was synthesized according to a literature procedure[9] that was adapted to our compound. **A2** (6.73 mmol, 2.82 g), $NaNO_2$ (20.9 mmol, 1.85 g) and AcOH (46.1 mmol, 2.83 g) were dissolved in a H_2O/THF (1:1) mixture (30 mL). After stirring at 50ºC for 2 hours, the reaction was cooled down to room temperature and the solvent was evaporated. The crude product was purified by column chromatography using $CHCl_3$/MeOH (20:1) as the eluent. **iG2** was obtained as a light orange solid (1.64 g, 70%). **^{1}H-NMR** (300 MHz, DMSO-d^6) δ(ppm) = 10.57 (s(broad), 1H, CON*H*), 6.21 (s(broad), 1H, NH_2), 5.95 (d, 1H, *J* = 4.5 Hz, $H^{1'}$), 5.24 (s(broad), 1H, NH_2), 4.94 (dd, 1H, *J* = 5.8, *J'* = 1.8 Hz, $H^{2'}$), 4.28 (s, 1H, $H^{3'}$), 4.00 (s, 1H, H^{11}), 3.75 (d, 1H, *J* = 12.5 Hz, $H^{4'}$), 3.60 (d, 1H, *J* = 10.5 Hz, $H^{5'}$), 1.52 (s, 3H, CH_3), 1.28 (s, 3H, CH_3). **MS (FAB+):** 348.1 $[M+H]^+$.

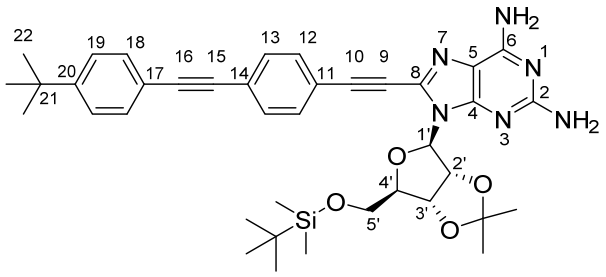


iG1. Into a 100 mL bottomed flask **iG2** (5.15 mmol, 2.16 g), imidazole (10.3 mmol, 71 mg) and *tert*-butyldimethylchlorosilane (10.3 mmol, 1.55 g) were dissolved in dry DMF (30 mL). The reaction was stirred for 2 hours at room temperature and then concentrated under vacuum. The residue was dissolved in $CHCl_3$ and washed with water (2 x 50 mL). The product was purified by column chromatography eluted with $CHCl_3$/ MeOH (30:1). An orange solid was obtained (2.02 g, 85%). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ(ppm) = 10.50 (s(broad), 1H, CON*H*), 7.43 (s(broad), 2H, NH_2), 6.02 (d, 1H, *J* = 2.1 Hz, $H^{1'}$), 5.54 d (, 1H, *J* = 6.6 Hz, $H^{2'}$), 4.94 (dd, 1H, *J* = 6.4, *J'* = 3.5 Hz, $H^{3'}$), 4.11 – 4.05 (m, 1H, $H^{4'}$), 3.80 – 3.66- (m, 3H, $H^{5'}$, H^{11}), 1.48 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 0.76 (s, 9H, -C(CH_3)$_3$), -0.11 (s, 6H, Si(CH_3)$_2$). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ(ppm) = 155.5, 113.1, 108.7, 88.9, 87.3, 84.4, 82.2, 81.6, 72.4, 63.2, 26.8, 25.4, 25.0, 17.7, -5.8. **HRMS (ESI+):** Calculated for $C_{21}H_{32}N_5O_5Si$: 462.2094 $[M+H]^+$. Found: 462.2168 $[M+H]^+$.

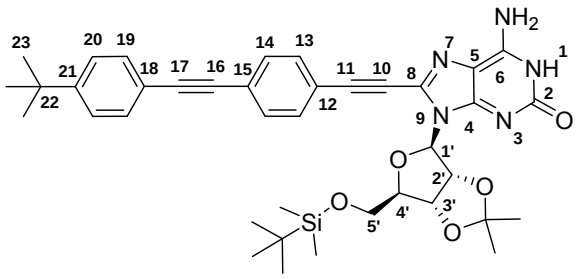
Lipophilic Nucleoside



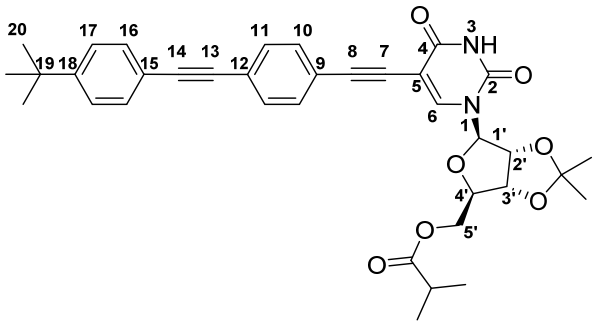
G. Lipophilic nucleoside **G** was prepared according to *Standard Procedure C*. **G1** (200 mg, 0.46 mmol), iodoarene **1**[6] (200 mg 0.56 mmol), $Pd(PPh_3)_4$ (6 mg), CuI (1 mg) and THF/NEt_3 (5 mL), the reaction was stirred during 12 h at 40 ºC. **G** was purified by chromatography on silica gel eluted with $CHCl_3$/MeOH (20:1), obtaining a yellow solid (232 mg, 76%). **^{1}H-NMR** (300 MHz, $CDCl_3$) *δ*(ppm) = 11.76 (s, 1H, N*H*), 7.59 – 7.37 (m, 8H, $H^{19,18,13,12}$), 6.75 (s, 2H, NH_2), 6.30 (d, *J* = 1.3 Hz, 1H, $H^{1'}$), 5.49 (d, *J* = 6.3 Hz, 1H, $H^{3'}$), 5.10 (dd, *J* = 11.1, *J'* = 7.2 Hz, 1H, $H^{2'}$), 4.80 (dd, *J* = 6.7, *J'* = 3.5 Hz, 1H, $H^{4'}$), 4.43 – 4.37 (m, 1H, $H^{5'}$), 4.09 (dd, *J* = 11.4, *J'* = 4.9 Hz, 1H, $H^{5'}$), 1.62 (s, 3H, -OC-(CH_3)), 1.40 (s, 3H, -OC-(CH_3)), 1.34 (s, 9H, -C-(CH_3)$_3$), 1.19 (s, 9H, -OCOC-(CH_3)$_3$). **^{13}C-NMR** (75 MHz, $CDCl_3$) *δ* = 177.4, 156.3, 153.7, 151.5, 131.2, 131.1, 130.8, 124.9, 124.0, 120.0, 119.0, 117.7, 113.3, 92.9, 91.9, 89.1, 87.7, 85.4, 83.7, 81.7, 79.7, 63.7, 38.1, 34.3, 30.6, 26.7, 26.6, 25.0.**HRMS (FAB+):** Calculated for $C_{38}H_{42}N_5O_6$: 664.3057 $[M+H]^+$. Found: 664.2686 $[M+H]^+$. **UV-Vis** ($CHCl_3$) = λ_{max} = 351 nm, 374 (sh) nm.



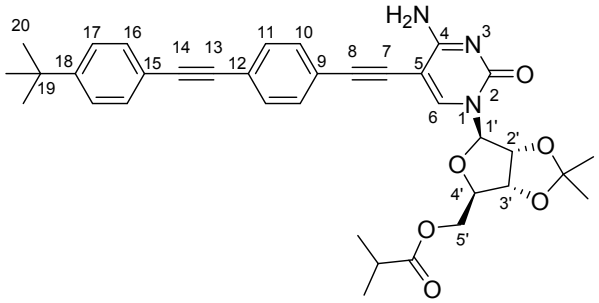
A. Lipophilic nucleoside **A** was prepared according to *Standard Procedure C*. **DAP1** (0.23 mmol, 159 mg), iodoarene **1**[6] (104 mg 0.3 mmol), $Pd(PPh_3)_4$ (6.7 mg, 0.006 mmol), CuI (0.003 mg) and THF/NEt_3 (2 mL) were mixed. The reaction was stirred during 12 h at 40 ºC. Compound **A** was purified by chromatography on silica gel using $CHCl_3$/MeOH (20:1) as eluent, obtaining a yellow solid (174 mg, 87%). **^{1}H-NMR** (300 MHz, $CDCl_3$) *δ* (ppm) = 7.63 – 7.29 (m, 8H, $H^{19,18,13,12}$), 6.27 (d, *J* = 2.0 Hz, 1H, $H^{4'}$), 5.80 (s, 2H, NH_2), 5.67 (dd, *J* = 6.3, *J'* = 2.0 Hz, 1H, $H^{1'}$), 5.09 (dd, *J* = 6.3, *J'* = 3.3 Hz, 1H, $H^{3'}$), 4.81 (s (broad), 2H, NH_2), 4.27 (dd, *J* = 6.7, *J'* = 3.3 Hz, 1H, $H^{2'}$), 3.77 (m, 2H, $H^{5'}$), 1.63 (s, 3H, , -OC-CH_3), 1.42 (s, 3H, -OC-CH_3), 1.33 (s, 9H, H^{20}), 0.85 (s, 9H, -SiC-(CH_3)$_3$), 0.00 (d, *J* = 5.3 Hz, 6H, -Si-(CH_3)$_2$). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ(ppm) = 160.2, 155.9, 152.2, 151.2, 132.2, 132.0, 131.7, 131.6, 125.6, 125.1, 120.5, 119.9, 115.1, 114.0, 94.7, 92.6, 90.2, 88.4, 87.9, 83.2, 82.6, 80.0, 77.6, 77.2, 76.7, 63.6, 35.0, 31.3, 27.5, 26.0, 25.8, 18.5, -5.2, -5.3. **HRMS (FAB+):** Calculated for $C_{39}H_{49}N_6O_4Si$: 693.3552 $[M+H]^+$. Found: 693.3596, $[M+H]^+$. **UV-Vis** ($CHCl_3$) = λ_{max} = 357 nm, 384 (sh) nm.



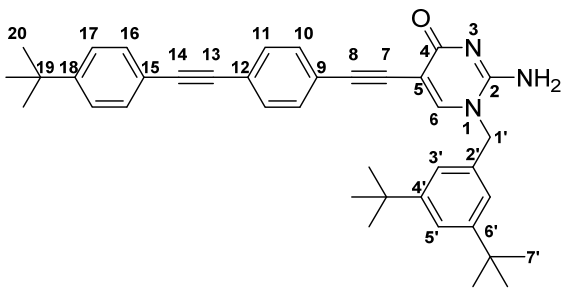
iG. Product **iG** was prepared according to *Standard Procedure C*. Compound **iG1** (0.43 mmol, 200 mg), iodoarene **1**[6] (0.52 mmol, 0.187 g), $Pd(PPh_3)_2Cl_2$ (0.02 eq, 8.66 µmol, 6.07 mg) and CuI (0.01 eq, 4.33 µmol, 0.83 mg) were dissolved in THF/NEt_3 4:1 (3 mL). The reaction was stirred during 12h at 40º C. The crude material was purified by column chromatography using $CHCl_3$/MeOH (30:1) as eluent. Recrystallization in MeCN yielded iG as a yellow solid (255 mg, 85%). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ(ppm) = 7.68 – 7.34 (m, 8H, H_{ar}), 6.17 (s, 1H, $H^{1'}$), 5.48 (s(broad), 1H, NH_2), 4.99 (s, 1H, $H^{2'}$), 4.37 (s, 1H, $H^{3'}$), 4.00 – 3.85 (m, 2H, $H^{5'}$), 3.12 (d, 1H, J = 7.3 Hz, $H^{4'}$), 1.62 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.31 (s, 9H, C(CH_3)$_3$), 0.86 (s, 9H, -C(CH_3)$_3$), 0.03 (s, 6H, Si(CH_3)$_2$). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ(ppm) = 151.9, 150.9, 149.5, 137.3, 132.9, 131.6, 131.5, 131.2, 131.1, 125.3, 124.8, 120.1, 119.4, 113.7, 92.4, 90.1, 88.0, 87.7, 82.0, 77.7, 63.7, 46.3, 34.6, 31.0, 27.1, 25.8, 25.4, 18.2, 8.7, -5.5. **HRMS (FAB+):** Calculated for $C_{39}H_{48}N_5O_5Si$: 694.3346 $[M+H]^+$. Found: 694.3435 $[M+H]^+$. **UV-Vis** ($CHCl_3$) = λ_{max} = 361 nm.



U. Lipophilic nucleoside **U** was prepared according to *Standard Procedure C*. Compound **U1** (0.41 mmol, 149 mg), iodoarene **1**[6] (0.33 mmol, 119 mg), $Pd(PPh_3)_4$ (8 mg) and CuI (0.01 eq, 3.3 µmol, 1 mg) were dissolved in THF/NEt_3 4:1 (3 mL). The reaction was stirred during 12h at 40º C. The crude material was purified by column chromatography using $CHCl_3$/ MeOH (30:1) as eluent. Recrystallization in MeOH yielded **U** as a yellow solid (168 mg, 84%). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ(ppm) = 9.25 (s (broad), 1H, CONH), 7.68 (s, 1H: H^6), 7.47 – 7.44 (m, 5H, H_{ar}), 7.38 (d, 2H, J = 8.5 Hz: H^{11}, H^{12}), 5.82 (d, 1H, J = 2.2 Hz, $H^{1'}$), 4.92 (dd, 1H, J = 6.4, J' = 2.3 Hz, $H^{2'}$), 4.80 (dd, 1H, J = 6.4, J' = 3.8 Hz, $H^{3'}$), 4.42 – 4.36 (m, 1H, $H^{4'}$), 4.34 (d, 2H, J = 4.3 Hz, $H^{5'}$),2.69 - 2.55 (m, 1H, J = 7.0 Hz, $H^{7'}$), 1.59 (s, 3H, -CH_3), 1.32 (s, 3H, -CH_3), 1.24 (s, 9H, -C(CH_3)$_3$), 1.17 (d, 3H, J = 5.2 Hz, ,-OCOCH-(CH_3)), 1.15 (d, 3H, J = 5.1 Hz,-OCOCH-(CH_3)). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ(ppm) = 176.5, 161.1, 152.0, 14.0, 143.6, 131.7, 131.6, 131.5, 125.5, 124.1, 122.0, 120.0, 115.0, 100.8, 94.0, 93.9, 91.9, 88.5, 85.1, 85.0, 81.4, 80.8, 63.8, 35.0, 34.0, 31.3, 27.3, 25.4, 19.2, 19.0. **HRMS (FAB+):** Calculated for $C_{36}H_{38}N_2O_7$: 610.2679 $[M+H]^+$. Found: 610.2689 $[M+H]^+$. **UV-Vis** ($CHCl_3$) = λ_{max} = 330 nm.



C: Lipophilic nucleoside **C** was prepared according to *Standard Procedure C*. **C1** (148.7 mg, 0.24 mmol), iodoarene **1**[6] (118 mg 0.3 mmol), $Pd(PPh_3)_4$ (7.6 mg), CuI (0.6 mg) and THF/NEt_3 (2 mL) were mixed. The reaction was stirred during 12 h at 40 ºC. The product was purified by chromatography on silica gel eluted with $CHCl_3$/MeOH (20:1), yielding **C** as a yellow solid (88 mg, 44%). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ(ppm) = 9.13 (s, 1H, N*H*), 7.74 (s, 1H, H^2), 7.52 – 7.36 (m, 8H, $H^{17,16,11,10}$), 6.00 (s, 1H, N*H*), 5.73 (d, J = 1.7 Hz, 1H, $H^{1'}$), 4.97 (d, J = 6.4, 1H, $H^{2'}$), 4.80 (dd, J = 6.3, J' = 3.6 Hz, 1H,$H^{3'}$), 4.45 – 4.31 (m, 3H, $H^{5'}$), 2.65 - 2.51 (m, 1H, -CO-C*H*-), 1.57 (s, 3H, -COCH-CH_3), 1.35 (s, 3H, -COCH-CH_3), 1.33 (s, 9H, H^{20}), 1.15 (dd, J = 7.0, J' = 2.2, 6H, -COCH-(CH_3)$_2$). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ(ppm) = 176.5, 164.7, 154.0, 151.9, 145.2, 131.6, 131.4, 131.3, 125.4, 124.3, 121.3, 119.8, 114.2, 95.7, 95.4, 92.1, 91.6, 88.4, 85.7, 85.6, 81.0, 81.1, 64.1, 34.8, 33.8, 31.1, 27.1, 25.3, 19.0, 18.9. **HRMS (FAB+):** Calculated for $C_{36}H_{40}N_3O_6$: 610.2811 $[M+H]^+$. Found: 610.2902, $[M+H]^+$. **UV-Vis** ($CHCl_3$) = λ_{max} = 331 nm, 335 (sh) nm.



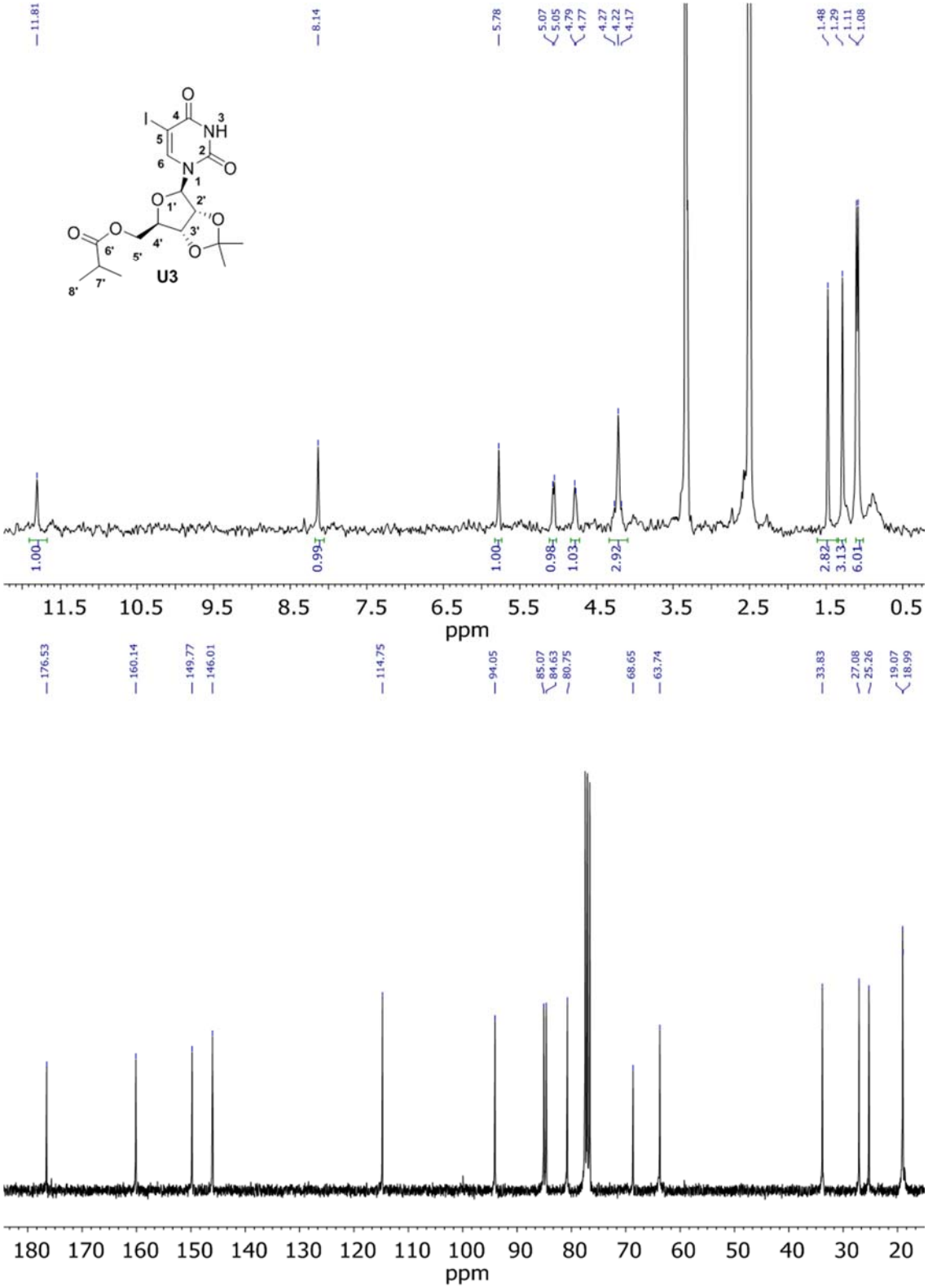
iC. Product **iC** was prepared according to *Standard Procedure C*. iodoarene **1**[6] (0.33 mmol, 0.120 g), **iC1** (0.40 mmol, 0.143 g), $Pd(PPh_3)_2Cl_2$ (0.02 eq, 6.6 µmol, 4 mg) and CuI (0.01 eq, 3.32 µmol, 1 mg) were dissolved in NEt_3/THF (4:1) (5 mL). The reaction was stirred during 12h at 40º C The crude material was purified by chromatography column using $CHCl_3$/MeOH (30:1) as eluent. Recrystallization in MeCN yielded **iC** as a yellow solid (76 mg, 40%). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ(ppm) = 7.46 – 7.43 (m, 8H, $H^{17,16,11,10}$), 7.37 (s, 1H, H^6), 7.35 (s, 1H, $H^{5'}$), 7.03 (s, 2H, $H^{3'}$), 6.42 (s (broad), 1H, NH_2), 4.93 (s, 2H, $H^{1'}$), 1.32 (s, 9H, H^{20}), 1.31 (s, 18H, $H^{7'}$). **^{13}C-NMR** (75 MHz, DMSO-d_6) δ(ppm) = 167.2, 154.4, 151.8, 150.7, 146.9, 134.7, 131.6, 131.2, 131.2, 125.6, 122.9, 122.1, 121.4, 121.0, 119.1, 102.4, 91.4, 90.8, 88.4, 87.1, 53.3, 34.6, 34.5, 31.2, 30.9. **HRMS (FAB+):** Calculated for $C_{39}H_{44}N_3O$: 569.3406 $[M+H]^+$. Found: 570.3499, $[M+H]^+$. **UV-Vis** ($CHCl_3$) = λ_{max} = 382 nm, 408(sh) nm.

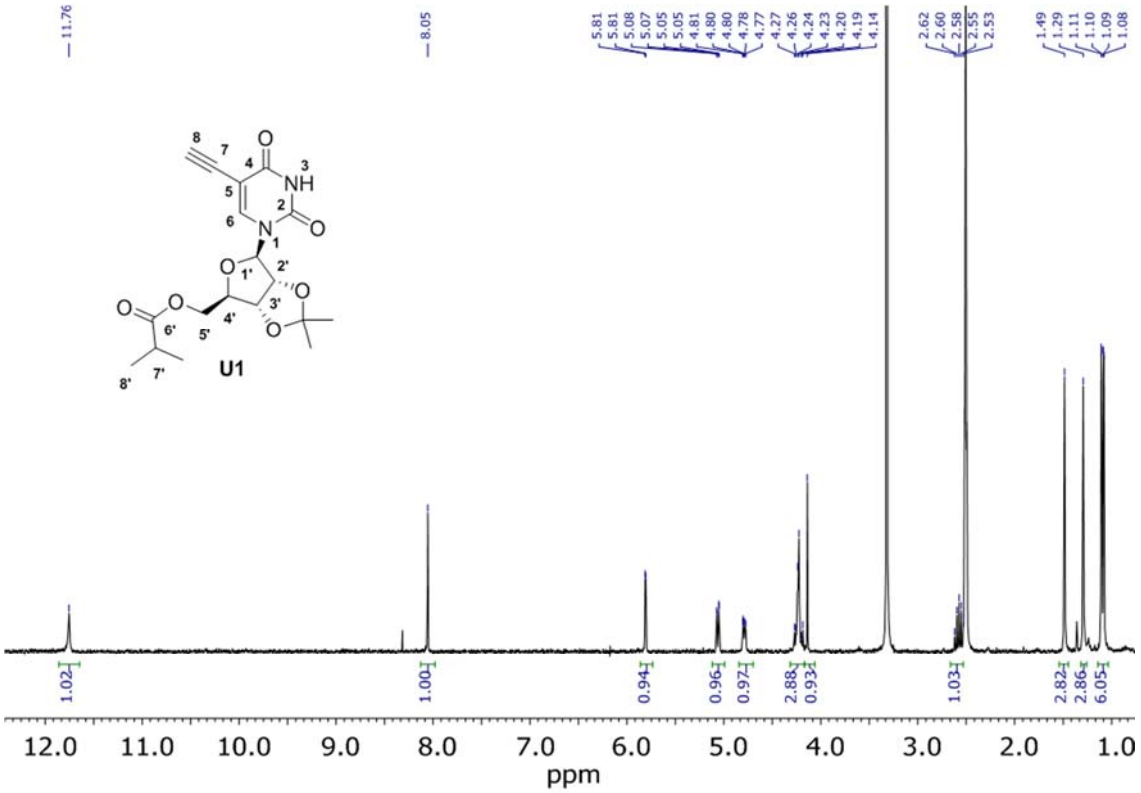
***Standard Procedure A*. Sonogashira coupling with TMSA.** A dry THF/NEt_3 (4:1) solvent mixture was subjected to deoxygenation by three freeze-pump-thaw cycles with argon. Then, this solvent was added over the system containing the corresponding halogenated base (1 eq.), CuI (0.01 eq.) and $Pd(PPh_3)_2Cl_2$ (0.02 eq.). The mixture was stirred at room temperature during a few minutes. Then, trimethylsilylacetylene (TMSA; 2 eq.) was added dropwise. The reaction is stirred under argon at a given temperature and for a period of time (indicated in each case) until completion, which was monitored by TLC. Then, the mixture was filtrated over celite and the solvent evaporated under vacuum. The resulting crude product was purified by column chromatography (eluent indicated in each case) or directly subjected to TMS deprotection without further purification.

***Standard procedure B*. Alkyne-TMS group deprotection.** In a round-bottomed flask equipped with a magnetic stirrer, the corresponding TMS-ethynyl-nucleobase was placed. THF was added and the mixture was stirred at room temperature until the solid was dissolved. Then hydrated tetrabutylammonium fluoride ($TBAF{\cdot}3H_2O$; 1 eq.) was slowly added at 0ºC, and the mixture was stirred at room temperature until reaction completion, which was monitored by TLC (approximately 1 h in all cases). The solvent was evaporated at reduced pressure and the product was purified by column chromatography (eluent indicated in each case).

***Standard Procedure C*. Sonogashira coupling between the ethynyl-nucleobase and iodoarene 1.** A dry THF/ NEt_3 (4:1) solvent mixture was subjected to deoxygenation by three freeze-pump-thaw cycles with argon. Then, this solvent was added over the system containing the corresponding ethynyl-substituted base (1.1 eq.), iodoarene **1**[6] (1 eq.), CuI (0.01 eq.) and $Pd(PPh_3)_2Cl_2$ (0.02 eq.). The reaction is stirred under argon at a given temperature and for a period of time (indicated in each case) until completion, which was monitored by TLC. Then, the mixture was filtrated over celite and the solvent evaporated under vacuum. The resulting crude product was purified by column chromatography (eluent indicated in each case).

^{1}H and ^{13}C NMR spectra for all new compounds

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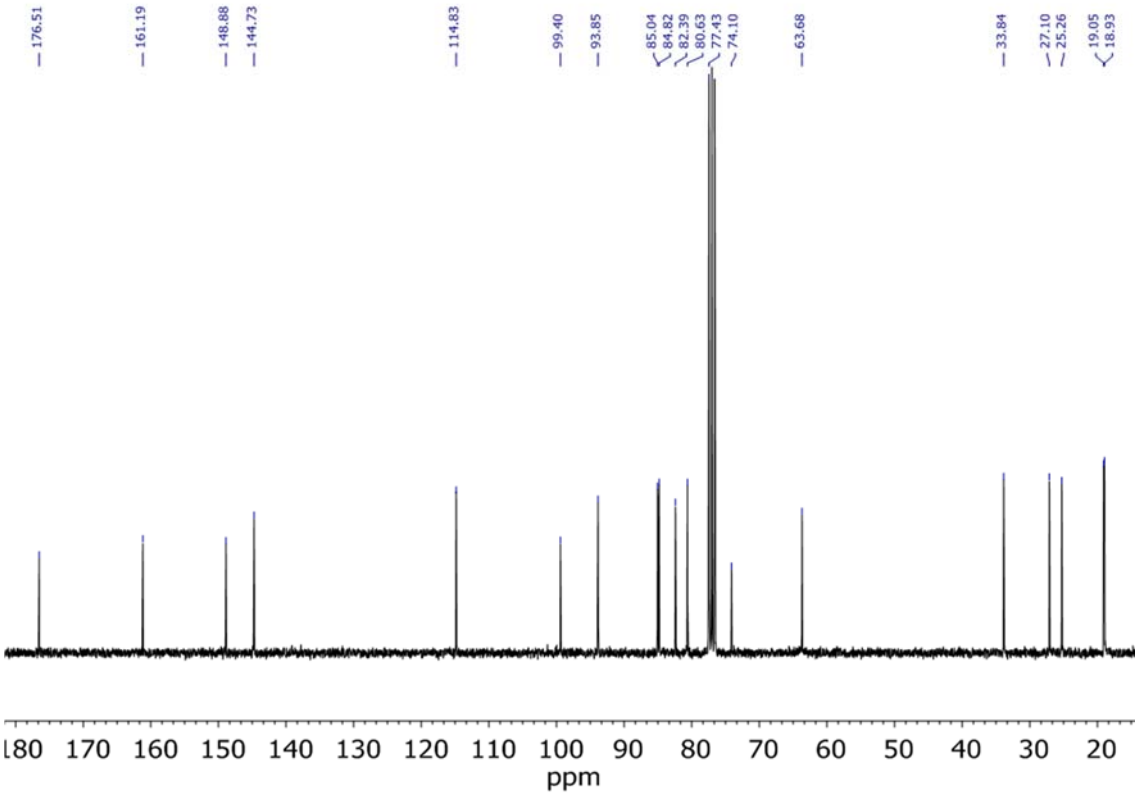
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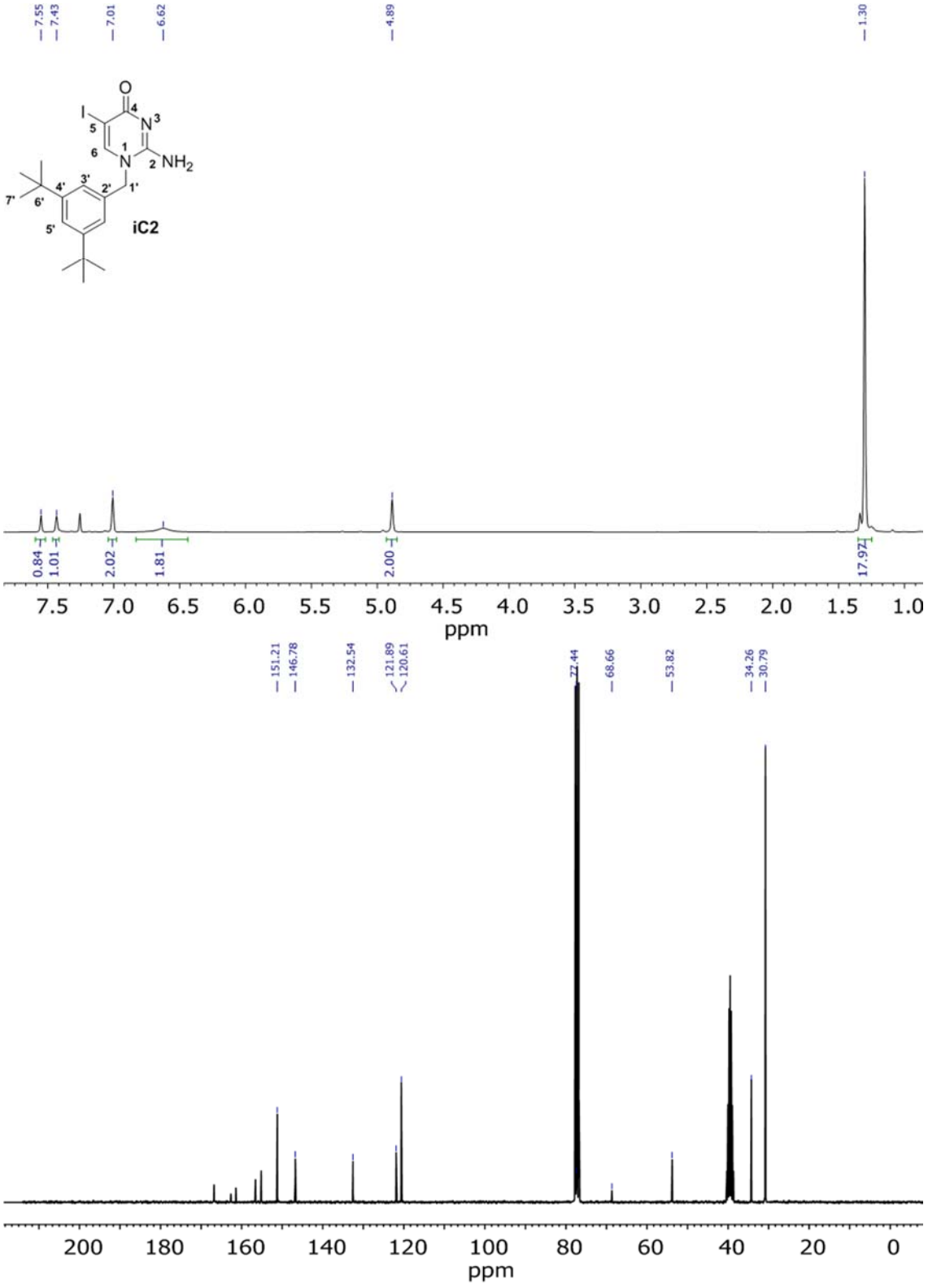
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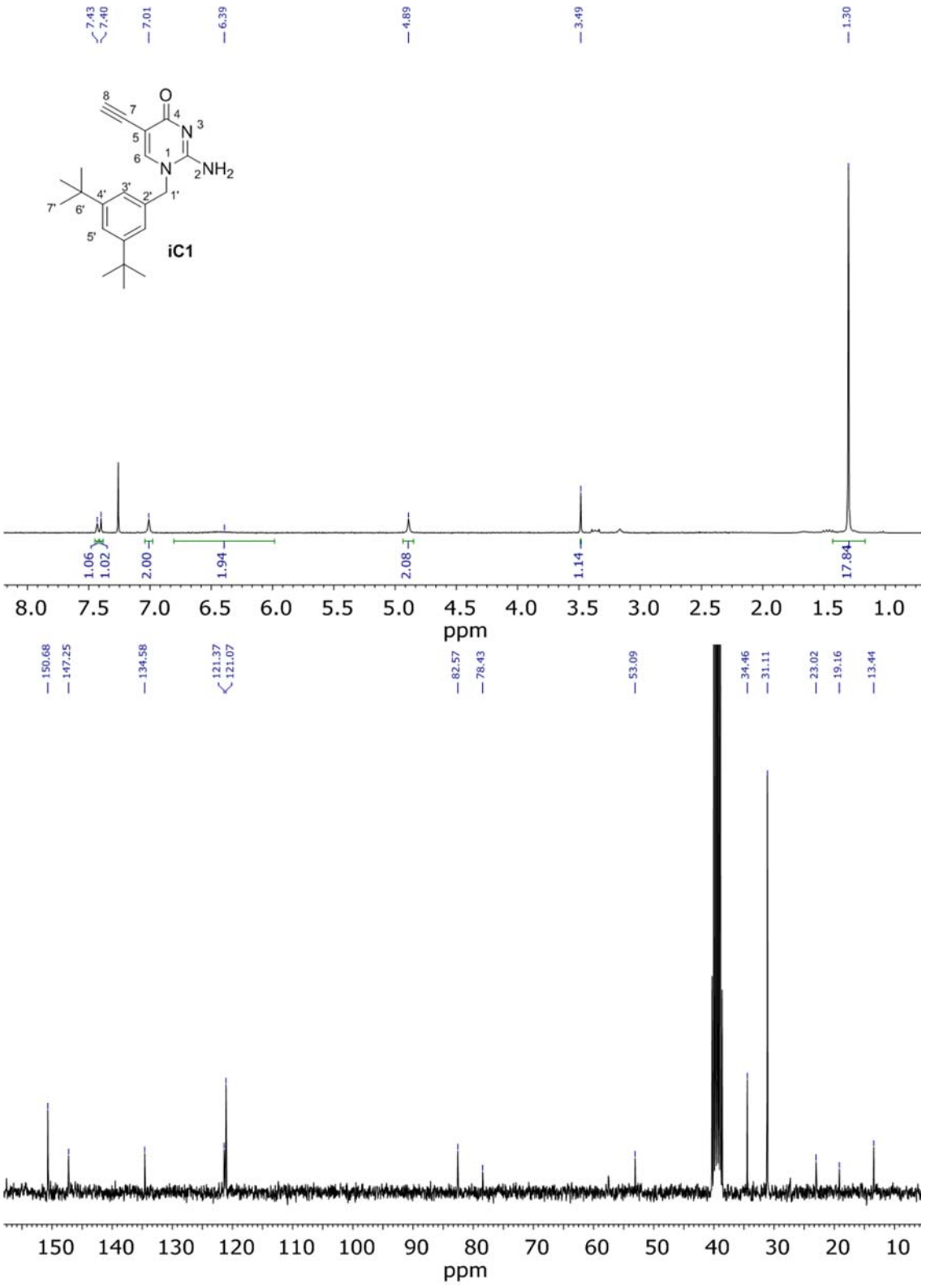
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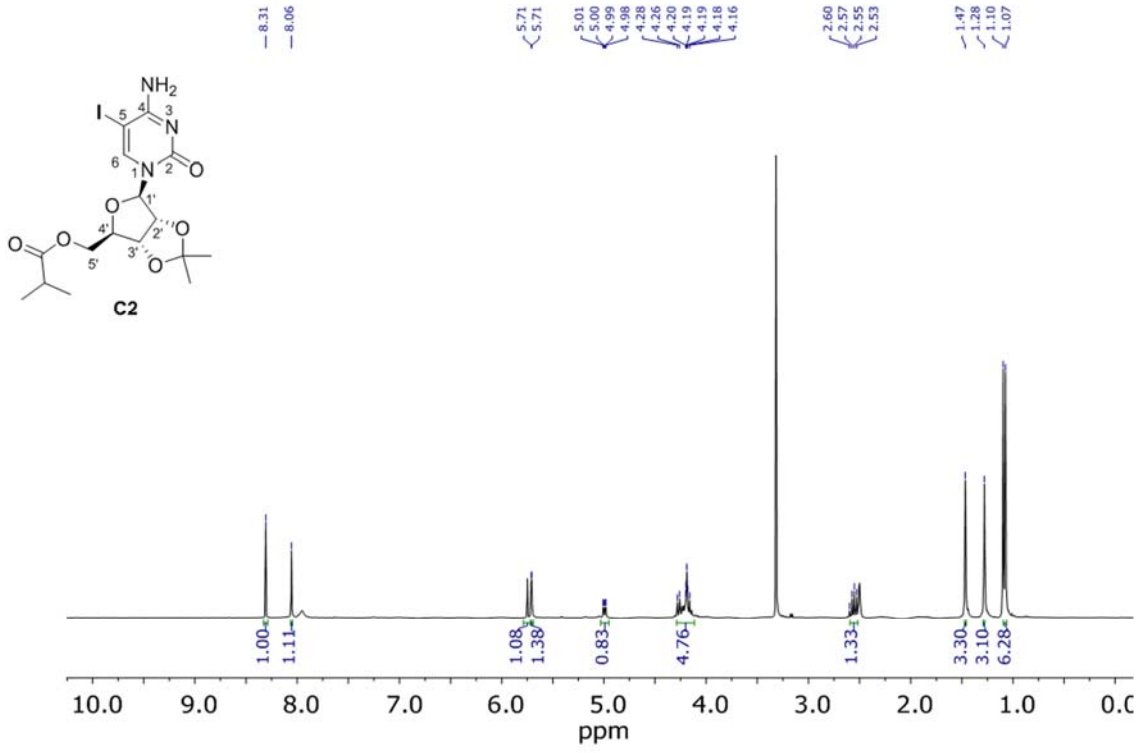
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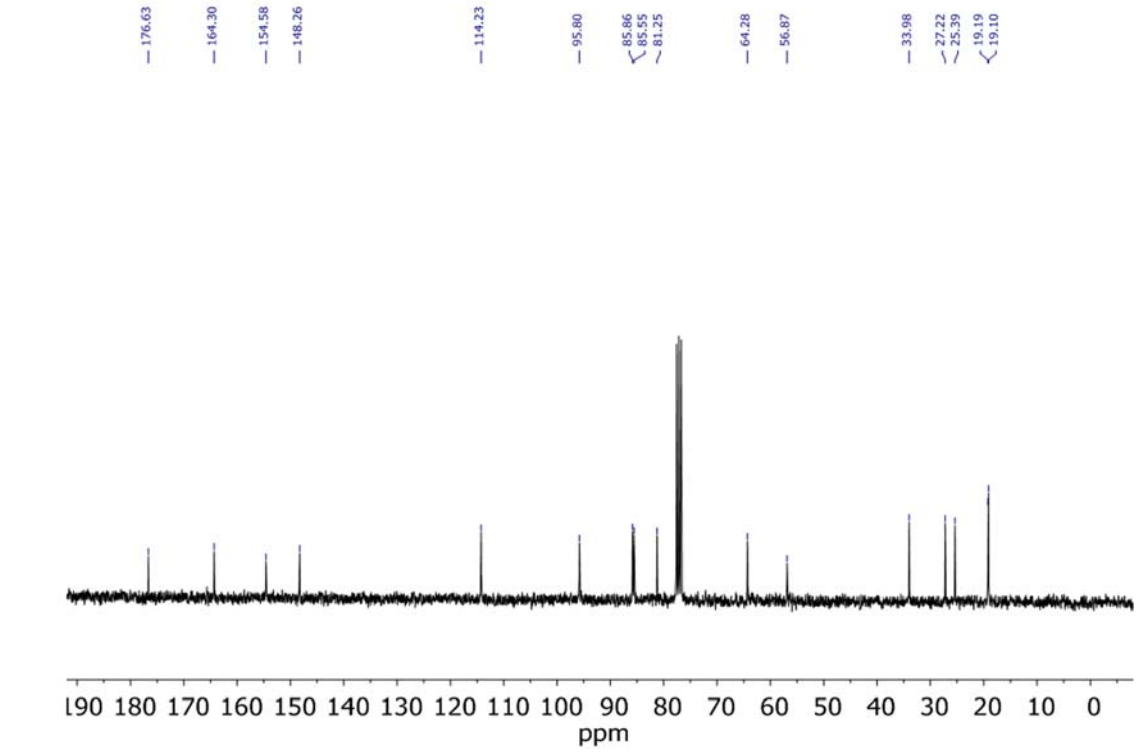
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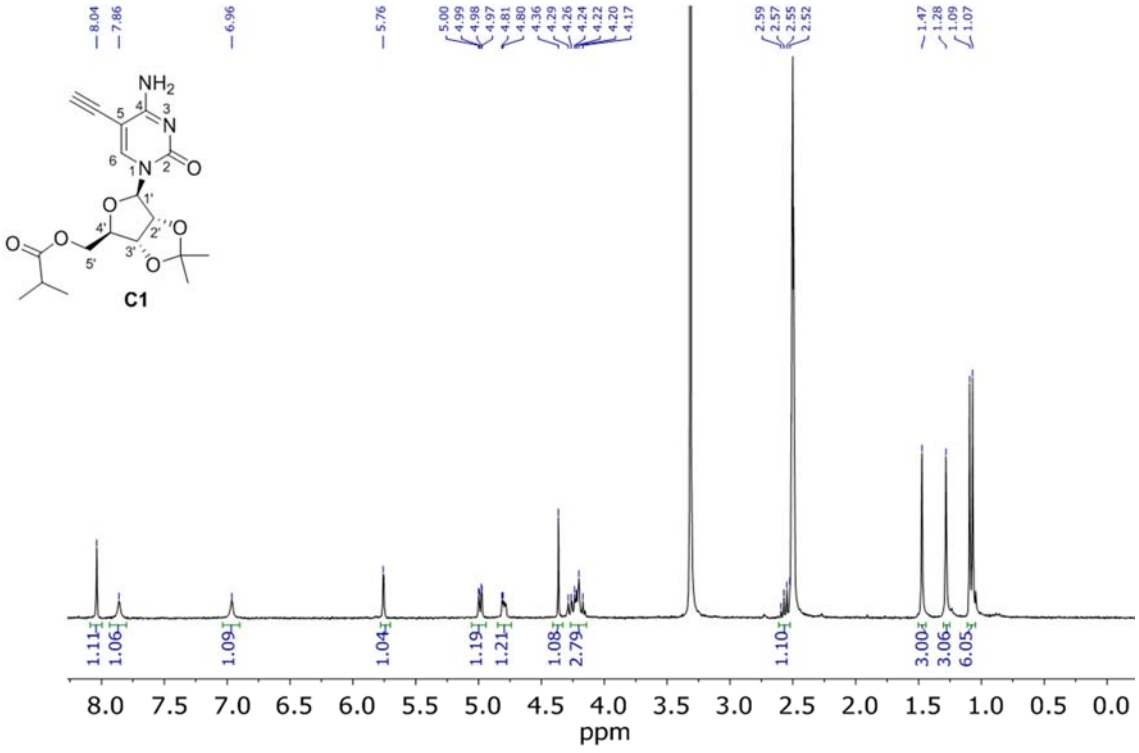
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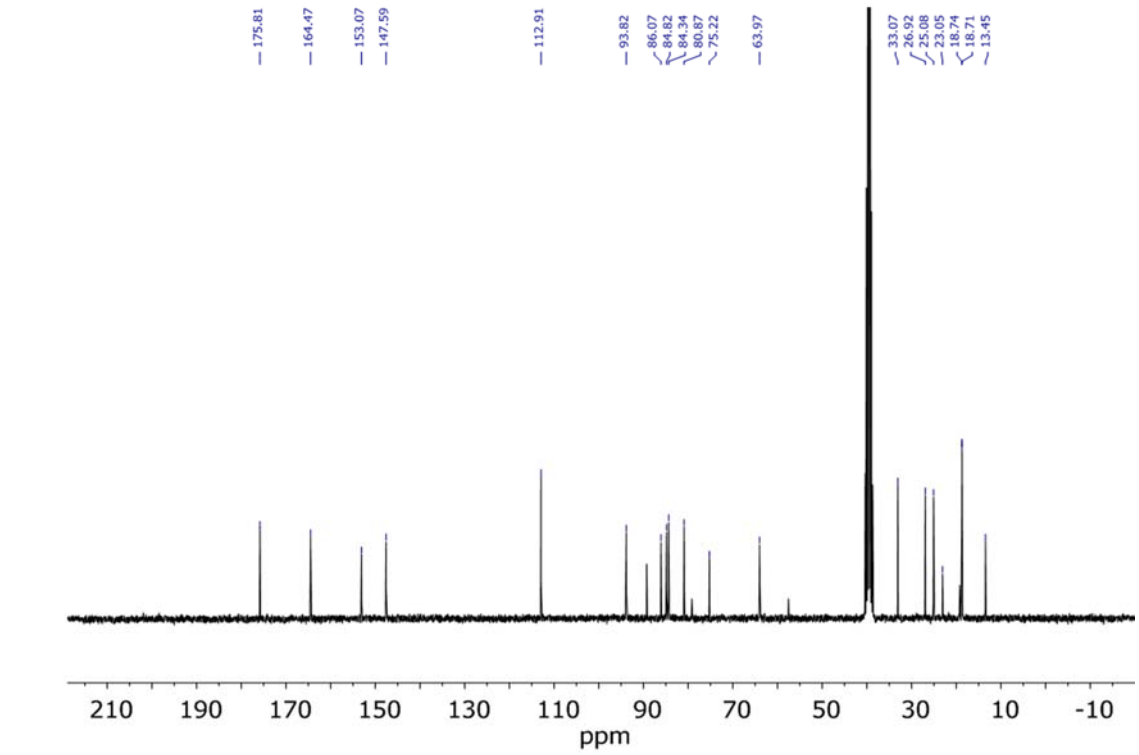
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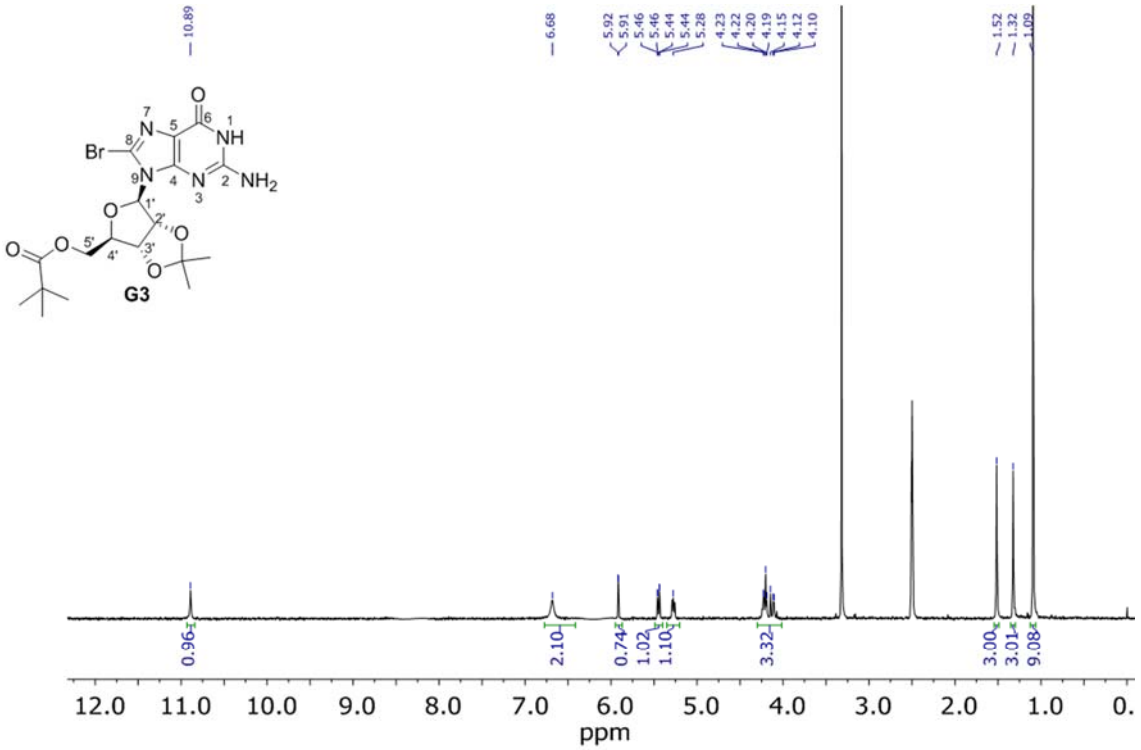
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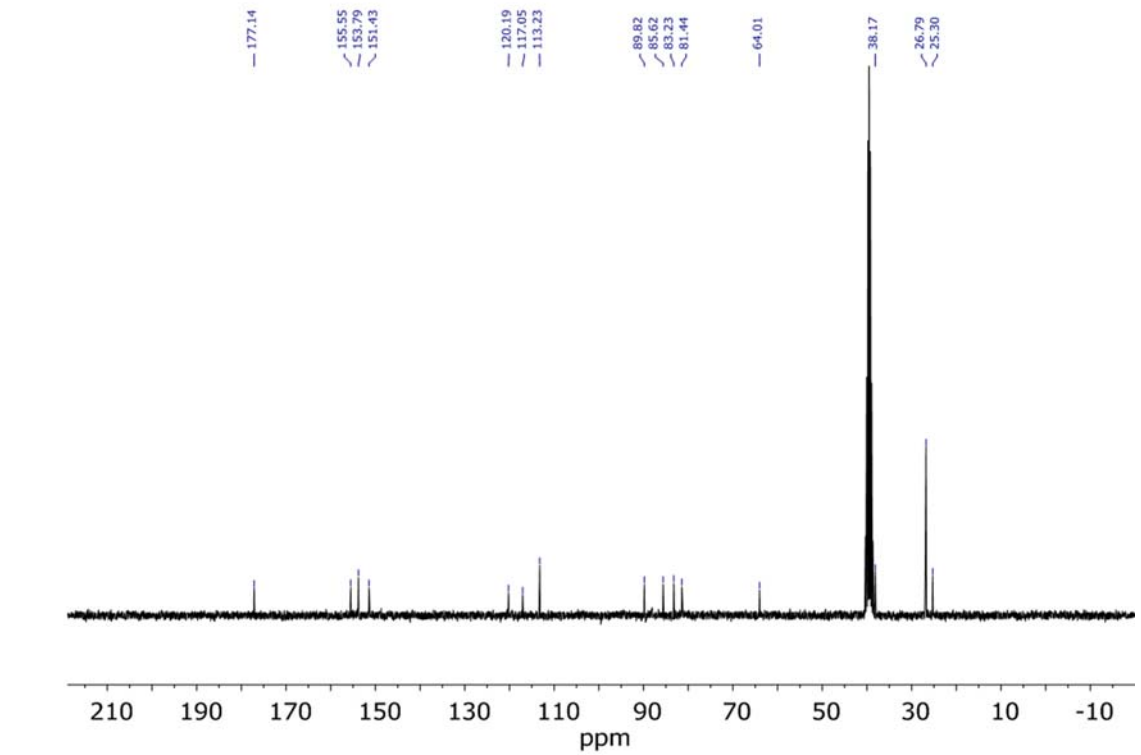
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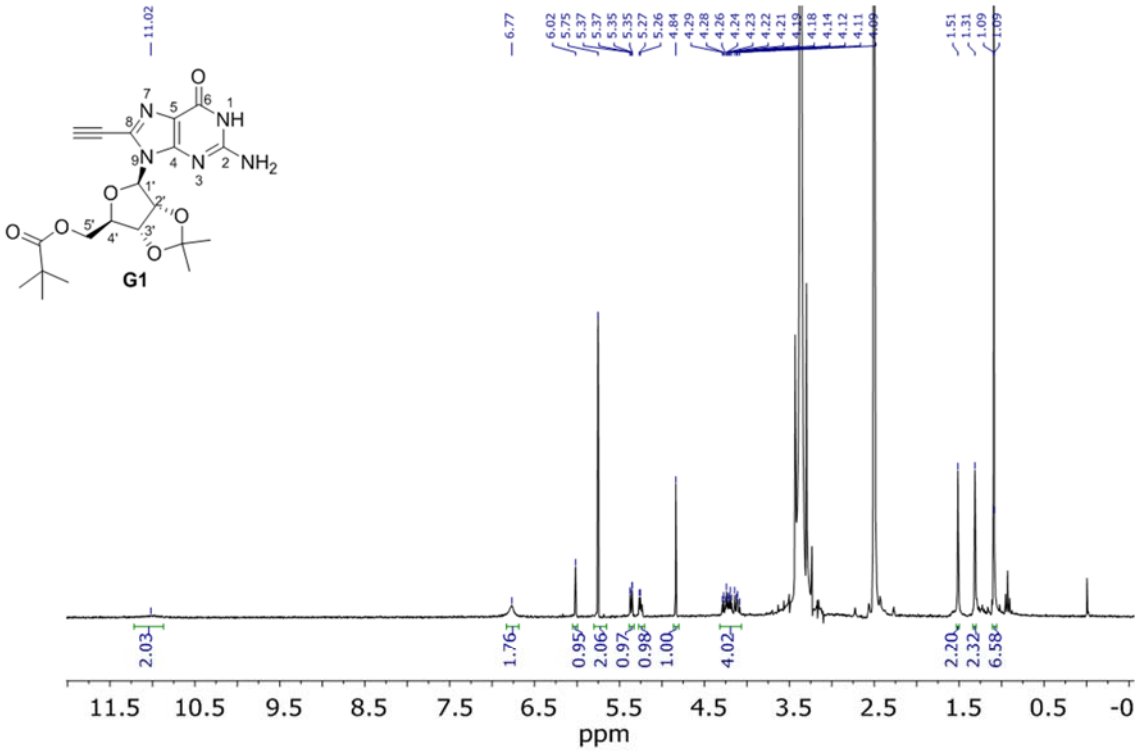
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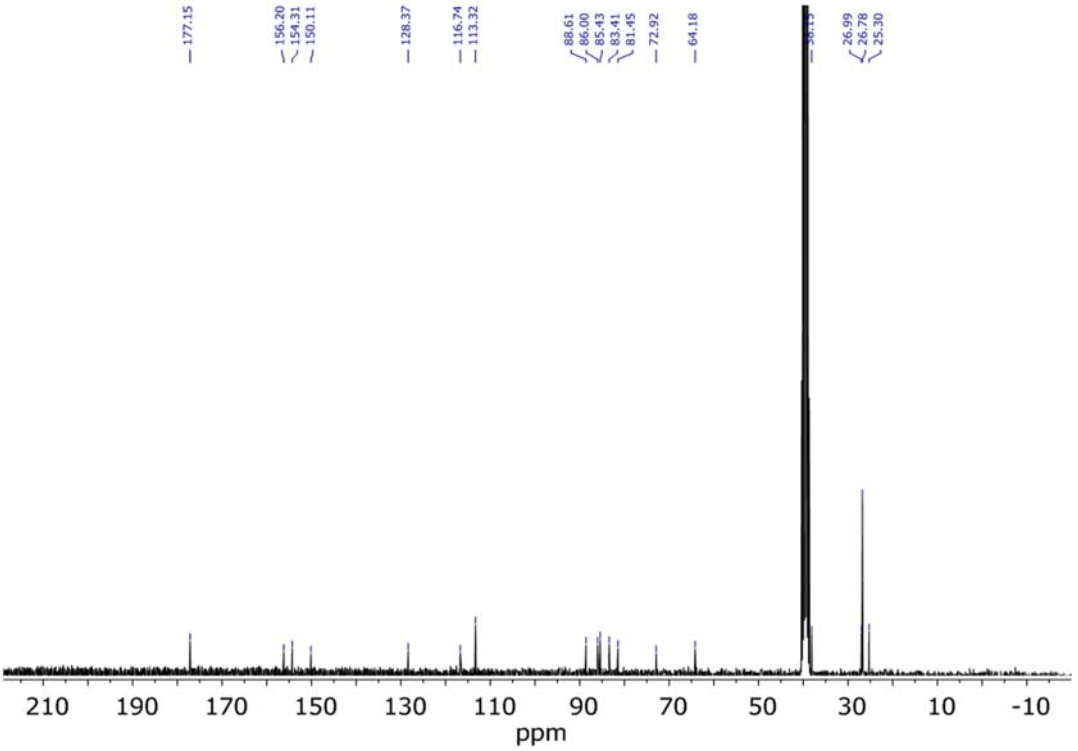
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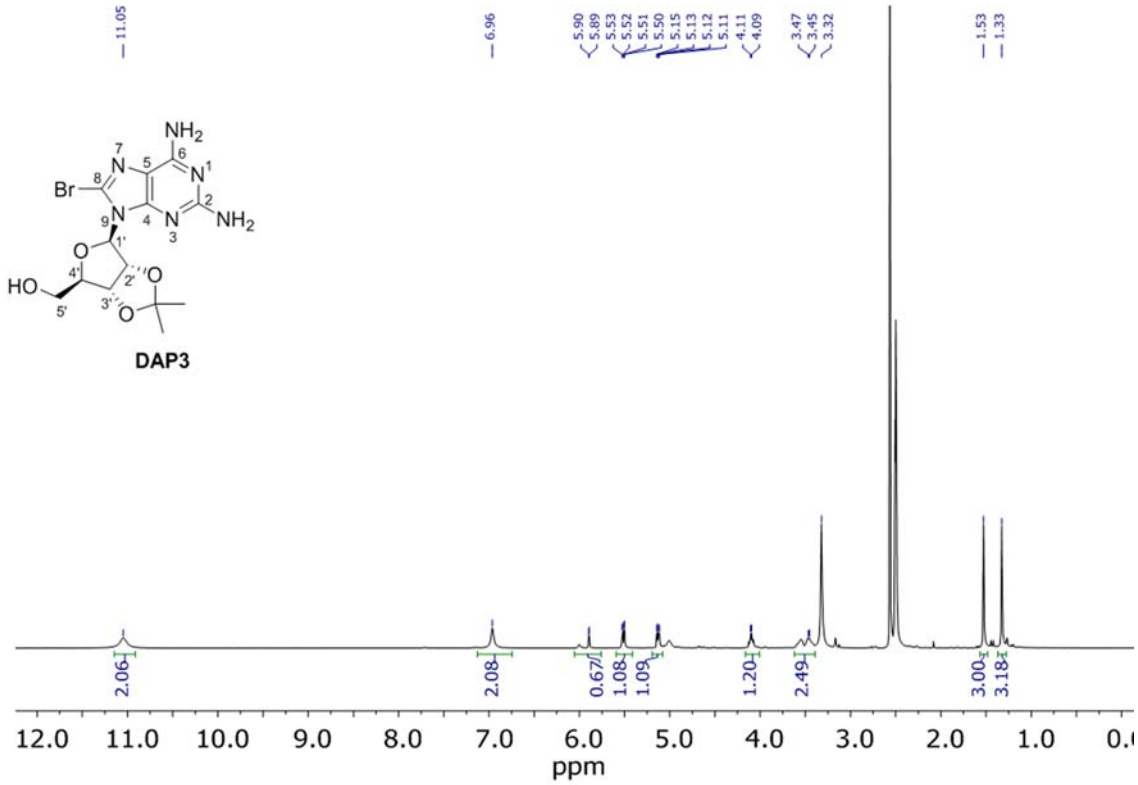
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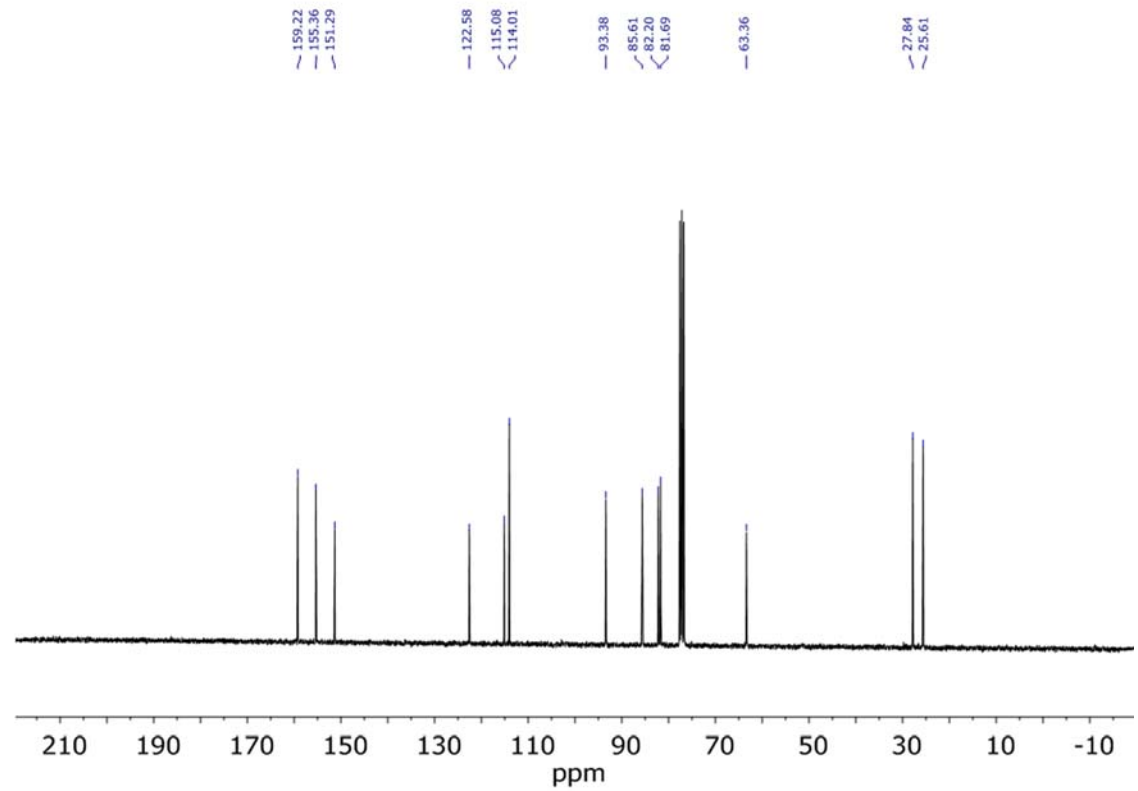
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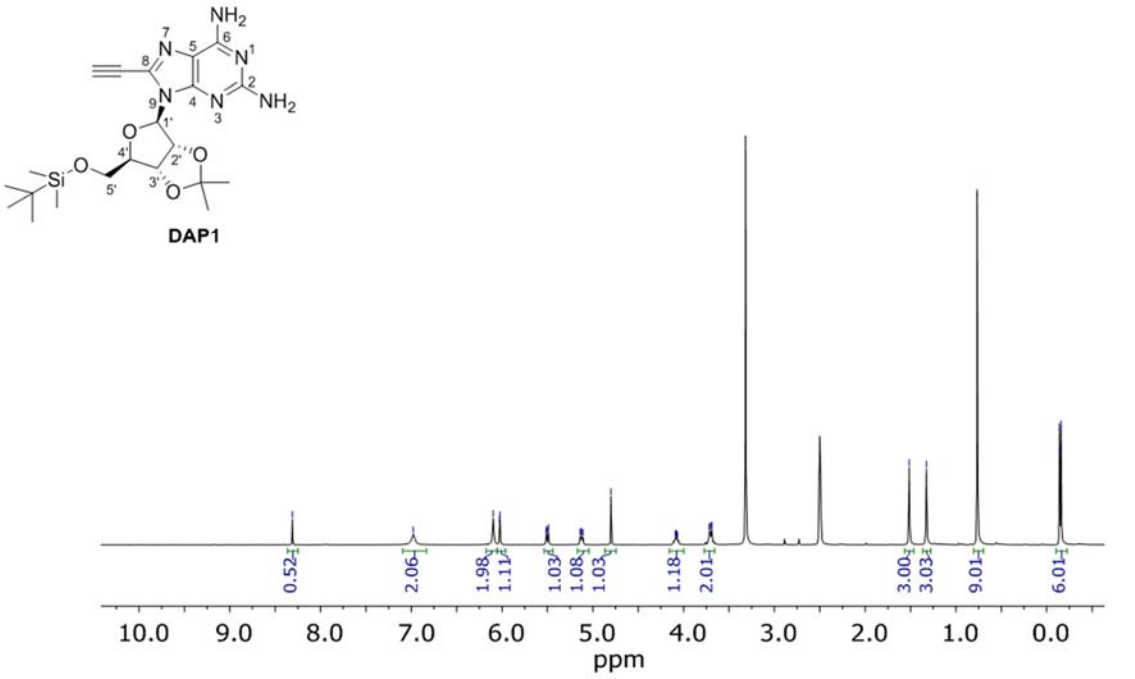
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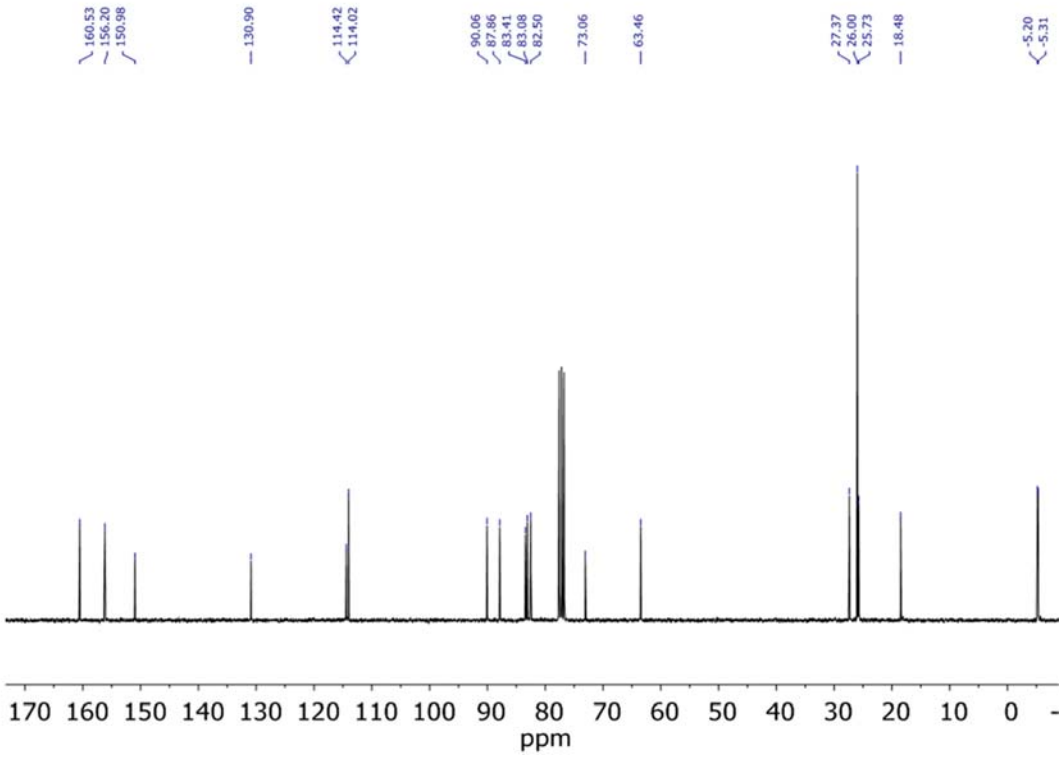
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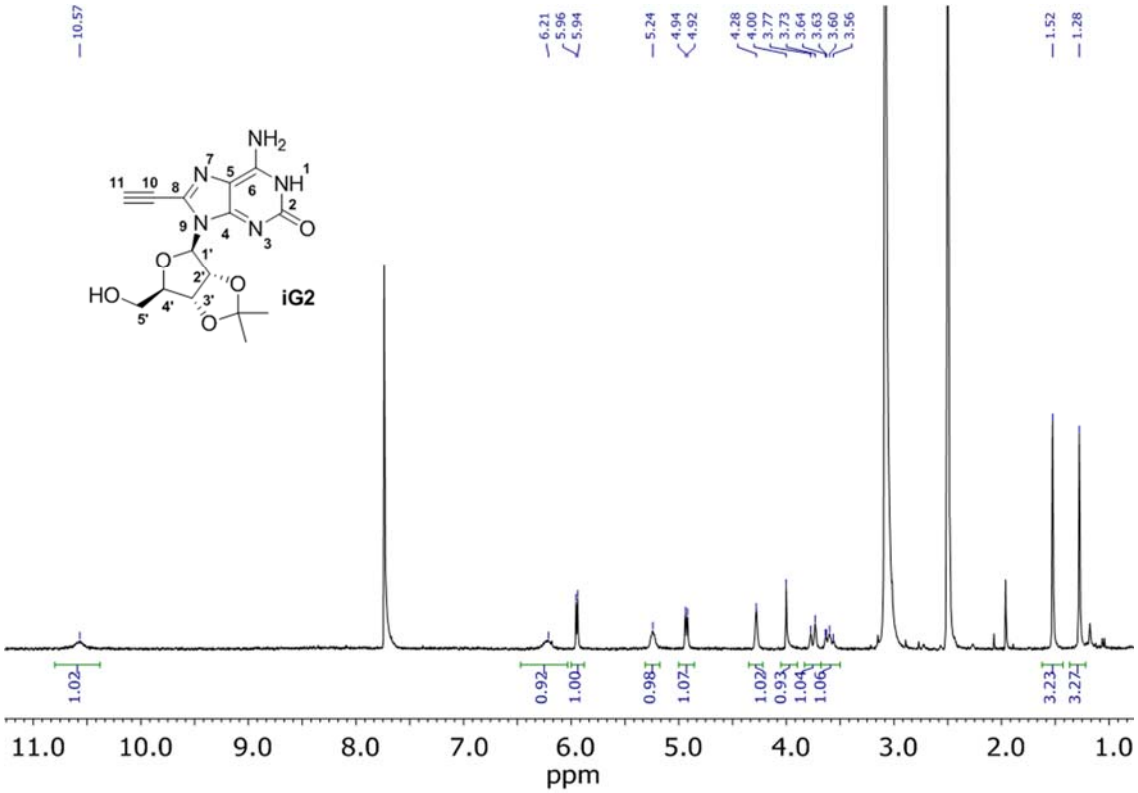
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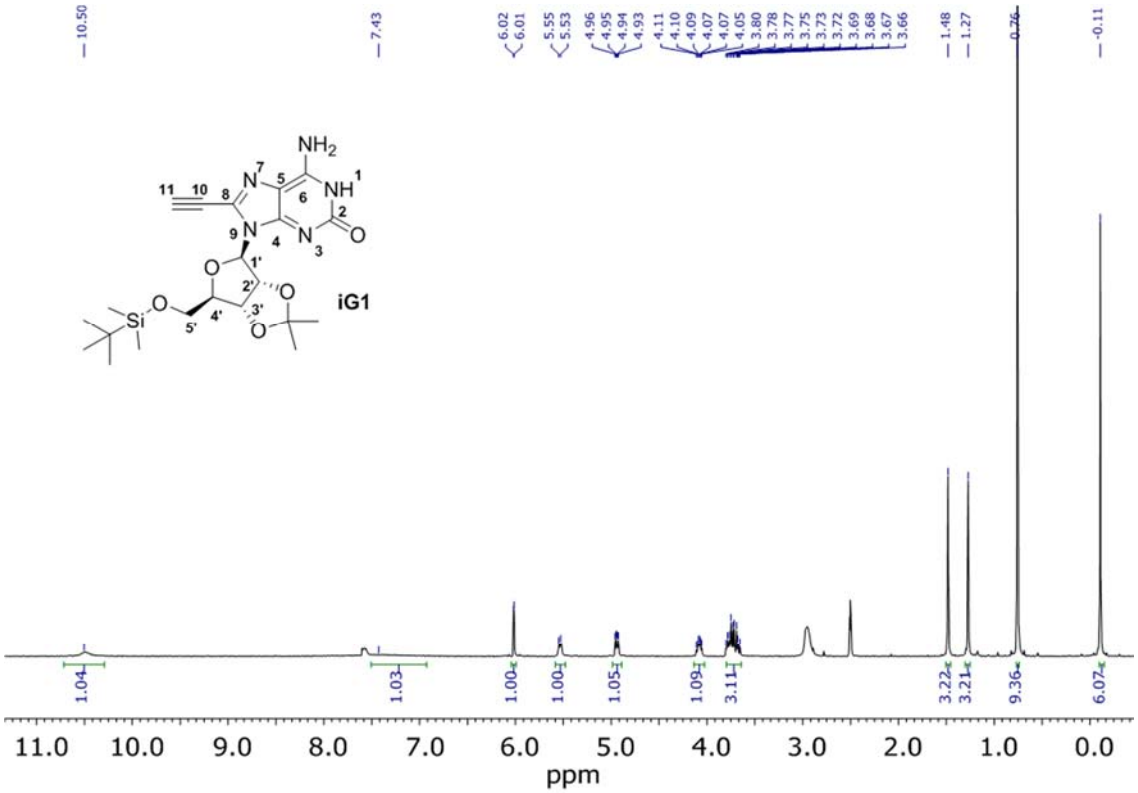
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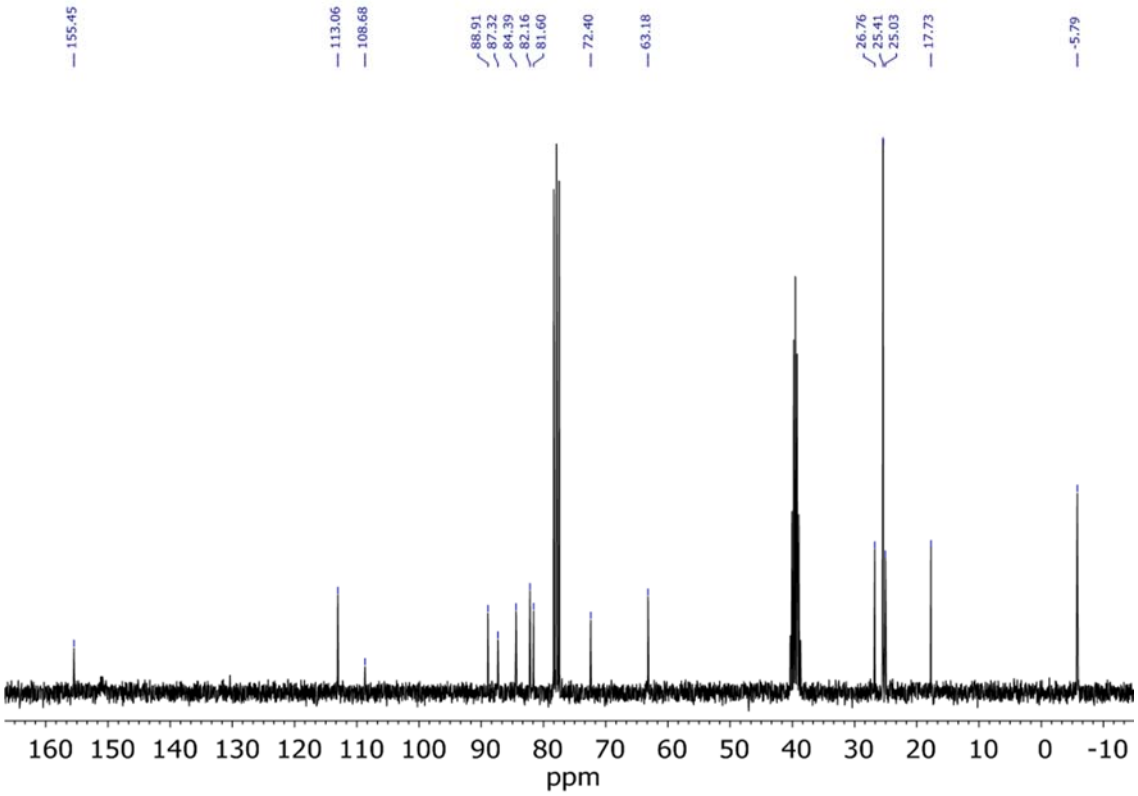
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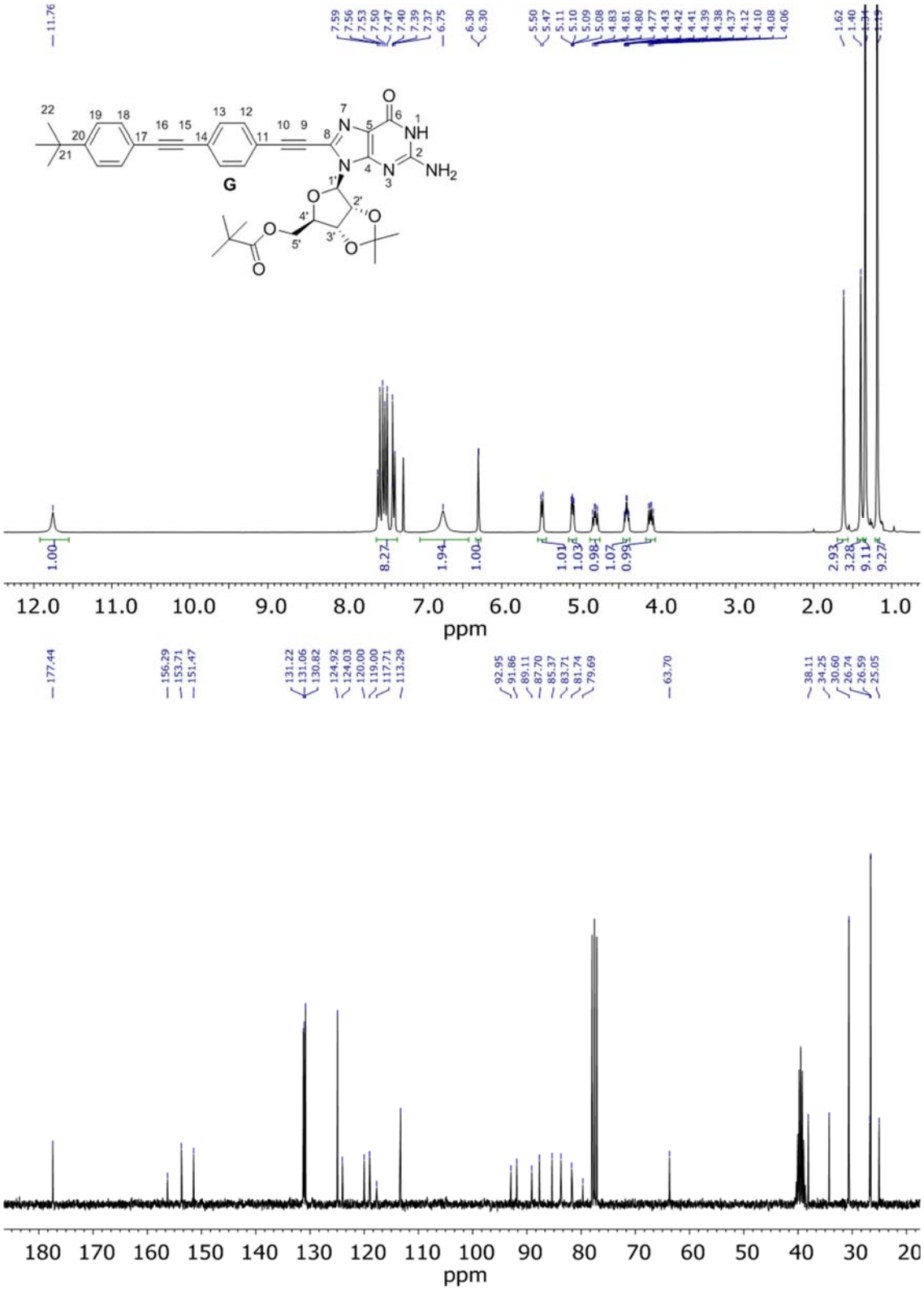
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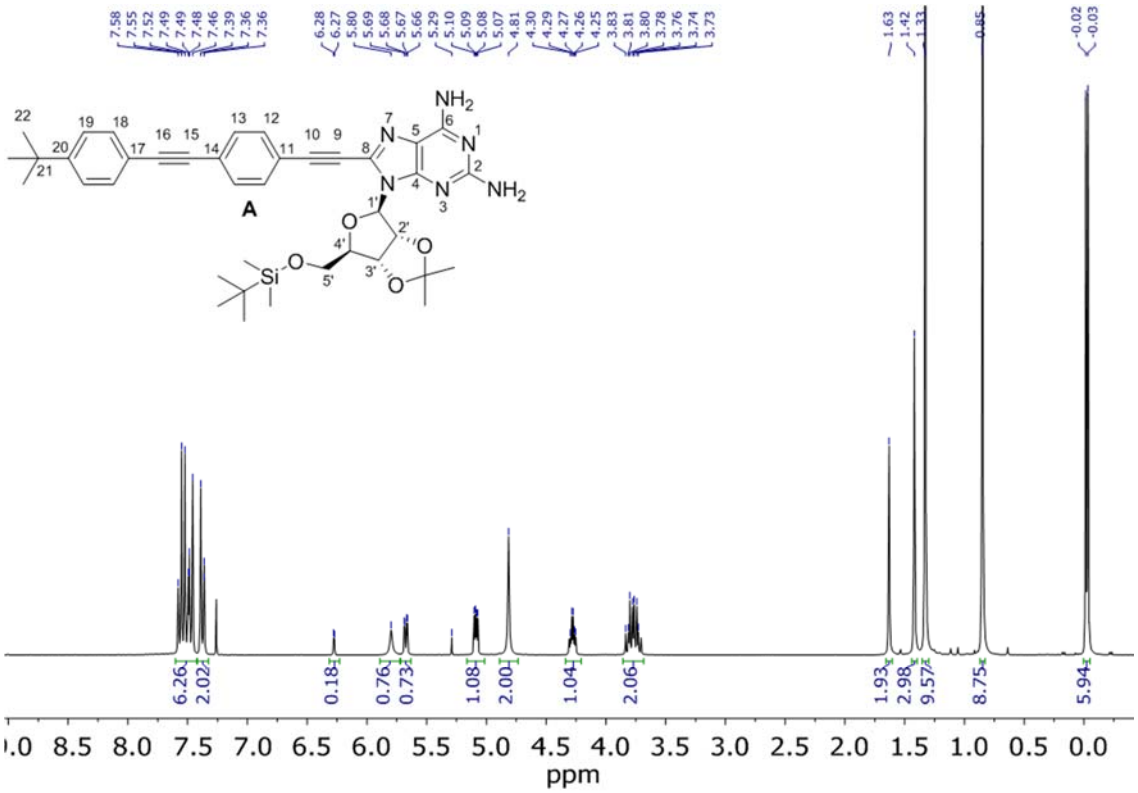
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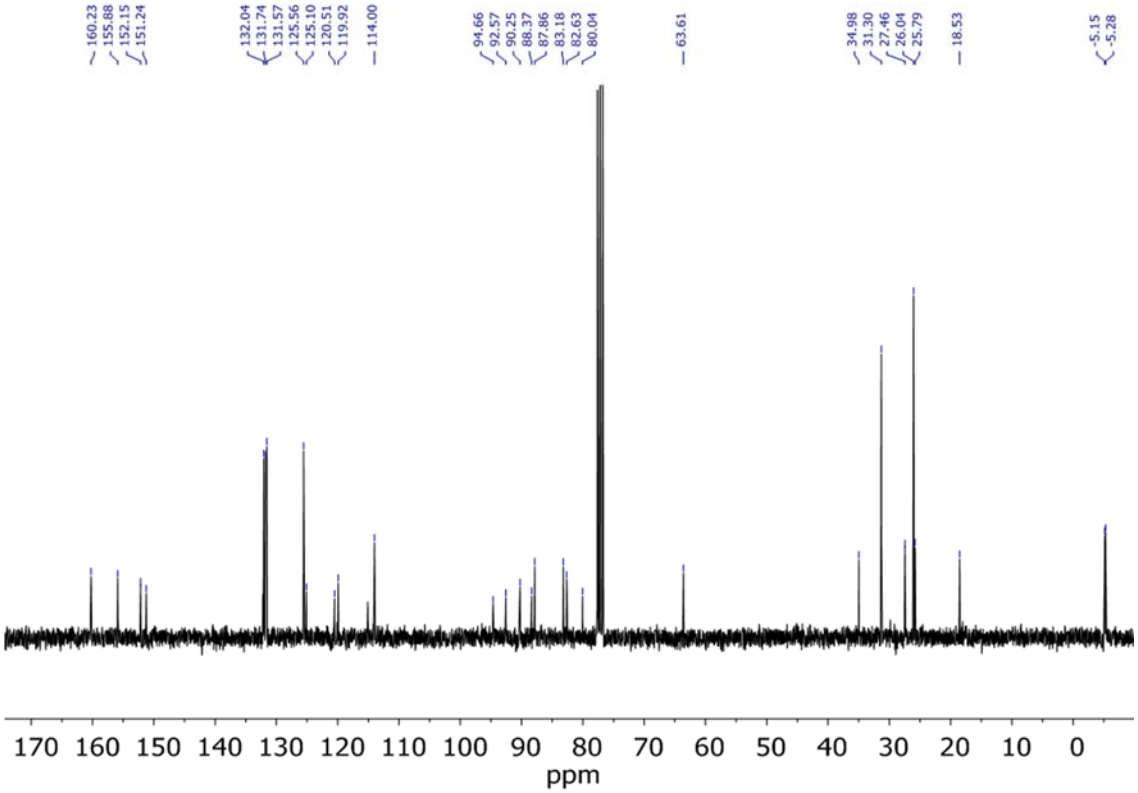
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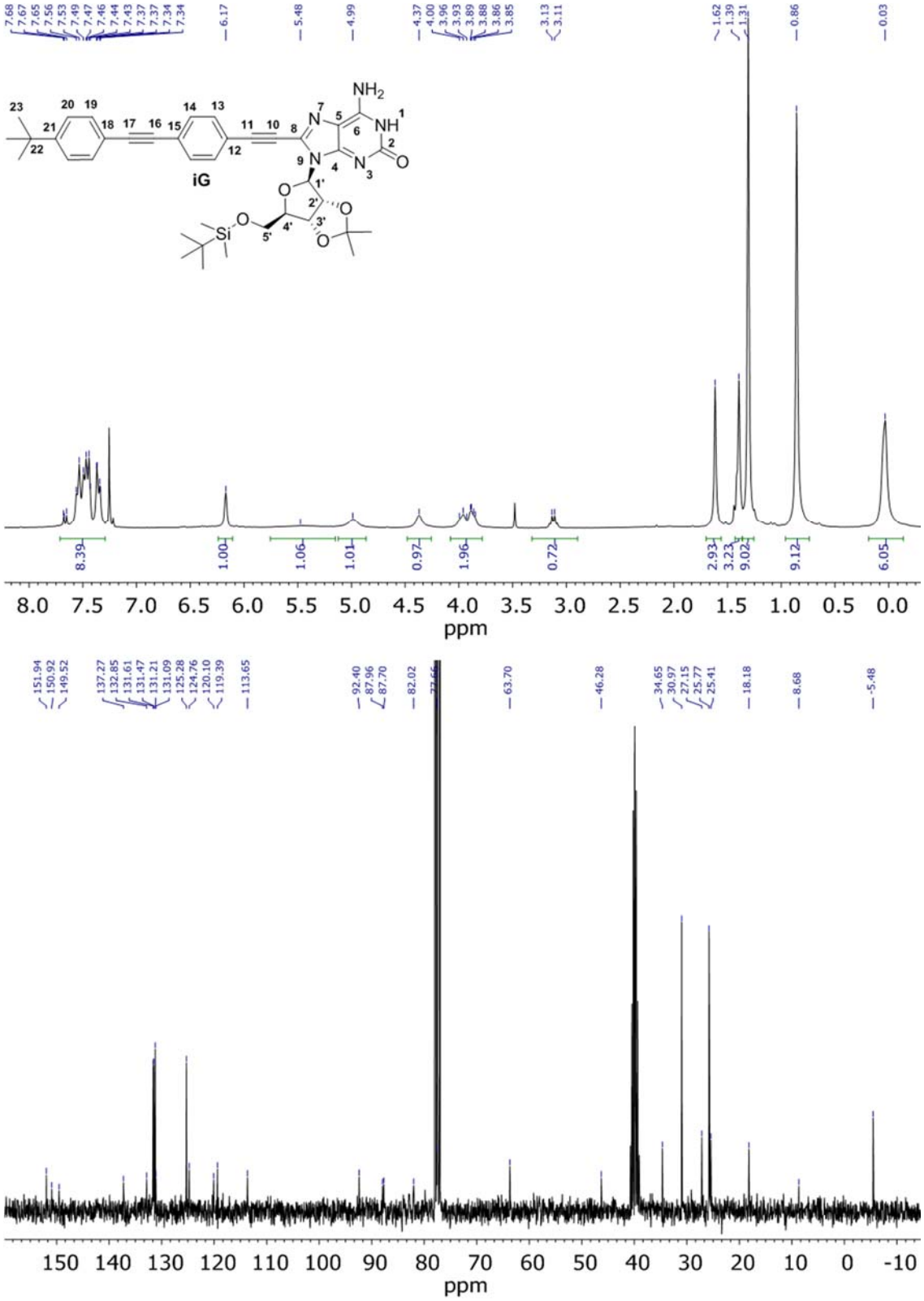
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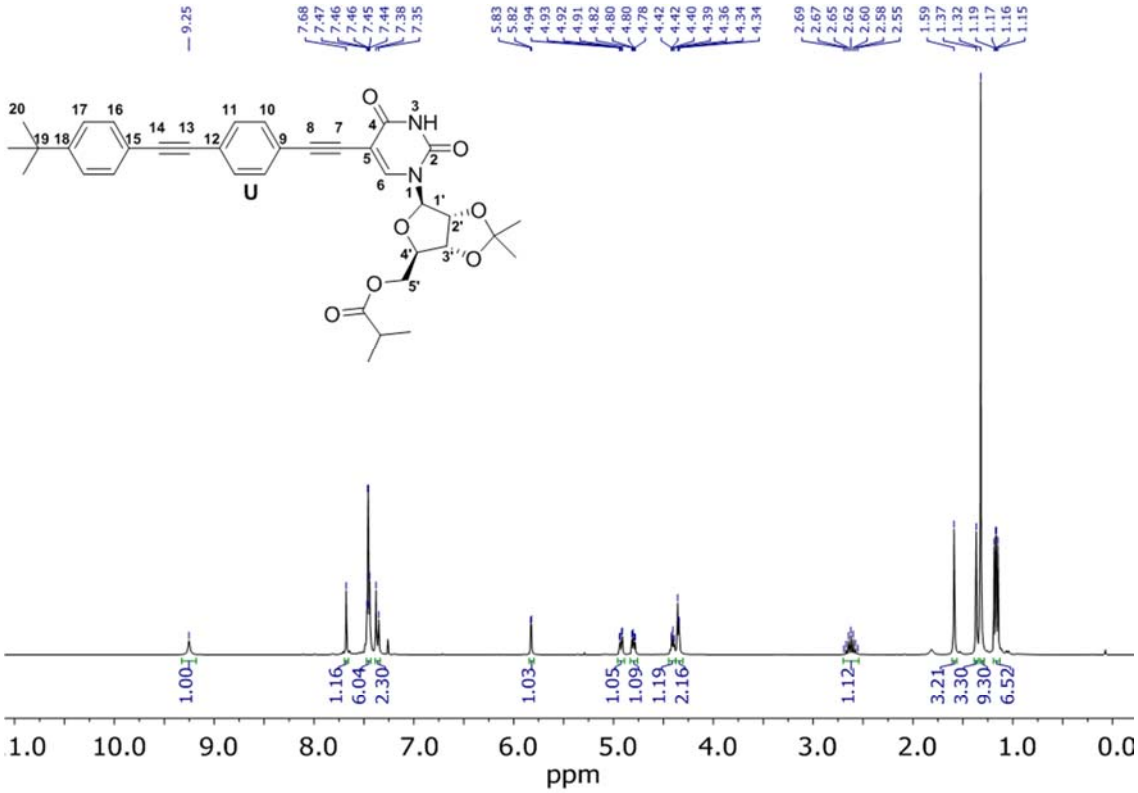
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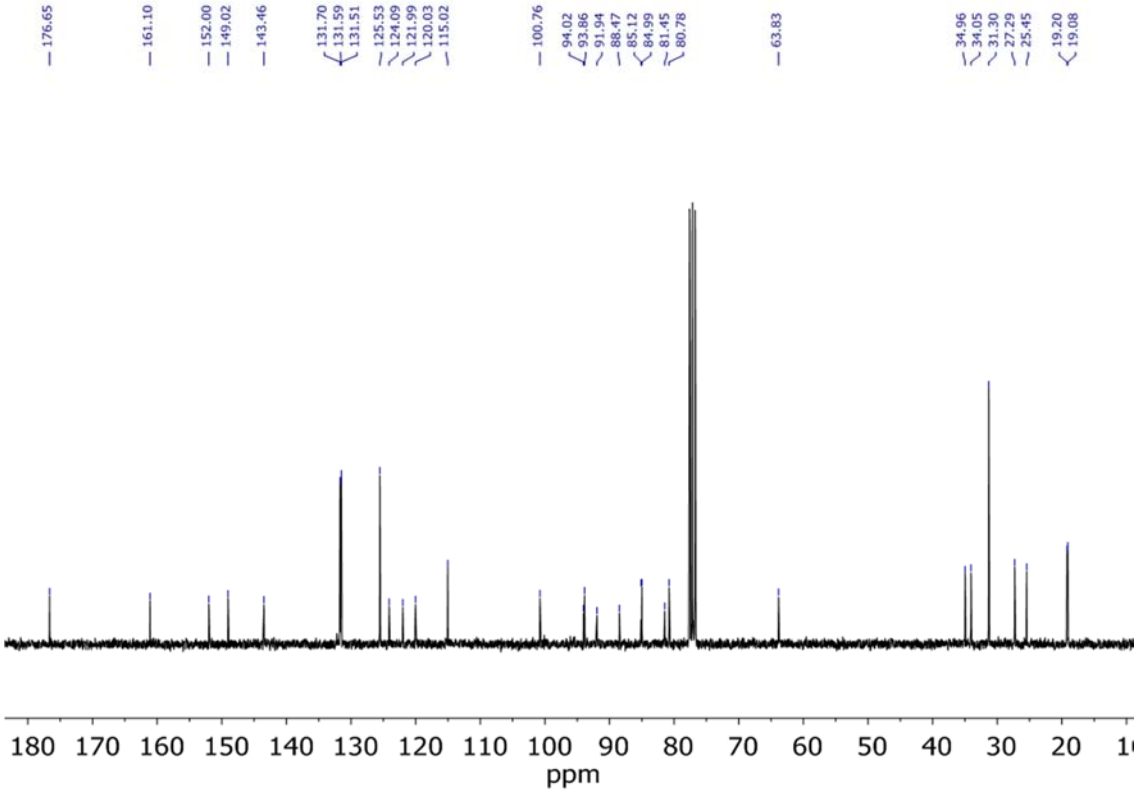
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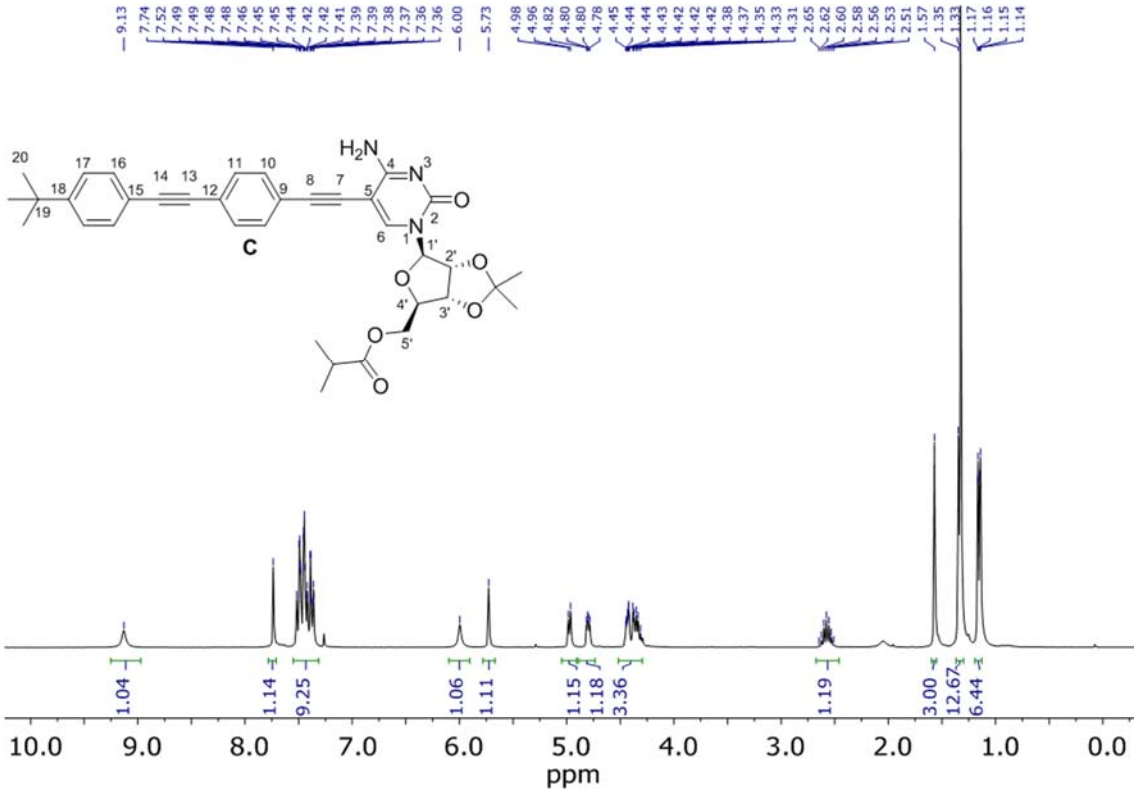
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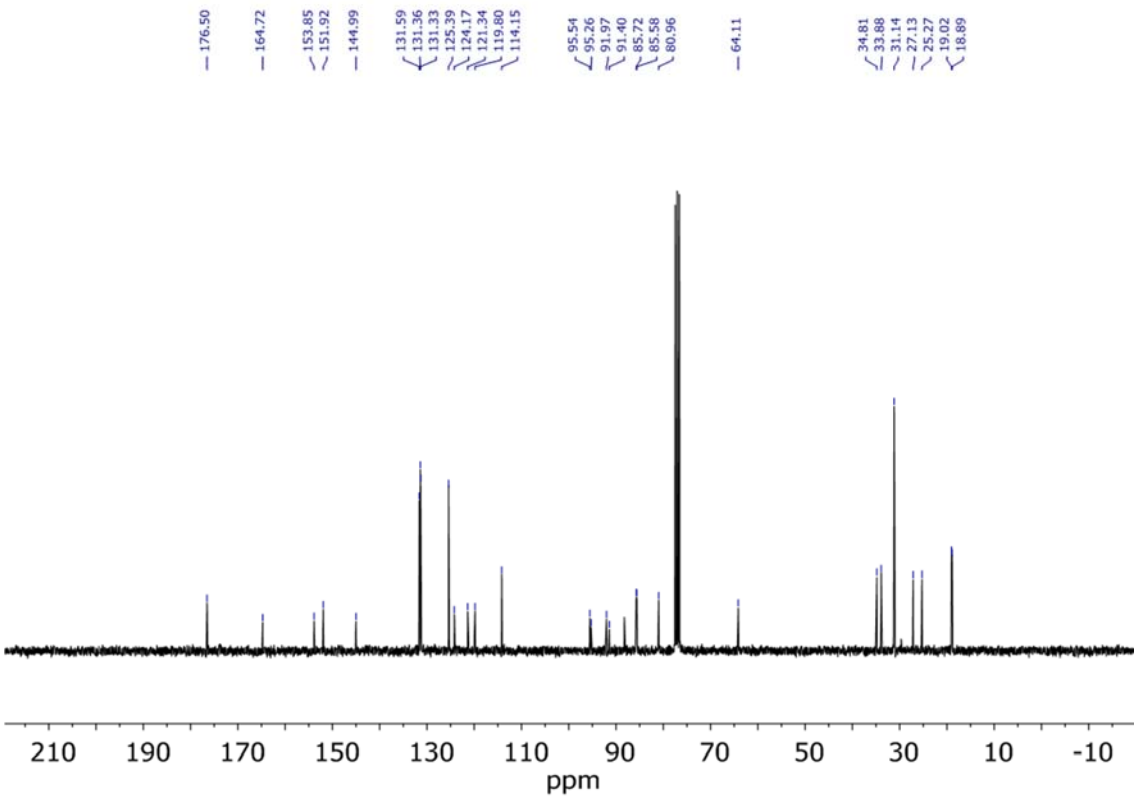
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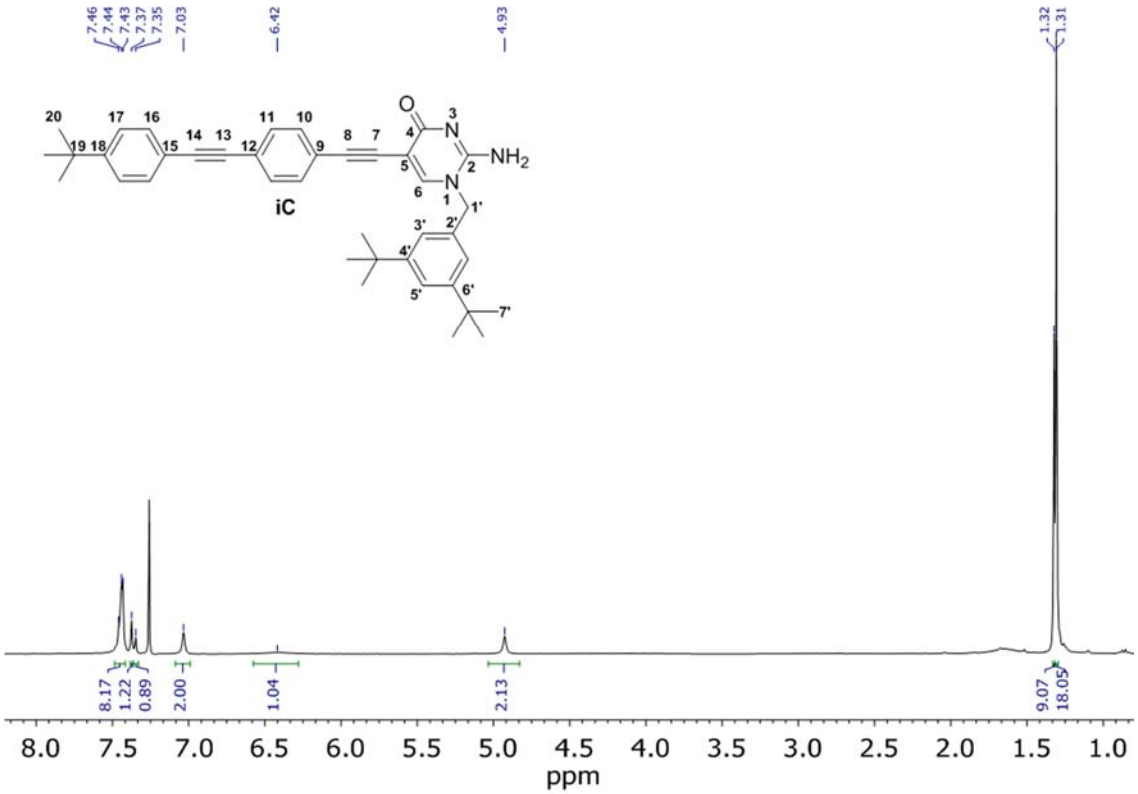
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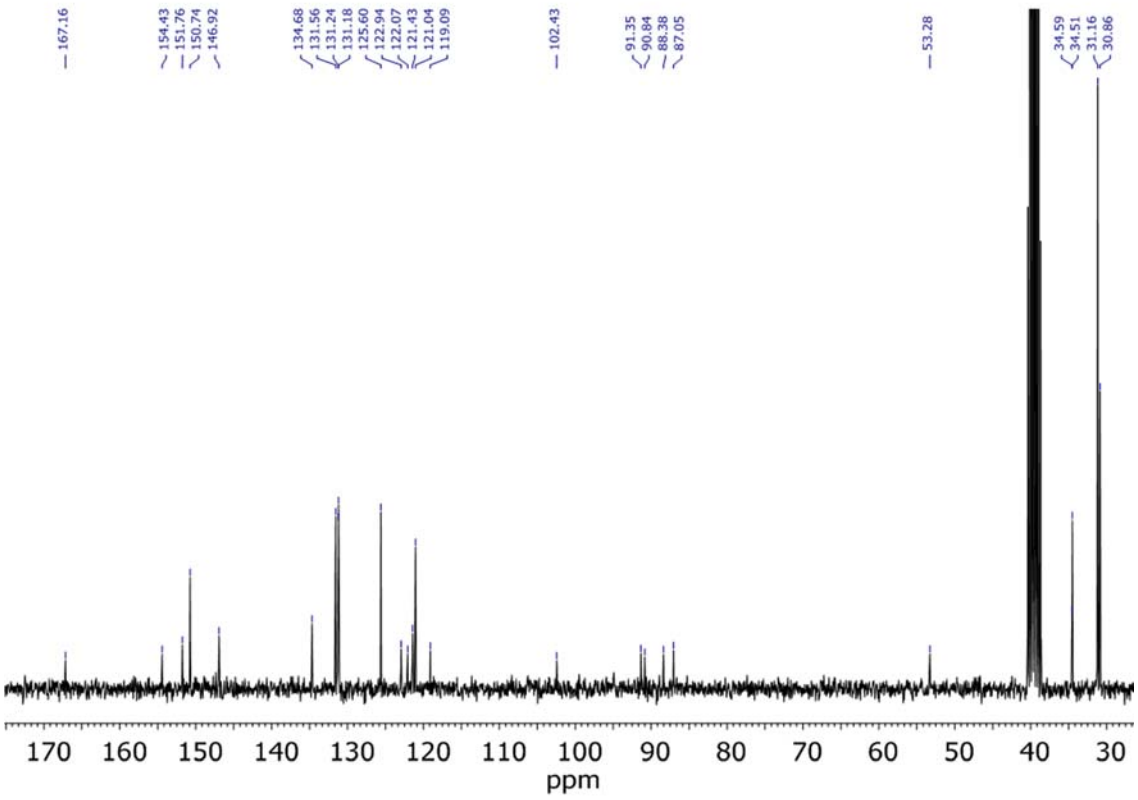
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3. NMR and UV-vis Dilution and Titration Experiments.

NMR dilutions and titrations were carried out in in 5 mm NMR tubes using $CDCl_3$ or $CDCl_3$:CCl_4 (2:3) as solvents. Deuterated solvents were purchased from Aldrich in ampoules and used as received. Residual $CHCl_3$ was used as the internal references (7.26 ppm), respectively. UV-vis dilutions and titrations were carried out in $CHCl_3$ or $CHCl_3$:CCl_4 (2:3) (Alfa Aesar, Spectrophotometric Grade). The experiments were performed in 1 cm or 1 mm path length quartz cuvettes. Volumes were added using Hamilton microsyringes. UV-vis absorbances were kept within the 0.2-3.5 range. Temperature control was set at 298 K in all cases.

Dilution experiments were carried out by successive injections of a stock solution of the corresponding nucleoside monomer into clean solvent, thus increasing the concentration along the experiment. We found this method more practical and reliable than performing successive dilutions of the concentrated starting sample. The full ^{1}H NMR/UV-vis spectra were recorded over at least 15 concentrations, considering, as far as possible, that most of them should yield chemical shift/absorbance data within the 20-80% saturation range. Hence, the concentration range targeted depended on the dimerization constant expected for each nucleobase. Each dilution experiment was repeated at least twice.

Titration experiments were performed as follows. A sample of the host nucleoside was dissolved in the appropriate solvent, whose concentration, indicated in each experiment below, varied depending on the technique employed (^{1}H NMR or UV-Vis) and the expected magnitude of the association constant. A portion of this solution was used as the host sample, and the remainder was used to dissolve the sample of the guest, so that the host concentration remained constant throughout the titration. Successive aliquots of the guest solution, typically 10-20 times more concentrated, were added to the host sample, and the whole ^{1}H NMR / UV-vis spectra were recorded after each of the 15-20 guest additions. Again, in order to cover as much as possible the 20%-80% probability of binding range, the initial host concentration and the number of guest equivalents targeted was lower or higher as a function of the expected association constant between complementary bases. Each titration experiment was repeated at least twice.

NMR Dilution and Titration Data Analysis with *Equilibria* to obtain K_{dim} and K_a

The *Equilibria* program is a software package developed by Christopher Marjo, Mark Wainwright Analytical Centre, University of New South Wales, Sydney, Australia (http://www.sseau.unsw.edu.au/). It has been written using C++, and the Microsoft® Foundation Classes.

The NMR models for i) dimerization and ii) the formation of 1:1 HG complex + H_2 dimer were employed in this work. Using the second model, K_a between host and guest can be determined with a known host dimerisation constant (K_{dim}) by measuring the change in NMR chemical shift of

a probe on the host in a set of solutions with constant host concentration and increasing guest concentration (see also reference 48 in the text).

The system equilibrium, and the corresponding binding constant equations are:

$$H + G \Leftrightarrow HG \qquad K_a = [HG] / [H][G] \qquad (1)$$

$$H + H \Leftrightarrow H_2 \qquad K_{dim} = [H_2] / [H]^2 \qquad (2)$$

The mass balances for the system are:

$$[H]_0 = [H] + [HG] + 2[H_2] \qquad (3)$$

$$[G]_0 = [G] + [HG] \qquad (4)$$

From equations (1) – (3), expressions can be derived for the concentration of all species in solution, for each titration point:

$$[H_2] = K_{dim}[H]^2 \qquad (5)$$

$$[HG] = [H]_0 - [H] - 2[H_2] \qquad (6)$$

$$[G] = [HG] / [H]\, K_a \qquad (7)$$

The NMR probe on the Host has 3 chemical shifts corresponding to the species in solution: the unbound chemical shift, δ_H, the chemical shift of the complex with the guest, δ_{HG}, and the chemical shift of any Host dimer that forms, δ_{H2}. The complex and the dimer chemical shifts are assumed to be the same, $\delta_{HG} = \delta_H$. The observed chemical shift will be a mixture of the 3 shifts according the mole fraction of each species present and can be calculated according to:

$$\delta_{calc} = (\delta_H[H] + \delta_{HG}[HG] + 2\delta_{H2}[H_2]) / ([H] + [HG] + 2[H_2]) \qquad (8)$$

The program searches for values of K_a , δ_H, and δ_{H2} (= δ_{HG}) that give δ_{calc} values that most closely match the experimental chemical shift, δ_{obs}, for each point in the titration curve. This process is described below.

The chemical shift of the Host dimer, δ_{H2}, and its binding constant, K_{dim}, is determined previously in an independent experiment. The program guesses a value for K_a, δ_H, and δ_{H2} (= δ_{HG}) then, for each point in the titration:

i. Use a numerical approach (Newton-Raphson) to find the value of free Host, [H] where:
   $[G]_0 - [G] - [HG] = 0$, where $[G]_0$ is known, and [G] and [HG] are given by (6) and (7).
ii. Use (5) to calculate the concentration of $[H_2]$.
iii. Use (6) to calculate the concentration of [HG].
iv. Use (8) to calculate the expected chemical shift for this point in the titration.
v. If it is not a good match try new values of K_a, δ_H, and δ_{H2} (= δ_{HG}).

Typically one or two different proton resonances were monitored at the same time giving the corresponding data sets. The association constant for a single run was calculated as the mean of the values obtained for each of the signals followed during the titration, weighted by the observed changes in chemical shift. The association constants from different runs were then averaged.

NMR Titration Data Analysis with Thordarson to obtain K_a

In some cases, when there were two shifting NH/NH_2 nuclei, the 1:1 binding constants were obtained from the ^{1}H NMR titration experiments using a custom written global nonlinear regression analysis program developed by P. Thordarson (ref. 22 in the text) within the Matlab R2012b package utilizing the Simplex algorithm.[10] This fitting method uses a global approach that considers both set of data simultaneously, which enhances the quality of the fitting procedure. However, host (nor guest) dimerization were considered using this fitting approach.

The standard errors (SEy) are calculated by :

$$\mathrm{SE}_y = \sqrt{\frac{\sum (y_{\mathrm{data}} - y_{\mathrm{calc}})^2}{N - k}}$$

Where *N* is the number of data points and *k* the number of parameters to be fitted.

UV-vis Dilution and Titration Data Analysis with *ReactLab*™ *EQUILIBRIA* to obtain K_{dim} and K_a

ReactLab EQUILIBRIA, a more sophisticated version of the previous SpecFit program, is a program developed and commercialized by Jplus Consulting Pty Ltd (http://jplusconsulting.com/ ; 8 Windsor Road, East Fremantle, WA 6158, Australia). It allows for the global fitting of multi-wavelength spectroscopic data in equilibrium titration measurements to chemical reaction schemes, and determines all equilibrium constants in the underlying mechanism. *ReactLab*™ algorithms fit complete reaction models directly to multivariate data and delivers all the required parameters in one step. The analysis also yields the concentration distributions of all species and the individual spectra of all the participating species. The program, including all algorithms and the GUI frontend has been developed in Matlab and compiled to produce the final deployable application.

A large wavelength region in the absorption spectra (from 250 to 450 nm; each wavelength representing one set of data) was fitted by this software. However, only a few selected wavelengths are plotted in the charts below. Both host and guest dimerization constants were considered in the analysis of the 1:1 host-guest binding constants.

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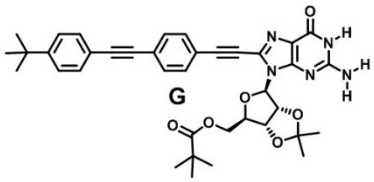
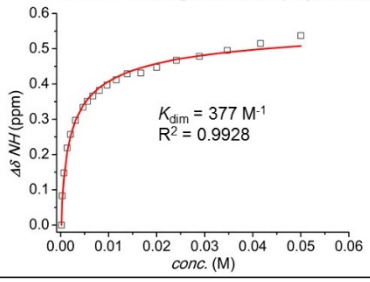
Self-association (Dimerization) Equilibria

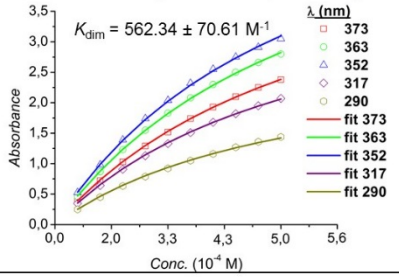


	Solvent	Concentration (M)
^{1}H NMR:	$CDCl_3$	$5.00 \times 10^{-2} – 1.78 \times 10^{-3}$
UV-vis:	$CHCl_3$	$5.00 \times 10^{-4} – 9.10 \times 10^{-5}$

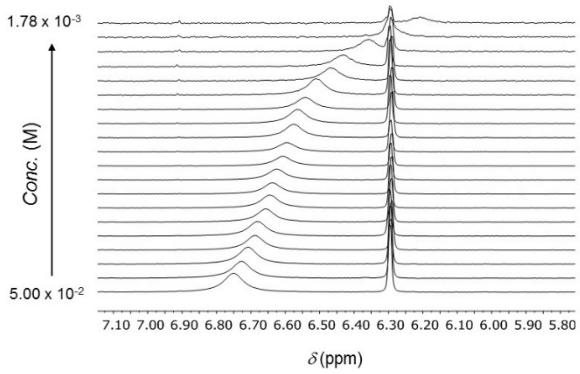
^{1}H-NMR: Binding Isotherm (Equilibria)



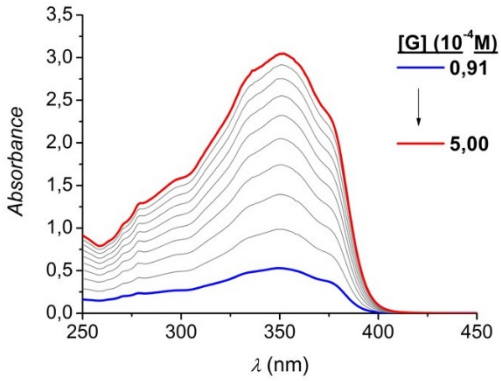
UV-Vis: Binding Isotherms (Reactlab)

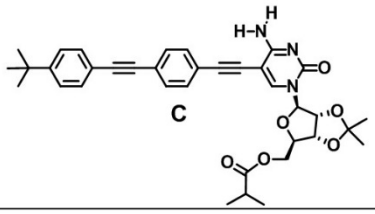


Concentration-dependent ^{1}H-NMR spectra



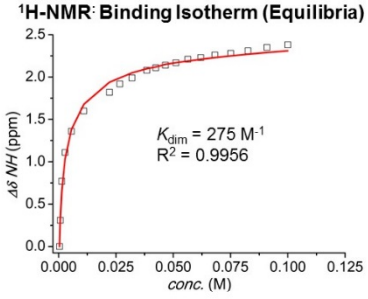
Concentration-dependent UV-Vis spectra





	Solvent	Concentration (M)
^{1}H NMR:	$CDCl_3$	$1.00 \times 10^{-1} – 7.47 \times 10^{-3}$
UV-vis:	$CHCl_3$	$5.24 \times 10^{-4} – 9.10 \times 10^{-5}$

^{1}H-NMR: Binding Isotherm (Equilibria)



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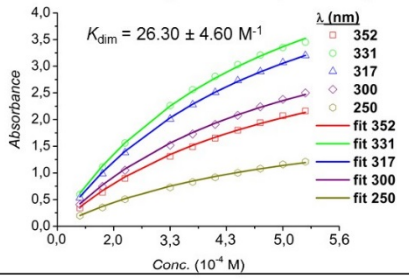
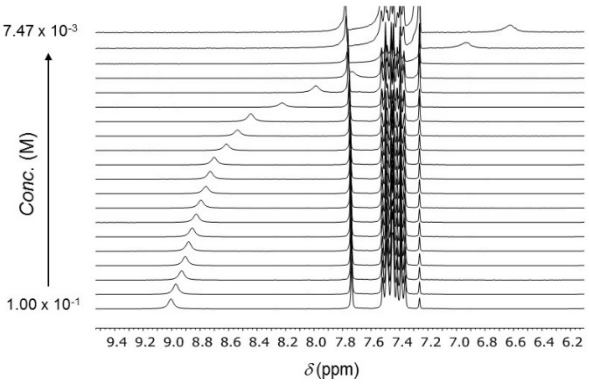


Concentration-dependent ^{1}H-NMR spectra



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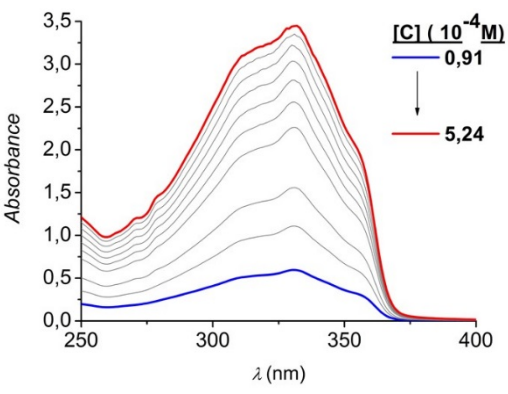
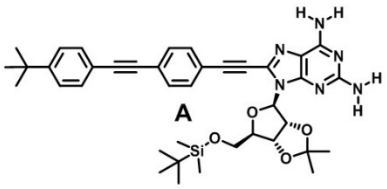
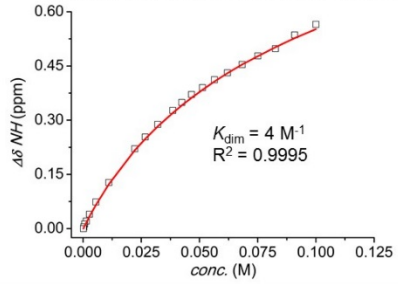


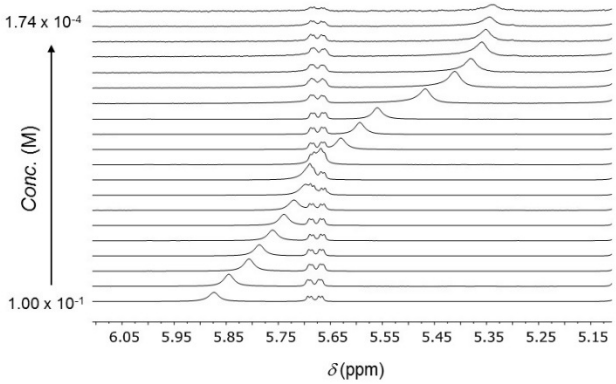


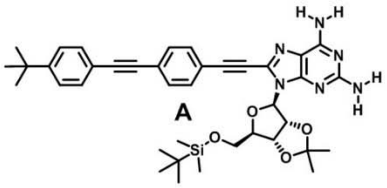
	Solvent	Concentration (M)
^{1}H NMR:	$CDCl_3$	$1.00 \times 10^{-1} – 1.74 \times 10^{-4}$

^{1}H-NMR: Binding Isotherm (Equilibria)



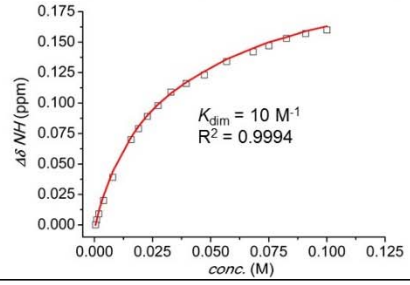
Concentration-dependent ^{1}H-NMR spectra



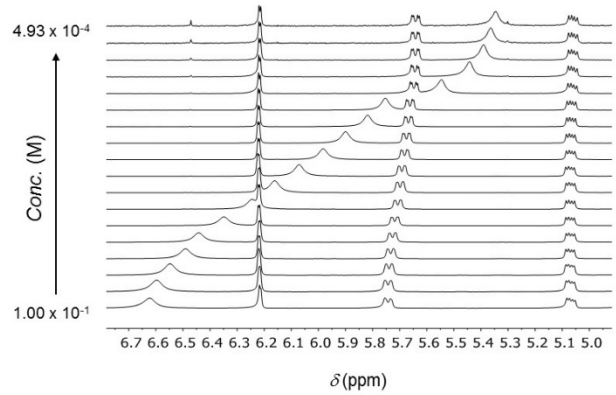


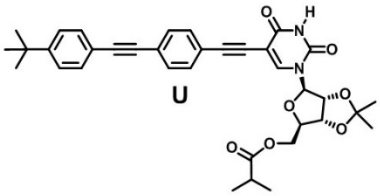
	Solvent	Concentration (M)
^{1}H NMR:	$CDCl_3$:CCl_4 (2:3)	$1.00 \times 10^{-1} – 4.93 \times 10^{-4}$

^{1}H-NMR: Binding Isotherm (Equilibria)



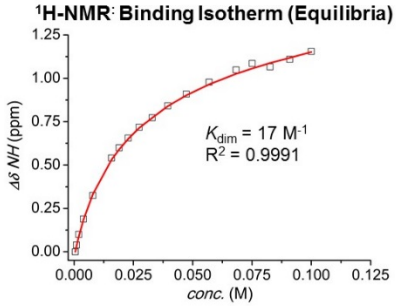
Concentration-dependent ^{1}H-NMR spectra



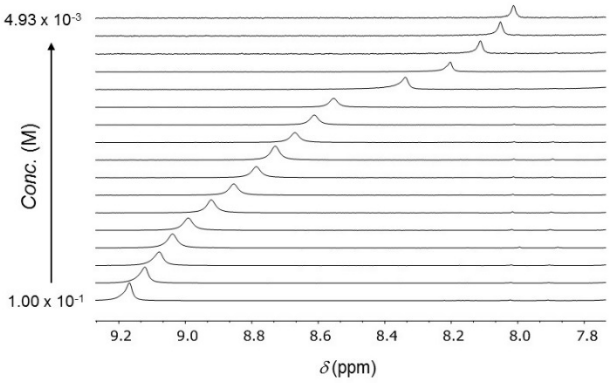


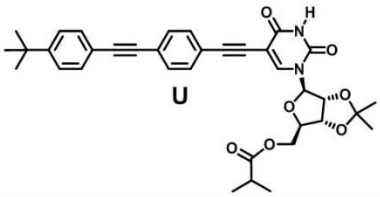
	Solvent	Concentration (M)
^{1}H NMR:	$CDCl_3$	$1.00 \times 10^{-1} – 4.93 \times 10^{-3}$

^{1}H-NMR: Binding Isotherm (Equilibria)



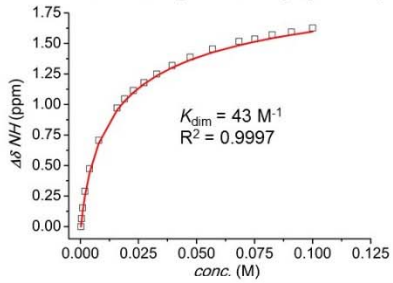
Concentration-dependent ^{1}H-NMR spectra



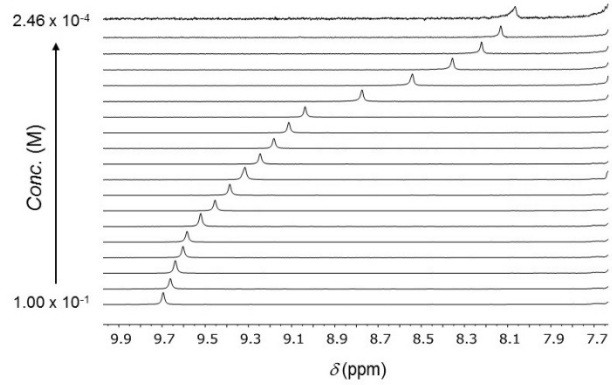


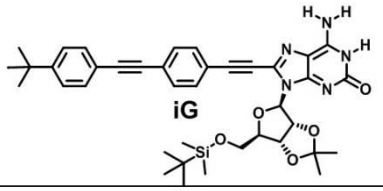
	Solvent	Concentration (M)
^{1}H NMR:	$CDCl_3$:CCl_4 (2:3)	$1.00 \times 10^{-1} – 2.46 \times 10^{-4}$

^{1}H-NMR: Binding Isotherm (Equilibria)



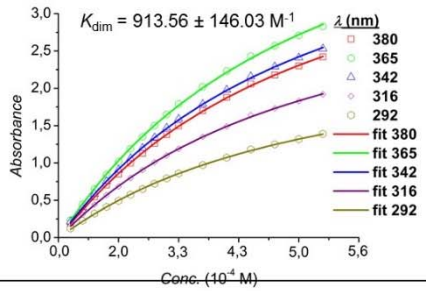
Concentration-dependent ^{1}H-NMR spectra



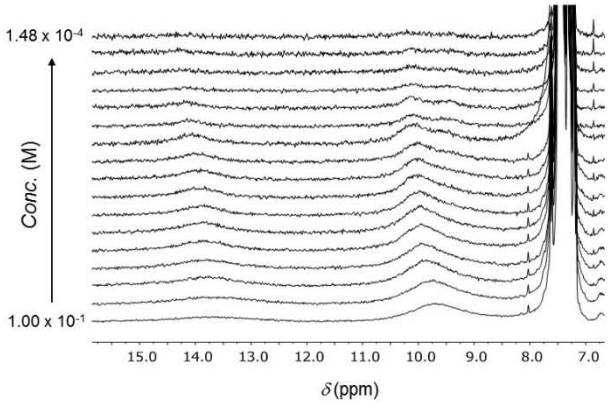


	Solvent	Concentration (M)
^{1}H NMR:	$CDCl_3$	$1.00 \times 10^{-1} – 1.48 \times 10^{-4}$
UV-vis:	$CHCl_3$	$5.24 \times 10^{-4} – 4.80 \times 10^{-5}$

UV-Vis: Binding Isotherms (Reactlab)



Concentration-dependent ^{1}H-NMR spectra



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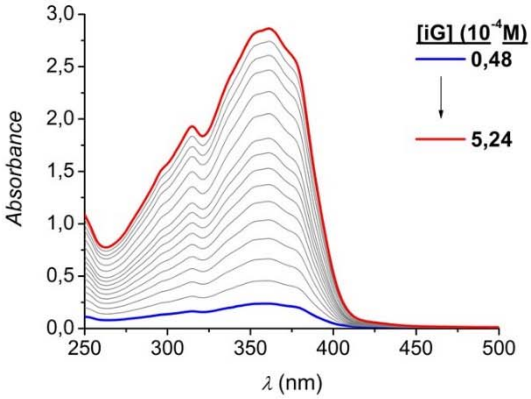
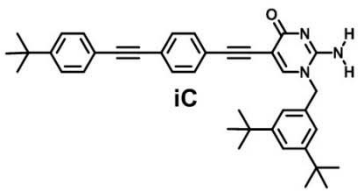
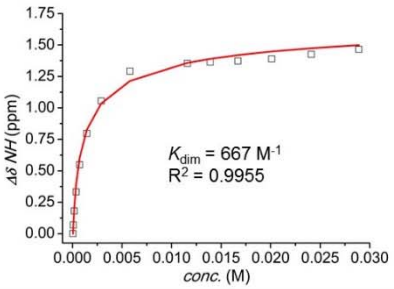


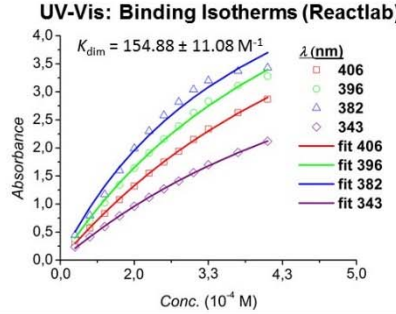


	Solvent	Concentration (M)
^{1}H NMR:	$CDCl_3$	$1.00 \times 10^{-1} – 7.47 \times 10^{-3}$
UV-vis:	$CHCl_3$	$7.50 \times 10^{-4} – 9.50 \times 10^{-5}$

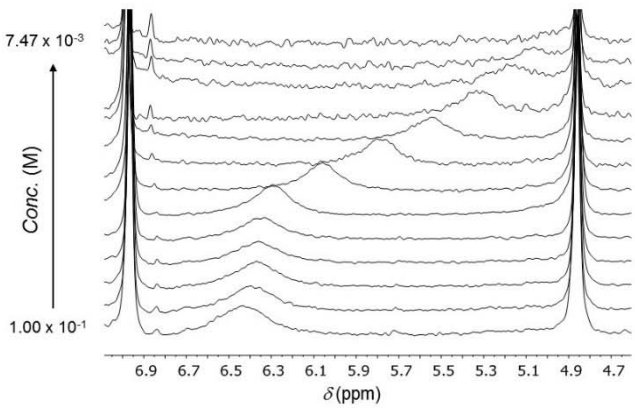
^{1}H-NMR: Binding Isotherm (Equilibria)



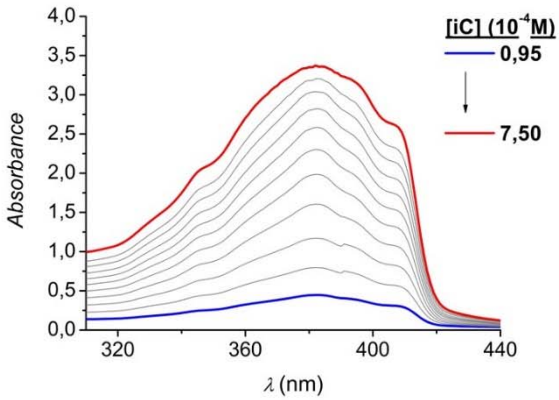
UV-Vis: Binding Isotherms (Reactlab)



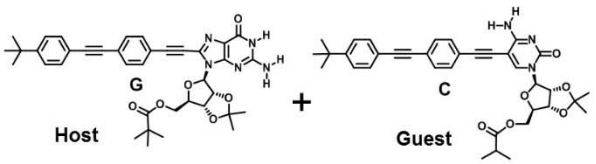
Concentration-dependent ^{1}H-NMR spectra



Concentration-dependent UV-Vis spectra

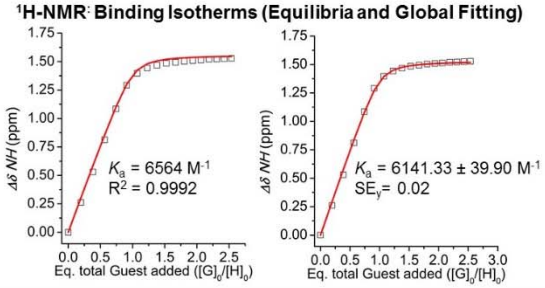


Nucleoside 1:1 H-bonding Binding Equilibria

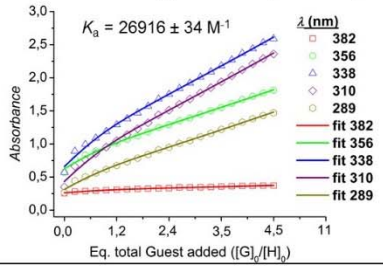


	Solvent	Concentration (M)
^{1}H NMR:	$CDCl_3$	**Host**: 1.00 x 10^{-2} M
		Guest: up to 2.52 x 10^{-2} M
UV-vis:	$CHCl_3$	**Host**: 1.00 x 10^{-5} M
		Guest: up to 4.60 x 10^{-5} M

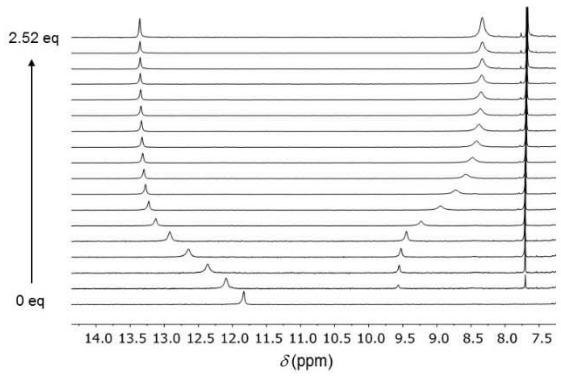
^{1}H-NMR: Binding Isotherms (Equilibria and Global Fitting)



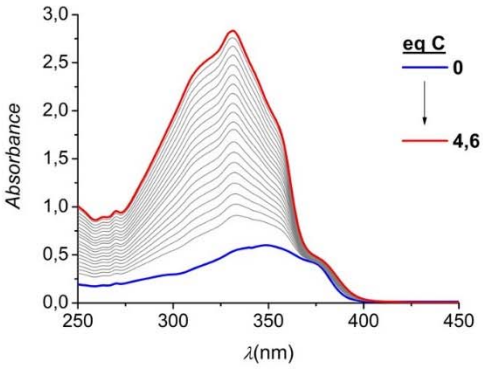
UV-Vis: Binding Isotherms (Reactlab)

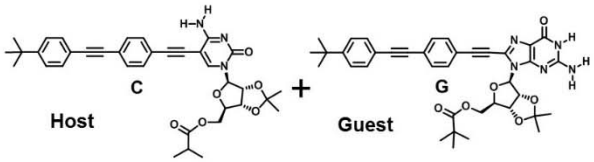


Titration ^{1}H-NMR spectra



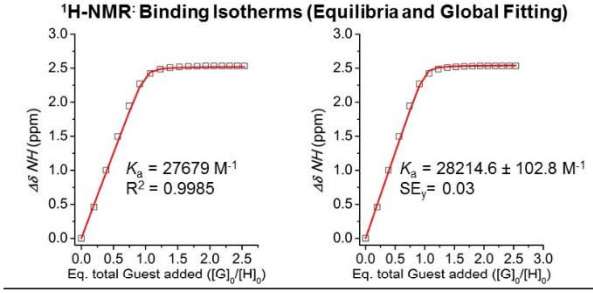
Concentration-dependent UV-Vis spectra



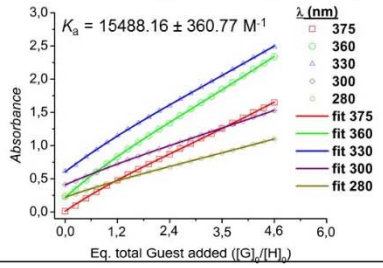


	Solvent	Concentration (M)
^{1}H NMR:	$CDCl_3$	**Host**: 1.00 x 10^{-2} M
		Guest: up to 2.54 x 10^{-2} M
UV-vis:	$CHCl_3$	**Host**: 1.00 x 10^{-5} M
		Guest: up to 4.50 x 10^{-5} M

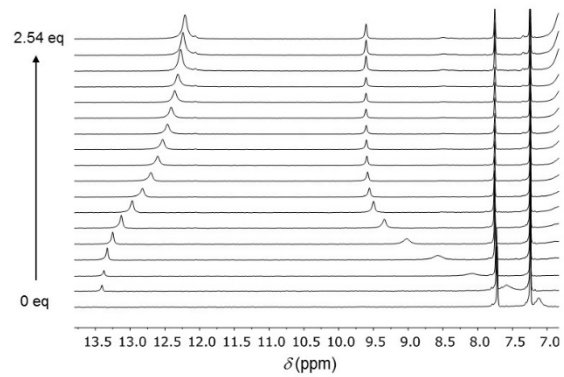
^{1}H-NMR: Binding Isotherms (Equilibria and Global Fitting)



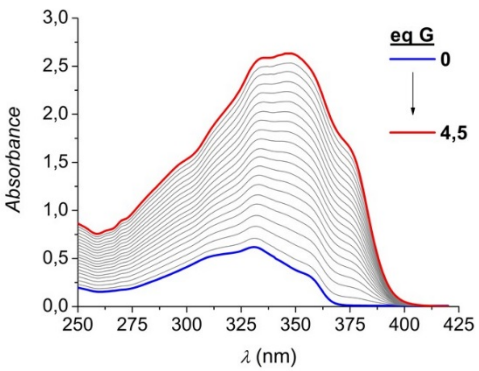
UV-Vis: Binding Isotherms (Reactlab)

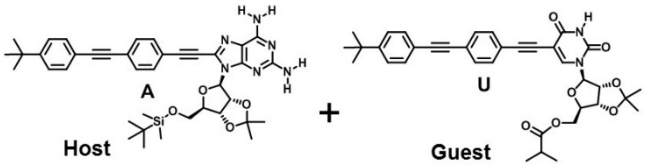


Titration ^{1}H-NMR spectra



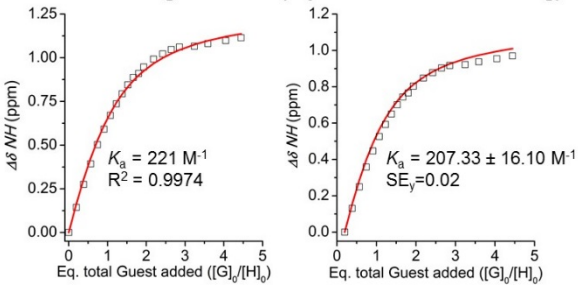
Concentration-dependent UV-Vis spectra



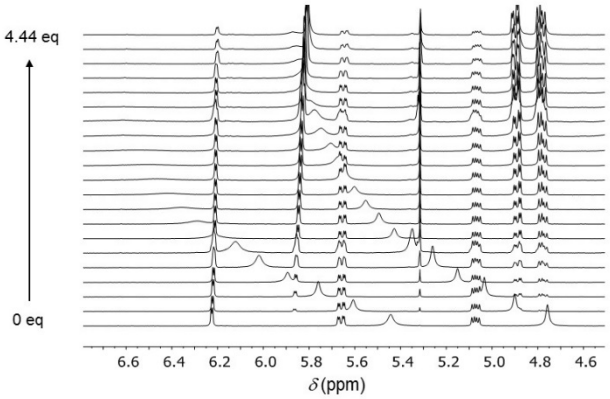


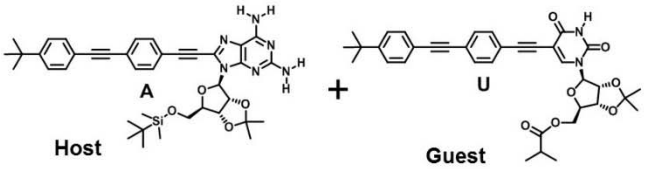
	Solvent	Concentration (M)
^{1}H NMR:	$CDCl_3$	**Host**: 1.00 x 10^{-2} M
		Guest: up to 4.44 x 10^{-2} M

^{1}H-NMR: Binding Isotherms (Equilibria and Global Fitting)



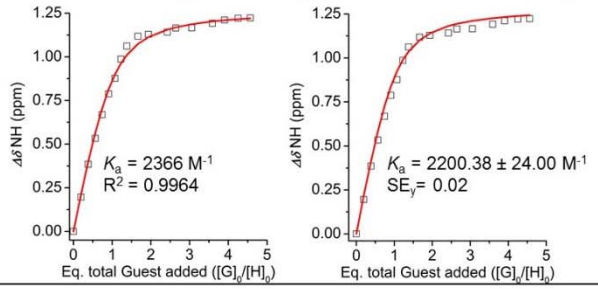
Titration ^{1}H-NMR spectra



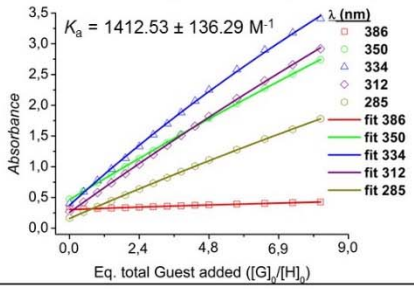


	Solvent	Concentration (M)
^{1}H NMR:	$CDCl_3$:CCl_4 (2:3)	**Host**: 1.00 x 10^{-2} M
		Guest: up to 4.52 x 10^{-2} M
UV-vis:	$CDCl_3$:CCl_4 (2:3)	**Host**: 1.00 x 10^{-5} M
		Guest: up to 8.30 x 10^{-5} M

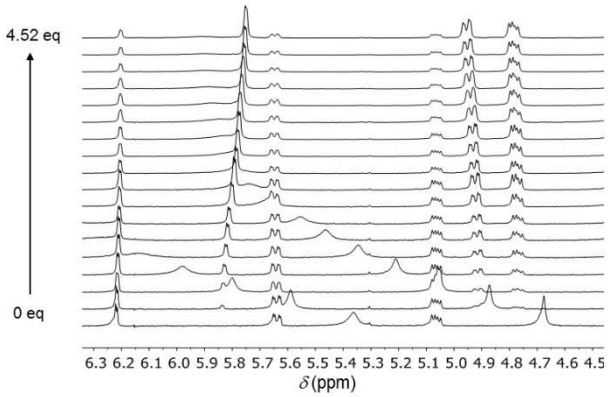
^{1}H-NMR: Binding Isotherms (Equilibria and Global Fitting)



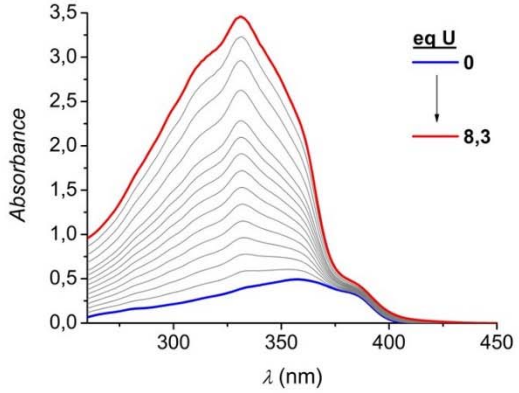
UV-Vis: Binding Isotherms (Reactlab)

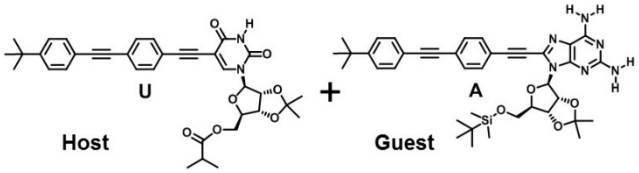


Titration ^{1}H-NMR spectra



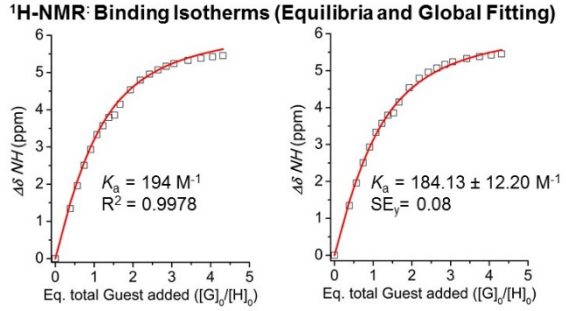
Concentration-dependent UV-Vis spectra



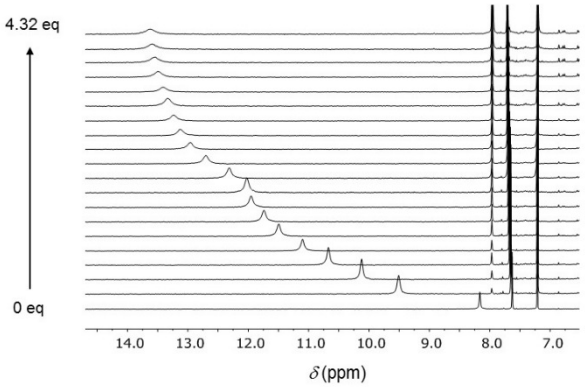


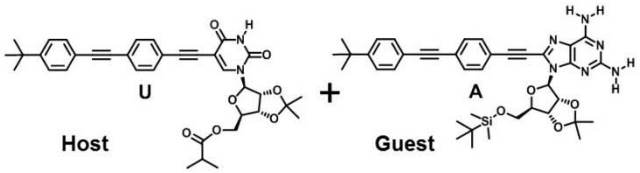
	Solvent	Concentration (M)
^{1}H NMR:	$CDCl_3$	**Host**: 1.00 x 10^{-2} M
		Guest: up to 4.32 x 10^{-2} M

^{1}H-NMR: Binding Isotherms (Equilibria and Global Fitting)



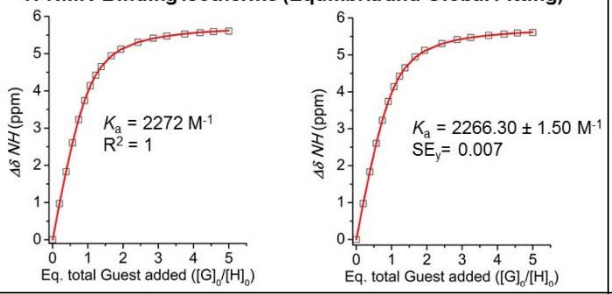
Titration ^{1}H-NMR spectra



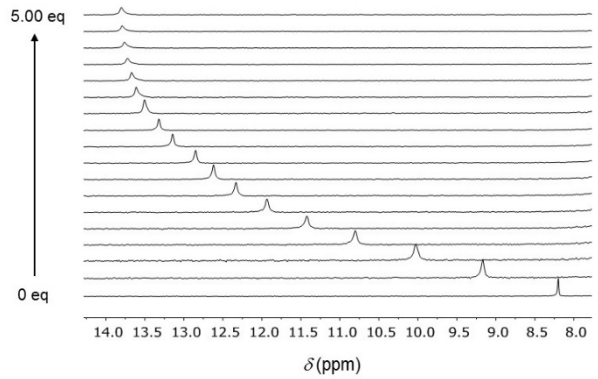


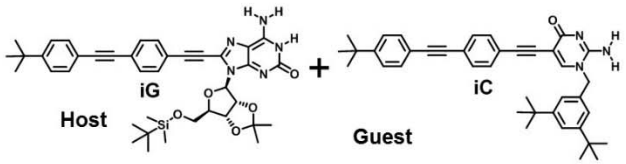
	Solvent	Concentration (M)
^{1}H NMR:	$CDCl_3$:CCl_4 (2:3)	**Host**: 1.00 x 10^{-2} M
		Guest: up to 5.00 x 10^{-2} M

^{1}H-NMR: Binding Isotherms (Equilibria and Global Fitting)



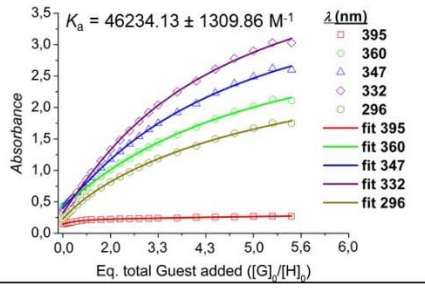
Titration ^{1}H-NMR spectra



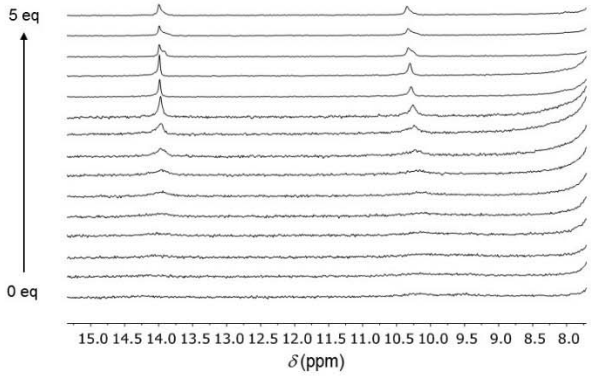


	Solvent	Concentration (M)
^{1}H NMR:	$CDCl_3$	**Host**: 3.00 x 10^{-3} M
		Guest: up to 1.50 x 10^{-2} M
UV-vis:	$CHCl_3$	**Host**: 1.00 x 10^{-5} M
		Guest: up to 5.45 x 10^{-5} M

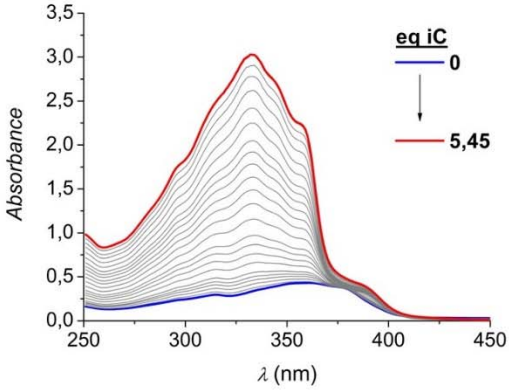
UV-Vis: Binding Isotherms (Reactlab)

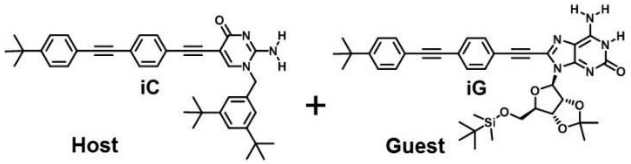


Titration ^{1}H-NMR spectra



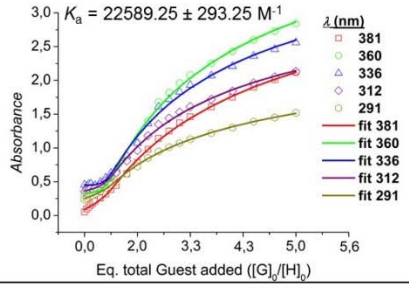
Concentration-dependent UV-Vis spectra



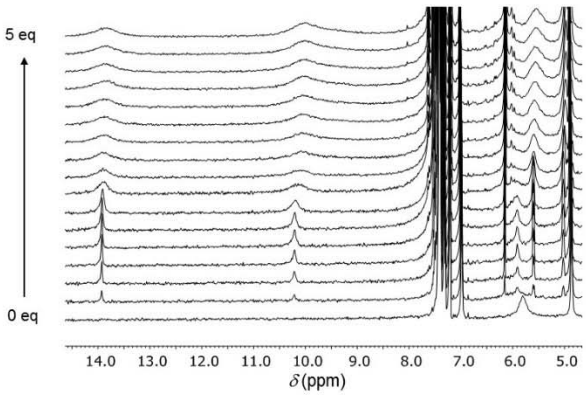


	Solvent	Concentration (M)
^{1}H NMR:	$CDCl_3$	**Host**: 3.00 x 10^{-3} M
		Guest: up to 1.50 x 10^{-2} M
UV-vis:	$CHCl_3$	**Host**: 1.00 x 10^{-4} M
		Guest: up to 5.00 x 10^{-4} M

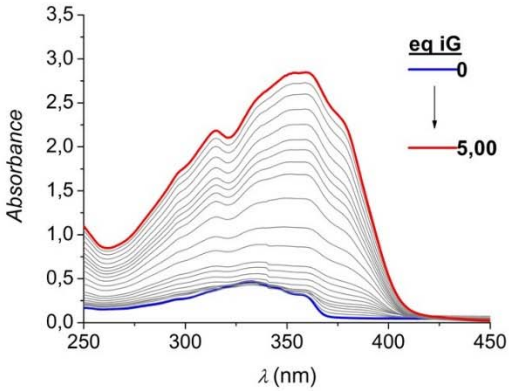
UV-Vis: Binding Isotherms (Reactlab)

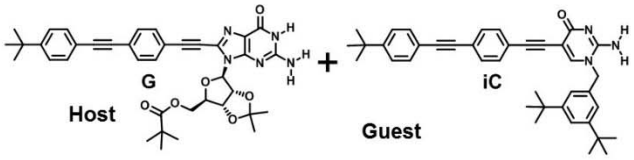


Titration ^{1}H-NMR spectra



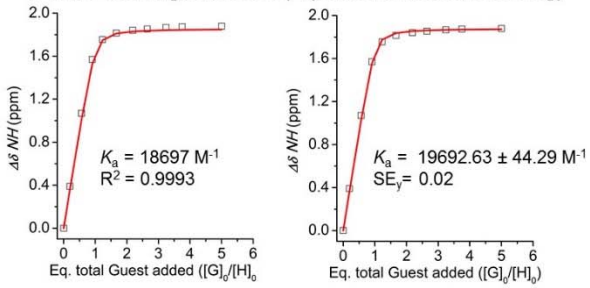
Concentration-dependent UV-Vis spectra



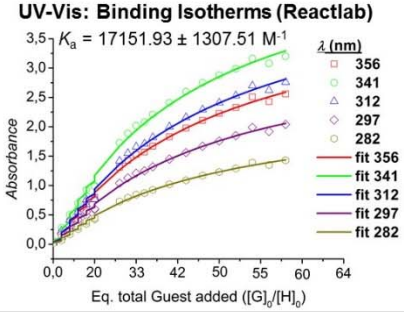


	Solvent	Concentration (M)
^{1}H NMR:	$CDCl_3$	**Host**: 3.00 x 10^{-3} M
		Guest: up to 1.50 x 10^{-2} M
UV-vis:	$CHCl_3$	**Host**: 1.00 x 10^{-5} M
		Guest: up to 5.80 x 10^{-4} M

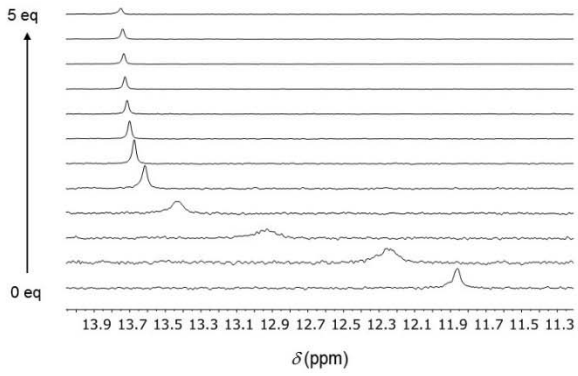
^{1}H-NMR: Binding Isotherms (Equilibria and Global Fitting)



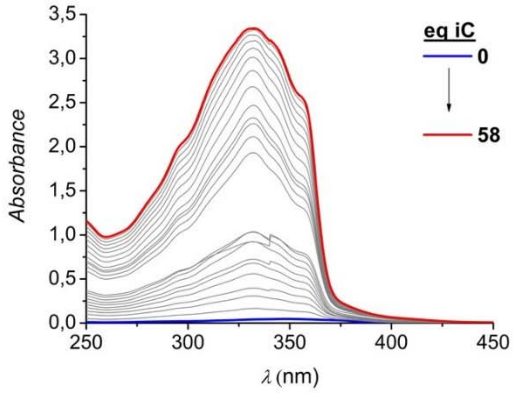
UV-Vis: Binding Isotherms (Reactlab)

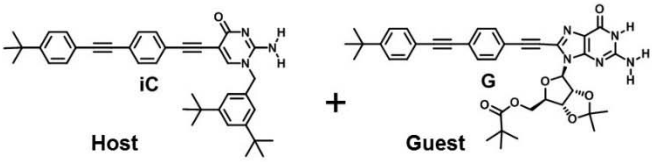


Titration ^{1}H-NMR spectra



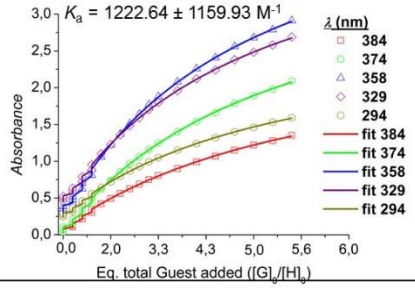
Concentration-dependent UV-Vis spectra



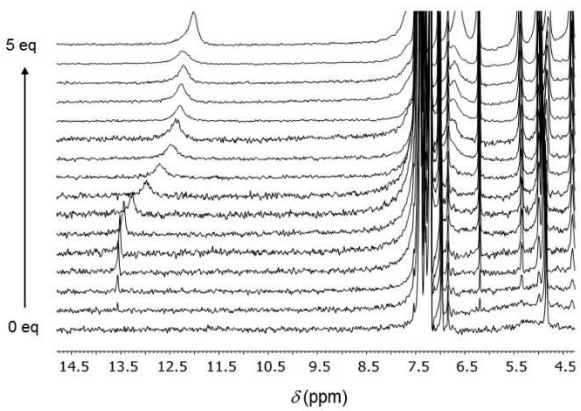


	Solvent	Concentration (M)
^{1}H NMR:	$CDCl_3$	**Host**: 1.00 x 10^{-3} M
		Guest: up to 5.00 x 10^{-3} M
UV-vis:	$CHCl_3$	**Host**: 1.00 x 10^{-4} M
		Guest: up to 5.45 x 10^{-4} M

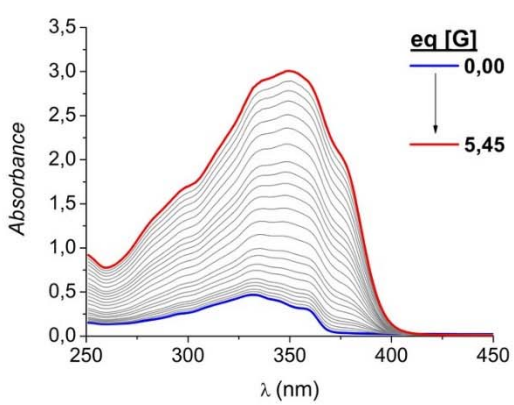
UV-Vis: Binding Isotherms (Reactlab)

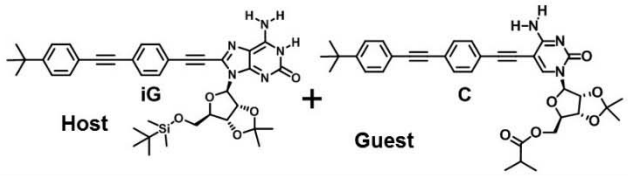


Titration ^{1}H-NMR spectra



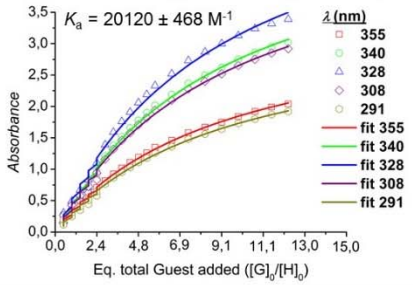
Concentration-dependent UV-Vis spectra



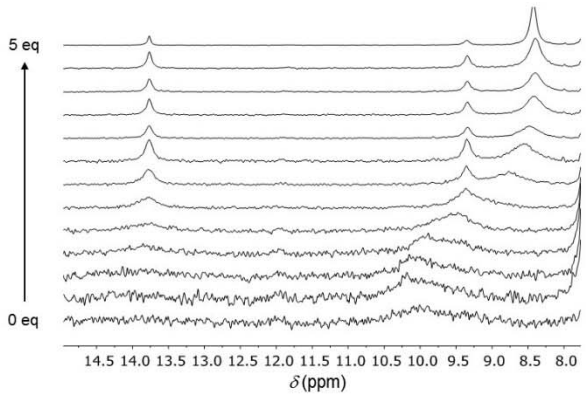


	Solvent	Concentration (M)
^{1}H NMR:	$CDCl_3$	**Host**: 3.00 x 10^{-3} M
		Guest: up to 1.50 x 10^{-2} M
UV-vis:	$CHCl_3$	**Host**: 1.00 x 10^{-5} M
		Guest: up to 1.20 x 10^{-4} M

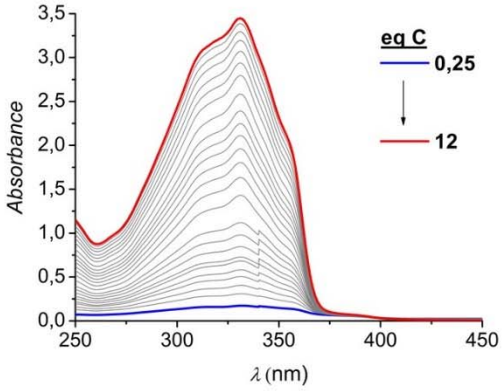
UV-Vis: Binding Isotherms (Reactlab)

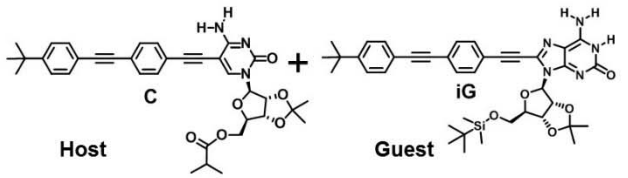


Titration ^{1}H-NMR spectra



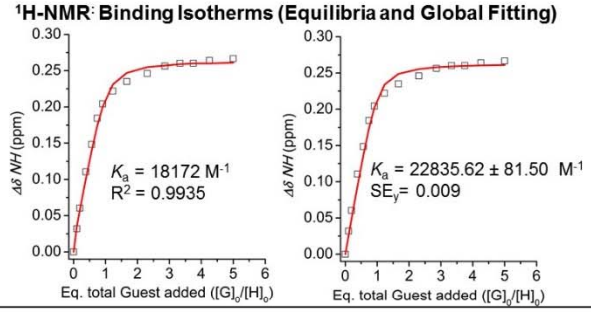
Concentration-dependent UV-Vis spectra



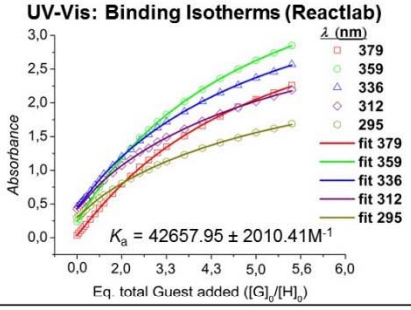


	Solvent	Concentration (M)
^{1}H NMR:	$CDCl_3$	**Host**: 1.00 x 10^{-3} M
		Guest: up to 5.00 x 10^{-3} M
UV-vis:	$CHCl_3$	**Host**: 1.00 x 10^{-4} M
		Guest: up to 5.45 x 10^{-4} M

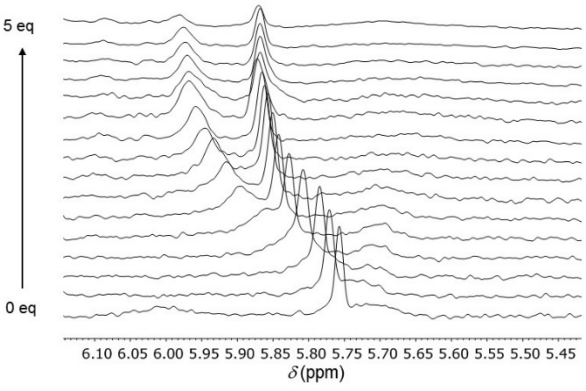
^{1}H-NMR: Binding Isotherms (Equilibria and Global Fitting)



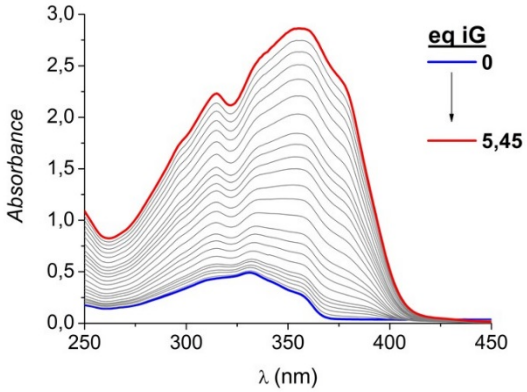
UV-Vis: Binding Isotherms (Reactlab)



Titration ^{1}H-NMR spectra



Concentration-dependent UV-Vis spectra



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