Supplementary Information

A Lewis acid-mediated conformational switch

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1. GENERAL INFORMATION

Reactions were carried out with stirring under a nitrogen or argon atmosphere in oven-dried glassware at room temperature unless otherwise stated. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents.

1.1 Solvent & reagents

Anhydrous tetrahydrofuran and dichloromethane (from commercial sources) were obtained by filtration through activated alumina (powder ~150 mesh, pore size 58 Å, basic, Sigma-Aldrich) columns, or were dried on an MB-SPS-800 dry solvent system. Other solvents and reagents were used directly as received from commercial suppliers. Petrol refers to distilled light petroleum of fraction (30 °C - 40 °C). Solutions of common salts were aqueous and saturated unless stated otherwise. Drying of organic layers was performed with anhydrous magnesium sulfate.

1.2 Chromatography

Flash column chromatography was carried out using VWR Kieselgel 60 silica gel (60-63 μm). Thin-layer chromatography was carried out using Merck Kieselgel 60 F254 (230-400 mesh) fluorescent treated silica, visualized under UV light (250 nm) and by staining with aqueous potassium permanganate solution.

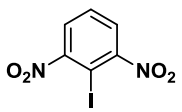
1.3 Spectroscopy

^{1}H and ^{13}C NMR spectra were recorded using a Bruker 700, 500, 400 or 300 MHz spectrometer running Topspin™ software and are quoted in ppm for measurement against a residual solvent peak as an internal standard. Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (*J*) are given in Hertz (Hz). The ^{1}H NMR spectra are reported as follows: δ / ppm (number of protons, multiplicity, coupling constant *J* / Hz (where appropriate),

assignment). Multiplicity is abbreviated as follows: s = singlet, br = broad, d = doublet, dd = doublet of doublets, t = triplet, dt = doublet of triplet, q = quartet, dq = doublet of quartet, qn = quintet, sept = septet, m = multiplet, v = very. Compound names are those generated by ChemBioDraw™ (CambridgeSoft) following IUPAC nomenclature. However, the NMR assignment numbering used is arbitrary and does not follow any particular convention. Numbering of compounds is illustrated on the spectra themselves; *vide infra*. The ^{13}C NMR spectra are reported in δ / ppm. Two-dimensional (COSY, HSQC, HMBC) NMR spectroscopy was used to assist the assignment of signals in the ^{1}H and ^{13}C NMR spectra. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer from a thin film deposited onto a diamond ATR module. Only selected maximum absorbances (ν_{max}) of the most intense peaks are reported (cm^{-1}). High-resolution mass spectra were recorded on a Bruker MicroTof mass spectrometer (ESI) by the internal service at the Department of Organic Chemistry, University of Oxford. Melting points were recorded using a Leica Galen III hot-stage microscope apparatus and are reported uncorrected in degrees Celsius (°C). For X-ray structural determinations, single crystals were mounted on a MiTeGen MicroMount using perfluoropolyether oil and cooled rapidly in a stream of cold nitrogen using an Oxford Cryosystems Cryostream unit. Crystallographic measurements were made using an Enraf-Nonius Kappa CCD diffractometer at 150(2) K using MoKα radiation. The structures were solved with SIR92, or SHELXS-97, and further refinements and all other crystallographic calculations were performed using either the CRYSTALS program suite or SHELXS-97. Other details of the structure solution and refinements are given in the CIF.

2. PROCEDURES

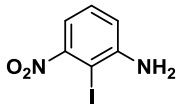
2-Iodo-1,3-dinitrobenzene (6)



Based on a literature procedure,[1] sodium nitrite (4.14 g, 60 mmol) was added portion-wise to sulfuric acid (conc., 45 mL), and the resulting suspension was warmed to 70 °C until the solids were completely dissolved. The solution was allowed to cool to below 40 °C, and 2,6-dinitroaniline (10 g, 55 mmol) in acetic acid (110 mL) was added dropwise at such a rate as to keep the temperature of the reaction mixture below 40 °C. The solution was stirred for a further

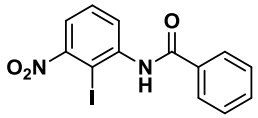
30 min, then poured into a stirred 70 °C solution of potassium iodide (9.97 g, 60 mmol) in water (100 mL). After 15 min the reaction mixture was poured into water (1 L), and the crude product was collected by filtration. The crude solid was taken up in dichloromethane (250 mL) and washed with sodium thiosulfate solution (2 x 100 mL). The organic layer was dried, filtered and concentrated *in vacuo* to give *the title compound* **6** (11.1 g, 69 %) as a pale brown solid. *The data obtained is consistent with that reported previously*;[1] δ_H ($CDCl_3$, 400 MHz) 7.84 (2H, d, *J* 8.3), 7.67 (1H, dd, *J* 8.6, 7.6); δ_C ($CDCl_3$, 100 MHz) 130.4, 126.9, 80.1.

2-Iodo-3-nitroaniline (7)



Based on a literature procedure,[2] iron powder (2.79 g, 50 mmol) was added cautiously in portions to a vigorously stirred 110 °C solution of nitro-compound **6** (5.0 g, 17.0 mmol) in glacial acetic acid (50 mL). After complete addition of the iron, the suspension was heated to reflux. After 30 min the reaction mixture was poured directly into cold water (500 mL). The aqueous layer was extracted with dichloromethane (3 x 250 mL), and the combined organic layers dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 2:1) and subsequent trituration with diethyl ether to give *the title compound* **7** (2.42 g, 54 %) as a golden yellow solid. *The data obtained is consistent with that reported previously*;[2] δ_H ($CDCl_3$, 400 MHz) 7.21 (1H, t, *J* 8.0), 7.06 (1H, dd, *J* 7.9, 1.3), 6.89 (1H, dd, *J* 8.1, 1.3), 4.57 (2H, s); δ_C ($CDCl_3$, 101 MHz) 149.3, 129.6, 117.2, 114.4;. HRMS (ESI): found 264.94674; $C_6H_6IN_2O_2$ $[M+H]^+$ requires 264.94685.

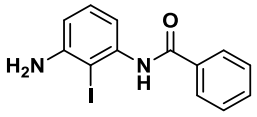
***N*-(2-Iodo-3-nitrophenyl)benzamide (8)**



Based on a literature procedure,[2] 4-dimethylaminopyridine (0.5 mg) was added to a solution of aniline **7** (1.5 g, 5.7 mmol) and pyridine (0.51 mL, 6.2 mmol) in dichloromethane (50 mL). Benzoyl chloride (0.71 mL, 6.3 mmol) was added dropwise to this solution. After 3 h the reaction mixture was diluted with dichloromethane (150 mL), washed with hydrochloric acid (2 M aq., 50 mL), and the combined organic extracts were dried, filtered and concentrated *in*

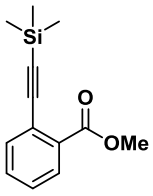
vacuo. The residue was triturated with diethyl ether to give *the title compound* **8** (1.36 g, 65 %). The remaining residue was purified by flash column chromatography (petrol:ethyl acetate, 7:3) to give *the title compound* **8** (0.49 g, 24 %; total mass 1.85 g, 89 %) as a yellow amorphous solid; δ_H ($CDCl_3$, 400 MHz) 8.71 (1H, m), 8.65 (1H, s), 8.00 (2H, d, *J* 7.9), 7.64 (1H, t, *J* 6.9), 7.63-7.50 (4H, m); δ_C ($CDCl_3$, 101 MHz) 165.7, 154.6, 140.7, 134.0, 132.9, 130.1, 129.3, 127.4, 124.8, 120.7, 83.3; HRMS (ESI): found 368.97263; $C_{13}H_{10}IN_2O_3$ $[M+H]^+$ requires 368.97306.

_N_-(3-Amino-2-iodophenyl)benzamide (9)



Based on a literature procedure,[2] tin(II) chloride dihydrate (1.91 g, 8.5 mmol) was added to a stirred solution of nitro-aromatic **8** (522 mg, 1.42 mmol) in ethyl acetate (15 mL). After 5 h the reaction mixture was diluted with ethyl acetate (50 mL) and sodium bicarbonate was added dropwise until a viscous aqueous layer formed, and the supernatant organic solution was decanted off and filtered over Celite®. The aqueous layer was washed with ethyl acetate (2 x 50 mL) and the organic layers were filtered over Celite®. The combined organic layers were washed with sodium bicarbonate (50 mL), dried, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 2:1) to give *the title compound* **9** (324 mg, 68 %) as a white solid; δ_H ($CDCl_3$, 500 MHz) 8.29 (1H, s), 7.98 (2H, d, *J* 7.4), 7.79 (1H, d, *J* 7.8), 7.58 (1H, t, *J* 7.2), 7.53 (2H, t, *J* 7.4), 7.18 (1H, t, *J* 8.0), 6.59 (1H, d, *J* 7.8), 4.21 (2H, s); δ_C ($CDCl_3$, 126 MHz) 165.4, 147.6, 138.8, 134.9, 132.2, 129.7, 129.0, 127.3, 112.1, 111.3, 81.4; HRMS (ESI): found 338.99796; $C_{13}H_{12}IN_2O$ $[M+H]^+$ requires 338.99888.

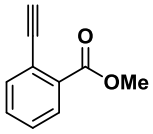
Methyl 2-((trimethylsilyl)ethynyl)benzoate (10)



Based on a literature procedure,[2] a solution of 2-iodomethylbenzoate (2.52 mL, 17 mmol) and ethynyltrimethylsilane (5.0 mL, 35 mmol) in triethylamine (150 mL) was degassed by sparging with nitrogen for 10 min. Palladium(II) chloride bis(triphenylphosphine) (440 mg, 0.62 mmol) and copper(I) iodide (350 mg, 1.8 mmol) were added, and the reaction mixture was heated to

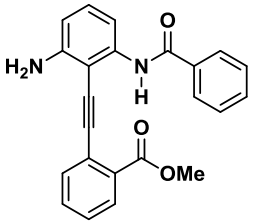
60 °C. After 16 h the reaction mixture was cooled to room temperature, filtered over Celite®, concentrated *in vacuo* and purified by flash column chromatography (petrol:diethyl ether, 5:1) to give *the title compound* **10** (3.23 g, 82%) as a colourless viscous oil; δ_H ($CDCl_3$, 400 MHz) 7.90 (1H, dd, *J* 7.8, 1.3), 7.58 (1H, dd, *J* 7.8, 1.3), 7.44 (1H, td, *J* 1.4, 7.6), 7.36 (1H, td, *J* 1.3, 7.7), 3.92 (3H, s), 0.28 (9H, s); δ_C ($CDCl_3$, 101 MHz) 167.0, 134.6, 132.6, 131.6, 130.4, 128.3, 123.3, 103.4, 99.8, 52.1, 0.0; HRMS (ESI): found 255.08064; $C_{13}H_{16}NaO_2Si$ $[M+Na]^+$ requires 255.08118.

Methyl 2-ethynylbenzoate (11)



Based on a literature procedure,[2] potassium carbonate (1.43 g, 10.3 mmol) was added to a solution of silylalkyne **10** (2.40 g, 10.3 mmol) in methanol (60 mL). After 15 min water (100 mL) was added and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo* to give *the title compound* **11** (1.41 g, 86 %) as a colourless oil which developed a brown colour on standing; δ_H ($CDCl_3$, 500 MHz) 7.94 (1H, dd, *J* 7.8, 1.2), 7.63 (1H, dd, *J* 7.7, 1.1), 7.48 (1H, td, *J* 1.4, 7.6), 7.40 (1H, td, *J* 7.7, 1.3), 3.93 (3H, s), 3.40 (1H, s); δ_C ($CDCl_3$, 126 MHz): 166.5, 135.1, 132.6, 131.8, 130.4, 128.6, 122.7, 82.4, 82.1, 52.3; HRMS (ESI): found 183.04150; $C_{10}H_8NaO_2$ $[M+Na]^+$ requires 183.04165.

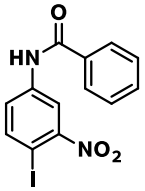
Methyl 2-((2-amino-6-benzamidophenyl)ethynyl)benzoate (2)



Based on a literature procedure,[2] a solution of acetylene **11** (78 mg, 0.49 mmol) and iodoaniline **9** (150 mg, 0.44 mmol) in 1:1 dimethylformamide:triethylamine (v/v, 10 mL) was degassed by sparging with nitrogen for 10 min. Copper(I) iodide (8.4 mg, 0.044 mmol) and palladium(II) chloride bis(triphenylphosphine) (19 mg, 0.027 mmol) were added, and the solution was warmed to 60 °C. After 2 h the solution was cooled to room temperature, filtered over Celite® and concentrated *in vacuo*. The residue was purified by flash column chromatography (dichloromethane:methanol, 97:3) to give *the title compound* **2** (130 mg, 80%) as a canary yellow

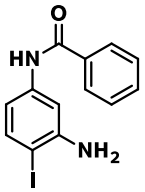
solid. *The data obtained is consistent with that reported previously*;[2] δ_H ($CDCl_3$, 500 MHz) 9.09 (1H, s), 8.06 (1H, dd, *J* 7.7, 1.1), 8.01-7.94 (3H, m), 7.62-7.46 (5H, m), 7.40 (1H, t, *J* 7.6), 7.21 (1H, td, *J* 8.1, 1.7), 6.52 (1H, d, *J* 8.2, 0.9), 4.84 (2H, s), 3.73 (3H, s); δ_C ($CDCl_3$, 126 MHz) 166.0, 165.9, 149.7, 140.1, 135.8, 133.1, 132.4, 131.8 , 131.2, 131.0, 130.1, 128.7, 128.1, 127.6, 124.1, 109.8, 108.8, 101.4, 97.6, 87.8, 52.4; HRMS (ESI): found 371.13874; $C_{23}H_{19}N_2O_3$ $[M+H]^+$ requires 371.13902.

_N_-(4-Iodo-3-nitrophenyl)benzamide (12)



Benzoyl chloride (0.54 mL, 4.7 mmol) was added dropwise over 5 min to a solution of 4-iodo-3-nitroaniline (500 mg, 1.89 mmol), pyridine (0.17 mL, 2.1 mmol) and 4-dimethylaminopyridine (0.2 mg) in dichloromethane (15 mL). After 15 min the reaction mixture was diluted with dichloromethane (25 mL) and sodium bicarbonate (20 mL) was added. The biphasic mixture was stirred for 30 min, after which the layers were separated, and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic layers were washed with hydrochloric acid (1 M, 10 mL), dried, filtered and concentrated *in vacuo*. The residue was purified by trituration (dichloromethane) to give *the title compound* **12** (596 mg, 86 %) as a canary-yellow solid; δ_H (400 MHz, $(CD_3)_2SO$) 10.73 (1H, s), 8.53 (1H, d, *J* 2.4), 8.10 (1H, d, *J* 8.6), 8.01-7.96 (2H, m), 7.83 (1H, dd, *J* 8.7, 2.5), 7.68-7.62 (1H, m), 7.60-7.54 (2H, m); δ_C (101 MHz, $(CD_3)_2SO$) 166.5, 153.4, 141.8, 140.7 134.5, 132.6, 129.0, 128.3, 125.5, 116.6, 80.5.; HRMS (ESI): found 390.9545; $C_{13}H_9IN_2NaO_3$ $[M+Na]^+$ requires 390.9550; ν_{max} (neat) 3406, 3141, 3071, 2161, 1524, 1307, 705.

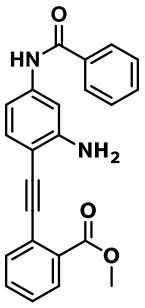
_N_-(3-Amino-4-iodophenyl)benzamide (13)



Tin(II) chloride dihydrate (1.84 g, 8.2 mmol) was added in one portion to a solution of nitro-aromatic **12** (500 mg, 1.36 mmol) in ethyl acetate (15 mL). After 16 h the reaction mixture was

diluted with ethyl acetate (25 mL) and sodium bicarbonate (10 mL) was added dropwise until a viscous white aqueous slurry had formed. The supernatant ethyl acetate was decanted, and passed over a plug of Celite®. The aqueous slurry was washed with ethyl acetate (3 x 10 mL) and the washings passed over Celite®. The organic washings were combined and washed with sodium bicarbonate (25 mL), dried, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (dichloromethane:methanol, 100:1) to give *the title compound* **13** (291 mg, 63 %) as a white powder; δ_H ($CDCl_3$, 400 MHz)* 9.10 (1H, s), 7.83 (1H, d, *J* 7.2), 7.4-7.42 (2H, m), 7.41-7.34 (3H, m), 6.71 (1H, d, *J* 8.3); δ_C ($CDCl_3$, 101 MHz)* 166.3, 147.4, 140.0, 138.6, 135.2, 131.6, 128.4, 127.5, 112.2, 106.5, 77.3; ν_{max} (neat): 3463, 3368, 2160, 1664, 1578, 1423, 1252, 1005, 762, 690; HRMS (ESI): found 360.9808; $C_{13}H_{11}IN_2NaO$ $[M+Na]^+$ requires 360.9808.

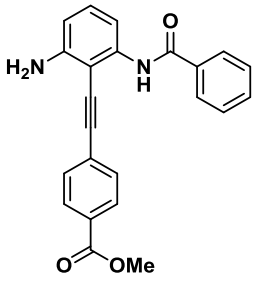
Methyl 2-((2-amino-4-benzamidophenyl)ethynyl)benzoate (14)



A stirred solution of iodoaniline **13** (150 mg, 0.44 mmol) and acetylene **11** (78 mg, 0.49 mmol) in triethylamine:*N*,*N*-dimethylformamide (1:1 v/v, 10 mL) was degassed by sparging with nitrogen for 10 min. Bis(triphenylphosphine)palladium(II) dichloride (19 mg, 0.027 mmol) and copper(I) iodide (8.4 mg, 0.044 mmol) were added, and the mixture was warmed to 60 °C. After 4 h the reaction mixture was allowed to cool and diluted with diethyl ether (50 mL). The organic layer was washed with hydrochloric acid (1 M aq., 3 x 25 mL), and the organic layer was dried, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1→3:2) to give *the title compound* **14** (144 mg, 88 %) as a yellow solid; δ_H ($CDCl_3$, 400 MHz) 8.03 (1H, dd, *J* 8.0, 1.0), 7.88-7.84 (2H, m), 7.76 (1H, s), 7.65 (1H, dd, *J* 7.8, 0.9), 7.58-7.46 (4H, m), 7.43 (1H, d, *J* 2.0), 7.38-7.31 (2H, m), 6.71 (1H, dd, *J* 8.3, 2.0), 5.17 (2H, s), 3.94 (3H, s); δ_C ($CDCl_3$, 101 MHz) 166.3, 165.6, 150.5, 139.7, 135.0, 133.5, 132.7, 132.0, 131.9, 130.6, 129.9, 128.8, 127.2, 127.0, 124.8, 108.8, 104.9, 103.5, 93.6, 92.5, 52.3; ν_{max} (neat): 3467, 3366, 3298, 2193, 1722, 1583, 1435, 1247, 1070, 694; HRMS (ESI): found 393.1210; $C_{23}H_{18}N_2NaO_3$ $[M+Na]^+$ requires 393.1210.

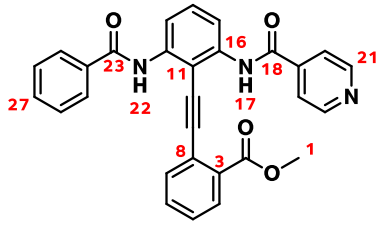
* *A few drops of d6-DMSO were added to aid dissolution.*

Methyl 4-((2-amino-6-benzamidophenyl)ethynyl)benzoate (15)



Based on a literature procedure,[2] a solution of methyl 4-ethynylbenzoate (78 mg, 0.49 mmol) and iodoaniline **9** (150 mg, 0.44 mmol) in *N*,*N*-dimethylformamide:triethylamine (1:1 v/v, 10 mL) was degassed by sparging with nitrogen for 10 min. Copper(I) iodide (8.4 mg, 0.044 mmol) and palladium(II) chloride bis(triphenylphosphine) (19 mg, 0.027 mmol) were added, and the solution was warmed to 60 °C. After 2 h the solution was cooled to room temperature, filtered over Celite® and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1) to give *the title compound* **15** (130 mg, 83 %) as a canary yellow solid. *The data obtained is consistent with that reported previously*;[2] δ_H ($CDCl_3$, 500 MHz) 8.75 (1H, s), 8.03 (2H, d, *J* 7.6), 7.96 (1H, d, *J* 8.2), 7.93 (2H, d, *J* 8.3), 7.59-7.53 (3H, m), 7.48 (2H, t, *J* 7.6), 7.18 (1H, t, *J* 8.2), 6.50 (1H, d, *J* 8.2), 4.39 (2H, s), 3.93 (3H, d, *J* 1.0); δ_C ($CDCl_3$, 126 MHz) 166.3, 165.1, 148.5, 139.6, 135.1, 132.1, 131.1, 131.0, 129.9, 129.8, 129.0, 127.0(2), 126.9(8), 110.1, 109.0, 101.6, 97.2, 84.6, 52.4; HRMS (ESI): found 371.13841; $C_{23}H_{19}N_2O_3$ $[M+H]^+$ requires 371.13902.

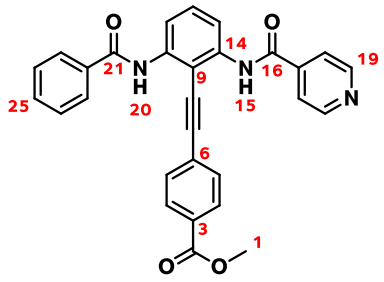
Methyl 2-((2-benzamido-6-(isonicotinamido)phenyl)ethynyl)benzoate (1)



Thionyl chloride (139 µL, 1.6 mmol) was added to a solution of isonicotinic acid (100 mg, 0.81 mmol) in dichloromethane (3 mL). A drop of dimethylformamide was added, causing the reaction mixture to bubble vigorously for several minutes. After gas evolution had ceased (*ca.* 10 min) the reaction mixture was concentrated under a stream of nitrogen gas. The solid residue was taken up as a suspension in dichloromethane (2 mL) and pyridine (130 µL, 1.6 mmol) was added. The supernatant solution was removed *via* syringe and added to a stirred suspension of **2**

(100 mg) and 4-dimethylaminopyridine (0.5 mg) in dichloromethane (2 mL). All solids were observed to dissolve immediately upon addition of the acid chloride solution. After 30 min the reaction mixture was diluted (dichloromethane, 25 mL) and water (10 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with brine, dried, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1 petrol:ethyl acetate) to give *the title compound* **1** (83 mg, 65 %) as a white powder. X-ray diffraction quality crystals were grown by vapour diffusion (chloroform/hexane); δ_H ($CDCl_3$, 500 MHz) 9.41 (1H, br s, H17), 9.07 (1H, br s, H22), 8.78 (2H, d, *J* 6.0, H21), 8.41 (1H, d, *J* 8.8, H13/H15), 8.35 (1H, d, *J* 8.2, H13/H15), 8.09 (1H, d, *J* 7.9, H4), 7.99 (2H, d, *J* 7.3, H25), 7.83–7.80 (2H, m, H20), 7.60–7.57 (3H, m, H6, H7 & H27), 7.54–7.45 (4H, m, H5, H14 & H26), 3.44 (3H, s, H1); δ_C ($CDCl_3$, 126 MHz) 165.8 (C23), 165.3 (C2), 164.9 (C18), 150.4 (C21), 142.6 (C19), 140.0 (C12/C16), 139.7 (C12/C16), 135.1 (C24), 132.9 (C6/C7), 132.6 (C6/C7), 132.0 (C27), 131.2 (C5), 131.1 (C4), 130.2 (C3), 129.0 (C5), 128.7 (C26), 127.4 (C25), 122.9 (C8), 121.8 (C20), 115.5 (C13 & C15)* 103.1 (C9), 102.5 (C11), 85.6 (C10), 52.1 (C1); ν_{max} (neat): 3398, 2952, 1719, 1684, 1583, 1487, 1469, 1304, 695; HRMS (ESI): found 498.1417; $C_{29}H_{21}N_3NaO_4$ $[M+Na]^+$ requires 498.1424; MP: 197-199 °C (chloroform/hexane).

Methyl 4-((2-benzamido-6-(isonicotinamido)phenyl)ethynyl)benzoate (3)

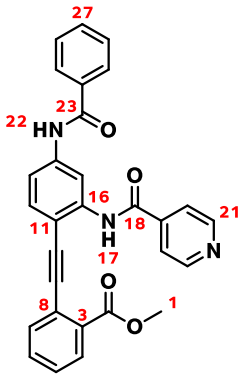


Thionyl chloride (139 μL, 1.6 mmol) was added to a solution of isonicotinic acid (100 mg, 0.81 mmol) in dichloromethane (3 mL). A drop of dimethylformamide was added, causing the reaction mixture to bubble vigorously for several minutes. After gas evolution had ceased (*ca.* 10 min) the reaction mixture was concentrated under a stream of nitrogen gas. The solid residue was taken up as a suspension in dichloromethane (2 mL) and pyridine (130 μL, 1.6 mmol) was added. The supernatant solution was removed *via* syringe and added to a stirred suspension of **15** (100 mg) and 4-dimethylaminopyridine (0.5 mg) in dichloromethane (2 mL). All solids were

* *Signals overlapping.*

observed to dissolve immediately upon addition of the acid chloride solution. After 30 min the reaction mixture was diluted (dichloromethane, 25 mL) and water (10 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with brine, dried, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (3:1 dichloromethane:ethyl acetate) to give *the title compound* **3** (41 mg, 32 %) as a cream coloured powder; δ_H ($CDCl_3$, 500 MHz) 8.84 (2H, dd, *J* 4.4, 1.6, H19), 8.71 (1H, s, H20), 8.69 (1H, s, H15), 8.41 (1H, d, *J* 8.5, H11), 8.30 (1H, d, *J* 8.2, H13), 8.11 (2H, dt, *J* 8.2, 1.7, H4), 7.96–7.92 (2H, m, H23), 7.77 (2H, dd, *J* 4.4, 1.6, H18), 7.62–7.56 (3H, m, H5 & H25), 7.54–7.49 (3H, m, H12 & H24), 3.97 (3H, s, H1); δ_C ($CDCl_3$, 126 MHz) 166.0 (C2), 165.1 (C21), 163.1 (C16), 151.0 (C19), 141.7 (C17), 139.6 (C10), 138.5 (C14), 134.6 (C22), 132.4 (C25), 131.5 (C12), 131.1 (C5 & C6)* 130.1 (C4), 129.0 (C24), 126.9 (C23), 125.5 (C3), 120.6 (C18), 115.8 (C11), 115.3 (C13), 103.6 (C7), 102.0 (C9), 82.5 (C8), 52.5 (C1); ν_{max} (neat): 3407, 3299, 3960, 2924, 1726, 1657, 1581, 1521, 1277, 696; HRMS (ESI): found 498.1416; $C_{29}H_{21}N_3NaO_4$ $[M+Na]^+$ requires 498.1424.

Methyl 2-((4-benzamido-2-(isonicotinamido)phenyl)ethynyl)benzoate (4)

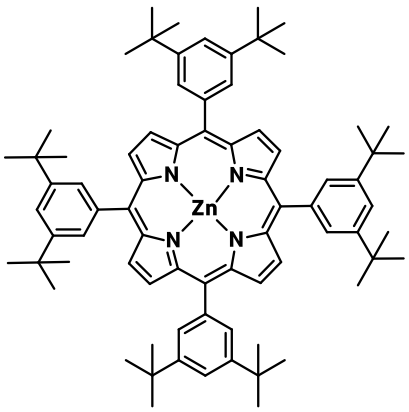


Thionyl chloride (139 μL, 1.6 mmol) was added to a solution of isonicotinic acid (100 mg, 0.81 mmol) in dichloromethane (3 mL). A drop of dimethylformamide was added, causing the reaction mixture to bubble vigorously for several minutes. After gas evolution had ceased (*ca.* 10 min) the reaction mixture was concentrated under a stream of nitrogen gas. The solid residue was taken up as a suspension in dichloromethane (2 mL) and pyridine (130 μL, 1.6 mmol) was added. The supernatant solution was removed *via* syringe and added to a stirred suspension of **14** (100 mg) and DMAP (0.5 mg) in dichloromethane (2 mL). All solids were observed to dissolve immediately upon addition of the acid chloride solution. After 30 min the reaction mixture was

* *Signals overlapping.*

diluted (dichloromethane, 25 mL) and water (10 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with brine, dried, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (3:1→2:1 dichloromethane:ethyl acetate) to give *the title compound* **4** (64 mg, 50 %) as a cream coloured powder; δ_H ($CDCl_3$, 500 MHz) 9.76 (1H, s, H17), 8.72 (2H, dd, *J* 4.6, 1.4, H21), 8.58 (1H, d, *J* 1.9, H15), 8.16 (1H, s, H22), 8.10 (1H, dd, *J* 8.5, 2.2, H13), 8.03 (1H, dd, *J* 7.9, 0.8, H4), 7.91–7.87 (2H, m, H25), 7.76 (2H, dd, *J* 4.4, 1.6, H20), 7.69 (1H, dd, *J* 7.9, 0.9, H7), 7.62 (1H, d, *J* 8.5, H12), 7.59-7.53 (2H, m, H6 & H27), 7.52–7.47 (2H, m, H26), 7.41 (1H, td, *J* 7.6, 1.2, H5)., 3.40 (3H, s, H1); δ_C ($CDCl_3$, 126 MHz) 165.9 (C18), 165.8 (C23), 165.6 (C2), 150.1 (C21), 142.7 (C19), 140.4 (C16), 139.6 (C14), 134.6 (C12), 133.7 (C7), 133.3 (C12), 132.5 (C6), 132.1 (C27), 130.74 (C4), 129.8 (C3), 128.8 (C26), 128.2 (C5), 127.1 (C25), 123.9 (C8), 122.1 (C20), 115.8 (C13), 110.8 (C15), 108.4 (C11), 95.1 (C9), 90.3 (C10), 51.9 (C1); ν_{max} (neat): 3330, 3171, 3065, 2849, 2201, 1707, 1678, 1660, 1256, 711; HRMS (ESI): found 498.1425; $C_{29}H_{21}N_3NaO_4$ $[M+Na]^+$ requires 498.1424.

Zinc(II) Tetra(3,5-di-*tert*-butyl)phenylporphyrin (5)



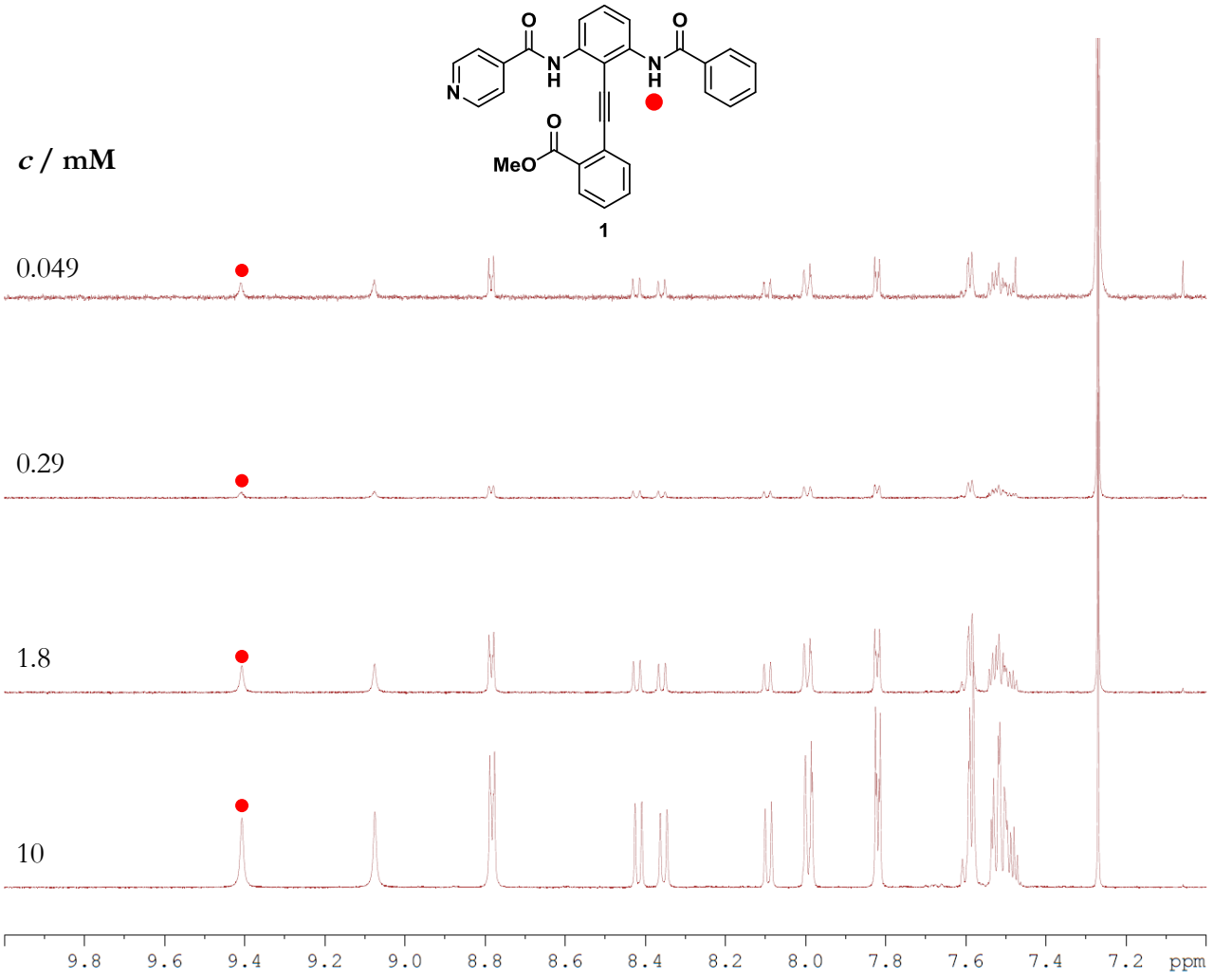
Based on a literature procedure,[3] pyrrole (83 μL, 1.3 mmol) was added to a solution of 3,5-di-*tert*-butylbenzaldehyde (250 mg, 1.15 mmol) in propionic acid (15 mL), and the resulting mixture was heated to reflux. After 3 h the reaction was allowed to cool to room temperature and was concentrated *in vacuo*. Residual propionic acid was removed by azeotrope with toluene (3 x 25 mL), and the resulting brown solid was taken up in dichloromethane, triethylamine (0.25 mL) was added and the mixture was stirred for 30 min. The solution was then passed twice through a plug of silica (eluent: dichloromethane) to remove polymeric impurities. The purple residue was concentrated *in vacuo* and re-dissolved in chloroform (40 mL), and a solution of zinc(II) acetate dihydrate (0.25 g, 1.15 mmol) in methanol (5 mL) was added in one portion. The reaction

mixture was stirred for 2 h then concentrated *in vacuo* and re-dissolved in dichloromethane:petrol (1:1 v/v). This solution was passed over a plug of silica (1:1 dichloromethane:petrol) and concentrated *in vacuo* to afford a purple solid. This was dissolved in chloroform (3 mL) and triturated by layering with methanol (3 mL) to give *the title compound* **5** (88 mg, 27 %) as a lustrous purple crystalline solid. δ_H ($CDCl_3$, 400 MHz) 9.02 (8H, s), 8.11 (8H, d, *J* 1.7), 7.79 (4H, t, *J* 1.8), 1.53 (72H, s).

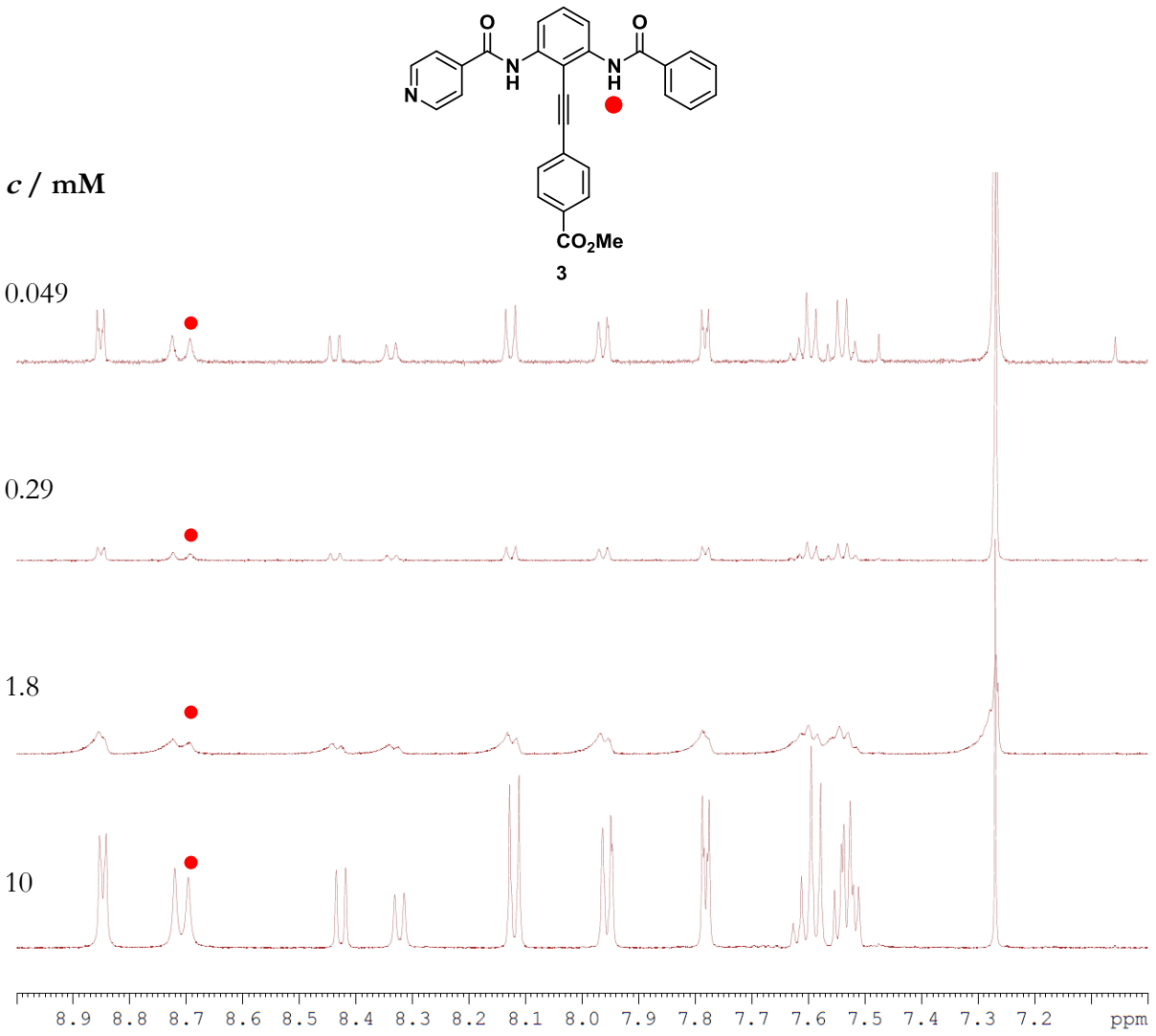
3. SWITCHING ANALYSIS

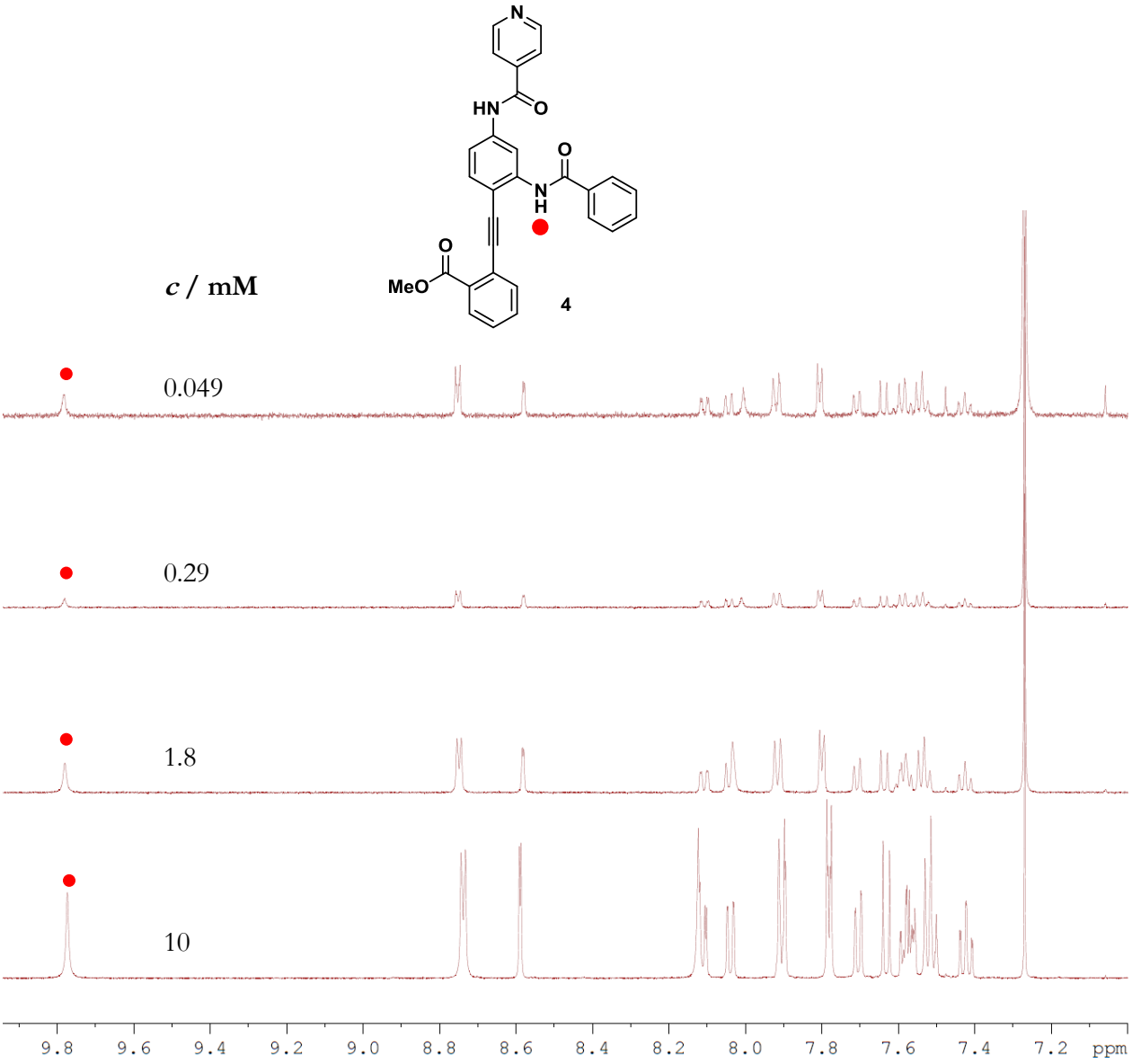
3.1 Dilution Studies

Serial dilution studies were carried out on switch **1** and controls **3** and **4** to verify that the chemical shifts examined in the switching analysis (*vide infra*) were determined by intra- rather than intermolecular hydrogen bonding interactions. A solution of the compound in question (**1**, **3** or **4**, 3 mg) was dissolved in $CDCl_3$ (0.60 mL, 10 mM). A ^1H NMR spectrum (500 MHz) was acquired, and 0.10 mL of the solution was added to $CDCl_3$ (0.50 mL). A ^1H spectrum of the resulting diluted sample was acquired, and the process was repeated two further times.



1


c / mM
0.049
0.29
1.8
10
CO2Me
3
8.9 8.8 8.7 8.6 8.5 8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2
ppm

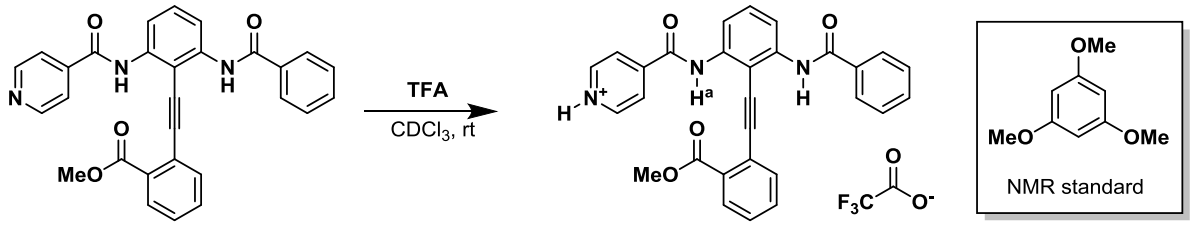


Given the extremely small changes in chemical shift across concentration changes of three orders of magnitude, it was deemed appropriate to assume that the changes in chemical shifts of the switch and control molecules in subsequent studies were a consequence of intramolecular hydrogen bonding alone.

3.2 TFA-Mediated Switching

3.2.1 Procedure

^{1}H NMR titrations with TFA were carried out by the following protocol:



A stock solution containing trifluoroacetic acid (0.1 M) and 1,3,5-trimethoxybenzene* (0.01 M) was made in $CDCl_3$. Switch **1** (1.0 mg) was dissolved in $CDCl_3$ (0.6 mL), and an initial ^{1}H NMR spectrum was acquired. The stock solution of TFA was added volumetrically (5 x 4 μL then 3 x 8 μL), and a new ^{1}H NMR spectrum was acquired after the addition of each aliquot.

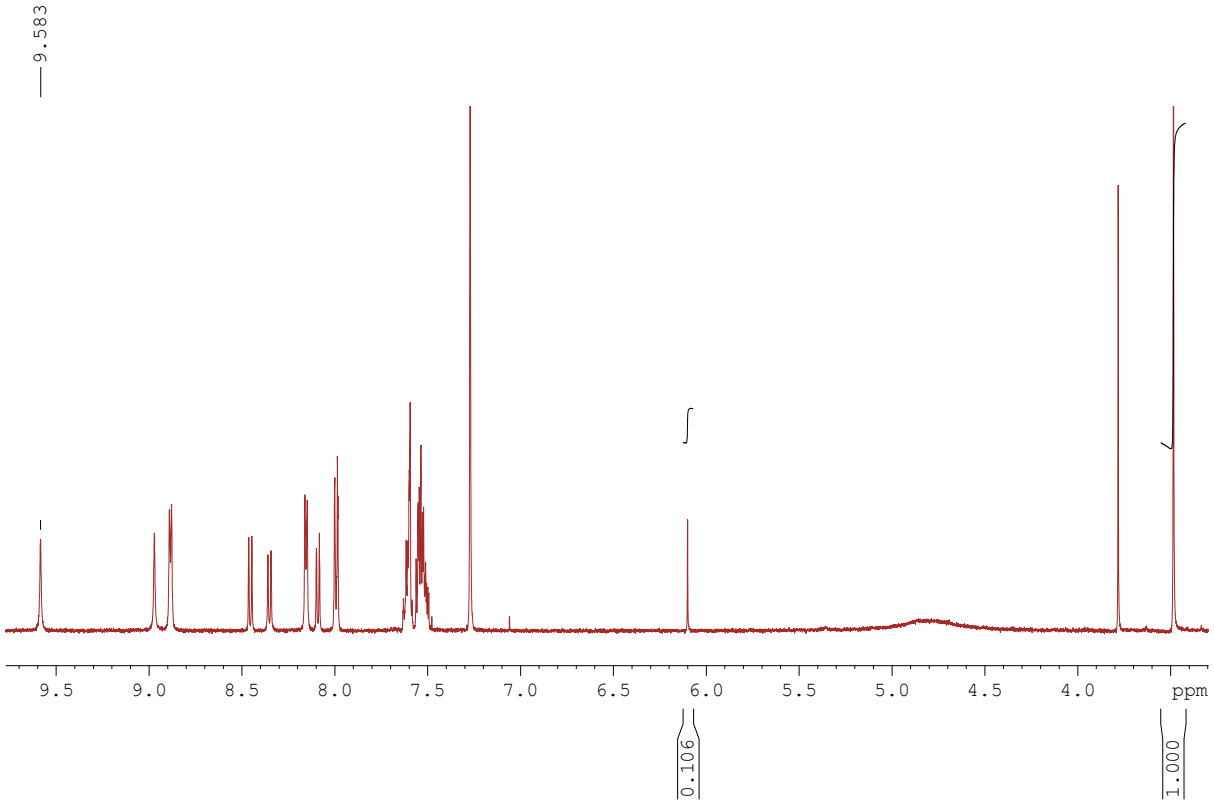
3.2.2 Analysis

The spectra acquired by the method described above were analysed as follows:

Each spectrum was individually integrated to determine the precise stoichiometry of TFA added. This was achieved by integrating the peak corresponding to the aromatic 3H singlet corresponding to 1,3,5-trimethoxybenzene relative to the 3H singlet corresponding to the ester in the switch **1**, and determining the ratio $\frac{I_{standard}}{I_{switch}}$. Since the concentration of TFA is 10x that of the 1,3,5-trimethoxybenzene, the concentration of TFA is simply $10 \times \left(\frac{I_{standard}}{I_{switch}}\right)$.

For example:

* Added as a ^{1}H NMR standard for integration.

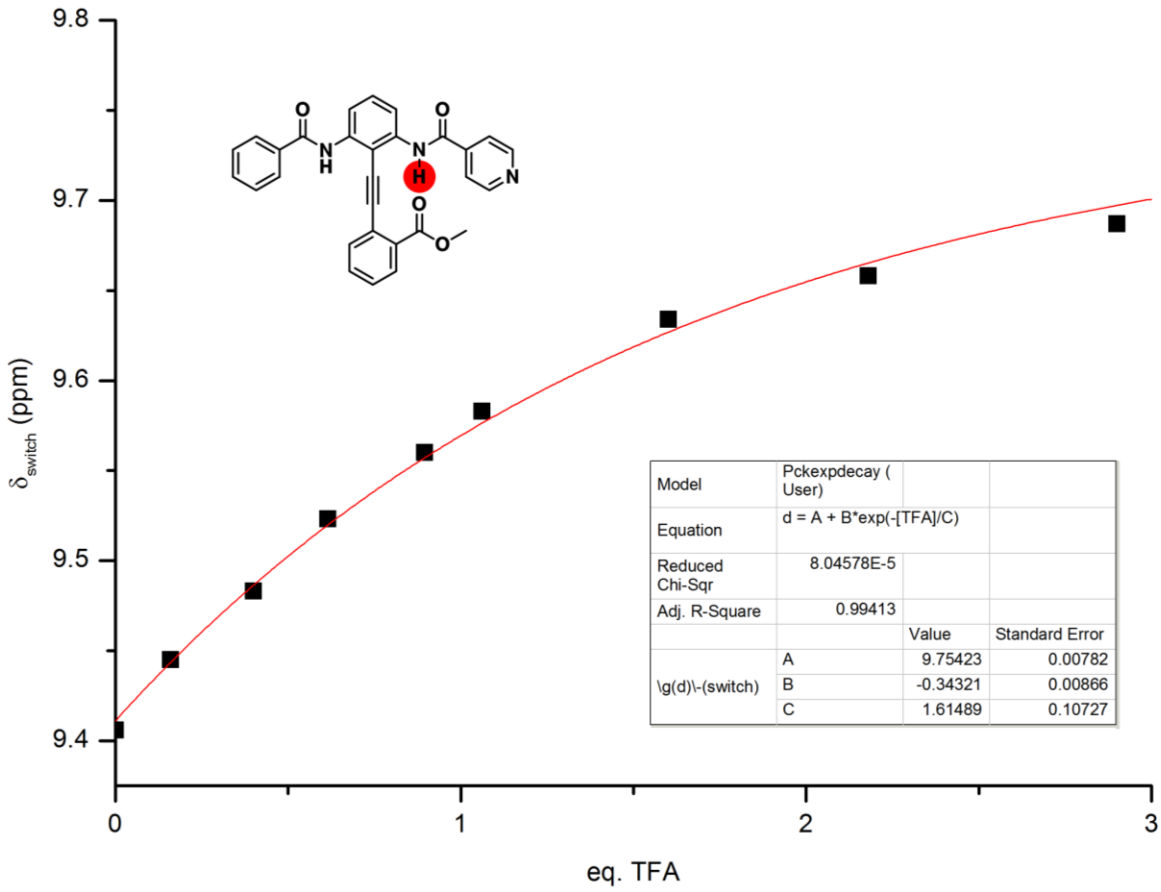


$\frac{I_{standard}}{I_{switch}} = 0.106 \therefore 1.06$ eq. TFA added.

The chemical shift of the proton of interest (H^a) was noted after each additional aliquot of TFA, and this chemical shift was plotted as a function of TFA equivalents (x). The resulting curve was fitted to the exponential decay function:

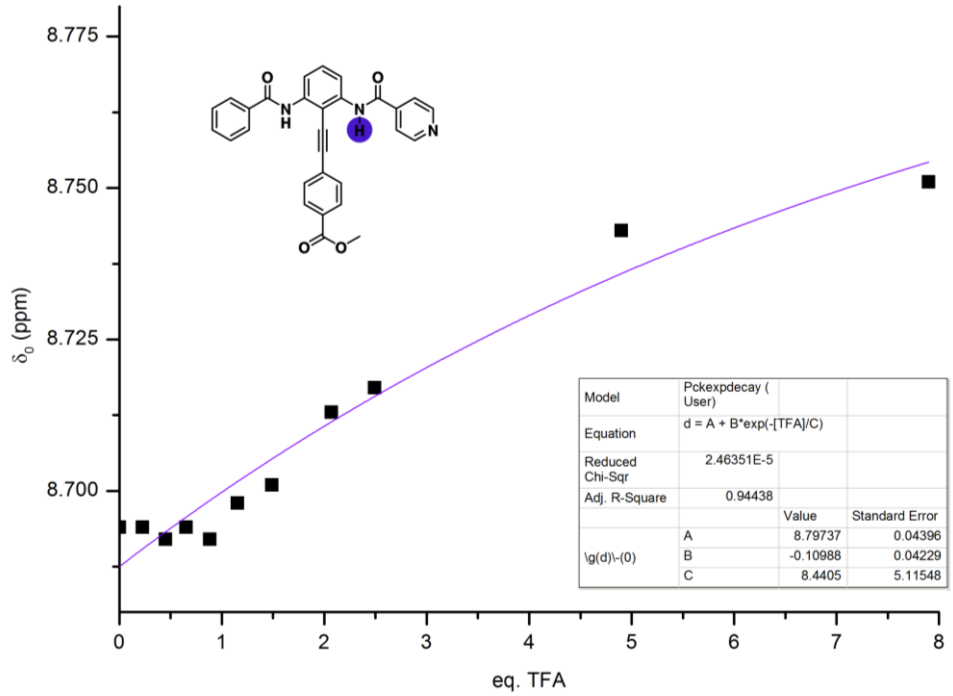
Equation (I) $$\delta_H([TFA]) = A + Be^{\frac{-x}{C}}$$

Where A, B and C are parameters to be determined. The fitting was carried out using OriginPro 8.1.2 SR2, and gave a curve with $r^2 = 0.99$, where $A_{sw} = 9.754$ ppm, $B_{sw} = -0.343$ ppm and $C_{sw} = 1.614$ eq^{-1}.

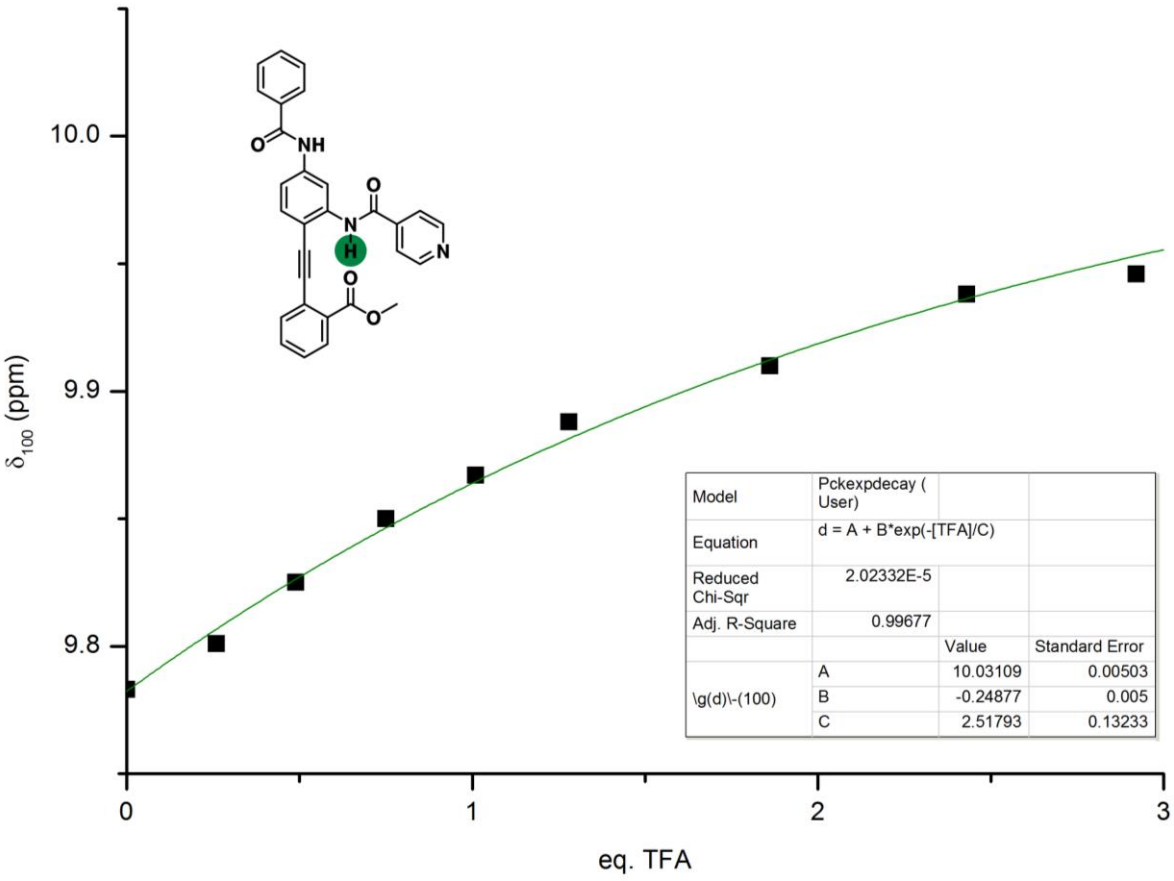


3.2.3 Switching Behaviour

To determine the extent of switching at a given stoichiometry of TFA, the analysis described above (see 3.2.1 and 3.2.2) was repeated on control compounds **3** and **4**. This generated an additional two fitted curves:



A_0 = 8.797 ppm, B_0 = -0.110 ppm, C_0 = 8.440 eq^{-1} (r^2 = 0.94)



A_{100} = 10.031 ppm, B_{100} = -0.249 ppm, C_{100} = 2.518 eq^{-1} (r^2 = 0.997)

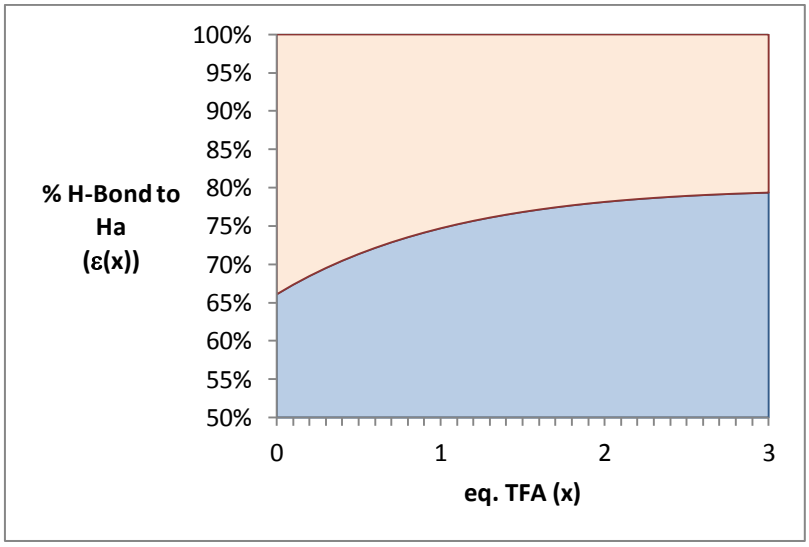
The extent of switching at a given concentration of TFA (ε(x)) can therefore be determined according to:

Equation (II) $$\varepsilon(x) = \frac{\delta_{sw} - \delta_0}{\delta_{100} - \delta_0}$$

Substituting expressions for δ_i with Equation (I), this gives:

Equation (III) $$\varepsilon(x) = \frac{(A_{Sw} - A_0) - \left[B_{Sw} \times e^{-\frac{x}{C_{Sw}}} - B_0 \times e^{-\frac{x}{C_0}}\right]}{(A_{100} - A_0) - \left[B_{100} \times e^{-\frac{x}{C_{100}}} - B_0 \times e^{-\frac{x}{C_0}}\right]}$$

Where A_i, B_i and C_i are the values of the fitted parameters corresponding to compound i (Sw = switch **1**, 0 = 0% control **3**, 100 = 100% control **4**). Plotting ε(x) against x therefore gives:

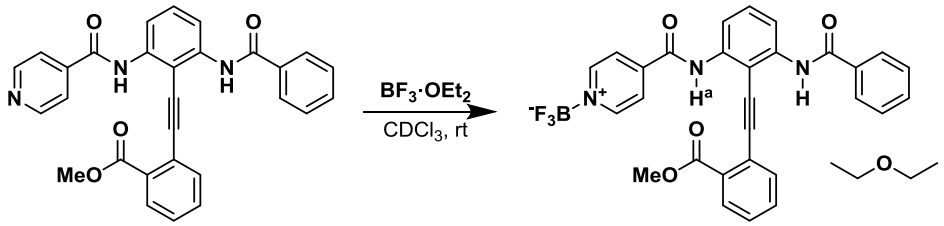


The value quoted in the main text of 4:1 switching after the addition of 3 eq. TFA is therefore obtained by evaluating Equation (III) where x = 3.

3.3 BF_3·OEt_2-Mediated Switching

The method of determining stoichiometry deployed above for the TFA titration could not be applied in this case since the BF_3 adducts of switch and control compounds was poorly soluble in $CDCl_3$ and visibly precipitated out of solution, confounding any analysis by integration of signals.

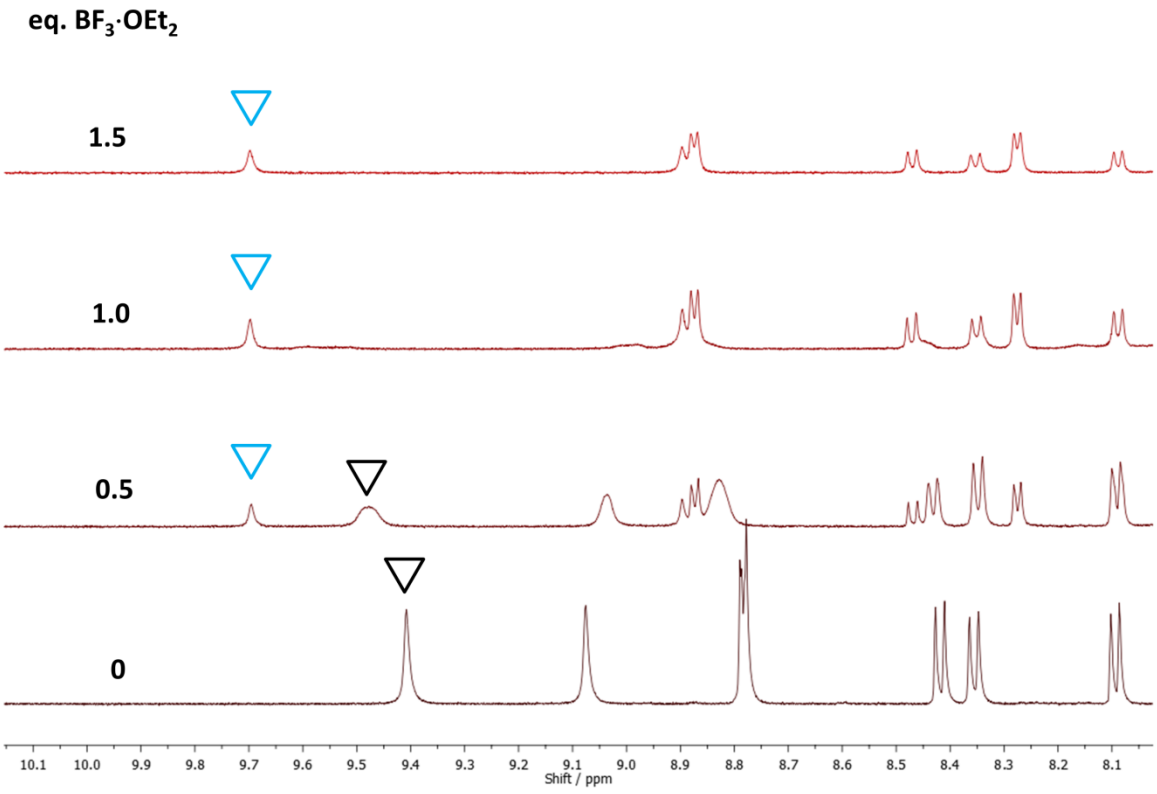
3.3.1 Procedure



A stock solution of boron trifluoride diethyl etherate (0.507 M) was initially made up in $CDCl_3$. Switch **1** (2.4 mg, 0.005 mmol) was dissolved in $CDCl_3$ (0.6 mL), and an initial ^1H NMR spectrum was acquired. The stock solution of $BF_3{\cdot}OEt_2$ was added volumetrically (3 x 0.5 µL; 3 x 0.5 eq.), and a new ^1H NMR spectrum was acquired after the addition of each aliquot.

3.3.2 Analysis and Switching

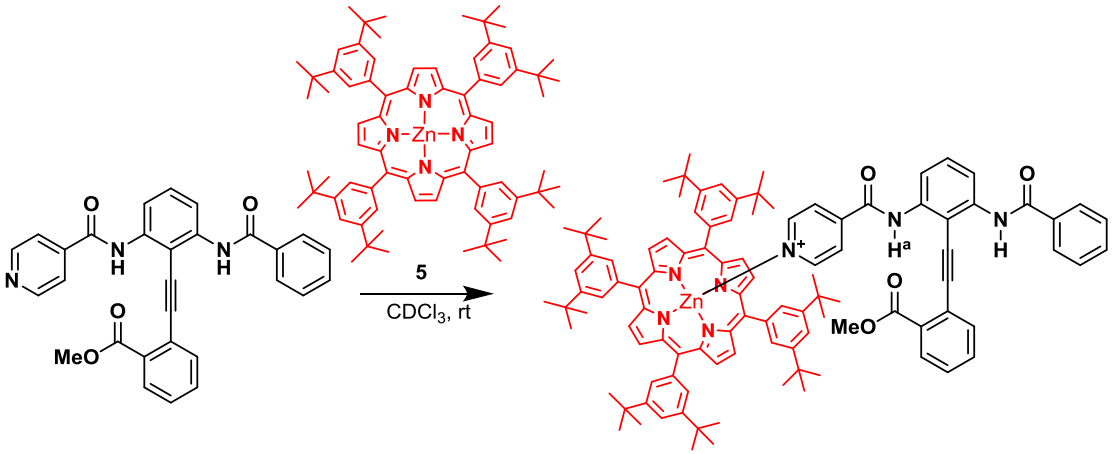
A 1:1 stoichiometric reaction was observed to occur between the switch **1** and the BF_3 (although a slight excess of BF_3 was required to drive the reaction to completion):



The extent of switching after the addition of one equivalent of BF_3 was therefore calculated by directly comparing the ^{1}H NMR peak corresponding to H^a of **1**·BF_3 (δ_{Sw} = 9.70 ppm) with the control complexes **3**·BF_3 (δ_0 = 8.71 ppm) and **4**·BF_3 (δ_{100} = 9.94 ppm), employing Equation (II), giving a value of ε = 0.81, corresponding to a ~4:1 bias in favour of hydrogen bonding to the isonicotinamide over the benzamide.

3.4 Zinc(II) Porphyrin 5-Mediated Switching

3.4.1 Procedure

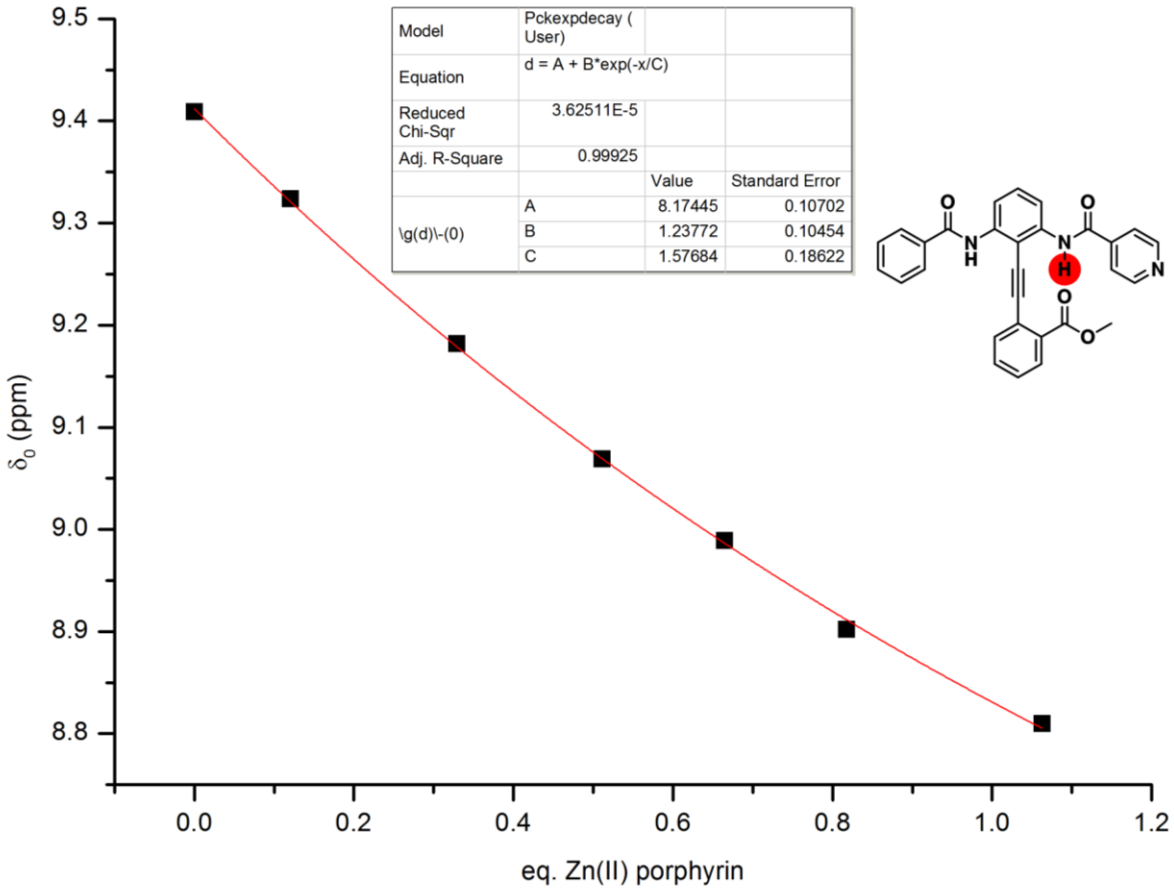


Switch **1** (2.4 mg, 0.005 mmol) was dissolved in $CDCl_3$ (0.6 mL), and an initial ^{1}H NMR spectrum was acquired. Zinc(II) porphyrin **5** was added in portions (6 x *ca.* 1 mg, 6 x *ca.* 0.17 eq.), and a new ^{1}H spectrum was acquired after the addition of each aliquot.

3.4.2 Analysis and Switching

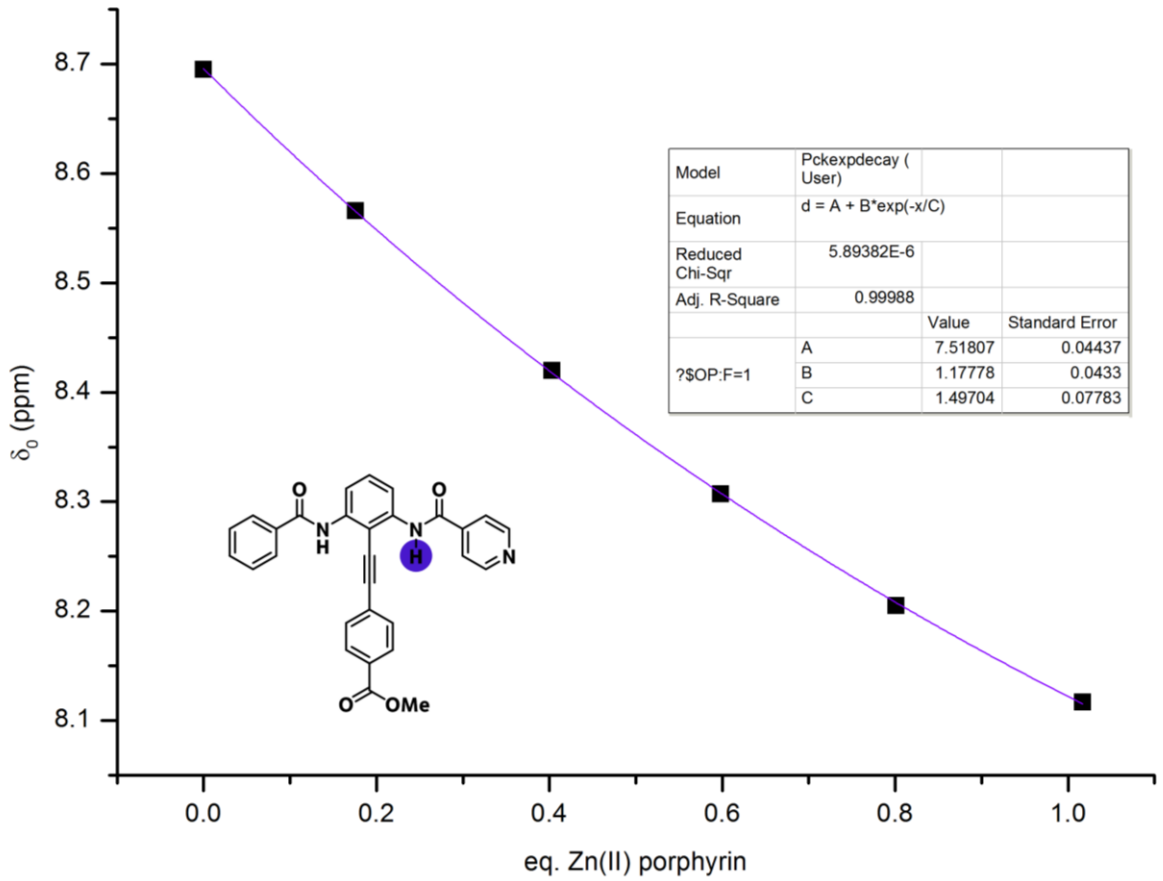
The analysis carried out was analogous to that described in section 3.2.2, but with the stoichiometry of ***5*** *calculated by integrating its 8H singlet at 8.97 ppm relative to the methyl group of the switch/control.*

The following fitted data was obtained for the switch **1**:

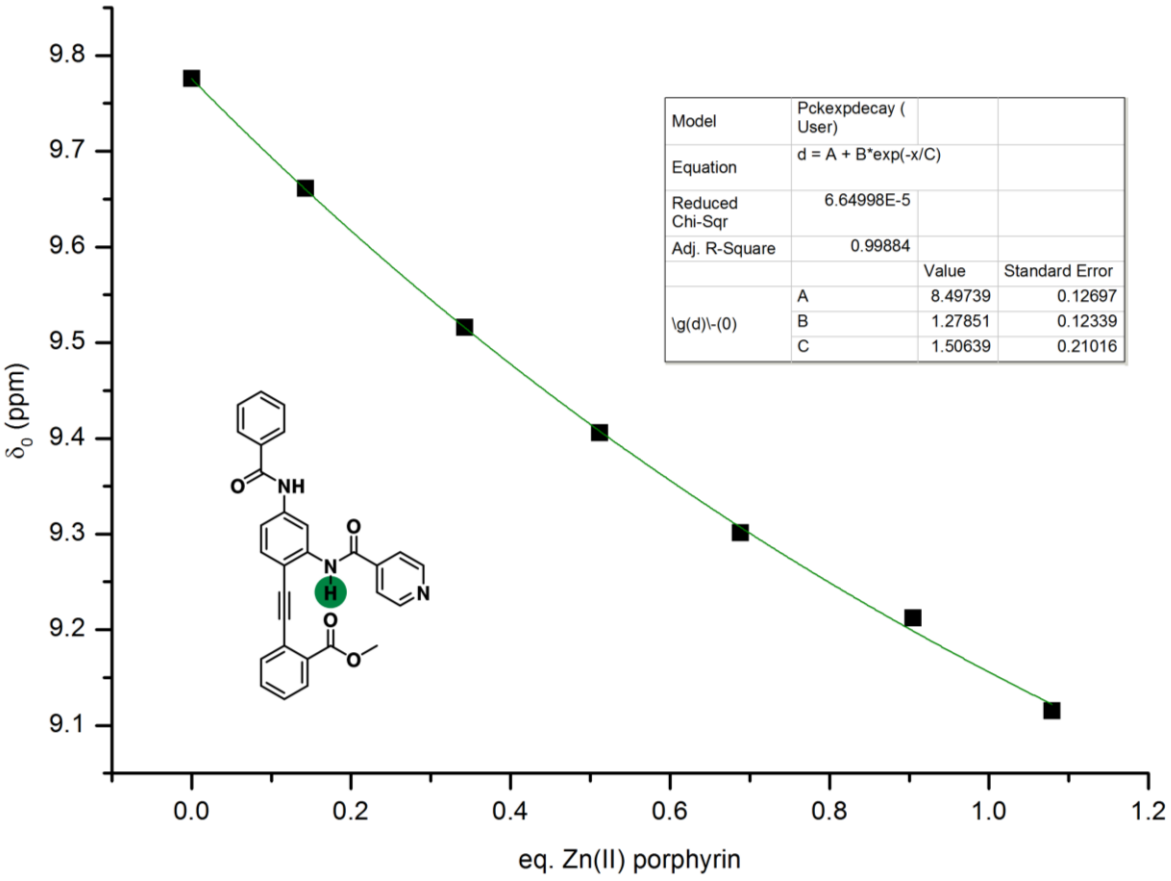


A_{Sw} = 8.174 ppm, B_{Sw} = 1.238 ppm, C_{Sw} = 1.577 eq^{-1} (r^2 = 0.999)

The same analysis was carried out for the control compounds **3** and **4**:

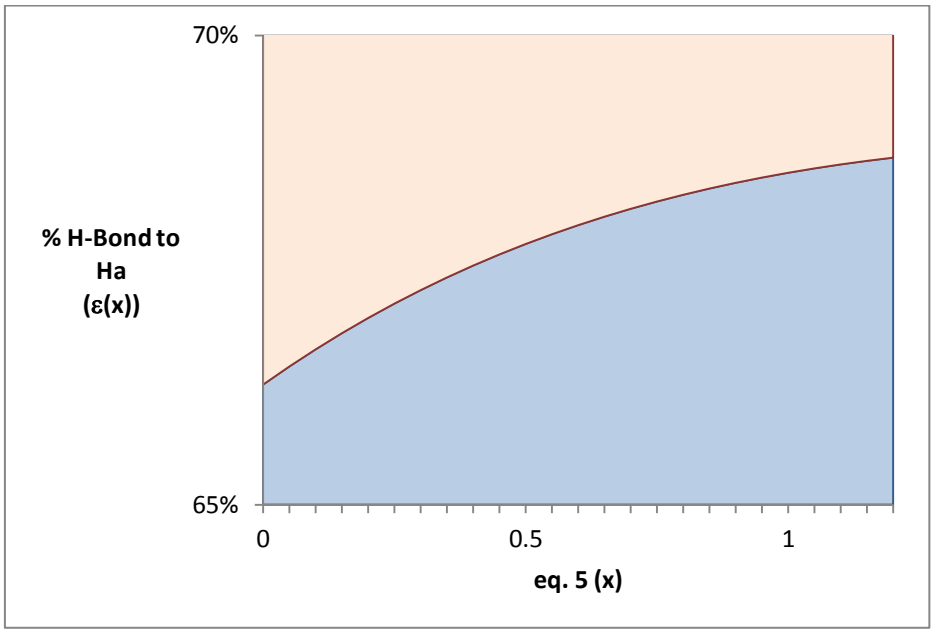


A_0 = 7.518 ppm, B_0 = 1.178 ppm, C_{Sw} = 1.497 eq^{-1} (r^2 = 0.9999)



A_{100} = 8.497 ppm, B_{100} = 1.279 ppm, C_{100} = 1.506 eq^{-1} (r^2 = 0.999)

By inserting these calculated parameters into Equation (III), a function relating the equivalents of **5** added to the position of the conformational equilibrium is obtained:



Inputting x = 1 into this expression gives the equilibrium position after the addition of 1 equivalent of **5**, which is determined to be $\varepsilon = 0.69$, equating to a ~7:3 bias in favour of hydrogen bonding to the isonicotinamide over the benzamide.

4. REFERENCES

(1) Sienkowska, M.; Benin, V.; Kaszynski, P. *Tetrahedron* **2000**, *56*, 165–173.

(2) Jones, I. M.; Hamilton, A. D. *Org. Lett.* **2010**, *12*, 3651–3653.

(3) Chabdon-Noblat, S.; Sauvage, J.-P. *Tetrahedron* **1991**, *47*, 5123.

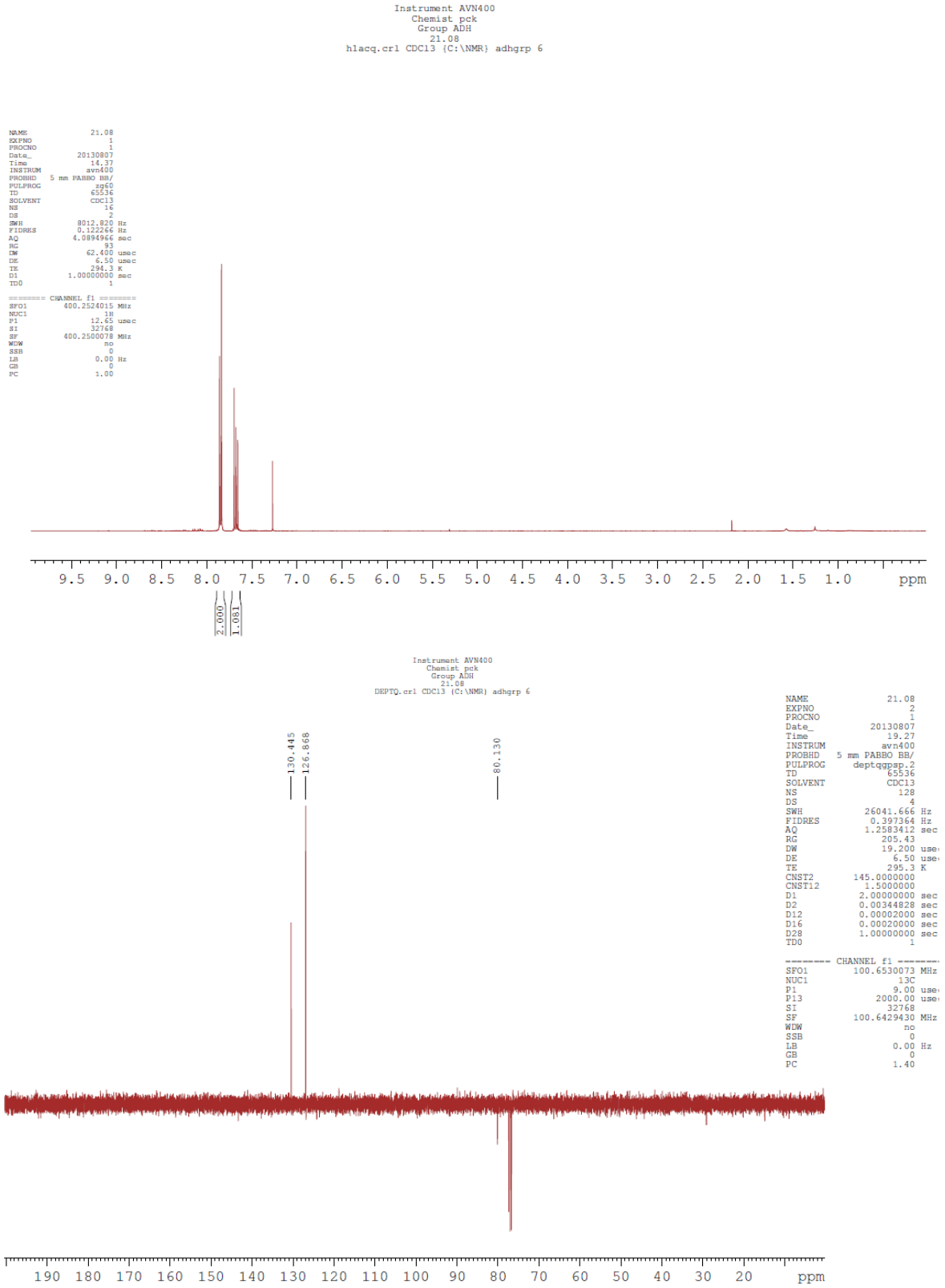
(4) Tamiaki, H.; Matsumoto, N.; Unno, S.; Shinoda, S.; Tsukube, H. *Inorganica Chim. Acta* **2000**, *300-302*, 243–249.

(5) Jones, I. M.; Hamilton, A. D. *Org. Lett.* **2010**, *12*, 3651–3653.

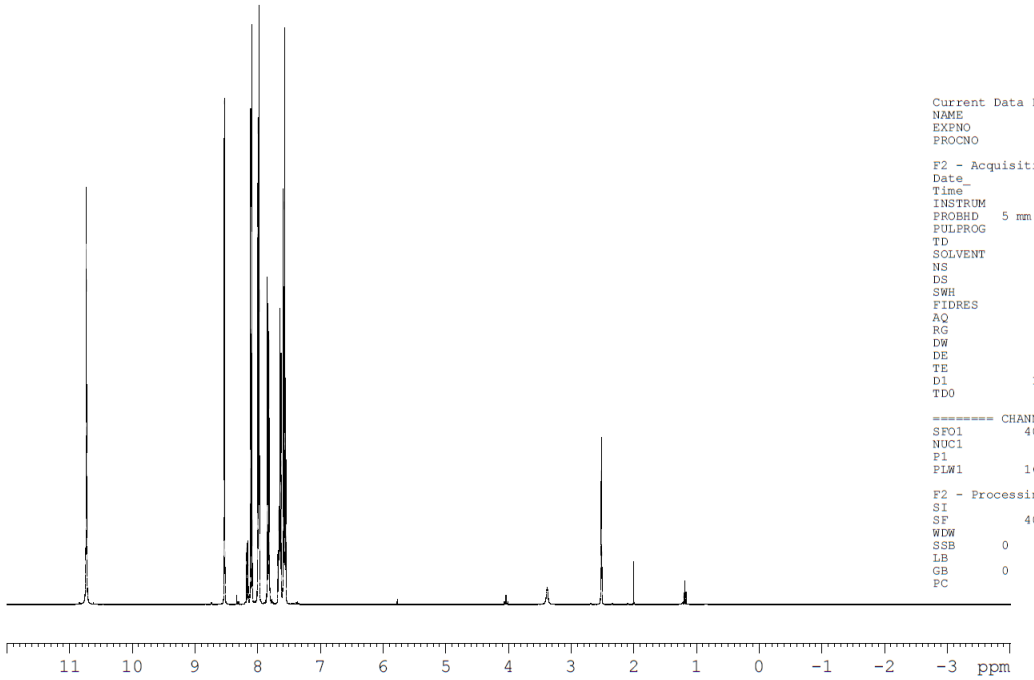
5. SPECTRA

*^{1}H and ^{13}C spectra for compounds **7-11** and **15** were reported previously.*[5]

2-Iodo-1,3-dinitrobenzene (6)



N-(4-Iodo-3-nitrophenyl)benzamide (12)




```
Current Data Parameters
NAME                  21.05
EXPNO                     1
PROCNO                    1

F2 - Acquisition Paramet
Date_              20130806
Time                  18.00
INSTRUM              avn400
PROBHD   5 mm PABBO BB/
PULPROG                zg60
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH                8012.820
FIDRES             0.122266
AQ                 4.0894465
RG                       93
DW                    62.400
DE                     6.50
TE                    294.5
D1                1.00000000
TD0                       1

======== CHANNEL f1 ====
SFO1             400.2524015
NUC1                      1H
P1                     12.65
PLW1             16.70000076

F2 - Processing paramete
SI                    32768
SF               400.2500000
WDW                      EM
SSB          0
LB                     0.30
GB           0
PC                     1.00
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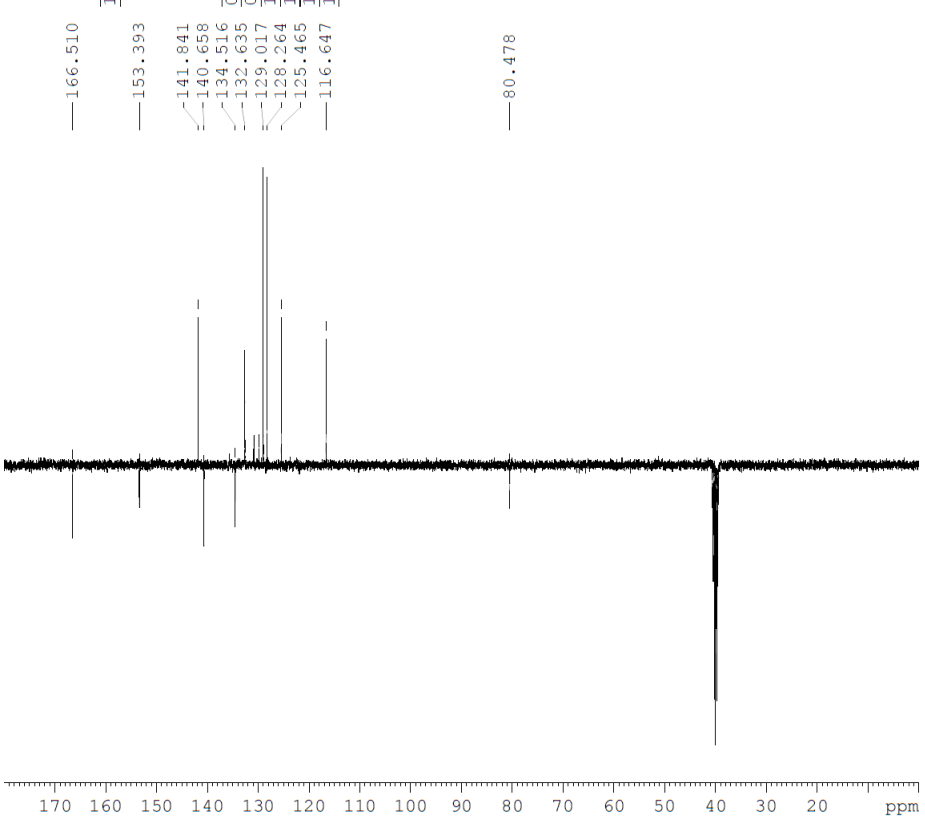


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Current Data Parameters
NAME                  21.05
EXPNO                     3
PROCNO                    1

F2 - Acquisition Parameters
Date_              20130806
Time                  18.21
INSTRUM              avn400
PROBHD   5 mm PABBO BB/
PULPROG     deptqgpsp.2
TD                    65536
SOLVENT                DMSO
NS                      128
DS                        4
SWH            26041.666 Hz
FIDRES          0.397364 Hz
AQ              1.2582912 sec
RG                   205.43
DW                 19.200 usec
DE                  6.50 usec
TE                 295.3 K
CNST2          145.0000000
CNST12           1.5000000
D1               2.00000000 sec
D2               0.00344828 sec
D12              0.00002000 sec
D16              0.00020000 sec
D28              1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1           100.6530073 MHz
NUC1                      13C
P1                   9.00 usec
P13                2000.00 usec
PLW0       0 W
PLW1            58.70000076 W
SPNAM[5]     Crp60comp.4
SPOAL5             0.500
SPOFFS5    0 Hz
SFW5             7.26459980 W

======== CHANNEL f2 ========
SFO2           400.2516010 MHz
NUC2                      1H
CPDPRG[2           waltz16
PO                   18.98 usec
P3                   12.65 usec
P4                   25.30 usec
PCPD2                90.00 usec
PLW2            16.70000076 W
PLW12            0.32991999 W
PLW13            0.26723999 W

====== GRADIENT CHANNEL =====
GPNAM[1]       SMSQ10.100
GPNAM[2]       SMSQ10.100
GPNAM[3]       SMSQ10.100
GPZ1                31.00 %
GPZ2                31.00 %
GPZ3                31.00 %
P16               1000.00 usec

F2 - Processing parameters
SI                    32768
SF             100.6429430 MHz
WDW                      EM
SSB          0
LB                  1.00 Hz
GB           0
PC                    1.40
```
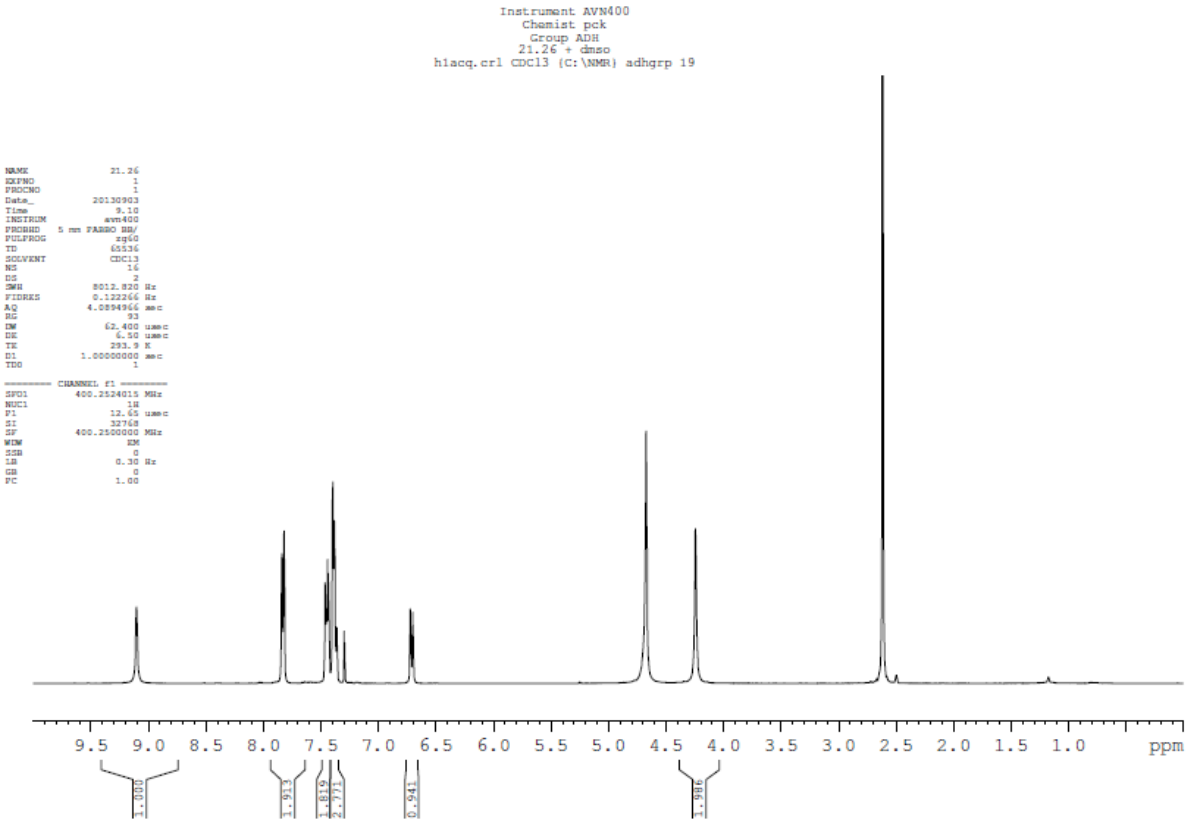
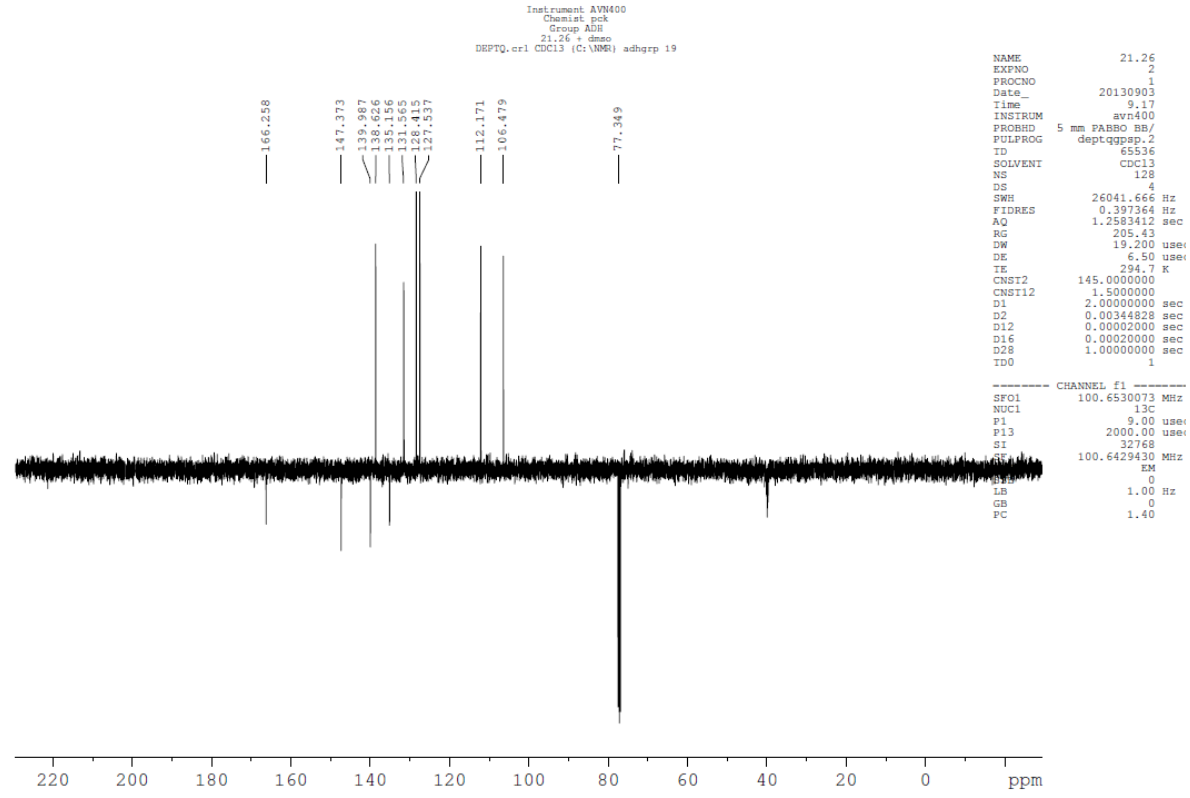
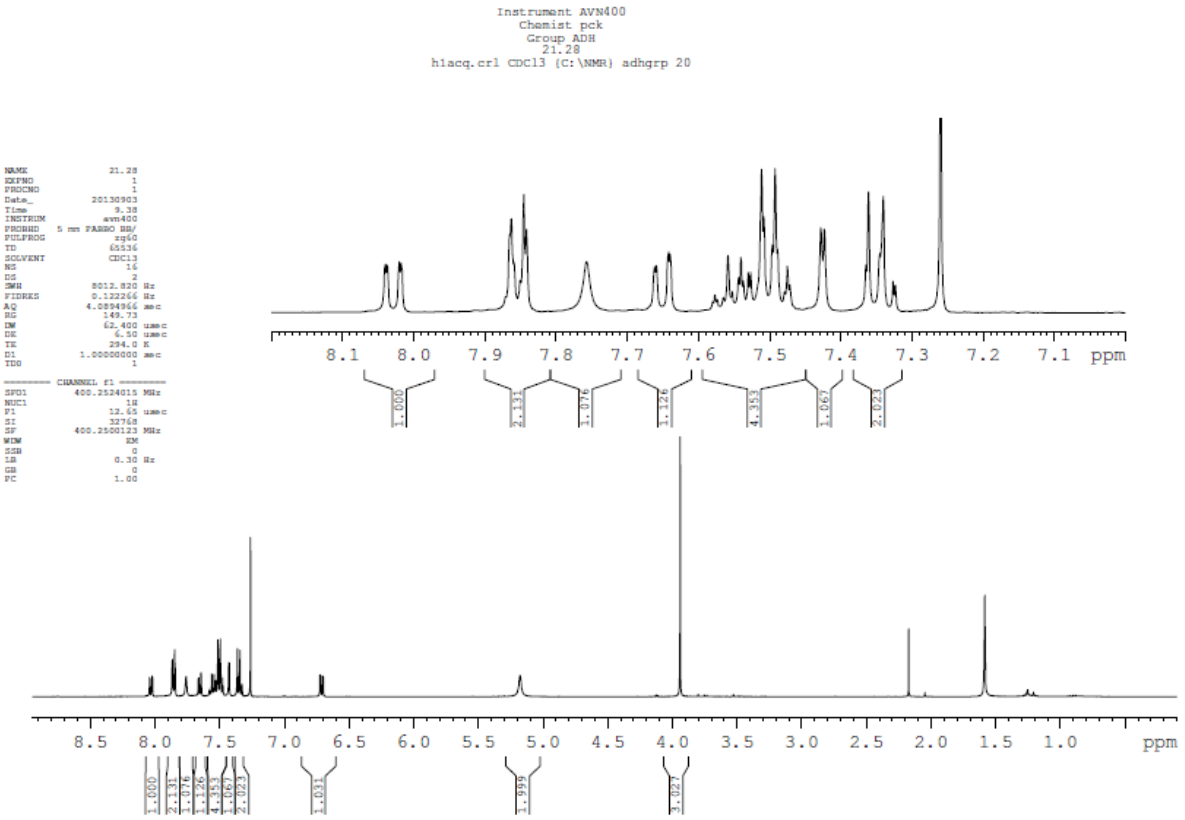
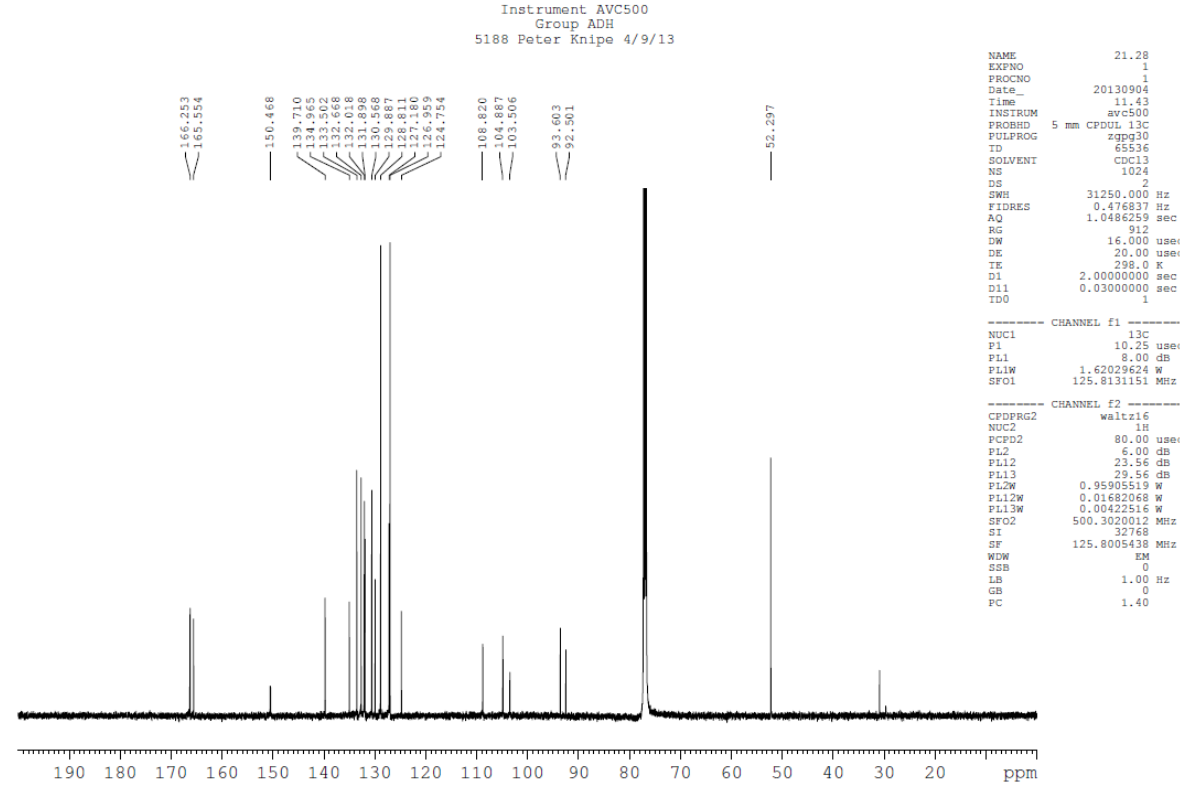

N-(3-Amino-4-iodophenyl)benzamide (13)



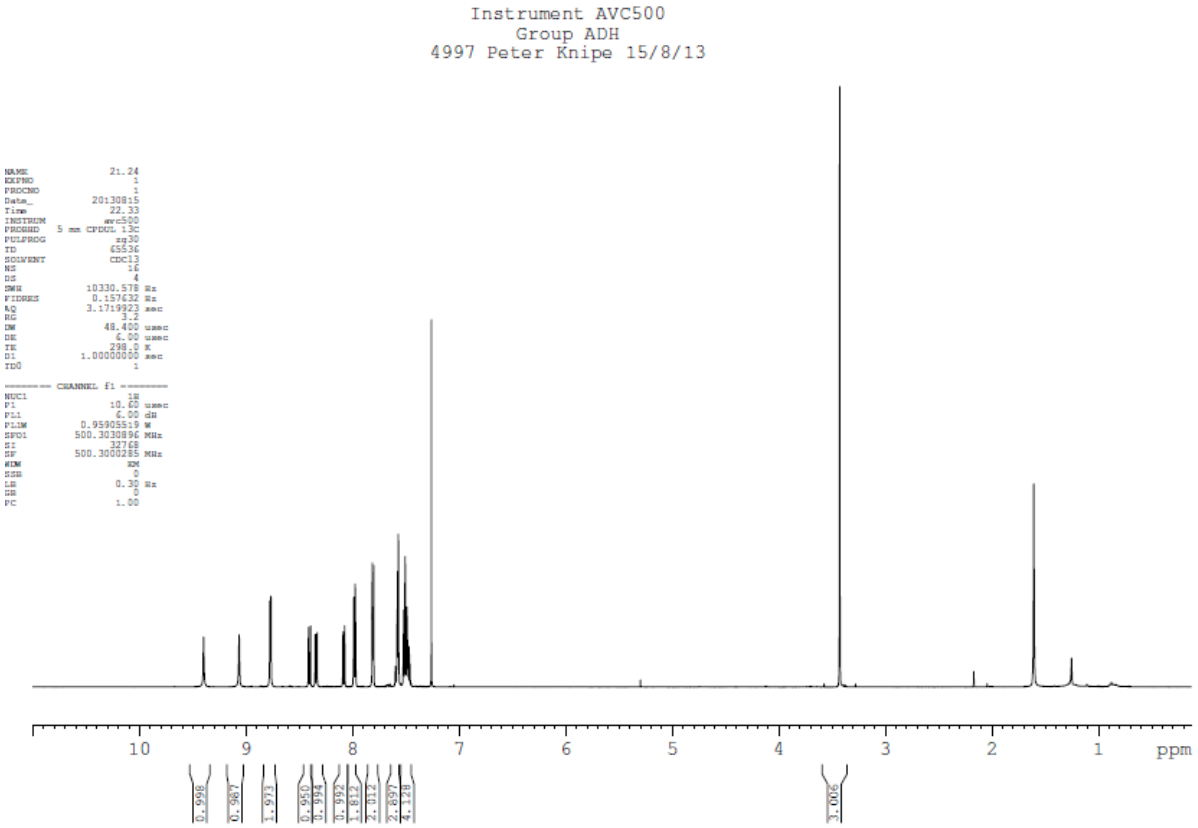


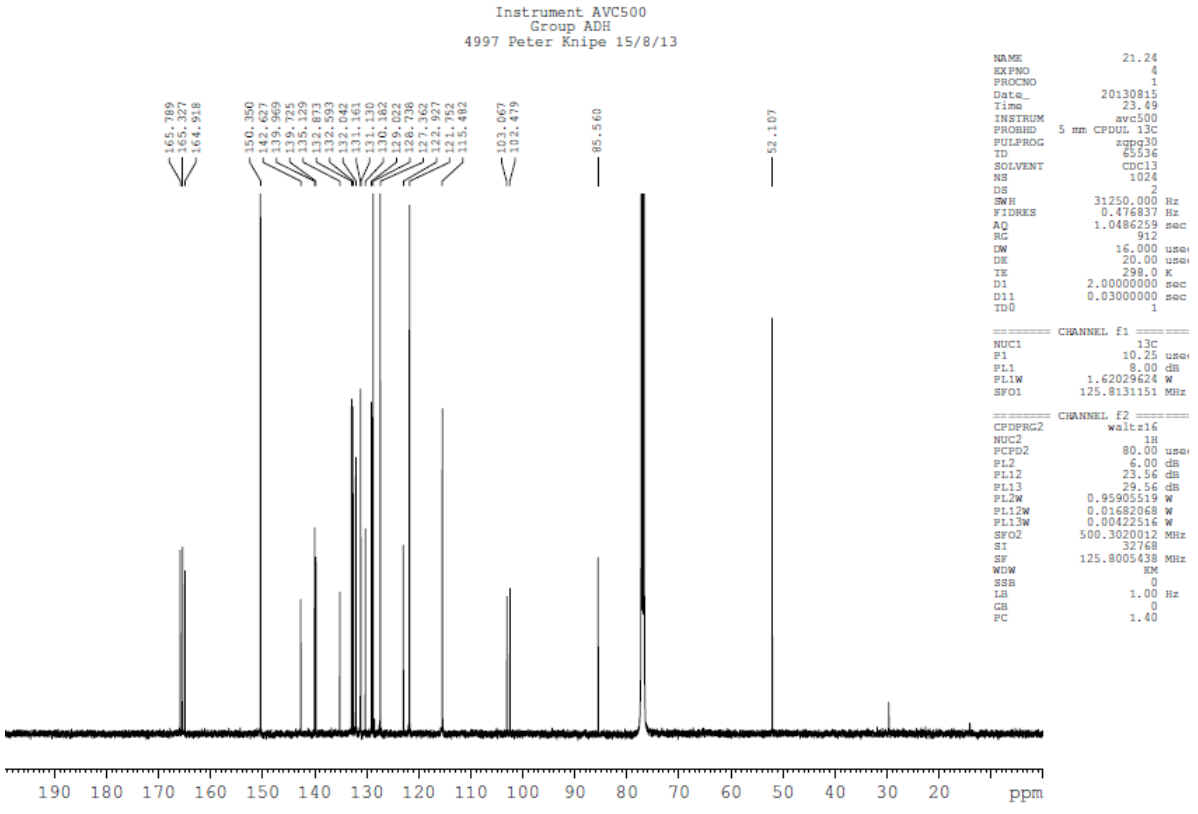
Methyl 2-((2-amino-4-benzamidophenyl)ethynyl)benzoate (14)



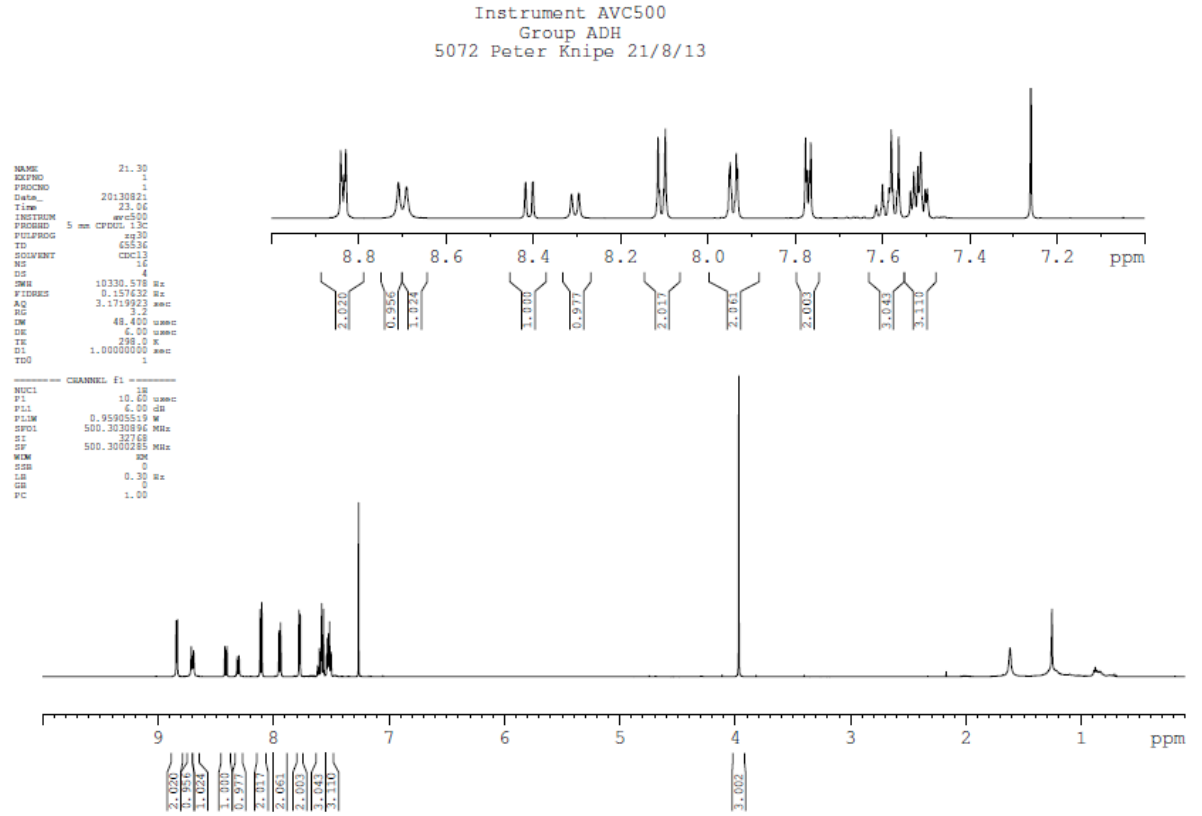


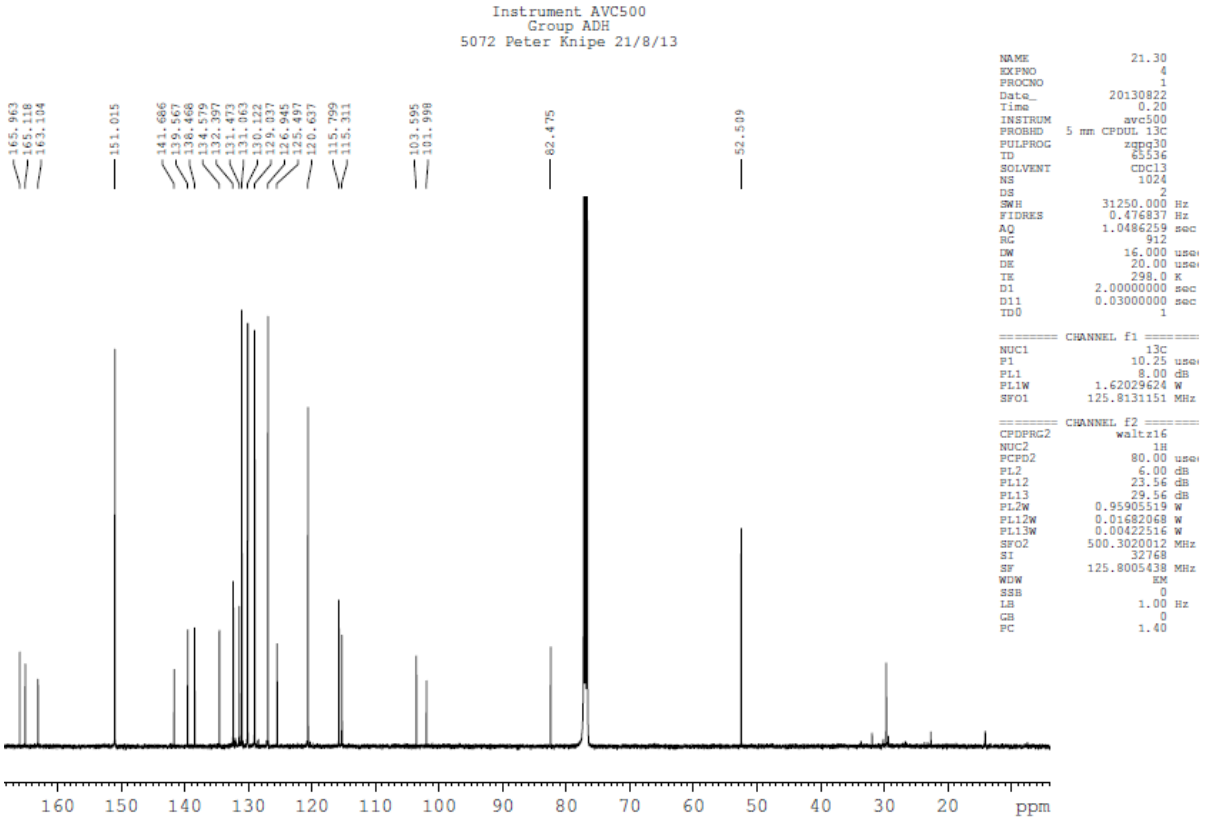
Methyl 2-((2-benzamido-6-(isonicotinamido)phenyl)ethynyl)benzoate (1)



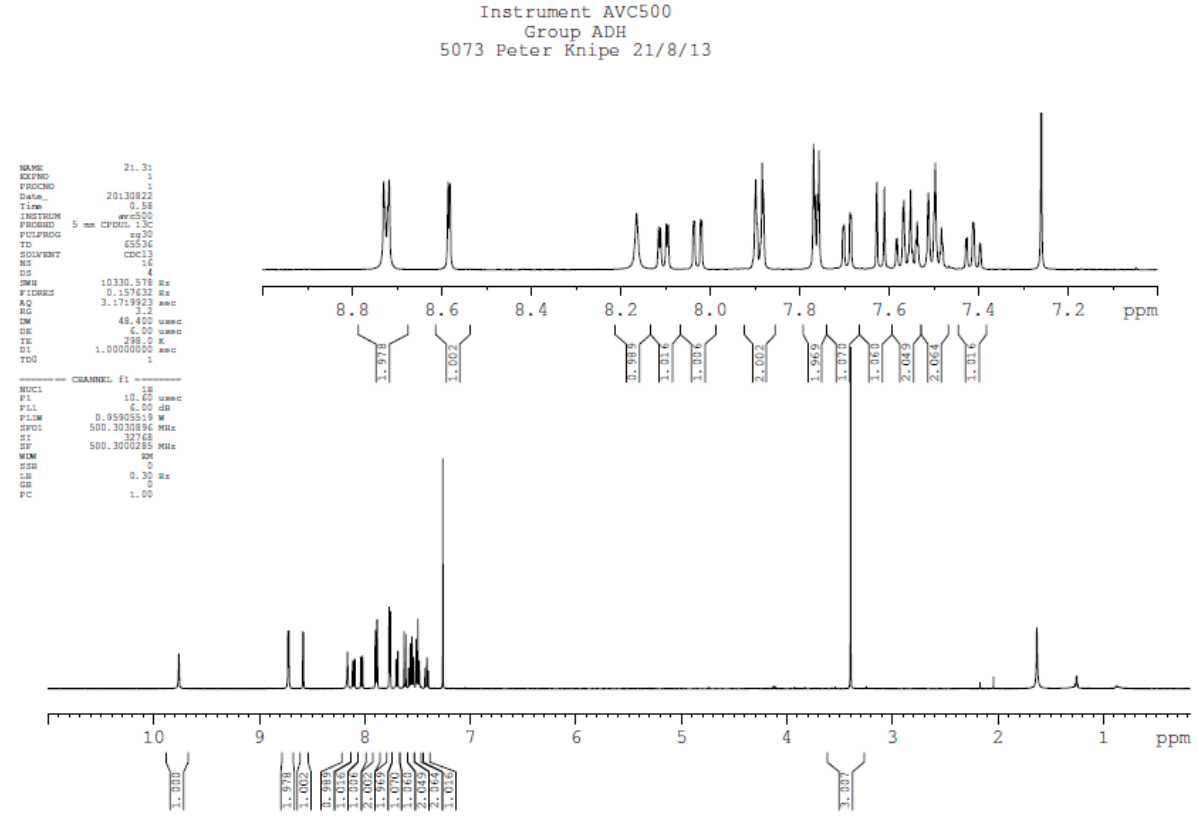


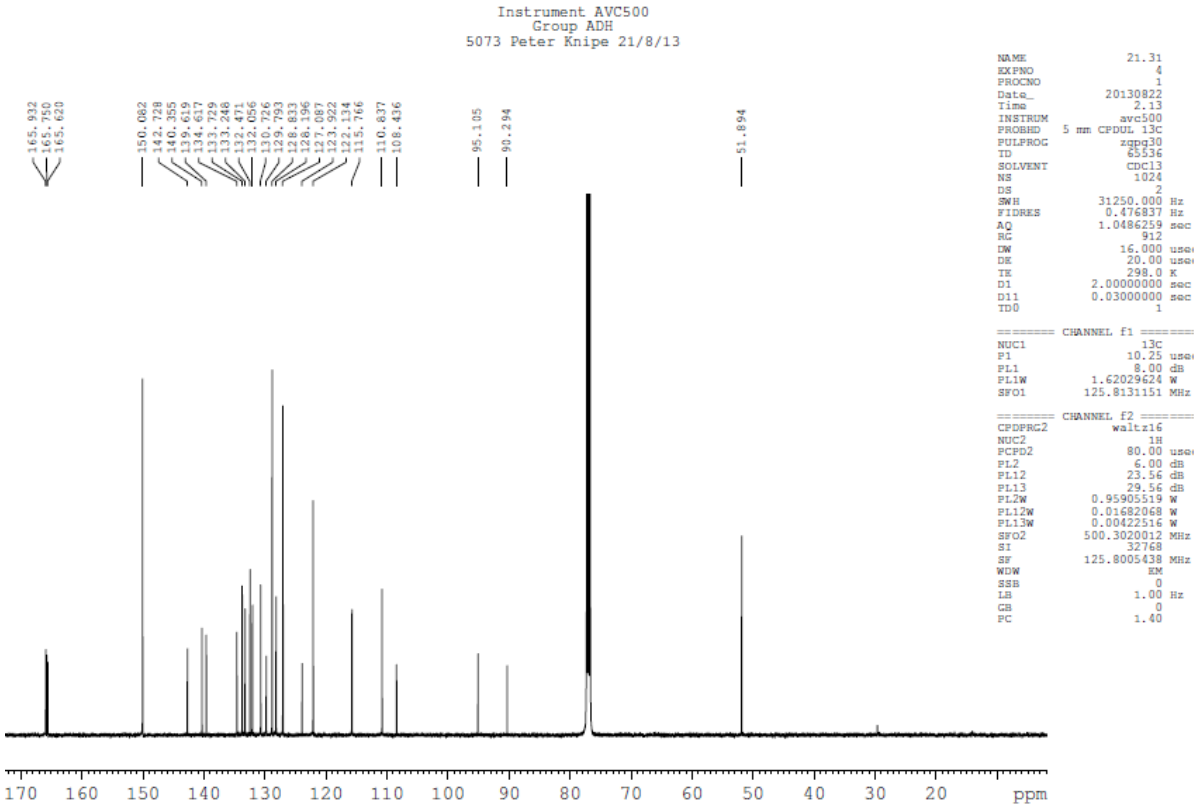
Methyl 4-((2-benzamido-6-(isonicotinamido)phenyl)ethynyl)benzoate (3)





Methyl 2-((4-benzamido-2-(isonicotinamido)phenyl)ethynyl)benzoate (4)





Zn Porphyrin (5)