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Synthesis and fungicidal activity of new 4-hydroxy-6-trifluoromethyl-2-phenylindoles

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Contents

1. Experimental Procedures and Characterization Data

The composition and structure of the prepared compounds were confirmed by ^{1}H-, ^{13}C- and ^{19}F-NMR spectroscopy, mass spectrometry and elemental analysis data. The NMR spectra of protons and ^{13}C and ^{19}F nuclei for compound **4a** and ROESY for compound **8** were recorded on a Bruker Avance II 600 spectrometer fitted with a broadband probe with Z-gradient in DMSO-d_6 at 30 ºC. The ^{1}H and ^{13}C chemical shifts were calibrated by signals of carbon atoms (39.50 ppm) and residual protons (2.50 ppm) of DMSO-d_6. The ^{19}F chemical shifts were calibrated by the signal of the external standard – $CFCl_3$ (0.0 ppm). The 2D experiments were set up according to Bruker standard procedures using Z-gradient pulses. The ^{1}H-^{13}C HMBC spectrum was optimized for the spin-spin coupling constant 10 Hz.

The ^{1}H NMR spectra of other compounds were recorded on a Bruker AM-300 spectrometer in DMSO-d_6, δ, ppm. The electron-impact mass spectra were obtained at 70 eV using a direct inlet system on a Finnigan MAT INCOS 50 instrument. Melting points were measured on a Kofler hot-stage microscope Boetius at a heating rate 4 deg min^{-1}. The reaction course and substance purity were controlled by HPLC ($MeCN/H_2O$ = 60/40; reversed phase C 18) using a Waters Binary HPLC Pump 1525 with Photodiode Array Detector Waters 2996. Silica gel 0.035-0.07 mm was used for column chromatography. All chemicals used in this study are commercially available. Oxime **2a** had been synthesized by us earlier [S. A. Shevelev et al., *Mendeleev Commun.*, 2002, **12**, 196].

O-(3-Nitro-5-trifluoromethylphenyl) propiophenone ketoxime (2b). A mixture of propiophenone oxime (14.92 g, 0.1 mol), NMP (96 ml), 3,5-dinitrobenzotrifluoride (23.61 g, 0.1 mol), and K_2CO_3 (27.58 g, 0.2 mol) was heated up to 50 ºC and was kept at this temperature for 13 hours until complete conversion (HPLC). The reaction mass was then poured with intensive stirring into cold water (500 ml) and and maintained for 10-15 min. The precipitate was filtered off, washed with water on a filter, air-dried, and recrystallized from EtOH.

Yield 71%. Mp = 105-107 ºC.

^{1} H NMR spectrum: 1.2 (t, 3H, ^{2}J=7.5); 3.05 (m, 2H); 7.49-7.51 (m, 3H); 7.71-7.74 (m, 2H); 8.04 (s, 1H); 8.15(s, 1H); 8.32 (s, 1H). Mass specrum, m/z: 338 (M^{+}).

^{13} C NMR spectrum: 11.1, 20.6, 112.9, 113.4, 114.2, 117.3, 118.0, 121.8, 125.6 126.6, 128.8, 130.6, 133.1, 149.1, 159.8, 165.0

^{19} F NMR spectrum: -60.14

Elemental analysis: found, %: C 56.98; H 3.99; N 8.10; calculated for $C_{16}H_{13}F_3N_2O_3$, % C 56.81; H 3.87; N 8.28.

Preparation of O-(3-amino-5-trifluoromethylphenyl) alky lphenyl ketone oximes

A mixture of *O*-(3-nitro-5-trifluoromethylphenyl) alkyl phenyl ketone oxime (0.01 mol), methanol (70 ml), $FeCl_3*6H_2O$ (0.014 g, 0.0008 mol), activated carbon (2.5 g), and hydrazine hydrate (3.8 ml, 0.08 mol) was boiled under reflux for 2-3 hours with stirring until complete conversion of the starting oxime (HPLC) and then filtered hot in vacuum. The filtrate was cooled and the precipitate was filtered off and air-dried.

***O*-(3-Amino-5-trifluoromethylphenyl) acetophenone ketoxime (3a)**:

Reaction time 2 h. Yield 85%. Mp = 52-53 ºC.

^1H NMR spectrum: 2.42 (s, 3H); 5.72 (br.s, 2H); 6.55 (s, 1H); 6.61 (s, 1H); 6.77 (s, 1H); 7.48-7.50 (m, 3H); 7.78-7.83 (m, 2H). Mass spectrum, m/z: 294 (M^+).

^{13}C NMR spectrum: 98.0, 102.1, 103.9, 114.2, 118.0, 121.8, 125.6, 126.5, 128.3, 130.1, 132.5, 134.2, 150.8, 159.9, 163.2

^{19}F NMR spectrum: -56.52

Elemental analysis: found, %: C 61.02; H 4.66; N 9.68; calculated for $C_{15}H_{13}F_3N_2O$, % C 61.22; H 4.45; N 9.52.

***O*-(3-Amino-5-trifluoromethylphenyl) propiophenone ketoxime (3b):**

Reactio time 3 h. Yield 88%. Mp = 53-55 ºC.

^1H NMR spectrum: 1.15 (t, 3H, ^2J=7.1); 2.95 (m, 2H); 6.22 (br.s, 2H); 6.55(s, 1H); 6.61 (s, 1H); 6.77 (s, 1H); 7.48-7.50 (m, 3H); 7.78-7.83 (m, 2H). Mass spectrum, m/z: 308 (M^+).

^{13}C NMR spectrum: 11.1, 20.2, 97.9, 102.5, 104.0, 114.2, 118.0, 121.8, 125.6, 126.7, 128.7, 130.1, 150.9, 160.2, 163.5

^{19}F NMR spectrum: -60.25

Elemental analysis: found, %: C 62.47; H 4.68; N 8.89; calculated for $C_{16}H_{15}F_3N_2O$, % C 62.33; H 4.90; N 9.09.

Preparation of 4-hydroxy-2-phenylindoles

A solution of acetyl chloride (3.6 ml) in MeOH, cooled in a glacial bath, was poured to a cooled ketoxime **3** (0.01 mol) solution in MeOH (total MeOH – 24 ml). The reaction mixture was refluxed for 4 hours, then cooled to room temperature and vacuum filtered. The filtrate was evaporated to dryness, benzene (40 ml) was added, and this was boiled with a Dean – Stark trap until full water removal. The precipitate was filtered in vacuum and the filtrate was evaporated to dryness. The remaining portion was then separated using column chromatography on silica gel, eluent – $CHCl_3$, to isolate the products **4**.

4-Hydroxy-6-trifluoromethyl-2-phenylindole 4a:

Yield 43%. Mp = 156-157 °C.

^{1} H NMR spectrum: 6.62 (s, 1H); 7.03 (s, 1H); 7,19 (s, 1H); 7.32-7.37 (m, 1H); 7.46-7.51 (m, 2H); 7.85-7.87 (m, 2H); 10.10 (s, 1H); 11.84 (s, 1H). Mass spectrum, m/z: 277 (M^+).

Elemental analysis: found, %: C 64.72; H 3.93; N 5,29; calculated for $C_{15}H_{10}F_3NO$, % C 64.98; H 3.64; N 5.05.

4-Hydroxy-3-methyl-6-trifluoromethyl-2-phenylindole 4b:

Yield 46%. Mp = 127-128 °C.

^{1} H NMR spectrum: 2.6 (s, 3H); 6.58 (s, 1H); 7.1 (s, 1H); 7.35-7.41 (m, 1H); 7.48-7.58 (m, 2H); 7.6-7.68 (m, 2H); 10.1 (s, 1H);11.42 (s, 1H). Mass spectrum, m/z: 291 (M^+).

^{13} C NMR spectrum: 10.5, 90.4, 91.5, 99.0, 112.0, 113.8, 115.6, 117.8, 118.6, 119.2, 120.0, 121.2, 123.9, 126.3, 128.1, 144.2

^{19} F NMR spectrum: -59.75

Elemental analysis: found, %: C 66.15; H 4.02; N 4.57; calculated for $C_{16}H_{12}F_3NO$, % C 65.98; H 4.15; N 4.81.

4-Hydroxy-5-dimethylaminomethyl-3-methyl-6-trifluoromethyl-2-phenylindole 8:

A mixture of 33% aqueous dimethylamine (1.9 ml, 0.01 mol) and 30% aqueous formalin (1 ml, 0.01 mol) was added dropwise to a suspension of indole **4b** (2.91 g, 0.01 mol) in MeOH (100 ml). The reaction mass was stirred for 36-48 hours at room temperature until complete conversion of the starting indole (HPLC). The solvent was then evacuated by a water-jet pump and the residue was purified by column chromatography on silica gel, eluent – $CHCl_3$, to isolate the product.

Yield 45%. Mp =121-122 °C.

^{1} H NMR spectrum: 2.31 (s, 6H); 2.61 (s, 3H); 3.80 (s, 2H); 4.9 (s, 1H); 7.1 (s, 1H); 7.31-7.41 (m, 1H); 7.45-7.53 (m, 2H); 7.6-7.68 (m, 2H); 11.35 (s, 1H). Mass spectrum, m/z: 348 (M^+).

^{13} C NMR spectrum: 11.4, 43.3, 57.3, 100.2, 105.8, 107.5, 112.5, 116.3, 120.1, 120.7, 123.5, 123.9, 127.3, 127.8, 128.6, 132.4, 135.2, 155.0

^{19} F NMR spectrum: -59.55

Elemental analysis: found, %: C 65.36; H 5.37; N 8.24; calculated for $C_{19}H_{19}F_3N_2O$, % C 65.51; H 5.50; N 8.04.

4-Hydroxy-3-dimethylaminomethyl-6-trifluoromethyl-2-phenylindole 9:

Aqueous 33% dimethylamine (1.9 m, 0.01 mol) and aqueous 30% formalin (1 ml, 0.01 mol) were added dropwise to a suspension of indole **4a** (3.34 g, 0.01 mol) in water (30 ml). The reaction was run at 50 °C for 30 min. After the starting compound had reacted (HPLC), the reaction mass was cooled. The obtained oily product was separated from the liquid phase and chromatographed on silica gel ($CHCl_3$).

Yield 50%. Mp = 87-88 ºC.

^{1}H NMR spectrum: 2.31 (s, 6H); 3.80 (s, 2H); 6.48 (s, 1H); 7.08 (s, 1H); 7.41-7.43 (m, 1H); 7.51-7.53 (m, 2H); 7.71-7.74 (m, 2H); 11.61 (s, 1H); 14.2 (s, 1H). Mass spectrum, m/z: 334 (M^+).

^{13}C NMR spectrum: 43.2, 98.7, 100.1, 108.5, 114.2, 118.0, 119.9, 121.8, 123.7, 125.1, 125.6, 128.0, 128.6, 128.7, 131.7, 135.9, 137.0

^{19}F NMR spectrum: -59.57

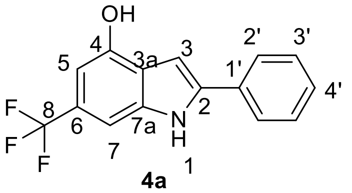
Elemental analysis: found, %: C 64.42; H 5.35; N 8.50; calculated for $C_{18}H_{17}F_3N_2O$, % C 64.66; H 5.13; N 8.38.

Bioassays of fungicidal activities

Antifungal activities were tested according to the conventional procedure [Ref. 8 of the main text] with six phytopathogenic fungi from different taxonomic classes: *S. sclerotiorum* (S.s.), *F. oxysporum* (F.o.), *F. moniliforme* (F.m.), *B. sorokiniana* (B.s.), *R. solani* (R.s.), and *V. inaequalis* (V.i.). The effect of the chemicals on mycelial radial growth was determined by dissolving them at the various concentration in acetone and suspending aliquots in potato-saccharose agar at 50 ºC to give the required series of concentration (1-60 μg cm^{-1}). The final acetone concentration of both fungicide-containing and control samples was 10 mL dm^{-1}. Petri dishes containing 15 ml of the agar medium were inoculated by placing 2-mm micelial agar discs on the agar surface. Plates were incubated at 25 ºC. The mixed medium without the sample was used as the blank control. Three replicates of each test were carried out. The mycelium elongation diameter (mm) of fungi settlements was measured after 72 h of culture. Growth inhibition rates were calculated by the following equation: $I = [(D_C - D_T)/D_C] \times 100\%$. Here I is a growth inhibition rate (%), D_C is the control settlement diameter (mm), and D_T is the treatment group fungi settlement diameter (mm). The results are summarized in Tables 2 and 3 of the mail text.

2. ^{1}H NMR, ^{13}C NMR and 2D-NMR spectra of compound 4a

Table S1. ^{1}H, ^{19}F and 1^{3}C NMR spectroscopy for compound 4a.



4a

Atom	^{1}H (19F)	^{13}C	HMBC interactions
1	11.85, s.	-	
2	-	131.67	H-1,3,2’
3	7.04, s.	96.55	H-1
3a	-	121.40	H-1,5,7
4	10.13 br. s. (4-OH)	151.00	H-3,5
5	6.64, s.	99.51, , q. J = 3.3 Hz	H-7
6	-	122.93, q. J = 32.3 Hz	H-5,7
8	(-59.95)	127.66, q. J = 329.1 Hz	H-5,7
7	7.21, s.	100.29, q. J = 4.4 Hz	H-5
7a	-	137.66	H-1,7
1’	-	138.56	H-1,2',3'
2’	7.87, d., J = 7.8 Hz	125.15	H-2’,4’
3’	7.47, t., J = 7.7 Hz	128.99	H-2’,3’,4’
4’	7.34, t., J = 7.7 Hz	127.81	H-2’,3’

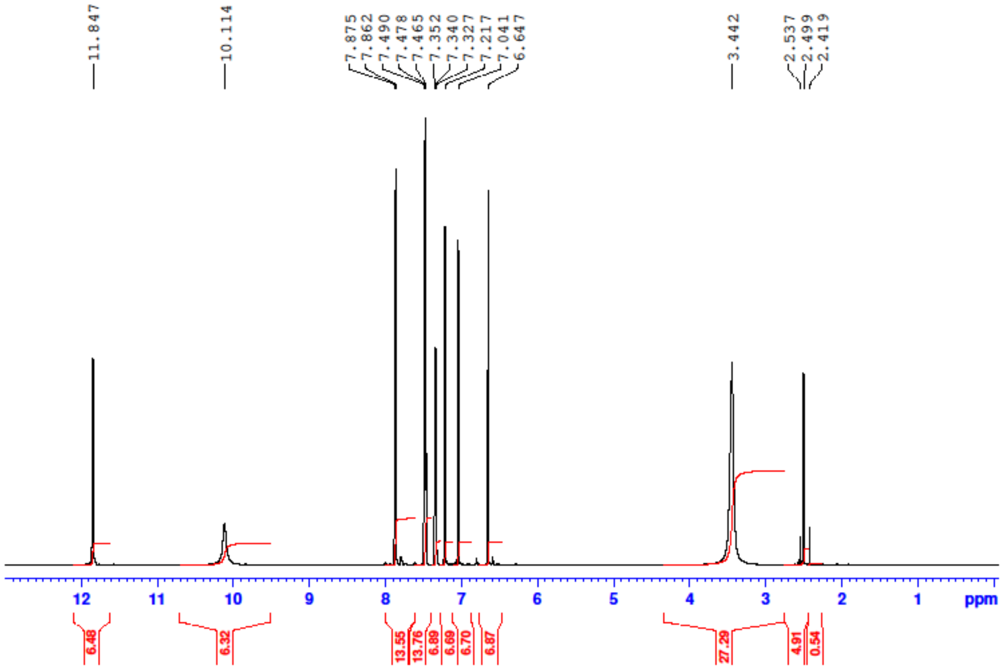


Figure S1. ^{1}H NMR spectrum at 600 MHz, DMSO-d$_6$ for compound 4a.

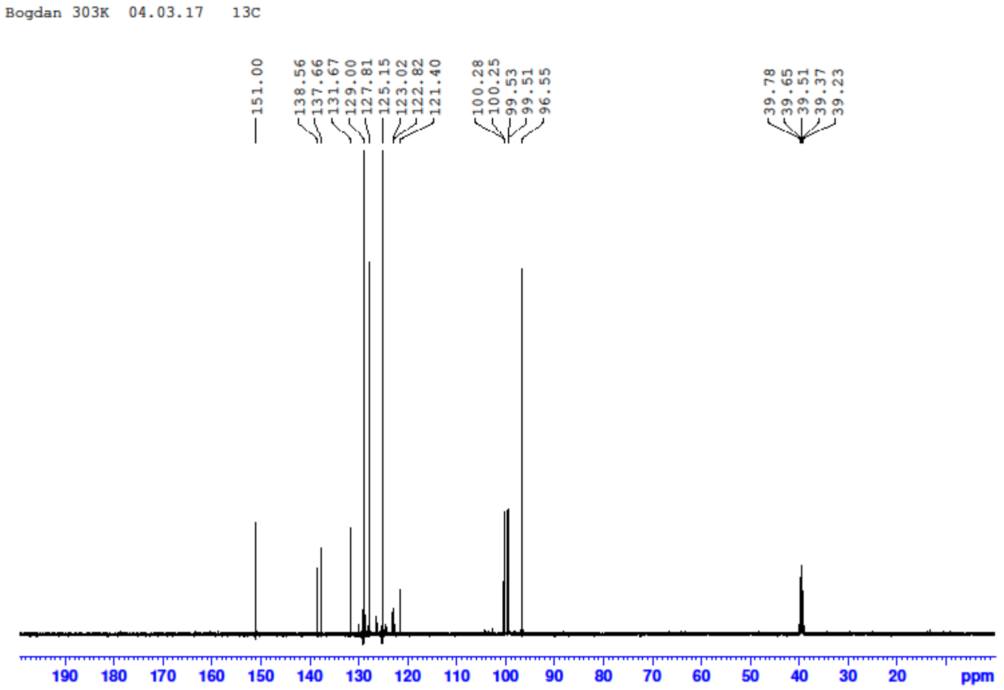


Figure S2. ^{13}C NMR spectrum at 150 MHz, DMSO-d$_6$ for compound 4a.

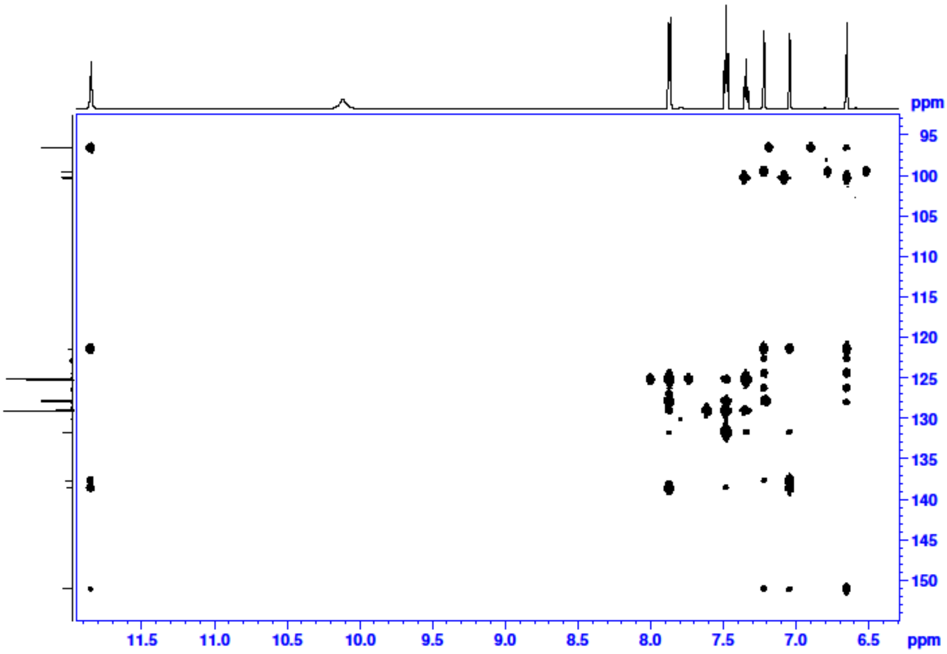


Figure S3. gHMBC NMR spectrum no 1 for compound 4a.

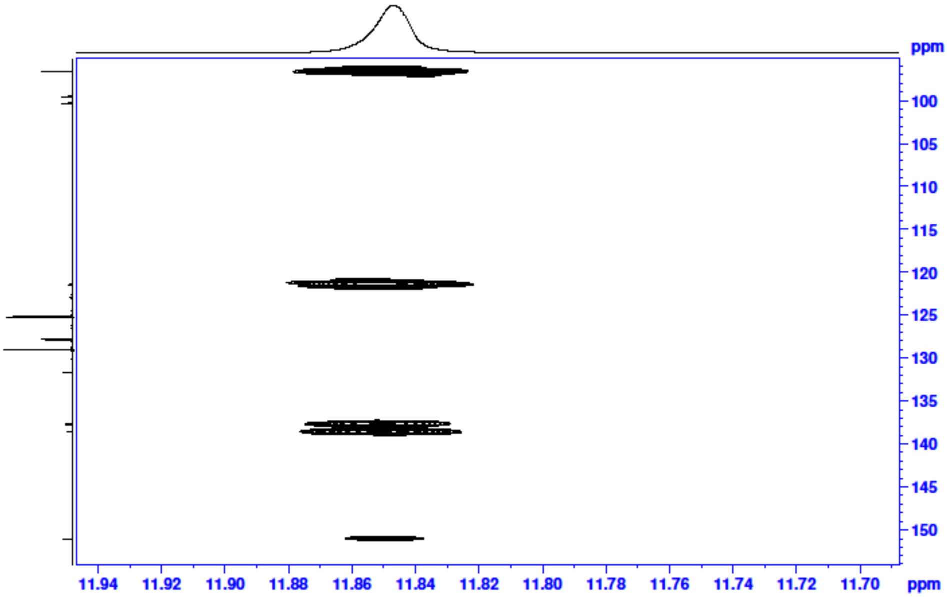


Figure S4. gHMBC NMR spectrum no 2 for compound 4a.

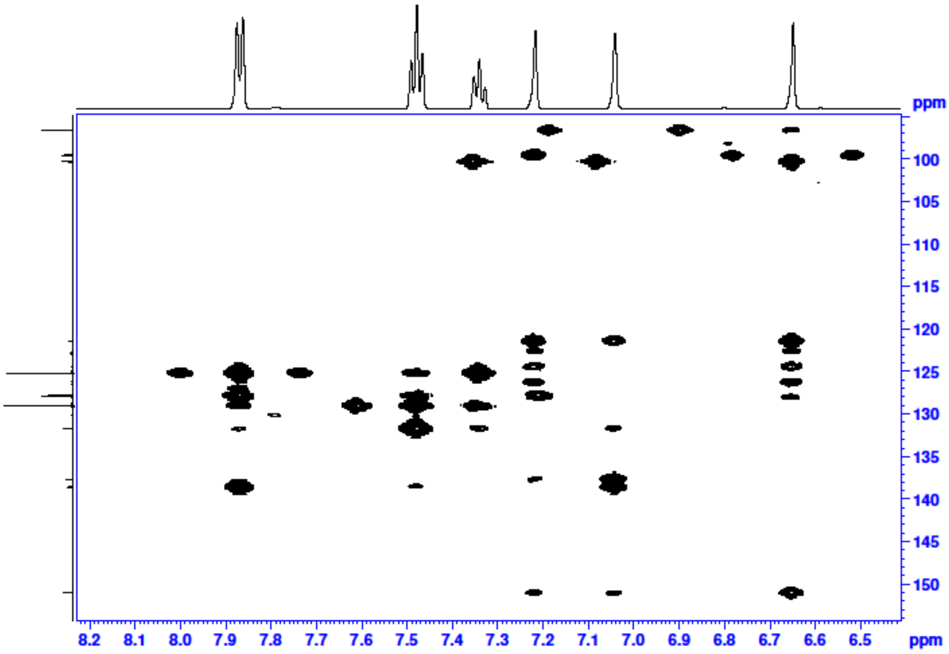


Figure S5. gHMBC NMR spectrum no 3 for compound 4a.

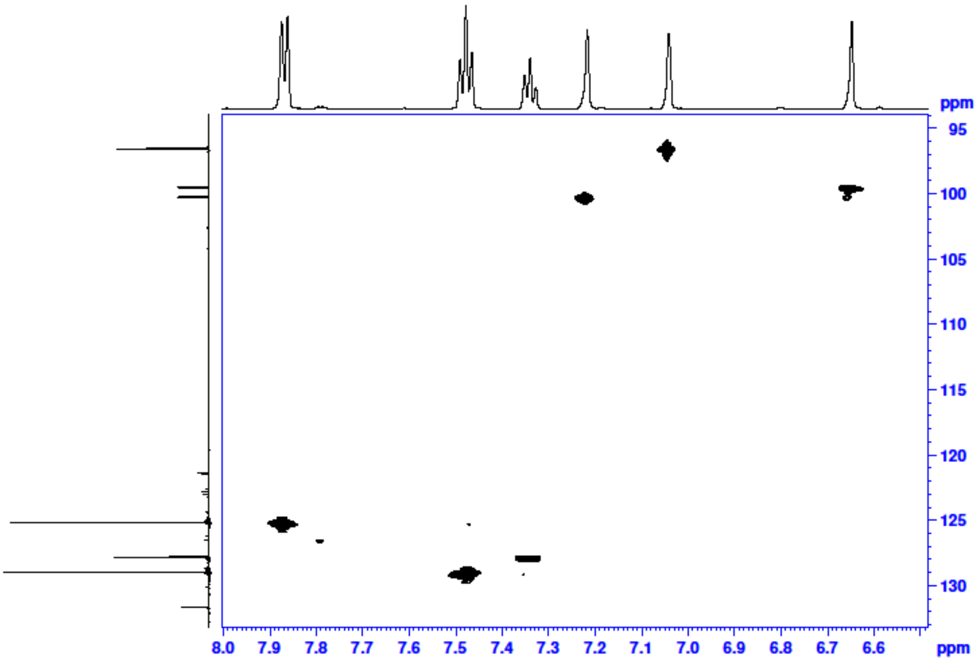


Figure S6. gHSQC NMR spectrum for compound 4a.

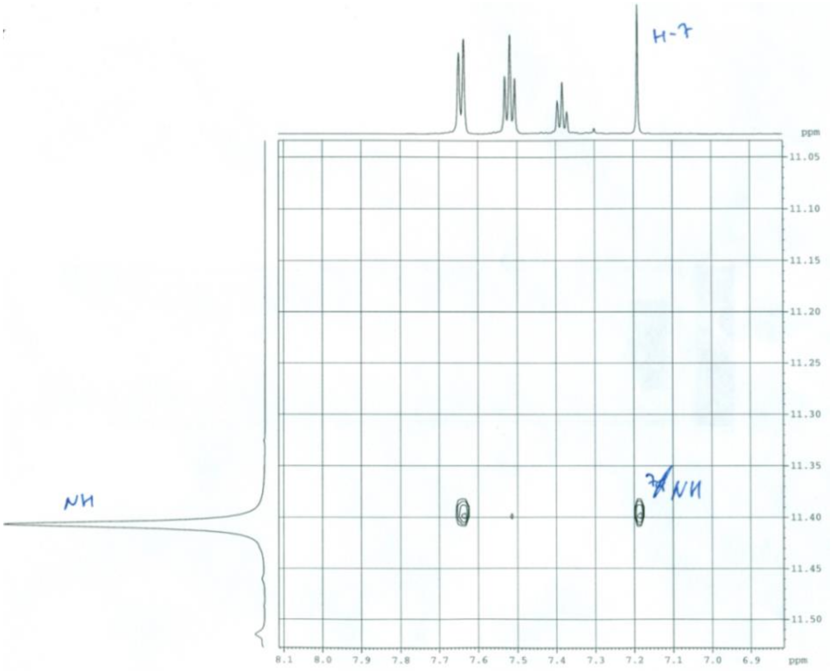


Figure S7. ROESY for compound 8.