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Supporting Information

for

Synthesis and characterisation of new antimalarial fluorinated triazolopyrazine compounds

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General experimental procedures, NMR spectra and characterisation data for all new triazolopyrazine compounds and X-ray crystallography data for compounds 5, 6 and 18

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S1: General experimental procedures

Melting points were measured using a Cole-Parmer melting point apparatus and are uncorrected. UV spectra were recorded using an Ocean Optics (USB-ISS-UV/VIS) spectrophotometer. NMR spectra were recorded at 25 °C on a Bruker AVANCE III HD 800 MHz NMR spectrometer equipped with a cryoprobe. The ^{1}H and ^{13}C chemical shifts were referenced to solvent peaks for $CDCl_3$ at δ_H 7.26 and δ_C 77.16, respectively. LRESIMS data were recorded on an Ultimate 3000 RS UHPLC coupled to a Thermo Fisher Scientific MSQ Plus single quadruple ESI mass spectrometer. HRESIMS data were acquired on a Bruker SolariX XR 12T FT-ICR-MS. GRACE Davisil C_{18}-bonded silica (35–70 µm, 60 Å) was used for pre-adsorption work before HPLC separations, and the pre-absorbed sample was packed into an Alltech stainless steel guard cartridge (10 × 30 mm). A Thermo Fisher Scientific Dionex Ultimate 3000 UHPLC was used for semipreparative HPLC separations. A Thermo Electron Betasil C_{18}-bonded silica column (5 µm, 100 Å, 150 × 21.2 mm) and a Thermo Betasil phenyl-bonded silica column (5 µm, 100 Å, 150 × 21.2 mm) were used for semipreparative HPLC separations. All solvents used for chromatography, UV and MS were Honeywell Burdick & Jackson or Lab-Scan HPLC grade. H_2O was filtered using a Sartorius Stedium Arium Pro VF ultrapure water system. All chemical reagents were purchased from Sigma-Aldrich.

S2: General procedure for coupling of primary alcohols with chloro-heterocycle scaffolds

The chloro-heterocycle scaffold (0.4 mmol), primary alcohol (0.4 mmol, 1.0 eq.), KOH (67 mg, 1.2 mmol, 3.0 eq.) and 18-crown-6 (8 mg, 32 µmol, 0.08 eq.) were dissolved in anhydrous acetonitrile (2 mL) and the reaction mixture stirred at room temperature for 2 h then preadsorbed to silica (~1 g) overnight. Purification was performed on an Isolute (10 g, silica, 55 µm, 54 Å) SPE cartridge using a 2% stepwise elution from 100% CH_2Cl_2 to 6% MeOH/94% CH_2Cl_2 with five fractions (10 mL each) collected for each elution. The 20 resulting fractions were all analysed by silica TLC (solvent system: 5% MeOH/96% CH_2Cl_2) and UV-active (254 nm) samples were further evaluated by ^{1}H NMR spectroscopy and LCMS in order to identify product of interest; only fractions containing the desired product in high purity (>95%) were combined. All ether triazolopyrazines eluted from the silica SPE cartridge with 4% MeOH/96% CH_2Cl_2 in yields ranging from 54 to 78%.

S3: X-ray crystallography analysis

Intensity data for compounds **5**, **6**, **18** were collected with an Oxford Diffraction Synergy diffractometer with Cu Kα radiation, and the temperature during data collection was maintained at 100.0(1) K using an Oxford Cryosystems cooling device. The structure of each

compound was solved by direct methods and difference Fourier synthesis [1]. Hydrogen atoms were placed in their idealized positions and included in subsequent refinement cycles. Thermal ellipsoid plots were generated in Mercury [2] within the WINGX suite of programs [3]. Crystallographic data for compounds **5** (CCDC 2195529), **6** (CCDC 2195531) and **18** (CCDC 2195530) have been deposited with the Cambridge Crystallographic Data Centre. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

S4: In vitro anti-plasmodial image-based assay

Plasmodium falciparum 3D7 and Dd2 parasites were cultured in RPMI1640 (Life Technologies, Camarillo, CA, USA) supplemented with 2.5 mg/mL Albumax II, 5% AB human serum, 25 mM HEPES, and 0.37mM hypoxanthine. Ring stage parasites were treated with compounds following two rounds of sorbitol synchronization, as previously described [4]. Artesunate and pyrimethamine were incorporated as controls. Following incubation of assay plates for 72 h at 37 °C, and 5% CO_2 and 5% O_2, parasites were stained with 2-(4-amidinophenyl)-1H-indole-6-carboxamidine (DAPI) and imaged using an Opera Phenix™ High Content Screening System (PerkinElmer, Waltham, MA, USA). Images were analysed using Harmony software (PerkinElmer, Waltham, MA, USA).

S5: In vitro cytotoxicity assay

Human embryonic kidney (HEK293) cells were maintained in DMEM (Life Technologies, Camarillo, CA, USA) containing 10% FBS (Hyclone™ ThermoFisher, Melbourne, Australia). Cytotoxicity testing was undertaken, as previously described [5]. In brief, 5 µL of test compound was added to the well of black/clear tissue culture-treated, 384-well plates containing 3000 adherent HEK 293 cells/well in 45 µL and incubated 72 h at 37 °C in 5% CO_2. After incubation, the supernatant was removed and replaced with 40 µL of 10% Alamar Blue per well. Plates were incubated for 5−6 h and measured for fluorescence at 530-nm excitation and 595-nm emission. The % inhibition was calculated using 0.4% DMSO (no inhibition) and 5 µM puromycin (100% inhibition) data. IC_{50} values were obtained by plotting % inhibition against log dose using GraphPad Prism v.6 (San Diego, CA, USA) nonlinear regression with a variable slope plot.

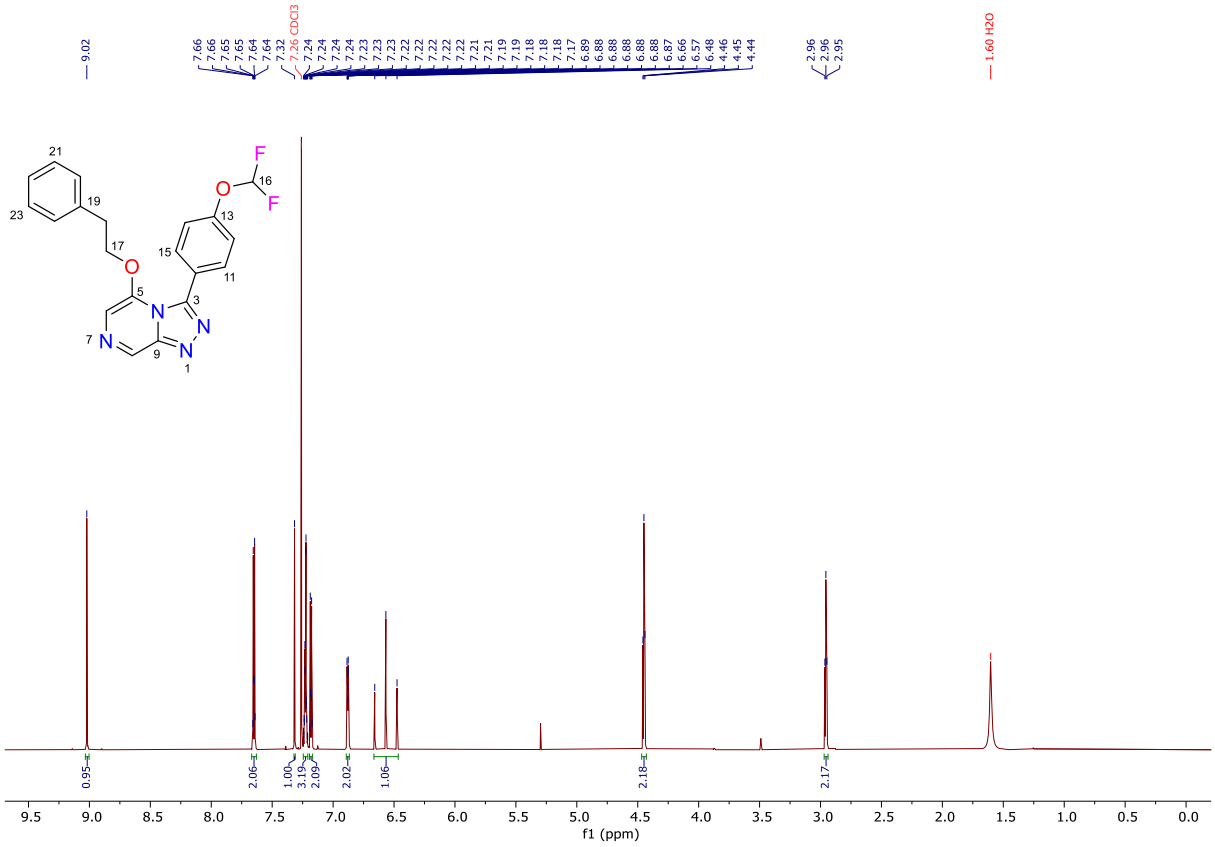
S6: *3-(4-(difluoromethoxy)phenyl)-5-phenethoxy-[1,2,4]triazolo[4,3-a]pyrazine* (**4**) [6] White amorphous solid (119 mg, 78%); UV (MeOH) λ_{max} (log ε) 240 (4.40), 285 (4.01), 307 (3.99) nm; LRESIMS *m/z* 383 $[M + H]^+$; HRESIMS *m/z* 383.1318 $[M + H]^+$ (calcd for $C_{20}H_{17}F_2N_4O_2$, 383.1314).

Table S1: NMR data of compound **4** in $CDCl_3$[a]

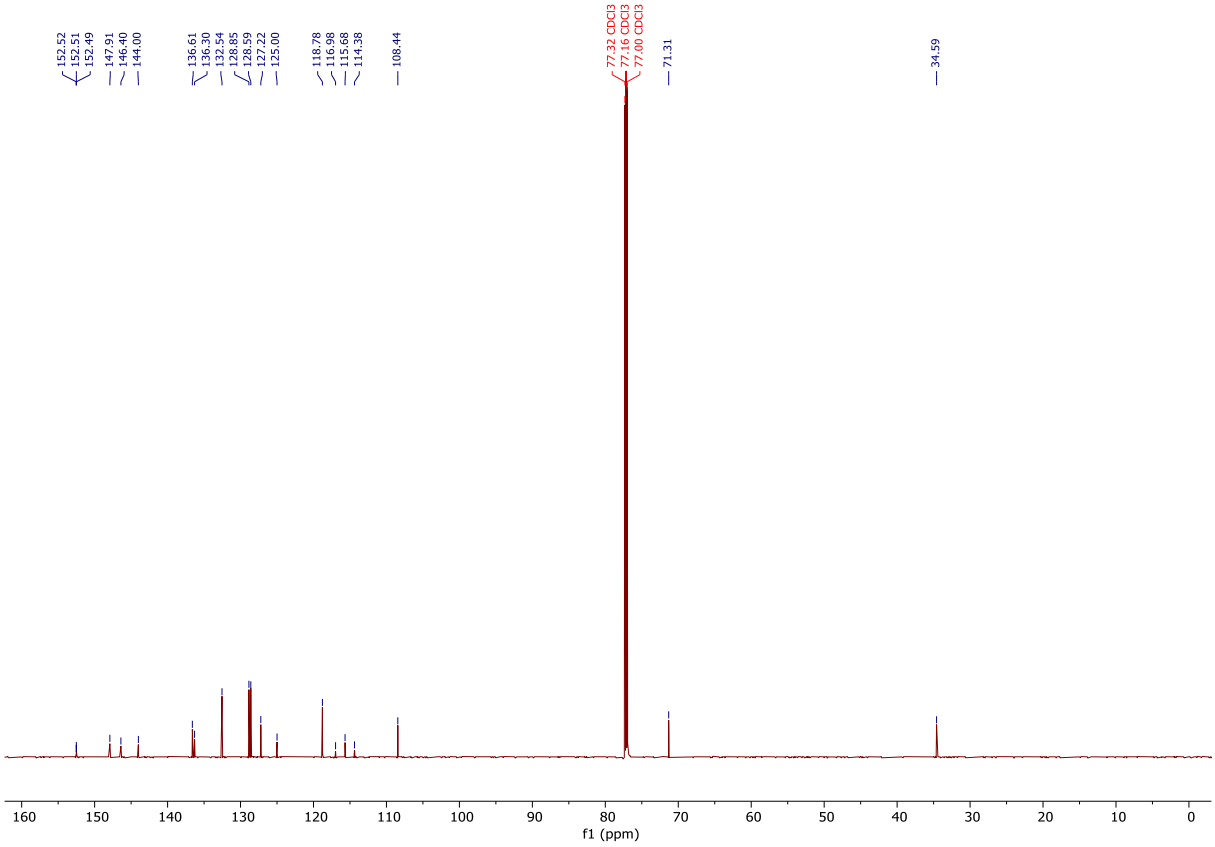
Position	δ_H, mult. (*J* in Hz), int.	δ_C, mult. (*J* in Hz)	COSY	HMBC	ROESY
3		146.4, s			
5		144.0, s			
6	7.32, s, 1H	108.4, s		5, 8	17
8	9.02, s, 1H	136.6, s		5, 6, 9	
9		147.9, s			
10		125.0, s			
11	7.65, m, 1H	132.5, s	12	3, 13, 15	12
12	7.18, m, 1H	118.8, s	11	10, 14	11
13		152.5, t (2.7)			
14	7.18, m, 1H	118.8, s	15	10, 12	15
15	7.65, m, 1H	132.5, s	14	3, 11, 13	14
16	6.57, t (73.1), 1H	115.7, t (261.1)		13	
17	4.45, t (6.5), 2H	71.3, s	18	5, 18, 19	6, 18
18	2.96, t (6.5), 2H	34.6, s	17	17, 19, 20, 24	17, 20, 24
19		136.3, s			
20	6.88, m, 1H	128.6, s	21	18, 22, 24	18, 21
21	7.23, m, 1H	128.9, s	20	19, 23	20
22	7.22, m, 1H	127.2, s		20, 24	
23	7.23, m, 1H	128.9, s	24	19, 21	24
24	6.88, m, 1H	128.6, s	23	18, 20, 22	18, 23

[a]Recorded at 800 MHz (^{1}H NMR) and 200 MHz (^{13}C NMR) at 25 °C.

S7: ^{1}H NMR spectrum of compound **4** in $CDCl_3$



S8: ^{13}C NMR spectrum of compound **4** in $CDCl_3$[a]



S9: *3-(4-chlorophenyl)-5-phenethoxy-[1,2,4]triazolo[4,3-a]pyrazine* (**5**)

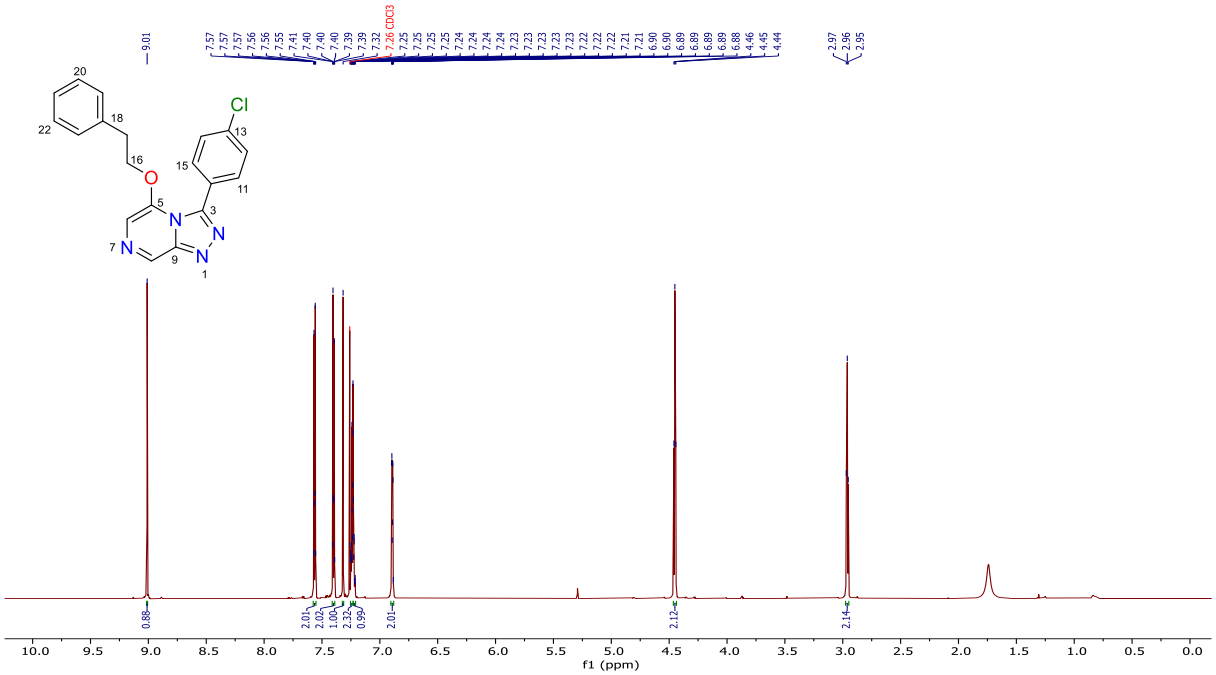
Yellow amorphous solid (107 mg, 75%); mp 131–132 °C; UV (MeOH) λ_{max} (log ε) 242 (4.30), 290 (3.96) nm; LRESIMS *m/z* 351 $[M + H]^+$; HRESIMS *m/z* 351.1007 $[M + H]^+$ (calcd for $C_{19}H_{16}ClN_4O$, 351.1007).

Table S2: NMR data of compound **5** in $CDCl_3$[a]

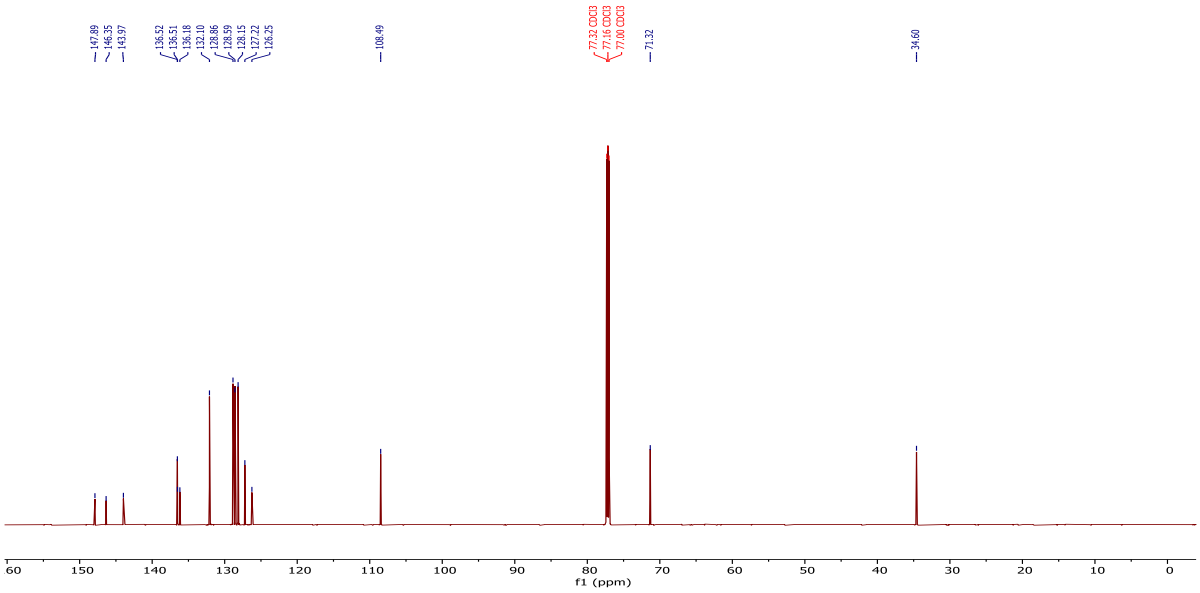
Position	δ_H, mult. (*J* in Hz), int.	δ_C, mult. (*J* in Hz)	COSY	HMBC	ROESY
3		146.4, s			
5		144.0, s			
6	7.32, s, 1H	108.5, s		5, 8	16
8	9.01, s, 1H	136.52, s		5, 6, 9	
9		147.9, s			
10		126.3, s			
11	7.56, m, 1H	132.1, s	12	3, 13, 15	12
12	7.40, m, 1H	128.2, s	11	10, 14	11
13		136.51, s			
14	7.40, m, 1H	128.2, s	15	10, 12	15
15	7.56, m, 1H	132.1, s	14	3, 11, 13	14
16	4.45, t (6.5), 2H	71.3, s	17	5, 17, 18	6, 17
17	2.96, t (6.5), 2H	34.6, s	16	16, 18, 19, 23	16, 19, 23
18		136.2, s			
19	6.89, m, 1H	128.6, s	20	17, 21, 23	16, 17, 20
20	7.24, m, 1H	128.9, s	19	18, 22	19
21	7.23, m, 1H	127.2, s		19, 23	
22	7.24, m, 1H	128.9, s	23	18, 20	23
23	6.89, m, 1H	128.6, s	22	17, 19, 21	16, 17, 22

[a]Recorded at 800 MHz (^{1}H NMR) and 200 MHz (^{13}C NMR) at 25 °C.

S10: ^{1}H NMR spectrum of compound **5** in $CDCl_3$



S11: ^{13}C NMR spectrum of compound **5** in $CDCl_3$



S12: *4-(5-phenethoxy-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)benzonitrile* (**6**)

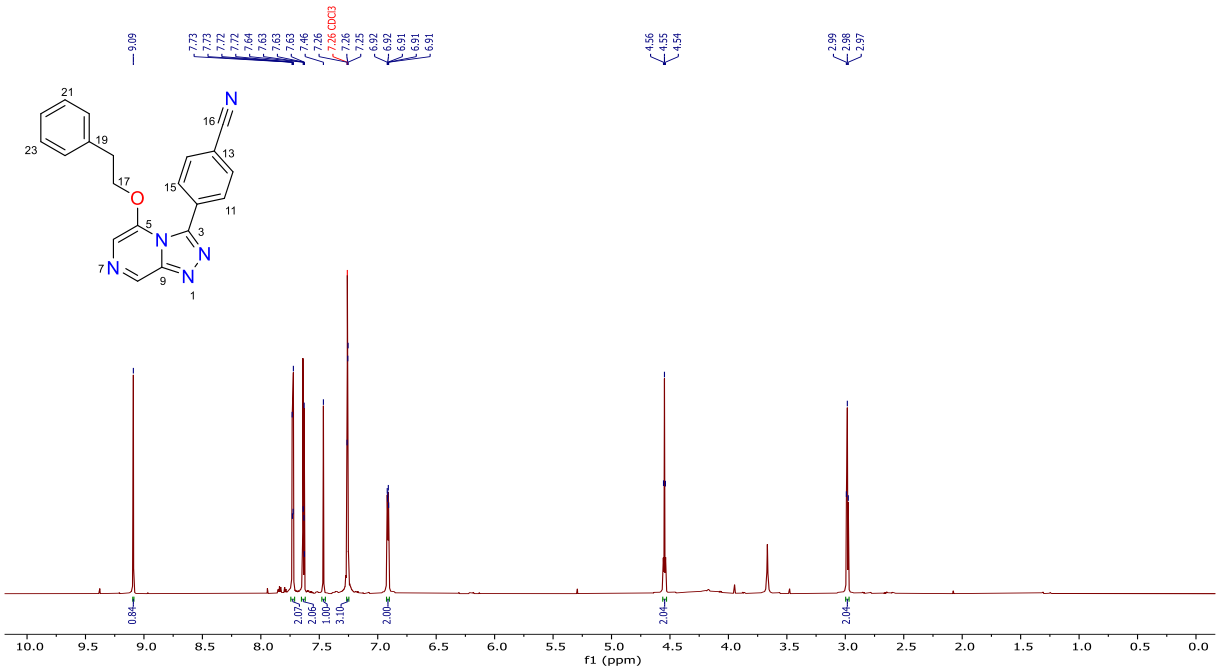
White amorphous solid (74 mg, 54%); mp 136–138 °C; UV (MeOH) λ_{max} (log ε) 261 (4.34), 311 (3.76) nm; LRESIMS *m/z* 342 $[M + H]^+$; HRESIMS *m/z* 342.1348 $[M + H]^+$ (calcd for $C_{20}H_{16}N_5O$, 342.1349).

Table S3: NMR data of compound **6** in $CDCl_3$[a]

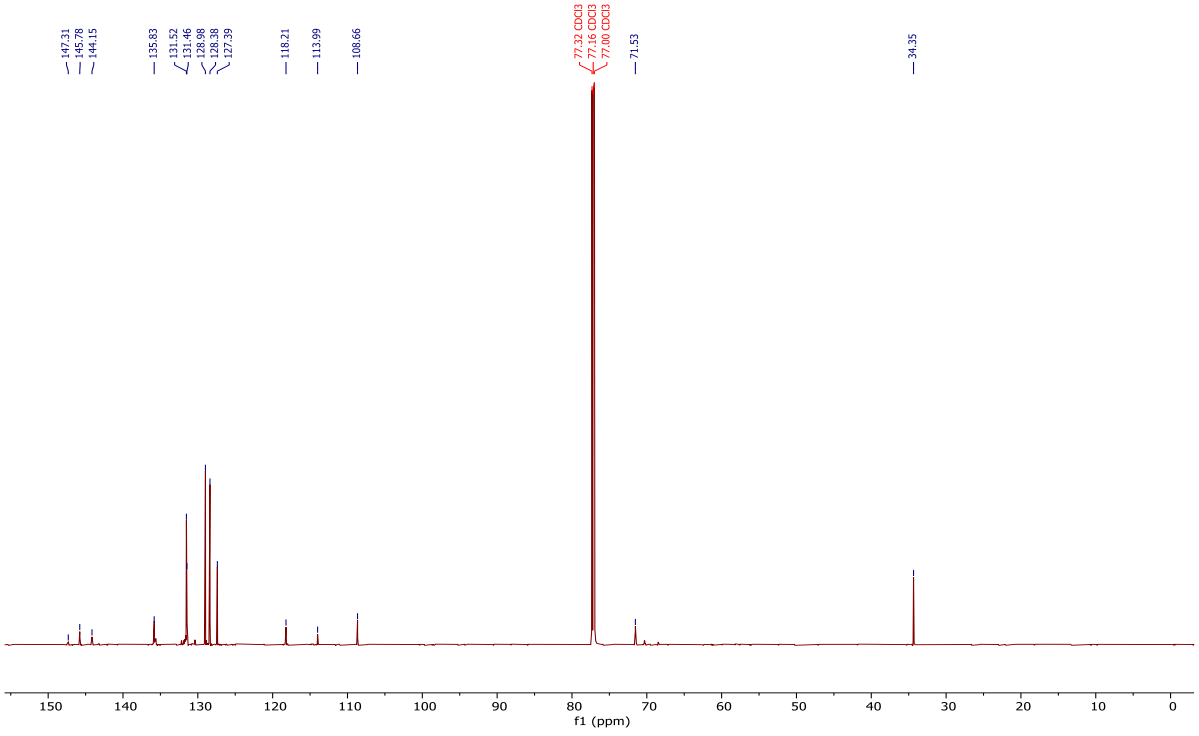
Position	δ_H, mult. (*J* in Hz), int.	δ_C, mult. (*J* in Hz)	COSY	HMBC	ROESY
3		145.8, s			
5		144.2, s			
6	7.46, s, 1H	108.7, s		5, 8	17
8	9.09, s, 1H	135.8, s		5, 6, 9	
9		147.3, s			
10		131.52, s			
11	7.73, m, 1H	131.46, s	12	3, 13, 15	
12	7.63, m, 1H	131.52, s	11	10, 14, 16	
13		114.0, s			
14	7.63, m, 1H	131.52, s	15	10, 12, 16	
15	7.73, m, 1H	131.46, s	14	3, 11, 13	
16		118.2, s			
17	4.55, t (6.5), 2H	71.5, s	18	5, 18, 19	6, 18, 20, 24
18	2.98, t (6.5), 2H	34.4, s	17	17, 19, 20, 24	17, 20, 24
19		135.8, s			
20	6.91, m, 1H	128.4, s	21	18, 22, 24	17,18, 21
21	7.26, m, 1H	129.0, s	20	19, 23	
22	7.25, m, 1H	127.4, s		20, 24	
23	7.26, m, 1H	129.0, s	24	19, 21	
24	6.91, m, 1H	128.4, s	23	18, 20, 22	17, 18, 23

[a]Recorded at 800 MHz (^1H NMR) and 200 MHz (^{13}C NMR) at 25 °C.

S13: ^{1}H NMR spectrum of compound **6** in $CDCl_3$



S14: ^{13}C NMR spectrum of compound **6** in $CDCl_3$



S15: *3-(4-(difluoromethoxy)phenyl)-5-ethoxy-[1,2,4]triazolo[4,3-a]pyrazine* (**7**)

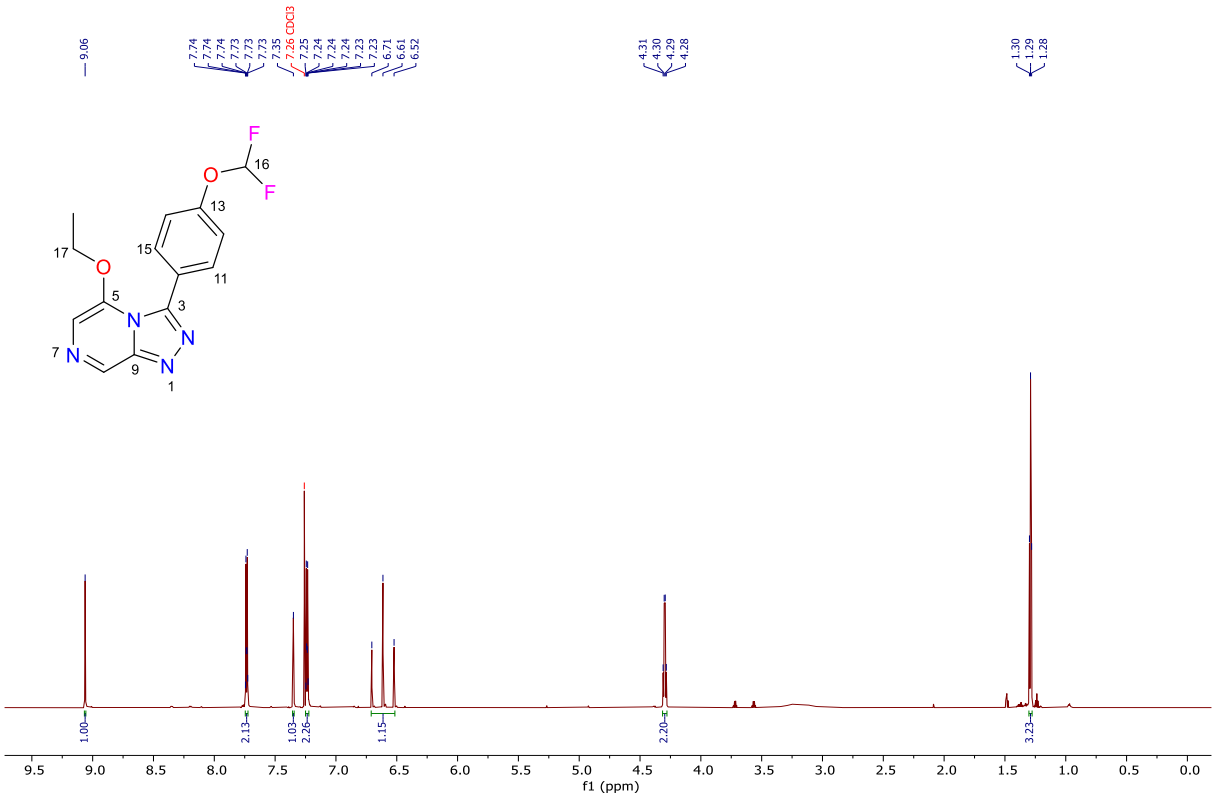
Yellow amorphous solid (72 mg, 58%); UV (MeOH) λ_{max} (log ε) 240 (4.21), 285 (3.83), 307 (3.78) nm; LRESIMS *m/z* 307 [M + H]$^+$; HRESIMS *m/z* 307.1000 [M + H]$^+$ (calcd for $C_{14}H_{13}F_2N_4O_2$, 307.1001).

Table S4: NMR data of compound **7** in $CDCl_3$[a]

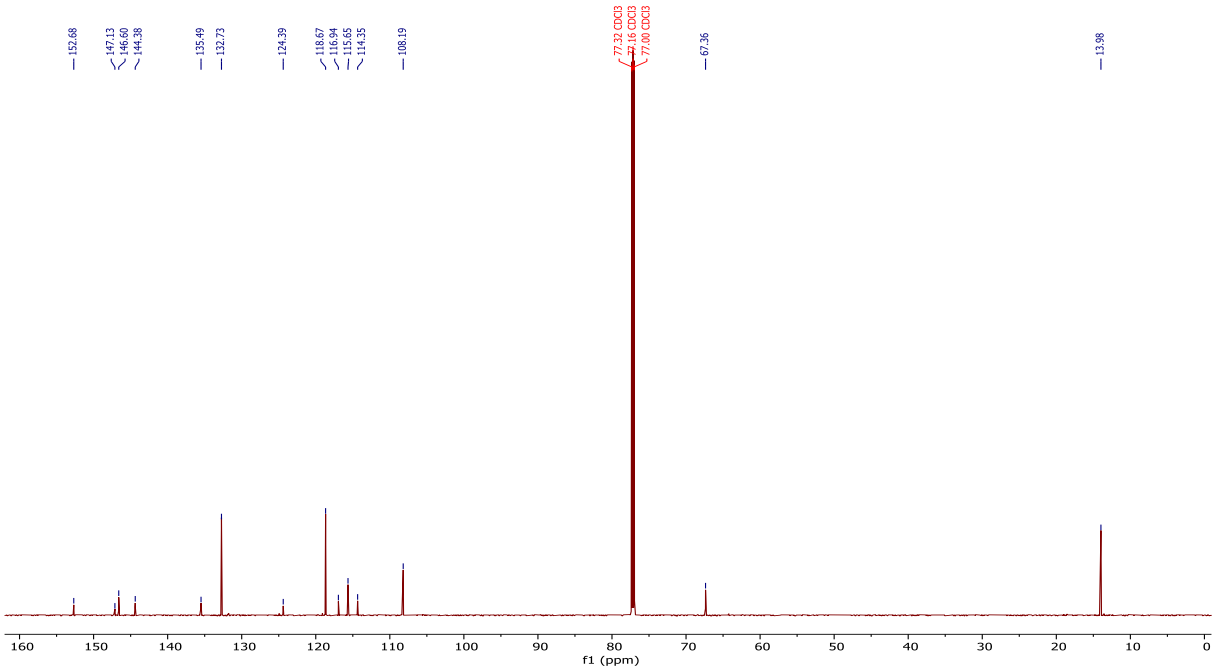
Position	δ_H, mult. (*J* in Hz), int.	δ_C, mult. (*J* in Hz)	COSY	HMBC	ROESY
3		146.6, s			
5		144.4, s			
6	7.35, s, 1H	108.2, s		5, 8	17
8	9.06, s, 1H	135.5, s		5, 6, 9	
9		147.1, s			
10		124.4, s			
11	7.73, m, 1H	132.7, s	12	3, 13, 15	12
12	7.24, m, 1H	118.7, s	11	10, 14	11
13		152.7, t (2.5)			
14	7.24, m, 1H	118.7, s	15	10, 12	15
15	7.73, m, 1H	132.7, s	14	3, 11, 13	14
16	6.61, t (73.6), 1H	115.7, t (262.2)		13	
17	4.30, q (7.0), 2H	67.4, s	18	5, 18	6, 18
18	1.29, t (7.0), 3H	14.0, s	17	17	17

[a]Recorded at 800 MHz (^{1}H NMR) and 200 MHz (^{13}C NMR) at 25 °C.

S16: ^{1}H NMR spectrum of compound **7** in $CDCl_3$



S17: ^{13}C NMR spectrum of compound **7** in $CDCl_3$



S18: *3-(4-chlorophenyl)-5-ethoxy-[1,2,4]triazolo[4,3-a]pyrazine* (**8**)

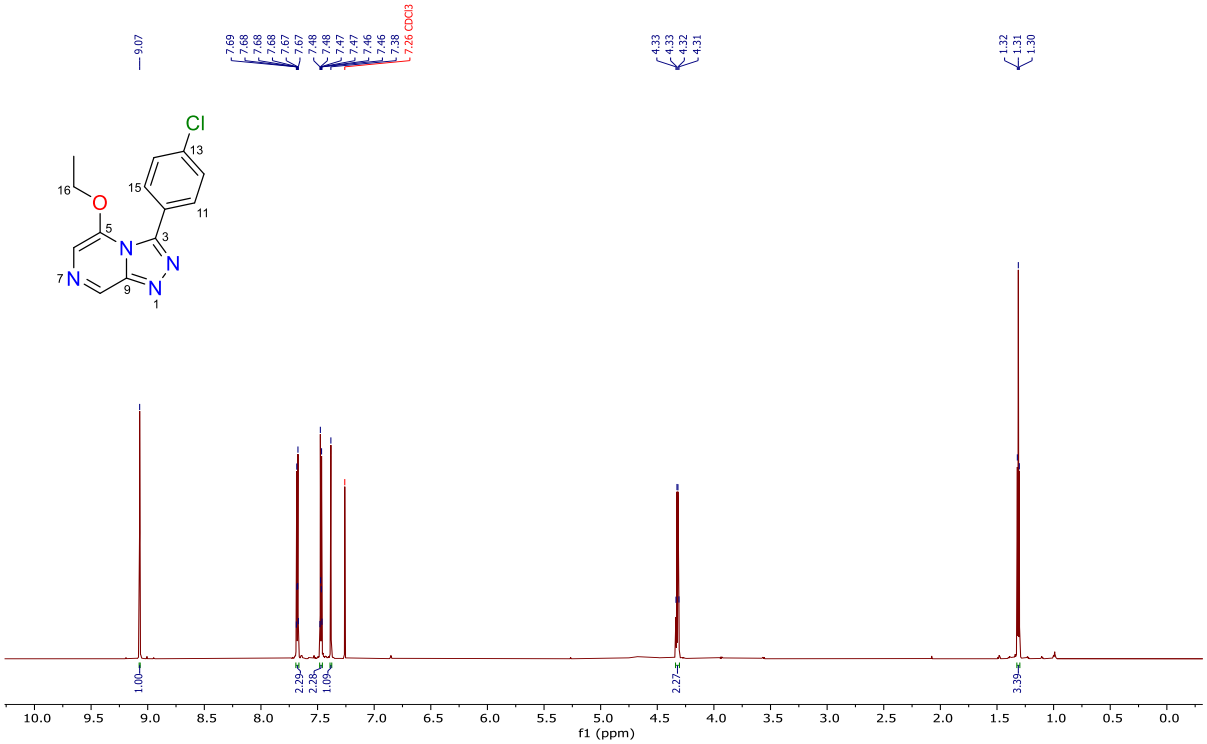
Pale yellow amorphous solid (35 mg, 64%); UV (MeOH) λ_{max} (log ε) 242 (4.12), 286 (3.76), 310 (3.70) nm; LRESIMS *m/z* 275 $[M + H]^+$; HRESIMS *m/z* 275.0698 $[M + H]^+$ (calcd for $C_{13}H_{12}ClN_4O$, 275.0694).

Table S5: NMR data of compound **8** in $CDCl_3$[a]

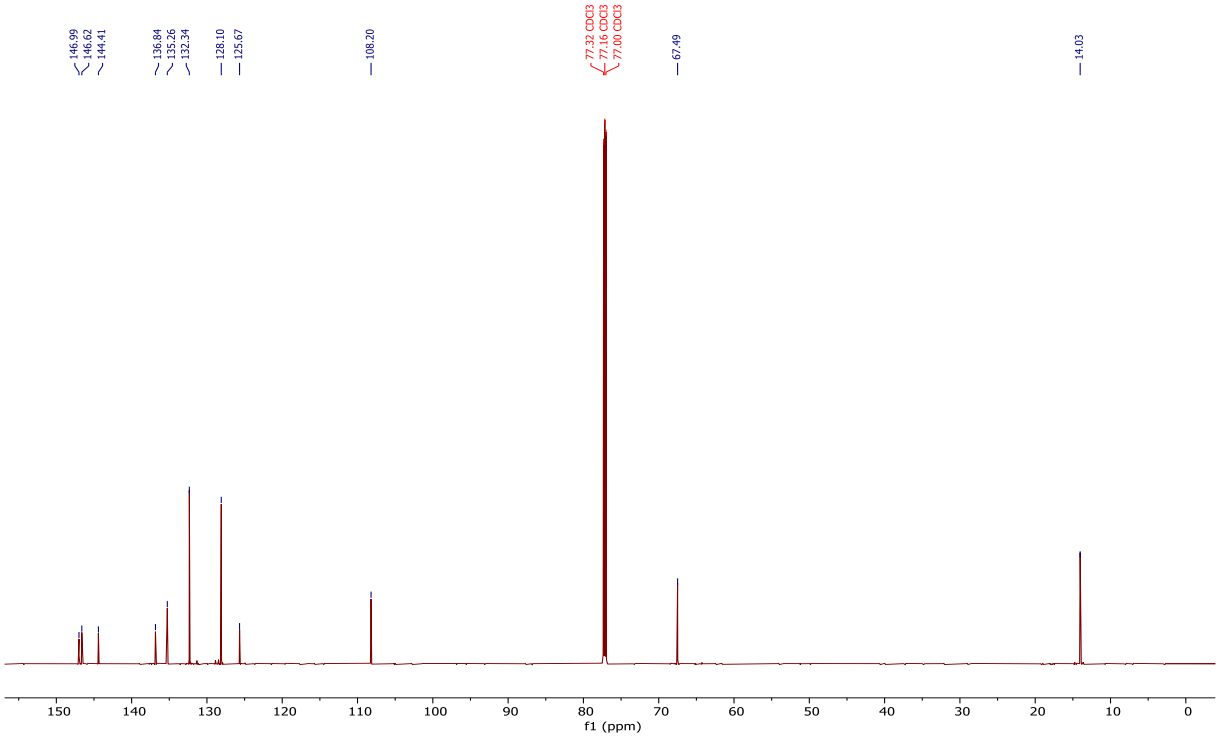
Position	δ_H, mult. (*J* in Hz), int.	δ_C, mult. (*J* in Hz)	COSY	HMBC	ROESY
3		146.6, s			
5		144.4, s			
6	7.38, s, 1H	108.2, s		5, 8	16
8	9.07, s, 1H	135.3, s		5, 6, 9	
9		147.0, s			
10		125.7, s			
11	7.68, m, 1H	132.3, s	12	3, 13, 15	12
12	7.47, m, 1H	128.1, s	11	10, 14	11
13		136.8, s			
14	7.47, m, 1H	128.1, s	15	10, 12	15
15	7.68, m, 1H	132.3, s	14	3, 11, 13	14
16	4.33, q (7.0), 2H	67.5, s	17	5, 17	6, 17
17	1.31, t (7.0), 3H	14.0, s	16	16	16

[a]Recorded at 800 MHz (^1H NMR) and 200 MHz (^{13}C NMR) at 25 °C.

S19: ^{1}H NMR spectrum of compound **8** in $CDCl_3$



S20: ^{13}C NMR spectrum of compound **8** in $CDCl_3$



S21: *4-(5-ethoxy-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)benzonitrile* (**9**)

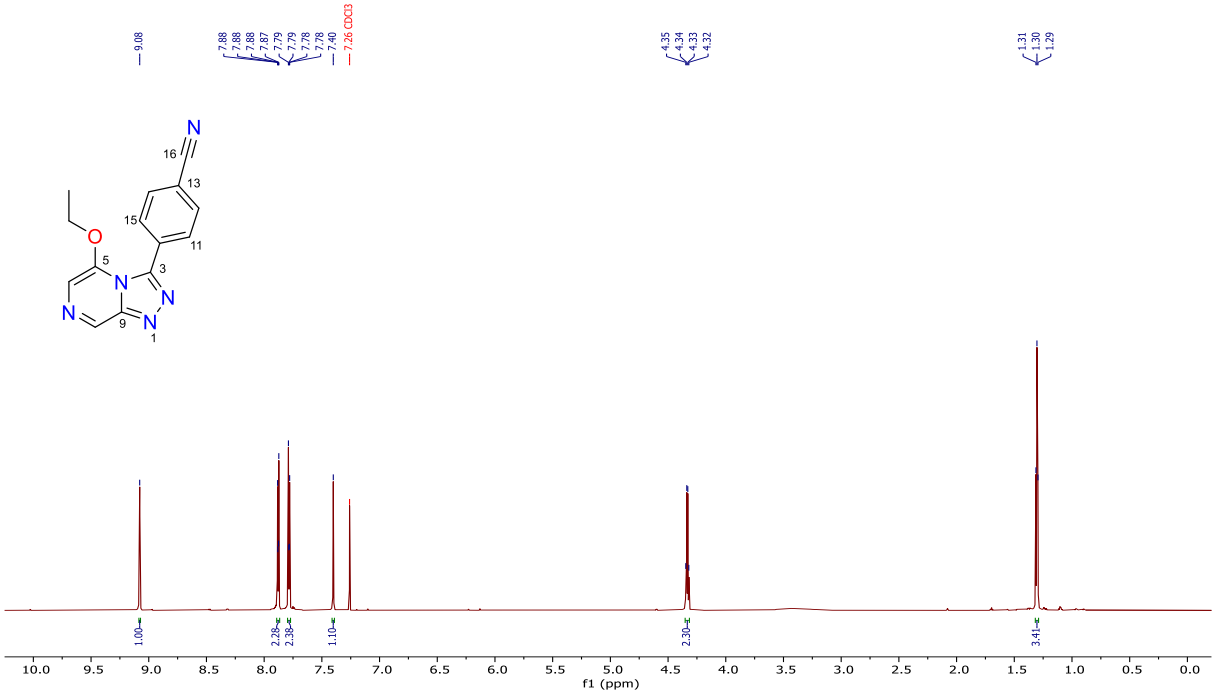
Pale yellow amorphous solid (43 mg, 41%); UV (MeOH) λ_{max} (log ε) 223 (4.03), 246 (3.97), 297 (3.83) nm; LRESIMS *m/z* 266 $[M + H]^+$; HRESIMS *m/z* 266.1036 $[M + H]^+$ (calcd for $C_{14}H_{12}N_5O$, 266.1036).

Table S6: NMR data of compound **9** in $CDCl_3$[a]

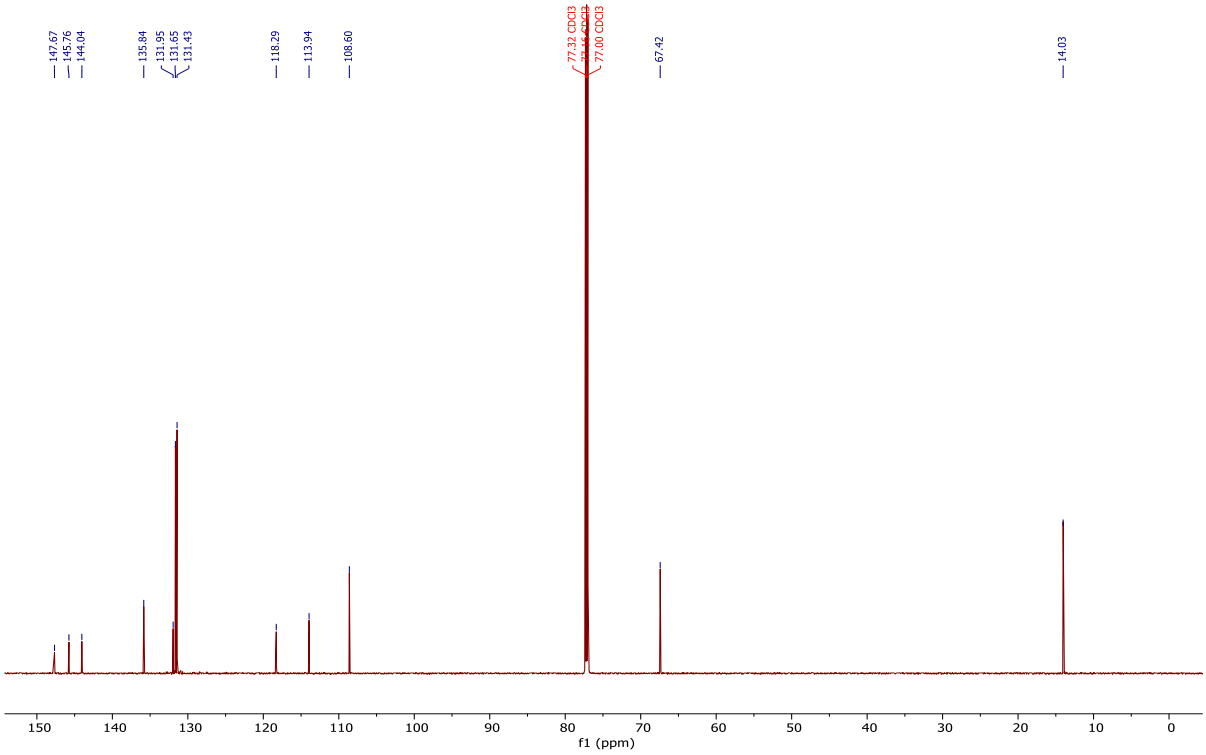
Position	δ_H, mult. (*J* in Hz), int.	δ_C, mult. (*J* in Hz)	COSY	HMBC	ROESY
3		145.8, s			
5		144.0, s			
6	7.40, s, 1H	108.6, s		5, 8	16
8	9.08, s, 1H	135.8, s		5, 6, 9	
9		147.7, s			
10		132.0, s			
11	7.88, m, 1H	131.7, s	12	3, 13, 15	12
12	7.78, m, 1H	131.4, s	11	10, 14, 16	11
13		113.9, s			
14	7.78, m, 1H	131.4, s	15	10, 12, 16	15
15	7.88, m, 1H	131.7, s	14	3, 11, 13	14
16		118.3, s			
17	4.33, q (7.0), 2H	67.4, s	18	5, 18	6, 18
18	1.30, t (7.0), 3H	14.0, s	17	17	17

[a]Recorded at 800 MHz (^{1}H NMR) and 200 MHz (^{13}C NMR) at 25 °C.

S22: ^{1}H NMR spectrum of compound **9** in $CDCl_3$



S23: ^{13}C NMR spectrum of compound **9** in $CDCl_3$

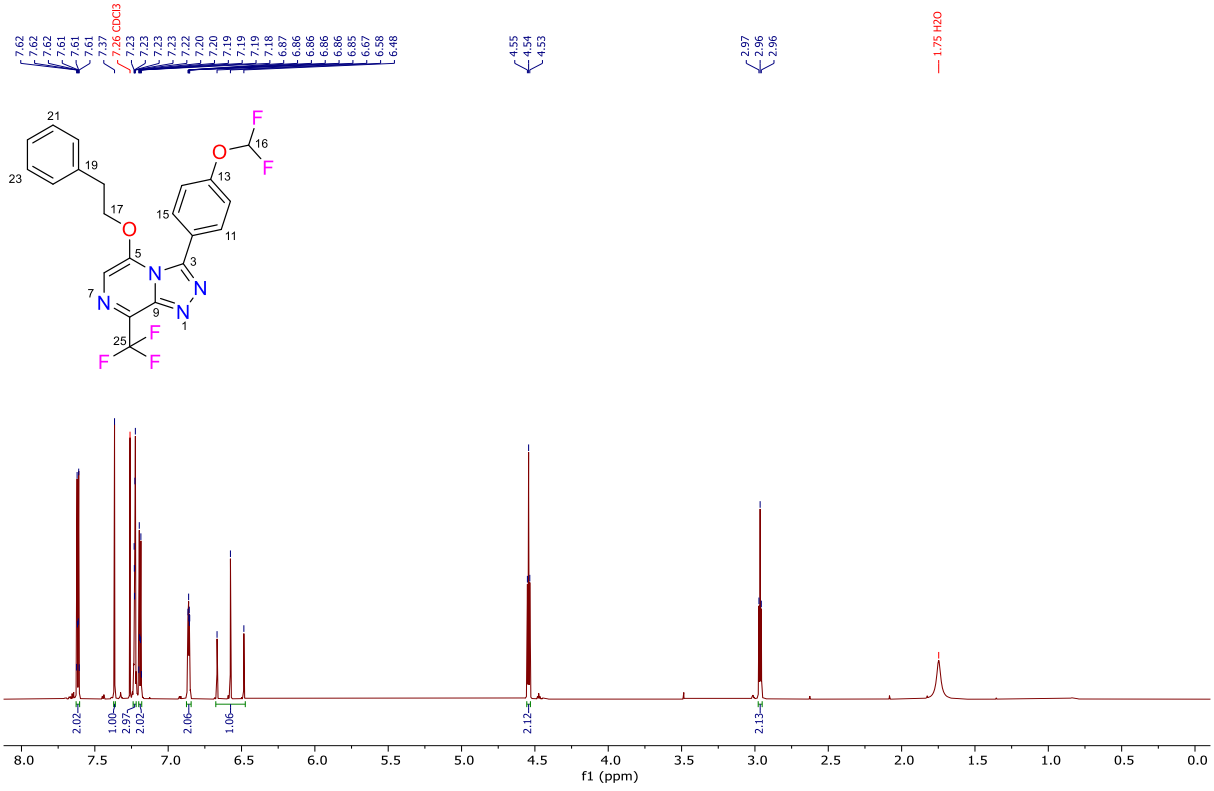


S24: NMR data of compound **10** in $CDCl_3$[a]

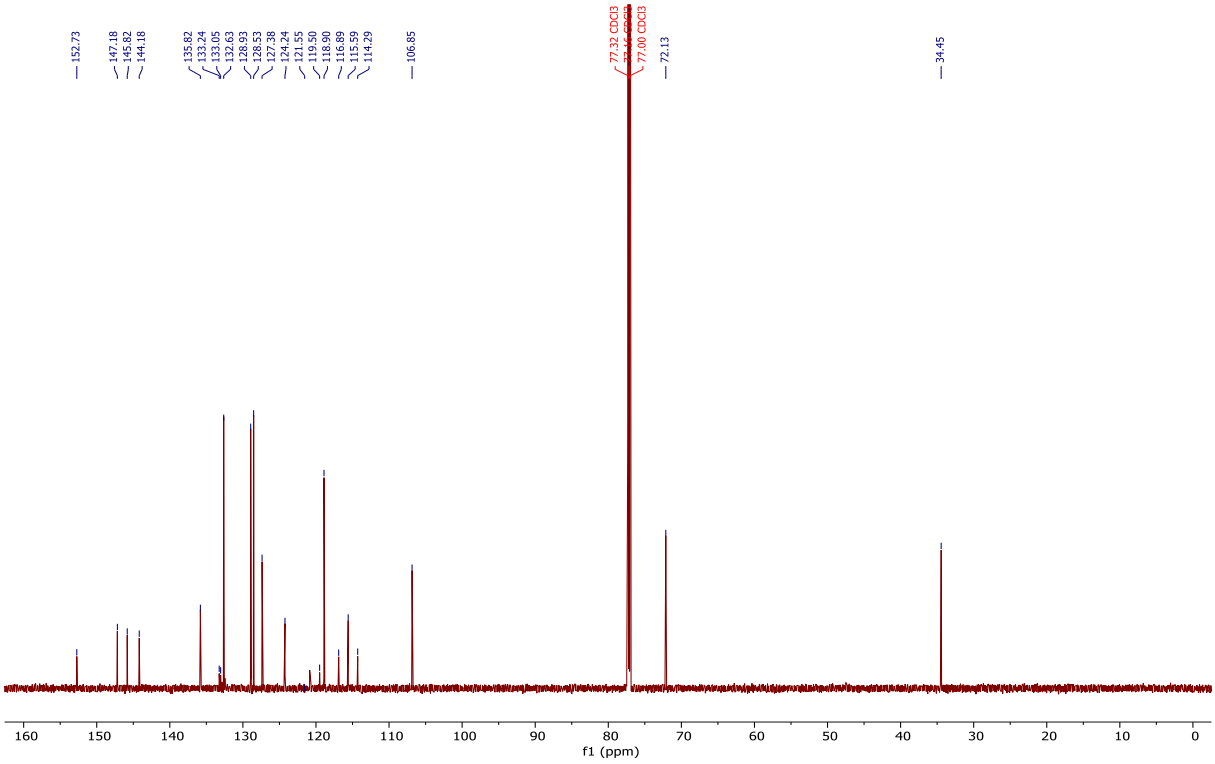
Position	δ_H, mult. (*J* in Hz), int.	δ_C, mult. (*J* in Hz)	COSY	HMBC	ROESY
3		147.2, s			
5		145.8, s			
6	7.37, s, 1H	106.9, s		5, 8	17
8		133.1, q (38.8)			
9		144.2, s			
10		124.2, s			
11	7.62, m, 1H	132.6, s	12	3, 13, 15	12
12	7.19, m, 1H	118.9, s	11	10, 14	11
13		152.7, t (2.7)			
14	7.19, m, 1H	118.9, s	15	10, 12	15
15	7.62, m, 1H	132.6, s	14	3, 11, 13	14
16	6.58, t (73.5), 1H	115.6, t (262.1)		13	
17	4.54, t (6.6), 2H	72.1, s	18	5, 18, 19	6, 18
18	2.96, t (6.6), 2H	34.5, s	17	17, 19, 20, 24	17, 20, 24
19		135.8, s			
20	6.86, m, 1H	128.5, s	21	18, 22, 24	18, 21
21	7.23, m, 1H	128.9, s	20	19, 23	20
22	7.22, m, 1H	127.4, s		20, 24	
23	7.23, m, 1H	128.9, s	24	19, 21	24
24	6.86, m, 1H	128.5, s	23	18, 20, 22	18, 23
25		120.2, q (273.3)			

[a]Recorded at 800 MHz (^{1}H NMR) and 200 MHz (^{13}C NMR) at 25 °C.

S25: ^{1}H NMR spectrum of compound **10** in $CDCl_3$



S26: ^{13}C NMR spectrum of compound **10** in $CDCl_3$

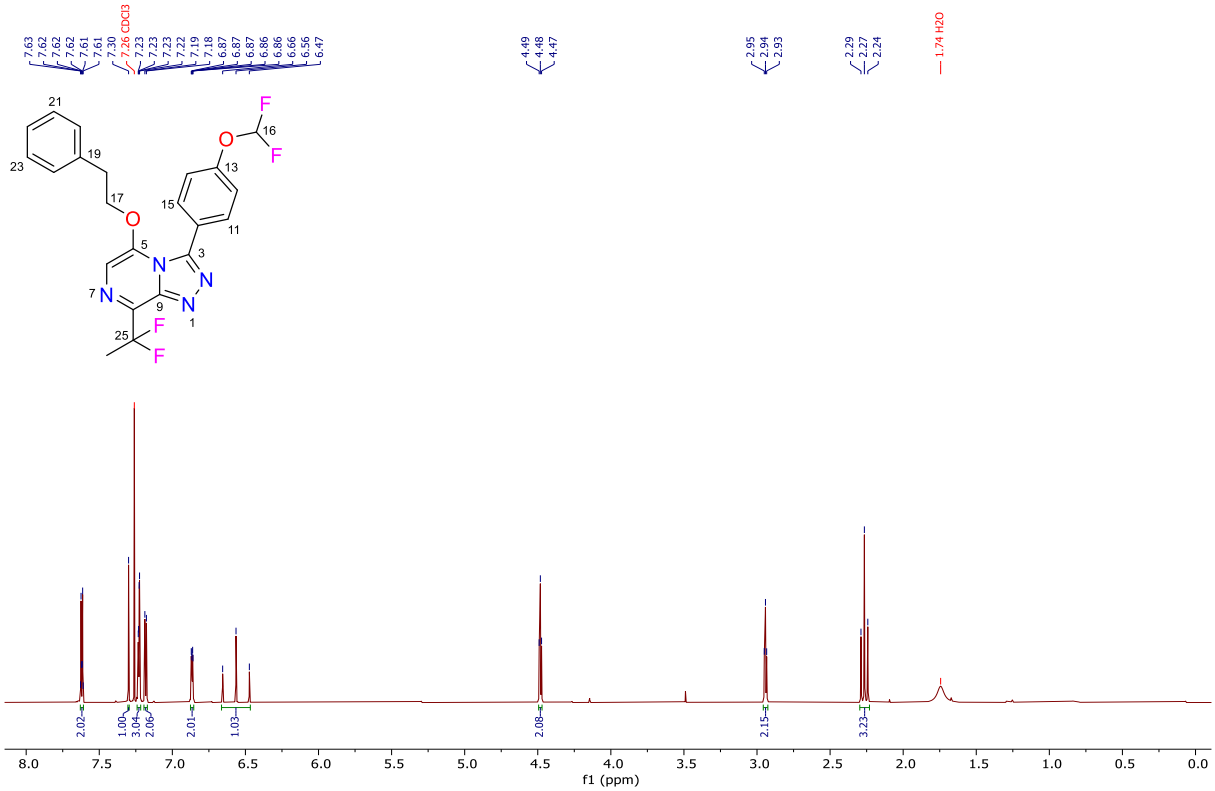


S27: NMR data of compound **11** in $CDCl_3$[a]

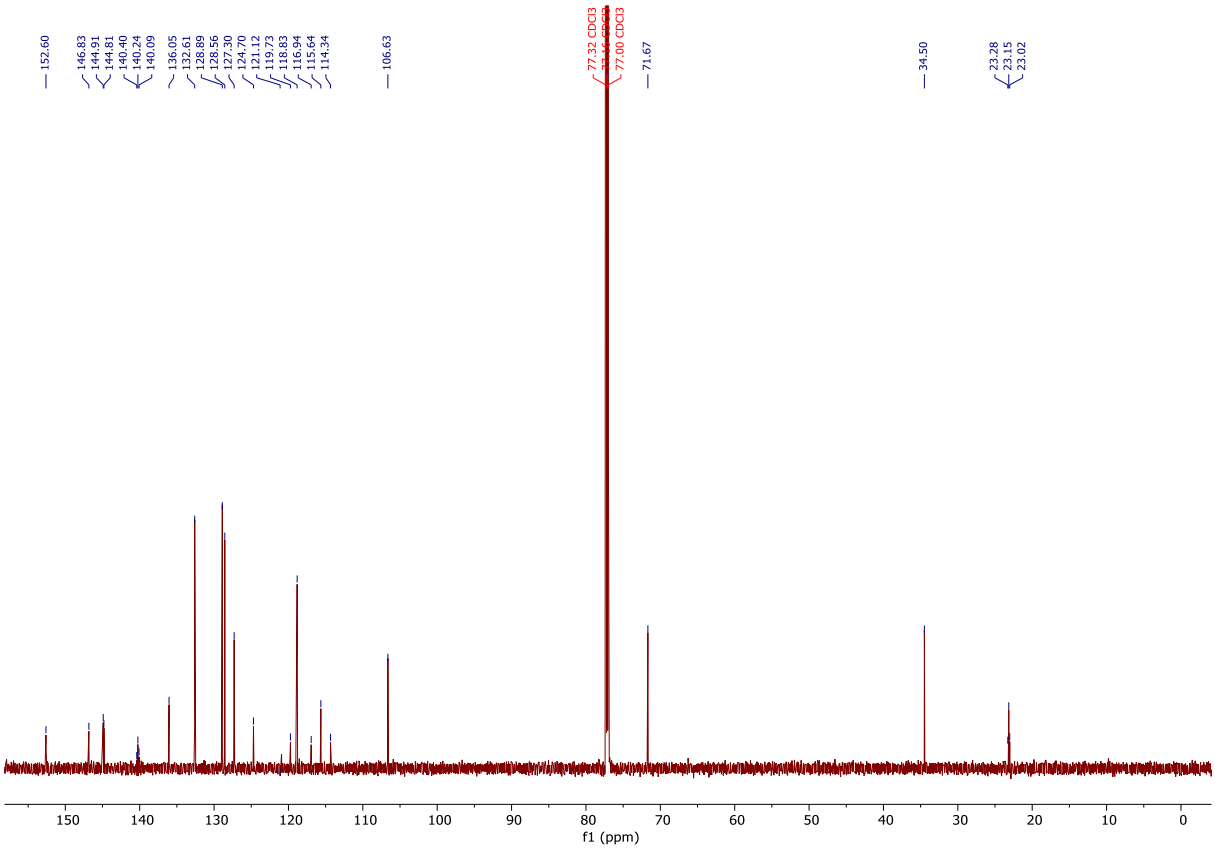
Position	δ_H, mult. (*J* in Hz), int.	δ_C, mult. (*J* in Hz)	COSY	HMBC	ROESY
3		146.8, s			
5		144.9, s			
6	7.30, s, 1H	106.6, s		5, 8	17
8		140.2, t (31.3)			
9		144.8, s			
10		124.7, s			
11	7.62, m, 1H	132.6, s	12	3, 13, 15	12
12	7.18, m, 1H	118.8, s	11	10, 14	11
13		152.6, t (2.8)			
14	7.18, m, 1H	118.8, s	15	10, 12	15
15	7.62, m, 1H	132.6, s	14	3, 11, 13	14
16	6.56, t (72.1), 1H	115.6, t (260.3)		13	
17	4.48, t (6.5), 2H	71.7, s	18	5, 18, 19	6, 18
18	2.94, t (6.5), 2H	34.5, s	17	19, 20, 24	17, 20, 24
19		136.1, s			
20	6.86, m, 1H	128.6, s	21	18, 22, 24	18, 21
21	7.23, m, 1H	128.9, s	20	19, 23	20
22	7.22, m, 1H	127.3, s		20, 24	
23	7.23, m, 1H	128.9, s	24	19, 21	24
24	6.86, m, 1H	128.6, s	23	18, 20, 22	18, 23
25		119.7, t (241.1)			
26	2.27, t (18.7), 3H	23.2, t (26.3)		8, 25	

[a]Recorded at 800 MHz (^1H NMR) and 200 MHz (^{13}C NMR) at 25 °C.

S28: ^{1}H NMR spectrum of compound **11** in $CDCl_3$



S29: ^{13}C NMR spectrum of compound **11** in $CDCl_3$

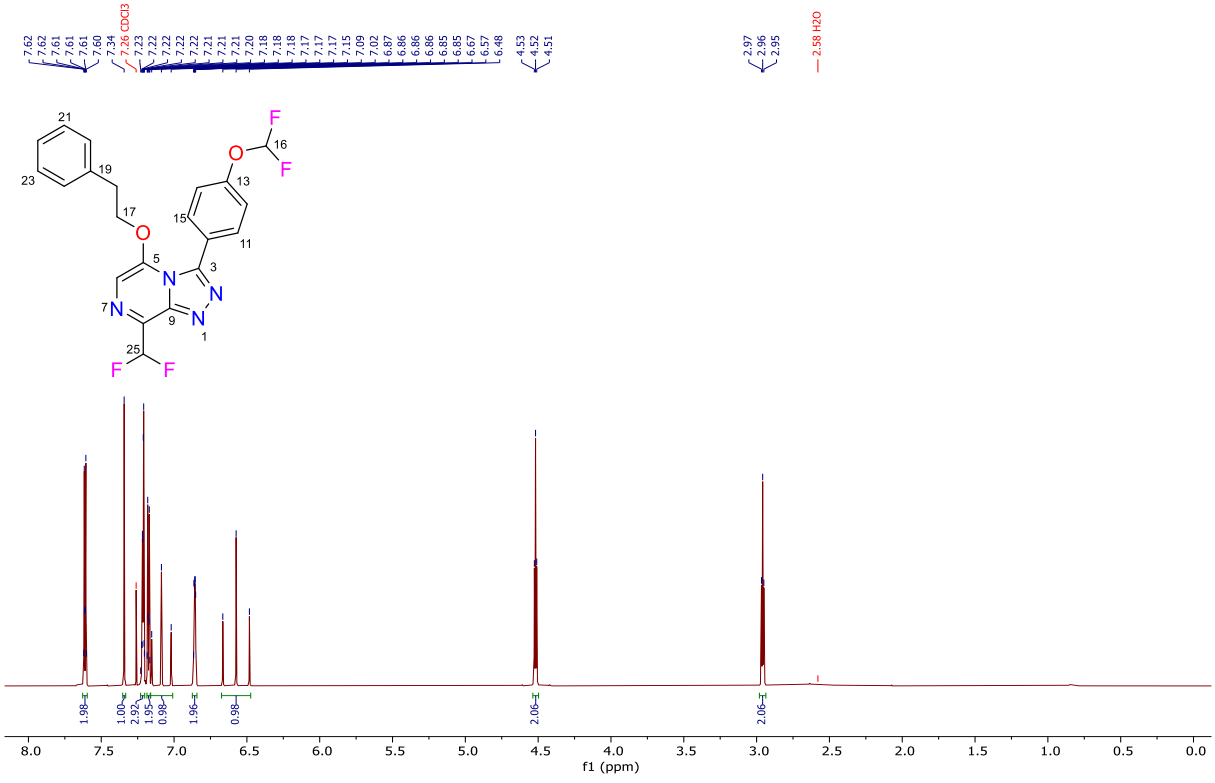


S30: NMR data of compound **12** in $CDCl_3$[a]

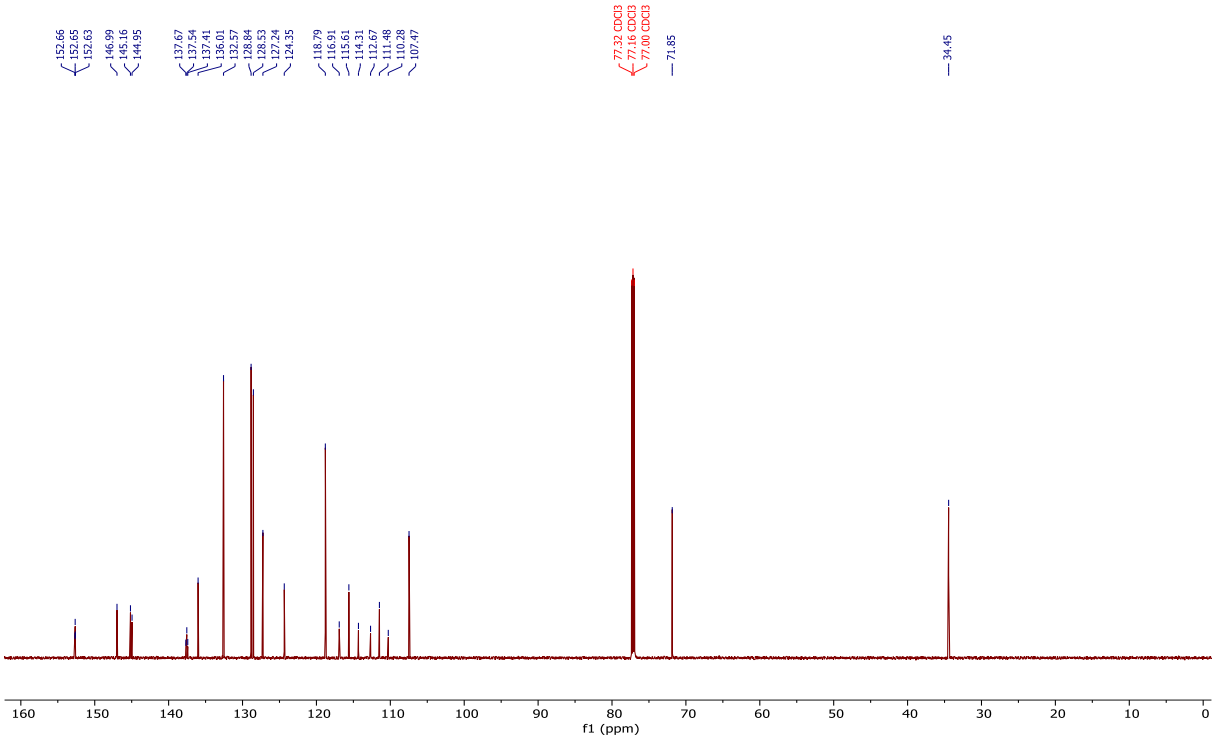
Position	δ_H, mult. (*J* in Hz), int.	δ_C, mult. (*J* in Hz)	COSY	HMBC	ROESY
3		147.0, s			
5		145.2, s			
6	7.34, s, 1H	107.5, s		5, 8	17
8		137.5, t (26.4)			
9		145.0, s			
10		124.4, s			
11	7.61, m, 1H	132.6, s	12	3, 13, 15	12
12	7.18, m, 1H	118.8, s	11	10, 14	11
13		152.7, t (2.7)			
14	7.18, m, 1H	118.8, s	15	10, 12	15
15	7.61, m, 1H	132.6, s	14	3, 11, 13	14
16	6.57, t (73.0), 1H	115.6, t (262.2)		13	
17	4.52, t (6.5), 2H	71.9, s	18	5, 18, 19	6, 18
18	2.96, t (6.5), 2H	34.4, s	17	17, 19, 20, 24	17, 20, 24
19		136.0, s			
20	6.86, m, 1H	128.5, s	21	18, 22, 24	18, 21
21	7.22, m, 1H	128.8, s	20	19, 23	20
22	7.21, m, 1H	127.2, s		20, 24	
23	7.22, m, 1H	128.8, s	24	19, 21	24
24	6.86, m, 1H	128.5, s	23	18, 20, 22	18, 23
25	7.09, t (54.0), 1H	111.5, t (241.3)		8, 9	

[a]Recorded at 800 MHz (^{1}H NMR) and 200 MHz (^{13}C NMR) at 25 °C.

S31: ^{1}H NMR spectrum of compound **12** in $CDCl_3$



S32: ^{13}C NMR spectrum of compound **12** in $CDCl_3$

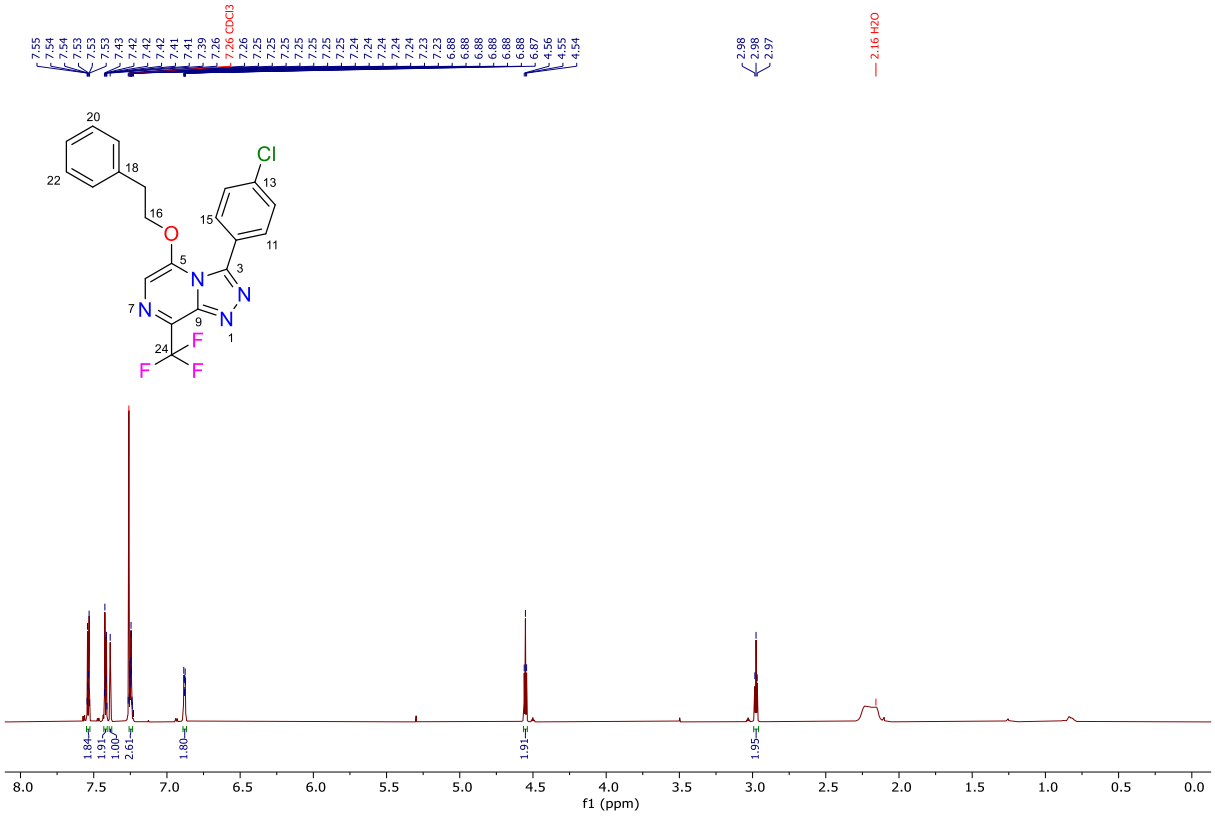


S33: NMR data of compound **13** in $CDCl_3$[a]

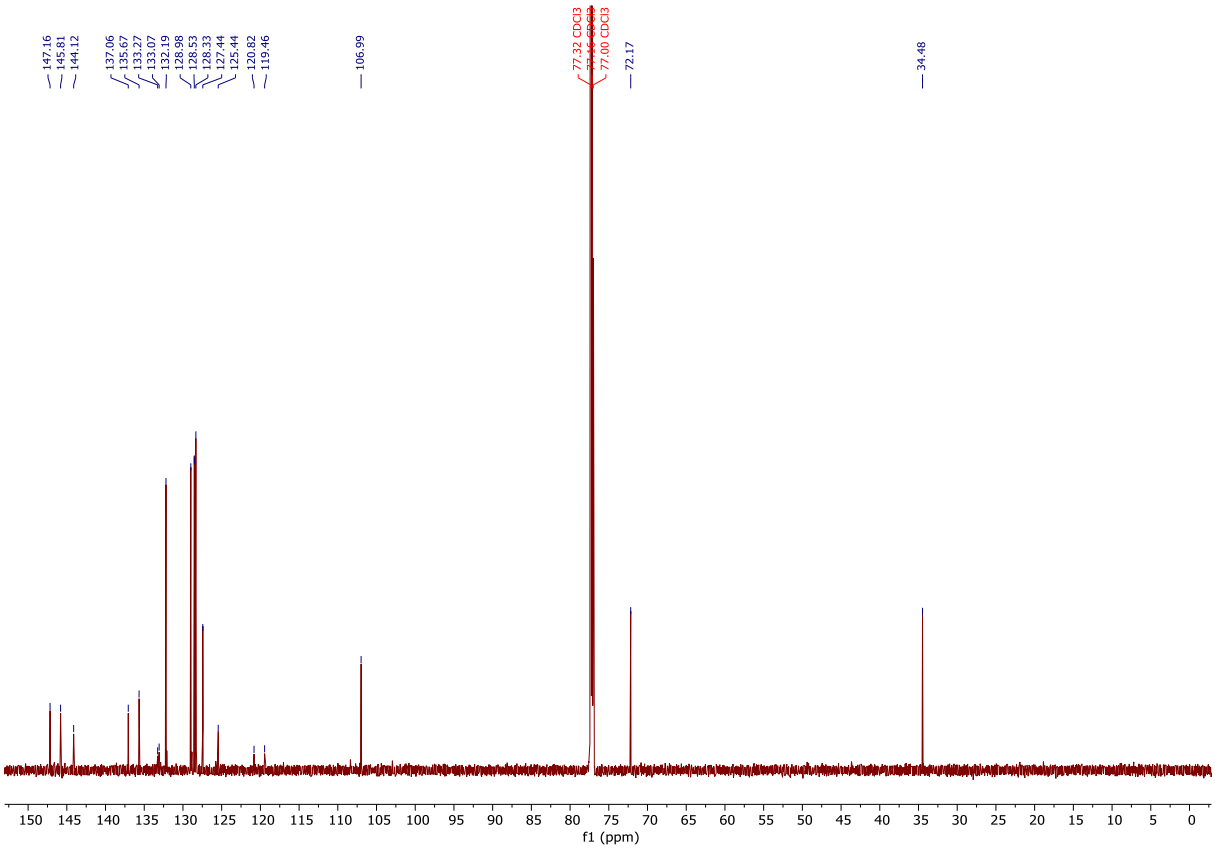
Position	δ_H, mult. (*J* in Hz), int.	δ_C, mult. (*J* in Hz)	COSY	HMBC	ROESY
3		147.2, s			
5		145.8, s			
6	7.39, s, 1H	107.0, s		5, 8	16
8		133.2, q (38.9)			
9		144.1, s			
10		125.4, s			
11	7.54, m, 1H	132.2, s	12	3, 13, 15	12
12	7.42, m, 1H	128.3, s	11	10, 14	11
13		137.1, s			
14	7.42, m, 1H	128.3, s	15	10, 12	15
15	7.54, m, 1H	132.2, s	14	3, 11, 13	14
16	4.55, t (6.6), 2H	72.2, s	17	5, 17, 18	6, 17
17	2.98, t (6.6), 2H	34.5, s	16	16, 18, 19, 23	16, 19, 23
18		135.7, s			
19	6.88, m, 1H	128.5, s	20	17, 21, 23	17, 20
20	7.25, m, 1H	129.0, s	19	18, 22	19
21	7.24, m, 1H	127.4, s		19, 23	
22	7.25, m, 1H	129.0, s	23	20, 20	23
23	6.88, m, 1H	128.5, s	22	17, 19, 21	17, 22
24		120.0, q (274.4)			

[a]Recorded at 800 MHz (^1H NMR) and 200 MHz (^{13}C NMR) at 25 °C.

S34: ^{1}H NMR spectrum of compound **13** in $CDCl_3$



S35: ^{13}C NMR spectrum of compound **13** in $CDCl_3$

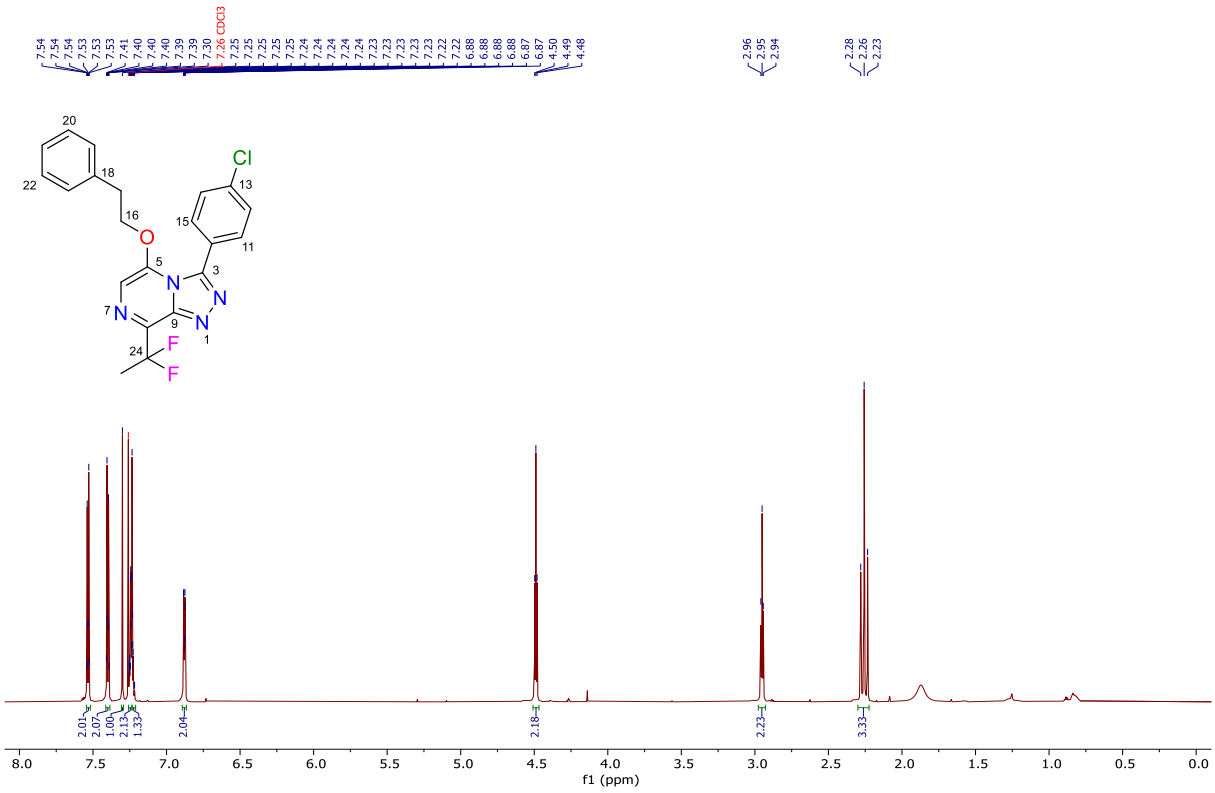


S36: NMR data of compound **14** in $CDCl_3$[a]

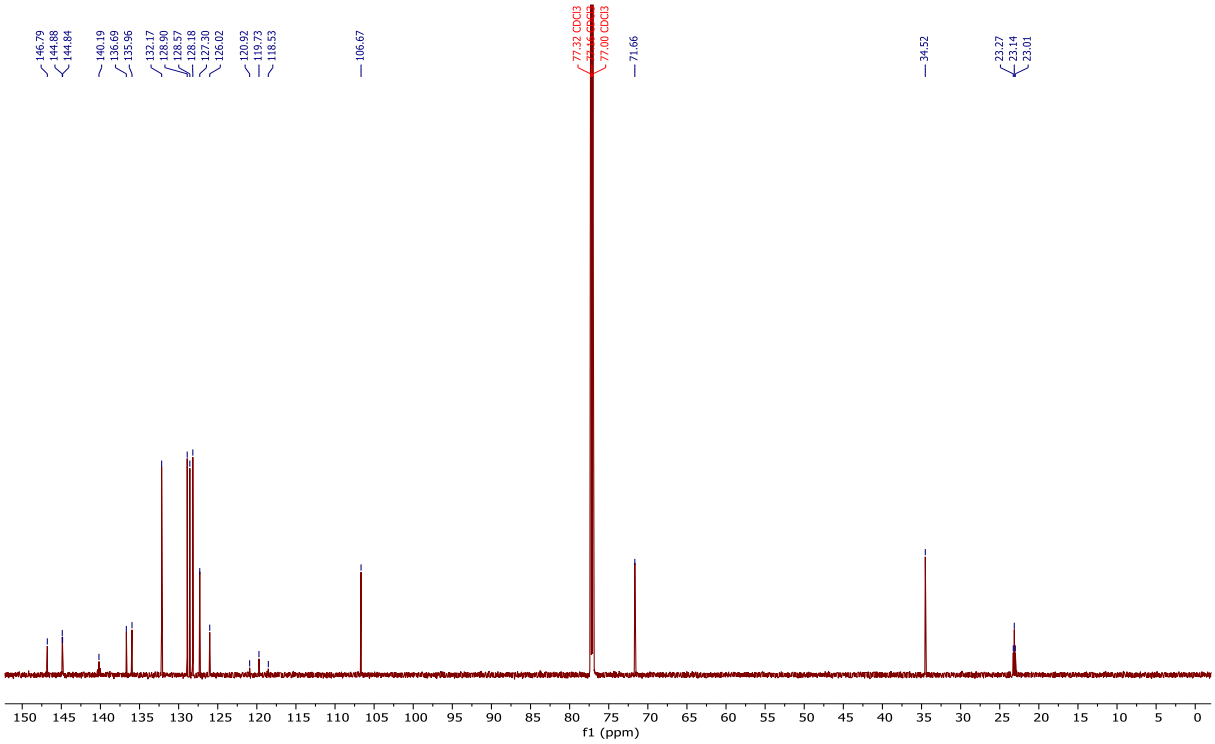
Position	δ_H, mult. (*J* in Hz), int.	δ_C, mult. (*J* in Hz)	COSY	HMBC	ROESY
3		146.8, s			
5		144.8, s			
6	7.30, s, 1H	106.7, s		5, 8	16
8		140.2, t (31.7)			
9		144.9, s			
10		126.0, s			
11	7.53, m, 1H	132.2, s	12	3, 13, 15	12
12	7.40, m, 1H	128.2, s	11	10, 14	11
13		136.7, s			
14	7.40, m, 1H	128.2, s	15	10, 12	15
15	7.53, m, 1H	132.2, s	14	3, 11, 13	14
16	4.49, t (6.5), 2H	71.7, s	17	5, 17, 18	6, 17
17	2.95, t (6.5), 2H	34.5, s	16	16, 18, 19, 23	16, 19, 23
18		136.0, s			
19	6.88, m, 1H	128.6, s	20	17, 21, 23	17, 20
20	7.24, m, 1H	128.9, s	19	18, 22	19
21	7.23, m, 1H	127.3, s		19, 23	
22	7.24, m, 1H	128.9, s	23	20, 20	23
23	6.88, m, 1H	128.6, s	22	17, 19, 21	17, 22
24		119.7, t (240.3)			
25	2.26, t (18.9), 3H	23.1, t (26.2)		8, 24	

[a]Recorded at 800 MHz (^{1}H NMR) and 200 MHz (^{13}C NMR) at 25 °C.

S37: ^{1}H NMR spectrum of compound **14** in $CDCl_3$



S38: ^{13}C NMR spectrum of compound **14** in $CDCl_3$

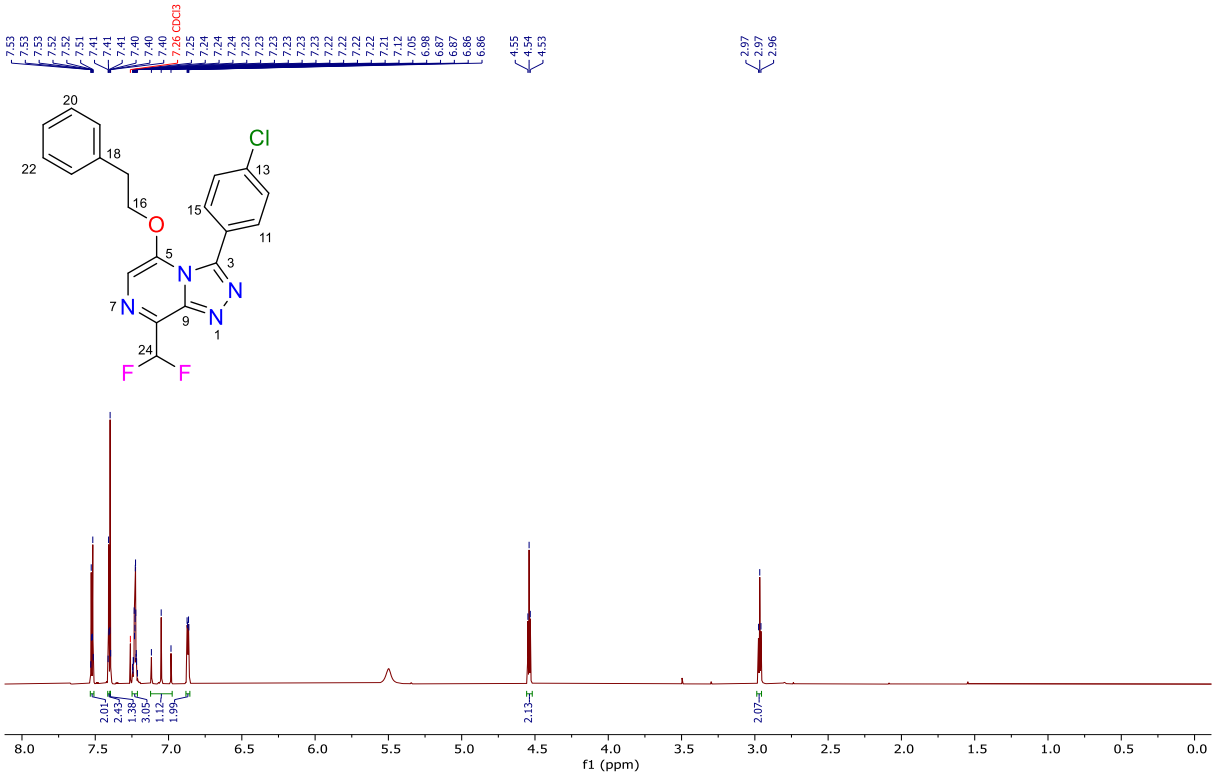


S39: NMR data of compound **15** in $CDCl_3$[a]

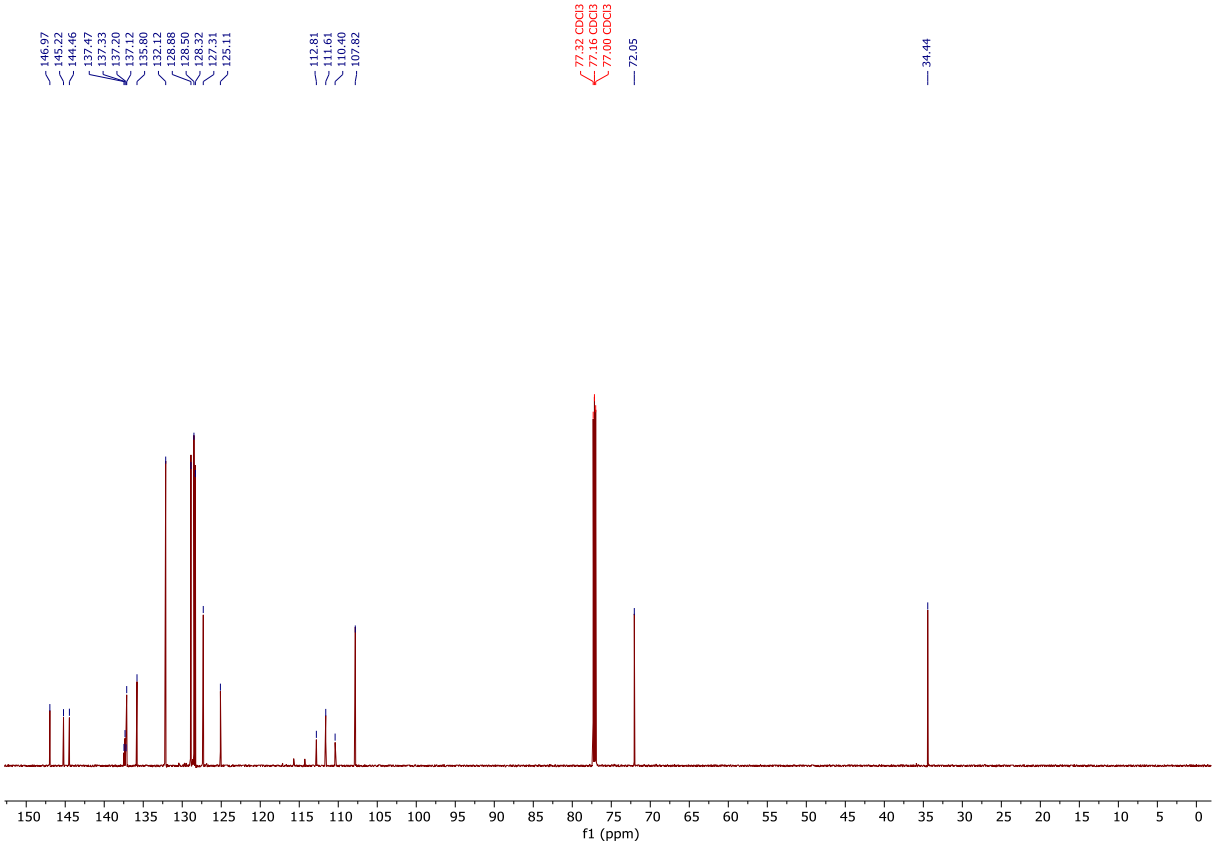
Position	δ_H, mult. (*J* in Hz), int.	δ_C, mult. (*J* in Hz)	COSY	HMBC	ROESY
3		147.0, s			
5		145.2, s			
6	7.40, s, 1H	107.8, s		5, 8	16
8		137.3, t (26.6)			
9		144.5, s			
10		125.1, s			
11	7.52, m, 1H	132.1, s	12	3, 13, 15	12
12	7.40, m, 1H	128.3, s	11	10, 14	11
13		137.1, s			
14	7.40, m, 1H	128.3, s	15	10, 12	15
15	7.52, m, 1H	132.1, s	14	3, 11, 13	14
16	4.54, t (6.5), 2H	72.1, s	17	5, 17, 18	6, 17
17	2.97, t (6.5), 2H	34.4, s	16	16, 18, 19, 23	16, 19, 23
18		135.8, s			
19	6.87, m, 1H	128.5, s	20	17, 21, 23	17, 20
20	7.23, m, 1H	128.9, s	19	18, 22	19
21	7.22, m, 1H	127.3, s		19, 23	
22	7.23, m, 1H	128.9, s	23	20, 20	23
23	6.87, m, 1H	128.5, s	22	17, 19, 21	17, 22
24	7.05, t (53.5), 1H	111.6, t (241.8)		8, 9	

[a]Recorded at 800 MHz (^1H NMR) and 200 MHz (^{13}C NMR) at 25 °C.

S40: ^{1}H NMR spectrum of compound **15** in $CDCl_3$



S41: ^{13}C NMR spectrum of compound **15** in $CDCl_3$

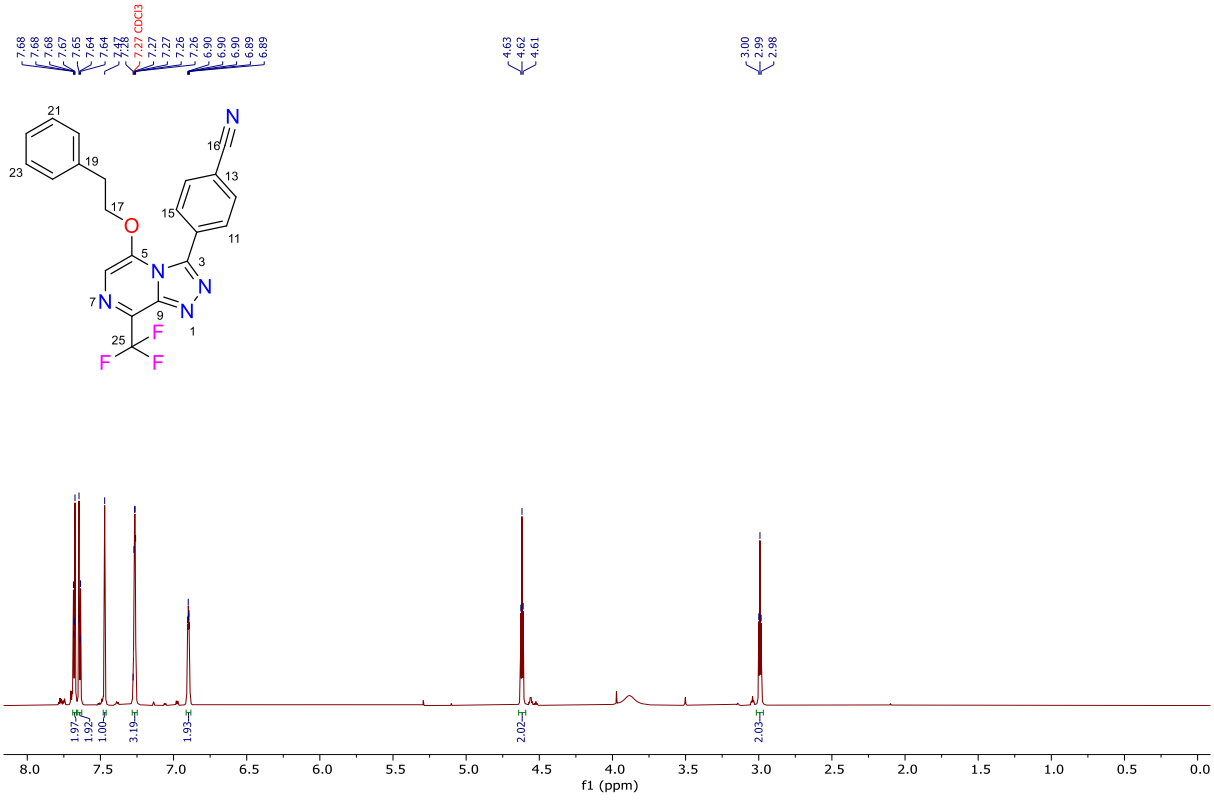


S42: NMR data of compound **16** in $CDCl_3$[a]

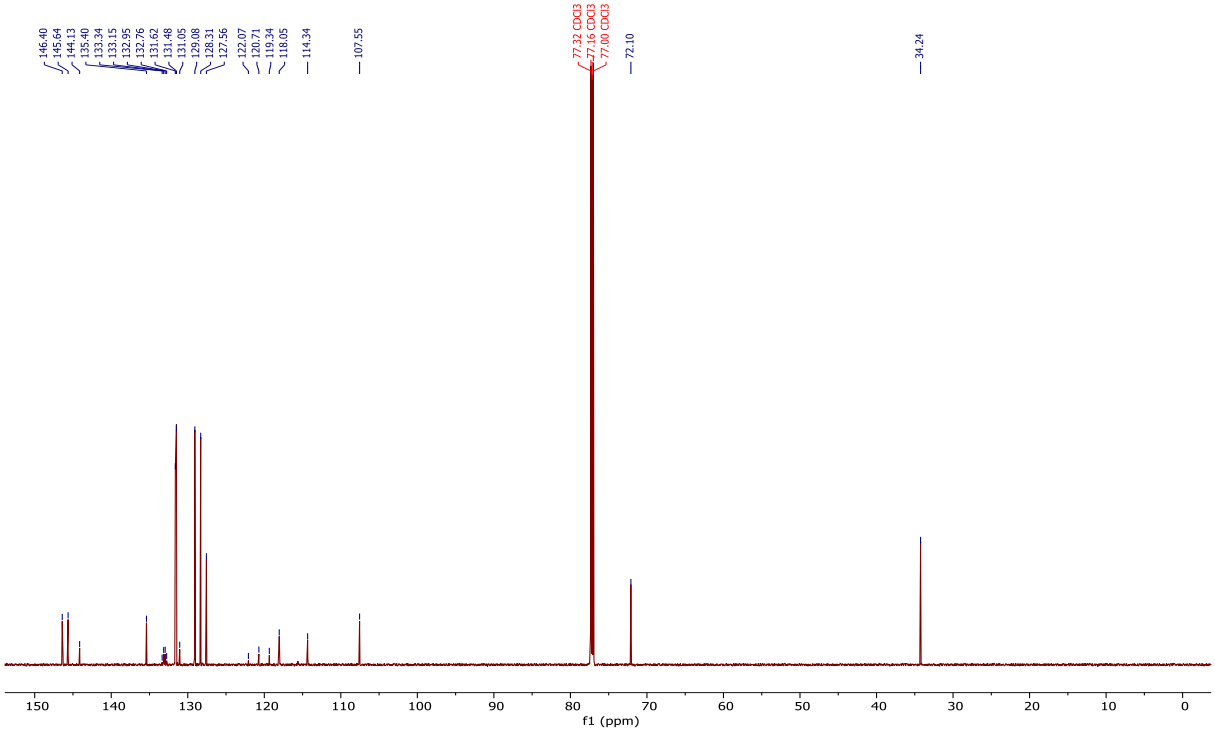
Position	δ_H, mult. (*J* in Hz), int.	δ_C, mult. (*J* in Hz)	COSY	HMBC	ROESY
3		146.4, s			
5		145.6, s			
6	7.47, s, 1H	107.6, s		5, 8	17, 18
8		133.1, q (39.1)			
9		144.1, s			
10		131.1, s			
11	7.68, m, 1H	131.5, s	12	3, 13, 15	12
12	7.64, m, 1H	131.6, s	11	10, 14, 16	11
13		114.3, s			
14	7.64, m, 1H	131.6, s	15	10, 12, 16	15
15	7.68, m, 1H	131.5, s	14	3, 11, 13	14
16		118.1, s			
17	4.62, t (6.5), 2H	72.1, s	18	5, 18, 19	6, 18, 20, 24
18	2.99, t (6.5), 2H	34.2, s	17	17, 19, 20, 24	6, 17, 20, 24
19		135.4, s			
20	6.90, m, 1H	128.3, s	21	18, 22, 24	17, 18, 21
21	7.27, m, 1H	129.1, s	20	19, 23	20
22	7.26, m, 1H	127.6, s		20, 24	
23	7.27, m, 1H	129.1, s	24	19, 21	24
24	6.90, m, 1H	128.3, s	23	18, 20, 22	17, 18, 23
25		120.0, q (274.6)			

[a]Recorded at 800 MHz (^{1}H NMR) and 200 MHz (^{13}C NMR) at 25 °C.

S43: ^{1}H NMR spectrum of compound **16** in $CDCl_3$



S44: ^{13}C NMR spectrum of compound **16** in $CDCl_3$

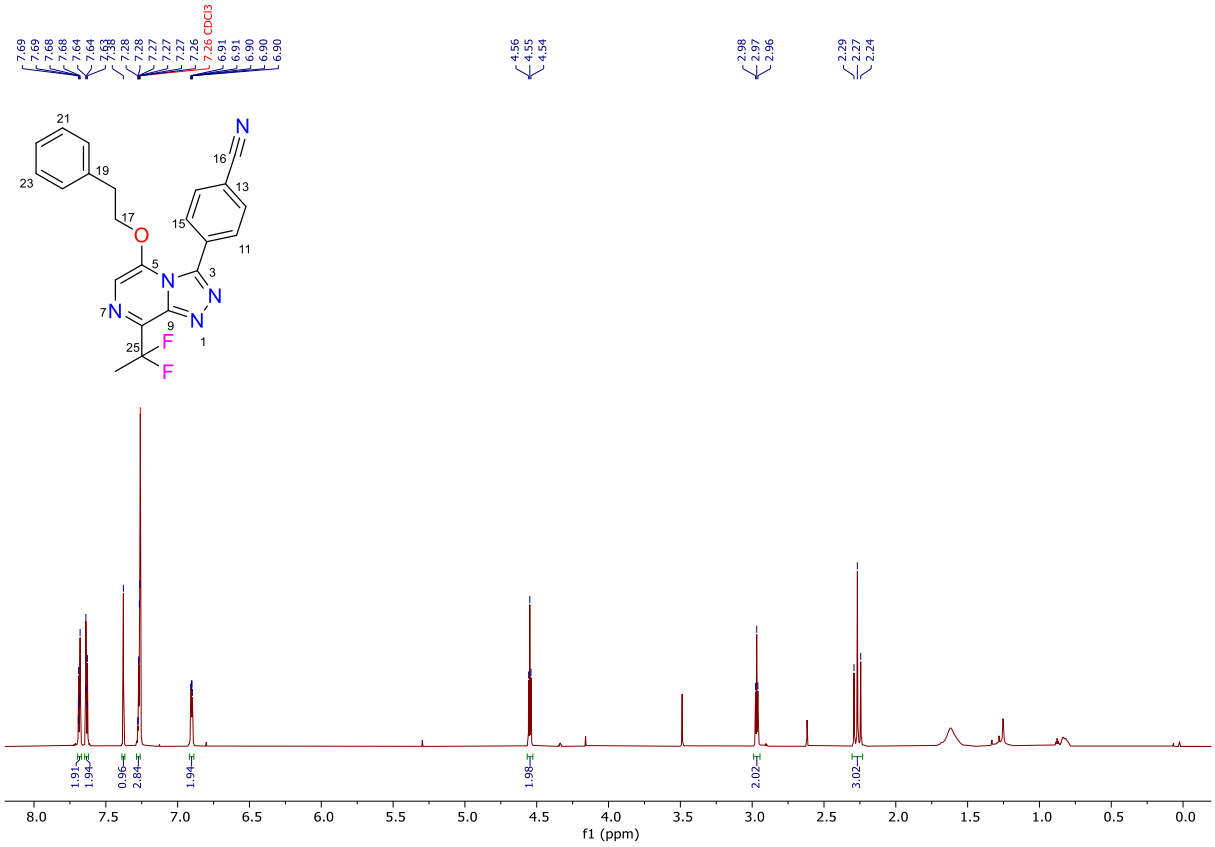


S45: NMR data of compound **17** in $CDCl_3$[a]

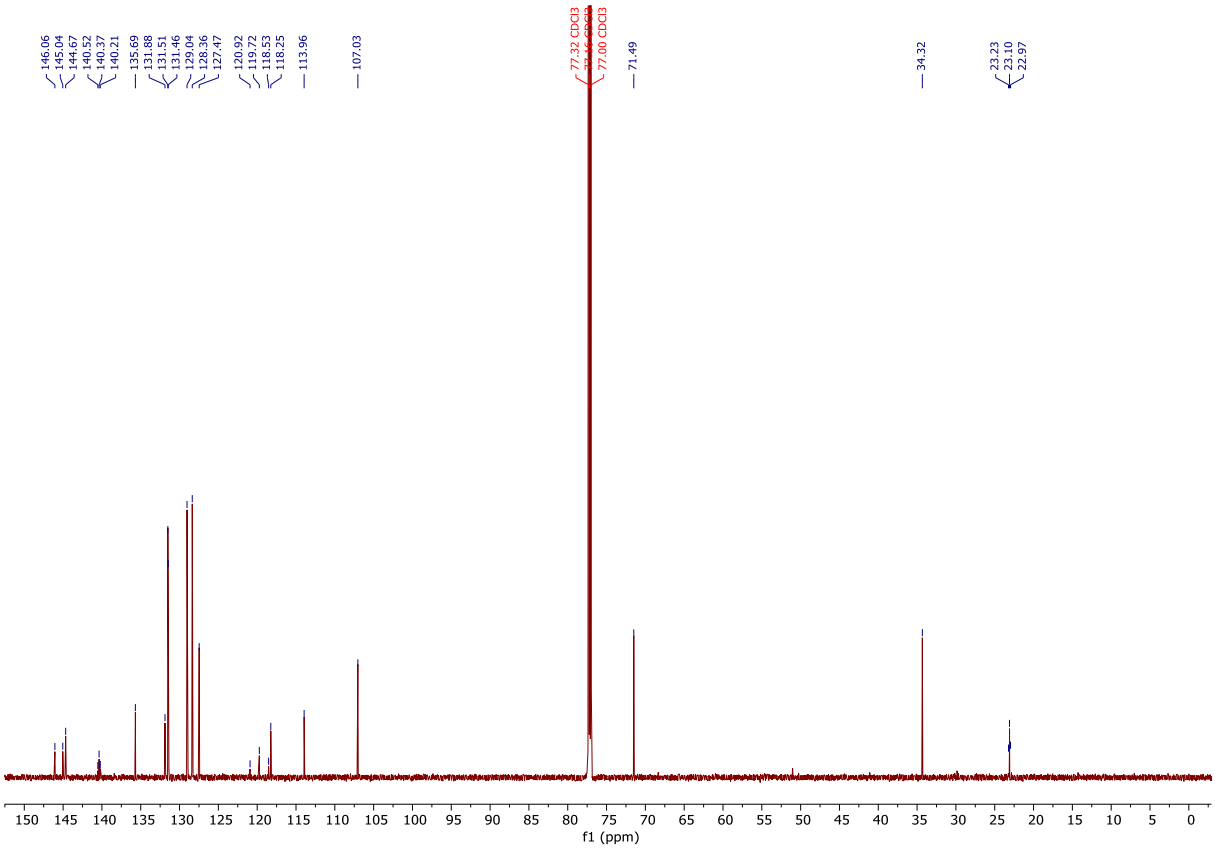
Position	δ_H, mult. (*J* in Hz), int.	δ_C, mult. (*J* in Hz)	COSY	HMBC	ROESY
3		146.1, s			
5		144.7, s			
6	7.38, s, 1H	107.0, s		5, 8	17
8		140.4, t (31.7)			
9		145.0, s			
10		131.9, s			
11	7.69, m, 1H	131.51, s	12	3, 13, 15	12
12	7.64, m, 1H	131.46, s	11	10, 14, 16	11
13		114.0, s			
14	7.64, m, 1H	131.46, s	15	10, 12, 16	15
15	7.69, m, 1H	131.51, s	14	3, 11, 13	14
16		118.3, s			
17	4.55, t (6.5), 2H	71.5, s	18	5, 18, 19	6, 18, 20, 24
18	2.97, t (6.5), 2H	34.3, s	17	19, 20, 24	17, 20, 24
19		135.7, s			
20	6.90, m, 1H	128.4, s	21	18, 22, 24	17, 18, 21
21	7.27, m, 1H	129.0, s	20	19, 23	20
22	7.27, m, 1H	127.5, s		20, 24	
23	7.27, m, 1H	129.0, s	24	19, 21	24
24	6.90, m, 1H	128.4, s	23	18, 20, 22	17, 18, 23
25		119.7, t (240.3)			
26	2.27, t (18.7), 3H	23.1, t (26.4)		8, 25	

[a]Recorded at 800 MHz (^1H NMR) and 200 MHz (^{13}C NMR) at 25 °C.

S46: ^{1}H NMR spectrum of compound **17** in $CDCl_3$



S47: ^{13}C NMR spectrum of compound **17** in $CDCl_3$

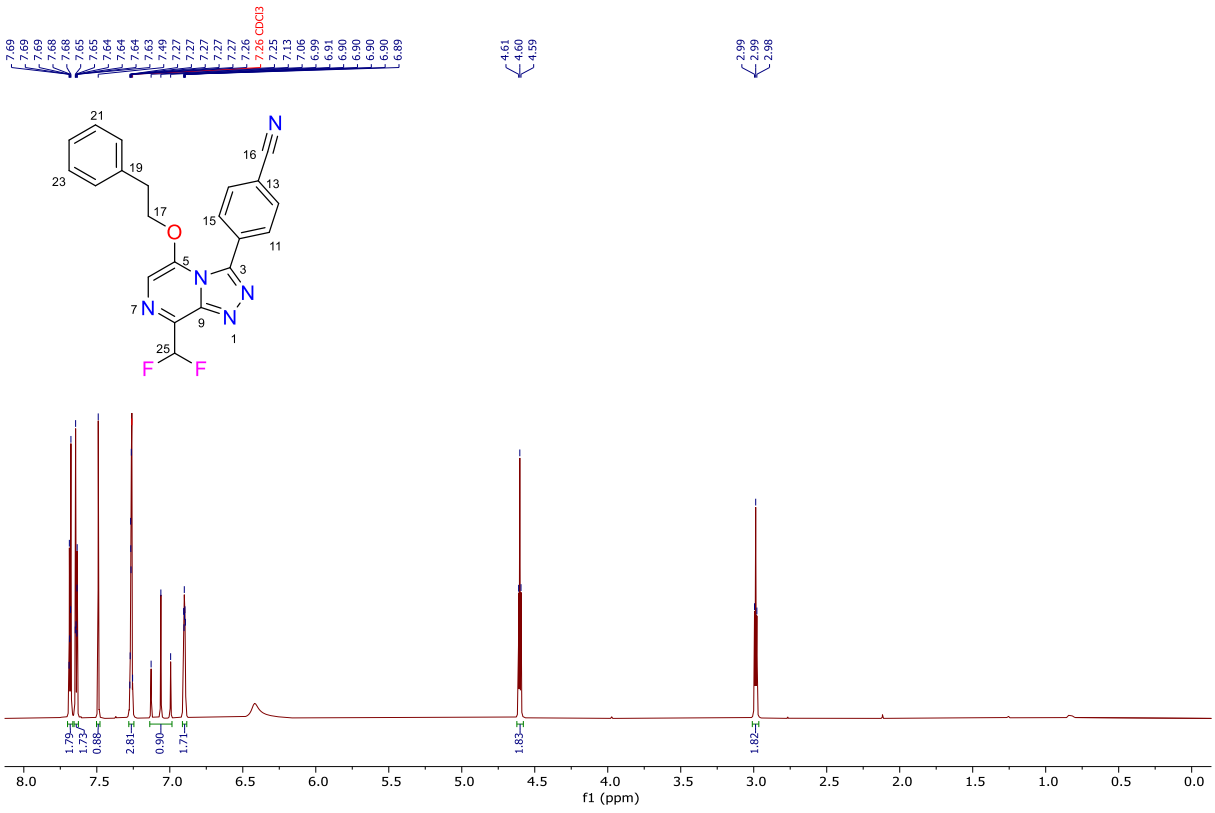


S48: NMR data of compound **18** in $CDCl_3$[a]

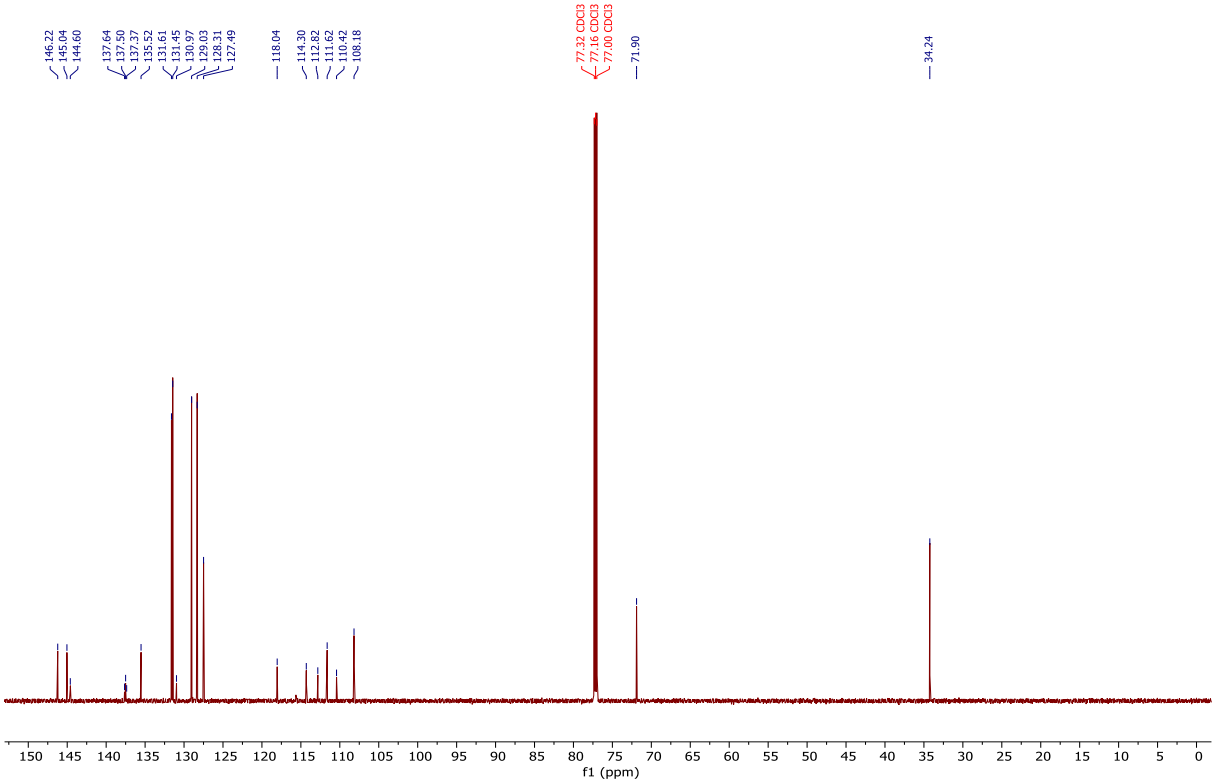
Position	δ_H, mult. (*J* in Hz), int.	δ_C, mult. (*J* in Hz)	COSY	HMBC	ROESY
3		146.2, s			
5		145.0, s			
6	7.49, s, 1H	108.2, s		5, 8	17
8		137.5, t (27.3)			
9		144.6, s			
10		131.0, s			
11	7.68, m, 1H	131.5, s	12	3, 13, 15	12
12	7.64, m, 1H	131.6, s	11	10, 14, 16	11
13		114.3, s			
14	7.64, m, 1H	131.6, s	15	10, 12, 16	15
15	7.68, m, 1H	131.5, s	14	3, 11, 13	14
16		118.0, s			
17	4.60, t (6.5), 2H	71.9, s	18	5, 18, 19	6, 18, 20, 24
18	2.99, t (6.5), 2H	34.3, s	17	19, 20, 24	17, 20, 24
19		135.5, s			
20	6.90, m, 1H	128.3, s	21	18, 22, 24	17, 18, 21
21	7.26, m, 1H	129.0, s	20	19, 23	20
22	7.26, m, 1H	127.5, s		20, 24	
23	7.26, m, 1H	129.0, s	24	19, 21	24
24	6.90, m, 1H	128.3, s	23	18, 20, 22	17, 18, 23
25	7.06, t (53.4), 1H	111.6, t (241.7)		8, 9	

[a]Recorded at 800 MHz (^{1}H NMR) and 200 MHz (^{13}C NMR) at 25 °C.

S49: ^{1}H NMR spectrum of compound **18** in $CDCl_3$



S50: ^{13}C NMR spectrum of compound **18** in $CDCl_3$



S51: Crystal data for compound **5**

$C_{19}H_{15}ClN_4O$, M = 350.80, T = 100.0(10) K, λ = 0.71073 Å, monoclinic, space group I2/a, a = 19.5831(3) Å, b = 8.89750(10) Å, c = 18.6547(3) Å, β= 93.5860(10)° V = 3244.04(8) $Å^3$, Z = 8, D_c = 1.437 Mg M^3 μ = 0.251 mm^{-1}, F(000) = 1456, crystal size 0.43 × 0.40 × 0.30 mm; θ_{max} = 51.26°, 51318 reflections measured, 17443 independent reflections (R_{int} = 0.0445); final R = 0.0439 [I > 2σ(I), 12147 data] and wR(F_2) = 0.1395 (all data); GOOF =1.045.

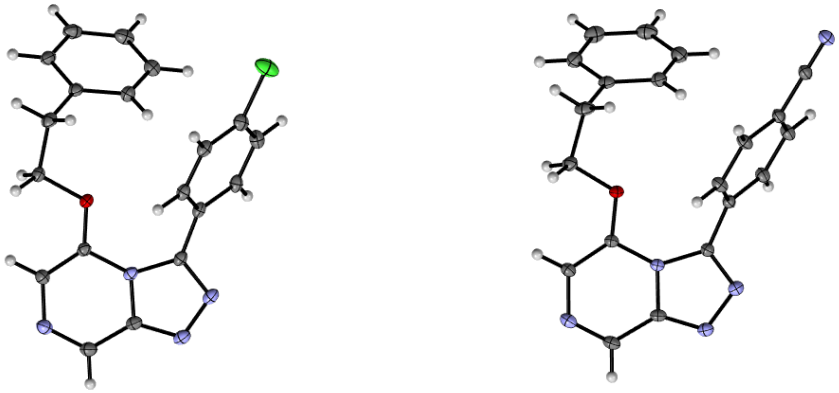
S52: Crystal data for compound **6**

$C_{20}H_{15}N_5O$, M = 341.37, T = 100.0(10) K, λ = 0.71073 Å, monoclinic, space group P21/n, a = 7.6152(1) Å, b = 16.8201(3) Å, c = 13.5669(2) Å, β= 90.877(2)°, V = 1737.56(5) $Å^3$, Z = 4, D_c = 1.305 Mg M^3 μ = 0.085 mm^{-1}, F(000) = 712, crystal size 0.56 × 0.33 × 0.30 mm; θ_{max} = 41.09°, 95562 reflections measured, 11148 independent reflections (R_{int} = 0.0417); final R = 0.0386 [I > 2σ(I), 9322 data] and wR(F_2) = 0.1182 (all data); GOOF =1.060.

S53: Crystal data for compound **18**

$C_{21}H_{15}F_2N_5O$, M = 391.38, T = 100.0(10) K, λ = 0.71073 Å, trigonal, space group R3cH, a = 25.1585(8) Å, c = 15.4454(6) Å, V = 8466.4(6) $Å^3$, Z = 18, D_c = 1.382 Mg M^3 μ = 0.103 mm^{-1}, F(000) = 3636, crystal size 0.42 × 0.29 × 0.16 mm; θ_{max} = 33.41°, 23922 reflections measured, 6267 independent reflections (R_{int} = 0.0419); final R = 0.0431 [I > 2σ(I), 4689 data] and wR(F_2) = 0.1003 (all data); GOOF =1.043.

S54: ORTEP drawing of compounds **5** and **6**



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