Temperature-Modulated Selective C(sp^3)−H or C(sp^2)−H Arylation through Palladium Catalysis

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1. General Information

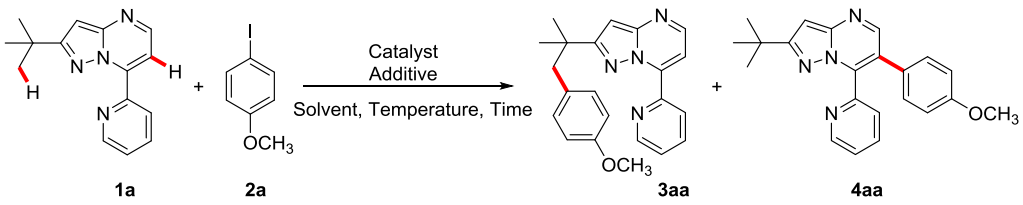
Catalytic reactions were carried out in sealed tubes using pre-dried glassware. 7-Pyridyl-pyrazolo[1,5-a]pyrimidines were synthesized according to reported procedures.[1] Unless otherwise noted, all the commercial material was used without further purification. Column chromatography purifications were performed using 200–300 mesh silica gel. NMR spectra were mostly recorded for ^{1}H NMR at 500 MHz and for ^{13}C NMR at 125 MHz. $CDCl_3$ were used as solvent. All chemical shifts are given as δ value (ppm) with reference to tetramethylsilane (TMS) as an internal standard. The following abbreviations are used to explain peak patterns: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants (*J*) are reported in Hertz (Hz). High resolution mass spectroscopy (HRMS) data of the products were collected on an Agilent Technologies 6224 TOF LC/MS apparatus (ESI).

2. General Procedure for the Preparation of Substrates (GP1)

Following a modified procedure,[1] a mixture of β-enaminone (1.0 mmol) and *NH*-5-aminopyrazole (1.0 mmol) was heated to 180 ℃ for 60 min in a sealed tube containing a 2yridi-coated magnetic stirring bar. The resulting reaction mixture was cooled to room temperature, and the precipitated product formed upon the addition of cold EtOH/H_2O (1:1) was filtered off, washed and dried to afford the pure 7-Pyridyl-pyrazolo[1, 5-a]pyrimidines **1**.

3. Optimization of Reaction Conditions

Table S1. Screening of Silver Additives[a,b]

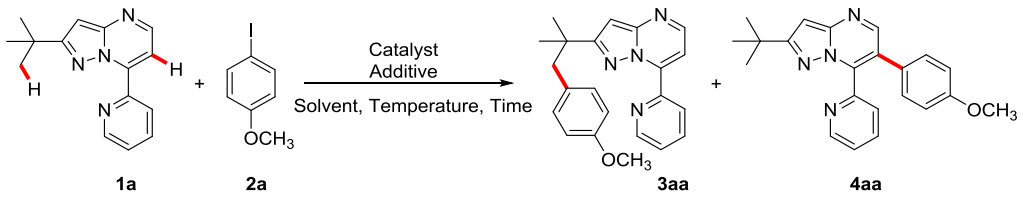


1a **2a** **3aa** **4aa**

entry	catalyst	solvent	additive	T (℃)	time (h)	yield (%)	
						3aa	**4aa**
1	$Pd(OAc)_2$	AcOH	AgTFA	120	24	18	6
2	$Pd(OAc)_2$	AcOH	AgOAc	120	24	11	<5
3	$Pd(OAc)_2$	AcOH	Ag_2CO_3	120	24	13	<5
4	$Pd(OAc)_2$	AcOH	AgF	120	24	8	<5
5[c]	$Pd(OAc)_2$	HFIP	$AgBr/(NMe_4)OC(CF_3)_3$	120	36	0	0
6[c]	$Pd(OAc)_2$	HFIP	$AgBr/(NMe_4)OC(CF_3)_3$	140	48	0	0

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.5 mmol), $Pd(OAc)_2$ (10 mol %), Additive (1.5 mmol), AcOH (3 mL). [b]Isolated Yield. [c] $Pd(OAc)_2$ (5 mol %), AgBr (2.0 mmol), $NMe_4)OC(CF_3)_3$ (2.0 mmol).

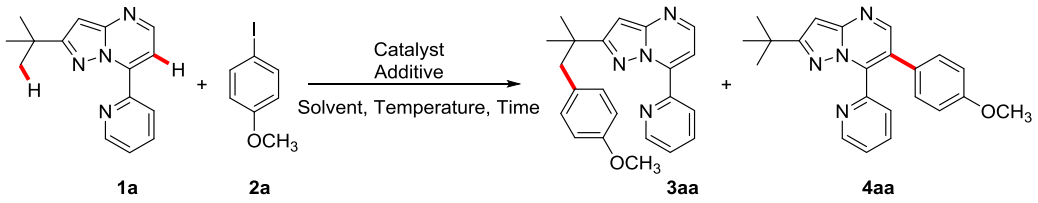
Table S2. Screening of Solvents[a,b]



entry	catalyst	solvent	additive	T (℃)	time (h)	yield (%)	
						3aa	**4aa**
1	$Pd(OAc)_2$	HFIP/AcOH (1:1)	AgTFA	120	24	24	18
2	$Pd(OAc)_2$	HFIP/AcOH (6:4)	AgTFA	120	24	33	14
3	$Pd(OAc)_2$	HFIP/AcOH (9:1)	AgTFA	120	24	46	10
4	$Pd(OAc)_2$	HFIP	AgTFA	120	24	58	<5
5	$Pd(OAc)_2$	TFE[c]	AgTFA	120	24	36	8
6	$Pd(OAc)_2$	DCE	AgTFA	120	24	<5	<5

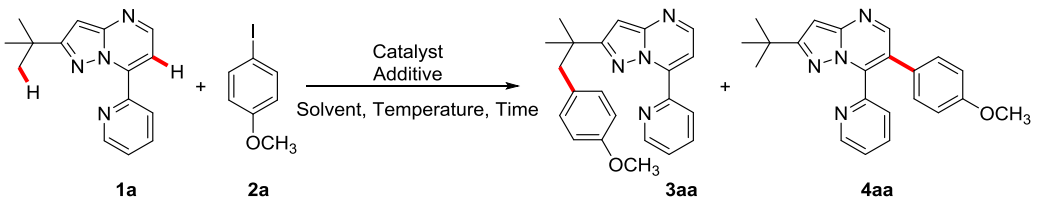
[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.5 mmol), $Pd(OAc)_2$ (10 mol %), AgTFA (1.5 mmol), Solvent (3 mL). [b]Isolated Yield. [c]2,2,2-trifluoroethanol.

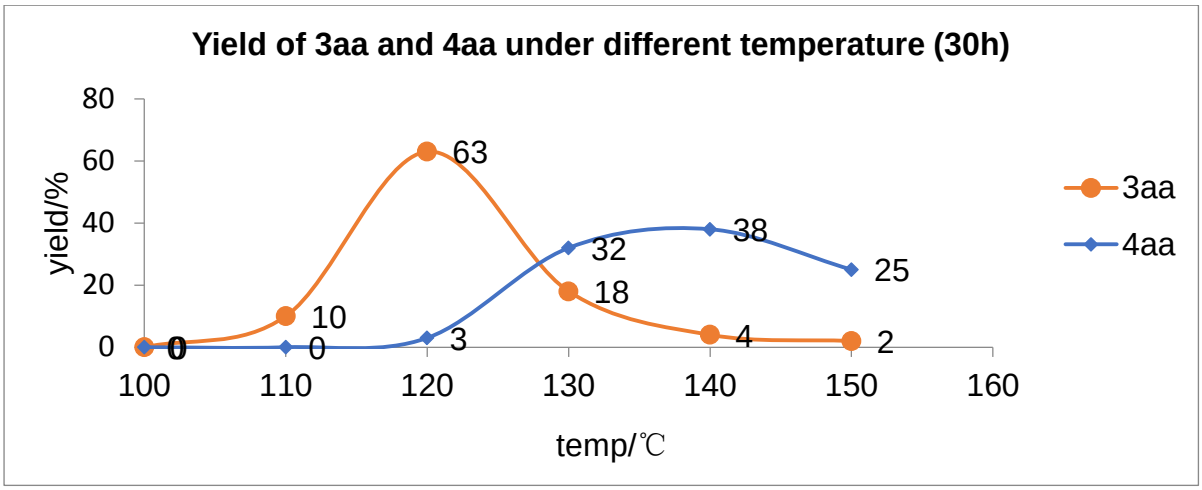
Table S3. Screening of Palladium Catalysts[a,b]

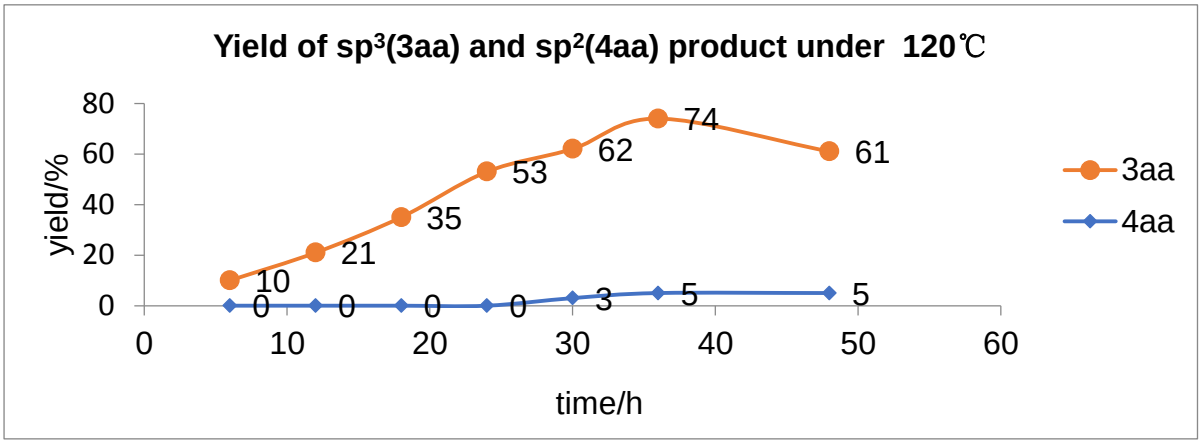


entry	catalyst	solvent	additive	T (℃)	time (h)	yield (%)	
						3aa	**4aa**
1	$PdCl_2$	HFIP	AgTFA	120	36	15	-
2	$PdCl_2$	HFIP	AgTFA	140	48	<5	<10
3	$Pd(TFA)_2$	HFIP	AgTFA	120	36	19	<5
4	$Pd(TFA)_2$	HFIP	AgTFA	140	48	<5	16

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.5 mmol), Catalyst (10 mol %), AgTFA (1.5 mmol), HFIP (3 mL). [b]Isolated Yield







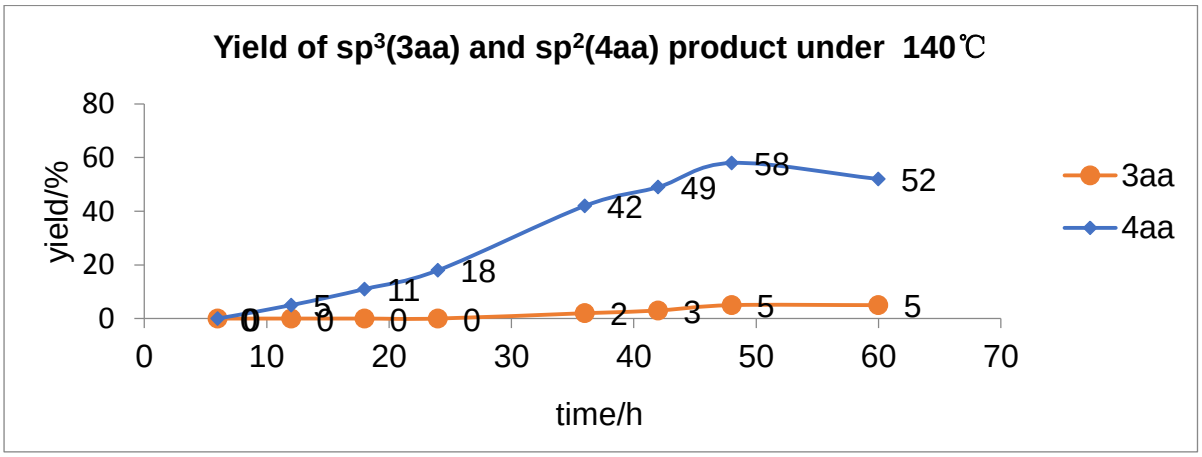
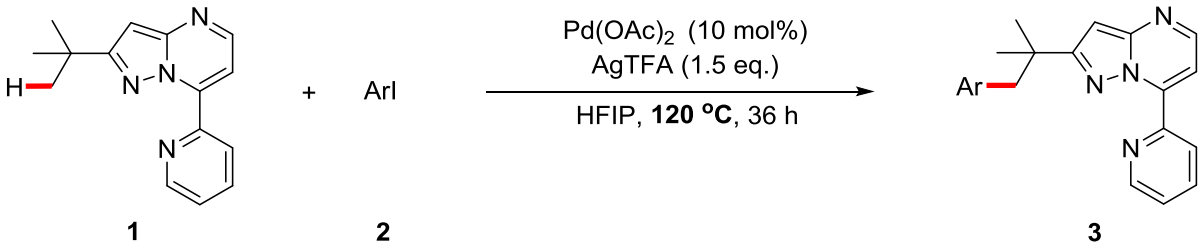


Figure S1 | Effect of Temperature and Time on the C(sp^3)-H and C(sp^2)-H Arylation. Reaction conditions: **1a** (1.0 mmol), **2a** (1.5 mmol), Catalyst (10 mol %), AgTFA (1.5 mmol), HFIP (3 mL).

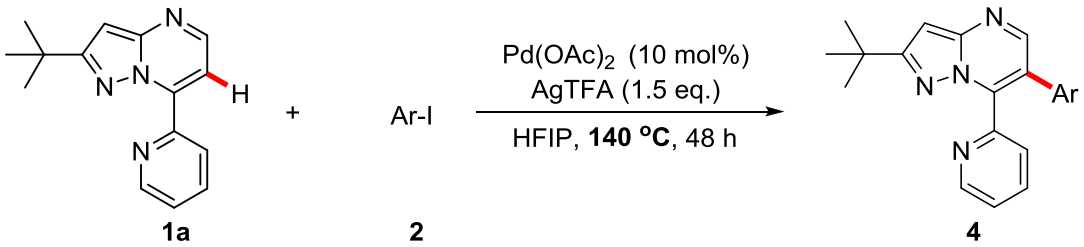
4. General Procedure for C(sp^3)-H and C(sp^2)-H Arylation Reactions

4.1 C(sp^3)-H Arylation Reaction (GP2)



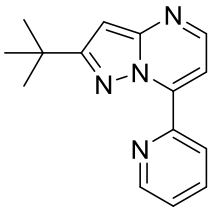
A 25 mL sealed tube was charged with 7-pyridyl-pyrazolo[1, 5-a]pyrimidine derivative **1** (0.1 mmol), aryl iodide **2** (0.15 mmol, 1.5 equiv), $Pd(OAc)_2$ (10 mol%), AgTFA (1.5 equiv) and HFIP (2.0 mL). The mixture was then stirred at 120 ℃ for 36 hours. Upon completion, the reaction mixture was cooled to room temperature and diluted with DCM. Then the reaction mixture was filtered through a pad of celite and the celite was further washed with DCM. The solvent was removed under vacuum directly and the obtained crude product was purified by silica gel column chromatography to afford the desired product **3**.

4.2 C(sp^2)-H Arylation Reaction (GP3)

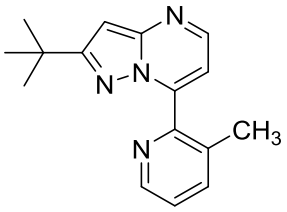


A 25 mL sealed tube was charged with 7-pyridyl-pyrazolo[1, 5-a]pyrimidine derivative **1** (0.15 mmol), aryl iodide **2** (0.15 mmol, 1.5 equiv), $Pd(OAc)_2$ (10 mol%), AgTFA (1.5 equiv) and HFIP (2.0 mL). The mixture was then stirred at 140 ℃ for 48 hours. Upon completion, the reaction mixture was cooled to room temperature and diluted with DCM. Then the reaction mixture was filtered through a pad of celite, which was further washed with DCM. The solvent was removed under vacuum directly and the obtained crude product was purified by silica gel column chromatography to afford the desired product **4**.

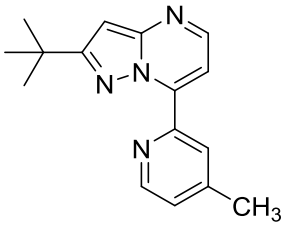
5. Characterization Data for the Substrates and the Products



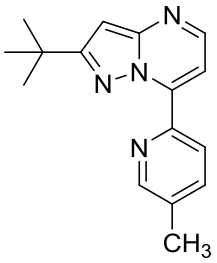
2-(*tert*-Butyl)-7-(pyridine-2-yl)pyrazolo[1,5-a]pyrimidine (1a): The title compound was obtained as a yellow solid in 86% yield according to the GP1. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.35 (d, J = 8.0 Hz, 1H), 8.80 (d, J = 4.0 Hz, 1H), 8.54 (d, J = 4.4 Hz, 1H), 7.94 (dd, J = 11.1, 4.4 Hz, 1H), 7.75 (d, J = 4.4 Hz, 1H), 7.45 (dd, J = 7.1, 4.9 Hz, 1H), 6.67 (s, 1H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 150.8, 149.7, 148.4, 148.3, 143.4, 136.6, 126.4, 125.3, 106.9, 93.0, 33.0, 30.5; HRMS (ESI) *m/z* calcd. For $C_{15}H_{17}N_4$ $[M+H]^+$ 253.1448, found 253.1451.



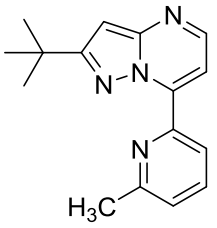
2-(*tert*-Butyl)-7-(3-methylpyridin-2-yl)pyrazolo[1,5-a]pyrimidine (1b): The title compound was obtained as a yellow solid in 86% yield according to the GP1. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.59 (dd, J = 4.7, 0.9 Hz, 1H), 8.50 (d, J = 4.2 Hz, 1H), 7.68 (dd, J = 7.8, 0.7 Hz, 1H), 7.39 (dd, J = 7.8, 4.8 Hz, 1H), 6.85 (d, J = 4.2 Hz, 1H), 6.62 (s, 1H), 2.16 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.0, 149.9, 149.5, 148.1, 147.0, 145.8, 138.2, 134.3, 124.6, 107.7, 92.9, 32.9, 30.4, 18.5; HRMS (ESI) *m/z* calcd. For $C_{16}H_{19}N_4$ $[M+H]^+$ 267.1604, found 267.1614.



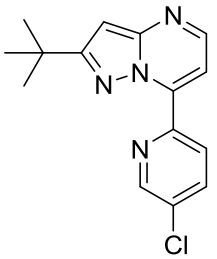
2-(*tert*-Butyl)-7-(4-methylpyridin-2-yl)pyrazolo[1,5-a]pyrimidine (1c): The title compound was obtained as a yellow solid in 84% yield according to the GP1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.64 (d, J = 4.9 Hz, 1H), 8.53 (d, J = 4.4 Hz, 1H), 7.71 (d, J = 4.4 Hz, 1H), 7.25 (d, J = 4.9 Hz, 1H), 6.66 (s, 1H), 2.50 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 150.9, 149.4, 148.4, 148.3, 147.7, 143.5, 127.4, 126.0, 106.9, 92.9, 33.0, 30.5, 21.5; HRMS (ESI) *m/z* calcd. For $C_{16}H_{19}N_4$ $[M+H]^+$ 267.1604, found 267.1611.



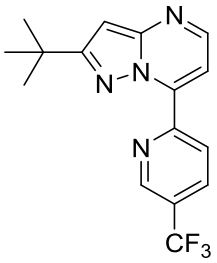
2-(*tert*-Butyl)-7-(5-methylpyridin-2-yl)pyrazolo[1,5-a]pyrimidine (1d): The title compound was obtained as a yellow solid in 63% yield according to the GP1. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.24 (d, J = 8.2 Hz, 1H), 8.62 (d, J = 1.7 Hz, 1H), 8.52 (d, J = 4.4 Hz, 1H), 7.73 (dd, J = 10.9, 3.0 Hz, 2H), 6.65 (s, 1H), 2.45 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 150.9, 150.3, 148.3, 145.8, 143.6, 136.9, 135.4, 125.9, 106.5, 92.9, 33.0, 30.5, 18.6; HRMS (ESI) *m/z* calcd. For $C_{16}H_{19}N_4$ $[M+H]^+$ 267.1604, found 267.1612.



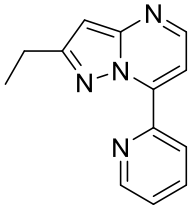
2-(*tert*-Butyl)-7-(6-methylpyridin-2-yl)pyrazolo[1,5-a]pyrimidine (1e): The title compound was obtained as a yellow solid in 68% yield according to the GP1. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.13 (d, J = 7.9 Hz, 1H), 8.53 (d, J = 4.4 Hz, 1H), 7.81 (t, J = 7.8 Hz, 1H), 7.76 (d, J = 4.4 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 6.65 (s, 1H), 2.67 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 158.6, 150.8, 148.3, 147.7, 143.7, 136.7, 125.0, 123.4, 106.9, 92.9, 33.0, 30.5, 24.7; HRMS (ESI) *m/z* calcd. For $C_{16}H_{19}N_4$ $[M+H]^+$ 267.1604, found 267.1612.



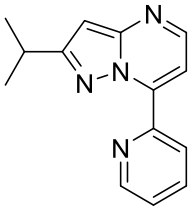
2-(*tert*-Butyl)-7-(5-chloropyridin-2-yl)pyrazolo[1,5-a]pyrimidine (1f): The title compound was obtained as a yellow solid in 59% yield according to the GP1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (d, J = 8.6 Hz, 1H), 8.74 (d, J = 2.3 Hz, 1H), 8.55 (d, J = 4.4 Hz, 1H), 7.93 (dd, J = 8.6, 2.5 Hz, 1H), 7.76 (d, J = 4.4 Hz, 1H), 6.69 (s, 1H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.7, 150.6, 148.8, 148.1, 146.4, 142.5, 136.3, 133.7, 127.0, 106.8, 93.2, 33.0, 30.5; HRMS (ESI) *m/z* calcd. For $C_{15}H_{16}ClN_4$ $[M+H]^+$ 287.1058, found 287.1048.



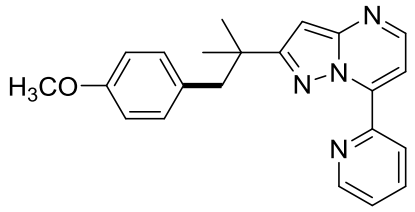
2-(*tert*-Butyl)-7-(5-(trifluoromethyl)pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (1g): The title compound was obtained as a yellow solid in 46% yield according to the GP1. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.56 (d, J = 8.4 Hz, 1H), 9.05 (dd, J = 1.5, 0.7 Hz, 1H), 8.58 (d, J = 4.4 Hz, 1H), 8.26 – 8.17 (m, 1H), 7.81 (d, J = 4.4 Hz, 1H), 6.71 (s, 1H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.8, 151.7, 150.9, 148.3, 146.4 (q, J = 3.9 Hz), 141.8, 134.0, 127.4 (q, J = 33.3 Hz), 125.8, 123.3 (q, J = 272.2 Hz, CF_3), 107.6, 93.5, 33.0, 30.5; HRMS (ESI) *m/z* calcd. For $C_{16}H_{16}F_3N_4$ $[M+H]^+$ 321.1322, found 321.1329.



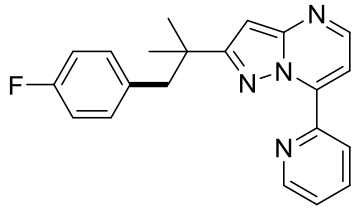
2-Ethyl-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (1h): The title compound was obtained as a yellow solid in 42% yield according to the GP1. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.16 (d, J = 8.0 Hz, 1H), 8.82 (d, J = 4.1 Hz, 1H), 8.55 (d, J = 4.4 Hz, 1H), 7.95 (td, J = 7.9, 1.6 Hz, 1H), 7.64 (d, J = 4.4 Hz, 1H), 7.46 (dd, J = 6.9, 4.8 Hz, 1H), 6.64 (s, 1H), 2.95 (q, J = 7.6 Hz, 2H), 1.41 (t, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.7, 151.0, 149.9, 148.6, 143.6, 136.7, 126.1, 125.3, 107.1, 94.9, 22.5, 13.7; HRMS (ESI) *m/z* calcd. For $C_{13}H_{13}N_4$ $[M+H]^+$ 225.1135, found 225.1148.



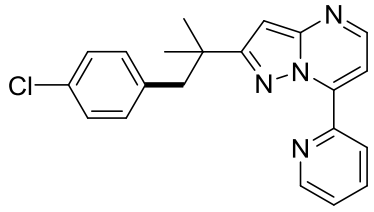
2-Isopropyl-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (1i): The title compound was obtained as a yellow solid in 49% yield according to the GP1. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.24 (d, J = 8.0 Hz, 1H), 8.81 (d, J = 3.7 Hz, 1H), 8.55 (d, J = 4.2 Hz, 1H), 7.95 (t, J = 7.2 Hz, 1H), 7.68 (d, J = 4.3 Hz, 1H), 7.46 (dd, J = 7.0, 4.7 Hz, 1H), 6.64 (s, 1H), 3.25 (dt, J = 13.8, 6.9 Hz, 1H), 1.43 (d, J = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.9, 150.9, 149.9, 148.6, 148.5, 143.5, 136.7, 126.3, 125.3, 107.1, 93.5, 28.8, 22.8; HRMS (ESI) *m/z* calcd. For $C_{14}H_{15}N_4$ $[M+H]^+$ 239.1291, found 239.1282.



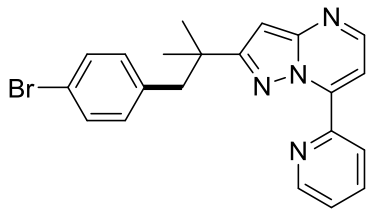
2-(1-(4-Methoxyphenyl)-2-methylpropan-2-yl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (3aa): The title compound was obtained as a pale yellow semi solid in 74% yield according to the GP2. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.19 (d, J = 8.1 Hz, 1H), 8.81 (d, J = 4.5 Hz, 1H), 8.56 (d, J = 4.4 Hz, 1H), 7.90 (td, J = 7.8, 1.7 Hz, 1H), 7.76 (d, J = 4.4 Hz, 1H), 7.45 (dd, J = 7.5, 4.8 Hz, 1H), 6.90 – 6.84 (m, 2H), 6.74 – 6.67 (m, 2H), 6.60 (s, 1H), 3.73 (s, 3H), 3.01 (s, 2H), 1.43 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.0, 158.0, 150.6, 149.6, 148.3, 148.2, 143.3, 136.7, 131.4, 130.8, 126.4, 125.3, 113.0, 107.0, 94.2, 55.1, 48.8, 37.3, 27.7; HRMS (ESI) *m/z* calcd. For C22H23N4O $[M+H]^+$ 359.1866, found 359.1874.



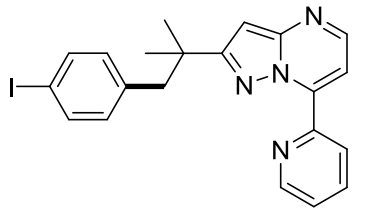
2-(1-(4-Fluorophenyl)-2-methylpropan-2-yl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (3ab): The title compound was obtained as a pale yellow semi solid in 68% yield according to the GP2. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.15 (d, J = 8.1 Hz, 1H), 8.85 – 8.78 (m, 1H), 8.57 (d, J = 4.4 Hz, 1H), 7.90 (td, J = 7.8, 1.8 Hz, 1H), 7.77 (d, J = 4.4 Hz, 1H), 7.46 (ddd, J = 7.6, 4.7, 0.9 Hz, 1H), 6.91 – 6.86 (m, 2H), 6.86 – 6.81 (m, 2H), 6.59 (s, 1H), 3.04 (s, 2H), 1.44 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.5, 161.5 (d, J = 243.2 Hz), 150.7, 149.7, 148.4, 148.3, 143.3, 136.7, 134.4 (d, J = 2.5 Hz), 131.7 (d, J = 7.7 Hz), 126.3, 125.3, 114.4 (d, J = 21.0 Hz), 107.1, 94.2, 48.8, 37.2, 27.7; HRMS (ESI) *m/z* calcd. For $C_{21}H_{20}FN_4$ $[M+H]^+$ 347.1667, found 347.1681.



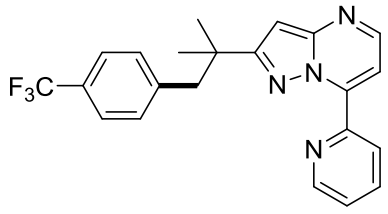
2-(1-(4-Chlorophenyl)-2-methylpropan-2-yl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (3ac): The title compound was obtained as a pale yellow solid in 65% yield according to the GP2. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.10 (d, J = 8.1 Hz, 1H), 8.86 – 8.77 (m, 1H), 8.57 (d, J = 4.4 Hz, 1H), 7.90 (dd, J = 11.6, 4.1 Hz, 1H), 7.76 (d, J = 4.4 Hz, 1H), 7.50 – 7.42 (m, 1H), 7.14 – 7.08 (m, 2H), 6.86 (t, J = 5.4 Hz, 2H), 6.59 (s, 1H), 3.03 (s, 2H), 1.44 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.3, 150.7, 149.7, 148.5, 148.3, 143.4, 137.2, 136.7, 131.9, 131.7, 127.7, 126.3, 125.3, 107.2, 94.2, 49.1, 37.2, 27.7; HRMS (ESI) *m/z* calcd. For $C_{21}H_{20}ClN_4$ $[M+H]^+$ 363.1371, found 363.1379.



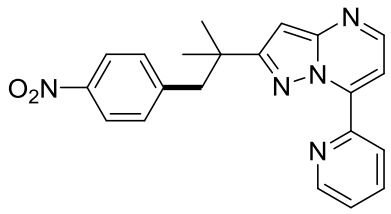
2-(1-(4-Bromophenyl)-2-methylpropan-2-yl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (3ad): The title compound was obtained as a pale yellow solid in 59% yield according to the GP2. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.12 – 9.05 (m, 1H), 8.81 (dd, *J* = 4.7, 0.8 Hz, 1H), 8.56 (d, *J* = 4.4 Hz, 1H), 7.90 (td, *J* = 7.8, 1.8 Hz, 1H), 7.76 (d, *J* = 4.4 Hz, 1H), 7.49 – 7.42 (m, 1H), 7.28 – 7.25 (m, 2H), 6.84 – 6.77 (m, 2H), 6.60 (s, 1H), 3.01 (s, 2H), 1.44 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.3, 150.7, 149.7, 148.4, 148.3, 143.4, 137.7, 136.7, 132.1, 130.7, 126.3, 125.3, 120.0, 107.2, 94.2, 49.1, 37.2, 27.7; HRMS (ESI) *m/z* calcd. For $C_{21}H_{20}BrN_4$ $[M+H]^+$ 407.0866, found 407.0876.



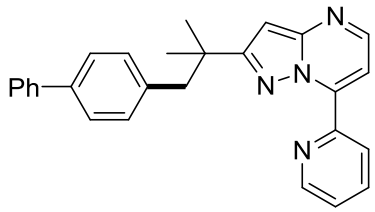
2-(1-(4-Iodophenyl)-2-methylpropan-2-yl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (3ae): The title compound was obtained as a pale yellow semi solid in 53% yield according to the GP2. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.08 (d, *J* = 8.0 Hz, 1H), 8.82 (d, *J* = 3.7 Hz, 1H), 8.57 (d, *J* = 4.4 Hz, 1H), 7.92 (t, *J* = 7.2 Hz, 1H), 7.77 (d, *J* = 4.4 Hz, 1H), 7.47 (dd, *J* = 7.3, 4.8 Hz, 1H), 7.28 – 7.25 (m, 3H), 6.80 (d, *J* = 8.3 Hz, 2H), 6.60 (s, 1H), 3.01 (s, 2H), 1.44 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.3, 150.6, 149.7, 148.4, 148.2, 143.3, 137.7, 136.8, 132.1, 130.7, 126.3, 125.4, 120.0, 107.2, 94.2, 49.1, 37.2, 27.8; HRMS (ESI) *m/z* calcd. For $C_{21}H_{20}IN_4$ $[M+H]^+$ 455.0727, found 455.0736.



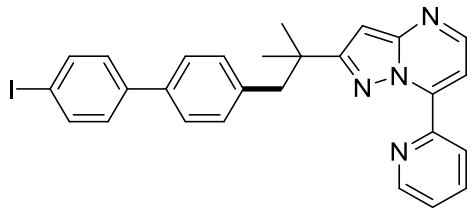
2-(2-Methyl-1-(4-(trifluoromethyl)phenyl)propan-2-yl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (3af): The title compound was obtained as a pale yellow semi solid in 52% yield according to the GP2. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.05 (d, *J* = 8.1 Hz, 1H), 8.81 (dd, *J* = 4.7, 0.8 Hz, 1H), 8.58 (d, *J* = 4.4 Hz, 1H), 7.87 (td, *J* = 7.9, 1.8 Hz, 1H), 7.77 (d, *J* = 4.4 Hz, 1H), 7.45 (ddd, *J* = 7.6, 4.7, 0.8 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.61 (s, 1H), 3.12 (s, 2H), 1.46 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0, 150.8, 149.8, 148.6, 148.3, 143.4, 142.9, 136.6, 130.7, 128.3 (q, *J* = 32.7 Hz), 126.2, 125.3, 124.4 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 272.3 Hz), 107.3, 94.1, 49.5, 37.3, 27.8; HRMS (ESI) *m/z* calcd. For $C_{22}H_{20}F_3N_4$ $[M+H]^+$ 397.1635, found 397.1644.



2-(2-Methyl-1-(4-nitrophenyl)propan-2-yl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (3ag): The title compound was obtained as a pale yellow semi solid in 38% yield according to the GP2. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.08 (d, J = 8.1 Hz, 1H), 8.85 – 8.79 (m, 1H), 8.59 (d, J = 4.4 Hz, 1H), 7.99 (d, J = 8.8 Hz, 2H), 7.89 (td, J = 7.9, 1.8 Hz, 1H), 7.80 (d, J = 4.4 Hz, 1H), 7.47 (ddd, J = 7.6, 4.7, 1.0 Hz, 1H), 7.07 (d, J = 8.7 Hz, 2H), 6.59 (s, 1H), 3.18 (s, 2H), 1.48 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.6, 150.7, 149.8, 148.7, 148.2, 146.8, 146.5, 143.4, 136.7, 131.1, 126.2, 125.5, 122.8, 107.4, 94.2, 49.5, 37.5, 27.9; HRMS (ESI) *m/z* calcd. For $C_{21}H_{20}N_5O_2$ $[M+H]^+$ 374.1612, found 374.1626.

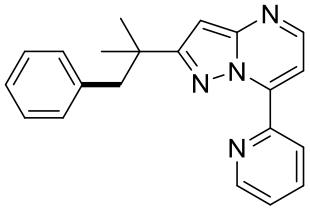


2-(1-([1,1'-Biphenyl]-4-yl)-2-methylpropan-2-yl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (3ah): The title compound was obtained as a yellow solid in 66% yield according to the GP2. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.15 (d, J = 8.0 Hz, 1H), 8.80 (d, J = 3.9 Hz, 1H), 8.57 (d, J = 4.2 Hz, 1H), 7.85 (t, J = 7.4 Hz, 1H), 7.77 (d, J = 4.3 Hz, 1H), 7.52 (d, J = 7.4 Hz, 2H), 7.41 (dt, J = 16.7, 6.6 Hz, 5H), 7.29 (t, J = 7.3 Hz, 1H), 7.02 (d, J = 8.0 Hz, 2H), 6.66 (s, 1H), 3.11 (s, 2H), 1.48 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.9, 150.6, 149.6, 148.3, 143.3, 141.0, 138.8, 137.9, 136.8, 130.9, 128.7, 127.0, 126.9, 126.4, 126.3, 125.4, 107.1, 94.2, 49.4, 37.4, 27.8; HRMS (ESI) *m/z* calcd. For $C_{27}H_{25}N_4$ $[M+H]^+$ 405.2074, found 405.2083.

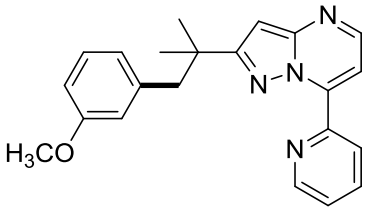


2-(1-(4-Methoxyphenyl)-2-methylpropan-2-yl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (3ai): The title compound was obtained as a yellow solid in 41% yield according to the GP2. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.15 (d, J = 8.1 Hz, 1H), 8.81 (dd, J = 4.7, 0.9 Hz, 1H), 8.57 (d, J = 4.4 Hz, 1H), 7.85 (td, J = 7.9, 1.8 Hz, 1H), 7.77 (d, J = 4.4 Hz, 1H), 7.73 – 7.68 (m, 2H), 7.43 (ddd, J = 7.6, 4.8, 0.9 Hz, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.27 (s, 1H), 7.25 (d, J = 1.9 Hz, 1H), 7.01 (d, J = 8.2 Hz, 2H), 6.63 (s, 1H), 3.11 (s, 2H), 1.48 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7, 150.7, 149.7, 148.4, 143.4, 140.5, 138.5, 137.8, 137.6,

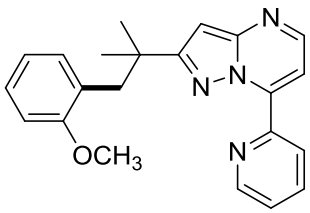
136.7, 131.0, 128.8, 126.3, 126.0, 125.3, 107.1, 94.2, 92.7, 49.4, 37.4, 27.8; HRMS (ESI) *m/z* calcd. For $C_{27}H_{24}IN_4$ $[M+H]^+$ 531.1040, found 531.1049.



2-(2-Methyl-1-phenylpropan-2-yl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (3aj): The title compound was obtained as a pale yellow semi solid in 58% yield according to the GP2. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.17 (d, J = 8.1 Hz, 1H), 8.81 (ddd, J = 4.7, 1.7, 0.8 Hz, 1H), 8.56 (d, J = 4.4 Hz, 1H), 7.90 (td, J = 7.9, 1.8 Hz, 1H), 7.76 (d, J = 4.4 Hz, 1H), 7.45 (ddd, J = 7.6, 4.7, 1.0 Hz, 1H), 7.19 – 7.13 (m, 3H), 6.99 – 6.93 (m, 2H), 6.61 (s, 1H), 3.08 (s, 2H), 1.45 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.9, 150.7, 149.7, 148.3, 143.3, 138.7, 136.7, 130.5, 127.6, 126.4, 125.9, 125.3, 107.0, 94.1, 49.7, 37.2, 27.7; HRMS (ESI) *m/z* calcd. For $C_{23}H_{23}N_4O_2$ $[M+H]^+$ 387.1816, found 387.1832.

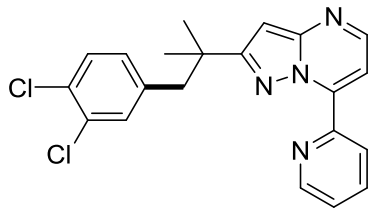


2-(1-(3-Methoxyphenyl)-2-methylpropan-2-yl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (3ak): The title compound was obtained as a pale yellow semi solid in 65% yield according to the GP2. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.18 (d, J = 8.1 Hz, 1H), 8.81 (ddd, J = 4.7, 1.7, 0.8 Hz, 1H), 8.56 (d, J = 4.4 Hz, 1H), 7.90 (td, J = 7.9, 1.8 Hz, 1H), 7.75 (d, J = 4.4 Hz, 1H), 7.45 (ddd, J = 7.6, 4.7, 1.1 Hz, 1H), 7.12 – 7.04 (m, 1H), 6.70 (ddd, J = 8.2, 2.6, 0.7 Hz, 1H), 6.62 (s, 1H), 6.58 (d, J = 7.6 Hz, 1H), 6.52 – 6.47 (m, 1H), 3.61 (s, 3H), 3.06 (s, 2H), 1.45 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.9, 158.9, 150.7, 149.7, 148.4, 148.4, 143.4, 140.3, 136.6, 128.5, 126.4, 125.3, 123.0, 116.1, 111.5, 107.0, 94.23, 54.9, 49.7, 37.3, 27.8; HRMS (ESI) *m/z* calcd. For $C_{22}H_{23}N_4O$ $[M+H]^+$ 359.1866, found 359.1876.

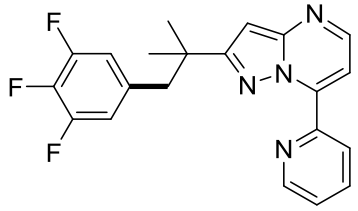


2-(1-(2-Methoxyphenyl)-2-methylpropan-2-yl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (3al): The title compound was obtained as a pale yellow semi solid in 58% yield according to the GP2. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.22 – 9.17 (m, 1H), 8.81 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 8.56 (d, J = 4.5 Hz, 1H), 7.90 (td, J = 7.9, 1.8 Hz, 1H), 7.76 (d, J = 4.5 Hz, 1H), 7.46 (ddd, J = 7.6, 4.7, 1.1 Hz, 1H), 7.14 (ddd, J = 8.2, 7.5,

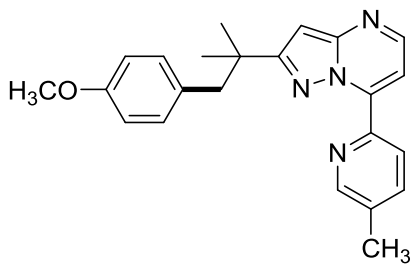
1.8 Hz, 1H), 6.87 (dd, *J* = 7.4, 1.7 Hz, 1H), 6.76 (ddd, *J* = 11.0, 5.9, 2.3 Hz, 2H), 6.62 (s, 1H), 3.60 (s, 3H), 3.12 (s, 2H), 1.45 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 158.1, 150.3, 149.5, 148.2, 147.9, 143.3, 136.9, 132.2, 127.3, 126.6, 125.4, 119.7, 110.1, 106.8, 94.1, 54.8, 42.3, 37.7, 27.5; HRMS (ESI) *m/z* calcd. For $C_{22}H_{23}N_4O$ $[M+H]^+$ 359.1866, found 359.1871.



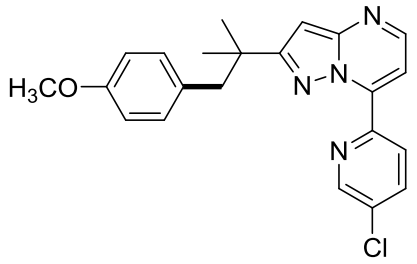
2-(1-(3,4-Dichlorophenyl)-2-methylpropan-2-yl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (3am): The title compound was obtained as a yellow solid in 46% yield according to the GP2. ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 9.06 (d, *J* = 8.1 Hz, 1H), 8.85 – 8.78 (m, 1H), 8.58 (d, *J* = 4.4 Hz, 1H), 7.91 (td, *J* = 7.8, 1.8 Hz, 1H), 7.77 (d, *J* = 4.4 Hz, 1H), 7.47 (ddd, *J* = 7.5, 4.7, 0.8 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.07 (d, *J* = 2.0 Hz, 1H), 6.71 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.61 (s, 1H), 3.01 (s, 2H), 1.45 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 164.9, 150.7, 149.7, 148.6, 148.2, 143.4, 139.1, 136.7, 132.2, 131.4, 130.05, 129.8, 129.5, 126.2, 125.4, 107.3, 94.1, 48.8, 37.2, 27.8; HRMS (ESI) *m/z* calcd. For $C_{21}H_{19}Cl_2N_4$ $[M+H]^+$ 397.0981, found 397.0996.



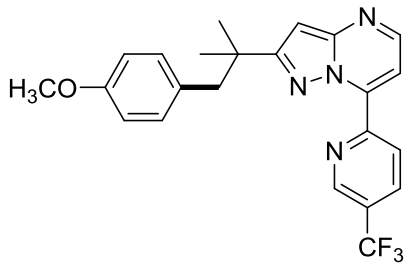
2-(2-Methyl-1-(3,4,5-trifluorophenyl)propan-2-yl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (3an): The title compound was obtained as a yellow semi solid in 40% yield according to the GP2. ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 9.15 (d, *J* = 8.1 Hz, 1H), 8.84 (dd, *J* = 4.6, 0.9 Hz, 1H), 8.59 (d, *J* = 4.4 Hz, 1H), 7.94 (td, *J* = 7.9, 1.7 Hz, 1H), 7.80 (d, *J* = 4.4 Hz, 1H), 7.49 (ddt, *J* = 7.8, 4.0, 2.0 Hz, 1H), 6.61 (s, 1H), 6.56 (dd, *J* = 8.7, 6.6 Hz, 2H), 3.02 (s, 2H), 1.45 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 164.8, 151.4 (dd, *J* = 9.8, 4.1 Hz), 150.7, 149.8, 149.4 (dd, *J* = 9.8, 4.1 Hz), 148.6, 148.2, 143.4, 136.8, 135.0, 126.2, 125.5, 114.2 (dd, *J* = 15.8, 4.5 Hz), 107.5, 94.1, 48.8, 37.2, 27.9; HRMS (ESI) *m/z* calcd. For $C_{21}H_{18}F_3N_4$ $[M+H]^+$ 383.1478, found 383.1486.



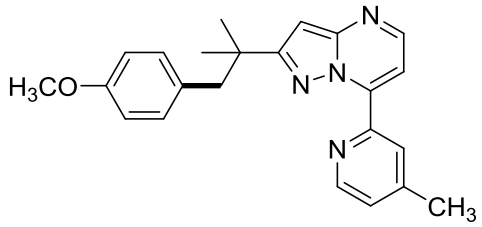
2-(1-(4-Methoxyphenyl)-2-methylpropan-2-yl)-7-(5-methylpyridin-2-yl)pyrazolo[1,5-a]pyrimidine (3ba): The title compound was obtained as a pale yellow solid in 46% yield according to the GP2. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.10 (d, J = 8.1 Hz, 1H), 8.63 (s, 1H), 8.53 (d, J = 4.3 Hz, 1H), 7.71 (dd, J = 11.0, 6.3 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 6.70 (d, J = 8.5 Hz, 2H), 6.57 (s, 1H), 3.73 (s, 3H), 3.01 (s, 2H), 2.46 (s, 3H), 1.42 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8, 157.9, 150.8, 150.4, 148.4, 145.8, 143.5, 136.9, 135.5, 131.4, 130.9, 125.9, 113.0, 106.6, 94.0, 55.2, 48.8, 37.3, 27.7, 18.6; HRMS (ESI) *m/z* calcd. For $C_{23}H_{25}N_4O$ $[M+H]^+$ 373.2023, found 373.2029.



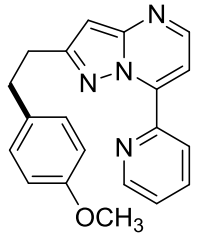
7-(5-Chloropyridin-2-yl)-2-(1-(4-methoxyphenyl)-2-methylpropan-2-yl)pyrazolo[1,5-a]pyrimidine (3ca): The title compound was obtained as a pale yellow solid in 38 % yield according to the GP2. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.21 (d, J = 8.6 Hz, 1H), 8.74 (d, J = 2.5 Hz, 1H), 8.56 (d, J = 4.5 Hz, 1H), 7.87 (dd, J = 8.6, 2.5 Hz, 1H), 7.75 (d, J = 4.4 Hz, 1H), 6.90 – 6.83 (m, 2H), 6.74 – 6.66 (m, 2H), 6.61 (s, 1H), 3.73 (s, 3H), 3.00 (s, 2H), 1.43 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.1, 158.0, 150.6, 148.8, 148.2, 146.4, 142.4, 136.2, 133.7, 131.4, 130.8, 127.0, 113.0, 106.9, 94.3, 55.1, 48.9, 37.3, 27.7; HRMS (ESI) *m/z* calcd. For $C_{22}H_{22}ClN_4O$ $[M+H]^+$ 393.1477, found 393.1479.



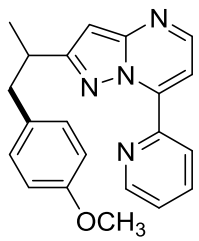
2-(1-(4-Methoxyphenyl)-2-methylpropan-2-yl)-7-(5-(trifluoromethyl)pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (3da): The title compound was obtained as a pale yellow solid in 32% yield according to the GP2. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.35 (d, J = 8.4 Hz, 1H), 9.05 (d, J = 0.7 Hz, 1H), 8.60 (d, J = 4.4 Hz, 1H), 8.15 (dd, J = 8.4, 1.8 Hz, 1H), 7.83 (d, J = 4.4 Hz, 1H), 6.86 (d, J = 8.6 Hz, 2H), 6.71 (d, J = 8.7 Hz, 2H), 6.66 (s, 1H), 3.73 (s, 3H), 3.00 (s, 2H), 1.44 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.2, 158.0, 151.6, 150.7, 148.3, 146.4 (q, J = 3.8 Hz), 141.8, 134.0 (q, J = 3.8 Hz), 131.4, 130.7, 127.5 (q, J = 32.8 Hz), 125.8, 123.3 (q, J = 272.2 Hz), 113.0, 107.7, 94.6, 55.1, 48.9, 37.4, 27.7; HRMS (ESI) *m/z* calcd. For $C_{23}H_{22}F_3N_4O$ $[M+H]^+$ 427.1740, found 427.1746.



2-(1-(4-Methoxyphenyl)-2-methylpropan-2-yl)-7-(4-methylpyridin-2-yl)pyrazolo[1,5-a]pyrimidine (3ea): The title compound was obtained as a pale yellow solid in 36% yield according to the GP2. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.97 (s, 1H), 8.65 (d, J = 4.9 Hz, 1H), 8.54 (d, J = 4.4 Hz, 1H), 7.71 (d, J = 4.4 Hz, 1H), 7.27 (d, J = 3.3 Hz, 1H), 6.88 – 6.83 (m, 2H), 6.74 – 6.67 (m, 2H), 6.60 (s, 1H), 3.72 (s, 3H), 3.00 (s, 2H), 2.46 (s, 3H), 1.43 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7, 157.9, 150.8, 149.3, 148.4, 148.1, 131.3, 130.8, 127.4, 126.1, 123.0, 107.1, 94.1, 55.1, 49.0, 37.3, 27.6, 21.5; HRMS (ESI) *m/z* calcd. For $C_{23}H_{25}N_4O$ $[M+H]^+$ 373.2023, found 373.2039.

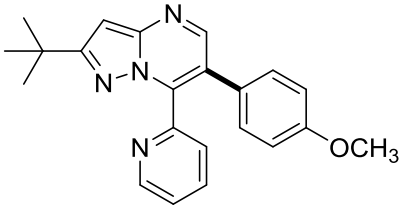


2-(4-Methoxyphenethyl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (3fa): The title compound was obtained as a pale yellow solid in 33% yield according to the GP2. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.12 – 9.04 (m, 1H), 8.83 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 8.56 (d, J = 4.4 Hz, 1H), 7.95 (td, J = 7.8, 1.8 Hz, 1H), 7.67 (d, J = 4.4 Hz, 1H), 7.49 (ddt, J = 7.1, 3.4, 1.7 Hz, 1H), 7.22 – 7.16 (m, 2H), 6.89 – 6.82 (m, 2H), 6.62 (s, 1H), 3.79 (s, 3H), 3.21 (dd, J = 9.1, 6.6 Hz, 2H), 3.08 (dd, J = 9.1, 6.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5, 157.9, 150.6, 149.7, 148.4, 148.2, 143.4, 137.0, 133.5, 129.4, 126.3, 125.5, 113.8, 107.3, 95.7, 55.3, 34.6, 31.2; HRMS (ESI) *m/z* calcd. For $C_{20}H_{19}N_4O$ $[M+H]^+$ 331.1553, found 331.1562.

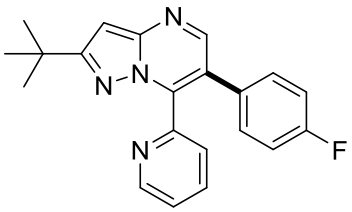


2-(1-(4-Methoxyphenyl)propan-2-yl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (3ga): The title compound was obtained as a pale yellow solid in 38% yield according to the GP2. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.04 (dt, J = 8.1, 1.0 Hz, 1H), 8.80 (ddd, J = 4.7, 1.8, 0.9 Hz, 1H), 8.55 (d, J = 4.4 Hz, 1H), 7.94 – 7.87 (m, 1H), 7.66 (d, J = 4.4 Hz, 1H), 7.44 (ddd, J = 7.6, 4.7, 1.1 Hz, 1H), 7.15 – 7.06 (m, 2H), 6.84 – 6.77 (m, 2H), 6.62 (s, 1H), 3.77 (s, 3H), 3.38 (dd, J = 14.9, 6.9 Hz, 1H), 3.14 (dd, J = 13.7, 6.7 Hz, 1H), 2.87 (dd, J = 13.7, 8.1 Hz, 1H), 1.38 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.2, 157.9,

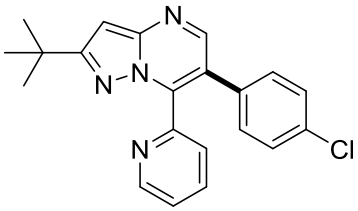
150.8, 149.8, 148.5, 143.5, 136.7, 132.6, 130.1, 126.2, 125.3, 113.6, 107.1, 94.1, 55.2, 42.7, 36.1, 20.1; HRMS (ESI) *m/z* calcd. For $C_{21}H_{21}N_4O$ $[M+H]^+$ 345.1710, found 345.1719.



2-(*tert*-Butyl)-6-(4-methoxyphenyl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (4aa): The title compound was obtained as a pale yellow solid in 58% yield according to the GP3. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.58 (s, 1H), 8.45 (s, 1H), 7.69 (t, *J* = 7.1 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 5.0 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 2H), 6.69 (d, *J* = 8.3 Hz, 2H), 6.53 (s, 1H), 3.68 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.0, 159.0, 150.8, 149.9, 148.8, 141.1, 136.5, 131.0, 127.1, 126.5, 124.2, 120.6, 114.0, 93.0, 55.4, 33.0, 30.4; HRMS (ESI) *m/z* calcd. For $C_{22}H_{23}N_4O$ $[M+H]^+$ 359.1866, found 359.1858.

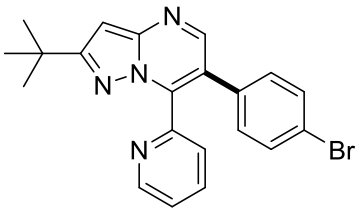


2-(*tert*-Butyl)-6-(4-fluorophenyl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (4ab): The title compound was obtained as a pale yellow solid in 56% yield according to the GP3. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (d, *J* = 4.5 Hz, 1H), 8.52 (s, 1H), 7.85 – 7.74 (m, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.34 (ddd, *J* = 7.6, 4.9, 0.9 Hz, 1H), 7.16 – 7.08 (m, 2H), 6.95 (dd, *J* = 9.7, 7.7 Hz, 2H), 6.64 (s, 1H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.4, 162.2 (d, *J* = 246 Hz), 161.2, 150.3, 149.1, 149.0, 148.9, 136.9, 131.6 (d, *J* = 8.2 Hz), 130.8, 126.7, 124.4, 120.1, 115.6 (d, *J* = 21.6 Hz), 93.3, 33.0, 30.3; HRMS (ESI) *m/z* calcd. For $C_{21}H_{20}FN_4$ $[M+H]^+$ 347.1667, found 347.1678.

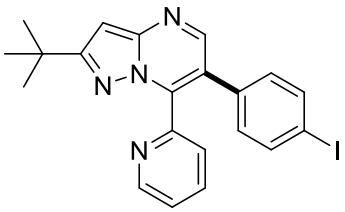


2-(*tert*-Butyl)-6-(4-chlorophenyl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (4ac): The title compound was obtained as a pale yellow solid in 51% yield according to the GP3. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.64 (d, *J* = 4.3 Hz, 1H), 8.52 (s, 1H), 7.82 (dd, *J* = 7.7, 6.6 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.37 (dd, *J* = 7.0, 4.8 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 2H), 6.65 (s, 1H), 1.34 (s, 9H); ^{13}C NMR

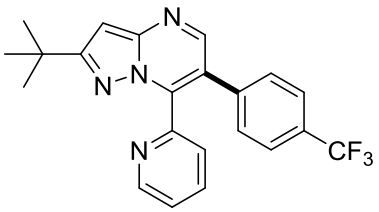
(125 MHz, $CDCl_3$): δ 168.5, 150.2, 149.4, 149.0, 141.5, 136.5, 133.7, 133.6, 131.1, 128.7, 126.6, 124.4, 119.8, 93.3, 33.0, 30.4; HRMS (ESI) *m/z* calcd. For $C_{21}H_{20}ClN_4$ $[M+H]^+$ 363.1371, found 363.1374.



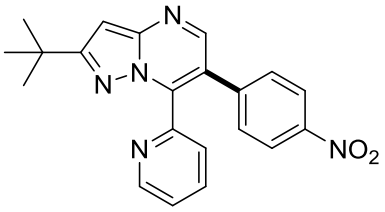
6-(4-Bromophenyl)-2-(*tert*-butyl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (4ad): The title compound was obtained as a pale yellow solid in 46% yield according to the GP3. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (s, 1H), 8.51 (s, 1H), 7.81 (t, *J* = 7.3 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 3H), 7.03 (d, *J* = 8.1 Hz, 2H), 6.65 (s, 1H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.4, 150.1, 149.8, 149.5, 149.1, 141.6, 136.4, 134.1, 131.6, 131.5, 126.5, 124.4, 121.9, 119.8, 93.3, 33.0, 30.4; HRMS (ESI) *m/z* calcd. For $C_{21}H_{20}BrN_4$ $[M+H]^+$ 407.0866, found 407.0874.



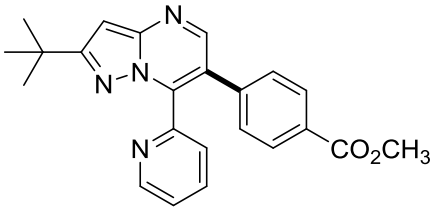
2-(*tert*-Butyl)-6-(4-iodophenyl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (4ae): The title compound was obtained as a pale yellow solid in 40% yield according to the GP3. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.65 (d, *J* = 3.3 Hz, 1H), 8.51 (s, 1H), 7.84 (t, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.40 (dd, *J* = 6.9, 4.0 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 2H), 6.66 (s, 1H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.5, 150.1, 149.4, 149.2, 149.0, 141.2, 137.6, 136.7, 134.6, 131.6, 126.6, 124.5, 119.9, 93.6, 93.4, 33.0, 30.3; HRMS (ESI) *m/z* calcd. For $C_{21}H_{20}IN_4$ $[M+H]^+$ 455.0727, found 455.0729.



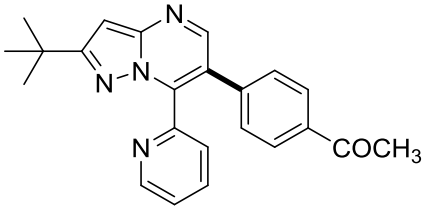
2-(*tert*-Butyl)-7-(pyridin-2-yl)-6-(4-(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidine (4af): The title compound was obtained as a pale yellow solid in 39% yield according to the GP3. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.62 (d, *J* = 4.0 Hz, 1H), 8.54 (s, 1H), 7.85 (t, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.44 – 7.37 (m, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 6.68 (s, 1H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.8, 150.0, 149.4, 149.1, 140.3, 138.9, 136.6, 130.2, 129.5 (q, *J* = 32.8 Hz), 126.7, 125.4 (q, *J* = 3.8 Hz), 124.6, 124.0 (q, *J* = 272.1 Hz), 119.6, 100.0, 93.5, 33.0, 30.4; HRMS (ESI) *m/z* calcd. For $C_{22}H_{20}F_3N_4$ $[M+H]^+$ 397.1635, found 397.1644.



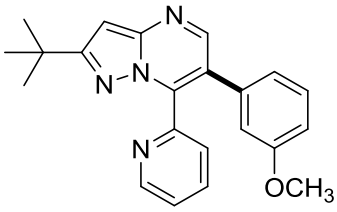
2-(*tert*-Butyl)-6-(4-nitrophenyl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (4ag): The title compound was obtained as a pale yellow solid in 36% yield according to the GP3. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.58 (d, J = 4.6 Hz, 1H), 8.54 (s, 1H), 8.13 (d, J = 8.7 Hz, 2H), 7.92 – 7.84 (m, 2H), 7.41 (t, J = 5.1 Hz, 1H), 7.33 (d, J = 8.7 Hz, 2H), 6.70 (s, 1H), 1.36 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 149.5, 149.3, 148.8, 146.9, 142.4, 142.0, 136.5, 130.7, 126.8, 124.8, 123.6, 118.9, 93.8, 33.0, 30.0; HRMS (ESI) *m/z* calcd. For $C_{21}H_{20}N_5O_2$ $[M+H]^+$ 374.1612, found 374.1628.



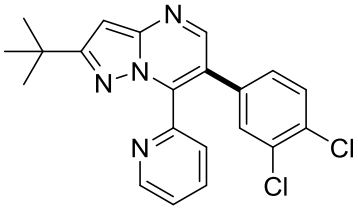
Methyl 4-(2-(tert-butyl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidin-6-yl)benzoate (4ah): The title compound was obtained as a pale yellow solid in 42% yield according to the GP3. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.58 (d, J = 4.7 Hz, 1H), 8.56 (s, 1H), 7.95 – 7.90 (m, 2H), 7.79 (td, J = 7.7, 1.6 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.33 (ddd, J = 7.5, 4.8, 0.8 Hz, 1H), 7.25 – 7.19 (m, 2H), 6.66 (s, 1H), 3.90 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.6, 166.7, 150.1, 149.6, 149.2, 141.9, 140.1, 136.2, 129.8, 129.6, 128.9, 126.5, 124.4, 119.9, 93.4, 52.2, 33.0, 30.5, 30.4; HRMS (ESI) *m/z* calcd. For $C_{23}H_{23}N_4O_2$ $[M+H]^+$ 387.1816, found 387.1832.



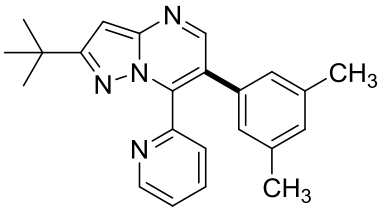
1-(4-(2-(*tert*-Butyl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidin-6-yl)phenyl)ethan-1-one (4ai): The title compound was obtained as a pale yellow solid in 40% yield according to the GP3. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.59 (d, J = 3.5 Hz, 1H), 8.56 (s, 1H), 7.85 (d, J = 8.2 Hz, 2H), 7.81 (t, J = 7.6 Hz, 1H), 7.74 (t, J = 8.7 Hz, 1H), 7.40 – 7.30 (m, 1H), 7.25 (d, J = 8.2 Hz, 2H), 6.67 (s, 1H), 2.58 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.6, 168.6, 150.0, 149.4, 149.2, 141.9, 140.3, 136.2, 135.7, 130.0, 128.4, 126.6, 124.4, 119.8, 93.5, 33.0, 30.4, 26.7; HRMS (ESI) *m/z* calcd. For $C_{23}H_{23}N_4O$ $[M+H]^+$ 371.1866, found 371.1876.



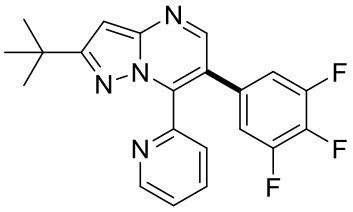
2-(*tert*-Butyl)-6-(3-methoxyphenyl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (4aj): The title compound was obtained as a pale yellow solid in 55% yield according to the GP3. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.67 (dd, J = 3.4, 0.9 Hz, 1H), 8.57 (s, 1H), 7.76 (td, J = 7.7, 1.7 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.34 (ddd, J = 7.6, 4.9, 1.1 Hz, 1H), 7.17 (t, J = 7.9 Hz, 1H), 6.82 – 6.73 (m, 2H), 6.70 – 6.66 (m, 1H), 6.64 (s, 1H), 3.65 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.2, 159.4, 150.5, 150.0, 149.5, 149.0, 141.6, 136.3, 136.3, 129.4, 126.3, 124.1, 122.2, 120.7, 115.2, 113.5, 93.1, 55.1, 33.0, 30.4; HRMS (ESI) *m/z* calcd. For $C_{22}H_{23}N_4O$ $[M+H]^+$ 359.1866, found 359.1855.



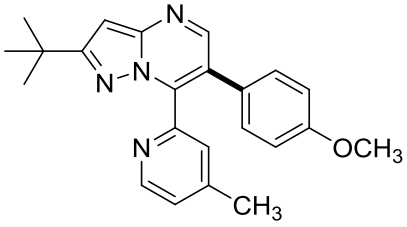
2-(*tert*-Butyl)-6-(3,4-dichlorophenyl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (4al): The title compound was obtained as a pale yellow solid in 44% yield according to the GP3. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.66 (d, J = 4.2 Hz, 1H), 8.51 (s, 1H), 7.90 (t, J = 7.7 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.44 (dd, J = 7.2, 4.7 Hz, 1H), 7.32 (d, J = 8.3 Hz, 1H), 7.28 (d, J = 1.9 Hz, 1H), 6.98 (dd, J = 8.3, 2.0 Hz, 1H), 6.68 (s, 1H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.8, 149.7, 149.2, 149.0, 148.6, 137.0, 135.0, 132.6, 132.0, 131.6, 130.4, 129.2, 126.8, 124.8, 118.8, 93.6, 33.1, 30.3; HRMS (ESI) *m/z* calcd. For $C_{21}H_{19}Cl_2N_4$ $[M+H]^+$ 397.0981, found 397.0999.



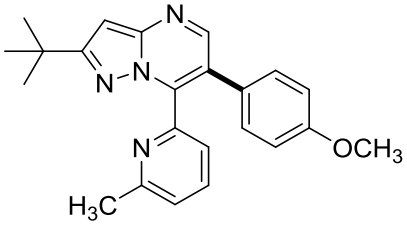
2-(*tert*-Butyl)-6-(3,5-dimethylphenyl)-7-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (4am): The title compound was obtained as a pale yellow solid in 44% yield according to the GP3. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.66 (d, J = 4.2 Hz, 1H), 8.56 (s, 1H), 7.80 (t, J = 7.6 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.40 – 7.33 (m, 1H), 6.87 (s, 1H), 6.75 (s, 2H), 6.63 (s, 1H), 2.20 (s, 6H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.1, 150.7, 149.8, 149.2, 148.8, 141.2, 137.9, 136.5, 134.6, 129.1, 127.6, 126.5, 124.1, 121.1, 93.0, 33.0, 30.4, 21.2; HRMS (ESI) *m/z* calcd. For $C_{23}H_{25}N_4$ $[M+H]^+$ 357.2074, found 357.2086.



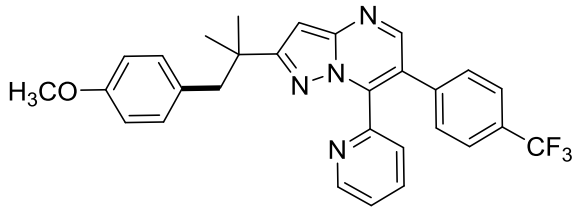
2-(*tert*-Butyl)-7-(pyridin-2-yl)-6-(3,4,5-trifluorophenyl)pyrazolo[1,5-a]pyrimidine (4an): The title compound was obtained as a pale yellow solid in 37% yield according to the GP3. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.65 (d, J = 4.4 Hz, 1H), 8.48 (s, 1H), 7.91 (dt, J = 7.7, 3.9 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.44 (dd, J = 6.8, 4.9 Hz, 1H), 6.80 (dd, J = 8.1, 6.5 Hz, 2H), 6.68 (s, 1H), 1.34 (s, 9H): ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.0, 150.0 (dd, J = 13.7, 4.0 Hz), 149.5, 149.4, 149.1, 148.5, 148.0 (dd, J = 6.1, 3.8 Hz), 141.5, 136.9, 126.7, 124.9, 118.3, 114.2 (dd, J = 16.7, 5.2 Hz), 99.7, 93.8, 33.1, 30.3; HRMS (ESI) *m/z* calcd. For $C_{21}H_{18}F_3N_4$ $[M+H]^+$ 383.1478, found 383.1488.



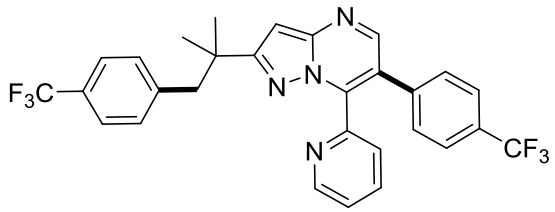
2-(*tert*-Butyl)-6-(4-methoxyphenyl)-7-(4-methylpyridin-2-yl)pyrazolo[1,5-a]pyrimidine (4ba): The title compound was obtained as a pale yellow solid in 32% yield according to the GP3. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.53 (s, 1H), 8.10 (d, J = 6.9 Hz, 1H), 7.42 (s, 1H), 7.19 (d, J = 4.1 Hz, 1H), 7.10 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 6.62 (s, 1H), 3.78 (s, 3H), 2.39 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.9, 165.1, 158.9, 150.8, 148.8, 131.0, 129.8, 129.3, 127.3, 125.2, 113.9, 113.1, 93.0, 55.2, 32.9, 30.4, 21.3; HRMS (ESI) *m/z* calcd. For $C_{23}H_{25}N_4O$ $[M+H]^+$ 373.2023, found 373.2041.



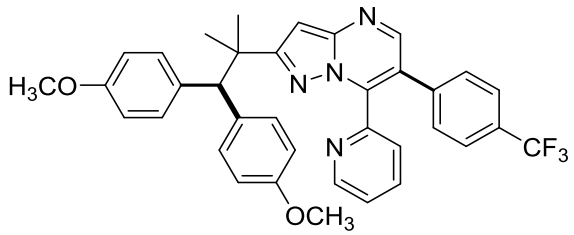
2-(*tert*-Butyl)-6-(4-methoxyphenyl)-7-(6-methylpyridin-2-yl)pyrazolo[1,5-a]pyrimidine (4ca): The title compound was obtained as a pale yellow solid in 41% yield according to the GP3. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.52 (s, 1H), 7.61 (t, J = 7.7 Hz, 1H), 7.29 (d, J = 7.7 Hz, 1H), 7.17 (d, J = 7.8 Hz, 1H), 7.14 – 7.06 (m, 2H), 6.79 (t, J = 5.8 Hz, 2H), 6.60 (s, 1H), 3.77 (s, 3H), 2.52 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.9, 158.9, 158.4, 150.7, 149.4, 149.0, 141.6, 136.5, 131.0, 127.4, 123.6, 123.2, 120.5, 113.8, 92.9, 55.2, 32.9, 30.4, 24.4; HRMS (ESI) *m/z* calcd. For $C_{23}H_{25}N_4O$ $[M+H]^+$ 373.2023, found 373.2014.



2-(1-(4-Methoxyphenyl)-2-methylpropan-2-yl)-7-(pyridin-2-yl)-6-(4-(trifluoromethyl)phenyl) pyrazolo[1,5-a]pyrimidine (5): The title compound was obtained as a pale yellow solid in 42% yield from **4af** according to the GP2. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.62 (d, J = 4.9 Hz, 1H), 8.55 (s, 1H), 7.88 (t, J = 7.7 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 8.2 Hz, 2H), 7.45 – 7.40 (m, 1H), 7.31 (d, J = 8.2 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.76 – 6.68 (m, 2H), 6.59 (s, 1H), 3.76 (s, 3H), 2.90 (s, 2H), 1.31 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 157.9, 149.9, 148.89, 148.87, 138.7, 137.2, 131.4, 130.8, 130.2, 129.7 (q, J = 32.7 Hz), 126.98, 126.97, 125.4 (q, J = 3.6 Hz), 124.89, 124.88, 123.9 (q, J = 273.7 Hz), 119.9, 113.0, 94.8, 55.2, 48.2, 37.4, 27.6; HRMS (ESI) *m/z* calcd. For $C_{29}H_{26}F_3N_4O$ $[M+H]^+$ 503.2053, found 503.2066.



2-(2-Methyl-1-(4-(trifluoromethyl)phenyl)propan-2-yl)-7-(pyridin-2-yl)-6-(4-(trifluoromethyl) phenyl)pyrazolo[1,5-a]pyrimidine (6): The title compound was obtained as a pale yellow solid in 26% yield from **3af** according to the GP3. This compound could also be prepared directly from **1a** by reaction at 120 ℃ for 36h and then at 140 ℃ for 48h with the yield of 23% according to the GP2 and GP3. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.61 (d, J = 4.5 Hz, 1H), 8.57 (s, 1H), 7.86 – 7.78 (m, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.53 (d, J = 8.1 Hz, 2H), 7.43 – 7.36 (m, 3H), 7.30 (d, J = 8.1 Hz, 2H), 7.02 (d, J = 8.0 Hz, 2H), 6.60 (s, 1H), 3.02 (s, 2H), 1.35 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.3, 150.3, 149.6, 149.1, 149.0, 142.9, 141.8, 138.7, 136.5, 130.8, 130.1, 129.6 (q, J = 32.8 Hz), 128.2 (q, J = 31.5 Hz), 126.5, 125.4 (q, J = 3.6 Hz), 124.6, 124.4 (q, J = 272.1 Hz), 124.38 (q, J = 3.8 Hz), 123.9 (q, J = 273.4 Hz), 119.9, 94.6, 48.8, 37.3, 27.9; HRMS (ESI) *m/z* calcd. For $C_{29}H_{23}F_6N_4$ $[M+H]^+$ 541.1821, found 541.1838.



2-(1,1-bis(4-Methoxyphenyl)-2-methylpropan-2-yl)-7-(pyridin-2-yl)-6-(4-(trifluoromethyl)phen yl)pyrazolo[1,5-a]pyrimidine (7): The title compound was obtained as a pale yellow solid from **8** in 31%

yield according to the GP2. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.59 – 8.55 (m, 1H), 8.53 (s, 1H), 7.83 (td, *J* = 7.8, 1.7 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.44 – 7.37 (m, 1H), 7.30 (d, *J* = 8.0 Hz, 3H), 7.14 – 7.08 (m, 4H), 6.74 – 6.68 (m, 4H), 6.47 (s, 1H), 4.25 (s, 1H), 3.74 (s, 6H), 1.42 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.3, 157.7, 150.0, 148.9, 148.5, 141.0, 138.7, 136.87, 136.88, 134.9, 131.0, 130.2, 129.5 (q, *J* = 32.2 Hz), 127.0, 125.4 (q, *J* = 3.8 Hz), 124.8, 124.4 (q, *J* = 272.1 Hz), 119.7, 113.0, 96.0, 61.1, 55.1, 40.5, 28.0; HRMS (ESI) *m/z* calcd. For $C_{36}H_{32}F_3N_4O_2$ $[M+H]^+$ 609.2472, found 609.2483.

6. Mechanistic Studies

6.1 Model Substrate for Function Confirmation of the Pyridine Nitrogen

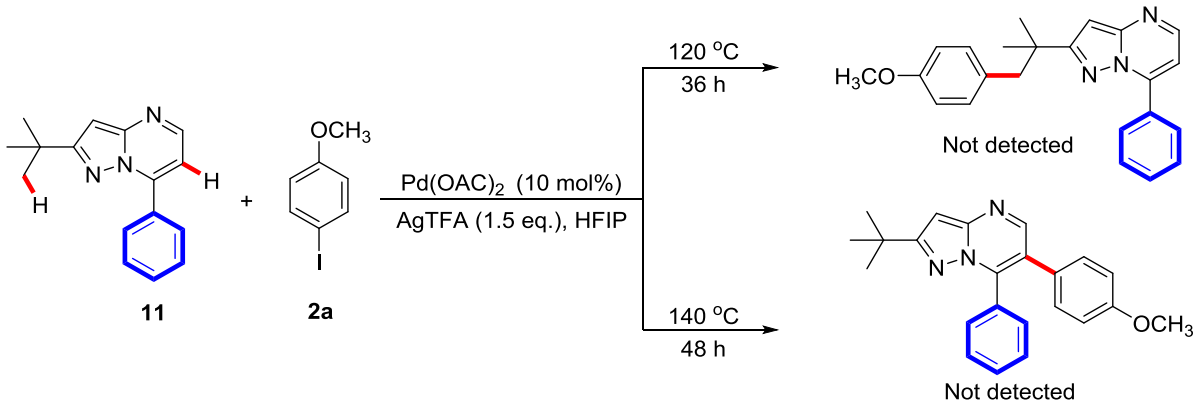


Figure S2 | Model substrate for function confirmation of the pyridine nitrogen

6.2 H/D exchange reaction

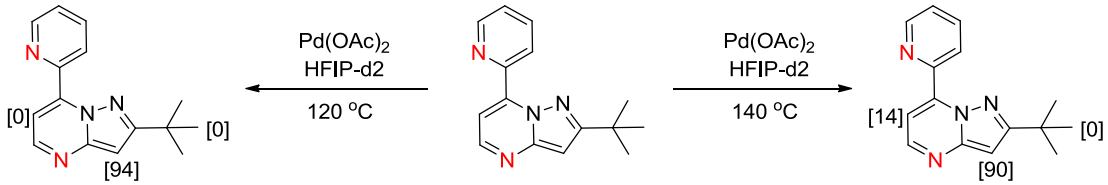
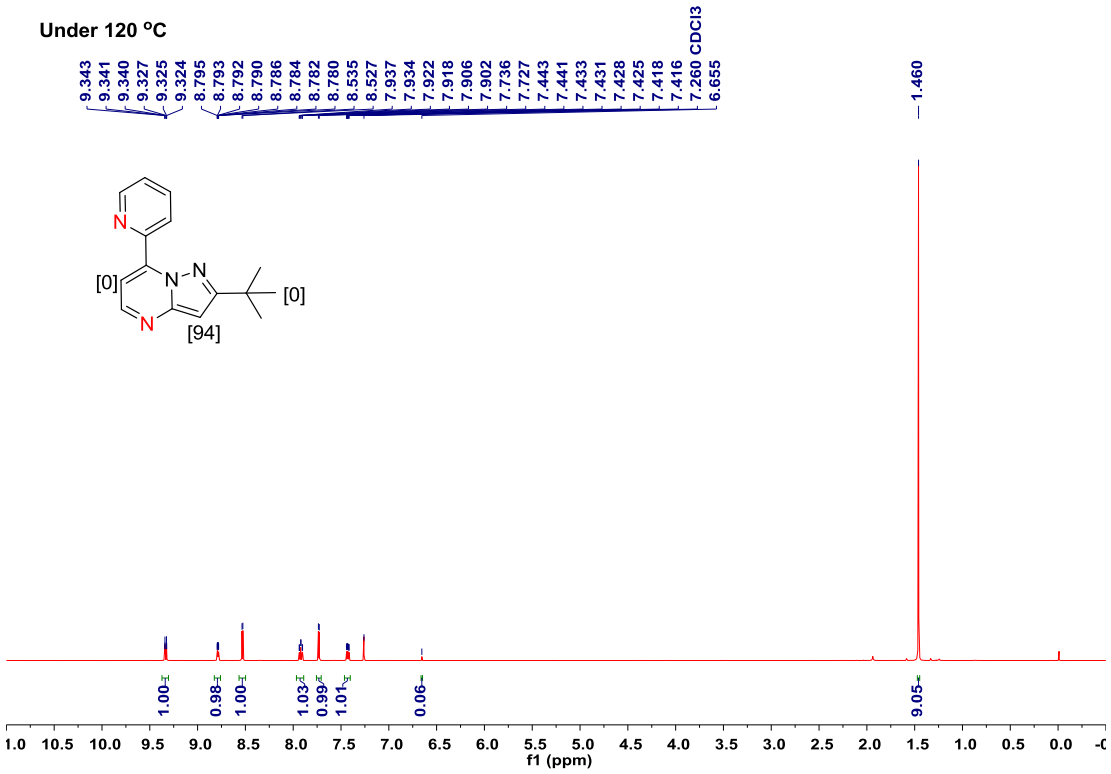
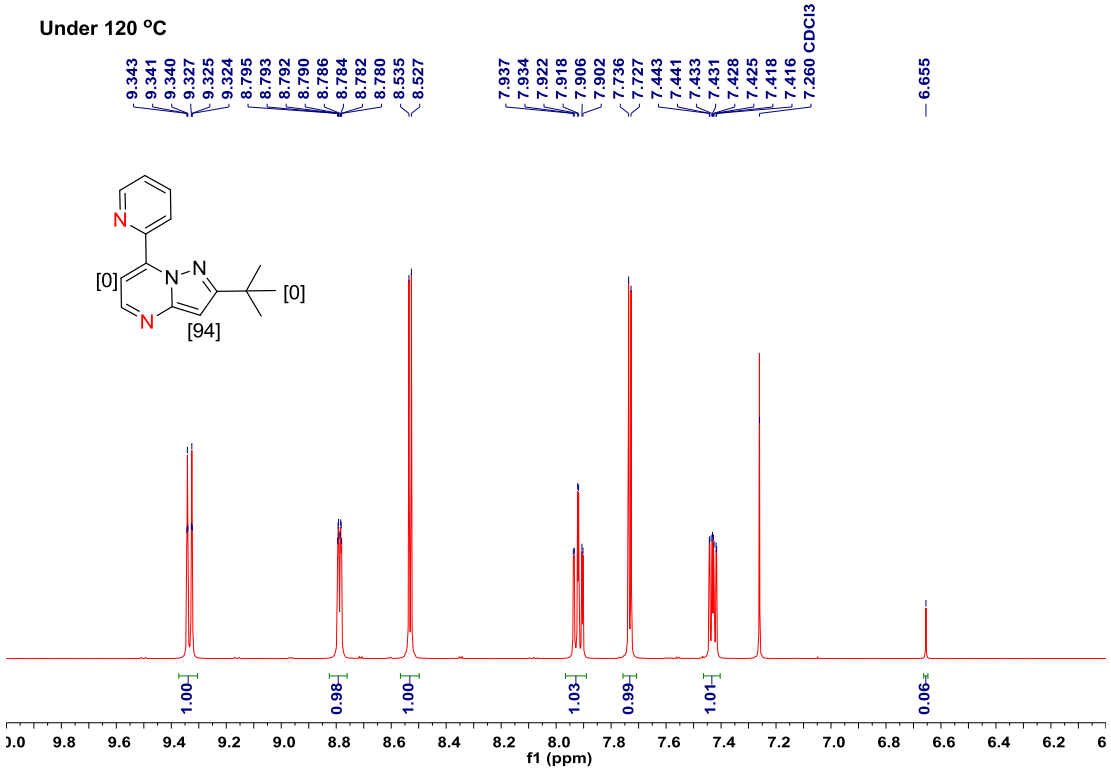
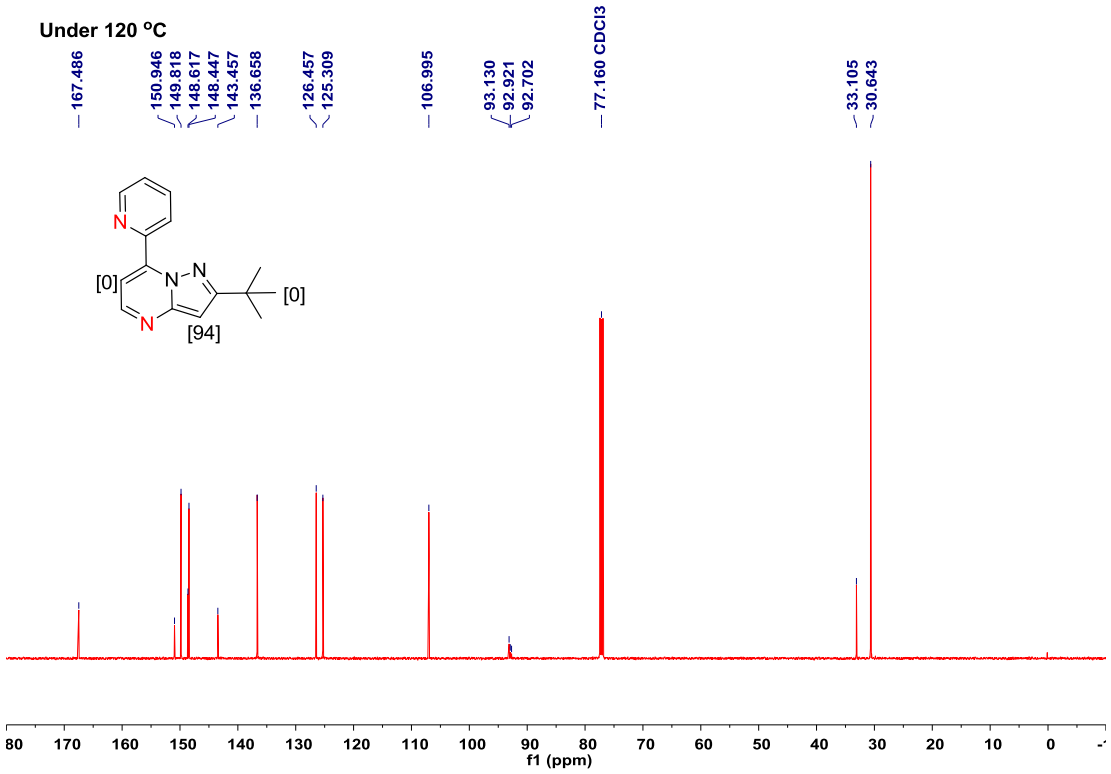
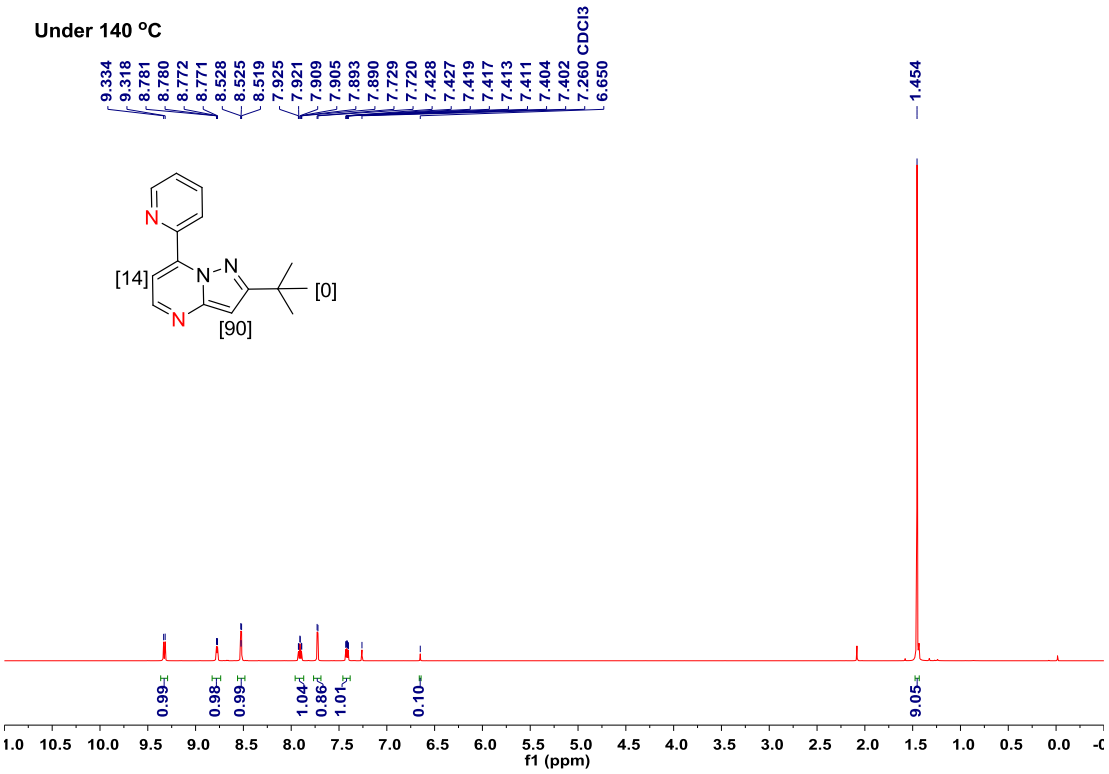


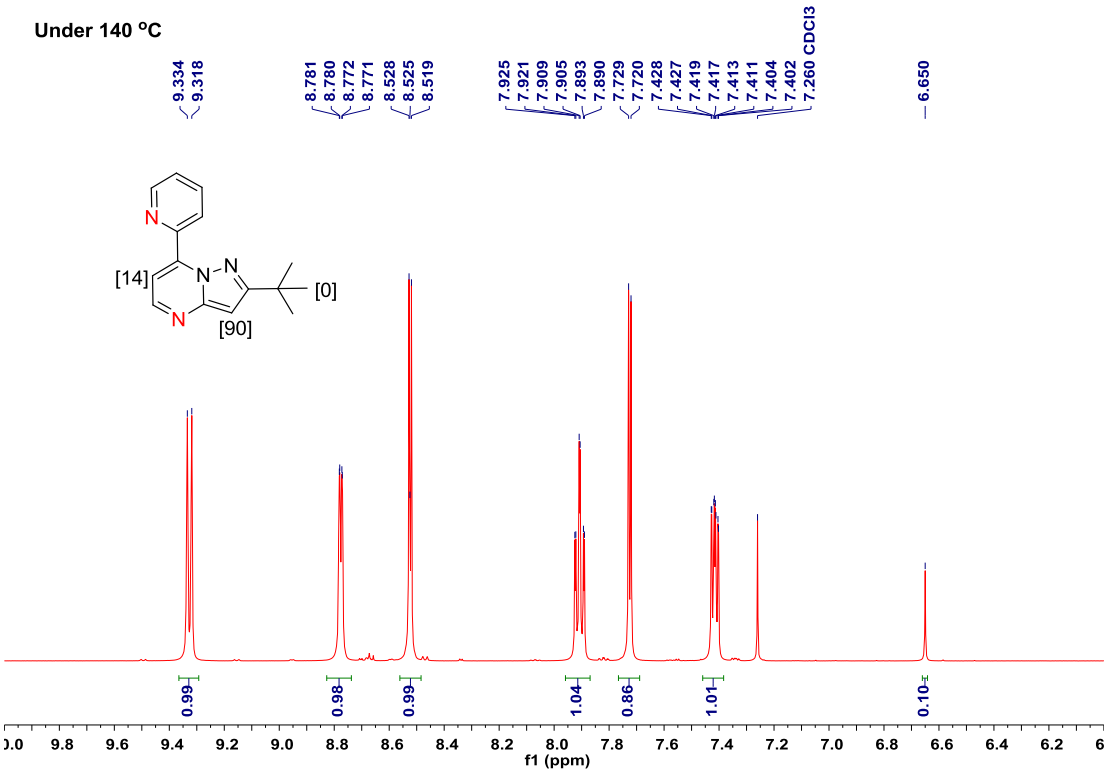
Figure S3 | H/D exchange reaction

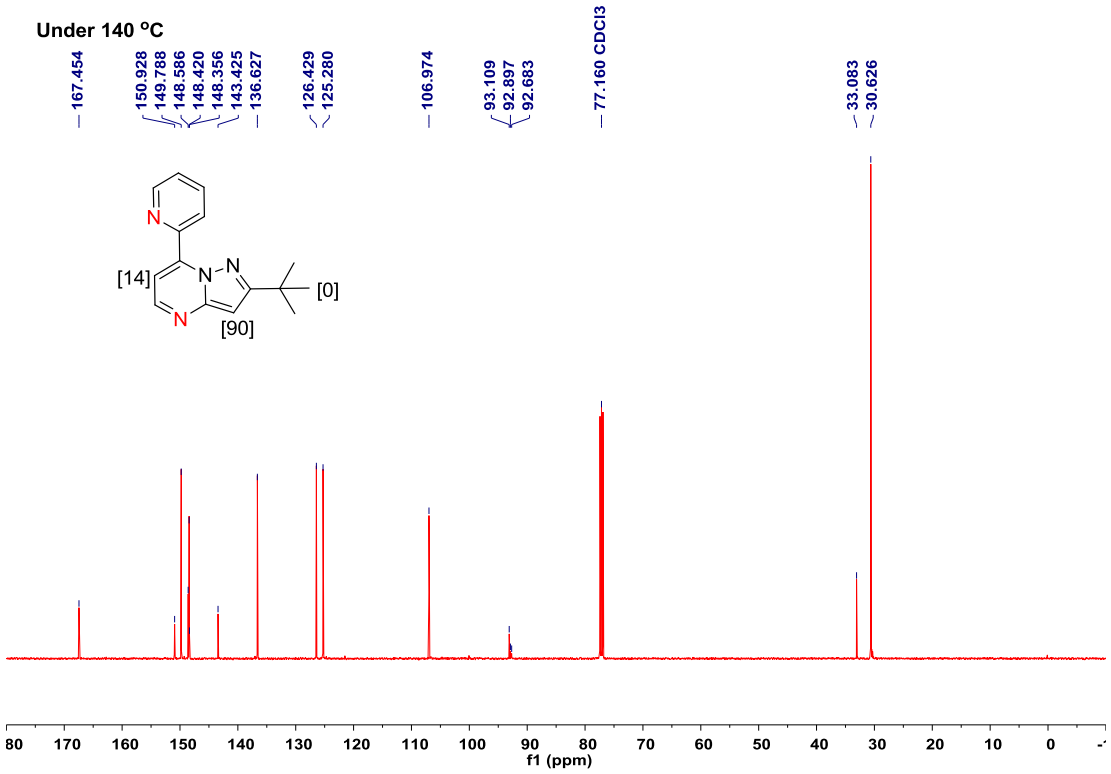

Under 120 °C
9.343
9.341
9.340
9.327
9.325
9.324
8.795
8.793
8.792
8.790
8.786
8.784
8.782
8.780
8.535
8.527
7.937
7.934
7.922
7.918
7.906
7.902
7.736
7.727
7.443
7.441
7.433
7.431
7.428
7.425
7.418
7.416
7.260 CDCl3
6.655
1.460
[0]
[0]
[94]
1.00
0.98
1.00
1.03
0.99
1.01
0.06
9.05
f1 (ppm)


Under 120 °C
9.343
9.341
9.340
9.327
9.325
9.324
8.795
8.793
8.792
8.790
8.786
8.784
8.782
8.780
8.535
8.527
7.937
7.934
7.922
7.918
7.906
7.902
7.736
7.727
7.443
7.441
7.433
7.431
7.428
7.425
7.418
7.416
7.260 CDCl3
6.655
[0]
[0]
[94]
1.00
0.98
1.00
1.03
0.99
1.01
0.06
f1 (ppm)

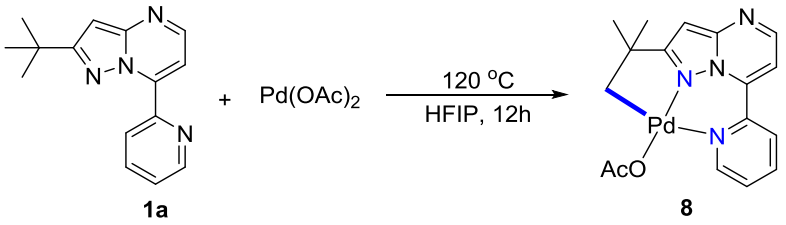

Under 120 °C
167.486
150.946
149.818
148.617
148.447
143.457
136.658
126.457
125.309
106.995
93.130
92.921
92.702
77.160 CDCl3
33.105
30.643
[0]
[0]
[94]
f1 (ppm)


Under 140 °C
9.334
9.318
8.781
8.780
8.772
8.771
8.528
8.525
8.519
7.925
7.921
7.909
7.905
7.893
7.890
7.729
7.720
7.428
7.427
7.419
7.417
7.413
7.411
7.404
7.402
7.260 CDCl3
6.650
1.454
[14]
[0]
[90]
0.99
0.98
0.99
1.04
0.86
1.01
0.10
9.05
f1 (ppm)


Under 140 °C
9.334
9.318
8.781
8.780
8.772
8.771
8.528
8.525
8.519
7.925
7.921
7.909
7.905
7.893
7.890
7.729
7.720
7.428
7.427
7.419
7.417
7.413
7.411
7.404
7.402
7.260 CDCl3
6.650
[14]
[0]
[90]
0.99
0.98
0.99
1.04
0.86
1.01
0.10
f1 (ppm)



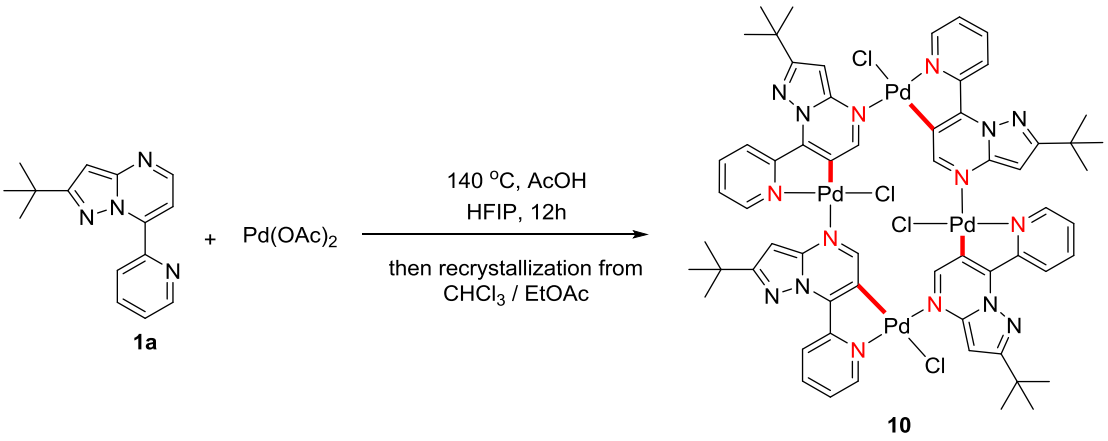
6.3 Preparation of the [6, 5]-Fused Palladacycle Intermediate for the C(sp^3)-H Arylation



A 25 mL sealed tube was charged with 7-pyridyl-pyrazolo[1, 5-a]pyrimidine **1a** (302 mg, 1.2 mmol), $Pd(OAc)_2$ (224 mg, 1 mmol) and HFIP (10 mL). The mixture was then stirred at 120 ℃ for 12 hours. After cooling to ambient temperature, the reaction mixture was evaporated to remove the solvent. The solid obtained was washed with ether to remove excess **1a**. Analytically pure **8** (212 mg, 51% yield) was obtained by recrystallization using chloroform and ethyl acetate. The nice crystal of **8** was also subjected to the X-ray Analysis.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.69 (dd, J = 5.2, 1.5 Hz, 1H), 8.62 (d, J = 4.8 Hz, 1H), 8.51 (d, J = 8.3 Hz, 1H), 8.31 (d, J = 4.8 Hz, 1H), 7.86 (td, J = 8.1, 1.8 Hz, 1H), 7.35 (ddd, J = 7.4, 5.3, 0.9 Hz, 1H), 6.50 (s, 1H), 2.56 (s, 2H), 2.17 (s, 3H), 1.46 (d, J = 6.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.1, 175.2, 151.0, 149.7, 149.3, 144.5, 139.1, 138.1, 126.4, 126.0, 109.9, 93.8, 42.2, 33.3, 29.6, 24.1.

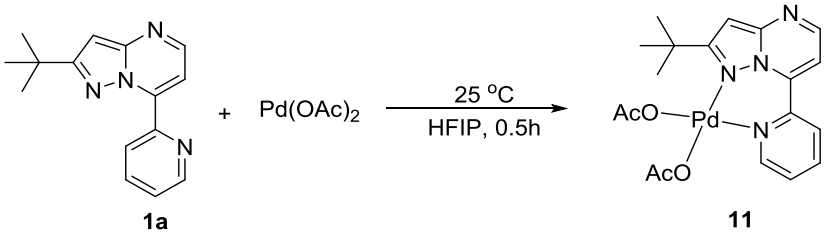
6.4 Preparation of the 16-Membered tetramer Intermediate for the C(sp^2)-H Arylation



A 25 mL sealed tube was charged with 7-pyridyl-pyrazolo[1, 5-a]pyrimidine **1a** (504 mg, 2 mmol), $Pd(OAc)_2$ (224 mg, 1 mmol), AcOH (2 mL) and HFIP (10 mL). The mixture was then stirred at 140 ℃ for 12 hours. After cooling to ambient temperature, the reaction mixture was evaporated to remove the solvent. The solid obtained was washed with ether to remove excess **1a**. Analytically pure **10** (138 mg, 35% yield) was obtained by recrystallization using chloroform and ethyl acetate.[3] The nice crystal of **10** was also subjected to the X-ray Analysis.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.70 (dd, J = 8.1, 0.9 Hz, 1H), 9.59 (dd, J = 5.6, 1.1 Hz, 1H), 8.11 (td, J = 7.9, 1.7 Hz, 1H), 7.52 (s, 1H), 7.47 – 7.39 (m, 1H), 7.14 (s, 1H), 1.37 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.8, 156.3, 152.0, 151.0, 146.8, 146.5, 139.2, 127.8, 125.4, 124.8, 95.2, 32.2, 29.4.

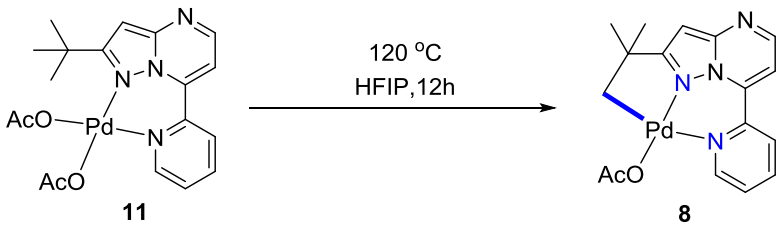
6.5 Preparation of the Shared Intermediate for the C(sp^2)-H and C(sp^3)-H Arylation



A 25 mL sealed tube was charged with 7-pyridyl-pyrazolo[1, 5-a]pyrimidine **1a** (302 mg, 1.2 mmol), $Pd(OAc)_2$ (224 mg, 1 mmol) and HFIP (10 mL). The mixture was then stirred at 25 ℃ for 0.5 hour. Upon completion, the reaction mixture was evaporated under 25 ℃ to remove the solvent. The solid obtained was washed with ether to remove excess **1a**. Analytically pure **11** (253 mg, 53% yield) was obtained by recrystallization using chloroform and ethyl acetate.

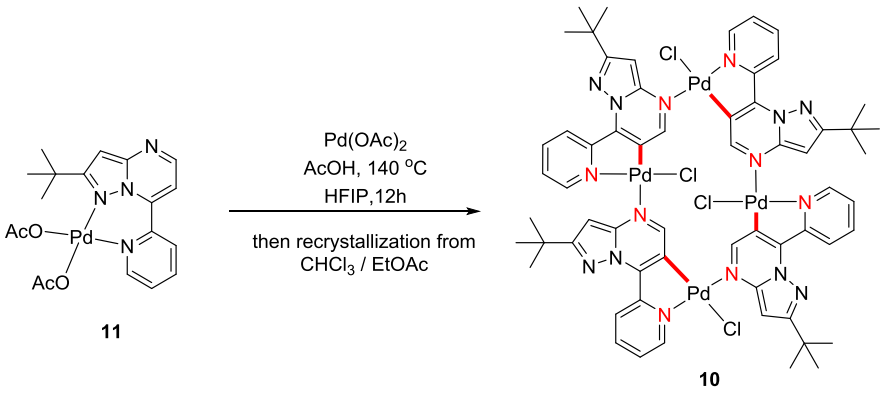
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.92 (dd, J = 7.2, 0.5 Hz, 1H), 8.80 (d, J = 7.3 Hz, 1H), 8.64 (d, J = 7.9 Hz, 1H), 8.15 (dd, J = 5.6, 1.2 Hz, 1H), 7.57 (td, J = 7.9, 1.4 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.07 (s, 1H), 2.22 (s, 3H), 2.20 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.8, 178.4, 171.4, 154.7, 153.9, 149.9, 146.3, 139.5, 139.4, 126.7, 125.8, 104.7, 94.7, 33.3, 30.2, 23.3, 23.2.

6.6 Transformation of the Shared Intermediate 13 to 10 for the C(sp^3)-H Arylation



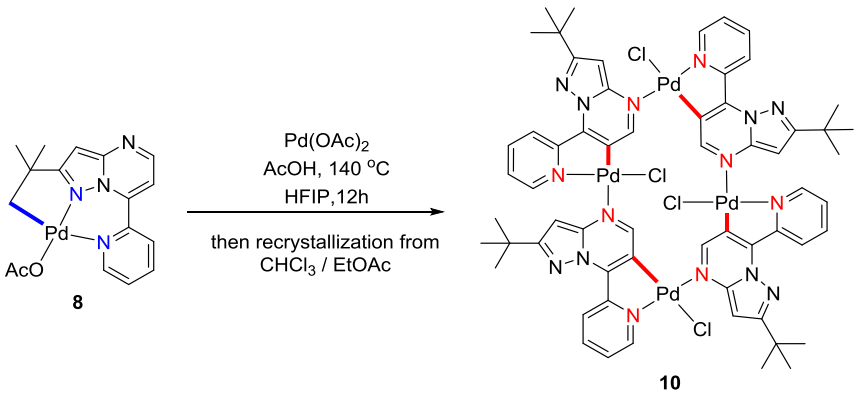
A 10 mL sealed tube was charged with **11** (48 mg, 0.1 mmol) and HFIP (2 mL). The mixture was then stirred at 120 ℃ for 12 hours. After cooling to ambient temperature, the reaction mixture was evaporated to remove the solvent. The solid obtained was washed with ether. Analytically pure **8** (37 mg, 89% yield) was obtained by recrystallization using chloroform and ethyl acetate.

6.7 Transformation of the Shared Intermediate 11 to 10 for the C(sp^2)-H Arylation



A 10 mL sealed tube was charged with **13** (48mg, 0.1 mmol), $Pd(OAc)_2$ (2mg, 0.01 mmol), AcOH (0.4 mL) and HFIP (2 mL). The mixture was then stirred at 140 ℃ for 12 hours. After cooling to ambient temperature, the reaction mixture was evaporated to remove the solvent. The solid obtained was washed with ether. Analytically pure **12** (23 mg, 59% yield) was obtained by recrystallization using chloroform and ethyl acetate.

6.8 Conversion of the C(sp^3)-H Arylation Intermediate 8 to the C(sp^2)-H Activation Intermediate 10



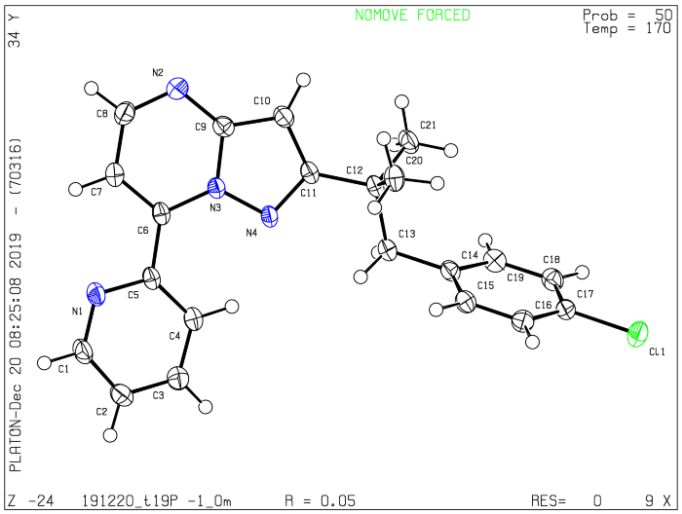
A 10 mL sealed tube was charged with **8** (42 mg, 0.1 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), AcOH (0.4 mL) and HFIP (2 mL). The mixture was then stirred at 140 ℃ for 12 hours. After cooling to ambient temperature, the reaction mixture was evaporated to remove the solvent. The solid obtained was washed with ether. Analytically pure **10** (25 mg, 64% yield) was obtained by recrystallization using chloroform and ethyl acetate.

6.9 General procedure for schemes 5b to 5e

A 10 mL sealed tube was charged with metal complex (**8** or **10** or **11**) (0.1 mmol), **2a** (0.1 mmol), AgTFA (0.15 mmol) and HFIP (2 mL). The mixture was then stirred at 120 ℃ for $C(sp^3)$-H arylation, 36 h and at 140 ℃ for $C(sp^2)$-H arylation, 48 h. Upon completion, the reaction mixture was cooled to room temperature and diluted with DCM. Then the reaction mixture was filtered through a pad of celite, which was further washed with DCM. The solvent was removed under vacuum directly and the obtained crude product was purified by silica gel column chromatography to afford the desired products **3aa** or **4aa**.

7. X-ray Crystallographic Data

7.1 Crystal Structure of 3ac

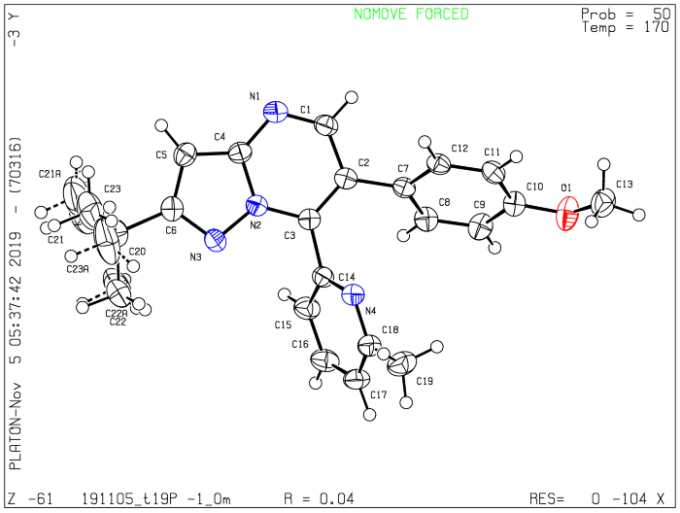


CCDC	1987484		
Bond precision:	C-C = 0.0025 A		Wavelength=0.71073
Cell:	a=8.907(6)	a=8.907(6)	a=8.907(6)
	alpha=68.74(4)	alpha=68.74(4)	alpha=68.74(4)
Temperature:	170 K		
	Calculated		Reported
Volume	864.0(13)		864.0(13)
Space group	P -1		P -1
Hall group	-P 1		-P 1
Moiety formula	C21 H19 Cl N4		C21 H19 Cl N4
Sum formula	C21 H19 Cl N4		C21 H19 Cl N4
Mr	362.85		362.85
Dx, g cm^{-3}	1.395		1.395
Z	2		2
Mu (mm-1)	0.234		0.234
F000	380.0		380.0
F000’	380.41		
h, k, lmax	11, 13, 14		11, 13, 14
Nref	3815		3792
Tmin, Tmax	0.937, 0.954		0.562, 0.746
Tmin’	0.915		

Correction method= # Reported T Limits: Tmin=0.562 Tmax=0.746
AbsCorr = MULTI-SCAN

Data completeness= 0.994 Theta(max)= 27.060
R(reflections)= 0.0450(3432) wR2(reflections)= 0.1185(3792)
S = 1.070 Npar= 237

7.2 Crystal Structure of 4ca

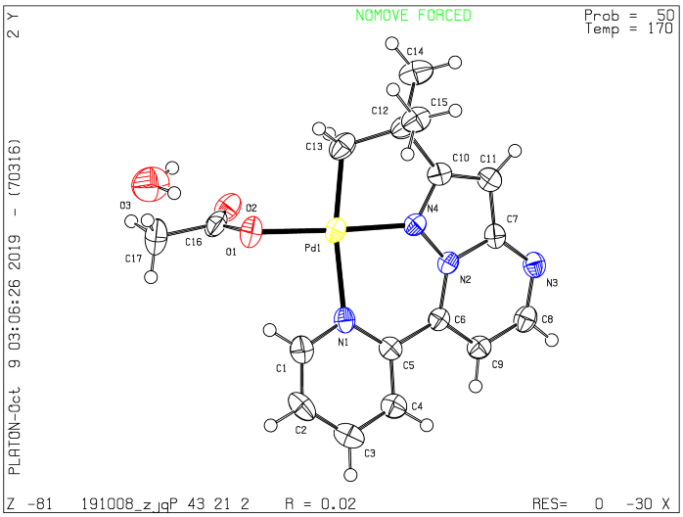


CCDC	1987483		
Bond precision:	C-C = 0.0016 A		Wavelength=0.71073
Cell:	a=9.4235(3)	b=9.4517(3)	c=11.8728(4)
	alpha=81.662(1)	beta=82.012(1)	gamma=79.093(1)
Temperature:	170 K		
	Calculated		Reported
Volume	1020.62(6)		1020.62(6)
Space group	P -1		P -1
Hall group	-P 1		-P 1
Moiety formula	C23 H24 N4 O		C23 H24 N4 O
Sum formula	C23 H24 N4 O		C23 H24 N4 O
Mr	372.46		372.46
Dx, g cm^{-3}	1.212		1.212
Z	2		2
Mu (mm-1)	0.076		0.076
F000	396.0		396.0
F000’	396.14		
h, k, lmax	12,12,15		12,12,15
Nref	4509		4492
Tmin, Tmax	0.986,0.992		0.688,0.746
Tmin’	0.985		

Correction method= # Reported T Limits: Tmin=0.688 Tmax=0.746
AbsCorr = MULTI-SCAN

Data completeness= 0.996 Theta(max)= 27.117
R(reflections)= 0.0407(4042) wR2(reflections)= 0.1103(4492)
S = 1.029 Npar= 289

7.3 Crystal Structure of 8

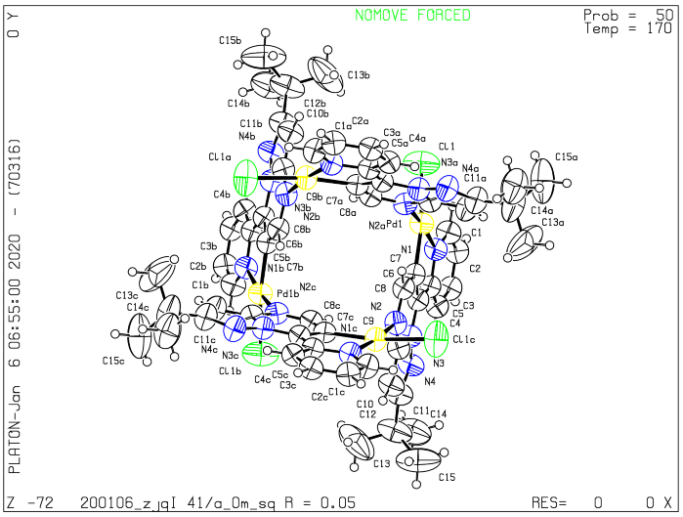


CCDC	1987481		
Bond precision:	C-C = 0.0056 A		Wavelength=0.71073
Cell:	a=15.890(8)	a=15.890(8)	a=15.890(8)
	alpha=90	alpha=90	alpha=90
Temperature:	170 K		
	Calculated		Reported
Volume	3565(4)		3565(4)
Space group	P 43 21 2		P 43 21 2
Hall group	P 4nw 2abw		P 4nw 2abw
Moiety formula	C17 H18 N4 O2 Pd, H2 O		C17 H18 N4 O2 Pd, H2 O
Sum formula	C17 H20 N4 O3 Pd		C17 H20 N4 O3 Pd
Mr	434.77		434.77
Dx, g cm^{-3}	1.620		1.620
Z	8		8
Mu (mm-1)	1.065		1.064
F000	1760.0		1760.0
F000’	1752.63		
h, k, lmax	20,20,18		20,20,18
Nref	3901[2266]		3866
Tmin, Tmax	0.815, 0.880		0.666, 0.746
Tmin’	0.727		

Correction method= # Reported T Limits: Tmin=0.666 Tmax=0.746
AbsCorr = MULTI-SCAN

Data completeness= 1.71/0.99 Theta(max)= 27.007
R(reflections)= 0.0225(3658) wR2(reflections)= 0.0510(3866)
S = 1.083 Npar= 235

7.4 Crystal Structure of 10



CCDC	1987482		
Bond precision:	C-C = 0.0073 A		Wavelength=0.71073
Cell:	a=20.0376(7)	a=20.0376(7)	a=20.0376(7)
	alpha=90	alpha=90	alpha=90
Temperature:	170 K		
	Calculated		Reported
Volume	9582.6(7)		3565(4)
Space group	I 41/a		P 43 21 2
Hall group	-I 4ad		P 4nw 2abw
Moiety formula	C60 H60 Cl4 N16 Pd4 [+solvent]		C60 H60 Cl4 N16 Pd4
Sum formula	C60 H60 Cl4 N16 Pd4 [+solvent]		C60 H60 Cl4 N16 Pd4
Mr	1572.64		1572.64
Dx, g cm^{-3}	1.090		1.090
Z	4		4
Mu (mm-1)	0.885		0.885
F000	3136.0		3136.0
F000’	3123.11		
h, k, lmax	25,25,30		25,25,30
Nref	5296		5296
Tmin, Tmax	0.783,0.838		0.650,0.746
Tmin’	0.708		

Correction method= # Reported T Limits: Tmin=0.650 Tmax=0.746
AbsCorr = MULTI-SCAN

Data completeness= 1.000 Theta(max)= 27.108
R(reflections)= 0.0463(3910) wR2(reflections)= 0.1468(5296)
S = 1.068 Npar= 193

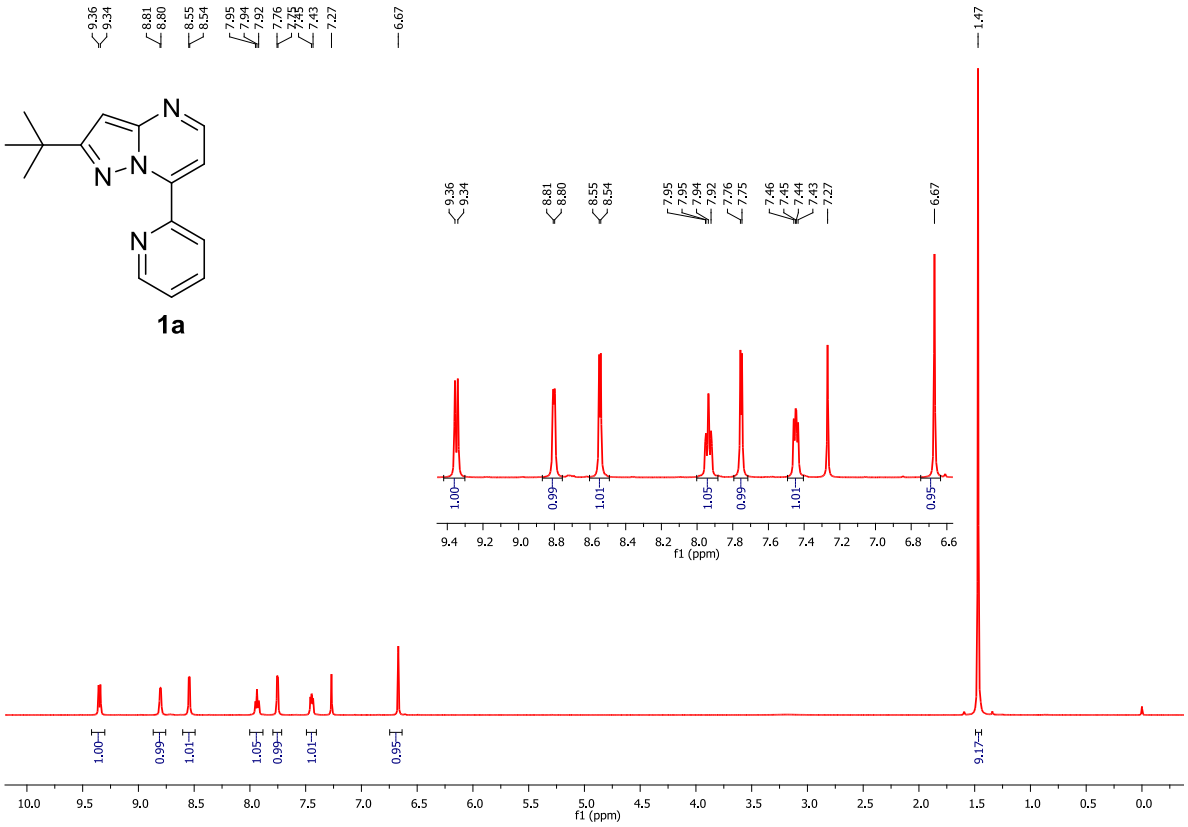
8. References

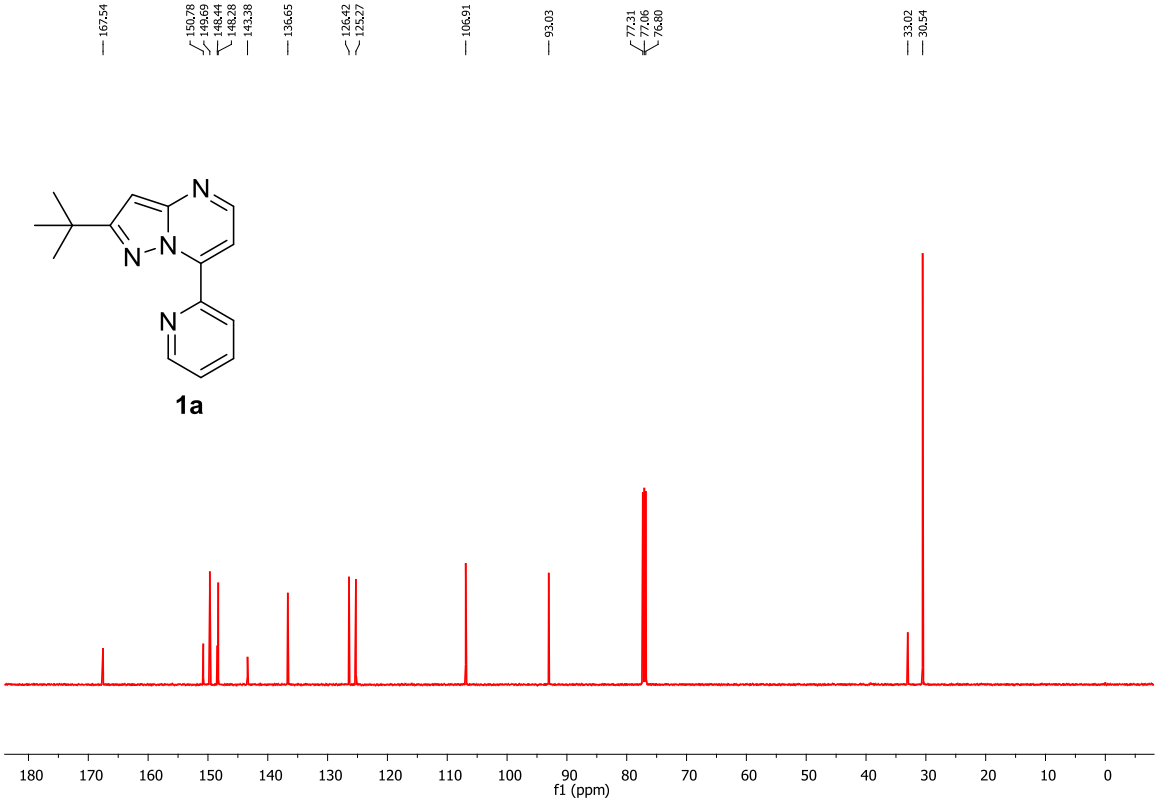
1. J. C. Castillo, H. A. Rosero, J. Portilla. *RSC Adv.* **2017**, *7*, 28483.

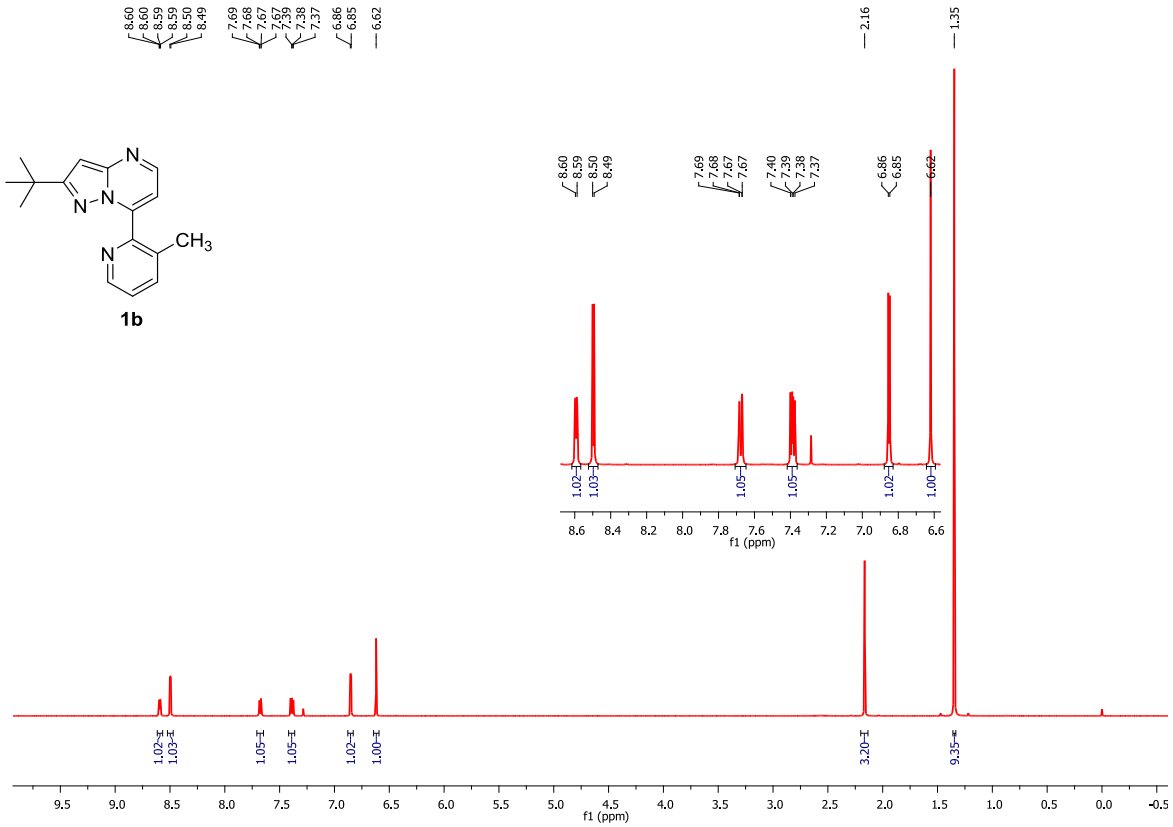
2. T. Gogula, J. Q. Zhang, H. B. Zou, H. B. *Org. Lett.* **2019**, *21*, 5933.

3. H. Park, P. Verma, K. Hong, J. Q. Yu, *Nat. Chem.* **2018**, *10*, 755.

9. NMR spectra



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7.68
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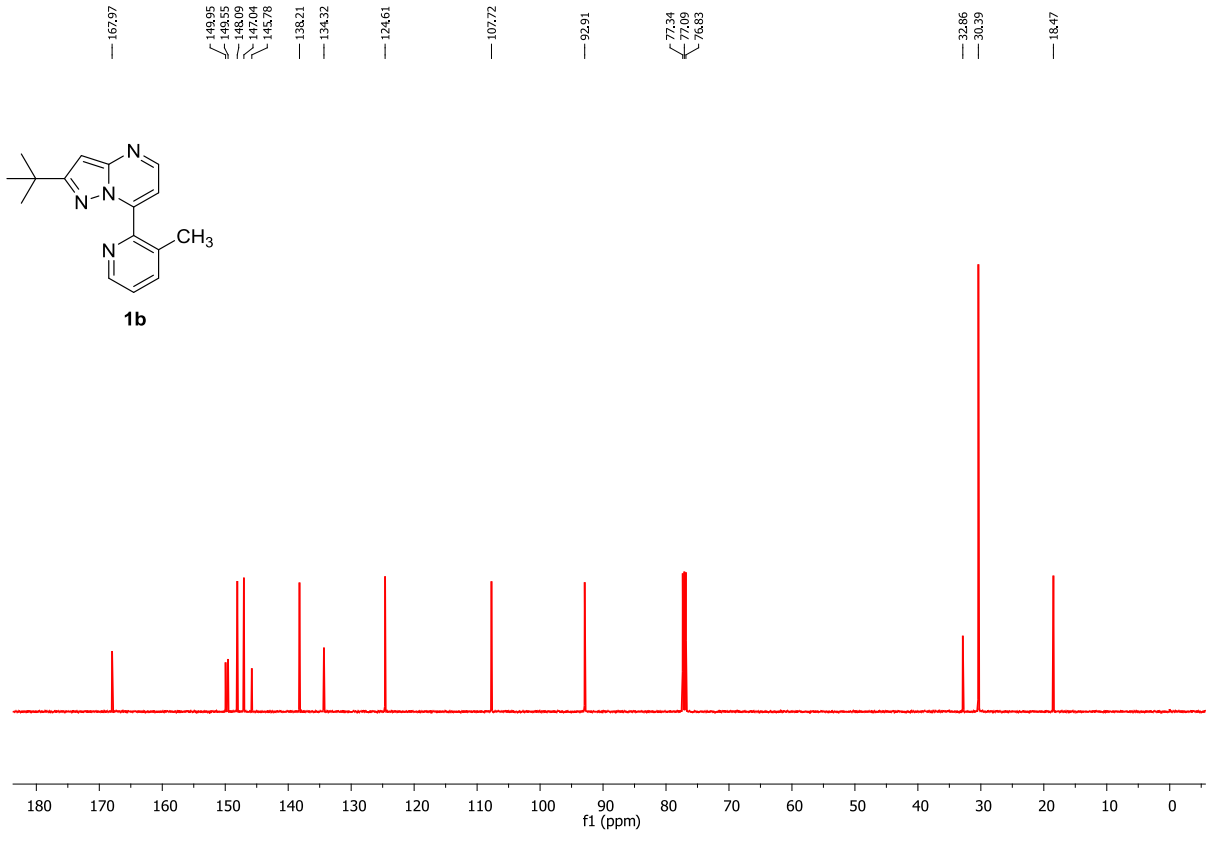
7.67
7.39
7.38
7.37
6.86
6.85
6.62
2.16
1.35
N
N
N
CH3
N
1b
1.02
1.03
1.05
1.05
1.02
1.00
3.20
9.35
f1 (ppm)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149.55
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147.04
145.78
138.21
134.32
124.61
107.72
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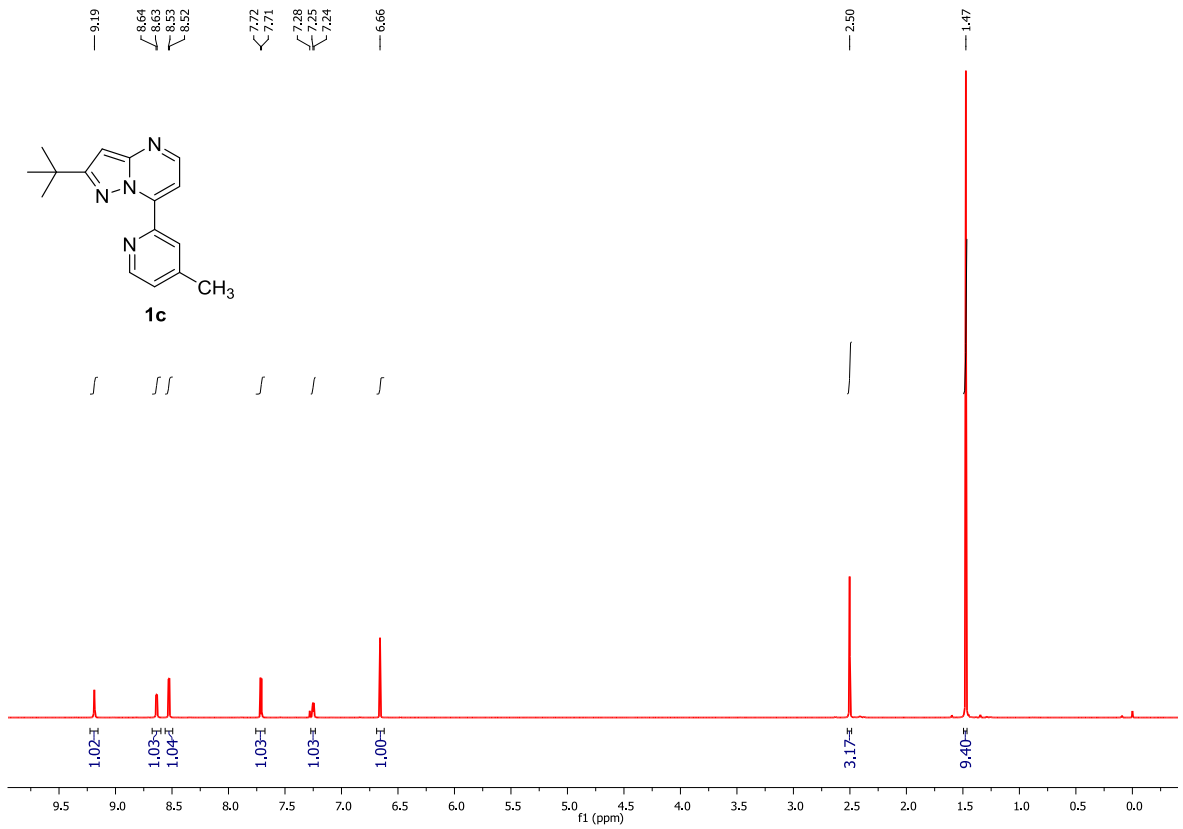
N
N
N
CH3
N
1b
f1 (ppm)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8.63
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8.52
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7.71
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7.25
7.24
6.66
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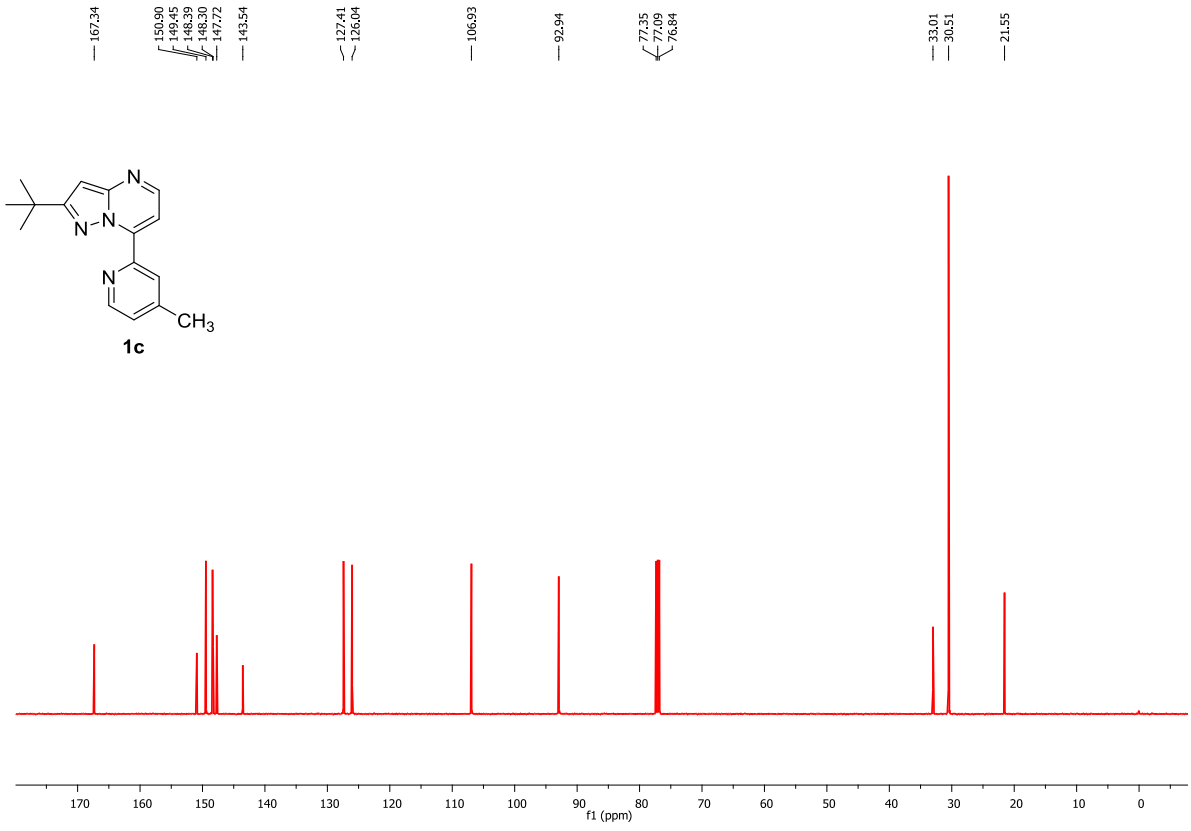
1.47
1c
1.02
1.03
1.04
1.03
1.03
1.00
3.17
9.40
f1 (ppm)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106.93
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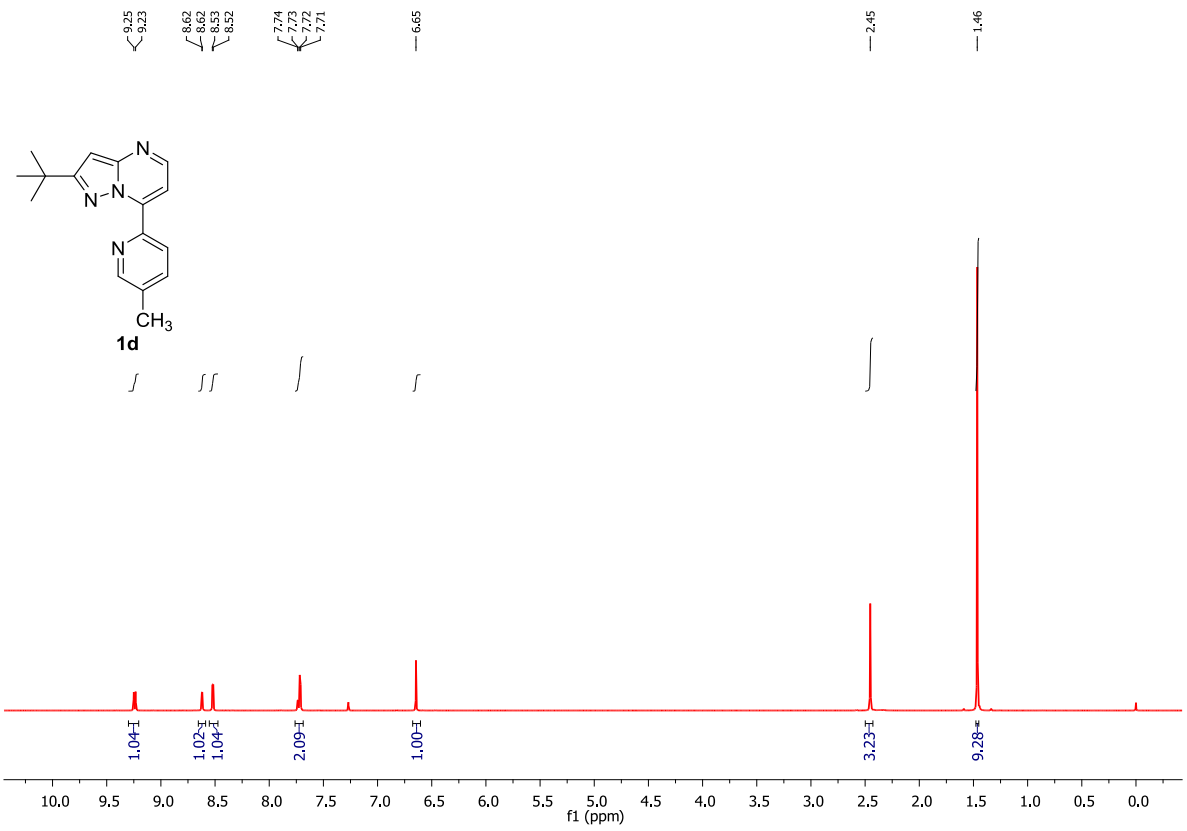
33.01
30.51
21.55
1c
f1 (ppm)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8.52
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1d
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1.02
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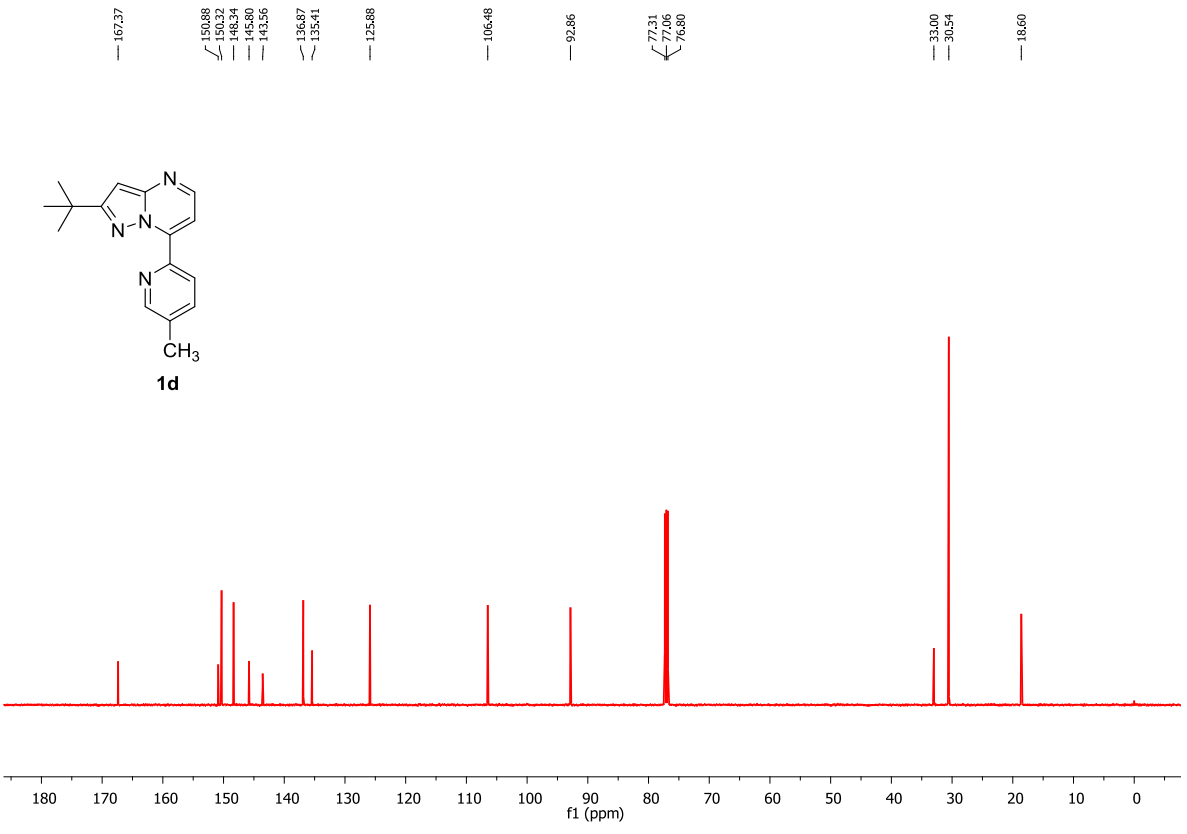
9.28
f1 (ppm)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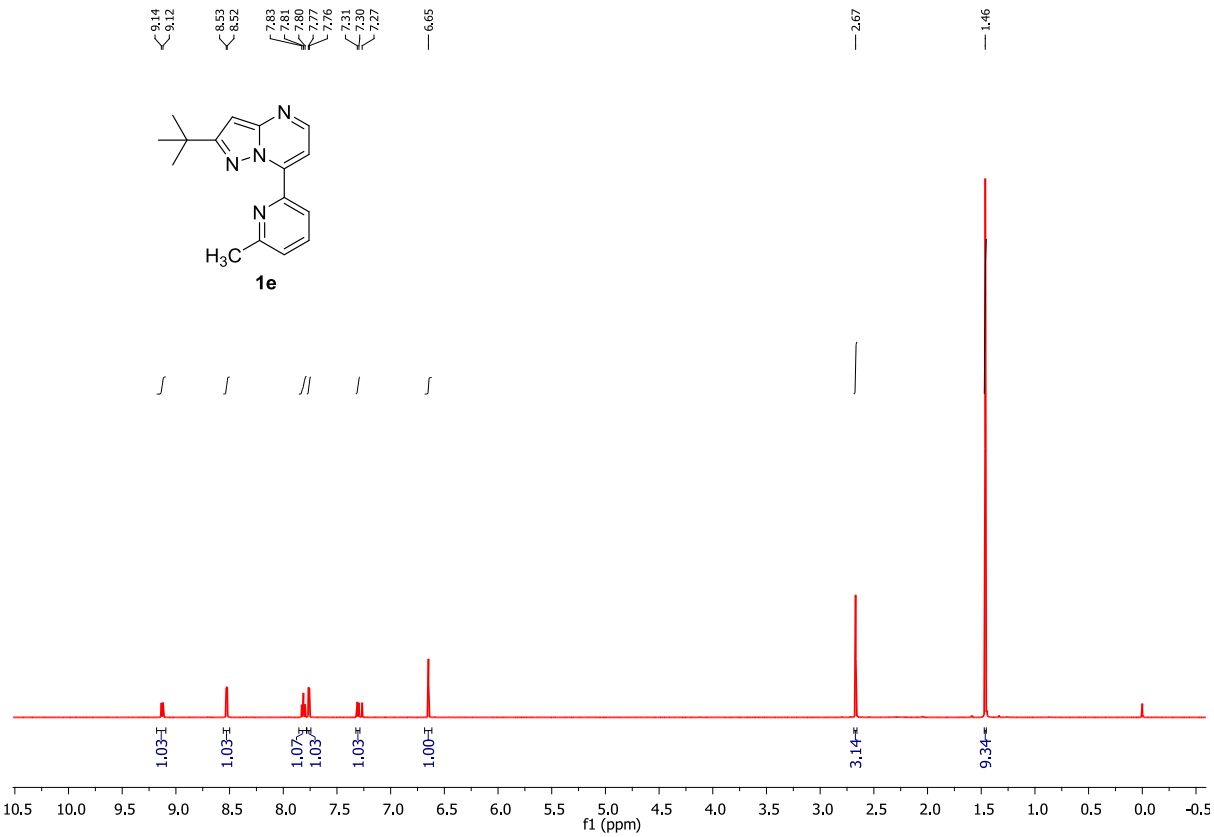
f1 (ppm)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7.77
7.76
7.31
7.30
7.27
6.65
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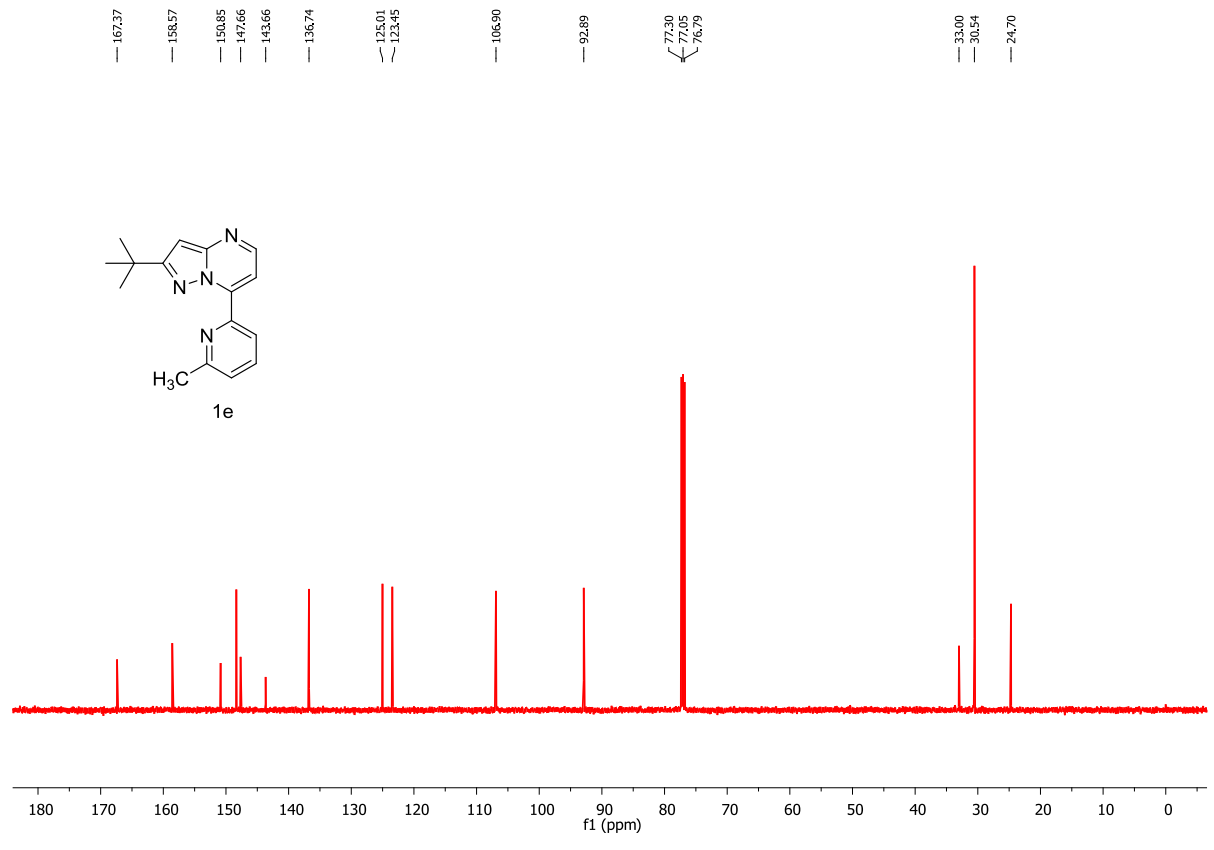
1e
1.03
1.03
1.07
1.03
1.03
1.00
3.14
9.34
f1 (ppm)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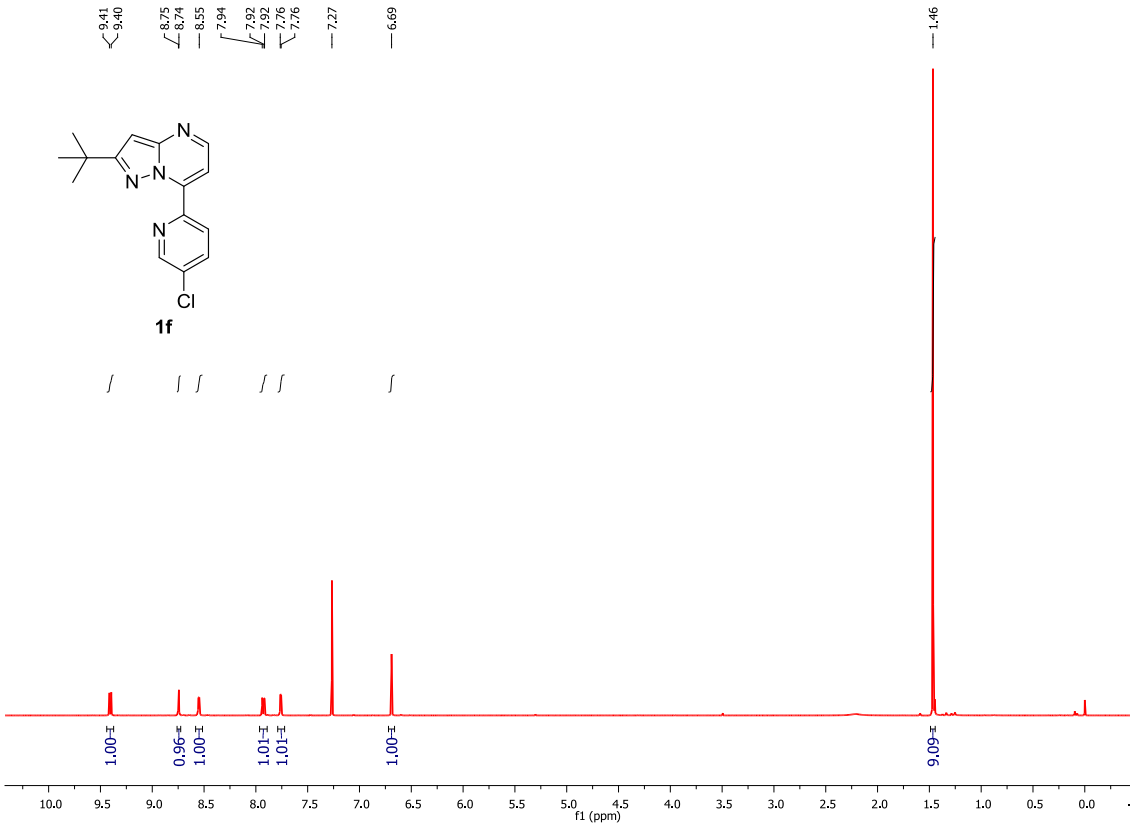
30.54
24.70
1e
f1 (ppm)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8.55
7.94
7.92
7.92
7.76
7.76
7.27
6.69
1.46
N
N
N
N
Cl
1f
1.00
0.96
1.00
1.01
1.01
1.00
9.09
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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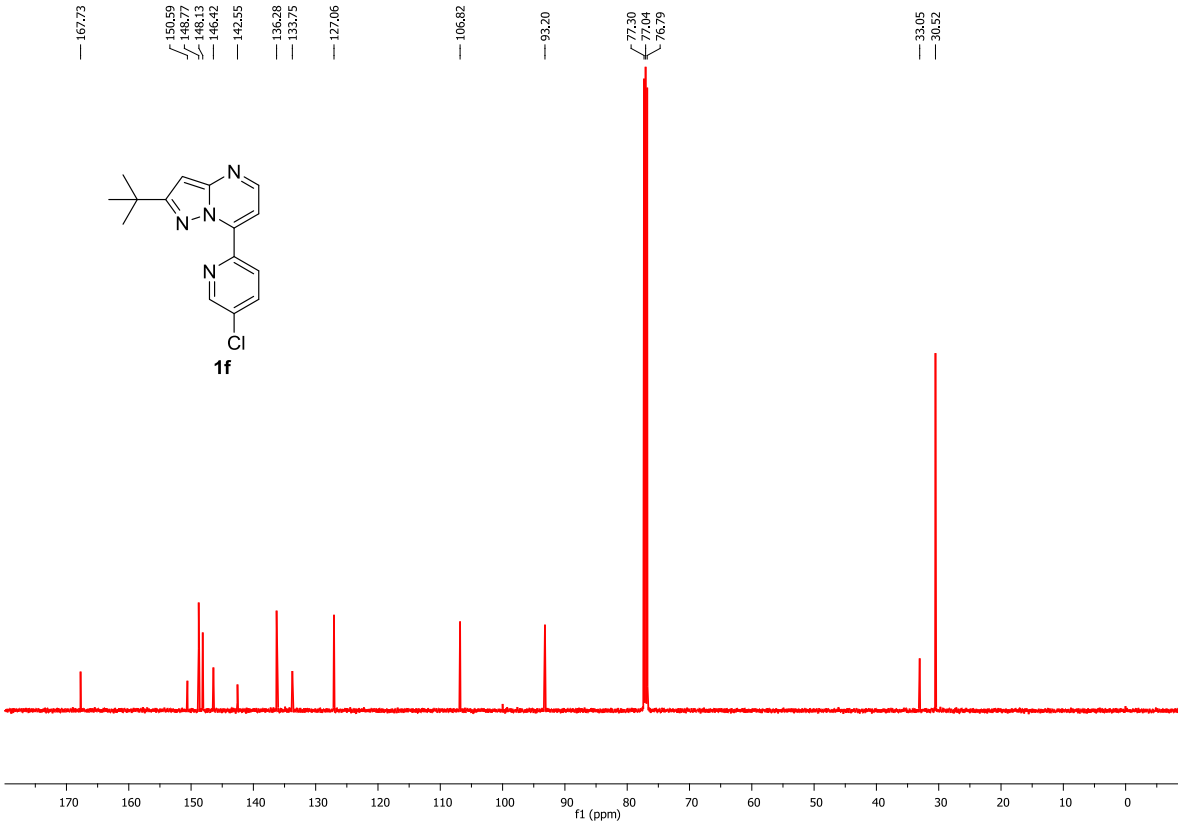
f1 (ppm)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Cl
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130
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110
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50
40
30
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10
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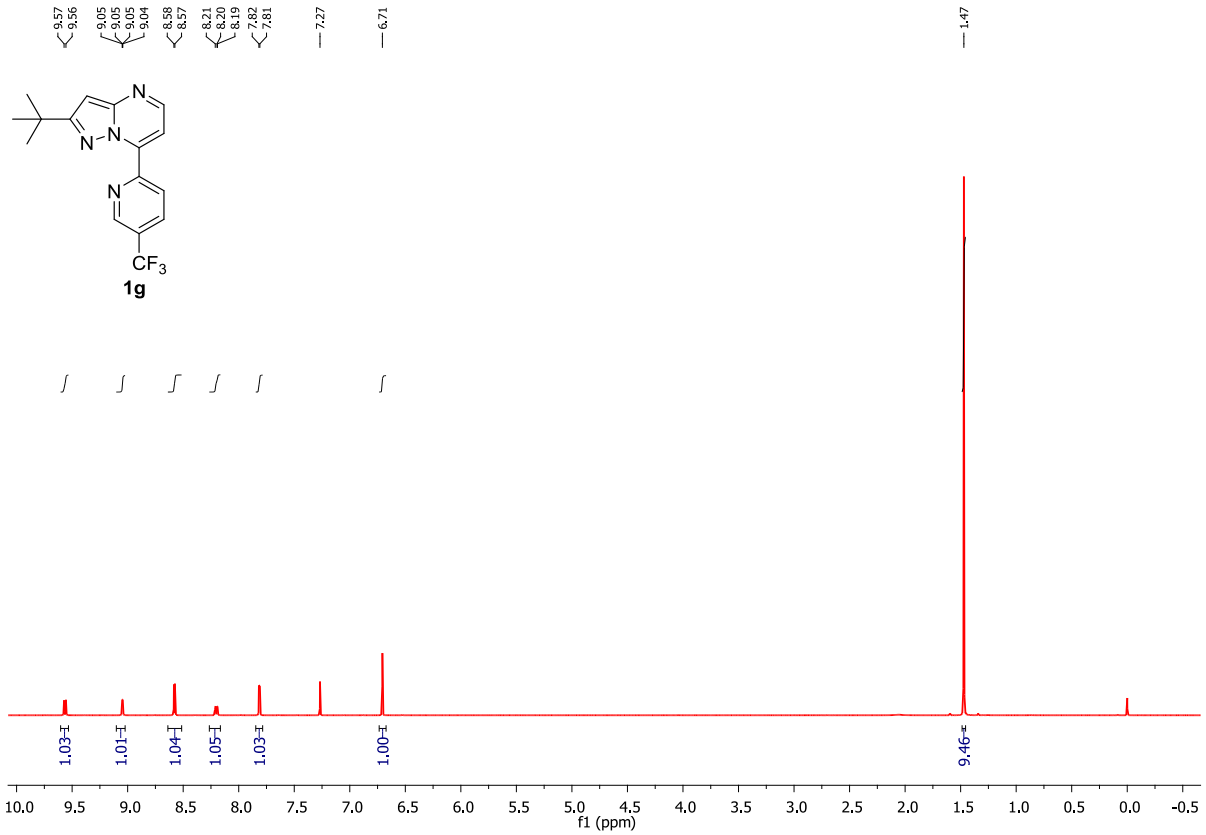
f1 (ppm)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9.05
9.05
9.04
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8.19
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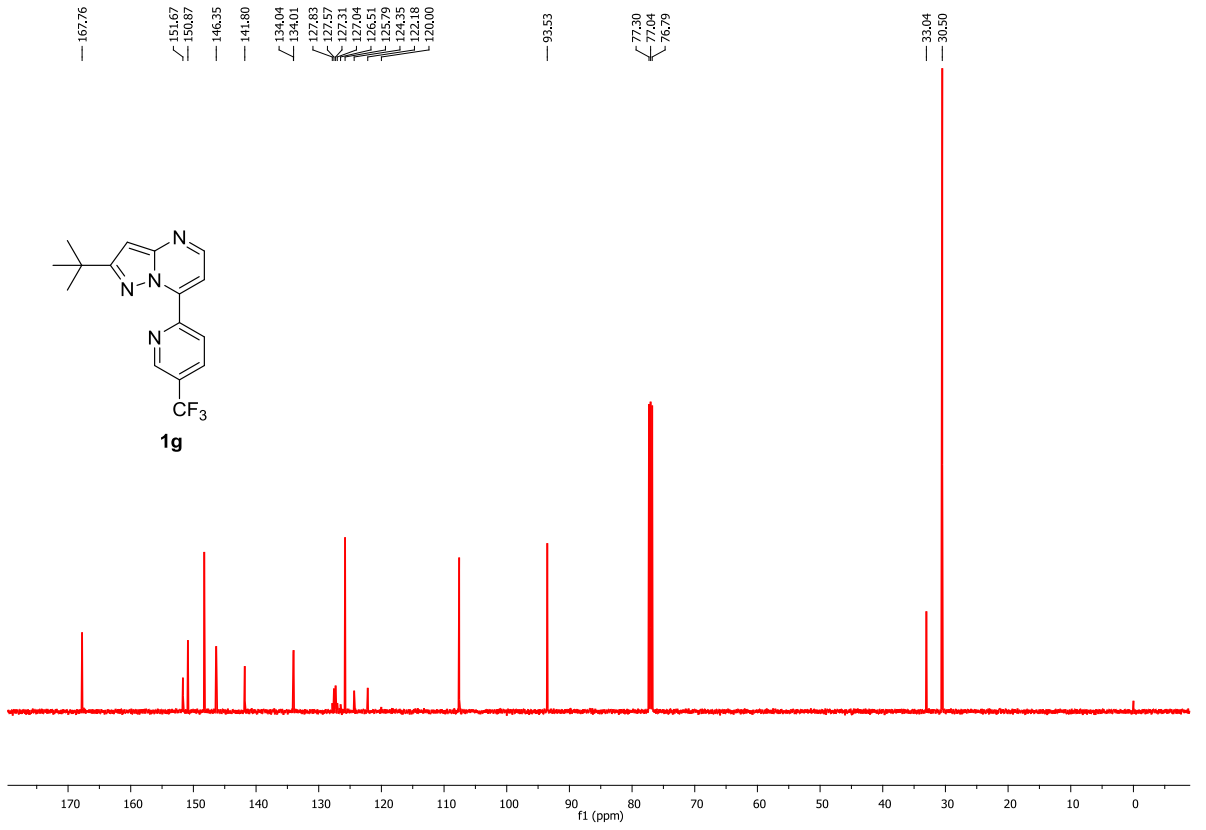
1.05
1.03
1.00
9.46
f1 (ppm)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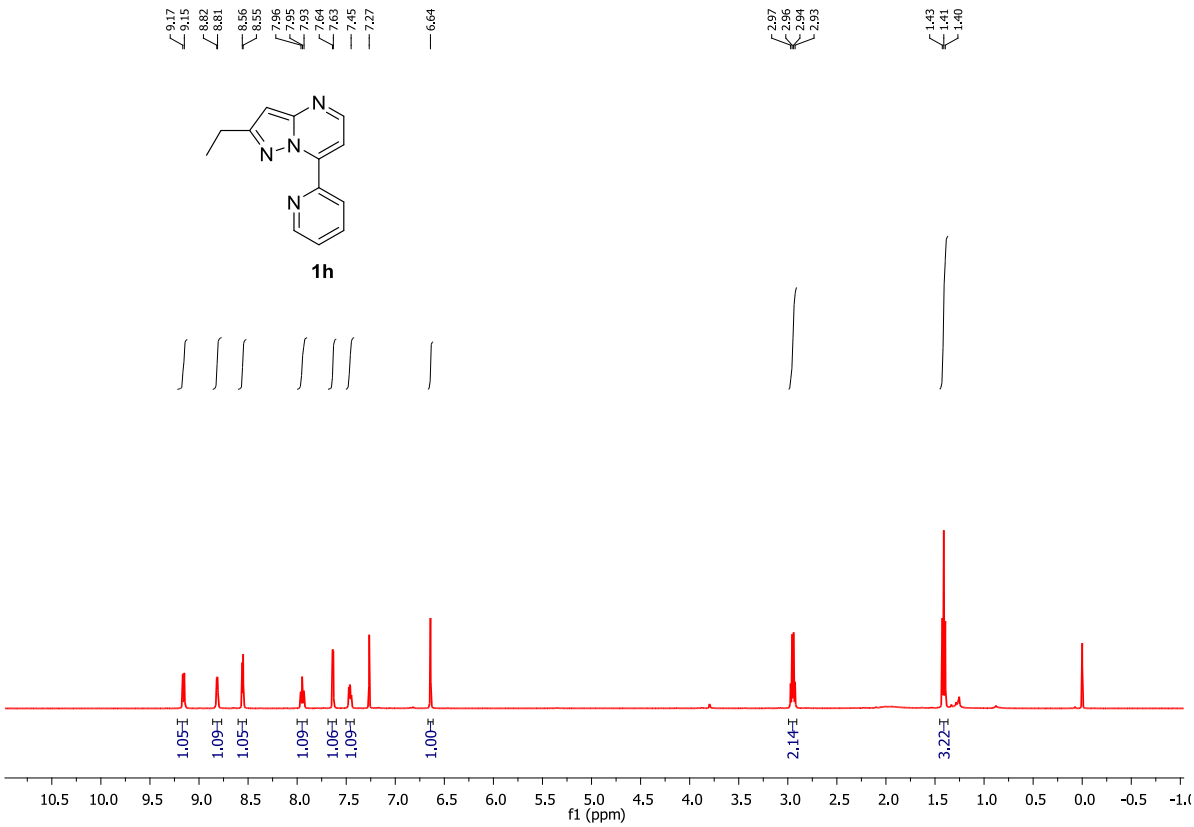
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2.94
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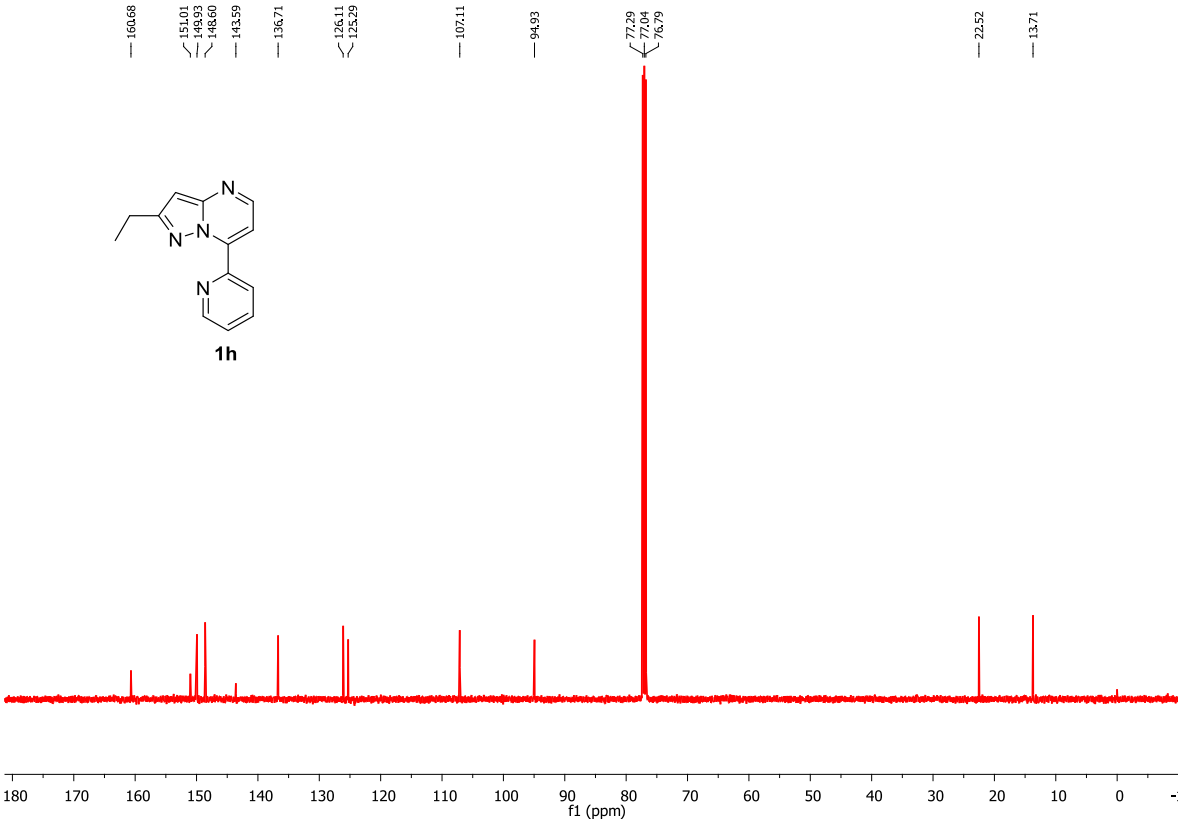
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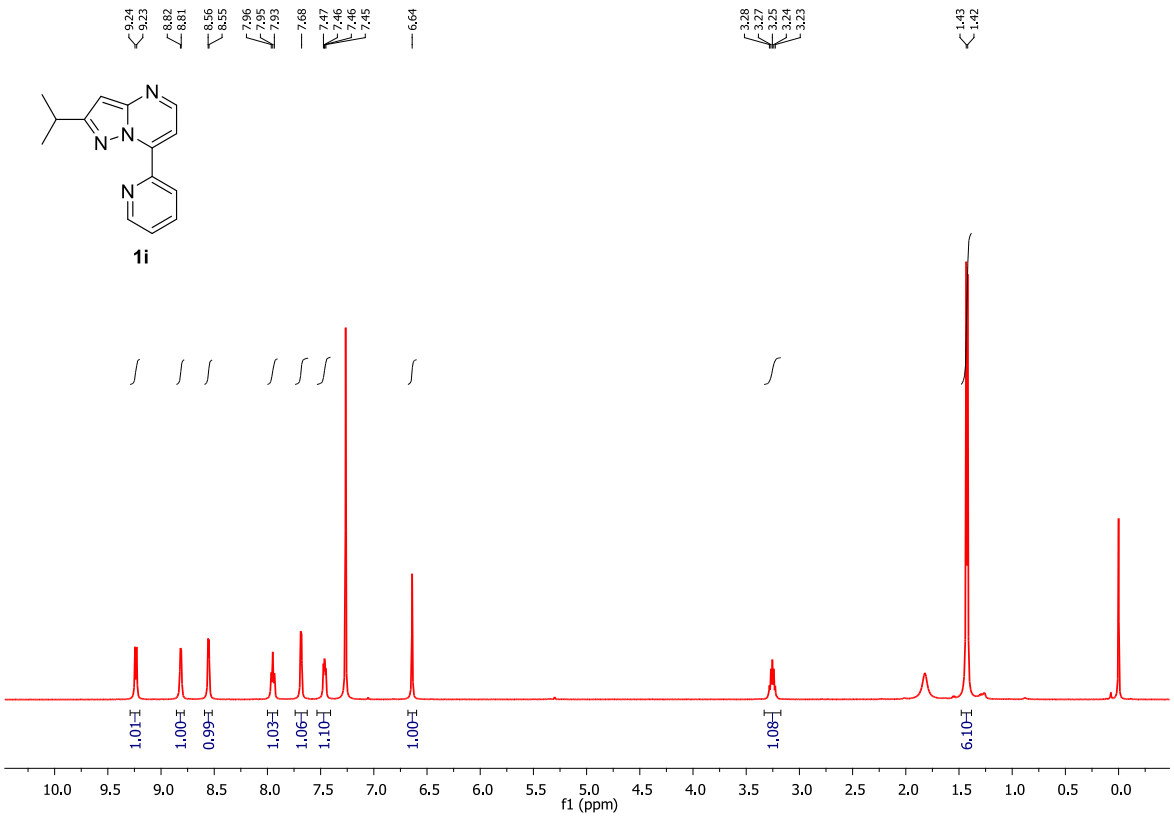
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3.24
3.23
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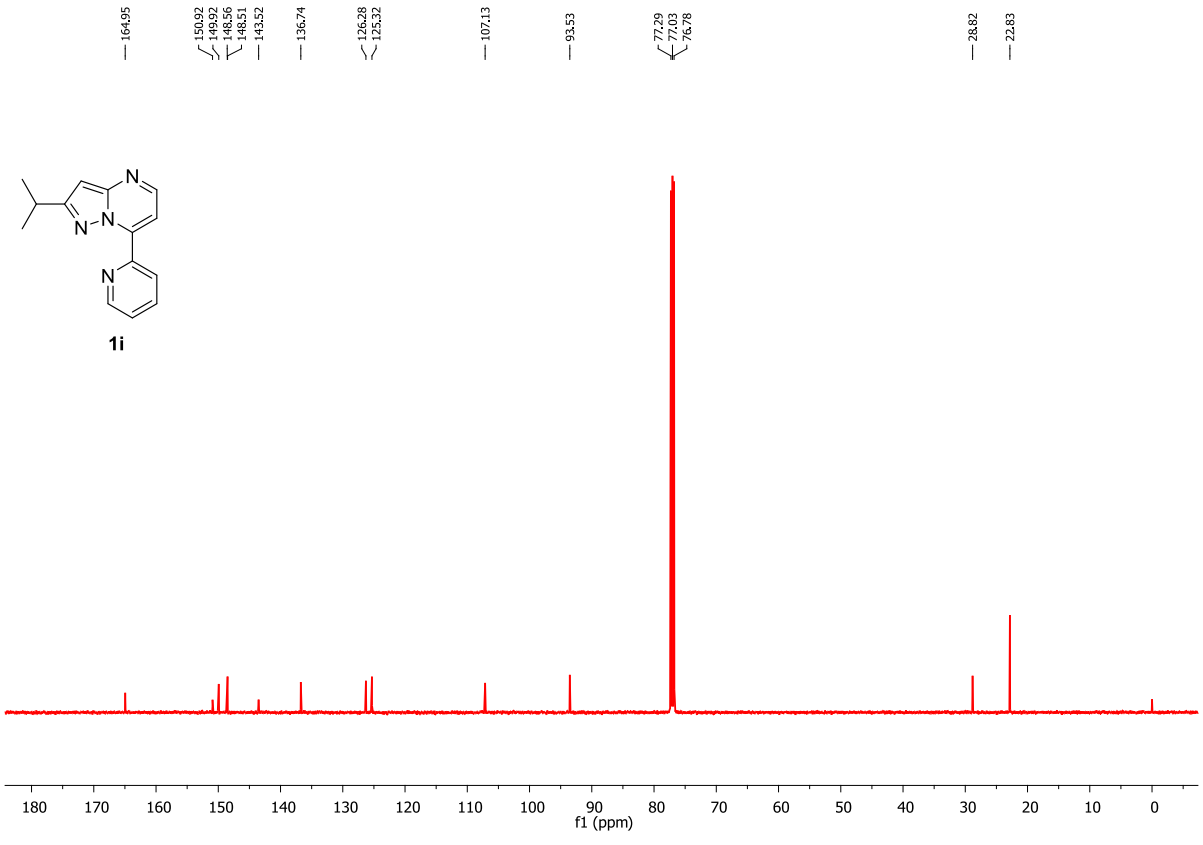
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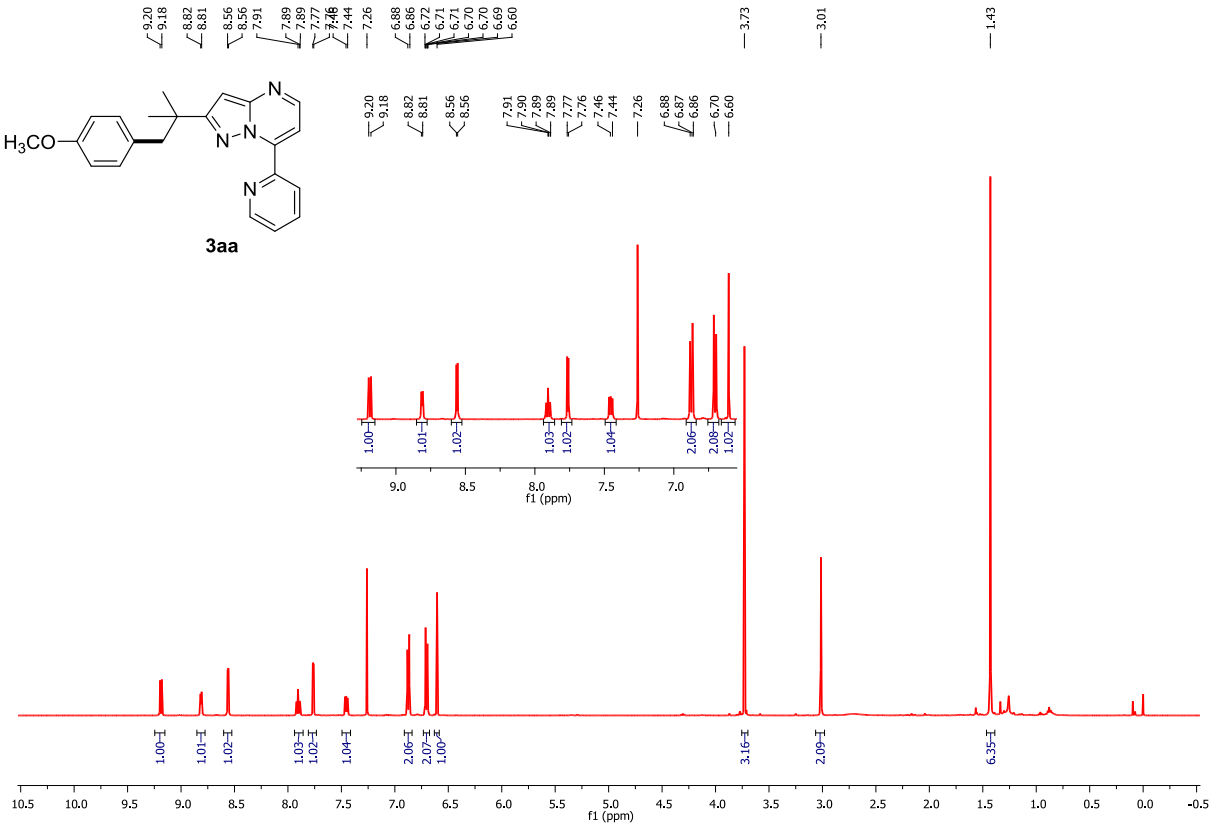
76.78
28.82
22.83
1i
f1 (ppm)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7.26
6.88
6.86
6.72
6.71
6.71
6.70
6.70
6.69
6.60
3.73
3.01
1.43
H3CO
N
N
N
3aa
1.00
1.01
1.02
1.03
1.02
1.04
2.06
2.08
1.02
f1 (ppm)
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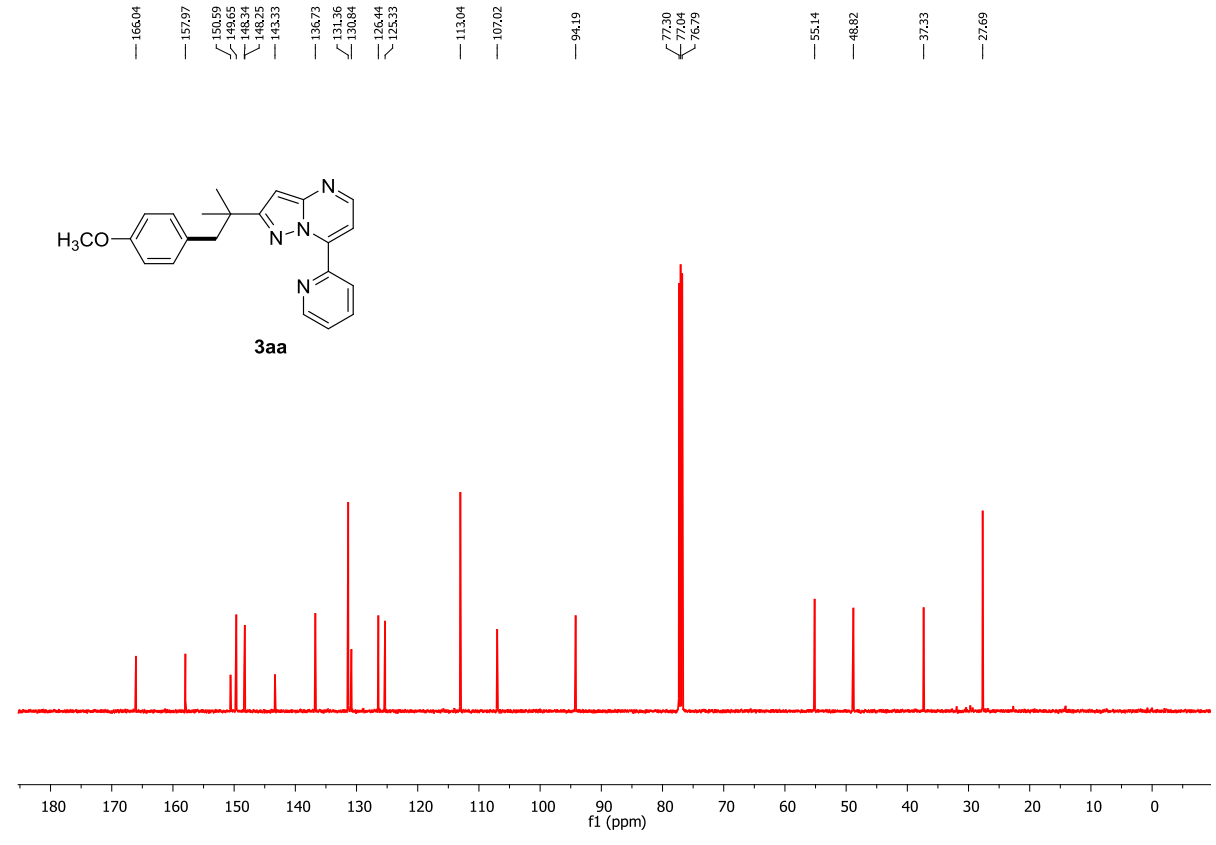
f1 (ppm)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113.04
107.02
94.19
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37.33
27.69
H3CO
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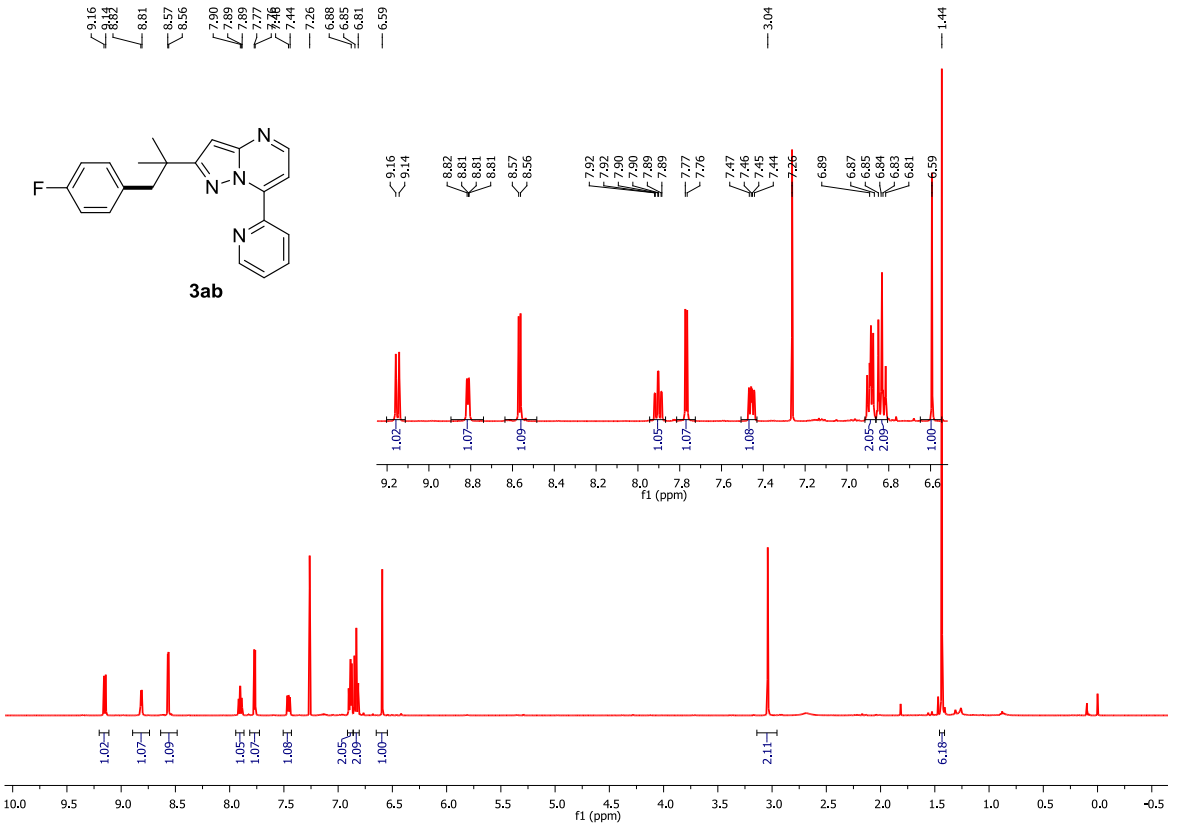
N
3aa
f1 (ppm)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6.59
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F
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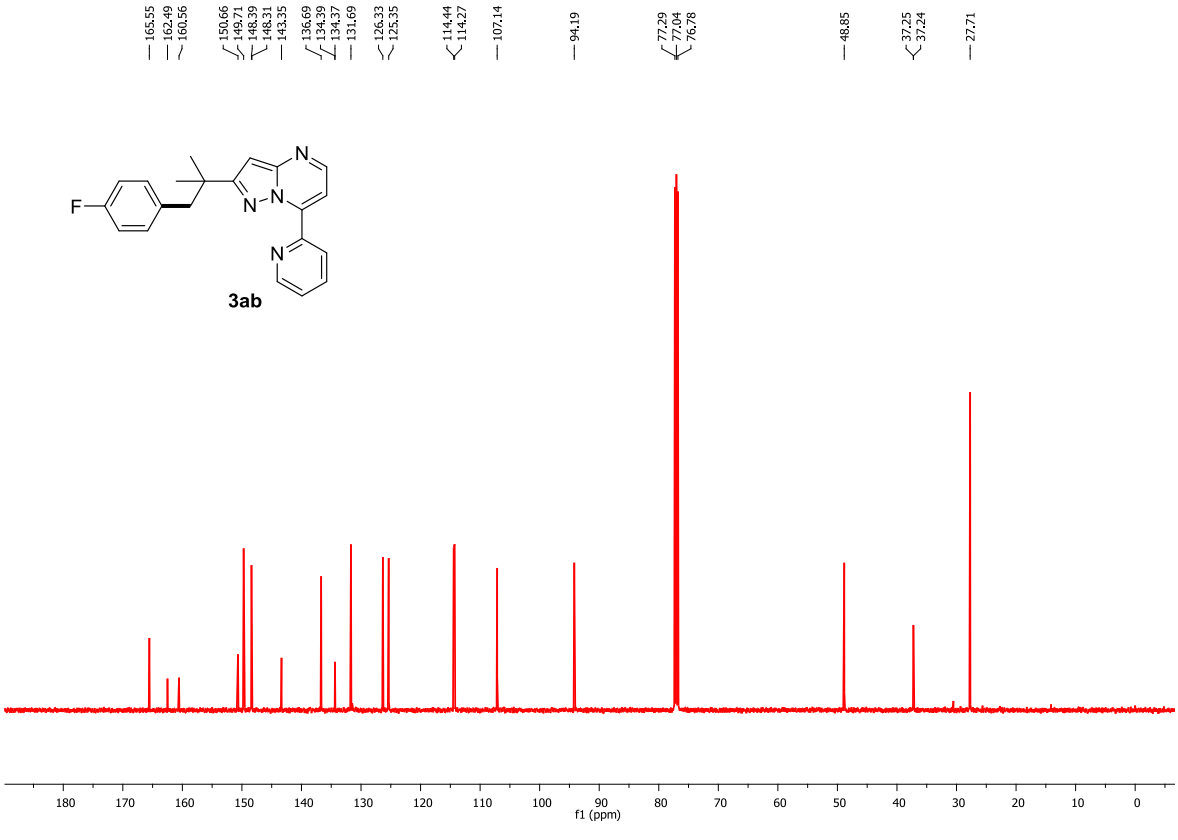
N
3ab
f1 (ppm)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114.27
107.14
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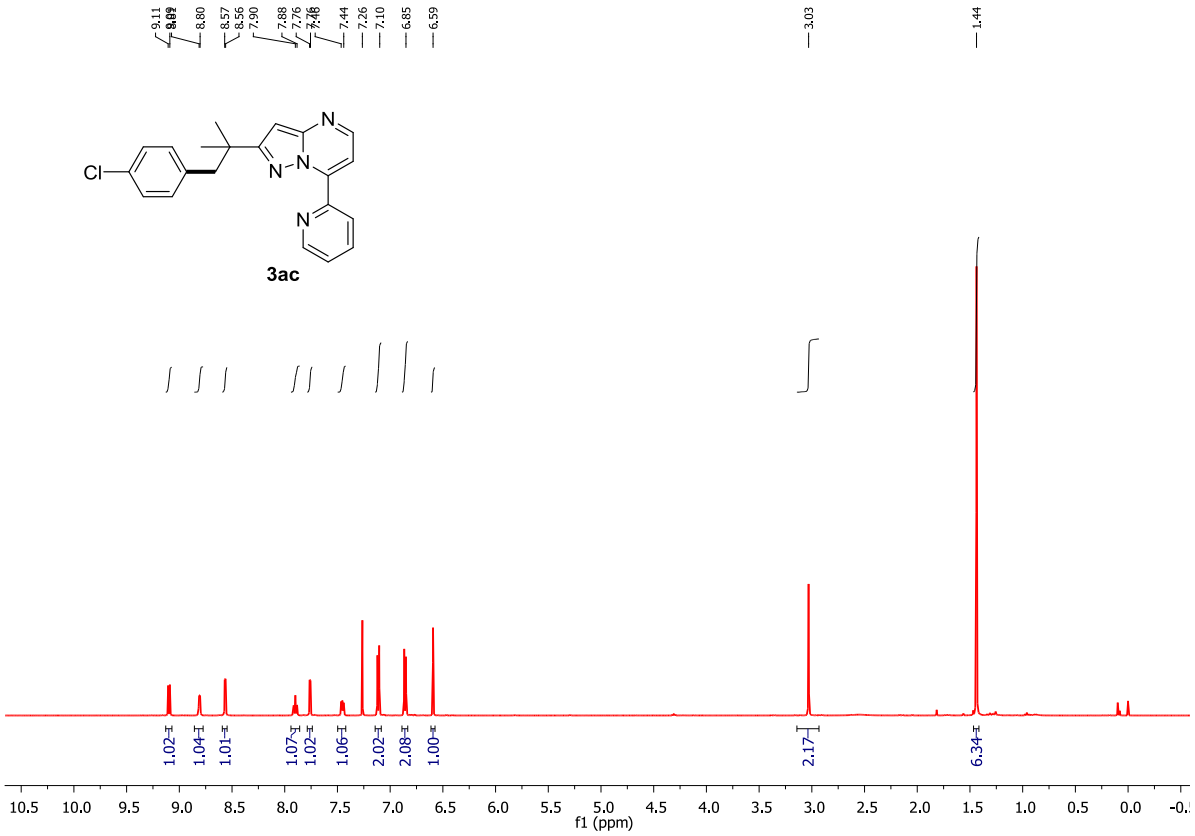
N
3ab
f1 (ppm)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6.59
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1.44
Cl
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N
N
3ac
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1.06
2.02
2.08
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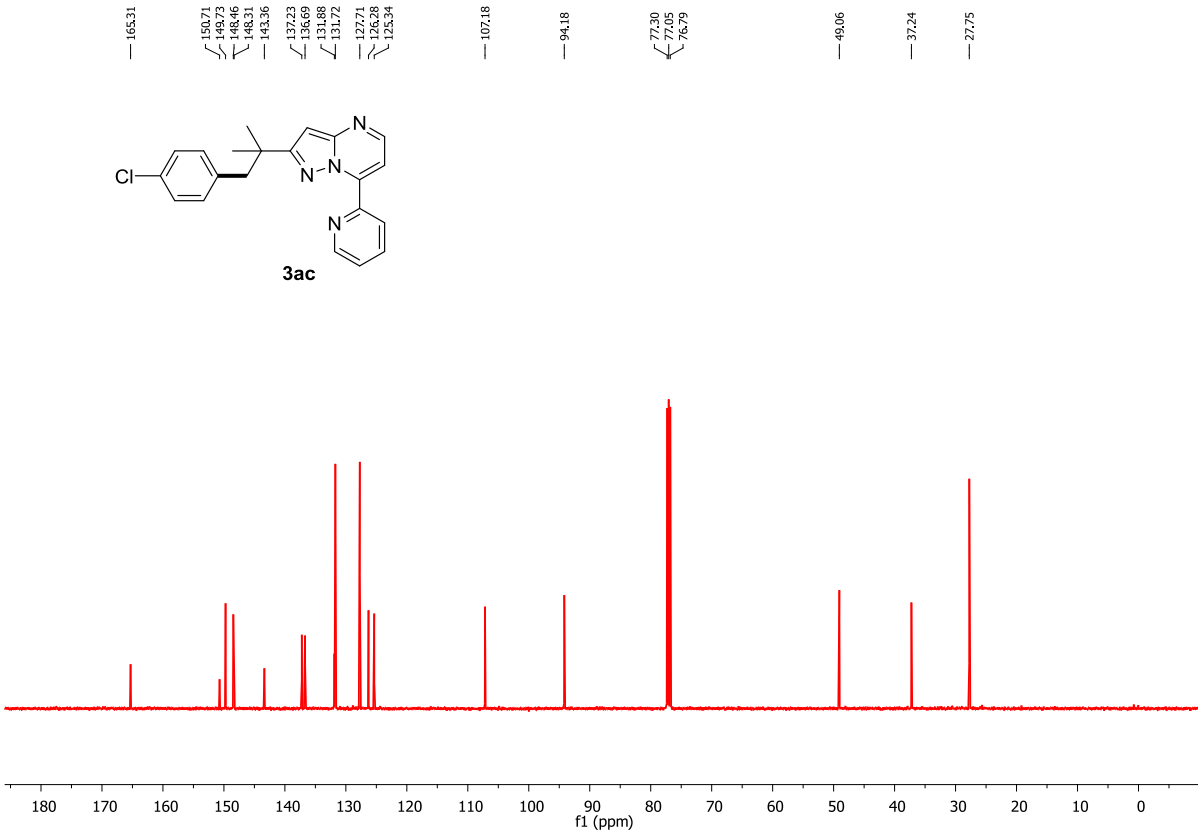
6.34
f1 (ppm)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49.06
37.24
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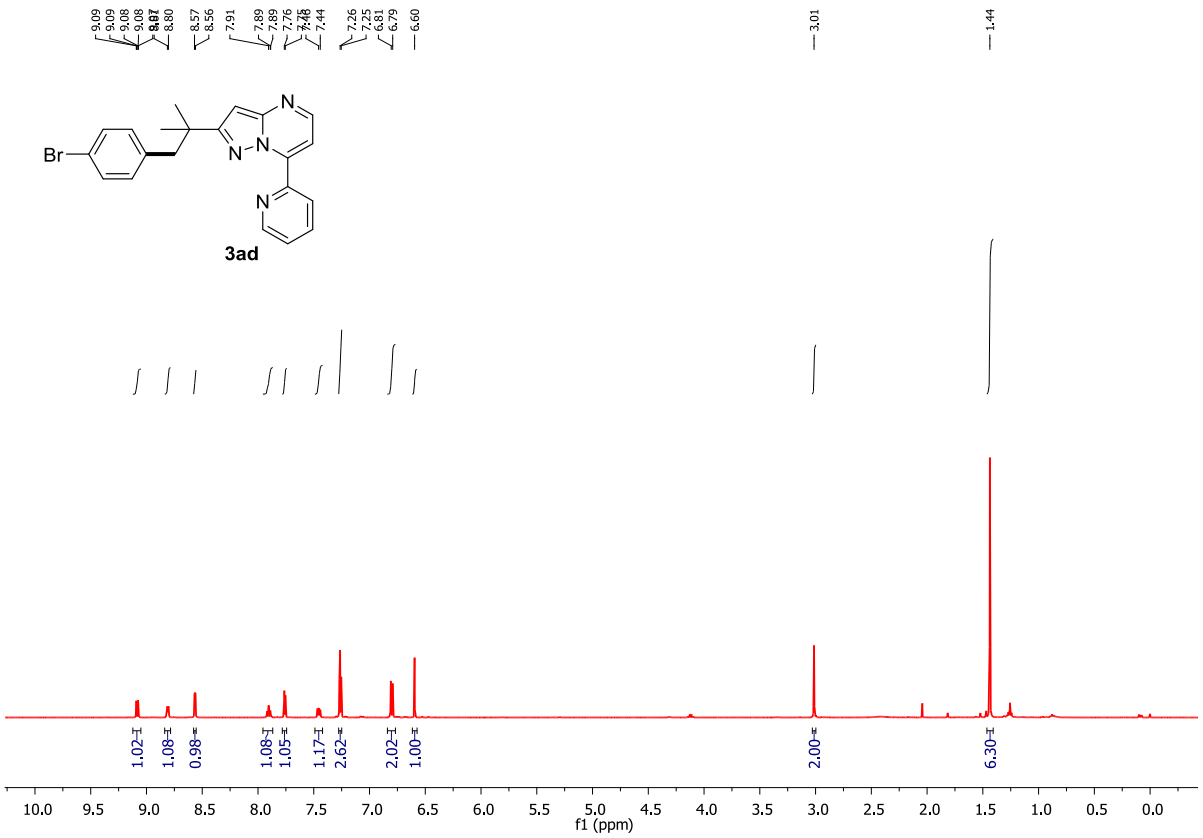
N
3ac
f1 (ppm)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6.81
6.79
6.60
3.01
1.44
Br
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N
N
N
3ad
1.02
1.08
0.98
1.08
1.05
1.17
2.62
2.02
1.00
2.00
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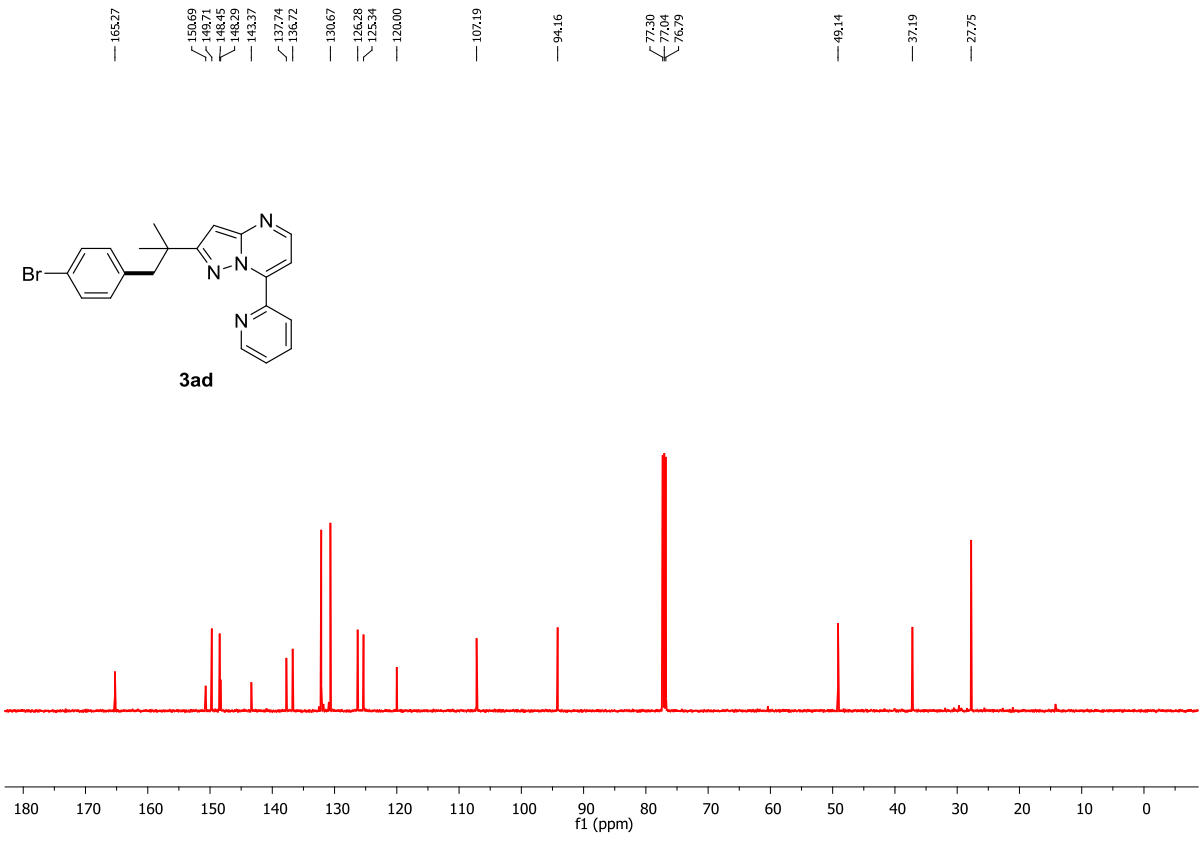
0.0
f1 (ppm)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94.16
77.30
77.04
76.79
49.14
37.19
27.75
Br
N
N
N
N
3ad
180
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110
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50
40
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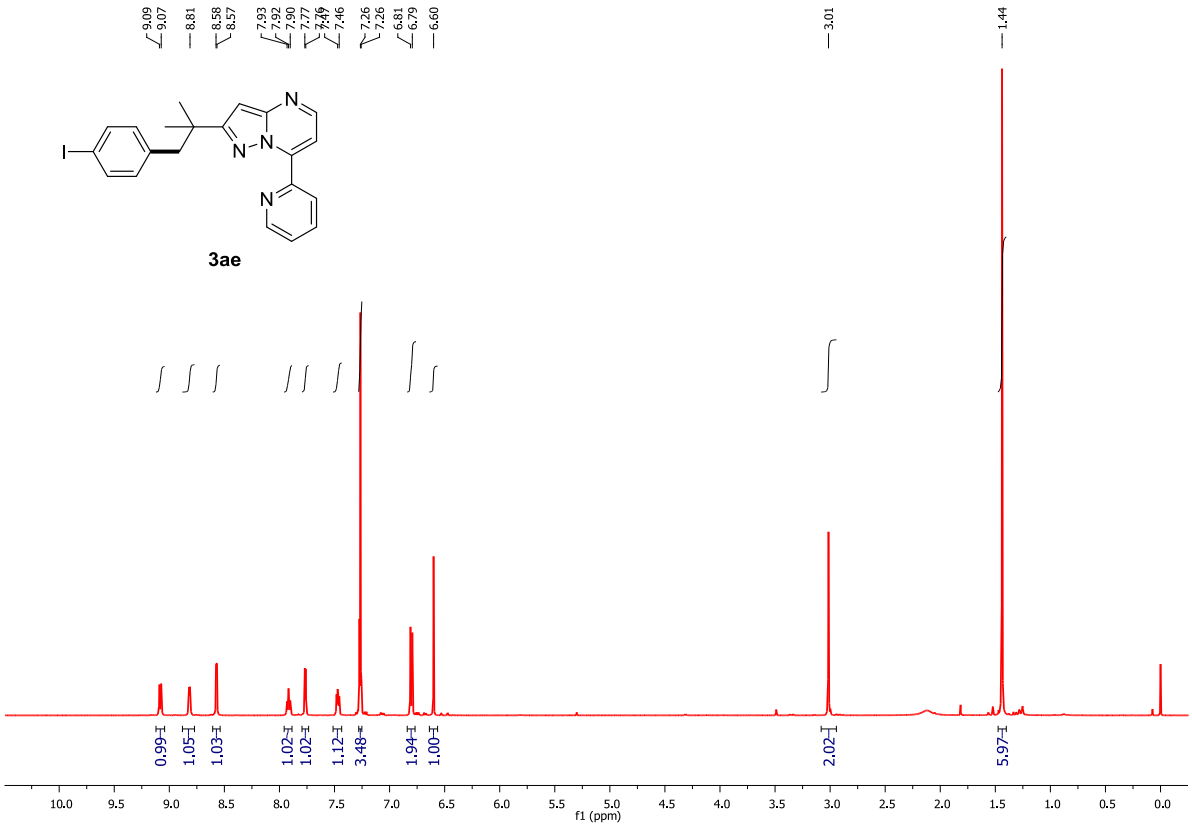
f1 (ppm)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7.26
6.81
6.79
6.60
3.01
1.44
I
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N
N
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1.05
1.03
1.02
1.02
1.12
3.48
1.94
1.00
2.02
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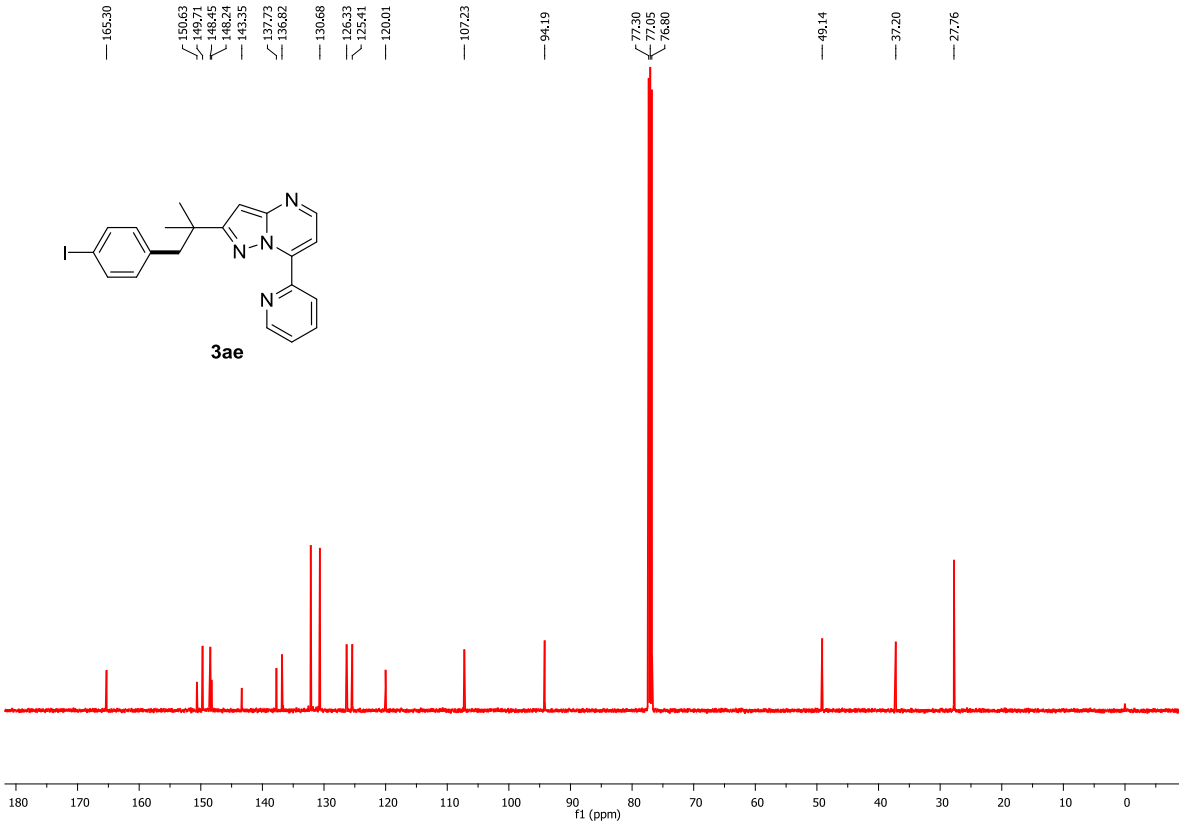
f1 (ppm)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77.30
77.05
76.80
49.14
37.20
27.76
I
N
N
N
N
3ae
180
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110
100
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50
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10
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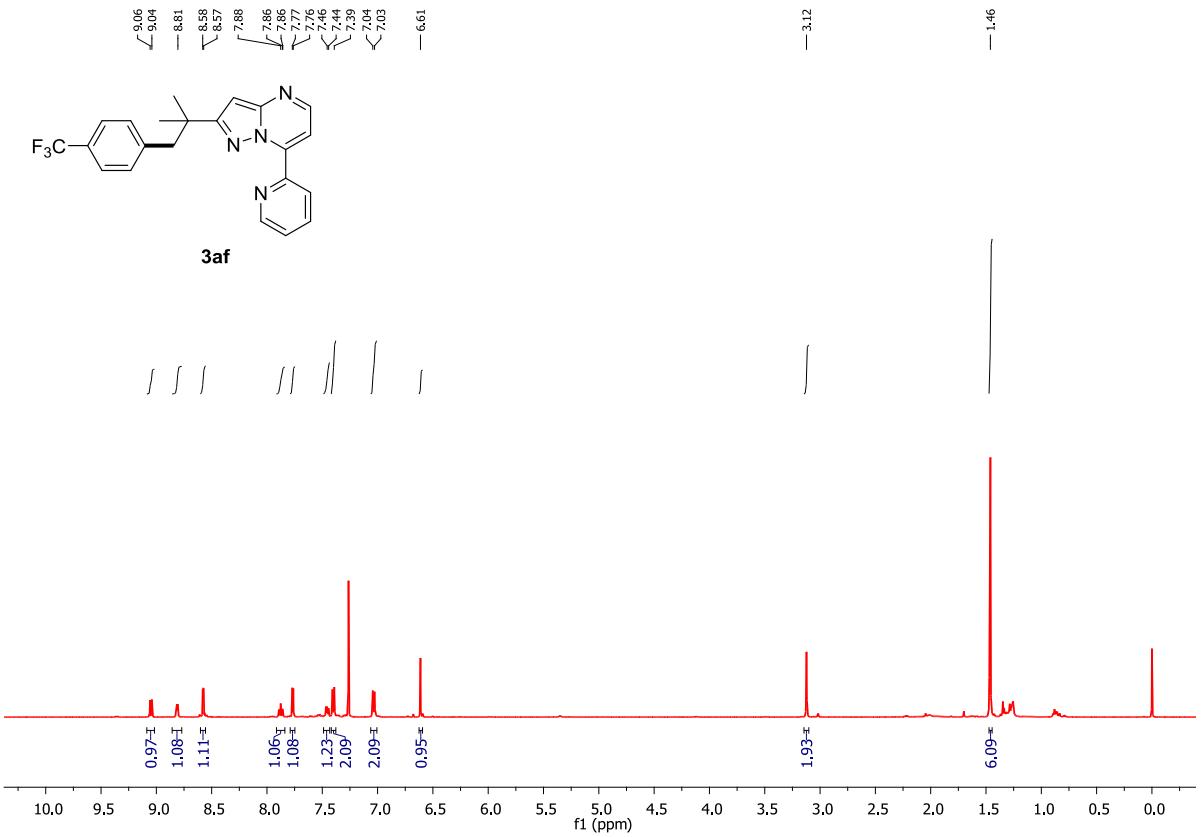
f1 (ppm)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6.61
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F3C
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N
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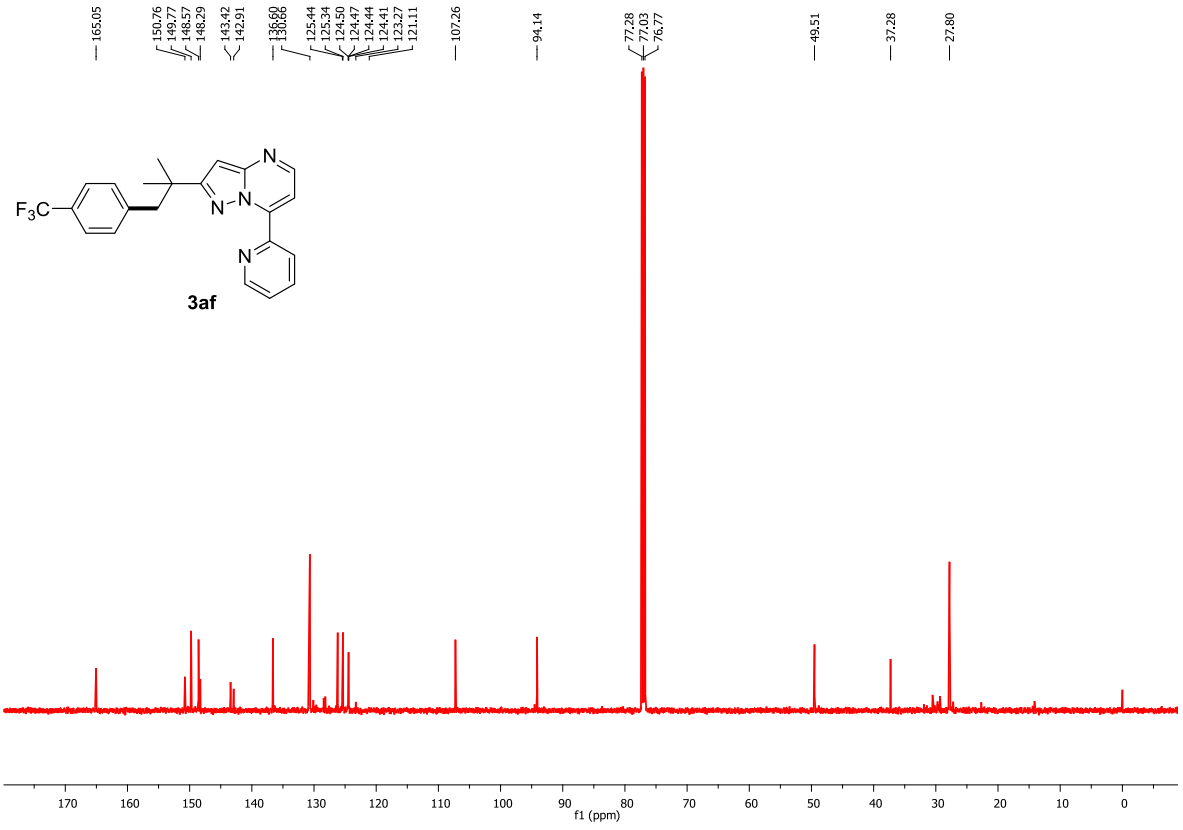
f1 (ppm)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F3C
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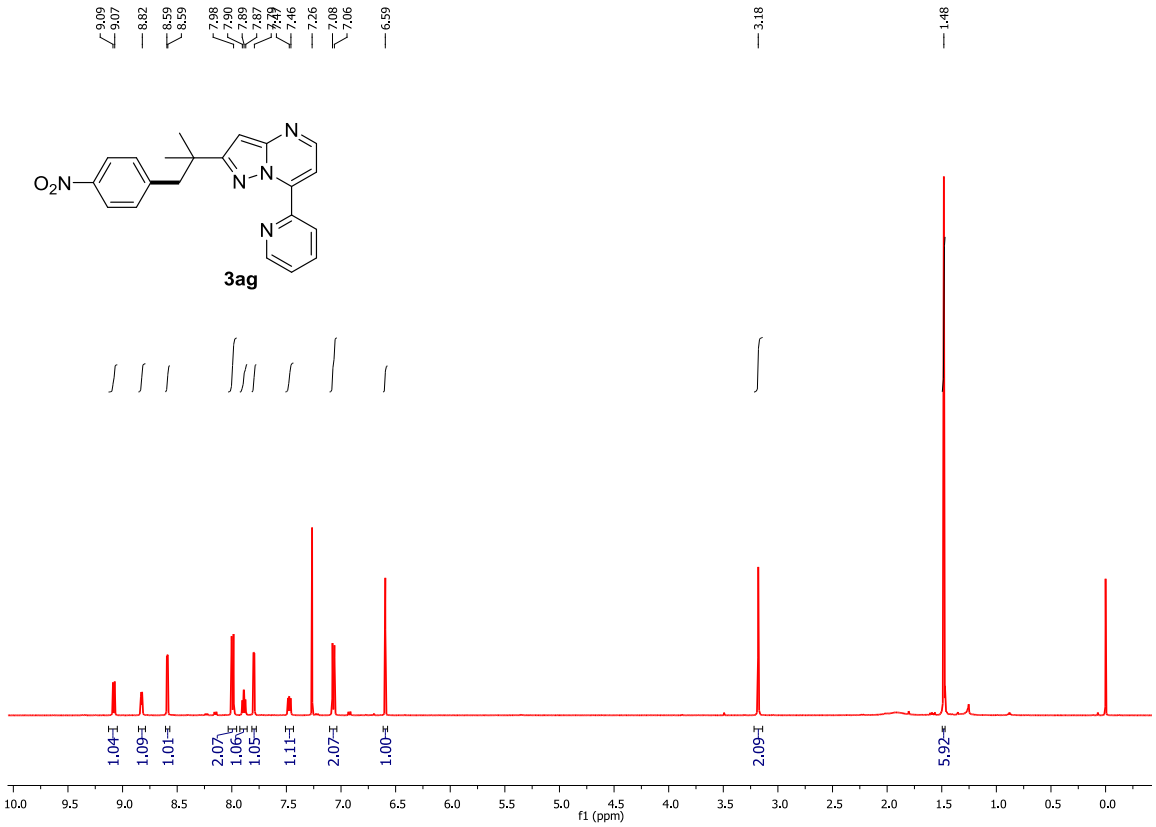
N
3af
f1 (ppm)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5.92
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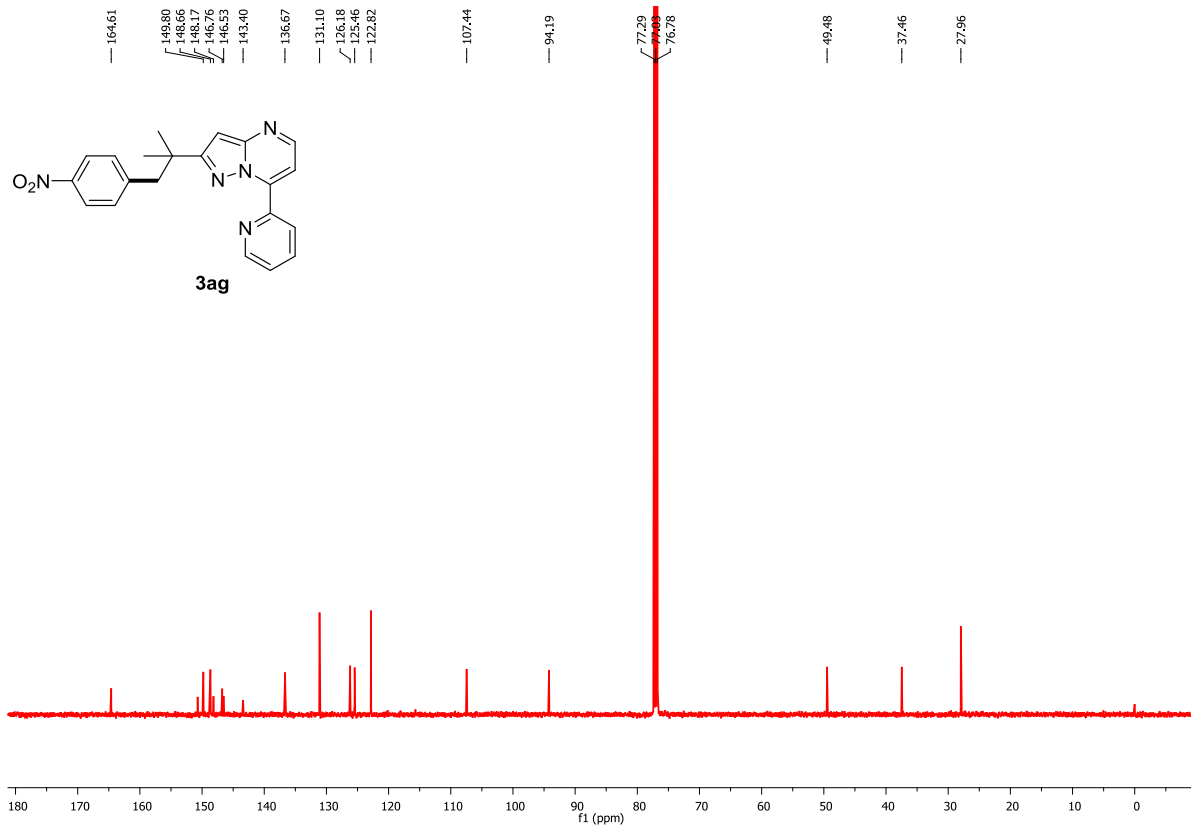
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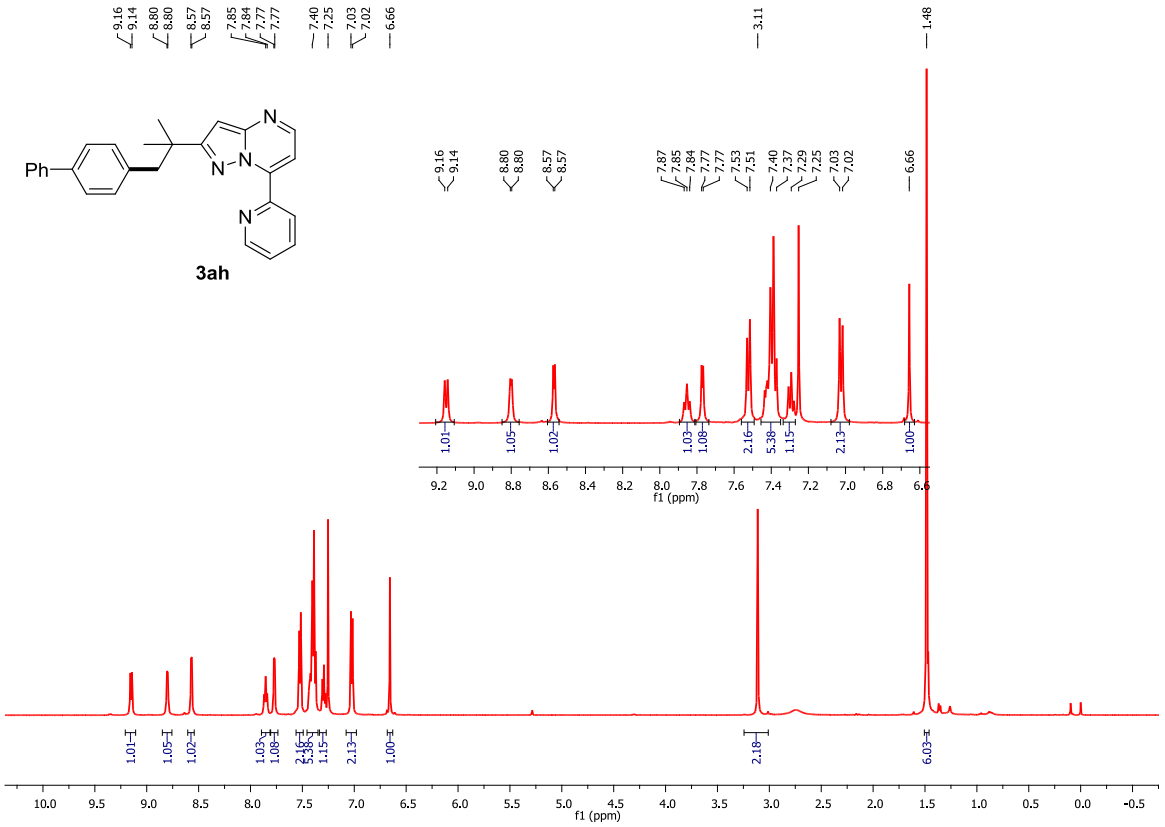
f1 (ppm)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7.02
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3.11
1.48
Ph
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6.03
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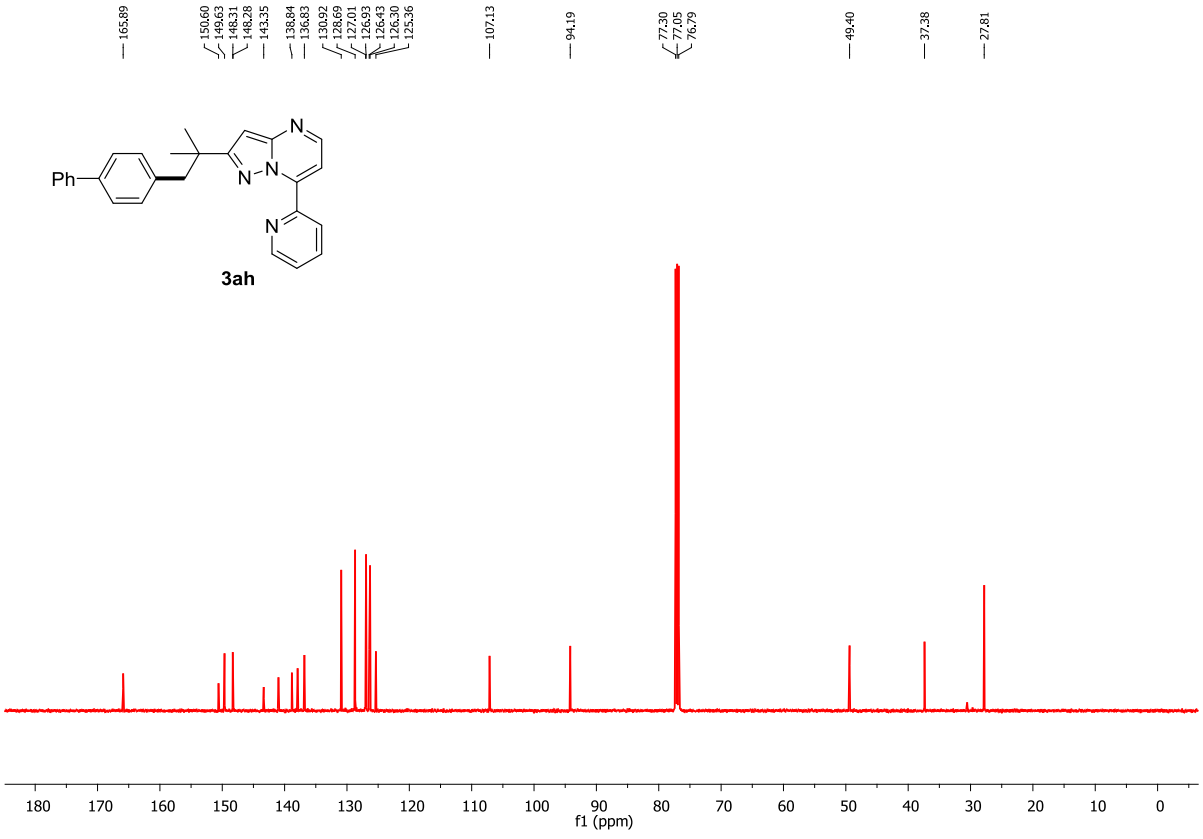
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125.36
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Ph
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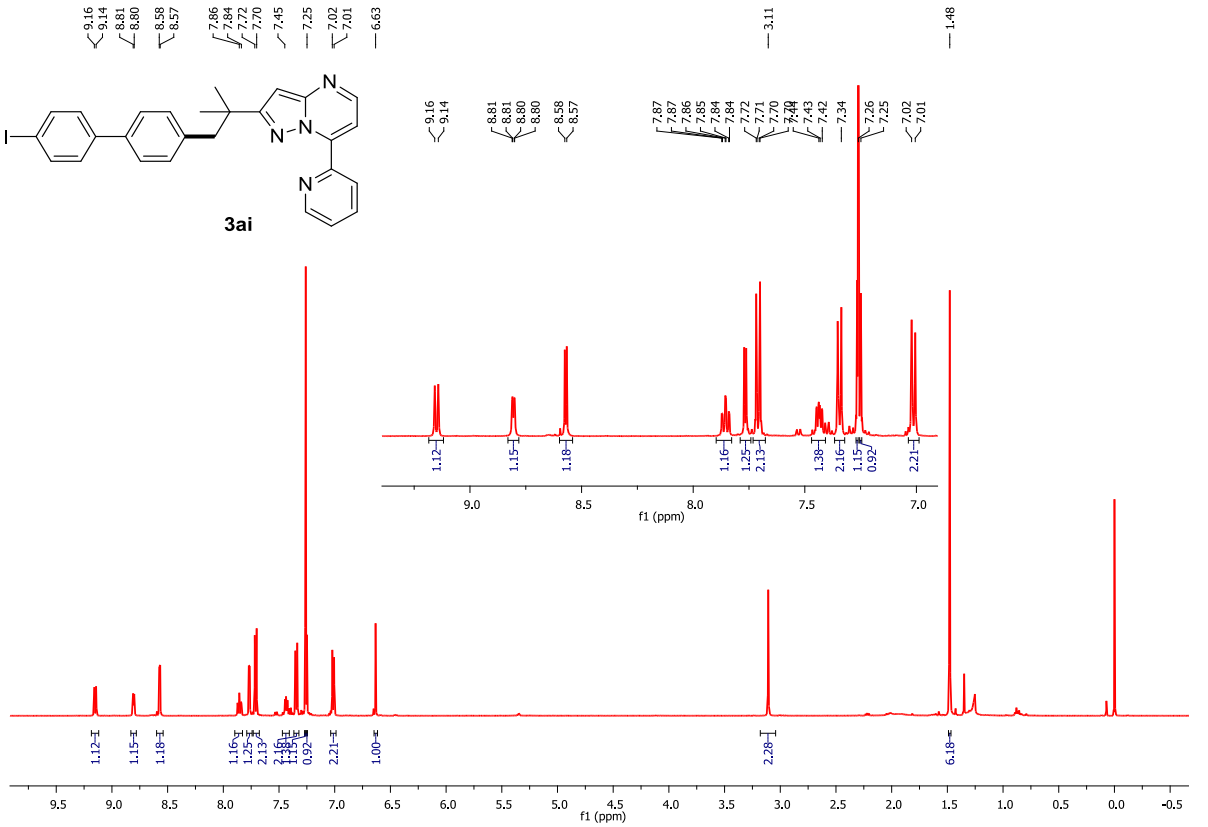
3ah
f1 (ppm)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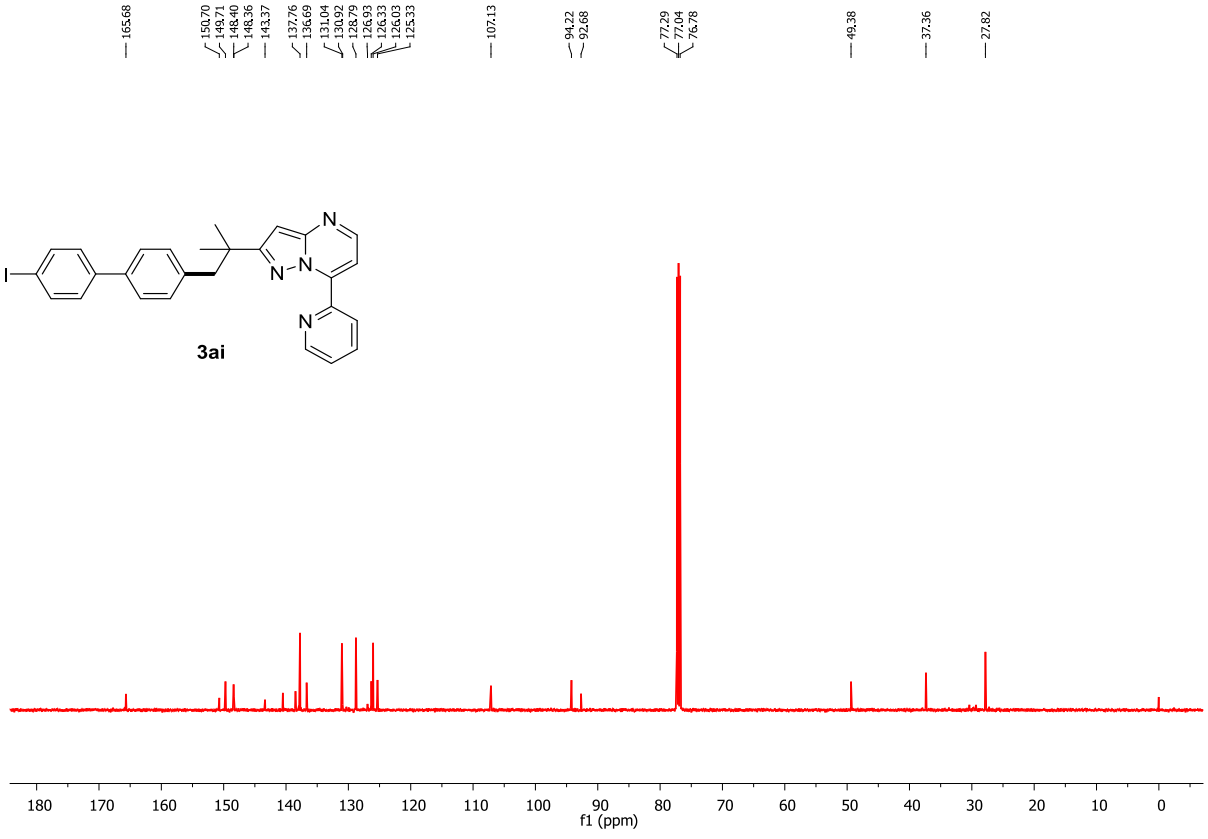
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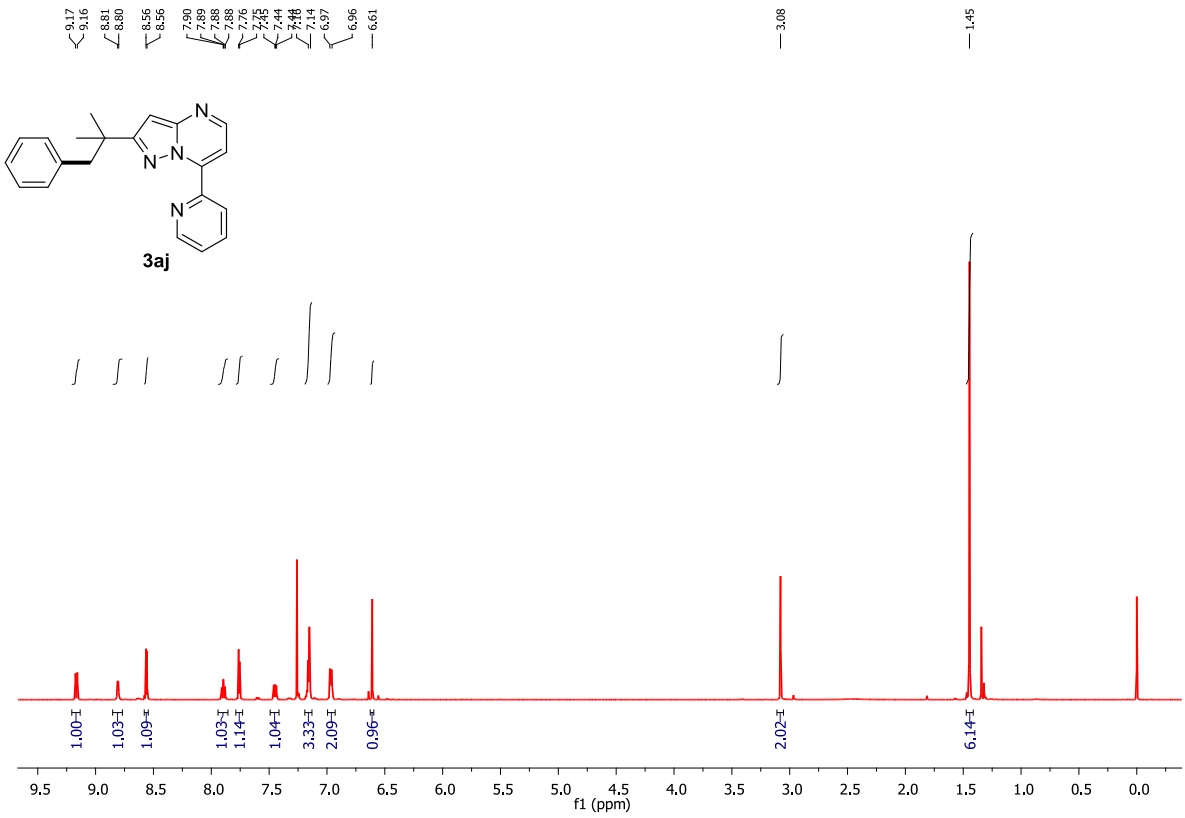
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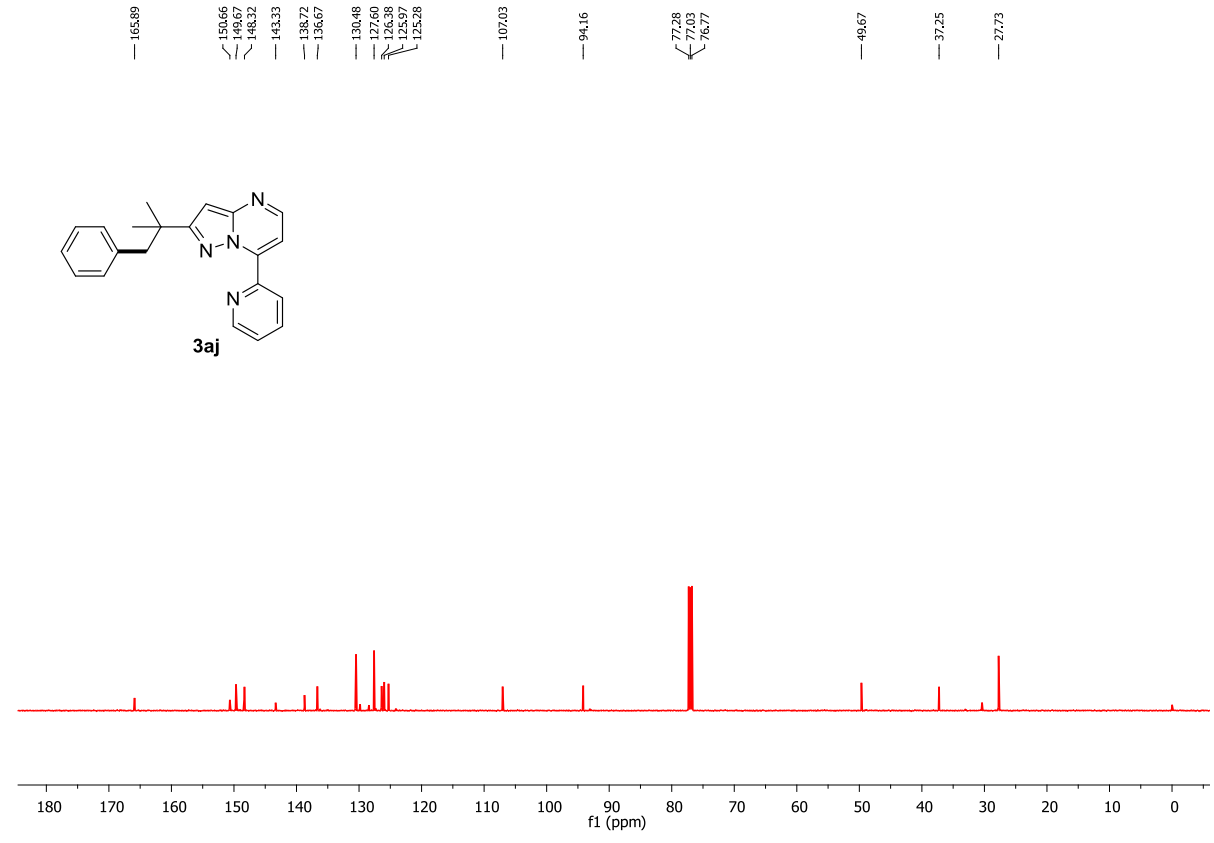
f1 (ppm)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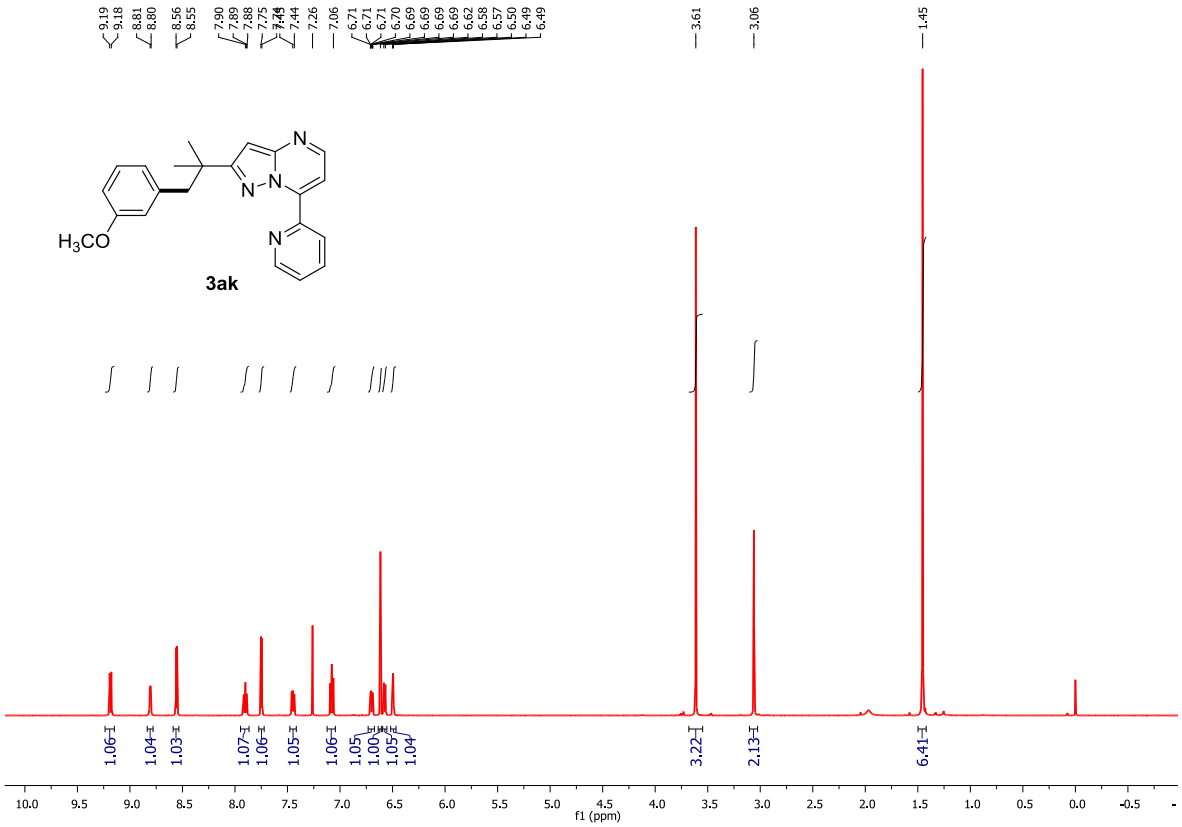
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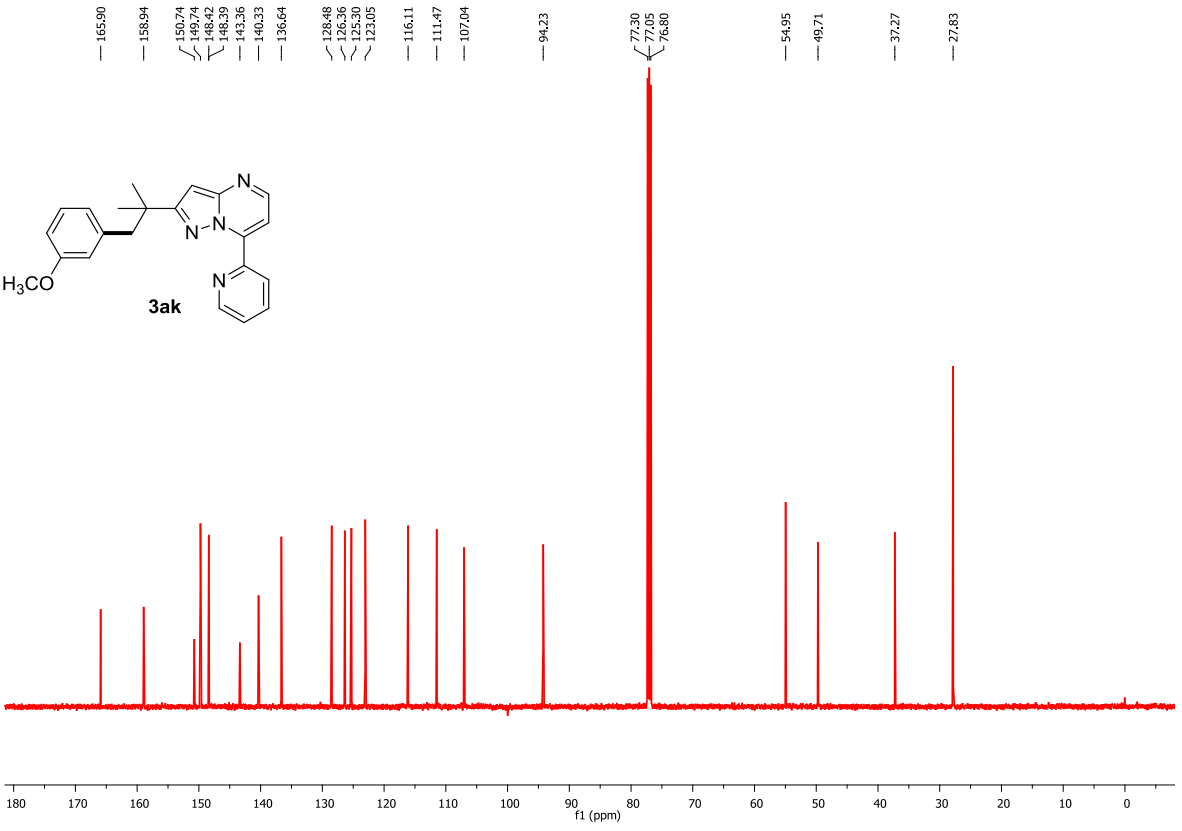
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N
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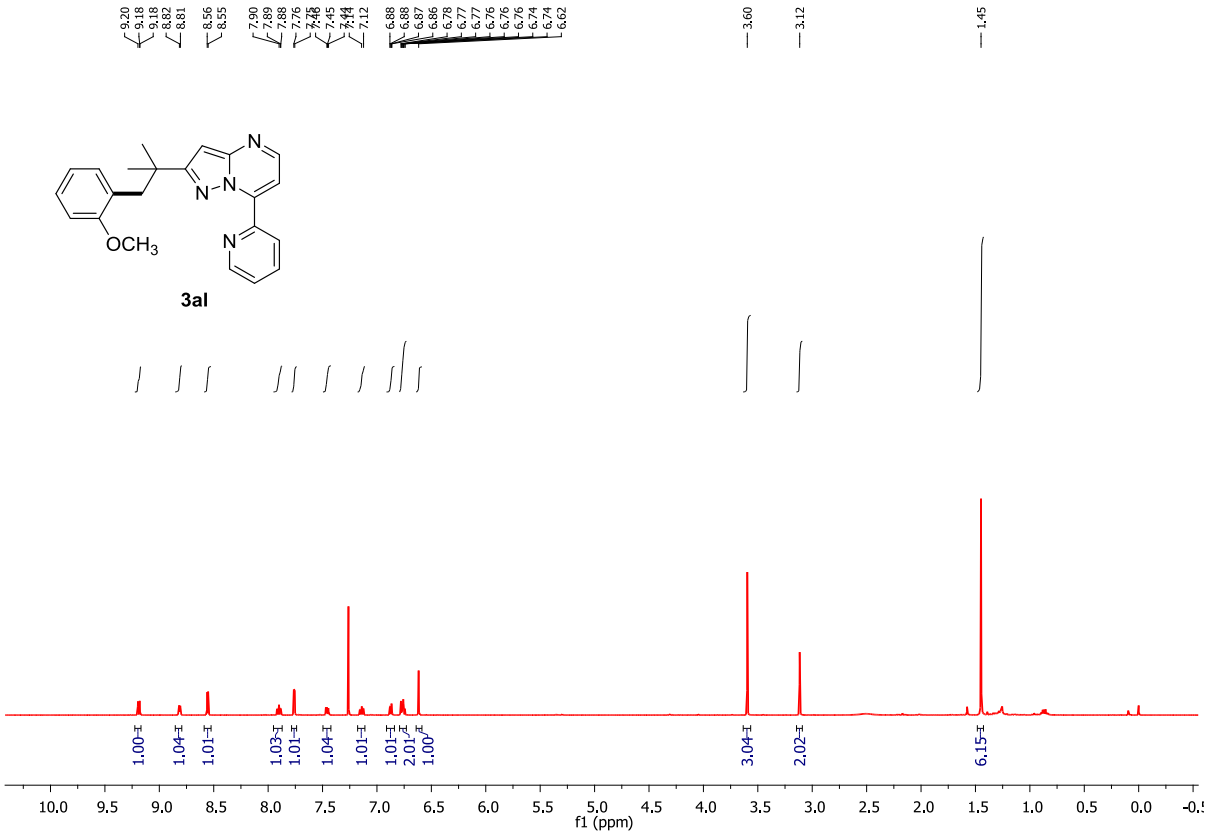
f1 (ppm)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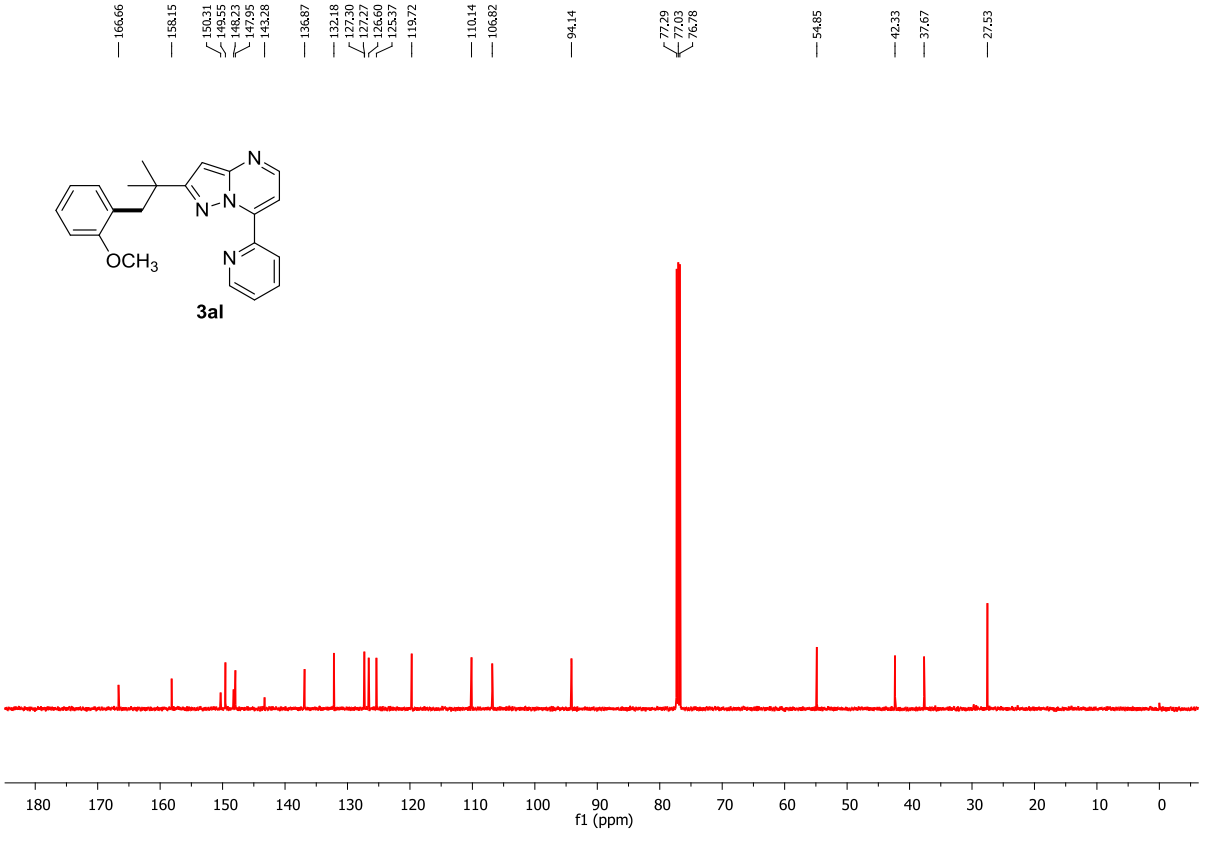
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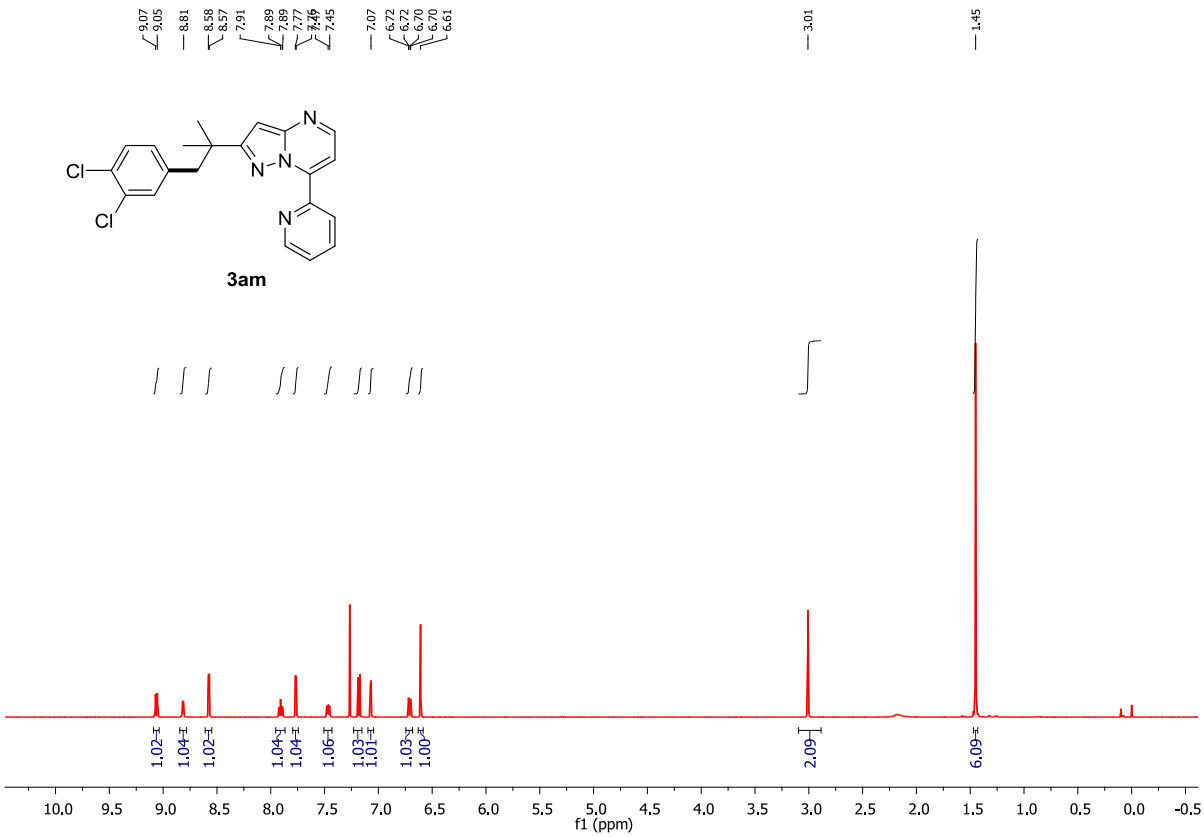
f1 (ppm)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6.70
6.70
6.61
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1.45
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Cl
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N
N
3am
1.02
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1.02
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1.04
1.06
1.03
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1.03
1.00
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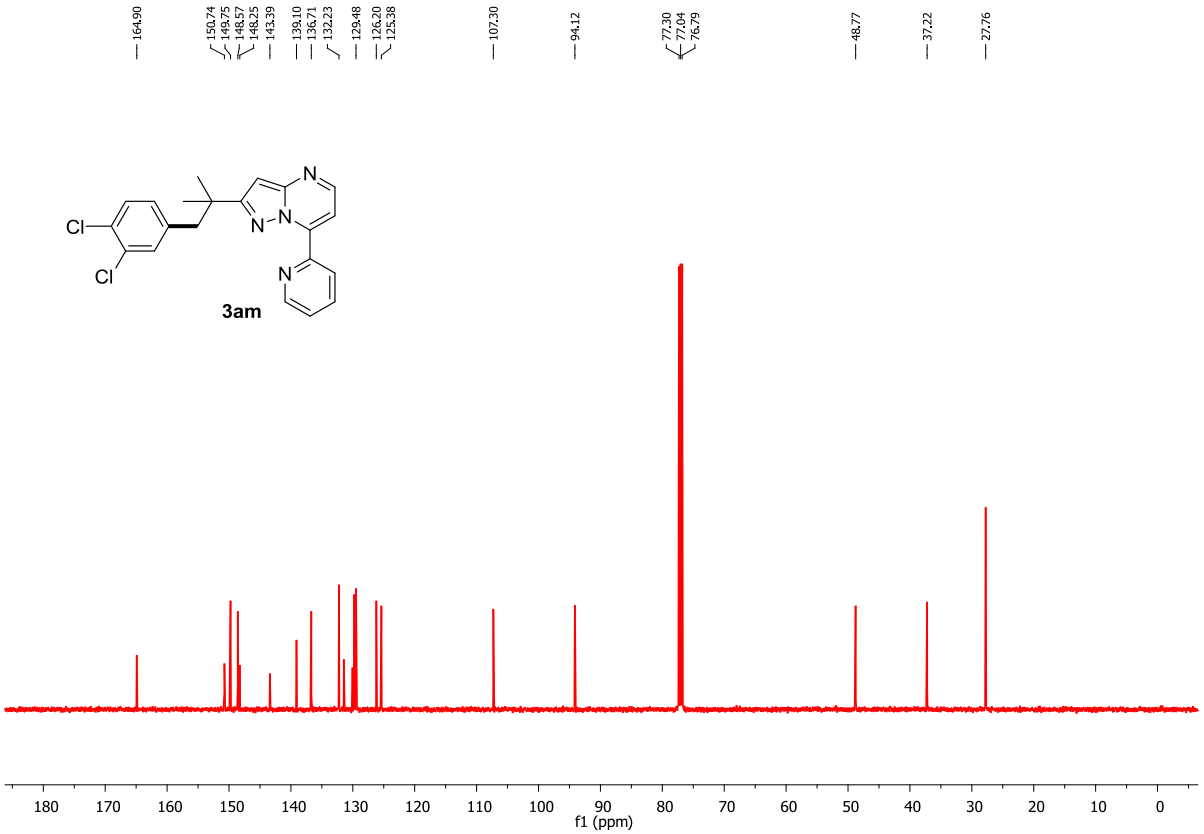
f1 (ppm)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Cl
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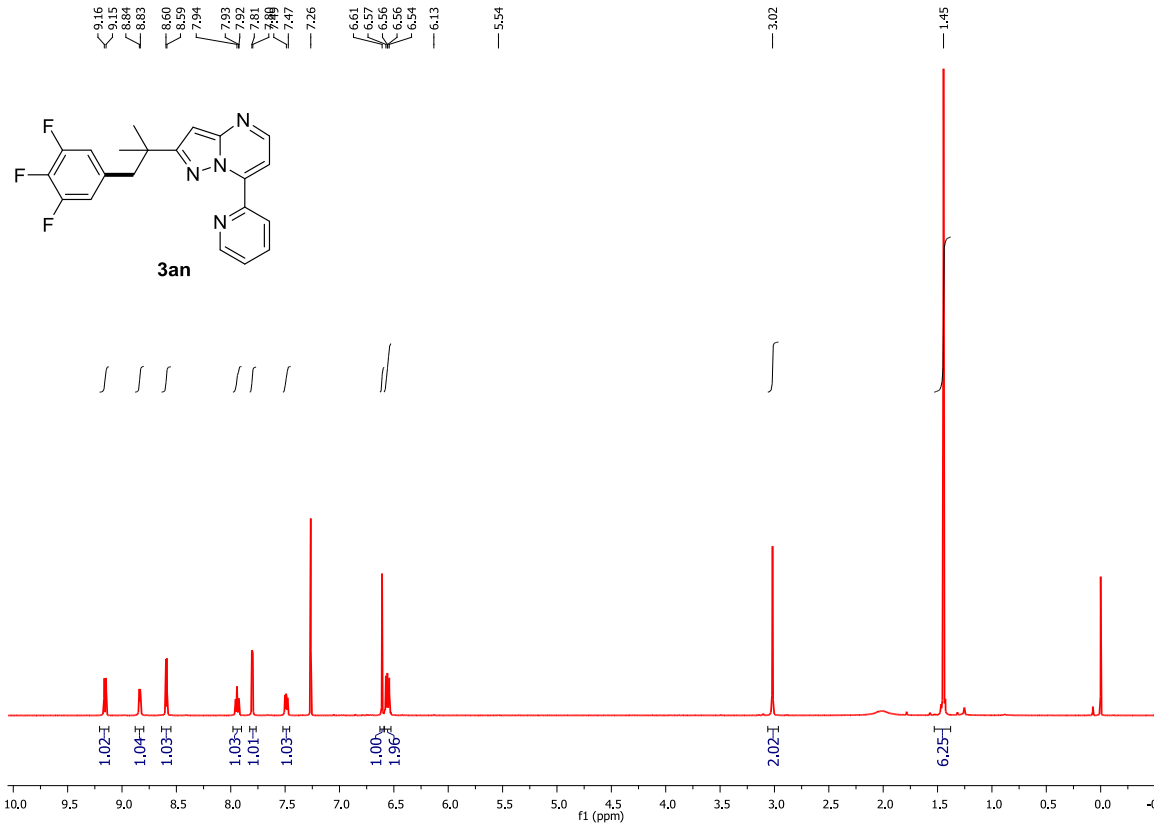
3am
f1 (ppm)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F
F
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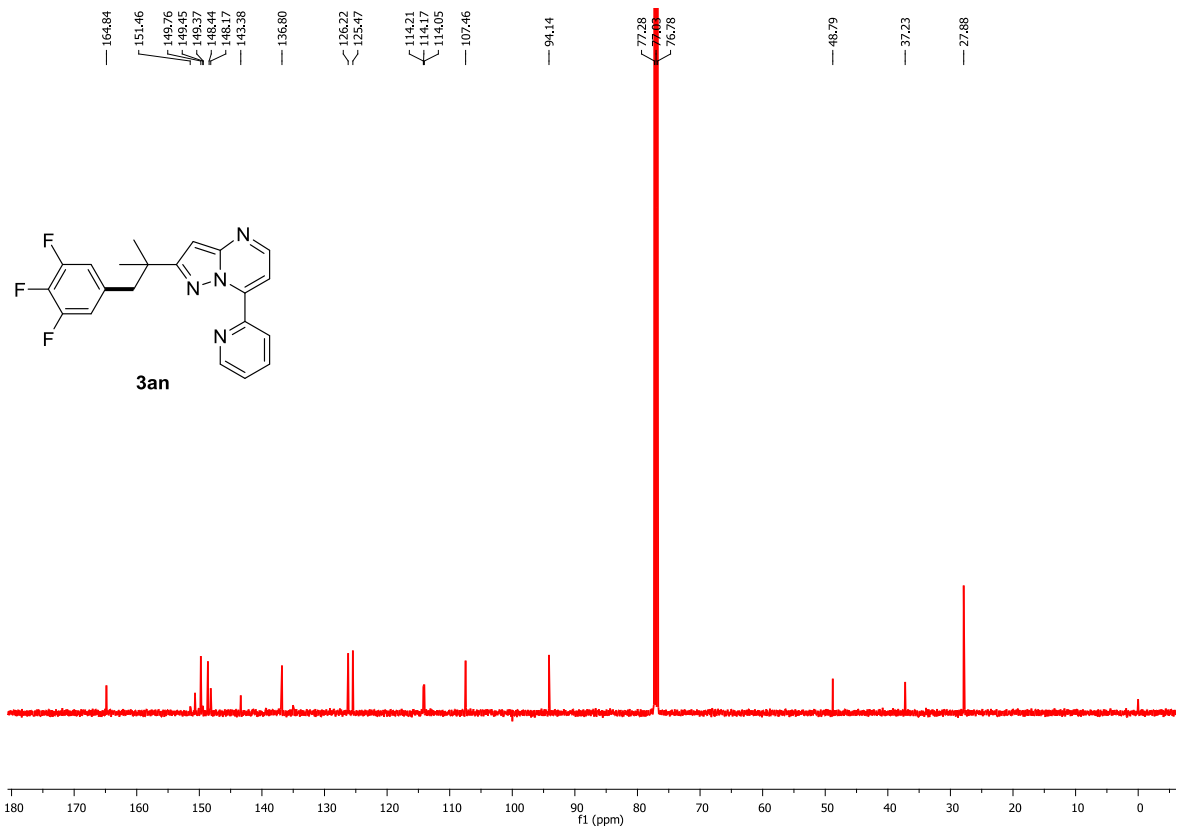
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114.05
107.46
94.14
77.28
77.03
76.78
48.79
37.23
27.88
F
F
F
N
N
N
3an
180
170
160
150
140
130
120
110
100
90
80
70
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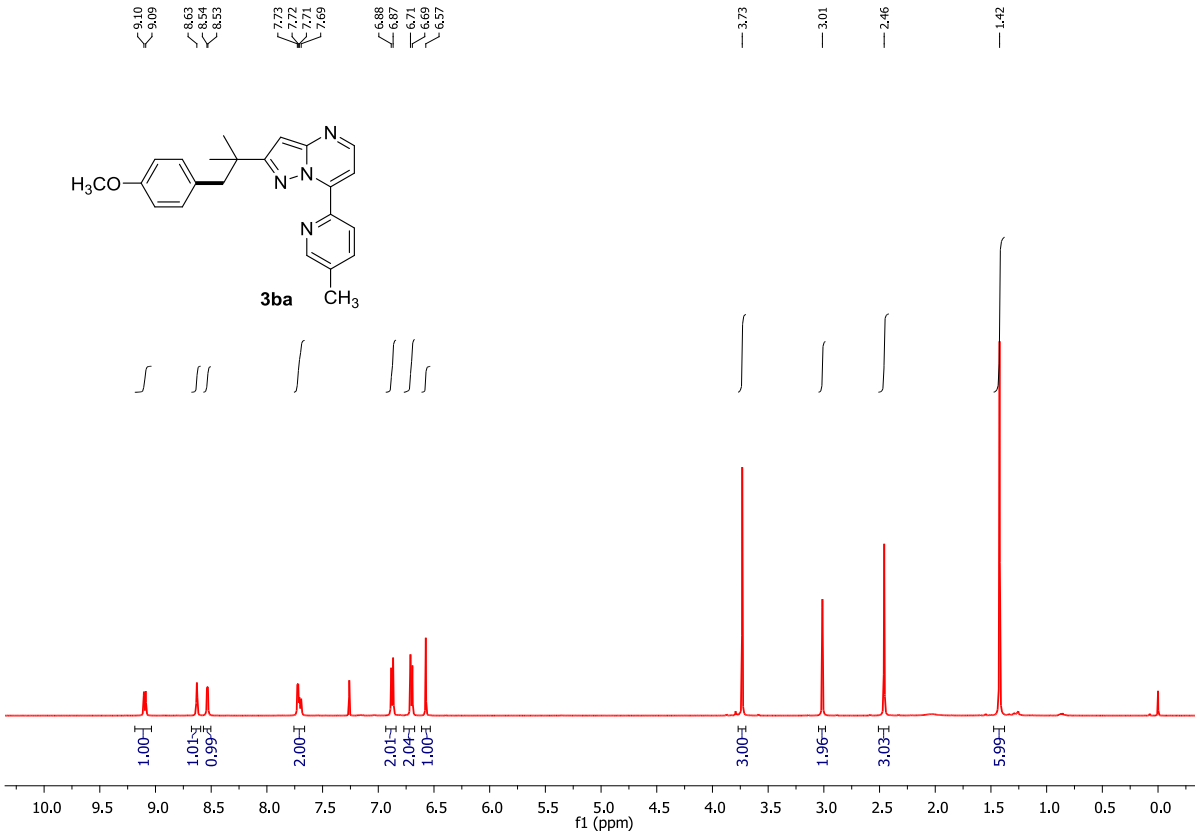
50
40
30
20
10
0
f1 (ppm)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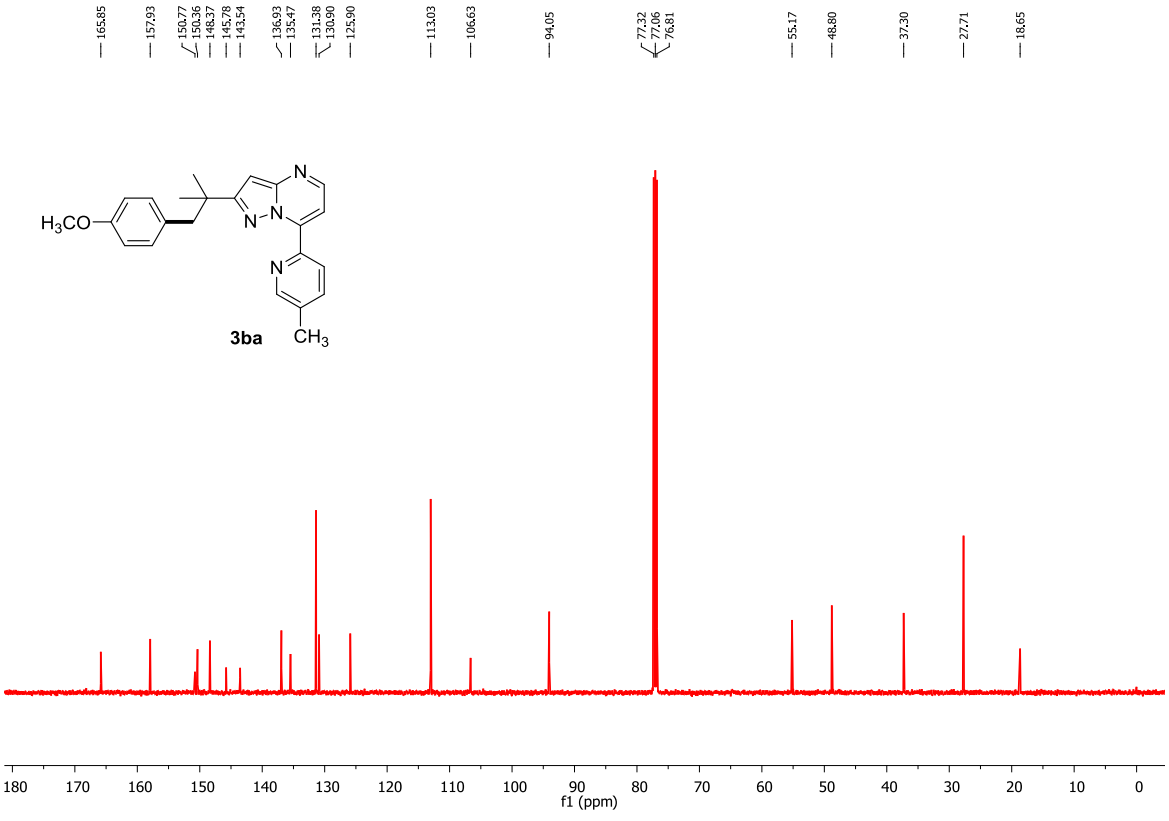
9.09
8.63
8.54
8.53
7.73
7.72
7.71
7.69
6.88
6.87
6.71
6.69
6.57
3.73
3.01
2.46
1.42
H3CO
N
N
N
3ba
CH3
1.00
1.01
0.99
2.00
2.01
2.04
1.00
3.00
1.96
3.03
5.99
f1 (ppm)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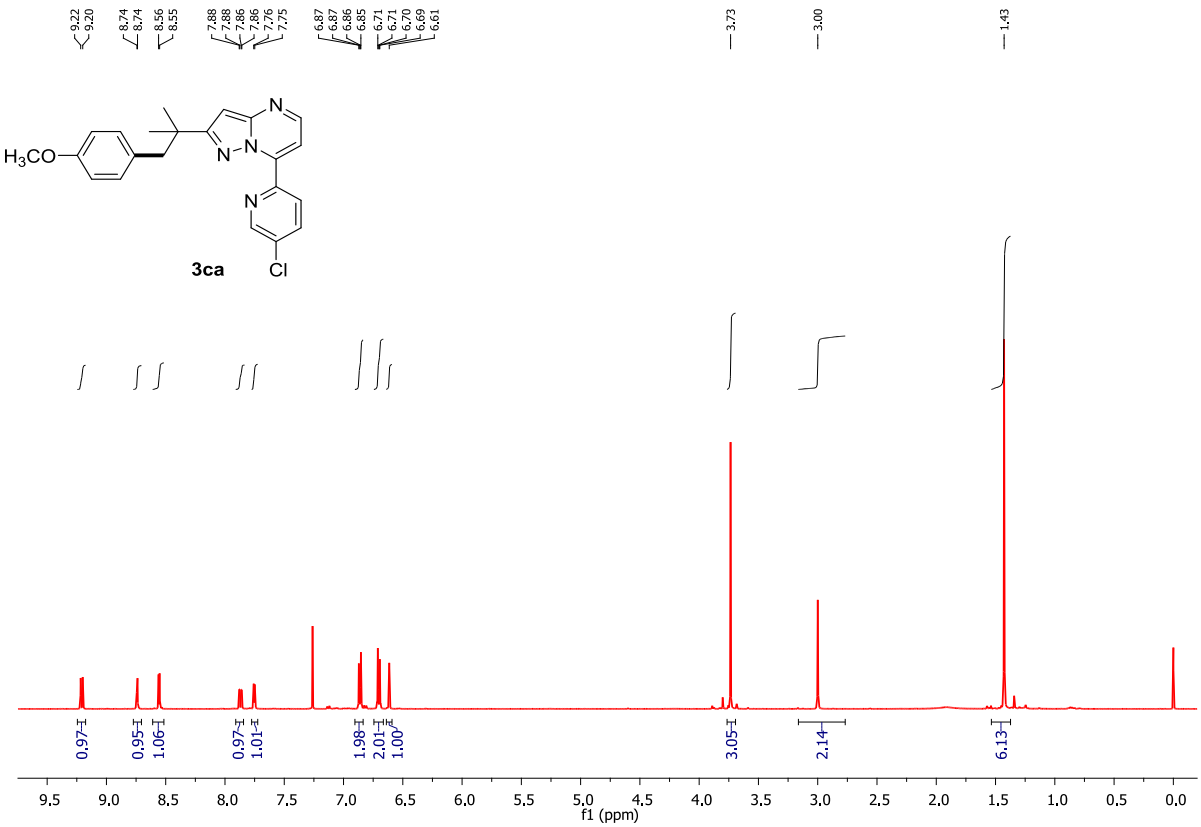
136.93
135.47
131.38
130.90
125.90
113.03
106.63
94.05
77.32
77.06
76.81
55.17
48.80
37.30
27.71
18.65
H3CO
N
N
N
3ba
CH3
f1 (ppm)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8.74
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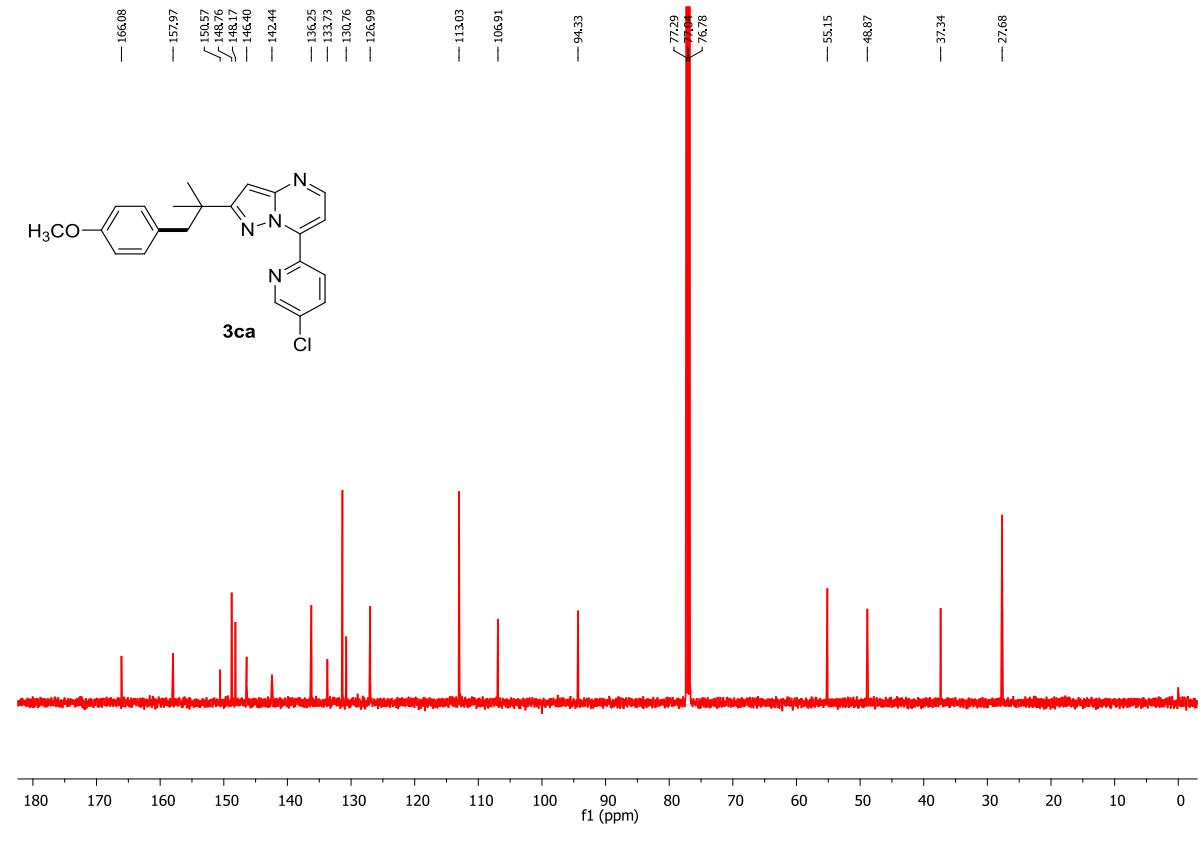
8.55
7.88
7.88
7.86
7.86
7.76
7.75
6.87
6.87
6.86
6.85
6.71
6.71
6.70
6.69
6.61
3.73
3.00
1.43
H3CO
N
N
N
N
Cl
3ca
0.97
0.95
1.06
0.97
1.01
1.98
2.01
1.00
3.05
2.14
6.13
f1 (ppm)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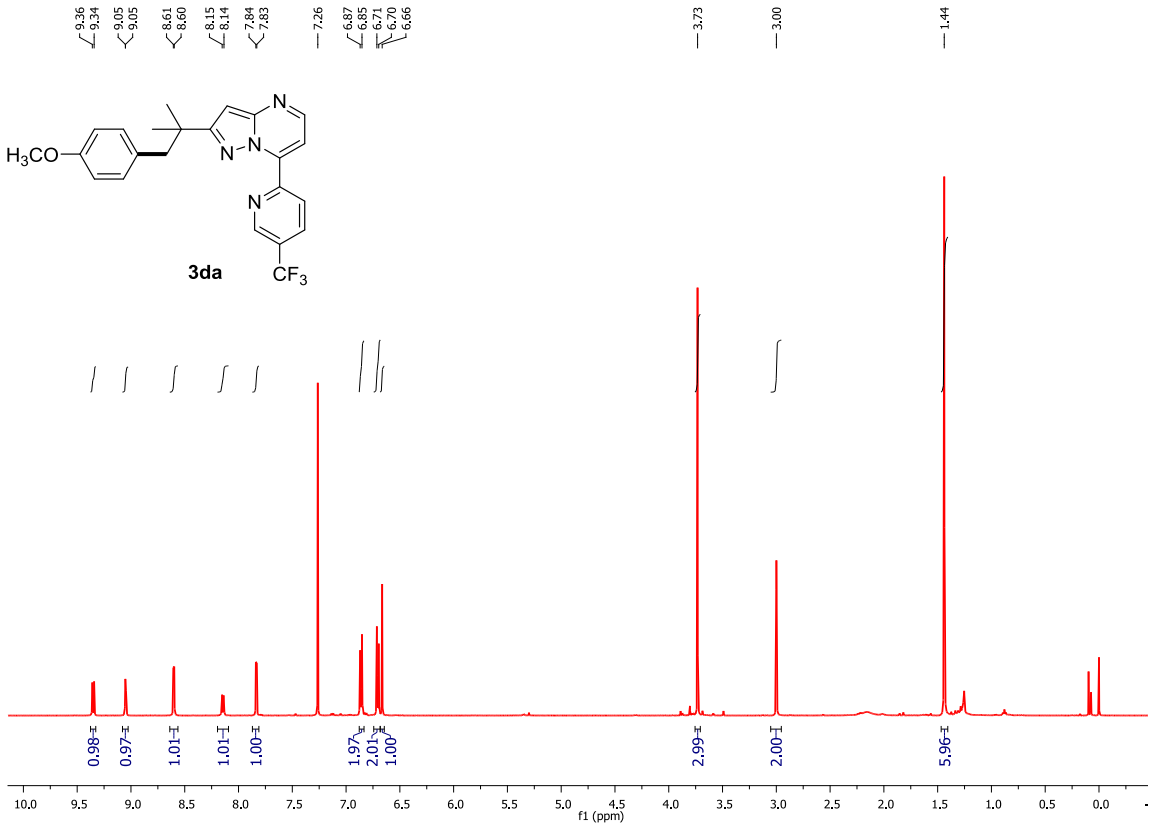
146.40
142.44
136.25
133.73
130.76
126.99
113.03
106.91
94.33
77.29
77.04
76.78
55.15
48.87
37.34
27.68
H3CO
N
N
N
N
Cl
3ca
f1 (ppm)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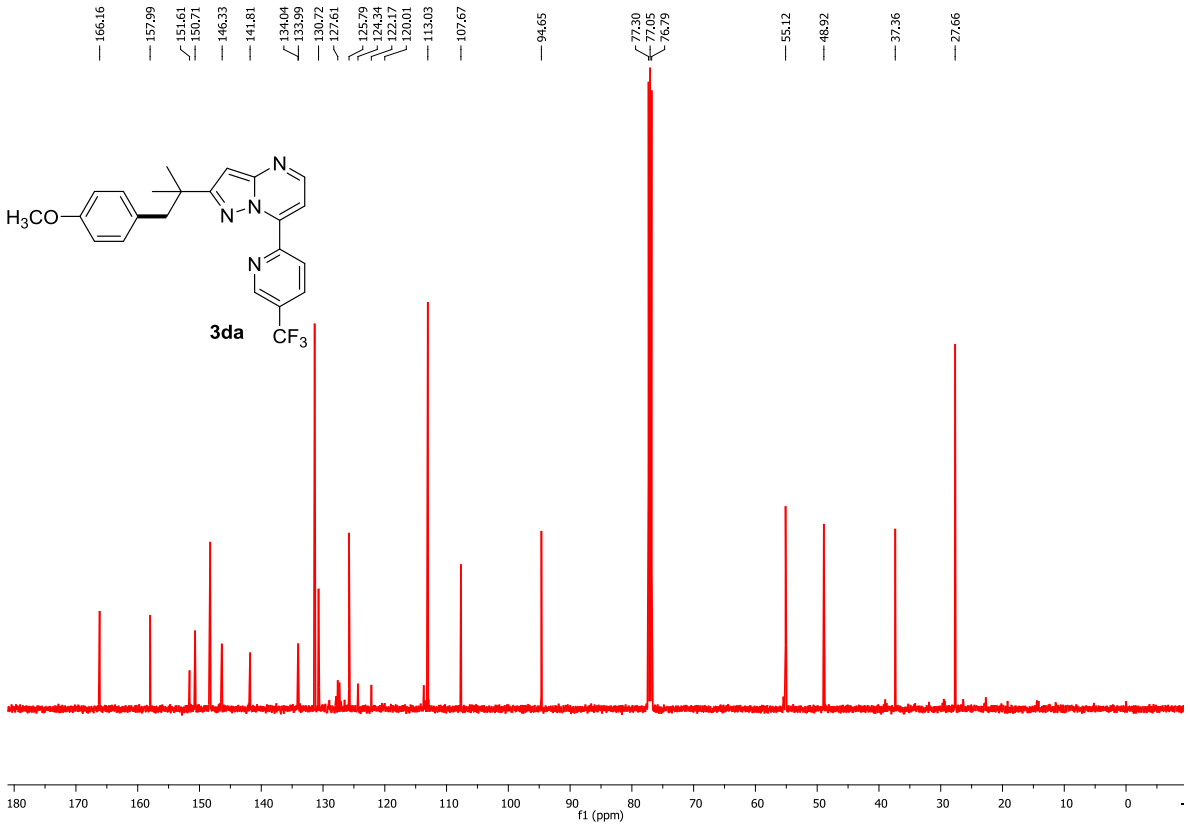
9.34
9.05
9.05
8.61
8.60
8.15
8.14
7.84
7.83
7.26
6.87
6.85
6.71
6.70
6.66
3.73
3.00
1.44
H3CO
N
N
N
3da
CF3
0.98
0.97
1.01
1.01
1.00
1.97
2.01
1.00
2.99
2.00
5.96
f1 (ppm)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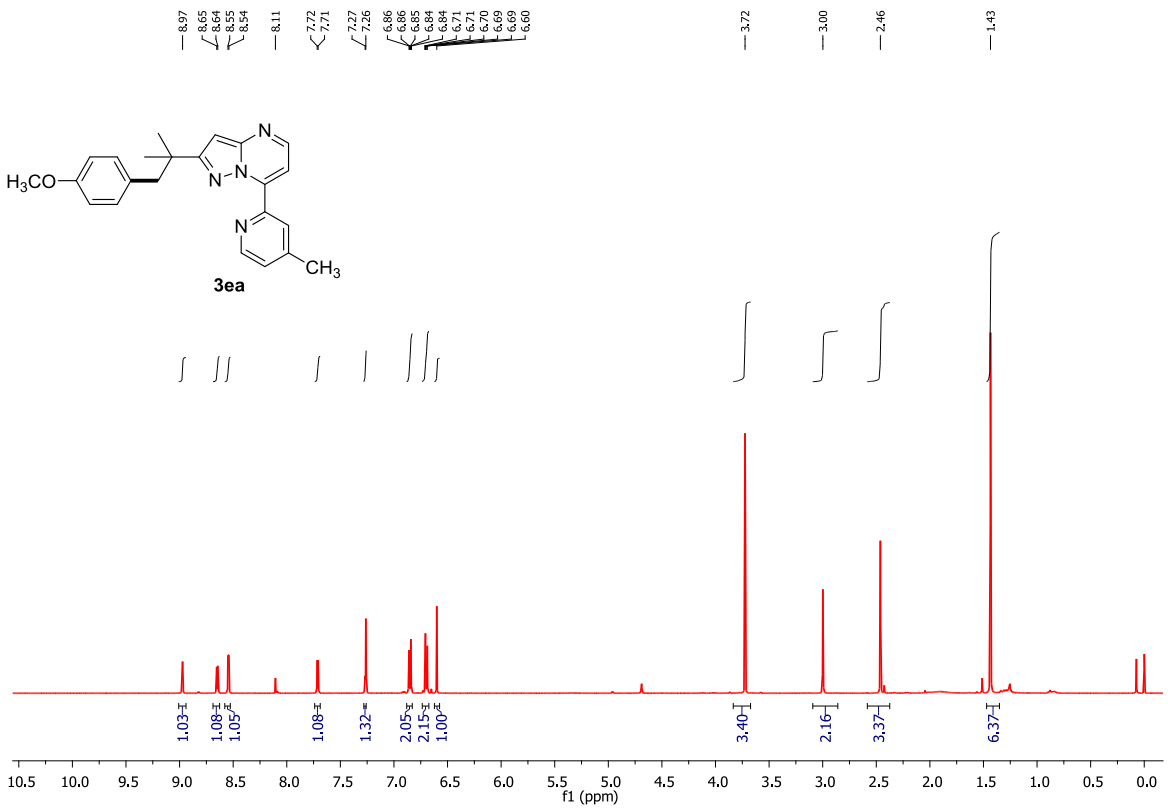
127.61
125.79
124.34
122.17
120.01
113.03
107.67
94.65
77.30
77.05
76.79
55.12
48.92
37.36
27.66
H3CO
N
N
N
3da
CF3
f1 (ppm)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7.71
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7.26
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6.86
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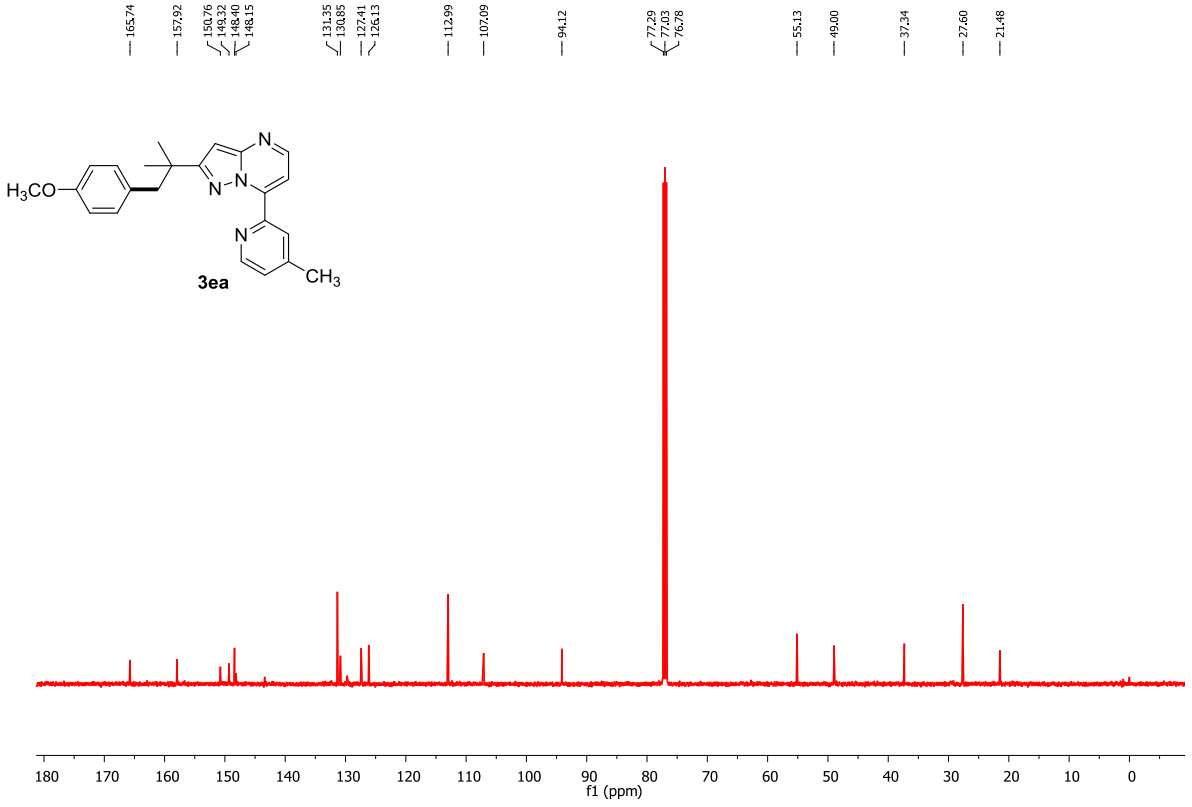
6.84
6.84
6.71
6.71
6.70
6.69
6.69
6.60
3.72
3.00
2.46
1.43
H3CO
N
N
N
CH3
3ea
1.03
1.08
1.05
1.08
1.32
2.05
2.15
1.00
3.40
2.16
3.37
6.37
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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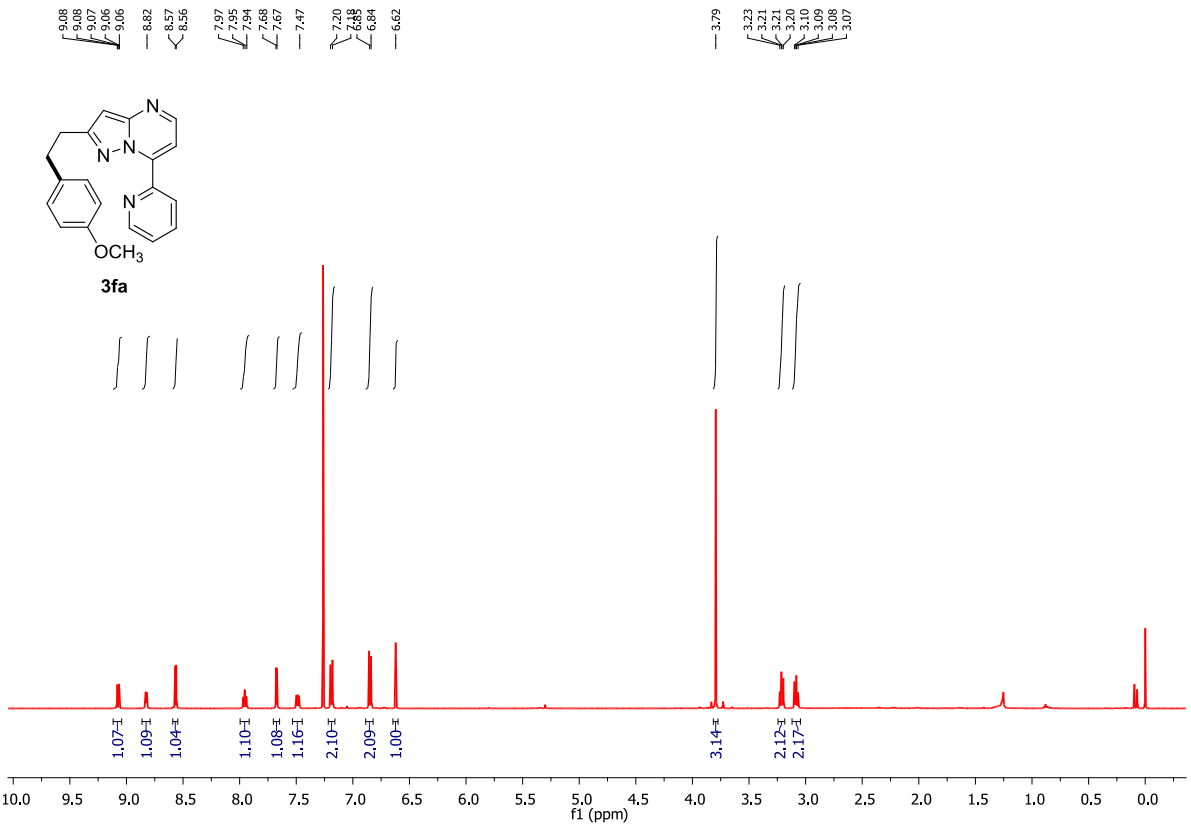
149.32
148.40
148.15
131.35
130.85
127.41
126.13
112.99
107.09
94.12
77.29
77.03
76.78
55.13
49.00
37.34
27.60
21.48
H3CO
N
N
N
CH3
3ea
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


9.08
9.08
9.07
9.06
9.06
8.82
8.57
8.56
7.97
7.95
7.94
7.68
7.67
7.47
7.20
6.84
6.62
3.79
3.23
3.21
3.21
3.20
3.10
3.09
3.08
3.07
N
N
N
N
OCH3
3fa
1.07
1.09
1.04
1.10
1.08
1.16
2.10
2.09
1.00
3.14
2.12
2.17
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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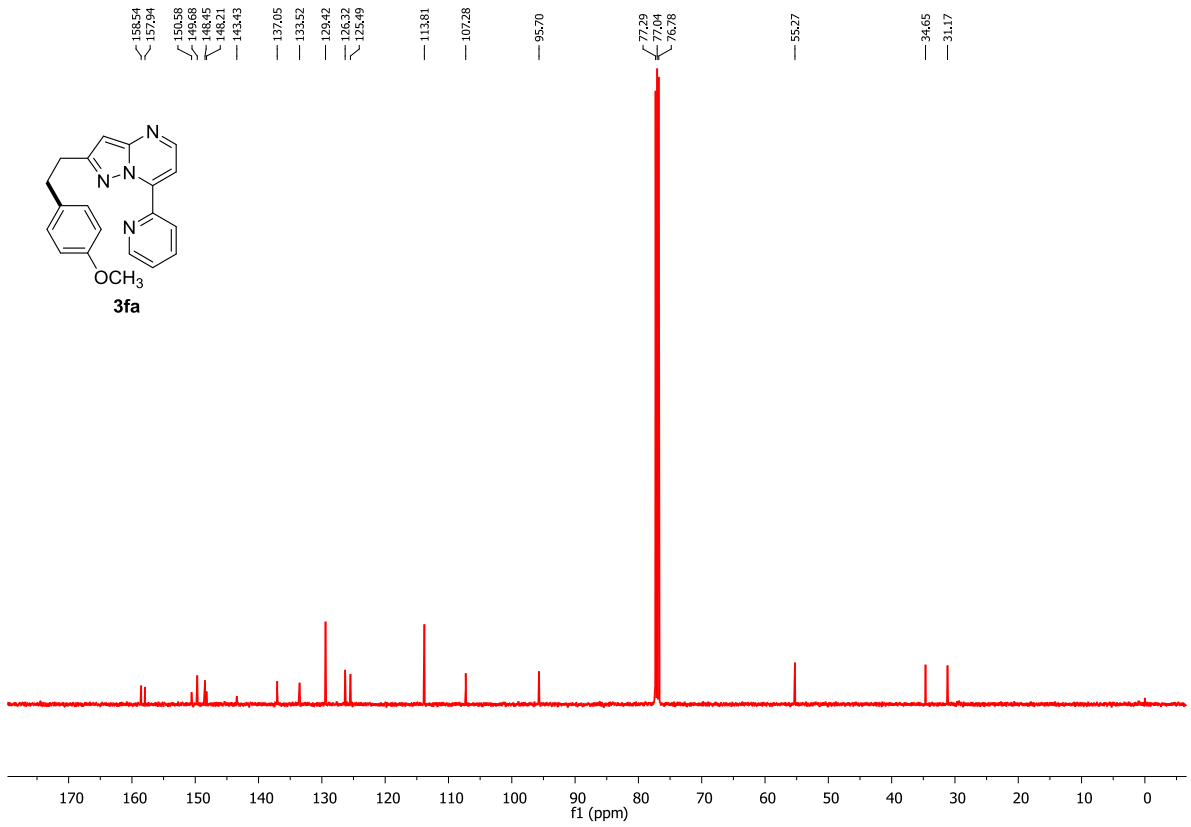
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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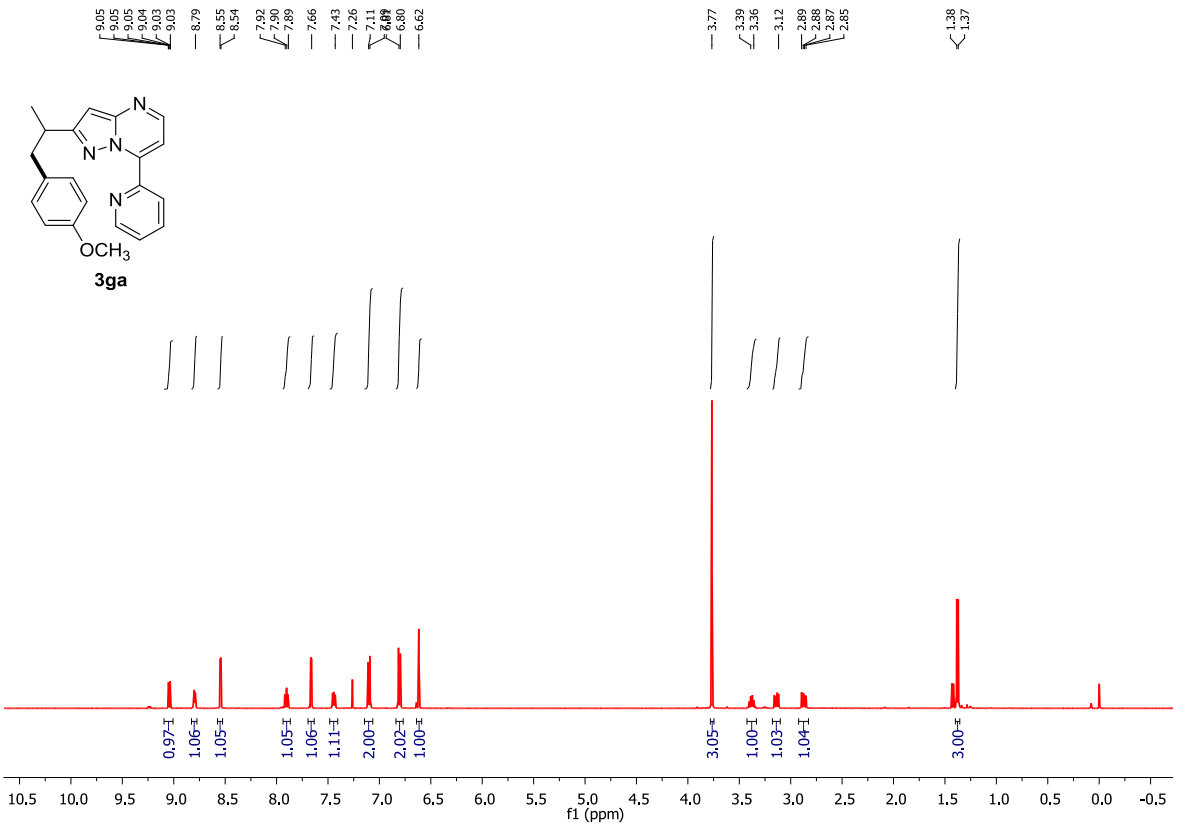
157.94
150.58
149.68
148.45
148.21
143.43
137.05
133.52
129.42
126.32
125.49
113.81
107.28
95.70
77.29
77.04
76.78
55.27
34.65
31.17
N
N
N
N
OCH3
3fa
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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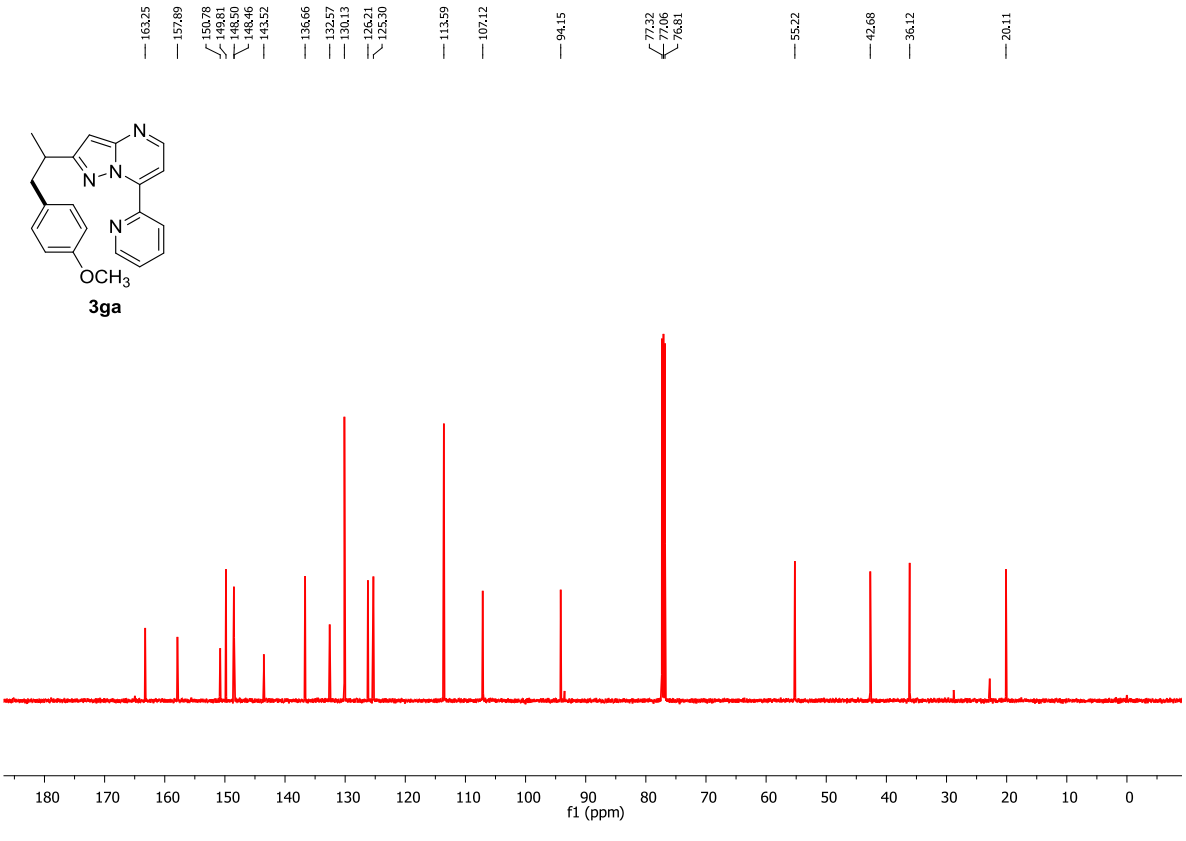
9.05
9.05
9.04
9.03
9.03
8.79
8.55
8.54
7.92
7.90
7.89
7.66
7.43
7.26
7.11
6.80
6.62
3.77
3.39
3.36
3.12
2.89
2.88
2.87
2.85
1.38
1.37
N
N
N
N
OCH3
0.97
1.06
1.05
1.05
1.06
1.11
2.00
2.02
1.00
3.05
1.00
1.03
1.04
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

3ga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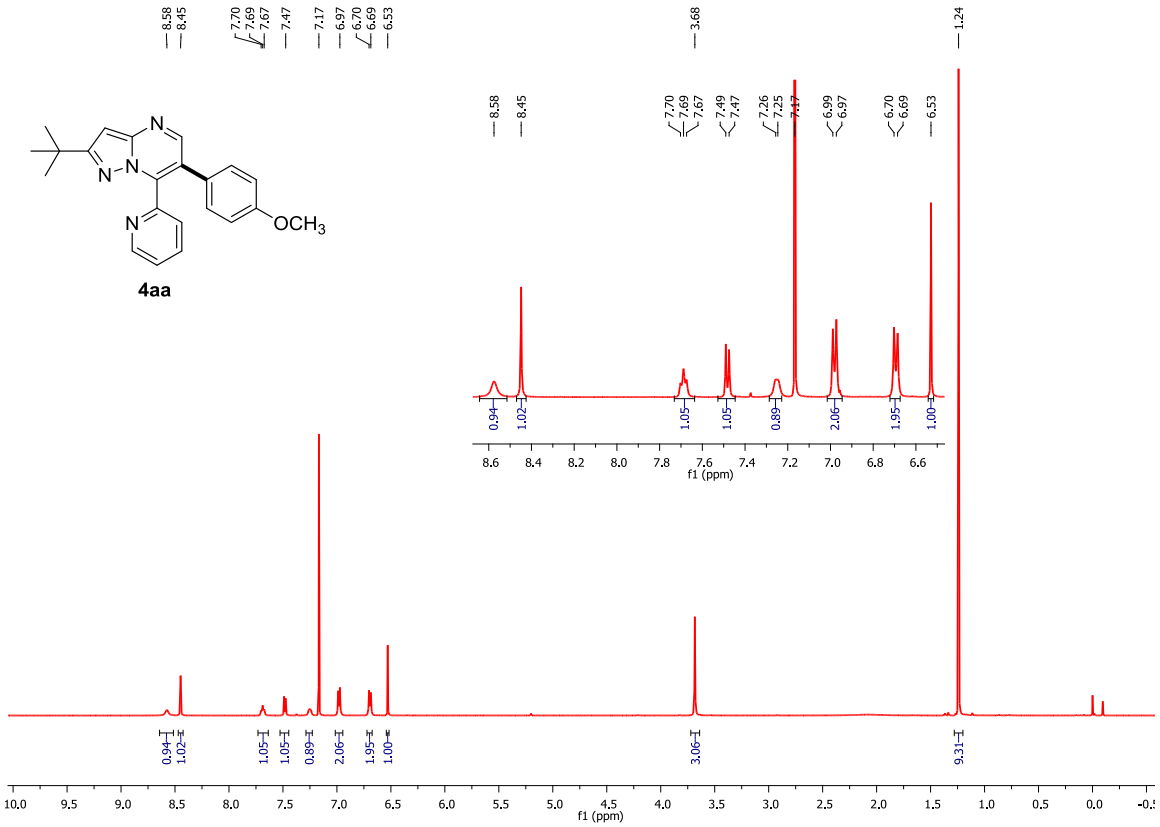
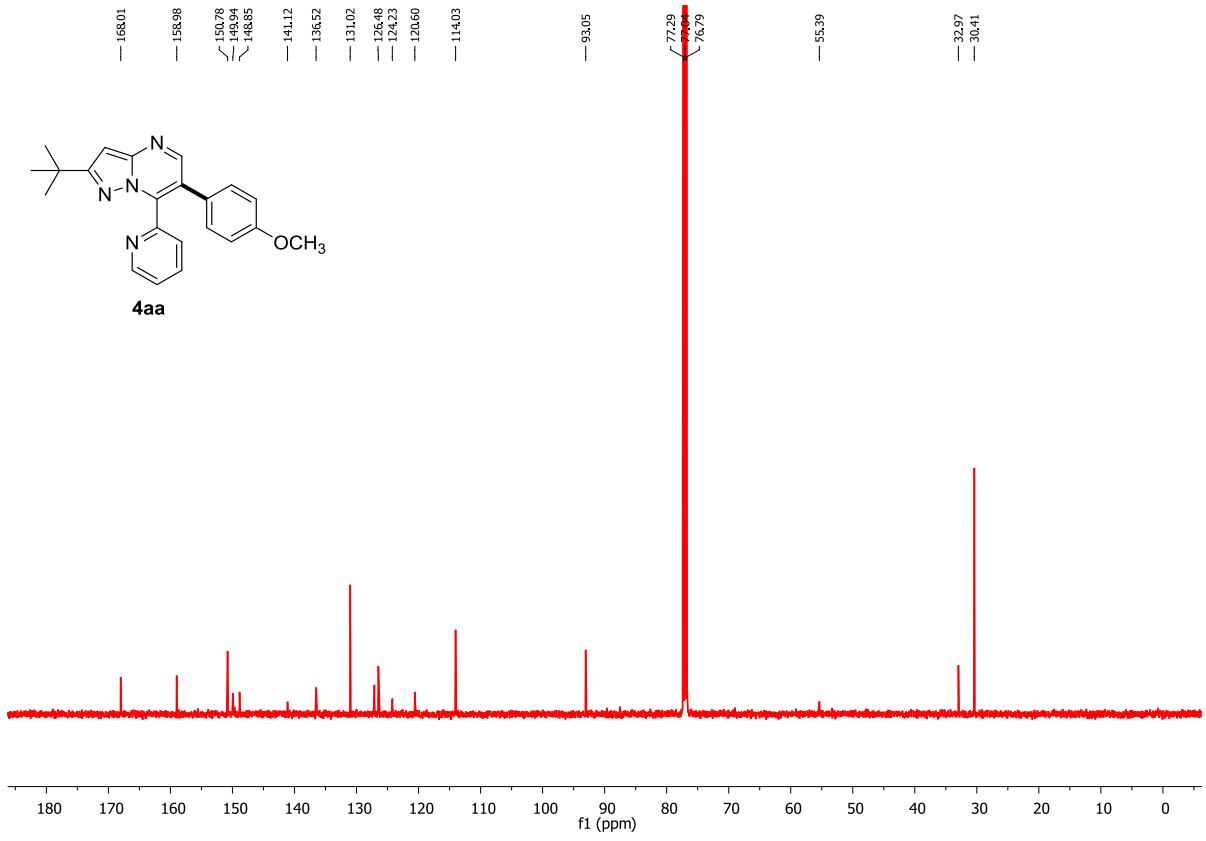
148.50
148.46
143.52
136.66
132.57
130.13
126.21
125.30
113.59
107.12
94.15
77.32
77.06
76.81
55.22
42.68
36.12
20.11
N
N
N
N
OCH3
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

3ga


8.58
8.45
7.70
7.69
7.67
7.47
7.17
6.97
6.70
6.69
6.53
3.68
1.24
OCH3
4aa
f1 (ppm)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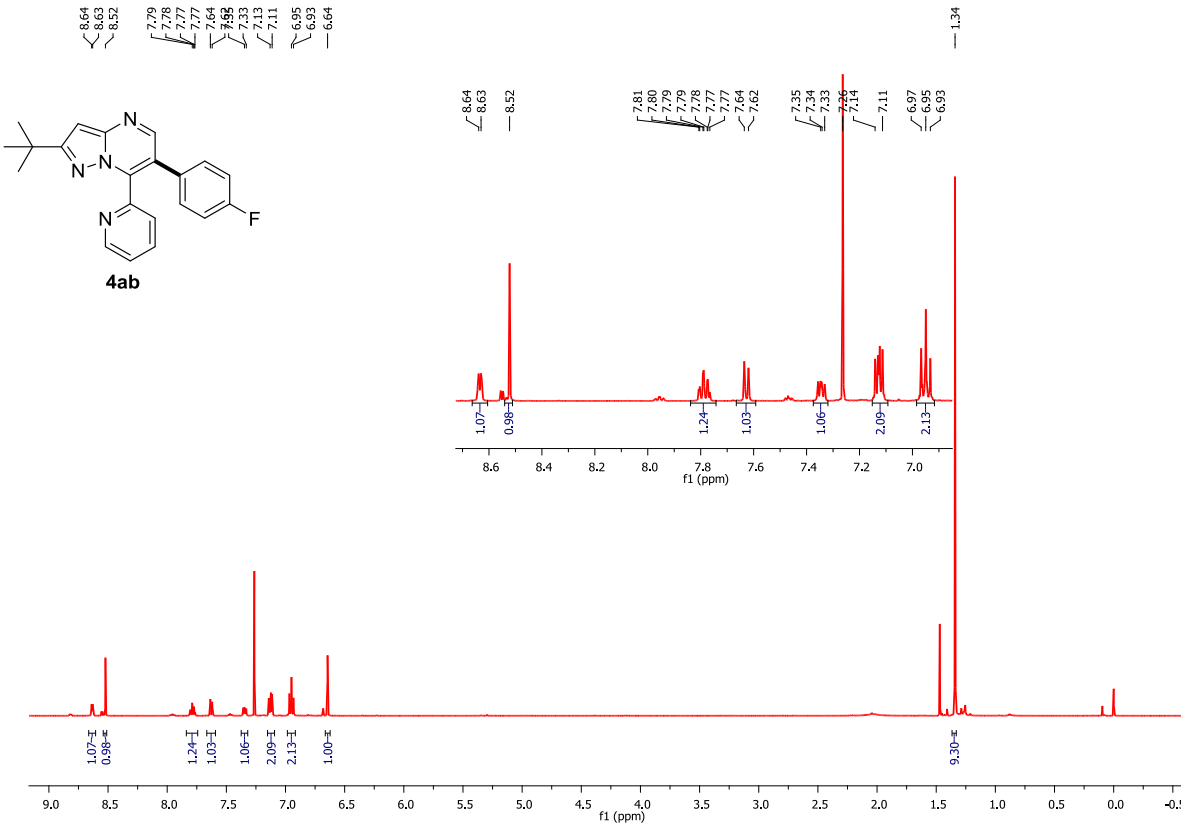
148.85
141.12
136.52
131.02
126.48
124.23
120.60
114.03
93.05
77.29
77.04
76.79
55.39
32.97
30.41
OCH3
4aa
f1 (ppm)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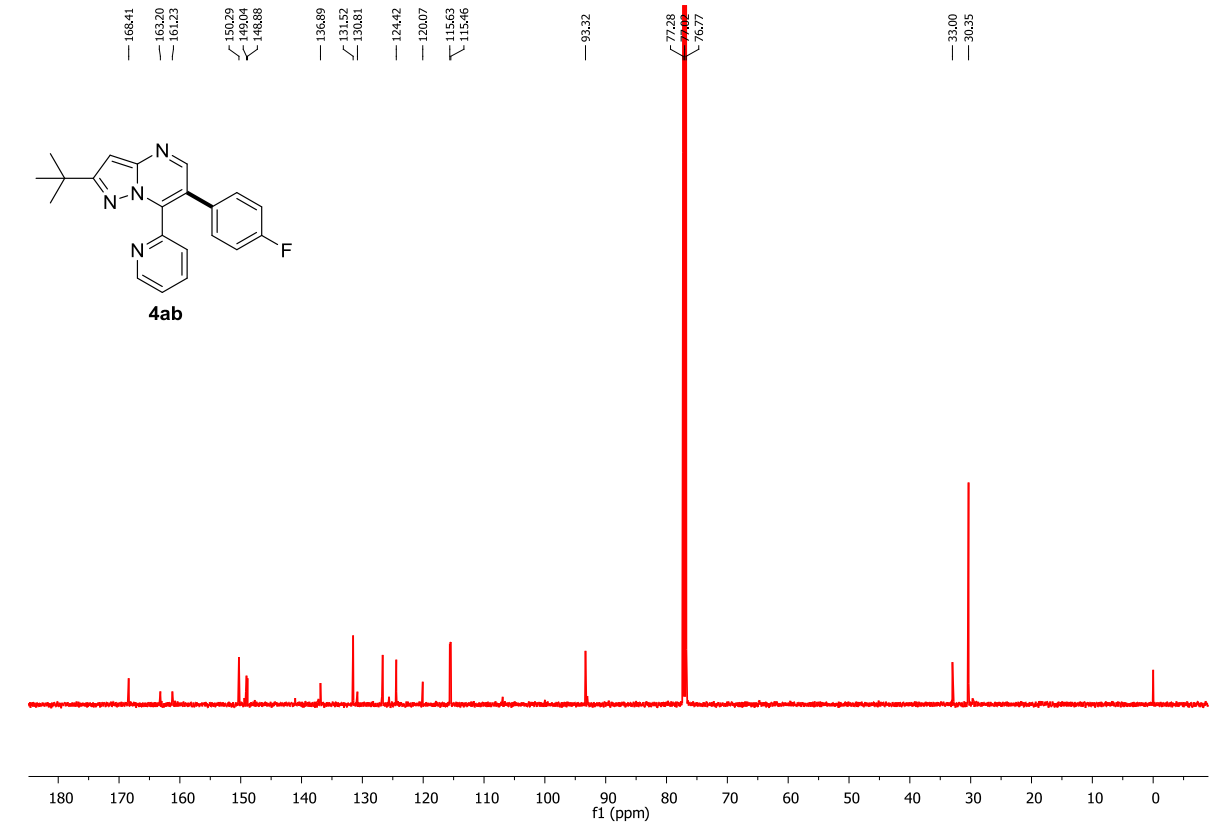
8.63
8.52
7.79
7.78
7.77
7.77
7.64
7.33
7.13
7.11
6.95
6.93
6.64
1.34
F
4ab
f1 (ppm)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161.23
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148.88
136.89
131.52
130.81
124.42
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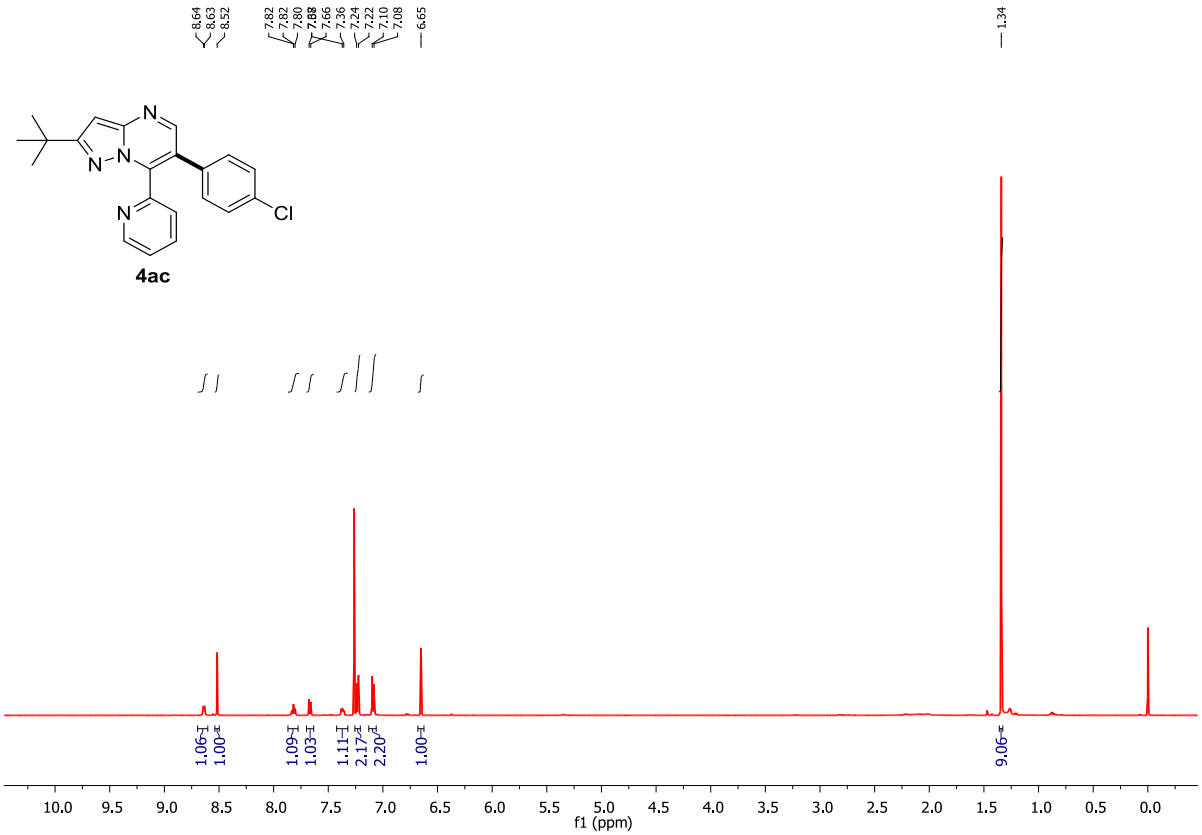
115.46
93.32
77.28
77.02
76.77
33.00
30.35
F
4ab
f1 (ppm)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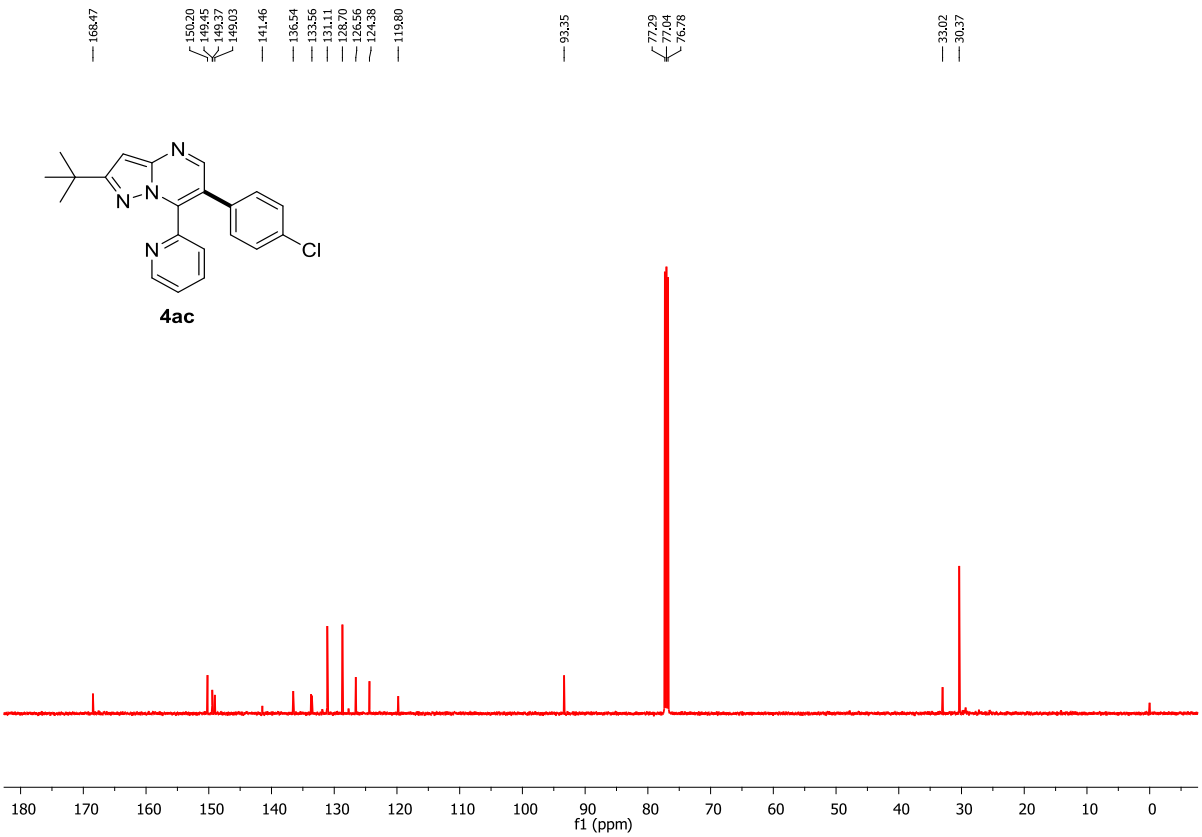
7.82
7.82
7.80
7.66
7.36
7.24
7.22
7.10
7.08
6.65
1.34
N
N
N
Cl
4ac
1.06
1.00
1.09
1.03
1.11
2.17
2.20
1.00
9.06
f1 (ppm)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149.37
149.03
141.46
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133.56
131.11
128.70
126.56
124.38
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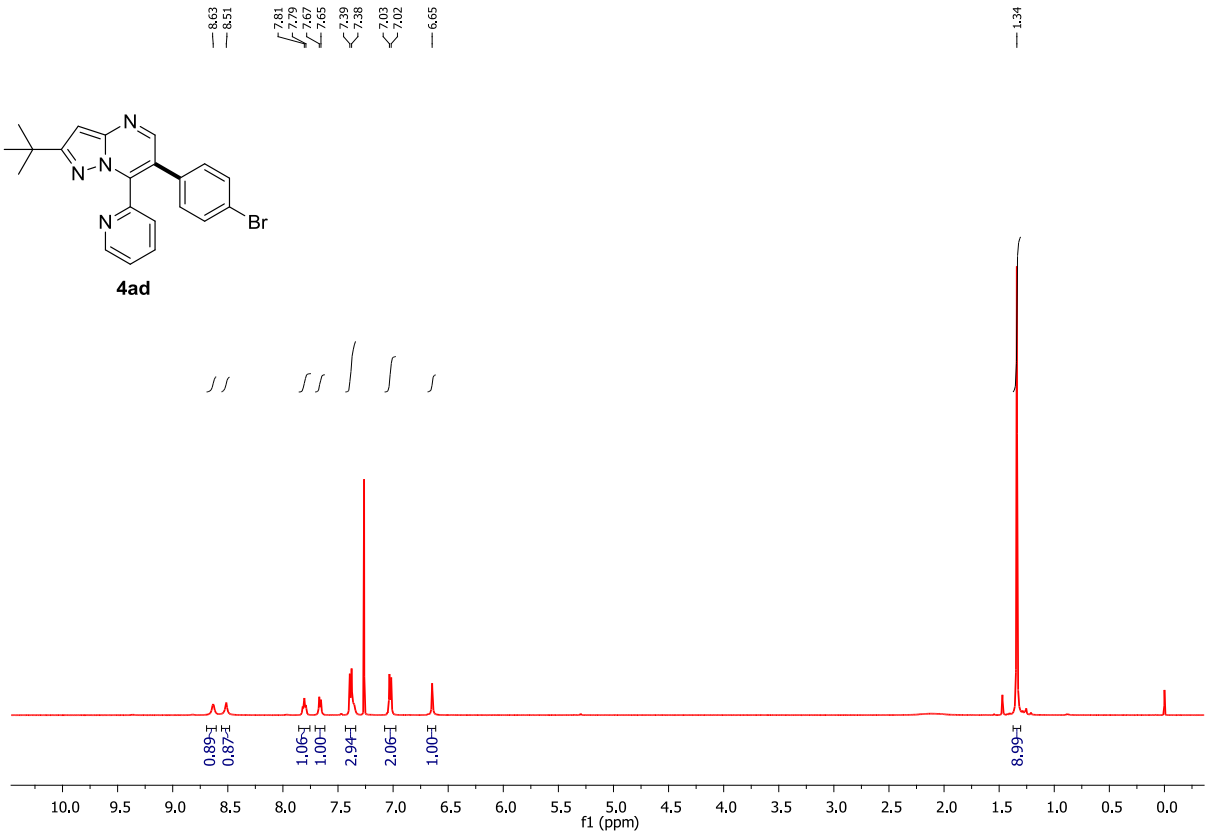
93.35
77.29
77.04
76.78
33.02
30.37
N
N
N
Cl
4ac
f1 (ppm)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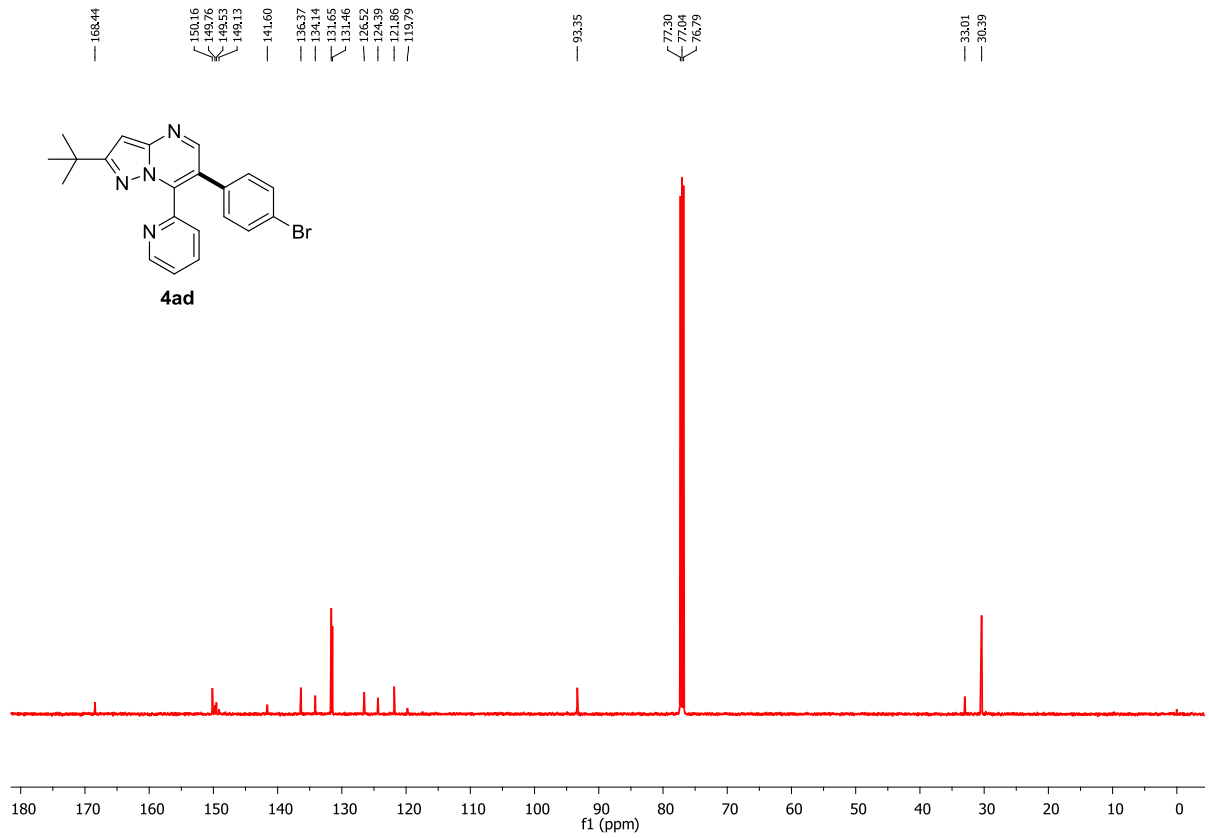
7.79
7.67
7.65
7.39
7.38
7.03
7.02
6.65
1.34
Br
4ad
0.89
0.87
1.06
1.00
2.94
2.06
1.00
8.99
f1 (ppm)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134.14
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131.46
126.52
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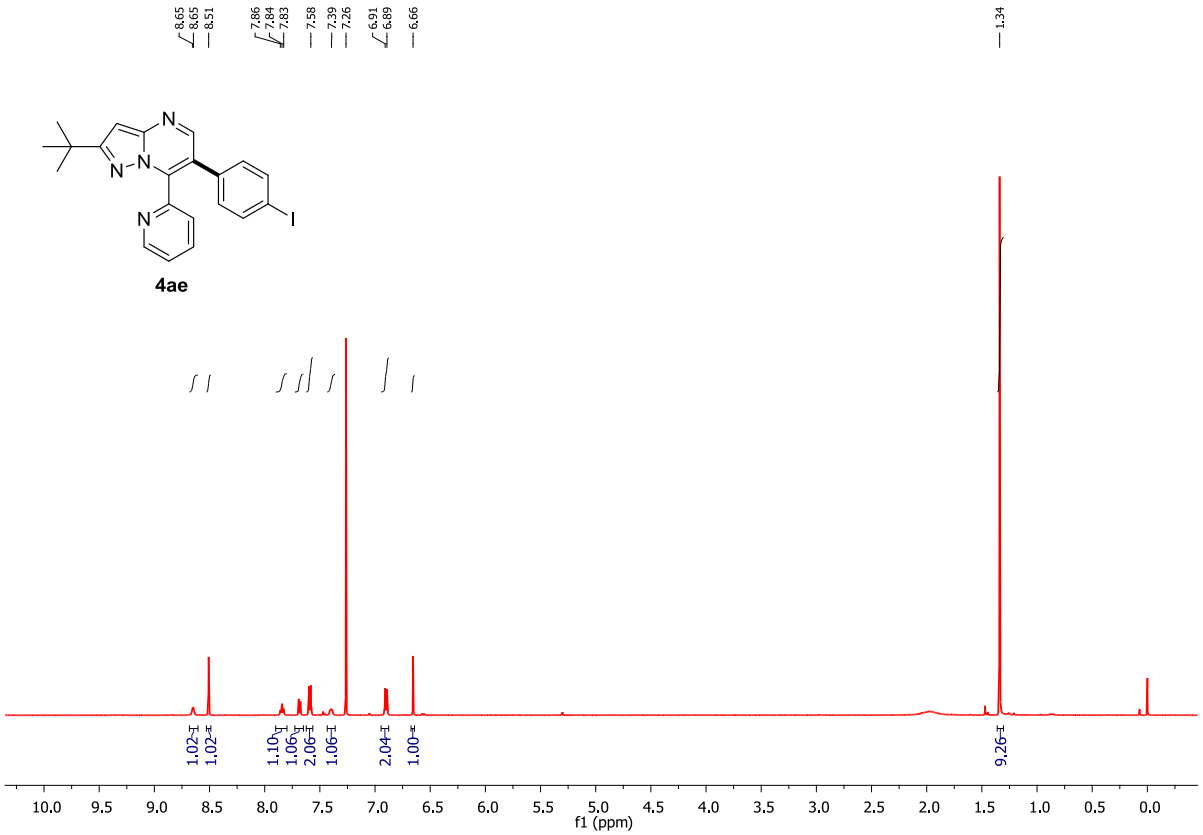
119.79
93.35
77.30
77.04
76.79
33.01
30.39
Br
4ad
f1 (ppm)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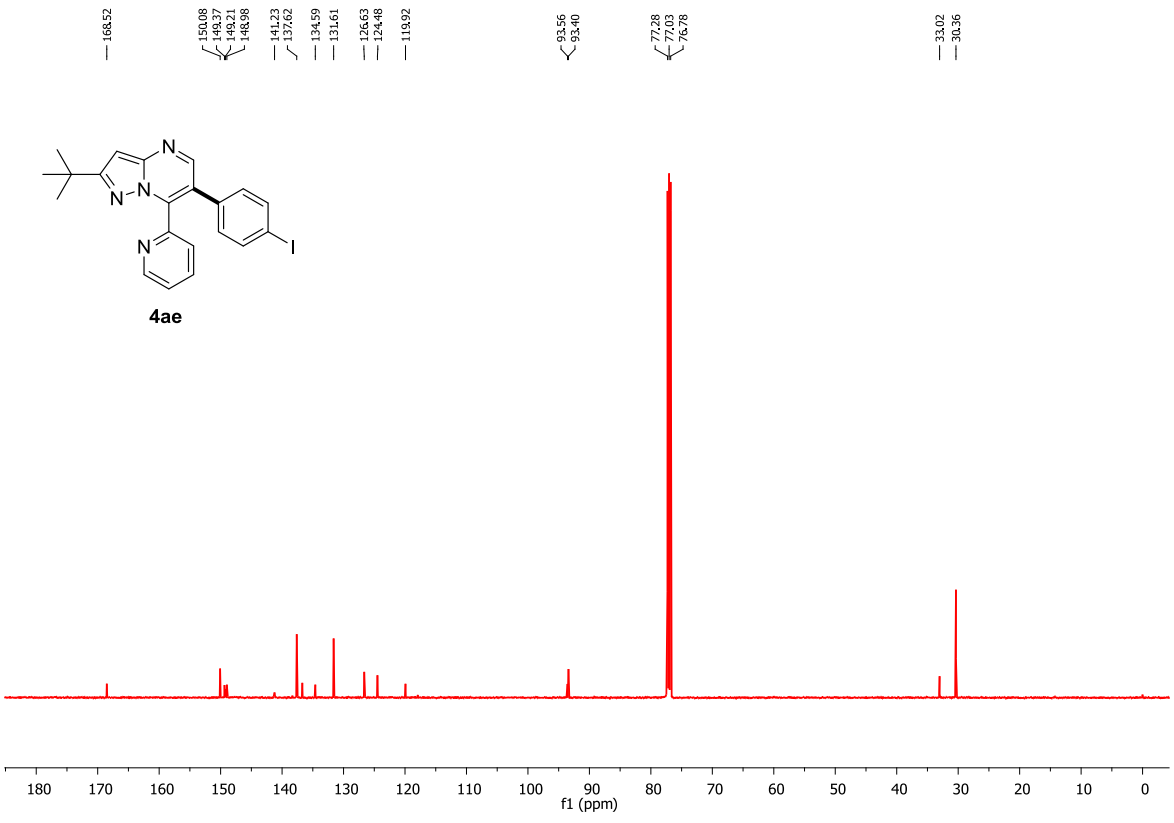
8.65
8.51
7.86
7.84
7.83
7.58
7.39
7.26
6.91
6.89
6.66
1.34
4ae
1.02
1.02
1.10
1.06
2.06
1.06
2.04
1.00
9.26
f1 (ppm)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141.23
137.62
134.59
131.61
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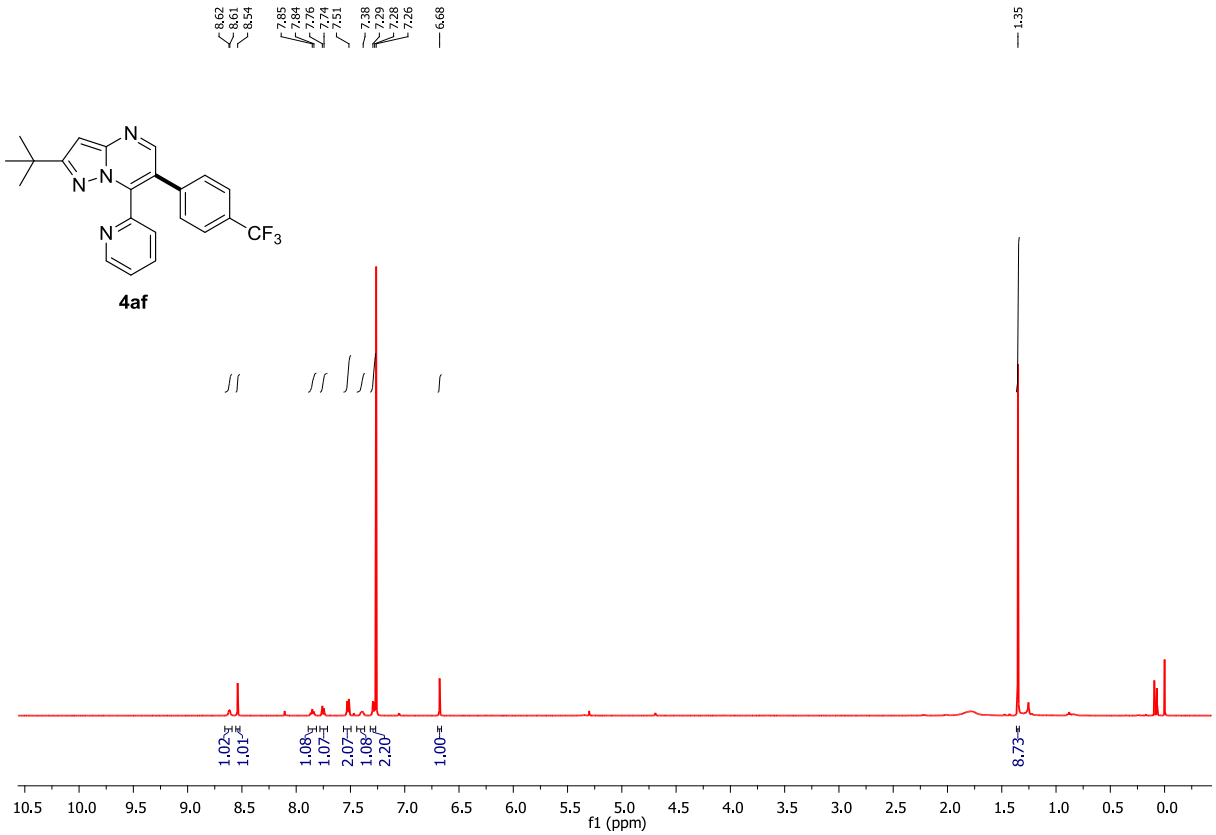
93.56
93.40
77.28
77.03
76.78
33.02
30.36
4ae
f1 (ppm)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7.76
7.74
7.51
7.38
7.29
7.28
7.26
6.68
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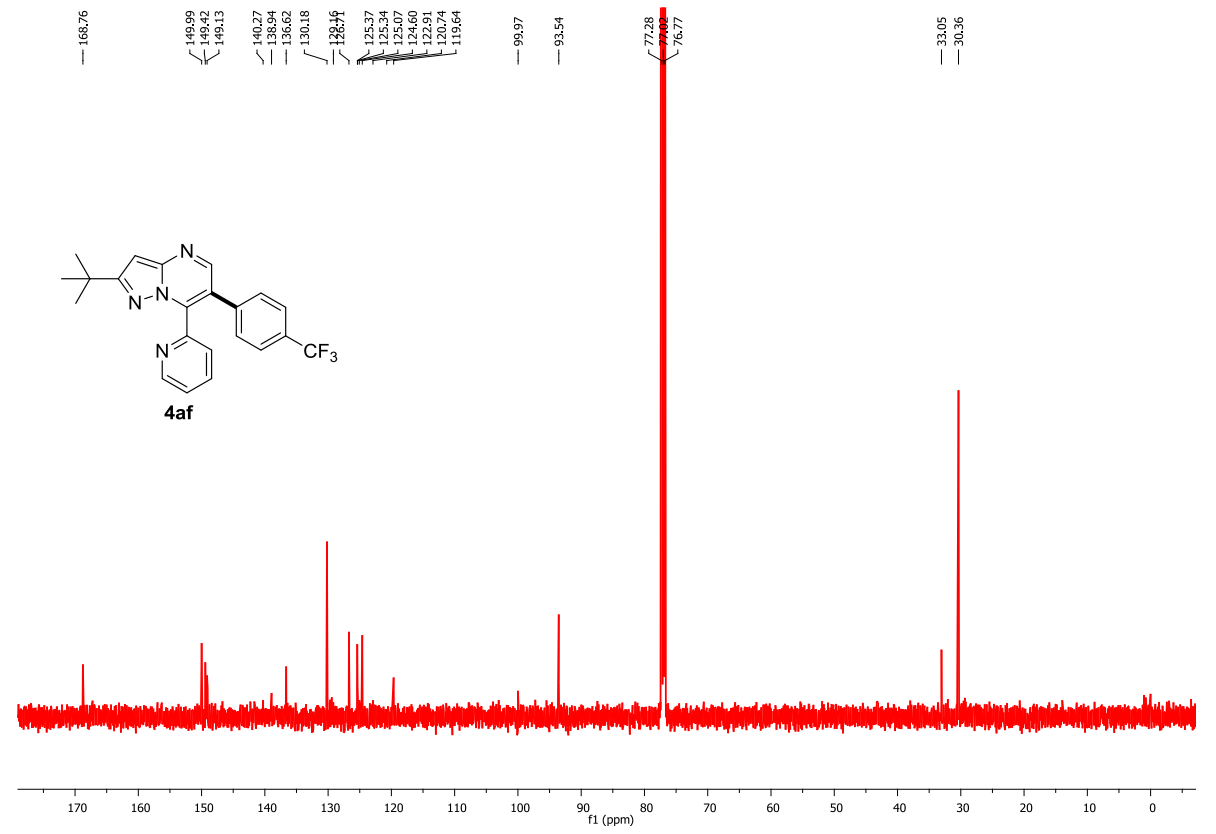
1.01
1.08
1.07
2.07
1.08
2.20
1.00
8.73
f1 (ppm)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149.13
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138.94
136.62
130.18
125.37
125.34
125.07
124.60
122.91
120.74
119.64
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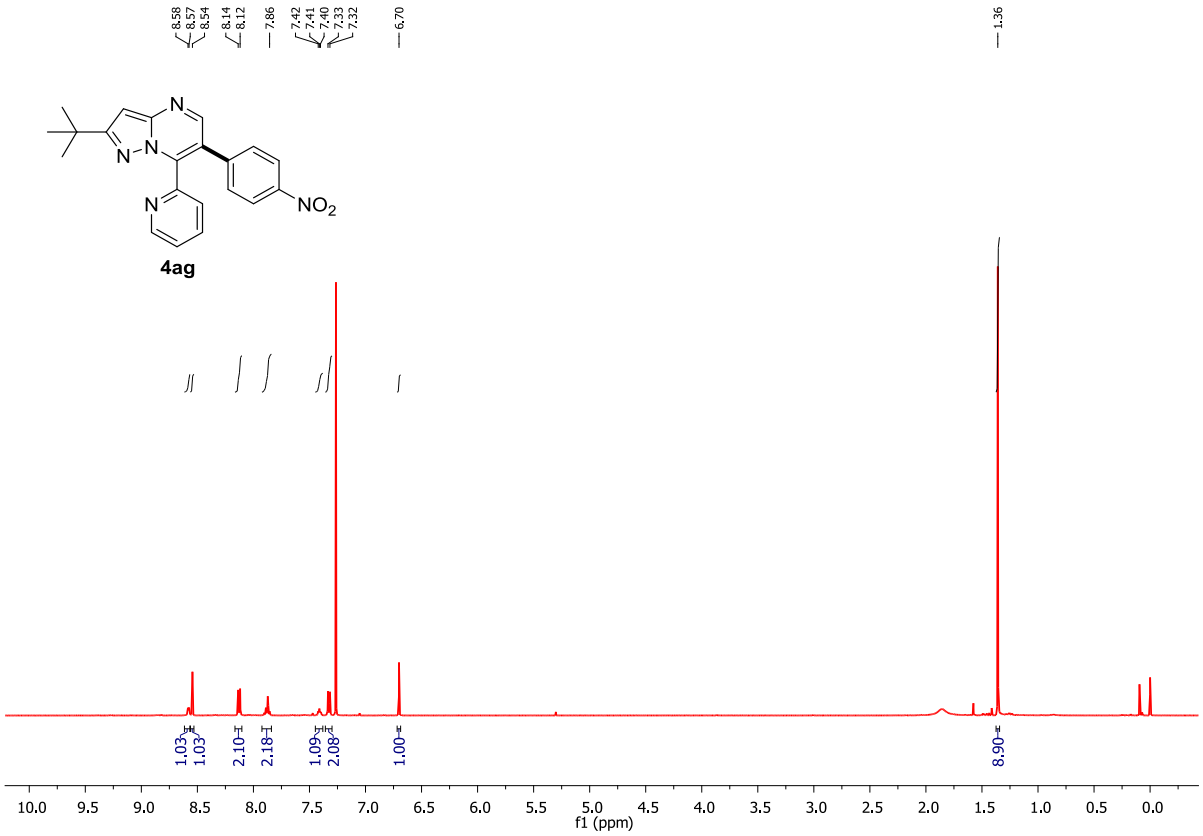
93.54
77.28
77.02
76.77
33.05
30.36
4af
f1 (ppm)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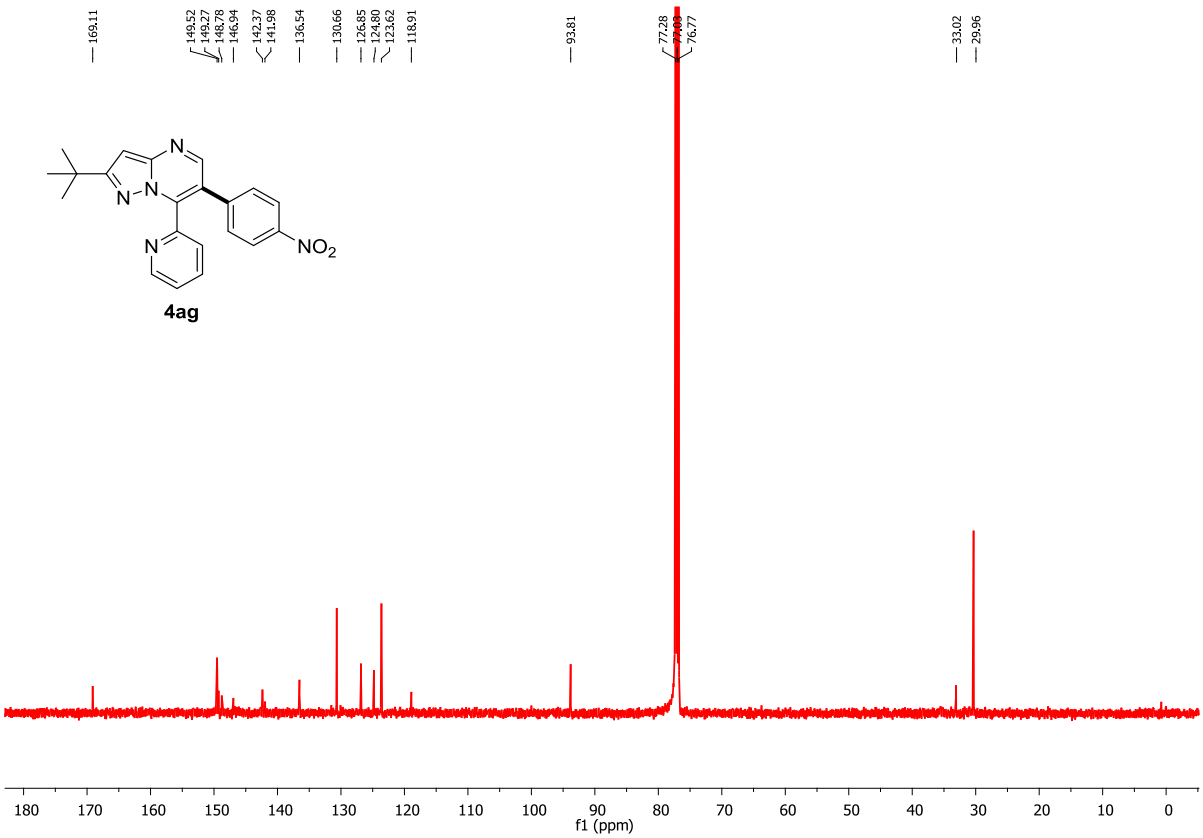
7.42
7.41
7.40
7.33
7.32
6.70
1.36
N
N
N
NO2
4ag
1.03
1.03
2.10
2.18
1.09
2.08
1.00
8.90
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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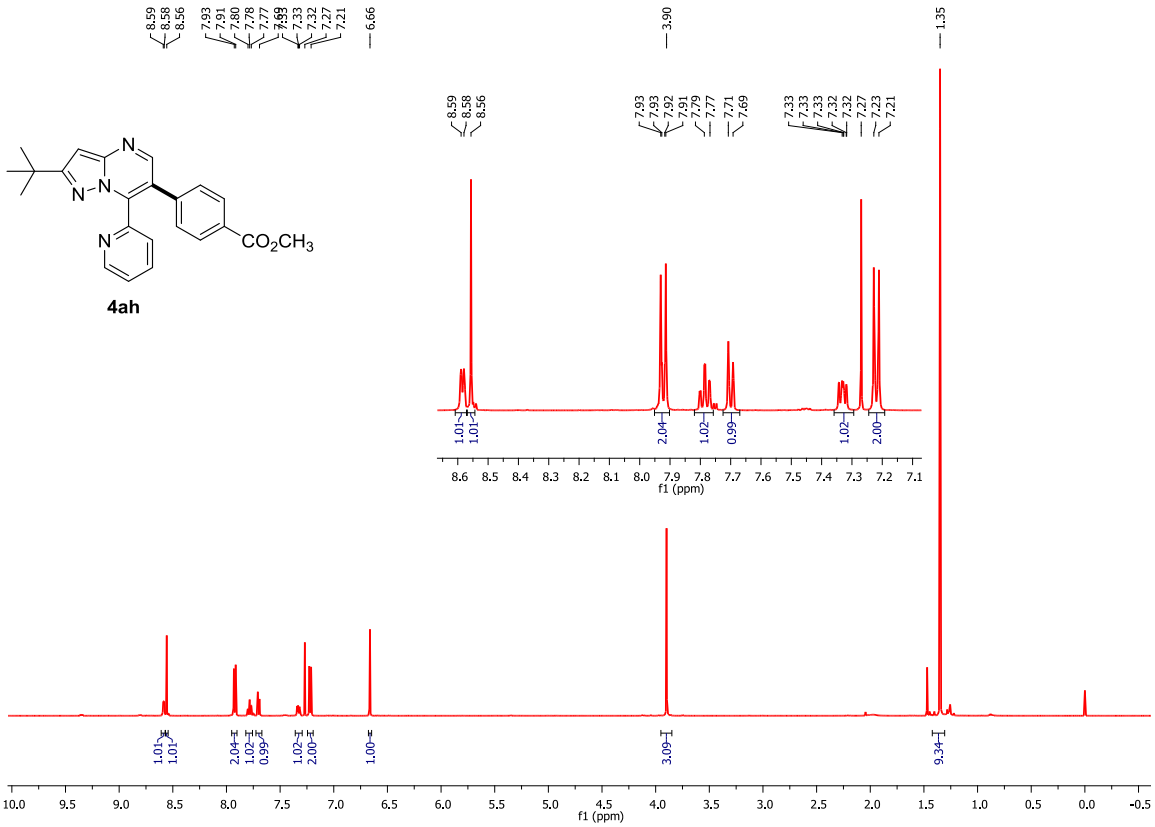
142.37
141.98
136.54
130.66
126.85
124.80
123.62
118.91
93.81
77.28
77.03
76.77
33.02
29.96
N
N
N
NO2
4ag
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.91
7.80
7.78
7.77
7.33
7.32
7.27
7.21
6.66
3.90
1.35
N
N
N
CO2CH3
4ah
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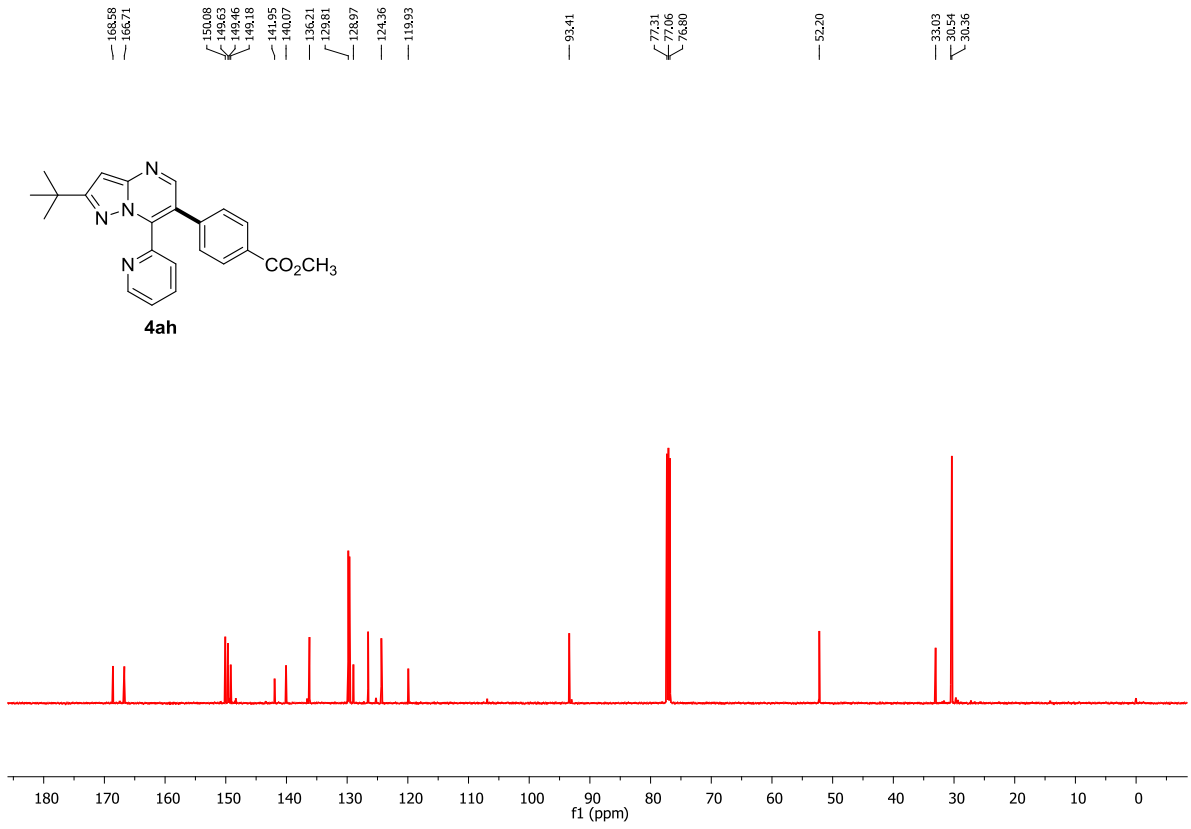
1.01
2.04
1.02
0.99
1.02
2.00
1.00
3.09
9.34
f1 (ppm)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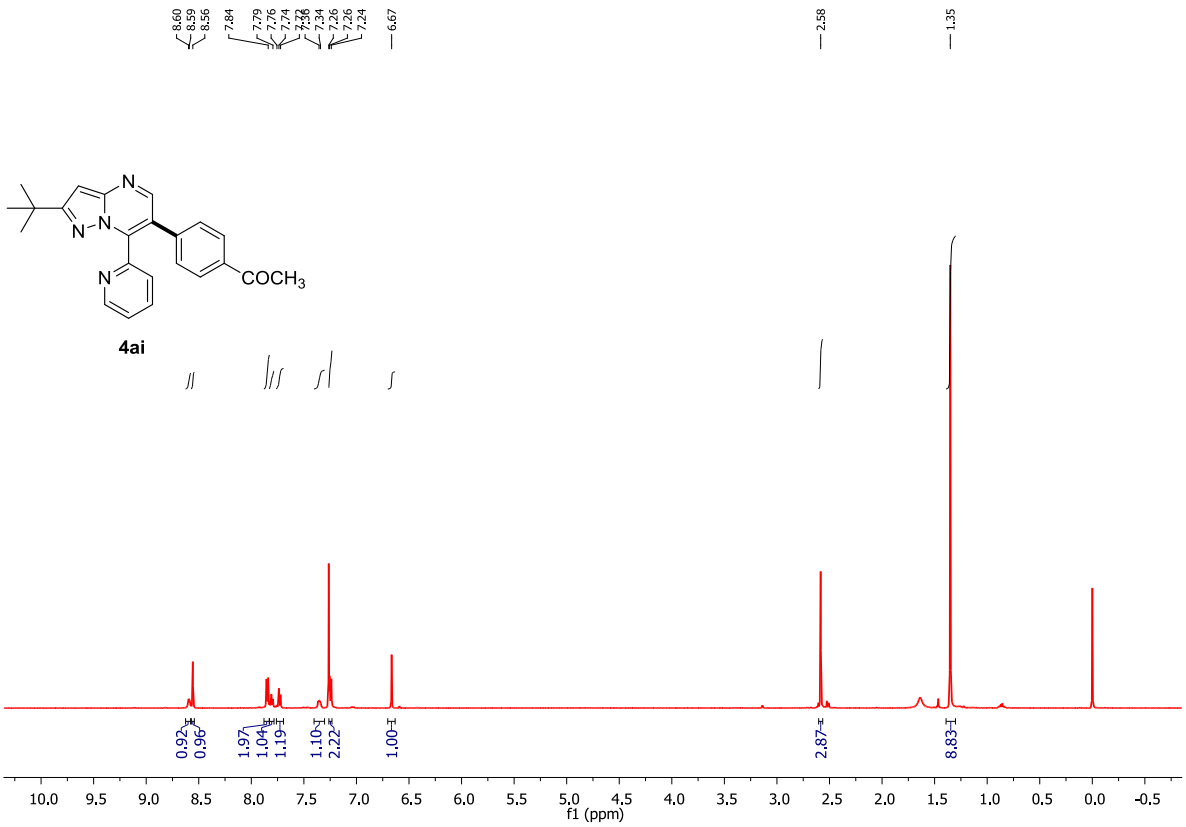
149.63
149.46
149.18
141.95
140.07
136.21
129.81
128.97
124.36
119.93
93.41
77.31
77.06
76.80
52.20
33.03
30.54
30.36
N
N
N
CO2CH3
4ah
f1 (ppm)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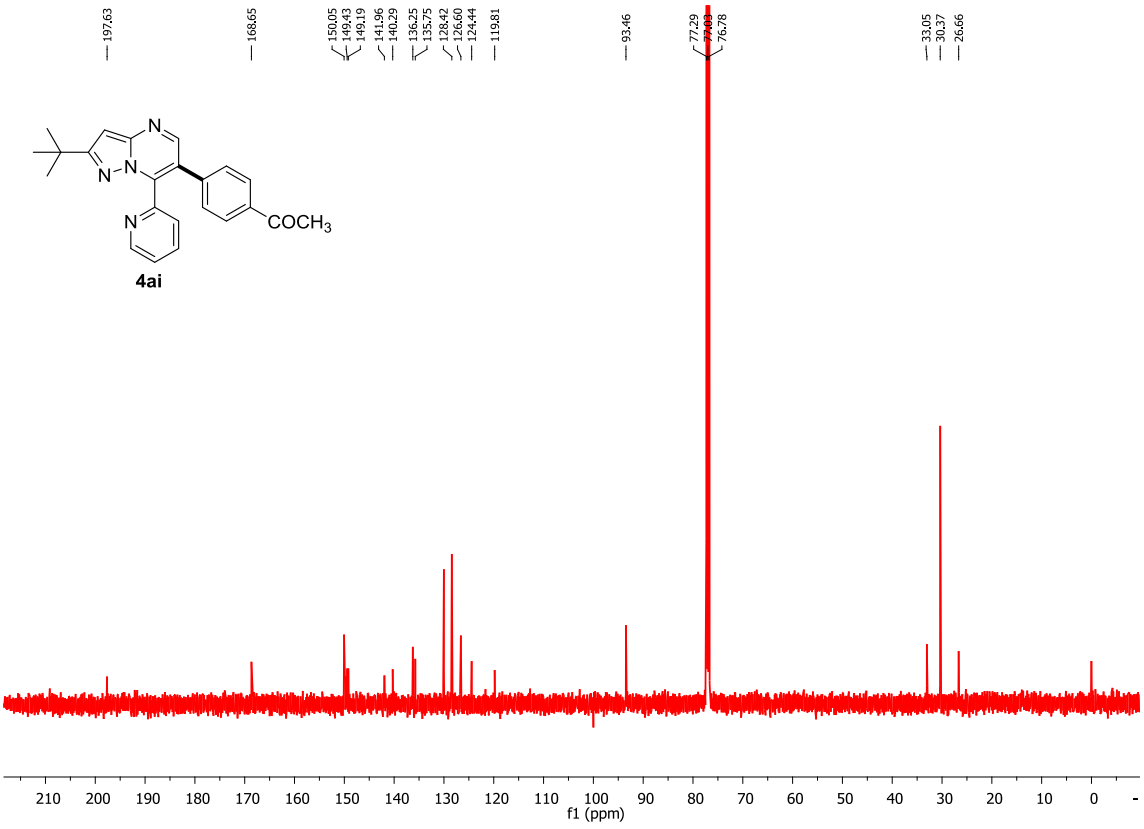
8.59
8.56
7.84
7.79
7.76
7.74
7.32
7.30
7.34
7.26
7.26
7.24
6.67
2.58
1.35
COCH3
4ai
0.92
0.96
1.97
1.04
1.19
1.10
2.22
1.00
2.87
8.83
f1 (ppm)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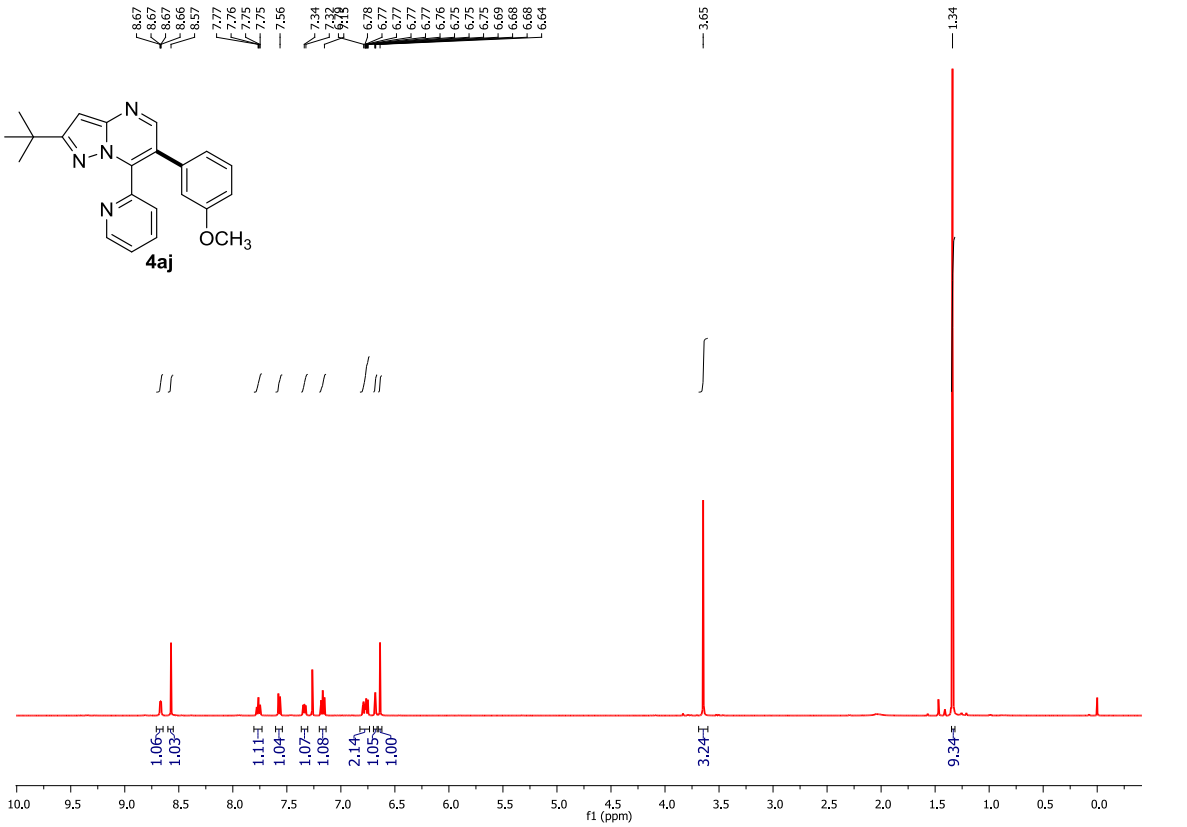
149.19
141.96
140.29
136.25
135.75
128.42
126.60
124.44
119.81
93.46
77.29
77.03
76.78
33.05
30.37
26.66
COCH3
4ai
f1 (ppm)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8.67
8.67
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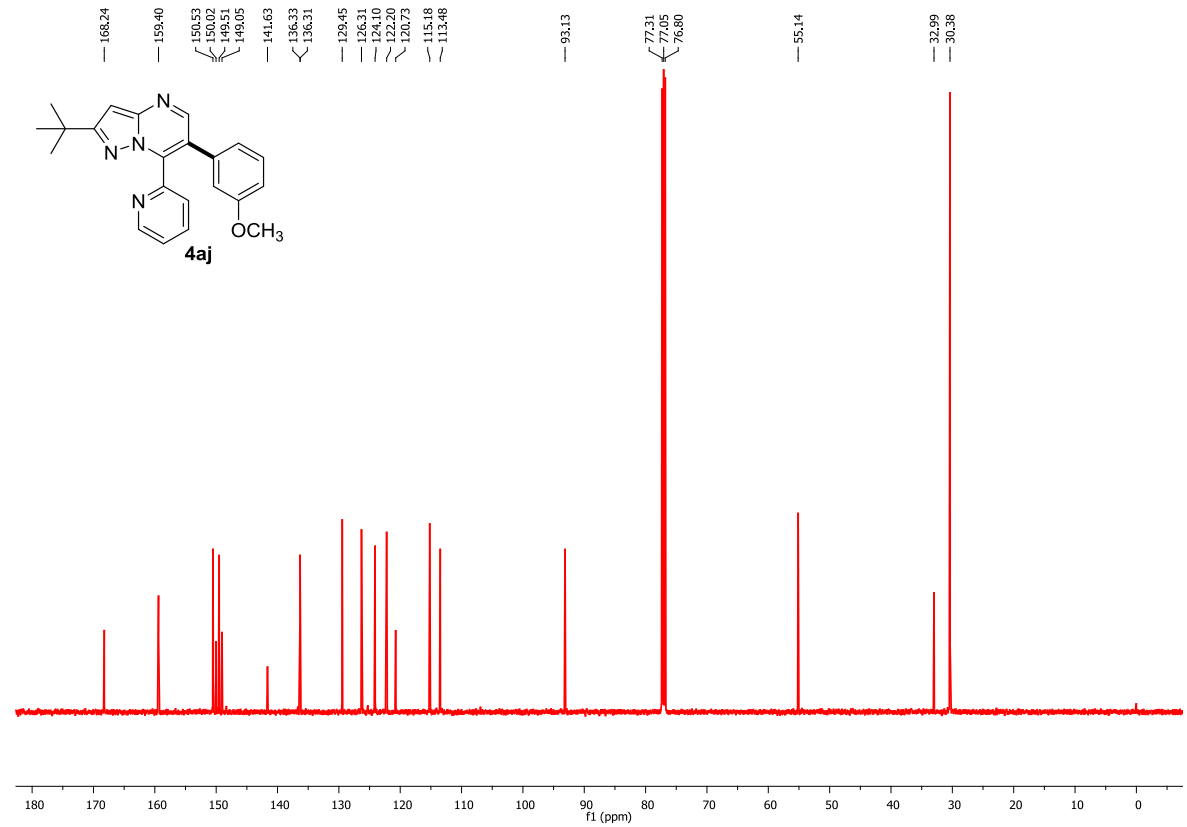
7.76
7.75
7.75
7.56
7.34
7.33
7.33
7.15
6.78
6.77
6.77
6.77
6.76
6.75
6.75
6.75
6.69
6.68
6.68
6.64
3.65
1.34
N
N
N
OCH3
4aj
1.06
1.03
1.11
1.04
1.07
1.08
2.14
1.05
1.00
3.24
9.34
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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159.40
150.53
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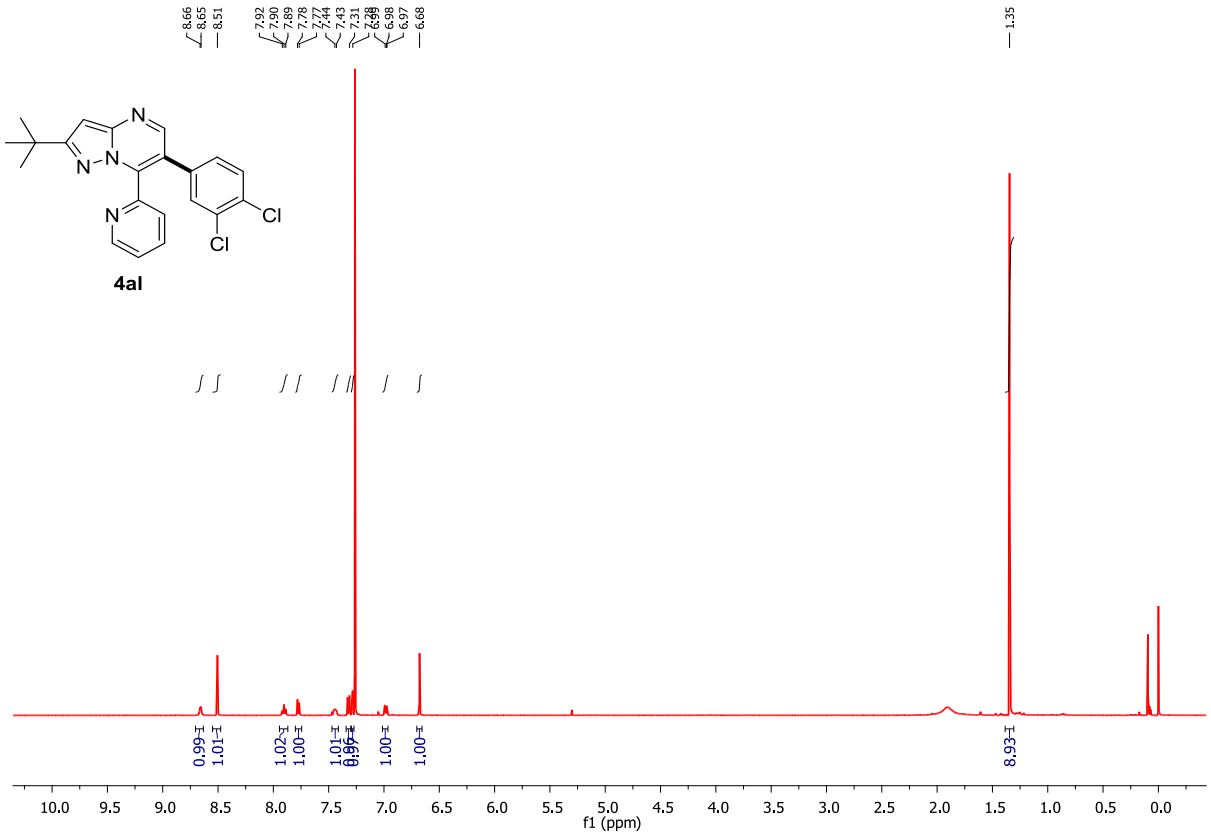
149.05
141.63
136.33
136.31
129.45
126.31
124.10
122.20
120.73
115.18
113.48
93.13
77.31
77.05
76.80
55.14
32.99
30.38
N
N
N
OCH3
4aj
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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8.65
8.51
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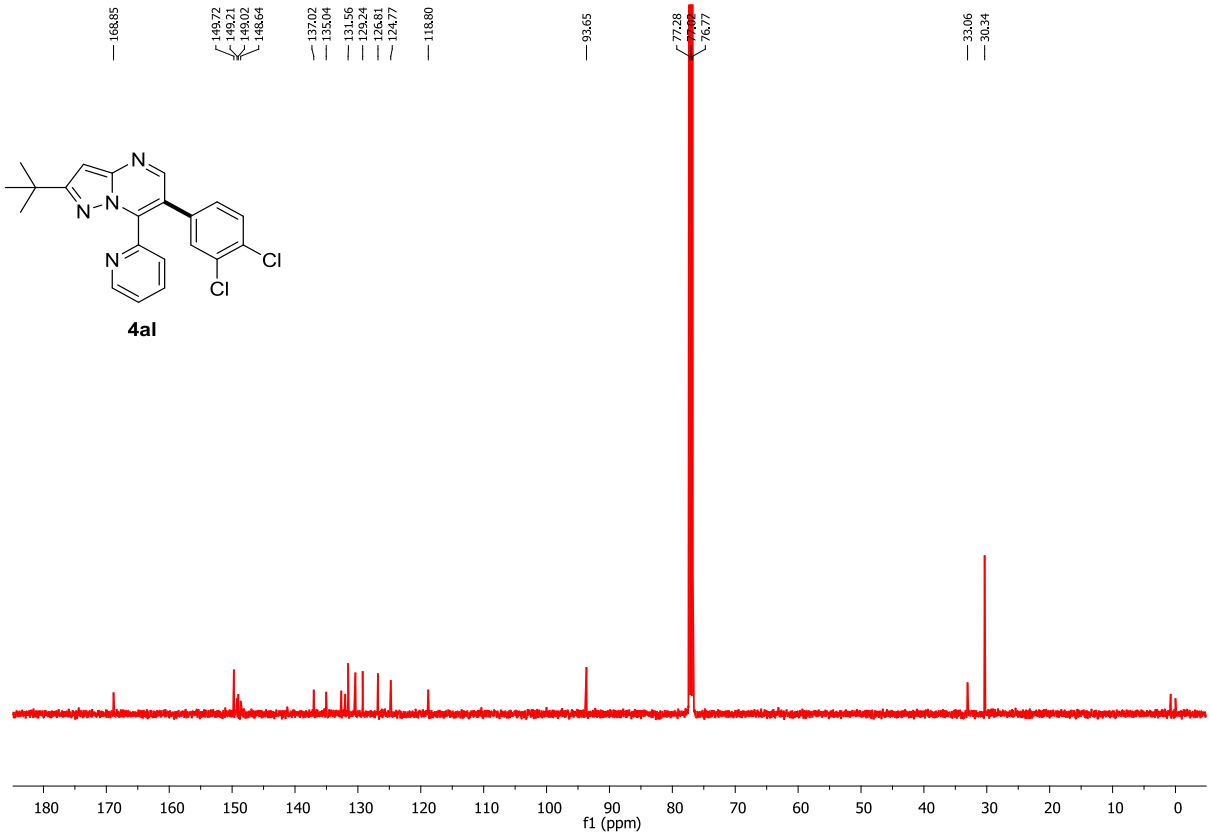
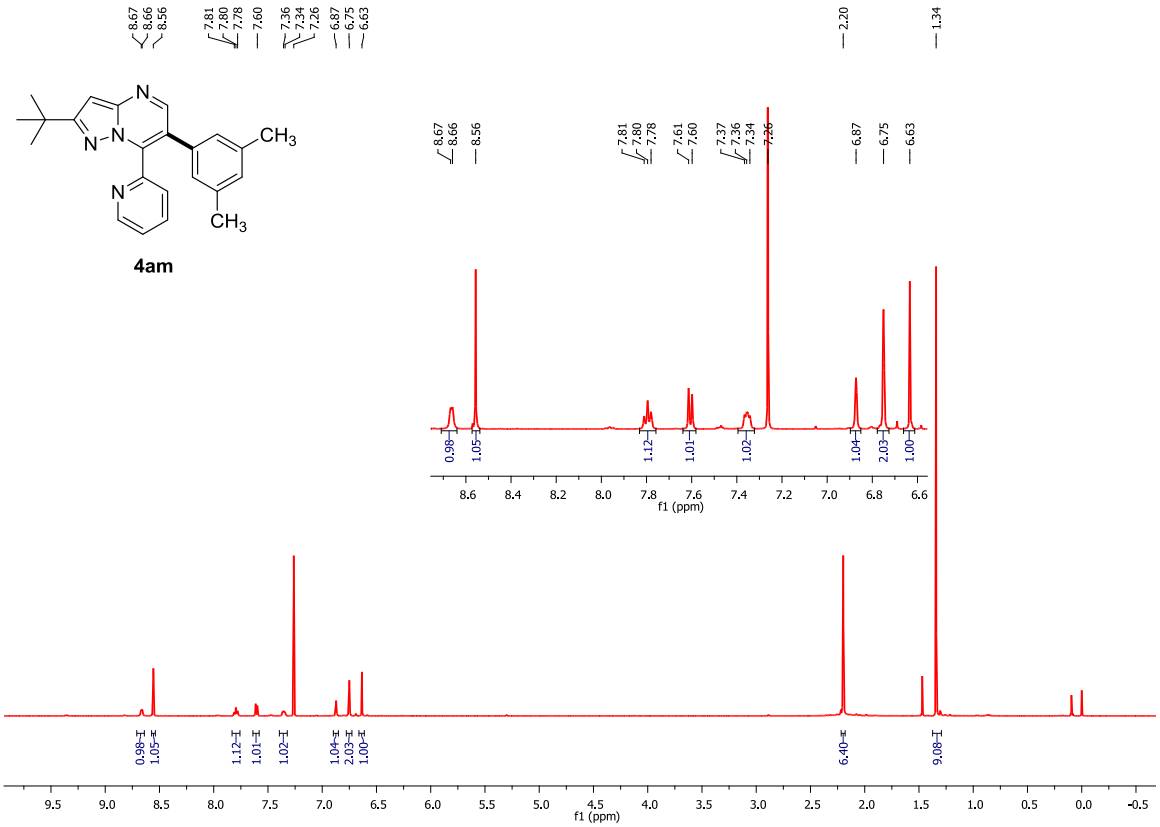
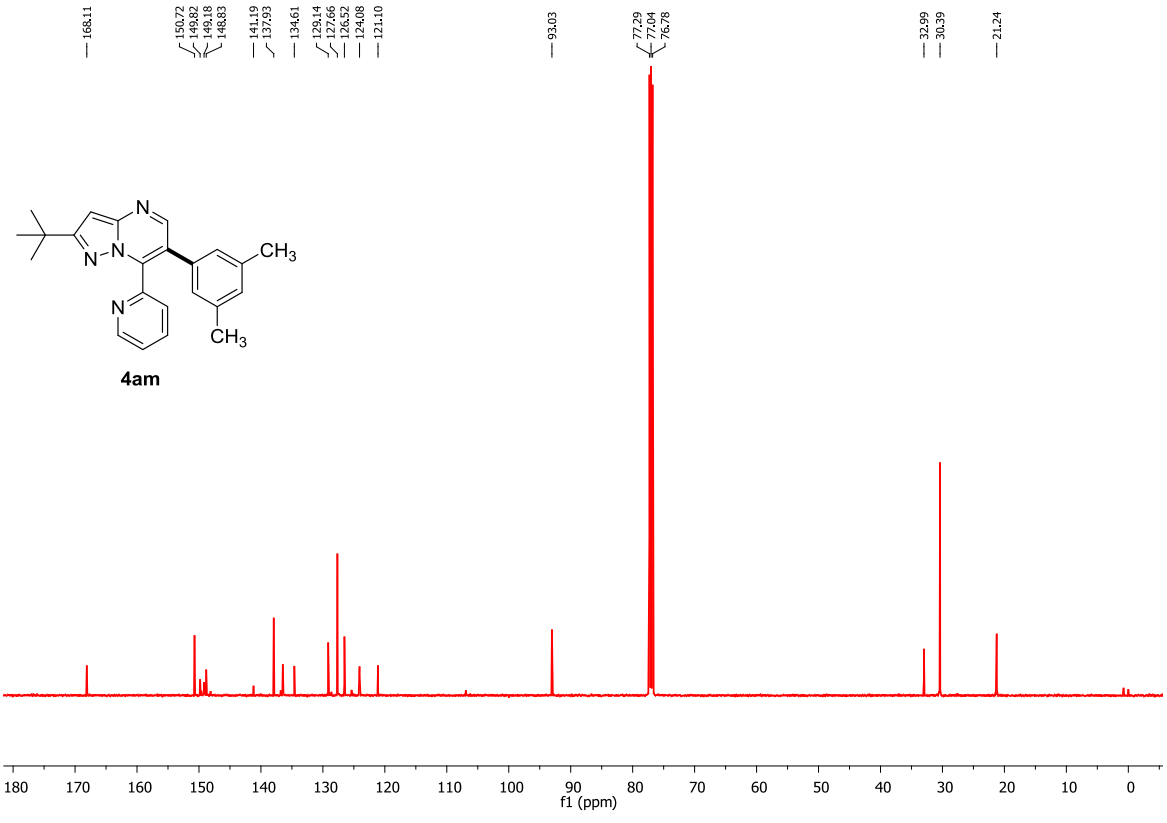
7.90
7.89
7.78
7.77
7.44
7.43
7.31
6.98
6.97
6.68
1.35
Cl
Cl
4al
0.99
1.01
1.02
1.00
1.01
1.00
1.00
8.93
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


168.85
149.72
149.21
149.02
148.64
137.02
135.04
131.56
129.24
126.81
124.77
118.80
93.65
77.28
77.03
76.77
33.06
30.34
Cl
Cl
4al
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.67
8.66
8.56
7.81
7.80
7.78
7.60
7.36
7.34
7.26
6.87
6.75
6.63
2.20
1.34
CH3
CH3
4am
f1 (ppm)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150.72
149.82
149.18
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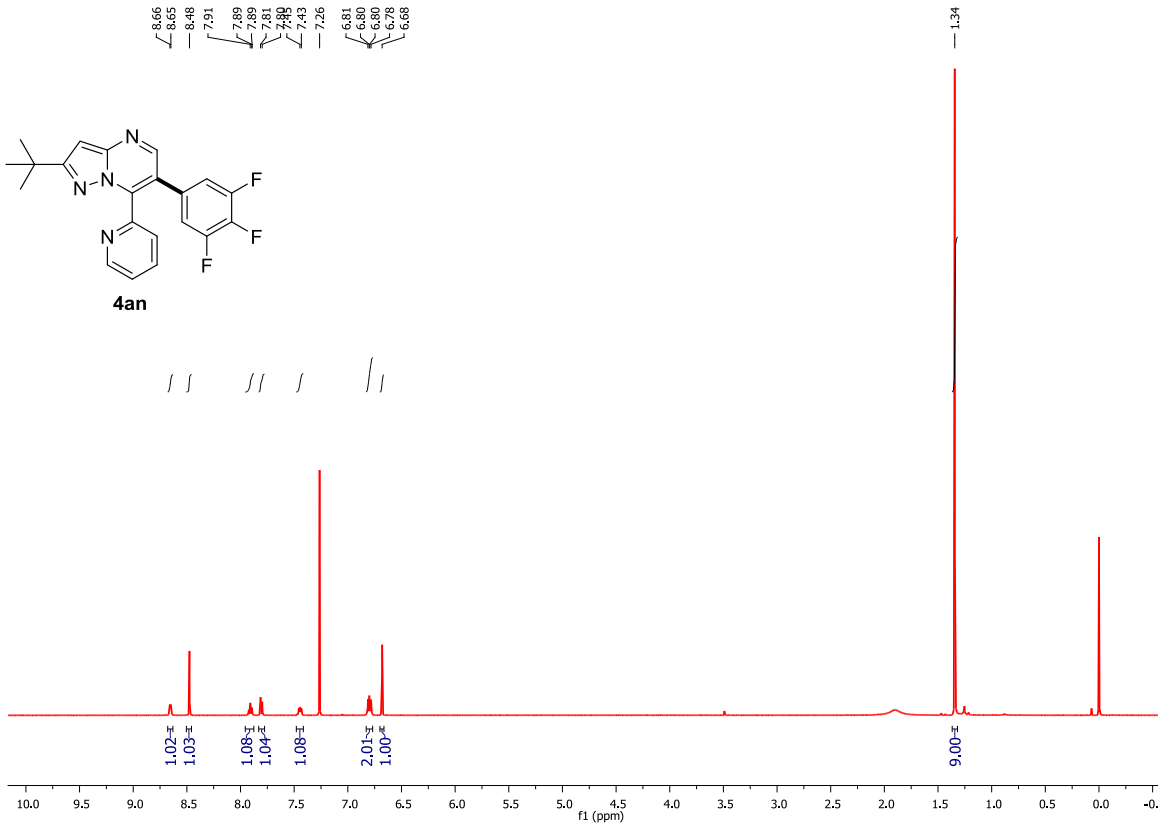
141.19
137.93
134.61
129.14
127.66
126.52
124.08
121.10
93.03
77.29
77.04
76.78
32.99
30.39
21.24
CH3
CH3
4am
f1 (ppm)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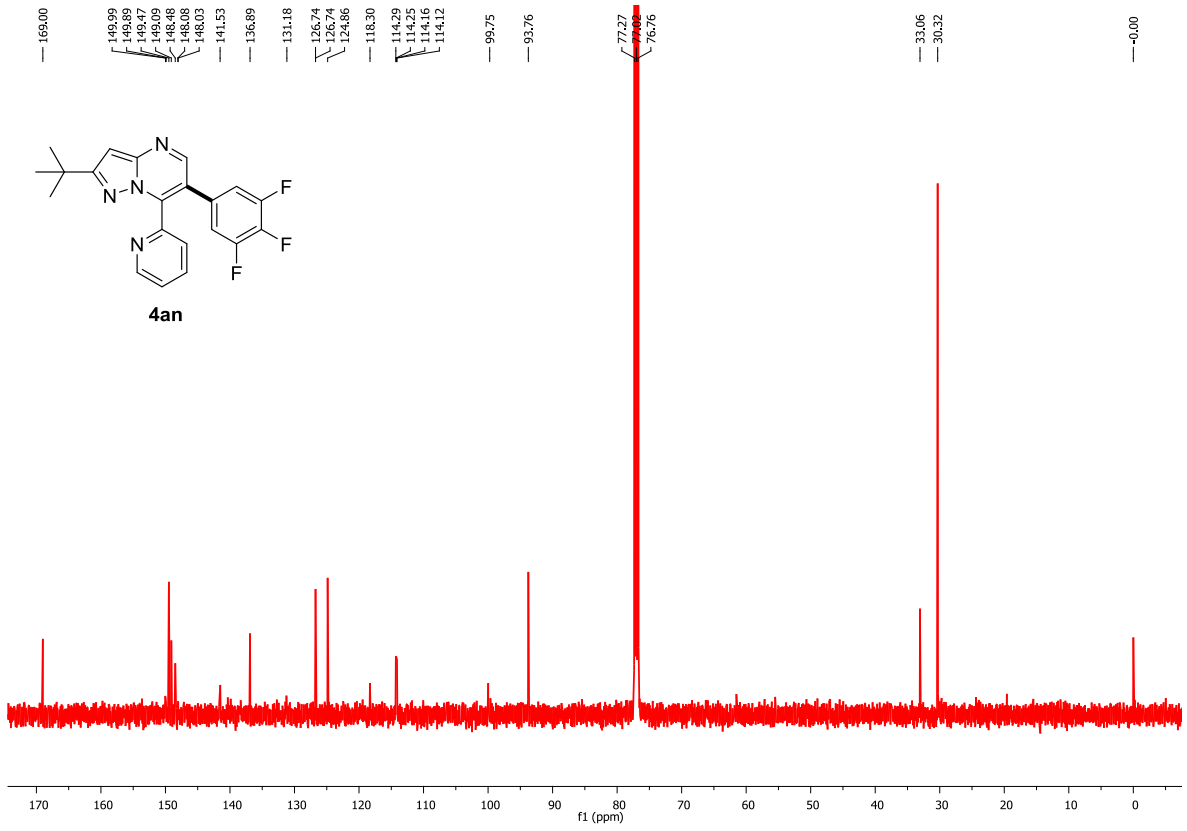
7.89
7.89
7.81
7.43
7.26
6.81
6.80
6.80
6.78
6.68
1.34
F
F
F
N
N
N
4an
1.02
1.03
1.08
1.04
1.08
2.01
1.00
9.00
f1 (ppm)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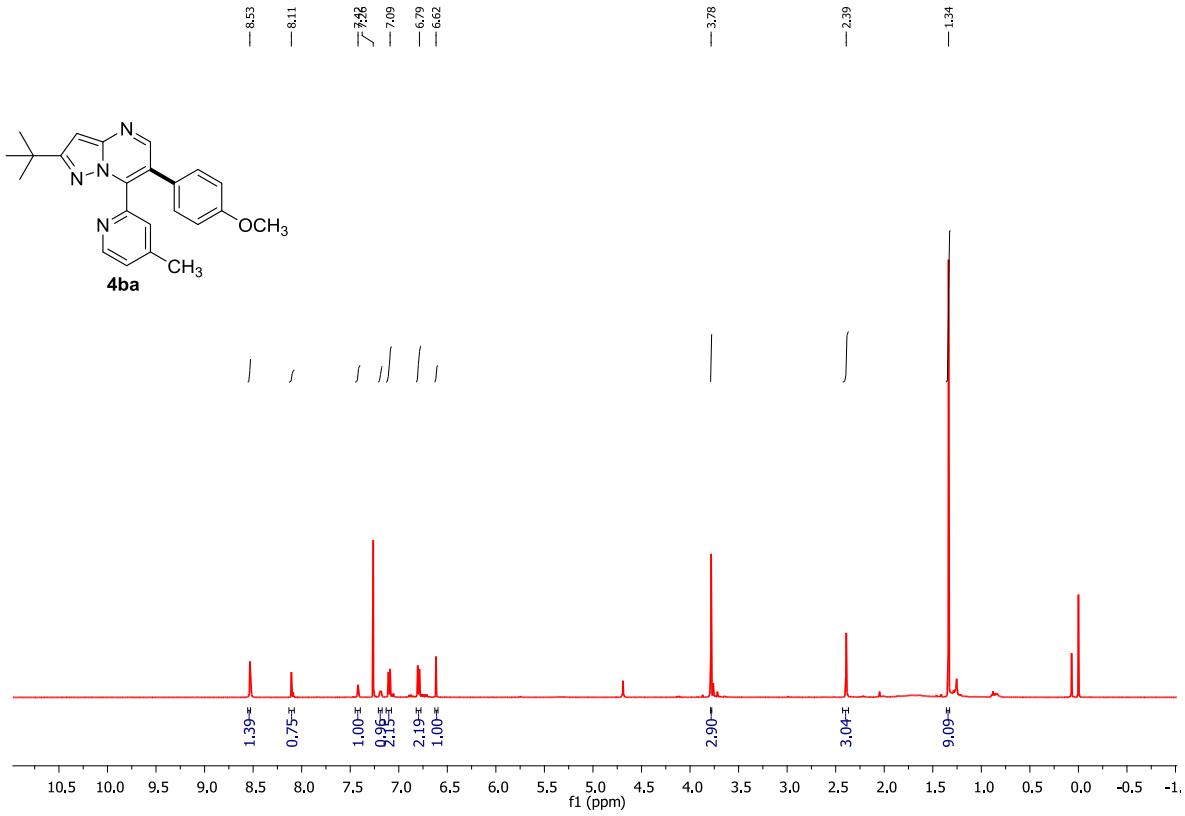
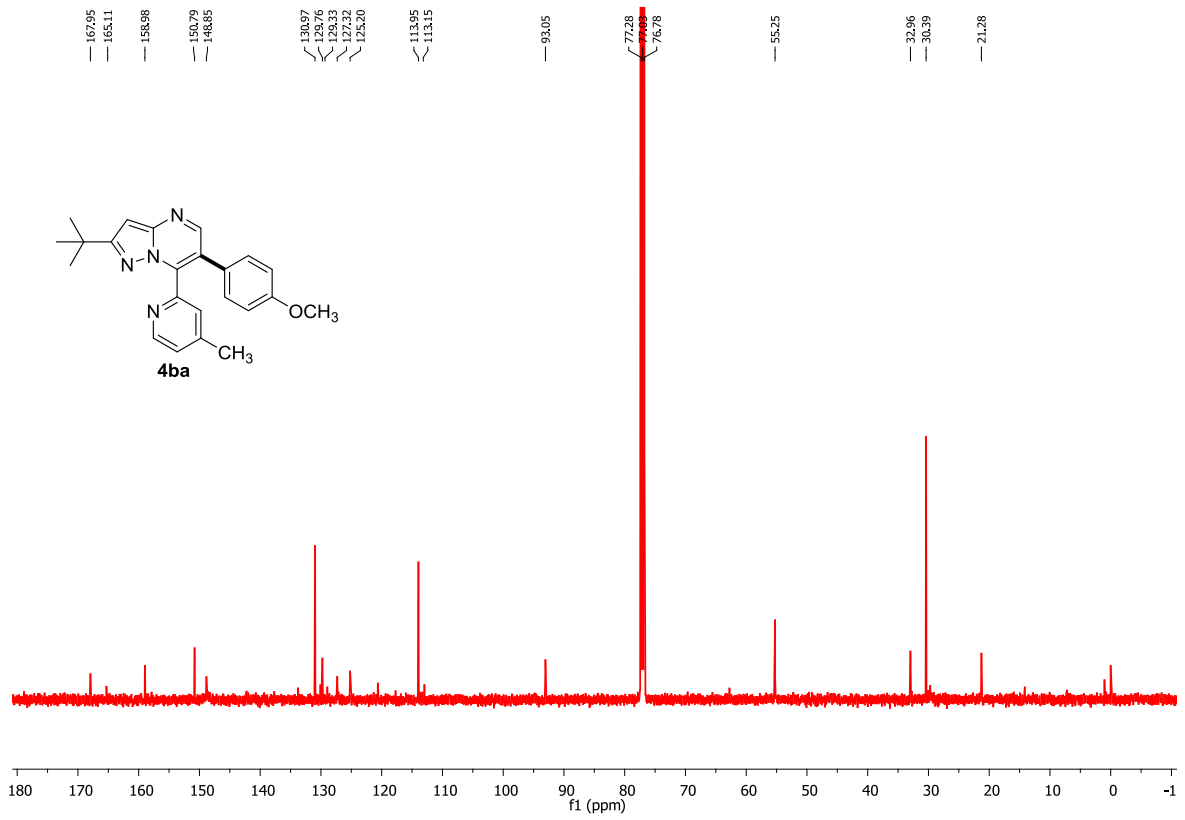
148.48
148.08
148.03
141.53
136.89
131.18
126.74
126.74
124.86
118.30
114.29
114.25
114.16
114.12
99.75
93.76
77.27
77.08
76.76
33.06
30.32
0.00
F
F
F
N
N
N
4an
f1 (ppm)


8.53
8.11
7.42
7.26
7.09
6.79
6.62
3.78
2.39
1.34
OCH3
CH3
4ba
1.39
0.75
1.00
0.96
2.15
2.19
1.00
2.90
3.04
9.09
f1 (ppm)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165.11
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130.97
129.76
129.33
127.32
125.20
113.95
113.15
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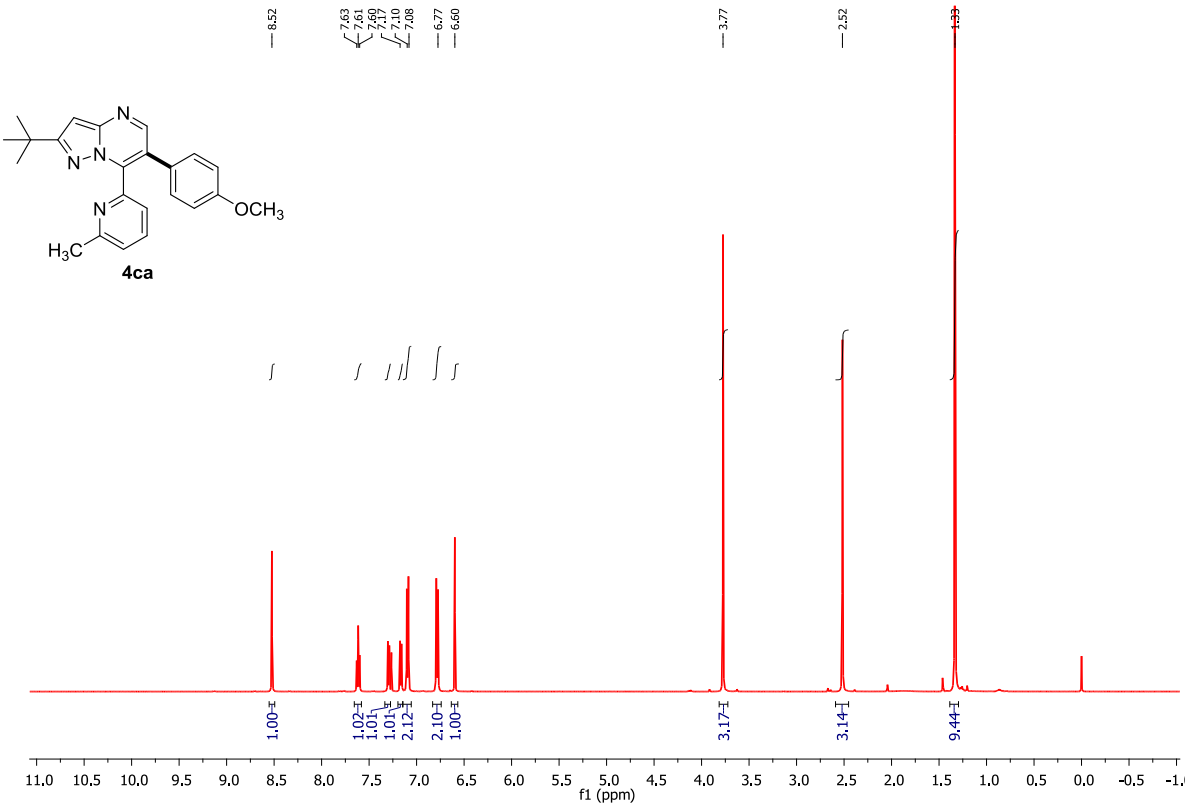
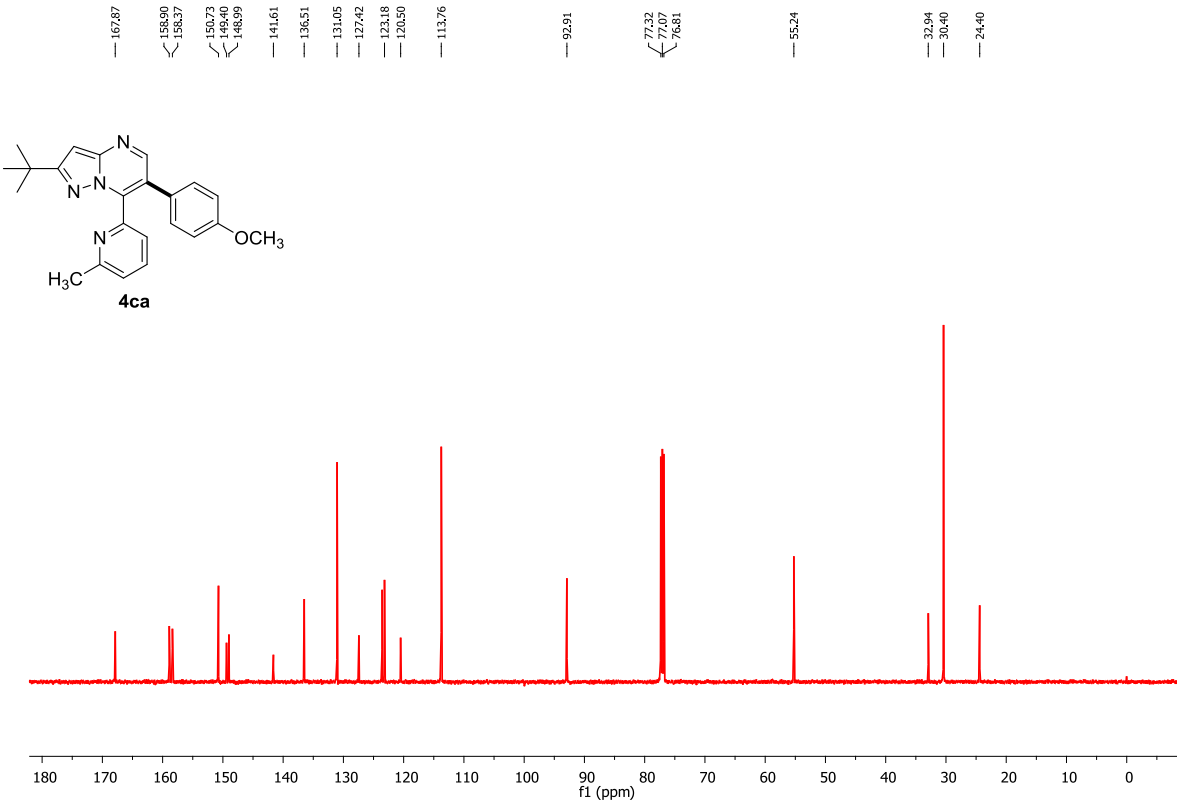
30.39
21.28
OCH3
CH3
4ba
f1 (ppm)


8.52
7.63
7.61
7.60
7.17
7.10
7.08
6.77
6.60
3.77
2.52
1.33
OCH3
H3C
4ca
1.00
1.02
1.01
1.01
2.12
2.10
1.00
3.17
3.14
9.44
f1 (ppm)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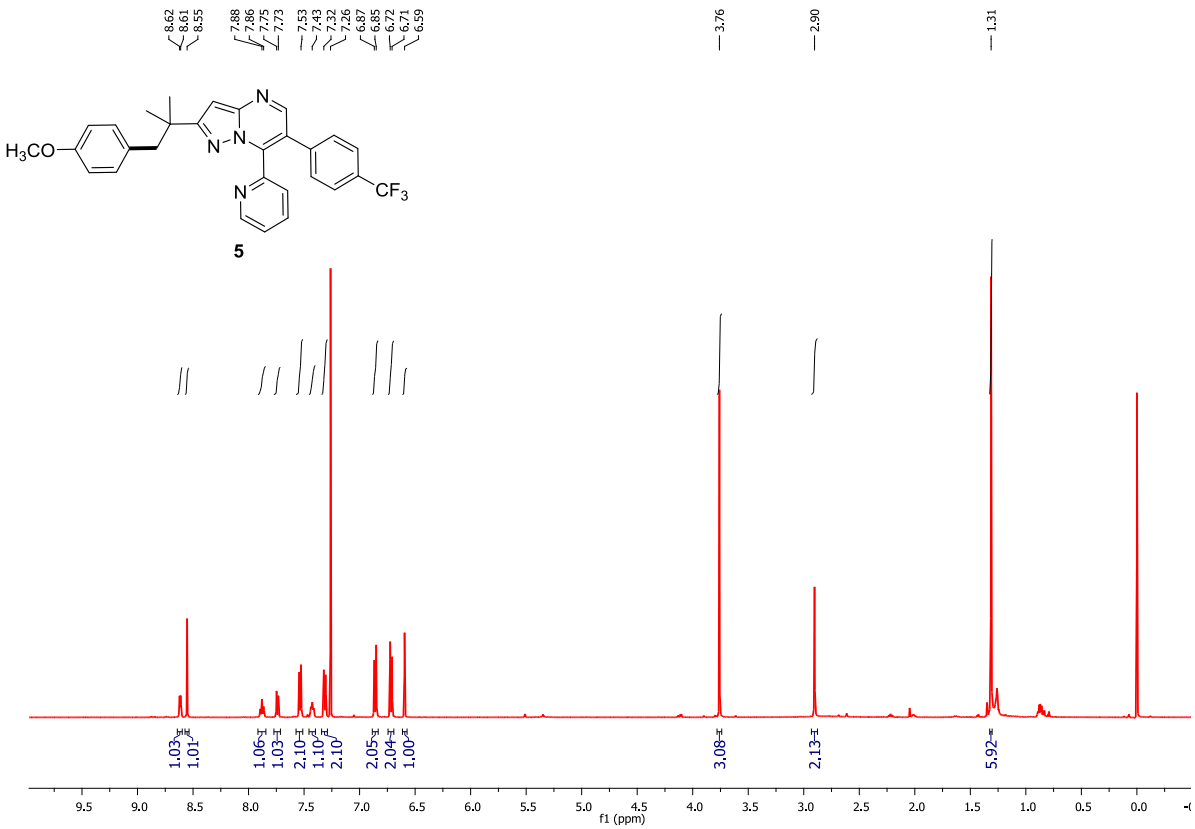
149.40
148.99
141.61
136.51
131.05
127.42
123.18
120.50
113.76
92.91
77.32
77.07
76.81
55.24
32.94
30.40
24.40
OCH3
H3C
4ca
f1 (ppm)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8.61
8.55
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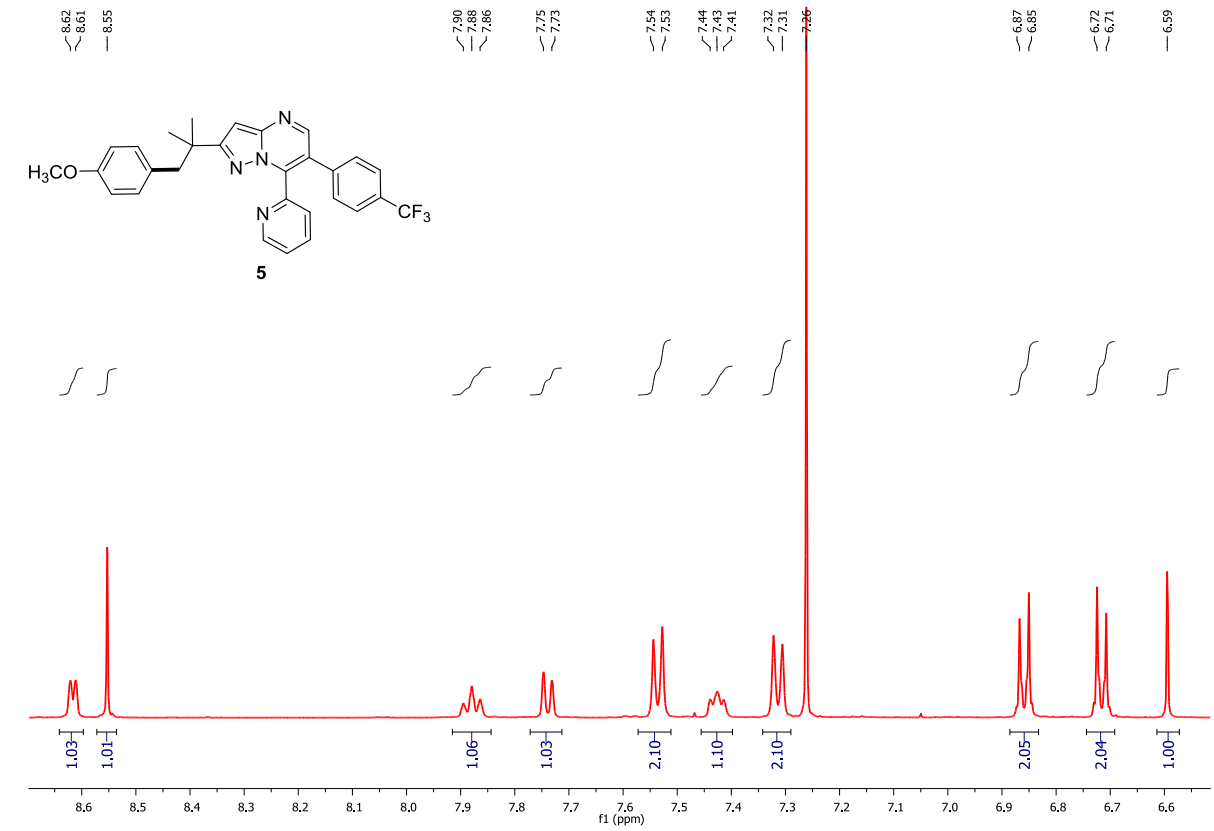
7.86
7.75
7.73
7.53
7.43
7.32
7.26
6.87
6.85
6.72
6.71
6.59
3.76
2.90
1.31
H3CO
N
N
N
CF3
5
1.03
1.01
1.06
1.03
2.10
1.10
2.10
2.05
2.04
1.00
3.08
2.13
5.92
f1 (ppm)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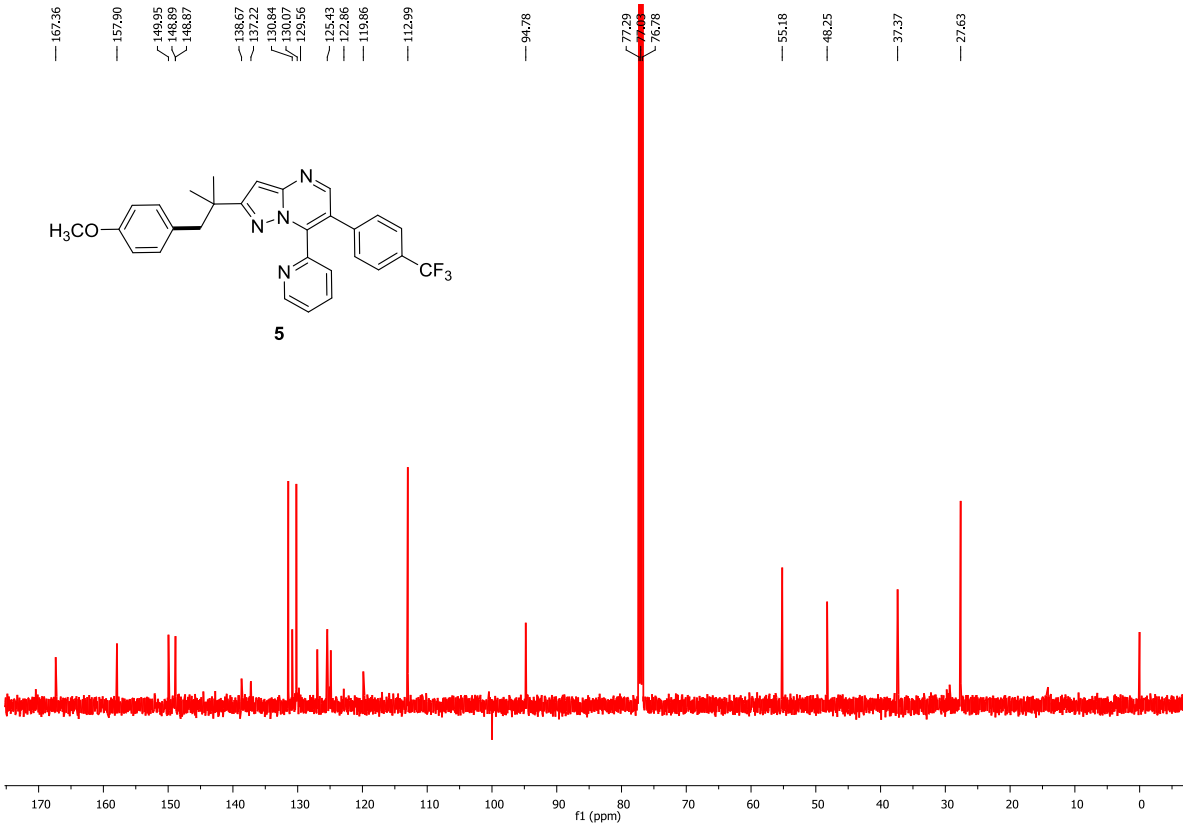
8.61
8.55
7.90
7.88
7.86
7.75
7.73
7.54
7.53
7.44
7.43
7.41
7.32
7.31
7.26
6.87
6.85
6.72
6.71
6.59
H3CO
N
N
N
CF3
5
1.03
1.01
1.06
1.03
2.10
1.10
2.10
2.05
2.04
1.00
f1 (ppm)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138.67
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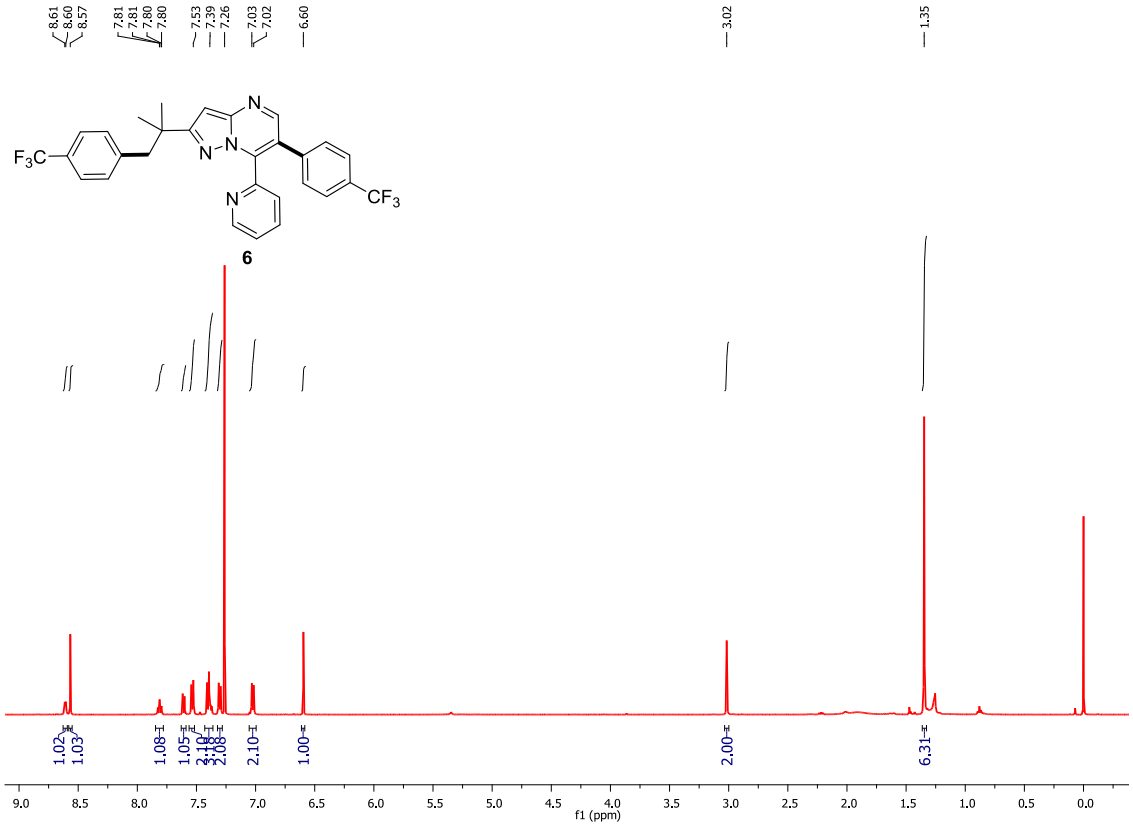
130.84
130.07
129.56
125.43
122.86
119.86
112.99
94.78
77.29
76.78
55.18
48.25
37.37
27.63
H3CO
CF3
N
N
N
f1 (ppm)

5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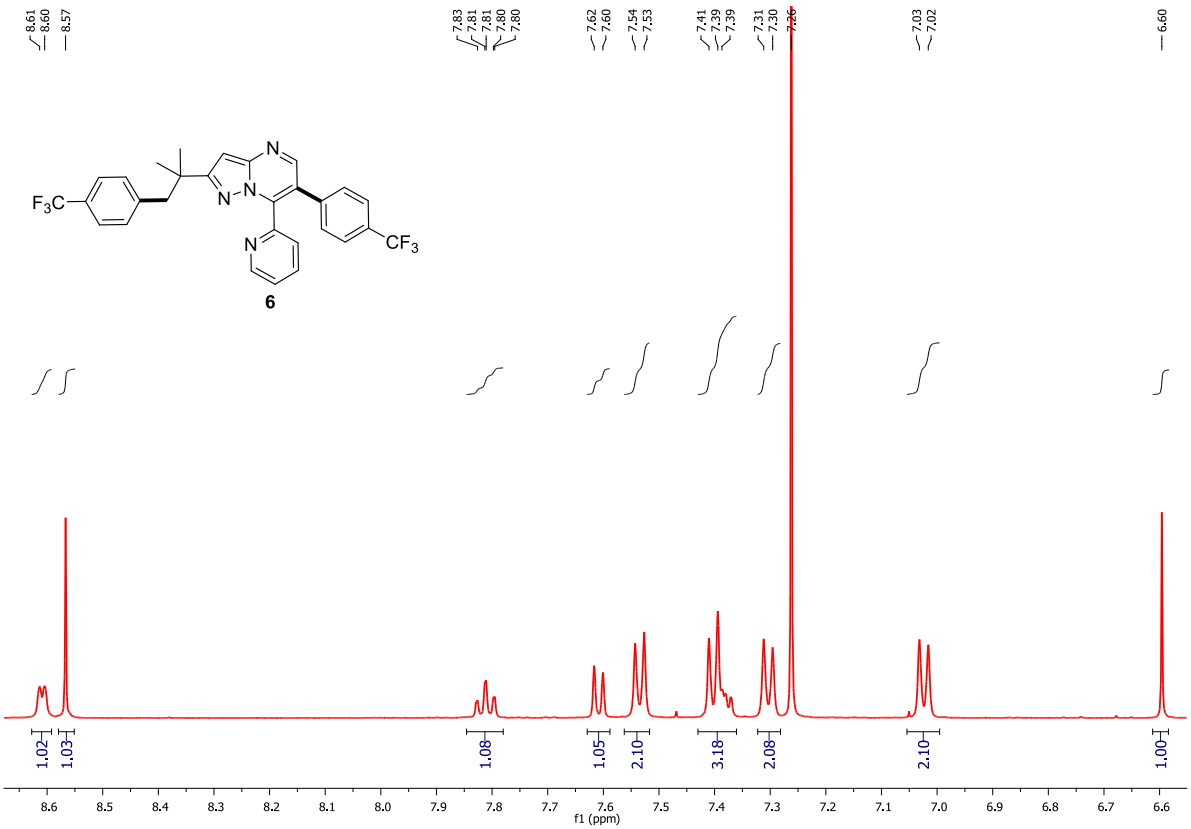
7.81
7.80
7.80
7.53
7.39
7.26
7.03
7.02
6.60
3.02
1.35
F3C
CF3
N
N
N
1.02
1.03
1.08
1.05
2.10
2.08
2.10
1.00
2.00
6.31
f1 (ppm)

6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7.80
7.80
7.62
7.60
7.54
7.53
7.41
7.39
7.39
7.31
7.30
7.26
7.03
7.02
6.60
F3C
CF3
N
N
N
6
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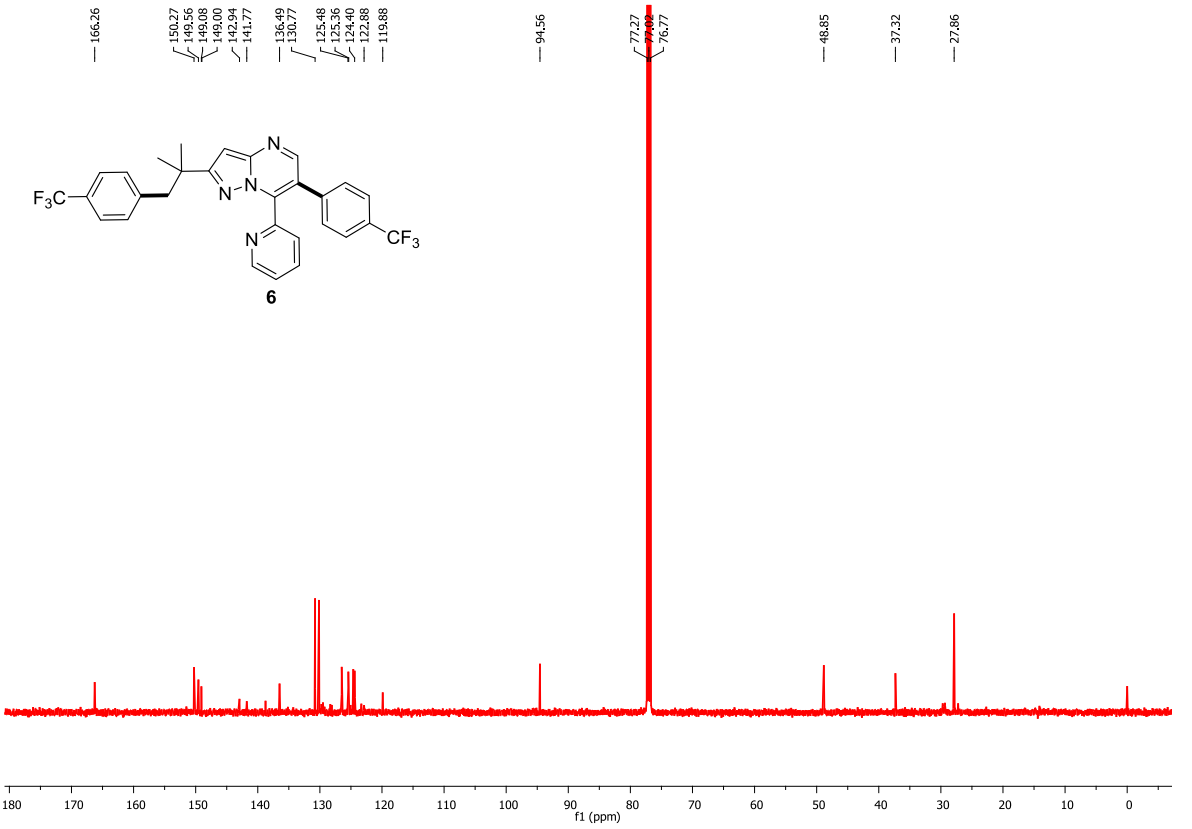
1.03
1.08
1.05
2.10
3.18
2.08
2.10
1.00
8.6
8.5
8.4
8.3
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
f1 (ppm)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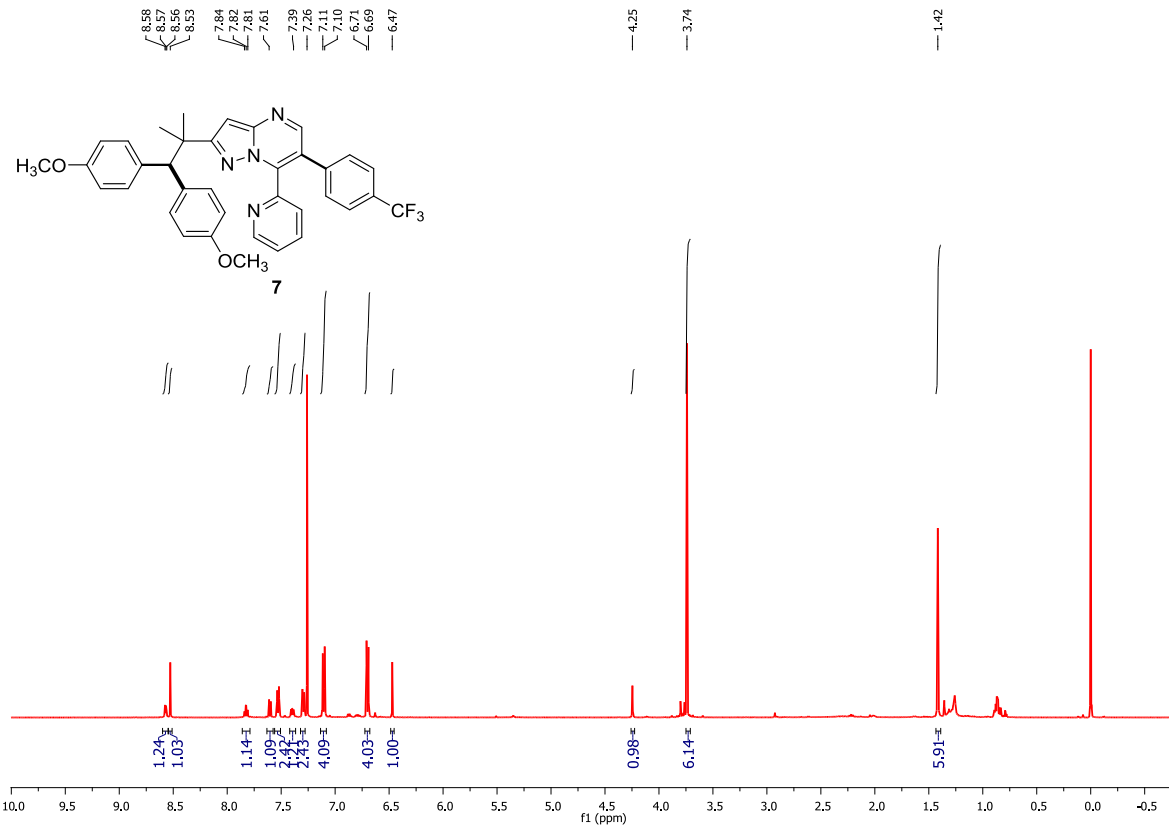
125.48
125.36
124.40
122.88
119.88
94.56
77.27
77.02
76.77
48.85
37.32
27.86
F3C
CF3
N
N
N
6
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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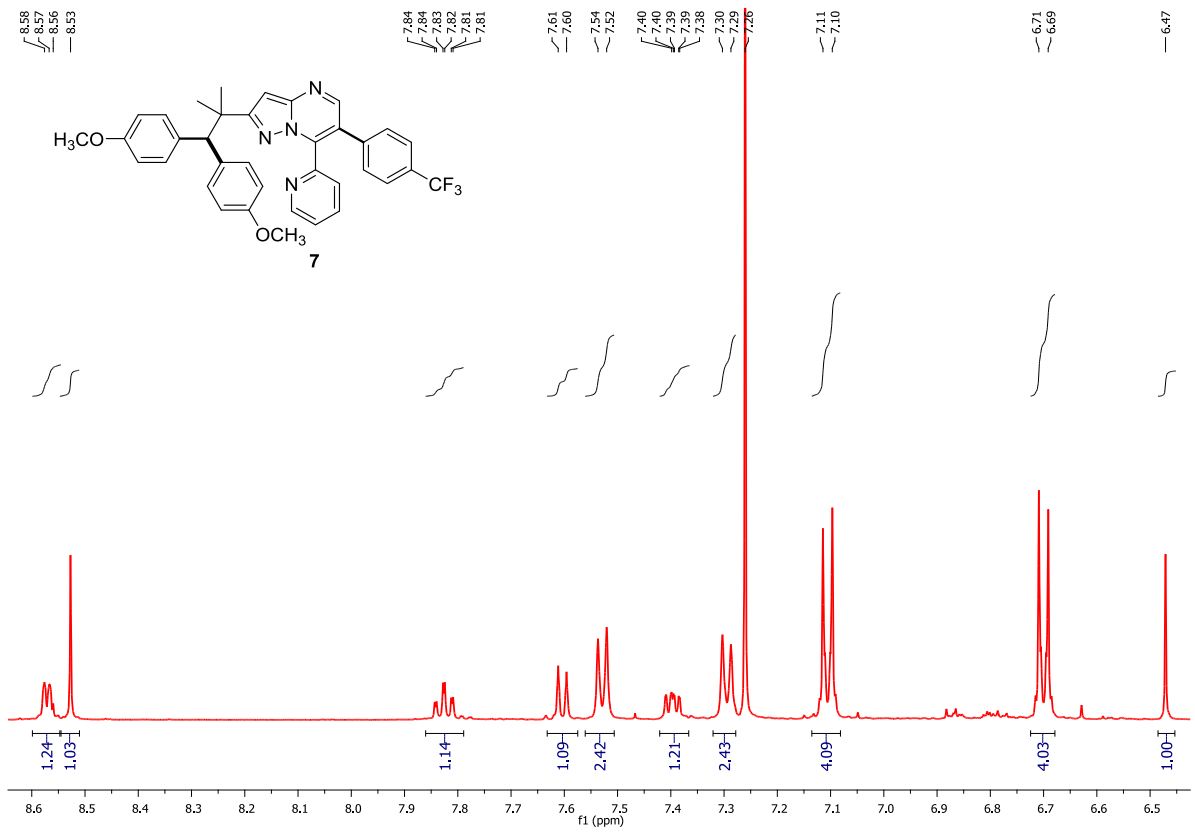
7.82
7.81
7.61
7.39
7.26
7.11
7.10
6.71
6.69
6.47
4.25
3.74
1.42
H3CO
CF3
OCH3
N
N
N
7
1.24
1.03
1.14
1.09
2.42
2.43
4.09
4.03
1.00
0.98
6.14
5.91
f1 (ppm)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7.82
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7.60
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7.52
7.40
7.40
7.39
7.39
7.38
7.30
7.29
7.26
7.11
7.10
6.71
6.69
6.47
H3CO
CF3
OCH3
N
N
N
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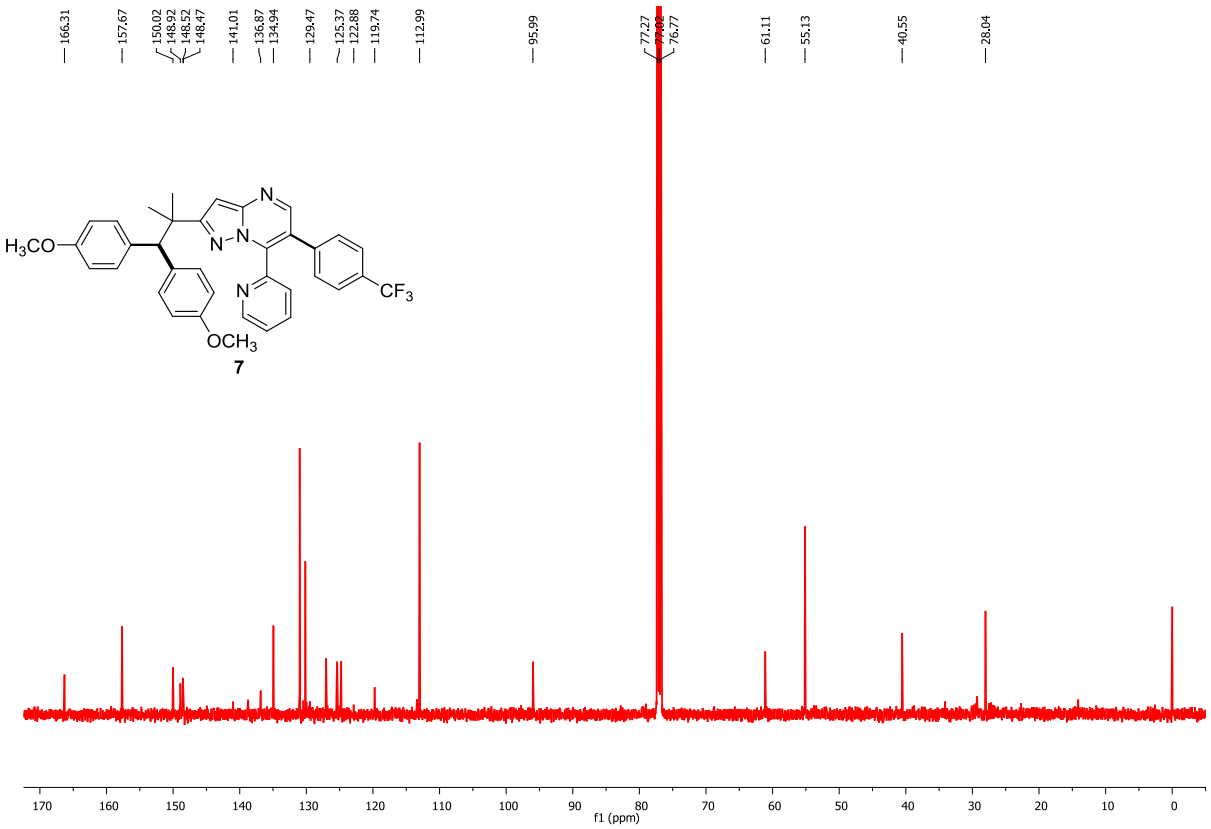
1.14
1.09
2.42
1.21
2.43
4.09
4.03
1.00
f1 (ppm)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141.01
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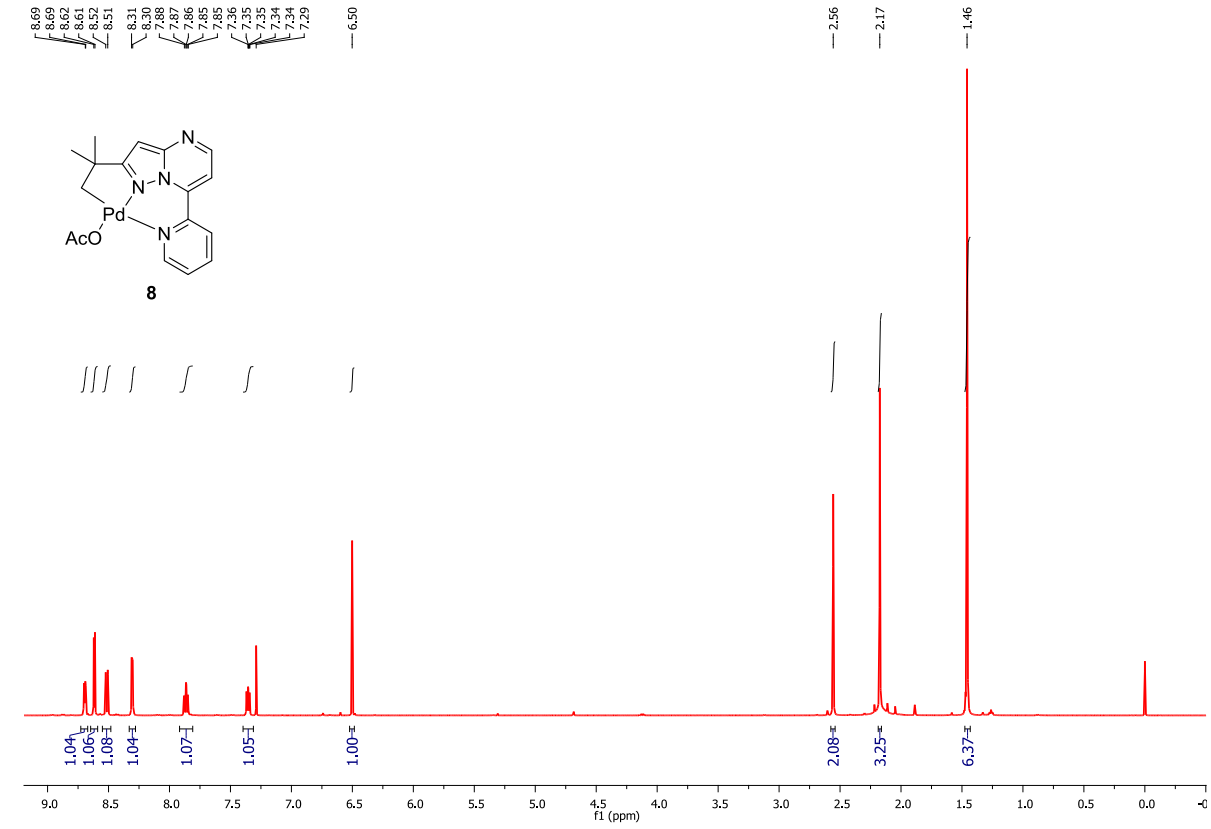
129.47
125.37
122.88
119.74
112.99
95.99
77.27
76.77
61.11
55.13
40.55
28.04
H3CO
CF3
OCH3
7
f1 (ppm)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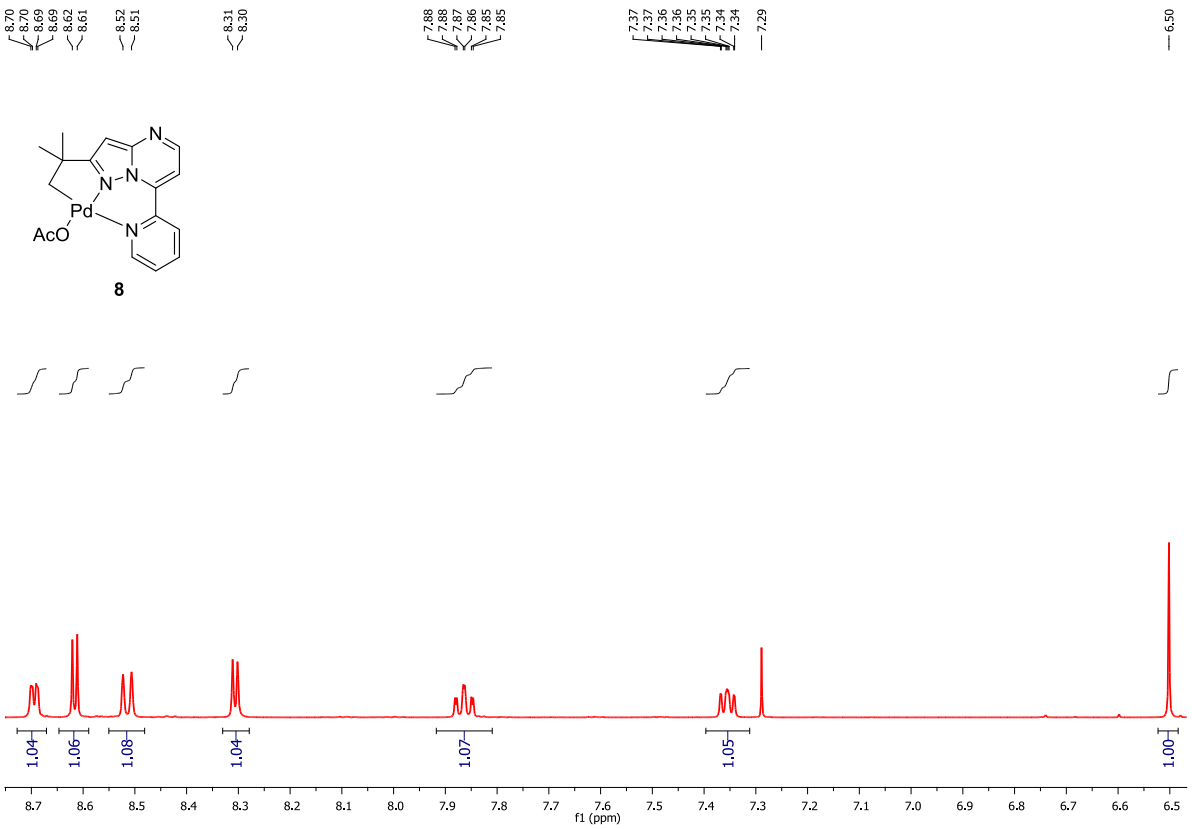
8.31
8.30
7.88
7.87
7.86
7.85
7.85
7.36
7.35
7.35
7.34
7.34
7.29
6.50
2.56
2.17
1.46
Pd
AcO
8
1.04
1.06
1.08
1.04
1.07
1.05
1.00
2.08
3.25
6.37
f1 (ppm)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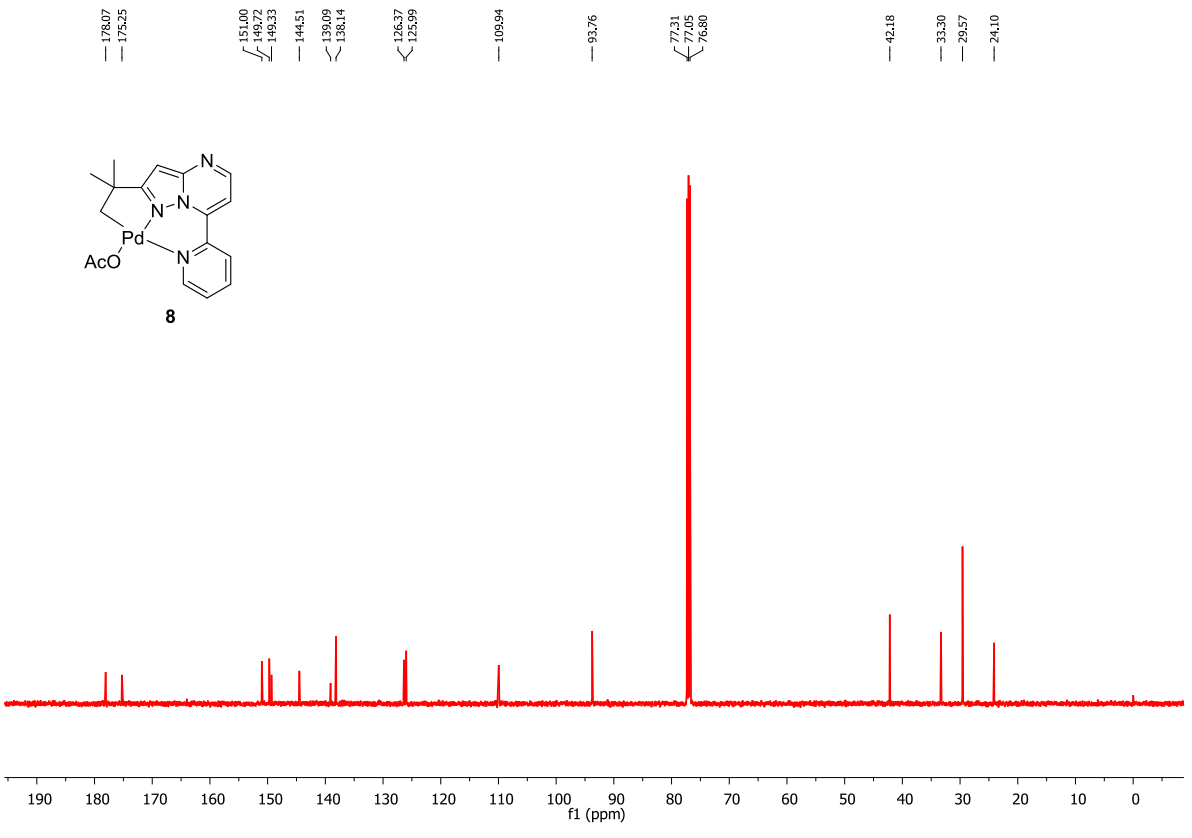
8.52
8.51
8.31
8.30
7.88
7.88
7.87
7.86
7.85
7.85
7.37
7.37
7.36
7.36
7.35
7.35
7.34
7.34
7.29
6.50
N
N
N
Pd
AcO
N
8
1.04
1.06
1.08
1.04
1.07
1.05
1.00
8.7
8.6
8.5
8.4
8.3
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
6.5
f1 (ppm)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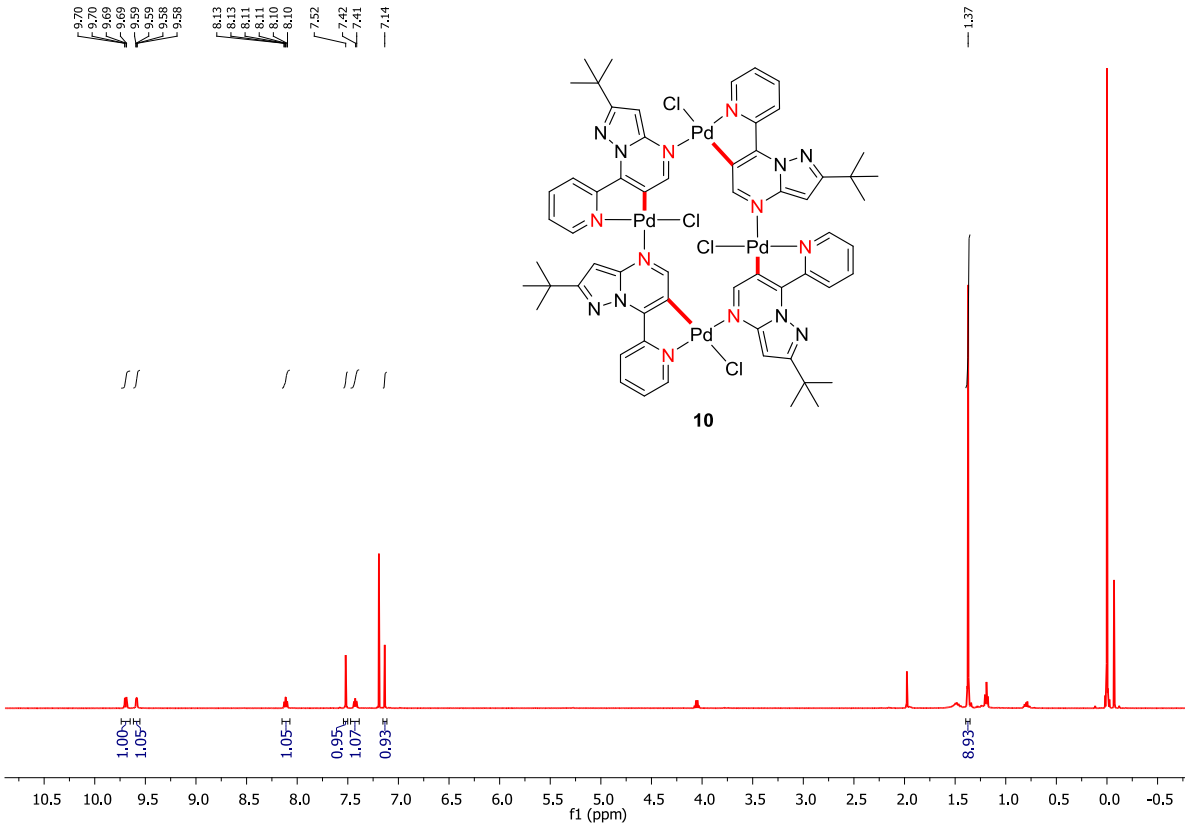
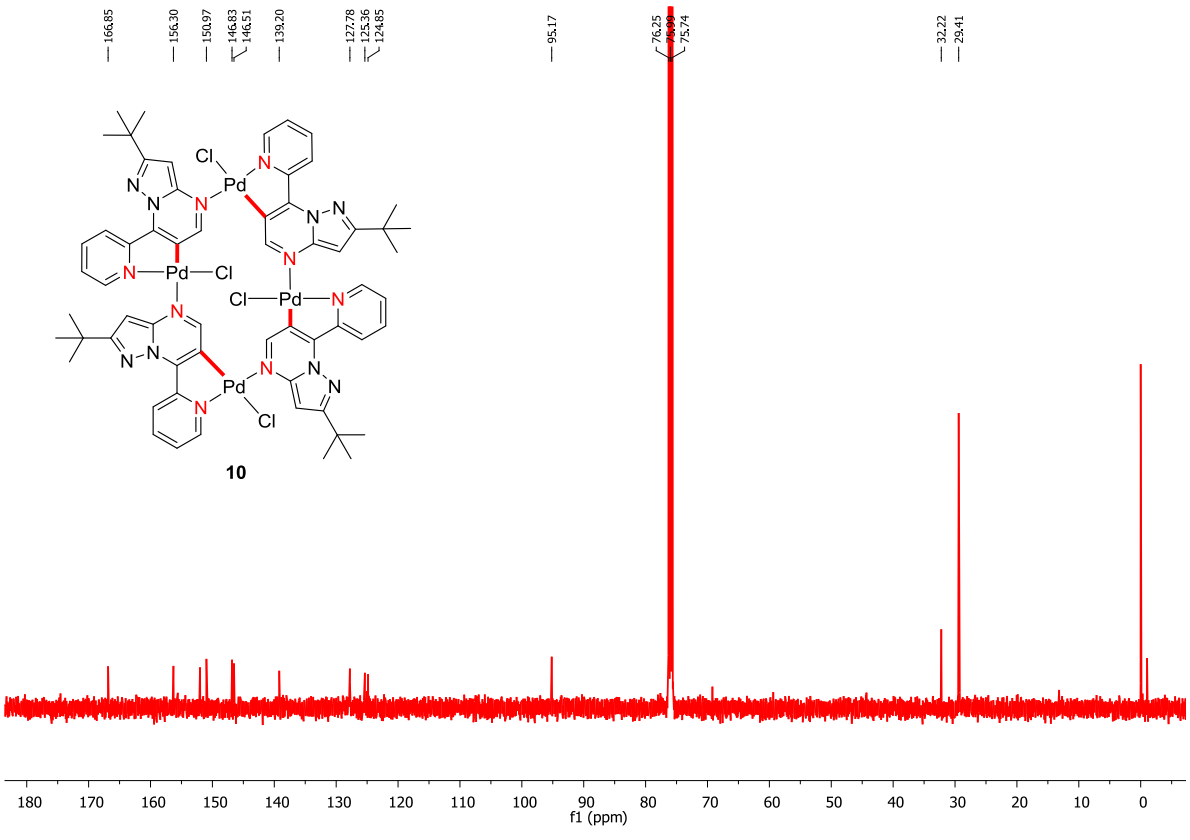
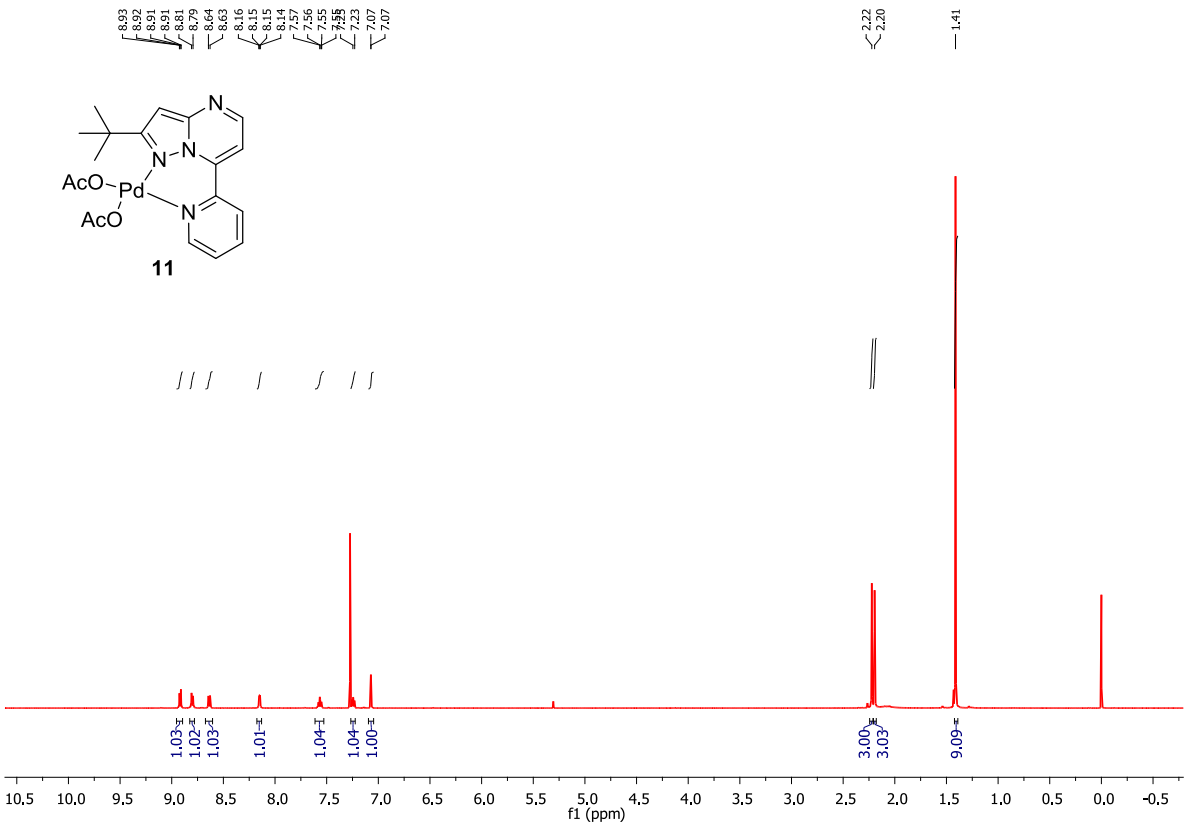
149.72
149.33
144.51
139.09
138.14
126.37
125.99
109.94
93.76
77.31
77.05
76.80
42.18
33.30
29.57
24.10
N
N
N
Pd
AcO
N
8
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

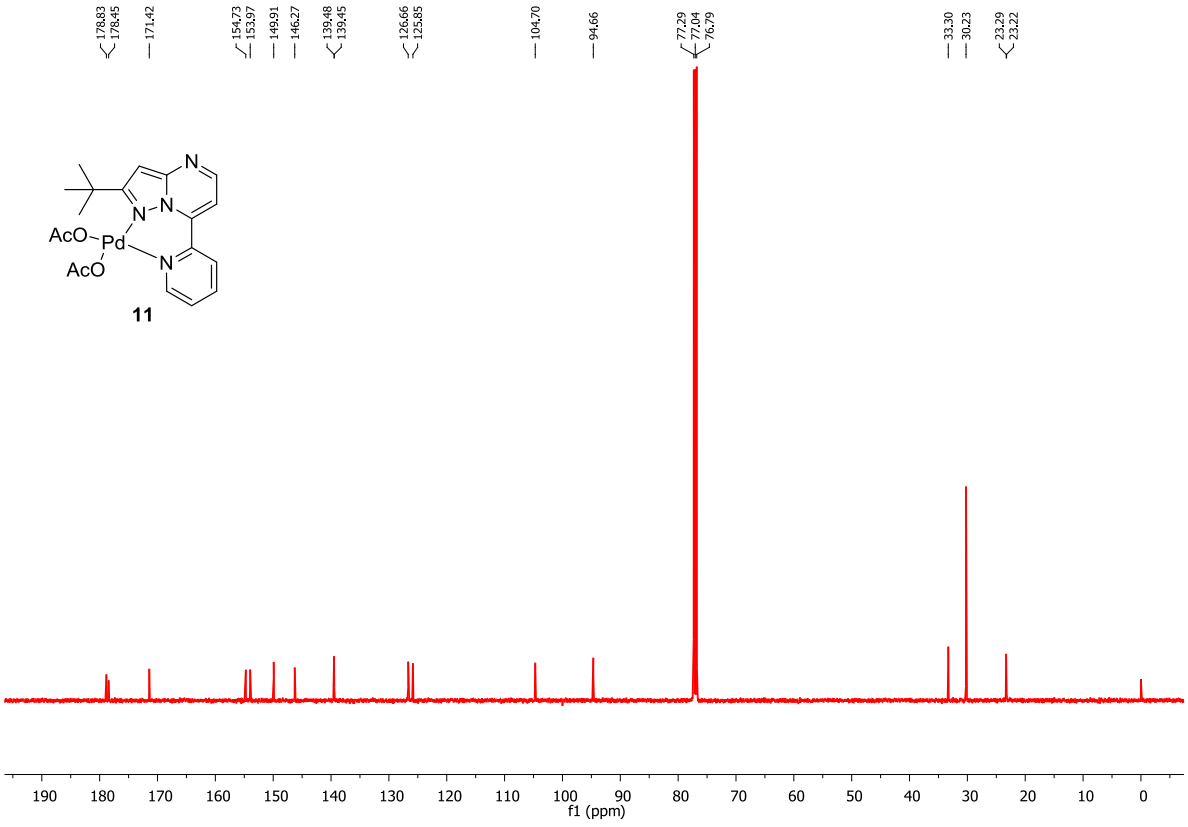

9.70
9.70
9.69
9.69
9.59
9.59
9.58
9.58
8.13
8.13
8.11
8.11
8.10
8.10
7.52
7.42
7.41
7.14
1.37
1.00
1.05
1.05
0.95
1.07
0.93
8.93
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

10


166.85
156.30
150.97
146.83
146.51
139.20
127.78
125.36
124.85
95.17
76.25
75.74
32.22
29.41
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

10


8.93
8.92
8.91
8.91
8.81
8.79
8.64
8.63
8.16
8.15
8.15
8.14
7.57
7.56
7.55
7.25
7.23
7.07
7.07
2.22
2.20
1.41
AcO
Pd
AcO
N
N
N
N
11
1.03
1.02
1.03
1.01
1.04
1.04
1.00
3.00
3.03
9.09
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


178.83
178.45
171.42
154.73
153.97
149.91
146.27
139.48
139.45
126.66
125.85
104.70
94.66
77.29
77.04
76.79
33.30
30.23
23.29
23.22
AcO
Pd
AcO
N
N
N
N
11
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)