Brønsted Acid Catalyzed Addition Reaction of 5-Aminopyrazoles with 4-Aryl-1,2,4-triazole-3,5-diones

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1. General Information:

All dry solvents were dried using activated 4Å molecular sieves and stored under argon. For thin layer chromatography (TLC), silica gel plates with fluorescence indicator 220 nm were used and compounds were visualized by irradiation with UV light and/or by I2. Celite® 512 medium was used for filtrations. Silica gel (60-120 mesh size) was used for the column chromatography. Petroleum ether and ethyl acetate for chromatography were acquired from commercial sources and were used without purification. NMR spectra were acquired on a Bruker 400 MHz, 500 MHz, 600MHz spectrometer. Chemical shifts (δ) are reported in ppm relative to residual solvent signals (the residual solvent peak was used as an internal reference: proton (chloroform δ 7.260, Methanol 3.31, acetone δ 2.05 and DMSO δ 2.50), carbon (chloroform δ 77.23, methanol 49.00, acetone δ 29.84 and DMSO δ 39.58). 13C spectra were acquired on a broad band decoupled mode. For 1H-NMR, data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = double doublet, ddd = doublet of doublet of doublets, t = triplet, q = quartet, dt = doublet of triplets, m = multiplet), coupling constants (Hz) and integration.

2. General procedure for the synthesis of 5-aminopyrazole:

5-aminopyrazole were prepared according to reported procedure. (1)

3. General procedure for the synthesis of urazole:

Urazoles were prepared according to reported procedures. (2)

4. Reaction condition optimization:

(a) Catalyst optimization:

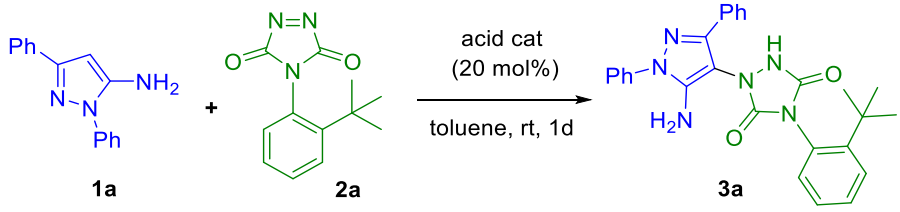


Table 1: Catalyst Optimization:

Entry[a]	Catalyst	Yield (%)[b]
1	DPP	65
2	PTSA	55
3	TFA	25
4	TFOH	NR
5	AcOH	62
6	TF_2NH	10
7	$SC(OTF)_3$	45
8	$BF_3.OEt_2$	NR

[a]Reaction condition: 0.1 mmol of **1** and 0.1 mmol of **2** using 20 mol% of catalysts in 2 ml of toluene at room temperature. [b] Isolated yield after silica gel column chromatography. DPP = Diphenyl phosphate

(b) Screening of different condition:

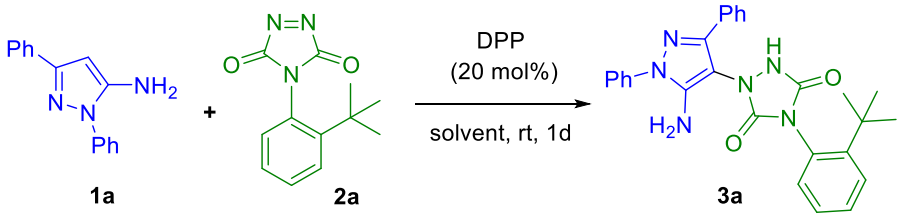
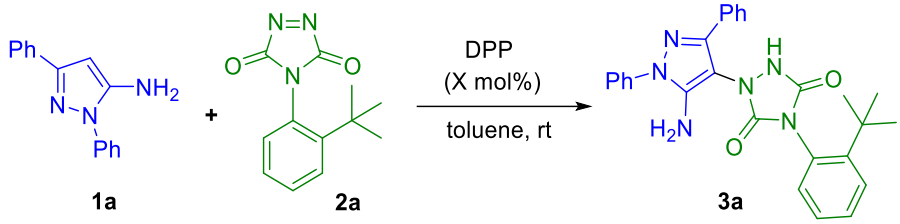


Table 2. Solvent optimization

Entry[a]	Solvent	Yield (%)[b]
1	DCM	61
2	THF	64
3	1,4 dioxane	50
4	ACN	48
5	EtOAc	47
6	Toluene	65
7	MeOH	60

[a] Reaction condition: 0.1 mmol of **1** and 0.1 mmol of **2** using 20 mol% of catalysts in 2 ml of solvent at room temperature. [b] Isolated yield after silica gel column chromatography.

Table 3. Catalyst loading optimization



Entry[a]	Catalyst loading(mol%)	Yield (%)[b]
1	5	45
2	10	55
3	20	65
4	30	60

[a] Reaction condition: 0.1 mmol of **1** and 0.1 mmol of **2** using different mol% of catalysts in 2 ml of toluene at room temperature.
[b] Isolated yield after silica gel column chromatography.

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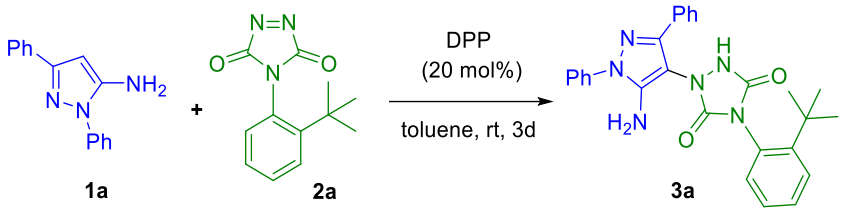
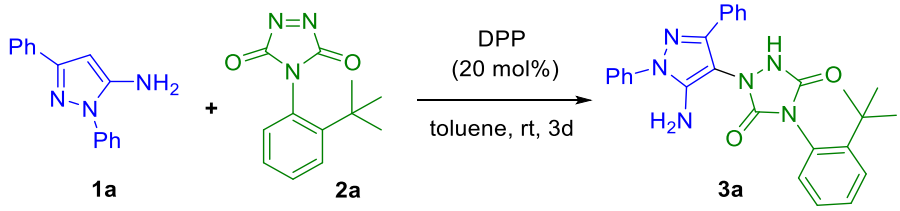
Table 4. Optimization of equivalency



entry[a]	X eq.	Yield (%)[b]
1	1	65
2	**1.5**	**62**
3	2	53

[a]Unless otherwise mentioned, reactions were carried out with (0.1*X) mmol of 2a with 0.1 mmol of 1a in 1 mL toluene using 20 mol% catalyst for 3days. [b] Isolated combined yield after silica gel column chromatography.

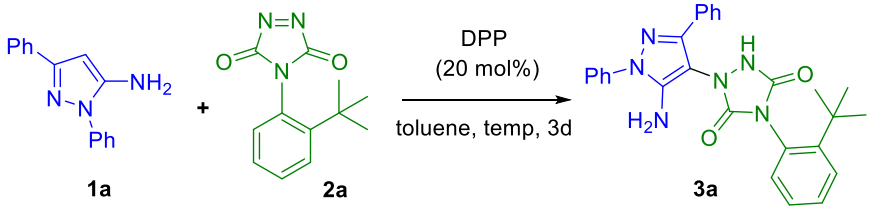
Table 5. Solvent concentration



entry[a]	Conc.	Yield (%)[b]
1	0.1	53
2	0.067	60
3	**0.050**	**65**
4.	0.033	50

[a]Reaction conditions: 0.1 mmol of 1a and 0.1 mmol of 2a, 20mol% of catalyst, toluene, rt. [b]Isolated yield after flash chromatography.

Table 6. Optimization of temperature



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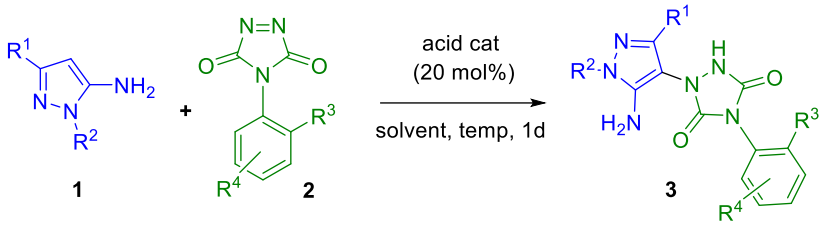
entry[a]	Temp.	Yield(%)[b]
1	**rt**	**65**
2	40	62
3	60	55
4	80	35

[a]Reaction conditions: 0.1 mmol of 1a and 0.1 mmol of 2a, 20mol% of catalyst, toluene with different temp. [b]Isolated yield after flash chromatography

5. General procedure for the synthesis of compound 3:



In an oven dried round bottom flask, **1** (0.1 mmol), **2** (0.1 mmol), 20 mol% of Catalsyt **DPP** were taken. 1 mL of toluene was added to the reaction mixture and stirred at rt for 1 day. Completion of reaction was checked by TLC. After the completion of reaction, solvent was concentrated and reaction mixture was directly purified by column chromatography on silica gel eluting with hexane/ethyl acetate (45/55) to afford desired product **3.**

References:

1. Tong,S.; Zhao,Z.; Hu,L.; Li,S.; *Org. Lett.* **2024**, *26* (46), 9877-9884
2. Zhang, J.-W.; Xu, J.-H.; Cheng, D.-J.; Shi, C.; Liu, X.-Y.; Tan, B.; *Nat. Commun.* **2016**, 7, 10677.

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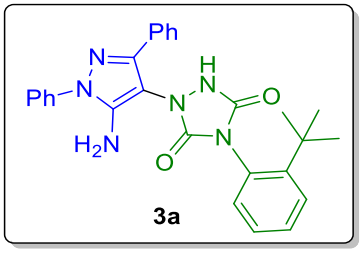
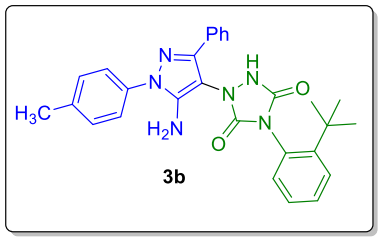
6. Characterisation of the products:

1-(5-amino-1,3-diphenyl-1H-pyrazol-4-yl)-4-(2-(tert-butyl)phenyl)-1,2,4-triazolidine-3,5-dione.



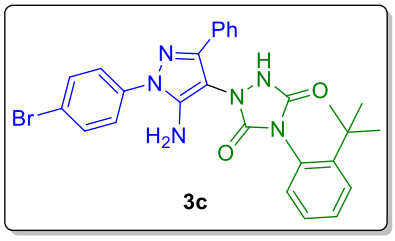
was obtained as a pale yellowish solid in 65% yield (30.29 mg) after column chromatography. R*f* = 0.40 in 3:2 ethyl acetate/hexane; M.P.: 210-215°C. **^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.59 (s, 2H), 7.41 (d, *J* = 15.8 Hz, 6H), 7.28 (s, 3H), 7.18 (s, 1H), 7.08 (s, 1H), 6.91 (s, 1H), 4.00 (s, 2H), 1.23 (s, 9H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 155.47, 154.48, 151.76, 149.22, 148.64, 144.20, 137.72, 131.59, 131.30, 130.26, 129.73, 128.82, 128.79, 128.20, 127.50, 127.43, 127.35, 124.12, 97.38, 35.70, 31.51. **HRMS (ESI) m/z**: $[M+Na]^+$ Calcd. for $C_{27}H_{26}N_6NaO_2^+$ 489.2010; Found 489.1968.

1-(5-amino-3-phenyl-1-(p-tolyl)-1H-pyrazol-4-yl)-4-(2-(tert-butyl)phenyl)-1,2,4-triazolidine-3,5-dione.



was obtained as a pale yellowish brown solid in 52% yield (25 mg) after column chromatography. R$_f$ = 0.60 in 3:2 ethyl acetate/hexane. M.P.: 230-235°C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.67 (d, *J* = 2.9 Hz, 1H), 7.65 (d, *J* = 1.8 Hz, 1H), 7.52 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.37 – 7.31 (m, 6H), 7.27 (s, 2H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 7.7 Hz, 1H), 2.40 (s, 3H), 1.31 (s, 9H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 154.37, 151.76, 149.20, 148.34, 144.11, 138.33, 135.09, 131.60, 131.33, 130.27, 130.23, 128.82, 128.79, 128.72, 127.48, 127.35, 124.13, 97.24, 35.70, 31.60, 21.18. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{28}H_{29}N_6O_2^+$ 481.2347; Found 481.2326.

1-(5-amino-1-(4-bromophenyl)-3-phenyl-1H-pyrazol-4-yl)-4-(2-(tert-butyl)phenyl)-1,2,4-triazolidine-3,5-dione.



was obtained as a pale yellowish brown solid in 38% yield (20.71 mg) after column chromatography. R$_f$ = 0.50 in 3:2 ethyl acetate/hexane. M.P.: 215-220°C. **^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.59 (d, *J* = 2.1 Hz, 2H), 7.55 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 8.7 Hz, 1H), 7.35 (s, 1H), 7.32 (s, 4H), 7.19 (d, *J* = 2.4 Hz, 2H), 6.95 (d, *J* = 7.8 Hz, 1H), 4.04 (s, 2H), 1.27 (s, 9H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 154.26, 151.81, 149.17, 148.72, 143.70, 136.80, 132.89, 131.45, 131.06, 130.38, 129.03, 128.92, 128.63, 127.55, 127.32, 125.48, 121.89, 98.23, 35.75, 31.54. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{27}H_{26}BrN_6O_2^+$ 545.1296; Found 545.1289.

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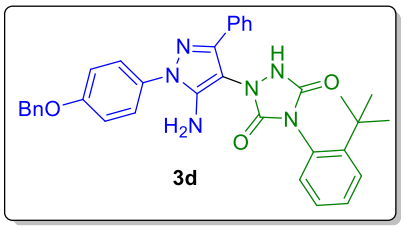
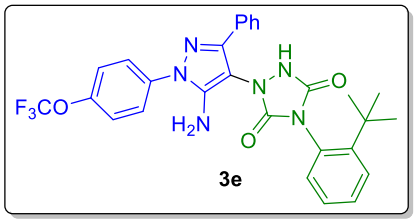
1-(5-amino-1-(4-(benzyloxy)phenyl)-3-phenyl-1H-pyrazol-4-yl)-4-(2-(tert-butyl)phenyl)-1,2,4-triazolidine-3,5-dione.



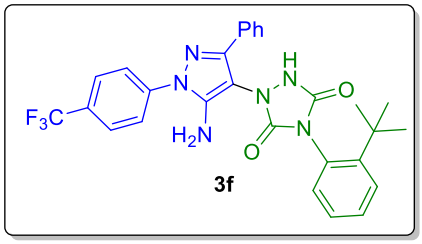
was obtained as a pale yellowish white solid in 55% yield (31.73 mg) after column chromatography. R*f* = 0.30 in 3:2 ethyl acetate/hexane. M.P.: 250-255°C. **^{1}H NMR (500 MHz, DMSO)** δ 7.67 (d, *J* = 7.6 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 8.9 Hz, 2H), 7.47 (d, *J* = 7.2 Hz, 2H), 7.41 (dq, *J* = 12.9, 7.5 Hz, 7H), 7.34 (d, *J* = 10.1 Hz, 2H), 7.18 (d, *J* = 8.9 Hz, 2H), 6.02 (s, 2H), 5.15 (s, 2H), 1.29 (s, 9H). **^{13}C NMR (126 MHz, DMSO)** δ 157.89, 155.13, 153.22, 151.37, 149.25, 148.01, 147.30, 137.18, 132.72, 132.03, 131.93, 130.61, 129.05, 129.02, 128.91, 128.49, 128.45, 128.19, 127.42, 126.89, 125.88, 125.77, 115.97, 70.01, 35.66, 31.67. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{34}H_{33}N_6O_3^+$573.2609; Found 573.2610.

1-(5-amino-3-phenyl-1-(4-(trifluoromethoxy)phenyl)-1H-pyrazol-4-yl)-4-(2-(tert-butyl)phenyl)-1,2,4-triazolidine-3,5-dione.



was obtained as a pale yellowish white solid in 47% yield (25.85 mg) after column chromatography. R*f* = 0.40 in 3:2 ethyl acetate/hexane. M.P.: 185-190°C. **^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.57 (d, *J* = 3.7 Hz, 2H), 7.43 (d, *J* = 9.1 Hz, 3H), 7.28 (d, *J* = 3.2 Hz, 3H), 7.24 (dd, *J* = 8.6, 3.4 Hz, 2H), 7.18 (d, *J* = 3.3 Hz, 1H), 7.08 (t, *J* = 9.1 Hz, 1H), 6.92 (d, *J* = 9.5 Hz, 1H), 4.00 (s, 2H), 1.23 (s, 9H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 151.81, 149.24, 148.90, 148.44, 144.23, 136.21, 131.53, 131.02, 130.29, 129.00, 128.87, 128.83, 128.73, 127.47, 127.25, 125.42, 122.19 (q, J = 258.3 Hz), 121.44, 119.39, 97.84, 35.70, 31.48. **^{19}F NMR (471 MHz, CDCl$_3$)** δ -57.93. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{28}H_{26}F_3N_6O_3^+$ 551.2013; Found 551.2002.

1-(5-amino-3-phenyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrazol-4-yl)-4-(2-(tert-butyl)phenyl)-1,2,4-triazolidine-3,5-dione.



was obtained as a white solid in 57% yield (30.49 mg) after column chromatography. R*f* = 0.45 in 3:2 ethyl acetate/hexane. M.P.: 210-215°C.**^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 4H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.29 (s, 3H), 7.19 (s, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 4.05 (s, 2H), 1.22 (s, 9H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 154.44, 151.86, 149.31, 149.22, 144.39, 140.75, 131.46, 130.86, 130.34, 129.12, 128.88, 128.68, 127.46, 127.27, 126.86, 126.83, 124.76, 123.47, 122.60, 98.32, 35.70, 31.48. **^{19}F NMR (471 MHz, CDCl$_3$)** δ -62.39. The coupling constant between C-F are as follow.

[1] JCF = (124.76-122.60) x 126= 272.16Hz

[2] JCF = (128.88-128.68) x 126= 25.2Hz

[3] JCF = (126.86-126.83) x 126= 3.78Hz

HRMS (ESI) m/z: $[M+H]^+$ Calcd. for $C_{28}H_{26}F_3N_6O_2^+$ 535.2064; Found 535.2055.

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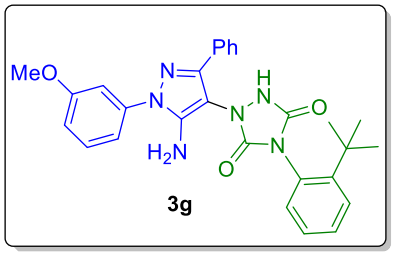
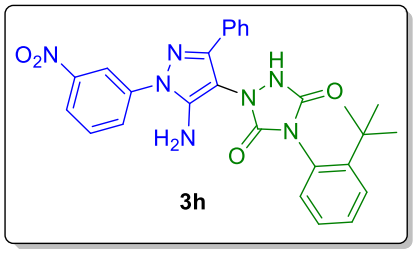
1-(5-amino-1-(3-methoxyphenyl)-3-phenyl-1H-pyrazol-4-yl)-4-(2-(tert-butyl)phenyl)-1,2,4-triazolidine-3,5-dione.



3g

was obtained as a white solid in 70% yield (34.72 mg) after column chromatography. R*f* = 0.35 in 3:2 ethyl acetate/hexane. M.P.: 150-155°C. **^{1}H NMR (400 MHz, CD_3OD_SPE)** δ 7.73 (d, *J* = 2.4 Hz, 1H), 7.71 (d, *J* = 1.9 Hz, 1H), 7.63 (d, *J* = 6.6 Hz, 1H), 7.46 (d, *J* = 2.1 Hz, 1H), 7.43 (dd, *J* = 6.0, 1.9 Hz, 3H), 7.35 – 7.31 (m, 1H), 7.28 (s, 1H), 7.20 (d, *J* = 7.4 Hz, 2H), 7.02 (dd, *J* = 9.2, 2.6 Hz, 2H), 3.86 (s, 3H), 1.34 (s, 9H) **^{13}C NMR (101 MHz, CD_3OD_SPE)** δ 160.71, 155.42, 152.06, 149.81, 149.22, 147.05, 139.08, 131.68, 131.50, 131.25, 130.13, 129.80, 129.40, 128.55, 128.42, 128.33, 127.26, 126.98, 116.07, 113.81, 109.88, 54.67, 35.27, 30.79. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{28}H_{29}N_6O_3^+$ 497.2296; Found 497.2296.

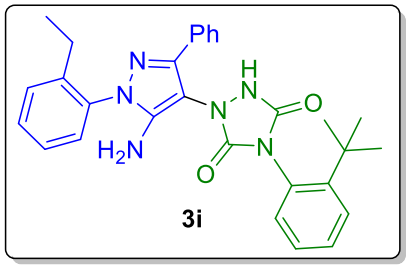
1-(5-amino-1-(3-nitrophenyl)-3-phenyl-1H-pyrazol-4-yl)-4-(2-(tert-butyl)phenyl)-1,2,4-triazolidine-3,5-dione.



3h

was obtained as a white solid in 59% yield (30.21 mg) after column chromatography. R*f* = 0.40 in 3:2 ethyl acetate/hexane. M.P.: 250-255°C. **^{1}H NMR (500 MHz, CD_3OD_SPE)** δ 8.58 (t, *J* = 2.2 Hz, 1H), 8.29 (s, 1H), 8.12 (d, *J* = 7.9 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.75 (dd, *J* = 7.5, 2.2 Hz, 2H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 5.8 Hz, 4H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 1.35 (s, 9H). **^{13}C NMR (126 MHz, CD_3OD_SPE)** δ 153.35, 150.73, 149.21, 148.85, 148.84, 147.77, 139.44, 131.66, 131.07, 130.49, 129.79, 129.38, 128.73, 128.44, 128.32, 127.23, 126.97, 126.96, 121.89, 118.43, 35.25, 30.77. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{27}H_{26}N_7O_4^+$ 512.2041; Found 512.2039.

1-(5-amino-1-(2-ethylphenyl)-3-phenyl-1H-pyrazol-4-yl)-4-(2-(tert-butyl)phenyl)-1,2,4-triazolidine-3,5-dione.



3i

was obtained as a brown solid in 65% yield (32.17 mg) after column chromatography. R*f* = 0.40 in 3:2 ethyl acetate/hexane. M.P.: 140-145°C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.71 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.53 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.43 (dd, *J* = 6.9, 4.9 Hz, 2H), 7.37 (d, *J* = 7.6 Hz, 3H), 7.30 (d, *J* = 11.6 Hz, 3H), 7.19 (t, *J* = 6.7 Hz, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 3.92 (s, 2H), 2.51 (q, *J* = 7.5 Hz, 2H), 1.35 (s, 9H), 1.12 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 154.42, 151.56, 149.23, 147.85, 144.66, 142.79, 135.13, 131.63, 131.51, 131.35, 130.30, 130.20, 129.98, 128.84, 128.78, 128.72, 128.68, 128.13, 127.47, 127.24, 127.09, 35.73, 31.55, 24.15, 14.50. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{29}H_{31}N_6O_2^+$ 495.2503; Found 495.2503.

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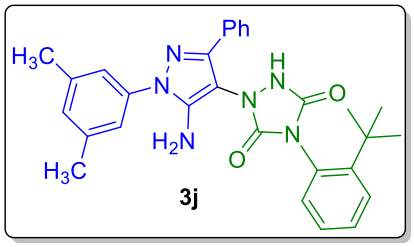
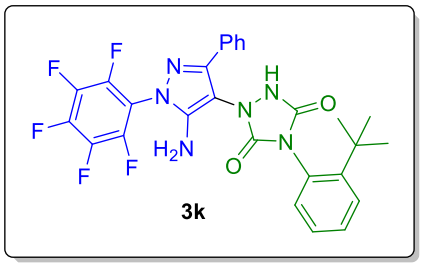
1-(5-amino-1-(3,5-dimethylphenyl)-3-phenyl-1H-pyrazol-4-yl)-4-(2-(tert-butyl)phenyl)-1,2,4-triazolidine-3,5-dione.



3j

was obtained as a green solid in 61% yield (31.19 mg) after column chromatography. R*f* = 0.40 in 3:2 ethyl acetate/hexane**.** M.P.: 210-215°C. **^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.60 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 7.1 Hz, 3H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 22.4 Hz, 4H), 4.12 (s, 2H), 2.27 (s, 6H), 1.23 (s, 9H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 154.48, 151.70, 149.20, 148.33, 144.14, 139.63, 137.40, 131.71, 131.29, 130.16, 129.94, 128.84, 128.80, 128.76, 127.45, 127.41, 121.83, 97.16, 35.67, 31.50, 21.29. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{29}H_{31}N_6O_2^+$ 495.2503; Found 495.2502.

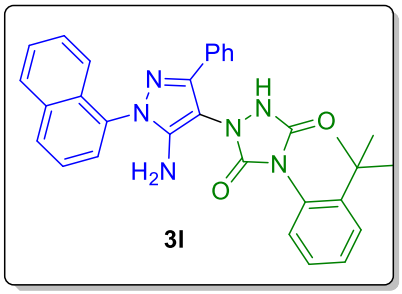
1-(5-amino-1-(perfluorophenyl)-3-phenyl-1H-pyrazol-4-yl)-4-(2-(tert-butyl)phenyl)-1,2,4-triazolidine-3,5-dione.



3k

was obtained as a light brown solid in 37% yield (20.57 mg) after column chromatography. R*f* = 0.40 in 3:2 ethyl acetate/hexane. M.P.: 185-190°C. **^{1}H NMR (500 MHz, CD$_3$OD_SPE)** δ 7.70 (s, 2H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.44 (d, *J* = 2.9 Hz, 4H), 7.32 (d, *J* = 7.4 Hz, 1H), 7.26 (s, 1H), 1.34 (s, 9H). **^{13}C NMR (126 MHz, CD$_3$OD_SPE)** δ 153.16, 152.35, 151.95, 149.75, 149.22, 131.63, 130.79, 129.78, 129.35, 128.90, 128.46, 128.34, 127.23, 126.95, 35.26, 30.77. **^{19}F NMR (471 MHz, MeOD)** δ -146.47, -146.52, -146.87, -146.92, -154.17, -154.21, -154.25, -154.26, -164.04, -164.08, -164.14, -164.20, -164.24. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{27}H_{31}F_5N_6O_2^+$ 557.1719; Found 557.1719.

1-(5-amino-1-(naphthalen-1-yl)-3-phenyl-1H-pyrazol-4-yl)-4-(2-(tert-butyl)phenyl)-1,2,4-triazolidine-3,5-dione.



3l

was obtained as a bwown solid in 48% yield (24.82 mg) after column chromatography. R*f* = 0.40 in 3:2 ethyl acetate/hexane. M.P.: 190-195°C. **^{1}H NMR (500 MHz, CDCl$_3$)** δ 8.00 (d, *J* = 7.4 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 1H), 7.58 – 7.52 (m, 3H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 1H), 7.35 (d, *J* = 7.2 Hz, 2H), 7.16 (t, *J* = 8.2 Hz, 1H), 7.06 (t, *J* = 7.7 Hz, 1H), 7.00 (d, *J* = 7.9 Hz, 1H), 1.31 (s, 3H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 154.32, 153.55, 150.60, 148.19, 147.62, 144.58, 133.52, 132.22, 130.59, 130.43, 129.19, 129.06, 128.84, 127.80, 127.75, 127.71, 127.65, 127.23, 126.80, 126.40, 126.29, 126.05, 124.74, 124.38, 122.19, 34.66, 30.56. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{31}H_{29}N_6O_2^+$ 517.2347; Found 517.2345.

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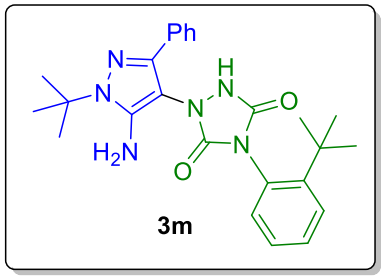
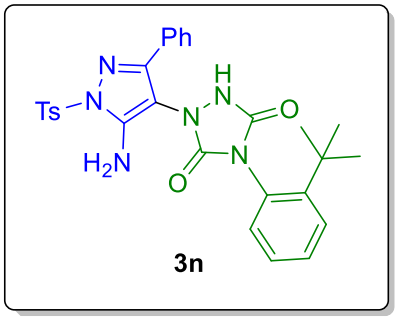
1-(5-amino-1-(tert-butyl)-3-phenyl-1H-pyrazol-4-yl)-4-(2-(tert-butyl)phenyl)-1,2,4-triazolidine-3,5-dione.



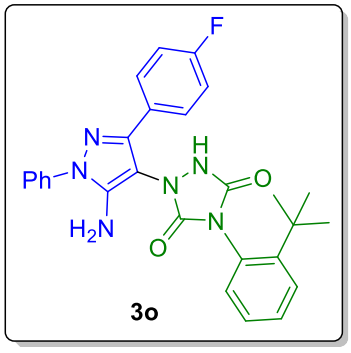
was obtained as a brown solid in 55% yield (24.53 mg) after column chromatography. R*f* = 0.40 in 3:2 ethyl acetate/hexane. M.P.: 130-135°C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.66 – 7.62 (m, 2H), 7.56 (d, *J* = 6.7 Hz, 1H), 7.40 – 7.31 (m, 4H), 7.22 (d, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 7.7 Hz, 1H), 3.95 (s, 2H), 1.60 (s, 9H), 1.34 (s, 9H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 154.36, 151.69, 149.20, 144.93, 143.91, 132.11, 131.65, 130.19, 128.95, 128.75, 128.69, 128.17, 127.50, 127.14, 99.08, 59.86, 35.70, 31.53, 29.10. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{25}H_{31}N_6O_2^+$ 447.2503; Found 447.2475.

1-(5-amino-3-phenyl-1-tosyl-1H-pyrazol-4-yl)-4-(2-(tert-butyl)phenyl)-1,2,4-triazolidine-3,5-dione.



was obtained as a pale yellowish solid in 38% yield (20.71mg) after column chromatography. R*f* = 0.40 in 3:2 ethyl acetate/hexane**.** M.P.: 130-135°C. **^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.80 (d, *J* = 7.1 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 4H), 7.18 (s, 2H), 6.94 (d, *J* = 7.8 Hz, 1H), 5.34 (s, 2H), 2.30 (s, 3H), 1.23 (s, 9H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 155.64, 154.69, 152.96, 151.55, 149.14, 147.84, 146.42, 133.60, 131.44, 130.53, 130.41, 130.21, 129.70, 129.06, 128.83, 128.71, 128.16, 127.65, 127.55, 35.67, 31.50, 22.70. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{28}H_{29}N_6O_4S^+$ 545.1966; Found 545.1961.

1-(5-amino-3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4-(2-(tert-butyl)phenyl)-1,2,4-triazolidine-3,5-dione.



was obtained as a yellowish white solid in 73% yield (35.40 mg) after column chromatography. R*f* = 0.40 in 3:2 ethyl acetate/hexane. M.P.: 220-225°C. **^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.62 – 7.57 (m, 2H), 7.47 (d, *J* = 6.7 Hz, 1H), 7.42 (d, *J* = 6.1 Hz, 3H), 7.34 (t, *J* = 6.1 Hz, 1H), 7.28 (t, *J* = 7.7 Hz, 1H), 7.19 (s, 1H), 7.16 – 7.10 (m, 1H), 7.02 – 6.93 (m, 3H), 4.05 (s, 2H), 1.26 (s, 9H).
^{13}C NMR (126 MHz, CDCl$_3$) δ 163.11, 161.14, 153.39, 150.79, 148.12, 146.73, 142.99, 136.52, 130.46, 129.33, 128.77, 128.32, 128.25, 127.88, 127.64, 127.36, 126.48, 123.13, 114.87, 114.70, 34.70, 30.50. **^{19}F NMR (471 MHz, CDCl$_3$)** δ -112.31.
The coupling constants between C-F are as follow,
^{1} JCF = (163.11-161.14) x 126= 248.22Hz
^{2} JCF = (114.87-114.70) x 126= 21.42Hz
^{3} JCF = (128.32-128.25) x 126= 8.82Hz
HRMS (ESI) m/z: $[M+H]^+$ Calcd. for $C_{27}H_{26}FN_6O_2^+$ 485.2096; Found 485.2083.

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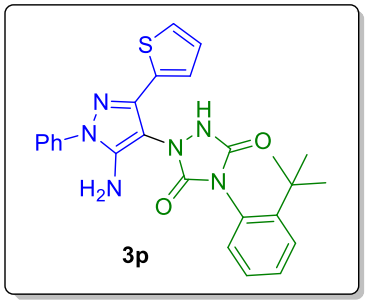
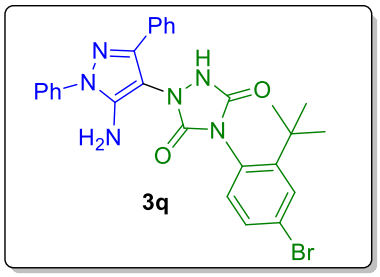
1-(5-amino-1-phenyl-3-(thiophen-2-yl)-1H-pyrazol-4-yl)-4-(2-(tert-butyl)phenyl)-1,2,4-triazolidine-3,5-dione.



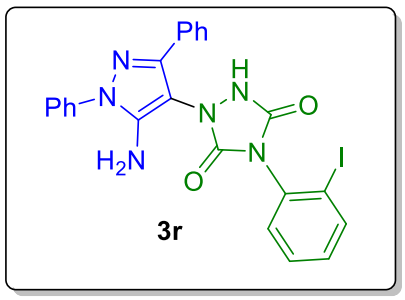
was obtained as a pale yellowish solid in 47% yield (22.23 mg) after column chromatography. R*f* = 0.45 in 3:2 ethyl acetate/hexane. M.P.: 240-245°C. **^{1}H NMR (500 MHz, CD_3OD_SPE)** δ 7.65 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 7.4 Hz, 2H), 7.57 (d, *J* = 7.4 Hz, 2H), 7.49 (s, 1H), 7.47 – 7.42 (m, 3H), 7.33 (dd, *J* = 14.6, 7.5 Hz, 2H), 7.13 (dd, *J* = 5.1, 3.6 Hz, 1H), 1.40 (s, 9H). **^{13}C NMR (126 MHz, CD_3OD_SPE)** δ 153.35, 152.13, 149.26, 146.90, 144.51, 137.99, 132.52, 131.72, 129.81, 129.73, 129.46, 129.36, 128.34, 128.06, 127.08, 127.00, 125.98, 125.77, 124.34, 35.30, 30.82. . **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{25}H_{25}N_6O_2S^+$ 473.1755; Found 473.1745.

1-(5-amino-1,3-diphenyl-1H-pyrazol-4-yl)-4-(4-bromo-2-(tert-butyl)phenyl)-1,2,4-triazolidine-3,5-dione.



was obtained as a brown solid in 53% yield (28.88 mg) after column chromatography. R*f* = 0.40 in 3:2 ethyl acetate/hexane. M.P.: 215-220°C. **^{1}H NMR (500 MHz, CD_3OD_SPE)** δ 7.75 (d, *J* = 2.2 Hz, 1H), 7.71 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.57 (t, *J* = 8.0 Hz, 2H), 7.50 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.47 (d, *J* = 9.2 Hz, 1H), 7.42 (d, *J* = 4.6 Hz, 3H), 7.21 (d, *J* = 8.6 Hz, 1H), 1.33 (s, 9H). **^{13}C NMR (126 MHz, CD_3OD_SPE)** δ 152.84, 151.78, 151.65, 149.82, 147.08, 138.13, 133.54, 131.73, 131.48, 131.26, 130.16, 129.36, 128.82, 128.52, 128.40, 128.00, 127.21, 124.28, 123.86, 35.46, 30.36. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{27}H_{26}BrN_6O_2^+$ 545.1296; Found 545.1286.

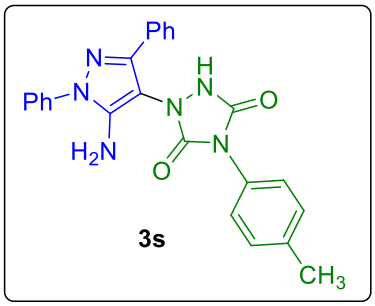
1-(5-amino-1,3-diphenyl-1H-pyrazol-4-yl)-4-(2-iodophenyl)-1,2,4-triazolidine-3,5-dione.



was obtained as a light brown solid in 77% yield (41.35mg) after column chromatography. R*f* = 0.40 in 3:2 ethyl acetate/hexane. M.P.: 210-215°C. **^{1}H NMR (500 MHz, CD_3OD_SPE)** δ 8.03 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.83 – 7.77 (m, 2H), 7.64 (dd, *J* = 7.8, 2.2 Hz, 2H), 7.59 – 7.52 (m, 3H), 7.51 (d, *J* = 6.6 Hz, 1H), 7.45 (dt, *J* = 14.7, 7.6 Hz, 3H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.26 (td, *J* = 7.6, 1.8 Hz, 1H). **^{13}C NMR (126 MHz, CD_3OD_SPE)** δ 153.61, 151.33, 149.36, 146.98, 139.65, 138.15, 134.37, 131.22, 131.12, 131.04, 130.27, 129.36, 129.31, 129.24, 128.49, 128.46, 127.99, 127.12, 124.27. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{23}H_{18}IN_6O_2^+$ 537.0531; Found 537.0523.

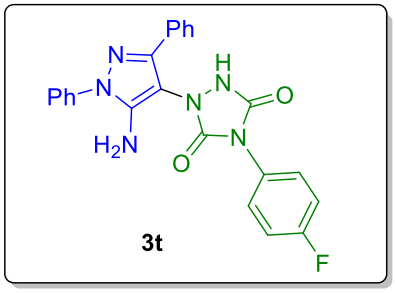
Synlett | DOI 10.1055/a-2726-4350 |

1-(5-amino-1,3-diphenyl-1H-pyrazol-4-yl)-4-(p-tolyl)-1,2,4-triazolidine-3,5-dione.



was obtained as a light brown solid in 75% yield 31.80mg) after column chromatography. R*f* = 0.45 in 3:2 ethyl acetate/hexane**.** M.P.: 240-245°C. **^{1}H NMR (400 MHz, CD$_3$OD_SPE)** δ 7.69 – 7.62 (m, 4H), 7.57 (t, *J* = 7.8 Hz, 2H), 7.48 – 7.39 (m, 4H), 7.33 (d, *J* = 6.4 Hz, 4H), 2.39 (s, 3H). **^{13}C NMR (101 MHz, CD$_3$OD_SPE)** δ 152.33, 151.68, 149.44, 147.10, 138.40, 138.15, 131.41, 129.36, 129.29, 128.97, 128.52, 128.42, 127.96, 126.76, 126.08, 125.95, 124.25, 19.80. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{24}H_{21}N_6O_2^+$ 425.1721; Found 425.1709.

1-(5-amino-1,3-diphenyl-1H-pyrazol-4-yl)-4-(4-fluorophenyl)-1,2,4-triazolidine-3,5-dione.



was obtained as a white solid in 66% yield 28.20mg) after column chromatography. R*f* = 0.40 in 3:2 ethyl acetate/hexane. M.P.: 220-225°C. **^{1}H NMR (400 MHz, CD$_3$OD_SPE)** δ 7.70 – 7.66 (m, 2H), 7.66 – 7.61 (m, 2H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.55 – 7.51 (m, 4H), 7.48 – 7.38 (m, 2H), 7.23 (d, *J* = 8.8 Hz, 2H). **^{13}C NMR (101 MHz, CD$_3$OD_SPE**) δ 163.35, 160.89, 151.99, 151.35, 149.45, 147.07, 138.13, 131.38, 129.37, 128.54, 128.45, 128.32, 128.23, 127.98, 127.79, 127.76, 126.77, 124.25, 115.66, 115.43.**^{19}F NMR (471 MHz, MeOD)** δ -114.93.

The coupling constants between C-F are as follow,

^{1} JCF = (163.35-160.89) x 101= 248.46Hz

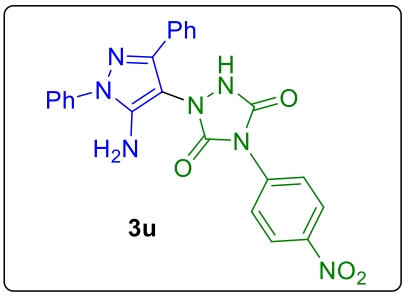
^{2} JCF = (115.66-115.43) x 101= 23.23Hz

^{3} JCF = (128.32-128.23) x 101= 9.09Hz

4 JCF = (127.79-127.76) x 101= 3.03Hz

HRMS (ESI) m/z: $[M+H]^+$ Calcd. for $C_{23}H_{18}FN_6O_2^+$ 429.1470; Found 429.1458.

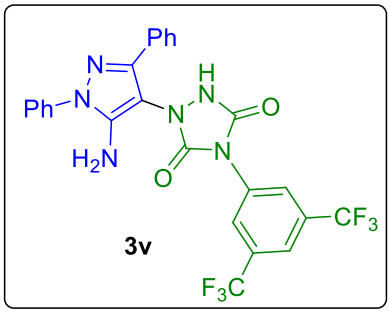
1-(5-amino-1,3-diphenyl-1H-pyrazol-4-yl)-4-(4-nitrophenyl)-1,2,4-triazolidine-3,5-dione



was obtained as a yellow solid in 72% yield 32.80mg) after column chromatography. R*f* = 0.30 in 3:2 ethyl acetate/hexane**.** M.P.: 200-205°C. **^{1}H NMR (500 MHz, MeOD)** δ 8.22 (d, *J* = 9.2 Hz, 2H), 7.78 (d, *J* = 9.1 Hz, 2H), 7.56 – 7.52 (m, 2H), 7.49 (d, *J* = 7.4 Hz, 2H), 7.43 (t, *J* = 7.9 Hz, 2H), 7.34 – 7.26 (m, 3H), 7.25 – 7.21 (m, 1H). **^{13}C NMR (126 MHz, MeOD)** δ 151.06, 150.40, 149.42, 146.98, 146.50, 138.14, 137.79, 131.35, 129.35, 128.51, 128.41, 127.98, 126.75, 125.72, 124.26, 123.81, 117.89. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{23}H_{18}N_7O_4^+$ 456.1415; Found 456.1379.

Synlett | DOI 10.1055/a-2726-4350 |

1-(5-amino-1,3-diphenyl-1H-pyrazol-4-yl)-4-(3,5-bis(trifluoromethyl)phenyl)-1,2,4-triazolidine-3,5-dione



3v

was obtained as a light brown solid in 56% yield 30.57mg) after column chromatography. R*f* = 0.45 in 3:2 ethyl acetate/hexane. M.P.: 210-215°C. **^{1}H NMR (400 MHz, CD_3OD_SPE)** δ 8.32 (s, 2H), 8.01 (s, 1H), 7.74 – 7.70 (m, 2H), 7.66 – 7.62 (m, 2H), 7.57 (s, 2H), 7.44 (s, 3H), 7.41 – 7.36 (m, 1H). **^{13}C NMR (101 MHz, CD_3OD_SPE)** δ 152.96, 150.86, 150.26, 149.49, 146.90, 138.10, 134.18, 134.12, 132.44, 132.11, 132.09, 131.77, 131.43, 131.27, 129.38, 128.55, 128.46, 128.00, 127.13, 126.82, 125.42, 125.38, 125.10, 124.42, 124.26, 121.72, 120.76, 120.72, 120.68, 119.02. **^{19}F NMR (471 MHz, MeOD)** δ -64.37. The coupling constants between C-F are as follow,

[1] JCF = (124.42.72-121.72) x 101= 272.7Hz

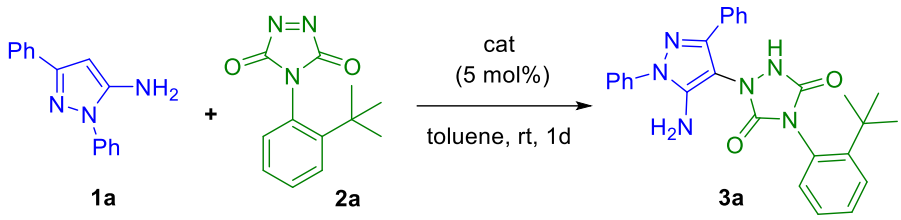
[2] JCF = (132.11-131.77) x 101= 34.34Hz

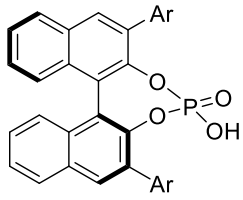
[3] JCF = (120.72-120.68) x 101= 4.04Hz

4 JCF = (125.72-125.38) x 101= Hz **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{25}H_{17}F_6N_6O_2^+$ 547.1312; Found 547.1297.

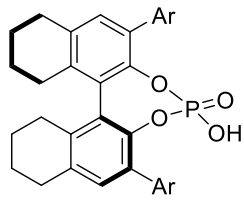
Synlett | DOI 10.1055/a-2726-4350 |

7. Preliminary results for asymmetric synthesis:





I, Ar=2,4,6-(^{i}Pr)$_3$C$_6$H$_6$
II, Ar=3,5-(CF$_3$)$_2$C$_6$H$_3$
III, Ar=2,4,6-(C$_6$H$_{11}$)$_3$-C$_6$H$_2$
IV, Ar=SiPh$_3$



V, Ar=2,4,6-(^{i}Pr)$_3$C$_6$H$_6$

Entry	catalyst	Yield(%)	Ee(%)
1.	**I**	**50**	**3**
2.	**II**	**60**	**1**
3.	**III**	**65**	**2**
4.	**IV**	**55**	**1**
5.	**V**	**40**	**9**

Synlett | DOI 10.1055/a-2726-4350 |

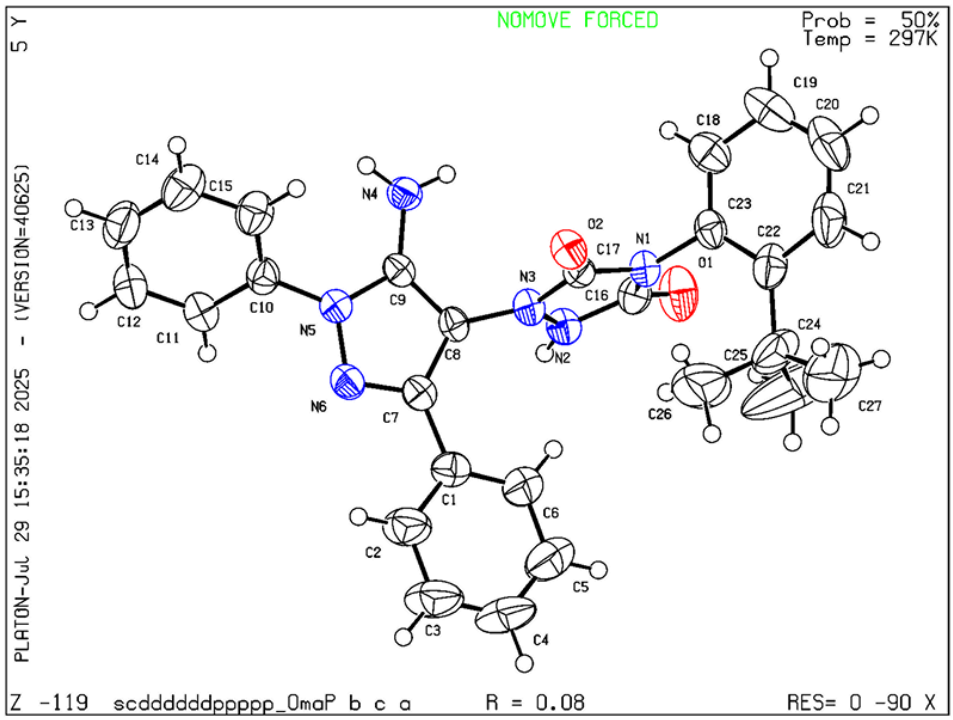
8. Single crystal X-ray diffraction analysis:

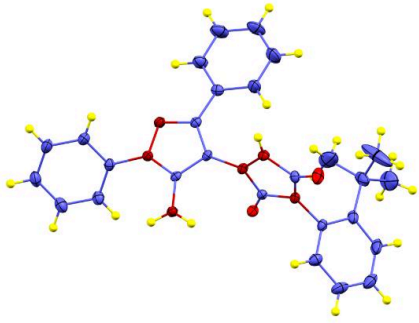
Single crystal X-ray diffraction analysis of **3a**: The compound 3aq was dissolved in minimum amount of hot ethyl acetate and kept the solution at room temperature for 96 h to give neddle like crystal. The crystallographic refinement parameters are given below:

Device type	Bruker APEX-II CCD
CCDC No.	2476941
Empirical formula	$C_{27}H_{26}N_6O_2$
Formula weight	466.54
Temperature/K	297.00
Crystal system	orthorhombic
Space group	Pbca
a/Å	24.385(11)
b/Å	7.612(3)
c/Å	26.681(12)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	4952(4)
Z	8
ρ_{calc}g/cm^3	1.251
μ/mm^{-1}	0.082
F(000)	1968.0
Crystal size/mm^3	0.30 × 0.19 × 0.18
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.526 to 49.982
Index ranges	-28 ≤ h ≤ 28, -9 ≤ k ≤ 9, -31 ≤ l ≤ 31
Reflections collected	88097
Independent reflections	4324 [R_{int} = 0.0718, R_{sigma} = 0.0269]
Data/restraints/parameters	4324/0/319
Goodness-of-fit on F^2	1.167
Final R indexes [I>=2σ (I)]	R_1 = 0.0766, wR_2 = 0.1636
Final R indexes [all data]	R_1 = 0.0897, wR_2 = 0.1738
Largest diff. peak/hole / e Å^{-3}	0.48/-0.43

Synlett | DOI 10.1055/a-2726-4350 |

Datablock scddddddppppp_0ma_a - ellipsoid plot





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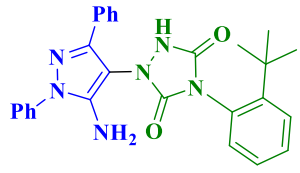
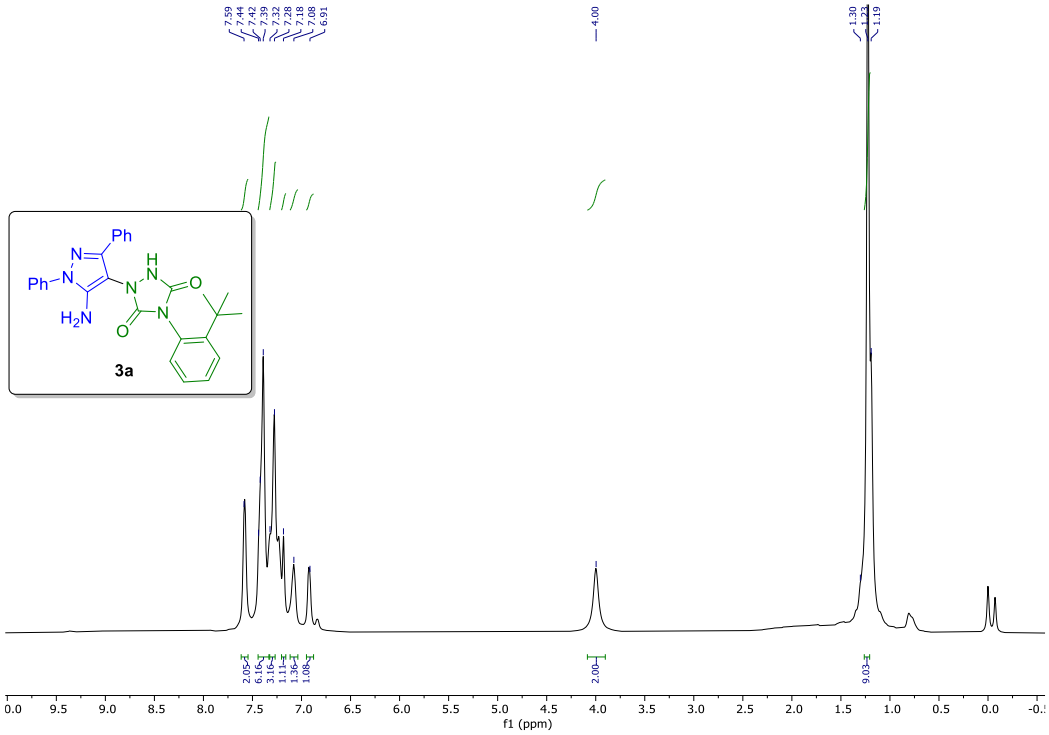


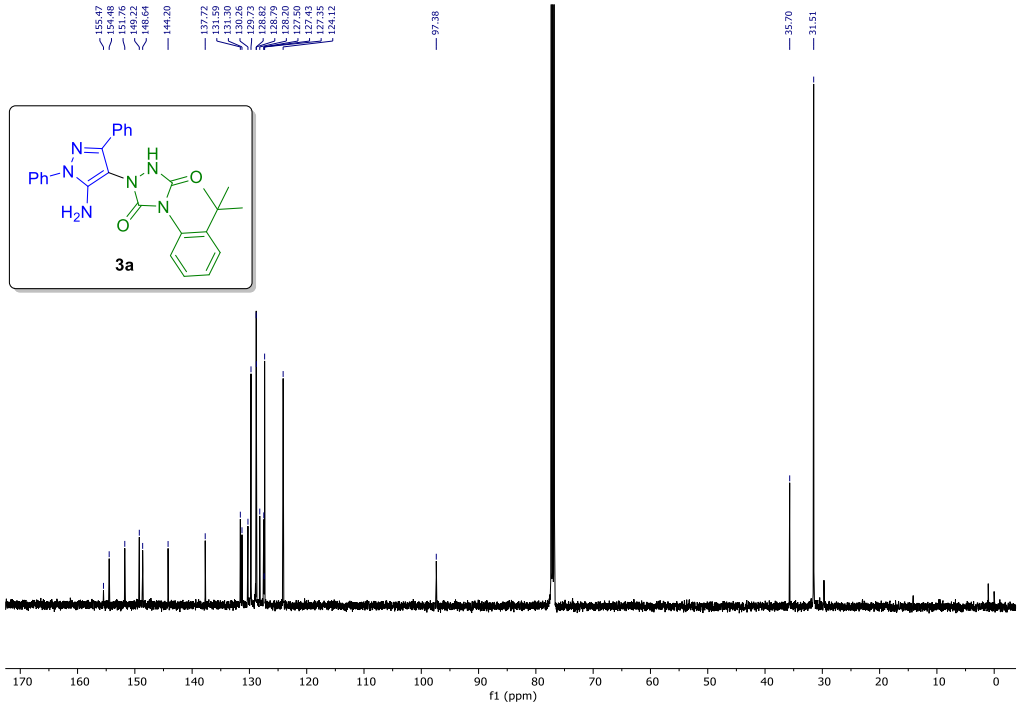
Synlett | DOI 10.1055/a-2726-4350 |

9. NMR spectra of the products:

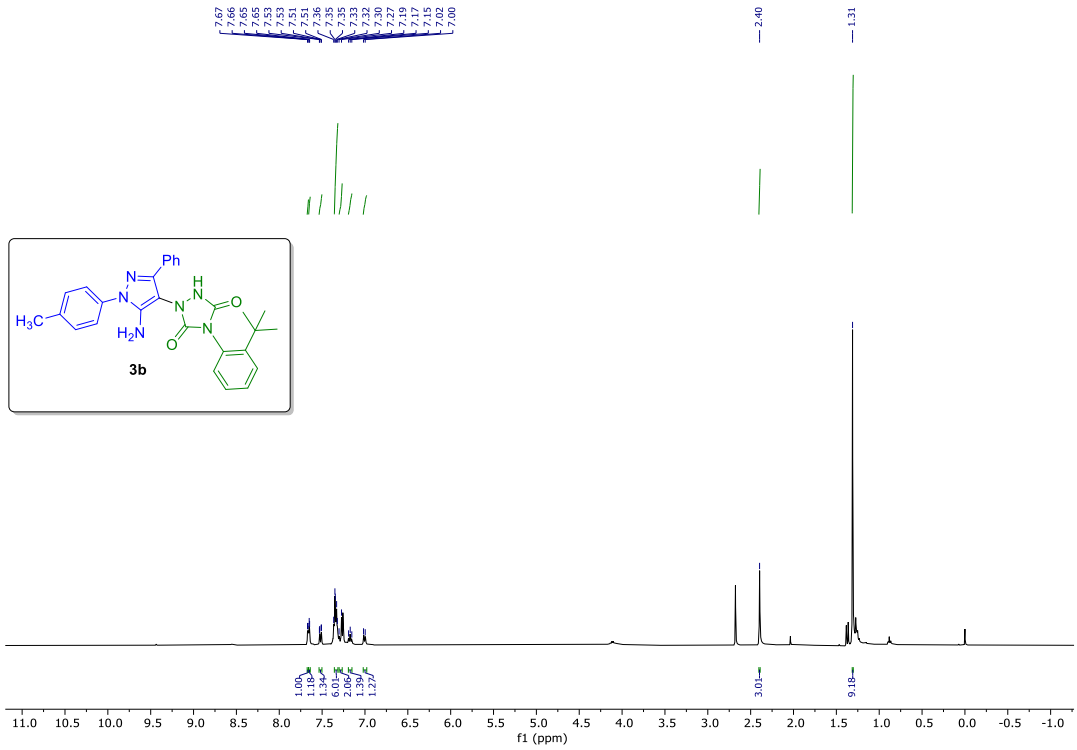
^{1}H NMR (500 MHz, $CDCl_3$)



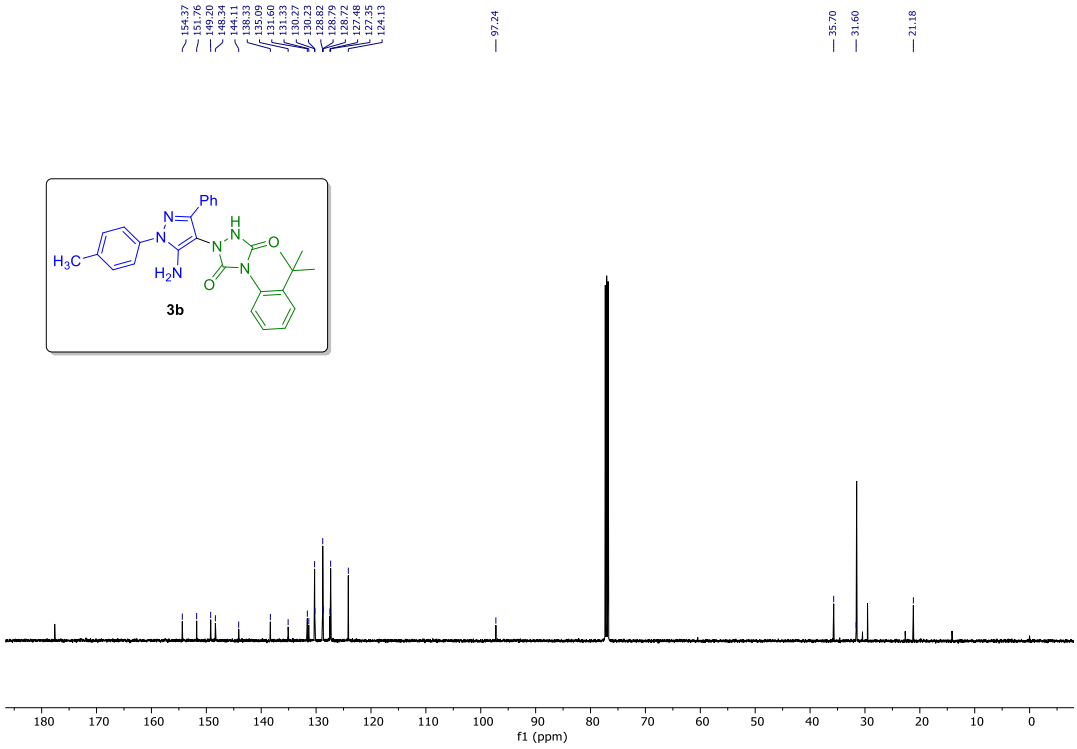
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)

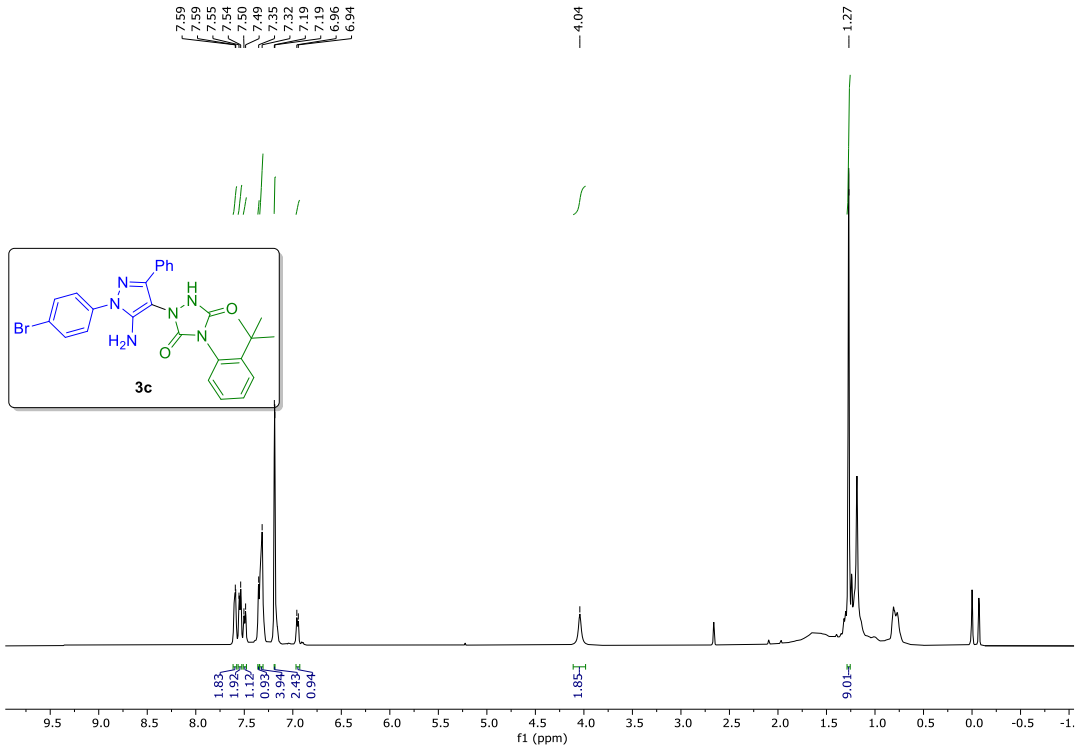


^{13}C NMR (126 MHz, $CDCl_3$)

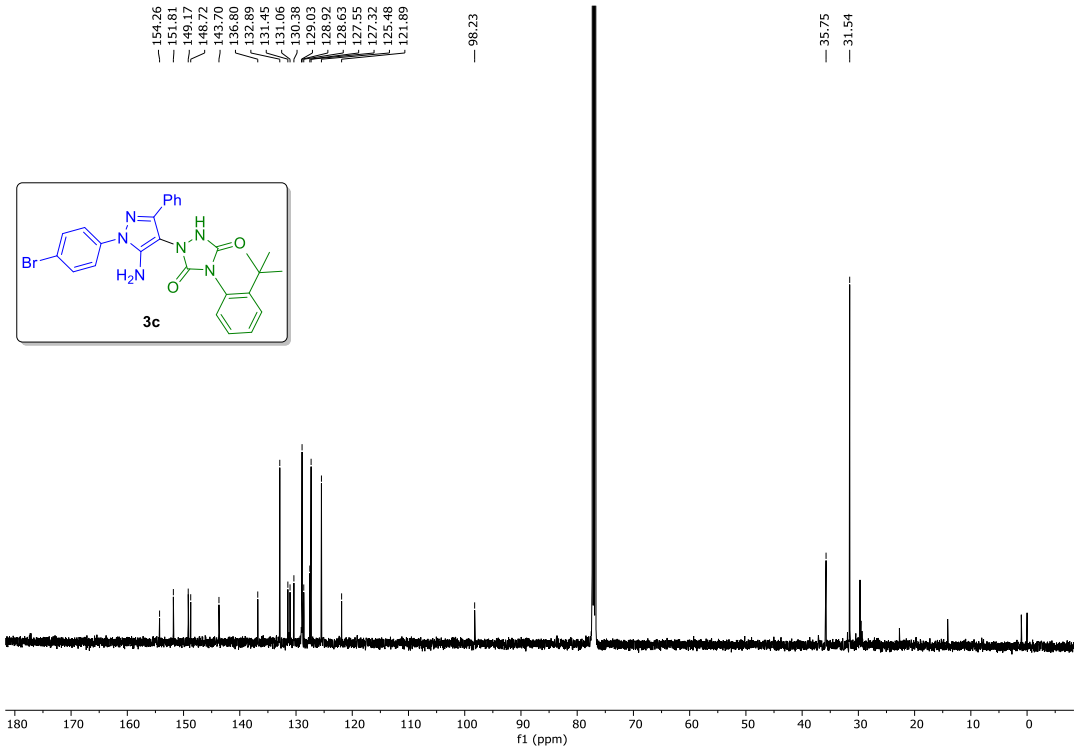


Synlett | DOI 10.1055/a-2726-4350 |

^{1}H NMR (500 MHz, $CDCl_3$)

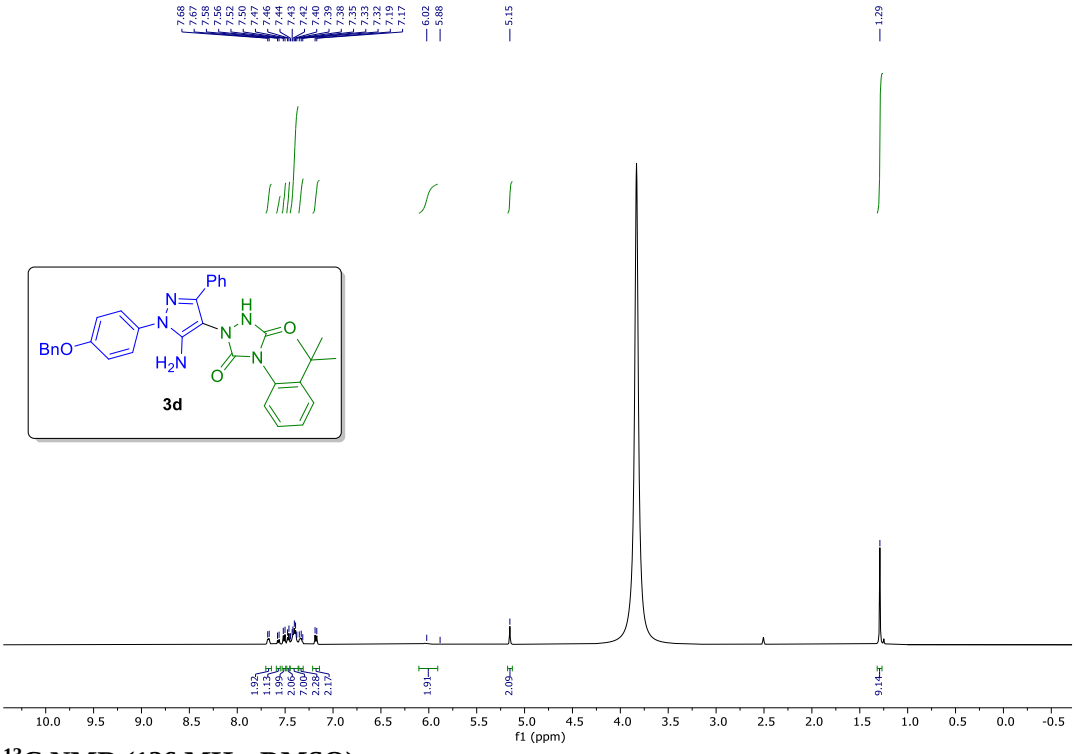


^{13}C NMR (126 MHz, $CDCl_3$)

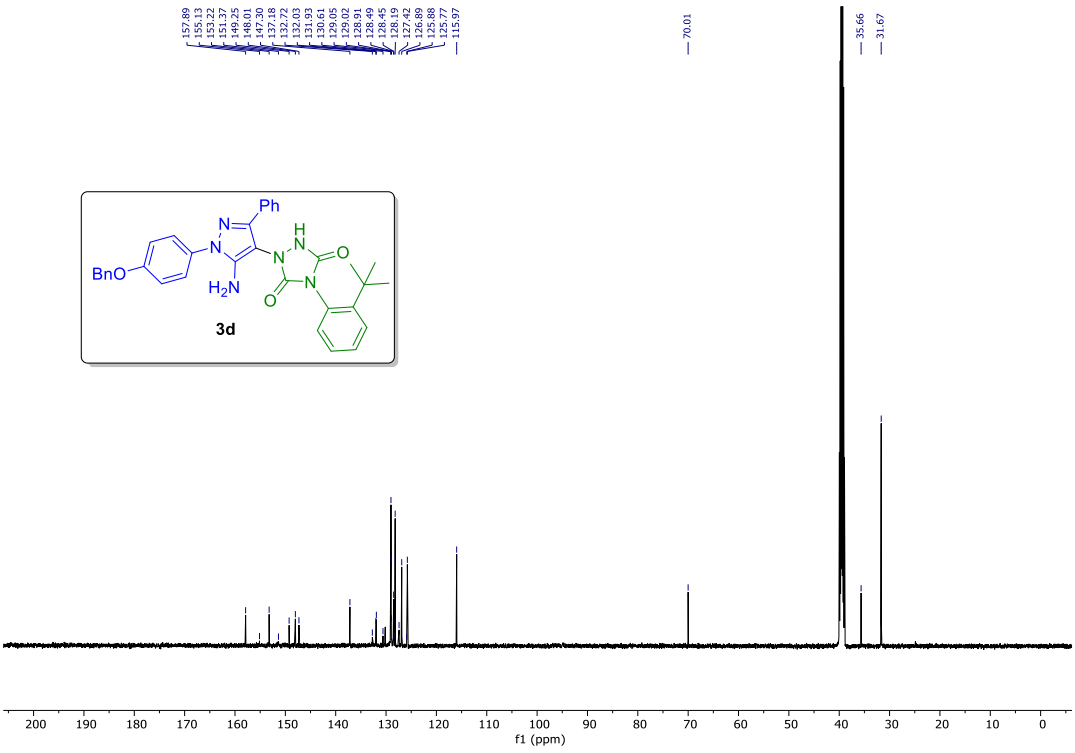


Synlett | DOI 10.1055/a-2726-4350 |

^{1}H NMR (500 MHz, DMSO)

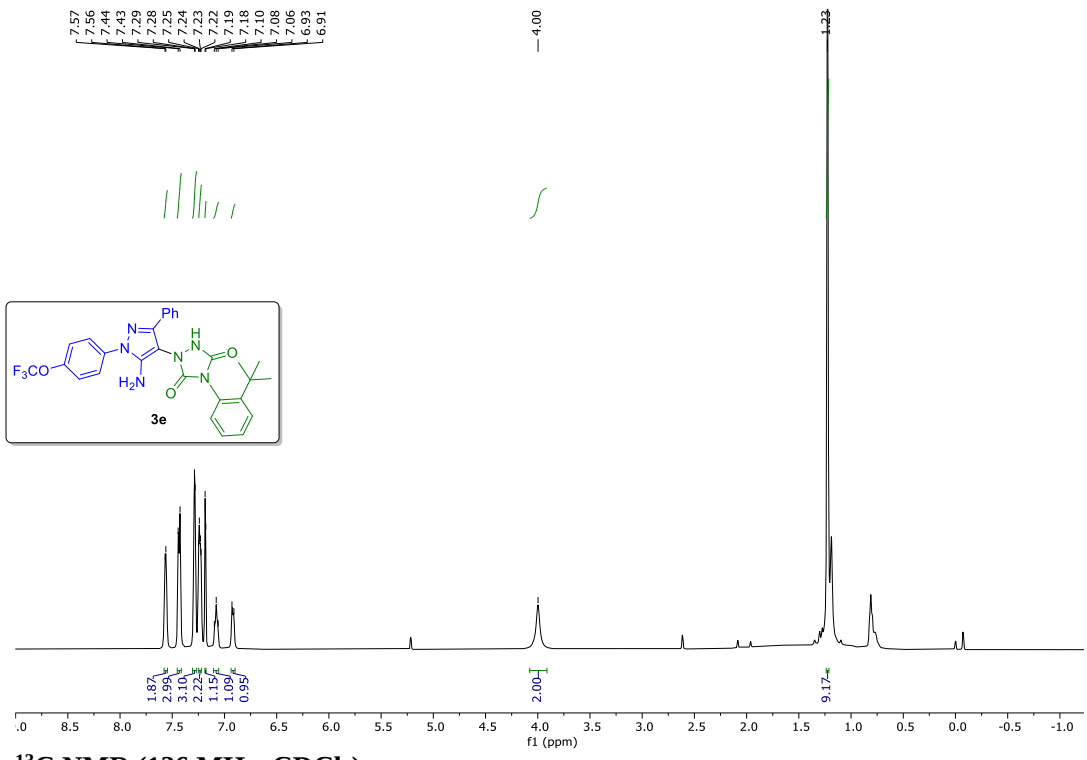


^{13}C NMR (126 MHz, DMSO)

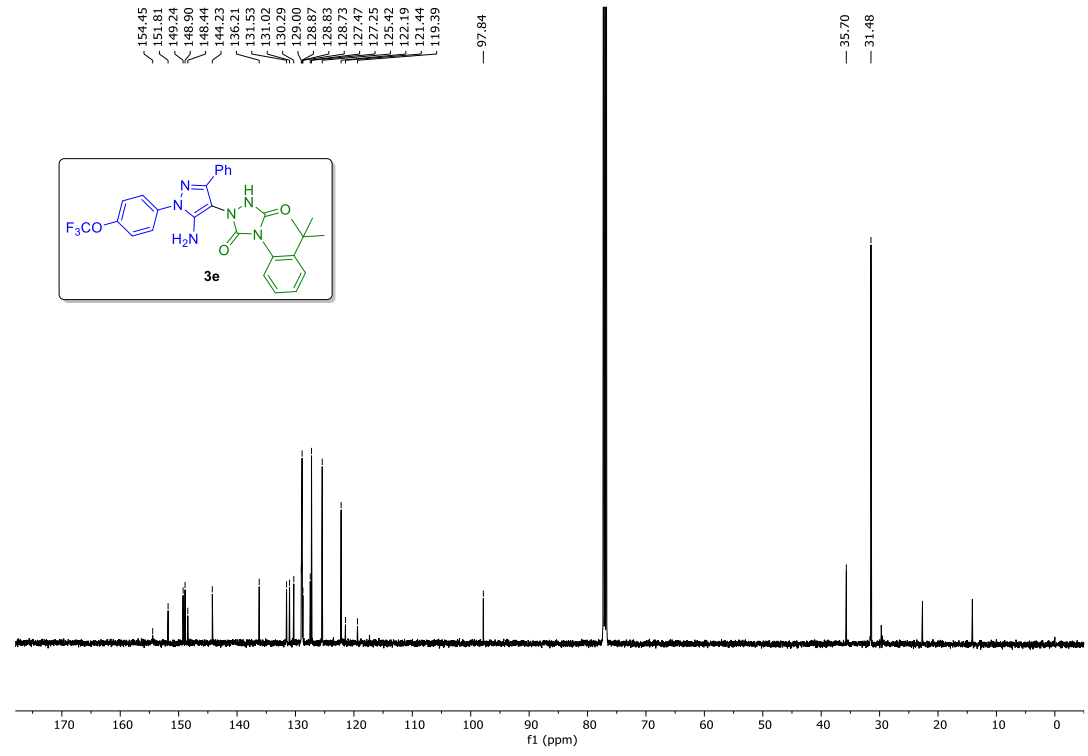


Synlett | DOI 10.1055/a-2726-4350 |

^{1}H NMR (500 MHz, $CDCl_3$)

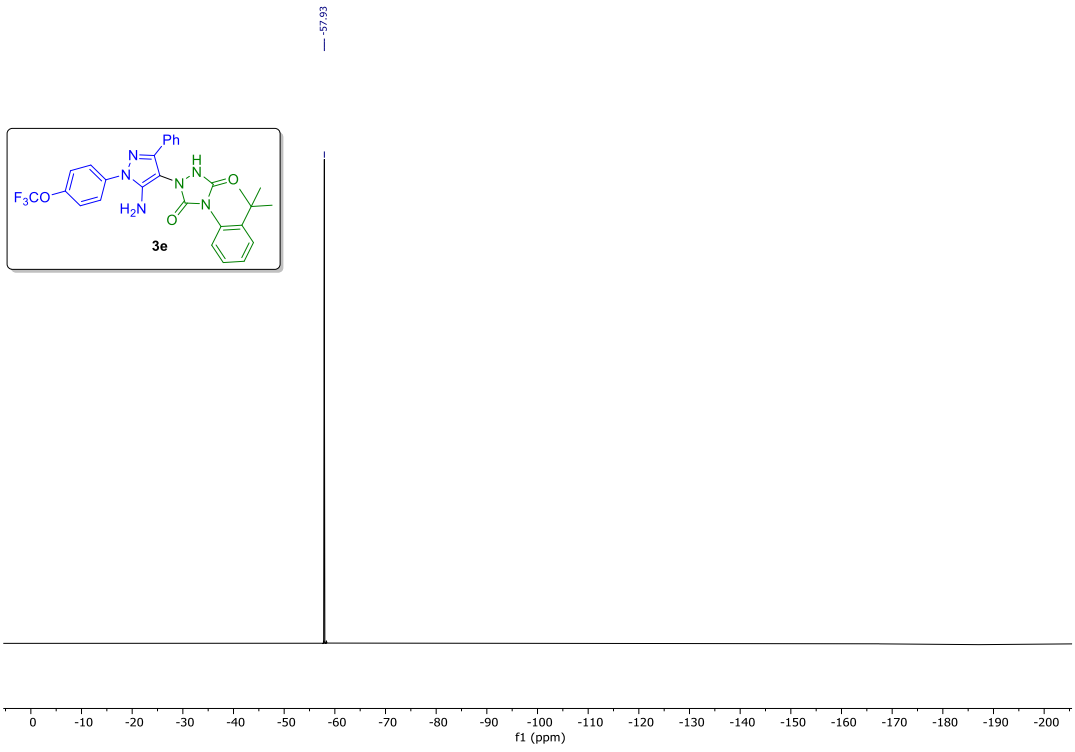


^{13}C NMR (126 MHz, $CDCl_3$)



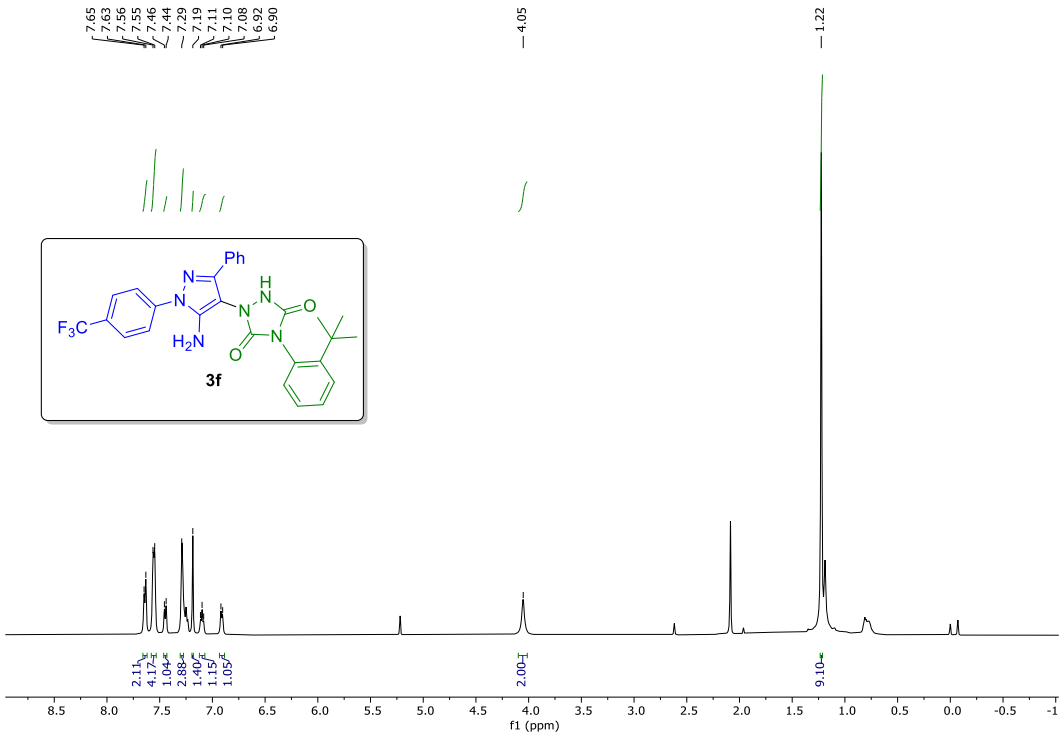
Synlett | DOI 10.1055/a-2726-4350 |

^{19}F NMR (471 MHz, $CDCl_3$)

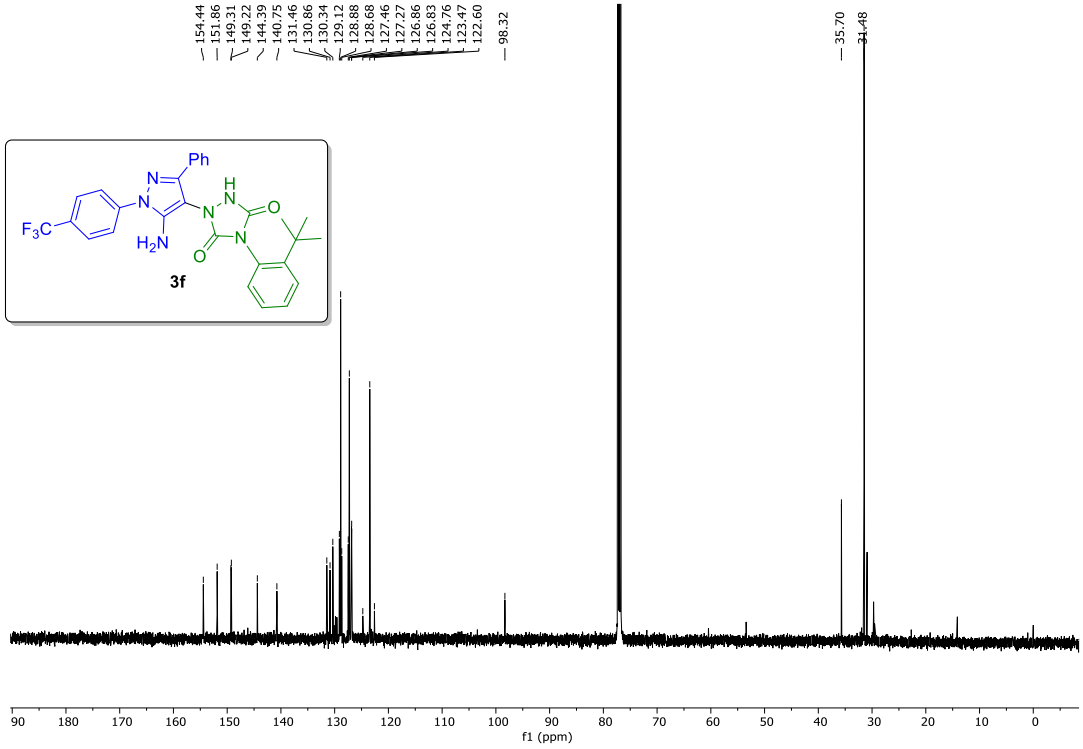


Synlett | DOI 10.1055/a-2726-4350 |

^{1}H NMR (500 MHz, $CDCl_3$)

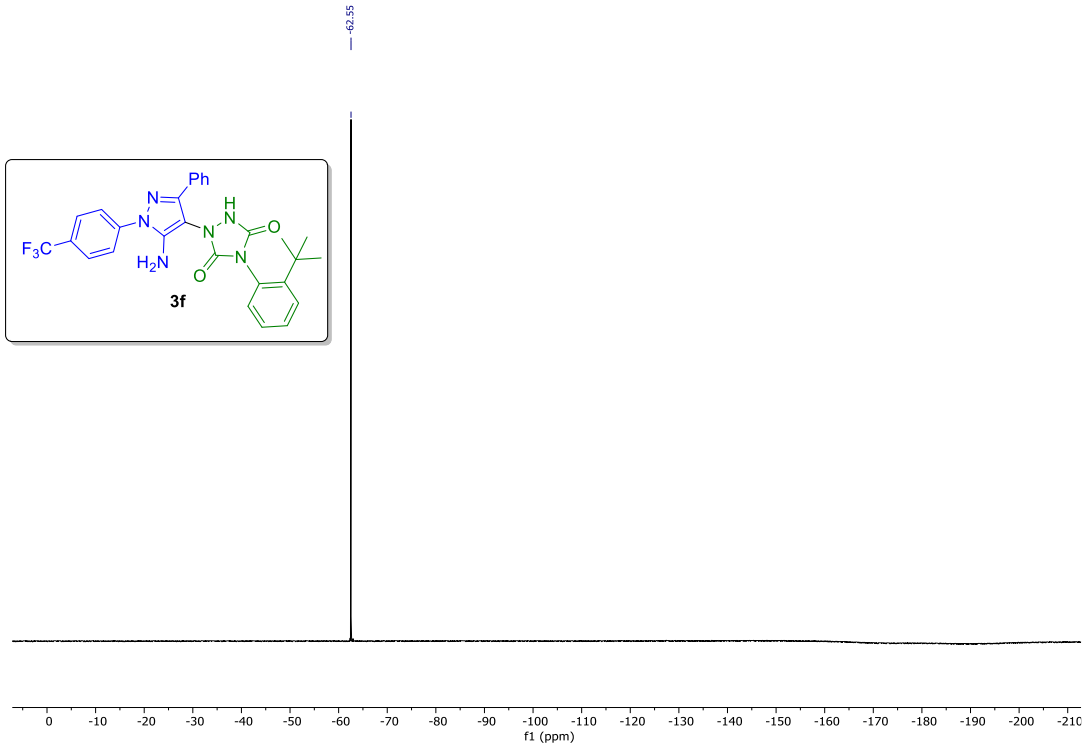


^{13}C NMR (126 MHz, $CDCl_3$)



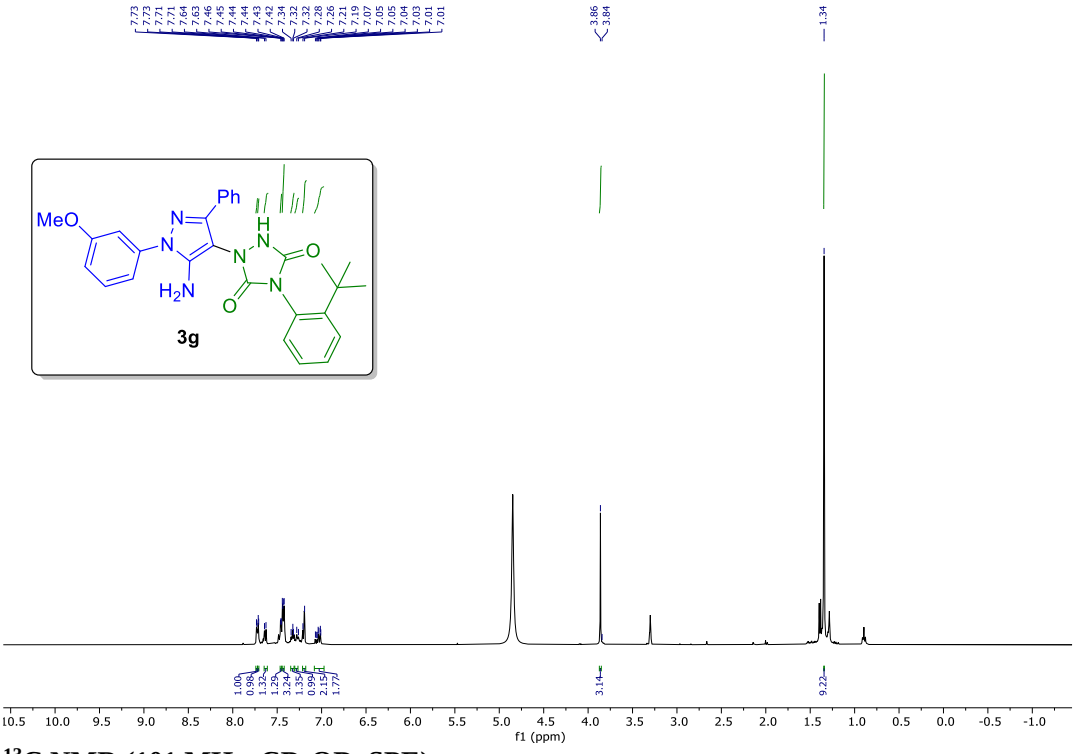
Synlett | DOI 10.1055/a-2726-4350 |

^{19}F NMR (471 MHz, CDCl$_3$)

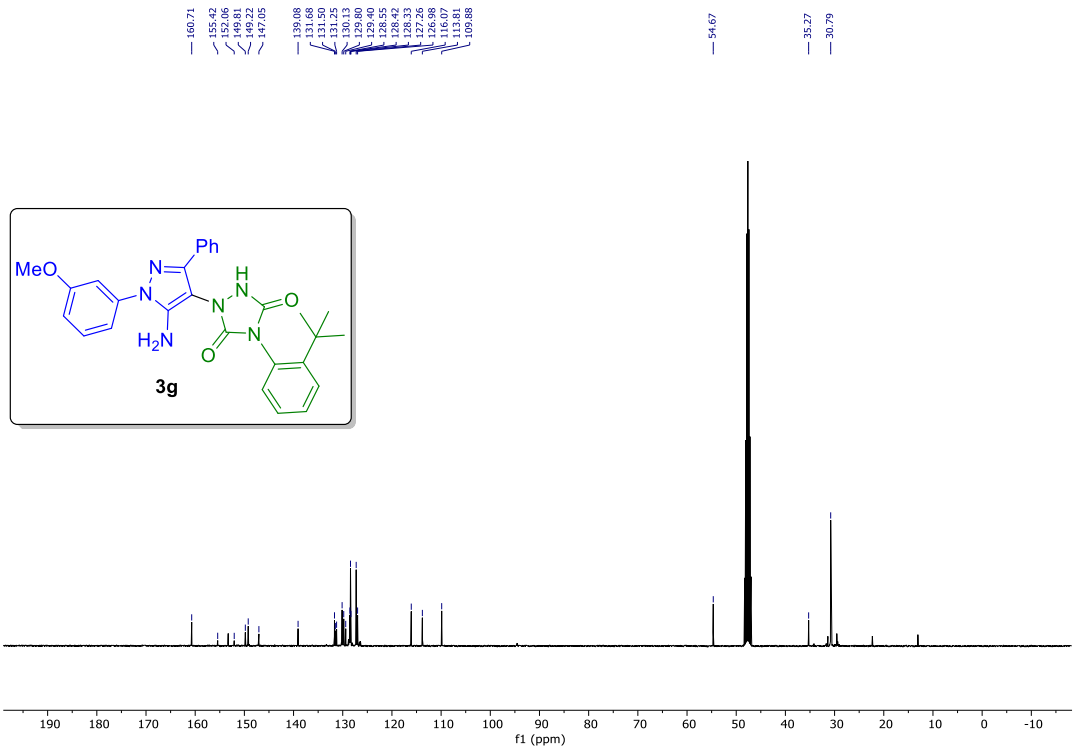


Synlett | DOI 10.1055/a-2726-4350 |

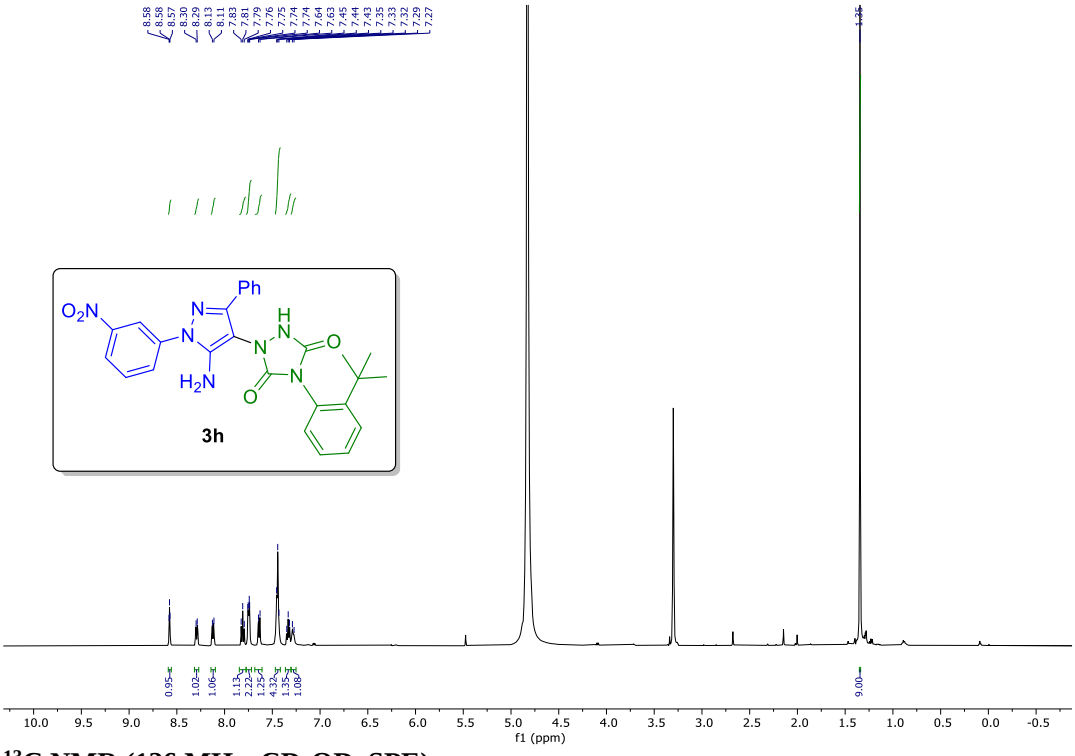
^{1}H NMR (400 MHz, CD_3OD_SPE)



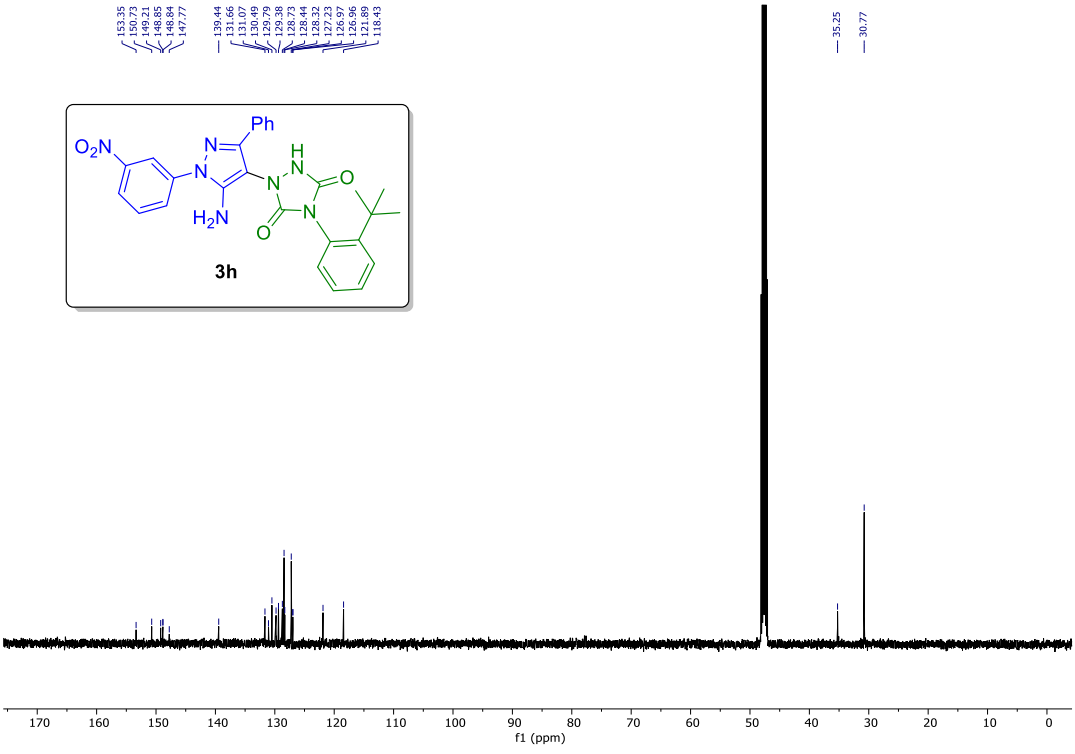
^{13}C NMR (101 MHz, CD_3OD_SPE)



^{1}H NMR (500 MHz, CD$_3$OD_SPE)

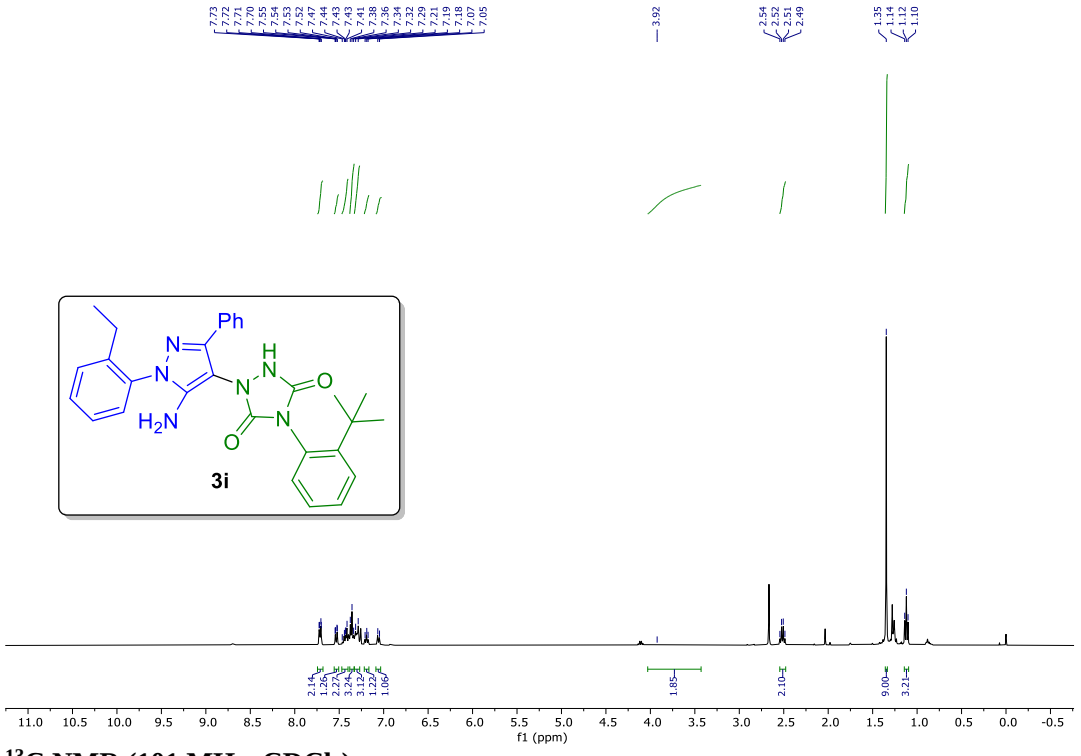


^{13}C NMR (126 MHz, CD$_3$OD_SPE)

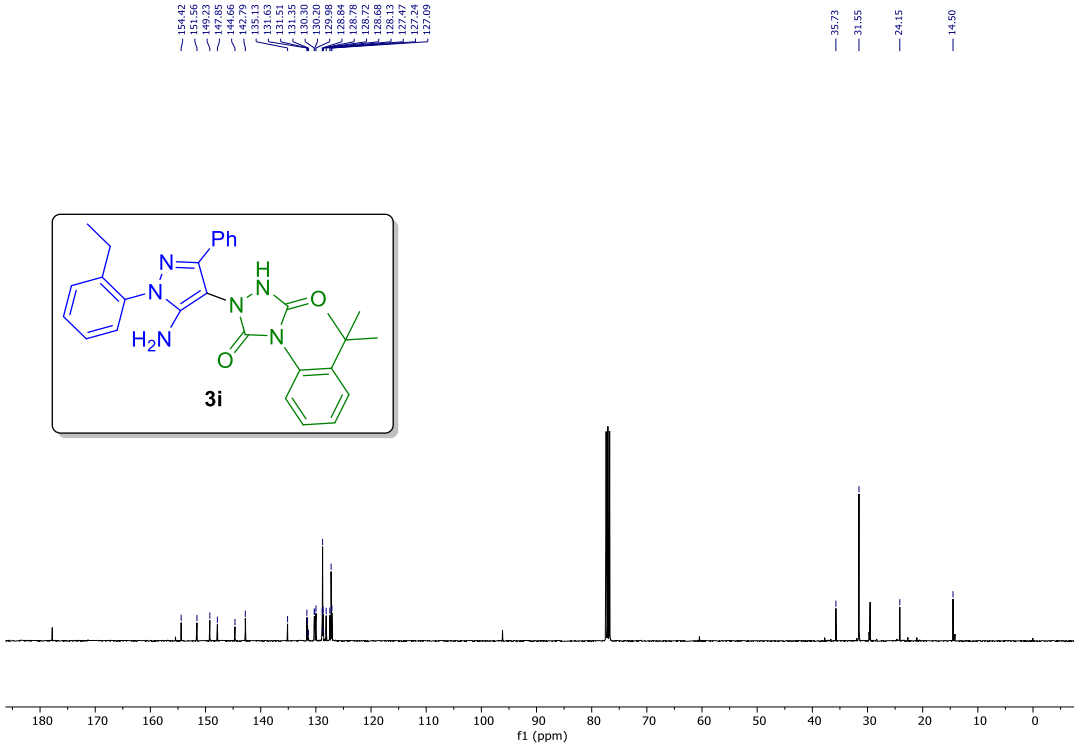


Synlett | DOI 10.1055/a-2726-4350 |

^{1}H NMR (400 MHz, $CDCl_3$)

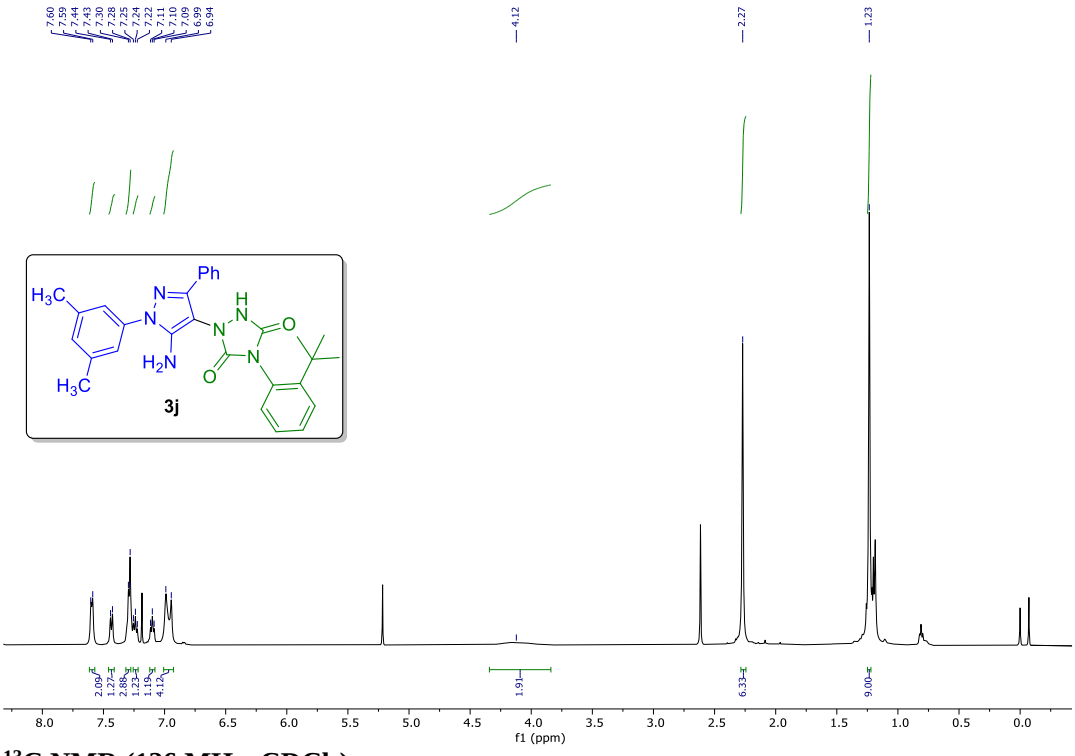


^{13}C NMR (101 MHz, $CDCl_3$)

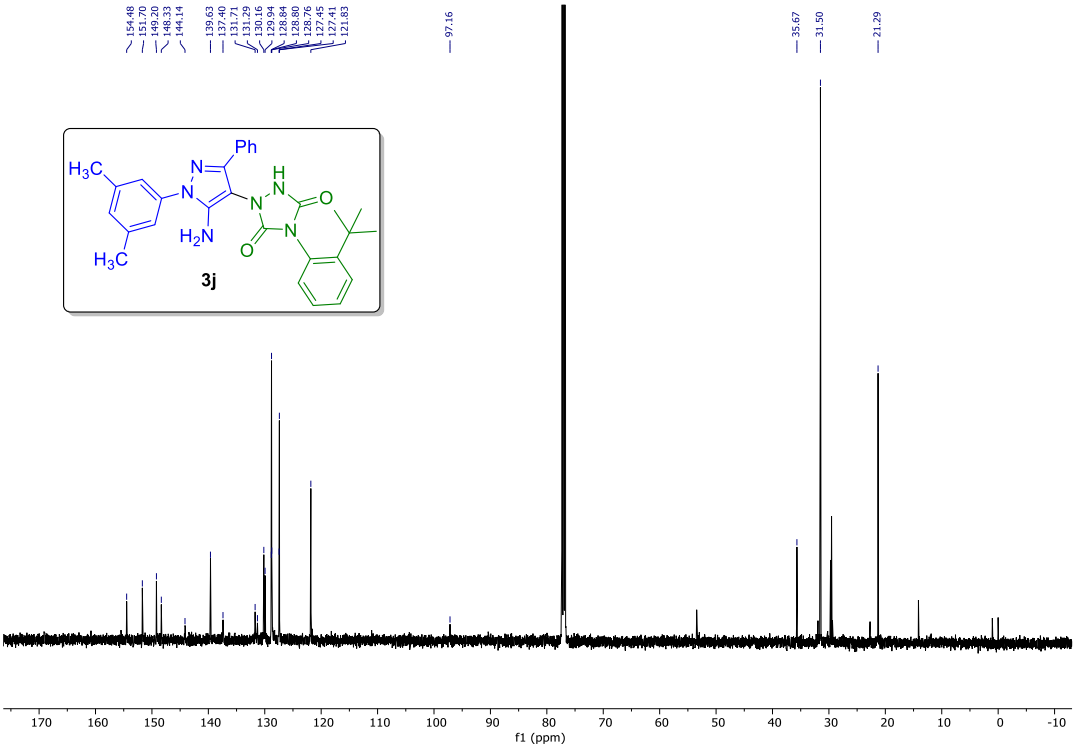


Synlett | DOI 10.1055/a-2726-4350 |

^{1}H NMR (500 MHz, $CDCl_3$)

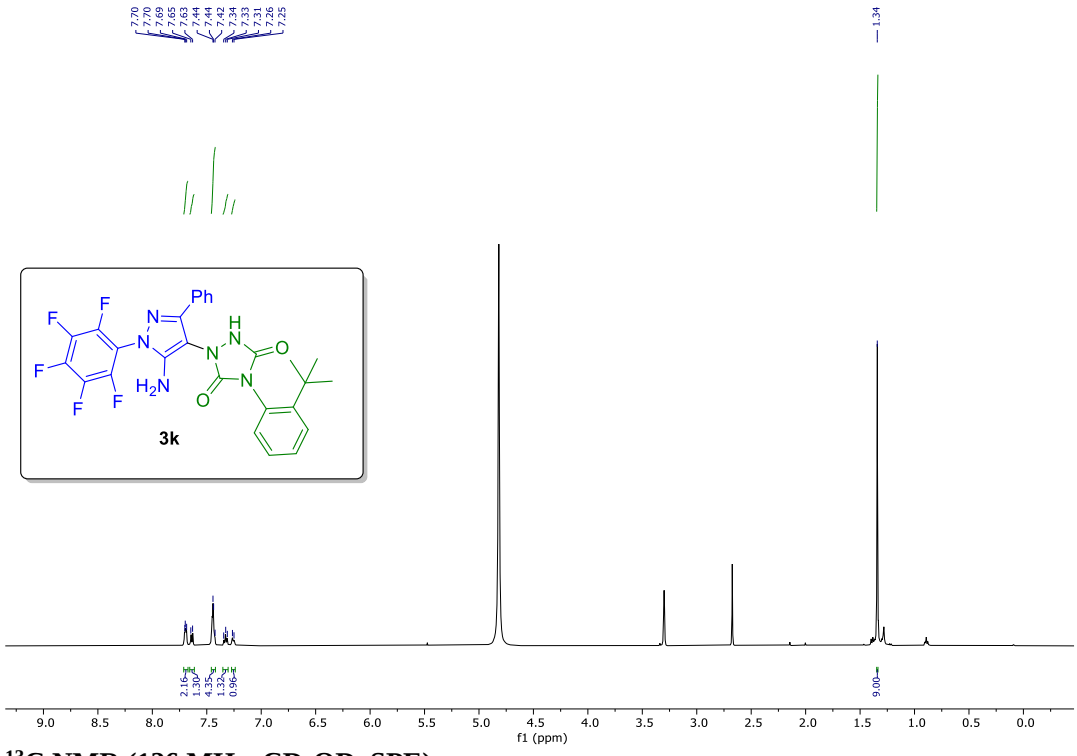


^{13}C NMR (126 MHz, $CDCl_3$)

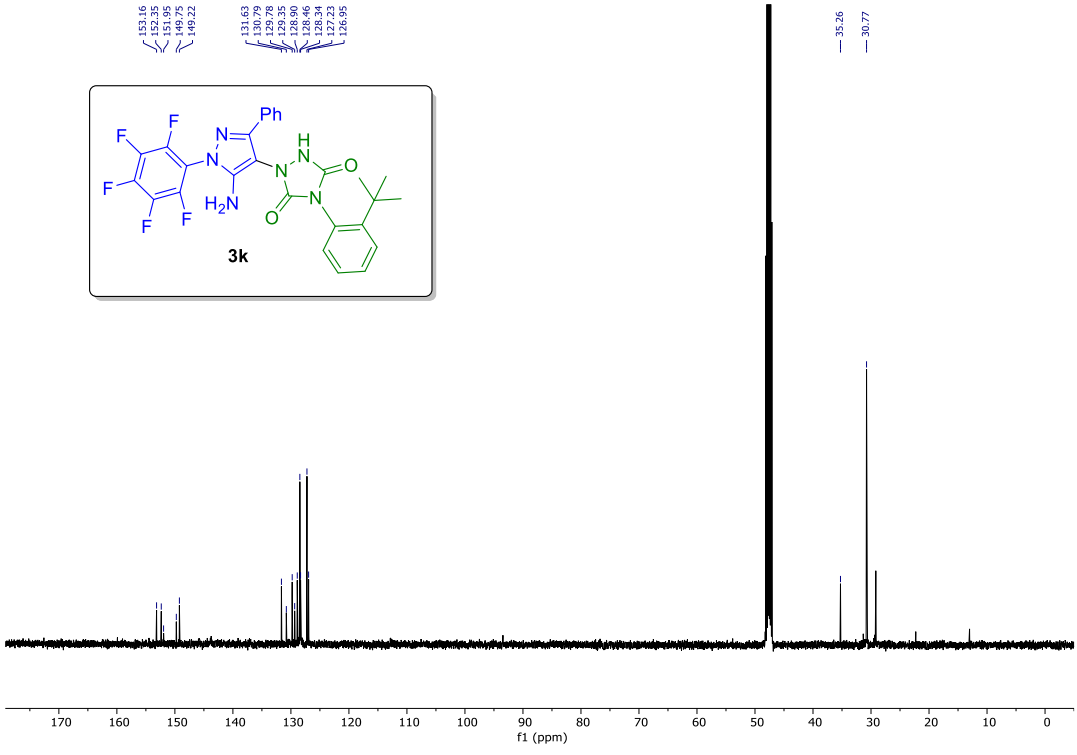


Synlett | DOI 10.1055/a-2726-4350 |

^{1}H NMR (500 MHz, CD_3OD_SPE)

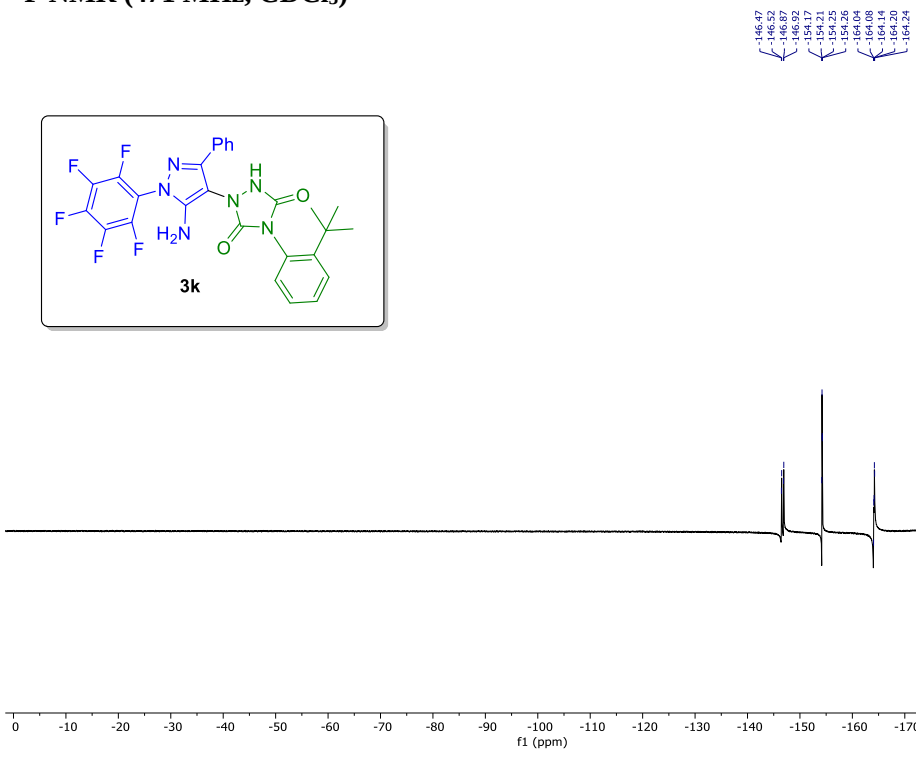


^{13}C NMR (126 MHz, CD_3OD_SPE)



Synlett | DOI 10.1055/a-2726-4350 |

^{19}F NMR (471 MHz, $CDCl_3$)



Synlett | DOI 10.1055/a-2726-4350 |

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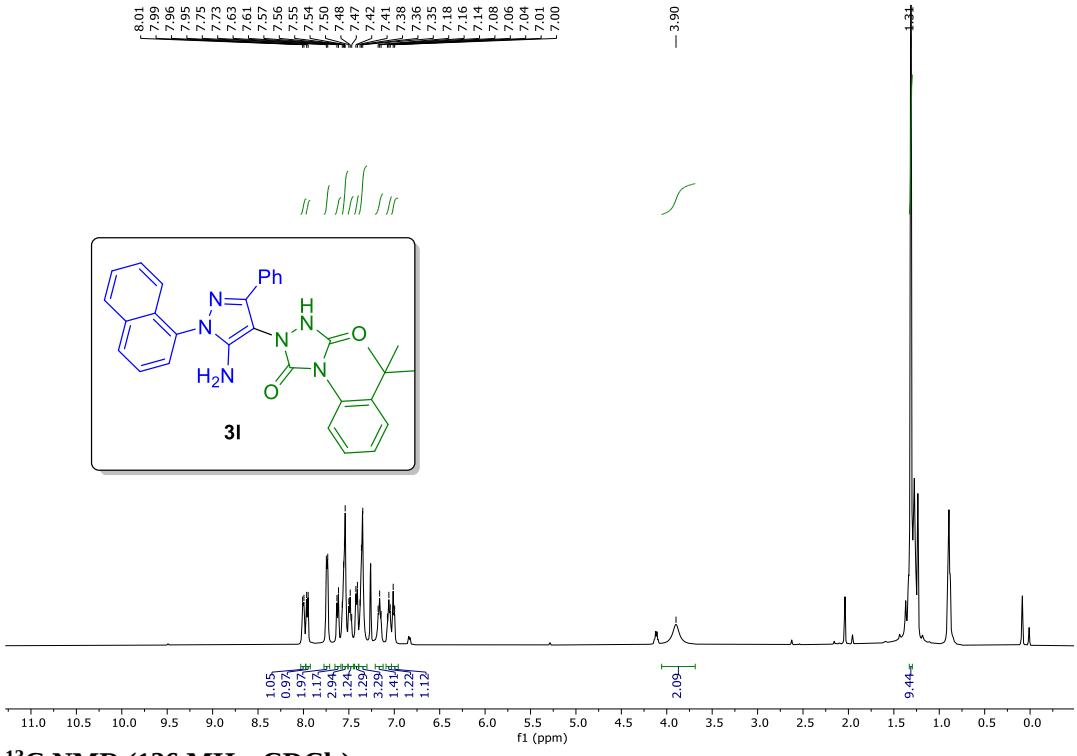
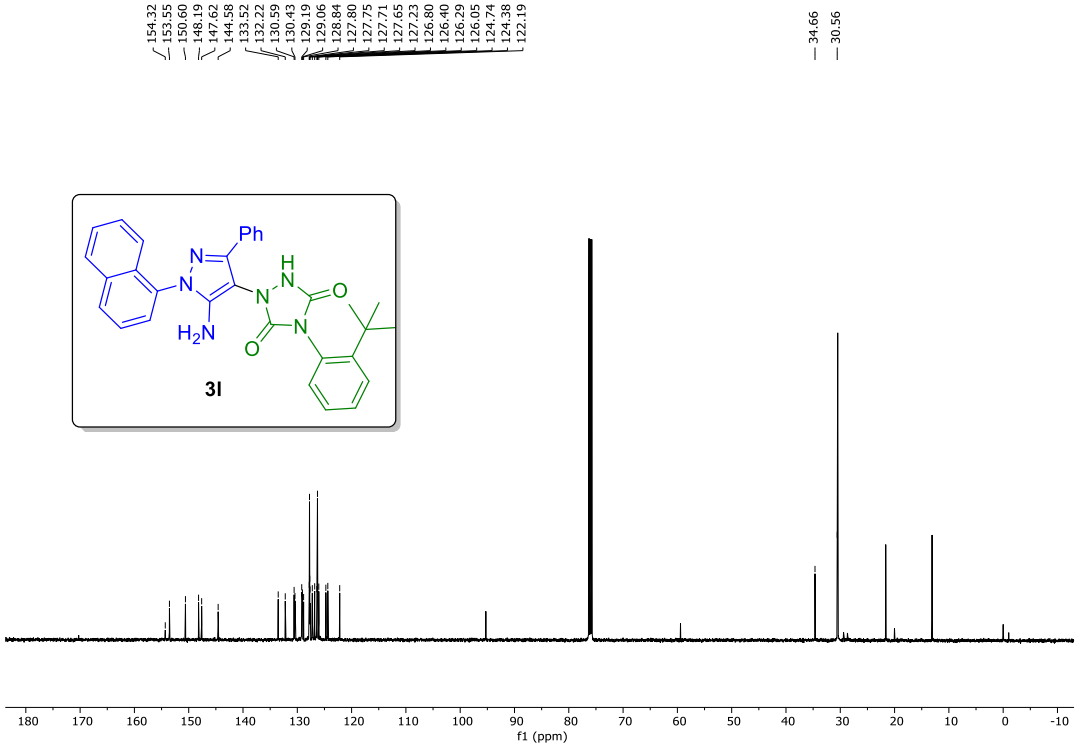
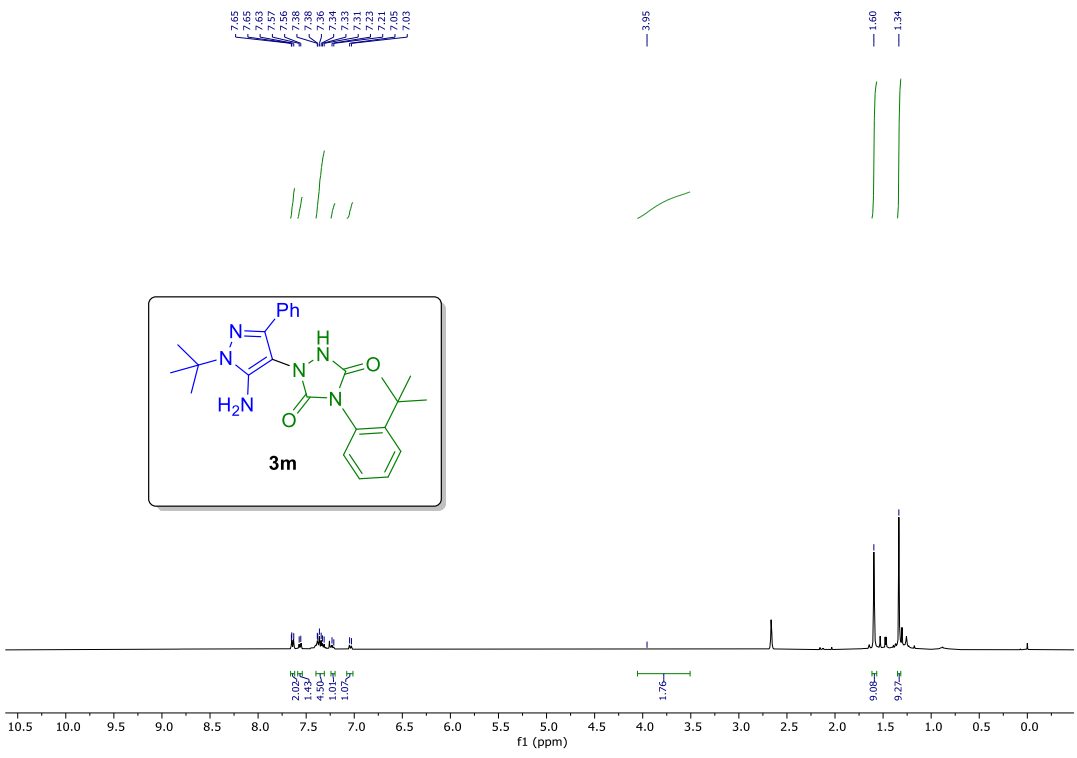


^{13}C NMR (126 MHz, $CDCl_3$)

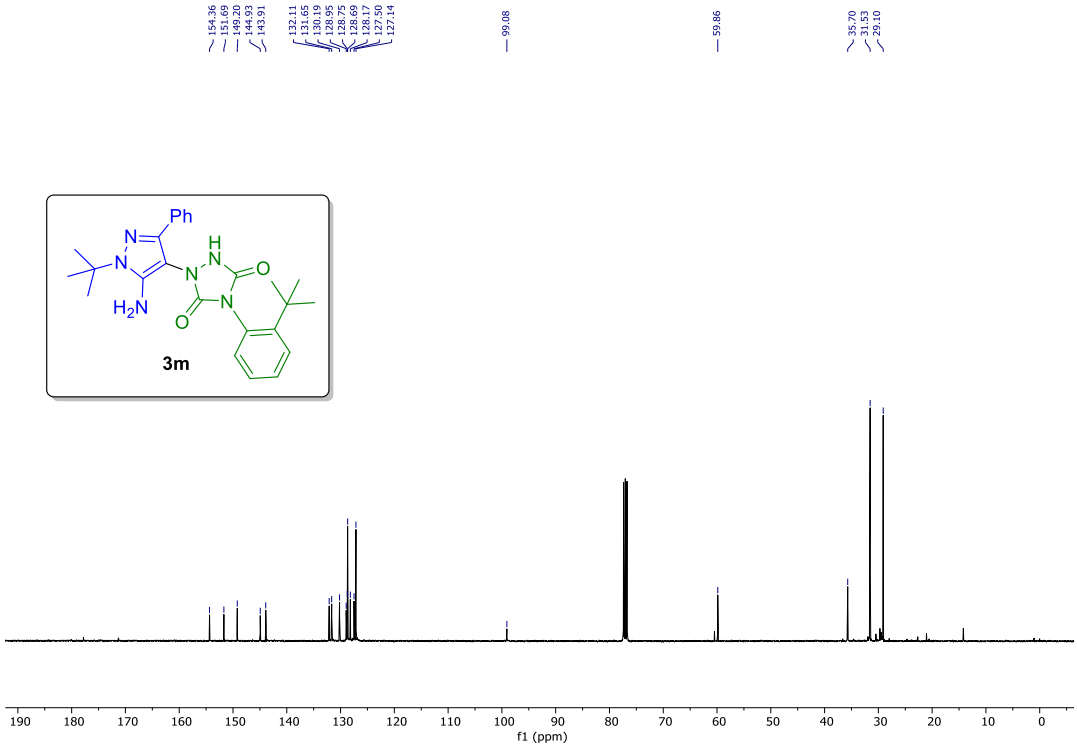


Synlett | DOI 10.1055/a-2726-4350 |

^{1}H NMR (400 MHz, $CDCl_3$)

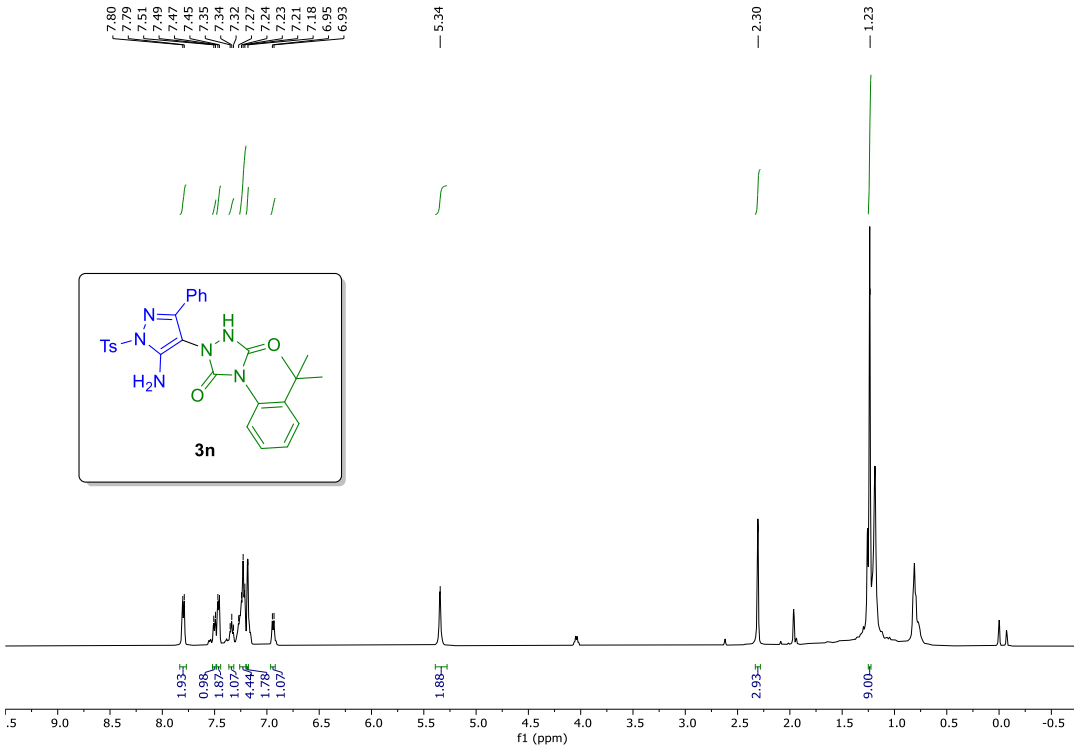


^{13}C NMR (101 MHz, $CDCl_3$)

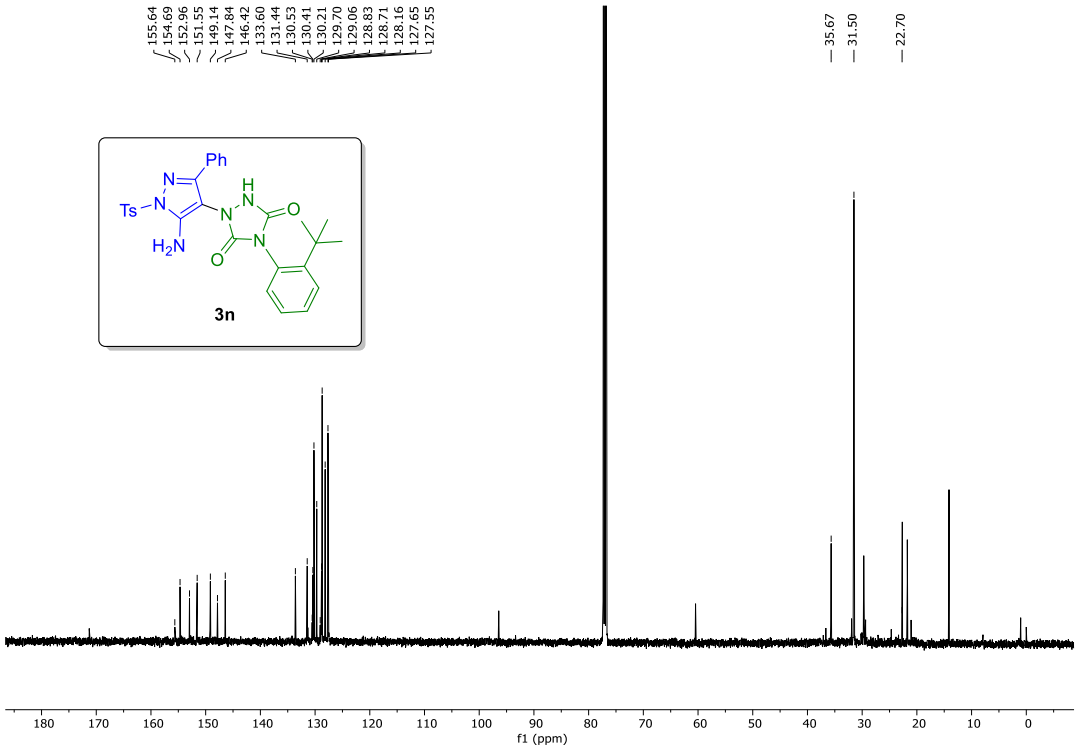


Synlett | DOI 10.1055/a-2726-4350 |

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (126 MHz, $CDCl_3$)



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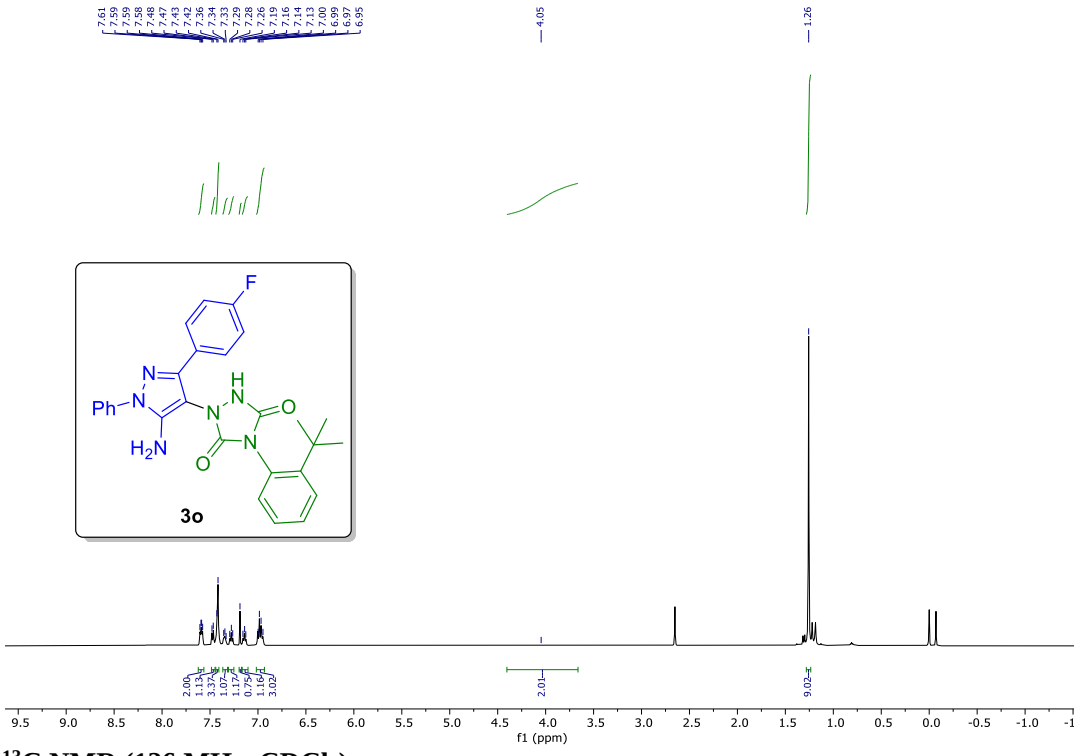

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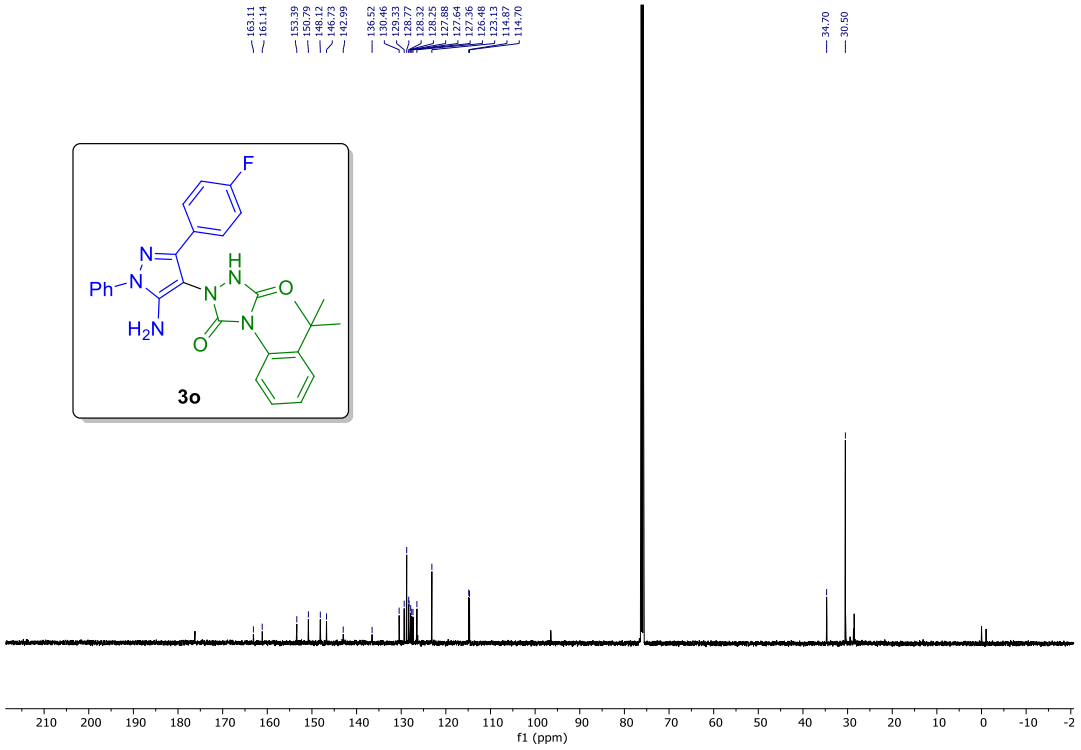
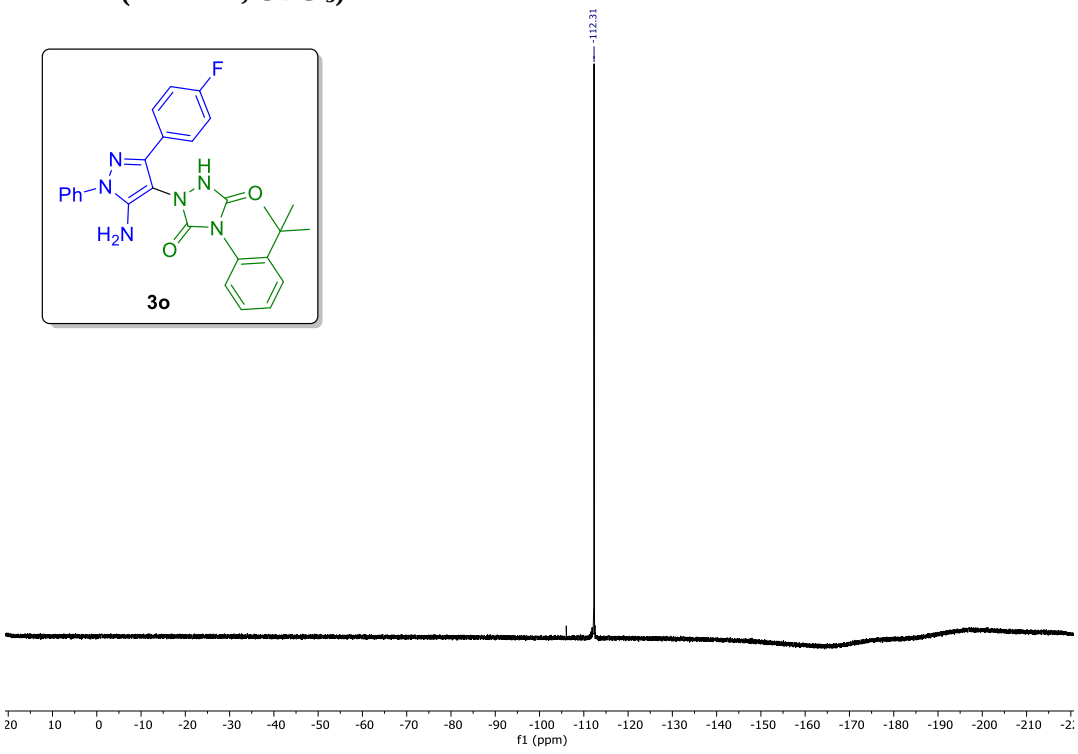


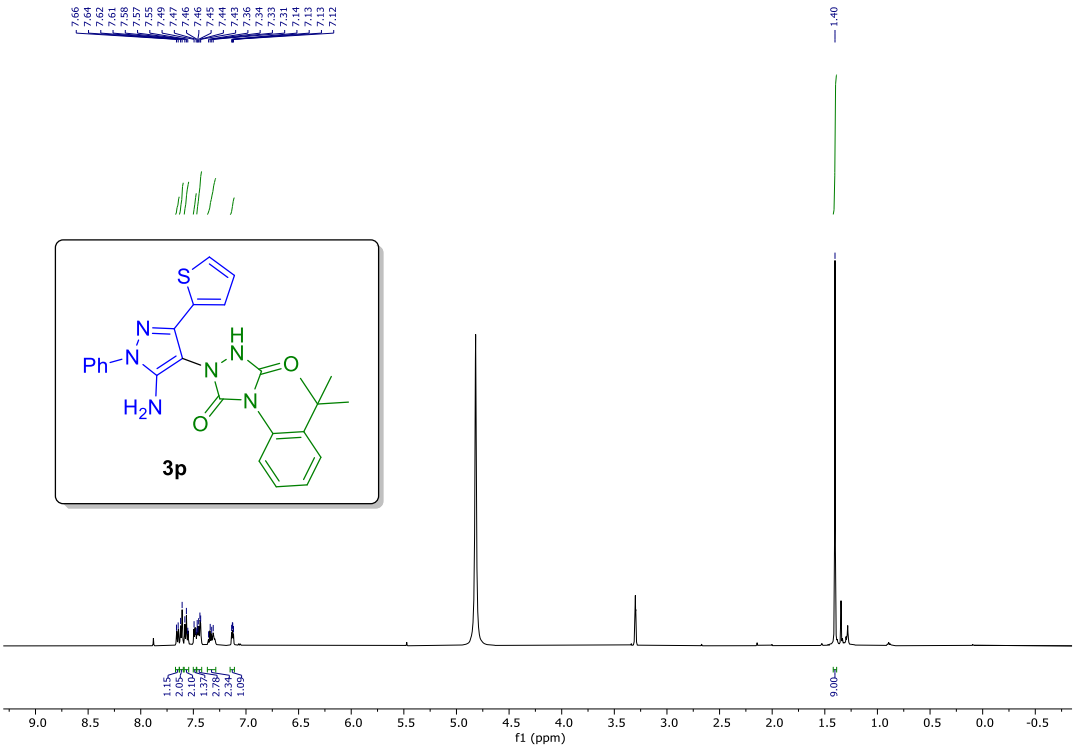
Synlett | DOI 10.1055/a-2726-4350 |

^{19}F NMR (471 MHz, $CDCl_3$)

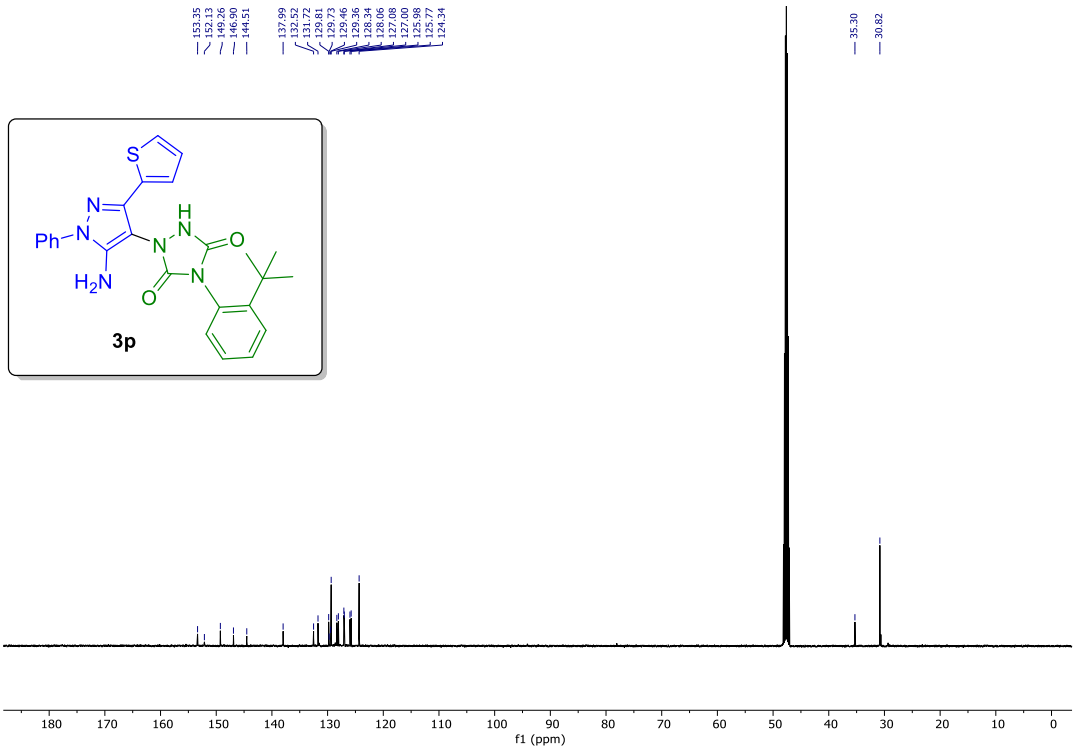


Synlett | DOI 10.1055/a-2726-4350 |

^{1}H NMR (500 MHz, CD_3OD_SPE)



^{13}C NMR (126 MHz, CD_3OD_SPE)



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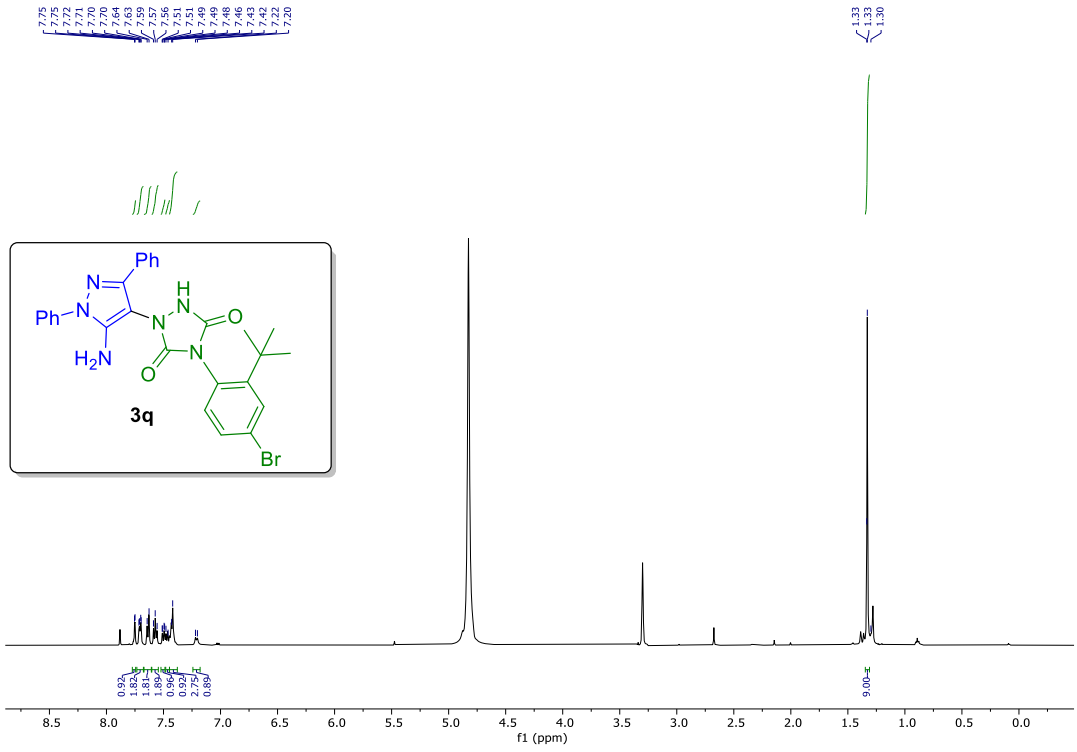
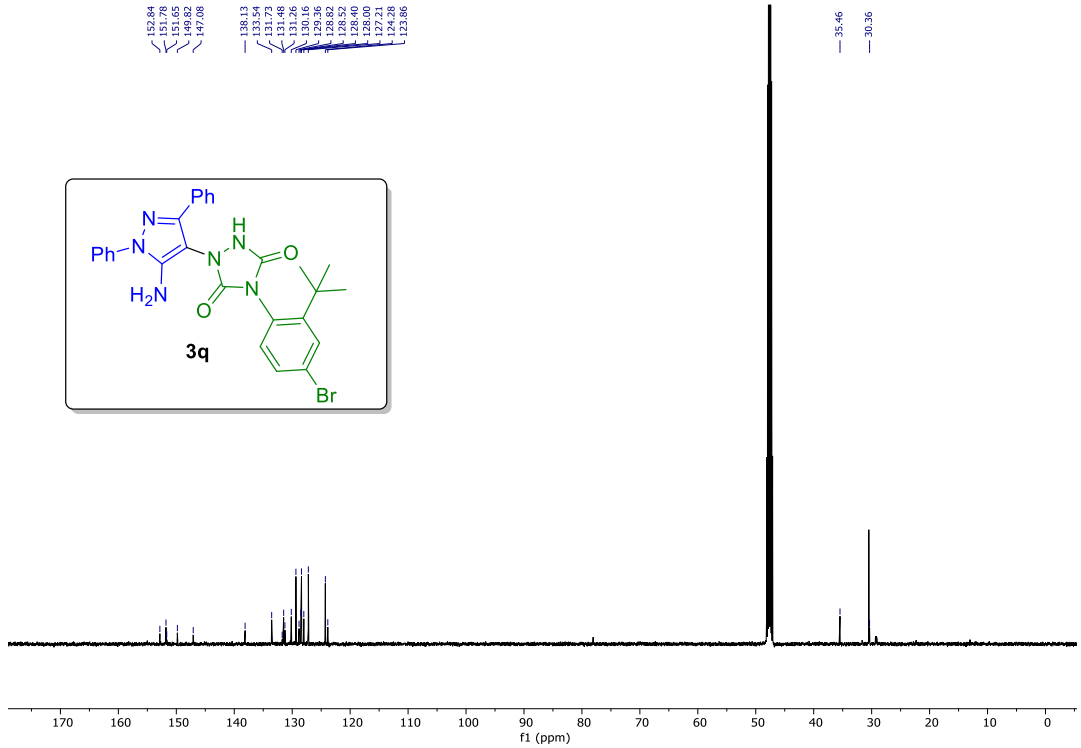
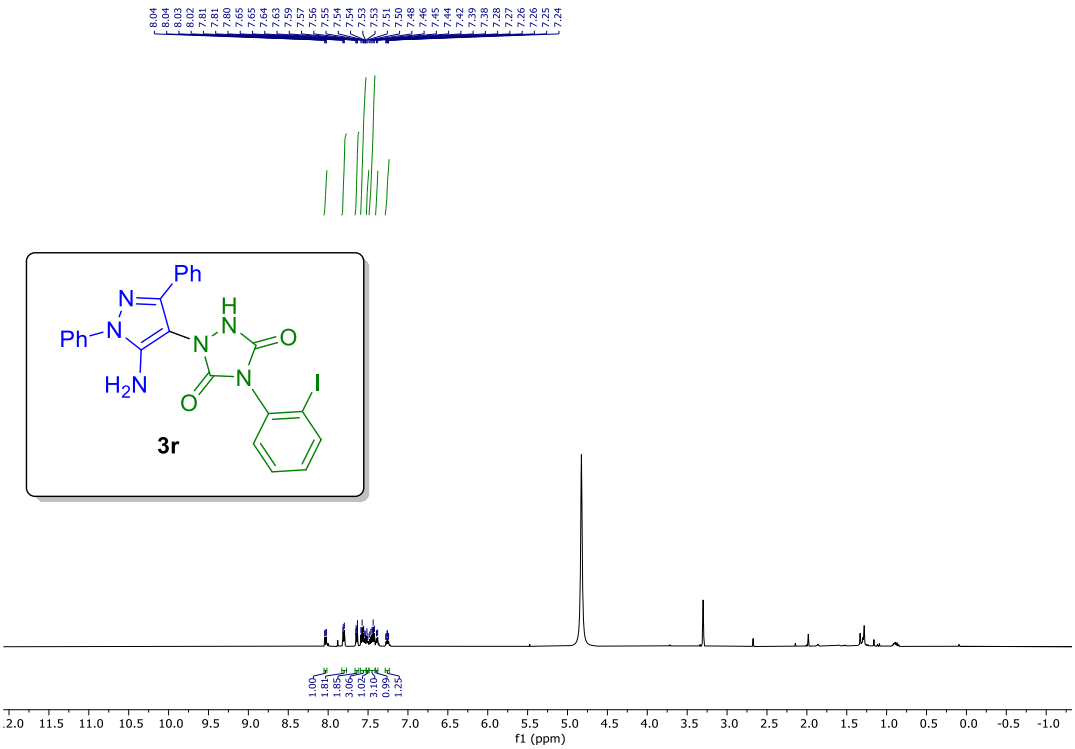


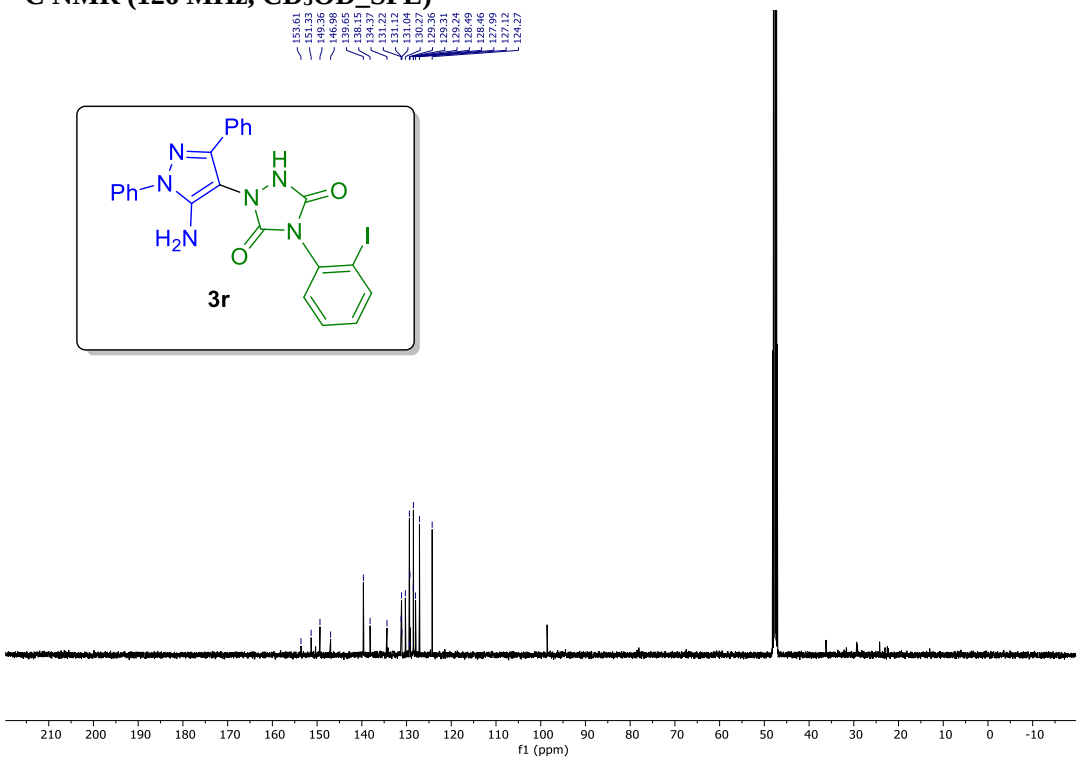
^{13}C NMR (126 MHz, CD_3OD_SPE)



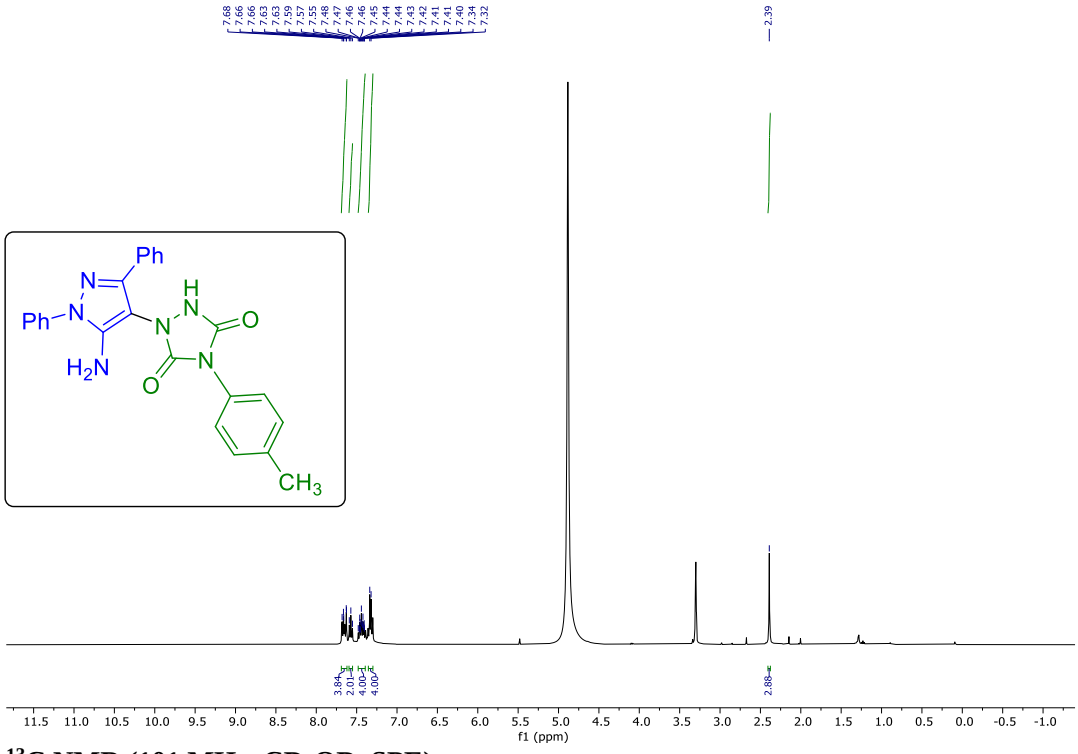
^{1}H NMR (500 MHz, CD_3OD_SPE)



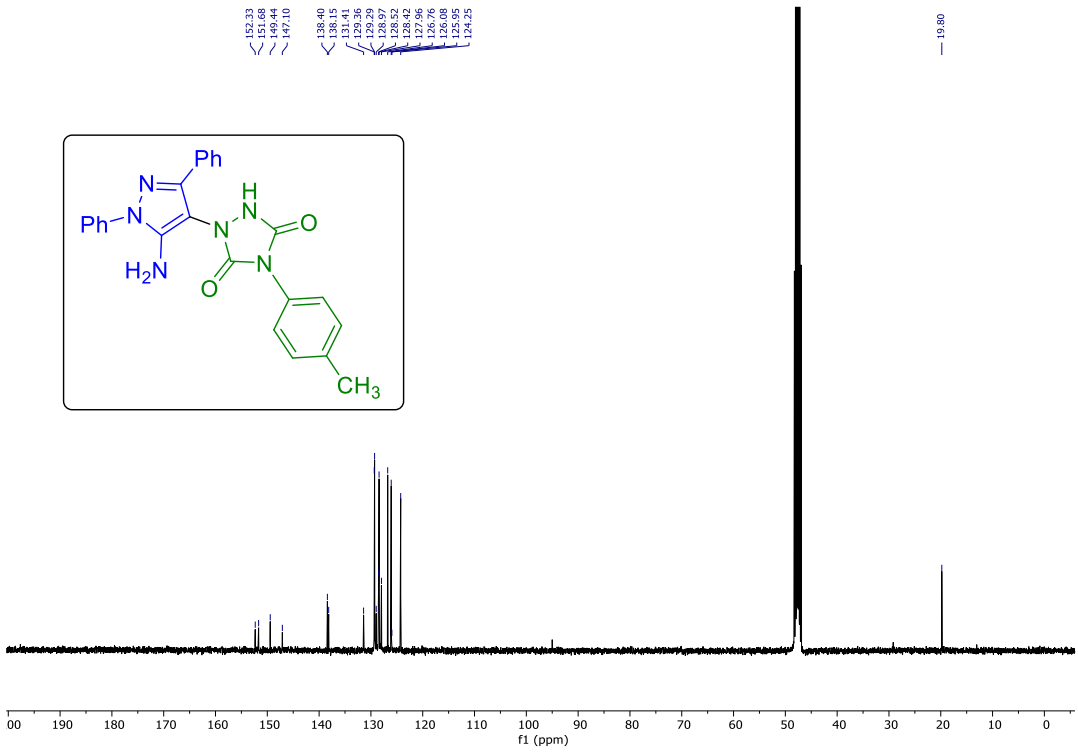
^{13}C NMR (126 MHz, CD_3OD_SPE)



^{1}H NMR (400 MHz, CD_3OD_SPE)

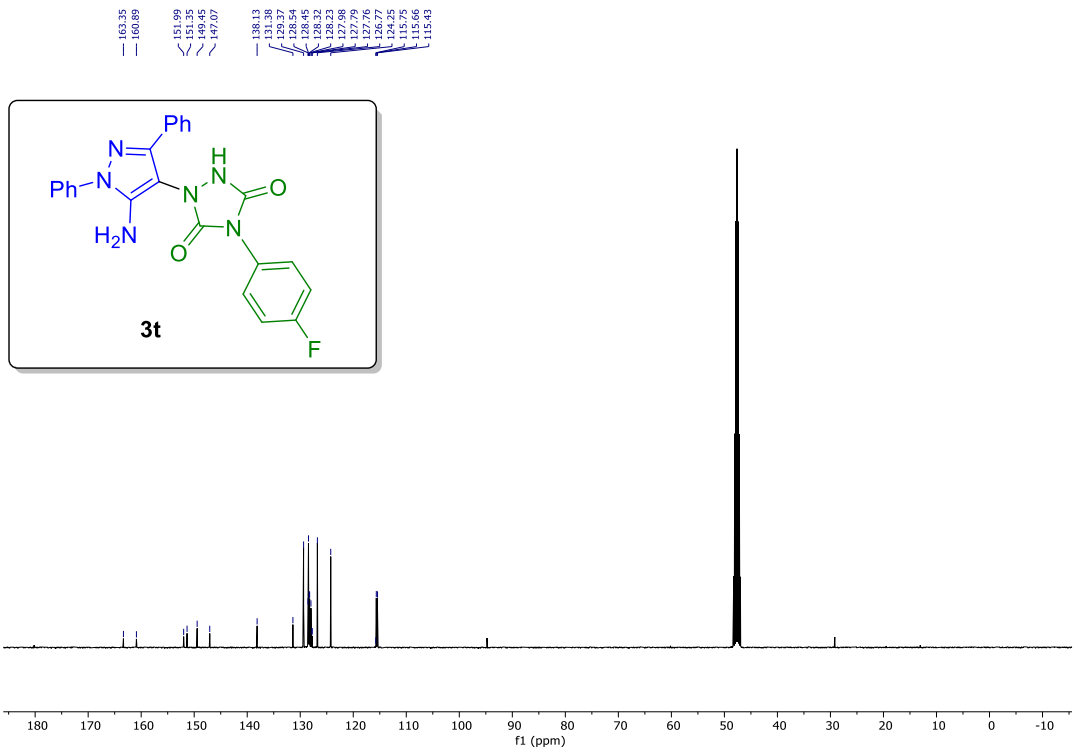


^{13}C NMR (101 MHz, CD_3OD_SPE)

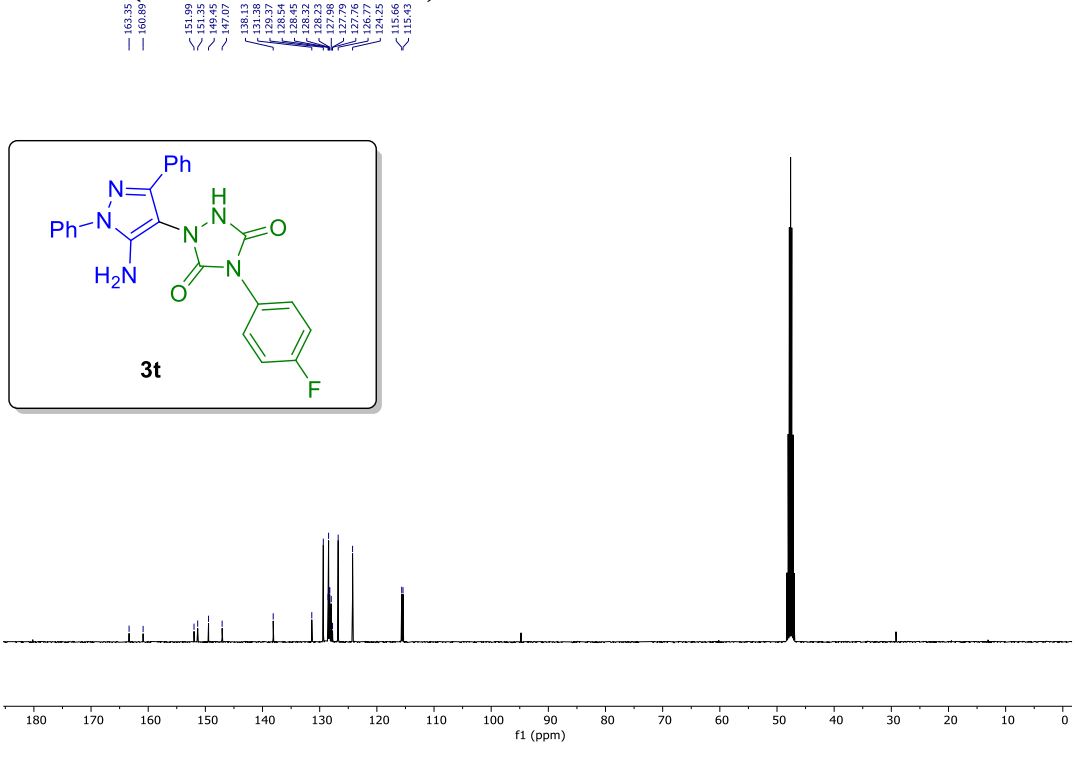


Synlett | DOI 10.1055/a-2726-4350 |

^{1}H NMR (400 MHz, CD_3OD_SPE)

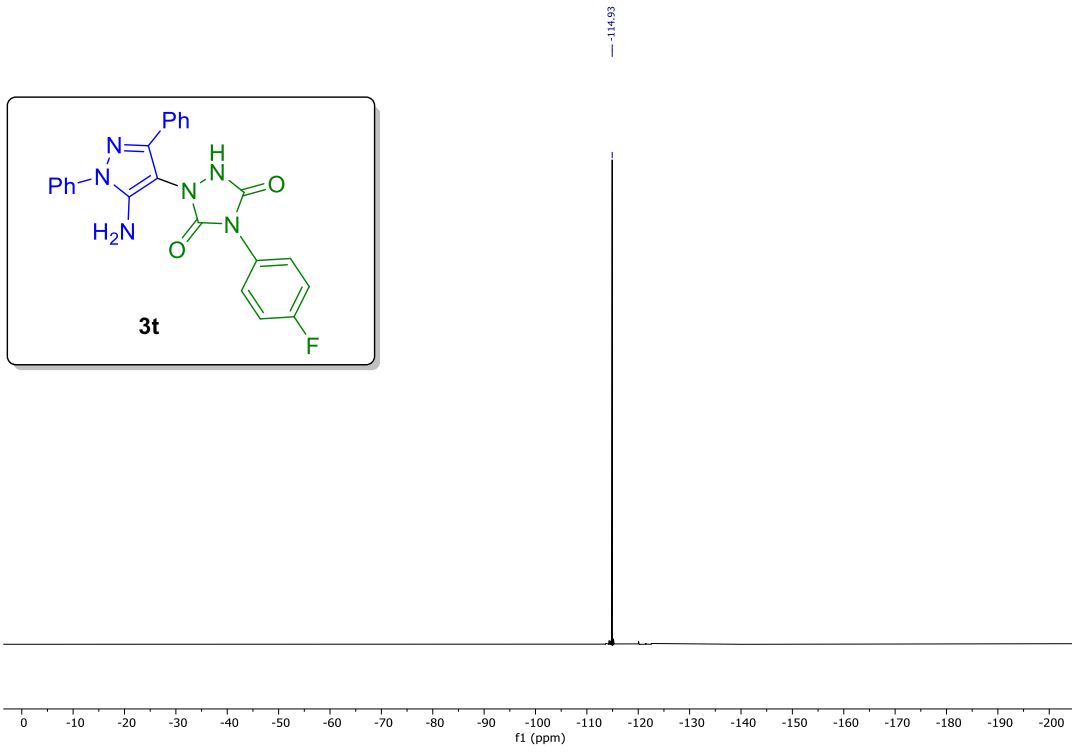


^{13}C NMR (101 MHz, CD_3OD_SPE)



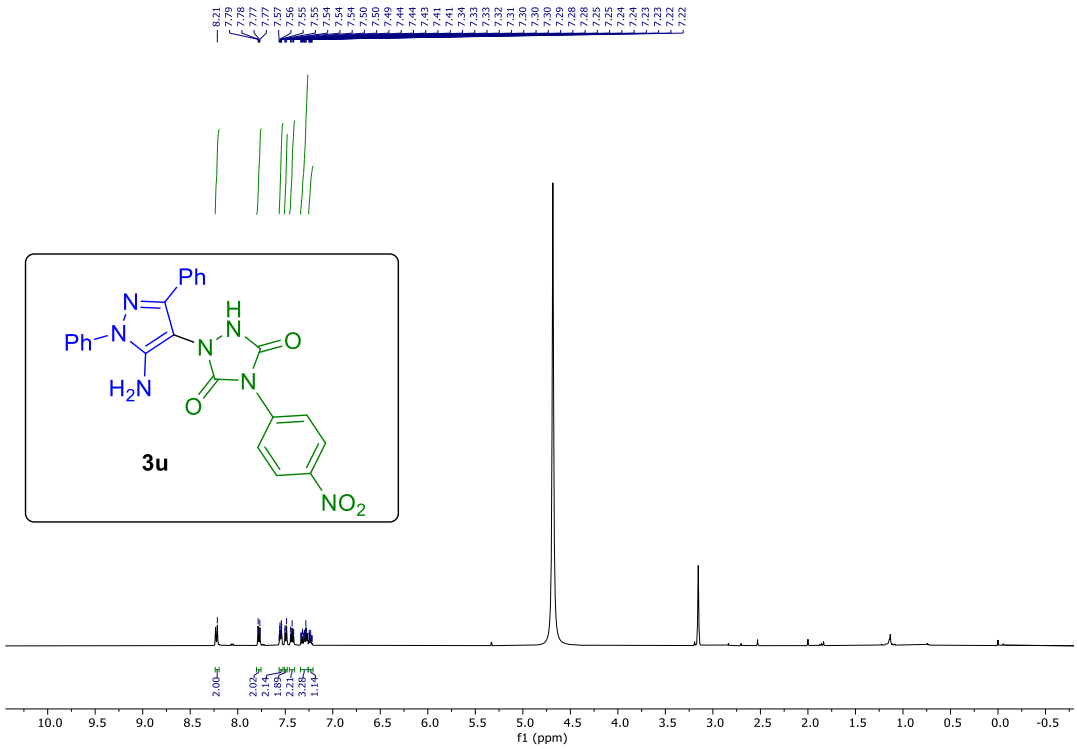
Synlett | DOI 10.1055/a-2726-4350 |

^{19}F NMR (471 MHz, MeOD)

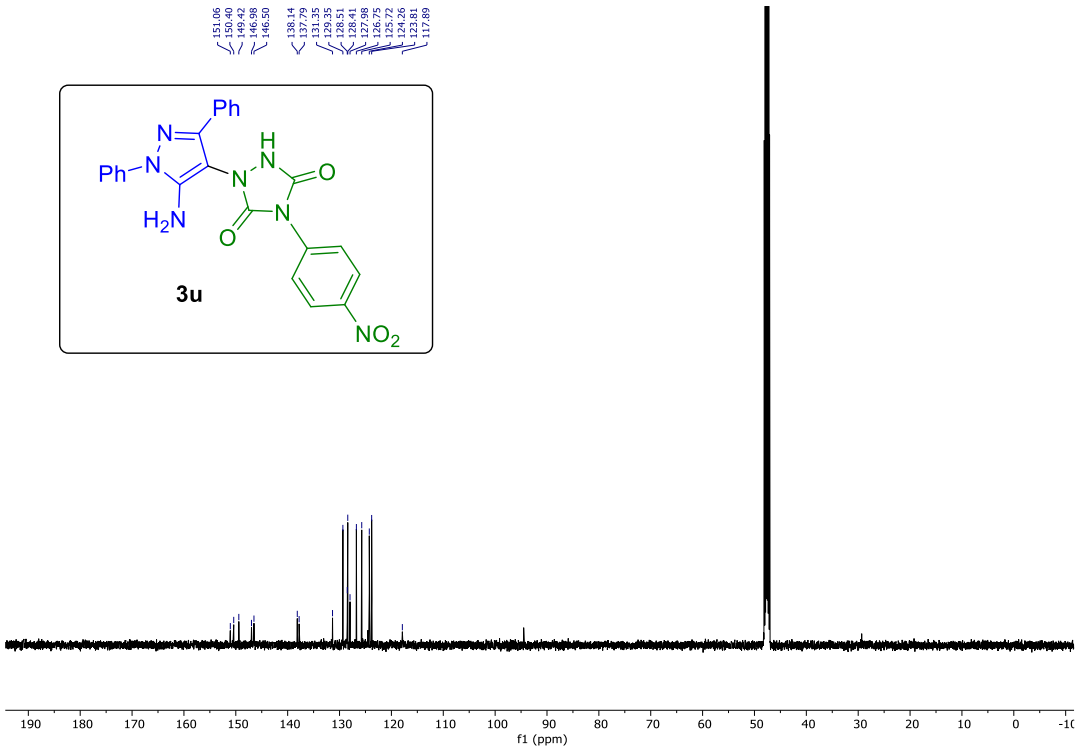


Synlett | DOI 10.1055/a-2726-4350 |

^{1}H NMR (500 MHz, MeOD)



^{13}C NMR (126 MHz, MeOD)



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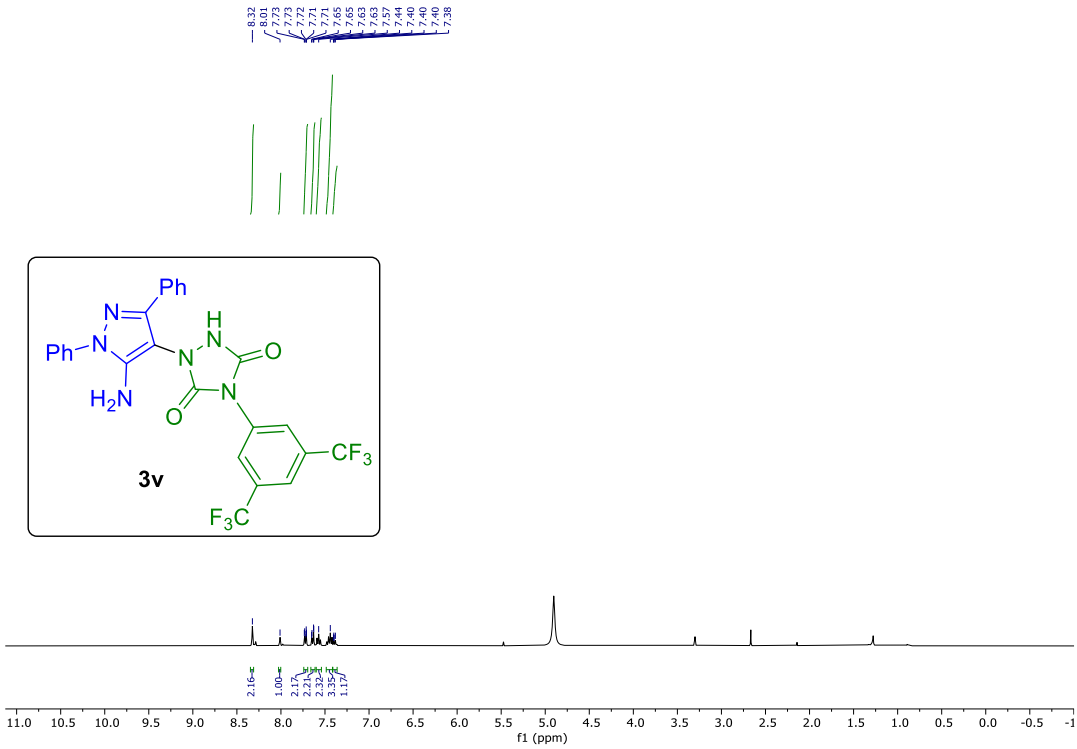
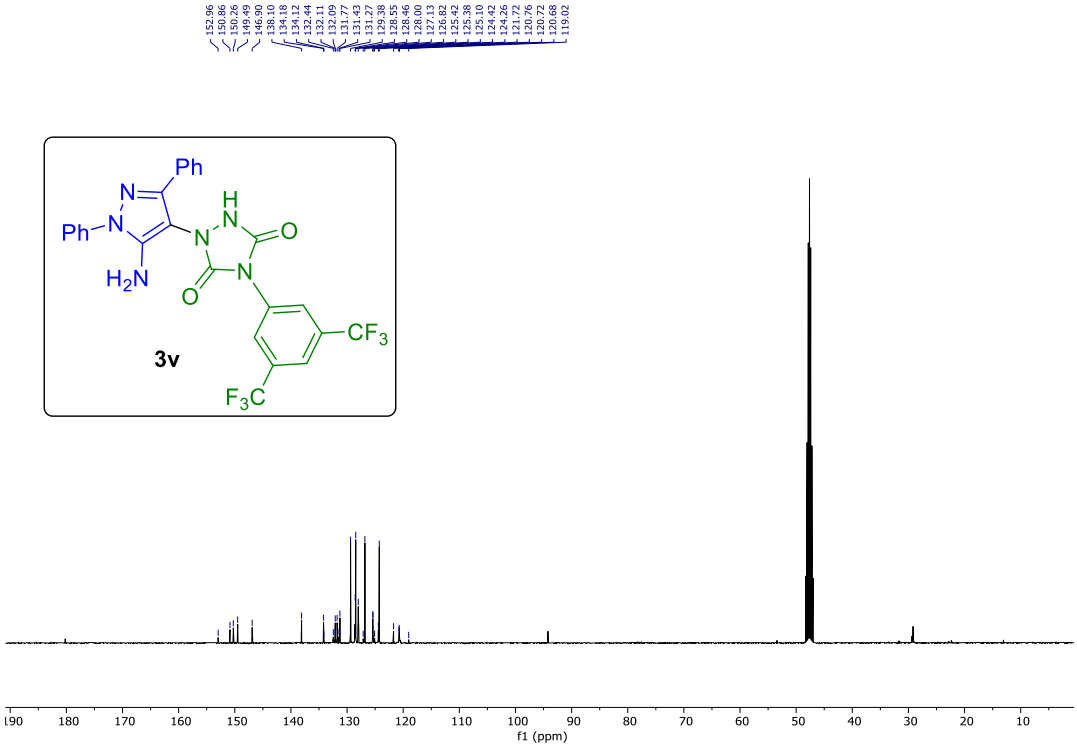
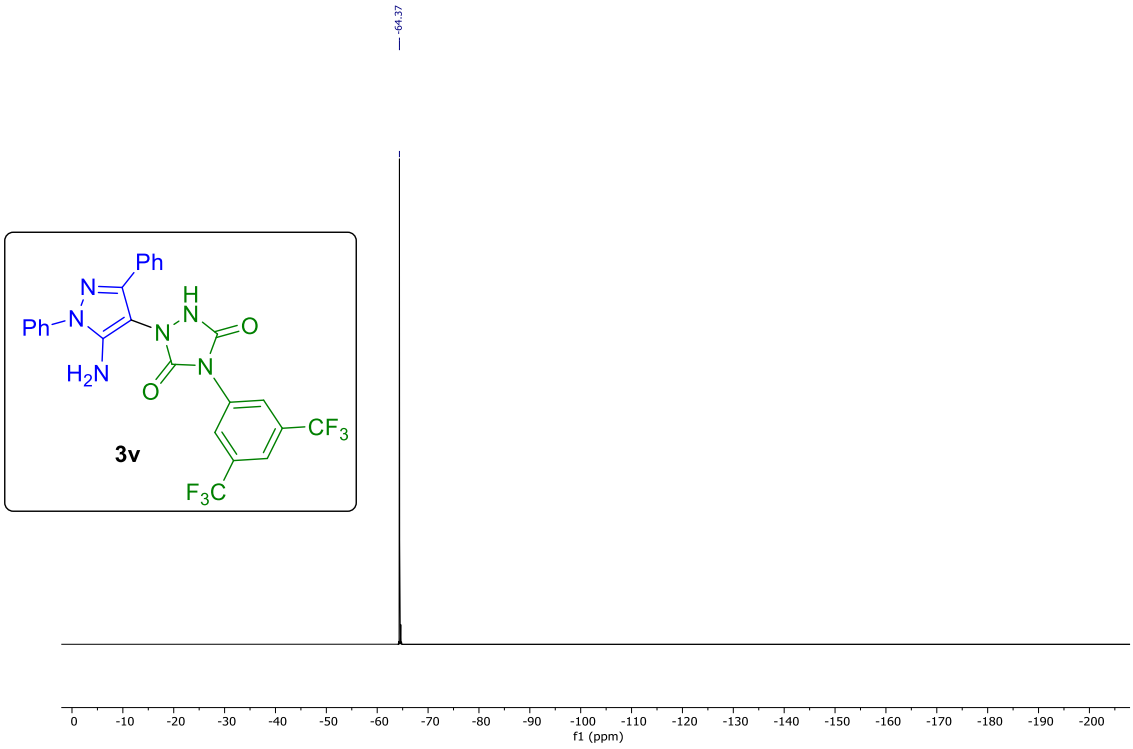
^{1}H NMR (400 MHz, CD_3OD_SPE)



^{13}C NMR (101 MHz, CD_3OD_SPE)



^{19}F NMR (471 MHz, MeOD)



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