Supporting information

Palladium catalyzed furan opening as a route to α,β-unsaturated aldehydes

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S4-19 : Characterization data of compounds **5a-5h** and their corresponding ^{1}H and ^{13}C NMR spectra.
S20 : General procedure for the synthesis of the phenol derived Ugi-Smiles adducts.
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S90 : General procedure for the synthesis of the *N*,*N* disubstitued-2-iodobenzamides.
S91-98 : Characterization data of compounds **9a-9d** and their corresponding ^{1}H and ^{13}C NMR spectra.
S99 : General procedure for the synthesis of the 4-vinyl isoquinolin-1-ones.
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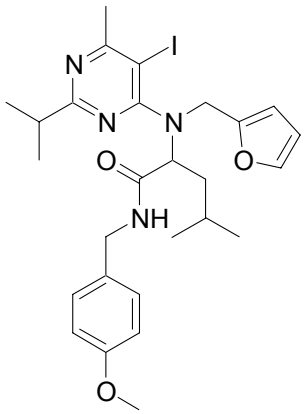
^{1}H NMR spectra were recorded on a 400 MHz spectrometer, using $CDCl_3$ solvent as reference and/or internal deuterium lock. ^{13}C NMR spectra were recorded on a 100.6 MHz spectrometer. Two-dimensional NMR spectroscopy [^{1}H -^{1}H COSY spectra, ^{1}H - ^{13}C COSY spectra (HSQC) and long-range ^{1}H -^{13}C COSY spectra (HMBC)], were carried out to determine the correlation between ^{1}H and ^{13}C. The chemical shifts for all NMR spectra are expressed in parts per million to high frequency of TMS reference. Coupling constants (J) are quoted in Hz and are recorded to the nearest 0.1 Hz.

The IR spectra were obtained using ATR accessories. High-resolution (HR) mass spectra were performed on a GC/MS system spectrometer. TLC was carried out using precoated plates of silica gel 60F254.

General procedure for the synthesis of the pyrimidin-4-ol derived Ugi-Smiles adducts :

To a 1 M solution of pyrimidin-4-ol in methanol were added successively 1.0 equiv of amine, 1.0 equiv of aldehyde and 1.0 equiv of isocyanide. The resulting mixture was stirred at 60°C for three days. The solvent was removed afterwards under reduced pressure to afford the Ugi-Smiles products after purification by flash chromatography on silica gel.

2-[furan-2-ylmethyl-(5-iodo-2-isopropyl-6-methylpyrimidin-4-yl)-amino]-4-methylpentanoic acid 4-methoxybenzylamide



$C_{27}H_{35}IN_4O_3$
MW = 590.50 g.mol^{-1}

5a

General procedure using isovaleraldehyde (220 µL, 2.0 mmol), furfurylamine (180 µL, 2.0 mmol), *p*-methoxybenzylisocyanide (300 µL, 2.0 mmol) and 5-iodo-2-isopropyl-6-methylpyrimidin-4-ol (560 mg, 2.0 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 70:30) gave **5a** as a brown oil.

Yield 62 % (730 mg).

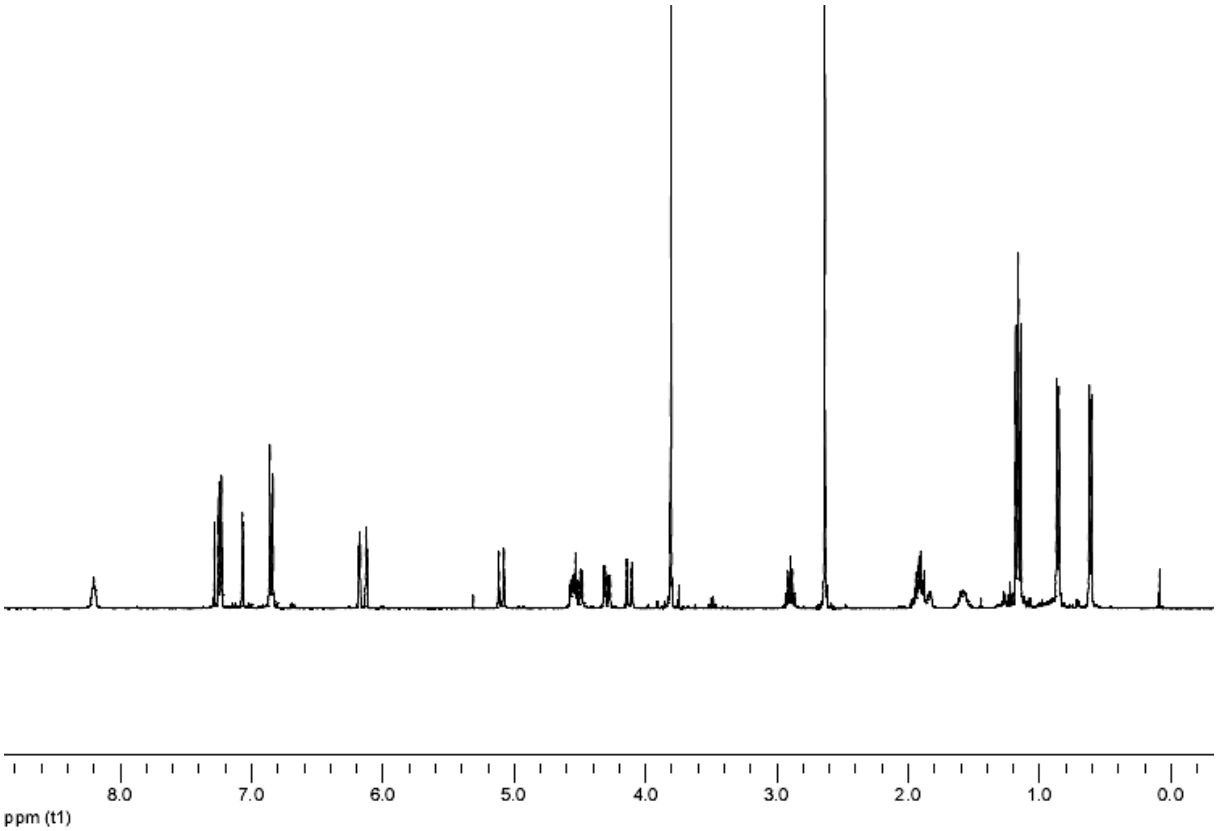
R_f 0.3 (70:30 petroleum ether / diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (t, *J* = 5.6 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 2H), 7.08-7.05 (s, 1H), 6.85 (d, *J* = 8.3 Hz, 2H), 6.16 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.10 (d, *J* = 3.1 Hz, 1H), 5.10 (d, *J* = 15.2 Hz, 1H), 4.58-4.46 (m, 2H), 4.27 (dd, *J* = 14.2, 4.9 Hz, 1H), 4.12 (d, *J* = 15.2 Hz, 1H), 3.80 (s, 3H), 2.90 (sept, *J* = 6.8 Hz, 1H), 2.63 (s, 3H), 1.98-1.84 (m, 2H), 1.65-1.52 (m, 1H), 1.17 (d, *J* = 6.8 Hz, 3H), 1.15 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.3 Hz, 3H), 0.61 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 172.8, 172.1, 171.3, 166.8, 159.3, 151.4, 142.2, 130.6, 130.0, 114.3, 110.5, 109.4, 84.6, 63.8, 55.7, 44.0, 43.9, 38.6, 37.0, 30.8, 25.2, 23.7, 22.1, 21.7, 21.4.

I.R. (thin film) 1655, 1568, 1512, 1467 cm^{-1}.

HRMS Calculated for $C_{27}H_{35}IN_4O_3$ 590.1754, found 590.1752.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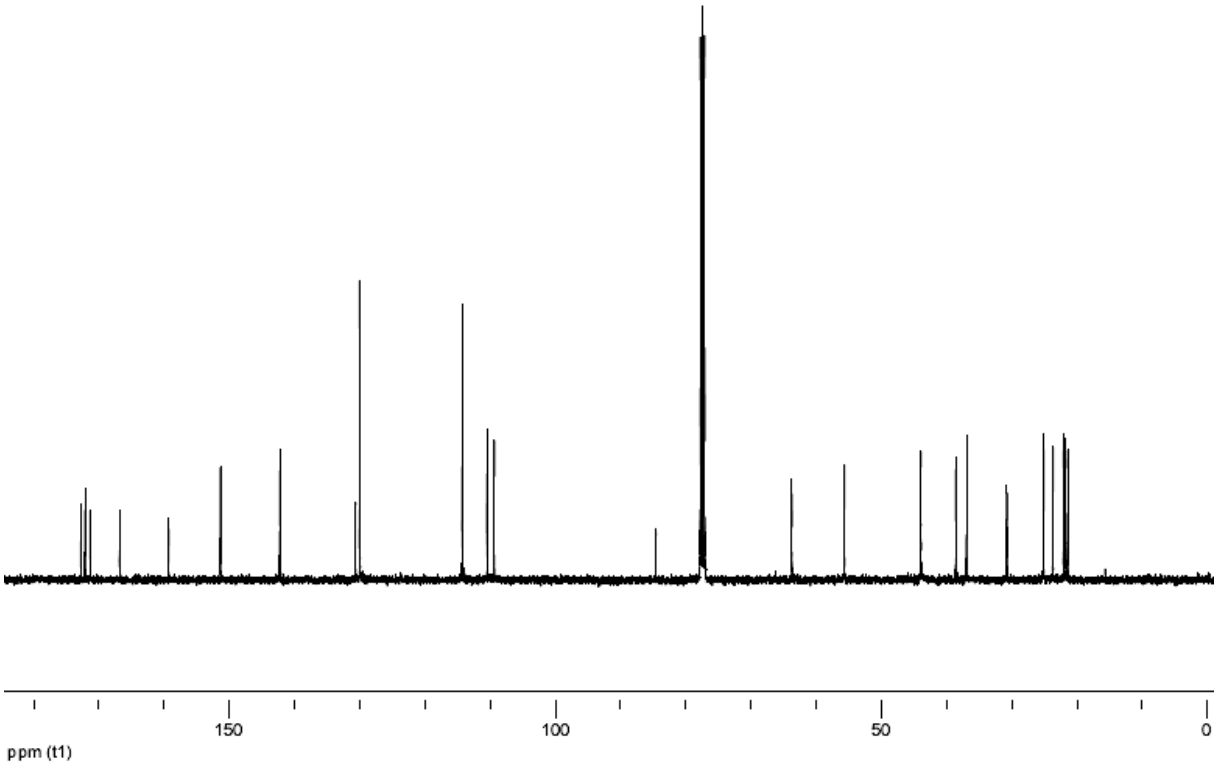
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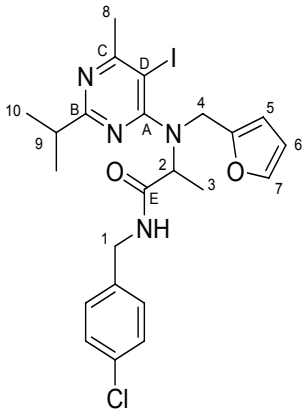
100
50
0
ppm (t1)

2-[furan-2-ylmethyl-(5-iodo-2-isopropyl-6-methylpyrimidin-4-yl)-amino]-*N*-(4-chlorobenzyl)-propionamide



$C_{23}H_{26}ClIN_4O_2$
MW = 552.84 g.mol^{-1}

5b

General procedure using acetaldehyde (110 µL, 2.0 mmol), furfurylamine (180 µL, 2.0 mmol), *p*-chlorobenzylisocyanide (260 µL, 2.0 mmol) and 5-iodo-2-isopropyl-6-methylpyrimidin-4-ol (560 mg, 2.0 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 70:30) gave **5b** as a yellow oil.

Yield 54 % (592 mg).

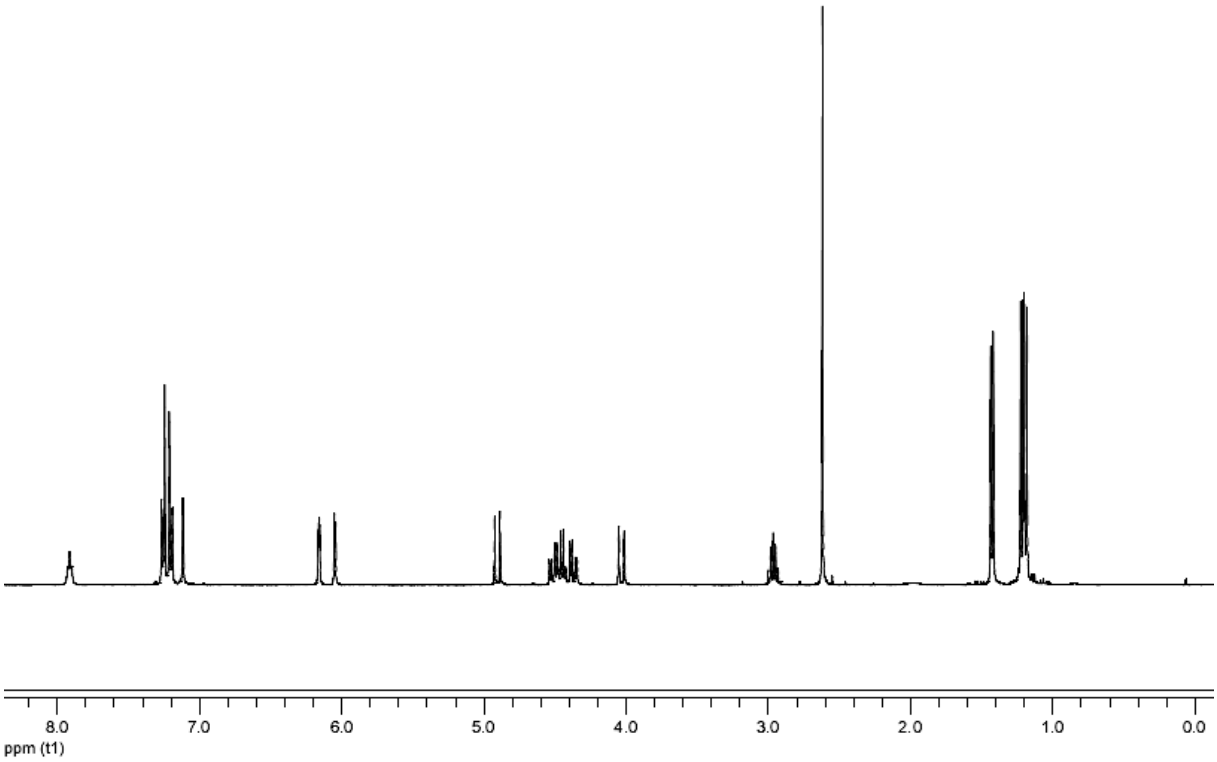
R_f 0.3 (70:30 petroleum ether / diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (t, *J* = 5.5 Hz, 1H), 7.26 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 1.9 Hz, 1H), 6.16 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.05 (d, *J* = 3.1 Hz, 1H), 4.91 (d, *J* = 15.0 Hz, 1H), 4.52 (dd, *J* = 14.7, 6.1 Hz, 1H), 4.45 (q, *J* = 7.0 Hz, 1H), 4.37 (dd, *J* = 14.7, 5.5 Hz, 1H), 4.03 (d, *J* = 15.0 Hz, 1H), 2.97 (sept, *J* = 6.9 Hz, 1H), 2.62 (s, 3H), 1.43 (d, *J* = 7.0 Hz, 3H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.19 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 172.9, 171.8, 171.1, 166.7, 151.1, 141.8, 129.3, 128.6, 110.1, 108.5, 87.5, 61.1, 43.3, 43.1, 36.5, 30.1, 21.7, 21.3, 13.3.

I.R. (thin film) 1660, 1570, 1536, 1492 cm^{-1}.

HRMS Calculated for $C_{23}H_{26}ClIN_4O_2$ 552.0789, found 552.0790.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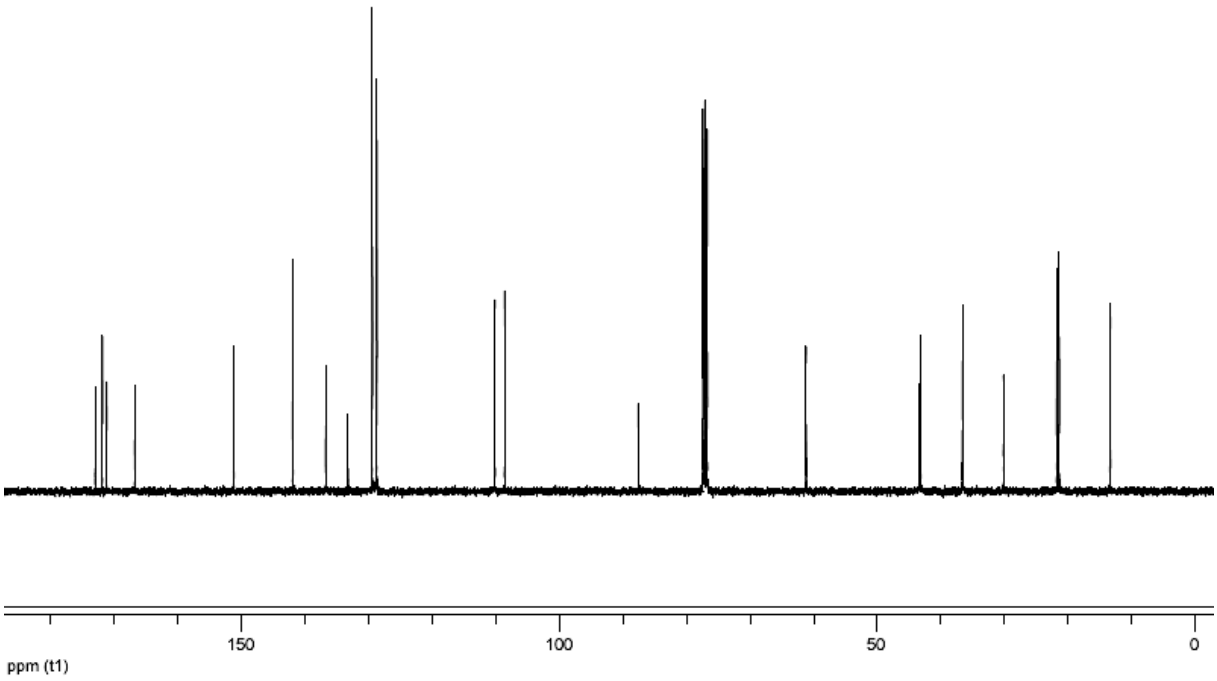
ppm (t1)


150
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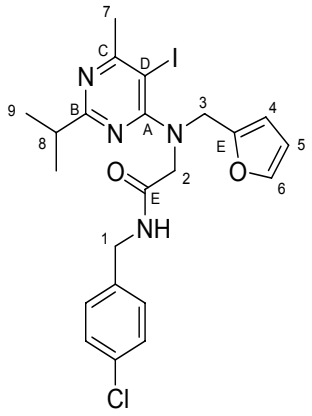
N-(4-chlorobenzyl)-2-[furan-2-ylmethyl-(5-iodo-2-isopropyl-6-methylpyrimidin-4-yl)-amino]-acetamide



$C_{22}H_{24}ClIN_4O_2$
MW = 538.81 g.mol^{-1}

5c

General procedure using formaldehyde (220 µL, 2.0 mmol), furfurylamine (180 µL, 2.0 mmol), *p*-chlorobenzylisocyanide (260 µL, 2.0 mmol) and 5-iodo-2-isopropyl-6-methylpyrimidin-4-ol (560 mg, 2.0 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 70:30) gave **5c** as a white solid.

MP 109-110 °C.

Yield 36 % (385 mg).

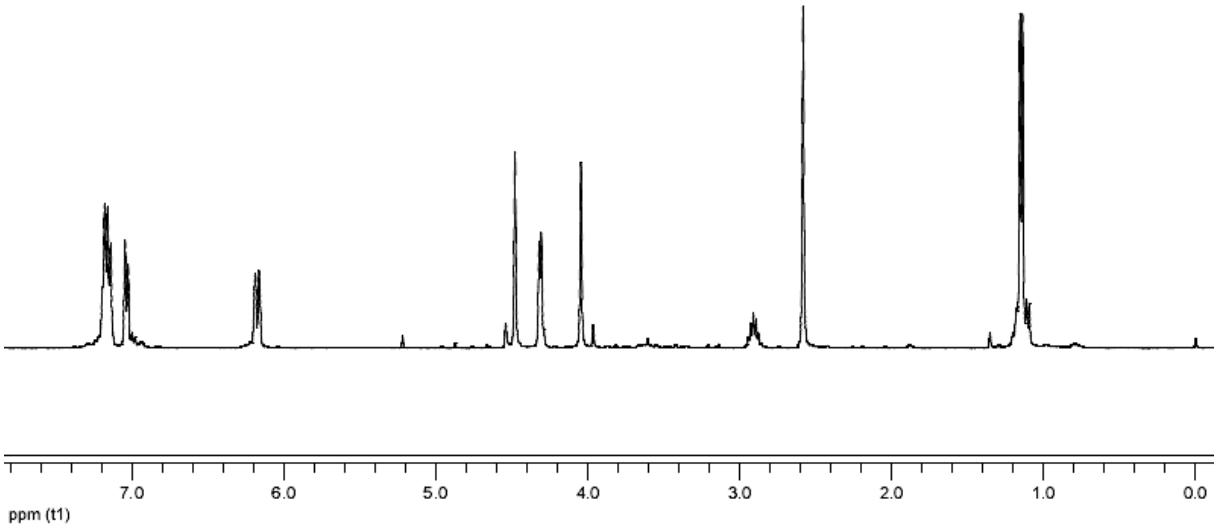
R_f 0.3 (70:30 petroleum ether / diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.18 (m, 4H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.25 (br s, 1H), 6.23 (br s, 1H), 4.57 (s, 2H), 4.38 (d, *J* = 5.8 Hz, 2H), 4.11 (s, 2H), 2.98 (sept, *J* = 6.9 Hz, 1H), 2.58 (s, 3H), 1.15 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.1, 171.1, 169.5, 166.3, 150.2, 142.3, 136.4, 133.2, 129.2, 128.7, 110.3, 109.4, 84.7, 54.8, 49.4, 42.7, 36.6, 30.2, 21.5.

I.R. (thin film) 1666, 1537, 1515, 1492 cm^{-1}.

HRMS Calculated for $C_{22}H_{24}ClIN_4O_2$ 538.0633, found 538.0625.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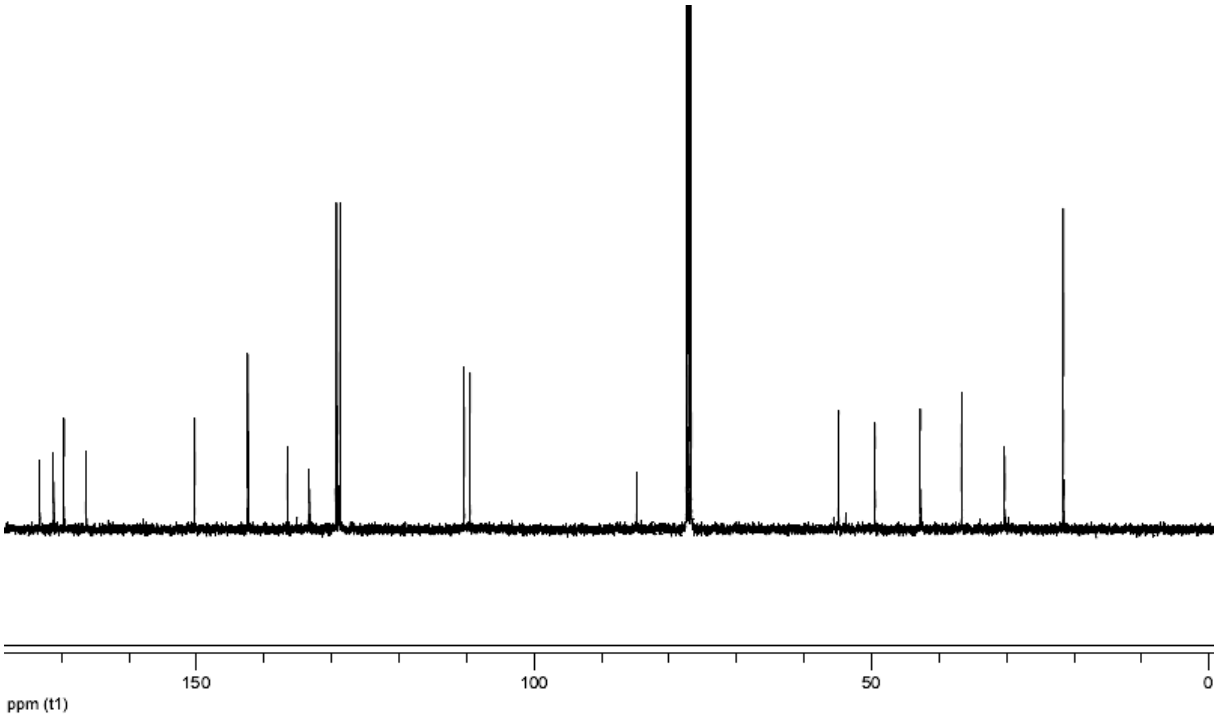
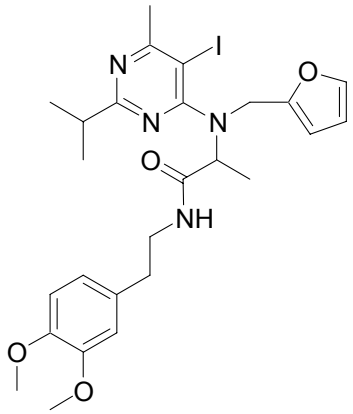
2.0
1.0
0.0
ppm (t1)


150
100
50
0
ppm (t1)

_N_-[2-(3,4-dimethoxyphenyl)-ethyl]-2-[furan-2-ylmethyl-(5-iodo-2-isopropyl-6-methylpyrimidin-4-yl)-amino]-propionamide



$C_{26}H_{33}IN_4O_4$
MW = 592.47 g.mol^{-1}

5d

General procedure using acetaldehyde (110 µL, 2.0 mmol), furfurylamine (180 µL, 2.0 mmol), 4-(2-isocyanoethyl)-1,2-dimethoxybenzene (382 mg, 2.0 mmol) and 5-iodo-2-isopropyl-6-methylpyrimidin-4-ol (560 mg, 2.0 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 20:80) gave **5d** as an orange oil.

Yield 42 % (490 mg).

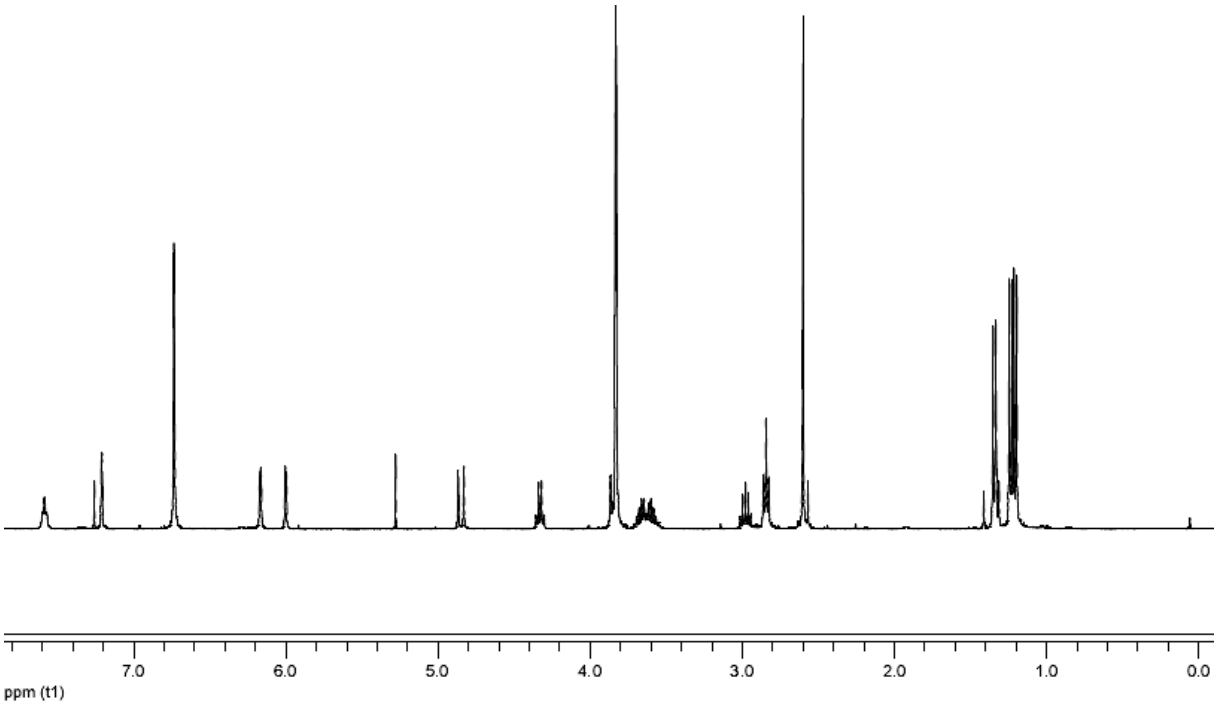
R_f 0.3 (20:80 petroleum ether / diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59 (t, *J* = 5.6 Hz, 1H), 7.21 (d, *J* = 1.8 Hz, 1H), 6.74 (br s, 3H), 6.17 (dd, *J* = 3.1, 1.8 Hz, 1H), 6.00 (d, *J* = 3.1 Hz, 1H), 4.85 (d, *J* = 14.8 Hz, 1H), 4.33 (q, *J* = 7.0 Hz, 1H), 3.85 (d, *J* = 14.8 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.72-3.53 (m, 2H), 2.98 (sept, *J* = 6.9 Hz, 1H), 2.84 (t, *J* = 7.0 Hz, 2H), 2.60 (s, 3H), 1.34 (d, *J* = 7.0 Hz, 1H), 1.24 (d, *J* = 6.9 Hz, 3H), 1.21 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 172.8, 171.5, 170.9, 166.7, 151.5, 148.9, 147.5, 141.7, 131.3, 120.6, 111.8, 111.1, 110.0, 108.2, 87.7, 61.4, 55.8, 55.8, 42.9, 40.6, 36.5, 34.9, 27.0, 21.8, 21.3, 12.8.

I.R. (thin film) 1669, 1535, 1515, 1463 cm^{-1}.

HRMS Calculated for $C_{26}H_{33}IN_4O_4$ 592.1547, found 592.1540.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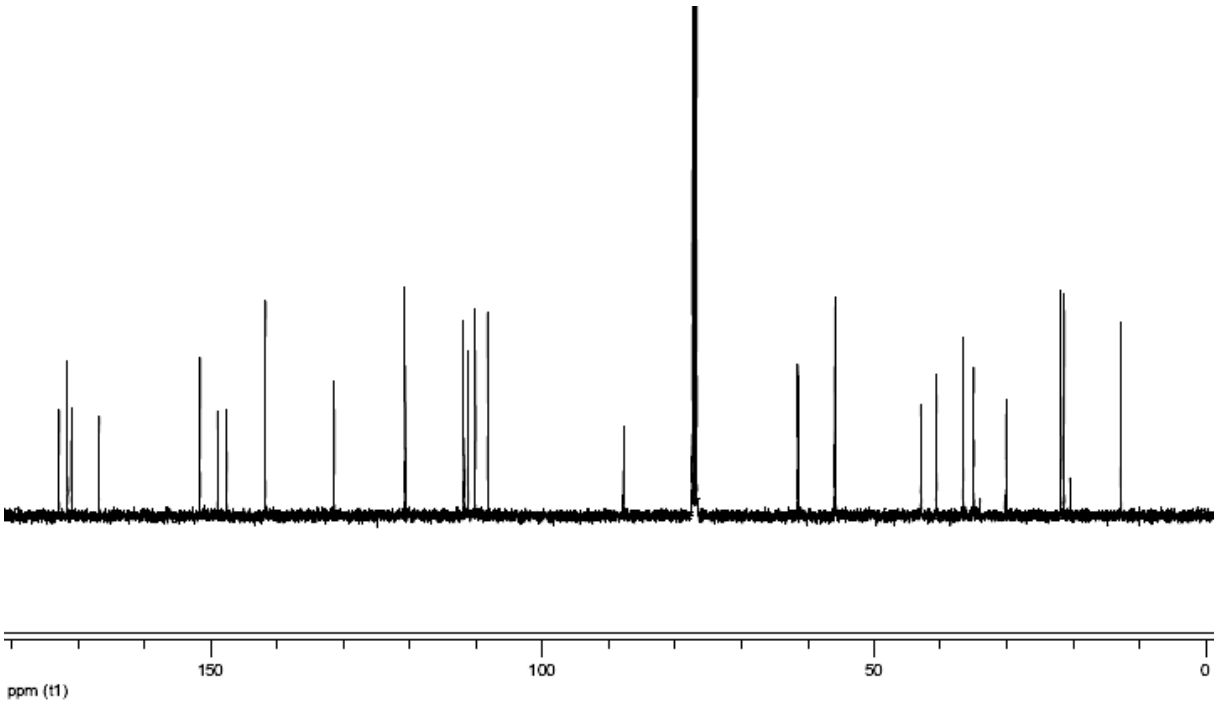
0.0
ppm (t1)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100
50
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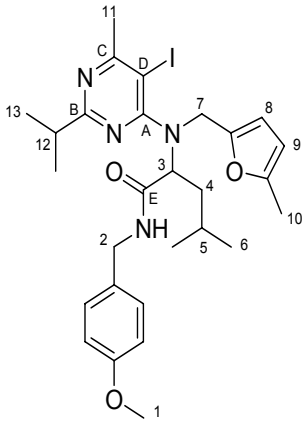
ppm (t1)

2-[(5-iodo-2-isopropyl-6-methylpyrimidin-4-yl)-(5-methylfuran-2-ylmethyl)-amino]-4-methylpentanoic acid 4-methoxybenzylamide



$C_{28}H_{37}IN_4O_3$
MW = 604.52 g.mol^{-1}

5e

General procedure using isovaleraldehyde (220 µL, 2.0 mmol), 5-methylfurfurylamine (250 µL, 2.0 mmol), *p*-methoxybenzylisocyanide (300 µL, 2.0 mmol) and 5-iodo-2-isopropyl-6-methylpyrimidin-4-ol (560 mg, 2.0 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 70:30) gave **5e** as a brown oil.

Yield 79 % (952 mg).

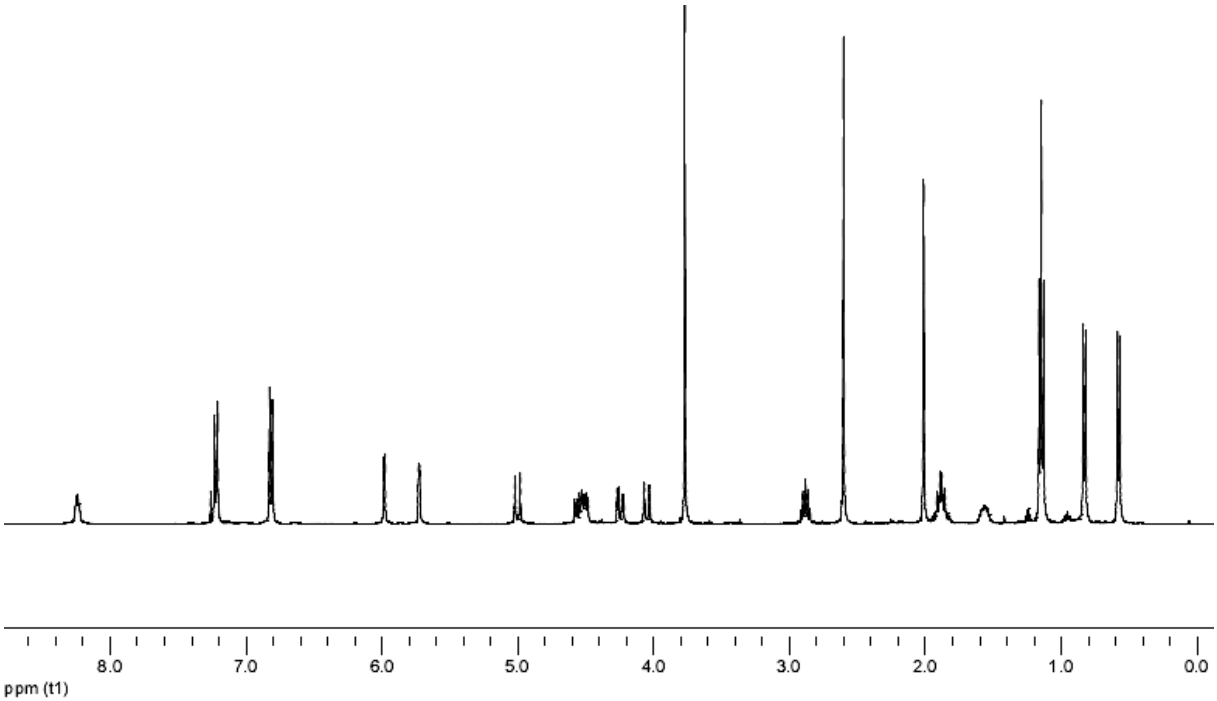
R_f 0.3 (70:30 petroleum ether / diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.18 (t, *J* = 5.8 Hz, 1H), 7.16 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 5.92 (d, *J* = 2.9 Hz, 1H), 5.66 (d, *J* = 2.9 Hz, 1H), 4.94 (d, *J* = 15.1 Hz, 1H), 4.49 (dd, *J* = 14.4, 6.3 Hz, 1H), 4.44 (d, *J* = 9.5, 5.4 Hz, 1H), 4.18 (dd, *J* = 14.4, 4.7 Hz, 1H), 3.99 (d, *J* = 15.1 Hz, 1H), 3.71 (s, 3H), 2.82 (sept, *J* = 6.9 Hz, 1H), 2.54 (s, 3H), 1.95 (s, 3H), 1.90-1.75 (m, 2H), 1.56-1.44 (m, 1H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.77 (d, *J* = 6.6 Hz, 3H), 0.52 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 172.2, 171.8, 170.7, 166.5, 158.8, 151.3, 149.0, 130.3, 129.4, 113.8, 109.9, 105.9, 84.4, 63.3, 55.3, 43.6, 43.3, 38.2, 36.5, 30.2, 24.6, 23.3, 21.6, 21.2, 20.9, 13.3.

I.R. (thin film) 1666, 1533, 1511, 1439 cm^{-1}.

HRMS Calculated for $C_{28}H_{37}IN_4O_3$ 604.1910, found 604.1903.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2.0
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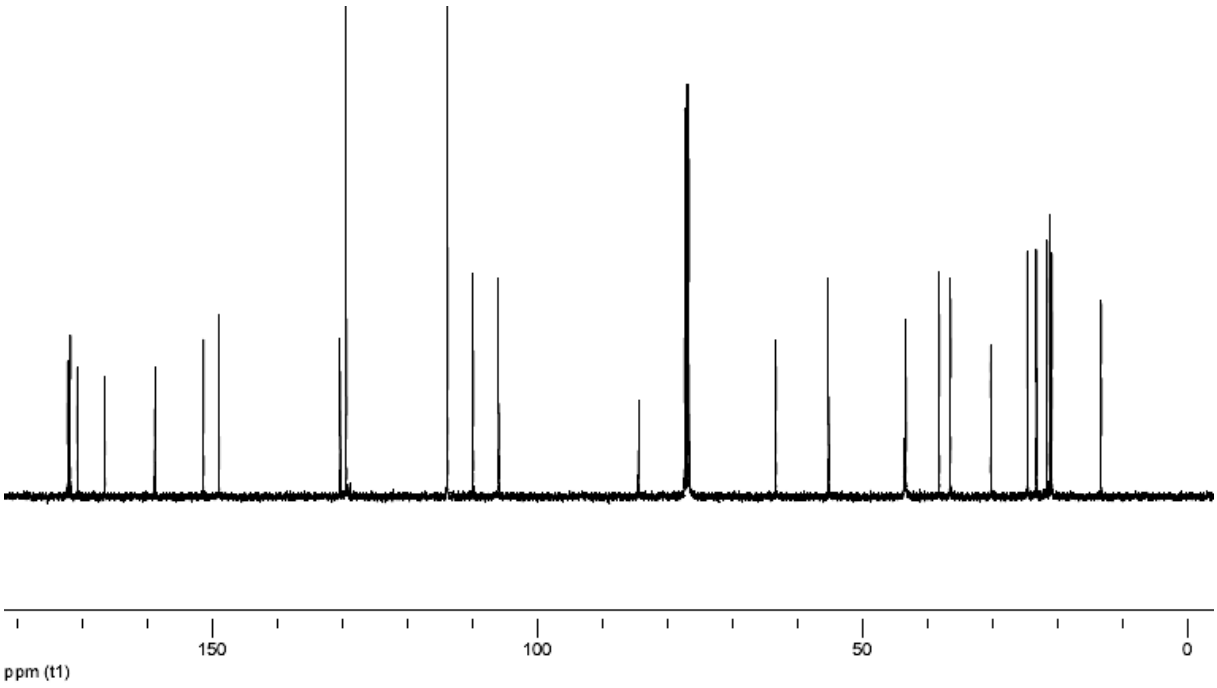
ppm (t1)


150
100
50
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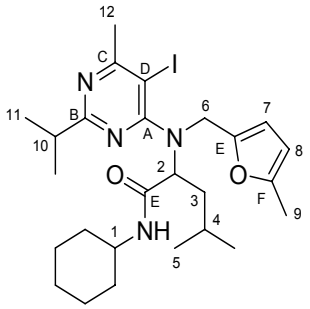
ppm (t1)

_N_-cyclohexyl-2-((5-iodo-2-isopropyl-6-methylpyrimidin-4-yl)((5-methylfuran-2-yl)methyl)amino)-4-methylpentanamide



$C_{26}H_{39}IN_4O_2$
MW = 566.52 g.mol^{-1}

5f

General procedure using isovaleraldehyde (220 µL, 2.0 mmol), 5-methylfurfurylamine (250 µL, 2.0 mmol), cyclohexylisocyanide (260 µL, 2.0 mmol) and 5-iodo-2-isopropyl-6-methylpyrimidin-4-ol (560 mg, 2.0 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 80:20) gave **5f** as an orange oil.

Yield 25 % (280 mg).

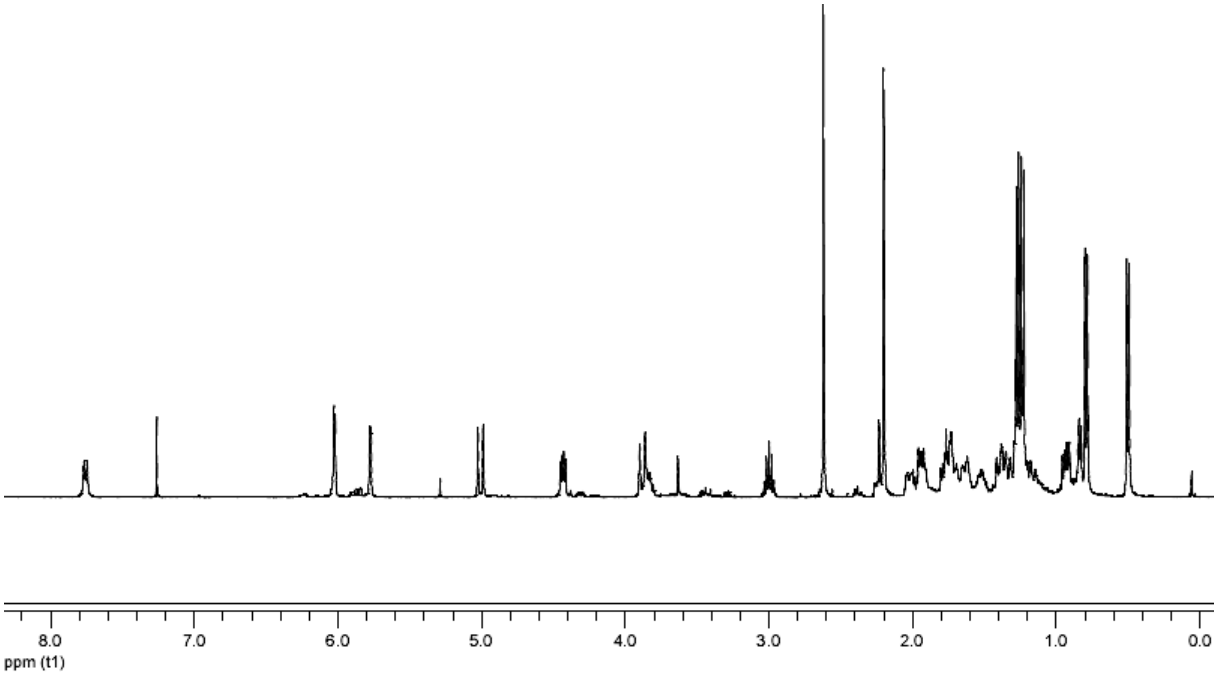
R_f 0.3 (80:20 petroleum ether / diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, *J* = 8.2 Hz, 1H), 6.02 (d, *J* = 2.9 Hz, 1H), 5.77 (d, *J* = 2.9 Hz, 1H), 5.00 (d, *J* = 14.7 Hz, 1H), 4.43 (dd, *J* = 9.9, 4.7 Hz, 1H), 3.88 (d, *J* = 14.7 Hz, 1H), 3.89-3.79 (m, 1H), 3.00 (sept, *J* = 6.9 Hz, 1H), 2.62 (s, 3H), 2.20 (s, 3H), 2.06-1.83 (m, 3H), 1.83-1.58 (m, 4H), 1.57-1.48 (m, 1H), 1.36-1.25 (m, 2H), 1.20-1.06 (m, 3H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.23 (d, *J* = 6.9 Hz, 3H), 0.79 (d, *J* = 6.6 Hz, 3H), 0.50 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 172.3, 170.6, 170.4, 166.8, 151.3, 149.4, 109.7, 106.0, 84.9, 63.8, 48.5, 42.8, 38.2, 36.6, 33.1, 33.0, 30.3, 25.7, 25.0, 24.9, 24.7, 23.7, 22.3, 21.8, 21.2, 13.6.

I.R. (thin film) 1669, 1567, 1537, 1451 cm^{-1}.

HRMS Calculated for $C_{26}H_{39}IN_4O_2$ 566.2118, found 566.2101.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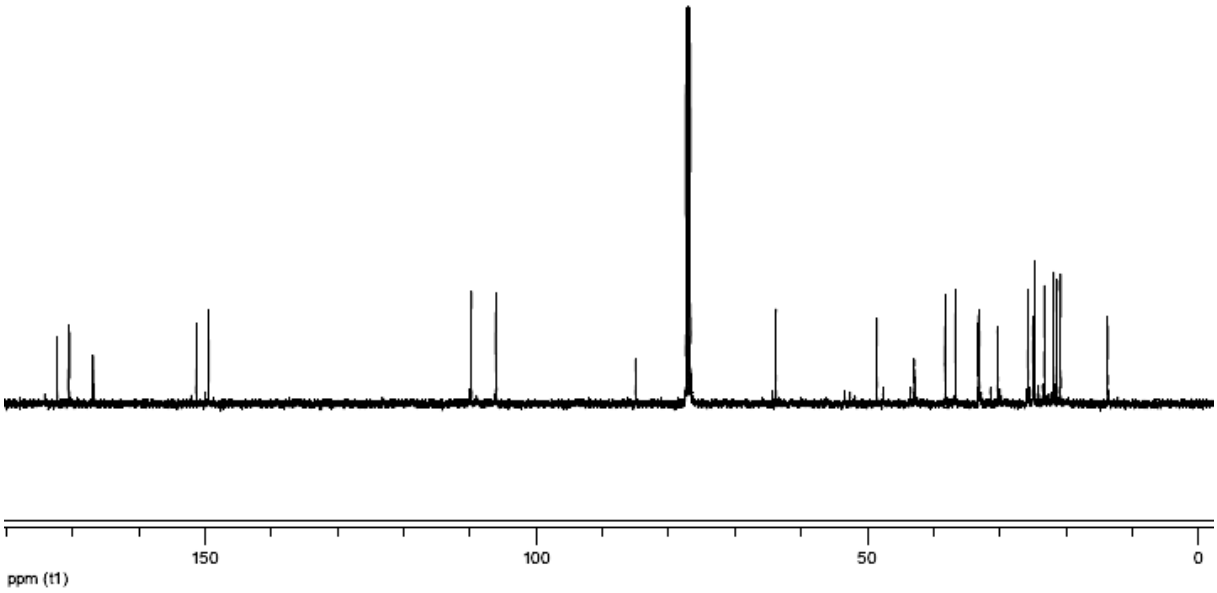
ppm (t1)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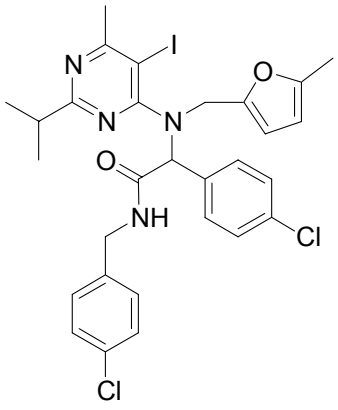
_N_-(4-chlorobenzyl)-2-(4-chlorophenyl)-2-[(5-iodo-2-isopropyl-6-methylpyrimidin-4-yl)-(5-methylfuran-2-ylmethyl)-amino]-acetamide



$C_{29}H_{29}Cl_2IN_4O_2$
MW = 663.38 g.mol^{-1}

5g

General procedure using *p*-chlorobenzaldehyde (280 mg, 2.0 mmol), 5-methylfurfurylamine (250 µL, 2.0 mmol), *p*-chlorobenzylisocyanide (260 µL, 2.0 mmol) and 5-iodo-2-isopropyl-6-methylpyrimidin-4-ol (560 mg, 2.0 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 70:30) gave **5g** as an orange oil.

Yield 35 % (461 mg).

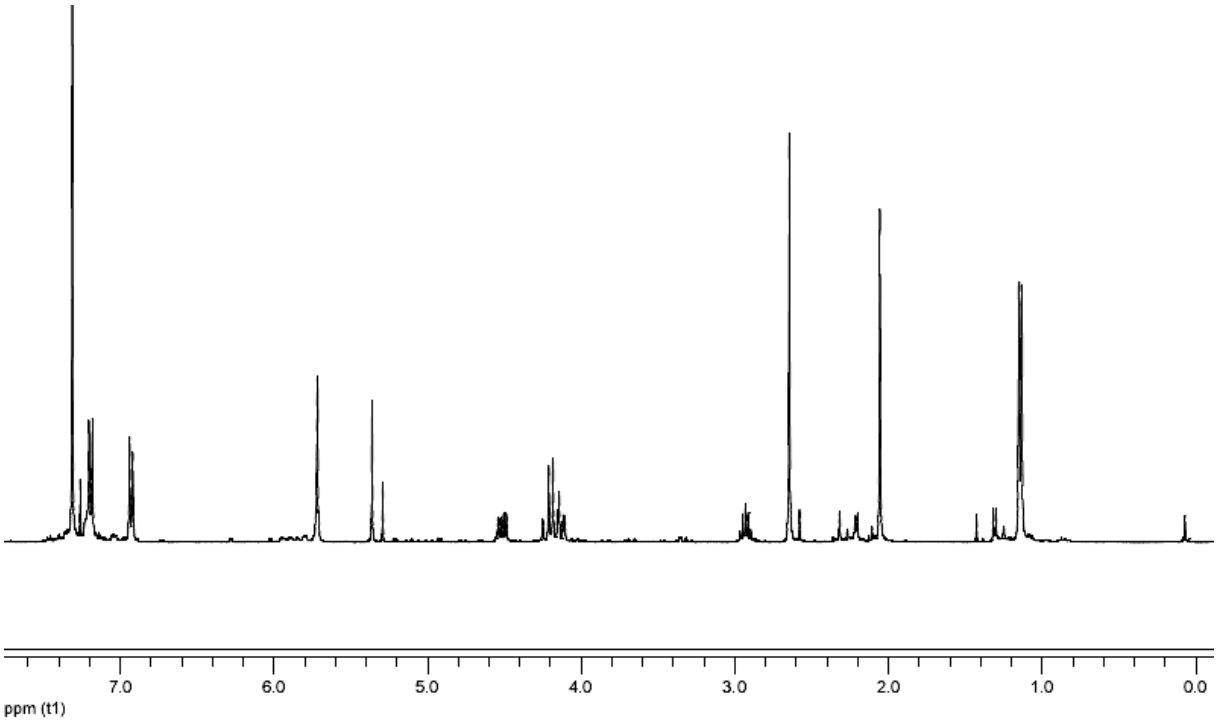
R_f 0.3 (70:30 petroleum ether / diethyl ether).

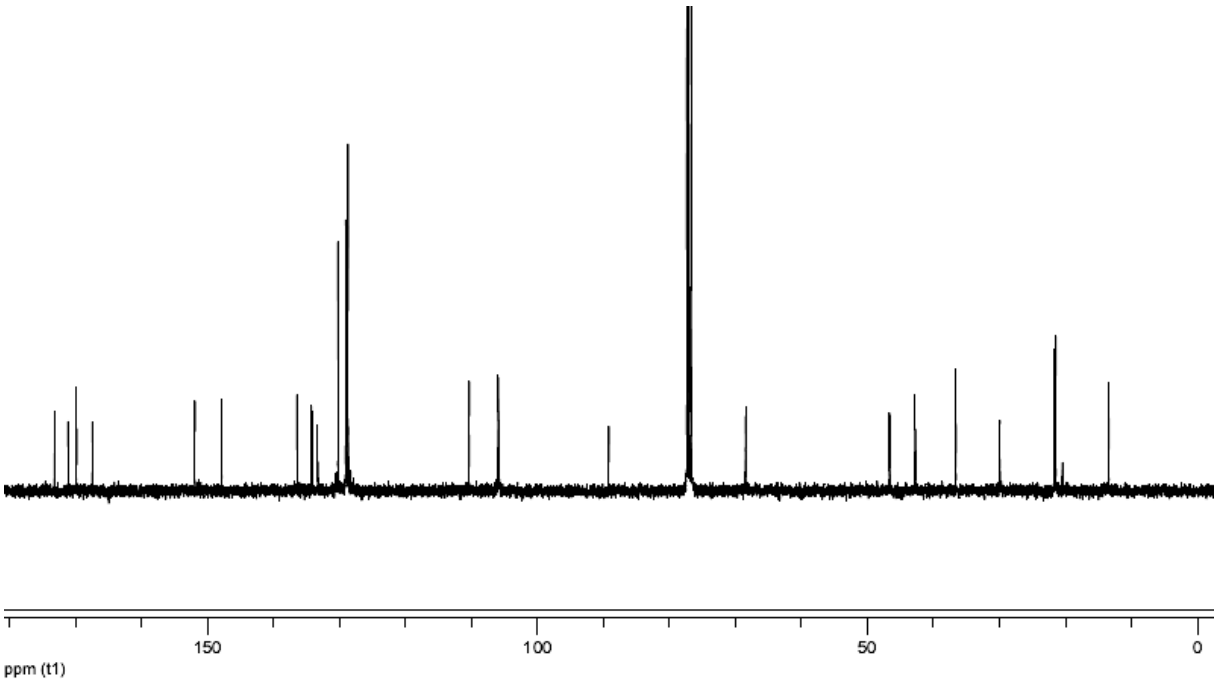
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31 (br s, 4H), 7.22 (br s, 1H), 7.19 (d, *J* = 8.3 Hz, 2H), 6.93 (d, *J* = 8.3 Hz, 2H), 5.72 (br s, 2H), 5.36 (s, 1H), 4.51 (dd, *J* = 14.7, 7.2 Hz, 1H), 4.32. (d, *J* = 15.6 Hz, 1H), 4.17 (d, *J* = 15.6 Hz, 1H), 4.13 (dd, *J* = 14.7, 4.5 Hz, 1H), 2.93 (sept, *J* = 6.9 Hz, 1H), 2.65 (s, 3H), 2.06 (s, 3H), 1.14 (d, *J* = 6.9 Hz, 1H), 1.14 (d, *J* = 6.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.2, 171.1, 169.8, 167.4, 151.9, 147.8, 136.4, 134.3, 134.1, 133.2, 130.2, 129.0, 128.7, 128.7, 110.3, 105.9, 89.1, 68.4, 46.6, 42.7, 36.6, 29.9, 21.6, 21.4, 13.4.

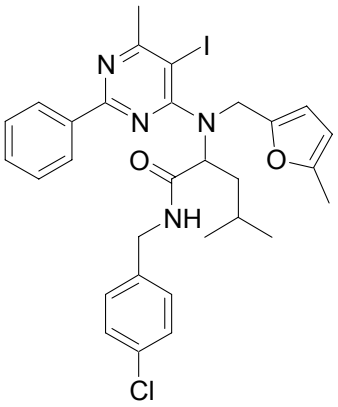
I.R. (thin film) 1670, 1558, 1539, 1491 cm^{-1}.

HRMS Calculated for $C_{29}H_{29}Cl_2IN_4O_2$ 662.0712, found 662.0691.


7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


150
100
50
0
ppm (t1)

2-[(5-iodo-6-methyl-2-phenylpyrimidin-4-yl)-(5-methylfuran-2-ylmethyl)-amino]-4-methylpentanoic acid 4-chlorobenzylamide



$C_{30}H_{32}ClIN_4O_2$
MW = 642.96 g.mol^{-1}

5h

General procedure using isovaleraldehyde (220 µL, 2.0 mmol), 5-methylfurfurylamine (250 µL, 2.0 mmol), *p*-chlorobenzylisocyanide (260 µL, 2.0 mmol) and 5-iodo-2-phenyl-6-methylpyrimidin-4-ol (624 mg, 2.0 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 80:20) gave **5h** as an orange oil.

Yield 82 % (1055 mg).

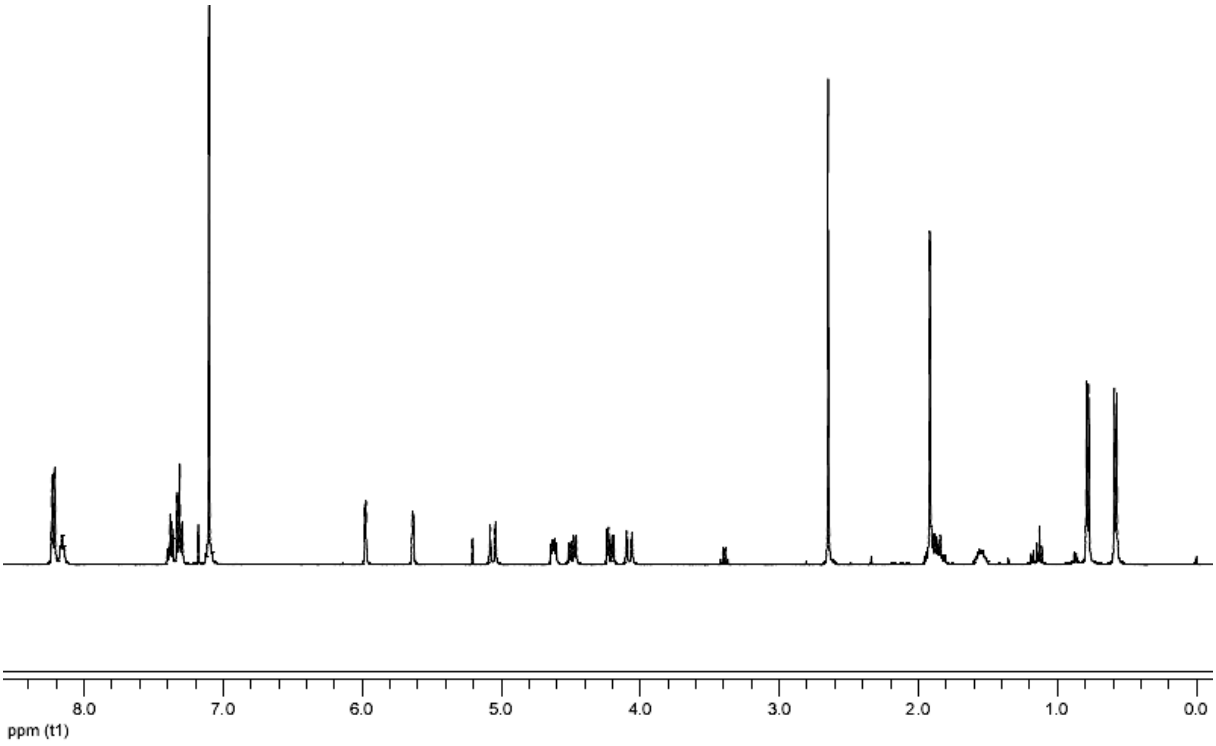
R_f 0.4 (70:30 petroleum ether / diethyl ether).

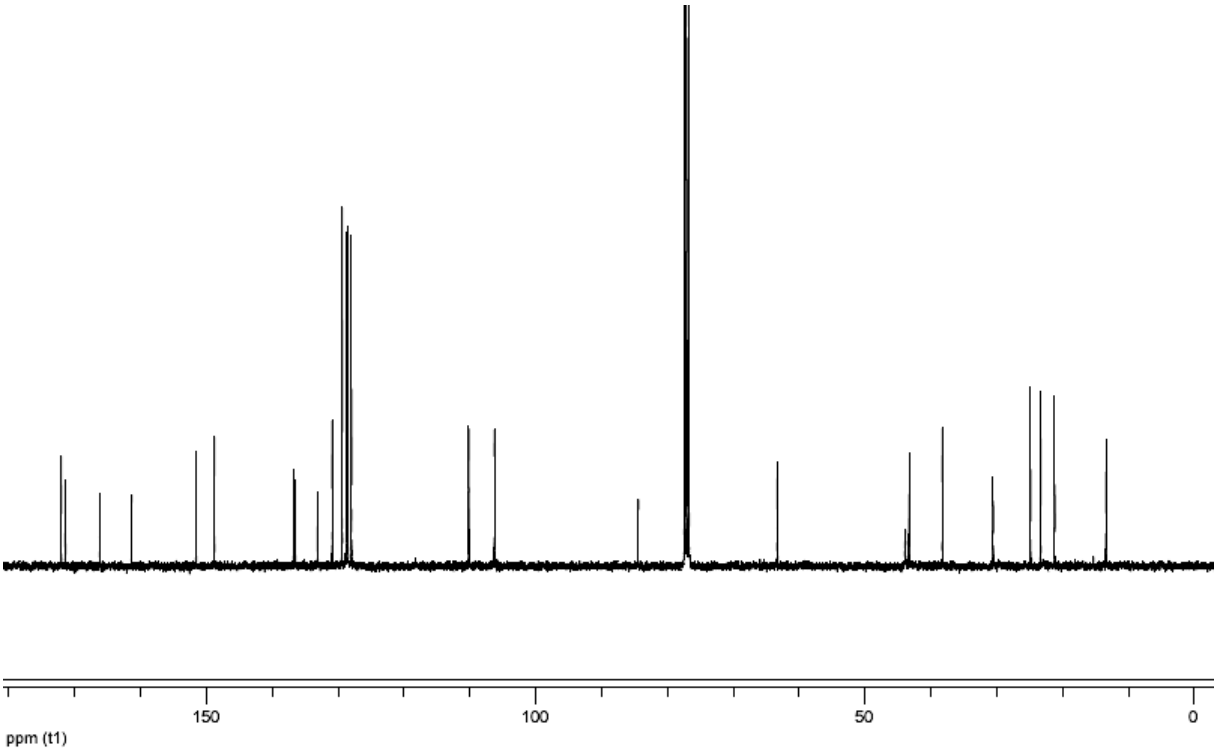
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32-8.28 (m, 2H), 8.24 (t, *J* = 5.6 Hz, 1H), 7.49-7.44 (m, 1H), 7.42-7.37 (m, 2H), 7.18 (br s, 4H), 6.06 (d, *J* = 3.0 Hz, 1H), 5.72 (dd, *J* = 3.0, 0.9 Hz, 1H), 5.14 (d, *J* = 15.2 Hz, 1H), 4.70 (dd, *J* = 9.6, 5.2 Hz, 1H), 4.57 (dd, *J* = 14.8, 6.4 Hz, 1H), 4.30 (dd, *J* = 14.8, 5.0 Hz, 1H), 4.14 (d, *J* = 15.2 Hz, 1H), 2.73 (s, 3H), 2.00 (s, 3H), 2.05-1.87 (m, 2H), 1.70-1.57 (m, 1H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.66 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 172.0, 171.3, 161.3, 166.1, 151.5, 148.7, 136.7, 136.4, 133.0, 130.8, 129.3, 128.6, 128.5, 127.9, 110.1, 106.2, 84.3, 63.2, 43.8, 43.2, 38.2, 30.5, 24.8, 23.3, 21.1, 13.3.

I.R. (thin film) 1670, 1530, 1510, 1428 cm^{-1}.

HRMS Calculated for [$C_{30}H_{32}ClIN_4O_2$ - C_8H_7ClNO] 474.1042, found 474.1058.
.

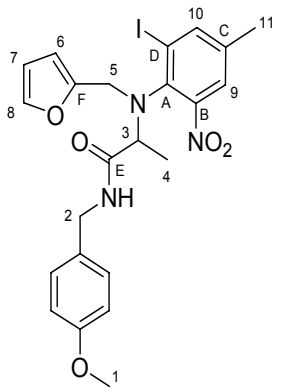

8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


150
100
50
0
ppm (t1)

General procedure for the synthesis of the phenol derived Ugi-Smiles adducts :

To a 1 M solution of 2-nitrophenol in toluene/water (ratio 9:1) were added successively 1.0 equiv of amine, 1.0 equiv of aldehyde and 1.0 equiv of isocyanide. The resulting mixture was stirred at 100°C for three days. The solvent was removed afterwards under reduced pressure to afford Ugi-Smiles products after purification by flash chromatography on silica gel.

2-((furan-2-ylmethyl)(2-iodo-4-methyl-6-nitrophenyl)amino)-*N*-(4-methoxybenzyl)propanamide



$C_{23}H_{24}IN_3O_5$
MW = 549.36 g.mol^{-1}

5i

General procedure using acetaldehyde (110 µL, 2.0 mmol), furfurylamine (180 µL, 2.0 mmol), *p*-methoxybenzylisocyanide (300 µL, 2.0 mmol) and 2-iodo-4-methyl-6-nitrophenol (558 mg, 2.0 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 40:60) gave **5i** as a yellow oil.

This product was isolated as a 1.5:1 mixture of two atropoisomers.

Yield 57 % (630 mg).

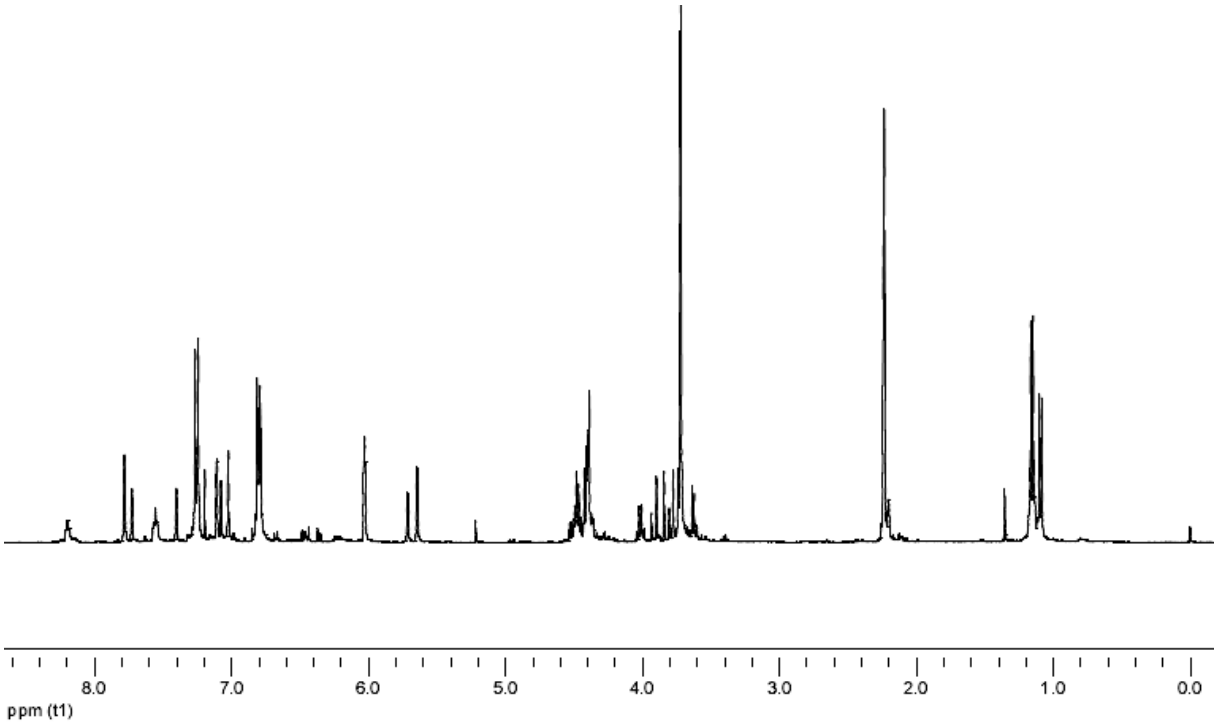
R_f 0.3 (40:60 petroleum ether / diethyl ether).

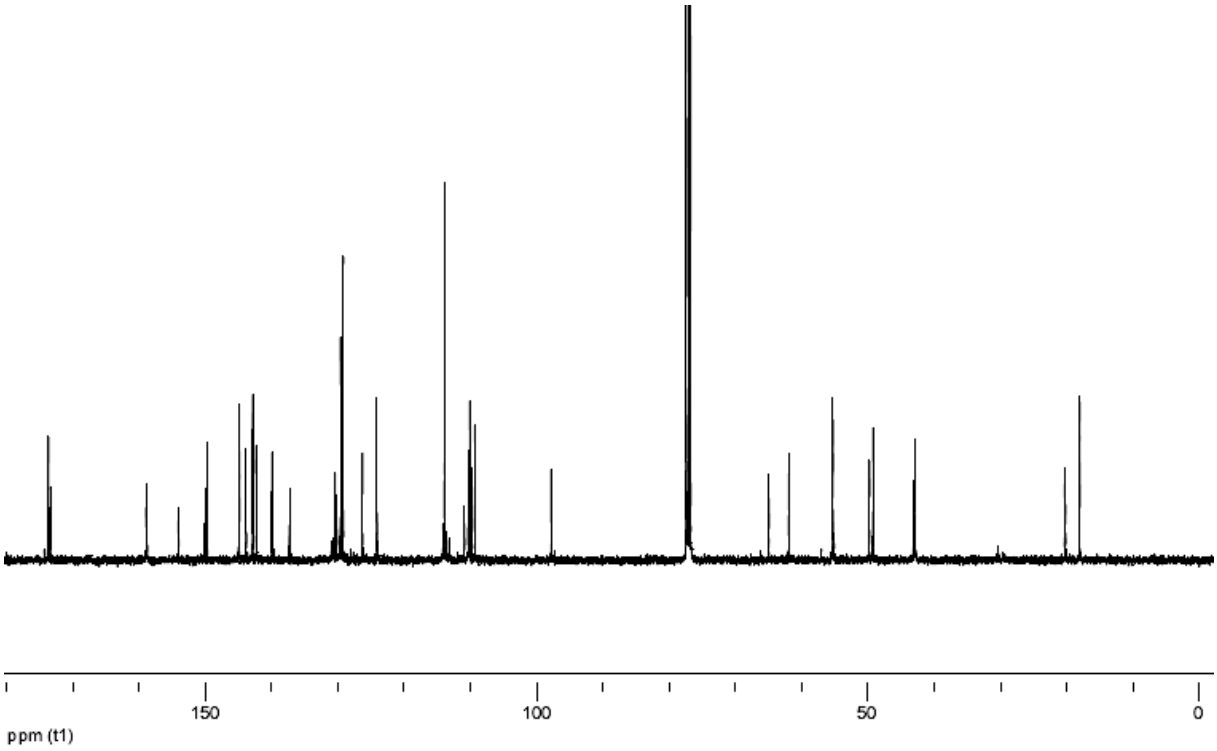
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26 (t, *J* = 5.3 Hz, 1H), 7.85 (d, *J* = 1.5 Hz, 1.5H), 7.79 (d, *J* = 1.5 Hz, 1H), 7.62 (t, *J* = 5.8 Hz, 1.5H), 7.47 (d, *J* = 1.5 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 5H), 7.17 (d, *J* = 1.5 Hz, 1.5H), 7.14 (d, *J* = 1.1 Hz, 1H), 7.09 (d, *J* = 1.1 Hz, 1.5H), 6.87 (d, *J* = 8.5 Hz, 3H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.11-6.08 (m, 2.5H), 5.78 (d, *J* = 3.1 Hz, 1H), 5.71 (d, *J* = 3.1 Hz, 1.5H), 4.61-4.50 (m, 3H), 4.50-4.41 (m, 5H), 4.08 (q, *J* = 7.1 Hz, 1H), 3.98 (d, *J* = 14.6 Hz, 1H), 3.89 (d, *J* = 14.6 Hz, 1H), 3.82 (d, *J* = 14.4 Hz, 1.5H), 3.79 (s, 3H), 3.78 (s, 4.5H), 2.31 (s, 3H), 2.30 (s, 4.5H), 1.22 (d, *J* = 7.1 Hz, 4.5H), 1.16 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.6, 173.3, 158.8, 158.7, 154.0, 150.1, 149.8, 149.6, 144.8, 143.7, 142.8, 142.2, 139.9, 139.8, 137.2, 137.1, 130.3, 130.1, 129.5, 129.1, 126.2, 124.0, 113.8, 113.8, 110.8, 110.2, 110.0, 109.7, 109.2, 97.7, 64.9, 61.8, 55.2, 55.2, 49.7, 49.1, 43.0, 42.9, 20.2, 20.1, 18.0, 17.9.

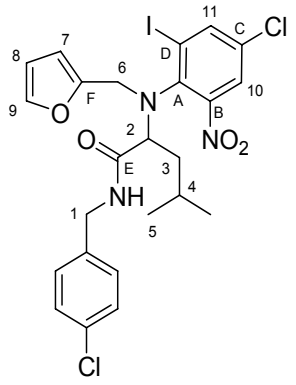
I.R. (thin film) 1659, 1612, 1528, 1513 cm^{-1}.

HRMS Calculated for $C_{23}H_{24}IN_3O_5$ 549.0761, found 549.0758.


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


150
100
50
0
ppm (t1)

2-((4-chloro-2-iodo-6-nitrophenyl)(furan-2-ylmethyl)amino)-*N*-(4-chlorobenzyl)-4-methylpentanamide



$C_{24}H_{24}Cl_2IN_3O_4$
MW = 616.28 g.mol^{-1}

5i

General procedure adduct using isovaleraldehyde (220 µL, 2.0 mmol), furfurylamine (180 µL, 2.0 mmol), *p*-chlorobenzylisocyanide (260 µL, 2.0 mmol) and 5-iodo-2-isopropyl-6-methyl-pyrimidin-4-ol (560 mg, 2.0 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 70:30) gave **5i** as a yellow oil.

This product was isolated as a 2.5:1 mixture of two atropoisomers.

Yield 75 % (920 mg).

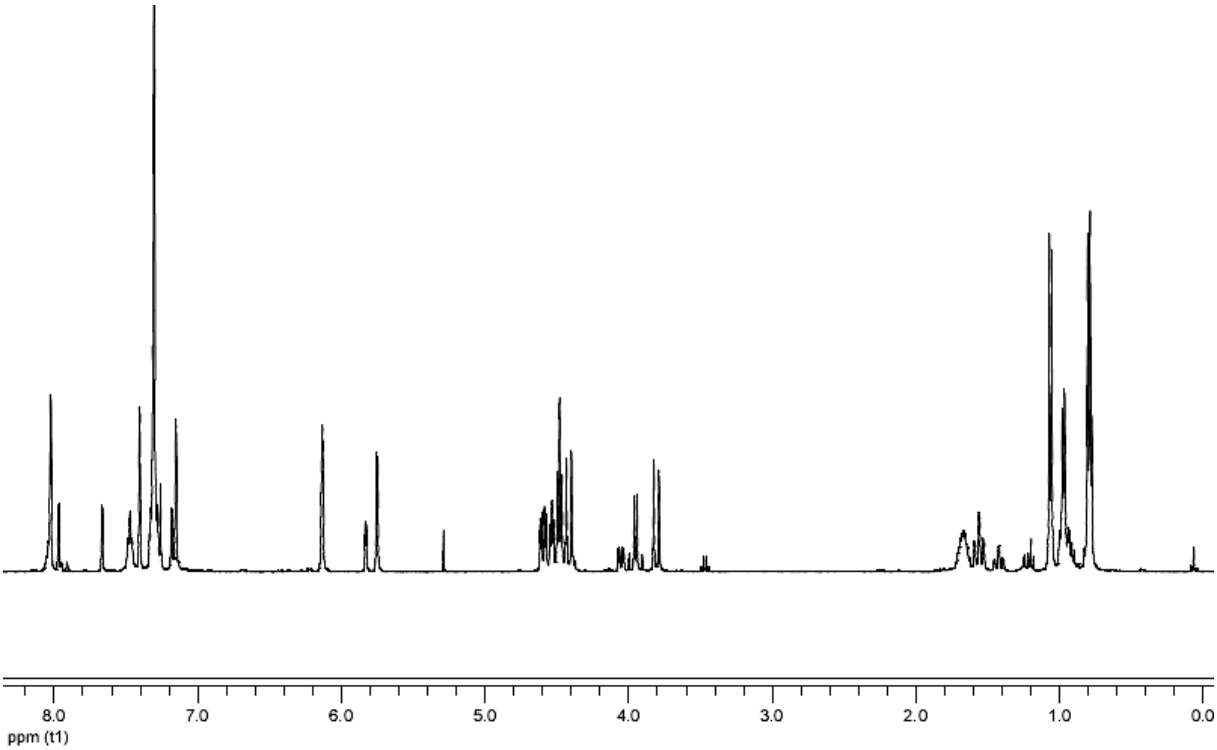
R_f 0.3 (70:30 petroleum ether / diethyl ether).

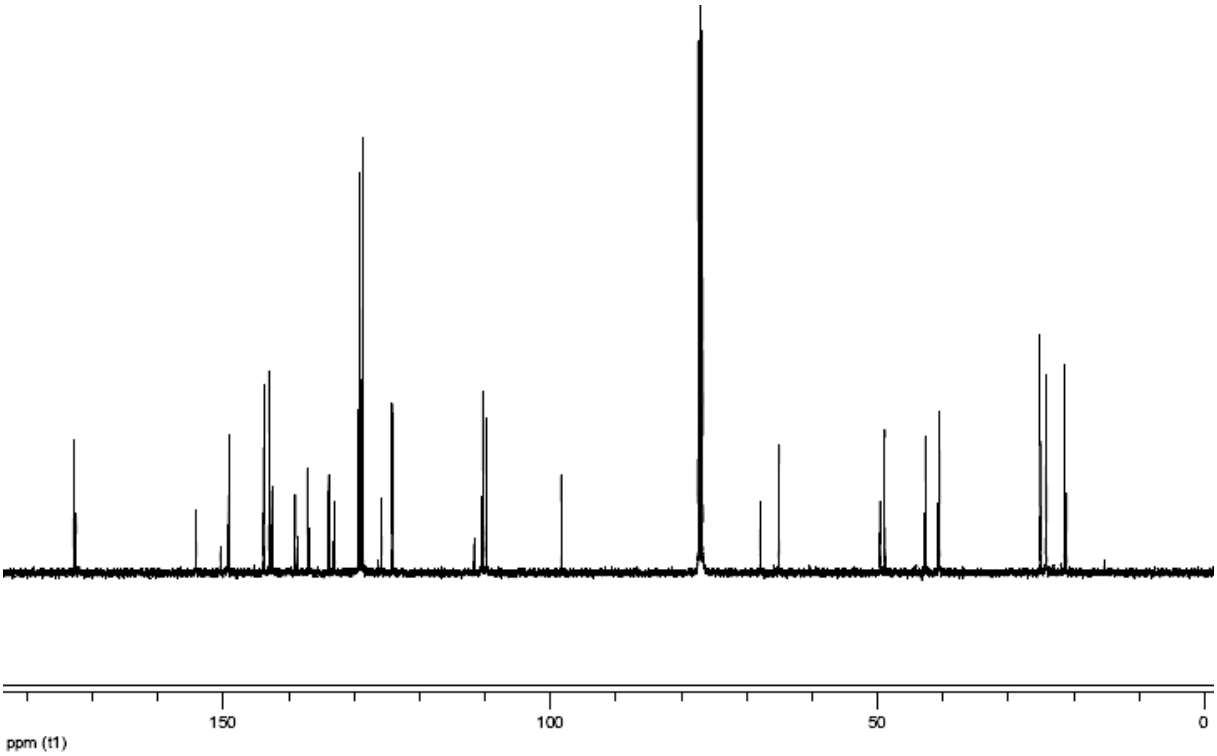
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (t, *J* = 5.8 Hz, 1H), 8.03 (d, *J* = 2.4 Hz, 2.5H), 7.97 (d, *J* = 2.4 Hz, 1H), 7.67 (d, *J* = 2.4 Hz, 1H), 7.47 (t, *J* = 5.8 Hz, 2.5H), 7.41 (d, *J* = 2.4 Hz, 2.5H), 7.35-7.27 (m, 14H), 7.18 (d, *J* = 1.1 Hz, 1H), 7.15 (d, *J* = 1.1 Hz, 2.5H), 6.15-6.12 (m, 3.5H), 5.83 (d, *J* = 3.1 Hz, 1H), 5.75 (d, *J* = 3.1 Hz, 2.5H), 4.60 (dd, *J* = 12.2, 4.5 Hz, 2.5H), 4.56-4.44 (m, 7H), 4.42 (d, *J* = 14.4 Hz, 2.5H), 4.05 (dd, *J* = 11.8, 4.2 Hz, 1H), 3.98 (d, *J* = 14.6 Hz, 1H), 3.92 (d, *J* = 14.6 Hz, 1H), 3.81 (d, *J* = 14.4 Hz, 2.5H), 1.73-1.62 (m, 3.5H), 1.56 (td, *J* = 12.6, 2.7 Hz, 2.5H), 1.42 (td, *J* = 12.6, 3.0 Hz, 1H), 1.10-0.88 (m, 3.5H), 1.07 (d, *J* = 6.6 Hz, 7.5H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 7.5H), 0.78 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 172.8, 172.5, 154.1, 150.3, 149.3, 149.1, 143.7, 142.9, 142.5, 142.4, 138.9, 138.6, 137.0, 136.8, 133.9, 133.8, 133.2, 132.9, 129.3, 129.1, 128.7, 128.6, 125.8, 124.1, 111.6, 110.4, 110.2, 110.2, 109.7, 98.3, 67.8, 65.0, 49.5, 48.8, 42.7, 42.6, 40.7, 40.5, 25.0, 25.0, 24.2, 24.1, 21.3, 21.1.

I.R. (thin film) 1669, 1617, 1539, 1459 cm^{-1}.

HRMS Calculated for [$C_{24}H_{24}Cl_2IN_3O_4$ - C_8H_7ClNO] 446.9972, found 446.9975.


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

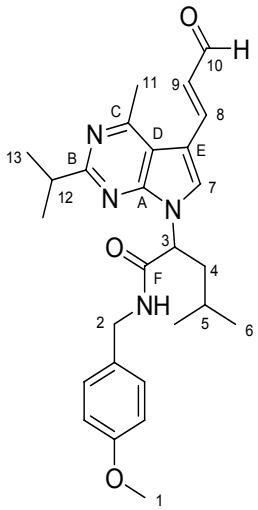

150
100
50
0
ppm (t1)

General Procedure for the synthesis of Ugi-Smiles derived 3-vinyl-[4,0,3]-heterocycles :

To a 0.1 M solution of Ugi-Smiles adduct in acetonitrile were successively added *bis*(triphenylphosphine)palladium chloride (5 mol %) and diisopropylethylamine (1 equiv). The resulting mixture was then stirred under microwave irradiation for 20 minutes at 130 °C (Power = 100 W, Pressure = 13 bars).

The crude mixture was first filtered and rinsed with methanol. After removal of the volatile materials, purification by flash chromatography gave the corresponding 3-vinyl-[4,0,3]-heterocycle.

(*E*)-2-[2-isopropyl-4-methyl-5-(3-oxopropenyl)-pyrrolo[2,3-*d*]pyrimidin-7-yl]-4-methyl-pentanoic acid 4-methoxybenzylamide



$C_{27}H_{34}N_4O_3$
MW = 462.58 g.mol^{-1}

6a

General procedure using **5a** (65 mg, 0.11 mmol), *bis*(triphenylphosphine)palladium chloride (4 mg, 5 mol %) and diisopropylethylamine (20 µL, 0.11 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 30:70) gave **6a** as a yellow solid.

MP 124-125 °C.

Yield 85 % (43 mg).

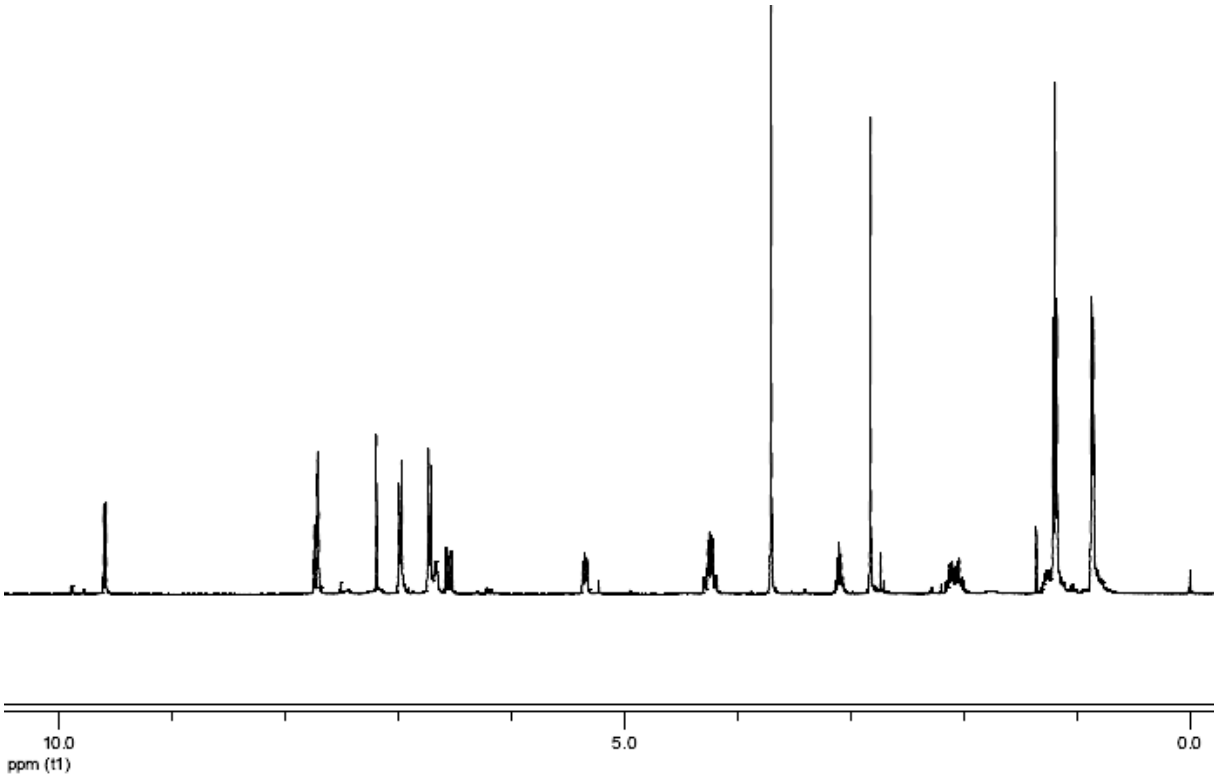
R_f 0.3 (70:30 petroleum ether / diethyl ether).

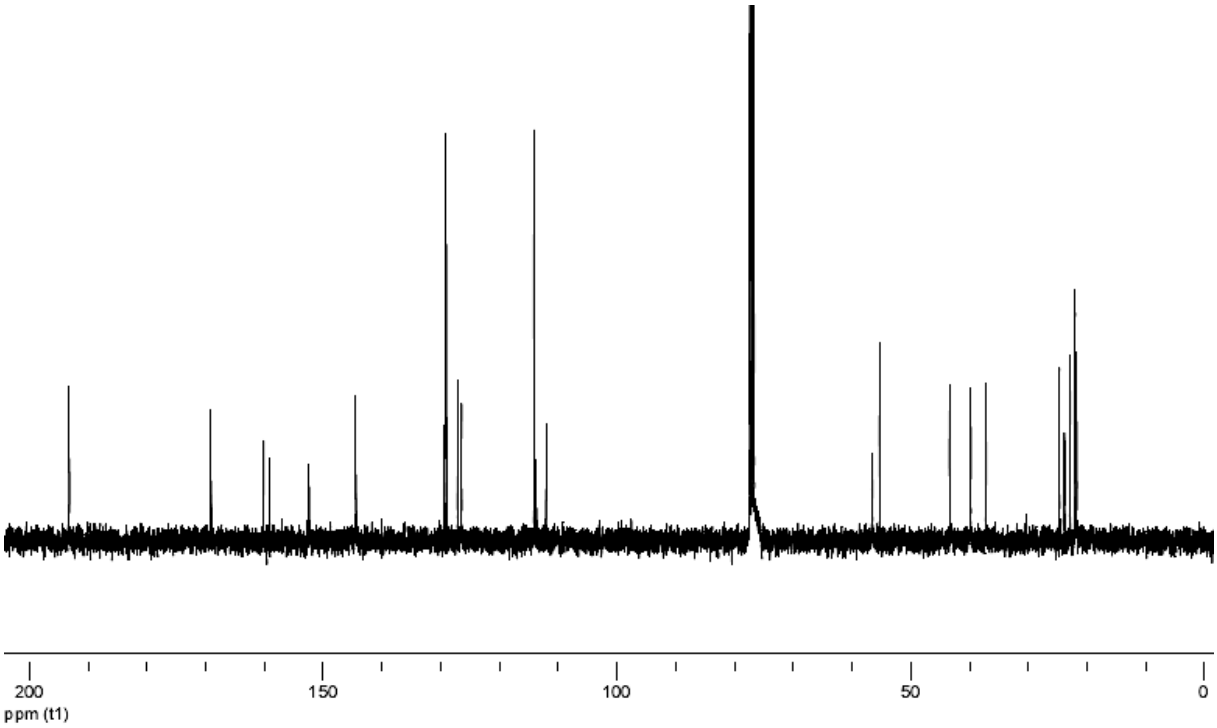
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.66 (d, *J* = 7.7 Hz, 1H), 7.79 (d, *J* = 15.6 Hz, 1H), 7.78 (s, 1H), 7.05 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 6.74 (t, *J* = 5.6 Hz, 1H), 6.62 (dd, *J* = 15.6, 7.7 Hz, 1H), 5.42 (dd, *J* = 9.6, 6.2 Hz, 1H), 4.34 (dd, *J* = 14.6, 5.5 Hz, 1H), 4.27 (dd, *J* = 14.6, 5.6 Hz, 1H), 3.77 (s, 3H), 3.17 (sept, *J* = 6.9 Hz, 1H), 2.89 (s, 3H), 2.25-2.06 (m, 2H), 1.39-1.29 (m, 1H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.25 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 193.2, 169.2, 169.1, 160.1, 159.1, 152.3, 144.4, 129.0, 127.5, 126.4, 113.6, 112.0, 56.5, 55.3, 39.7, 37.2, 24.7, 23.8, 22.9, 22.0, 21.7.

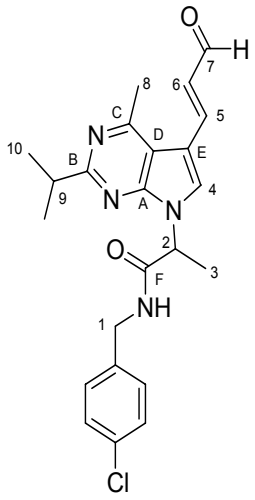
I.R. (thin film) 1667, 1615, 1560, 1515 cm^{-1}.

HRMS Calculated for $C_{27}H_{34}N_4O_3$ 462.2631, found 462.2633.


10.0
ppm (t1)
5.0
0.0


200
ppm (t1)
150
100
50
0

(*E*)-*N*-(4-chlorobenzyl)-2-[2-isopropyl-4-methyl-5-(3-oxopropenyl)-pyrrolo[2,3-*d*]pyrimidin-7-yl]-propionamide



$C_{23}H_{25}ClN_4O_2$
MW = 424.92 g.mol^{-1}

6b

General procedure using **5b** (90 mg, 0.16 mmol), *bis*(triphenylphosphine)palladium chloride (6 mg, 5 mol %) and diisopropylethylamine (30 µL, 0.16 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 30:70) gave **6b** as a white solid.

MP 216-217 °C.

Yield 88 % (60 mg).

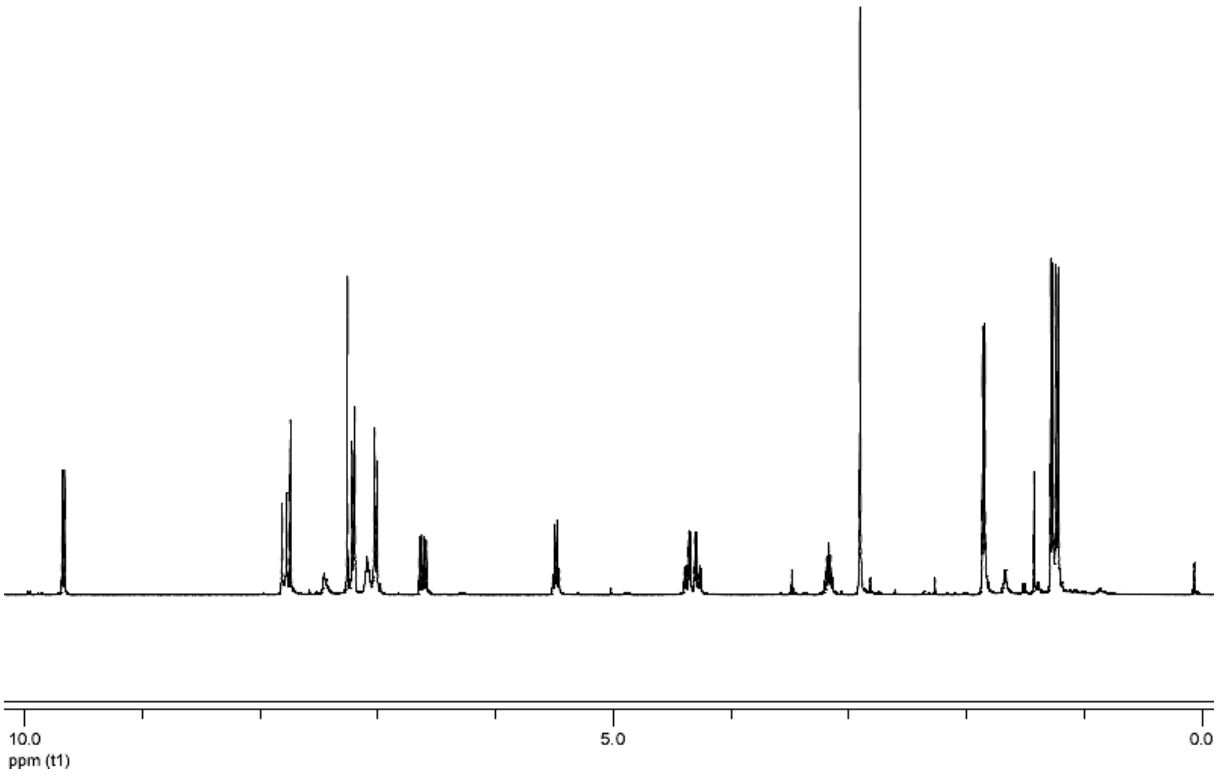
R_f 0.3 (30:70 petroleum ether / diethyl ether).

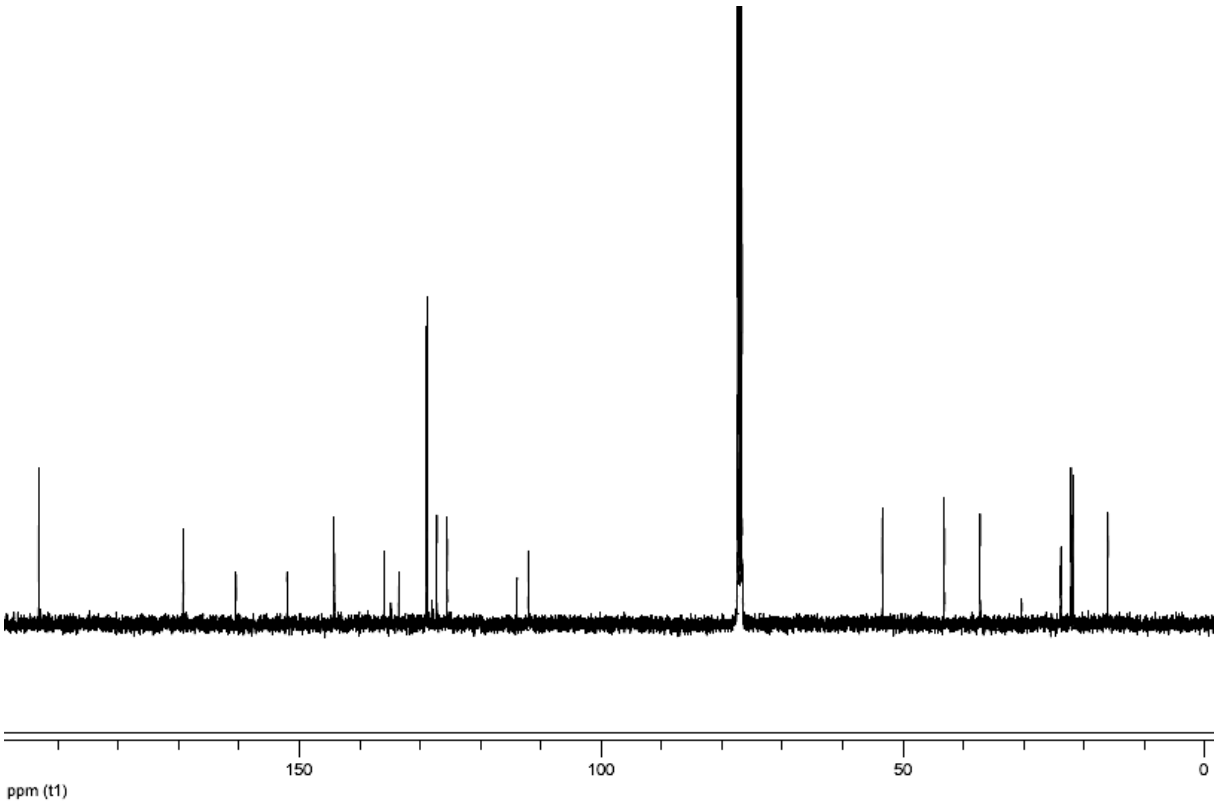
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.67 (d, *J* = 7.7 Hz, 1H), 7.79 (d, *J* = 15.9 Hz, 1H), 7.74 (s, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.09 (t, *J* = 5.7 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.62 (dd, *J* = 15.9, 7.7 Hz, 1H), 5.49 (q, *J* = 7.2 Hz, 1H), 4.37 (dd, *J* = 14.9, 5.7 Hz, 1H), 4.28 (dd, *J* = 14.9, 5.8 Hz, 1H), 3.17 (sept, *J* = 6.9 Hz, 1H), 2.91 (s, 3H), 1.86 **(**d, *J* = 7.2 Hz, 3H**),** 1.28 (d, *J* = 6.9 Hz, 3H), 1.23 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 193.1, 169.2, 169.2, 160.5, 152.0, 144.2, 135.9, 133.5, 128.9, 128.8, 127.2, 125.5, 113.9, 112.0, 53.4, 43.1, 37.2, 23.8, 22.1, 21.8, 16.1.

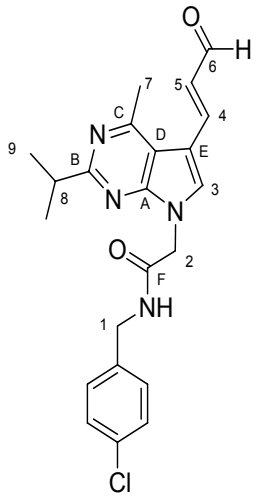
I.R. (thin film) 1661, 1614, 1560, 1522 cm^{-1}.

HRMS Calculated for $C_{23}H_{25}ClN_4O_2$ 424.1666, found 424.1662.


10.0
5.0
0.0
ppm (t1)


150
100
50
0
ppm (t1)

(*E*)-*N*-(4-chlorobenzyl)-2-[2-isopropyl-4-methyl-5-(3-oxopropenyl)-pyrrolo[2,3-*d*]pyrimidin-7-yl]-acetamide



$C_{22}H_{23}ClN_4O_2$
MW = 410.90 g.mol^{-1}

6c

General procedure using **5c** (120 mg, 0.22 mmol), *bis*(triphenylphosphine)palladium chloride (8 mg, 5 mol %) and diisopropylethylamine (40 µL, 0.22 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 30:70) gave **6c** as a white solid.

MP 195-196 °C.

Yield 68 % (62 mg).

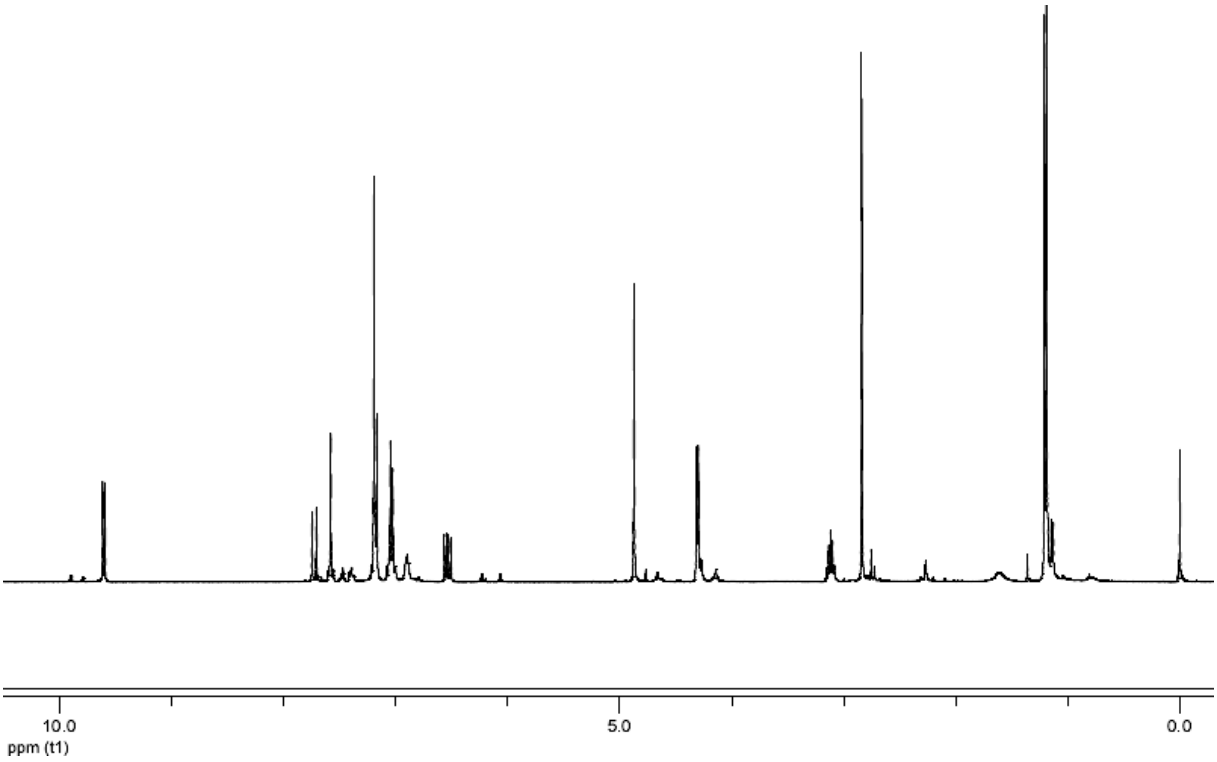
R_f 0.3 (30:70 petroleum ether / diethyl ether).

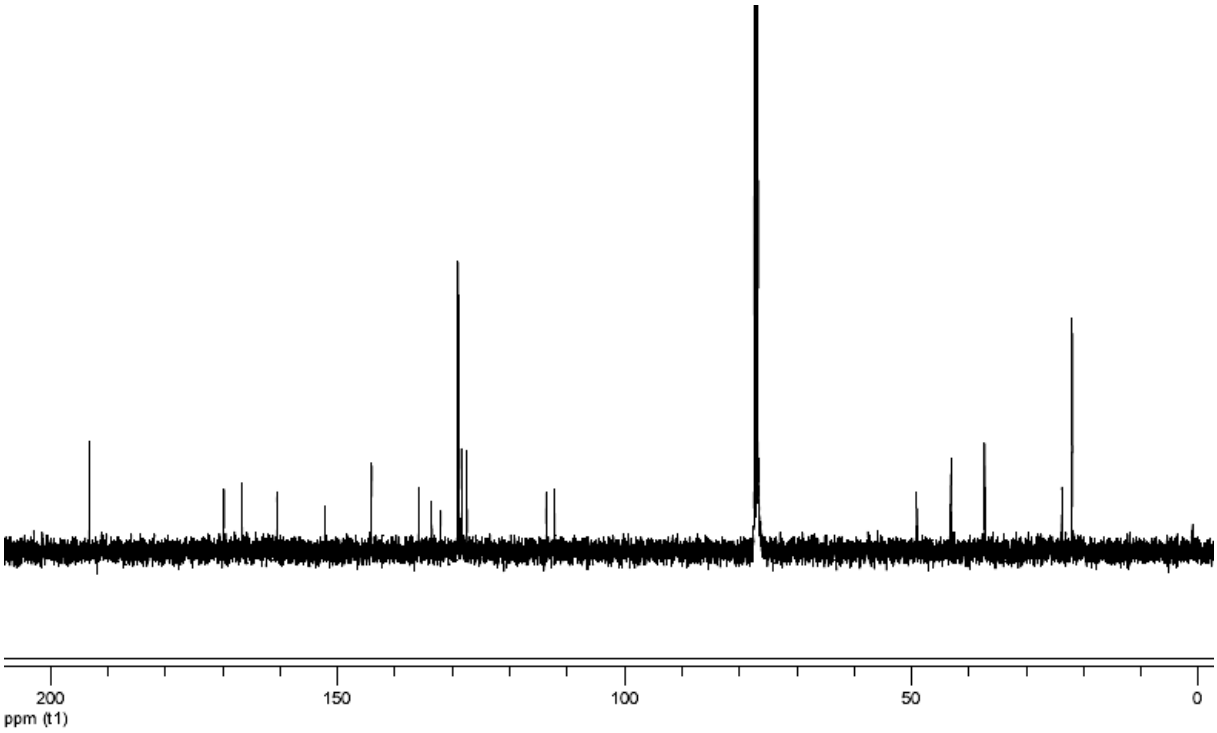
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.66 (d, *J* = 7.7 Hz, 1H), 7.79 (d, *J* = 15.8 Hz, 1H), 7.65 (s, 1H), 7.24 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 2H), 6.96 (t, *J* = 5.8 Hz, 1H), 6.60 (dd, *J* = 15.8, 7.7 Hz, 1H), 4.94 (s, 2H), 4.37 (d, *J* = 5.8 Hz, 2H), 3.18 (sept, *J* = 6.9 Hz, 1H), 2.90 (s, 3H), 1.27 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 193.2, 169.7, 166.6, 160.4, 152.1, 144.1, 135.8, 133.6, 129.0, 128.9, 128.4, 127.4, 113.5, 112.1, 48.9, 43.0, 37.2, 23.8, 21.9.

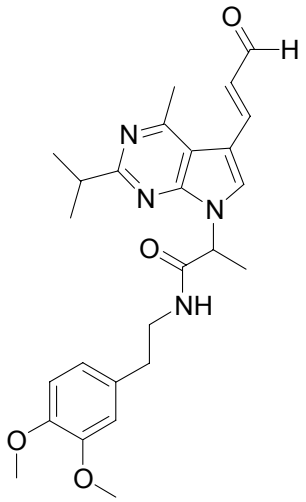
I.R. (thin film) 1671, 1616, 1558, 1527 cm^{-1}.

HRMS Calculated for $C_{22}H_{23}ClN_4O_2$ 410.1510, found 410.1512.


10.0
5.0
0.0
ppm (t1)


200
150
100
50
0
ppm (t1)

(*E*)-*N*-[2-(3,4-dimethoxyphenyl)-ethyl]-2-[2-isopropyl-4-methyl-5-(3-oxopropenyl)-pyrrolo[2,3-*d*]pyrimidin-7-yl]-propionamide



$C_{26}H_{32}N_4O_4$
MW = 464.56 g.mol^{-1}

6d

General procedure using **5d** (120 mg, 0.20 mmol), *bis*(triphenylphosphine)palladium chloride (7 mg, 5 mol %) and diisopropylethylamine (35 µL, 0.20 mmol). Purification by flash chromatography (ethyl acetate-diethyl ether, 20:80) gave **6d** as a yellow solid.

MP 144-145 °C.

Yield 71 % (66 mg).

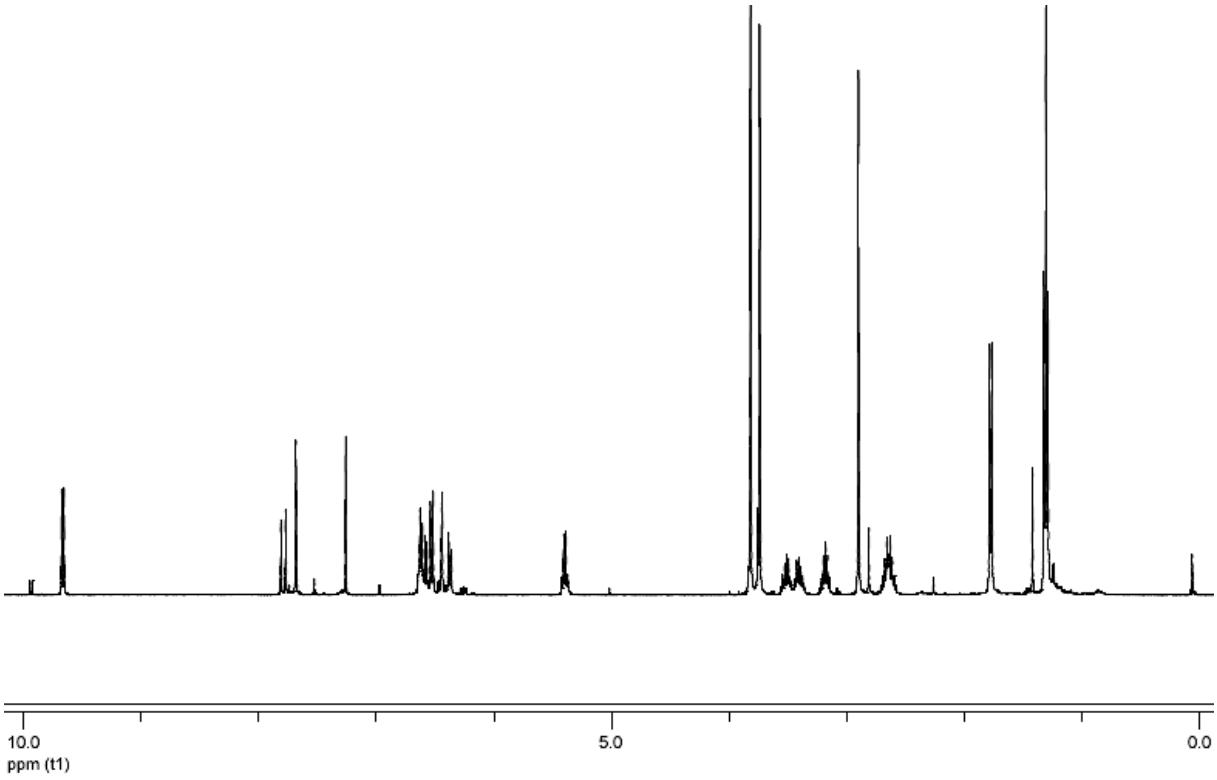
R_f 0.3 (20:80 ethyl acetate / diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.67 (d, *J* = 7.7 Hz, 1H), 7.79 (d, *J* = 15.9 Hz, 1H), 7.68 (s, 1H), 6.64 (br s, 1H), 6.60 (dd, *J* = 15.9, 7.7 Hz, 1H), 6.53 (d, *J* = 8.1 Hz, 1H), 6.44 (d, *J* = 1.8 Hz, 1H), 6.38 (dd, *J* = 8.1, 1.8 Hz, 1H), 5.40 (q, *J* = 7.2 Hz, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 3.57-3.47 (m, 1H), 3.45-3.35 (m, 1H), 3.18 (sept, *J* = 6.9 Hz, 1H), 2.90 (s, 3H), 2.72-2.57 (m, 2H), 1.78 (d, *J* = 7.2 Hz, 3H), 1.32 (d, *J* = 6.9 Hz, 3H), 1.30 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 193.), 169.2, 169.0, 160.3, 151.9, 148.7, 147.4, 144.4, 130.4, 126.9, 125.2, 119.9, 113.7, 111.9, 111.4, 110.8, 55.7, 55.6, 53.0, 40.5, 37.1, 34.6, 23.7, 22.2, 21.8, 16.2.

I.R. (thin film) 1668, 1615, 1561, 1517 cm^{-1}.

HRMS Calculated for $C_{26}H_{32}N_4O_4$ 464.2424, found 464.2425.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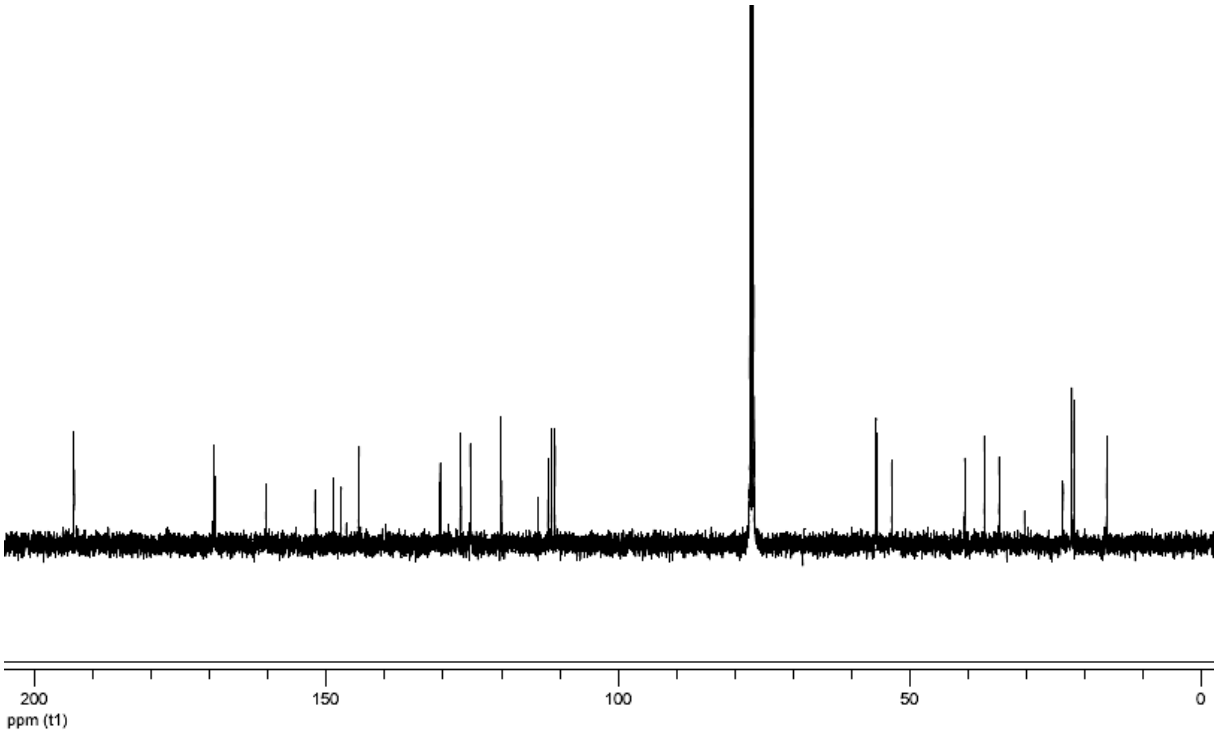
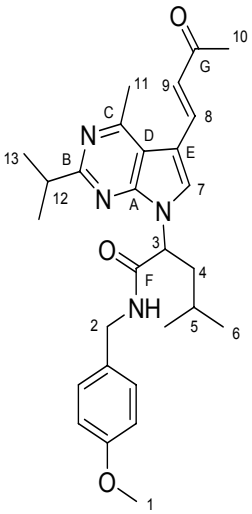
5.0
0.0
ppm (t1)


200
150
100
50
0
ppm (t1)

(*E*)-2-[2-isopropyl-4-methyl-5-(3-oxobut-1-enyl)-pyrrolo[2,3-*d*]pyrimidin-7-yl]-4-methylpentanoic acid 4-methoxybenzylamide



$C_{28}H_{36}N_4O_3$
MW = 476.61 g.mol^{-1}

6e

General procedure using **5e** (120 mg, 0.20 mmol), *bis*(triphenylphosphine)palladium chloride (7 mg, 5 mol %) and diisopropylethylamine (35 µL, 0.20 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 20:80) gave **6e** as a brown oil.

Yield 76 % (72 mg).

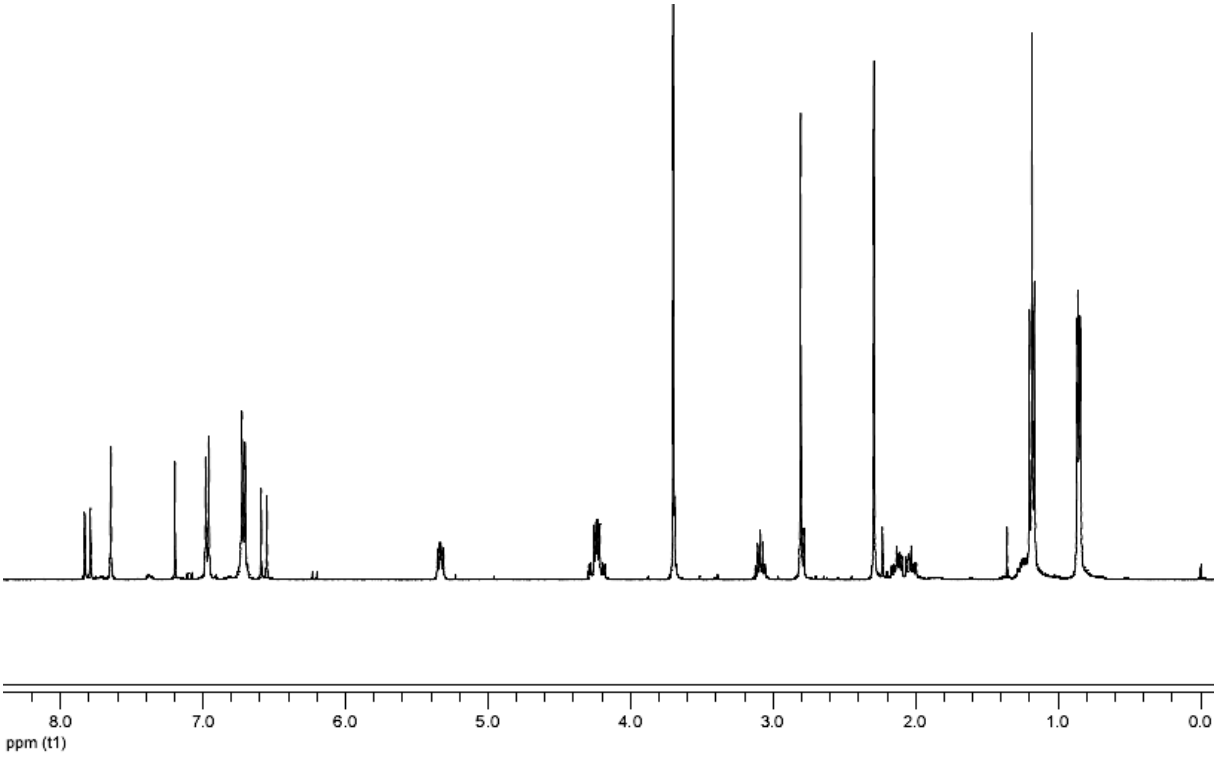
R_f 0.3 (20:80 petroleum ether / diethyl ether).

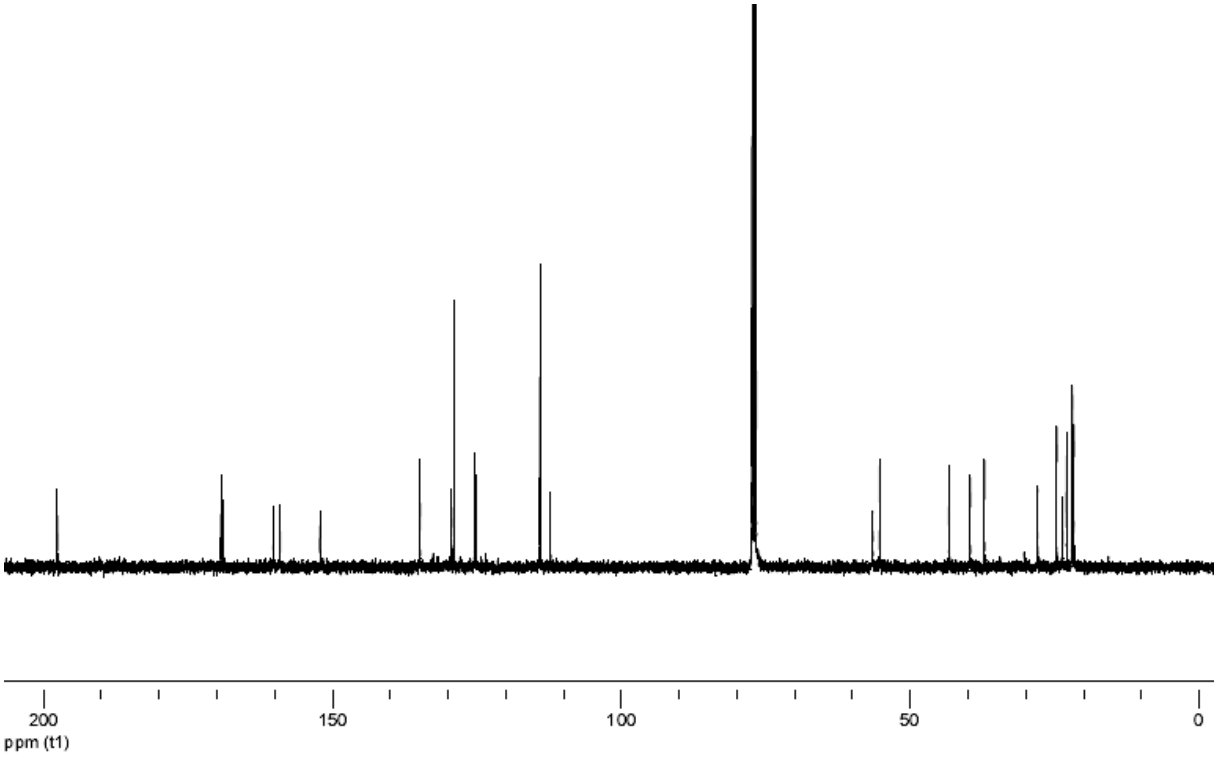
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, *J* = 16.0 Hz, 1H), 7.71 (s, 1H), 7.03 (d, *J* = 8.6 Hz, 2H), 6.84-6.79 (m, 1H), 6.78 (d, *J* = 8.6 Hz, 2H), 6.64 (d, *J* = 16.0 Hz, 1H), 5.33 (dd, *J* = 9.7, 6.1 Hz, 1H), 4.27 (dd, *J* = 14.6, 5.5 Hz, 1H), 4.21 (dd, *J* = 14.6, 5.6 Hz, 1H), 3.70 (s, 3H), 3.09 (sept, *J* = 6.9 Hz, 1H), 2.81 (s, 3H), 2.29 (s, 3H), 2.22-2.09 (m, 1H), 2.08-1.99 (m, 1H), 1.31-1.21 (m, 1H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.18 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 197.6, 169.3, 168.9, 160.2, 159.1, 152.1, 134.8, 129.4, 129.0, 125.4, 125.1, 114.0, 114.0, 112.2, 56.5, 55.2, 39.6, 37.1, 28.0, 24.6, 23.6, 22.9, 22.0, 22.0, 21.7.

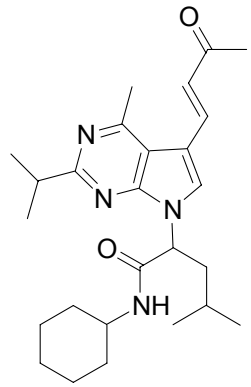
I.R. (thin film) 1665, 1614, 1558, 1513 cm^{-1}.

HRMS Calculated for $C_{28}H_{36}N_4O_3$ 476.2787, found 476.2785.


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


200
150
100
50
0
ppm (t1)

(*E*)-2-[2-isopropyl-4-methyl-5-(3-oxobut-1-enyl)-pyrrolo[2,3-*d*]pyrimidin-7-yl]-4-methylpentanoic acid cyclohexylamide



$C_{26}H_{38}N_4O_2$
MW = 438.61 g.mol^{-1}

6f

General procedure using **5f** (100 mg, 0.18 mmol), *bis*(triphenylphosphine)palladium chloride (6 mg, 5 mol %) and diisopropylethylamine (30 µL, 0.18 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 30:70) gave **6f** as a white solid.

MP 138-139 °C.

Yield 58 % (45 mg).

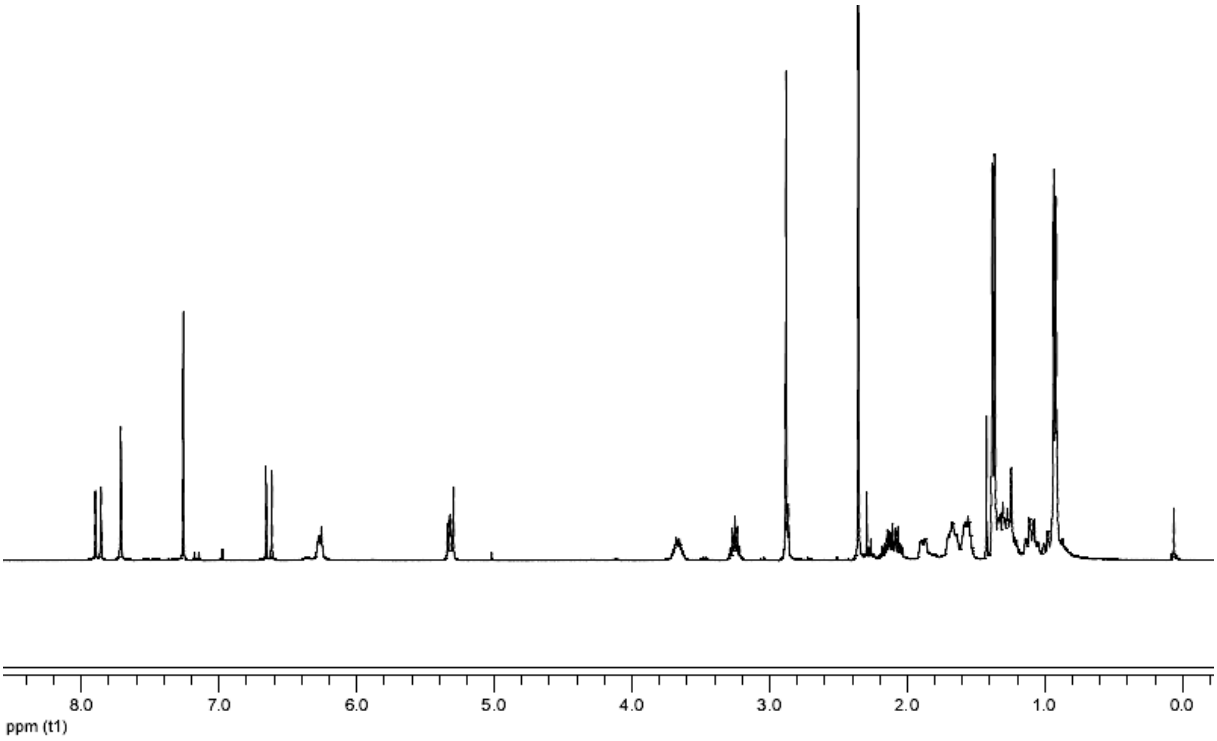
R_f 0.3 (30:70 petroleum ether / diethyl ether).

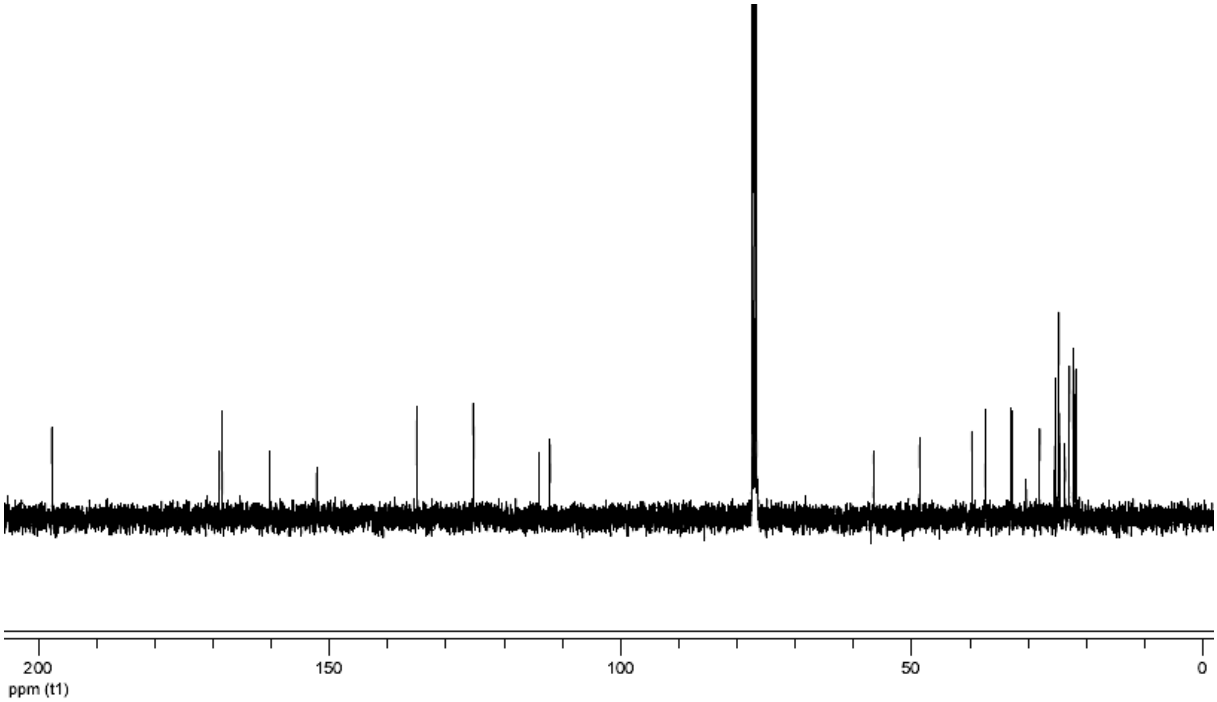
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (d, *J* = 16.0 Hz, 1H), 7.71 (s, 1H), 6.64 (d, *J* = 16.0 Hz, 1H), 6.30-6.22 (m, 1H), 5.32 (dd, *J* = 9.5, 6.5 Hz, 1H), 3.73-3.61 (m, 1H), 3.25 (sept, *J* = 6.9 Hz, 1H), 2.88 (s, 3H), 2.36 (s, 3H), 2.19-2.02 (m, 2H), 1.93-1.85 (m, 1H), 1.72-1.51 (m, 5H), 1.37 (d, *J* = 6.9 Hz, 6H), 1.23-1.18 (m, 2H), 1.16-1.02 (m, 2H), 1.02-0.94 (m, 1H), 0.93 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 197.6, 168.8, 168.4, 160.2, 152.1, 134.9, 125.3, 125.2, 113.9, 112.0, 56.5, 48.6, 39.6, 37.3, 32.9, 32.7, 28.0, 25.3, 24.7, 24.7, 24.6, 23.7, 22.9, 22.2, 22.1, 21.8.

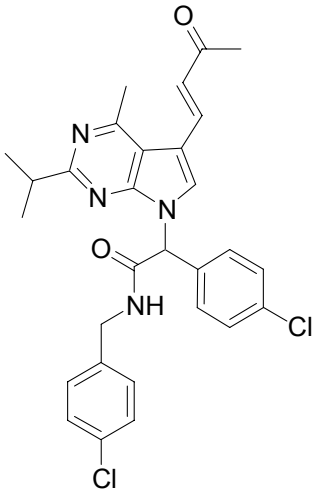
I.R. (thin film) 1666, 1593, 1580, 1558 cm^{-1}.

HRMS Calculated for $C_{26}H_{38}N_4O_2$ 438.2995, found 438.2979.


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


200
150
100
50
0
ppm (t1)

(*E*)-*N*-(4-chlorobenzyl)-2-(4-chlorophenyl)-2-[2-isopropyl-4-methyl-5-(3-oxobut-1-enyl)-pyrrolo[2,3-*d*]pyrimidin-7-yl]-acetamide



$C_{29}H_{28}Cl_2N_4O_2$

MW = 535.46 g.mol^{-1}

6g

General procedure using **5g** (115 mg, 0.17 mmol), *bis*(triphenylphosphine)palladium chloride (6 mg, 5 mol %) and diisopropylethylamine (30 µL, 0.17 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 30:70) gave **6g** as a brown solid.

MP 178-179 °C.

Yield 66 % (60 mg).

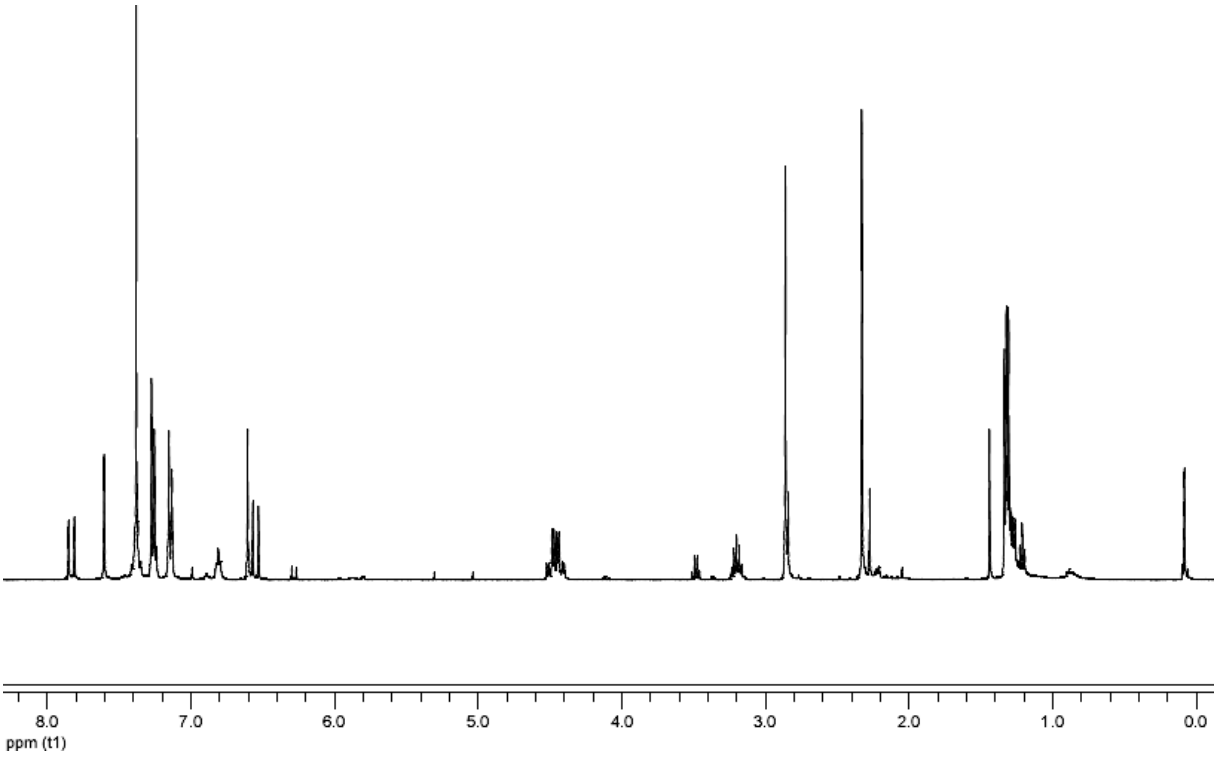
R_f 0.3 (30:70 petroleum ether / diethyl ether).

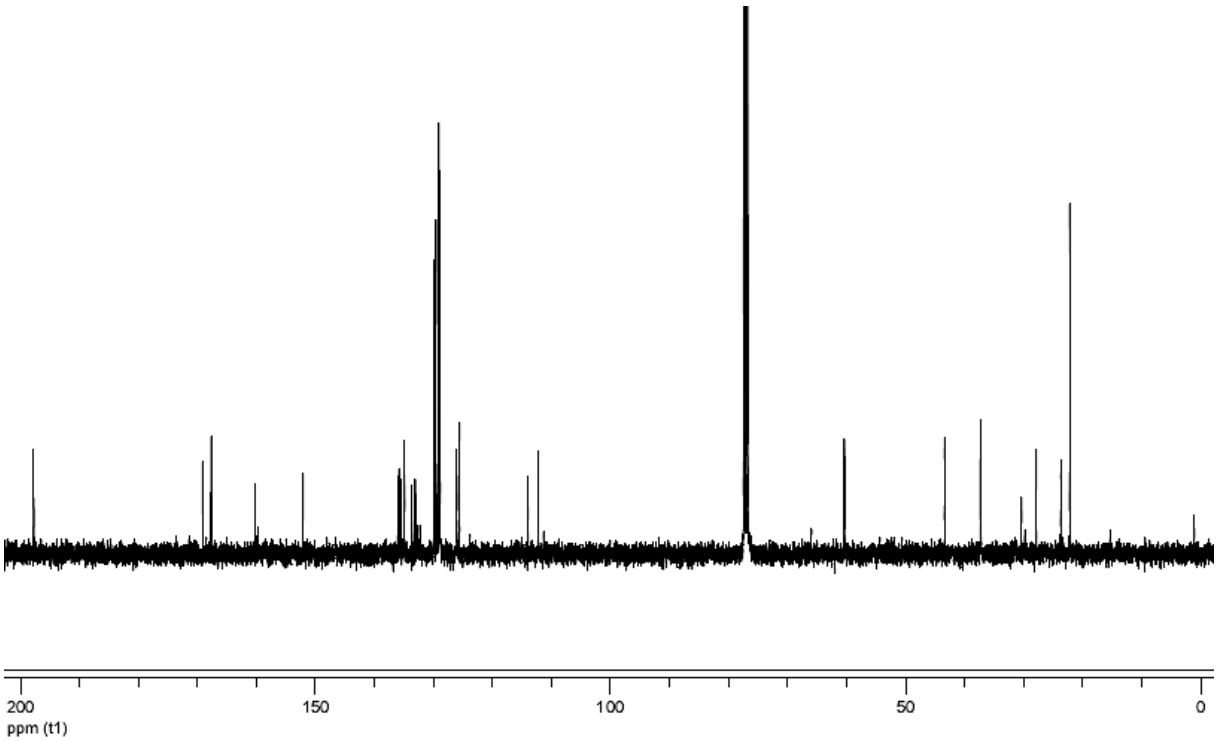
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, *J* = 16.0 Hz, 1H), 7.59 (s, 1H), 7.37 (br s, 4H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.80 (t, *J* = 5.7 Hz, 1H), 6.59 (s, 1H), 6.54 (d, *J* = 16.0 Hz, 1H), 4.48 (dd, *J* = 14.9, 6.0 Hz, 1H), 4.41 (dd, *J* = 14.9, 5.7 Hz, 1H), 3.19 (sept, *J* = 6.9 Hz, 1H), 2.85 (s, 3H), 2.31 (s, 3H), 1.31 (d, *J* = 6.9 Hz, 3H), 1.30 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 197.7, 169.0, 167.6, 160.2, 152.1, 135.8, 135.4, 134.9, 133.6, 133.0, 129.8, 129.5, 129.0, 128.9, 125.9, 125.6, 113.9, 112.2, 60.3, 43.3, 37.2, 27.8, 23.6, 22.1.

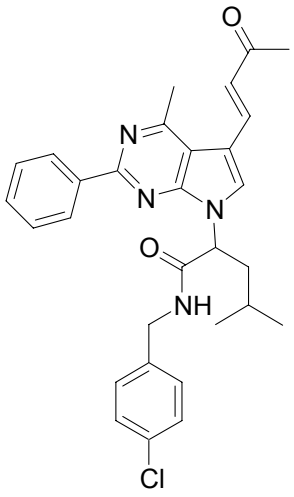
I.R. (thin film) 1670, 1617, 1559, 1522 cm^{-1}.

HRMS Calculated for $C_{29}H_{28}Cl_2N_4O_2$ 534.1589, found 534.1607.


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


200
150
100
50
0
ppm (t1)

(*E*)-4-methyl-2-[4-methyl-5-(3-oxobut-1-enyl)-2-phenylpyrrolo[2,3-*d*]pyrimidin-7-yl]-pentanoic acid 4-chlorobenzylamide



$C_{30}H_{31}ClN_4O_2$
MW = 515.05 g.mol^{-1}

6h

General procedure using **5h** (128 mg, 0.20 mmol), *bis*(triphenylphosphine)palladium chloride (7 mg, 5 mol %) and diisopropylethylamine (35 µL, 0.20 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 30:70) gave **6h** as an orange solid.

MP 205-206 °C.

Yield 78 % (80 mg).

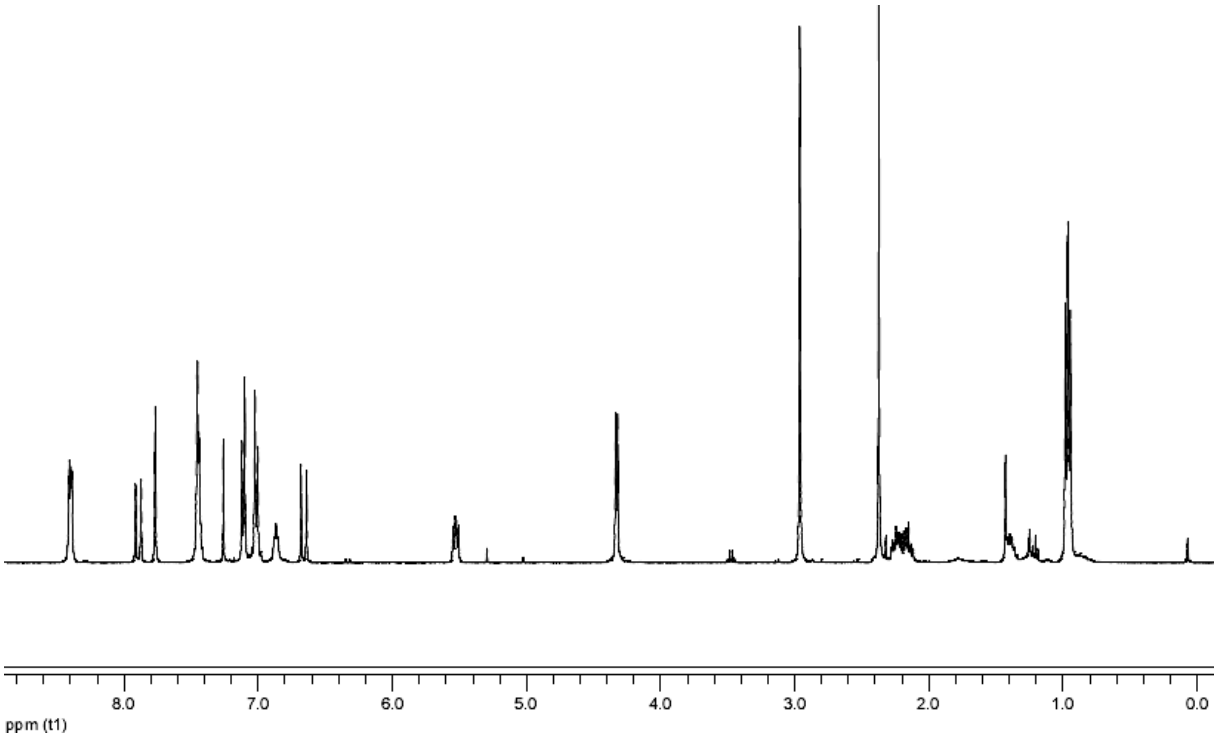
R_f 0.3 (30:70 petroleum ether / diethyl ether).

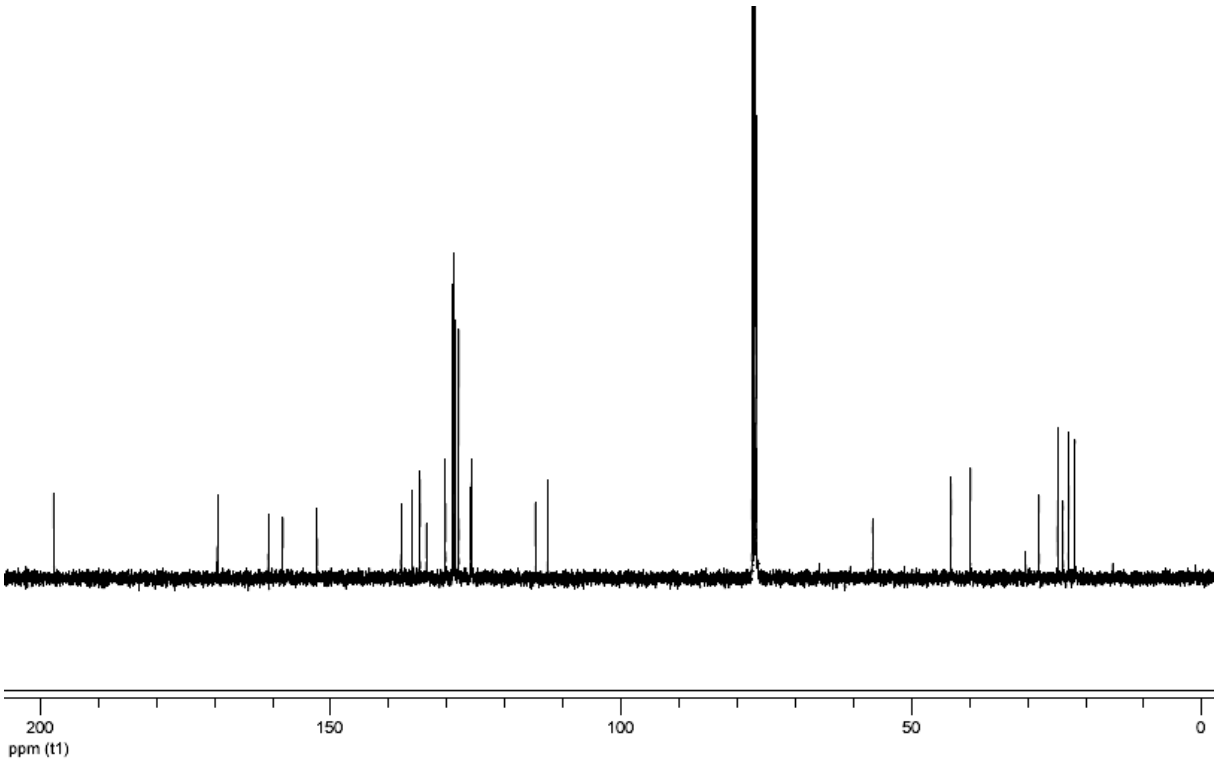
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.44 (m, 2H), 7.90 (d, *J* = 16.0 Hz, 1H), 7.77 (s, 1H), 7.50-7.41 (m, 3H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.87 (t, *J* = 5.7 Hz, 1H), 6.66 (d, *J* = 16.0 Hz, 1H), 5.53 (dd, *J* = 9.6, 6.1 Hz, 1H), 4.33 (d, *J* = 5.7 Hz, 2H), 2.96 (s, 3H), 2.37 (s, 3H), 2.30-2.10 (m, 2H), 1.46-1.34 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 197.6, 169.4, 160.6, 158.1, 152.2, 137.8, 135.8, 134.5, 133.4, 130.2, 128.9, 128.8, 128.5, 127.9, 125.8, 125.7, 114.6, 112.5, 56.6, 43.1, 39.8, 28.0, 24.7, 23.9, 22.9, 21.8.

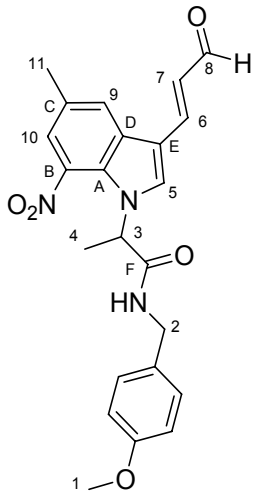
I.R. (thin film) 1667, 1614, 1557, 1525 cm^{-1}.

HRMS Calculated for $C_{30}H_{31}ClN_4O_2$ 514.2136, found 514.2155.


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


200
150
100
50
0
ppm (t1)

(*E*)-*N*-(4-methoxybenzyl)-2-(5-methyl-7-nitro-3-(3-oxoprop-1-enyl)-1*H*-indol-1-yl)propanamide



$C_{23}H_{23}N_3O_5$
MW = 421.45 g.mol^{-1}

6i

General procedure using **5i** (72 mg, 0.13 mmol), *bis*(triphenylphosphine)palladium chloride (5 mg, 5 mol %) and diisopropylethylamine (25 μL, 0.13 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 20:80) gave **6i** as a yellow oil.

Yield 66 % (36 mg).

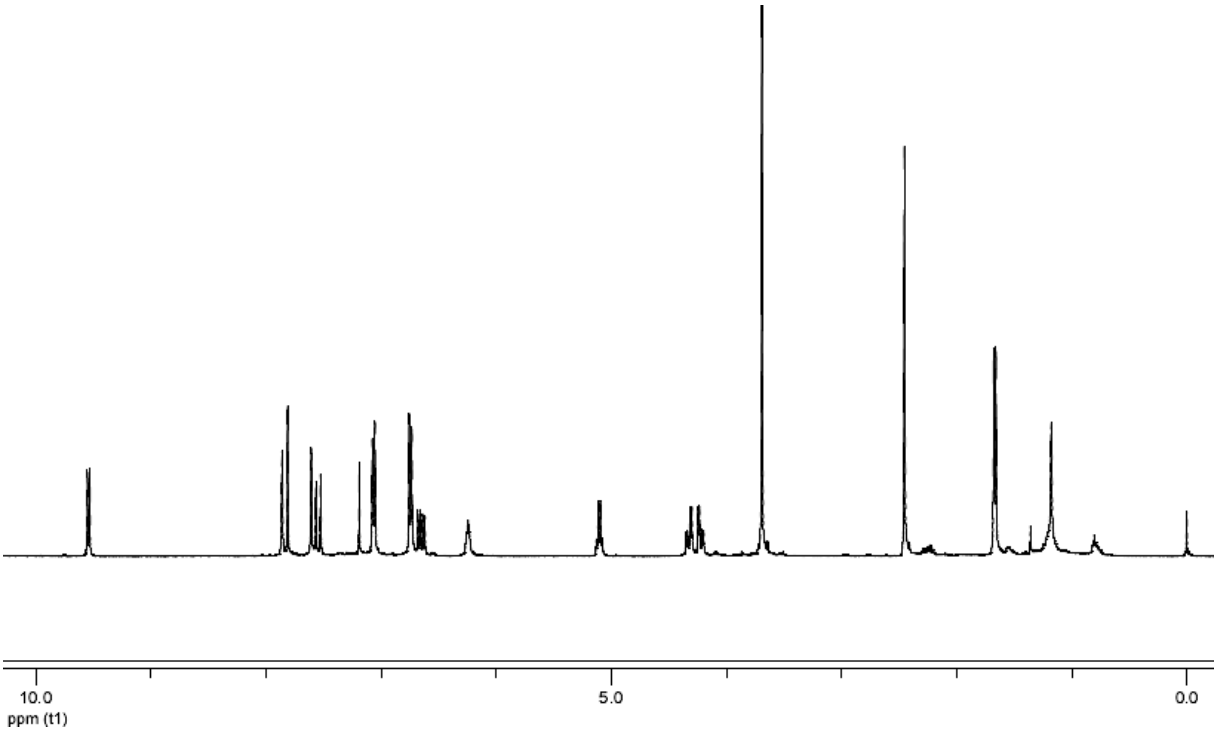
R_f 0.3 (20:80 petroleum ether / diethyl ether).

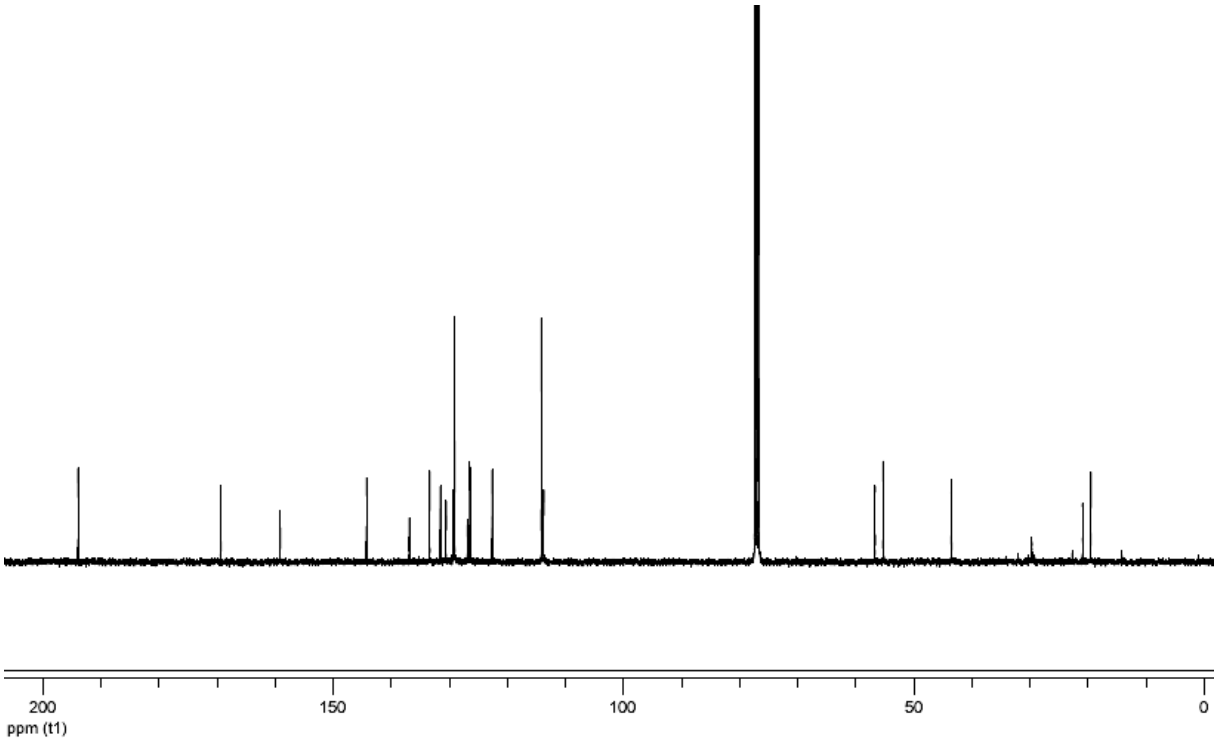
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.64 (d, *J* = 7.7 Hz, 1H), 7.94 (s, 1H), 7.87 (s, 1H), 7.69 (s, 1H), 7.63 (d, *J* = 16.0 Hz, 1H), 7.15 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.74 (dd, *J* = 16.0, 7.7 Hz, 1H), 6.15 (t, *J* = 5.3 Hz, 1H), 5.17 (q, *J* = 7.0 Hz, 1H), 4.42 (dd, *J* = 14.5, 5.8 Hz, 1H), 4.31 (dd, *J* = 14.5, 5.3 Hz, 1H), 3.78 (s, 3H), 2.53 (s, 3H), 1.74 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 193.8, 169.3, 159.1, 144.2, 136.8, 133.3, 131.5, 130.5, 129.3, 129.1, 126.8, 126.7, 122.5, 114.1, 113.7, 56.6, 52.2, 43.5, 20.9, 19.5.

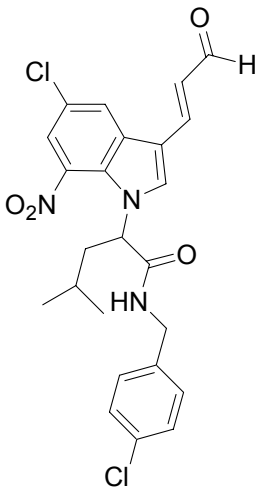
I.R. (thin film) 1668, 1615, 1529, 1514 cm^{-1}.

HRMS Calculated for $C_{23}H_{23}N_3O_5$ 421.1638, found 421.1631.


10.0
5.0
0.0
ppm (t1)


200
150
100
50
0
ppm (t1)

(*E*)-2-(5-chloro-7-nitro-3-(3-oxoprop-1-enyl)-1*H*-indol-1-yl)-*N*-(4-chlorobenzyl)-4-methylpentanamide



$C_{24}H_{23}Cl_2N_3O_4$

MW = 488.36 $g.mol^{-1}$

6j

General procedure using **5j** (125 mg, 0.20 mmol), *bis*(triphenylphosphine)palladium chloride (7 mg, 5 mol %) and diisopropylethylamine (35 µL, 0.20 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 40:60) gave **6j** as a brown oil.

Yield 71 % (69 mg).

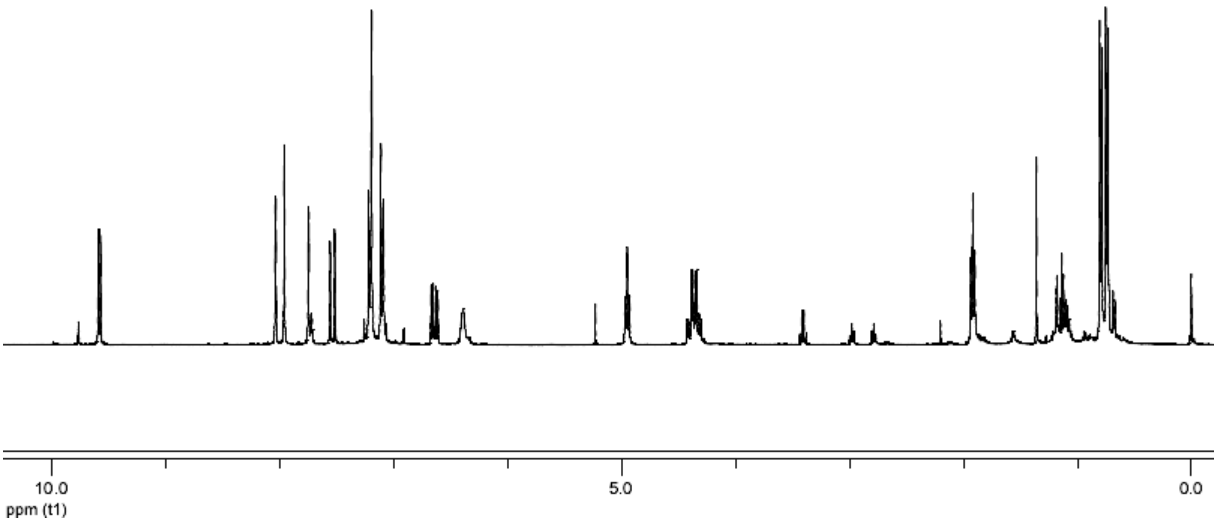
R_f 0.3 (40:60 petroleum ether / diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.65 (d, *J* = 7.6 Hz, 1H), 8.10 (d, *J* = 1.9 Hz, 1H), 8.03 (s, 1H), 7.81 (d, *J* = 1.9 Hz, 1H), 7.61 (d, *J* = 16.1 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.71 (dd, *J* = 16.1, 7.6 Hz, 1H), 6.46 (t, *J* = 5.8 Hz, 1H), 5.02 (dd, *J* = 7.7, 7.5 Hz, 1H), 4.47 (dd, *J* = 14.9, 5.8 Hz, 1H), 4.40 (dd, *J* = 14.9, 6.0 Hz, 1H), 1.99 (dd, *J* = 7.5, 7.1 Hz, 2H), 1.17 (sept, *J* = 6.6 Hz, 1H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 193.5, 168.8, 142.8, 136.9, 135.7, 134.2, 133.6, 131.0, 129.0, 128.9, 127.2, 126.9, 126.7, 125.5, 121.2, 113.9, 59.1, 43.3, 42.6, 24.6, 22.7, 21.7.

I.R. (thin film) 1670, 1622, 1534, 1525 cm^{-1}.

HRMS Calculated for $C_{24}H_{23}Cl_2N_3O_4$ 487.1066, found 487.1078.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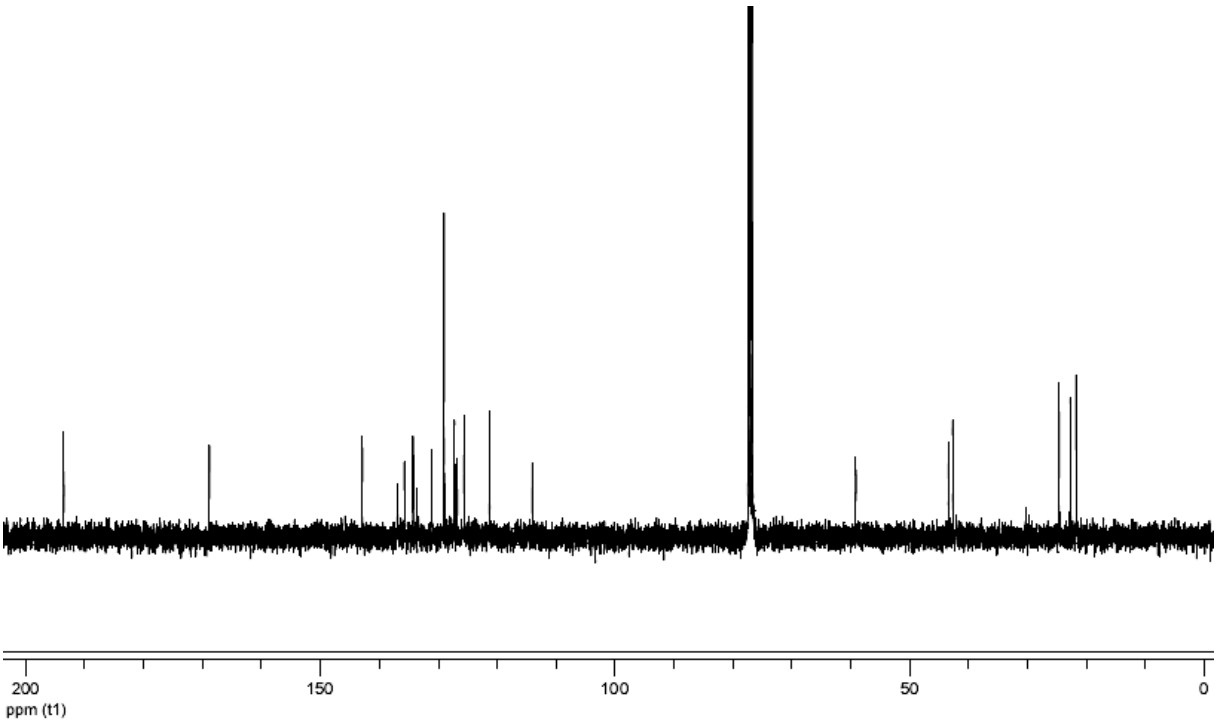
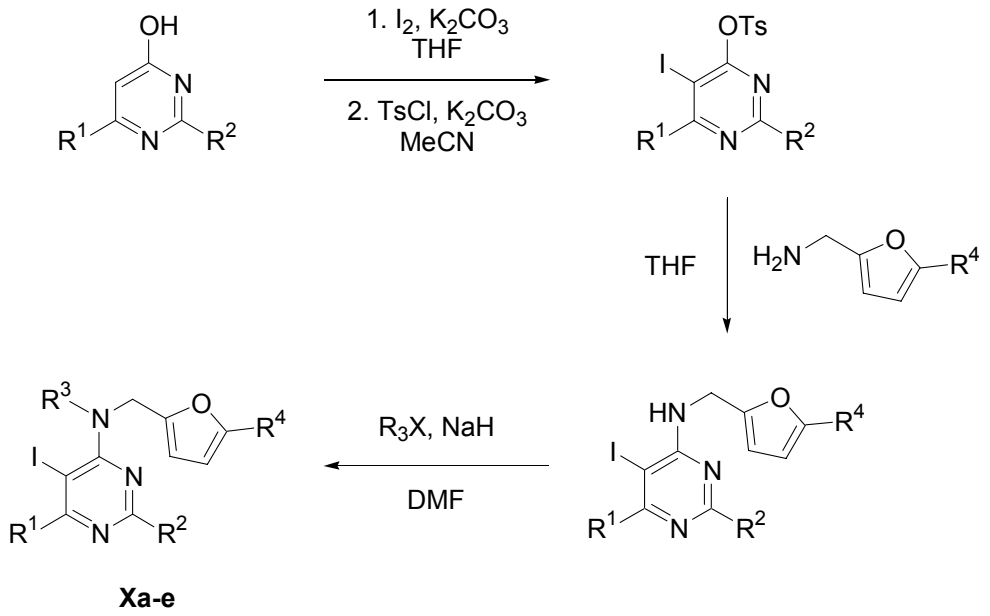
5.0
0.0
ppm (t1)


200
150
100
50
0
ppm (t1)

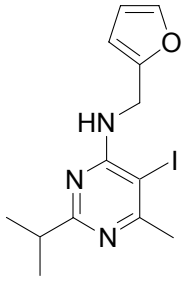
General procedure for the synthesis of *N*,*N*-disubstituted 2,6-substituted 4-amino-5-iodopyrimidines :



Xa-e

- Non commercial pyrimidin-4-ols were prepared according to Liu, Z; Li, D.; Li, S.; Bai, D.; He X.; Hu, Y. *Tetrahedron,* **2007**, *63*, 1931-1936.
- Iodinated hydroxy pyrimidines were obtained according to Elokdah, H. M. *Biorg. Med. Chem. Lett.* **2002**, *12*, 1967-1971.
- Tosylation was accomplished according to Benderitter, P.; De Araujo Junior, J. X.; Schmitt, M.; Bourguignon, J.-J. *Tetrahedron*, **2007**, *63*, 12465–12470.
- *N*-monosubstitued aminopyrimidines were prepared according to Mugnaini, C.; Petricci E.; Botta, M.; Corelli, F.; Mastromarino, P.; Giorgi, G. *Eur. J. of Med. Chem.*, **2007**, *42*, 256-262.

N-(furan-2-ylmethyl)-5-iodo-2-isopropyl-6-methylpyrimidin-4-amine



$C_{13}H_{16}IN_3O$
MW = 357.19 g.mol^{-1}

To a solution of 2-isopropyl-6-methylpyrimidin-4-ol (1.52 g, 10 mmol) in THF (70 mL) were added iodide (5.10 g, 20 mmol) and potassium carbonate (3.00 g, 22 mmol). The resulting mixture was refluxed overnight and then poured into 100 mL of water. After acidification to pH = 5 using citric acid, the solution was extracted three times with dichloromethane. The organic extracts were collected, washed with a saturated sodium sulfite aqueous solution and dried over $MgSO_4$. The volatile materials were finally removed under reduced pressure to yield the crude 5-iodo-2-isopropyl-6-methylpyrimidin-4-ol (2.70 g, 97 %).

To a solution of the above iodopyrimidin-4-ol (2.70 g, 9.7 mmol) in acetonitrile (30 mL) were added tosylchloride (1.84 g, 9.7 mmol) and potassium carbonate (1.61 g, 11.7 mmol). The resulting mixture was refluxed for 5 hours and then poured into 100 mL of water. The solution was extracted three times with dichloromethane and the organic phases were dried over $MgSO_4$ and concentrated to yield the crude toluene-4-sulfonic acid 5-iodo-2-isopropyl-6-methyl-pyrimidin-4-yl ester (4.10 g, 98 %).

To a solution of the above sulfonic acid ester (4.10 g, 9.5 mmol) in THF (20 mL) was added furfurylamine (1.28 mL, 14.3 mmol). The resulting mixture was refluxed for three days. After removal of the volatile materials, purification by flash chromatography (petroleum ether-diethyl ether, 90:10) afforded *N*-(furan-2-ylmethyl)-5-iodo-2-isopropyl-6-methylpyrimidin-4-amine as a brown oil (2.51 g, 74 %).

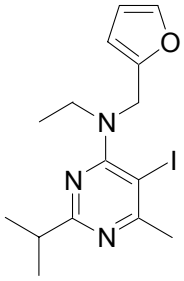
Yield (over three steps) 70 % (2.51 g).

R_f 0.3 (90:10 petroleum ether / diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.35 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.29 (dd, *J* = 3.2, 0.8 Hz, 1H), 5.69 (t, *J* = 5.6 Hz, 1H), 4.71 (d, *J* = 5.6 Hz, 2H), 2.98 (sept, *J* = 6.9 Hz, 1H), 2.56 (s, 3H), 1.30 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 174.0, 166.9, 160.6, 152.3, 142.5, 110.8, 107.8, 79.3, 39.1, 37.2, 29.4, 22.2.

N-ethyl-*N*-(furan-2-ylmethyl)-5-iodo-2-isopropyl-6-methylpyrimidin-4-amine



$C_{15}H_{20}IN_3O$

MW = 385.24 $g.mol^{-1}$

7a

To a solution of *N*-(furan-2-ylmethyl)-5-iodo-2-isopropyl-6-methylpyrimidin-4-amine (130 mg, 0.36 mmol) in DMF (1 mL) were added sodium hydride (12 mg, 0.44 mmol) and ethyl iodide (35 µL, 0.44 mmol). After one night at room temperature, the reaction mixture was poured into a diethyl ether solution and washed ten times with 1 mL of water. The organic phase was dried over $MgSO_4$ and concentrated to yield **7a** as a brown oil. The crude product was used in the cyclization step without any further purification.

Yield 87 % (120 mg).

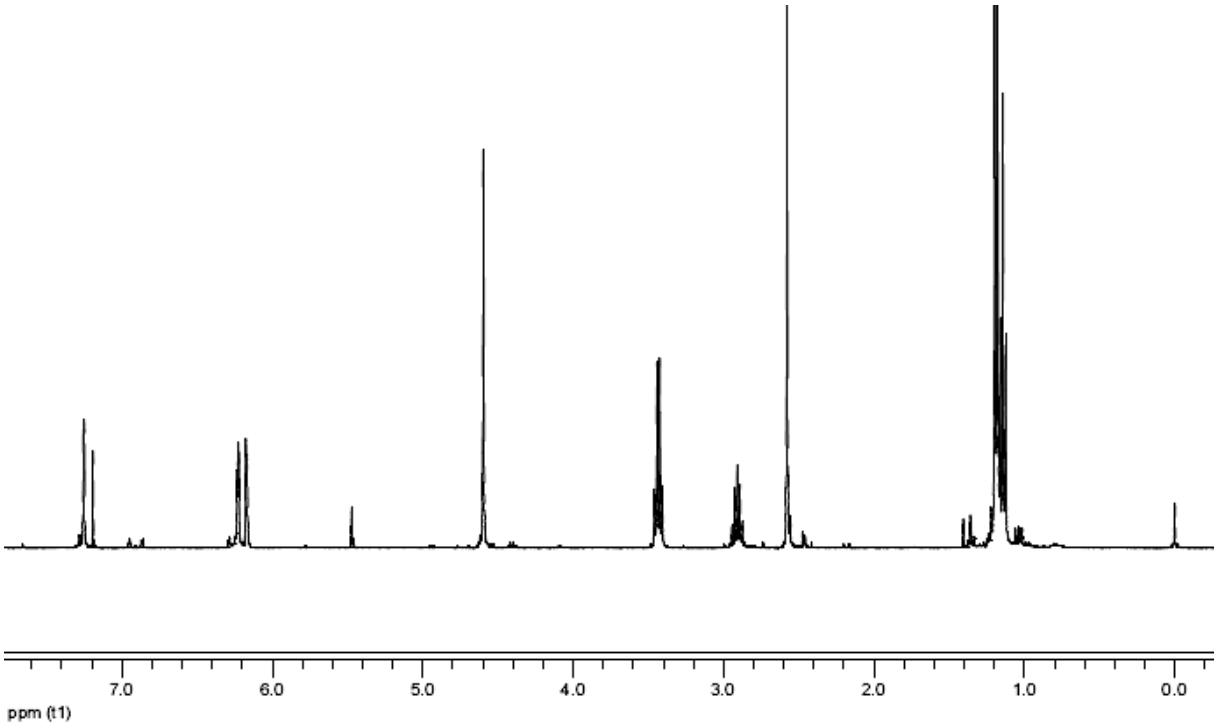
R_f 0.3 (95:5 petroleum ether / diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (d, *J* = 1.8 Hz, 1H), 6.30 (dd, *J* = 3.1, 1.8 Hz, 1H), 6.24 (d, *J* = 3.1 Hz, 1H), 4.67 (s, 2H), 3.50 (q, *J* = 7.0 Hz, 2H), 2.98 (sept, *J* = 6.9 Hz, 1H), 2.65 (s, 3H), 1.26 (d, *J* = 6.9 Hz, 6H), 1.21 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 172.2, 169.7, 166.0, 152.4, 141.5, 110.2, 108.0, 81.1, 46.4, 45.4, 36.6, 30.6, 21.7, 12.9.

I.R. (thin film) 1573, 1536, 1506, 1431 cm^{-1}.

HRMS Calculated for $C_{15}H_{20}IN_3O$ 385.0651, found 385.0652.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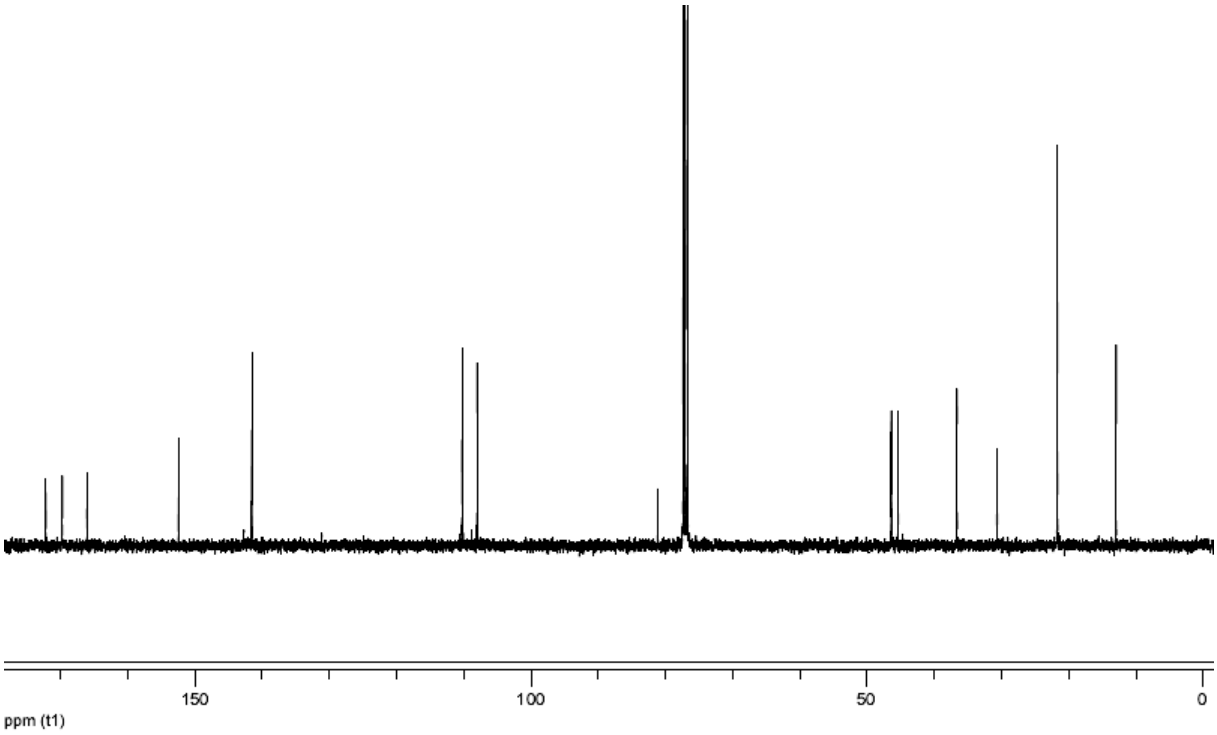
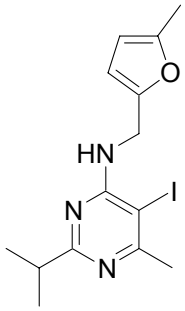
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


150
100
50
0
ppm (t1)

_N_-(5-methylfuran-2-ylmethyl)-5-iodo-2-isopropyl-6-methylpyrimidin-4-amine



$C_{14}H_{18}IN_3O$
MW = 371.22 g.mol^{-1}

To a solution of the sulfonic acid ester used in **7a**'s synthesis (4.10 g, 9.5 mmol) in THF (20 mL) was added 5-methylfurfurylamine (1.78 mL, 14.3 mmol). The resulting mixture was refluxed for three days. After removal of the volatile materials, purification by flash chromatography (petroleum ether-diethyl ether, 90:10) afforded *N*-(5-methylfuran-2-ylmethyl)-5-iodo-2-isopropyl-6-methylpyrimidin-4-amine as a brown oil (2.74 g, 75 %).

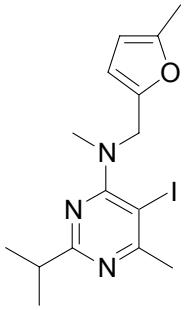
Yield 71 % (2.74 g).

R_f 0.3 (90:10 petroleum ether / diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.15 (d, *J* = 3.0 Hz, 1H), 5.89 (dd, *J* = 3.0, 0.9 Hz, 1H), 5.62 (t, *J* = 5.5 Hz, 1H), 4.62 (d, *J* = 5.5 Hz, 2H), 2.96 (sept, *J* = 6.9 Hz, 1H), 2.54 (s, 3H), 2.28 (s, 3H), 1.28 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.5, 166.4, 160.1, 151.8, 150.0, 108.3, 106.2, 78.9, 38.7, 36.8, 29.0, 21.8, 13.5.

_N_-methyl-_N_-(5-methylfuran-2-ylmethyl)-5-iodo-2-isopropyl-6-methylpyrimidin-4-amine



$C_{15}H_{20}IN_3O$
MW = 385.24 $g.mol^{-1}$

7b

To a solution of *N*-(5-methylfuran-2-ylmethyl)-5-iodo-2-isopropyl-6-methylpyrimidin-4-amine (170 µL, 0.46 mmol) in DMF (1 mL) were added sodium hydride (13 mg, 0.55 mmol) and methyl iodide (35 µL, 0.55 mmol). After one night at room temperature, the reaction mixture was poured into a diethyl ether solution and washed ten times with 1 mL of water. The organic phase was dried over $MgSO_4$ and concentrated to yield **7b** as a brown oil. The crude product was used in the cyclization step without any further purification.

Yield 97 % (150 mg).

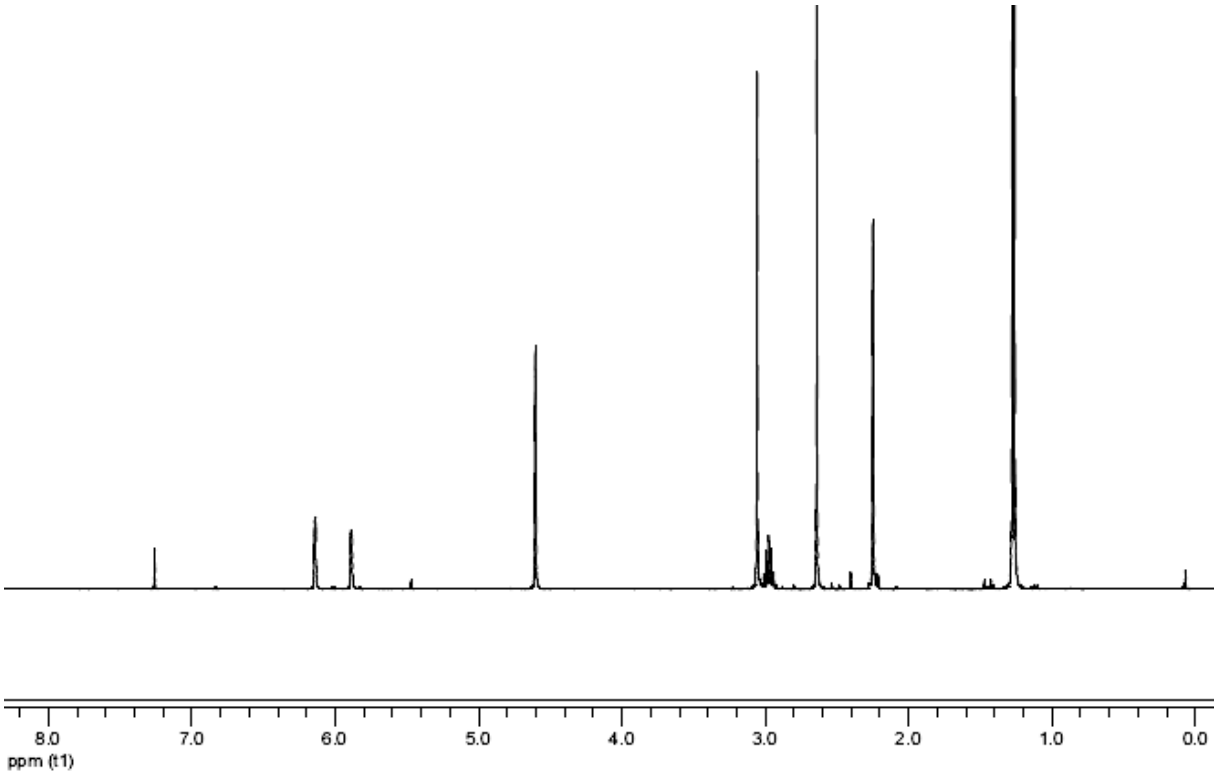
R_f 0.3 (95:05 petroleum ether / diethyl ether).

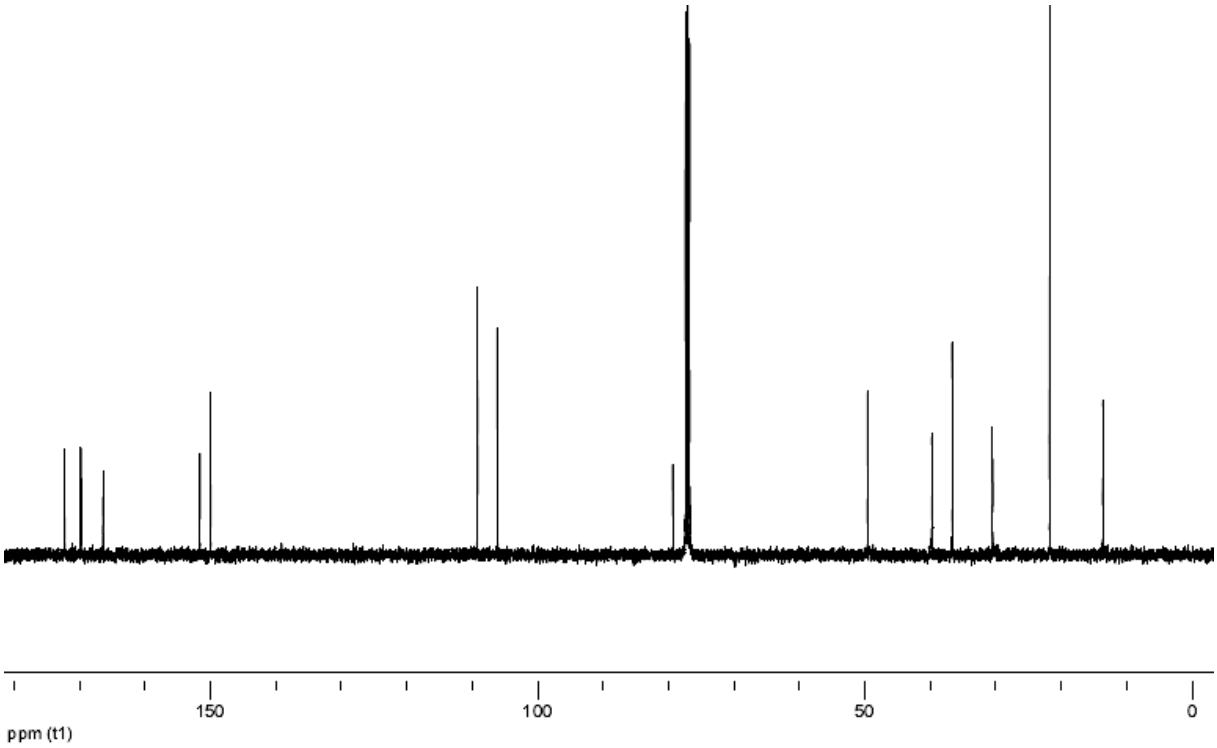
^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.14 (d, *J* = 2.9 Hz, 1H), 5.89 (dd, *J* = 2.9, 0.8 Hz, 1H), 4.60 (s, 2H), 3.06 (s, 3H), 2.98 (sept, *J* = 6.9 Hz, 1H), 2.64 (s, 3H), 2.25 (s, 3H), 1.27 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 172.2, 169.6, 166.3, 151.5, 149.9, 109.1, 106.1, 79.3, 49.5, 39.7, 36.6, 30.4, 21.7, 13.6.

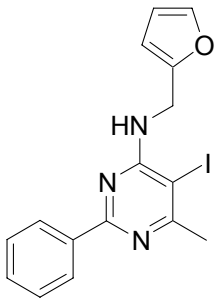
I.R. (thin film) 1547, 1507, 1402, 1387 cm^{-1}.

HRMS Calculated for $C_{15}H_{20}IN_3O$ 385.0651, found 385.0654.


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


150
100
50
0
ppm (t1)

N-(furan-2-ylmethyl)-5-iodo-2-phenyl-6-methylpyrimidin-4-amine



$C_{16}H_{14}IN_3O$
MW = 391.21 $g.mol^{-1}$

To a solution of sodium (0.6 g, 25 mmol) in ethanol (15 mL) was added 3-oxobutyric acid ethyl ester (1.6 mL, 12.5 mmol) and benzamidine (2.0 g, 12.5 mmol). The resulting mixture was refluxed overnight and then acidified to pH = 5 using citric acid. The solution was then extracted with dichloromethane and the organic extracts were collected, dried over $MgSO_4$ and concentrated to yield the crude 2-phenyl-6-methylpyrimidin-4-ol (2.0 g, 86 %).

To a solution of the above pyrimidin-4-ol (1.86 g, 10 mmol) in THF (70 mL) were added iodide (5.1 g, 20 mmol) and potassium carbonate (3.0 g, 22 mmol). The resulting mixture was refluxed overnight and then poured into 100 mL of water. After acidification to pH = 5 using citric acid, the solution was extracted with dichloromethane. The organic extracts were collected, dried over $MgSO_4$ and washed with a saturated sodium sulfite solution. The volatile materials were finally removed under reduced pressure to yield the crude 5-iodo-2-isopropyl-6-methylpyrimidin-4-ol (3.06 g, 98 %).

To a solution of the above iodopyrimidin-4-ol (3.06 g, 9.8 mmol) in acetonitrile (30 mL) were added tosylchloride (1.86 g, 9.8 mmol) and potassium carbonate (1.65 g, 11.8 mmol). The resulting mixture was refluxed for 5 hours and then poured into 100 mL of water. The solution was extracted with dichloromethane and the organic phases were dried over $MgSO_4$ and concentrated to yield the crude toluene-4-sulfonic acid 5-iodo-2-isopropyl-6-methyl-pyrimidin-4-yl ester (4.48 g, 98 %).

To a solution of the above sulfonic acid ester (4.48 g, 9.6 mmol) in THF (20 mL) was added furfurylamine (1.30 mL, 14.4 mmol). The resulting mixture was refluxed for three days. After removal of the volatile materials, purification by flash chromatography (petroleum ether-diethyl ether, 90:10) afforded *N*-(furan-2-ylmethyl)-5-iodo-2-isopropyl-6-methylpyrimidin-4-amine as a brown oil.

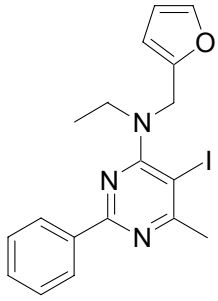
Yield (over four steps) 58 % (2.78 g).

R_f 0.3 (30:70 petroleum ether / diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.45-8.39 (m, 2H), 7.48-7.42 (m, 3H), 7.41-7.39 (m, 1H), 6.36-6.31 (m, 2H), 5.75 (t, *J* = 5.5 Hz, 1H), 4.82 (d, *J* = 5.5 Hz, 2H), 2.66 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 167.0, 162.4, 160.1, 151.7, 142.1, 137.3, 130.4, 128.2, 128.1, 110.4, 107.4, 79.8, 38.8, 29.2.

N-ethyl-*N*-(furan-2-ylmethyl)-5-iodo-2-phenyl-6-methylpyrimidin-4-amine



$C_{18}H_{18}IN_3O$
MW = 419.26 g.mol^{-1}

7c

To a solution of *N*-(furan-2-ylmethyl)-5-iodo-2-phenyl-6-methylpyrimidin-4-amine (180 mg, 0.46 mmol) in DMF (1 mL) were added sodium hydride (13 mg, 0.55 mmol) and ethyl iodide (44 µL, 0.55 mmol). After one night at room temperature, the reaction mixture was poured into a diethyl ether solution and washed ten times with 1 mL of water. The organic phase was dried over $MgSO_4$ and concentrated to yield **7c** as a brown oil. The crude product was used in the cyclization step without any further purification.

Yield 99 % (190 mg).

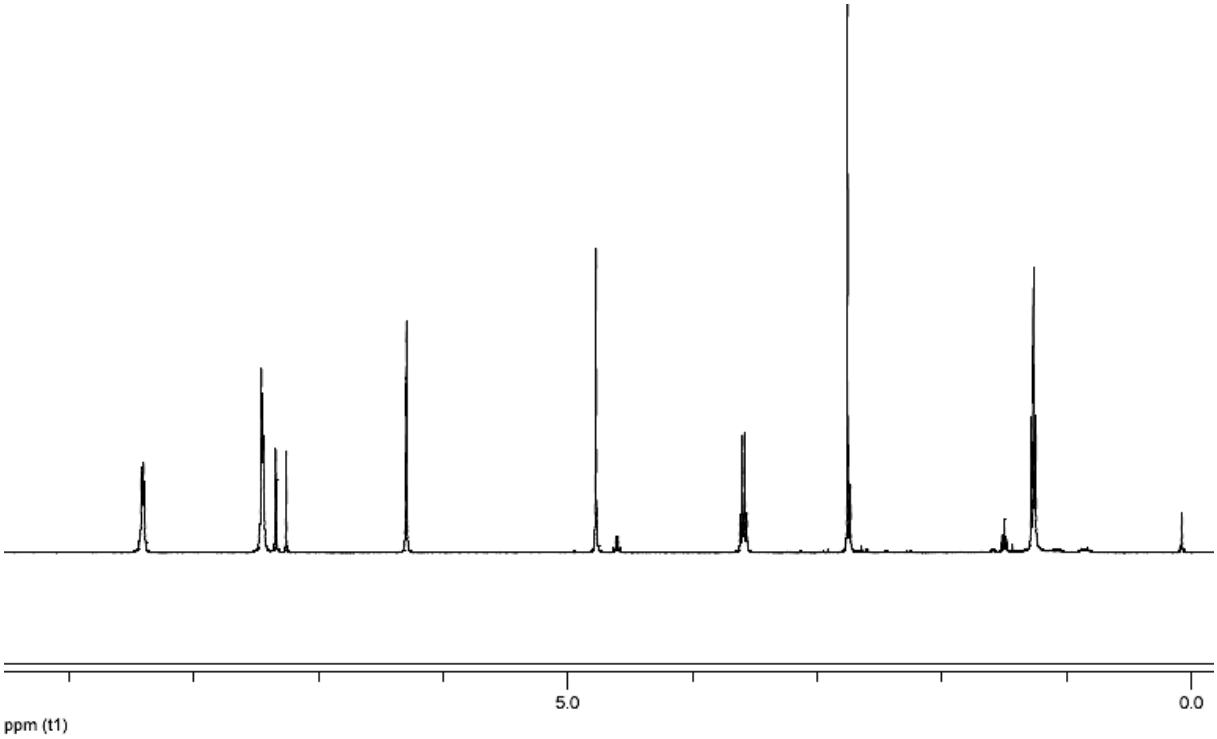
R_f 0.3 (30:70 petroleum ether / diethyl ether).

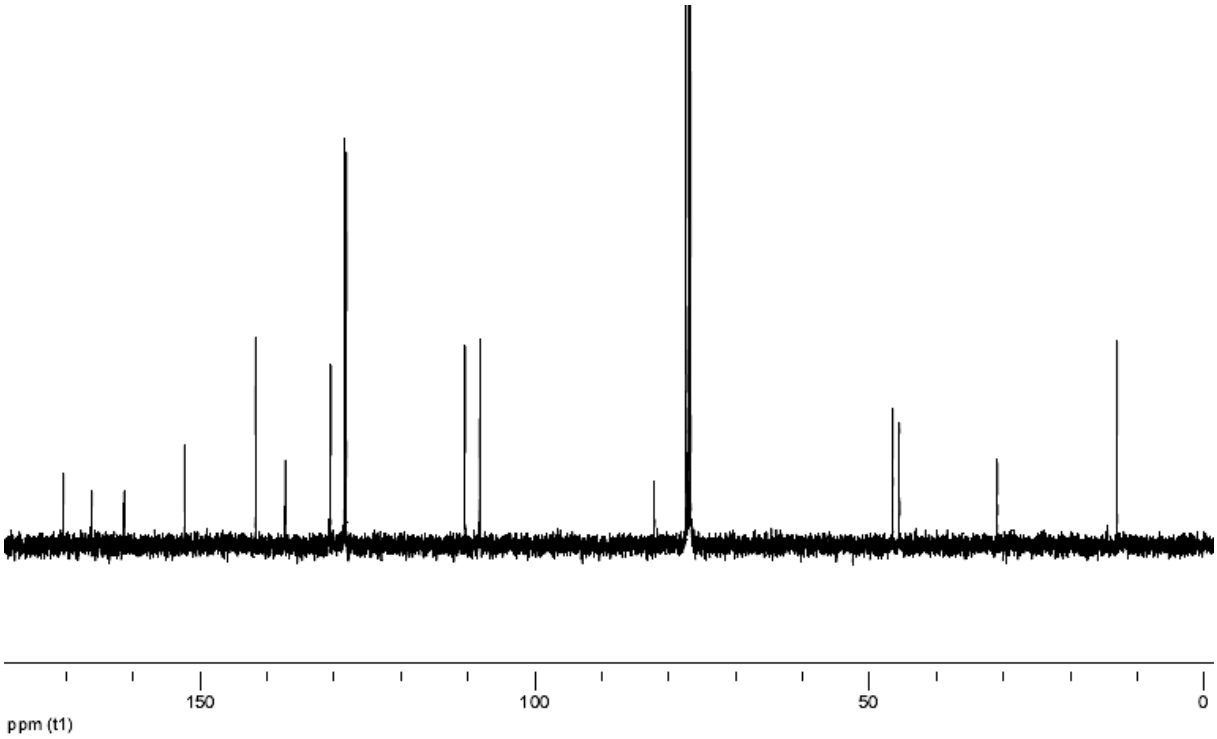
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.44-8.38 (m, 2H), 7.48-7.42 (m, 3H), 7.34 (br s, 1H), 6.30 (br s, 2H), 4.78 (s, 2H), 3.59 (q, *J* = 7.0 Hz, 2H), 2.76 (s, 3H), 1.27 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.4, 166.1, 161.4, 152.3, 141.6, 137.2, 130.4, 128.3, 128.1, 110.3, 108.2, 82.0, 46.5, 45.5, 30.8, 12.9.

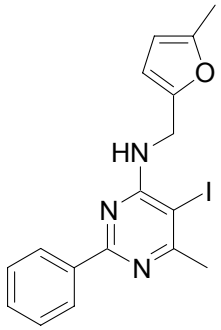
I.R. (thin film) 1531, 1502, 1426, 1372 cm^{-1}.

HRMS Calculated for $C_{18}H_{18}IN_3O$ 419.0495, found 419.0487.


5.0
0.0
ppm (t1)


150
100
50
0
ppm (t1)

N-(5-methylfuran-2-ylmethyl)-5-iodo-6-methyl-2-phenylpyrimidin-4-amine



$C_{17}H_{16}IN_3O$
MW = 405.23 g.mol^{-1}

To a solution of the same sulfonic acid ester used in **7c**'s synthesis (482 mg, 1.03 mmol) in THF (2 mL) was added 5-methylfurfurylamine (195 µL, 1.55 mmol). The resulting mixture was refluxed for three days. After removal of the volatile materials, purification by flash chromatography (petroleum ether-diethyl ether, 90:10) afforded *N*-(furan-2-ylmethyl)-5-iodo-2-isopropyl-6-methylpyrimidin-4-amine as a brown oil.

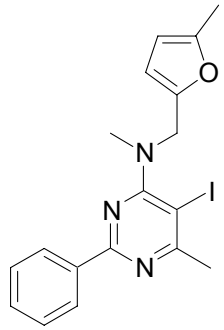
Yield 69 % (280 mg).

R_f 0.3 (95:5 petroleum ether / diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.47-8.40 (m, 2H), 7.50-7.42 (m, 3H), 6.21 (d, *J* = 3.0 Hz, 1H), 5.92 (d, *J* = 3.0, 0.8 Hz, 1H), 5.72 (t, *J* = 5.4 Hz, 1H), 4.75 (d, *J* = 5.4 Hz, 2H), 2.66 (s, 3H), 2.30 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.9, 162.5, 160.2, 151.9, 149.8, 137.4, 130.3, 128.4, 128.1, 108.3, 106.3, 79.8, 39.0, 29.2, 13.6.

N-methyl-*N*-(5-methylfuran-2-ylmethyl)-5-iodo-6-methyl-2-phenylpyrimidin-4-amine



$C_{18}H_{18}IN_3O$
MW = 419.26 g.mol^{-1}

7d

To a solution of *N*-(5-methylfuran-2-ylmethyl)-5-iodo-2-phenyl-6-methylpyrimidin-4-amine (150 mg, 0.37 mmol) in DMF (1 mL) were added sodium hydride (11 mg, 0.44 mmol) and methyl iodide (28 μL, 0.44 mmol). After one night at room temperature, the reaction mixture was poured into a diethyl ether solution and washed ten times with 1 mL of water. The organic phase was dried over $MgSO_4$ and concentrated to yield **7d** as a yellw oil. The crude product was used in the cyclization step without any further purification.

Yield 97 % (150 mg).

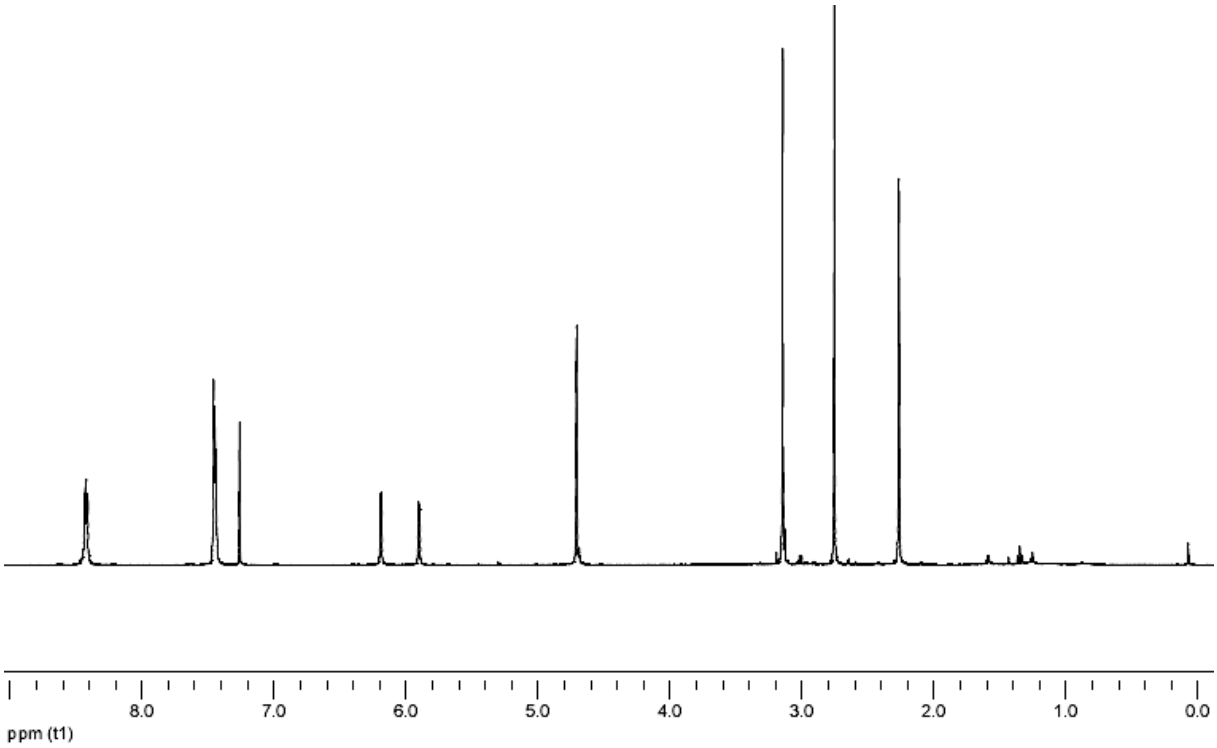
R_f 0.3 (90:10 petroleum ether / diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.45-8.40 (m, 2H), 7.47-7.42 (m, 3H), 6.19 (d, *J* = 2.9 Hz, 1H), 5.90 (dd, *J* = 2.9, 0.8 Hz, 1H), 4.71 (s, 2H), 3.15 (s, 3H), 2.76 (s, 3H), 2.27 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.3, 166.4, 161.3, 151.6, 149.8, 137.2, 130.4, 128.3, 128.1, 109.3, 106.2, 80.3, 49.7, 39.7, 30.6, 13.6.

I.R. (thin film) 1534, 1504, 1422, 1373 cm^{-1}.

HRMS Calculated for $C_{18}H_{18}IN_3O$ 419.0495, found 419.0496.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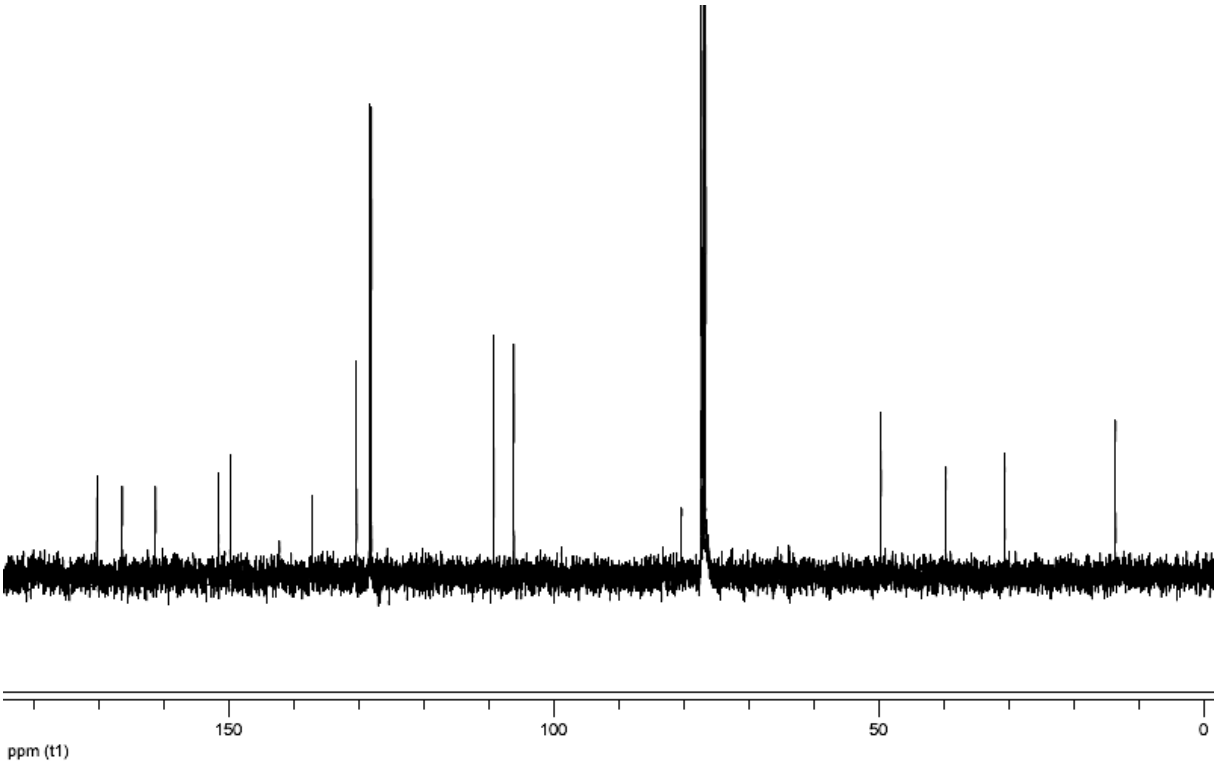
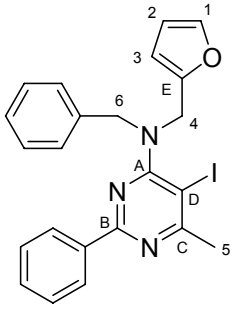
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


150
100
50
0
ppm (t1)

N-benzyl-*N*-(furan-2-ylmethyl)-5-iodo-6-methyl-2-phenylpyrimidin-4-amine



$C_{23}H_{20}IN_3O$
MW = 481.33 g.mol^{-1}

7e

To a solution of *N*-(furan-2-ylmethyl)-5-iodo-2-phenyl-6-methylpyrimidin-4-amine (190 mg, 0.49 mmol) in DMF (1 mL) were added sodium hydride (14 mg, 0.58 mmol), benzyl bromide (72 µL, 0.58 mmol) and tetrabutylammonium iodide (37 mg, 0.10 mmol). After one night at room temperature, the reaction mixture was poured into a diethyl ether solution and washed ten times with 1 mL of water. The organic phase was dried over $MgSO_4$ and concentrated to yield **7e** as a yellow oil. The crude product was used in the cyclization step without any further purification.

Yield 87 % (205 mg).

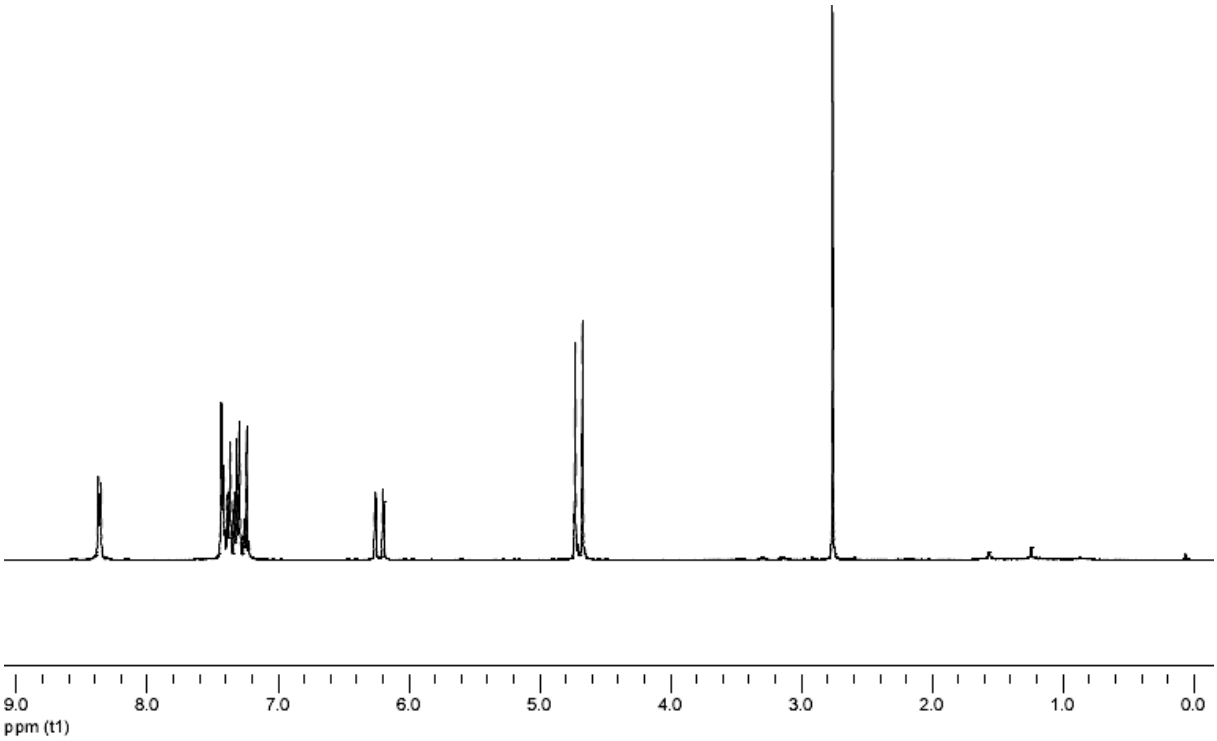
R_f 0.3 (30:70 petroleum ether / diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.38-8.34 (m, 2H), 7.45-7.40 (m, 3H), 7.40-7.35 (m, 2H), 7.34-7.28 (m, 3H), 7.27-7.21 (m, 1H), 6.26 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.20 (d, *J* = 3.1 Hz, 1H), 4.73 (s, 2H), 4.67 (s, 2H), 2.76 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.7, 166.6, 161.6, 151.6, 141.9, 137.9, 137.1, 130.5, 128.4, 128.3, 128.1, 128.0, 127.1, 110.2, 108.5, 83.3, 54.0, 47.0, 30.6.

I.R. (thin film) 1530, 1504, 1426, 1373 cm^{-1}.

HRMS Calculated for $C_{23}H_{20}IN_3O$ 481.0651, found 481.0669.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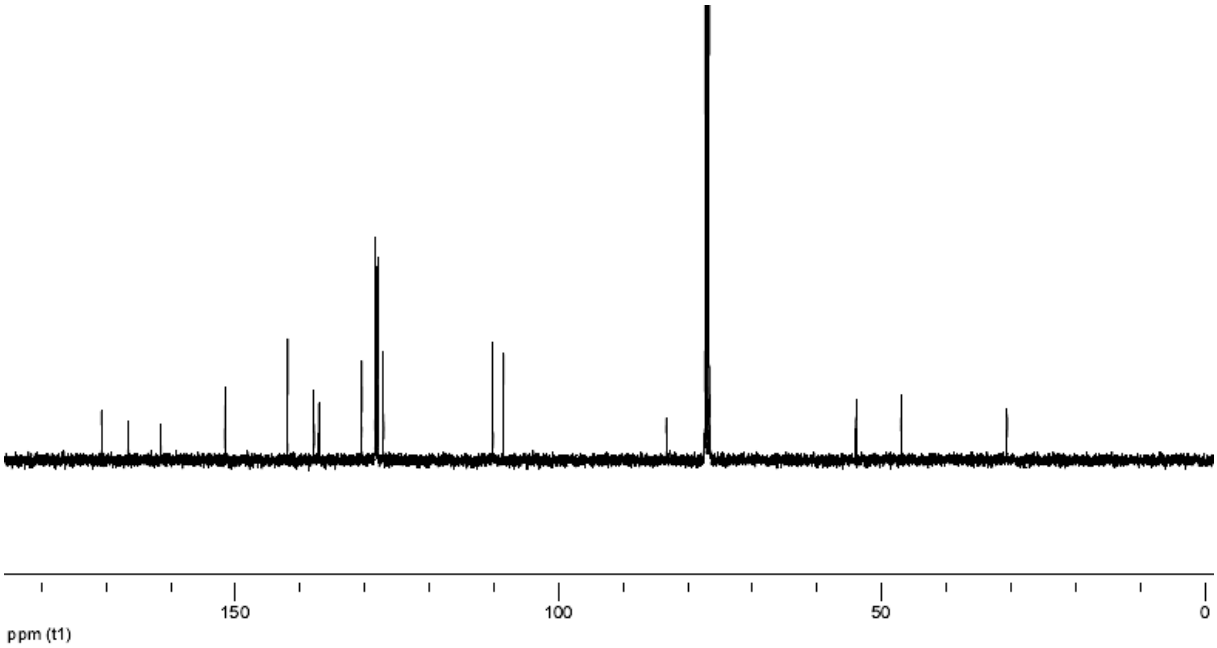
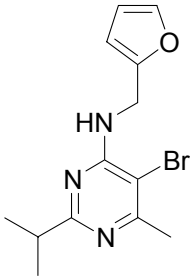
3.0
2.0
1.0
0.0
ppm (t1)


150
100
50
0
ppm (t1)

N-(furan-2-ylmethyl)-5-bromo-2-isopropyl-6-methylpyrimidin-4-amine



$C_{13}H_{16}BrN_3O$
MW = 310.19 g.mol^{-1}

To a solution of 2-isopropyl-6-methylpyrimidin-4-ol (760 mg, 5.0 mmol) in acetic acid (10 mL) was added bromine (250 µL, 5.0 mmol). After one night at room temperature, iced water was poured into the solution. The precipitate was filtered off, washed with water, dissolved in dichloromethaneand finally dried over $MgSO_4$. The volatile materials were removed under reduce pressure to yield the crude 5-bromo-2-isopropyl-6-methylpyrimidin-4-ol (630 mg, 55 %).

To a solution of the above bromopyrimidin-4-ol (630 mg, 2.73 mmol) in acetonitrile (7 mL) were added tosylchloride (518 mg, 2.73 mmol) and potassium carbonate (452 mg, 3.28 mmol). The resulting mixture was refluxed for 5 hours and then poured into 100 mL of water. The solution was extracted with dichloromethane and the organic phases were dried over $MgSO_4$ and concentrated to yield the crude toluene-4-sulfonic acid 5-iodo-2-isopropyl-6-methyl-pyrimidin-4-yl ester (980 mg, 93 %).

To a solution of the above sulfonic acid ester (980 mg, 2.54 mmol) in THF (5 mL) was added furfurylamine (340 µL, 3.81 mmol). The resulting mixture was refluxed for three days. After removal of the volatile materials, purification by flash chromatography (petroleum ether-diethyl ether, 90:10) afforded *N*-(furan-2-ylmethyl)-5-iodo-2-isopropyl-6-methylpyrimidin-4-amine as a brown oil.

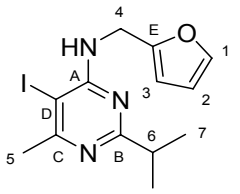
Yield (over three steps) 35 % (540 mg).

R_f 0.3 (90:10 petroleum ether / diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36 (dd, *J* = 1.9, 0.7 Hz, 1H), 6.32 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.27 (d, *J* = 3.1 Hz, 1H), 5.66 (t, *J* = 5.6 Hz, 1H), 4.70 (d, *J* = 5.6 Hz, 2H), 2.96 (sept, *J* = 6.9 Hz, 1H), 2.46 (s, 3H), 1.28 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 172.4, 162.5, 158.0, 151.9, 142.1, 110.4, 107.5, 102.1, 38.2, 37.1, 24.4, 21.8.

N-methyl-*N*-(furan-2-ylmethyl)-5-bromo-2-isopropyl-6-methylpyrimidin-4-amine



$C_{13}H_{16}IN_3O$
MW = 357.19 g.mol^{-1}

7f

To a solution of *N*-(furan-2-ylmethyl)-5-bromo-2-isopropyl-6-methylpyrimidin-4-amine (190 mg, 0.61 mmol) in DMF (1.2 mL) were added sodium hydride (18 mg, 0.73 mmol), methyl iodide (46 µL, 0.73 mmol). After one night at room temperature, the reaction mixture was poured into a diethyl ether solution and washed ten times with 1 mL of water. The organic phase was dried over $MgSO_4$ and concentrated to yield **7f** as a colorless oil. The crude product was used in the cyclization step without any further purification.
Yield 99 % (195 mg).

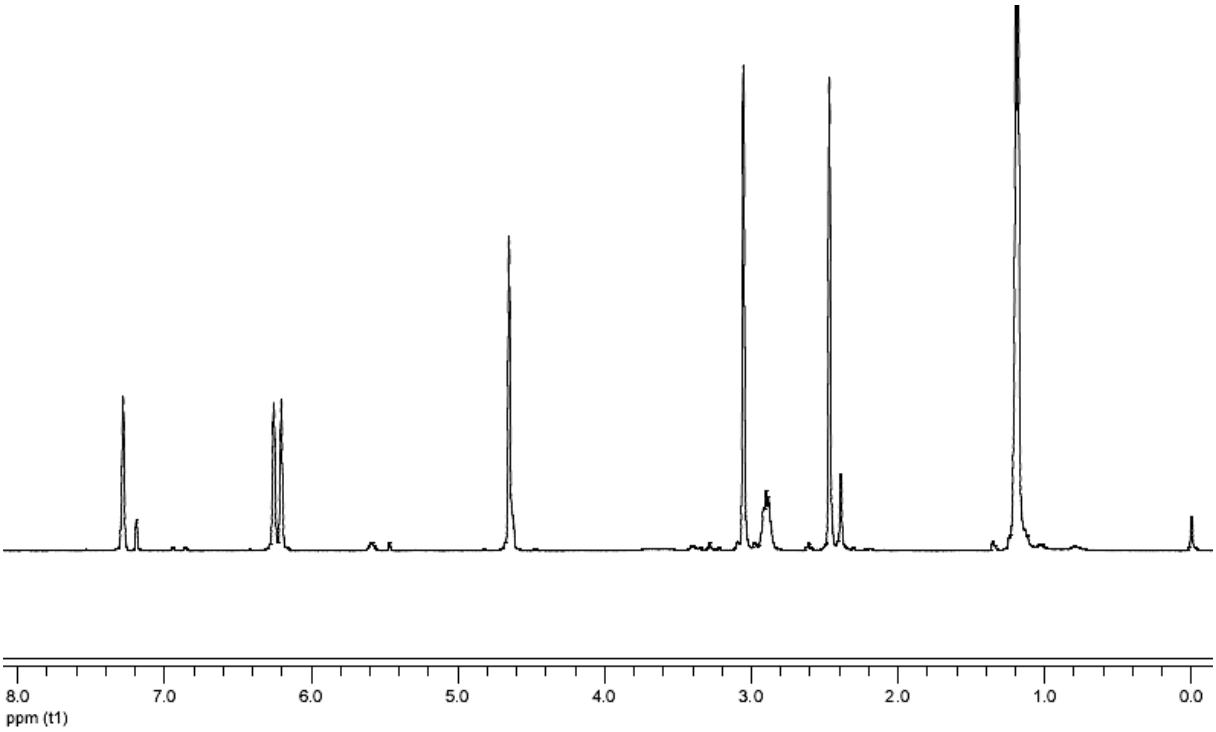
R_f 0.3 (90:10 petroleum ether / diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.34 (m, 1H), 6.33 (dd, *J* = 3.1, 1.8 Hz, 1H), 6.27 (d, *J* = 3.1 Hz, 1H), 4.72 (s, 2H), 3.12 (s, 3H), 2.97 (sept, *J* = 6.9 Hz, 1H), 2.54 (s, 3H), 1.26 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 171.1, 166.0, 162.1, 151.9, 141.9, 110.3, 108.1, 103.2, 48.8, 38.9, 36.8, 25.7, 21.7.

I.R. (thin film) 1581, 1548, 1516, 1404 cm^{-1}.

HRMS Calculated for $C_{14}H_{18}BrN_3O$ 323.0633, found 323.0621.


8.0
7.0
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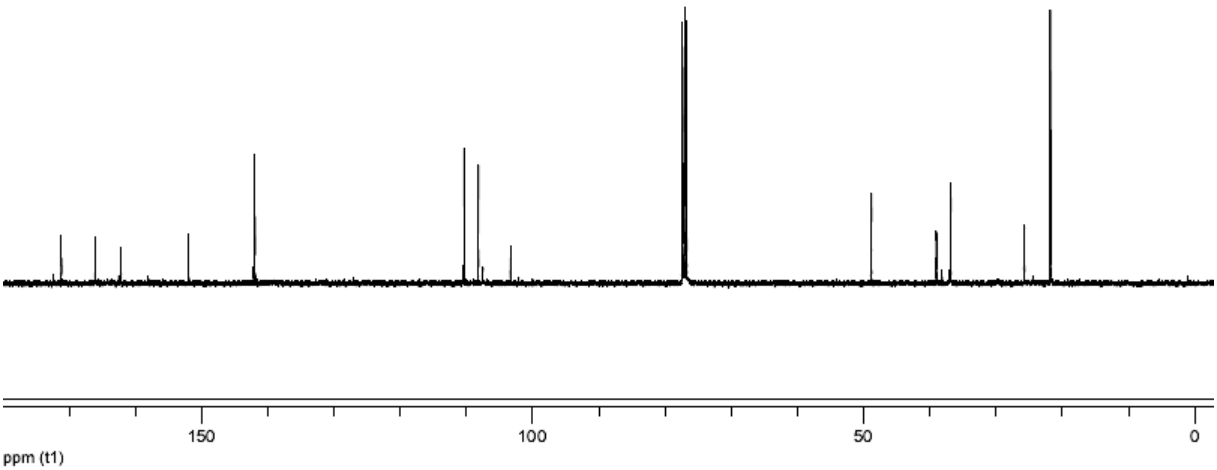
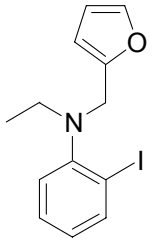
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


150
100
50
0
ppm (t1)

General procedure for the synthesis of *N,N* disubstitued 5-iodoanilines :

- Reductive amination was performed using Solé's conditions : Solé, D.; Vallverdu, L; Solans, X.; Font-Bardia, M.; Bonjoch, J. *J. Am. Chem. Soc.* **2003**, *125*, 1587.

N-ethyl-*N*-furan-2-ylmethyl-(2-iodophenyl)-amine



$C_{13}H_{14}INO$
MW = 327.16 g.mol^{-1}

7g

To a solution of furfuraldehyde (200 µL, 2.4 mmol) in dichloromethane were added 2-iodoaniline (440 mg, 2.0 mmol), acetic acid (340 µL, 6.0 mmol) and sodium triacetoxyborohydride (1.0 g, 4.8 mmol). After one night at room temperature, the reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution and extracted with dichloromethane. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude furfurylaniline in a quantitative yield.

To a solution of the above aniline (140 mg, 0.47 mmol) in DMF (1 mL) were added sodium hydride (15 mg, 0.56 mmol) and ethyl iodide (45 µL, 0.56 mmol). After one night at room temperature, the reaction mixture was poured into a diethyl ether solution and washed ten times with 1 mL of water. The organic phase was dried over $MgSO_4$ and concentrated. Purification by flash column chromatography (petroleum ether) gave **7g** as a yellow oil.

Yield 68 % (105 mg).

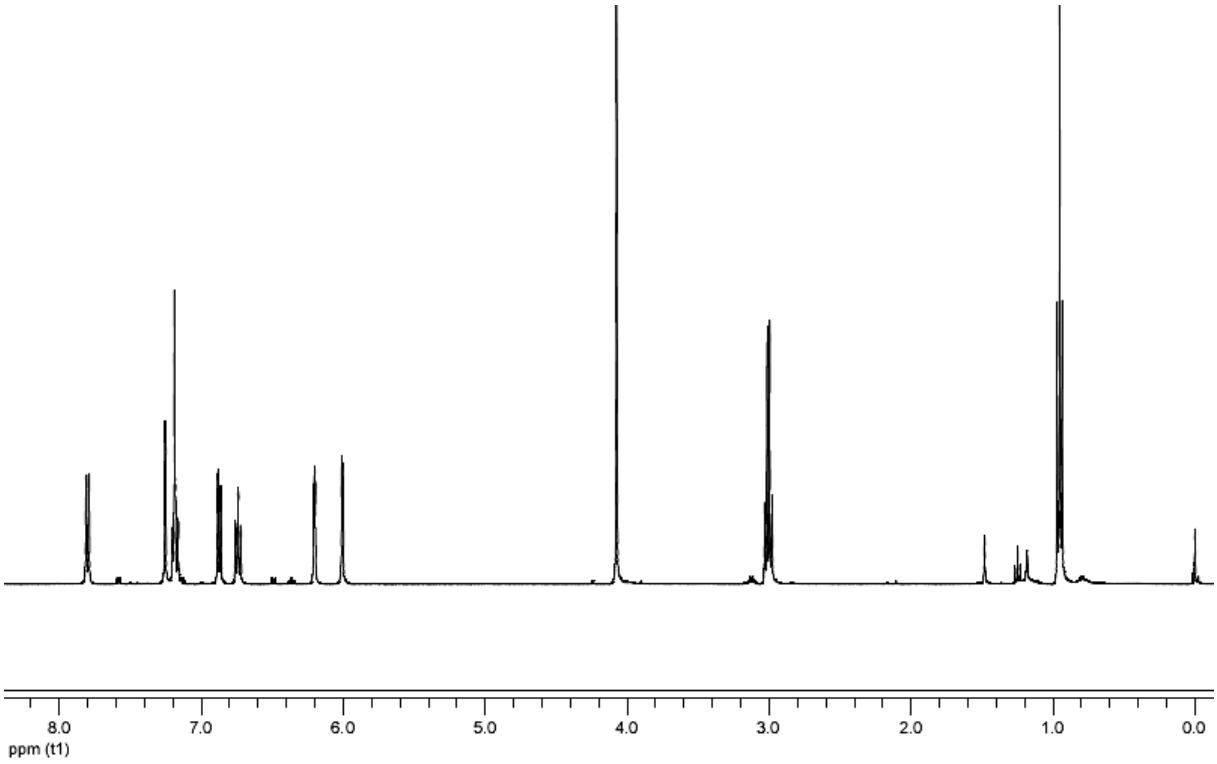
R_f 0.3 (petroleum ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.32 (dd, *J* = 1.9, 0.7 Hz, 1H), 7.28-7.23 (m, 1H), 6.94 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.81 (td, *J* = 7.9, 1.5 Hz, 1H), 6.27 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.08 (d, *J* = 3.1 Hz, 1H), 4.15 (s, 2H), 3.08 (q, *J* = 7.1 Hz, 2H), 1.03 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 152.3, 151.3, 141.6, 139.8, 128.5, 126.0, 124.5, 110.1, 108.4, 101.2, 50.9, 47.0, 12.6.

I.R. (thin film) 1578, 1502, 1468, 1434 cm^{-1}.

HRMS Calculated for $C_{13}H_{14}INO$ 327.0120, found 327.0134.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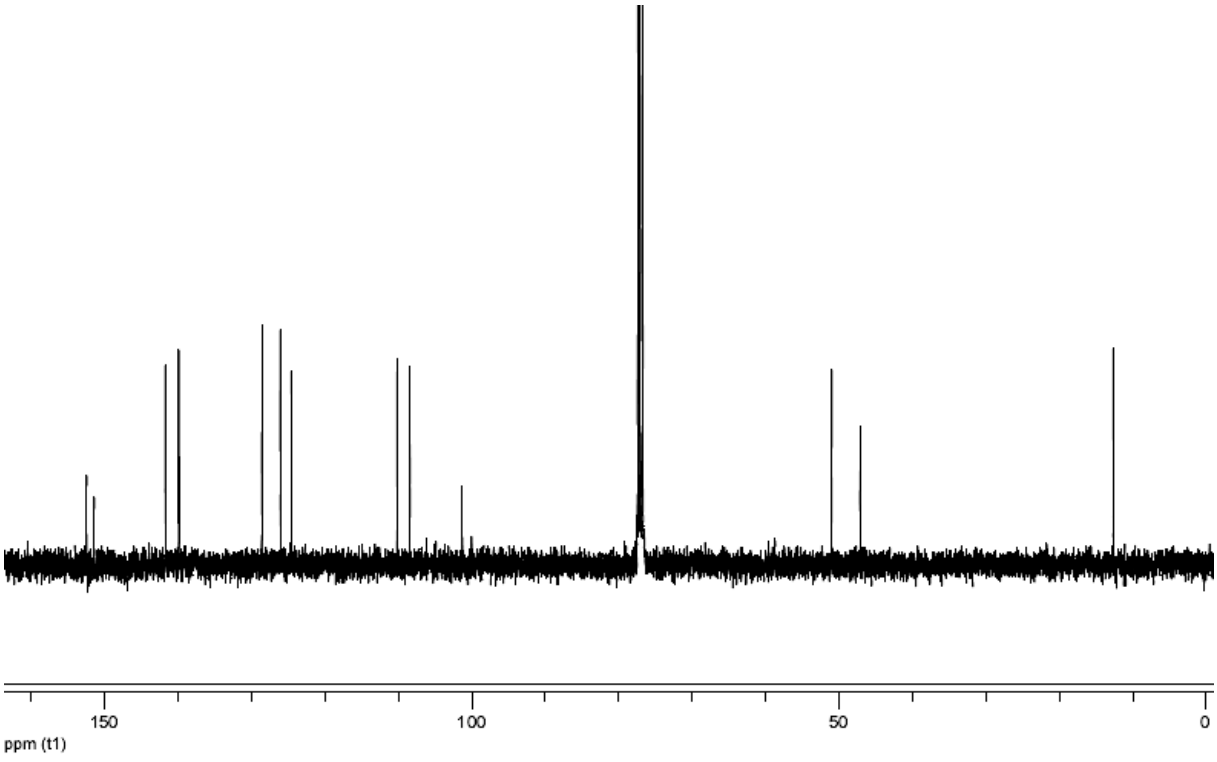
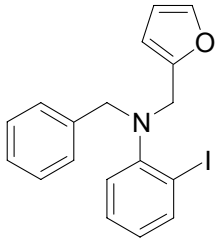
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


150
100
50
0
ppm (t1)

N-benzyl-*N*-furan-2-ylmethyl-(2-iodophenyl)-amine



$C_{18}H_{16}INO$
MW = 389.23 $g.mol^{-1}$

7h

To a solution of *N*-(furan-2-ylmethyl)-2-iodobenzenamine (180 mg, 0.60 mmol) in DMF (1 mL) were added sodium hydride (18 mg, 0.72 mmol), benzyl bromide (80 µL, 0.72 mmol), tetrabutylammonium iodide (44 mg, 0.12 mmol). After one night at room temperature, the reaction mixture was poured into a diethyl ether solution and washed ten times with 1 mL of water. The organic phase was dried over $MgSO_4$ and concentrated. Purification by flash column chromatography (petroleum ether) gave **7h** as a colorless oil.

Yield 78 % (182 mg).

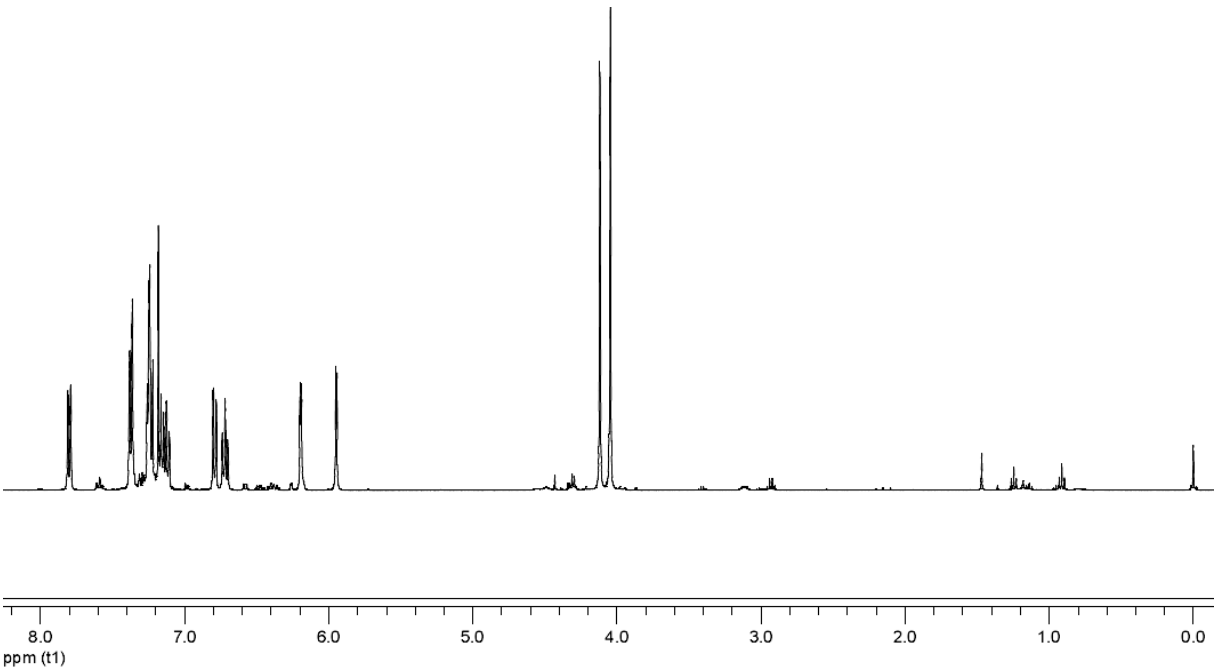
R_f 0.3 (30:70 petroleum ether / diethyl ether).

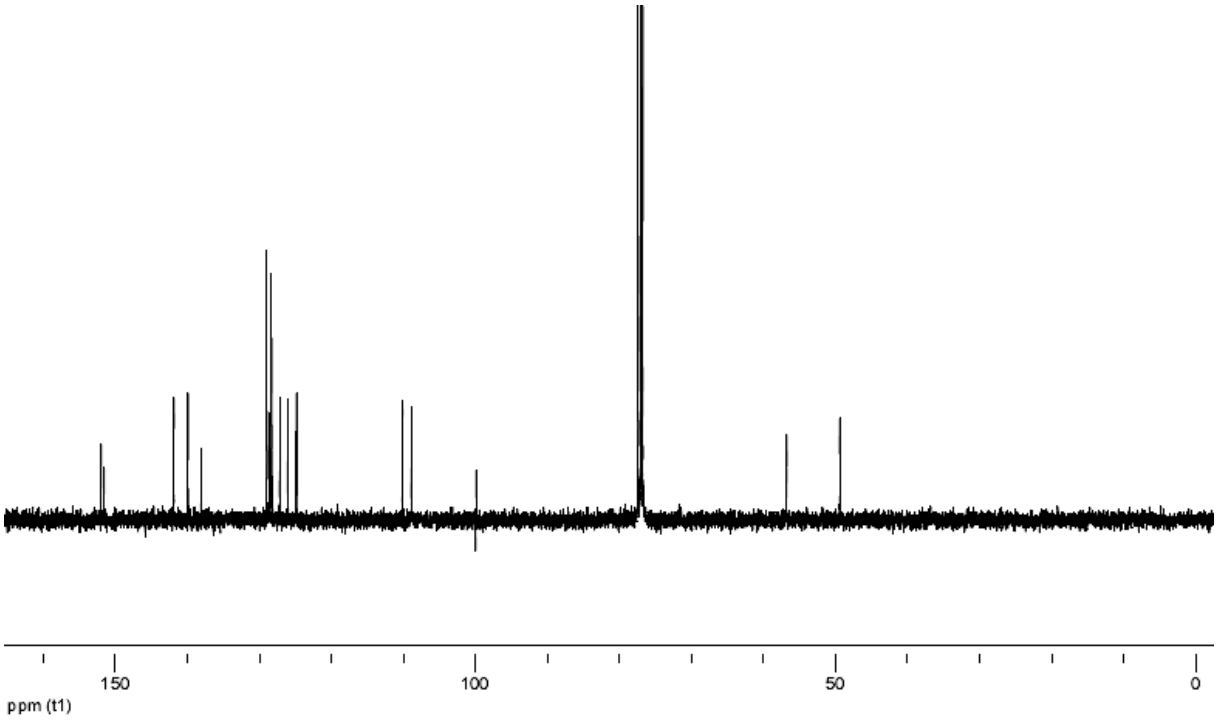
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.47-7.43 (m, 2H), 7.35-7.29 (m, 3H), 7.27-7.24 (m, 1H), 7.23-7.18 (m, 1H), 6.87 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.80 (td, *J* = 7.5, 1.4 Hz, 1H), 6.27 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.03 (d, *J* = 3.1 Hz, 1H), 4.20 (s, 2H), 4.12 (s, 2H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 151.9, 151.5, 141.8, 139.8, 138.0, 128.9, 128.5, 128.2, 127.1, 126.0, 124.7, 110.0, 108.8, 99.8, 56.7, 49.3.

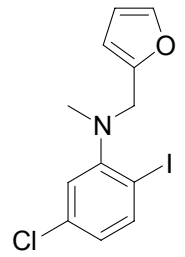
I.R. (thin film) 1579, 1505, 1497, 1469 cm^{-1}.

HRMS Calculated for $C_{18}H_{16}INO$ 389.0277, found 389.0270.


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


150
100
50
0
ppm (t1)

(5-chloro-2-iodophenyl)-furan-2-ylmethylmethylamine



$C_{12}H_{11}ClINO$
MW = 347.58 g.mol^{-1}

7i

To a solution of furfuraldehyde (200 µL, 2.4 mmol) in dichloromethane were added 5-chloro-2-iodoaniline (506 mg, 2.0 mmol), acetic acid (340 µL, 6.0 mmol) and sodium triacetoxyborohydride (1.0 g, 4.8 mmol). After one night at room temperature, the reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution and extracted with dichloromethane. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude furfurylaniline in a quantitative yield.

To a solution of the above aniline (260 mg, 0.78 mmol) in DMF (1.5 mL) were added sodium hydride (28 mg, 0.94 mmol) and methyl iodide (100 µL, 0.94 mmol). After one night at room temperature, the reaction mixture was poured into a diethyl ether solution and washed ten times with 1 mL of water. The organic phase was dried over $MgSO_4$ and concentrated to yield **7i** as an orange oil. The crude product was used in the cyclization step without any further purification.

Yield 89 % (240 mg).

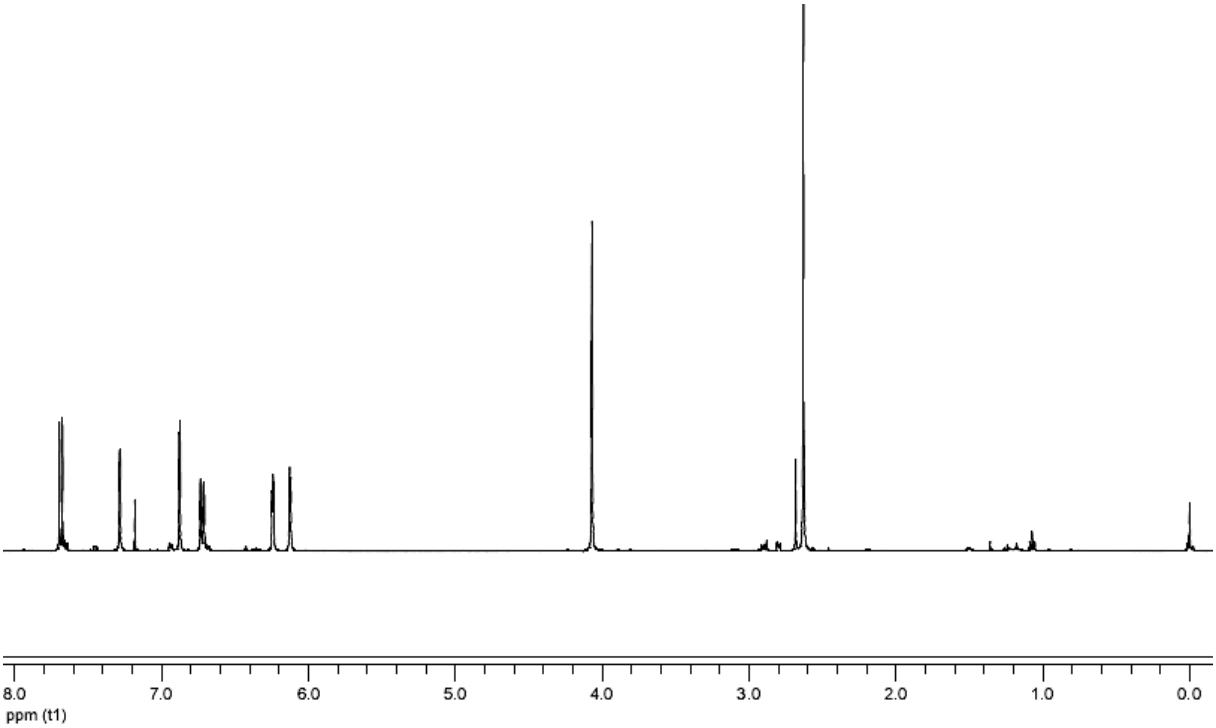
R_f 0.3 (30:70 petroleum ether / diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, *J* = 8.4 Hz, 1H), 7.36 (dd, *J* = 1.9, 0.7 Hz, 1H), 6.96 (d, *J* = 2.4 Hz, 1H), 6.80 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.32 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.20 (d, *J* = 3.1 Hz, 1H), 4.15 (s, 2H), 2.71 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 154.4, 151.5, 142.0, 140.7, 134.7, 125.5, 122.8, 110.2, 108.8, 94.7, 53.2, 40.9.

I.R. (thin film) 1570, 1504, 1470, 1455 cm^{-1}.

HRMS Calculated for $C_{12}H_{11}ClINO$ 346.9574, found 346.9583.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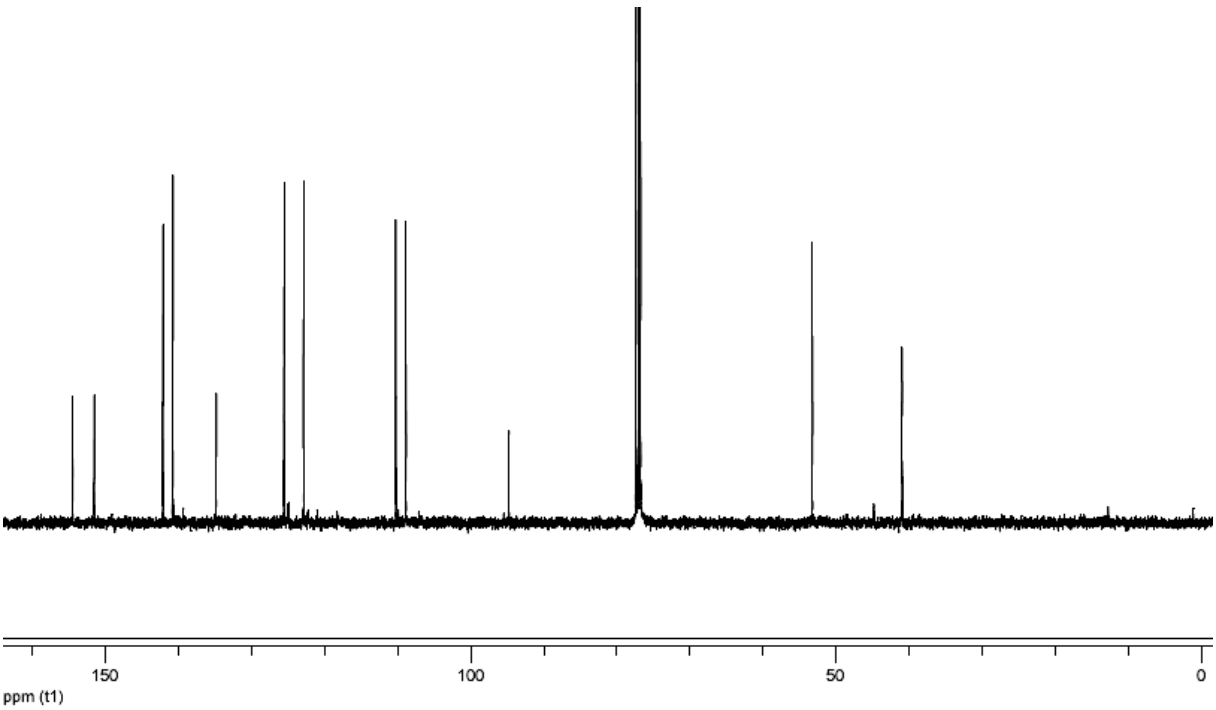
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

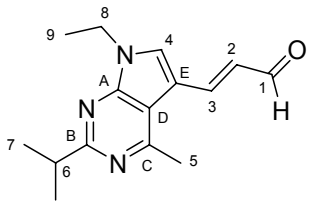

150
100
50
0
ppm (t1)

General Procedure for the synthesis of 3-vinyl-[4,0,3]-heterocycles :

To a 0.25 M solution of the corresponding aminopyrimidine or aniline in acetonitrile were successfully added *bis*(triphenylphosphine)palladium chloride (5 mol %) and diisopropylethylamine (1 equiv). The resulting mixture was then stirred under microwave activation for 20 minutes at 130 °C (Power = 100 W, Pressure = 13 bars).

The crude mixture was first filtered and rinsed with methanol. After removal of the volatile materials, purification by flash chromatography gave the corresponding 3-vinyl-[4,0,3]-heterocycle.

(*E*)-3-(7-ethyl-2-isopropyl-4-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)acrylaldehyde



$C_{15}H_{19}N_3O$
MW = 257.33 g.mol^{-1}

8a

General procedure using **7a** (180 mg, 0.47 mmol), *bis*(triphenylphosphine)palladium chloride (18 mg, 5 mol %) and diisopropylethylamine (80 µL, 0.47 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 50:50) gave **8a** as an orange solid.

MP 96-97 °C.

Yield 72 % (87 mg).

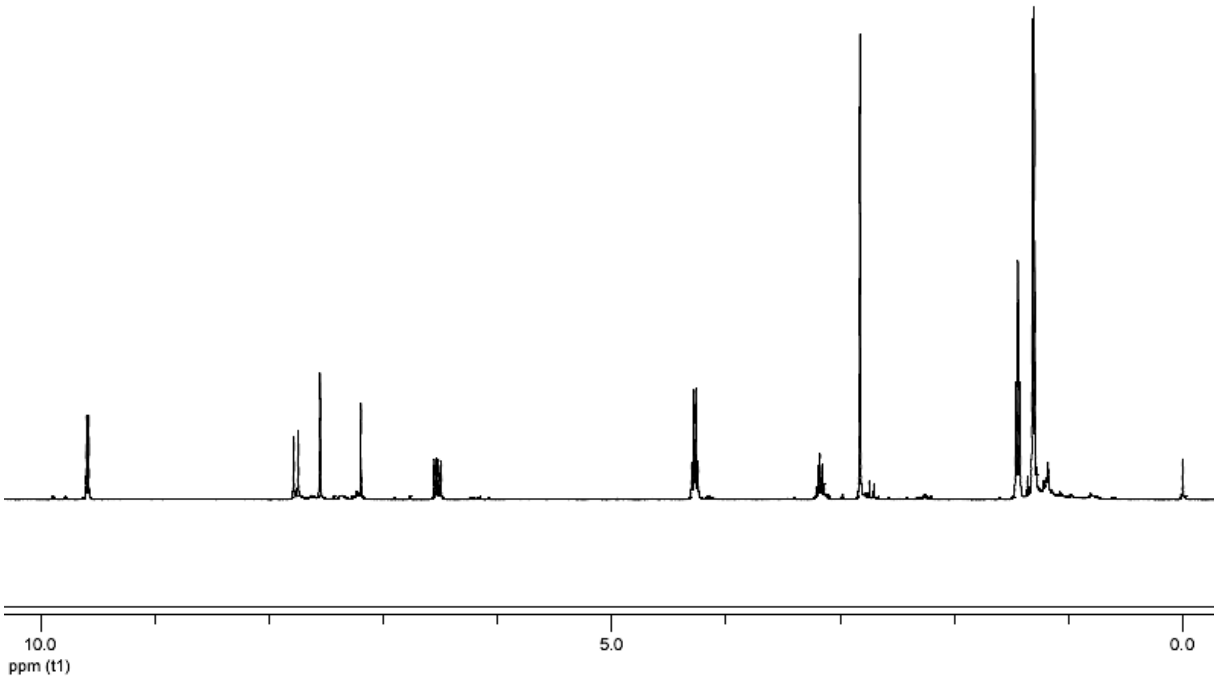
R_f 0.3 (50:50 petroleum ether / diethyl ether).

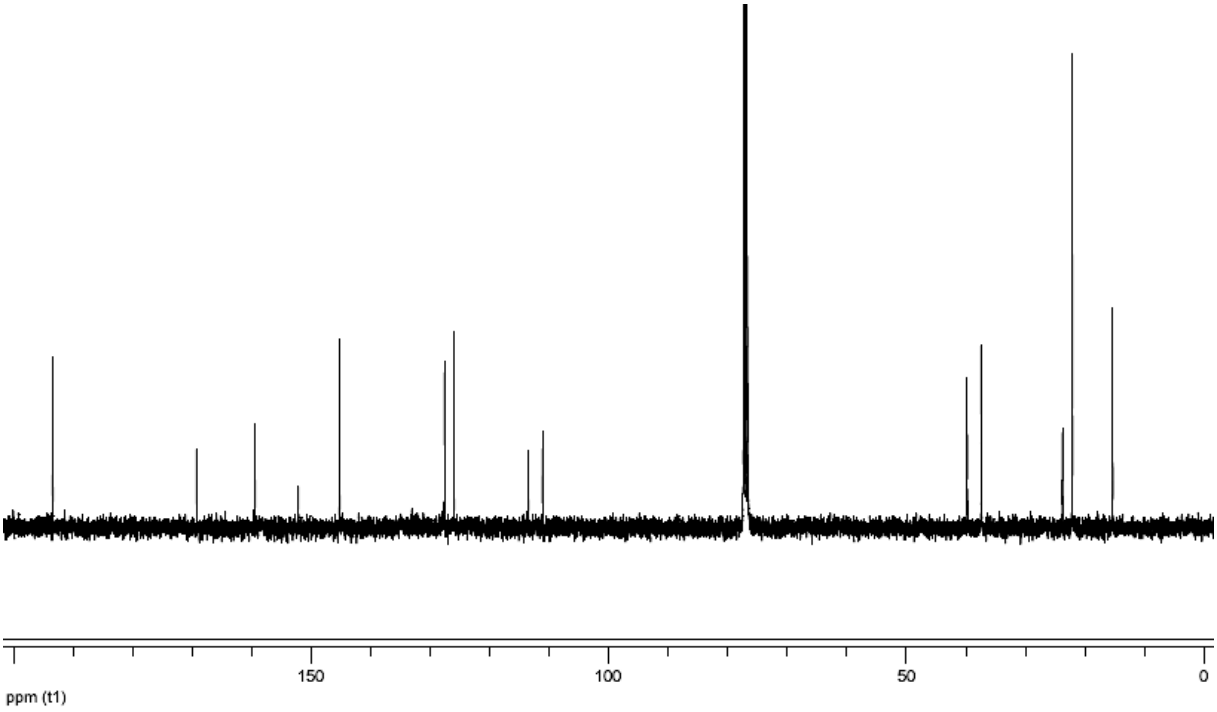
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.67 (d, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 15.7 Hz, 1H), 7.62 (s, 1H), 6.59 (dd, *J* = 15.7, 7.8 Hz, 1H), 4.34 (q, *J* = 7.3 Hz, 2H), 3.24 (sept, *J* = 6.9 Hz, 1H), 2.89 (s, 3H), 1.51 (t, *J* = 7.3 Hz, 3H), 1.37 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 193.4, 169.2, 159. 4, 152.2, 145.2, 127.6, 126.0, 113.5, 110.1, 39.7, 37.4, 23.7, 22.1, 15.3.

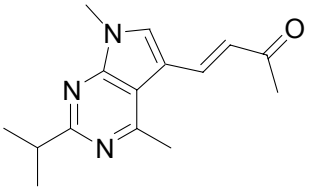
I.R. (thin film) 1668, 1615, 1560, 1525 cm^{-1}.

HRMS Calculated for $C_{15}H_{19}N_3O$ 257.1528, found 257.1525.


10.0
5.0
0.0
ppm (t1)


150
100
50
0
ppm (t1)

(*E*)-4-(2-isopropyl-4,7-dimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-but-3-en-2-one



$C_{15}H_{19}N_3O$
MW = 257.33 g.mol^{-1}

8b

General procedure using **7b** (140 mg, 0.36 mmol), *bis*(triphenylphosphine)palladium chloride (13 mg, 5 mol %) and diisopropylethylamine (60 µL, 0.36 mmol). Purification by flash chromatography (diethyl ether) gave **8b** as a yellow solid.

MP 138-139 °C.

Yield 77 % (71 mg).

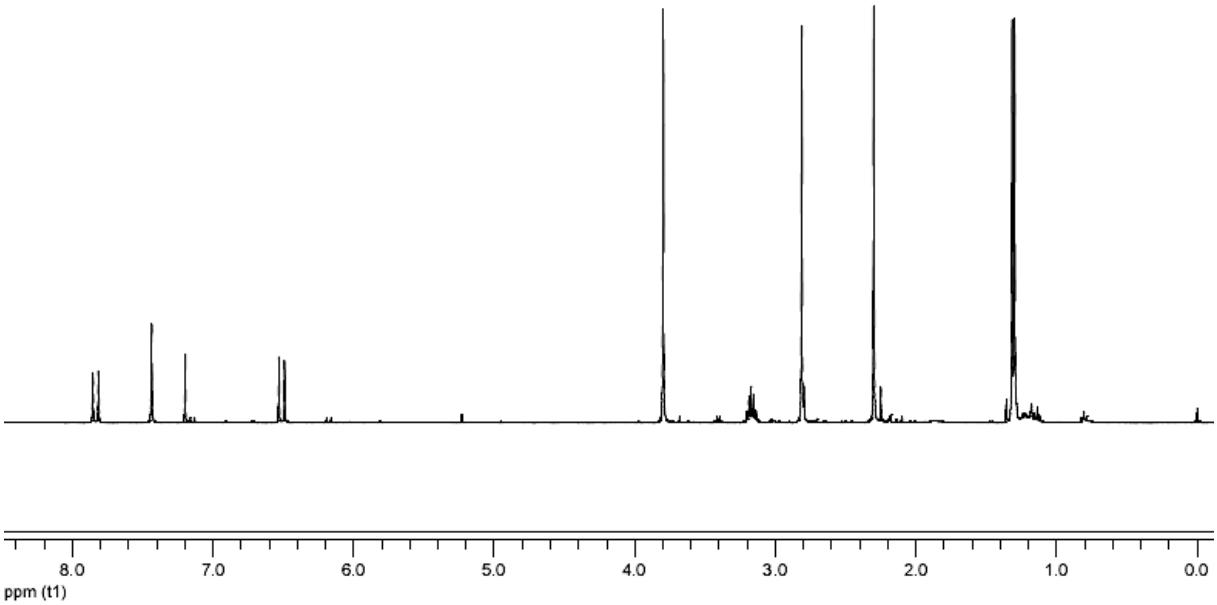
R_f 0.3 (diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (d, *J* = 16.0 Hz, 1H), 7.50 (s, 1H), 6.57 (d, *J* = 16.0 Hz, 1H), 3.86 (s, 3H), 3.23 (sept, *J* = 6.9 Hz, 1H), 2.88 (s, 3H), 2.36 (s, 3H), 1.37 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 197.8, 169.1, 159.4, 152.4, 135.7, 127.8, 124.7, 113.6, 111.2, 37.4, 31.2, 27.4, 23.6, 22.1.

I.R. (thin film) 1663, 1636, 1613, 1531 cm^{-1}.

HRMS Calculated for $C_{15}H_{19}N_3O$ 257.1528, found 257.1538.


8.0
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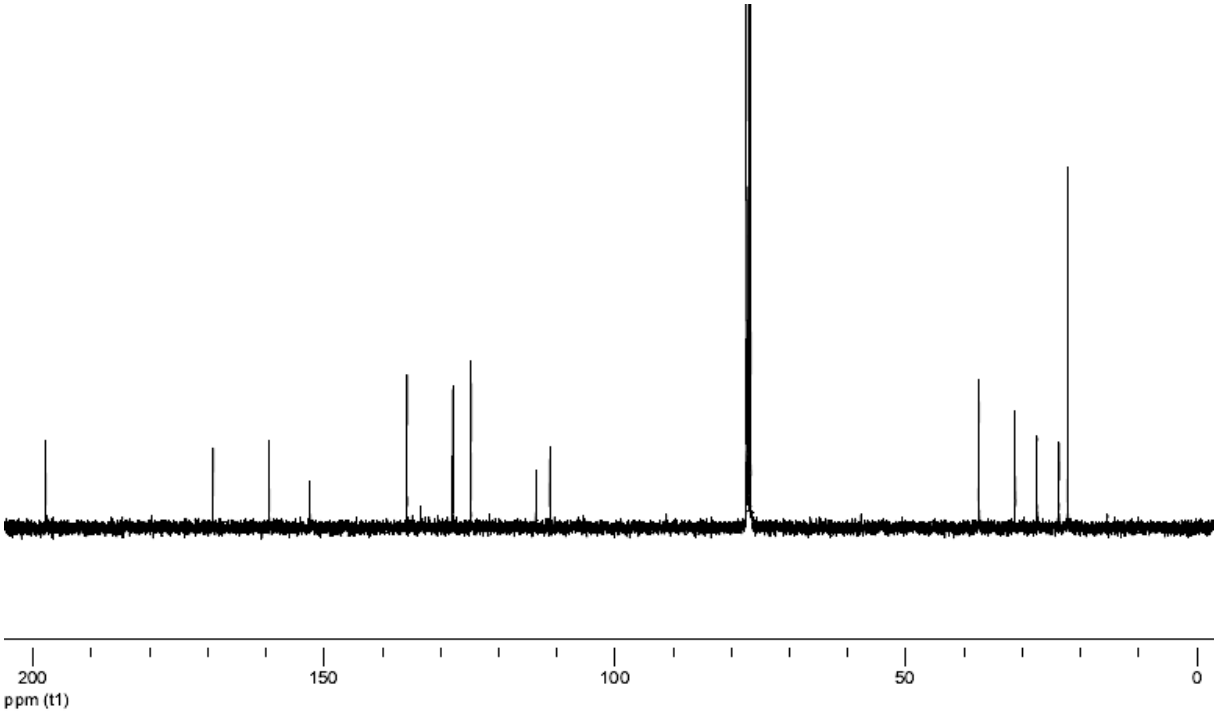
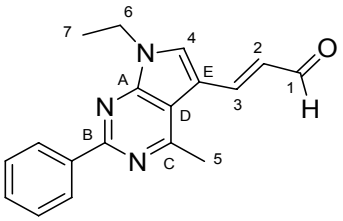
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


200
150
100
50
0
ppm (t1)

(*E*)-3-(7-ethyl-4-methyl-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-propenal



$C_{18}H_{17}N_3O$
MW = 291.35 g.mol^{-1}

8c

General procedure using **7c** (150 mg, 0.36 mmol), *bis*(triphenylphosphine)palladium chloride (13 mg, 5 mol %) and diisopropylethylamine (60 µL, 0.36 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 50:50) gave **8c** as an orange solid.

MP 217-218 °C.

Yield 76 % (80 mg).

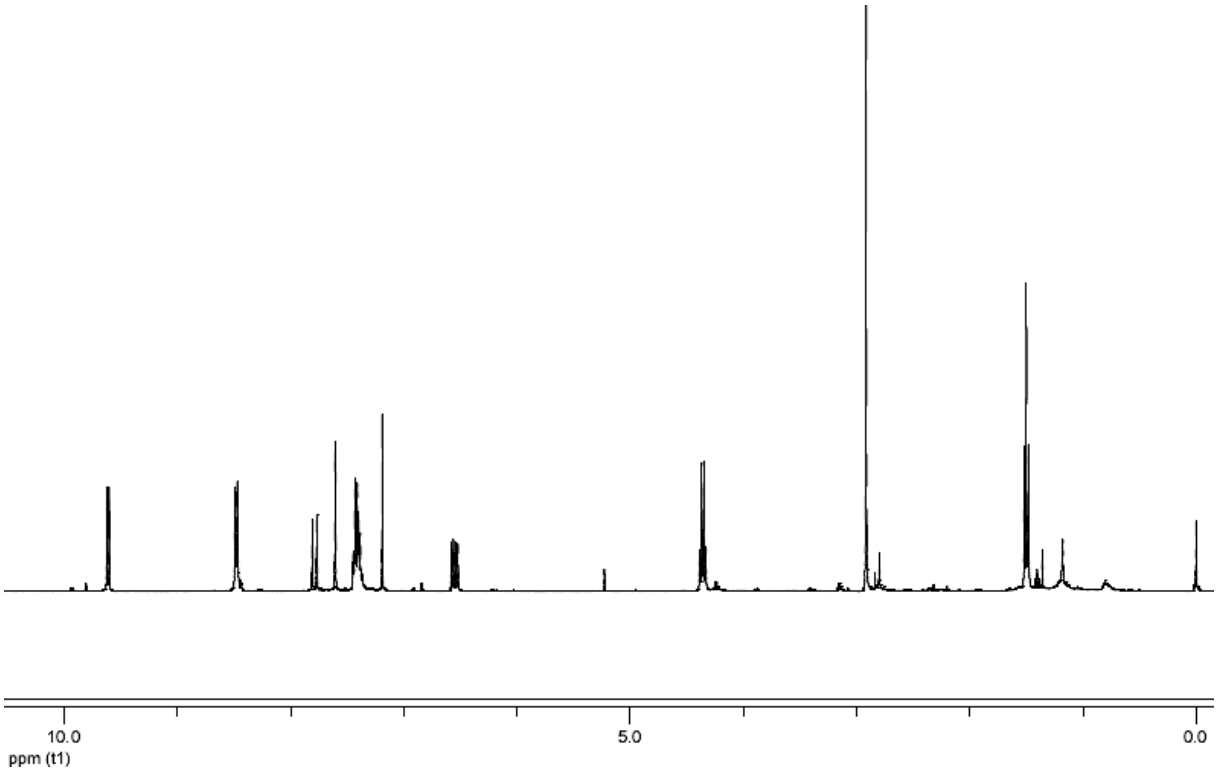
R_f 0.3 (50:50 petroleum ether / diethyl ether).

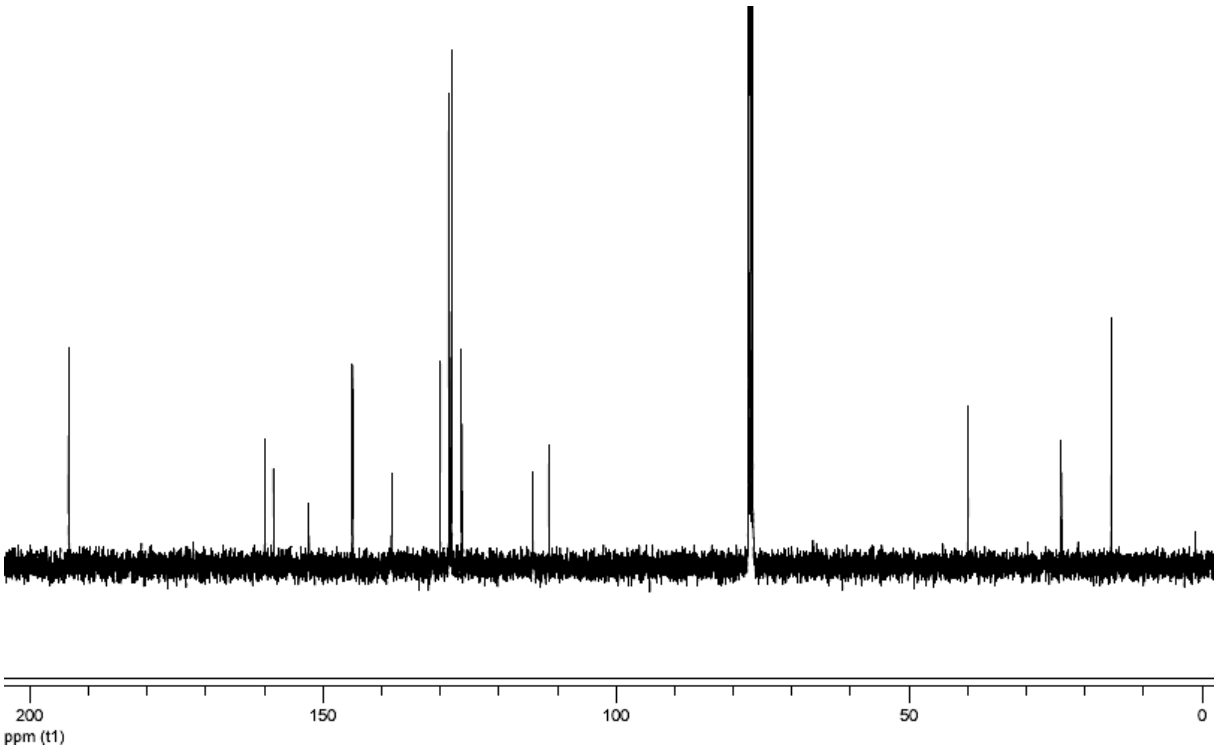
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.68 (d, *J* = 7.8 Hz, 1H), 8.57-8.53 (m, 2H), 7.86 (d, *J* = 15.8 Hz, 1H), 7.68 (s, 1H), 7.53-7.45 (m, 3H), 6.62 (dd, *J* = 15.8, 7.8 Hz, 1H), 4.43 (q, *J* = 7.3 Hz, 2H), 2.99 (s, 3H), 1.57 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 193.3, 159.8, 158.3, 152.3, 144.9, 138.2, 129.9, 128.4, 128.3, 128.0, 126.2, 114.1, 111.4, 39.9, 23.9, 15.4.

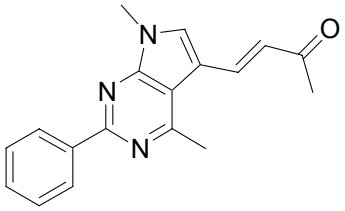
I.R. (thin film) 1670, 1616, 1558, 1523 cm^{-1}.

HRMS Calculated for $C_{18}H_{17}N_3O$ 291.1372, found 291.1369.


10.0
5.0
0.0
ppm (t1)


200
150
100
50
0
ppm (t1)

(*E*)-4-(4,7-dimethyl-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-but-3-en-2-one



$C_{18}H_{17}N_3O$
MW = 291.35 g.mol^{-1}

8d

General procedure using **7d** (150 mg, 0.36 mmol), *bis*(triphenylphosphine)palladium chloride (13 mg, 5 mol %) and diisopropylethylamine (60 µL, 0.36 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 10:90) gave **8d** as a brown solid.

MP 181-182 °C.

Yield 81 % (85 mg).

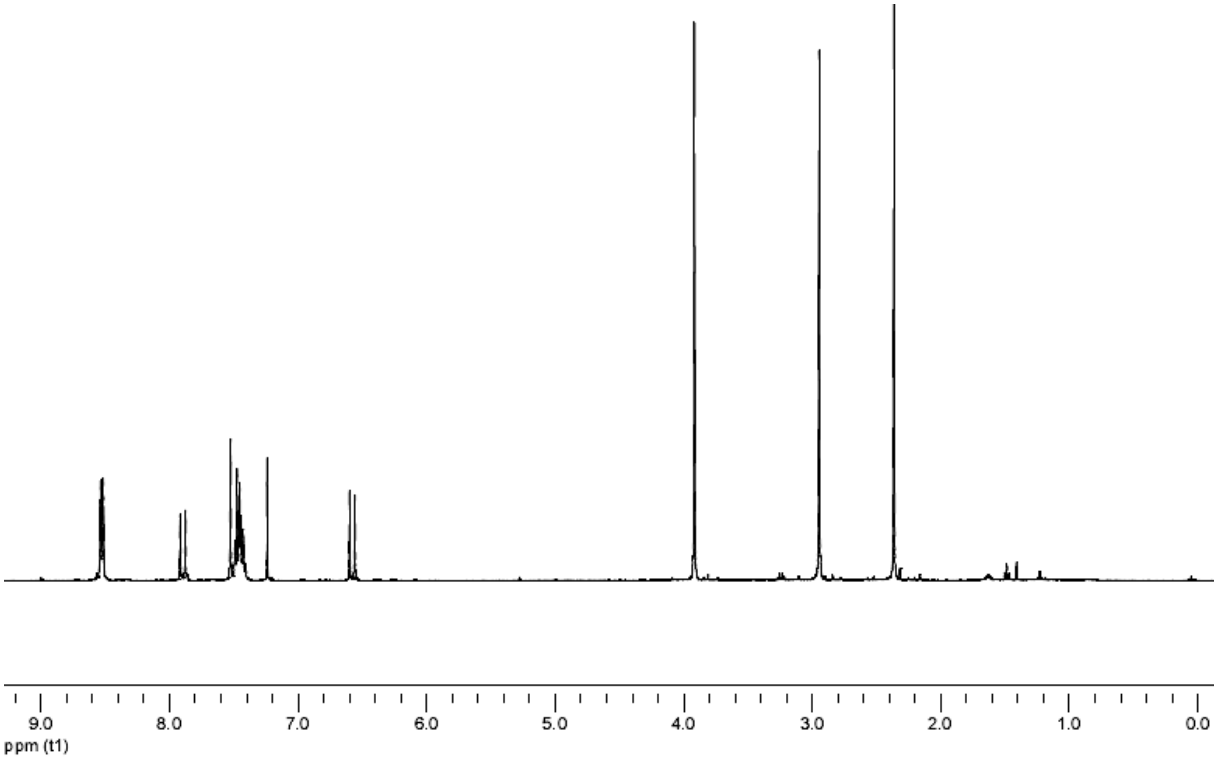
R_f 0.3 (10:90 petroleum ether / diethyl ether).

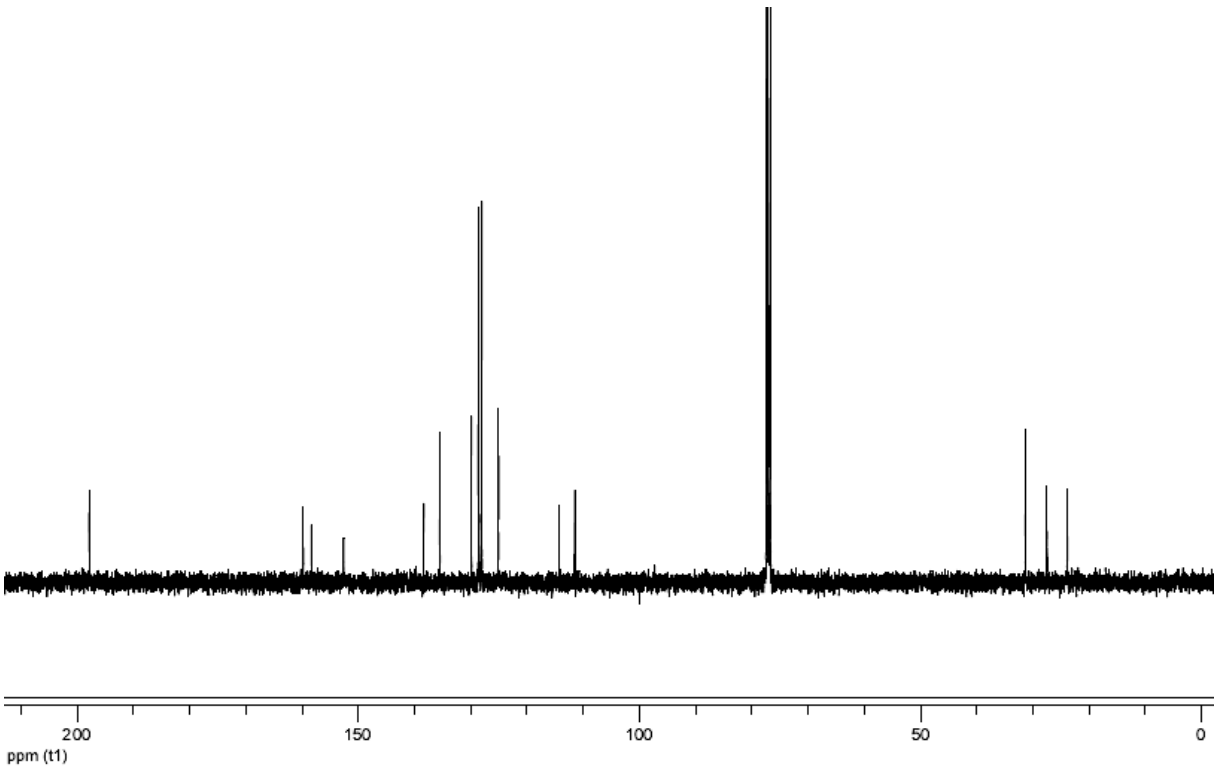
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.56-8.50 (m, 2H), 7.90 (d, *J* = 16.1 Hz, 1H), 7.53 (s, 1H), 7.50-7.39 (m, 3H), 6.58 (d, *J* = 16.1 Hz, 1H), 3.92 (s, 3H), 2.95 (s, 3H), 2.37 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 197.8, 159.7, 158.2, 152.5, 138.3, 135.4, 129.0, 128.6, 128.4, 128.0, 125.0, 114.2, 111.4, 31.3, 27.4, 23.8.

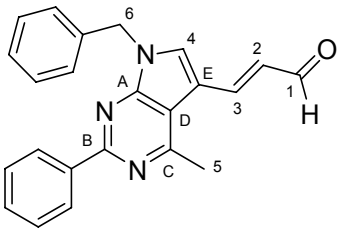
I.R. (thin film) 1661, 1638, 1620, 1531 cm^{-1}.

HRMS Calculated for $C_{18}H_{17}N_3O$ 291.1372, found 291.1361.


9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


200
150
100
50
0
ppm (t1)

(*E*)-3-(7-benzyl-4-methyl-2-phenyl-*7H*-pyrrolo[2,3-d]pyrimidin-5-yl)-propenal



$C_{23}H_{19}N_3O$
MW = 353.42 g.mol^{-1}

8e

General procedure using **7e** (120 mg, 0.25 mmol), *bis*(triphenylphosphine)palladium chloride (9 mg, 5 mol %) and diisopropylethylamine (45 µL, 0.25 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 10:90) gave **8e** as a white solid.

MP 204-205 °C.

Yield 75 % (66 mg).

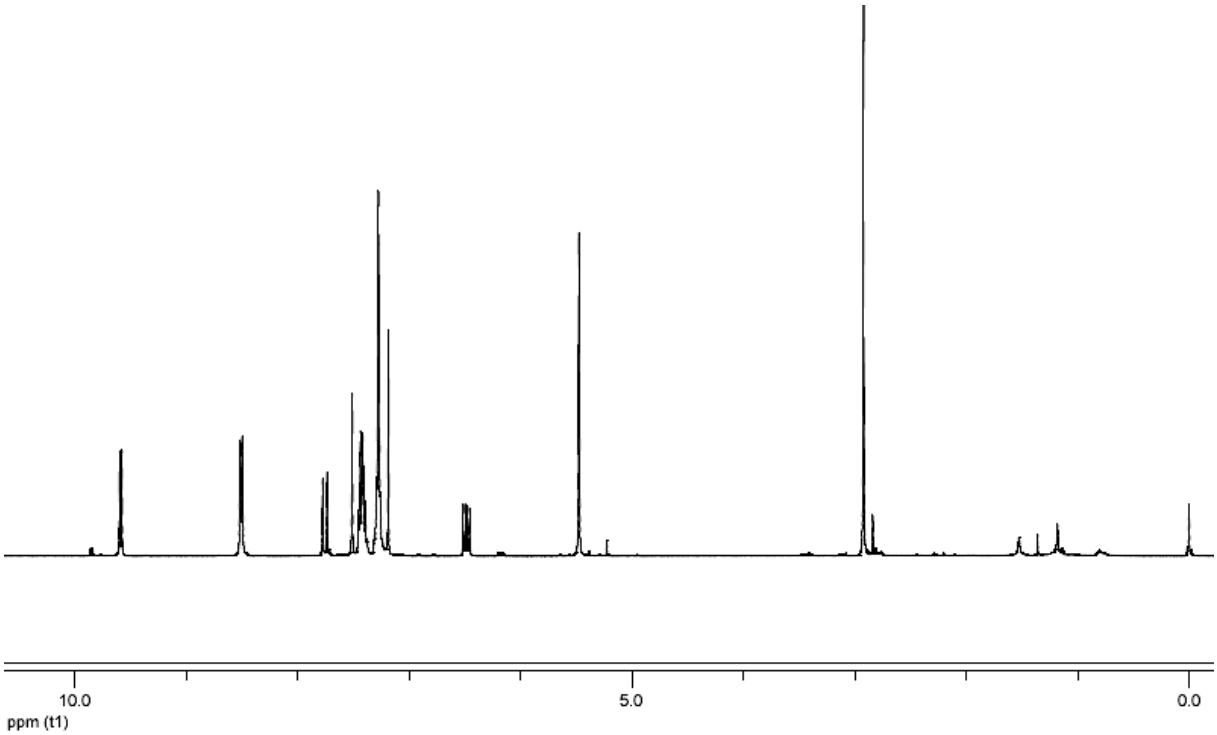
R_f 0.3 (30:70 petroleum ether / diethyl ether).

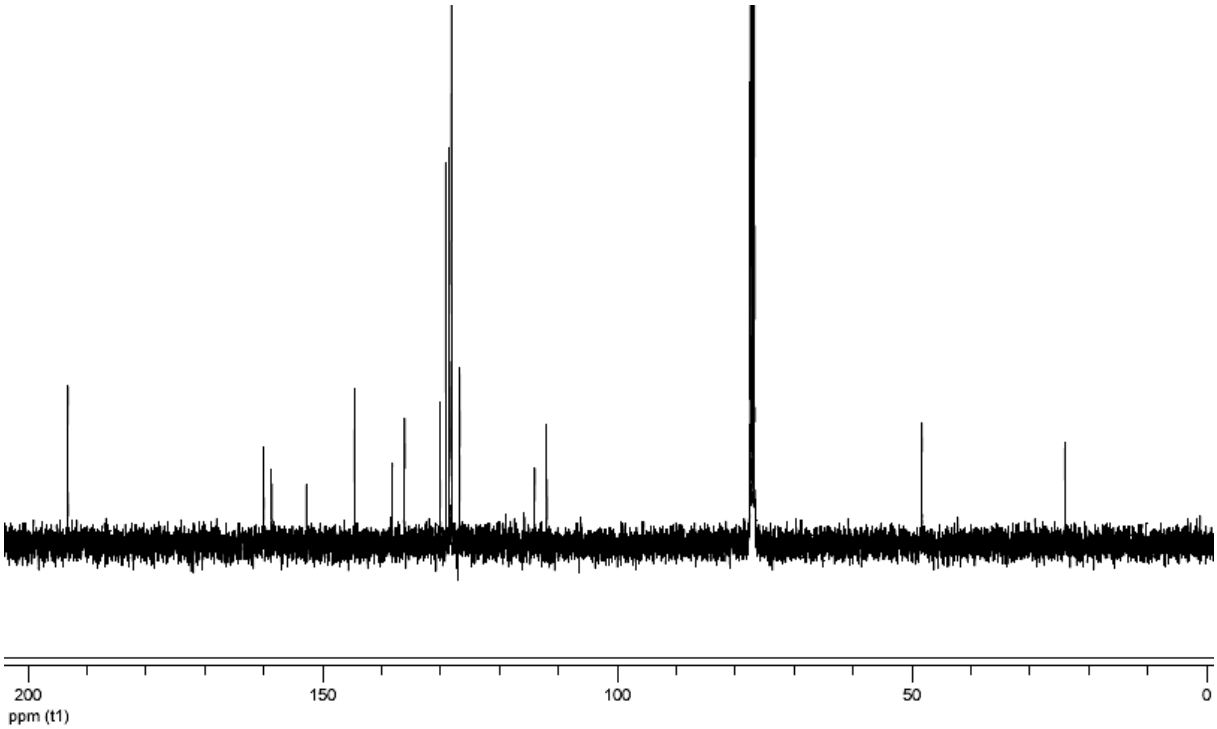
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.66 (d, *J* = 7.8 Hz, 1H), 8.60-8.56 (m, 2H), 7.83 (d, *J* = 15.8 Hz, 1H), 7.56 (s, 1H), 7.54-7.46 (m, 3H), 7.38-7.32 (m, 5H), 6.56 (dd, *J* = 15.8, 7.8 Hz, 1H), 5.55 (s, 2H), 3.00 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 193.2, 159.9, 158.6, 152.7, 144.5, 138.1, 136.0, 130.0, 129.1, 128.5, 128.4, 128.4, 128.1, 126.7, 114.0, 112.0, 48.3, 24.0.

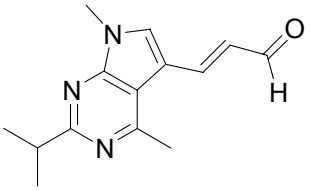
I.R. (thin film) 1664, 1614, 1556, 1448 cm^{-1}.

HRMS Calculated for $C_{23}H_{19}N_3O$ 353.1528, found 353.1530.


10.0
5.0
0.0
ppm (t1)


200
150
100
50
0
ppm (t1)

(*E*)-3-(2-isopropyl-4,7-dimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-propenal



$C_{14}H_{17}N_3O$
MW = 243.30 g.mol^{-1}

8f

General procedure using **7f** (115 mg, 0.36 mmol), *bis*(triphenylphosphine)palladium chloride (12 mg, 5 mol %) and diisopropylethylamine (60 μL, 0.36 mmol). Purification by flash chromatography (diethyl ether) gave **8f** as an orange solid.

MP 145-146 °C.

Yield 59 % (50 mg).

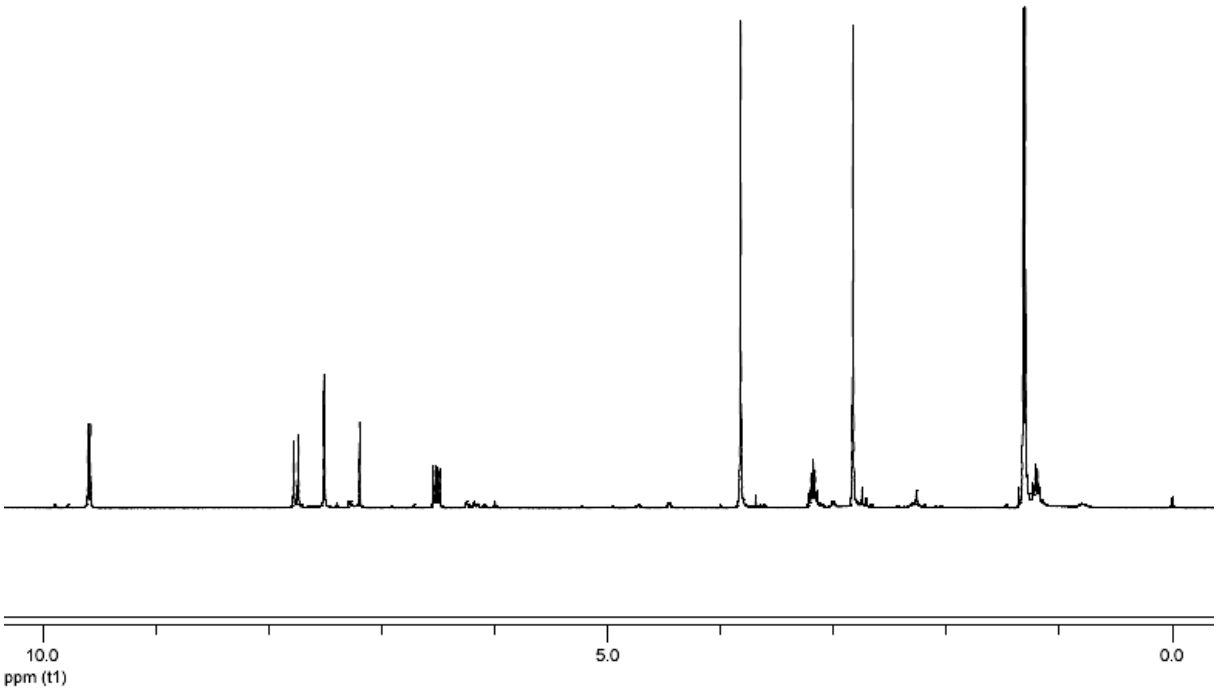
R_f 0.3 (diethyl ether).

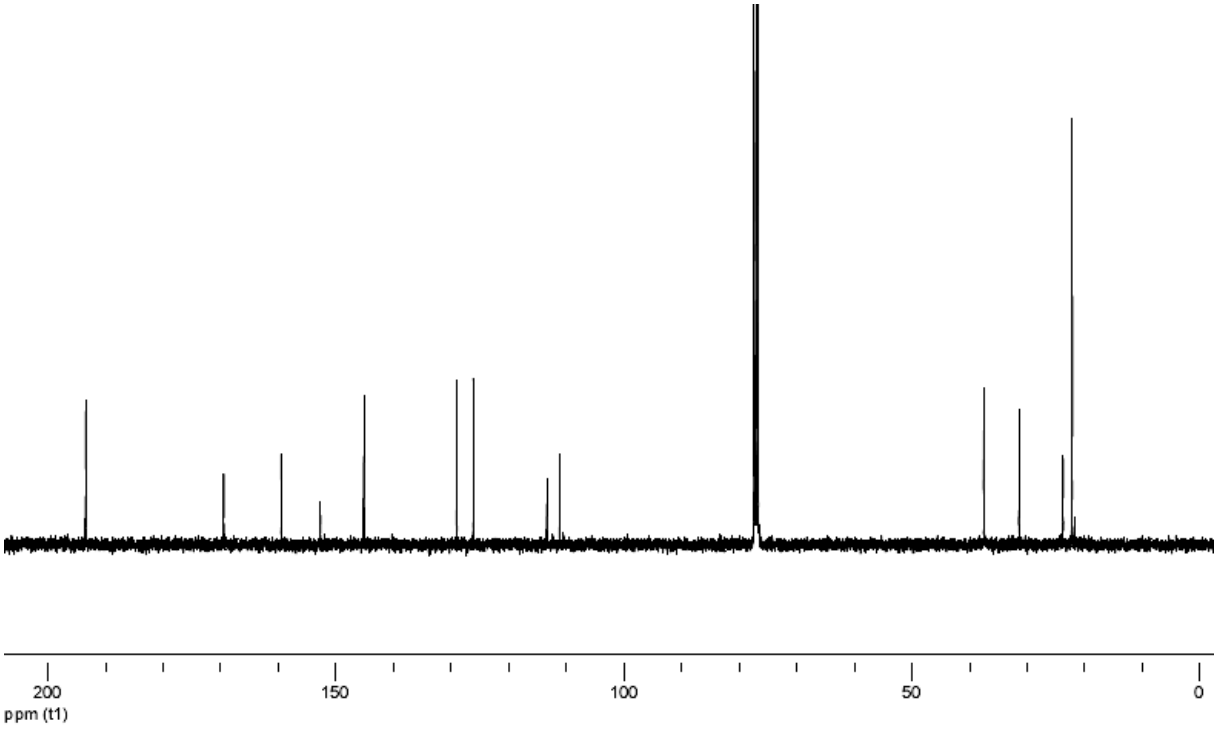
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.65 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 15.8 Hz, 1H), 7.57 (s, 1H), 6.58 (dd, *J* = 15.8, 7.8 Hz, 1H), 3.89 (s, 3H), 3.24 (sept, *J* = 6.9 Hz, 1H), 2.89 (s, 3H), 1.38 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 193.3, 169.4, 159.4, 152.6, 145.0, 128.9, 126.1, 113.3, 111.1, 37.4, 31.3, 23.7, 22.1.

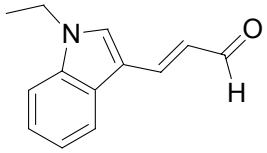
I.R. (thin film) 1696, 1669, 1616, 1532 cm^{-1}.

HRMS Calculated for $C_{14}H_{17}N_3O$ 243.1372, found 243.1366.


10.0
5.0
0.0
ppm (t1)


200
150
100
50
0
ppm (t1)

(*E*)-3-(1-ethyl-1*H*-indol-3-yl)-propenal



$C_{13}H_{13}NO$
MW = 199.25 g.mol^{-1}

8g

General procedure using **7g** (56 mg, 0.17 mmol), *bis*(triphenylphosphine)palladium chloride (6 mg, 5 mol %) and diisopropylethylamine (30 µL, 0.17 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 50:50) gave **8g** as a white solid.

MP 99-100 °C.

Yield 83 % (28 mg).

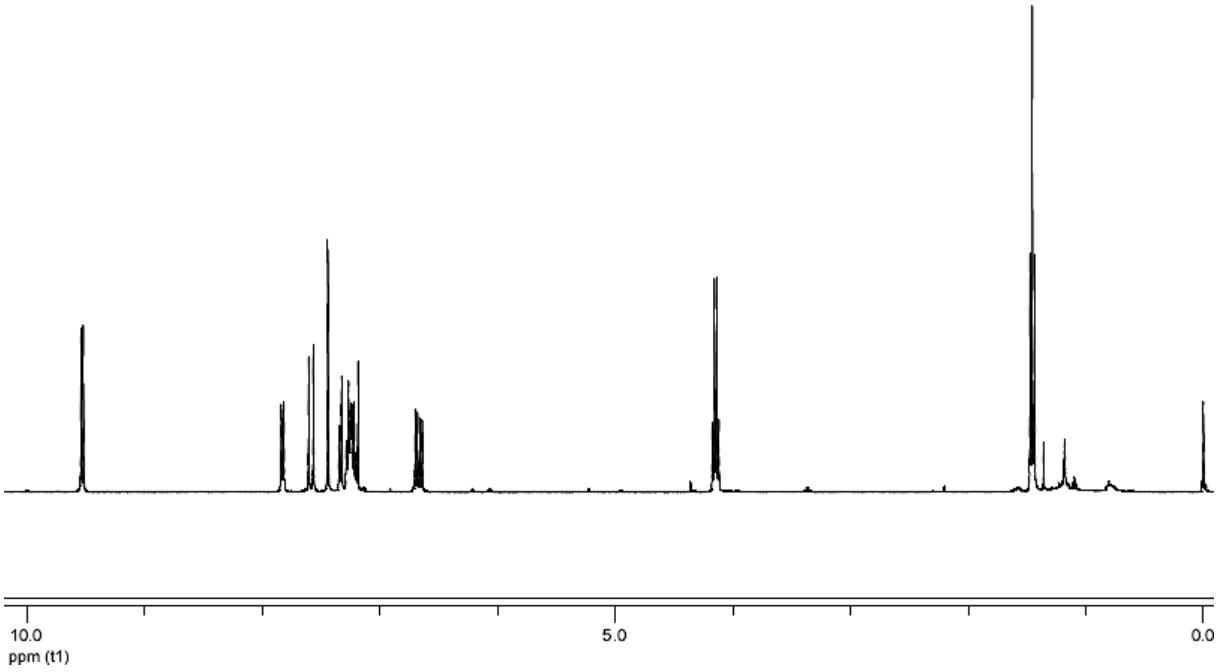
R_f 0.3 (50:50 petroleum ether / diethyl ether).

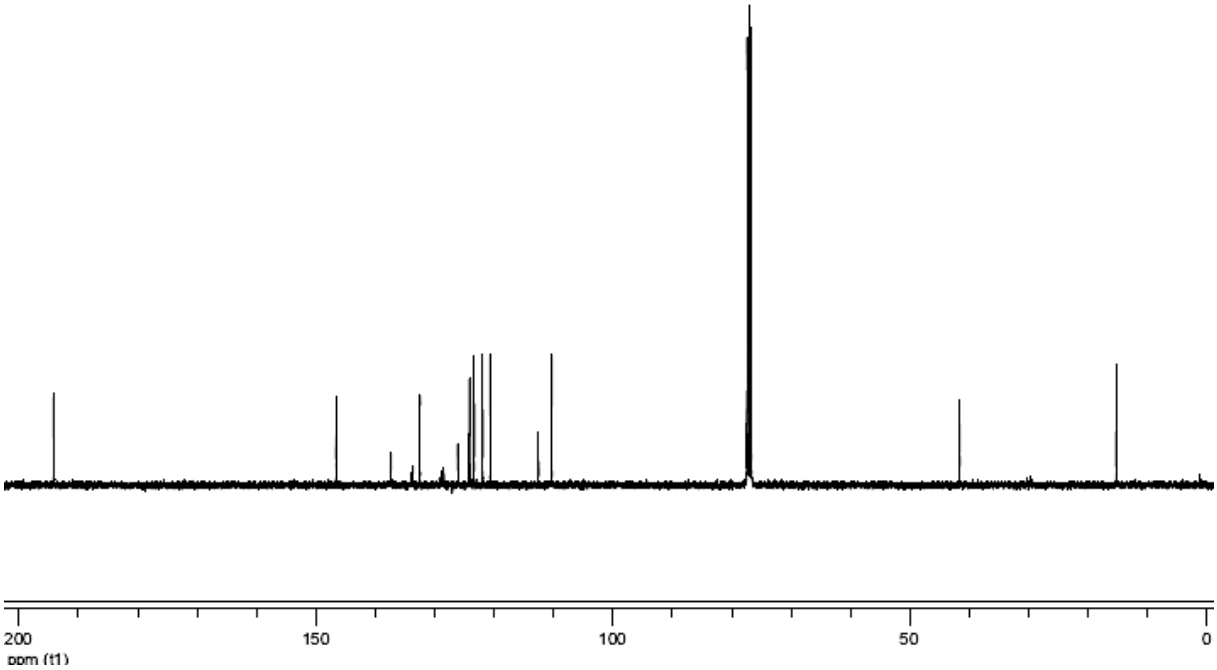
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.60 (d, *J* = 7.9 Hz, 1H), 7.90 (d, *J* = 7.4 Hz, 1H), 7.66 (d, *J* = 15.7 Hz, 1H), 7.52 (s, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.37-7.27 (m, 2H), 6.74 (dd, *J* = 15.7, 7.9 Hz, 1H), 4.22 (q, *J* = 7.3 Hz, 2H), 1.53 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 194.1, 146.5, 137.4, 132.4, 126.1, 124.1, 123.3, 121.9, 120.6, 112.5, 110.2, 41.6, 15.2.

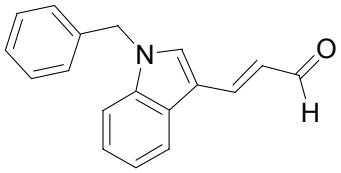
I.R. (thin film) 1663, 1611, 1521, 1388 cm^{-1}.

HRMS Calculated for $C_{13}H_{13}NO$ 199.0997, found 199.0991.


10.0
5.0
0.0
ppm (t1)


200
150
100
50
0
ppm (t1)

(*E*)-3-(1-phenyl-1*H*-indol-3-yl)-propenal



$C_{18}H_{15}NO$
MW = 261.32g .mol^{-1}

8h

General procedure using **7h** (110 mg, 0.28 mmol), *bis*(triphenylphosphine)palladium chloride (10 mg, 5 mol %) and diisopropylethylamine (48 µL, 0.28 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 50:50) gave **8h** as an orange solid.

MP 118-119 °C.

Yield 78 % (57 mg).

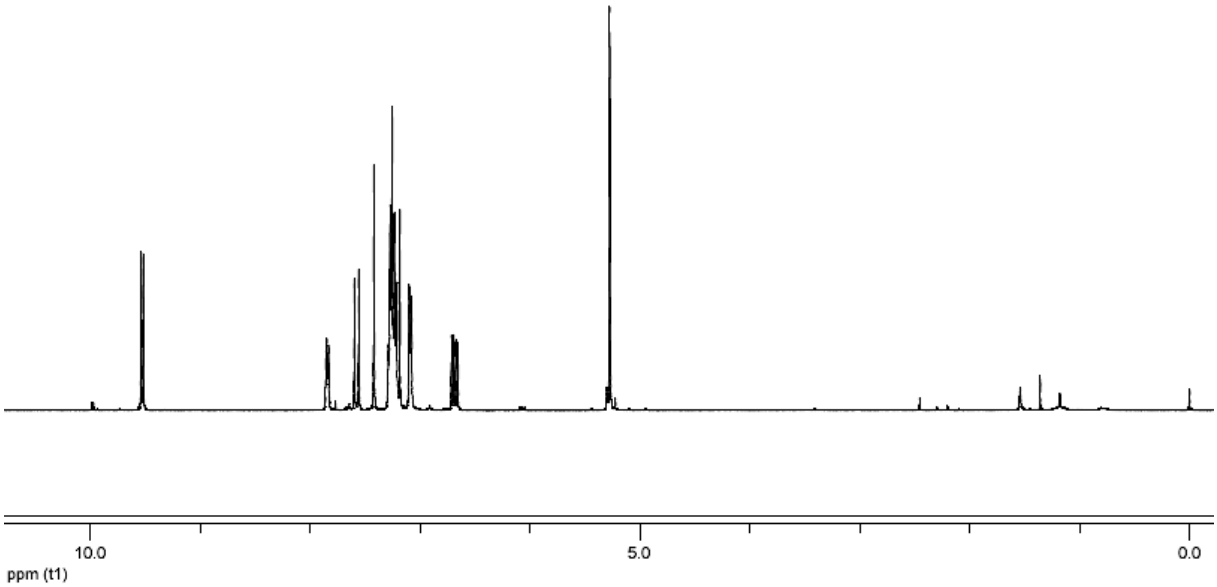
R_f 0.3 (30:70 petroleum ether / diethyl ether).

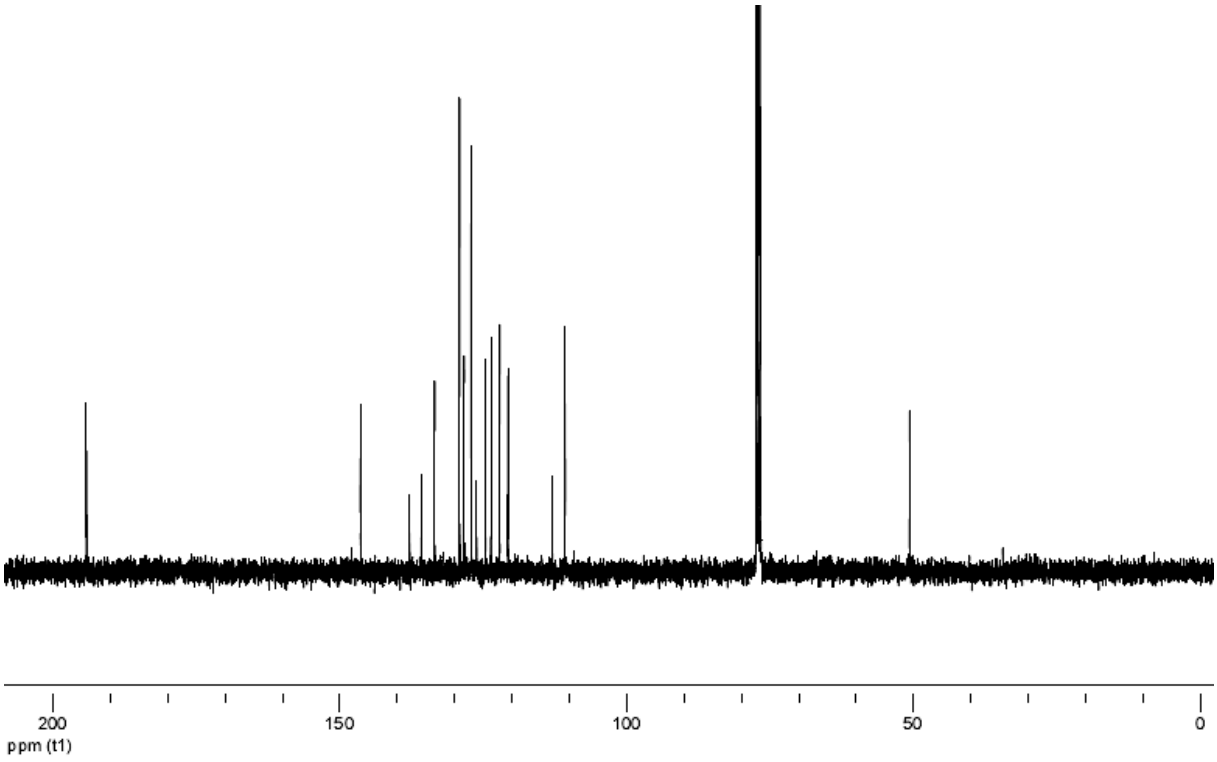
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.60 (d, *J* = 7.9 Hz, 1H), 7.95-7.90 (m, 1H), 7.65 (d, *J* = 15.8 Hz, 1H), 7.50 (s, 1H), 7.38-7.27 (m, 6H), 7.19-7.14 (m, 2H), 6.76 (dd, *J* = 15.8, 7.9 Hz, 1H), 5.35 (s, 2H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 194.1, 146.3, 137.8, 135.7, 133.4, 129.0, 128.2, 127.0, 126.1, 124.5, 123.6, 122.1, 120.6, 112.9, 110.7, 50.6.

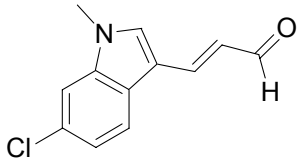
I.R. (thin film) 1658, 1605, 1520, 1467 cm^{-1}.

HRMS Calculated for $C_{18}H_{15}NO$ 261.1154, found 261.1155.


10.0
5.0
0.0
ppm (t1)


200
150
100
50
0
ppm (t1)

(*E*)-3-(6-chloro-1-methyl-1*H*-indol-3-yl)-propenal



$C_{12}H_{10}ClNO$
MW = 219.67 $g.mol^{-1}$

8i

General procedure using **7i** (105 mg, 0.31 mmol), *bis*(triphenylphosphine)palladium chloride (11 mg, 5 mol %) and diisopropylethylamine (55 µL, 0.31 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 40:60) gave **8i** as a white solid.

MP 128-129 °C.

Yield 77 % (53 mg).

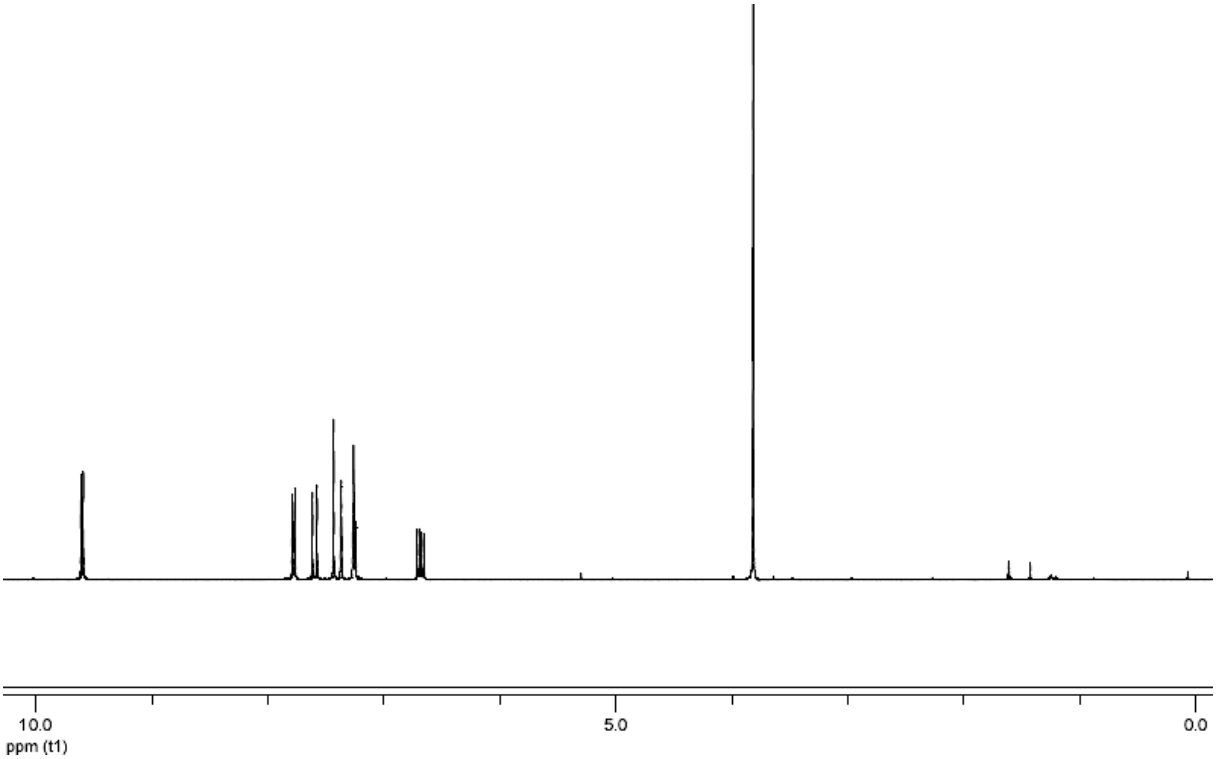
R_f 0.3 (40:60 petroleum ether / diethyl ether).

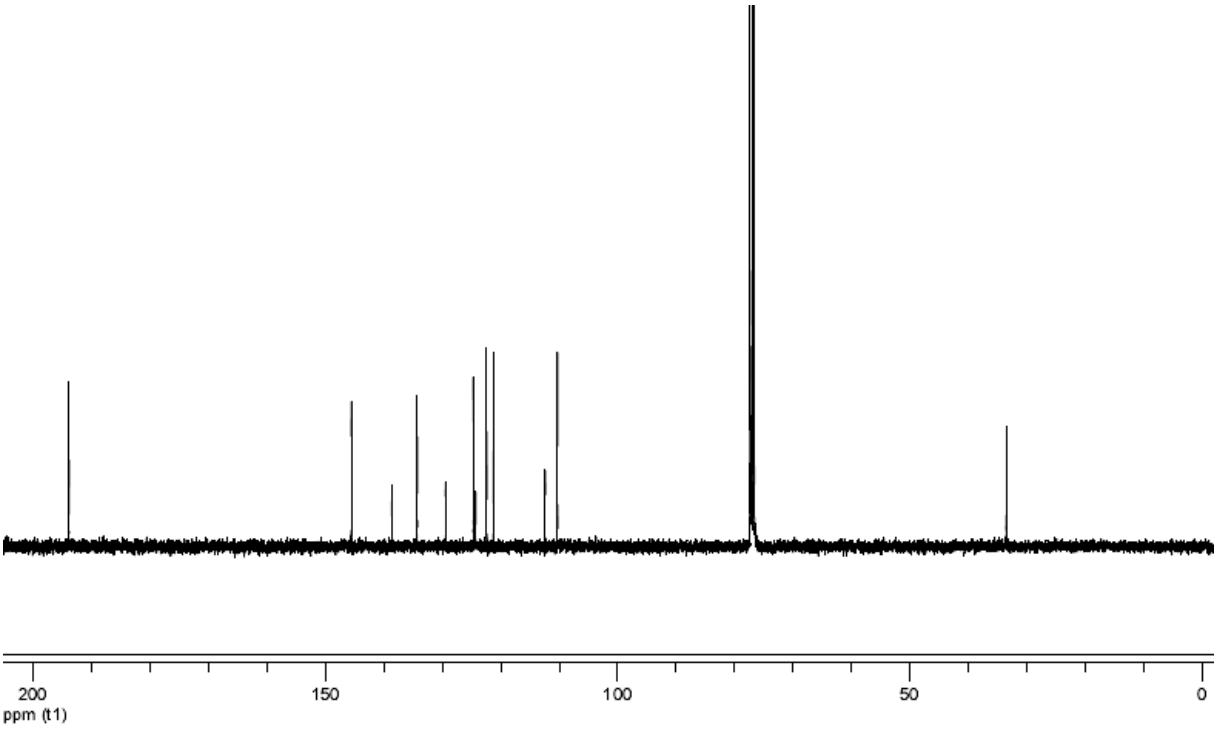
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.60 (d, *J* = 7.9 Hz, 1H), 7.78 (d, *J* = 8.5 Hz, 1H), 7.60 (d, *J* = 15.8 Hz, 1H), 7.43 (s, 1H), 7.37 (d, *J* = 1.7 Hz, 1H), 7.26 (dd, *J* = 8.5, 1.7 Hz, 1H), 6.69 (dd, *J* = 15.8, 7.9 Hz, 1H), 3.82 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 193.9, 145.6, 138.6, 134.3, 129.4, 124.7, 124.3, 122.4, 121.3, 112.4, 110.3, 33.5.

I.R. (thin film) 1664, 1612, 1526, 1467 cm^{-1}.

HRMS Calculated for [$C_{12}H_{10}ClNO$ - H] 218.0373, found 218.0379.


10.0
5.0
0.0
ppm (t1)


200
150
100
50
0
ppm (t1)

General procedure for the synthesis of tertiary amides :

Amidation step :

To a 0.5 M solution of *o*-iodobenzoic acid (1.24 g, 5 mmol) in DCM (10 mL) were added 1.1 equiv of oxalyl chloride (470 µL, 5.5 mmol) and a few drops of DMF. The resulting mixture was stirred under argon for two hours at room temperature.
A 5 mL solution containing 1.1 equiv of the corresponding amine (5.5 mmol) and 1.1 equiv of triethylamine (770 µL, 5.5 mmol) was then added dropwise to the former solution.

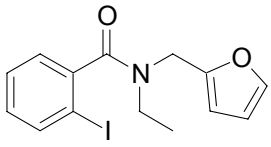
The reaction mixture was then poured onto an aqueous solution of citric acid and the aqueous layer was extracted three times with dichloromethane. After removal of the volatile materials under reduced pressure, the crude amide was directly used in the next step.

Alkylation step :

To a 0.5 M solution of amide in DMF were successively added 1.2 equiv of sodium hydride and 1.2 equiv of the corresponding alkyl halogen derivative. In the case of benzyl bromide, a catalytic amount (20 mol %) of tetrabutylammonium iodide was required. The resulting mixture was stirred under argon overnight at room temperature.

The reaction mixture was then dissolved in ether and washed ten times with 1 mL of water. After removal of the volatile materials under reduced pressure, the crude mixture was purified by flash column chromatography on silica gel to yield the corresponding tertiary amide as a mixture of two rotamers.

N-ethyl-*N*-furan-2-ylmethyl-2-iodobenzamide



$C_{14}H_{14}INO_2$
MW = 355.17 g.mol^{-1}

9a

General procedure using *o*-iodobenzoic acid (1.24 g, 5 mmol), oxalyl chloride (470 µL, 5.5 mmol), triethylamine (770 µL, 5.5 mmol) and furfurylamine (500 µL, 5.5 mmol). The crude secondary amide was used in the following step without any further purification.

To a solution of the above secondary amide (517 mg, 1.58 mmol) in DMF (3 mL) were added sodium hydride (45 mg, 1.90 mmol) and ethyl iodide (130 µL, 1.90 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 70:30) gave **9a** as an orange oil.

9a was isolated as a mixture of two rotamers in a 1.1 : 1 ratio.

Yield 63 % (360 mg).

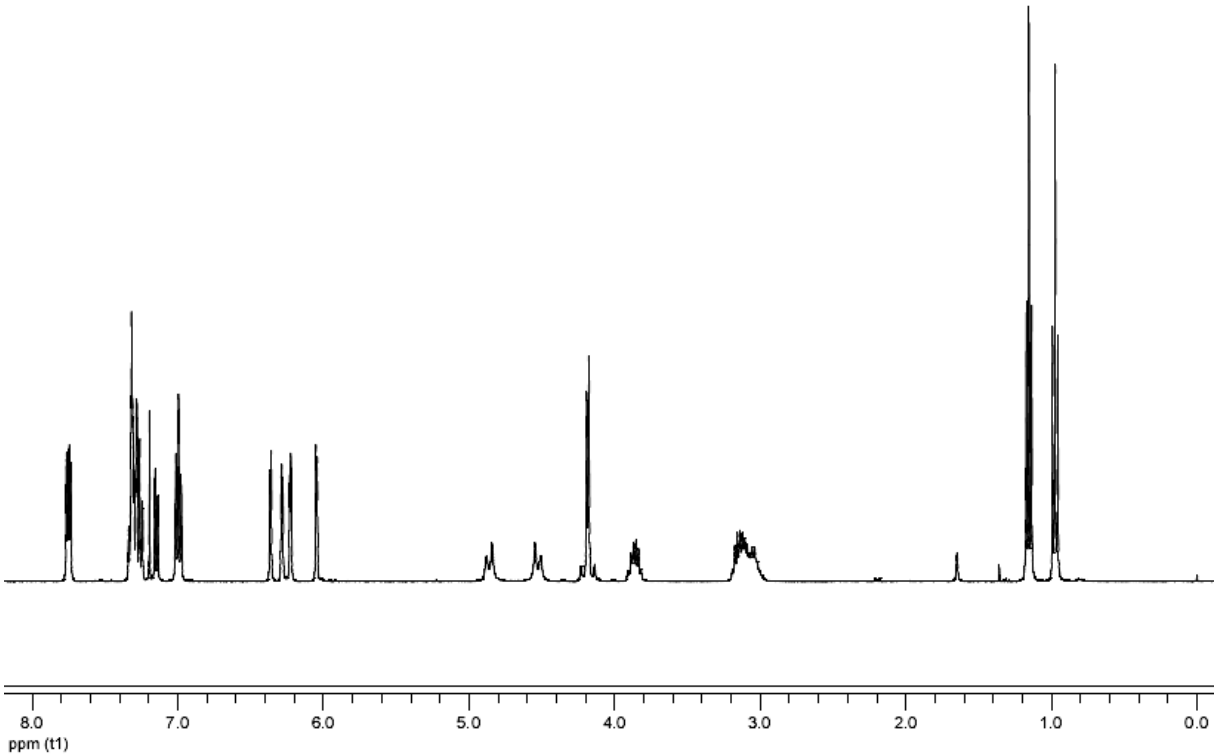
R_f 0.3 (70:30 petroleum ether / diethyl ether).

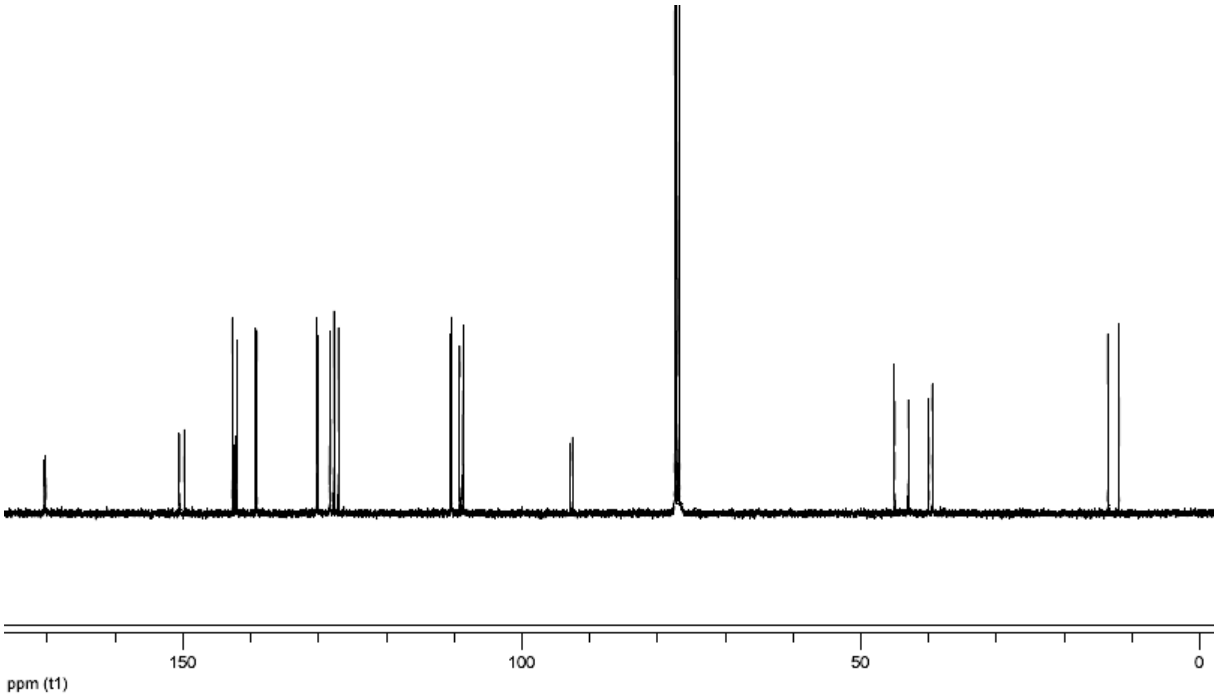
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84-7.79 (m, 2.1H), 7.42-7.30 (m, 5.2H), 7.21 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.09-7.03 (m, 2.2H), 6.43 (d, *J* = 3.1 Hz, 1H), 6.35 (dd, *J* = 3.1, 1.8 Hz, 1H), 6.29 (dd, *J* = 3.1, 1.9 Hz, 1.1H), 6.11 (d, *J* = 3.1 Hz, 1.1H), 4.93 (d, *J* = 15.2 Hz, 1H), 4.59 (d, *J* = 15.2 Hz, 1H), 4.28 (d, *J* = 15.9 Hz, 1.1H), 4.22 (d, *J* = 15.9 Hz, 1.1H), 3.99-3.87 (m, 1.1H), 3.27-3.04 (m, 3.1H), 1.22 (t, *J* = 7.1 Hz, 3.3H), 1.04 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.3, 170.2, 150.4, 149.7, 142.6, 142.3, 142.1, 142.0, 139.2, 139.0, 130.1, 130.0, 128.2, 128.1, 127.6, 126.9, 110.5, 110.3, 109.1, 108.6, 92.8, 92.4, 44.9, 42.9, 39.9, 39.3, 13.4, 11.8.

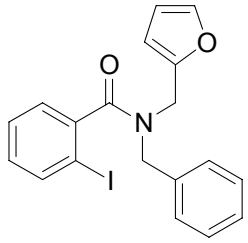
I.R. (thin film) 1638, 1424 cm^{-1}.

HRMS Calculated for $C_{14}H_{14}INO_2$ 355.0069, found 355.0074.


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


150
100
50
0
ppm (t1)

N-benzyl-*N*-furan-2-ylmethyl-2-iodobenzamide



$C_{19}H_{16}INO_2$
MW = 417.24 g.mol^{-1}

9b

Genral procedure using *N*-(furan-2-ylmethyl)-2-iodobenzamide (530 mg, 1.62 mmol) in DMF (3 mL), sodium hydride (50 mg, 1.94 mmol), benzyl bromide (240 µL, 1.94 mmol) and tetrabutylammonium iodide (120 mg, 0.32 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 70:30) gave **9b** as a white solid.

9b was isolated as a mixture of two rotamers in a 1.3 : 1 ratio.

MP 106-107 °C.

Yield 65 % (440 mg).

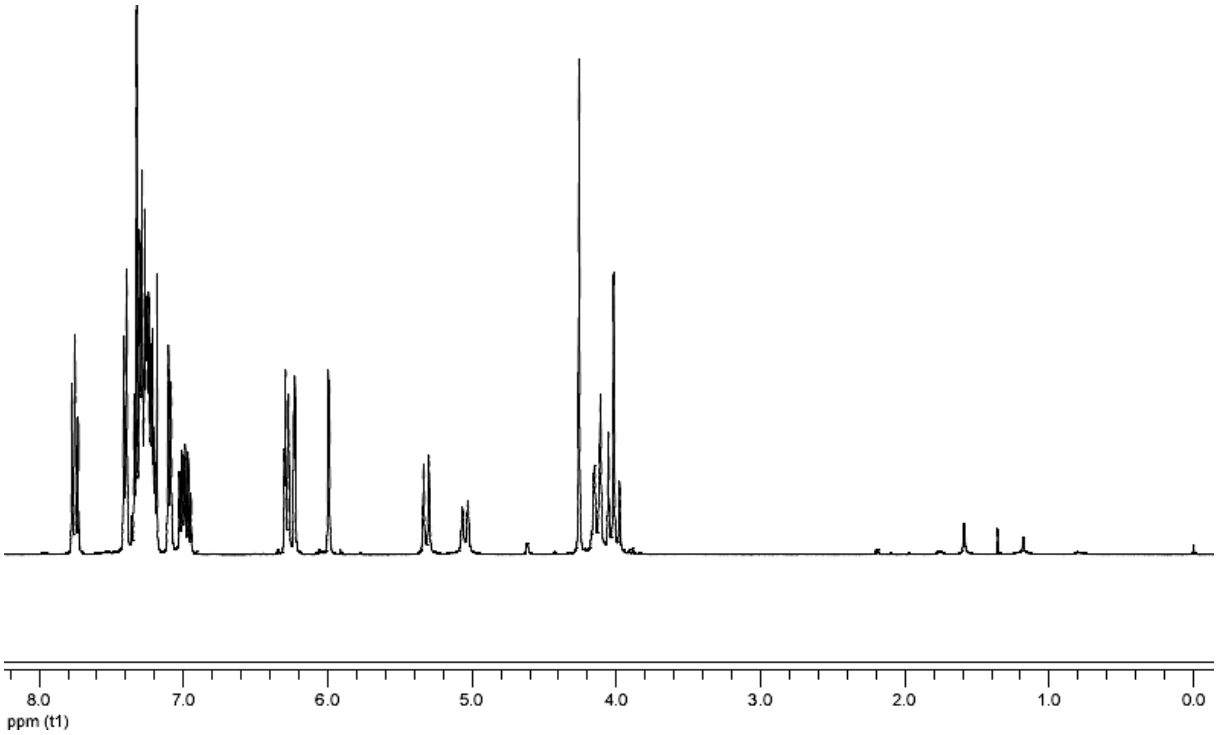
R_f 0.3 (70:30 petroleum ether / diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86-7.79 (m, 2.3H), 7.50-7.45 (m, 2.6H), 7.43-7.26 (m, 13.8H), 7.20-7.15 (m, 2H), 7.11-7.02 (m, 2.3H), 6.37 (d, *J* = 3.0 Hz, 1H), 6.35 (dd, *J* = 3.0, 1.8 Hz, 1H), 6.31 (dd, *J* = 3.1, 1.9 Hz, 1.3H), 6.07 (d, *J* = 3.1 Hz, 1.3H), 5.39 (d, *J* = 14.6 Hz, 1.3H), 5.12 (d, *J* = 15.2 Hz, 1H), 4.34 (s, 2H), 4.25-4.17 (m, 2.3H), 4.15-4.04 (m, 2.6H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.7, 150.1, 149.3, 142.7, 142.1, 141.8, 141.7, 139.3, 139.2, 136.1, 135.8, 130.2, 130.2, 129.3, 128.7, 128.5, 128.2, 128.0, 127.8, 127.6, 127.5, 127.4, 110.4, 110.3, 109.6, 109.1, 92.7, 92.5, 51.6, 46.8, 44.0, 39.6.

I.R. (thin film) 1649, 1423 cm^{-1}.

HRMS Calculated for $C_{19}H_{16}INO_2$ 417.0226, found 417.0218.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2.0
1.0
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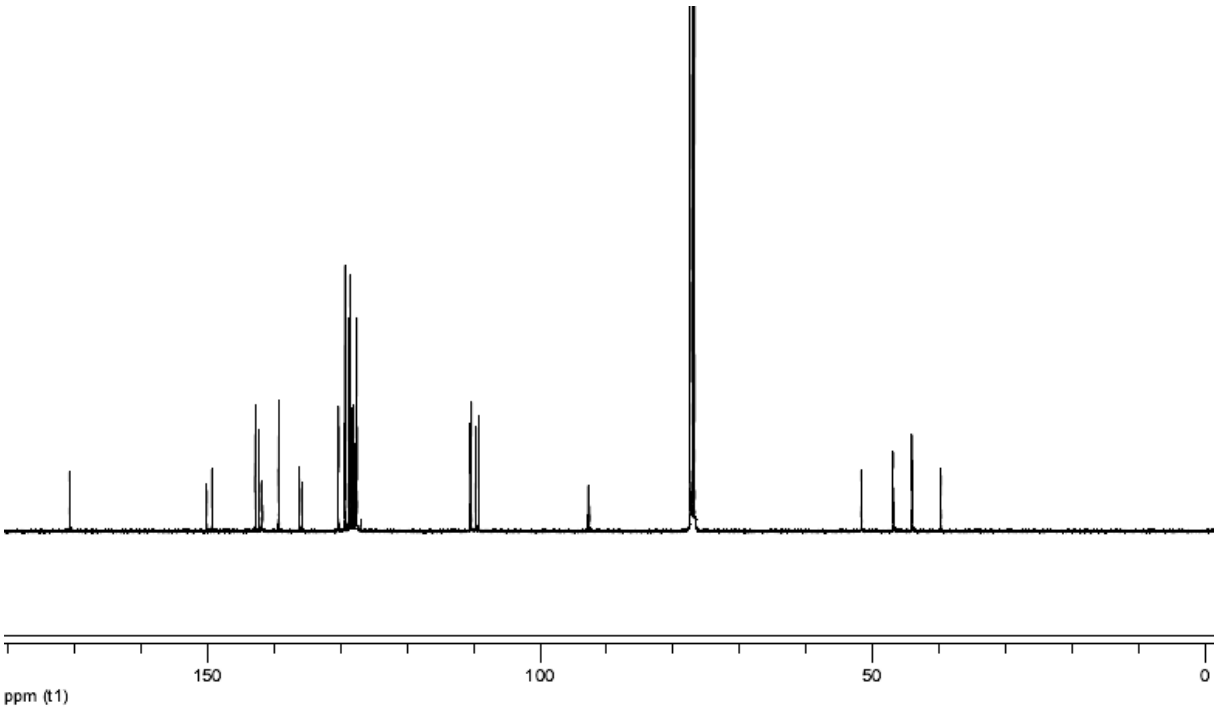
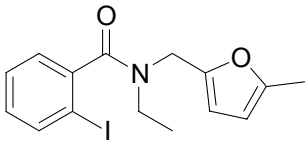
ppm (t1)


150
100
50
0
ppm (t1)

N-ethyl-2-iodo-*N*-(5-methylfuran-2-ylmethyl)-benzamide



$C_{15}H_{16}INO_2$
MW = 369.20 g.mol^{-1}

9c

General procedure using *o*-iodobenzoic acid (1.24 g, 5 mmol), oxalyl chloride (620 µL, 5.5 mmol), triethylamine (770 µL, 5.5 mmol) and furfurylamine (500 µL, 5.5 mmol). The crude secondary amide was used in the following step without any further purification.

General procedure using the above secondary amide (445 mg, 1.30 mmol) in DMF (2.5 mL), sodium hydride (40 mg, 1.56 mmol) and ethyl iodide (130 µL, 1.56 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 70:30) gave **9c** as a yellow oil.

9c was isolated as a mixture of two rotamers in a 1.4 : 1 ratio.

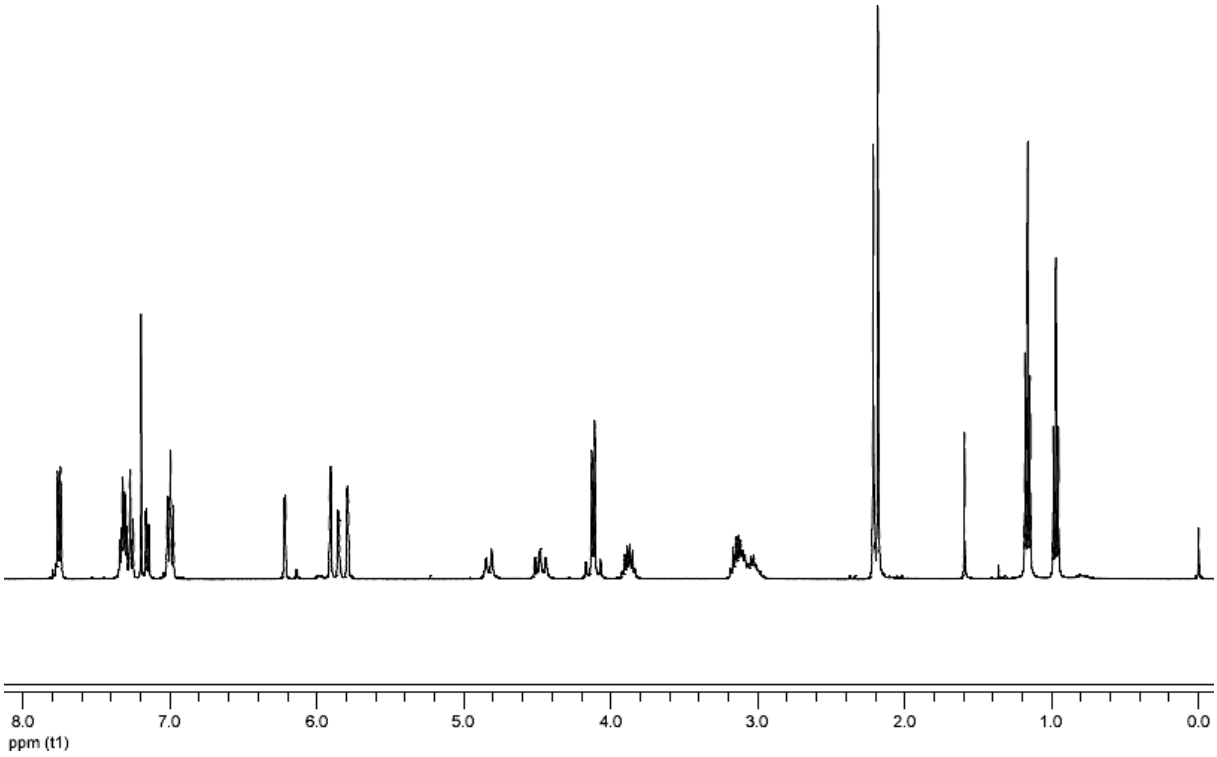
Yield 65 % (310 mg).

R_f 0.3 (40:60 petroleum ether / diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, *J* = 8.0 Hz, 2.4H), 7.41-7.31 (m, 3.8H), 7.22 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.10-7.03 (m, 2.4H), 6.28 (d, *J* = 3.0 Hz, 1H), 5.97 (d, *J* = 3.0 Hz, 1.4H), 5.92 (dd, *J* = 3.0, 0.8 Hz, 1H), 5.86 (dd, *J* = 3.0, 0.8 Hz, 1.4H), 4.89 (d, *J* = 15.2 Hz, 1H), 4.53 (d, *J* = 15.2 Hz, 1H), 4.21 (d, *J* = 15.9 Hz, 1.4H), 4.16 (d, *J* = 15.9 Hz, 1.4H), 4.00-3.89 (m, 1.4H), 3.26-3.03 (m, 3.4H), 2.28 (s, 3H), 2.25 (s, 4.2H), 1.23 (t, *J* = 7.1 Hz, 4.2H), 1.04 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.3, 170.2, 152.4, 151.7, 148.4, 147.7, 142.4, 142.2, 139.7, 139.5, 130.5, 130.5, 128.7, 128.6, 128.2, 127.5, 109.9, 109.4, 106.3, 106.1, 92.9, 92.5, 45.0, 42.6, 39.9, 39.2, 13.7, 13.6, 13.5, 11.9.

I.R. (thin film) 1638, 1424 cm^{-1}.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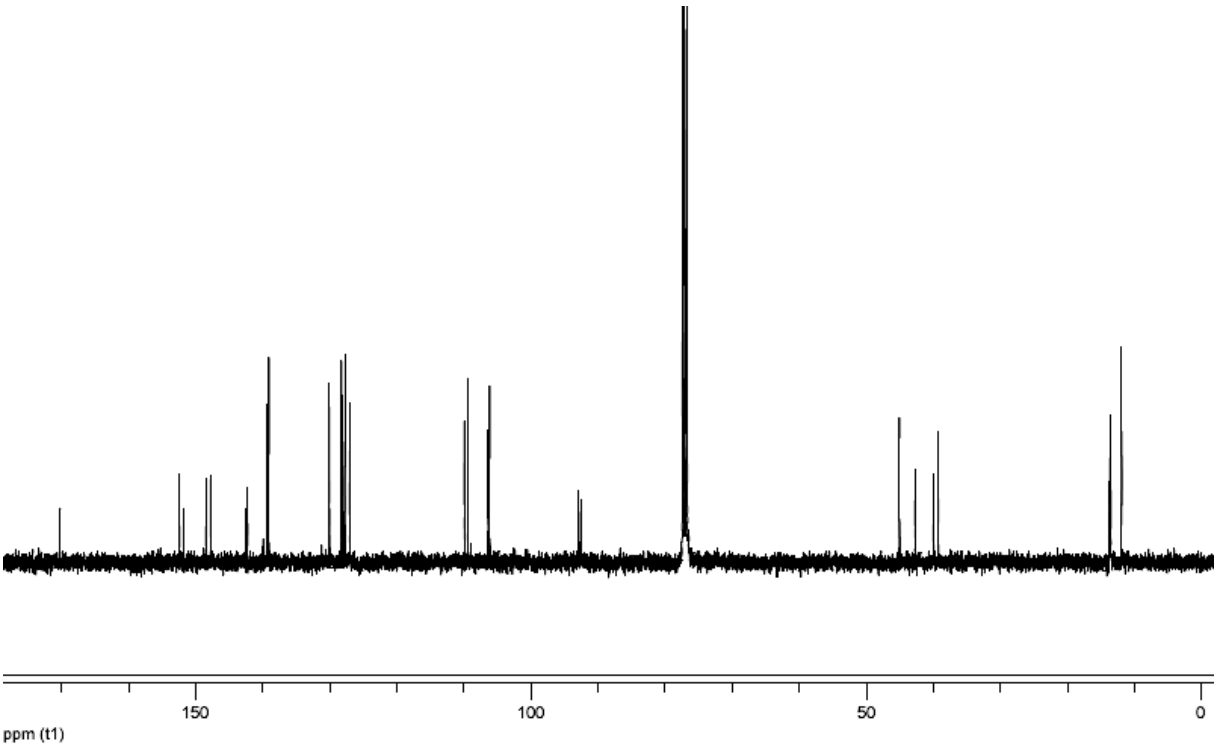
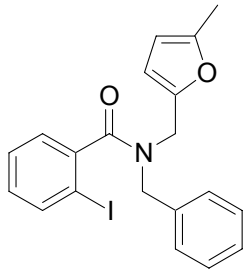
ppm (t1)


150
100
50
0
ppm (t1)

N-benzyl-2-iodo-*N*-(5-methylfuran-2-ylmethyl)-benzamide



$C_{20}H_{18}INO_2$
MW = 431.27 g.mol^{-1}

9d

General procedure using *N*-(5-methylfuran-2-ylmethyl)-2-iodobenzamide (525 mg, 1.53 mmol) in DMF (3 mL), sodium hydride (45 mg, 1.84 mmol), benzyl bromide (200 µL, 184 mmol) and tetrabutylammonium iodide (110 mg, 0.31 mmol). The reaction mixture was then dissolved in ether and washed ten times with 1 mL of water. The volatile materials were removed under reduced pressure. Purification by flash chromatography (petroleum ether-diethyl ether, 70:30) gave **9d** as a white solid.

9d was isolated as a mixture of two rotamers in a 1.6 : 1 ratio.

MP 95-96 °C.

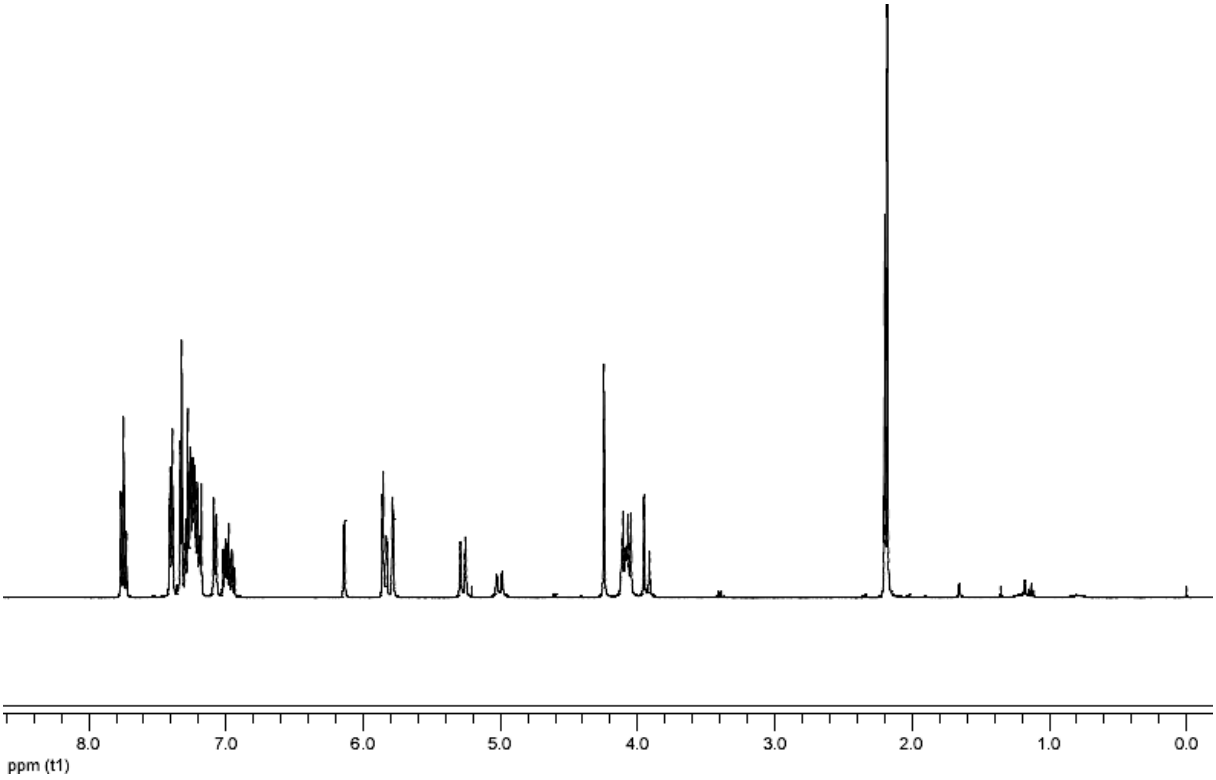
Yield 65 % (430 mg).

R_f 0.3 (70:30 petroleum ether / diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (d, *J* = 8.0 Hz, 1.6H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.50-7.46 (m, 3.2H), 7.43-7.39 (m, 3.2H), 7.39-7.26 (m, 9.8H), 7.18-7.14 (m, 2H), 7.11-7.01 (m, 2.6H), 6.22 (d, *J* = 3.0 Hz, 1H), 5.94 (d, *J* = 3.0 Hz, 1.6H), 5.91 (dd, *J* = 3.0, 0.9 Hz, 1H), 5.87 (dd, *J* = 3.0, 0.9 Hz, 1.6H), 5.36 (d, *J* = 14.5 Hz, 1.6H), 5.09 (d, *J* = 15.2 Hz, 1H), 4.33 (s, 2H), 4.21-4.12 (m, 4.2H), 4.01 (d, *J* = 15.9 Hz, 1.6H), 2.28 (s, 3H), 2.26 (s, 4.8H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.6, 152.5, 151.8, 147.9, 147.2, 141.9, 141.8, 139.3, 139.2, 136.3, 135.9, 130.1, 129.2, 128.6, 128.4, 128.2, 128.1, 128.0, 127.7, 127.5, 127.4, 127.4, 110.4, 110.0, 106.2, 106.0, 92.7, 92.5, 51.4, 46.7, 44.1, 39.8, 13.7, 13.6.

I.R. (thin film) 1638, 1421 cm^{-1}.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3.0
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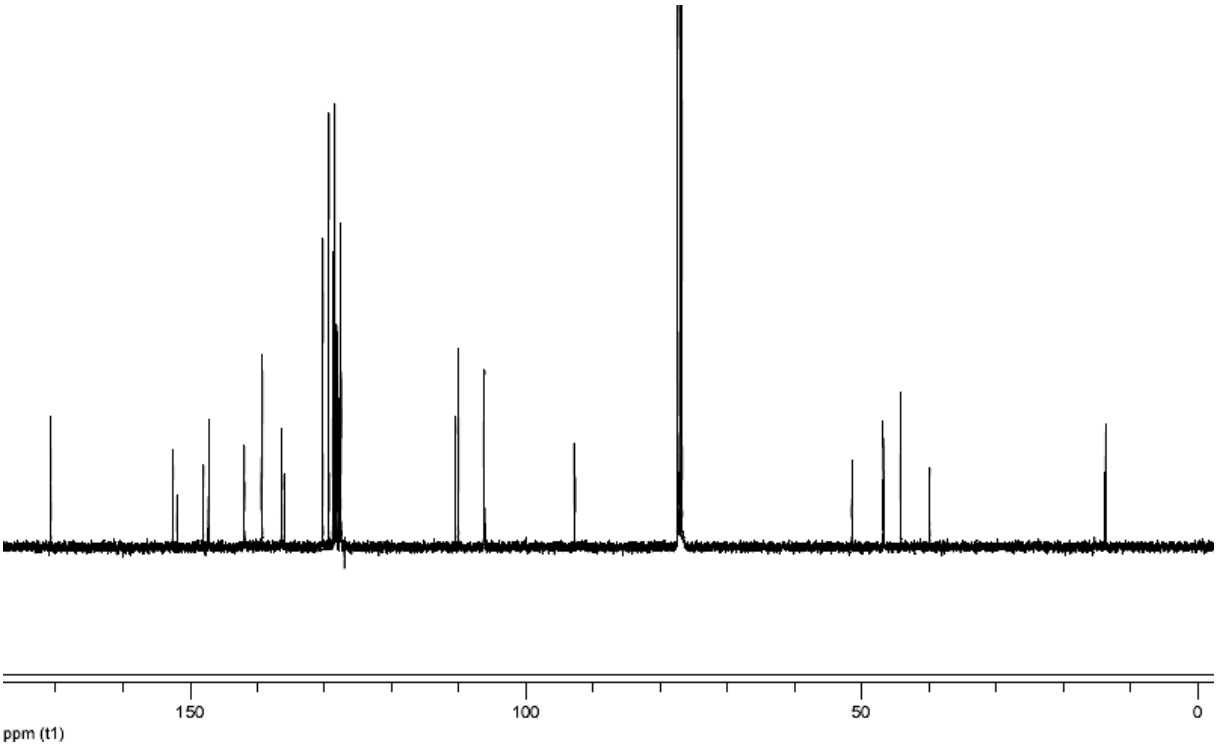
1.0
0.0
ppm (t1)

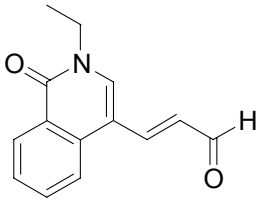

150
100
50
0
ppm (t1)

General procedure for the synthesis of isoquinolin-1-ones :

To a 0.25 M solution of tertiary amide in acetonitrile were successively added a catalytic amount of *bis*(triphenylphosphine)palladium(II) chloride (5 mol %) and 1 equiv of *N*,*N*-diisopropylethylamine. The resulting mixture was then stirred for twenty minutes at 130 °C under microwave irradiation (100 W, 13 bars).

The reaction mixture was then filtered under reduced pressure and rinsed with methanol. After removal of the volatile materials under reduced pressure, the crude mixture was purified by flash column chromatography on silica gel to yield the corresponding isoquinolin-1-one.

(*E*)-3-(2-ethyl-1-oxo-1,2-dihydroisoquinolin-4-yl)-propenal



$C_{14}H_{13}NO_2$
MW = 227.26 g.mol^{-1}

10a

General procedure using **9a** (140 mg, 0.39 mmol), *bis*(triphenylphosphine)palladium chloride (14 mg, 5 mol %) and diisopropylethylamine (70 µL, 0.39 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 20:80) gave **10a** as a white solid.

MP 194-195 °C.

Yield 52 % (46 mg).

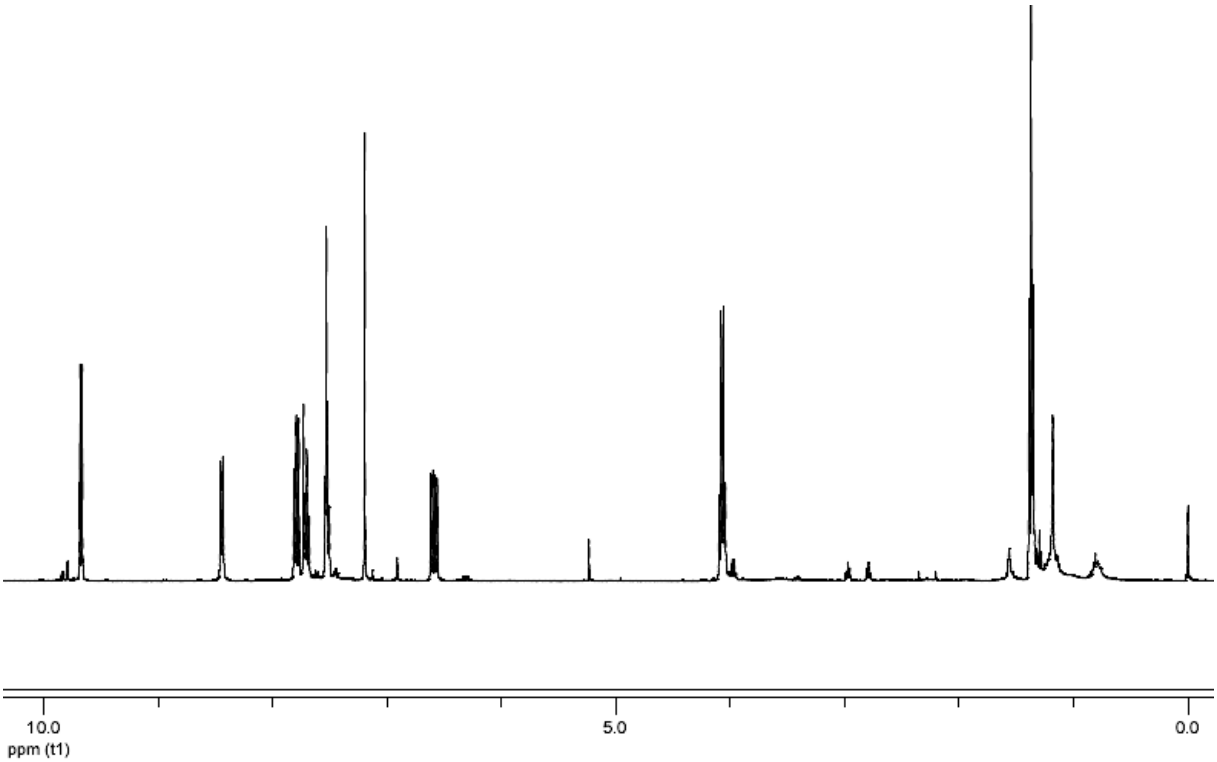
R_f 0.3 (20:80 petroleum ether / diethyl ether).

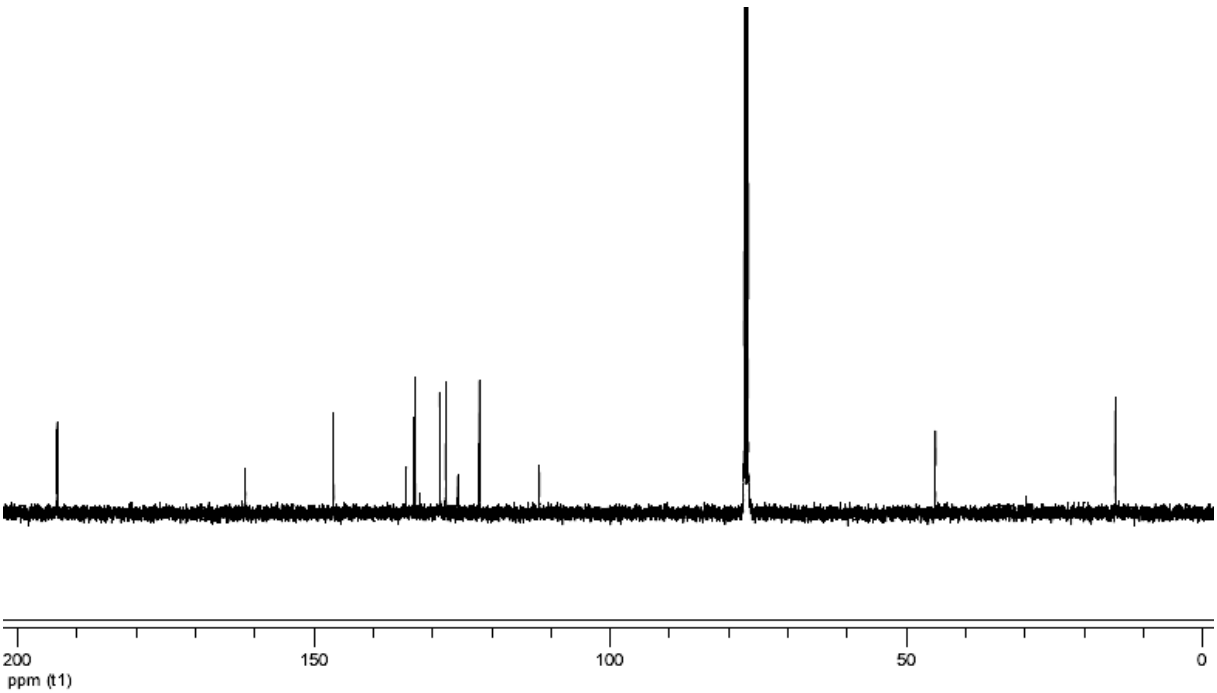
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.74 (d, *J* = 7.6 Hz, 1H), 8.51 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 15.8 Hz, 1H), 7.79-7.74 (m, 1H), 7.62-7.56 (m, 1H), 7.60 (s, 1H), 6.65 (dd, *J* = 15.8, 7.6 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 193.3, 161.5, 146.6, 134.4, 133.0, 132.8, 128.7, 127.7, 127.6, 125.7, 122.0, 111.9, 45.1, 14.7.

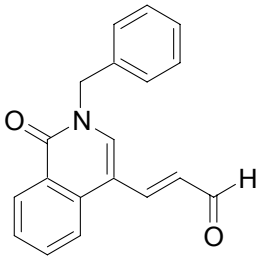
I.R. (thin film) 1680, 1647, 1604 cm^{-1}.

HRMS Calculated for $C_{14}H_{13}NO_2$ 227.0946, found 227.0948.


10.0
5.0
0.0
ppm (t1)


200
150
100
50
0
ppm (t1)

(*E*)-3-(2-benzyl-1-oxo-1,2-dihydroisoquinolin-4-yl)-propenal



$C_{19}H_{15}NO_2$
MW = 289.33 g.mol^{-1}

10b

General procedure using **9b** (180 mg, 0.43 mmol), *bis*(triphenylphosphine)palladium chloride (16 mg, 5 mol %) and diisopropylethylamine (80 µL, 0.43 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 20:80) gave **10b** as a yellow solid.

MP 164-165 °C.

Yield 56 % (70 mg).

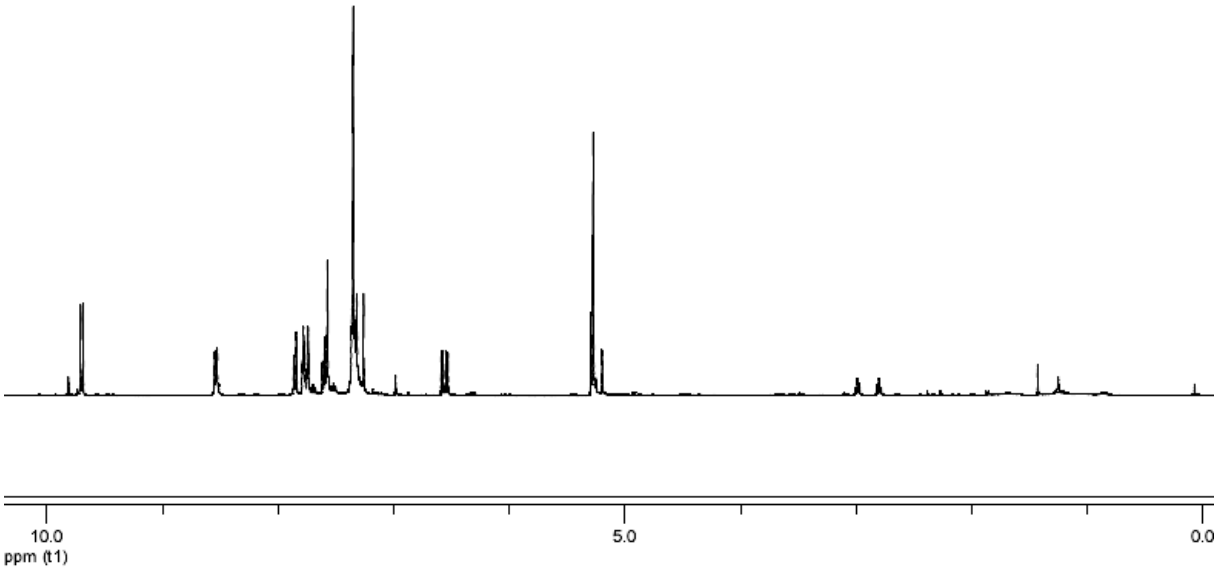
R_f 0.3 (20:80 petroleum ether / diethyl ether).

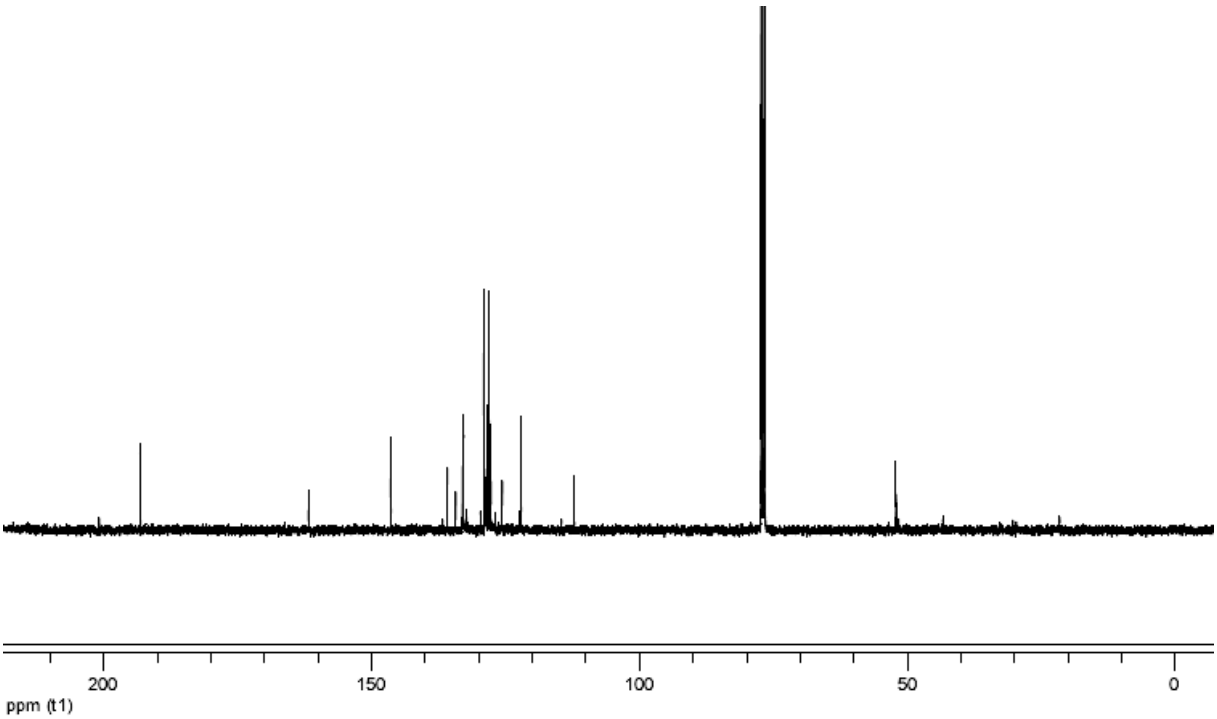
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.70 (d, *J* = 7.6 Hz, 1H), 8.54 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.80-7.75 (m, 1H), 7.76 (d, *J* = 15.8 Hz, 1H), 7.63-7.58 (m, 1H), 7.57 (s, 1H), 7.38-7.30 (m, 5H), 6.56 (dd, *J* = 15.8, 7.6 Hz, 1H), 5.28 (s, 2H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 193.2, 161.8, 146.4, 135.9, 134.3, 133.0, 132.8, 129.1, 129.0, 128.3, 128.1, 128.0, 127.8, 125.7, 122.6, 112.2, 52.1.

I.R. (thin film) 1653, 1627, 1604 cm^{-1}.

HRMS Calculated for $C_{19}H_{15}NO_2$ 289.1103, found 289.1106.


10.0
5.0
0.0
ppm (t1)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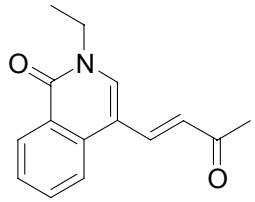
ppm (t1)

(*E*)-2-ethyl-4-(3-oxobut-1-enyl)-2*H*-isoquinolin-1-one



$C_{15}H_{15}NO_2$
MW = 241.29 g.mol^{-1}

10c

General procedure using **9c** (155 mg, 0.42 mmol), *bis*(triphenylphosphine)palladium chloride (15 mg, 5 mol %) and diisopropylethylamine (75 µL, 0.42 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 10:90) gave **10c** as a white solid.

MP 98-99 °C.

Yield 74 % (75 mg).

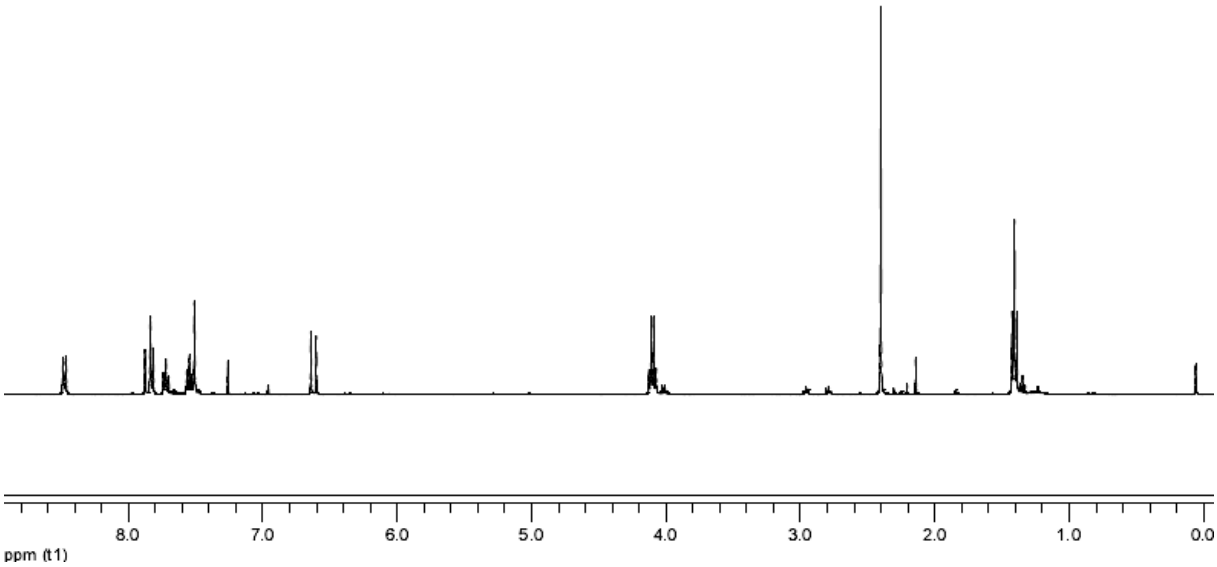
R_f 0.3 (10:90 petroleum ether / diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.48 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.86 (d, *J* = 16.0 Hz, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.75-7.69 (m, 1H), 7.56-7.52 (m, 1H), 7.51 (s, 1H), 6.62 (d, *J* = 16.0 Hz, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 197.7, 161.5, 137.3, 134.8, 132.6, 131.8, 128.5, 127.4, 126.4, 125.6, 122.3, 112.3, 44.8, 27.9, 14.7.

I.R. (thin film) 1649, 1622, 1605 cm^{-1}.

HRMS Calculated for $C_{15}H_{15}NO_2$ 241.1103, found 241.1114.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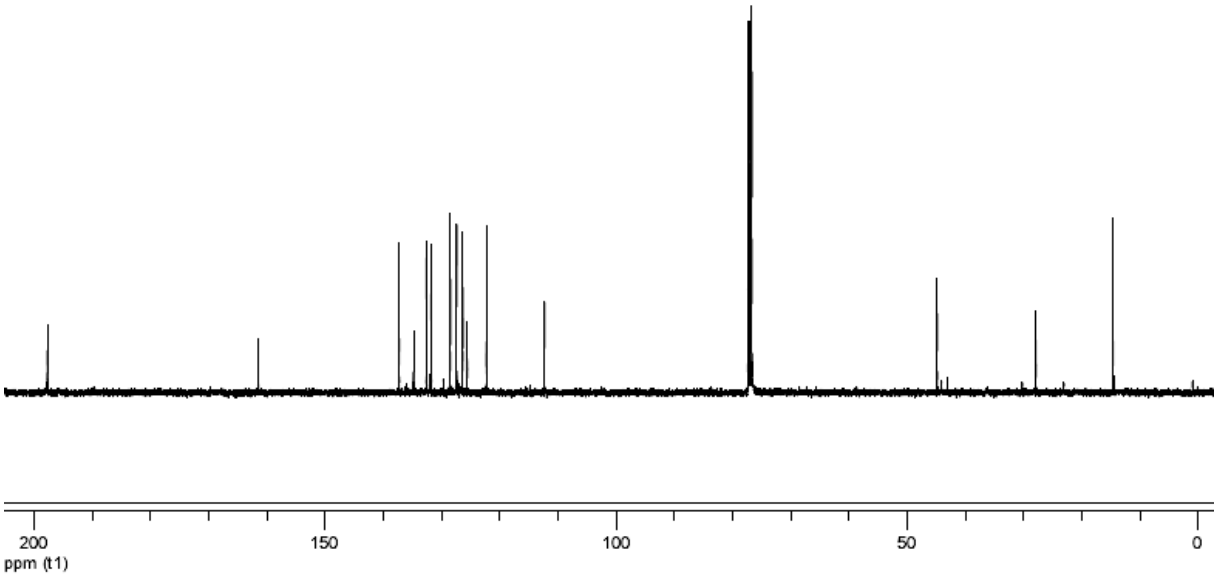
4.0
3.0
2.0
1.0
0.0
ppm (t1)


200
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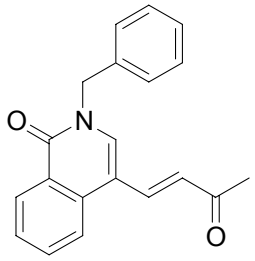
ppm (t1)

(*E*)-2-benzyl-4-(3-oxobut-1-enyl)-2*H*-isoquinolin-1-one



$C_{20}H_{17}NO_2$
MW = 303.35 $g.mol^{-1}$

10d

General procedure using **9d** (150 mg, 0.35 mmol), *bis*(triphenylphosphine)palladium chloride (12 mg, 5 mol %) and diisopropylethylamine (60 μL, 0.35 mmol). Purification by flash chromatography (petroleum ether-diethyl ether, 20:80) gave **10d** as a white solid.

MP 155-156 °C.

Yield 80 % (85 mg).

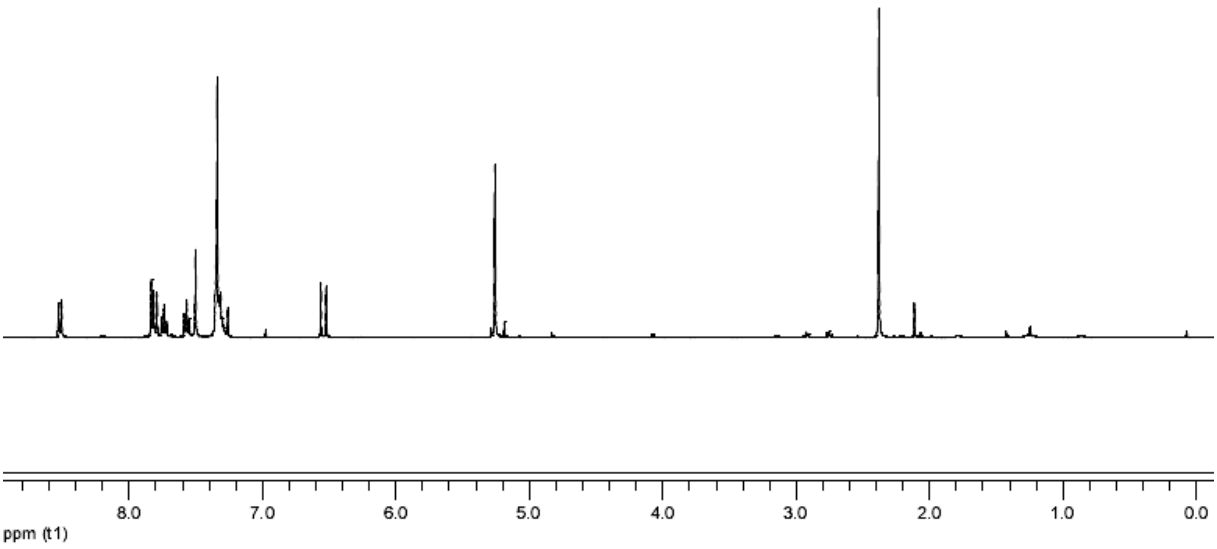
R_f 0.3 (20:80 petroleum ether / diethyl ether).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.52 (d, *J* = 7.7 Hz, 1H), 7.83 (d, *J* = 7.0 Hz, 1H), 7.81 (d, *J* = 16.0 Hz, 1H), 7.77-7.71 (m, 1H), 7.60-7.54 (m, 1H), 7.50 (s, 1H), 7.36-7.28 (m, 5H), 6.54 (d, *J* = 16.0 Hz, 1H), 5.26 (s, 2H), 2.38 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 197.7, 161.8, 137.2, 136.1, 134.8, 132.8, 131.7, 129.0, 128.8, 128.1, 128.0, 127.6, 125.6, 122.4, 112.6, 52.0, 27.8.

I.R. (thin film) 1649, 1622, 1602 cm^{-1}.

HRMS Calculated for $C_{20}H_{17}NO_2$ 303.1259, found 303.1271.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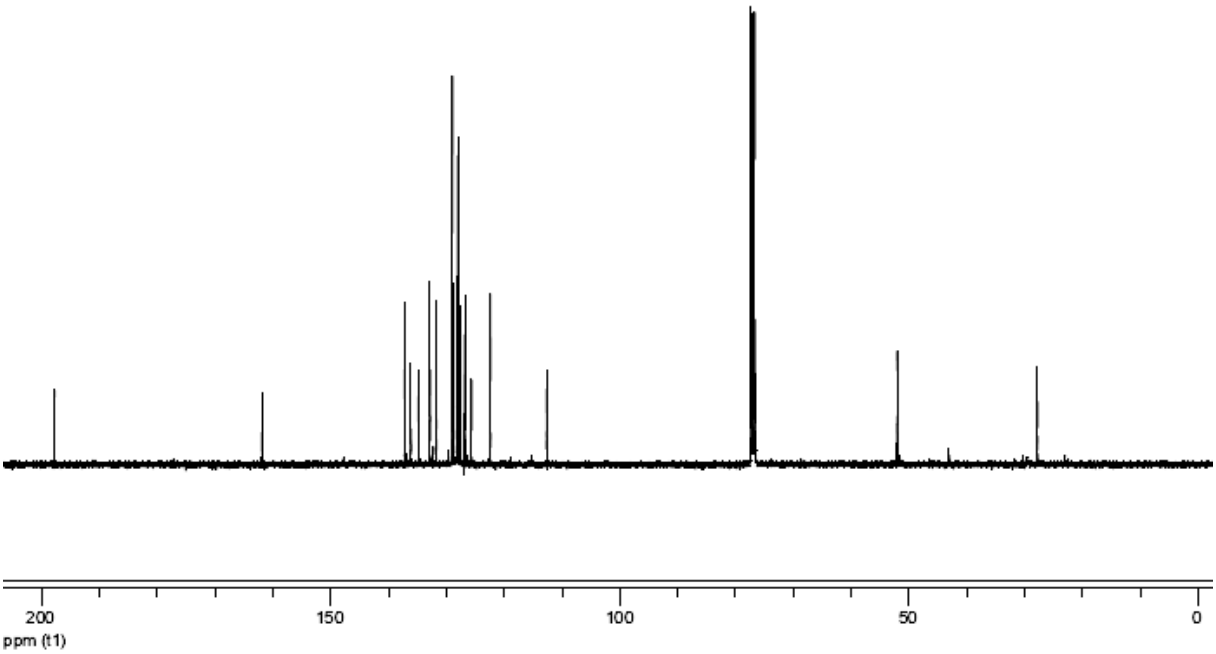
4.0
3.0
2.0
1.0
0.0
ppm (t1)


200
150
100
50
0
ppm (t1)