SUPPORTING INFORMATION SECTION

Intramolecular Hydrogen Bonding in Medicinal Chemistry

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Table of Contents

S2-48: Synthesis and Characterisation Data for Model Compounds

All compounds were purified by chromatography and / or crystallization – if necessary - as indicated below individually to a purity of at least 95 % as determined by HPLC. Proton NMR's were obtained on a Bruker AVIII 600 CP instrument (600 MHz) with chemical shifts (δ in ppm) reported relative to tetramethylsilane as an internal standard; 13C NMR were recorded at 150.9 MHz. Column chromatography was carried out on silica gel 60 (Chemie Brunschwig, 32-60 mesh, 60Å). LC/MS analytics was done on an Agilent 1200 RRLC with Agilent 6520 QTOF. Separation was achieved on a standard C18 column eclipse plus 2.1*50 mm filled with 1.8 µm particles. A gradient was applied from 5% water with 0.01 % formic acid to 99 % of a mixture containing 20% 2-propanol, 80 % acetonitrile and 0.01 % formic acid. To improve ionization, especially in negative mode, post column a splitting and dilution interface was built from two T-pieces and an additional isocratic pump with diluted ammonia in methanol. For simultaneous ESI and APCI ionization, a multimode source was used with standard parameters. For very high resolution MS a ThermoFinigan LTQ-FTMS was used.

1a] 2-Ethyl-*N*,*N*-dimethyl-benzamide

2-Ethyl-benzoic acid (510 mg, 3.40 mmol) was dissolved in 8 ml of toluene and treated at 0°C with 575 µl (6.79 mmol, 2 eq.) of oxalyl chloride and 1 drop of DMF. The mixture was kept for 2 h at ambient temperature. Careful evaporation left the acid chloride as pale yellow oil which was reacted with 3.4 ml of 2M dimethylamine (2 eq.) in THF; stirring was continued for 1 h. Pouring onto crashed ice, twofold extraction with ethyl acetate, washing with water, drying over $MgSO_4$, and evaporation gave 588 mg of the title compound as light yellow oil.

MS: $C_{11}H_{15}NO$, expected: 177.1154, found: 177.1151.

IR:

1a = 2-Ethyl-N,N-dimethyl-benzamide

17 Dec 2009

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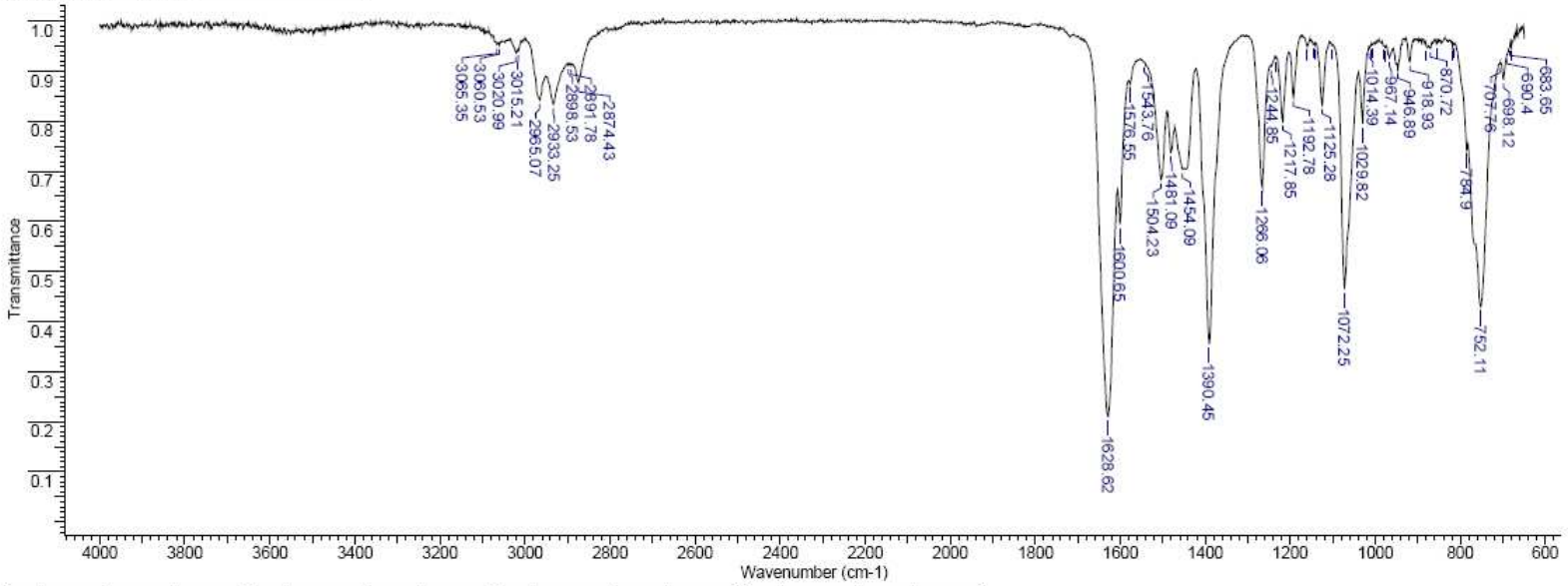

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2	683.65	0.949	VW	15	967.14	0.926	W	28	1192.78	0.848	W	41	2874.43	0.876	W
3	690.40	0.933	VW	16	976.78	0.947	VW	29	1217.85	0.800	W	42	2891.78	0.912	W
4	698.12	0.884	W	17	981.61	0.951	VW	30	1233.27	0.926	W	43	2898.53	0.912	W
5	707.76	0.914	W	18	1006.68	0.952	VW	31	1244.85	0.910	W	44	2933.25	0.834	W
6	752.11	0.430	S	19	1010.53	0.950	VW	32	1266.06	0.668	M	45	2965.07	0.843	W
7	784.90	0.743	M	20	1014.39	0.945	VW	33	1390.45	0.356	S	46	3015.21	0.940	VW
8	814.79	0.953	VW	21	1029.82	0.795	W	34	1454.09	0.704	M	47	3020.99	0.936	VW
9	818.65	0.948	VW	22	1072.25	0.466	S	35	1481.09	0.738	M	48	3060.53	0.952	VW
10	856.25	0.954	VW	23	1101.17	0.951	VW	36	1504.23	0.684	M	49	3065.35	0.953	VW
11	870.72	0.946	VW	24	1125.28	0.833	W	37	1543.76	0.916	W				
12	880.36	0.948	VW	25	1142.64	0.952	VW	38	1576.55	0.876	W				
13	918.93	0.919	W	26	1145.53	0.954	VW	39	1600.65	0.594	M				

1H-NMR:

1a = 2-Ethyl-N,N-dimethyl-benzamide

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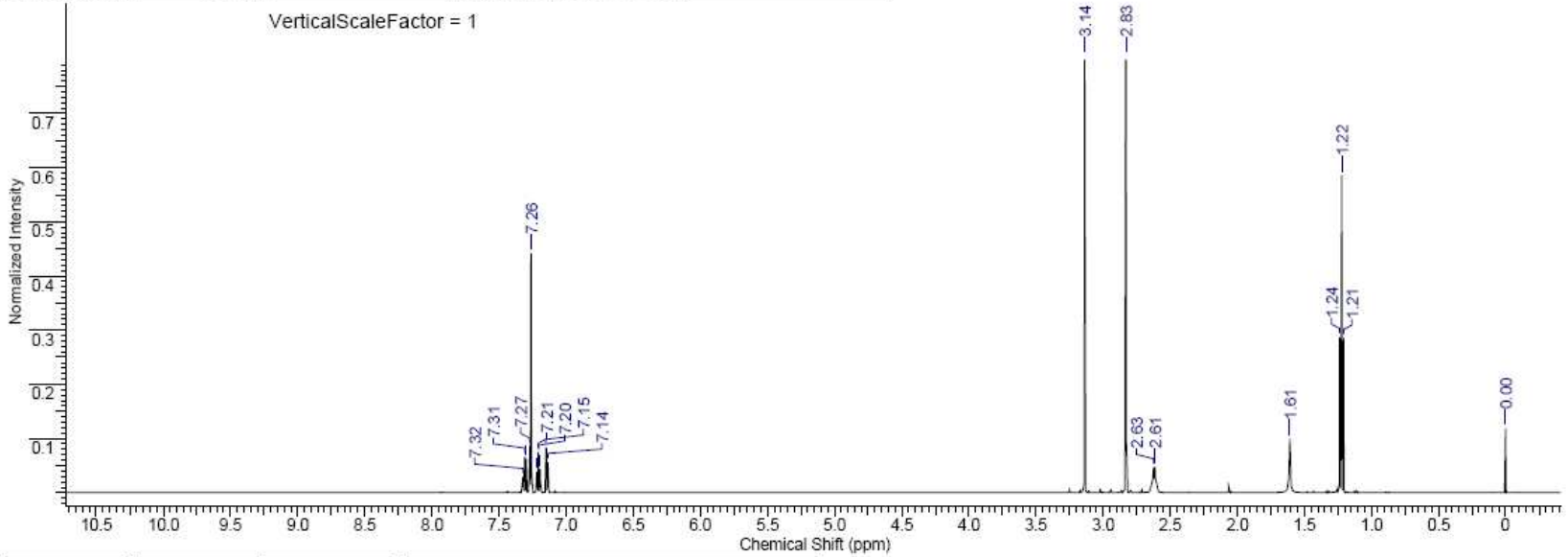

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1.22	733.6	7.15	4290.6	7.27	4362.9
1.24	741.2	7.19	4316.2	7.27	4363.6
1.61	965.7	7.19	4317.6	7.29	4377.7
2.61	1567.9	7.20	4323.7	7.30	4379.3
2.63	1575.5	7.21	4325.1	7.31	4385.2
2.83	1697.2	7.22	4331.0	7.31	4386.6
3.14	1882.6	7.22	4332.3	7.32	4392.8
7.13	4281.7	7.26	4355.3	7.32	4394.2

No	Color	Structure	Visible
1			True

13C-NMR:

1a = 2-Ethyl-N,N-dimethyl-benzamide

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Comment	ARC= 2009000161424 Labjournal 23718B092 Labgroup ID mohrp Contact Person Name Stefan Buerli Contact Person Address 092/4.36A Theme 7299				
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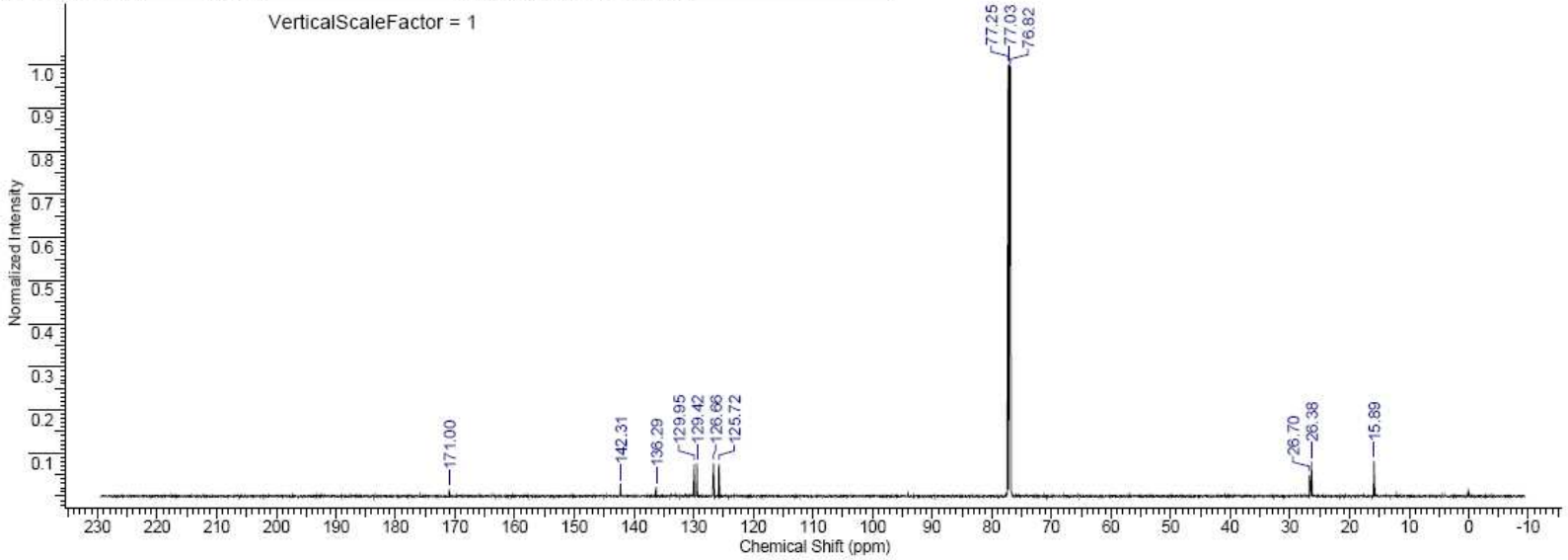

(ppm)	(Hz)
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26.38	3981.4
26.70	4029.2
76.82	11594.2
77.03	11626.1
77.25	11658.3
125.72	18973.9

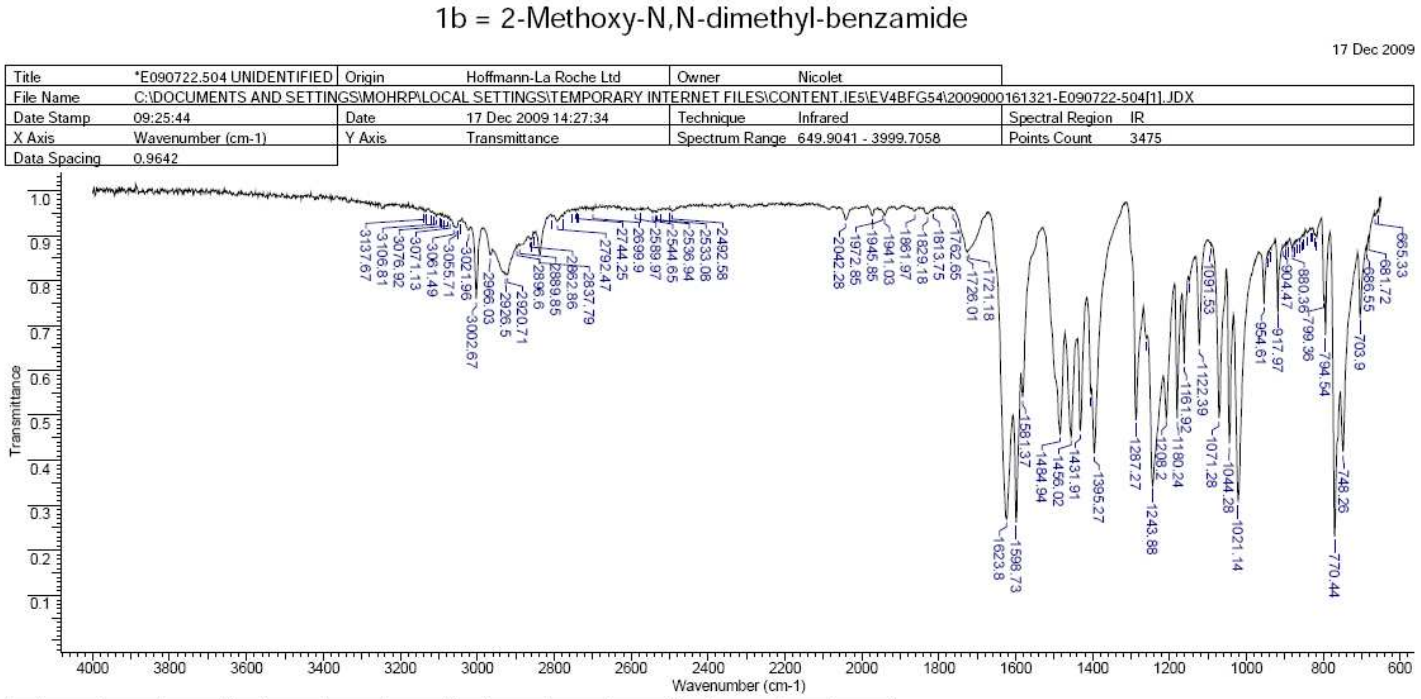
(ppm)	(Hz)
126.66	19114.8
129.42	19532.4
129.95	19611.4
136.29	20569.5
142.31	21477.3
171.00	25806.8

No	Color	Structure	Visible
1			True

1b] 2-Methoxy-*N*,*N*-dimethyl-benzamide

MS: $C_{10}H_{13}NO_2$, expected: 179.0946, found: 179.0948.

IR:



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2	665.33	0.943	VW	27	954.61	0.748	M	52	1829.18	0.948	VW	77	2862.86	0.892	W
3	681.72	0.886	W	28	1021.14	0.308	VS	53	1861.97	0.954	VW	78	2889.85	0.878	W
4	686.55	0.867	W	29	1044.28	0.438	S	54	1941.03	0.945	VW	79	2896.60	0.874	W
5	703.90	0.720	M	30	1071.28	0.494	S	55	1945.85	0.952	VW	80	2920.71	0.813	W
6	748.26	0.419	S	31	1091.53	0.880	W	56	1972.85	0.944	VW	81	2926.50	0.812	W
7	770.44	0.231	VS	32	1122.39	0.656	M	57	2042.28	0.935	W	82	2966.03	0.857	W
8	794.54	0.679	M	33	1148.42	0.800	W	58	2492.58	0.955	VW	83	3002.67	0.759	M
9	799.36	0.758	M	34	1161.92	0.616	M	59	2501.26	0.957	VW	84	3021.96	0.912	W
10	816.72	0.893	W	35	1180.24	0.494	S	60	2521.51	0.956	VW	85	3044.13	0.932	W
11	822.50	0.901	W	36	1208.20	0.494	S	61	2533.08	0.952	VW	86	3051.85	0.918	W
12	828.29	0.914	W	37	1243.88	0.345	S	62	2536.94	0.952	VW	87	3055.71	0.918	W
13	833.11	0.913	W	38	1260.27	0.672	M	63	2544.65	0.951	VW	88	3061.49	0.920	W
14	841.79	0.905	W	39	1287.27	0.490	S	64	2575.51	0.957	VW	89	3071.13	0.933	W

1H-NMR:

1b = 2-Methoxy-N,N-dimethyl-benzamide

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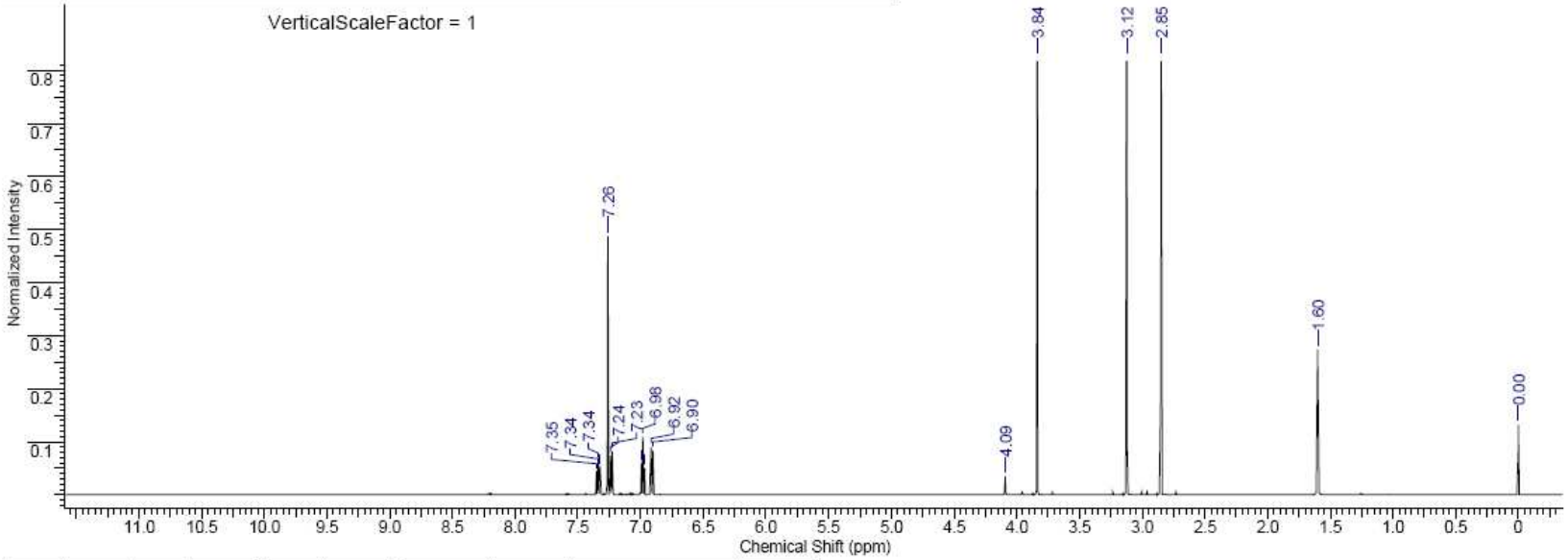

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2.85	1709.7	6.98	4190.3	7.33	4396.5
3.12	1873.0	6.99	4196.9	7.34	4402.3
3.84	2302.2	6.99	4197.8	7.34	4403.2
4.09	2454.6	7.23	4336.1	7.34	4404.0
6.90	4142.3	7.23	4337.8	7.34	4404.9
6.92	4150.6	7.24	4343.6	7.35	4410.7
6.97	4182.0	7.24	4345.3	7.35	4412.4

No	Color	Structure	Visible
1			True

13C-NMR:

1b = 2-Methoxy-N,N-dimethyl-benzamide

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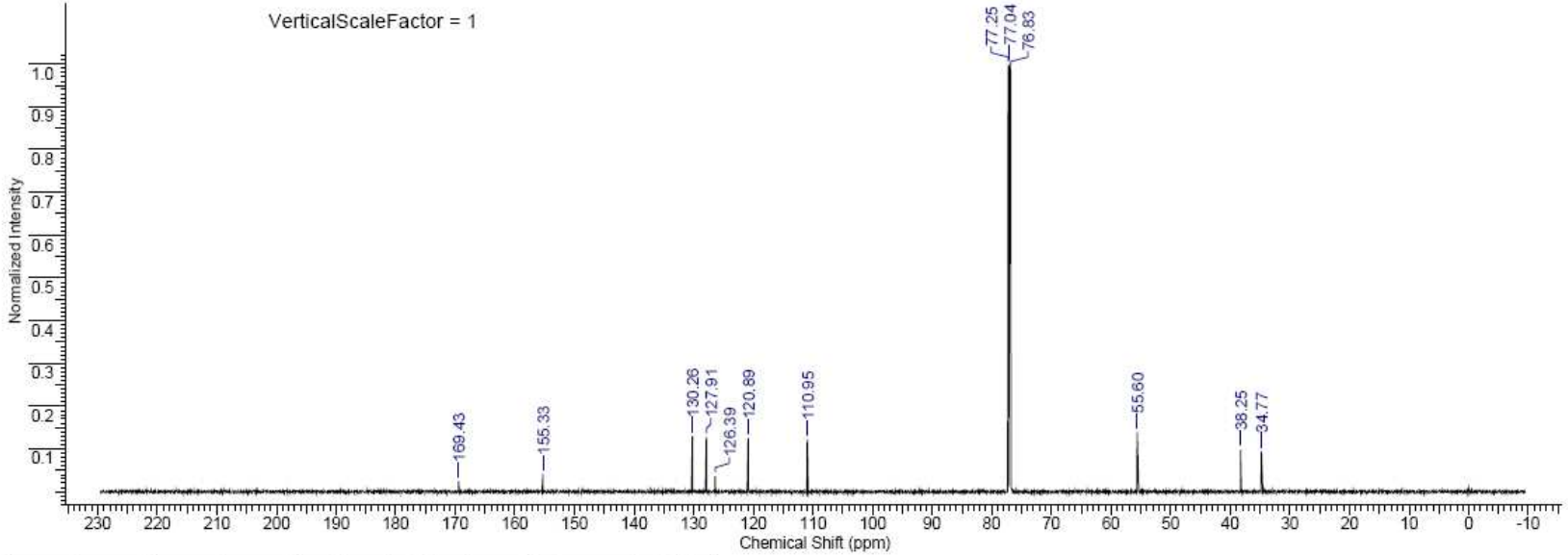

(ppm)	(Hz)
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38.25	5772.9
55.60	8390.5
76.83	11594.8
77.04	11626.7
77.25	11658.6
110.95	16744.4

(ppm)	(Hz)
120.89	18245.0
126.39	19075.3
127.91	19303.9
130.26	19659.1
155.33	23441.7
169.43	25569.8

No	Color	Structure	Visible
1			True

1c] 2-Ethyl-*N*-methyl-benzamide

2-Ethyl-benzoic acid (510 mg, 3.40 mmol) was dissolved in 8 ml of toluene and treated at 0^{o}C with 575 µl (6.79 mmol, 2 eq.) of oxalyl chloride and 1 drop of DMF. The mixture was kept for 2 h at ambient tempertature. Careful evaporation left the acid chloride as pale yellow oil which was reacted with 3.4 ml of 2M methylamine (2 eq.) in THF; stirring was continued for 1 h. Pouring onto crashed ice, twofold extraction with ethyl acetate, washing with water, drying over $MgSO_4$, and evaporation gave 538 mg of the title compound as off-white crystals.

MS: $C_{10}H_{13}NO$, expected: 163.0997, found: 163.0994.

IR:

1c = 2-Ethyl-N-methyl-benzamide

17 Dec 2009

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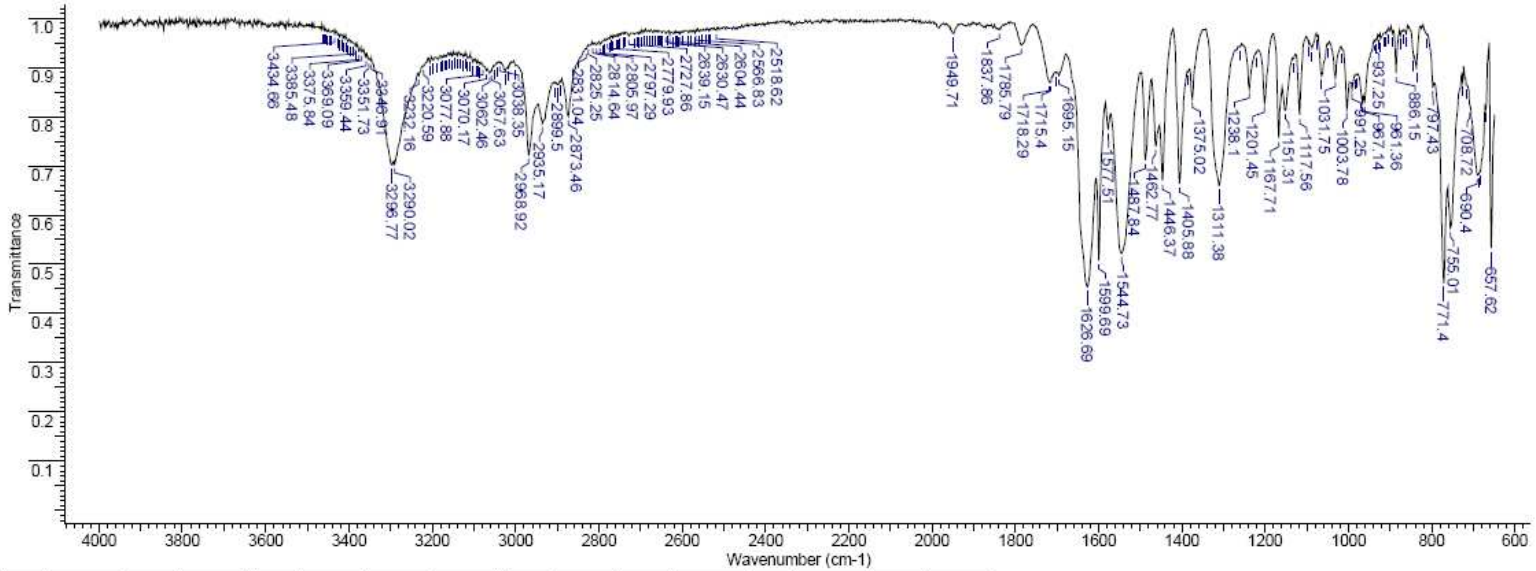

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2	670.15	0.816	M	28	967.14	0.828	M	54	1487.84	0.712	M	80	2616.01	0.971	VW
3	683.65	0.688	M	29	978.71	0.885	W	55	1544.73	0.523	S	81	2620.83	0.968	VW
4	687.51	0.684	M	30	983.53	0.883	W	56	1577.51	0.774	M	82	2630.47	0.967	VW
5	690.40	0.682	M	31	991.25	0.854	W	57	1599.69	0.508	VS	83	2634.33	0.972	VW
6	708.72	0.816	M	32	1003.78	0.814	M	58	1626.69	0.454	VS	84	2639.15	0.969	VW
7	717.40	0.865	W	33	1015.35	0.936	W	59	1695.15	0.884	W	85	2648.79	0.971	VW
8	726.08	0.870	W	34	1031.75	0.878	W	60	1701.90	0.890	W	86	2652.65	0.973	VW
9	755.01	0.573	S	35	1049.10	0.947	VW	61	1715.40	0.870	W	87	2655.54	0.973	VW
10	771.40	0.462	VS	36	1064.53	0.882	W	62	1718.29	0.870	W	88	2659.40	0.972	VW
11	797.43	0.860	W	37	1075.14	0.963	VW	63	1785.79	0.946	W	89	2664.22	0.973	VW
12	811.90	0.966	VW	38	1087.67	0.940	W	64	1837.86	0.977	VW	90	2670.01	0.971	VW
13	836.97	0.897	W	39	1095.39	0.949	VW	65	1949.71	0.969	VW	91	2677.72	0.973	VW
14	843.72	0.921	W	40	1117.56	0.804	M	66	2518.62	0.976	VW	92	2684.47	0.973	VW

1H-NMR:

1c = 2-Ethyl-N-methyl-benzamide

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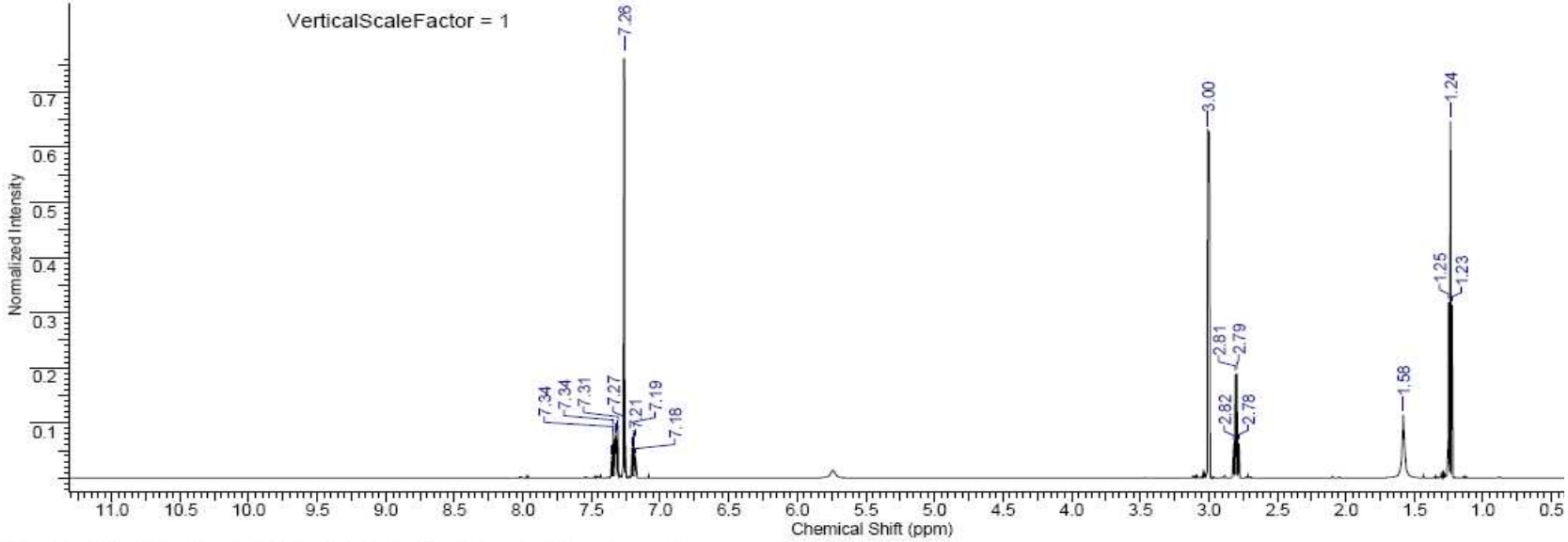

(ppm)	(Hz)	(ppm)	(Hz)	(ppm)	(Hz)
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1.23	735.3	7.18	4308.4	7.32	4392.4
1.24	742.9	7.18	4309.5	7.32	4393.7
1.25	750.4	7.19	4315.7	7.33	4398.0
1.26	756.8	7.19	4317.1	7.33	4399.5
1.58	948.3	7.20	4323.3	7.34	4405.5
2.78	1668.4	7.21	4324.4	7.34	4406.9
2.79	1675.9	7.25	4353.8	7.35	4413.1
2.81	1683.6	7.26	4358.2	7.36	4414.5
2.82	1691.2	7.27	4361.0		
3.00	1798.3	7.31	4384.9		

No	Color	Structure	Visible
1			True

13C-NMR:

1c = 2-Ethyl-N-methyl-benzamide

Acquisition Time (sec)	3.6351				
Comment	ARC= 2009000161424 Labjournal 23718B092 Labgroup ID mohrp Contact Person Name Stefan Buerli Contact Person Address 092/4.36A Theme 7299				
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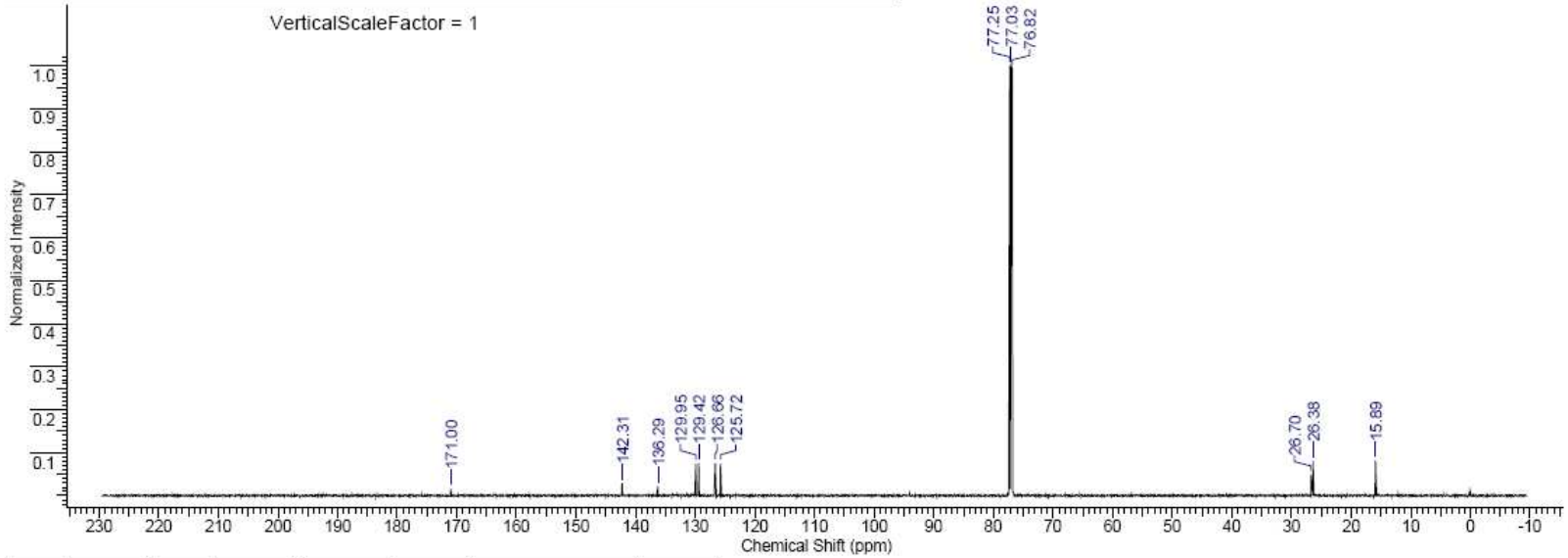
Sweep Width (Hz)	36057.42	Temperature (degree C)	25.027		



(ppm)	(Hz)
15.89	2397.6
26.38	3981.4
26.70	4029.2
76.82	11594.2
77.03	11626.1
77.25	11658.3
125.72	18973.9

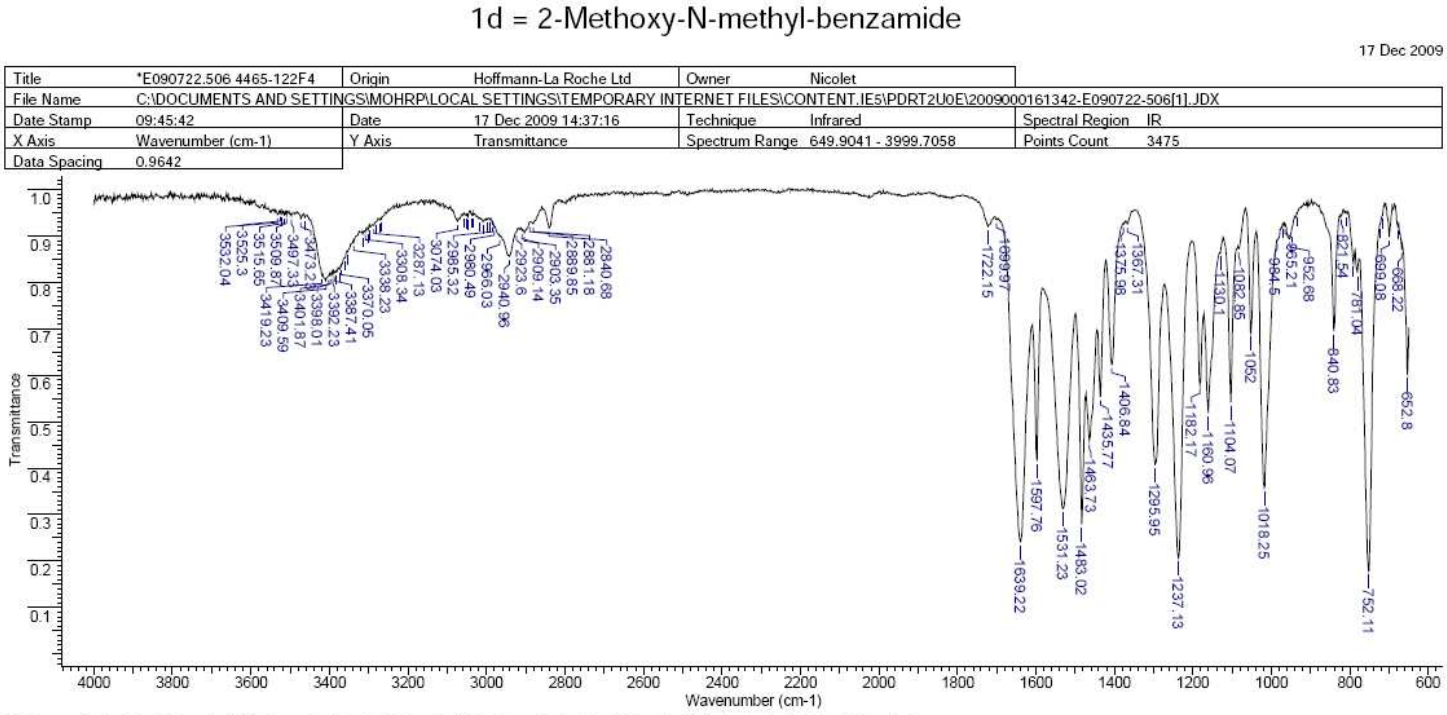
(ppm)	(Hz)
126.66	19114.8
129.42	19532.4
129.95	19611.4
136.29	20569.5
142.31	21477.3
171.00	25806.8

No	Color	Structure	Visible
1			True

1d] 2-Methoxy-*N*-methyl-benzamide

MS: $C_9H_{11}NO_2$, expected: 165.079, found: 165.079.

IR:

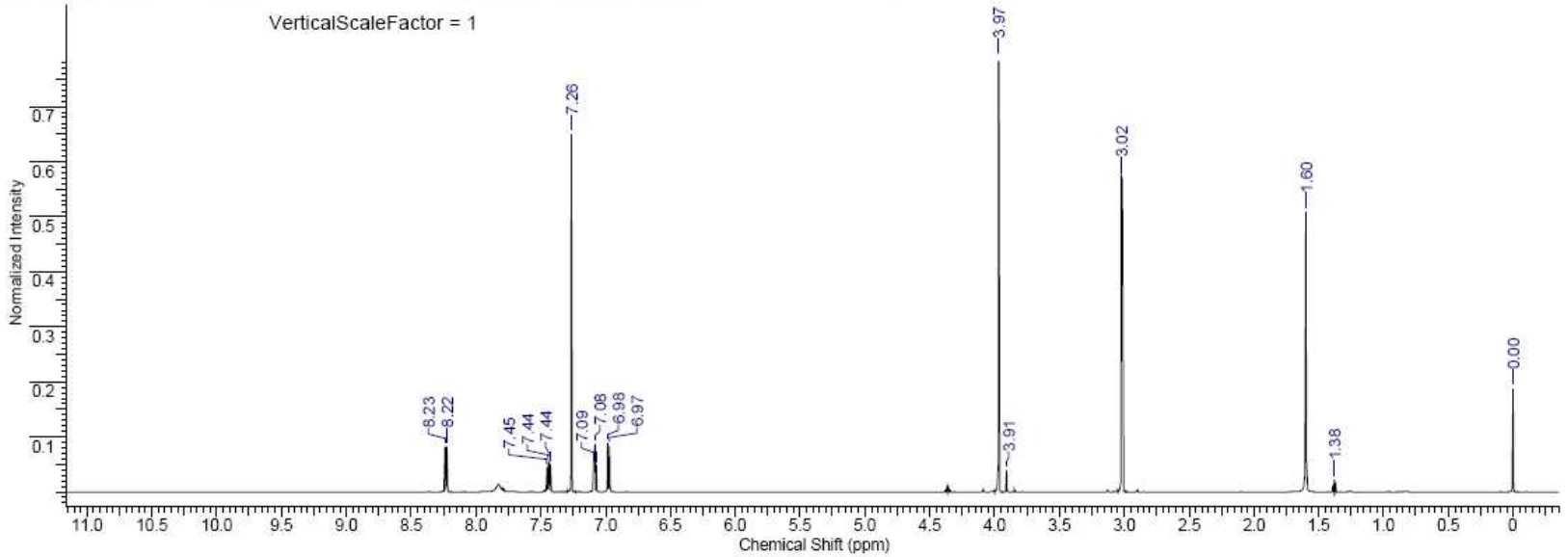


No	cm-1	T	Intensity	No	cm-1	T	Intensity	No	cm-1	T	Intensity	No	cm-1	T	Intensity
1	652.80	0.602	M	23	1160.96	0.518	M	45	2966.03	0.898	W	67	3353.66	0.866	W
2	668.22	0.871	W	24	1182.17	0.579	M	46	2980.49	0.919	W	68	3361.37	0.852	W
3	677.87	0.920	W	25	1237.13	0.207	VS	47	2985.32	0.927	VW	69	3370.05	0.834	W
4	699.08	0.897	W	26	1295.95	0.408	S	48	2991.10	0.935	VW	70	3373.91	0.828	W
5	716.44	0.944	VW	27	1367.31	0.926	VW	49	2997.85	0.935	VW	71	3381.62	0.823	W
6	722.22	0.924	VW	28	1375.98	0.926	VW	50	3008.46	0.930	VW	72	3387.41	0.821	W
7	752.11	0.178	VS	29	1406.84	0.623	M	51	3019.06	0.937	VW	73	3392.23	0.816	W
8	781.04	0.820	W	30	1435.77	0.554	M	52	3033.53	0.945	VW	74	3398.01	0.815	W
9	790.68	0.841	W	31	1463.73	0.460	S	53	3037.39	0.945	VW	75	3401.87	0.813	W
10	809.97	0.949	VW	32	1483.02	0.279	S	54	3047.99	0.941	VW	76	3409.59	0.803	W
11	821.54	0.943	VW	33	1531.23	0.313	S	55	3051.85	0.944	VW	77	3419.23	0.815	W
12	840.83	0.696	M	34	1597.76	0.415	S	56	3055.71	0.946	VW	78	3462.62	0.940	VW
13	934.36	0.947	VW	35	1639.22	0.242	VS	57	3074.03	0.931	VW	79	3473.23	0.937	VW

1H-NMR:

1d = 2-Methoxy-N-methyl-benzamide

Acquisition Time (sec)	9.9266				
Comment	ARC= 2009000161342 Labjournal 4465.122F4 Labgroup ID mohrp Contact Person Name Stefan Buerli Contact Person Address 092/4.36A Theme 7299				
Date	27 Jul 2009 21:45:34	Date Stamp	27 Jul 2009 21:45:34		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\OLS5AZO5\2009000161342_2000[1].JDX				
Frequency (MHz)	600.14	Nucleus	1H	Number of Transients	8
Origin	NMR_Roche_Basel	Original Points Count	131072	Owner	serv
Points Count	131072	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	5690.8535
Sweep Width (Hz)	13204.13	Temperature (degree C)	25.027		



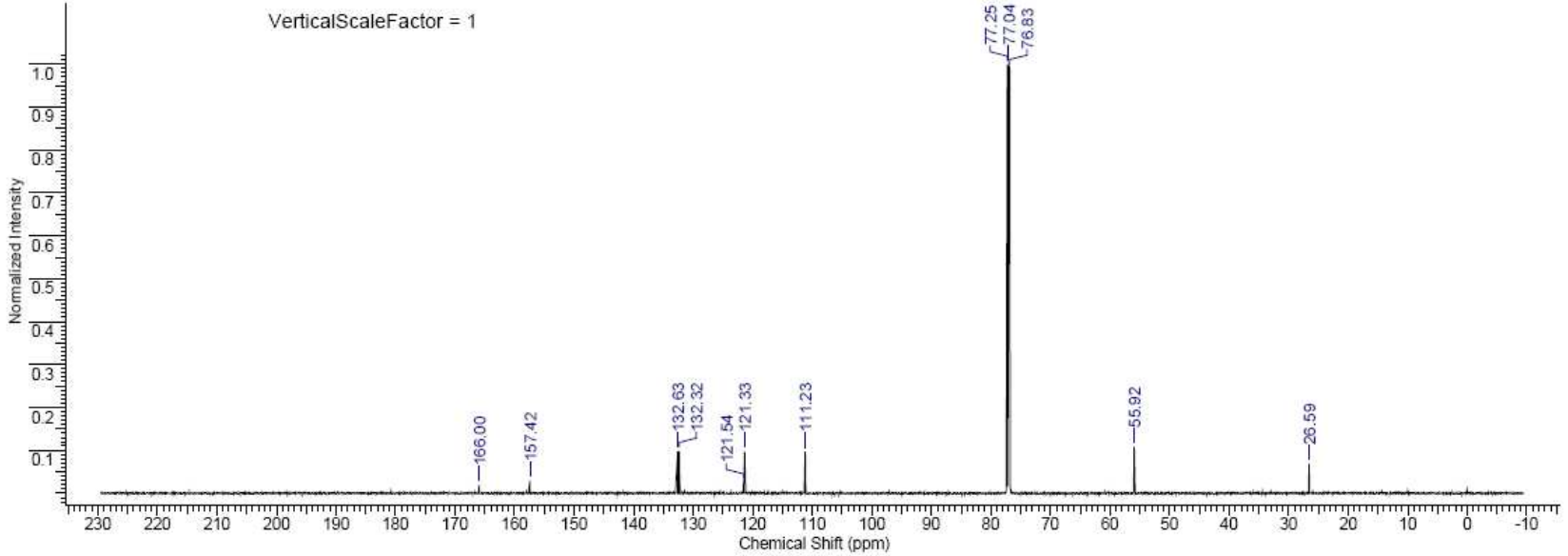
(ppm)	(Hz)	(ppm)	(Hz)	(ppm)	(Hz)
0.00	0.1	7.07	4243.1	7.44	4465.4
1.38	828.0	7.08	4249.9	7.44	4466.4
1.60	960.2	7.08	4250.4	7.45	4471.8
3.01	1808.1	7.09	4257.2	7.45	4473.8
3.02	1812.9	7.10	4258.2	8.22	4933.4
3.91	2343.9	7.26	4358.5	8.22	4935.4
3.97	2381.5	7.43	4456.2	8.23	4941.2
6.97	4181.8	7.43	4458.1	8.24	4943.1
6.98	4190.1	7.44	4463.6		
7.07	4242.1	7.44	4464.6		

No	Color	Structure	Visible
1			True

13C-NMR:

1d = 2-Methoxy-N-methyl-benzamide

Acquisition Time (sec)	3.6351				
Comment	ARC= 2009000161342 Labjournal 4465.122F4 Labgroup ID mohrp Contact Person Name Stefan Buerli Contact Person Address 092/4.36A Theme 7299				
Date	27 Jul 2009 22:05:22	Date Stamp	27 Jul 2009 22:05:22		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\M14NAXY5\2009000161342_2001[1].JDX				
Frequency (MHz)	150.92	Nucleus	13C	Number of Transients	512
Origin	NMR_Roche_Basel	Original Points Count	131072	Owner	serv
Points Count	131072	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	16603.6582
Sweep Width (Hz)	36057.42	Temperature (degree C)	25.027		



(ppm)	(Hz)	(ppm)	(Hz)
26.59	4013.1	121.33	18311.1
55.92	8439.2	121.54	18343.2
76.83	11594.5	132.32	19970.2
77.04	11626.4	132.63	20016.9
77.25	11658.4	157.42	23757.5
111.23	16787.0	166.00	25052.1

No	Color	Structure	Visible
1			True

2a] 1,1-Dimethyl-3-phenyl-urea

Aniline (175 mg, 1.88 mmol) was dissolved in 3.6 ml of CH_2Cl_2 and treated at 0°C with 260 µl (1.88 mmol, 1 eq.) of triethylamine and 207 µl (1.2 eq.) of dimethylcarbamoyl chloride. The mixture was kept over night at ambient temperature. Pouring onto crashed ice, twofold extraction with ethyl acetate, washing with water, drying over $MgSO_4$, and evaporation of all solvents, followed by flash chromatography (SiO_2, heptane / ethyl acetate = 1 / 1) produced 152 mg of the title compound as white solid.

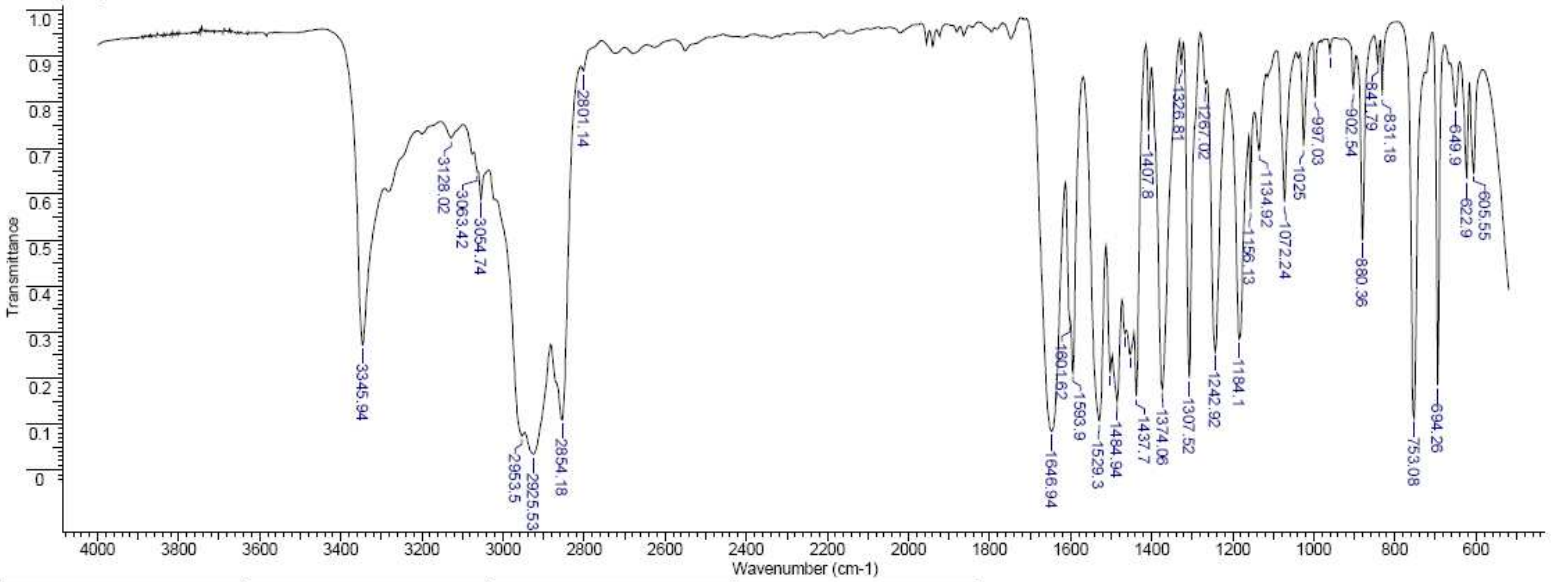
MS: $C_9H_{12}N_2O$, expected: 164.095, found: 164.095.

IR:

2a = 1,1-Dimethyl-3-phenyl-urea

17 Dec 2009

Title	*E090924.106 24041B029	Origin	Hoffmann-La Roche Ltd	Owner	Nicolet		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\MT92FAHG\2009000164788-E090924-106[1].JDX						
Date Stamp	09:04:05	Date	17 Dec 2009 14:44:30	Technique	Infrared	Spectral Region	IR
X Axis	Wavenumber (cm-1)	Y Axis	Transmittance	Spectrum Range	519.7302 - 3999.7058	Points Count	3610
Data Spacing	0.9642						

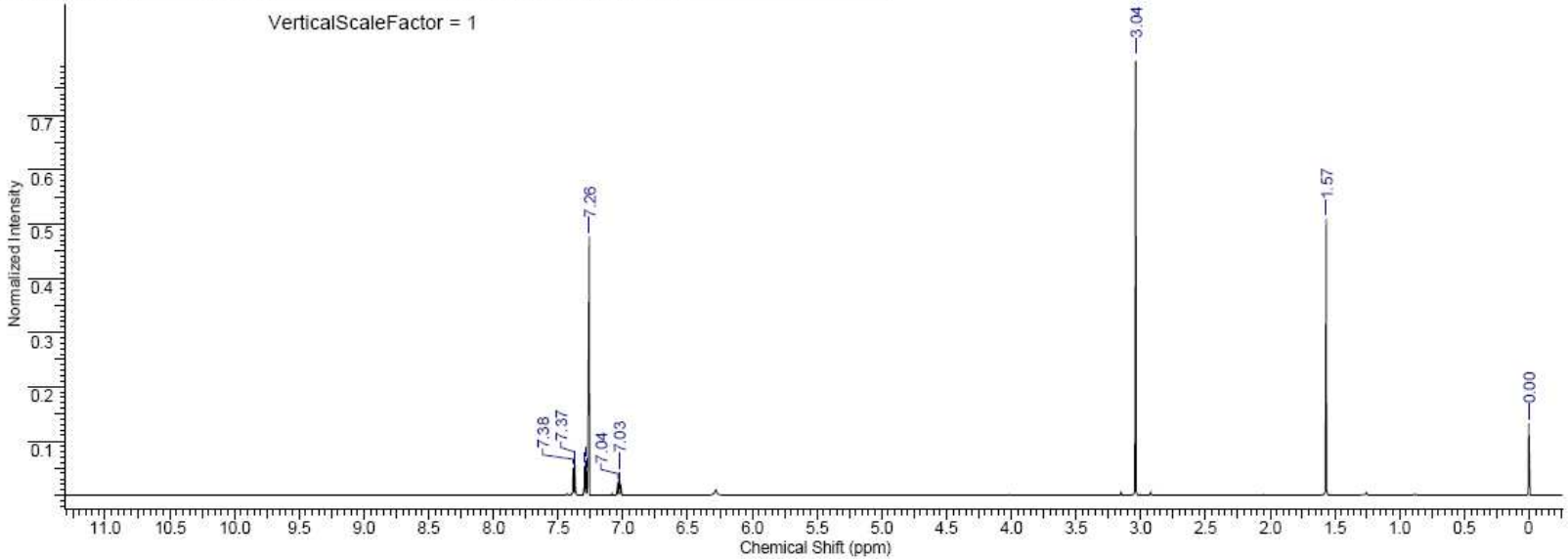


No	cm-1	T	Intensity	No	cm-1	T	Intensity	No	cm-1	T	Intensity	No	cm-1	T	Intensity
1	605.55	0.648	M	11	997.03	0.810	W	21	1374.06	0.176	S	31	1646.94	0.085	VS
2	622.90	0.633	M	12	1025.00	0.706	W	22	1407.80	0.737	W	32	2801.14	0.868	W
3	649.90	0.790	W	13	1072.24	0.583	M	23	1437.70	0.161	S	33	2854.18	0.109	VS
4	694.26	0.184	S	14	1134.92	0.694	M	24	1453.12	0.251	S	34	2925.53	0.035	VS
5	753.08	0.112	VS	15	1156.13	0.568	M	25	1466.62	0.297	S	35	2953.50	0.074	VS
6	831.18	0.815	W	16	1184.10	0.284	S	26	1484.94	0.149	S	36	3054.74	0.589	M
7	841.79	0.884	W	17	1242.92	0.257	S	27	1502.30	0.212	S	37	3063.42	0.649	M
8	880.36	0.501	M	18	1267.02	0.841	W	28	1529.30	0.107	VS	38	3128.02	0.723	W
9	902.54	0.828	W	19	1307.52	0.200	S	29	1593.90	0.211	S	39	3345.94	0.272	S
10	960.39	0.904	VW	20	1326.81	0.880	W	30	1601.62	0.319	S				

1H-NMR:

2a = 1,1-Dimethyl-3-phenyl-urea

Acquisition Time (sec)	9.9266				
Comment	ARC= 2009000164788 Labjournal 24041B029 Labgroup ID mohrp Contact Person Name Stefan Buerli Contact Person Address 092/4.36A Theme 4652				
Date	23 Sep 2009 12:29:47	Date Stamp	23 Sep 2009 12:29:47		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\450Z4V4Z\2009000164788_1000[1].JDX				
Frequency (MHz)	600.14	Nucleus	1H	Number of Transients	8
Origin	NMR_Roche_Basel	Original Points Count	131072	Owner	serv
Points Count	131072	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	5690.3428
Sweep Width (Hz)	13204.13	Temperature (degree C)	25.027		



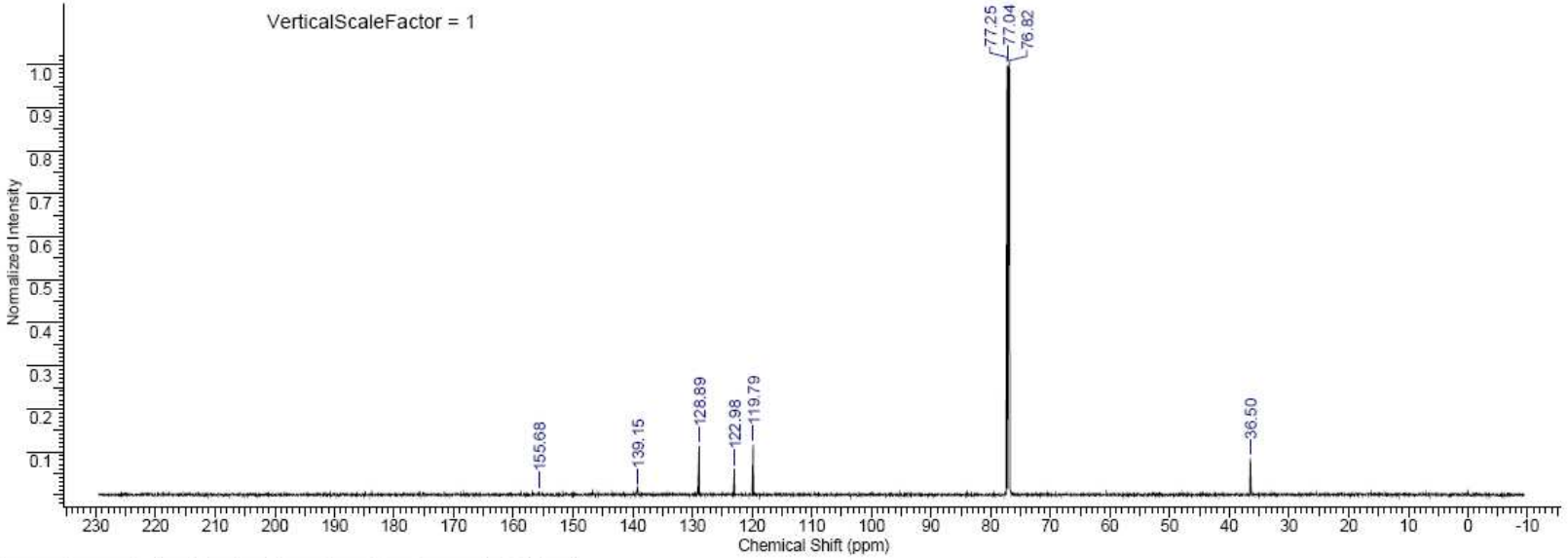
(ppm)	(Hz)	(ppm)	(Hz)
0.00	0.1	7.28	4370.6
1.57	941.0	7.28	4371.7
3.04	1823.1	7.30	4379.1
7.03	4217.4	7.37	4422.4
7.04	4224.8	7.37	4423.5
7.26	4357.7	7.38	4430.9
7.27	4363.1	7.39	4432.1

No	Color	Structure	Visible
1			True

13-C NMR:

2a = 1,1-Dimethyl-3-phenyl-urea

Acquisition Time (sec)	3.6351				
Comment	ARC= 2009000164788 Labjournal 24041B029 Labgroup ID mohrp Contact Person Name Stefan Buerli Contact Person Address 092/4.36A Theme 4652				
Date	23 Sep 2009 12:43:45	Date Stamp	23 Sep 2009 12:43:45		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\RUC7ZL0X\2009000164788_1002[1].JDX				
Frequency (MHz)	150.92	Nucleus	13C	Number of Transients	256
Origin	NMR_Roche_Basel	Original Points Count	131072	Owner	serv
Points Count	131072	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	16603.6113
Sweep Width (Hz)	36057.42	Temperature (degree C)	25.027		



(ppm)	(Hz)
36.50	5507.9
76.82	11594.2
77.04	11626.1
77.25	11658.0
119.79	18078.0
122.98	18559.4
128.89	19451.6
139.15	21000.4
155.68	23494.4

No	Color	Structure	Visible
1			True

2b] 1,1-Dimethyl-3-pyridin-2-yl-urea

Pyridin-2-ylamine (222 mg, 2.36 mmol) was dissolved in 2.5 ml of CH_2Cl_2 and treated at 0°C with 401 µl (2.36 mmol, 1 eq.) of ethyl-diisopropyl-amine and 325 µl (1.5 eq.) of dimethylcarbamoyl chloride. The mixture was kept over night at ambient temperature. Pouring onto crashed ice, twofold extraction with ethyl acetate, washing with water, drying over $MgSO_4$, and evaporation of all solvents, followed by threefold flash chromatography (SiO_2, CH_2Cl_2 / MeOH = 97 / 3, then SiO_2, ethyl acetate / heptane = 75 / 25, then SiO_2, CH_2Cl_2 / MeOH = 95 / 5), yielded 31 mg of the title compound as light yellow viscous oil.

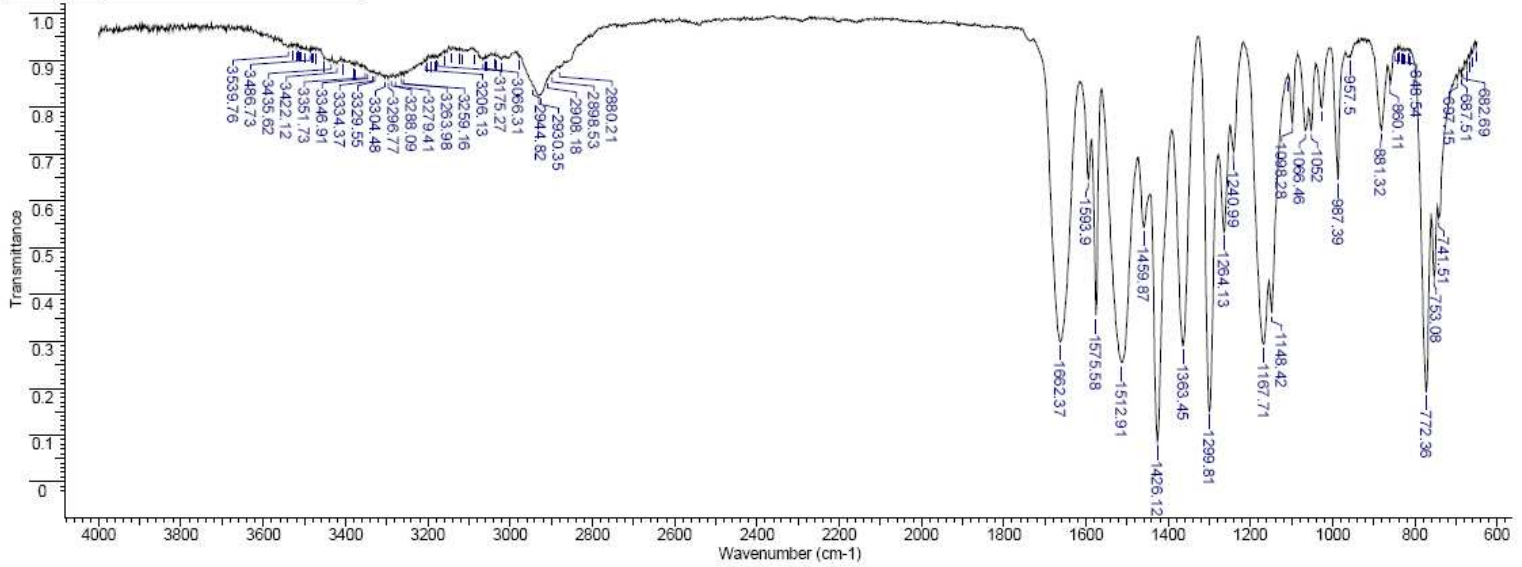
MS: $C_8H_{11}N_3O$, expected ($M+H^+$): 166.09749, found: 166.09746 ($M+H^+$).

IR:

2b = 1,1-Dimethyl-3-pyridin-2-yl-urea

17 Dec 2009

Title	*E090903.501 24-041B015	Origin	Hoffmann-La Roche Ltd	Owner	Nicolet		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\YJU36DM3\2009000163658-E090903-501[1].JDX						
Date Stamp	07:55:41	Date	17 Dec 2009 14:47:18	Technique	Infrared	Spectral Region	IR
X Axis	Wavenumber (cm-1)	Y Axis	Transmittance	Spectrum Range	649.9041 - 3999.7058	Points Count	3475
Data Spacing	0.9642						

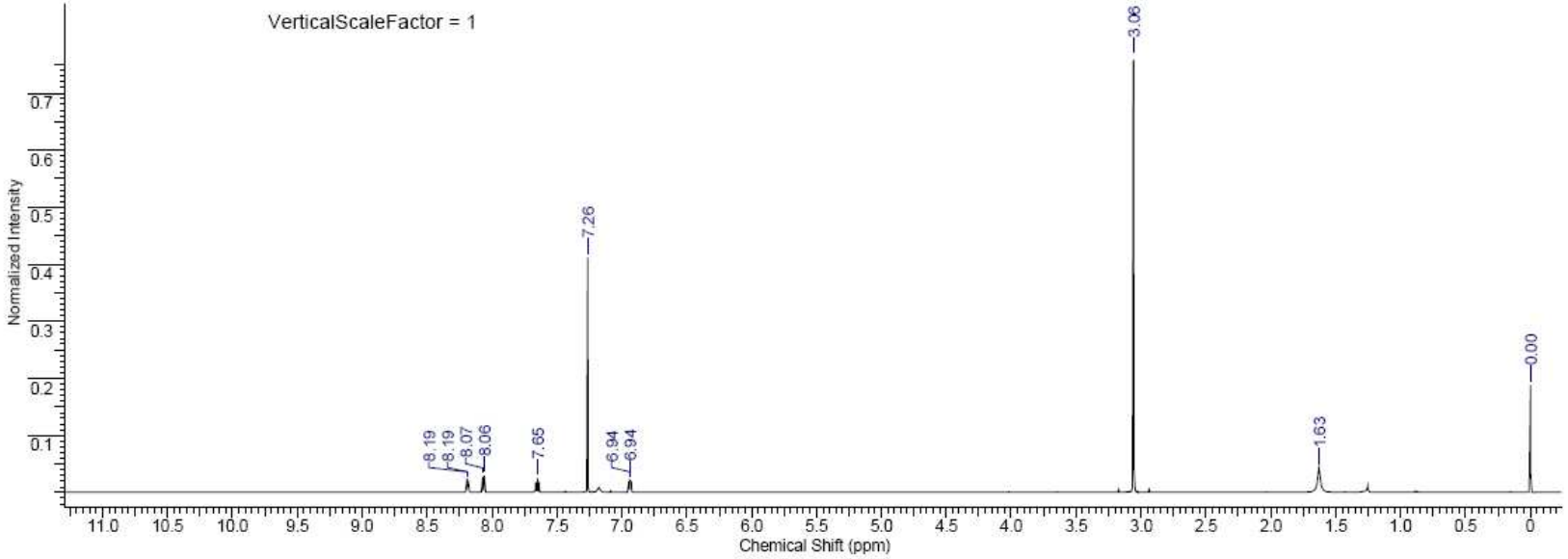


No	cm-1	T	Intensity	No	cm-1	T	Intensity	No	cm-1	T	Intensity	No	cm-1	T	Intensity
1	651.83	0.926	VW	24	1052.00	0.751	W	47	3034.49	0.908	VW	70	3334.37	0.874	W
2	661.48	0.913	VW	25	1066.46	0.751	W	48	3038.35	0.911	VW	71	3346.91	0.879	W
3	667.26	0.905	W	26	1098.28	0.765	W	49	3055.71	0.906	VW	72	3351.73	0.881	W
4	674.01	0.885	W	27	1110.82	0.862	W	50	3058.60	0.906	VW	73	3375.84	0.889	W
5	682.69	0.880	W	28	1148.42	0.361	S	51	3066.31	0.902	W	74	3380.66	0.890	W
6	687.51	0.869	W	29	1167.71	0.294	S	52	3085.60	0.920	VW	75	3408.62	0.898	W
7	697.15	0.860	W	30	1240.99	0.704	M	53	3114.53	0.920	VW	76	3422.12	0.893	W
8	741.51	0.563	M	31	1264.13	0.534	M	54	3121.27	0.921	VW	77	3435.62	0.900	W
9	753.08	0.439	S	32	1299.81	0.151	VS	55	3143.45	0.923	VW	78	3452.98	0.905	W
10	772.36	0.192	S	33	1363.45	0.291	S	56	3159.84	0.916	VW	79	3473.23	0.922	VW
11	810.93	0.918	VW	34	1426.12	0.086	VS	57	3175.27	0.905	VW	80	3479.01	0.923	VW
12	815.75	0.921	VW	35	1459.87	0.543	M	58	3179.13	0.907	VW	81	3483.83	0.922	VW
13	824.43	0.920	VW	36	1512.91	0.255	S	59	3182.99	0.907	VW	82	3486.73	0.918	VW
14	829.25	0.921	VW	37	1575.58	0.356	S	60	3193.59	0.904	W	83	3499.26	0.923	VW

1H-NMR:

2b = 1,1-Dimethyl-3-pyridin-2-yl-urea

Acquisition Time (sec)	9.9266				
Comment	ARC= 2009000163658 Labjournal 24'041B015 Labgroup ID mohrp Contact Person Name Stefan Buerli Contact Person Address 092/4.36A Theme 4652				
Date	03 Sep 2009 05:25:19	Date Stamp	03 Sep 2009 05:25:19		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\BAZDHLFF\2009000163658_1000[1].JDX				
Frequency (MHz)	600.14	Nucleus	1H	Number of Transients	8
Origin	NMR_Roche_Basel	Original Points Count	131072	Owner	serv
Points Count	131072	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	5691.0381
Sweep Width (Hz)	13204.13	Temperature (degree C)	25.027		



(ppm)	(Hz)
0.00	0.1
1.63	977.5
3.06	1834.7
6.93	4161.4
6.94	4162.8
6.94	4163.8
7.26	4358.6
7.65	4589.9

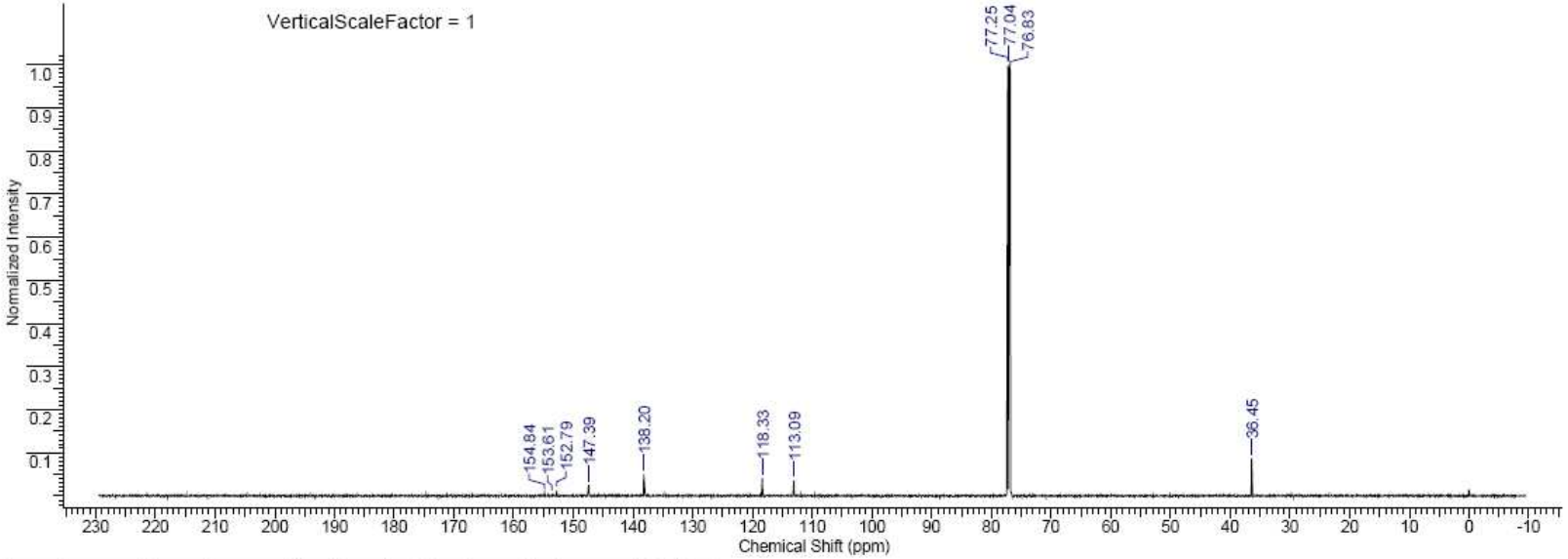
(ppm)	(Hz)
7.65	4590.4
7.65	4591.7
8.06	4835.7
8.07	4844.2
8.19	4912.4
8.19	4916.3
8.19	4917.3

No	Color	Structure	Visible
1			True

13C-NMR:

2b = 1,1-Dimethyl-3-pyridin-2-yl-urea

Acquisition Time (sec)	3.6351				
Comment	ARC= 2009000163658 Labjournal 24'041B015 Labgroup ID mohrp Contact Person Name Stefan Buerli Contact Person Address 092/4.36A Theme 4652				
Date	03 Sep 2009 05:48:34	Date Stamp	03 Sep 2009 05:48:34		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\5RNHBLZW\2009000163658_1002[1].JDX				
Frequency (MHz)	150.92	Nucleus	13C	Number of Transients	512
Origin	NMR Roche Basel	Original Points Count	131072	Owner	serv
Points Count	131072	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	16603.7012
Sweep Width (Hz)	36057.42	Temperature (degree C)	25.027		



(ppm)	(Hz)
36.45	5501.4
76.83	11594.6
77.04	11626.5
77.25	11658.4
113.09	17067.9
118.33	17857.7

(ppm)	(Hz)
138.20	20857.1
147.39	22244.7
152.79	23059.0
153.61	23183.1
154.84	23368.2

No	Color	Structure	Visible
1			True

2c] 1-Methyl-3-phenyl-urea

Aniline (220 mg, 2.36 mmol) was dissolved in 2.3 ml of DMF and treated at 0°C with 293 µl (4.73 mmol, 2 eq.) of isocyanatomethane. The flask was sealed with a rubber septum and the mixture stirred over night at ambient temperature. Pouring onto crashed ice, twofold extraction with ethyl acetate, washing with water, drying over $MgSO_4$, and evaporation of all solvents, followed by crystallization from ethyl acetate / hexane, yielded 301 mg of the title compound as white crystals.

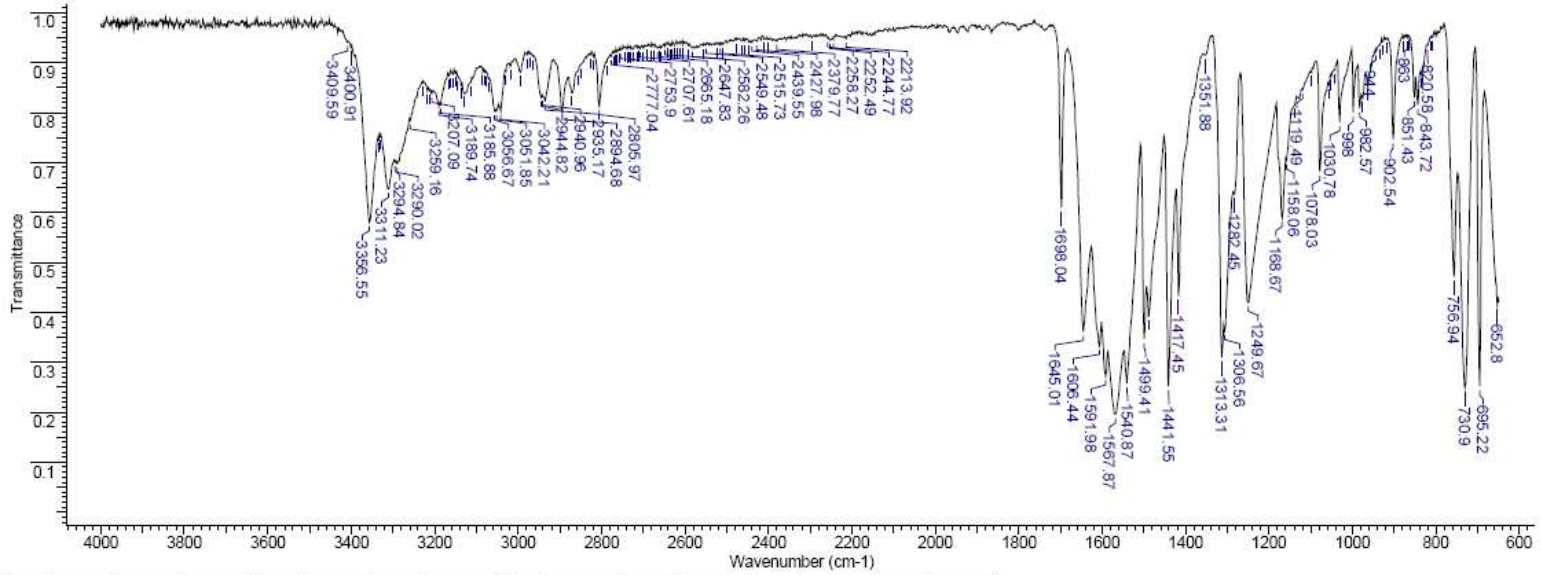
MS: $C_8H_{10}N_2O$, expected: 150.079, found: 150.079.

IR:

2c = 1-Methyl-3-phenyl-urea

17 Dec 2009

Title	*E091016.502 24041B041	Origin	Hoffmann-La Roche Ltd	Owner	Nicolet		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\EV4BFG54\20090090165978-E091016-502[1].JDX						
Date Stamp	08:47:08	Date	17 Dec 2009 14:51:54	Technique	Infrared	Spectral Region	IR
X Axis	Wavenumber (cm-1)	Y Axis	Transmittance	Spectrum Range	649.9041 - 3999.7058	Points Count	3475
Data Spacing	0.9642						



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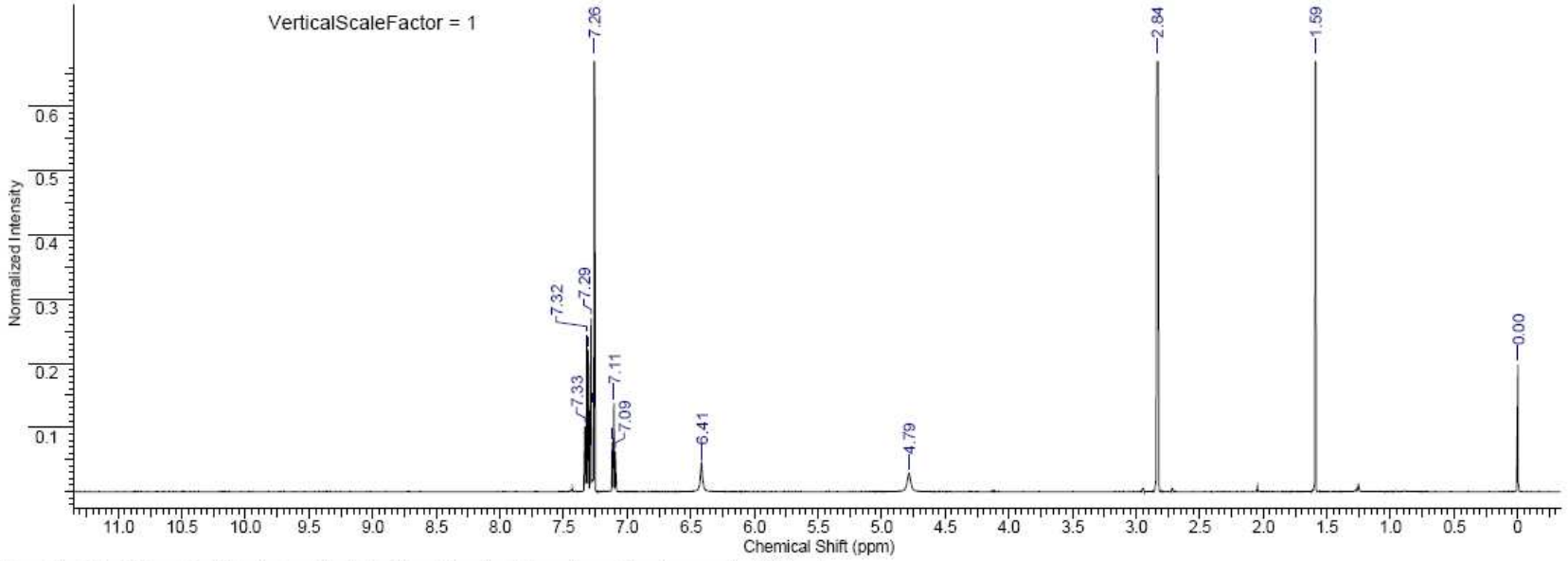
1	652.80	0.414	S	27	1051.03	0.872	W	53	2258.27	0.949	VW	79	2647.83	0.933	VW
2	695.22	0.252	VS	28	1056.82	0.854	W	54	2295.88	0.950	VW	80	2657.47	0.929	VW
3	730.90	0.249	VS	29	1078.03	0.681	M	55	2379.77	0.944	VW	81	2661.33	0.930	VW
4	756.94	0.471	S	30	1098.28	0.880	W	56	2400.98	0.946	VW	82	2665.18	0.929	VW
5	808.04	0.951	VW	31	1119.49	0.846	W	57	2409.66	0.946	VW	83	2672.90	0.932	VW
6	811.90	0.950	VW	32	1138.78	0.815	W	58	2427.98	0.943	VW	84	2678.68	0.934	VW
7	820.58	0.934	VW	33	1158.06	0.704	M	59	2439.55	0.940	VW	85	2681.58	0.932	VW
8	831.18	0.884	W	34	1168.67	0.589	M	60	2447.26	0.941	VW	86	2691.22	0.933	VW
9	835.04	0.877	W	35	1249.67	0.420	S	61	2457.87	0.944	VW	87	2699.90	0.929	VW
10	843.72	0.815	W	36	1282.45	0.637	M	62	2462.69	0.943	VW	88	2707.61	0.928	VW
11	851.43	0.830	W	37	1306.56	0.362	S	63	2465.59	0.945	VW	89	2711.47	0.930	VW
12	863.00	0.948	VW	38	1313.31	0.310	S	64	2478.12	0.945	VW	90	2715.33	0.929	VW
13	865.90	0.952	VW	39	1351.88	0.915	VW	65	2511.87	0.936	VW	91	2723.04	0.928	VW

1H-NMR:

2c = 1-Methyl-3-phenyl-urea

Acquisition Time (sec)	9.9266				
Comment	ARC= 2009000165978 Labjournal 24041B041 Labgroup ID mohrp Contact Person Name Stefan Buerli Contact Person Address 092/4.36A Theme 4652				
Date	16 Oct 2009 06:32:34	Date Stamp	16 Oct 2009 06:32:34		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\OLS5AZO5\2009000165978_1000[1].JDX				
Frequency (MHz)	600.14	Nucleus	1H	Number of Transients	8
Origin	NMR_Roche_Basel	Original Points Count	131072	Owner	serv
Points Count	131072	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	5690.5352
Sweep Width (Hz)	13204.13	Temperature (degree C)	25.027		



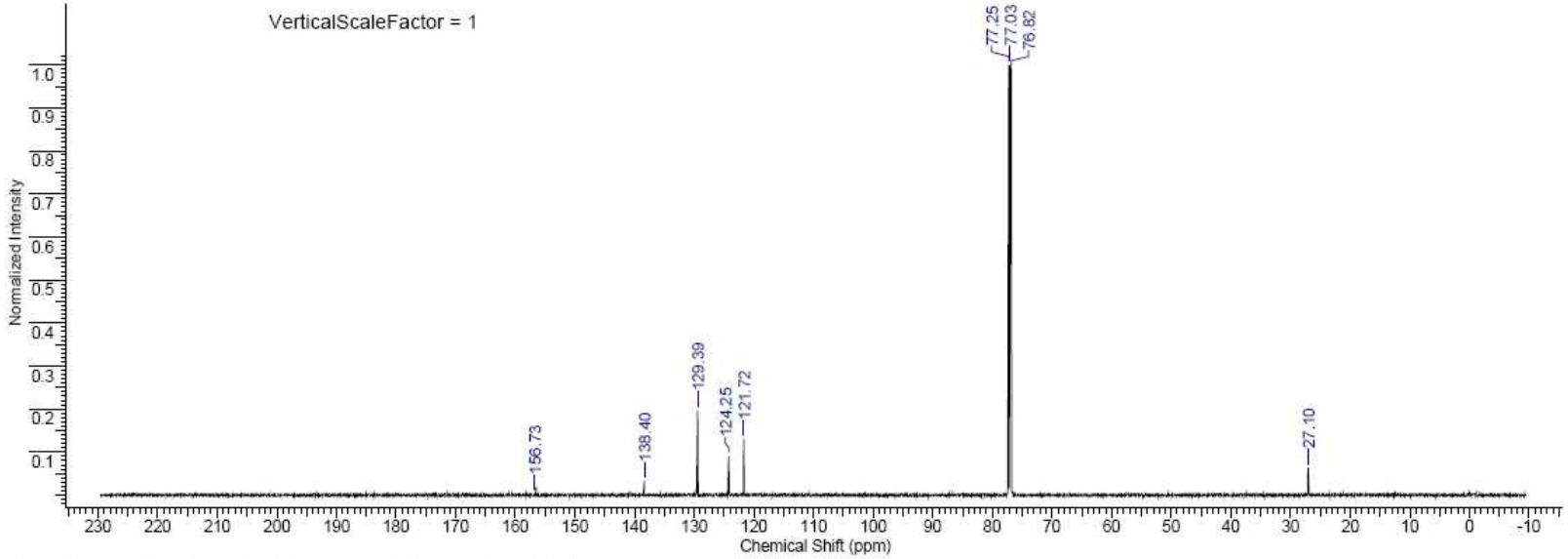
(ppm)	(Hz)	(ppm)	(Hz)	(ppm)	(Hz)
0.00	0.1	7.11	4264.1	7.29	4372.0
1.59	955.5	7.11	4265.4	7.29	4373.3
2.83	1698.2	7.11	4269.9	7.30	4383.2
2.84	1703.1	7.12	4271.3	7.31	4384.8
4.79	2872.7	7.12	4272.7	7.31	4386.9
6.41	3849.8	7.26	4357.9	7.32	4392.0
7.09	4255.5	7.27	4361.6	7.32	4393.3
7.09	4256.9	7.27	4363.4	7.33	4398.6
7.10	4258.3	7.27	4364.6	7.33	4400.5
7.10	4262.9	7.28	4369.8		

No	Color	Structure	Visible
1			True

13C-NMR:

2c = 1-Methyl-3-phenyl-urea

Acquisition Time (sec)	3.6351				
Comment	ARC= 2009000165978 Labjournal 24041B041 Labgroup ID mohrp Contact Person Name Stefan Buerli Contact Person Address 092/4.36A Theme 4652				
Date	16 Oct 2009 06:46:33	Date Stamp	16 Oct 2009 06:46:33		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\M14NAXY5\2009000165978_1002[1].JDX				
Frequency (MHz)	150.92	Nucleus	13C	Number of Transients	256
Origin	NMR Roche Basel	Original Points Count	131072	Owner	serv
Points Count	131072	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	16603.6426
Sweep Width (Hz)	36057.42	Temperature (degree C)	25.027		



(ppm)	(Hz)
27.10	4089.3
76.82	11594.0
77.03	11625.9
77.25	11657.8
121.72	18370.2
124.25	18751.5
129.39	19528.1
138.40	20887.3
156.73	23654.3

No	Color	Structure	Visible
1			True

2d] 1-Methyl-3-pyridin-2-yl-urea

Pyridin-2-ylamine (59 mg, 0.627 mmol) was dissolved in 1.0 ml of DMF and treated at 0°C with 78 µl (1.25 mmol, 2 eq.) of isocyanatomethane. The flask was sealed with a rubber septum and the mixture stirred over night at ambient temperature. Pouring onto crashed ice, twofold extraction with ethyl acetate, washing with water, drying over $MgSO_4$, and evaporation of all solvents, followed by crystallization from ethyl acetate / hexane, yielded 66 mg of the title compound as white crystals.

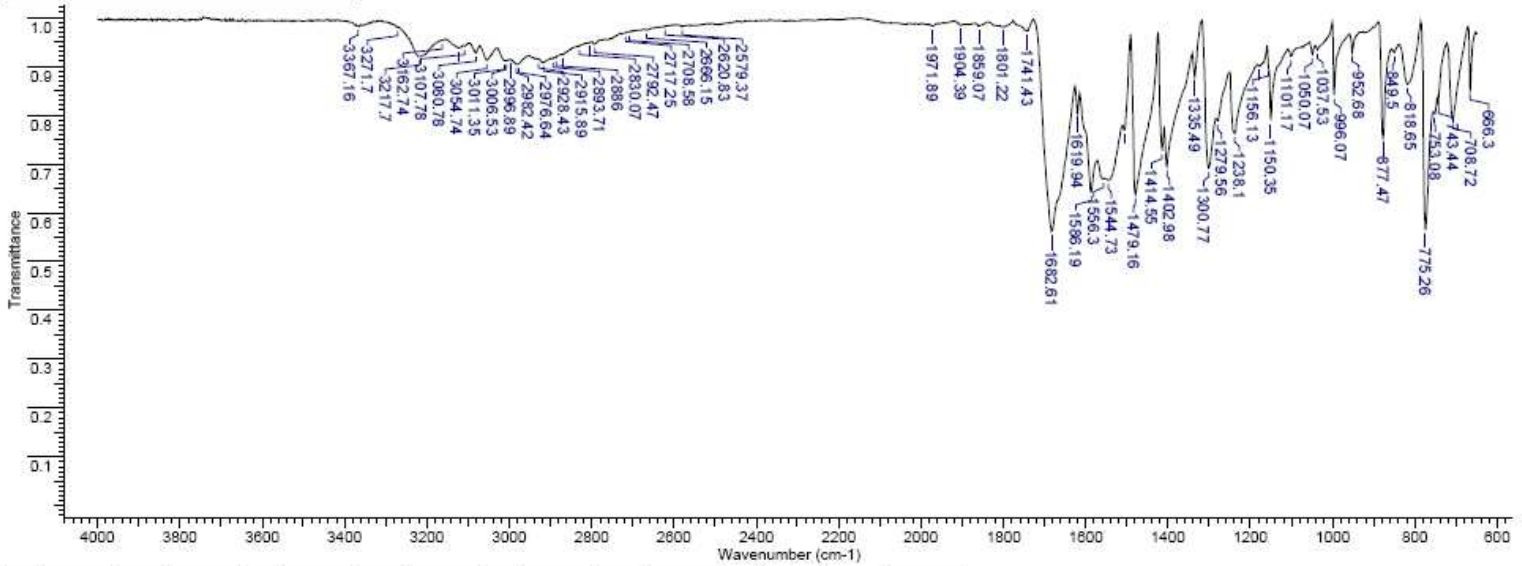
MS: $C_7H_9N_3O$, expected: 151.0746, found: 151.0744.

IR:

2d = 1-Methyl-3-pyridin-2-yl-urea

17 Dec 2009

Title	*E090820.539 24041B011	Origin	Hoffmann-La Roche Ltd	Owner	Nicolet		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\M14NAXY5\2009000162941-E090820-539[1].JDX						
Date Stamp	15:49:48	Date	17 Dec 2009 15:27:34	Technique	Infrared	Spectral Region	IR
X Axis	Wavenumber (cm-1)	Y Axis	Transmittance	Spectrum Range	649.9041 - 3999.7058	Points Count	3475
Data Spacing	0.9642						

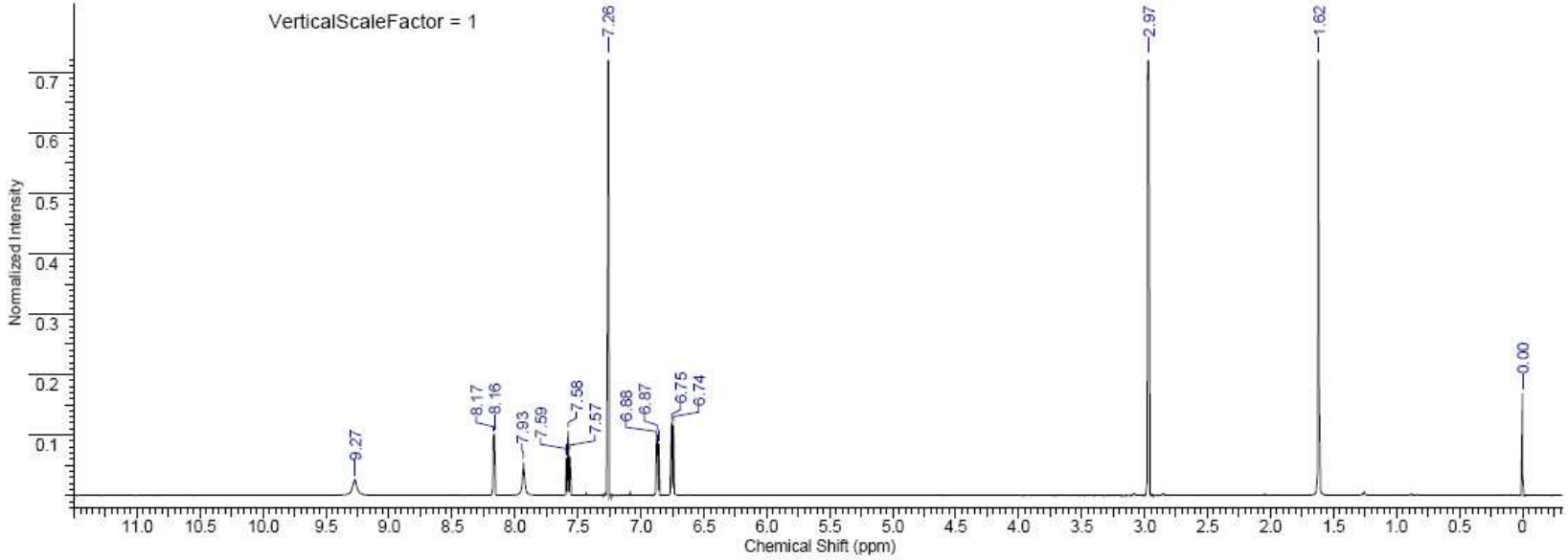


No	cm-1	T	Intensity	No	cm-1	T	Intensity	No	cm-1	T	Intensity	No	cm-1	T	Intensity
1	666.30	0.848	M	17	1238.10	0.762	M	33	1904.39	0.983	VW	49	2982.42	0.904	W
2	708.72	0.790	M	18	1279.56	0.788	M	34	1971.89	0.982	VW	50	2996.89	0.913	W
3	743.44	0.821	M	19	1300.77	0.691	S	35	2579.37	0.982	VW	51	3006.53	0.911	W
4	753.08	0.802	M	20	1335.49	0.878	W	36	2620.83	0.981	VW	52	3011.35	0.911	W
5	775.26	0.566	VS	21	1402.98	0.694	S	37	2666.15	0.974	VW	53	3054.74	0.913	W
6	818.65	0.863	M	22	1414.55	0.727	S	38	2708.58	0.970	VW	54	3080.78	0.928	W
7	849.50	0.929	W	23	1479.16	0.637	S	39	2717.25	0.968	VW	55	3107.78	0.941	W
8	877.47	0.752	M	24	1506.16	0.769	M	40	2792.47	0.945	W	56	3122.24	0.937	W
9	952.68	0.927	W	25	1544.73	0.667	S	41	2805.97	0.948	W	57	3162.74	0.952	W
10	996.07	0.841	M	26	1556.30	0.669	S	42	2830.07	0.941	W	58	3214.81	0.920	W
11	1037.53	0.933	W	27	1586.19	0.642	S	43	2870.57	0.923	W	59	3217.70	0.919	W
12	1050.07	0.923	W	28	1619.94	0.803	M	44	2886.00	0.918	W	60	3271.70	0.979	VW
13	1101.17	0.920	W	29	1682.61	0.561	VS	45	2893.71	0.915	W	61	3367.16	0.981	VW
14	1150.35	0.789	M	30	1741.43	0.972	VW	46	2915.89	0.907	W				

1H-NMR:

2d = 1-Methyl-3-pyridin-2-yl-urea

Acquisition Time (sec)	9.9266				
Comment	ARC= 2009000162941 Labjournal 24041B011 Labgroup ID mohrp Contact Person Name Stefan Buerli Contact Person Address 092/4.36A Theme 4652				
Date	20 Aug 2009 08:55:07	Date Stamp	20 Aug 2009 08:55:07		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\OLS5AZO5\2009000162941_1000[1].JDX				
Frequency (MHz)	600.14	Nucleus	1H	Number of Transients	8
Origin	NMR_Roche_Basel	Original Points Count	131072	Owner	serv
Points Count	131072	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	5690.8223
Sweep Width (Hz)	13204.13	Temperature (degree C)	25.027		



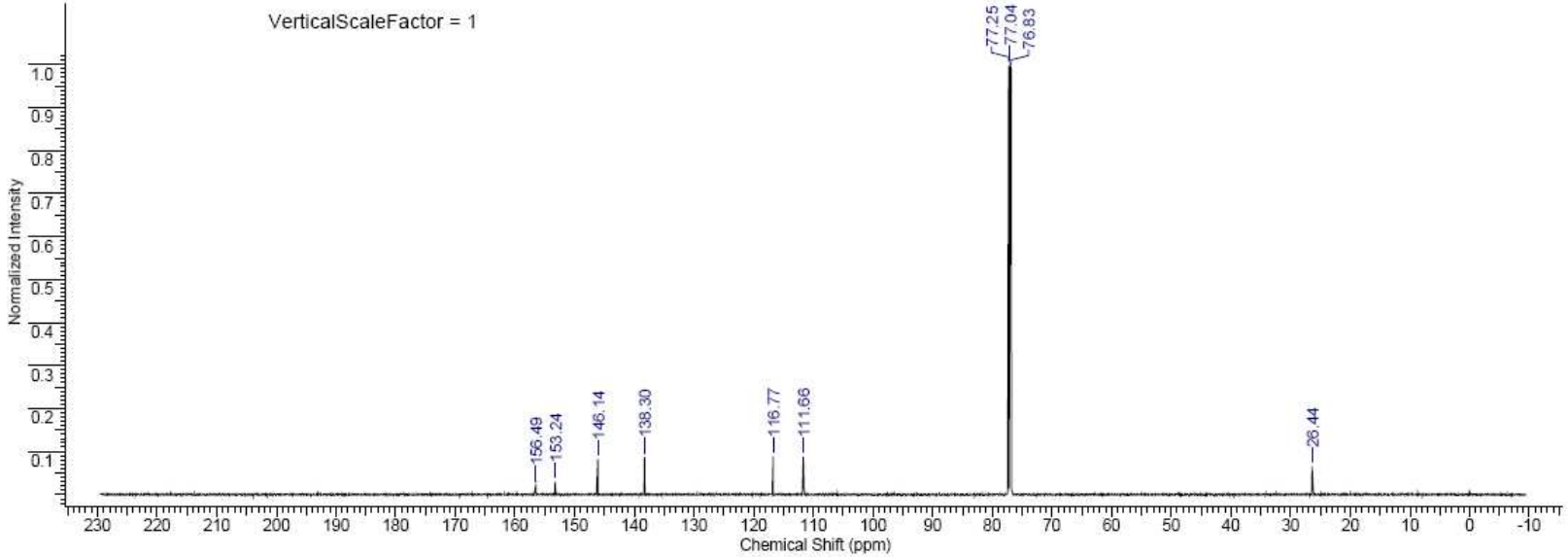
(ppm)	(Hz)	(ppm)	(Hz)	(ppm)	(Hz)
0.00	0.2	6.87	4121.9	7.59	4556.4
1.62	971.2	6.88	4127.2	7.93	4759.9
2.97	1779.8	7.26	4358.7	8.16	4898.2
2.97	1784.6	7.56	4539.0	8.16	4899.2
6.74	4045.5	7.57	4540.9	8.17	4902.6
6.75	4053.7	7.58	4546.5	8.17	4903.3
6.86	4114.8	7.58	4547.5	8.17	4904.3
6.86	4119.9	7.58	4548.3	9.27	5564.2
6.87	4120.7	7.59	4554.6		

No	Color	Structure	Visible
1			True

13C-NMR:

2d = 1-Methyl-3-pyridin-2-yl-urea

Acquisition Time (sec)	3.6351				
Comment	ARC= 2009000162941 Labjournal 24041B011 Labgroup ID mohrp Contact Person Name Stefan Buerli Contact Person Address 092/4.36A Theme 4652				
Date	20 Aug 2009 09:18:44	Date Stamp	20 Aug 2009 09:18:44		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\2CZSS3VR\2009000162941_1002[1].JDX				
Frequency (MHz)	150.92	Nucleus	13C	Number of Transients	512
Origin	NMR Roche Basel	Original Points Count	131072	Owner	serv
Points Count	131072	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	16603.7480
Sweep Width (Hz)	36057.42	Temperature (degree C)	25.027		



(ppm)	(Hz)
26.44	3989.8
76.83	11594.6
77.04	11626.5
77.25	11658.4
111.66	16852.0
116.77	17622.9
138.30	20872.9
146.14	22056.1
153.24	23126.5
156.49	23617.5

No	Color	Structure	Visible
1			True

3a] *N*-(1-Methyl-1*H*-benzoimidazol-2-yl)-acetamide

1-Methyl-1*H*-benzoimidazol-2-ylamine (428 mg, 2.91 mmol) was dissolved in 9.0 ml of CH_2Cl_2 and successively treated at -10°C with 258 µl (3.20 mmol, 1.1 eq.) of pyridine and 218 µl (3.05 mmol, 1.05 eq.) of acetyl chloride. MS indicated after 2 h a mixture of starting material, mono- and di-acetate. Pouring onto crashed ice, twofold extraction with ethyl acetate, washing with water, drying over $MgSO_4$, and evaporation of all solvents, followed by flash chromatography (SiO_2, ethyl acetate / heptane = 6 / 4) and ensuing crystallization from hexane / ethyl acetate afforded 94 mg of the title compound as white crystals.

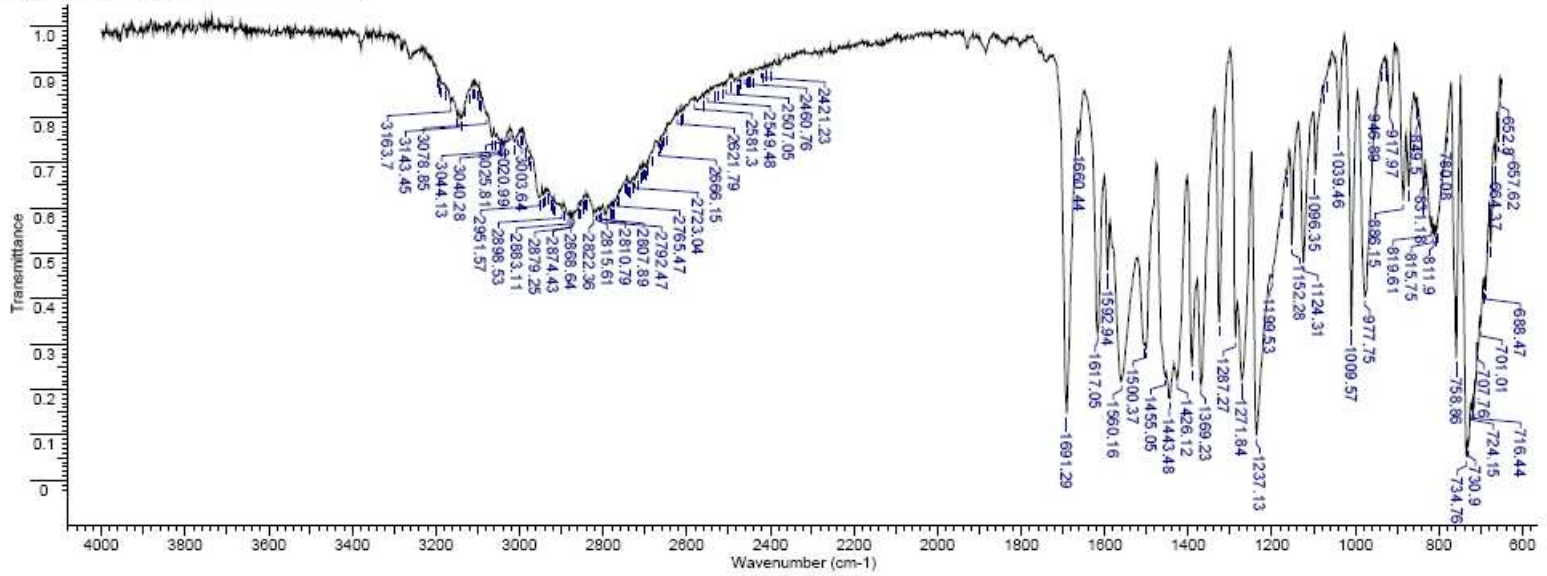
MS: $C_{10}H_{11}N_3O$, expected: 189.0902, found: 189.0905.

IR:

3a = N-(1-Methyl-1H-benzoimidazol-2-yl)-acetamide

17 Dec 2009

Title	*E090807.507 24041B004	Origin	Hoffmann-La Roche Ltd	Owner	Nicolet		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\OLS5AZO5\2009000162265-E090807-507[1].JDX						
Date Stamp	13:30:02	Date	17 Dec 2009 15:31:08	Technique	Infrared	Spectral Region	IR
X Axis	Wavenumber (cm-1)	Y Axis	Transmittance	Spectrum Range	649.9041 - 3999.7058	Points Count	3475
Data Spacing	0.9642						

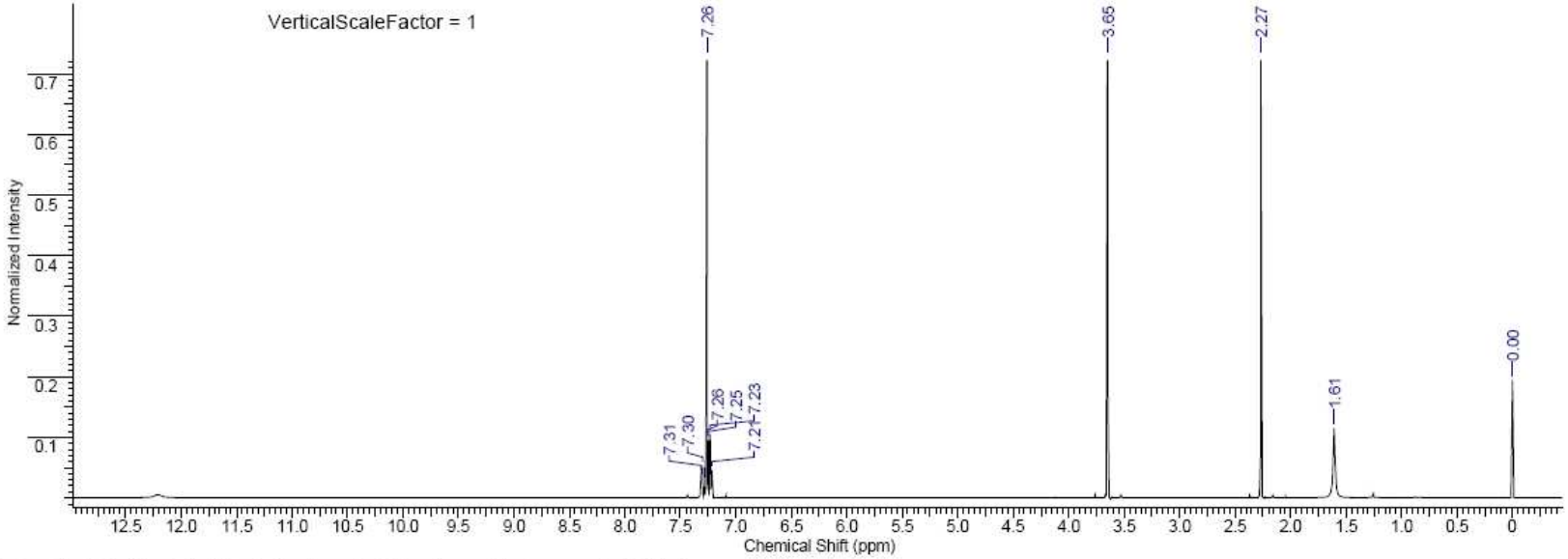


No	cm-1	T	Intensity	No	cm-1	T	Intensity	No	cm-1	T	Intensity	No	cm-1	T	Intensity
1	652.80	0.843	W	27	886.15	0.616	M	53	1506.16	0.300	S	79	2607.33	0.815	W
2	657.62	0.745	W	28	917.97	0.813	W	54	1560.16	0.218	S	80	2613.12	0.811	W
3	664.37	0.699	M	29	926.64	0.910	W	55	1592.94	0.464	M	81	2621.79	0.805	W
4	675.94	0.522	M	30	937.25	0.909	W	56	1617.05	0.324	S	82	2648.79	0.769	W
5	688.47	0.419	S	31	946.89	0.849	W	57	1660.44	0.758	W	83	2653.61	0.764	W
6	692.33	0.420	S	32	977.75	0.405	S	58	1691.29	0.148	VS	84	2657.47	0.757	W
7	701.01	0.337	S	33	1009.57	0.340	S	59	2400.02	0.909	W	85	2661.33	0.751	W
8	707.76	0.285	S	34	1039.46	0.767	W	60	2409.66	0.910	W	86	2666.15	0.734	W
9	716.44	0.156	S	35	1069.35	0.886	W	61	2415.44	0.906	W	87	2682.54	0.723	M
10	720.29	0.166	S	36	1077.07	0.859	W	62	2421.23	0.906	W	88	2691.22	0.700	M
11	724.15	0.153	S	37	1096.35	0.672	M	63	2441.48	0.895	W	89	2697.01	0.690	M
12	728.01	0.087	VS	38	1124.31	0.480	M	64	2446.30	0.897	W	90	2700.86	0.693	M
13	730.90	0.073	VS	39	1152.28	0.517	M	65	2452.09	0.896	W	91	2703.75	0.691	M
14	734.76	0.051	VS	40	1163.85	0.677	M	66	2455.94	0.896	W	92	2709.54	0.685	M

1H-NMR:

3a = N-(1-Methyl-1H-benzoimidazol-2-yl)-acetamide in CDCl3 at ambient temperature

Acquisition Time (sec)	9.9266				
Comment	ARC= 2009000162265 Labjournal 24041B004 Labgroup ID mohrp Contact Person Name Stefan Buerli Contact Person Address 092/4.36A Theme 4652				
Date	08 Aug 2009 04:19:26	Date Stamp	08 Aug 2009 04:19:26		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\MT92FAHG\2009000162265_1000[2].JDX				
Frequency (MHz)	600.14	Nucleus	1H	Number of Transients	8
Origin	NMR_Roche_Basel	Original Points Count	131072	Owner	serv
Points Count	131072	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	5690.5703
Sweep Width (Hz)	13204.13	Temperature (degree C)	25.027		

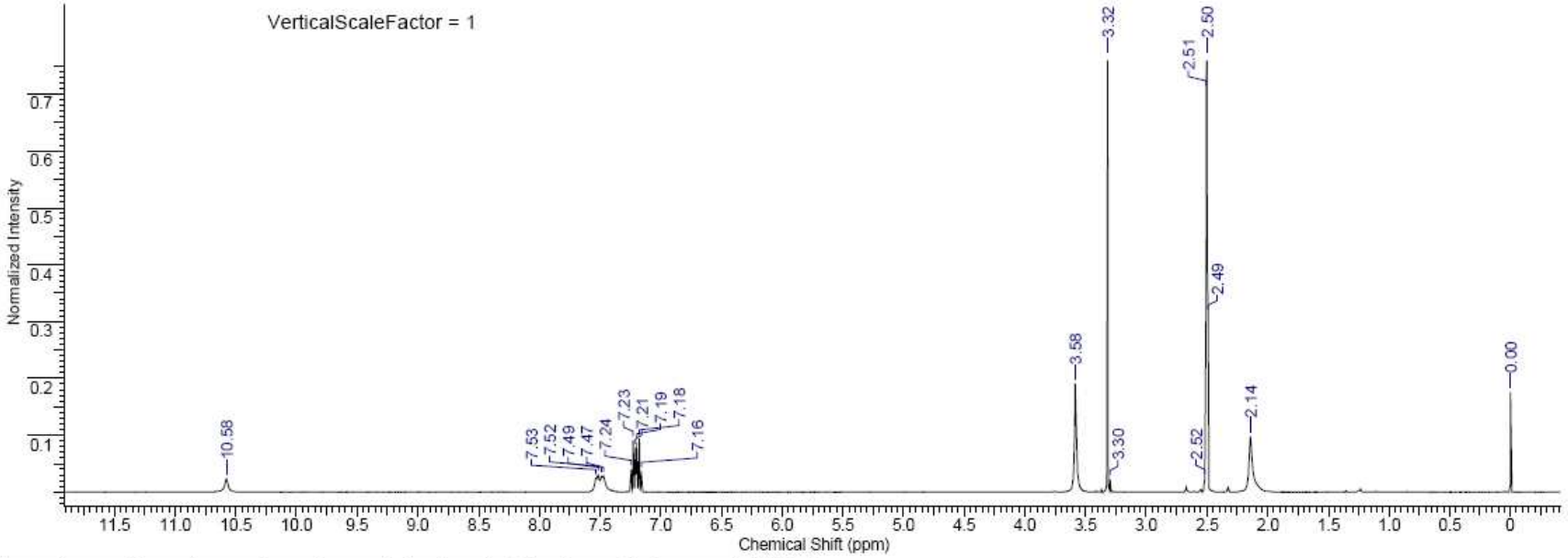


(ppm)	(Hz)	(ppm)	(Hz)
0.00	0.1	7.25	4349.8
1.61	965.4	7.25	4352.9
2.27	1360.4	7.26	4354.4
3.65	2189.5	7.26	4358.3
7.21	4329.8	7.27	4360.3
7.22	4333.1	7.27	4361.8
7.22	4334.6	7.28	4368.0
7.23	4338.2	7.28	4369.2
7.23	4340.7	7.30	4380.9
7.24	4342.2	7.31	4388.6
7.25	4348.1		

No	Color	Structure	Visible
1			True

3a = N-(1-Methyl-1H-benzoimidazol-2-yl)-acetamide in DMSO at ambient temperature

Acquisition Time (sec)	3.7224				
Comment	ARC= 2009000162265 Labjournal 24041B004 Labgroup ID mohrp Contact Person Name Stefan Buerli Contact Person Address 092/4.36A Theme 4652				
Date	21 Oct 2009 05:58:41	Date Stamp	21 Oct 2009 05:58:41		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\RUC7ZL0X\2009000162265_21[1].JDX				
Frequency (MHz)	400.13	Nucleus	1H	Number of Transients	256
Origin	NMR_Roche_Basel	Original Points Count	32768	Owner	serv
Points Count	32768	Solvent	DMSO-d6	Spectrum Offset (Hz)	3997.6646
Sweep Width (Hz)	8802.82	Temperature (degree C)	25.000		

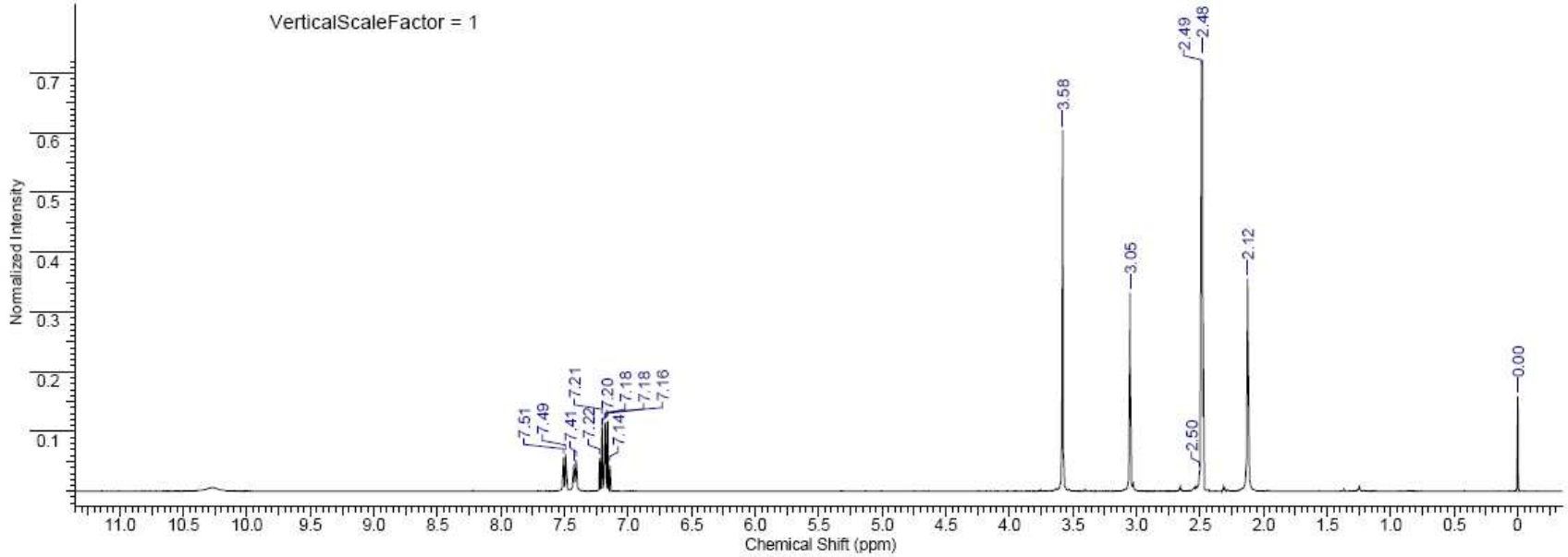


(ppm)	(Hz)	(ppm)	(Hz)	(ppm)	(Hz)
-0.00	-0.2	3.58	1434.4	7.23	2891.2
2.14	856.8	7.16	2863.8	7.24	2897.4
2.49	997.0	7.16	2865.2	7.24	2898.5
2.50	998.9	7.18	2871.4	7.47	2989.3
2.50	1000.8	7.18	2872.7	7.49	2995.5
2.51	1002.6	7.19	2878.9	7.52	3007.6
2.51	1004.2	7.20	2880.2	7.53	3014.3
2.52	1007.7	7.20	2882.1	10.58	4231.8
3.30	1318.8	7.21	2883.7		
3.32	1328.2	7.22	2889.9		

No	Color	Structure	Visible
1			True

3a = N-(1-Methyl-1H-benzoimidazol-2-yl)-acetamide in DMSO 80 degree C

Acquisition Time (sec)	3.7224				
Comment	ARC= 2009000162265 Labjournal 24041B004 Labgroup ID mohrp Contact Person Name Stefan Buerli Contact Person Address 092/4.36A Theme 4652				
Date	21 Oct 2009 07:49:33	Date Stamp	21 Oct 2009 07:49:33		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\2CZSS3VR\2009000162265_27[1].JDX				
Frequency (MHz)	400.13	Nucleus	1H	Number of Transients	256
Origin	NMR Roche Basel	Original Points Count	32768	Owner	serv
Points Count	32768	Solvent	DMSO-d6	Spectrum Offset (Hz)	3990.9780
Sweep Width (Hz)	8802.82	Temperature (degree C)	80.000		



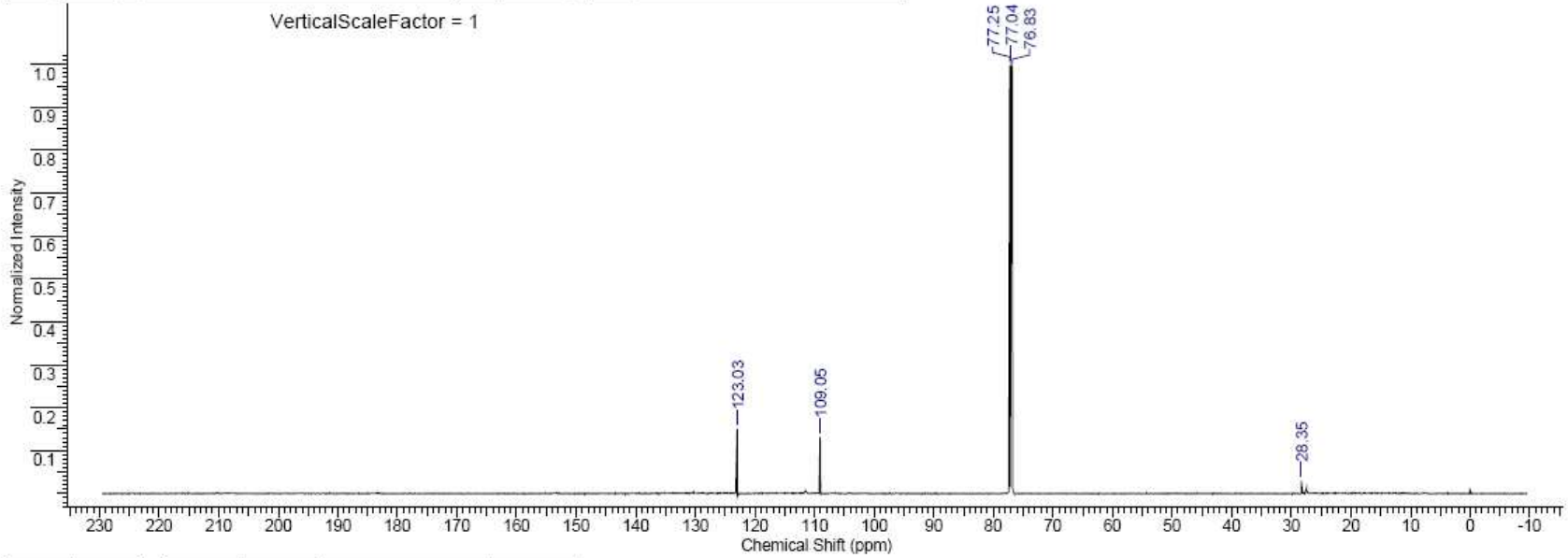
(ppm)	(Hz)	(ppm)	(Hz)	(ppm)	(Hz)
-0.00	-0.2	3.05	1220.3	7.20	2882.1
2.12	849.8	3.58	1432.5	7.21	2883.5
2.47	990.0	7.14	2857.1	7.22	2889.4
2.48	991.9	7.14	2858.5	7.22	2890.7
2.48	993.8	7.16	2864.4	7.41	2964.3
2.49	995.7	7.16	2865.7	7.43	2971.9
2.49	997.6	7.18	2871.9	7.49	2997.4
2.50	1000.8	7.18	2873.5	7.51	3004.6
2.51	1002.7	7.19	2876.0		

No	Color	Structure	Visible
1			True

13C-NMR: most peaks not visible due to very strong line broadening

3a = N-(1-Methyl-1H-benzoimidazol-2-yl)-acetamide in CDCl3 at ambient temperature

Acquisition Time (sec)	3.6351				
Comment	ARC= 2009000162265 Labjournal 24041B004 Labgroup ID mohrp Contact Person Name Stefan Buerli Contact Person Address 092/4.36A Theme 4652				
Date	13 Oct 2009 03:10:59	Date Stamp	13 Oct 2009 03:10:59		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\MT92FAHG\2009000162265_3013[1].JDX				
Frequency (MHz)	150.92	Nucleus	13C	Number of Transients	4048
Origin	NMR_Roche_Basel	Original Points Count	131072	Owner	serv
Points Count	131072	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	16603.8066
Sweep Width (Hz)	36057.42	Temperature (degree C)	25.027		



(ppm)	(Hz)
28.35	4278.2
76.83	11594.7
77.04	11626.6
77.25	11658.5
109.05	16458.4
123.02	18565.4
123.03	18567.3

No	Color	Structure	Visible
1			True

3b] *N*-(1*H*-Benzoimidazol-2-yl)-acetamide

1H-Benzoimidazol-2-ylamine (266 mg, 2.00 mmol) was treated with 10 ml of acetic anhydride and stirred for 4 h at ambient temperature. The initially heterogeneous solution became gradually homogeneous, before a solid started precipitating. TLC indicated then complete disappearance of starting material. The reaction mixture was heated to reflux for 30 minutes. Cooling, pouring onto crashed ice, twofold extraction with ethyl acetate, washing with water, drying over Na_2SO_4, and evaporation of all solvents, followed by flash chromatography (SiO_2, gradient CH_2Cl_2 to CH_2Cl_2 / MeOH = 92 / 8) and ensuing crystallization from heptane / ethyl acetate afforded 25 mg of the title compound as off-white crystals. The diacetate in the less polar fractions was discarded.

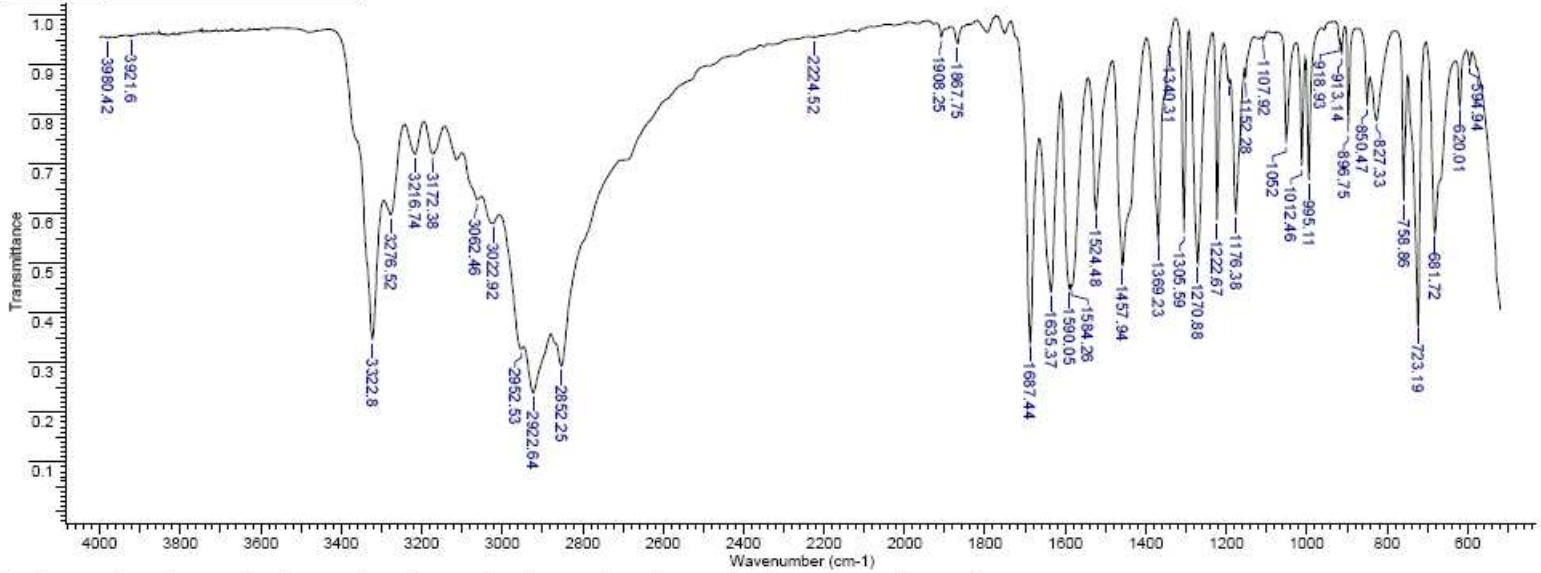
MS: $C_9H_9N_3O$, expected: 175.075, found: 175.074.

IR:

3b = N-(1H-Benzoimidazol-2-yl)-acetamide

17 Dec 2009

Title	*E091110.102 23925-B032	Origin	Hoffmann-La Roche Ltd	Owner	Nicolet		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\BAZDHLFF\20090001675 31-E091110-102[1].JDX						
Date Stamp	08:49:42	Date	17 Dec 2009 15:36:04	Technique	Infrared	Spectral Region	IR
X Axis	Wavenumber (cm-1)	Y Axis	Transmittance	Spectrum Range	519.7302 - 3999.7058	Points Count	3610
Data Spacing	0.9642						

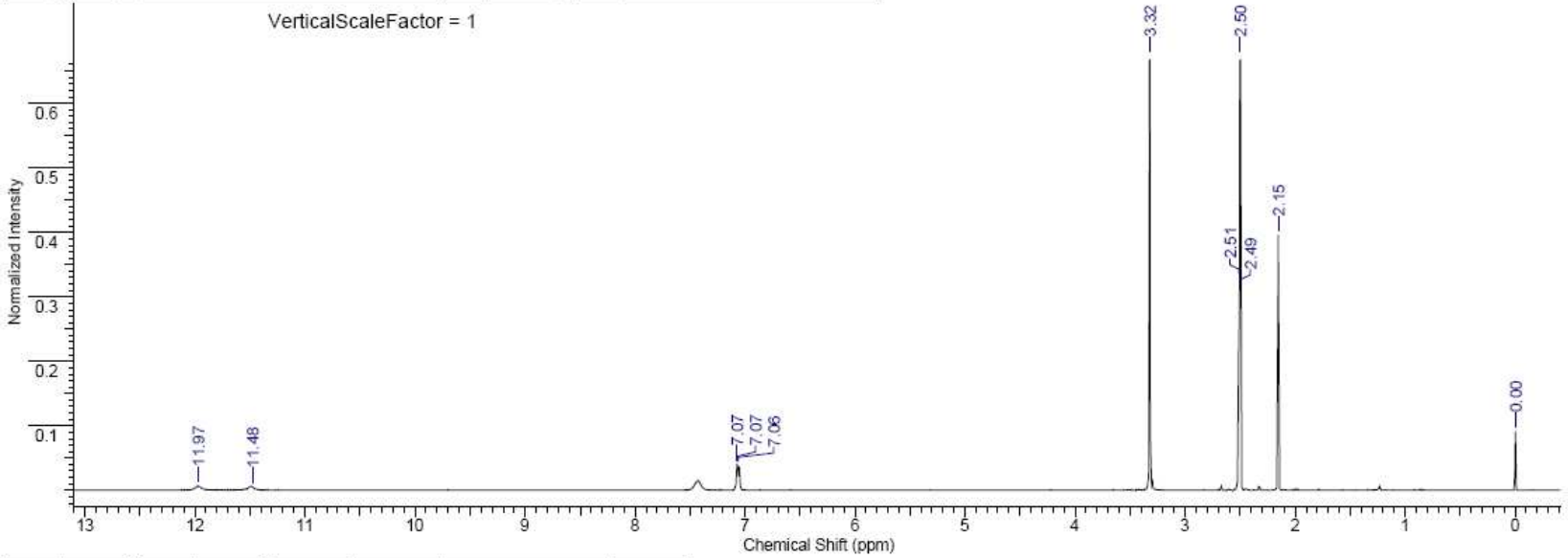


No	cm-1	T	Intensity	No	cm-1	T	Intensity	No	cm-1	T	Intensity	No	cm-1	T	Intensity
1	594.94	0.900	W	12	1012.46	0.695	M	23	1457.94	0.495	S	34	2952.53	0.327	S
2	620.01	0.816	W	13	1052.00	0.741	M	24	1524.48	0.606	M	35	3022.92	0.580	M
3	681.72	0.561	M	14	1107.92	0.949	VW	25	1584.26	0.453	S	36	3062.46	0.627	M
4	723.19	0.376	S	15	1152.28	0.872	W	26	1590.05	0.448	S	37	3172.38	0.720	M
5	758.86	0.625	M	16	1176.38	0.599	M	27	1635.37	0.441	S	38	3216.74	0.720	M
6	827.33	0.788	W	17	1193.74	0.865	W	28	1687.44	0.338	S	39	3276.52	0.597	M
7	850.47	0.818	W	18	1222.67	0.586	M	29	1867.75	0.942	VW	40	3322.80	0.346	S
8	896.75	0.765	M	19	1270.88	0.498	S	30	1908.25	0.956	VW	41	3921.60	0.957	VW
9	913.14	0.921	W	20	1305.59	0.563	M	31	2224.52	0.955	VW	42	3980.42	0.954	VW
10	918.93	0.945	VW	21	1340.31	0.935	VW	32	2852.25	0.293	VS				
11	995.11	0.666	M	22	1369.23	0.544	M	33	2922.64	0.239	VS				

1H-NMR:

3b = N-(1H-Benzoimidazol-2-yl)-acetamide

Acquisition Time (sec)	3.7224				
Comment	ARC= 2009000166479 Labjournal 23925.B032 Labgroup ID mohrp Contact Person Name Peter Mohr Contact Person Address 092/4.30C Theme 4652				
Date	28 Oct 2009 07:50:05	Date Stamp	28 Oct 2009 07:50:05		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\RUC7ZL0X\2009000166479_10[1].JDX				
Frequency (MHz)	400.13	Nucleus	1H	Number of Transients	30
Origin	NMR_Roche_Basel	Original Points Count	32768	Owner	serv
Points Count	32768	Solvent	DMSO-d6	Spectrum Offset (Hz)	3997.7241
Sweep Width (Hz)	8802.82	Temperature (degree C)	25.000		



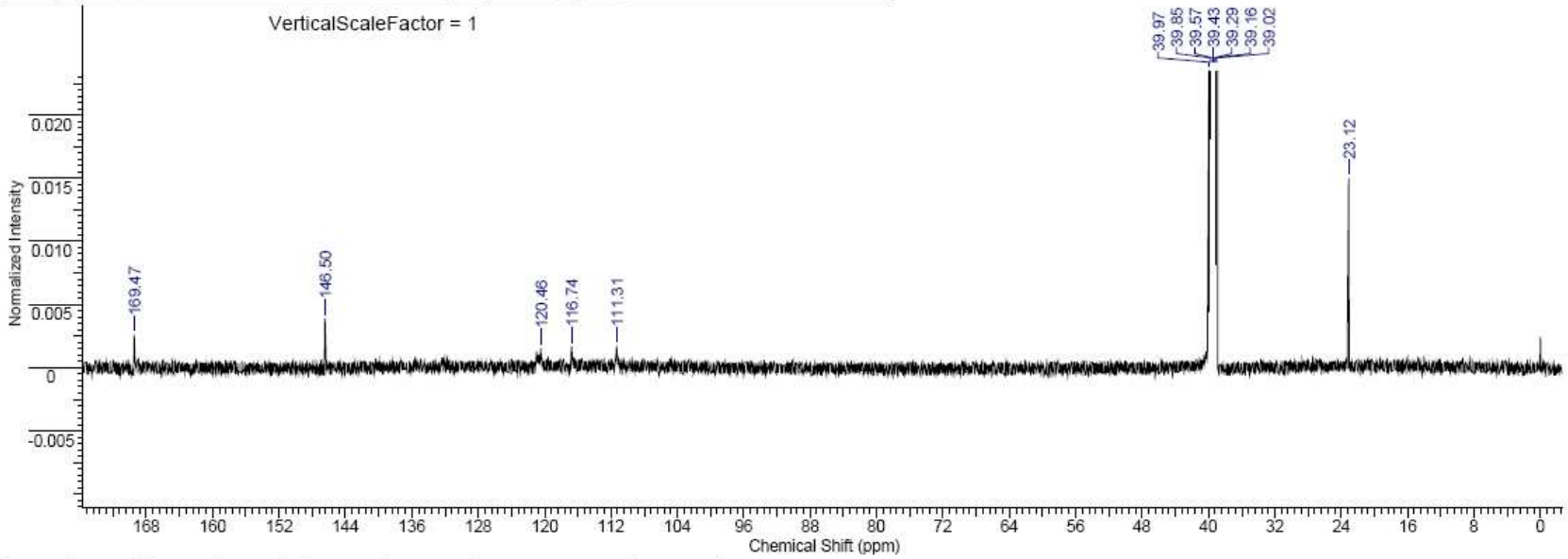
(ppm)	(Hz)	(ppm)	(Hz)
-0.00	-0.2	3.32	1328.6
2.15	861.9	7.05	2821.7
2.49	997.1	7.06	2824.7
2.50	998.9	7.07	2827.9
2.50	1000.8	7.07	2830.8
2.51	1002.7	11.48	4593.2
2.51	1004.3	11.97	4790.6

No	Color	Structure	Visible
1			True

13C-NMR: some peaks not visible due to very strong line broadening

3b = N-(1H-Benzoimidazol-2-yl)-acetamide

Acquisition Time (sec)	3.6351				
Comment	ARC= 2009000166479 Labjournal 23925.B032 Labgroup ID mohrp Contact Person Name Peter Mohr Contact Person Address 092/4.30C Theme 4652				
Date	26 Oct 2009 12:34:55	Date Stamp	26 Oct 2009 12:34:55		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\OLS5AZO5\2009000166479_2004[1].JDX				
Frequency (MHz)	150.92	Nucleus	13C	Number of Transients	1024
Origin	NMR Roche Basel	Original Points Count	131072	Owner	serv
Points Count	131072	Solvent	DMSO-d6	Spectrum Offset (Hz)	16515.2637
Sweep Width (Hz)	36057.42	Temperature (degree C)	25.027		



(ppm)	(Hz)	(ppm)	(Hz)
23.12	3489.2	39.85	6014.1
39.02	5888.4	39.97	6032.2
39.16	5909.3	111.31	16798.8
39.29	5930.2	116.74	17618.3
39.43	5951.3	120.46	18179.5
39.57	5972.3	146.50	22109.5
39.71	5993.2	169.47	25576.9

No	Color	Structure	Visible
1			True

4a] *N*-(1-Methyl-1*H*-benzoimidazol-2-ylmethyl)-acetamide

C-(1-Methyl-1*H*-benzoimidazol-2-yl)-methylamine (229 mg, 1.42 mmol) was dissolved in 4.5 ml of CH_2Cl_2 and successively treated at -10°C with 126 µl (1.56 mmol, 1.1 eq.) of pyridine and 106 µl (1.49 mmol, 1.05 eq.) of acetyl chloride. The reaction mixture was kept over night at ambient temperature. Pouring onto crashed ice / ammonium chloride / ethyl acetate, additional extraction with ethyl acetate, washing with water, drying over $MgSO_4$, and evaporation of all solvents, followed by flash chromatography (SiO_2, CH_2Cl_2 / MeOH = 92 / 8) and ensuing crystallization from hexane / ethyl acetate yielded 54 mg of the title compound as white crystals.

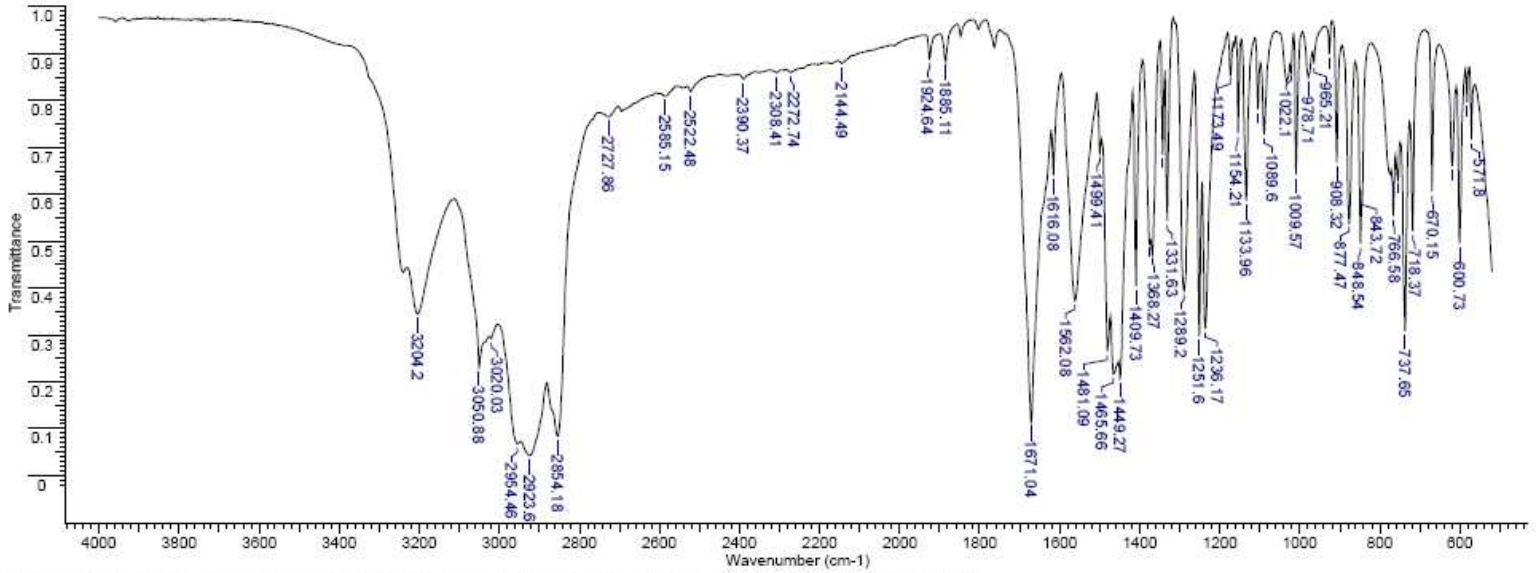
MS: $C_{11}H_{13}N_3O$, expected: 204.11314, found: 204.11304.

IR:

4a = N-(1-Methyl-1H-benzoimidazol-2-ylmethyl)-acetamide

17 Dec 2009

Title	*E091027.101 24041B046	Origin	Hoffmann-La Roche Ltd	Owner	Nicolet		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\RXKDEEBG\20090001666621-E091027-101[1].JDX						
Date Stamp	07:26:46	Date	17 Dec 2009 15:39:46	Technique	Infrared	Spectral Region	IR
X Axis	Wavenumber (cm-1)	Y Axis	Transmittance	Spectrum Range	519.7302 - 3999.7058	Points Count	3610
Data Spacing	0.9642						

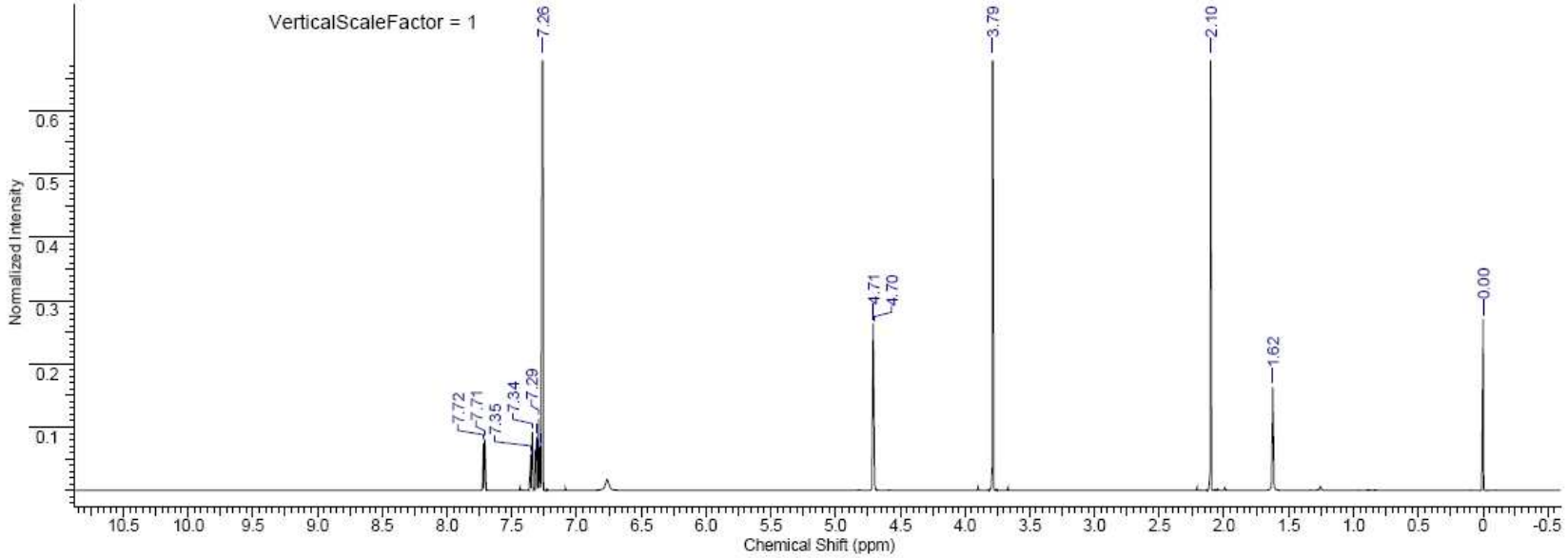


No	cm-1	T	Intensity	No	cm-1	T	Intensity	No	cm-1	T	Intensity	No	cm-1	T	Intensity
1	571.80	0.717	W	15	965.21	0.878	W	29	1368.27	0.471	M	43	2308.41	0.859	W
2	582.41	0.795	W	16	978.71	0.849	W	30	1375.98	0.495	M	44	2390.37	0.846	W
3	600.73	0.495	M	17	1009.57	0.642	M	31	1409.73	0.404	S	45	2522.48	0.818	W
4	620.01	0.659	M	18	1022.10	0.861	W	32	1449.27	0.207	S	46	2585.15	0.809	W
5	670.15	0.605	M	19	1089.60	0.727	W	33	1465.66	0.217	S	47	2727.86	0.765	W
6	718.37	0.521	M	20	1105.03	0.781	W	34	1481.09	0.265	S	48	2854.18	0.084	VS
7	737.65	0.308	S	21	1133.96	0.586	M	35	1499.41	0.687	M	49	2923.60	0.042	VS
8	755.01	0.631	M	22	1154.21	0.731	W	36	1562.08	0.372	S	50	2954.46	0.068	VS
9	766.58	0.553	M	23	1173.49	0.854	W	37	1616.08	0.639	M	51	3020.03	0.292	S
10	843.72	0.596	M	24	1236.17	0.313	S	38	1671.04	0.114	VS	52	3050.88	0.230	S
11	848.54	0.494	M	25	1251.60	0.296	S	39	1885.11	0.883	W	53	3204.20	0.345	S
12	877.47	0.538	M	26	1289.20	0.394	S	40	1924.64	0.889	VW				
13	908.32	0.668	M	27	1331.63	0.543	M	41	2144.49	0.879	W				
14	926.64	0.898	VW	28	1343.20	0.684	M	42	2272.74	0.860	W				

1H-NMR:

4a = N-(1-Methyl-1H-benzoimidazol-2-ylmethyl)-acetamide

Acquisition Time (sec)	9.9266				
Comment	ARC= 2009000166621 Labjournal 24041B046 Labgroup ID mohrp Contact Person Name Stefan Buerli Contact Person Address 092/4.36A Theme 4652				
Date	26 Oct 2009 15:28:25	Date Stamp	26 Oct 2009 15:28:25		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\PDRT2U0E\2009000166621_1000[1].JDX				
Frequency (MHz)	600.14	Nucleus	1H	Number of Transients	8
Origin	NMR_Roche_Basel	Original Points Count	131072	Owner	serv
Points Count	131072	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	5690.6846
Sweep Width (Hz)	13204.13	Temperature (degree C)	25.027		



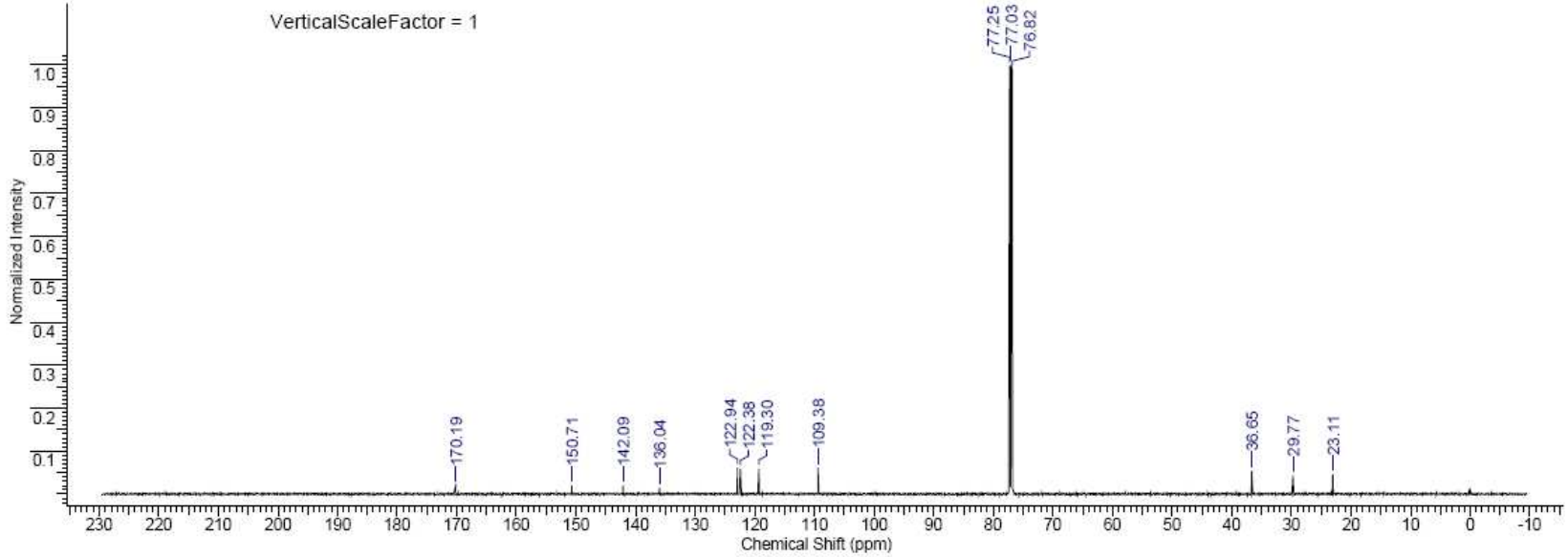
(ppm)	(Hz)	(ppm)	(Hz)	(ppm)	(Hz)
0.00	0.1	7.28	4367.5	7.34	4406.1
1.62	974.3	7.28	4368.8	7.34	4407.3
2.10	1262.4	7.29	4374.9	7.35	4413.2
3.79	2272.4	7.29	4376.6	7.36	4414.8
4.70	2821.2	7.30	4378.2	7.71	4624.2
4.71	2826.2	7.31	4384.4	7.71	4625.5
7.26	4357.8	7.31	4385.7	7.72	4632.7
7.27	4360.2	7.32	4391.6		
7.27	4361.7	7.32	4392.8		

No	Color	Structure	Visible
1			True

13C-NMR:

4a = N-(1-Methyl-1H-benzoimidazol-2-ylmethyl)-acetamide

Acquisition Time (sec)	3.6351				
Comment	ARC= 2009000166621 Labjournal 24041B046 Labgroup ID mohrp Contact Person Name Stefan Buerli Contact Person Address 092/4.36A Theme 4652				
Date	26 Oct 2009 15:51:42	Date Stamp	26 Oct 2009 15:51:42		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\YJU36DM3\2009000166621_1002[1].JDX				
Frequency (MHz)	150.92	Nucleus	13C	Number of Transients	512
Origin	NMR_Roche_Basel	Original Points Count	131072	Owner	serv
Points Count	131072	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	16603.5645
Sweep Width (Hz)	36057.42	Temperature (degree C)	25.027		



(ppm)	(Hz)	(ppm)	(Hz)
23.11	3488.1	119.30	18004.8
29.77	4493.0	122.38	18470.2
36.65	5531.3	122.94	18553.9
76.82	11594.2	136.04	20531.0
77.03	11626.1	142.09	21444.3
77.25	11658.0	150.71	22745.3
109.38	16508.0	170.19	25685.0

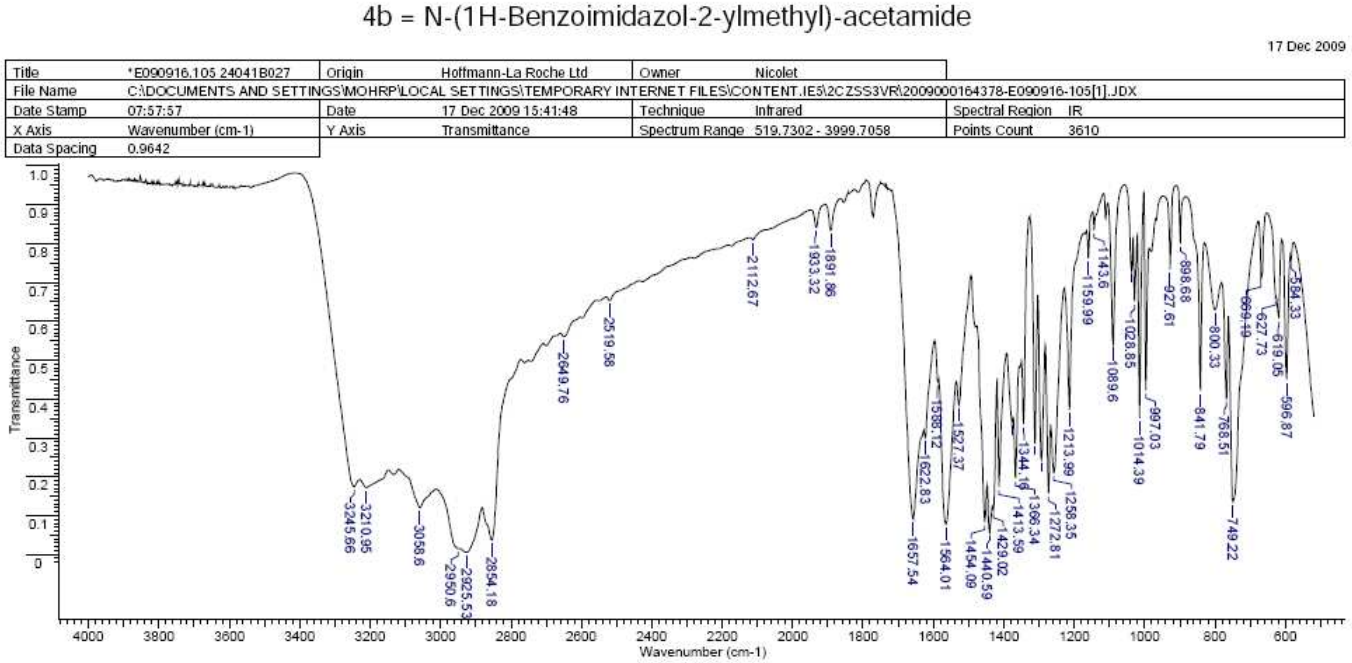
No	Color	Structure	Visible
1			True

4b] *N*-(1*H*-Benzoimidazol-2-ylmethyl)-acetamide

Was bought from Princeton.

MS: $C_{10}H_{11}N_3O$, expected: 190.09749, found: 190.09740 $(M+H)^+$.

IR:

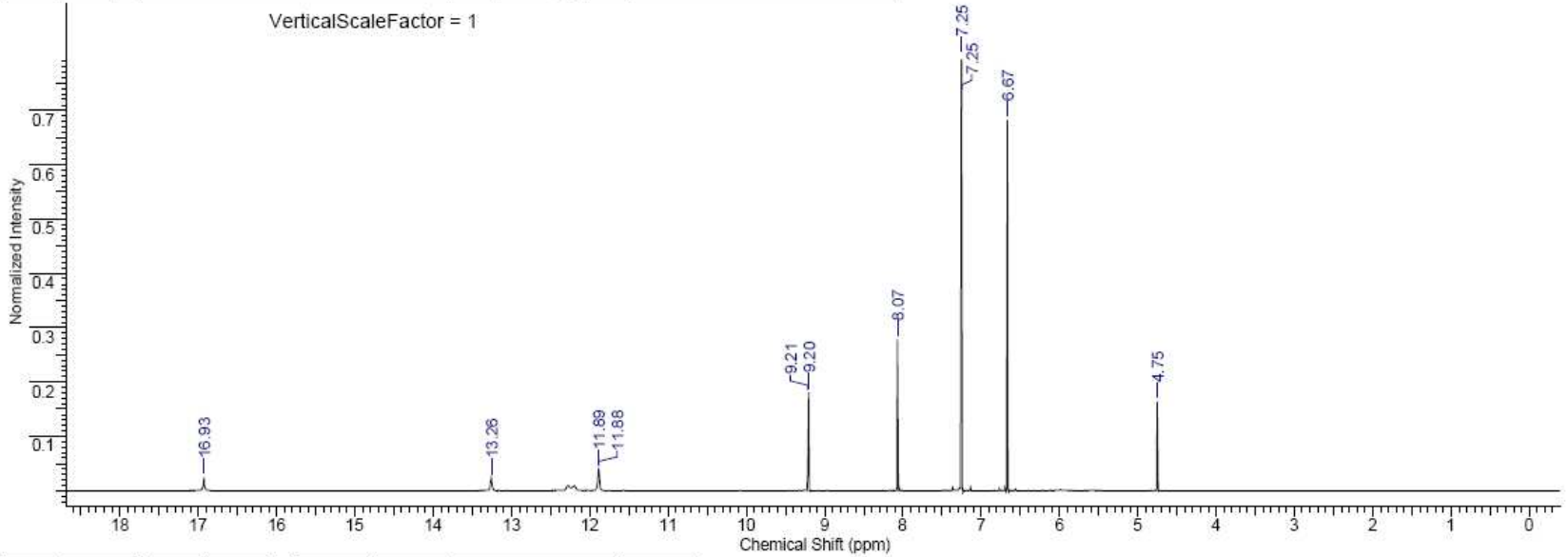


No	cm-1	T	Intensity	No	cm-1	T	Intensity	No	cm-1	T	Intensity	No	cm-1	T	Intensity
1	584.33	0.754	W	13	1014.39	0.350	S	25	1366.34	0.196	S	37	1933.32	0.842	W
2	596.87	0.450	M	14	1028.85	0.651	M	26	1376.95	0.339	S	38	2112.67	0.810	W
3	619.05	0.606	M	15	1037.53	0.730	W	27	1413.59	0.173	S	39	2519.58	0.652	M
4	627.73	0.661	M	16	1089.60	0.543	M	28	1429.02	0.114	S	40	2649.76	0.560	M
5	669.19	0.708	W	17	1143.60	0.834	W	29	1440.59	0.056	VS	41	2854.18	0.037	VS
6	749.22	0.135	S	18	1159.99	0.762	W	30	1454.09	0.083	VS	42	2925.53	0.005	VS
7	768.51	0.400	M	19	1213.99	0.372	S	31	1527.37	0.385	S	43	2950.60	0.015	VS
8	800.33	0.629	M	20	1258.35	0.209	S	32	1564.01	0.078	VS	44	3058.60	0.119	S
9	841.79	0.421	M	21	1272.81	0.157	S	33	1588.12	0.443	M	45	3210.95	0.172	S
10	898.68	0.800	W	22	1293.06	0.244	S	34	1622.83	0.301	S	46	3245.66	0.174	S
11	927.61	0.733	W	23	1311.38	0.287	S	35	1657.54	0.091	VS				
12	997.03	0.423	M	24	1344.16	0.335	S	36	1891.86	0.833	W				

1H-NMR:

4b = N-(1H-Benzoimidazol-2-ylmethyl)-acetamide

Acquisition Time (sec)	9.9266				
Comment	ARC= 2009000164378 Labjournal 24041B027 Labgroup ID mohrp Contact Person Name Stefan Buerli Contact Person Address 092/4.36A Theme 4652				
Date	16 Sep 2009 08:35:02	Date Stamp	16 Sep 2009 08:35:02		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\M14NAXY5\2009000164378_1000[1].JDX				
Frequency (MHz)	600.14	Nucleus	1H	Number of Transients	8
Origin	NMR Roche Basel	Original Points Count	131072	Owner	serv
Points Count	131072	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	5701.4033
Sweep Width (Hz)	13204.13	Temperature (degree C)	25.027		



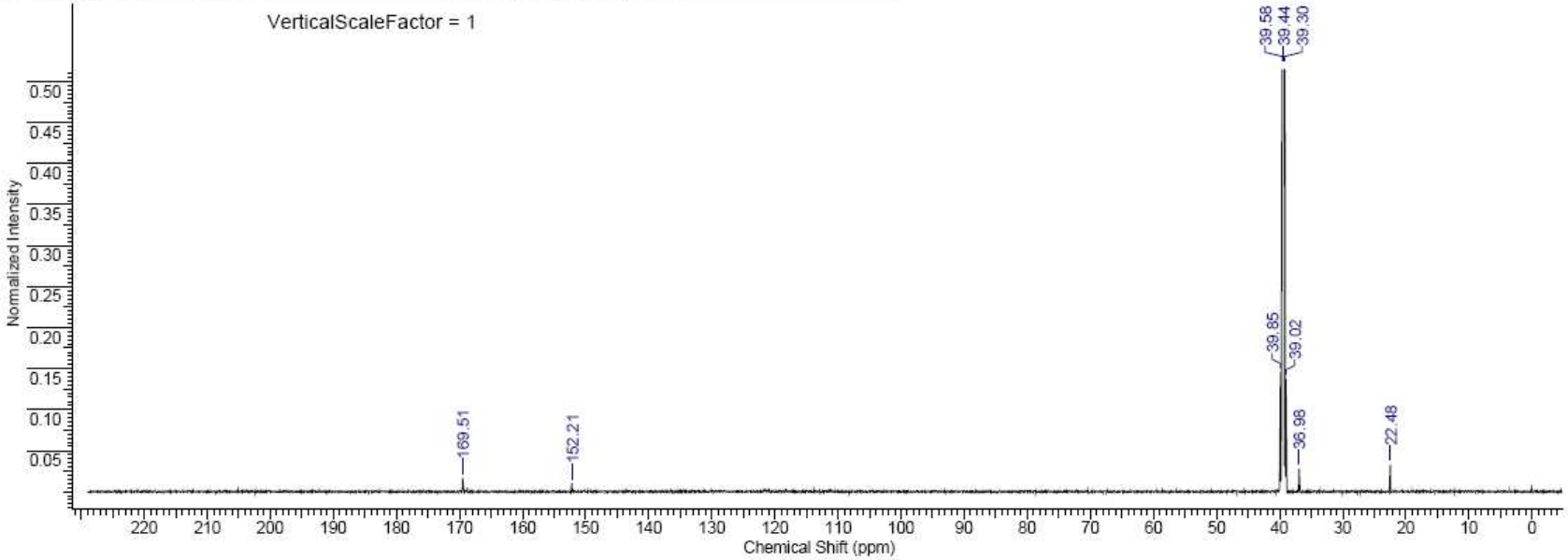
(ppm)	(Hz)	(ppm)	(Hz)
4.75	2852.0	8.07	4845.0
6.67	4001.1	9.20	5524.2
7.25	4349.2	9.21	5529.8
7.25	4351.0	11.88	7131.4
7.25	4352.8	11.89	7135.8
7.26	4354.8	13.26	7956.8
7.26	4356.6	16.93	10159.3

No	Color	Structure	Visible
1			True

13C-NMR: some peaks not visible due to very strong line broadening

4b = N-(1H-Benzoimidazol-2-ylmethyl)-acetamide

Acquisition Time (sec)	3.6351				
Comment	ARC= 2009000164378 Labjournal 24041B027 Labgroup ID mohrp Contact Person Name Stefan Buerli Contact Person Address 092/4.36A Theme 4652				
Date	16 Sep 2009 08:59:25	Date Stamp	16 Sep 2009 08:59:25		
File Name	C:\DOCUMENTS AND SETTINGS\MOHRP\LOCAL SETTINGS\TEMPORARY INTERNET FILES\CONTENT.IE5\RUC7ZL0X\2009000164378_1002[1].JDX				
Frequency (MHz)	150.92	Nucleus	13C	Number of Transients	256
Origin	NMR_Roche_Basel	Original Points Count	131072	Owner	serv
Points Count	131072	Solvent	DMSO-d6	Spectrum Offset (Hz)	16515.3691
Sweep Width (Hz)	36057.42	Temperature (degree C)	25.027		



(ppm)	(Hz)	(ppm)	(Hz)
22.48	3392.2	39.58	5972.6
36.98	5580.3	39.71	5993.5
39.02	5888.7	39.85	6014.5
39.16	5909.6	39.97	6032.6
39.30	5930.5	152.21	22970.7
39.44	5951.7	169.51	25581.9

No	Color	Structure	Visible
1			True

S49-50: Methods for Measurement of Physicochemical Properties

LIPOPHILICITY DETERMINATION (LOG D):

Lipophilicity was determined by the new CAMDIS® method as described in US 2006211121 A1 and EP 1705474 A1. We found excellent quantitative agreement with the conventional shake-flask method (M.M. Abraham, H.S. Chadha, J.P.Dixon, and A.J. Leo, Hydrogen bonding, Part 9. The partition of solutes between water and various alcohols, Phys. Org. Chem. 7:712-716, 1994). However, for some of the more lipophilic molecules only the former procedure was applicable.

LYOPHILISATION SOLUBILITY ASSAY (LYSA):

Samples were prepared in duplicate from 10 mM dimethylsulfoxide stock solutions. After evaporation (1h) of dimethylsulfoxide with a centrifugal vacuum evaporator (Genevac Technologies), the compounds were dissolved in 0.05 M phosphate buffer (pH 6.5), stirred for one hour and shaken two hours. After one night, the solutions were filtered using a microtiter filter plate (Millipore MSDV N65) and the filtrate and its 1/10 dilution were analyzed by direct UV measurement or by HPLC-UV. In addition a four point calibration curve is prepared from the 10 mM stock solutions and used for the solubility determination of the compounds. The results are expressed in µg/ml. Starting from a 10 mM stock solution, the measurement range for MW 500 was 0-666 µg/ml. In case the percentage of sample measured in solution after evaporation divided by the calculated maximum of sample amount was larger than 80% the solubility was reported as larger than this value.

PARALLEL ARTIFICIAL MEMBRANE PERMEABILITY ASSAY (PAMPA):

PAMPA PSR4p is an automated assay which is based on 96 well microplates. The permeation of drugs is measured using a "sandwich" construction. A filterplate is coated with phospholipids (membrane) and placed into a donor plate containing a drug/buffer solution. Finally the filterplate is filled with buffer solution (acceptor). The donor concentration is measured at t-start (reference) and compared with the donor and acceptor concentration after a certain time t-end.

The following setup is used for the PAMPA PSR4p assay:

Donor: 0.05 M MOPSO buffer at pH 6.5 + 0.5% (w/v) Glyco Cholic Acid

Membrane: 10% (w/v) Egg Lecithin + 0.5% (w/v) Cholesterol in Dodecane

Acceptor: 0.05 M MOPSO buffer at pH 6.5.

The liquid handling is done with a TECAN TeMO pipetting robot. The drug analysis is based on UV spectroscopy. All samples are transferred into 96 well UV plates. A SpectraMax 190 UV plate reader is used to collect the UV spectras.

S51-52: Summary of C=O···H-N interaction statistics (CSD)

Topology	CSD % H-bond (# entries)	# Prous entries	CSD / PDB example
C=O···H-N (5-membered)			
aC3a	40.4 (297)	12	BEFSOU / 1jd2
aNa	9.1 (297)	8	LAGFUV / 1afe
aC4a	8.8 (1476)	420	DEZTAD / 1gbm
C=O···H-N (6-membered)			
cC3aC3a	93.0 (242)	18	ACEMEB / 3ce3
aC3cC3a	89.5 (447)	49	ABEKIC / 2nq6
cNaC3a	96.0 (25)	6	ADILOP / –
aNaC3c	93.5 (31)	6	CIVRUV / 1bwb
aNaC3a	85.3 (312)	18	ABEFAP / 2ati
aC4aC3a	17.5 (103)	7	COYMOS / 1jaq
aC4aC4a	8.8 (331)	82	BAWXED / 2huw
C=O···H-N (7-membered)			

aC4aC3cC3a	61.1 (18)	7	MISBEW / 1pxx
aNaC3cC3a	36.6 (41)	8	BEDLUR / 1inf
aNaC4aC4a	17.8 (45)	40	XEMLIL / 4hvp
aNaC4aC3a	0.8 (799)	91	BXGLAL / 1eld
C=O···H-N (8-membered)			
aNaC4aC4aC4a	28.6 (21)	17	WUGJIR / 1bzl

S53: Summary of C=O···H-O interaction statistics (CSD)

Topology	CSD % H-bond (# entries)	# Prous entries	CSD / PDB example
C=O···H-O (5-membered)			
aC4a	18.6 (732)	108	AFEZER / 13pk
C=O···H-O (6-membered)			
aC3cC3a	84.7 (901)	49	ABENAX / 1bx6
aC4cC4a	25.5 (274)	19	AVAZIG / 1kws
cC4aC4a	16.5 (284)	33	ALAROU / 1bck
aC4aC4a	14.0 (607)	42	AKUYAG / 1b52
C=O···H-O (7-membered)			
aNaC4aC4a	6.0 (215)	57	ARULOO / 1a7c

S54: Summary of N···H-N and N···H-O interaction statistics (CSD)

Topology	CSD % H-bond (# entries)	# Prous entries	CSD / PDB example
N···H-N (5-membered)			
aC3a	60.5 (377)	49	JAYBAN / 2h96
aC4a	17.4 (138)	32	CIJGAE / 1o07
N···H-N (6-membered)			
aNaC3a	80.9 (183)	11	AWUBID / 1iky
aC3aC3a	66.7 (27)	36	BOJYII / 1pzp
aC4aC4a	12.7 (63)	29	GADBOC / 1ewj
N···H-O (5-membered)			
aC4a	15.7 (166)	7	ABINOP / 1b66
N···H-O (6-membered)			
aC4aC4a	27.6 (98)	15	AFADEQ / 1dr1

S55: Summary of Alkoxy···H-N interaction statistics (CSD)

Topology aC3aC3cC3a is predominantly represented by ester groups as H-bond acceptors. Due to the competition between C=O and alkoxy acceptors, which is strongly in favor of C=O (Fig. 7), the propensity for this topology is unusually low.

Topology	CSD % H-bond (# entries)	# Prous entries	CSD / PDB example
C-O···H-N (5-membered)			
aC4aC3a	74.5 (51)	8	AFEVOW / 1jcq
aC3cC3a	71.2 (170)	31	AFIJUV / 1y6a
aC4aC4a	10.1 (79)	47	FIHPAO / 1the
C-O···H-N (6-membered)			
aC3cC3aC3a	87.9 (99)	50	BEZJIA / 1t40
aC3cC3aC3c	70.0 (20)	7	AFOFAC / 2chm
aC3aC3cC3a	6.0 (184)	9	BUBNOB / –

S56: Comparison between CSD and PDB statistics of C=O···H-N and C=O···H-O interactions

Topology	CSD % H-bond (# entries)	PDB % H-bond (# entries)	CSD / PDB example
C=O···H-N (6-membered)			
cC3aC3a	93.0 (242)	66.7 (9)	ACEMEB / 3ce3
aC3cC3a	89.5 (447)	71.0 (31)	ABEKIC / 2nq6
aNaC3a	85.3 (312)	57.1 (21)	ABEFAP / 2ati
aC4aC4a	8.8 (331)	9.2 (541)	BAWXED / 2huw
C=O···H-N (7-membered)			
aNaC4aC3a	0.8 (799)	4.4 (1111)	BXGLAL / 1eld
C=O···H-O (6-membered)			
aC3cC3a	84.7 (901)	47.7 (86)	ABENAX / 1bx6
aC4aC4a	14.0 (607)	9.0 (578)	AKUYAG / 1b52
C=O···H-O (7-membered)			
aNaC4aC4a	6.0 (215)	2.6 (773)	ARULOO / 1a7c

S57: Crystal structure examples of N···H-N and Alkoxy···H-N interactions in 5-membered rings with particular high propensities

a) N···NH interaction with topology aC3a, 61% hbond (jnk1 complex 2h96), b) alkoxy···NH interaction with topology aC4aC3a, 75% hbond (farnesyltransferase complex 1jcq), c) alkoxy···NH interaction with topology aC3cC3a, 71% hbond (kdr complex 1y6a).