Supporting Information

Structure-based Optimization of Inhibitors of the Tyrosine Kinase EphB4. Part 2: Cellular Potency Improvement and Binding Mode Validation by X-ray Crystallography

Karine Lafleur,[†,‡,#] Jing Dong,[‡,#] Danzhi Huang,[‡] Amedeo Caflisch,*[,‡] and Cristina Nevado*[,†]

[†]*Department of Organic Chemistry and* [‡]*Department of Biochemistry, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland*

Table of contents

[*] To whom correspondence should be addressed. Phone: (41) 446353945. Fax: (41) 446353948.
E-mail: nevado@oci.uzh.ch, caflisch@bioc.uzh.ch
# These two authors contributed equally to this work.
[†] Dept. of Organic Chemistry
[‡] Dept. of Biochemistry

---

[*] To whom correspondence should be addressed. Phone: (41) 446353945. Fax: (41) 446353948.
E-mail: nevado@oci.uzh.ch, caflisch@bioc.uzh.ch
# These two authors contributed equally to this work.
[†] Dept. of Organic Chemistry
[‡] Dept. of Biochemistry

Table S1. Selectivity of compound **40** tested on a panel of 124 protein kinases at the University of Dundee. The percentage of kinase activity is measured in the presence of 3 µM of **40** compared to a 100% DMSO control.

Kinase	% act.	Kinase	% act.	Kinase	% act.	Kinase	% act.	Kinase	% act.
MKK1	56	MNK1	105	CK1	97	MEKK1	112	EPH-B4	18
MKK2	86	MNK2	103	CK2	91	MLK1	106	FGF-R1	88
MKK6	105	MAPKAP-K2	99	TTBK1	97	MLK3	101	HER4	91
ERK1	96	MAPKAP-K3	70	DYRK1A	96	TESK1	84	IGF-1R	112
ERK2	105	PRAK	99	DYRK2	93	TAO1	107	IR	99
JNK1	96	CAMKKb	99	DYRK3	101	ASK1	111	IRR	111
JNK2	95	CAMK1	84	NEK2a	108	TAK1	107	TrkA	90
JNK3	87	SmMLCK	104	NEK6	90	IRAK1	118	VEG-FR	87
p38a MAPK	107	PHK	93	IKKb	80	IRAK4	97		
p38b MAPK	98	DAPK1	115	IKKe	93	RIPK2	12		
p38g MAPK	108	CHK1	108	TBK1	101	OSR1	104		
p38d MAPK	102	CHK2	107	PIM1	98	TTK	104		
ERK8	94	GSK3b	123	PIM2	96	MPSK1	83		
RSK1	98	CDK2-Cyclin A	114	PIM3	92	Src	2		
RSK2	84	PLK1	102	SRPK1	91	Lck	5		
PDK1	104	Aurora A	77	EF2K	97	CSK	57		
PKBa	103	Aurora B	95	EIF2AK3	96	YES1	14		
PKBb	74	TLK1	116	HIPK1	120	ABL	43		
SGK1	134	LKB1	91	HIPK2	87	BTK	58		
S6K1	114	AMPK	100	HIPK3	87	JAK2	108		
PKA	83	MARK1	101	CLK2	118	SYK	137		
ROCK 2	101	MARK2	111	PAK2	100	ZAP70	103		
PRK2	100	MARK3	84	PAK4	106	TIE2	101		
PKCa	105	MARK4	97	PAK5	104	BRK	79		
PKCγ	99	BRSK1	92	PAK6	96	EPH-A2	6		
PKCz	101	BRSK2	83	MST2	111	EPH-A4	5		
PKD1	80	MELK	101	MST4	103	EPH-B1	10		
STK33	84	NUAK1	109	GCK	93	EPH-B2	8		
MSK1	85	TSSK1	98	MINK1	99	EPH-B3	13		

NCI-data on the anti-proliferative activity of compound 3

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : 752203 / 1	Experiment ID : 1004NS26	Test Type : 08	Units : Molar
Report Date : May 30, 2010	Test Date : April 05, 2010	QNS :	MC :
COMI : compound 66 (92094)	Stain Reagent : SRB Dual-Pass Related	SSPL : 0XTH	

			Log10 Concentration												
	Time		Mean Optical Densities					Percent Growth							
Panel/Cell Line	Zero	Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.475	2.192	2.244	2.267	2.259	2.153	1.392	103	104	104	98	53	> 1.00E-4	> 1.00E-4	> 1.00E-4
HL-60(TB)	0.317	2.180	2.019	2.117	2.529	2.602	1.302	91	97	119	123	53	> 1.00E-4	> 1.00E-4	> 1.00E-4
K-562	0.137	1.947	1.869	1.513	0.555	0.532	0.590	96	76	23	22	25	3.10E-7	> 1.00E-4	> 1.00E-4
MOLT-4	0.389	2.145	2.142	2.083	1.902	1.883	1.224	100	96	86	85	48	8.59E-5	> 1.00E-4	> 1.00E-4
RPMI-8226	0.815	2.124	2.248	2.324	2.357	2.277	1.633	109	115	118	112	63	> 1.00E-4	> 1.00E-4	> 1.00E-4
SR	0.274	1.928	1.755	1.803	1.650	1.521	1.009	90	92	83	75	44	6.60E-5	> 1.00E-4	> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.326	1.730	1.664	1.627	1.624	1.137	0.684	95	93	92	58	25	1.74E-5	> 1.00E-4	> 1.00E-4
EKVX	0.620	1.705	1.651	1.591	1.509	1.163	0.924	95	90	82	50	28	1.01E-5	> 1.00E-4	> 1.00E-4
HOP-62	0.355	1.045	1.055	1.042	1.064	0.655	0.559	101	100	103	43	30	7.74E-6	> 1.00E-4	> 1.00E-4
NCI-H226	0.675	1.216	1.232	1.211	1.190	1.156	0.921	103	99	95	89	45	7.87E-5	> 1.00E-4	> 1.00E-4
NCI-H23	0.321	0.966	0.944	0.929	0.874	0.793	0.603	97	94	86	73	44	6.09E-5	> 1.00E-4	> 1.00E-4
NCI-H322M	0.659	1.714	1.702	1.725	1.647	0.973	1.035	99	101	94	30	36	4.82E-6	> 1.00E-4	> 1.00E-4
NCI-H460	0.212	1.778	1.792	1.662	1.680	1.470	1.079	101	93	94	80	55	> 1.00E-4	> 1.00E-4	> 1.00E-4
NCI-H522	0.610	1.689	1.660	1.586	1.222	0.934	0.920	97	90	57	30	29	1.79E-6	> 1.00E-4	> 1.00E-4
Colon Cancer															
COLO 205	0.378	1.520	1.621	1.664	1.624	1.301	0.235	109	113	109	81	-38	1.82E-5	4.80E-5	> 1.00E-4
HCC-2998	0.635	1.679	1.624	1.605	1.730	1.639	1.476	95	93	105	96	81	> 1.00E-4	> 1.00E-4	> 1.00E-4
HCT-116	0.254	1.523	1.507	1.518	1.449	1.047	0.559	99	100	94	62	24	2.11E-5	> 1.00E-4	> 1.00E-4
HCT-15	0.304	2.087	1.959	1.926	1.849	1.563	1.065	93	91	87	71	43	5.47E-5	> 1.00E-4	> 1.00E-4
HT29	0.186	1.000	1.010	0.908	0.715	0.174	0.117	101	89	65	-6	-37	1.62E-6	8.12E-6	> 1.00E-4
KM12	0.412	2.034	2.037	1.936	1.893	1.773	1.431	100	94	91	84	63	> 1.00E-4	> 1.00E-4	> 1.00E-4
SW-620	0.202	1.044	1.026	1.015	1.017	1.103	0.893	98	96	97	107	82	> 1.00E-4	> 1.00E-4	> 1.00E-4
CNS Cancer															
SF-268	0.523	1.687	1.695	1.612	1.429	0.969	0.902	101	94	78	38	33	5.07E-6	> 1.00E-4	> 1.00E-4
SF-295	0.649	1.455	1.287	1.305	1.243	0.980	0.936	79	81	74	41	36	5.34E-6	> 1.00E-4	> 1.00E-4
SF-539	0.735	2.227	2.188	2.116	1.980	1.454	1.005	97	93	83	48	18	8.86E-6	> 1.00E-4	> 1.00E-4
SNB-19	0.589	1.914	1.908	2.066	2.056	1.527	1.310	100	111	111	71	54	> 1.00E-4	> 1.00E-4	> 1.00E-4
SNB-75	0.629	1.081	1.000	0.882	0.638	0.400	0.406	82	56	2	-36	-35	1.29E-7	1.12E-6	> 1.00E-4
U251	0.286	1.497	1.480	1.464	1.414	0.966	0.752	99	97	93	56	38	2.22E-5	> 1.00E-4	> 1.00E-4
Melanoma															
LOX IMVI	0.184	1.070	1.017	0.968	0.827	0.269	0.116	94	88	72	10	-37	2.28E-6	1.60E-5	> 1.00E-4
MALME-3M	0.710	1.611	1.523	1.531	1.426	1.364	1.340	90	91	79	73	70	> 1.00E-4	> 1.00E-4	> 1.00E-4
M14	0.221	0.806	0.813	0.779	0.718	0.690	0.506	101	95	85	80	49	9.08E-5	> 1.00E-4	> 1.00E-4
MDA-MB-435	0.475	1.684	1.602	1.593	1.539	1.435	1.102	93	93	88	79	52	> 1.00E-4	> 1.00E-4	> 1.00E-4
SK-MEL-2	0.702	1.858	1.923	1.796	1.961	1.743	1.511	106	95	109	90	70	> 1.00E-4	> 1.00E-4	> 1.00E-4
SK-MEL-28	0.510	1.336	1.365	1.327	1.289	1.290	1.065	103	99	94	94	67	> 1.00E-4	> 1.00E-4	> 1.00E-4
SK-MEL-5	0.663	2.508	2.441	2.407	2.371	1.999	1.430	96	95	93	72	42	5.32E-5	> 1.00E-4	> 1.00E-4
UACC-257	0.658	1.680	1.631	1.633	1.590	1.462	1.329	95	95	91	79	66	> 1.00E-4	> 1.00E-4	> 1.00E-4
UACC-62	0.723	2.437	2.453	2.501	2.329	1.961	1.581	101	104	94	72	50	> 1.00E-4	> 1.00E-4	> 1.00E-4
Ovarian Cancer															
IGROV1	0.476	1.846	2.041	2.117	1.954	0.504	0.418	114	120	108	2	-12	3.52E-6	1.39E-5	> 1.00E-4
OVCAR-3	0.464	1.425	1.458	1.441	1.224	0.781	0.744	103	102	79	33	29	4.28E-6	> 1.00E-4	> 1.00E-4
OVCAR-4	0.513	1.304	1.328	1.253	1.292	1.233	0.985	103	93	98	91	60	> 1.00E-4	> 1.00E-4	> 1.00E-4
OVCAR-5	0.588	1.420	1.356	1.347	1.336	1.165	0.807	92	91	90	69	26	2.81E-5	> 1.00E-4	> 1.00E-4
OVCAR-8	0.301	1.230	1.336	1.292	1.210	0.773	0.574	111	107	98	51	29	1.09E-5	> 1.00E-4	> 1.00E-4
NCI/ADR-RES	0.389	1.169	1.165	1.139	1.130	1.069	0.822	99	96	95	87	55	> 1.00E-4	> 1.00E-4	> 1.00E-4
SK-OV-3	0.453	0.956	0.967	0.938	0.823	0.557	0.472	102	96	73	21	4	2.78E-6	> 1.00E-4	> 1.00E-4
Renal Cancer															
786-0	0.635	1.573	1.691	1.689	1.536	0.993	0.874	113	112	96	38	25	6.24E-6	> 1.00E-4	> 1.00E-4
A498	1.024	1.564	1.489	1.415	1.413	1.456	1.050	86	72	72	80	5	2.50E-5	> 1.00E-4	> 1.00E-4
ACHN	0.392	1.698	1.663	1.619	1.269	0.521	0.383	97	94	67	10	-2	1.99E-6	6.35E-5	> 1.00E-4
CAKI-1	0.828	1.224	1.256	1.263	1.272	0.662	0.234	108	110	112	-20	-72	2.95E-6	7.05E-6	3.80E-5
RXF 393	0.833	1.395	1.353	1.343	1.100	0.585	0.618	92	91	47	-30	-26	8.72E-7	4.11E-6	> 1.00E-4
SN12C	0.625	2.387	2.364	2.323	1.966	1.296	1.098	99	96	76	38	27	4.85E-6	> 1.00E-4	> 1.00E-4
TK-10	0.715	1.394	1.394	1.375	1.348	1.128	0.518	100	97	93	61	-28	1.33E-5	4.87E-5	> 1.00E-4
UO-31	0.464	1.639	1.605	1.599	1.469	1.039	0.708	97	97	86	49	21	9.33E-6	> 1.00E-4	> 1.00E-4
Prostate Cancer															
PC-3	0.557	1.787	1.775	1.749	1.749	1.648	1.174	99	97	97	89	50	> 1.00E-4	> 1.00E-4	> 1.00E-4
DU-145	0.304	1.151	1.169	1.133	1.089	0.663	0.481	102	98	93	42	21	7.04E-6	> 1.00E-4	> 1.00E-4
Breast Cancer															
MCF7	0.376	1.841	1.748	1.683	1.628	1.421	1.314	94	89	85	71	64	> 1.00E-4	> 1.00E-4	> 1.00E-4
MDA-MB-231/ATCC	0.571	1.359	1.431	1.375	1.149	0.770	0.594	109	102	73	25	3	3.06E-6	> 1.00E-4	> 1.00E-4
HS 578T	0.680	1.187	1.173	1.108	0.877	0.597	0.578	97	84	39	-12	-15	5.67E-7	5.75E-6	> 1.00E-4
BT-549	1.008	1.393	1.442	1.575	1.574	1.282	1.022	113	147	147	71	4	2.05E-5	> 1.00E-4	> 1.00E-4
T-47D	0.407	0.905	0.881	0.907	0.905	0.708	0.625	95	101	100	60	44	4.24E-5	> 1.00E-4	> 1.00E-4
MDA-MB-468	0.563	1.386	1.314	1.334	1.285	1.072	0.573	91	94	88	62	1	1.56E-5	> 1.00E-4	> 1.00E-4

Experimental section

Chemistry

Experimental details can be found in the main text of the article. For compounds **24**, **28**, **30**, **31**, **37**, **39**, **40**, **46** and **50** further spectroscopic data can also be found under the Experimental Section of the article.

1-(4-Fluoro-2-methylphenyl)ethanol (6)

To a solution of 4-fluoro-2-methylbenzaldehyde (**5**, 0.8 mL, 6.62 mmol) in THF (20 mL) at -78 °C was added MeLi (1.6 M, 5.2 mL, 8.28 mmol) dropwise. The reaction was allowed to warm to room temperature and stirred for an additional hour. The reaction was quenched by addition of EtOAc, followed by water. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was immediately purified by column chromatography (gradient hexane:EtOAc 20:1 to 10:1) to afford the desired compound as a colorless oil (559 mg, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (dd, *J* = 8.6 Hz, *J* = 5.9 Hz, 1H), 6.93-6.88 (m, 1H), 6.83 (dd, *J* = 9.7 Hz, *J* = 2.7 Hz, 1H), 5.08 (q, *J* = 6.4 Hz, 1H), 2.33 (s, 3H), 1.44 (d, *J* = 6.4 Hz, 3H), OH not observed; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.7 (d, *J* = 244.7 Hz), 139.5 (d, *J* = 3 Hz), 136.6 (d, *J* = 7.7 Hz), 126.3 (d, *J* = 8.4 Hz), 116.8 (d, *J* = 20.9 Hz), 112.9 (d, *J* = 20.8 Hz), 66.4, 24.1, 18.9 (d, *J* = 1.4 Hz); IR (film): $\tilde{\upsilon}$ = 2975, 2929, 1681, 1580, 1354, 1234, 1115, 972, 865, 813 cm^{-1}; MS (GC/MS): *m/z*: calcd for $C_9H_{11}FO$: 154.1, found: 154.0.

1-(4-Fluoro-2-methylphenyl)ethanone (7)

1-(4-Fluoro-2-methylphenyl)ethanol (**6**, 559 mg, 3.62 mmol) was dissolved in CH_2Cl_2 (6 mL), and PCC (1.58 g, 7.33 mmol) was added to the mixture. After 1 h at 25 °C, the solution was filtered off over celite, concentrated under reduced pressure, and purified by flash chromatography on silica gel (gradient hexane:EtOAc 99:1 to 95:5) to afford **7** as a colorless oil (403 mg, 73% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.74 (dd, *J* = 9.4 Hz, *J* = 5.8 Hz, 1H), 6.96-6.92 (m, 2H), 2.56 (s, 3H), 2.55 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.8, 164.1 (d, *J* = 253.2 Hz), 142.5 (d, *J* = 8.9 Hz), 133.7 (d, *J* = 2.9 Hz), 132.1 (d, *J* = 9.5 Hz), 118.9 (d, *J* = 21.2 Hz), 112.5

(d, J = 21.4 Hz), 29.4, 21.9 (d, J = 1.6 Hz); IR (film): $\tilde{\upsilon}$ = 2975, 2929, 1681, 1580, 1354, 1234, 1115, 972, 865, 813 cm^{-1}; MS (ESI): m/z: calcd for $C_9H_9FONa^+$: 175.1, found: 174.9.

1-(2,6-Dimethylphenyl)ethanone (10)

To a solution of 2-bromo-1,3-dimethylbenzene (**8**, 2 mL, 15.01 mmol) in anhydrous THF (20 mL) at -78 °C was added *n*BuLi (2.5 M in hexane, 9.6 mL, 24.02 mmol). The reaction was stirred 30 min at -78 °C. After addition of acetaldehyde (21.8 mL, 390.3 mmol), stirring was continued at -78 °C for 1 h. The reaction was quenched with water, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude alcohol (**9**). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.07-7.03 (m, 1H), 7.00-6.98 (m, 2H), 5.40 (q, J = 6.7 Hz, 1H), 2.45 (s, 6H), 1.54 (d, J = 6.7 Hz, 3H), OH not observed; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.5, 135.7, 129.4, 126.9, 67.7, 21.4, 20.6; IR (film): $\tilde{\upsilon}$ = 3302, 3019, 2925, 2856, 1583, 1468, 1366, 1298, 1191, 1071, 892 cm^{-1}; MS (ESI): m/z: calcd for $C_{10}H_{14}ONa^+$: 173.1, found: 173.0.

The crude intermediate (**9**) was dissolved in CH_2Cl_2 (20 mL), and PCC (3.56 g, 16.51 mmol) was added to the mixture. After 1 h at 25 °C, the solution was filtrated over celite, concentrated under reduced pressure, and purified by flash chromatography on silica gel (hexane/EtOAc 100:1) to afford **10** as a light yellow oil (1.24 g, 56% yield over two steps). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.15 (t, J = 7.6 Hz, 1H), 7.02 (d, J = 7.6 Hz, 2H), 2.47 (s, 3H), 2.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.4, 142.6, 132.2, 128.5, 127.8, 32.1, 19.1; IR (film): $\tilde{\upsilon}$ = 3066, 2954, 2923, 2854, 1697, 1462, 1421, 1350, 1254, 1055, 769 cm^{-1}; MS (ESI): m/z: calcd for $C_{10}H_{12}ONa^+$: 171.1, found: 171.0.

1-(3-Amino-2,6-dimethylphenyl)ethanone (12)

To a solution of 1-(2,6-dimethylphenyl)ethanone (**10**, 1.24 g, 8.10 mmol) in H_2SO_4 (10 mL) at 0 °C was added dropwise a solution of KNO_3 (819 mg, 8.10 mmol) in H_2SO_4 (10 mL) over 1 h. The reaction was then quenched by pouring into ice, and the aqueous layer was extracted with EtOAc. The organic solution was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude intermediate (**11**). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, J = 8.3 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 2.51 (s, 3H), 2.42 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.9, 148.1, 144.7, 138.1, 128.9, 127.7, 124.5, 32.2, 19.4, 16.4; IR (film): $\tilde{\upsilon}$ = 3089, 2979, 2915, 2846, 1706, 1514, 1338, 1237, 1094, 841, 754 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{10}H_{11}NO_3Na^+$: 216.0631, found: 216.0631.

The intermediate (**11**) was dissolved in a 1 : 1 glacial acetic acid–ethanol solution (10 mL) and iron (2.26 g, 40.5 mmol) was added in portions. The resulting mixture was stirred at 90 °C for 2 h, filtered through celite, concentrated under reduced pressure, and neutralized with $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (hexane/EtOAc 5:1) afforded the desired compound as a light yellow oil (626 mg, 47% yield over two steps). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.85 (d, *J* = 8.1 Hz, 1H), 6.60 (d, *J* = 8.1 Hz, 1H), 3.57 (s, 2H), 2.45 (s, 3H), 2.14 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 208.9, 143.2, 142.6, 128.6, 121.8, 116.4, 115.3, 32.4, 18.3, 13.8; IR (film): $\tilde{\upsilon}$ = 3455, 3369, 3235, 2919, 2862, 1691, 1624, 1482, 1350, 1302, 1242, 815 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{10}H_{13}NOH^+$: 164.1070, found: 164.1068.

1,1'-(5-Methyl-1H-indazole-1,4-diyl)diethanone (13)

To a mixture of 1-(3-amino-2,6-dimethylphenyl)ethanone (**12**, 285 mg, 1.74 mmol) and NaOAc (172 mg, 2.09 mmol) in $CHCl_3$ (3 mL) at 0 °C was added acetic anhydride (0.49 mL, 25.1 mmol) dropwise. After stirring for 30 min at 25 °C, the reaction was heated to 40 °C, and isoamyl nitrite (0.469 mL, 3.49 mmol) was added. The reaction was stirred at 60 °C for 7 h and quenched by the addition of a saturated solution of $NaHCO_3$. The resulting solution was extracted with $CHCl_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (hexane/EtOAc 9:1) afforded the desired compound as a white solid (219 mg, 58% yield). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 8.5 Hz, 1H), 8.18 (d, *J* = 0.8 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 2.79 (s, 3H), 2.69 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.3, 171.2, 138.6, 137.8, 133.0, 132.4, 132.0, 124.2, 117.5, 32.1, 23.0, 20.3; IR (film): $\tilde{\upsilon}$ = 3107, 2979, 2927, 1719, 1686, 1412, 1380, 1356, 1160, 942, 818 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{12}H_{12}N_2O_2Na^+$: 239.0791, found: 239.0790.

2-Bromo-1-(4-fluoro-2-methylphenyl)ethanone (17)

Colorless oil; Yield: 64%; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (dd, *J* = 8.5 Hz, *J* = 5.7 Hz, 1H), 7.00-6.94 (m, 2H), 4.38 (s, 2H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.6, 164.5 (d, *J* = 254.8 Hz), 143.9 (d, *J* = 8.9 Hz), 131.8 (d, *J* = 9.7 Hz), 130.4 (d, *J* = 2.9 Hz), 119.3 (d, *J* = 21.2 Hz), 112.8 (d, J = 21.7 Hz), 33.2, 21.8 (d, J = 1.3 Hz); IR (film): $\tilde{\upsilon}$ = 2974, 2927, 1678, 1605, 1579, 1258, 1235, 1104, 989, 866, 818 cm^{-1}; MS (ESI): *m/z*: calcd for $C_9H_8BrFONa^+$: 253.0, found: 252.9.

2-Bromo-1-(2,6-dimethylphenyl)ethanone (18)

Colorless oil; Yield: 21%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23-7.19 (m, 1H), 7.06-7.04 (m, 2H), 4.28 (s, 2H), 2.26 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.1, 138.8, 133.4, 129.6, 127.9, 36.5, 19.4; IR (film): $\tilde{\upsilon}$ = 3066, 2925, 2854, 1716, 1695, 1462, 1381, 1261, 1185, 983, 771 cm^{-1}; MS (ESI): *m/z*: calcd for $C_{10}H_{11}BrONa^+$: 249.0, found: 248.9.

1-(1-Acetyl-5-methyl-1H-indazol-4-yl)-2-bromoethanone (19)

White solid; Yield: 37%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (d, J = 8.6 Hz, 1H), 8.12 (s, 1H), 7.44 (d, J = 8.6 Hz, 1H), 4.43 (s, 2H), 2.80 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.8, 171.1, 138.0, 137.8, 132.8, 132.5, 129.2, 124.5, 118.2, 34.9, 23.0, 20.0; IR (film): $\tilde{\upsilon}$ = 2928, 2852, 1712, 1415, 1382, 1152, 946, 823, 677 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{12}H_{11}BrN_2O_2Na^+$: 316.9896, found: 316.9896.

2-Bromo-1-(2-chlorophenyl)ethanone (20)

Light brown oil; Yield: 52%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.58-7.56 (m, 1H), 7.46-7.44 (m, 2H), 7.39-7.34 (m, 1H), 4.53 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 194.0, 136.2, 132.7, 131.3, 130.6, 130.2, 127.1, 34.5; IR (film): $\tilde{\upsilon}$ = 3067, 2940, 1697, 1589, 1432, 1285, 1192, 1064, 988, 755 cm^{-1}; MS (ESI): *m/z*: calcd for $C_8H_6BrClONa^+$: 254.9, found: 254.9.

2-Bromo-1-(3-chlorophenyl)ethanone (21)

Light brown oil; Yield: 31%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (t, J = 1.9 Hz, 1H), 7.87-7.84 (m, 1H), 7.58 (ddd, J = 7.9 Hz, J = 1.9 Hz, J = 0.9 Hz, 1H), 7.44 (t, J = 7.9 Hz, 1H), 4.42 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.1, 135.4, 135.2, 133.9, 130.2, 128.9, 127.0, 30.5; IR (film): $\tilde{\upsilon}$ = 3067, 3003, 2950, 1698, 1571, 1422, 1269, 1016, 781 cm^{-1}; MS (ESI): *m/z*: calcd for $C_8H_6BrClONa^+$: 254.9, found: 254.9.

2-Bromo-1-(2-(trifluoromethyl)phenyl)ethanone (22)

Light brown oil; Yield: 55%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75 (dd, *J* = 7.2 Hz, *J* = 1.5 Hz, 1H), 7.67-7.61 (m, 2H), 7.52 (dd, *J* = 7.2 Hz, *J* = 1.5 Hz, 1H), 4.40 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 194.9, 136.3 (q, *J* = 2 Hz), 132.0, 131.1, 127.8, 127.4 (q, *J* = 32.4 Hz), 126.9 (q, *J* = 4.9 Hz), 123.2 (q, *J* = 273.6 Hz), 34.4 (q, *J* = 2.2 Hz); IR (film): $\tilde{\upsilon}$ = 2943, 1725, 1703, 1312, 1275, 1167, 1125, 1063, 1034, 766 cm^{-1}; MS (ESI): *m/z*: calcd for $C_9H_6BrF_3ONa^+$: 289.0, found: 288.9.

8-Bromo-3-methyl-7-(2-oxo-2-(*o*-tolyl)ethyl)-1H-purine-2,6(3H,7H)-dione (24)

^{13}C NMR (125 MHz, DMSO-d_6): δ = 194.1, 153.9, 150.4, 148.9, 138.3, 133.7, 132.7, 131.9, 129.1, 129.0, 126.1, 108.8, 54.3, 28.5, 20.6; IR (film): $\tilde{\upsilon}$ = 3154, 3025, 2814, 1676, 1535, 1364, 1208, 768 cm^{-1}.

8-Bromo-7-(2-(4-fluoro-2-methylphenyl)-2-oxoethyl)-3-methyl-1H-purine-2,6(3H,7H)-dione (25)

White solid; Yield: 56%; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.35 (s, 1H), 8.20-8.17 (m, 1H), 7.30-7.29 (m, 2H), 5.79 (s, 2H), 3.36 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 192.7, 164.0 (d, *J* = 252 Hz), 154.0, 150.5, 149.0, 142.9 (d, *J* = 9.2 Hz), 132.4 (d, *J* = 9.9 Hz), 130.3 (d, *J* = 2.7 Hz), 129.2, 118.8 (d, *J* = 21.5 Hz), 113.1 (d, *J* = 21.4 Hz), 108.8, 54.3, 28.6, 20.9; IR (film): $\tilde{\upsilon}$ = 3152, 3032, 2813, 1671, 1534, 1369, 1237, 1200, 990, 865 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{15}H_{12}BrFN_4O_3Na^+$: 416.9969, found: 416.9967.

8-Bromo-7-(2-(3-chlorophenyl)-2-oxoethyl)-3-methyl-1H-purine-2,6(3H,7H)-dione (26)

White solid; Yield: 75%; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.34 (s, 1H), 8.16 (t, *J* = 1.9 Hz, 1H), 8.07-8.05 (m, 1H), 7.85 (ddd, *J* = 7.9 Hz, *J* = 1.9 Hz, *J* = 0.9 Hz, 1H), 7.66 (t, *J* = 7.9 Hz, 1H), 5.96 (s, 2H), 3.36 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 190.7, 153.9, 150.5, 149.1, 135.4, 134.2, 134.0, 131.1, 129.1, 128.0, 126.9, 108.9, 53.0, 28.6; IR (film): $\tilde{\upsilon}$ = 3143, 3000, 2818, 1680, 1537, 1438, 1364, 1210, 876 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{14}H_{10}BrClN_4O_3Na^+$: 418.9517, found: 418.9515.

8-Bromo-7-(2-(2-chlorophenyl)-2-oxoethyl)-3-methyl-1H-purine-2,6(3H,7H)-dione (27)

White solid; Yield: 63%; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.38 (s, 1H), 7.96-7.94 (m, 1H), 7.68-7.65 (m, 2H), 7.61-7.56 (m, 1H), 5.80 (s, 2H), 3.36 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 193.0, 154.0, 150.5, 149.0, 134.4, 133.8, 131.0, 130.6, 130.1, 129.1, 127.7, 108.7, 54.9, 28.6; IR (film): $\tilde{\upsilon}$ = 3161, 3052, 2948, 2835, 1680, 1541, 1430, 1353, 1199, 838, 746 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{14}H_{10}BrClN_4O_3Na^+$: 418.9517, found: 418.9517.

8-Bromo-3-methyl-7-(2-oxo-2-(2-(trifluoromethyl)phenyl)ethyl)-1H-purine-2,6(3H,7H)-dione (28)

^{13}C NMR (125 MHz, DMSO-d_6): δ = 194.8, 154.1, 150.5, 149.1, 135.2 (q, *J* = 2 Hz), 132.9, 132.3, 129.0, 128.5, 127.2 (q, *J* = 4.9 Hz), 126.2 (q, *J* = 32.2 Hz), 123.3 (q, *J* = 273.8 Hz), 108.7, 55.1, 28.6; IR (film): $\tilde{\upsilon}$ = 3163, 3046, 2940, 2807, 1708, 1674, 1359, 1318, 1213, 1165, 1111, 773 cm^{-1}.

8-Bromo-7-(2-(2,6-dimethylphenyl)-2-oxoethyl)-3-methyl-1H-purine-2,6(3H,7H)-dione (29)

3-Methyl-8-bromoxanthine (**4**, 240 mg, 0.98 mmol) was dissolved in DMF (2.5 mL), and *N,N*-diisopropylethylamine (0.256 mL, 1.47 mmol) was added. After stirring for 5 min at 25 °C, 2-bromo-1-(2,6-dimethylphenyl)ethanone (**18**, 222 mg, 0.98 mmol) was added. The reaction was stirred at 110 °C for 2 h. The mixture was then concentrated under reduced pressure, methanol was added and the formed precipitate was filtered off and washed with water to afford the product as a white solid (226 mg, 59% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.38 (s, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 2H), 5.63 (s, 2H), 3.37 (s, 3H), 2.34 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6, $CDCl_3$): δ = 201.0, 154.0, 150.4, 149.1, 137.5, 133.5, 129.7, 129.2, 127.8, 108.8, 56.5, 28.6, 18.8; IR (film): $\tilde{\upsilon}$ = 3150, 3019, 2956, 2829, 1668, 1363, 1199, 969, 780 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{16}H_{15}BrN_4O_3H^+$: 391.0400, found: 391.0405.

7-(2-(1-Acetyl-5-methyl-1H-indazol-4-yl)-2-oxoethyl)-8-bromo-3-methyl-1H-purine-2,6(3H,7H)-dione (30)

^{13}C NMR (125 MHz, DMSO-d_6): δ = 196.5, 170.8, 154.2, 150.5, 149.2, 137.8, 136.9, 133.0, 132.2, 129.3, 128.7, 123.5, 117.2, 108.8, 56.5, 28.6, 22.7, 19.0; IR (film): $\tilde{\upsilon}$ = 3165, 3049, 2948, 2820, 1722, 1702, 1675, 1371, 1207, 1154, 1105, 942, 816 cm^{-1}.

8-(Butylamino)-7-(2-(butylimino)-2-(*o*-tolyl)ethyl)-3-methyl-1H-purine-2,6(3H,7H)-dione (31)

^{13}C NMR (125 MHz, DMSO-d_6): δ = 163.7, 155.2, 153.1, 150.9, 150.0, 135.7, 134.4, 129.8, 128.6, 126.8, 125.7, 102.0, 51.0, 49.3, 41.9, 32.1, 31.4, 28.3, 19.5, 19.3, 18.6, 13.7, 13.6; IR (film): $\tilde{\upsilon}$ = 3329, 3141, 2954, 2929, 2869, 2806, 1671, 1611, 1573, 1438, 1300, 1225, 1113, 753 cm^{-1}.

3-Methyl-8-(pentylamino)-7-(2-(pentylimino)-2-(*o*-tolyl)ethyl)-1H-purine-2,6(3H,7H)-dione (32)

White solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.53 (s, 1H), 7.31-7.25 (m, 4H), 6.90 (t, *J* = 5.6 Hz, 1H), 4.97 (d, *J* = 18.2 Hz, 1H), 4.86 (d, *J* = 18.2 Hz, 1H), 3.33 (s, 2H), 3.29 (s, 3H), 3.01-2.97 (m, 1H), 2.82-2.77 (m, 1H), 2.17 (s, 3H), 1.58-1.55 (m, 2H), 1.33-1.26 (m, 6H), 1.10-1.00 (m, 4H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.75 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 163.6, 155.3, 153.1, 150.9, 150.0, 135.7, 134.4, 129.8, 128.6, 126.7, 125.7, 102.0, 51.1, 49.4, 42.2, 29.5, 28.9, 28.6, 28.4, 28.3, 21.9, 21.8, 18.6, 13.9, 13.8; IR (film): $\tilde{\upsilon}$ = 3340, 3144, 3015, 2955, 2924, 2855, 2802, 1657, 1614, 1579, 1437, 1219, 1098, 752 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{25}H_{36}N_6O_2H^+$: 453.2973, found: 453.2970.

8-(Hexylamino)-7-(2-(hexylimino)-2-(*o*-tolyl)ethyl)-3-methyl-1H-purine-2,6(3H,7H)-dione (33)

White solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.52 (s, 1H), 7.31-7.25 (m, 4H), 6.90 (t, *J* = 5.6 Hz, 1H), 4.97 (d, *J* = 17.7 Hz, 1H), 4.86 (d, *J* = 17.7 Hz, 1H), 3.33 (s, 2H), 3.29 (s, 3H), 3.00-2.96 (m, 1H), 2.82-2.77 (m, 1H), 2.17 (s, 3H), 1.58-1.52 (m, 2H), 1.35-1.25 (m, 8H), 1.17-1.02 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H), 0.78 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 163.6, 155.3, 153.1, 150.9, 150.0, 135.8, 134.4, 129.8, 128.6, 126.8, 125.6, 102.0, 51.1, 49.3, 42.2, 31.0, 30.9, 29.8, 29.2, 28.2, 26.0, 25.9, 22.1, 21.9, 18.6, 13.9, 13.8; IR (film): $\tilde{\upsilon}$ = 3338, 3149, 3015, 2953, 2924, 2854, 1659, 1614, 1550, 1486, 1439, 1301, 1218, 1099, 752 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{27}H_{40}N_6O_2H^+$: 481.3286, found: 481.3286.

8-(Butylamino)-7-(2-(butylimino)-2-(4-fluoro-2-methylphenyl)ethyl)-3-methyl-1H-purine-2,6(3H,7H)-dione (34)

Light brown solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.50 (s, 1H), 7.37-7.32 (m, 1H), 7.15-7.13 (m, 2H), 6.87 (t, J = 5.7 Hz, 1H), 4.98 (d, J = 18.4 Hz, 1H), 4.83 (d, J = 18.4 Hz, 1H), 3.31 (s, 5H), 3.04-2.98 (m, 1H), 2.83-2.77 (m, 1H), 2.18 (s, 3H), 1.58-1.51 (m, 2H), 1.38-1.32 (m, 2H), 1.29-1.24 (m, 2H), 1.14-1.03 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H), 0.70 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.9, 161.9 (d, J = 244.7 Hz), 155.2, 153.1, 150.9, 150.0, 137.8 (d, J = 8.2 Hz), 132.0 (d, J = 3.1 Hz), 129.0 (d, J = 8.8 Hz), 116.4 (d, J = 21.2 Hz), 112.6 (d, J = 21.0 Hz), 101.9, 51.0, 49.4, 41.9, 32.0, 31.4, 28.3, 19.5, 19.3, 18.6, 13.7, 13.6; IR (film): $\tilde{\upsilon}$ = 3330, 3141, 2956, 2930, 2870, 1672, 1656, 1612, 1573, 1439, 1300, 1226, 1116, 856, 754 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{23}H_{31}FN_6O_2H^+$: 443.2565, found: 443.2564.

8-(Butylamino)-7-(2-(butylimino)-2-(3-chlorophenyl)ethyl)-3-methyl-1H-purine-2,6(3H,7H)-dione (35)

White solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.53 (s, 1H), 7.52-7.50 (m, 2H), 7.43 (s, 1H), 7.24-7.21 (m, 1H), 6.86 (t, J = 5.4 Hz, 1H), 4.97 (s, 2H), 3.31 (s, 2H), 3.28 (s, 3H), 3.08 (t, J = 6.6 Hz, 2H), 1.58-1.51 (m, 2H), 1.40-1.27 (m, 4H), 1.06-1.15 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H), 0.71 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.0, 154.9, 153.2, 150.9, 150.0, 137.6, 133.3, 130.5, 128.7, 126.7, 125.6, 101.8, 51.2, 49.3, 41.9, 32.3, 31.4, 28.3, 19.5, 19.4, 13.7, 13.6; IR (film): $\tilde{\upsilon}$ = 3361, 3154, 2956, 2862, 1668, 1615, 1570, 1544, 1443, 1223, 749 cm^{-1}.

8-(Butylamino)-7-(2-(butylimino)-2-(2-chlorophenyl)ethyl)-3-methyl-1H-purine-2,6(3H,7H)-dione (36)

White solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.52 (s, 1H), 7.53-7.39 (m, 4H), 6.81 (t, J = 5.4 Hz, 1H), 5.08 (d, J = 17.7 Hz, 1H), 4.92 (d, J = 17.7 Hz, 1H), 3.34 (s, 2H), 3.28 (s, 3H), 3.09-3.07 (m, 1H), 2.86-2.84 (m, 1H), 1.53 (quint, J = 7.3 Hz, 2H), 1.39-1.29 (m, 4H), 1.15-1.06 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H), 0.71 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 160.8, 155.2, 153.1, 150.9, 150.0, 134.5, 130.6, 130.1, 129.1, 129.0, 127.3, 102.0, 51.5, 49.1, 41.9, 31.9, 31.3, 28.3, 19.5, 19.3, 13.7, 13.6; IR (film): $\tilde{\upsilon}$ = 3316, 3139, 2955, 2858, 2812, 1672, 1614, 1444, 1303, 1225, 1133, 875, 750 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{22}H_{29}ClN_6O_2H^+$: 445.2113, found: 445.2115.

8-Butyl-1-methyl-7-(*o*-tolyl)-1H-imidazo[2,1-*f*]purine-2,4(3H,8H)-dione (40)

^{13}C NMR (125 MHz, DMSO-d_6): δ = 153.3, 152.7, 151.0, 147.3, 138.2, 131.5, 130.4, 130.3, 129.8, 127.0, 125.9, 105.7, 98.9, 42.8, 30.1, 28.8, 19.6, 18.7, 13.0; IR (film): $\tilde{\upsilon}$ = 3165, 3062, 2955, 2872, 1698, 1670, 1505, 1456, 1146, 774, 721 cm^{-1}.

1-Methyl-8-pentyl-7-(*o*-tolyl)-1H-imidazo[2,1-*f*]purine-2,4(3H,8H)-dione (41)

White solid; Yield: 37% over two steps; mp 206-208 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.94 (s, 1H), 7.62 (s, 1H), 7.47-7.33 (m, 4H), 3.82 (t, *J* = 7.1 Hz, 2H), 3.40 (s, 3H), 2.24 (s, 3H), 1.56 (quint, *J* = 7.1 Hz, 2H), 1.12-0.99 (m, 4H), 0.71 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 153.3, 152.7, 151.0, 147.3, 138.1, 131.5, 130.4, 130.3, 129.8, 127.1, 125.9, 105.7, 98.9, 43.0, 28.8, 27.6, 27.6, 21.2, 19.6, 13.5; IR (film): $\tilde{\upsilon}$ = 3156, 3013, 2930, 2868, 2820, 1674, 1514, 1455, 1297, 1153, 848, 725 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{20}H_{23}N_5O_2Na^+$: 388.1744, found: 388.1742.

8-Hexyl-1-methyl-7-(*o*-tolyl)-1H-imidazo[2,1-*f*]purine-2,4(3H,8H)-dione (42)

White solid; Yield: 38% over two steps; mp 202-204 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.94 (s, 1H), 7.62 (s, 1H), 7.46-7.33 (m, 4H), 3.82 (t, *J* = 7.1 Hz, 2H), 3.40 (s, 3H), 2.24 (s, 3H), 1.56 (quint, *J* = 7.1 Hz, 2H), 1.12-1.02 (m, 6H), 0.74 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 153.3, 152.7, 151.0, 147.3, 138.1, 131.5, 130.4, 130.3, 129.8, 127.1, 125.9, 105.7, 98.9, 43.0, 30.2, 28.8, 27.8, 25.1, 21.7, 19.6, 13.7; IR (film): $\tilde{\upsilon}$ = 3155, 3016, 2928, 2856, 2823, 1671, 1514, 1455, 1154, 851, 725 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{21}H_{25}N_5O_2Na^+$: 402.1901, found: 402.1905.

8-Butyl-7-(4-fluoro-2-methylphenyl)-1-methyl-1H-imidazo[2,1-*f*]purine-2,4(3H,8H)-dione (43)

White solid; Yield: 43% over two steps; mp 240-242 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.94 (s, 1H), 7.63 (s, 1H), 7.49-7.46 (m, 1H), 7.30 (d, *J* = 9.3 Hz, 1H), 7.22-7.19 (m, 1H), 3.81 (t, *J* = 7.1 Hz, 2H), 3.40 (s, 3H), 2.24 (s, 3H), 1.55 (quint, *J* = 7.1 Hz, 2H), 1.08 (sext, *J* = 7.1 Hz, 2H), 0.70 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.6 (d, *J* = 246.7 Hz), 153.3, 152.7, 151.0, 147.3, 141.5 (d, *J* = 8.5 Hz), 133.7 (d, *J* = 8.5 Hz), 129.2, 123.5 (d, *J* = 2.9 Hz), 116.9 (d, *J* = 21.5 Hz), 112.9 (d, *J* = 21.4 Hz), 106.0, 98.9, 42.8, 30.1, 28.8, 19.6, 18.8, 13.1; IR (film): $\tilde{\upsilon}$ = 3161, 3034, 2952, 2871, 2819, 1698, 1672, 1509, 1445, 1311, 1192, 1141, 861, 746 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{19}H_{20}FN_5O_2Na^+$: 392.1493, found:.392.1495.

8-Butyl-7-(3-chlorophenyl)-1-methyl-1H-imidazo[2,1-*f*]purine-2,4(3H,8H)-dione (44)

White solid; Yield: 41% over two steps; mp 259-261 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.98 (s, 1H), 7.84 (s, 1H), 7.72-7.71 (m, 1H), 7.58-7.56 (m, 3H), 4.12 (t, *J* = 7.3 Hz, 2H), 3.40 (s, 3H), 1.61 (quint, *J* = 7.3 Hz, 2H), 1.12 (sext, *J* = 7.3 Hz, 2H), 0.74 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 153.2, 152.9, 151.0, 148.0, 133.6, 130.8, 130.6, 130.1, 128.9, 128.5, 127.5, 106.0, 98.9, 43.5, 30.2, 28.9, 18.8, 13.1; IR (film): $\tilde{\upsilon}$ = 3153, 3027, 2969, 2929, 2859, 2826, 1686, 1507, 1442, 1226, 1138, 786 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{18}H_{18}ClN_5O_2H^+$: 372.1222, found: 372.1223.

8-Butyl-7-(2-chlorophenyl)-1-methyl-1H-imidazo[2,1-*f*]purine-2,4(3H,8H)-dione (45)

White solid; Yield: 34% over two steps; mp 236-238 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.97 (s, 1H), 7.72-7.69 (m, 2H), 7.64-7.59 (m, 2H), 7.55-7.52 (m, 1H), 3.87 (t, *J* = 7.3 Hz, 2H), 3.40 (s, 3H), 1.57 (quint, *J* = 7.3 Hz, 2H), 1.08 (sext, *J* = 7.3 Hz, 2H), 0.69 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 153.3, 152.9, 151.0, 147.3, 134.2, 133.6, 131.9, 129.8, 128.4, 127.6, 126.6, 106.5, 98.9, 43.3, 30.1, 28.9, 18.7, 13.0; IR (film): $\tilde{\upsilon}$ = 3176, 3064, 2963, 2875, 2804, 1698, 1669, 1504, 1455, 1148, 768 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{18}H_{18}ClN_5O_2H^+$: 372.1222, found: 372.1224.

7-(3-Chlorophenyl)-8-(2-methoxyphenyl)-1-methyl-1H-imidazo[2,1-*f*]purine-2,4(3H,8H)-dione (47)

White solid; Yield: 45%; mp 313-315 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.98 (s, 1H), 8.16 (s, 1H), 7.58 (dd, *J* = 7.7 Hz, *J* = 1.6 Hz, 1H), 7.54 (td, *J* = 7.7 Hz, *J* = 1.6 Hz, 1H), 7.38-7.30 (m, 3H), 7.22-7.19 (m, 2H), 7.14 (td, *J* = 7.6 Hz, *J* = 1.1 Hz, 1H), 3.58 (s, 3H), 3.28 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 154.7, 153.3, 152.9, 151.0, 148.1, 133.0, 131.5, 131.3, 130.3, 130.2, 129.8, 128.1, 126.9, 125.7, 122.3, 121.1, 113.0, 106.3, 99.2, 55.7, 28.9; IR (film): $\tilde{\upsilon}$ = 3169, 3022, 2826, 1708, 1670, 1505, 1434, 1161, 849, 740 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{21}H_{16}ClN_5O_3H^+$: 422.1014, found: 422.1012.

7-(2-Chlorophenyl)-8-(2-methoxyphenyl)-1-methyl-1H-imidazo[2,1-*f*]purine-2,4(3H,8H)-dione (48)

White solid; Yield: 32%; mp 305-307 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.00 (s, 1H), 7.89 (s, 1H), 7.52-7.46 (m, 2H), 7.43-7.36 (m, 3H), 7.31-7.27 (m, 1H), 7.08-7.02 (m, 2H), 3.57 (s, 3H), 3.28 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 154.3, 153.4, 152.9, 151.0, 147.3, 133.7, 133.0, 131.1, 131.1, 129.6, 129.5, 129.3, 126.8, 126.7, 121.7, 120.6, 112.5, 107.2, 99.1, 55.4, 28.8; IR (film): $\tilde{\upsilon}$ = 3150, 3044, 2821, 1665, 1509, 1490, 1422, 1280, 1159, 764 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{21}H_{16}ClN_5O_3H^+$: 422.1014, found: 422.1016.

Synthesis of compound 46

8-(Butylamino)-3-methyl-7-(2-oxo-2-(2-(trifluoromethyl)phenyl)ethyl)-1H-purine-2,6(3H,7H)-dione (37)

^{13}C NMR (125 MHz, DMSO-d_6): δ = 195.2, 154.8, 153.2, 150.8, 150.2, 135.3, 132.6, 132.2, 129.3, 127.2 (q, *J* = 5.4 Hz), 126.4 (q, *J* = 32.2 Hz), 123.2 (q, *J* = 273.8 Hz), 101.6, 51.5, 41.9, 31.2, 28.3, 19.2, 13.6; IR (film): $\tilde{\upsilon}$ = 3379, 3153, 3035, 2939, 2875, 2804, 1671, 1618, 1573, 1547, 1317, 1223, 1170, 1130, 778, 750 cm^{-1}.

8-Butyl-1-methyl-7-(2-(trifluoromethyl)phenyl)-1H-imidazo[2,1-*f*]purine-2,4(3H,8H)-dione (46)

^{13}C NMR (125 MHz, DMSO-d_6): δ = 153.3, 152.9, 151.0, 147.3, 134.2, 132.6, 130.8, 129.3 (q, *J* = 29.2 Hz), 127.0, 126.6 (q, *J* = 5.2 Hz), 125.4 (q, *J* = 1.7 Hz), 123.6 (q, *J* = 273.7 Hz), 106.6, 98.8, 43.2, 30.0, 28.9, 18.8, 13.1; IR (film): $\tilde{\upsilon}$ = 3169, 3034, 2959, 2873, 2820, 1701, 1671, 1509, 1443, 1309, 1179, 1136, 781 cm^{-1}.

Synthesis of compounds 49 and 50

8-(Butylamino)-7-(2-(2,6-dimethylphenyl)-2-oxoethyl)-3-methyl-1H-purine-2,6(3H,7H)-dione (38)

A mixture of 8-bromo-7-(2-(2,6-dimethylphenyl)-2-oxoethyl)-3-methyl-1H-purine-2,6(3H,7H)-dione (**29**, 88 mg, 0.22 mmol) and butyl amine (0.088 mL, 0.89 mmol) in EtOH (2 mL) was heated in a sealed tube at 175 °C for 2 h. The reaction was cooled to room temperature and the solid was filtered off to afford the crude product as a light yellow solid (68 mg, 81% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.70 (s, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 2H), 6.91 (t, *J* = 5.4 Hz, 1H), 5.35 (s, 2H), 3.34 (s, 5H), 2.27 (s, 6H), 1.52 (quint, *J* = 7.3 Hz, 2H), 1.34 (sext, *J* = 7.3 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 202.7, 155.0, 153.2, 150.9, 150.2, 138.2, 133.5, 129.3, 127.7, 102.3, 53.3, 41.9, 31.1, 28.4, 19.3, 18.7, 13.6; IR (film): $\tilde{\upsilon}$ = 3342, 3152, 2987, 2934, 1673, 1614, 1545, 1439, 1223, 750 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{20}H_{25}N_5O_3H^+$: 384.2030, found: 384.2032.

8-(Butylamino)-3-methyl-7-(2-(5-methyl-1H-indazol-4-yl)-2-oxoethyl)-1H-purine-2,6(3H,7H)-dione (39)

^{13}C NMR (125 MHz, DMSO-d_6): δ = 197.2, 154.9, 153.2, 150.9, 150.3, 138.8, 132.6, 129.9, 129.4, 127.3, 120.4, 113.3, 101.7, 53.1, 41.9, 31.2, 28.4, 19.8, 19.3, 13.6; IR (film): $\tilde{\upsilon}$ = 3325, 3141, 3031, 2933, 2862, 2783, 1685, 1671, 1489, 1443, 1223, 1159, 1107, 921, 819, 748 cm^{-1}.

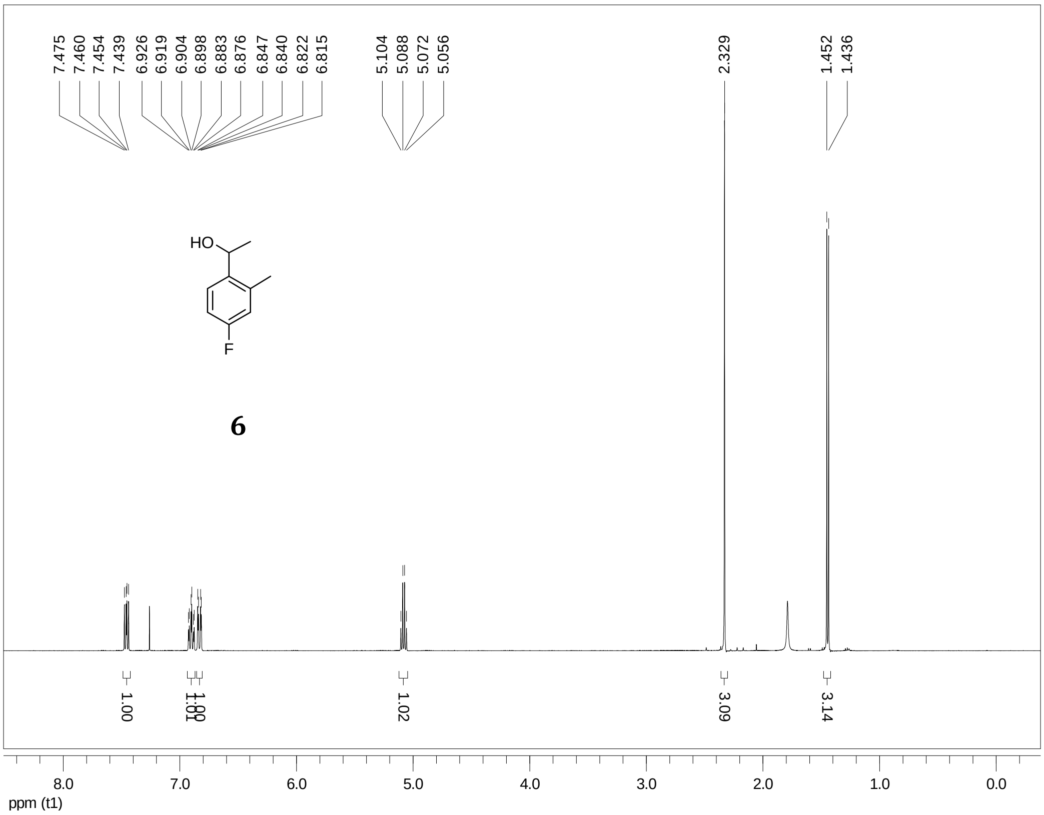
8-Butyl-7-(2,6-dimethylphenyl)-1-methyl-1H-imidazo[2,1-*f*]purine-2,4(3H,8H)-dione (49)

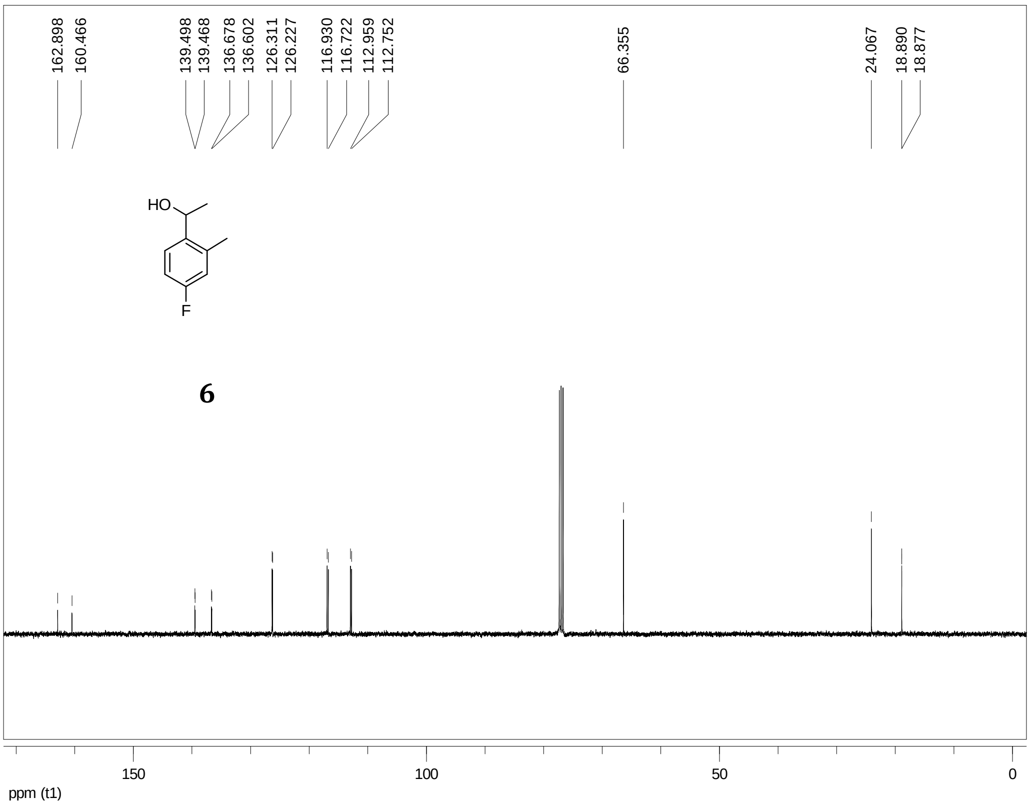
8-(butylamino)-7-(2-(2,6-dimethylphenyl)-2-oxoethyl)-3-methyl-1H-purine-2,6(3H,7H)-dione (**38**, 175 mg, 0.46 mmol) was heated in a sealed tube at 175 °C in CH_2Cl_2 (3 mL) in the presence of $BF_3{\cdot}OEt_2$ (2 mL, 16.2 mmol) for 6 h. The reaction was poured in water, extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (EtOAc/Toluene 1:2) followed by recrystallization in acetone afforded the desired compound as a white solid (43 mg, 26% yield) and ca. 87% purity. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.88 (s, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.26 (s, 1H), 7.18 (d, *J* = 7.6 Hz, 2H), 3.72 (t, *J* = 7.4 Hz, 2H), 3.60 (s, 3H), 2.15 (s, 6H), 1.65 (quint, *J* = 7.4 Hz, 2H), 1.23 (sext, *J* = 7.4 Hz, 2H), 0.82 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.6, 153.1, 151.1, 148.1, 139.4, 130.1, 129.4, 127.8, 126.5, 105.7, 99.8, 43.5, 30.9, 29.4, 20.4, 19.6, 13.4; IR (film): $\tilde{\upsilon}$ = 3152, 3044, 2958, 2871, 2820, 1675, 1607, 1512, 1457, 781 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{20}H_{23}N_5O_2H^+$: 366.1925, found: 366.1921.

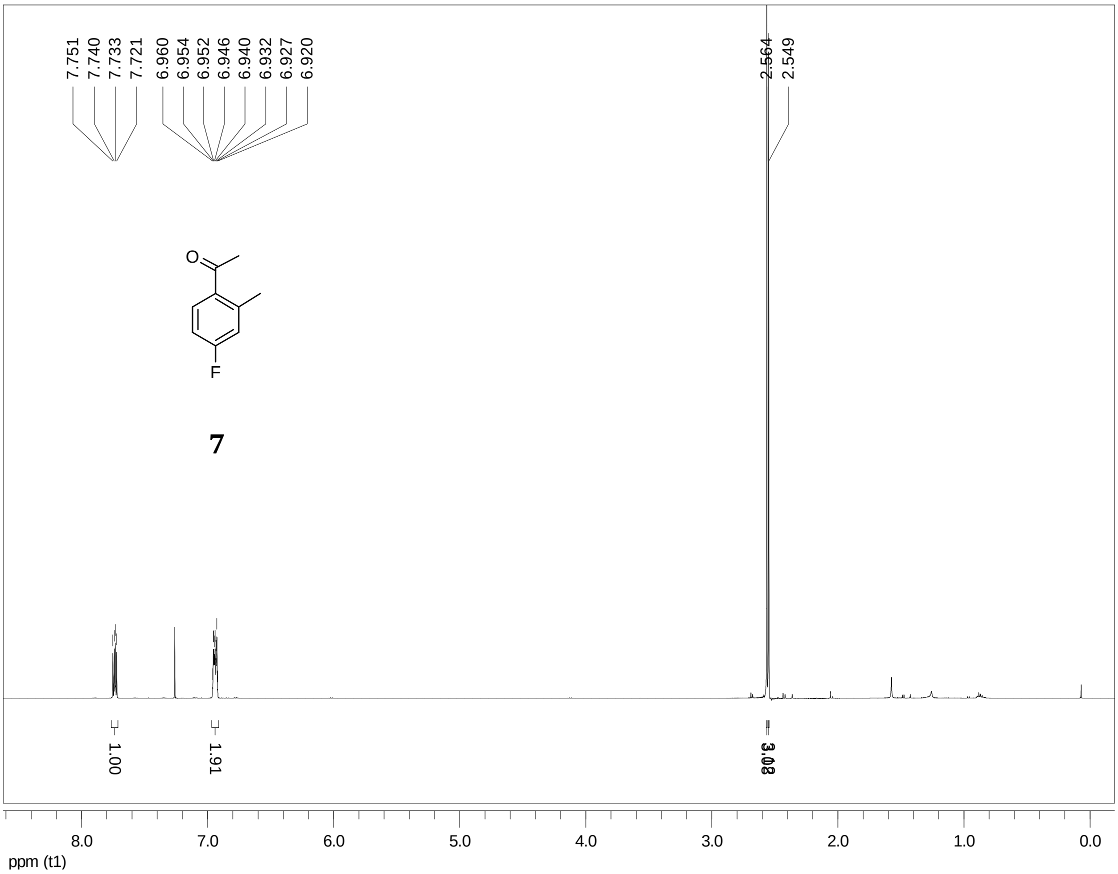
8-Butyl-1-methyl-7-(5-methyl-1H-indazol-4-yl)-1H-imidazo[2,1-*f*]purine-2,4(3H,8H)-dione (50)

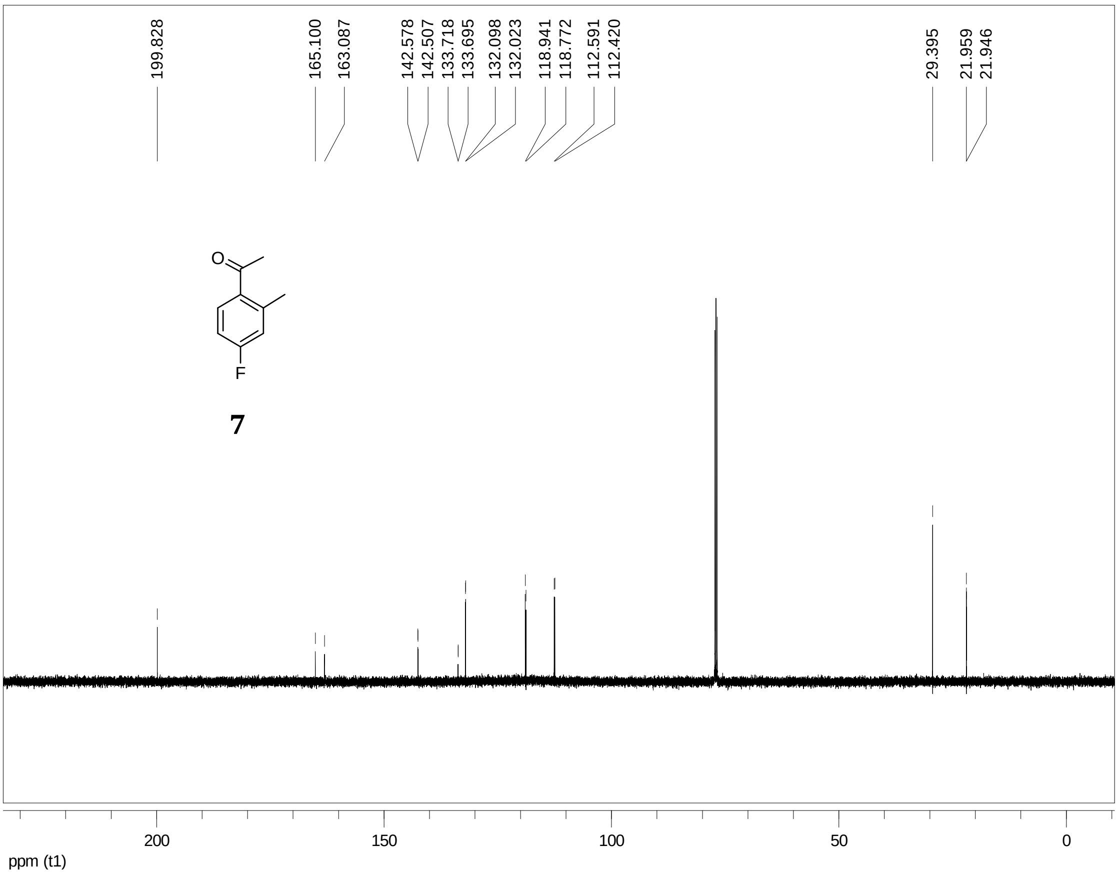
^{13}C NMR (125 MHz, DMSO-d_6): δ = 153.3, 152.8, 151.0, 147.6, 138.4, 132.2, 130.5, 128.9, 127.8, 124.3, 117.7, 111.8, 106.2, 99.0, 43.1, 30.0, 28.8, 18.8, 18.6, 12.9; IR (film): $\tilde{\upsilon}$ = 3356, 3194, 2956, 2925, 2857, 1687, 1607, 1513, 1456, 1054, 754 cm^{-1}.

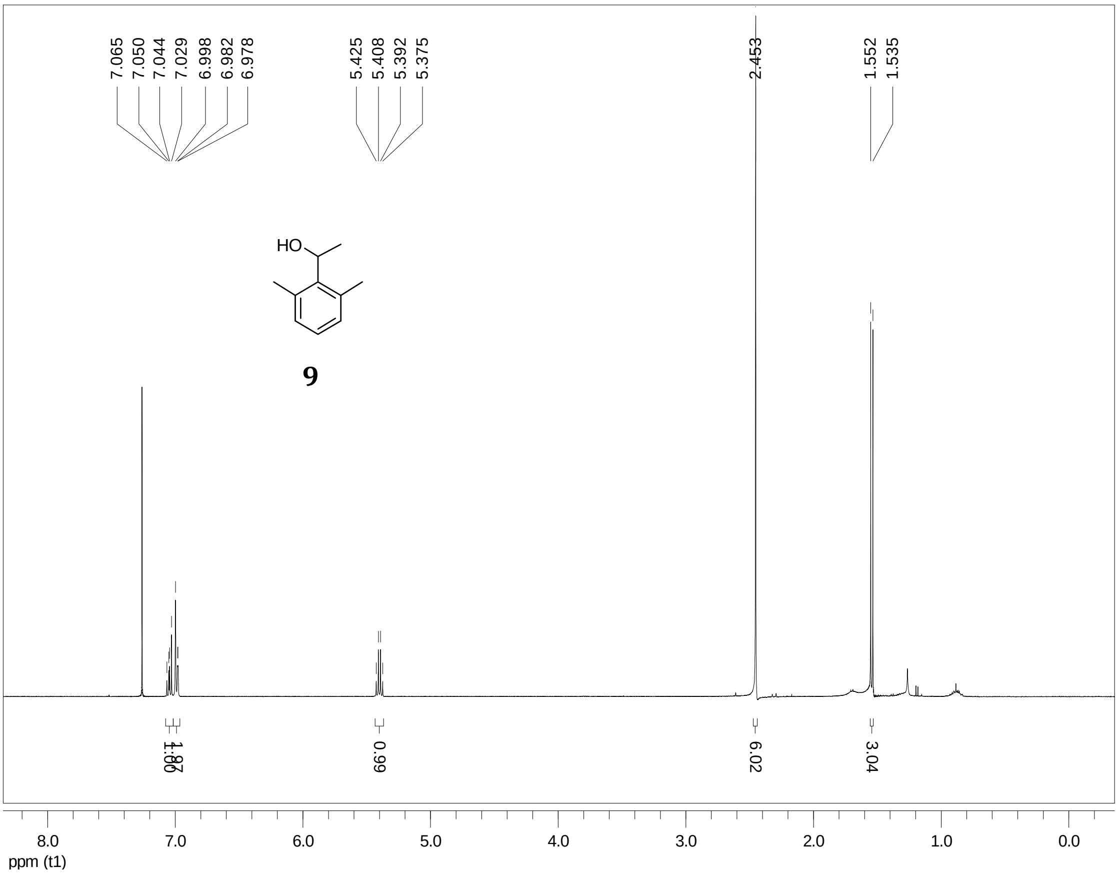
NMR TRACES

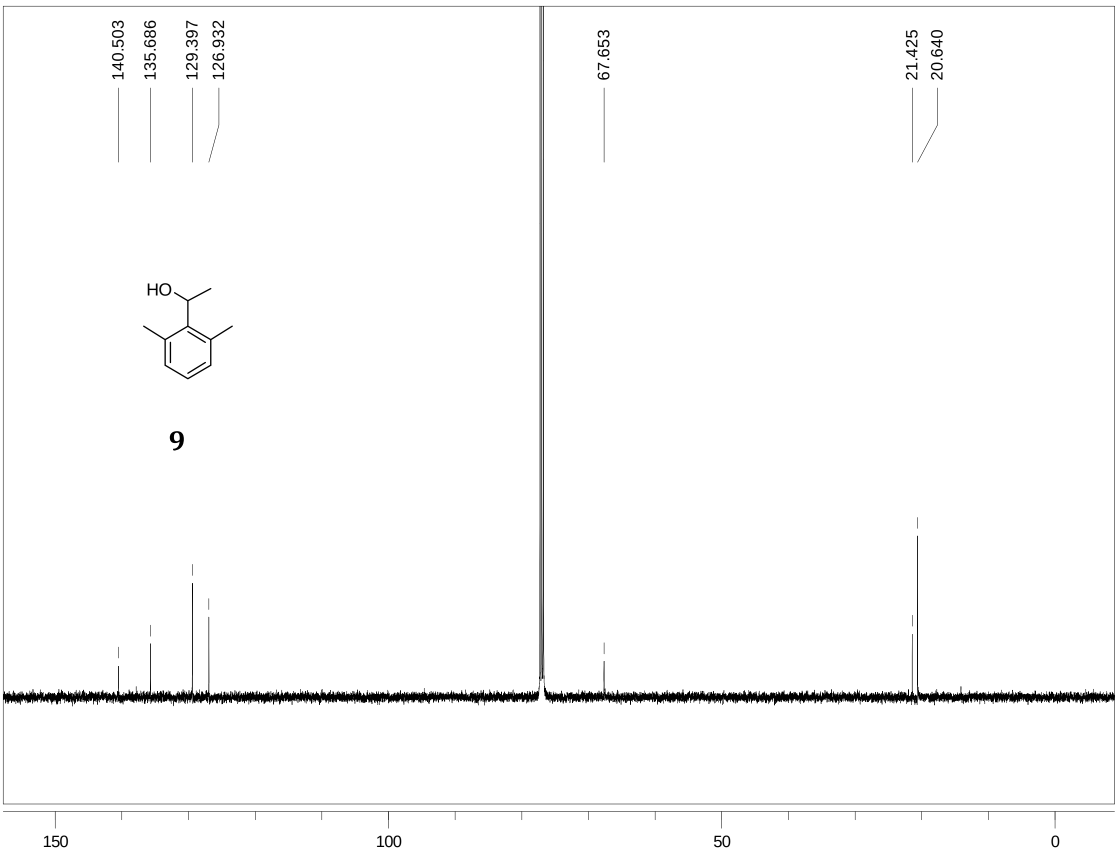

7.475
7.460
7.454
7.439
6.926
6.919
6.904
6.898
6.883
6.876
6.847
6.840
6.822
6.815
5.104
5.088
5.072
5.056
2.329
1.452
1.436
HO
F
6
1.00
1.01
1.00
1.02
3.09
3.14
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

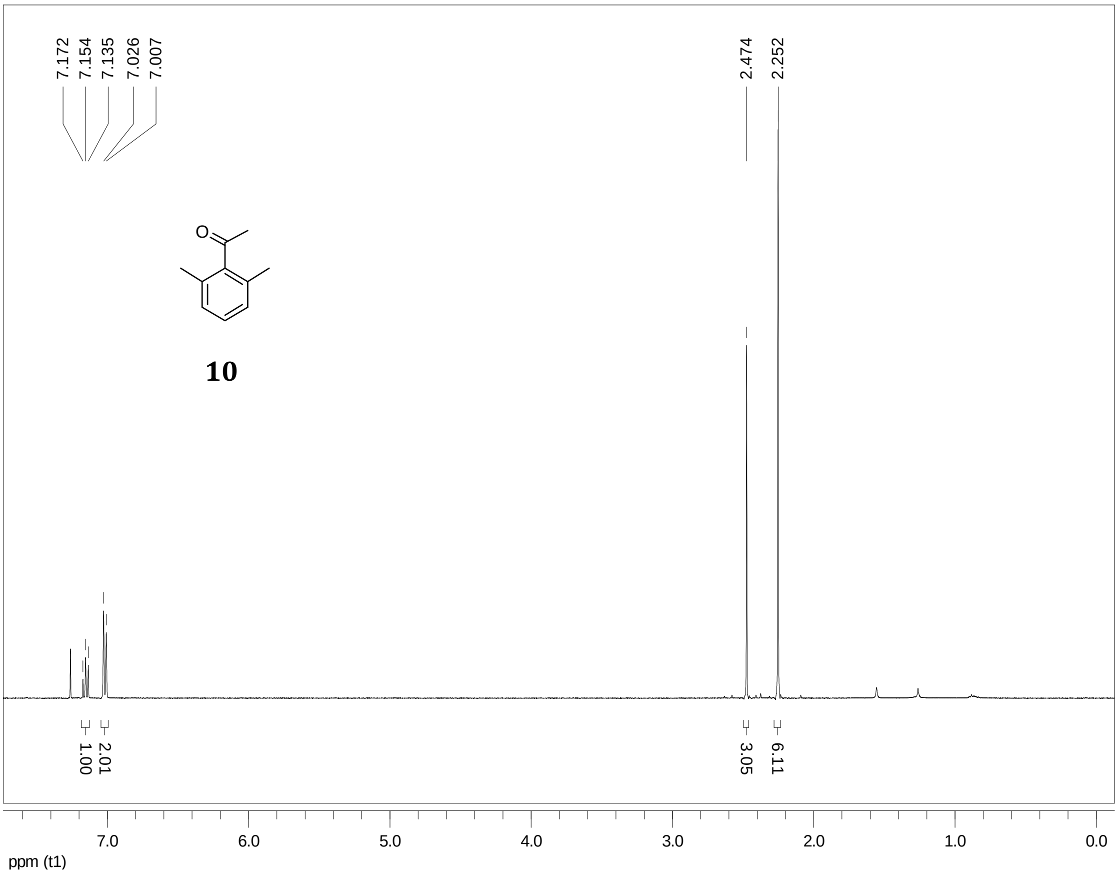

162.898
160.466
139.498
139.468
136.678
136.602
126.311
126.227
116.930
116.722
112.959
112.752
66.355
24.067
18.890
18.877
HO
F
6
150
100
50
0
ppm (t1)

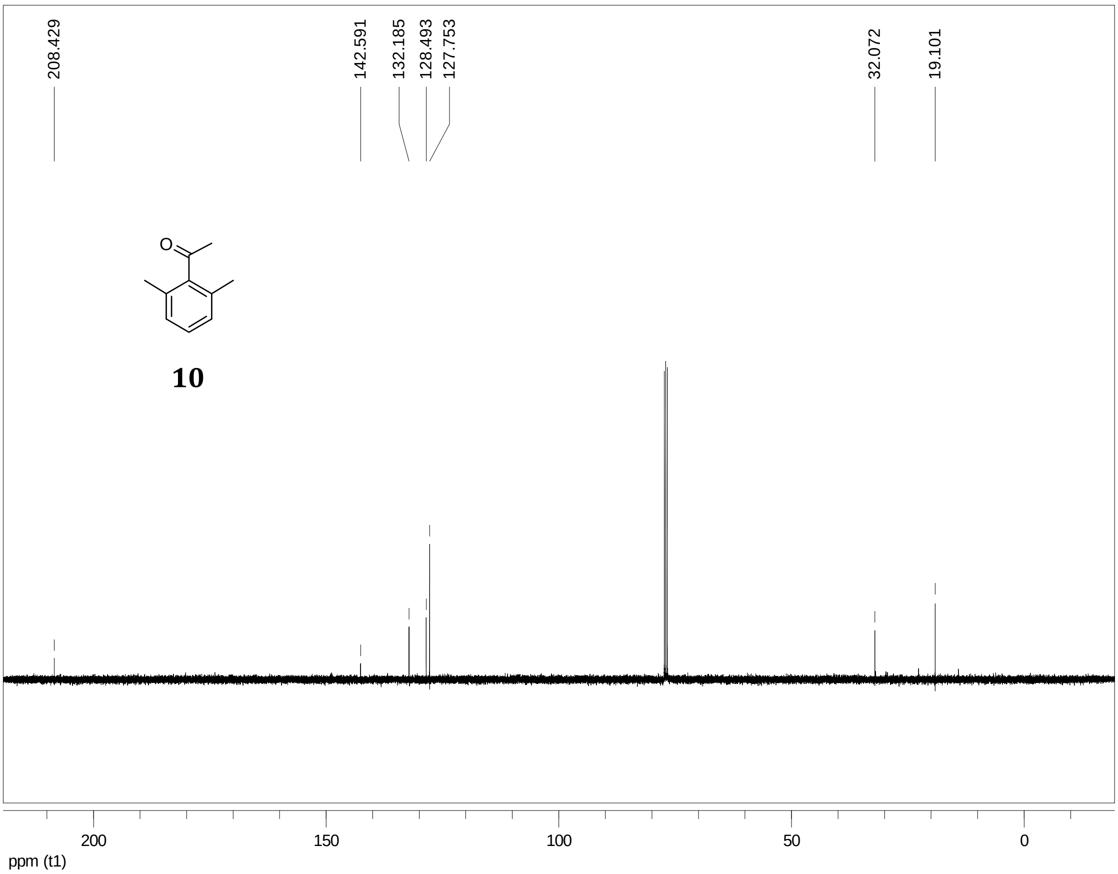

7.751
7.740
7.733
7.721
6.960
6.954
6.952
6.946
6.940
6.932
6.927
6.920
2.564
2.549
O
F
7
1.00
1.91
3.08
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

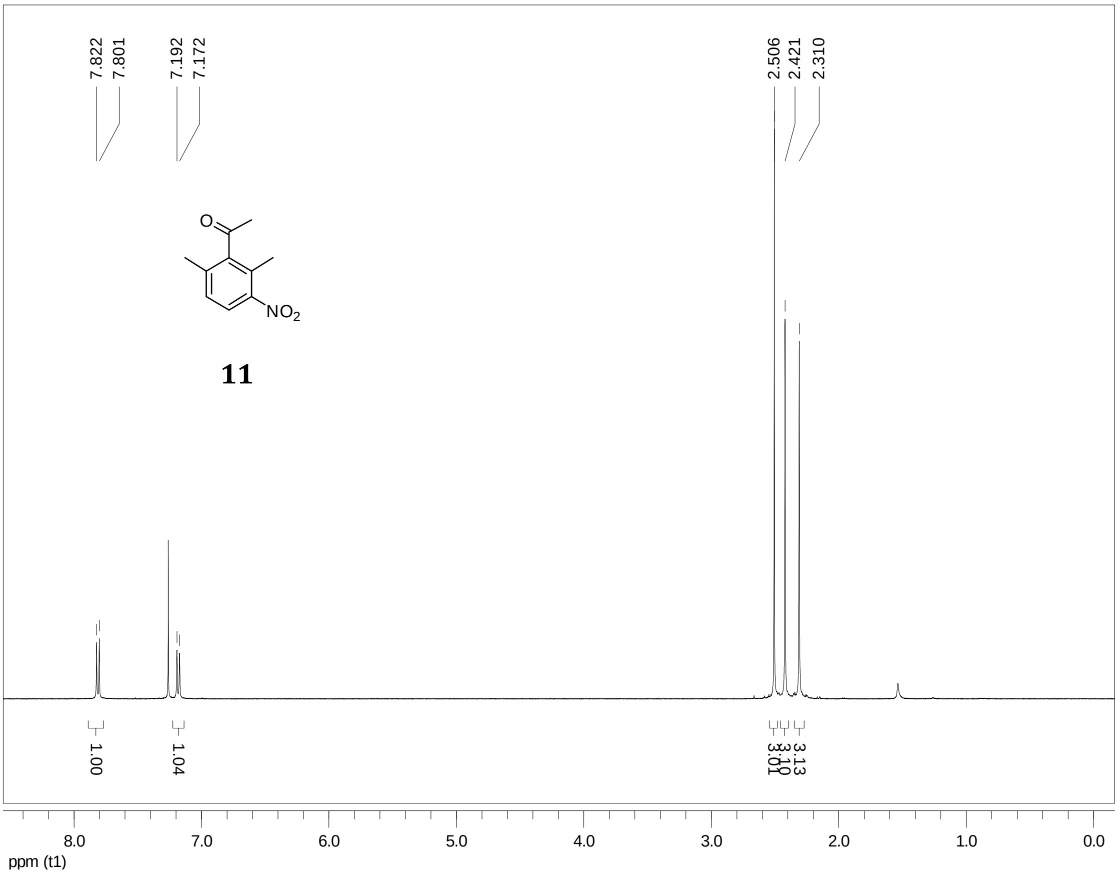

199.828
165.100
163.087
142.578
142.507
133.718
133.695
132.098
132.023
118.941
118.772
112.591
112.420
29.395
21.959
21.946
O
F
7
200
150
100
50
0
ppm (t1)

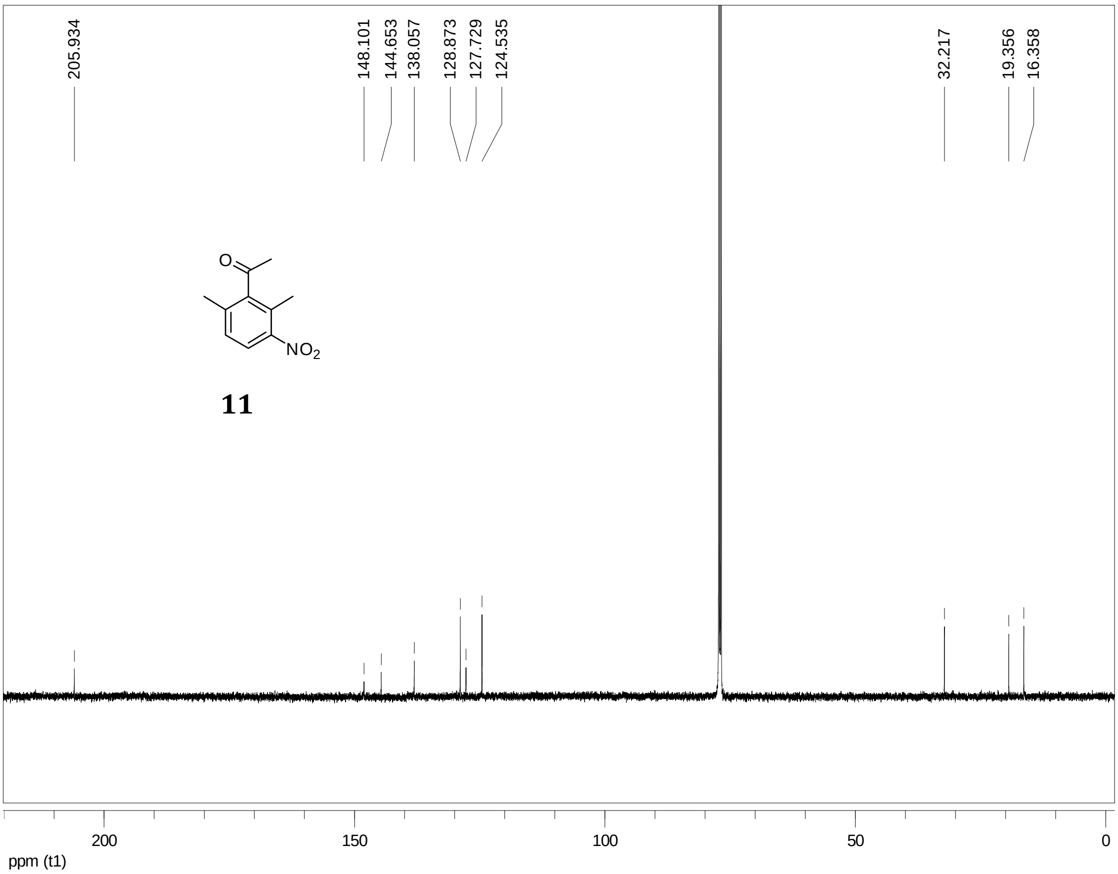

7.065
7.050
7.044
7.029
6.998
6.982
6.978
5.425
5.408
5.392
5.375
2.453
1.552
1.535
HO
9
1.87
1.00
0.99
6.02
3.04
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

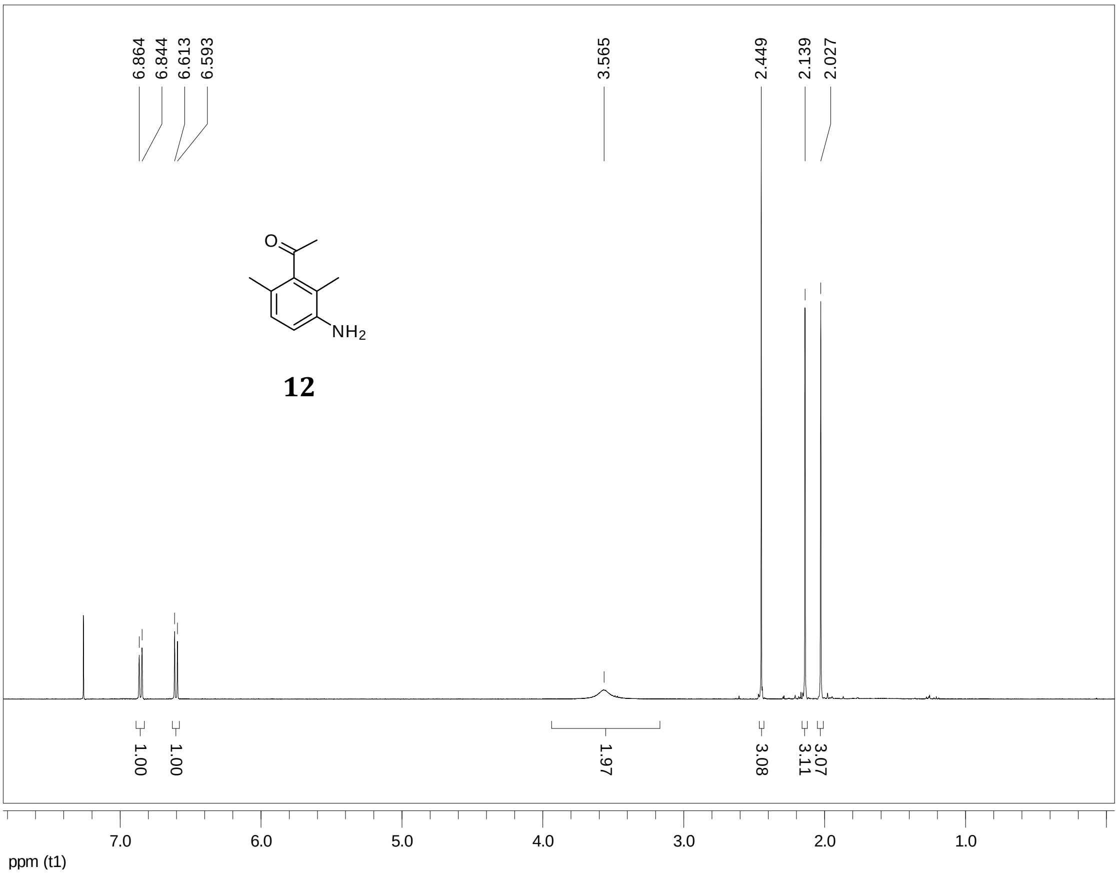

140.503
135.686
129.397
126.932
67.653
21.425
20.640
HO
9
150
100
50
0
ppm (t1)

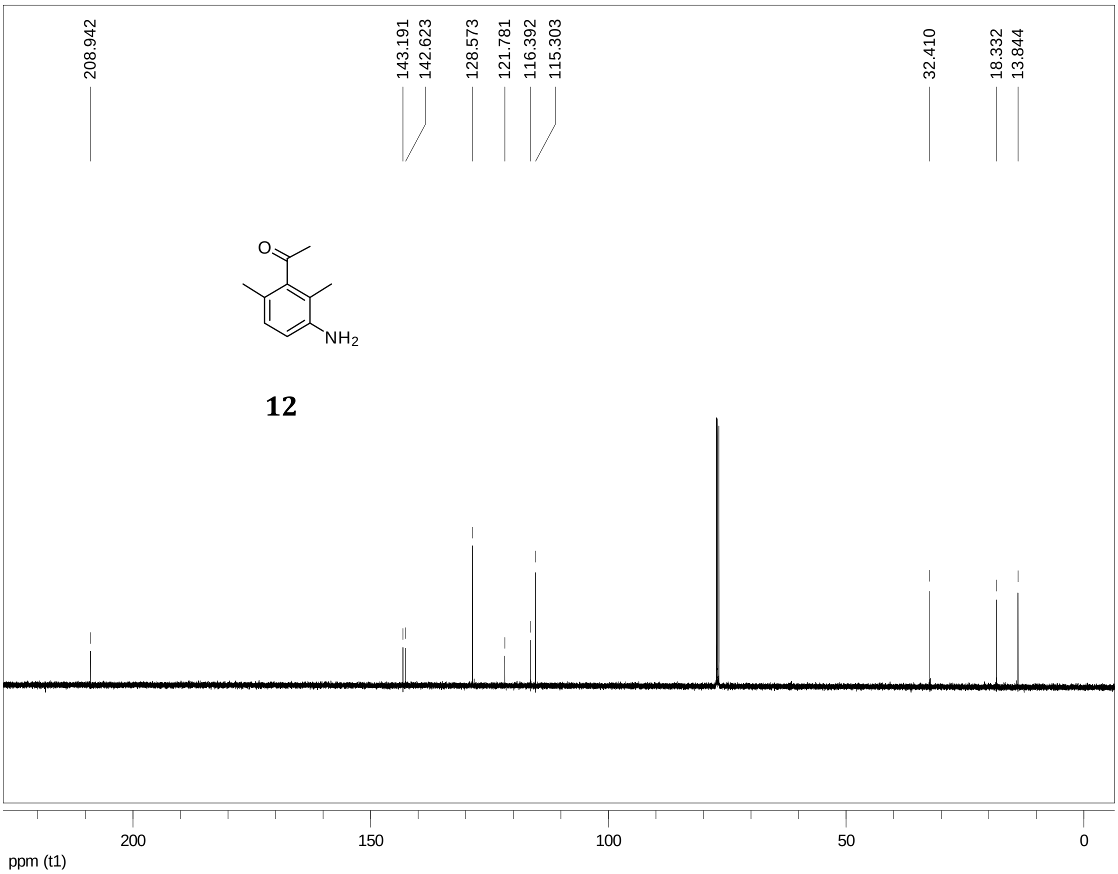

7.172
7.154
7.135
7.026
7.007
2.474
2.252
O
10
1.00
2.01
3.05
6.11
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

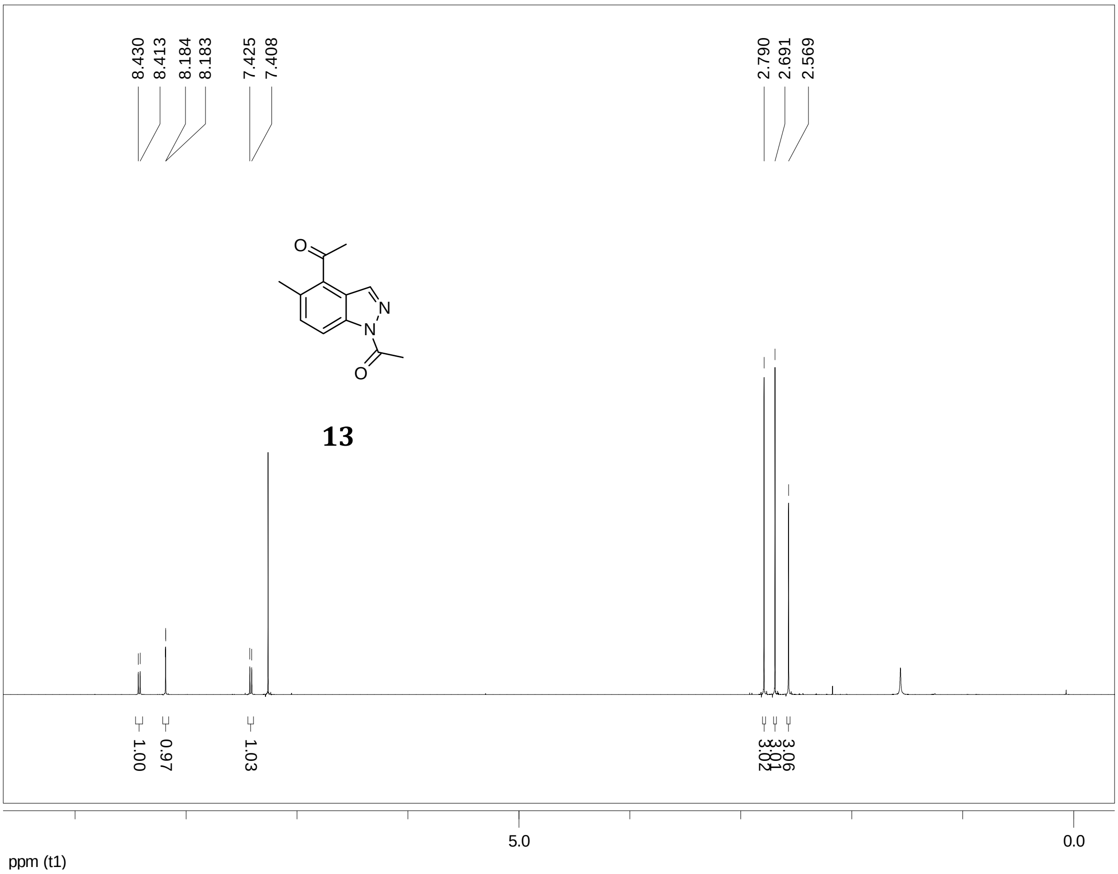

208.429
142.591
132.185
128.493
127.753
32.072
19.101
O
10
200
150
100
50
0
ppm (t1)

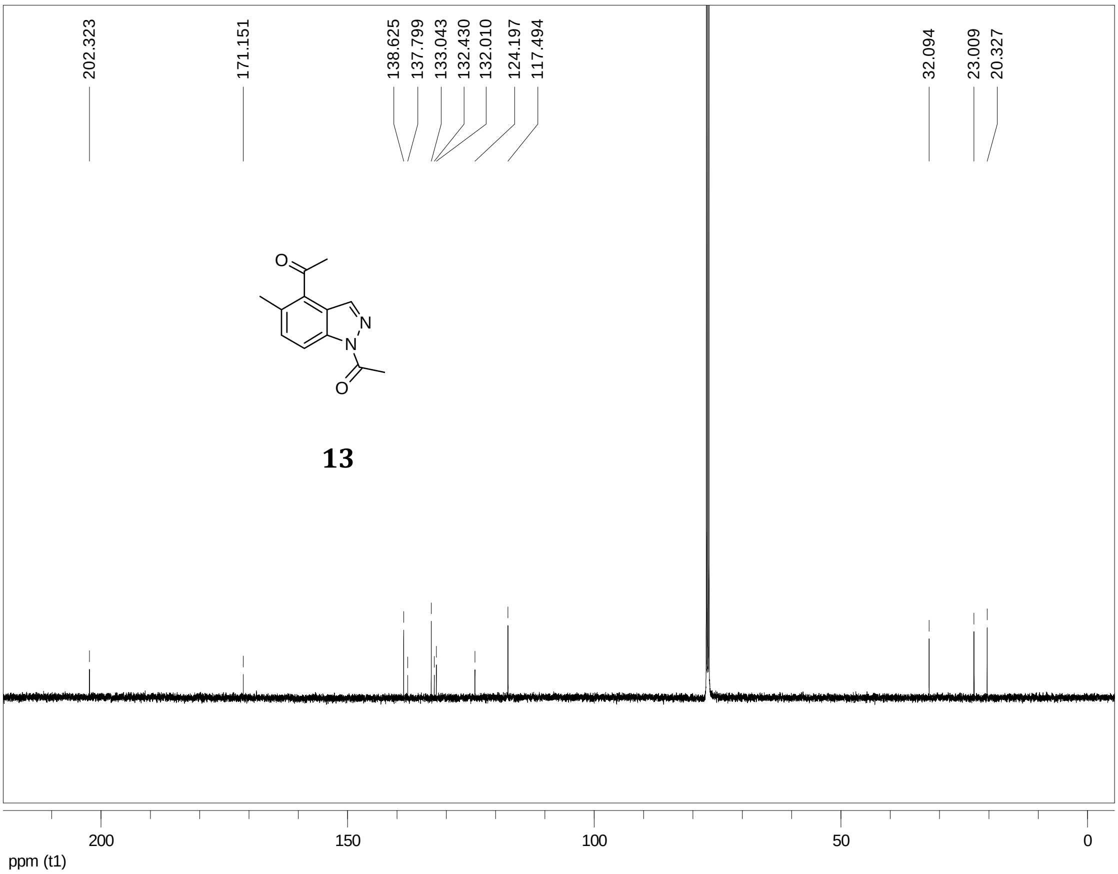

7.822
7.801
7.192
7.172
2.506
2.421
2.310
O
NO2
11
1.00
1.04
3.01
3.10
3.13
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

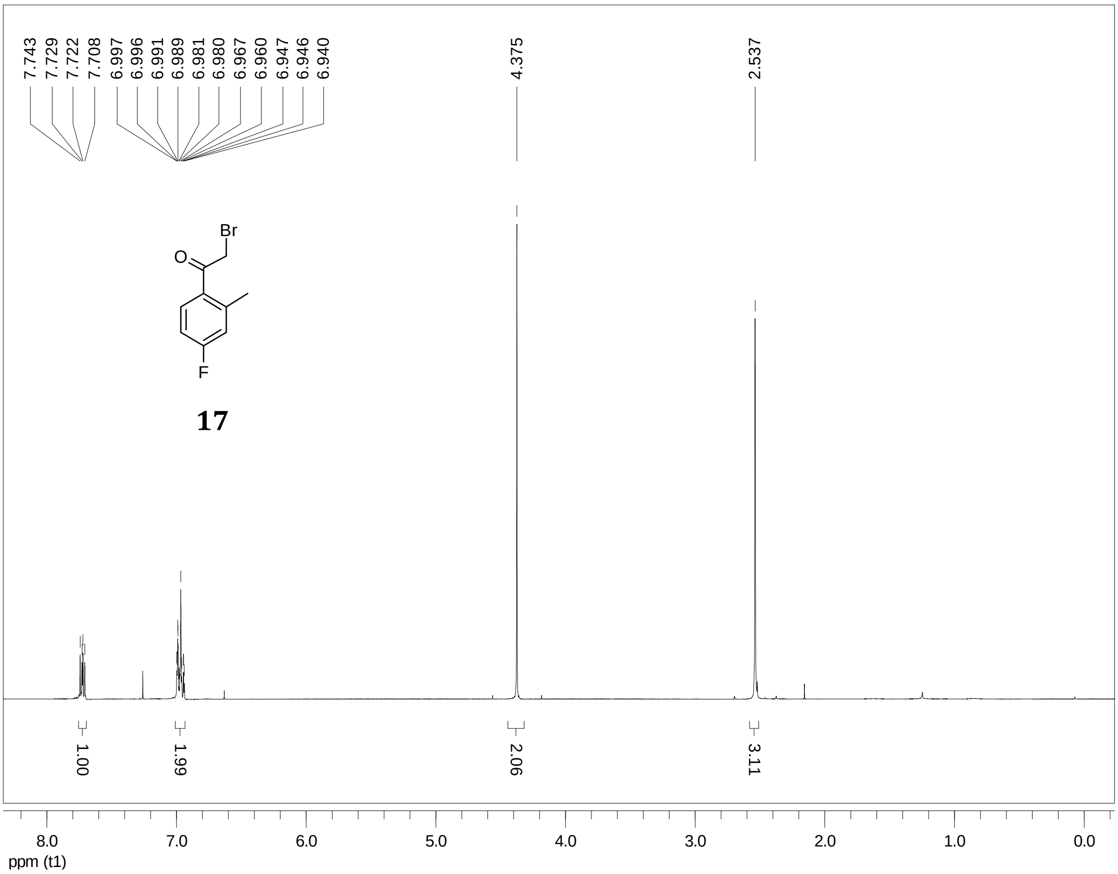

205.934
148.101
144.653
138.057
128.873
127.729
124.535
32.217
19.356
16.358
O
NO2
11
200
150
100
50
0
ppm (t1)

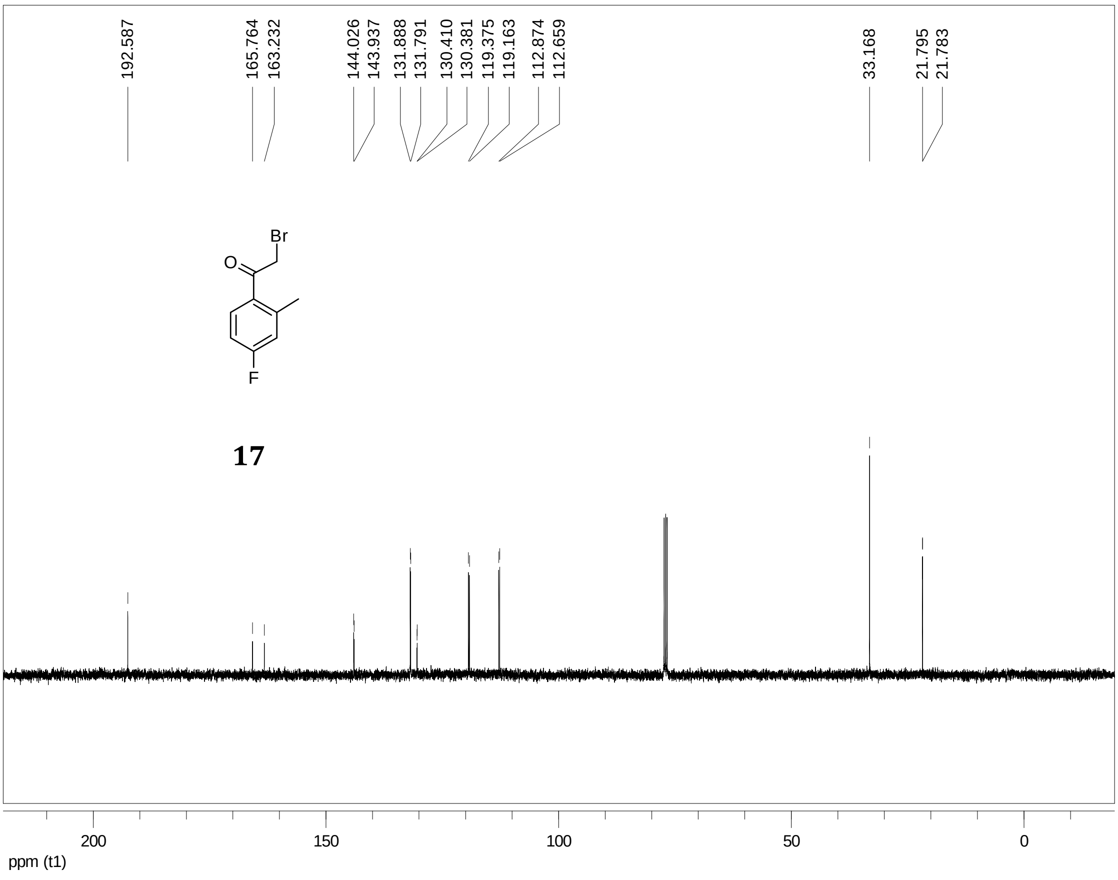

6.864
6.844
6.613
6.593
3.565
2.449
2.139
2.027
NH2
12
1.00
1.00
1.97
3.08
3.11
3.07
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

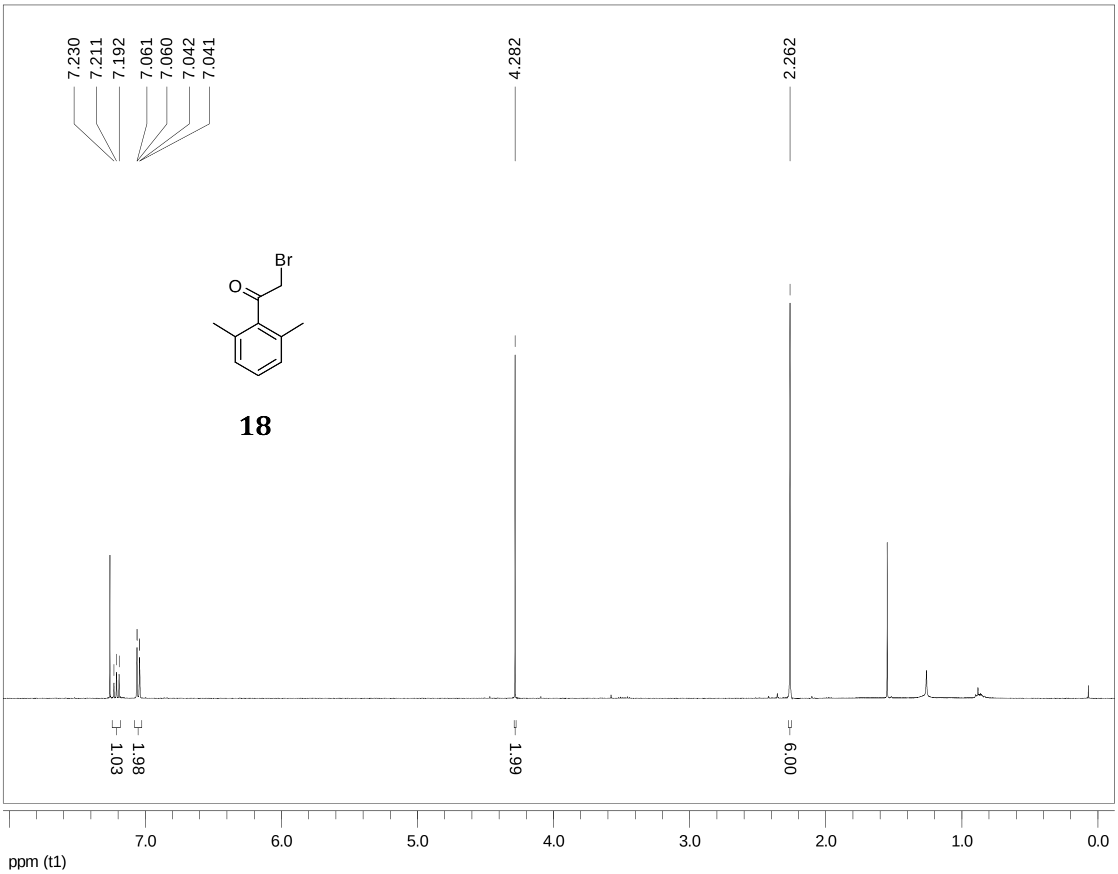

208.942
143.191
142.623
128.573
121.781
116.392
115.303
32.410
18.332
13.844
NH2
12
200
150
100
50
0
ppm (t1)

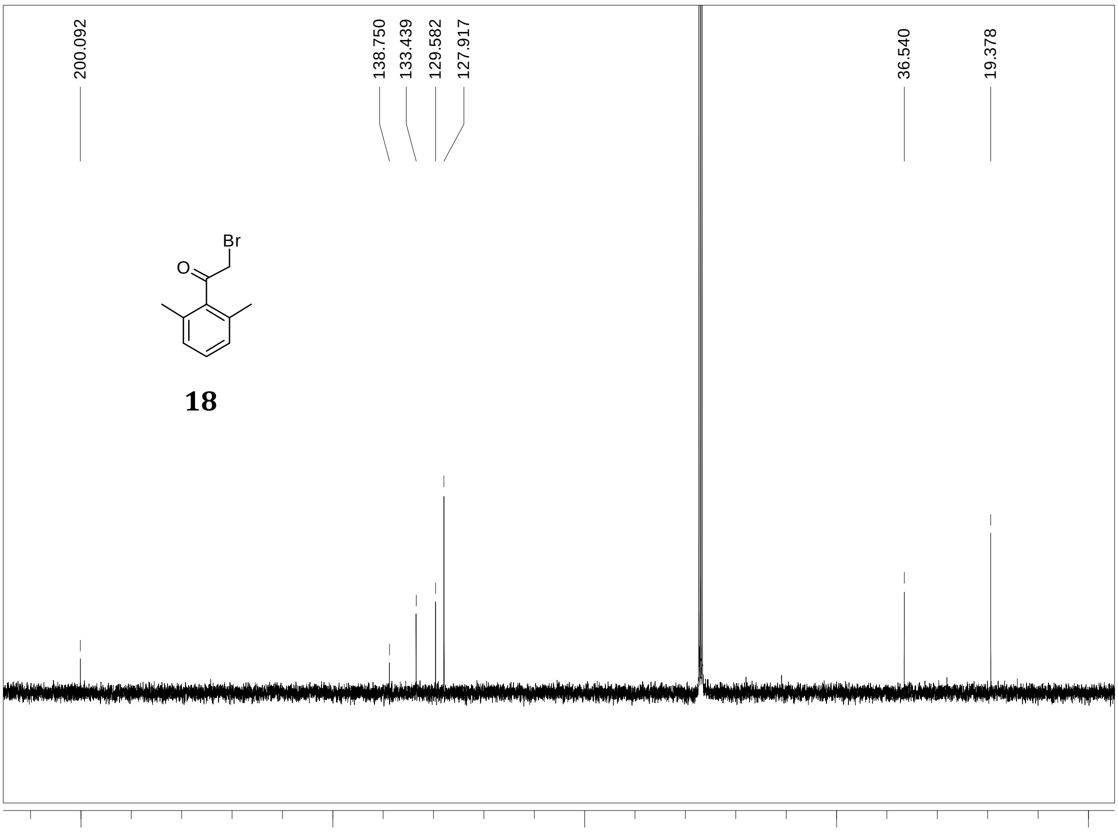

8.430
8.413
8.184
8.183
7.425
7.408
2.790
2.691
2.569
13
1.00
0.97
1.03
3.02
3.01
3.06
5.0
0.0
ppm (t1)

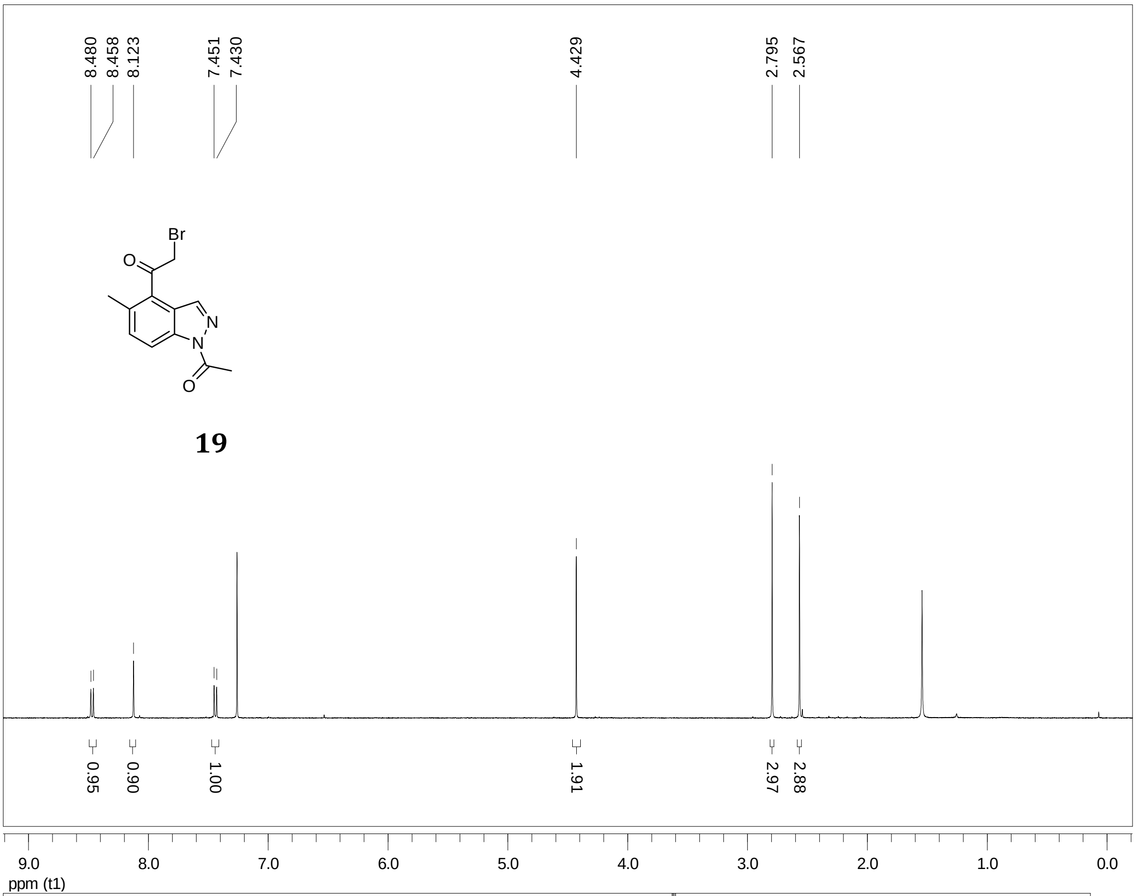

202.323
171.151
138.625
137.799
133.043
132.430
132.010
124.197
117.494
32.094
23.009
20.327
13
200
150
100
50
0
ppm (t1)

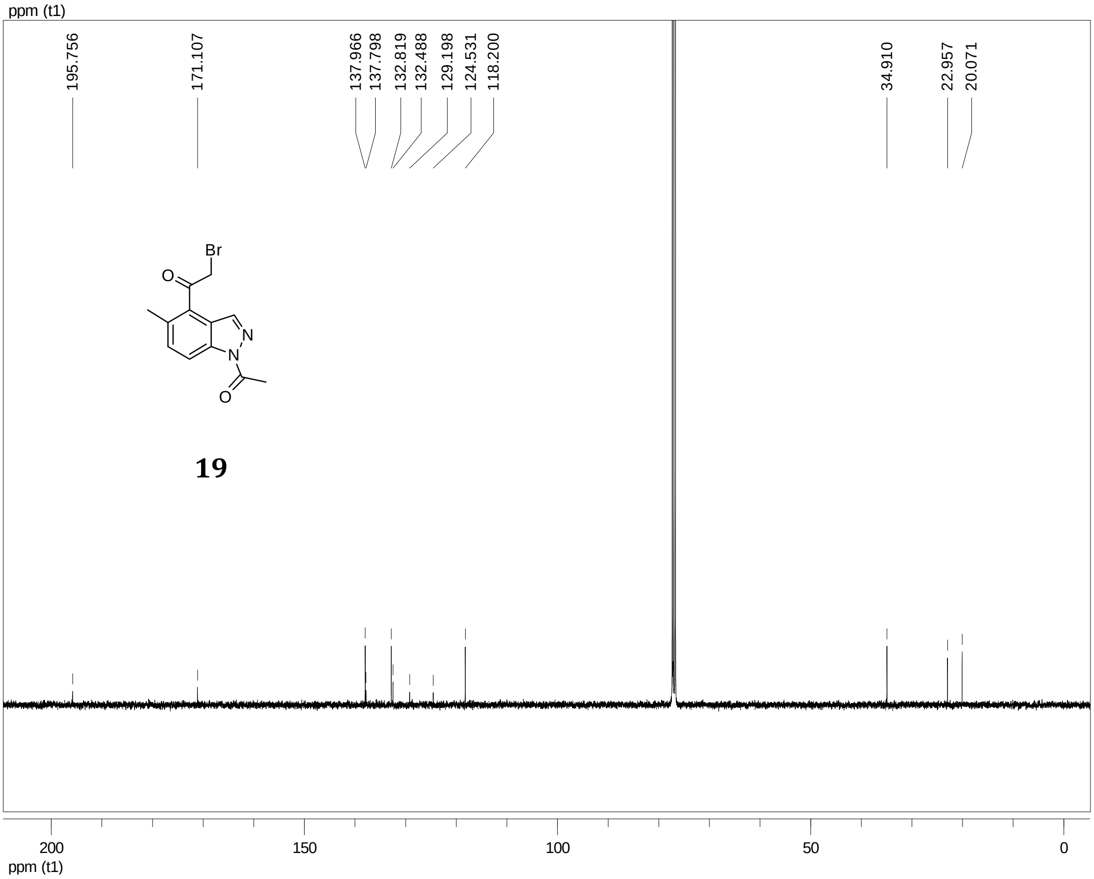

7.743
7.729
7.722
7.708
6.997
6.996
6.991
6.989
6.981
6.980
6.967
6.960
6.947
6.946
6.940
4.375
2.537
Br
O
F
17
1.00
1.99
2.06
3.11
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

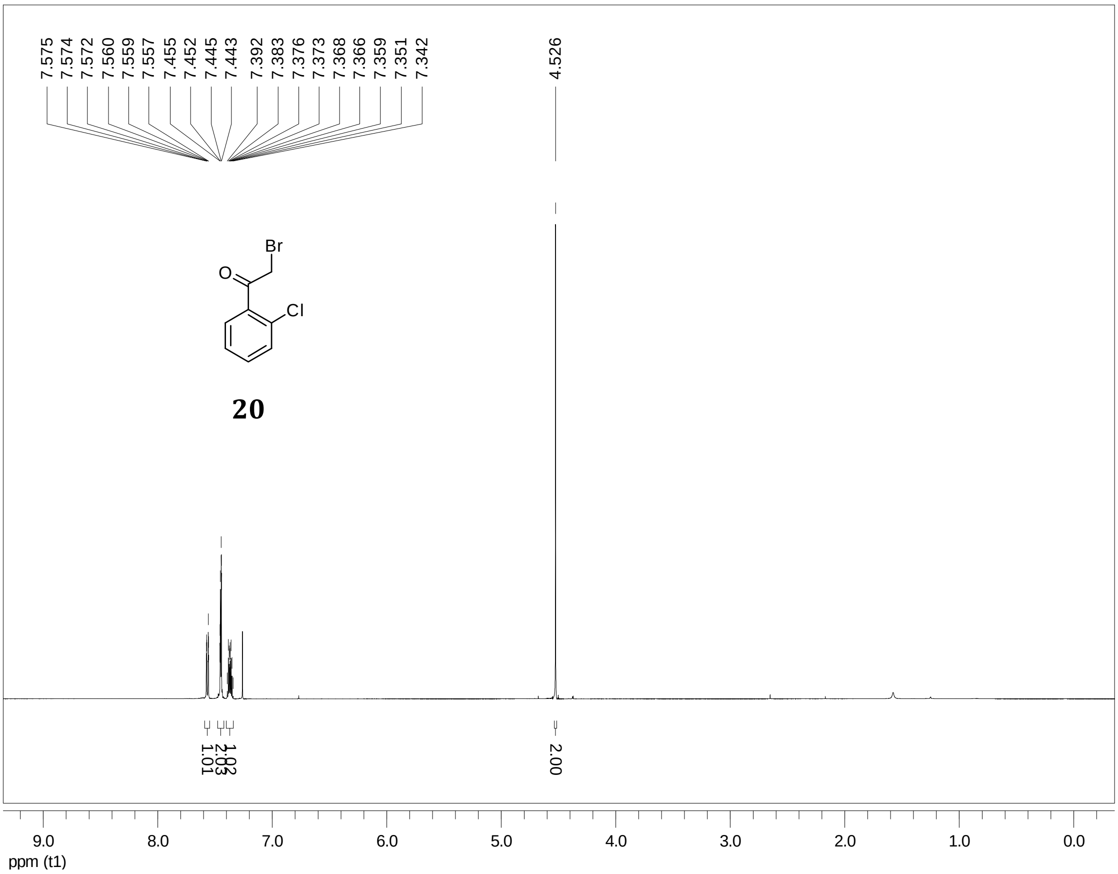

192.587
165.764
163.232
144.026
143.937
131.888
131.791
130.410
130.381
119.375
119.163
112.874
112.659
33.168
21.795
21.783
Br
O
F
17
200
150
100
50
0
ppm (t1)

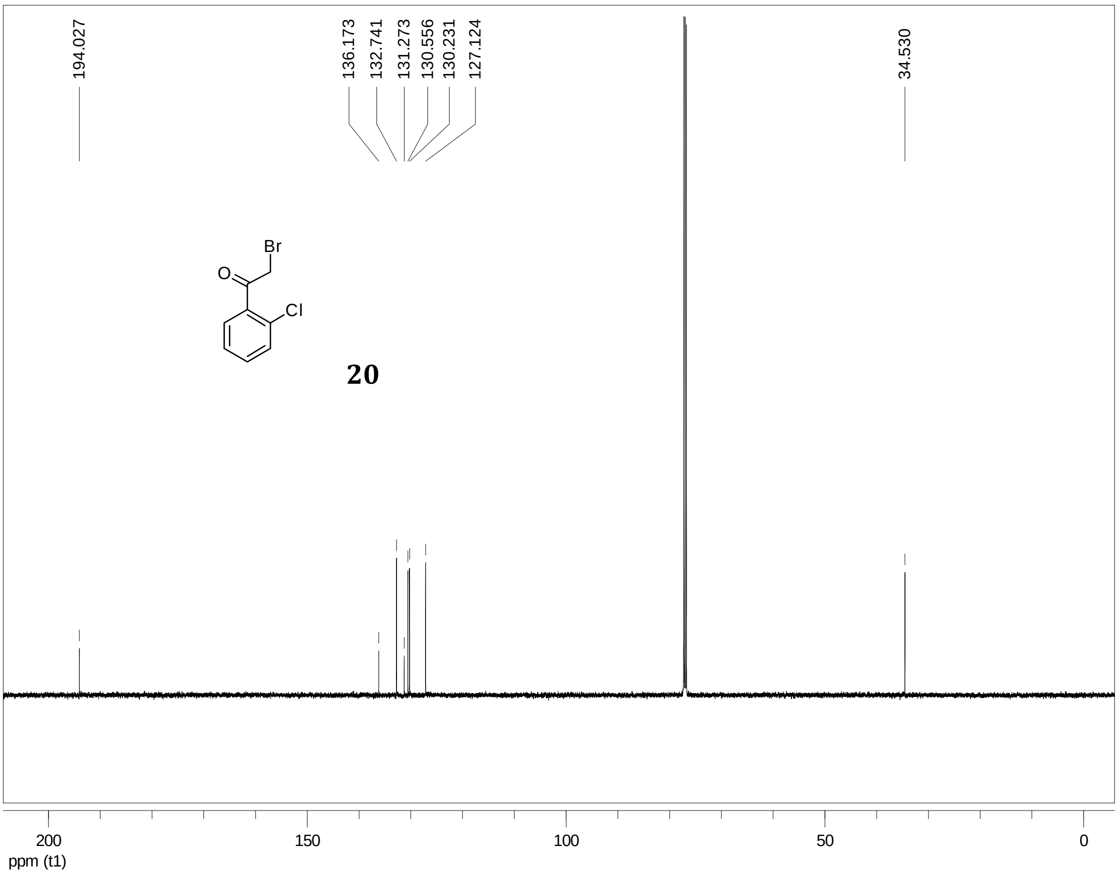

7.230
7.211
7.192
7.061
7.060
7.042
7.041
4.282
2.262
Br
O
18
1.03
1.98
1.99
6.00
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

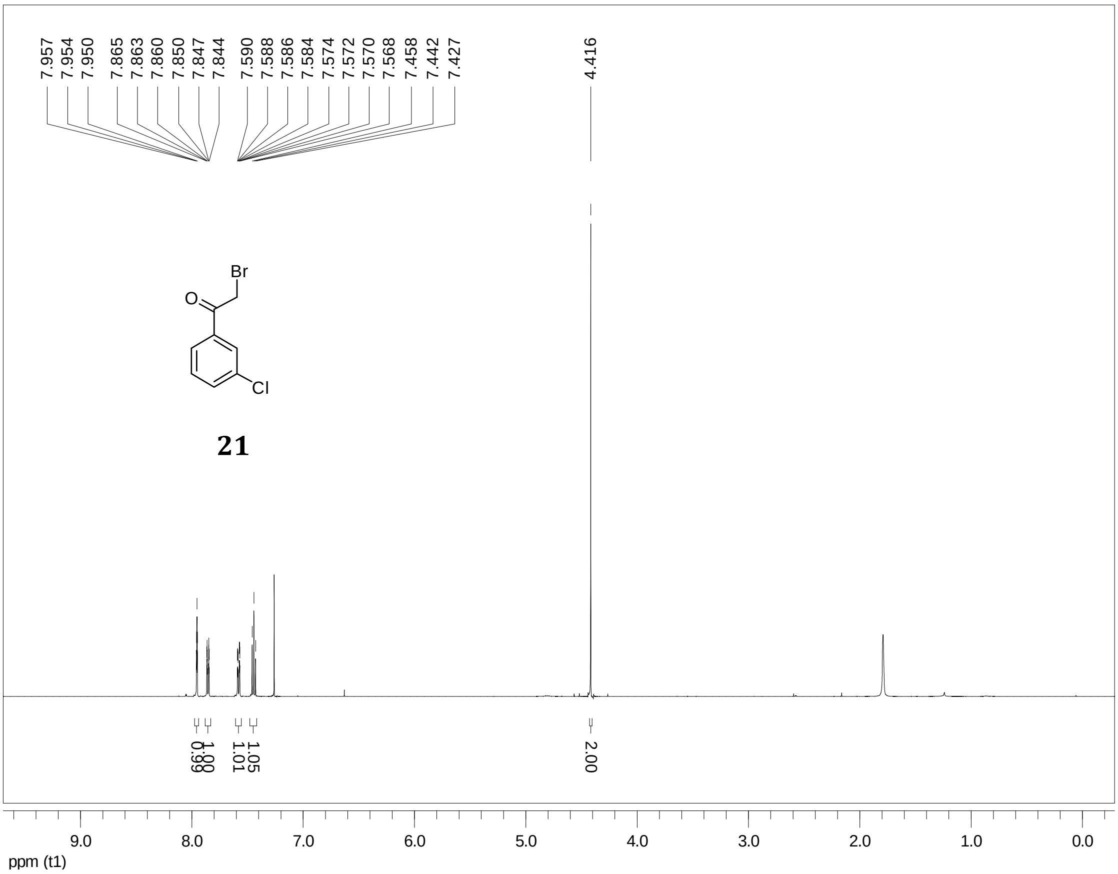

200.092
138.750
133.439
129.582
127.917
36.540
19.378
Br
O
18
200
150
100
50
0
ppm (t1)


8.480
8.458
8.123
7.451
7.430
4.429
2.795
2.567
Br
O
N
N
O
19
0.95
0.90
1.00
1.91
2.97
2.88
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

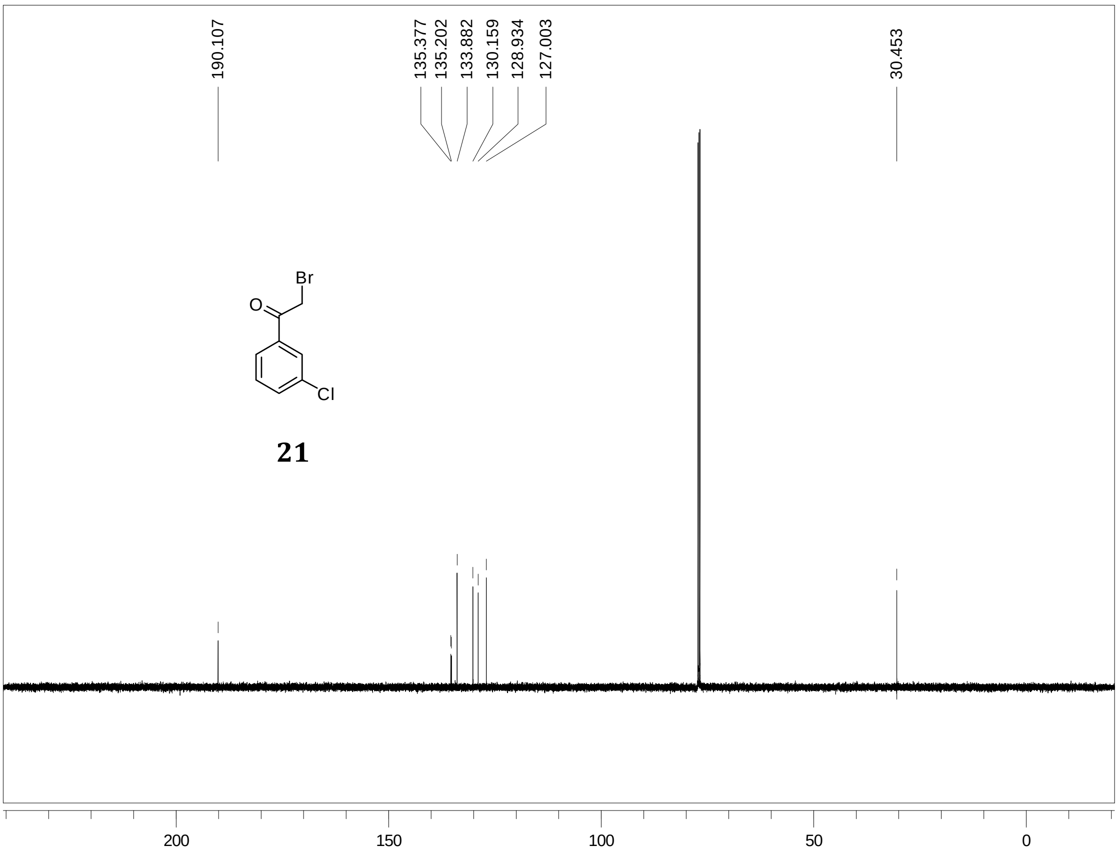

195.756
171.107
137.966
137.798
132.819
132.488
129.198
124.531
118.200
34.910
22.957
20.071
Br
O
N
N
O
19
200
150
100
50
0
ppm (t1)


7.575
7.574
7.572
7.560
7.559
7.557
7.455
7.452
7.445
7.443
7.392
7.383
7.376
7.373
7.368
7.366
7.359
7.351
7.342
4.526
Br
O
Cl
20
1.01
2.03
1.02
2.00
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

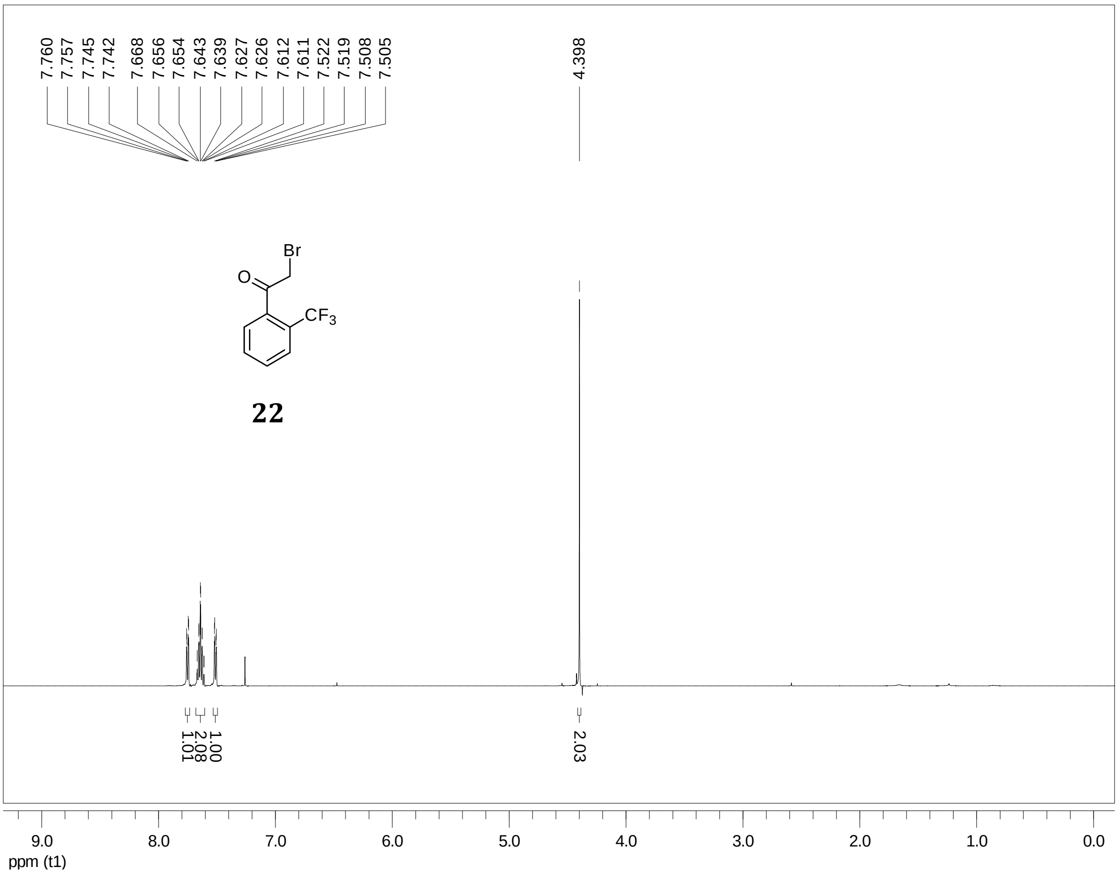

194.027
136.173
132.741
131.273
130.556
130.231
127.124
34.530
Br
O
Cl
20
200
150
100
50
0
ppm (t1)

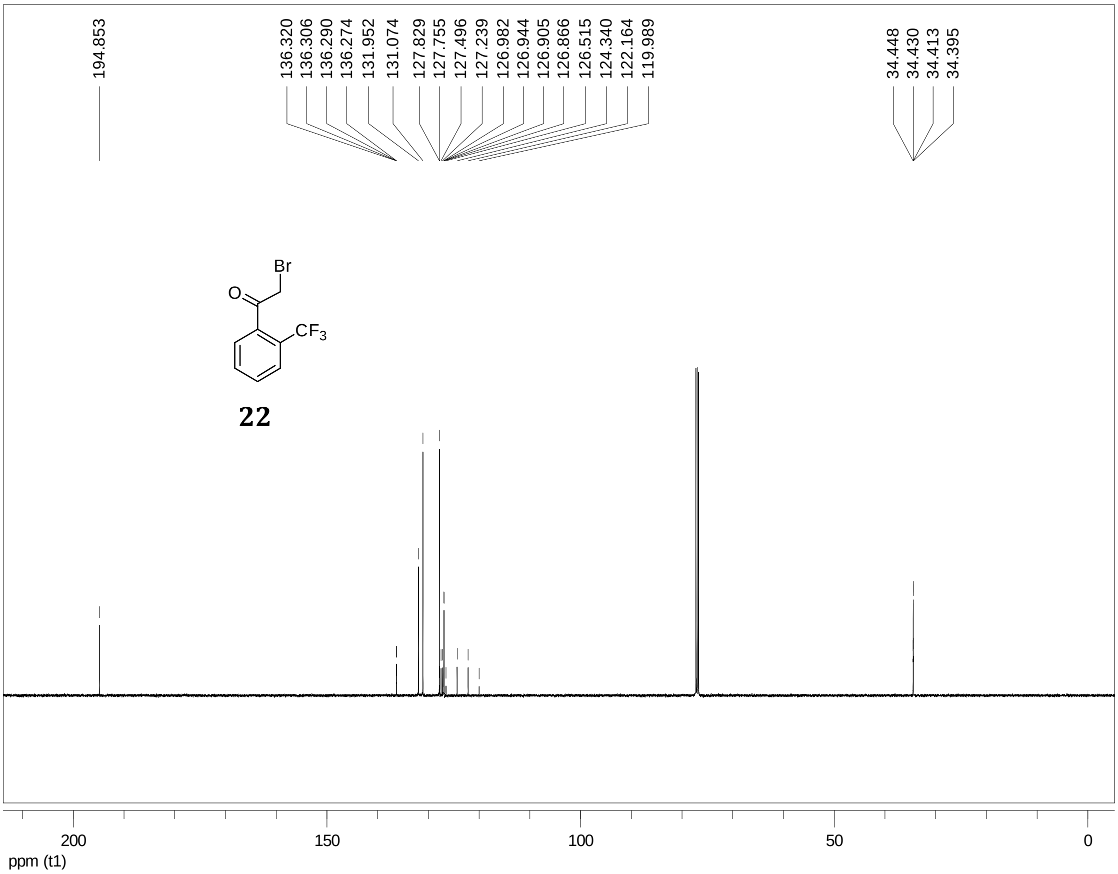

7.957
7.954
7.950
7.865
7.863
7.860
7.850
7.847
7.844
7.590
7.588
7.586
7.584
7.574
7.572
7.570
7.568
7.458
7.442
7.427
4.416
Br
O
Cl
0.99
1.00
1.01
1.05
2.00
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

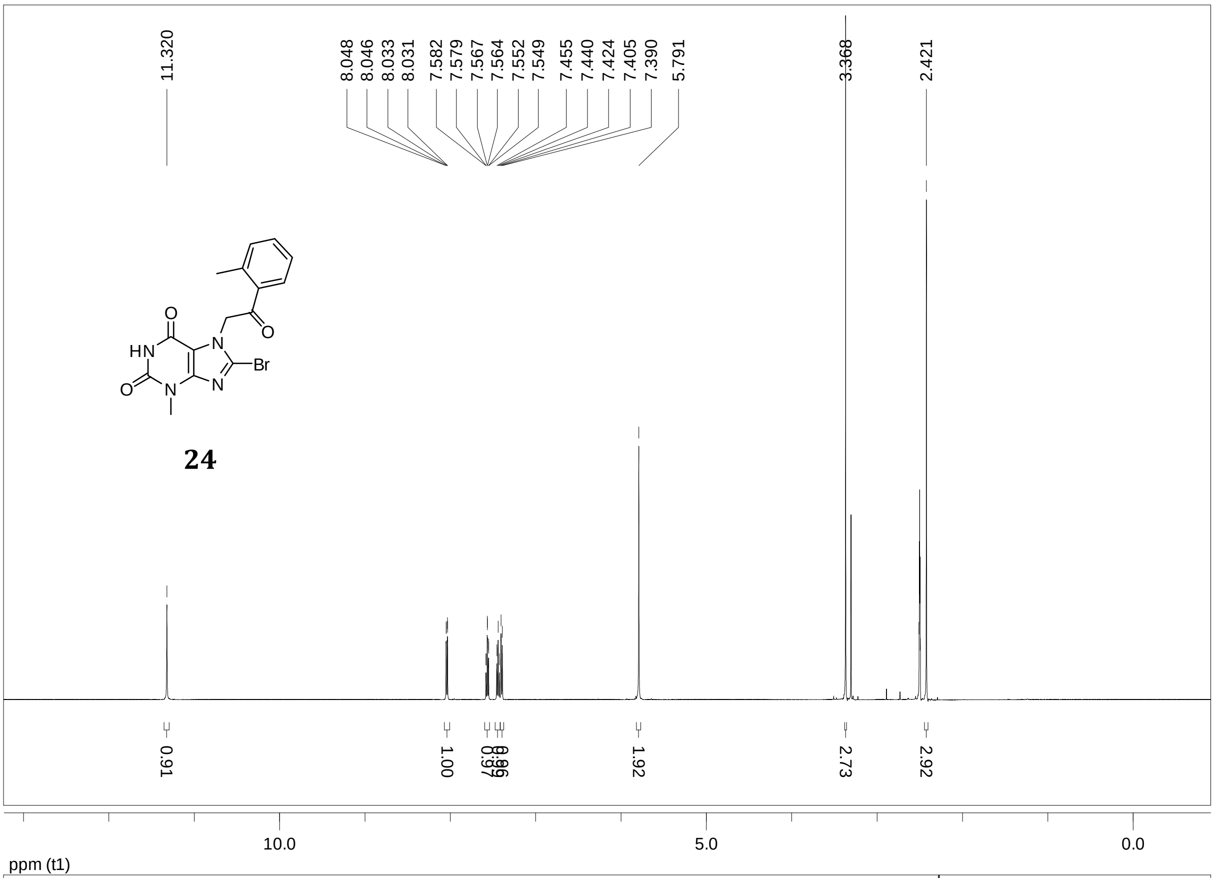
21

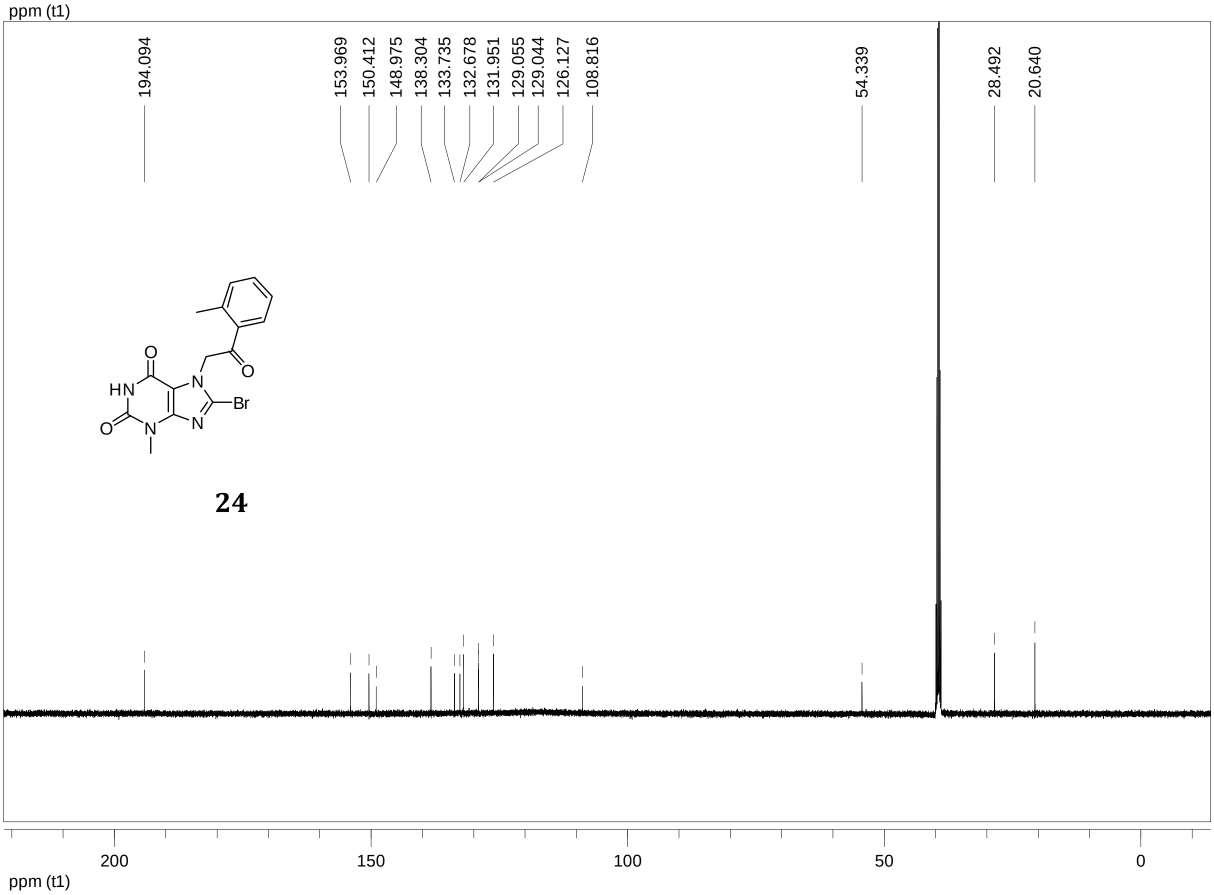

190.107
135.377
135.202
133.882
130.159
128.934
127.003
30.453
Br
O
Cl
200
150
100
50
0
ppm (t1)

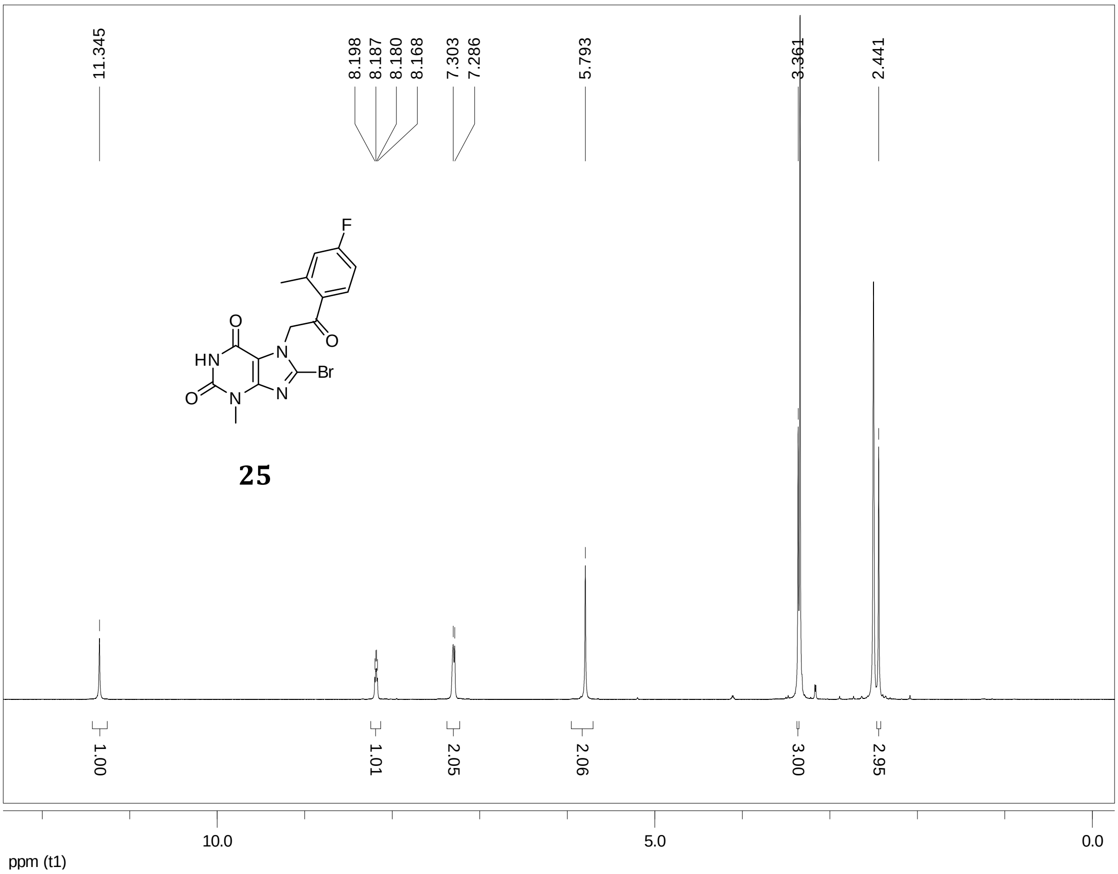
21

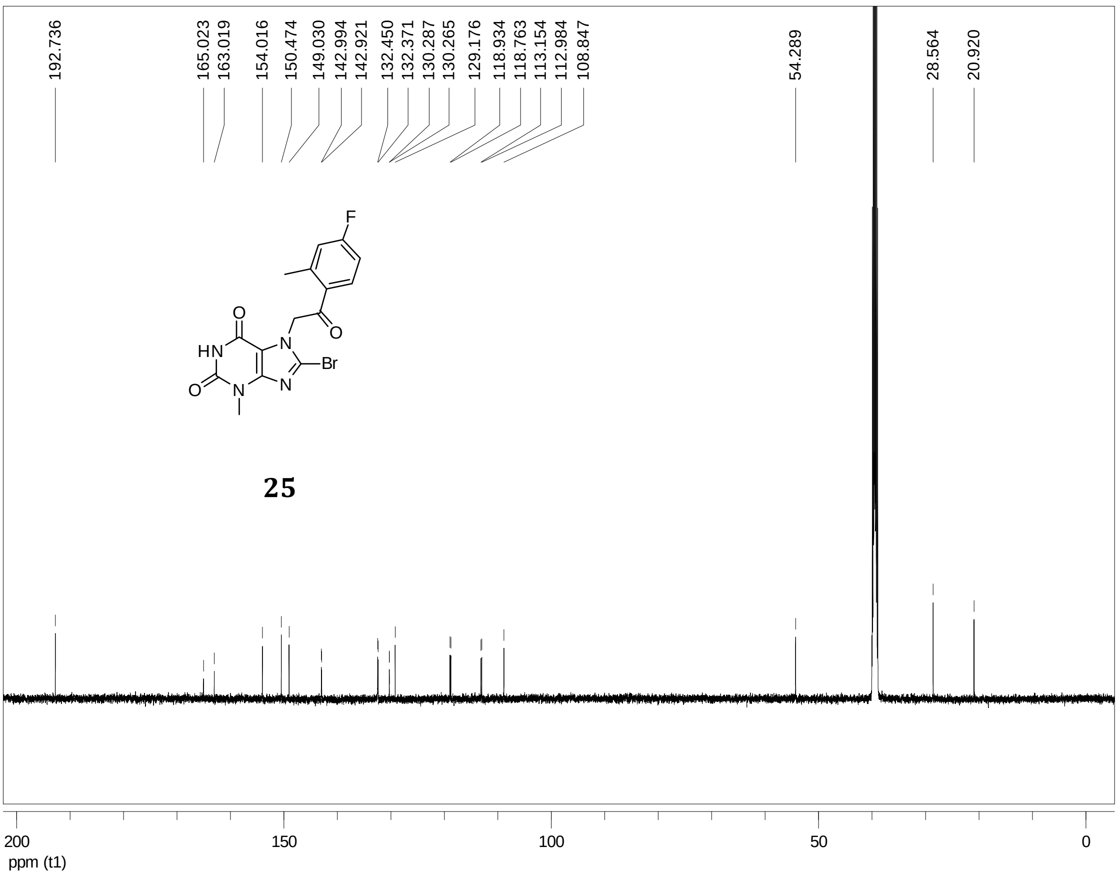

7.760
7.757
7.745
7.742
7.668
7.656
7.654
7.643
7.639
7.627
7.626
7.612
7.611
7.522
7.519
7.508
7.505
4.398
Br
O
CF3
22
1.01
2.08
1.00
2.03
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

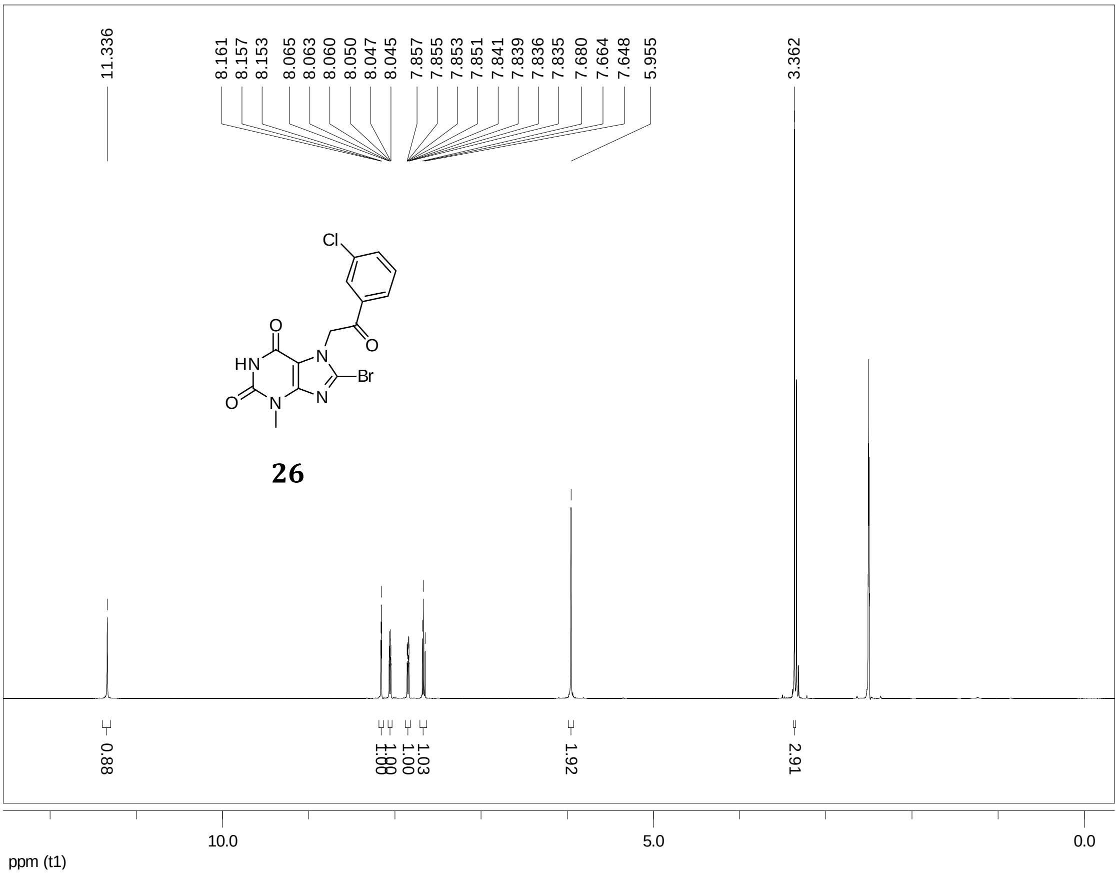

194.853
136.320
136.306
136.290
136.274
131.952
131.074
127.829
127.755
127.496
127.239
126.982
126.944
126.905
126.866
126.515
124.340
122.164
119.989
34.448
34.430
34.413
34.395
Br
O
CF3
22
200
150
100
50
0
ppm (t1)

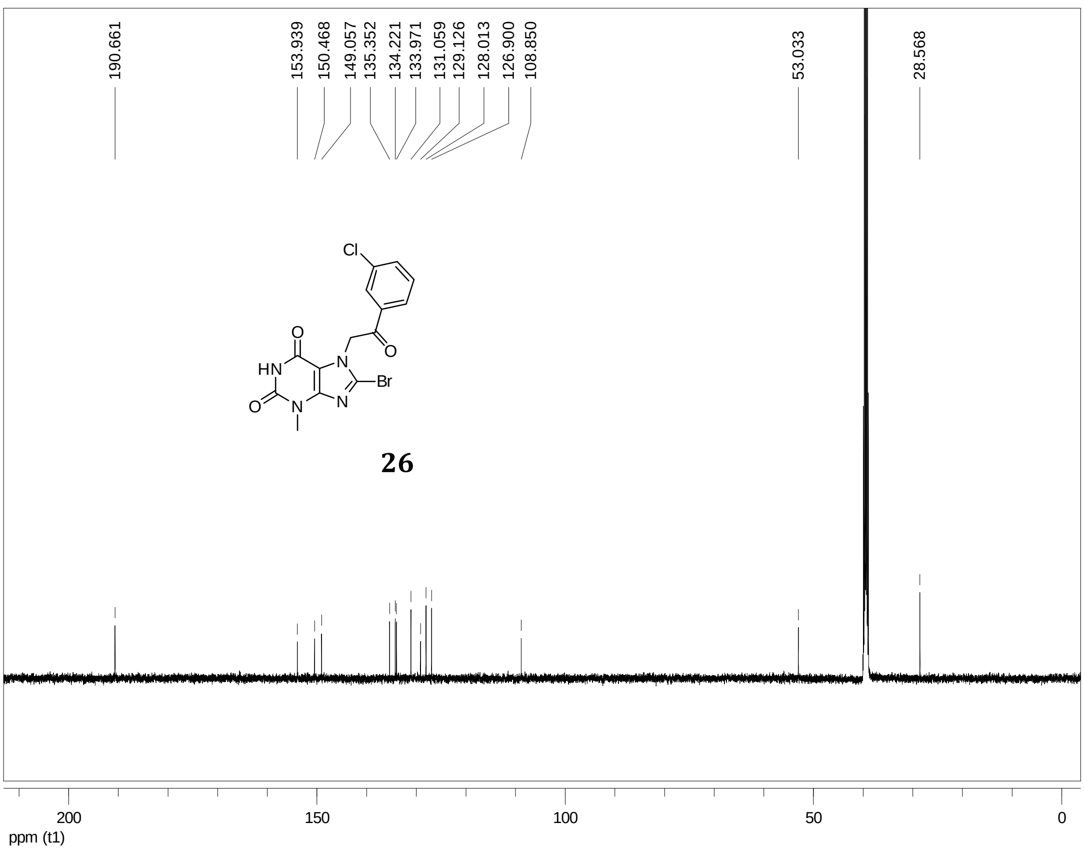

11.320
8.048
8.046
8.033
8.031
7.582
7.579
7.567
7.564
7.552
7.549
7.455
7.440
7.424
7.405
7.390
5.791
3.368
2.421
HN
O
N
O
N
N
Br
O
24
0.91
1.00
0.97
0.96
0.96
1.92
2.73
2.92
10.0
5.0
0.0
ppm (t1)

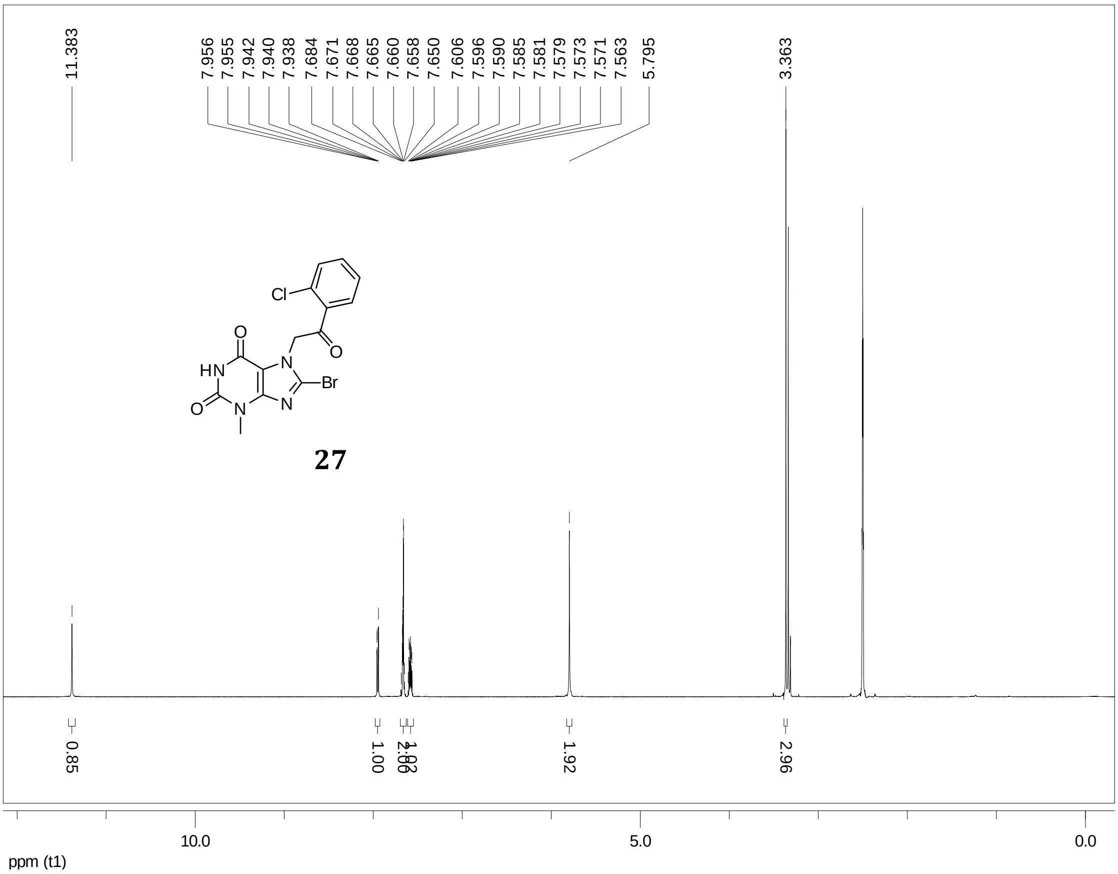

194.094
153.969
150.412
148.975
138.304
133.735
132.678
131.951
129.055
129.044
126.127
108.816
54.339
28.492
20.640
HN
O
N
O
N
N
Br
O
24
200
150
100
50
0
ppm (t1)

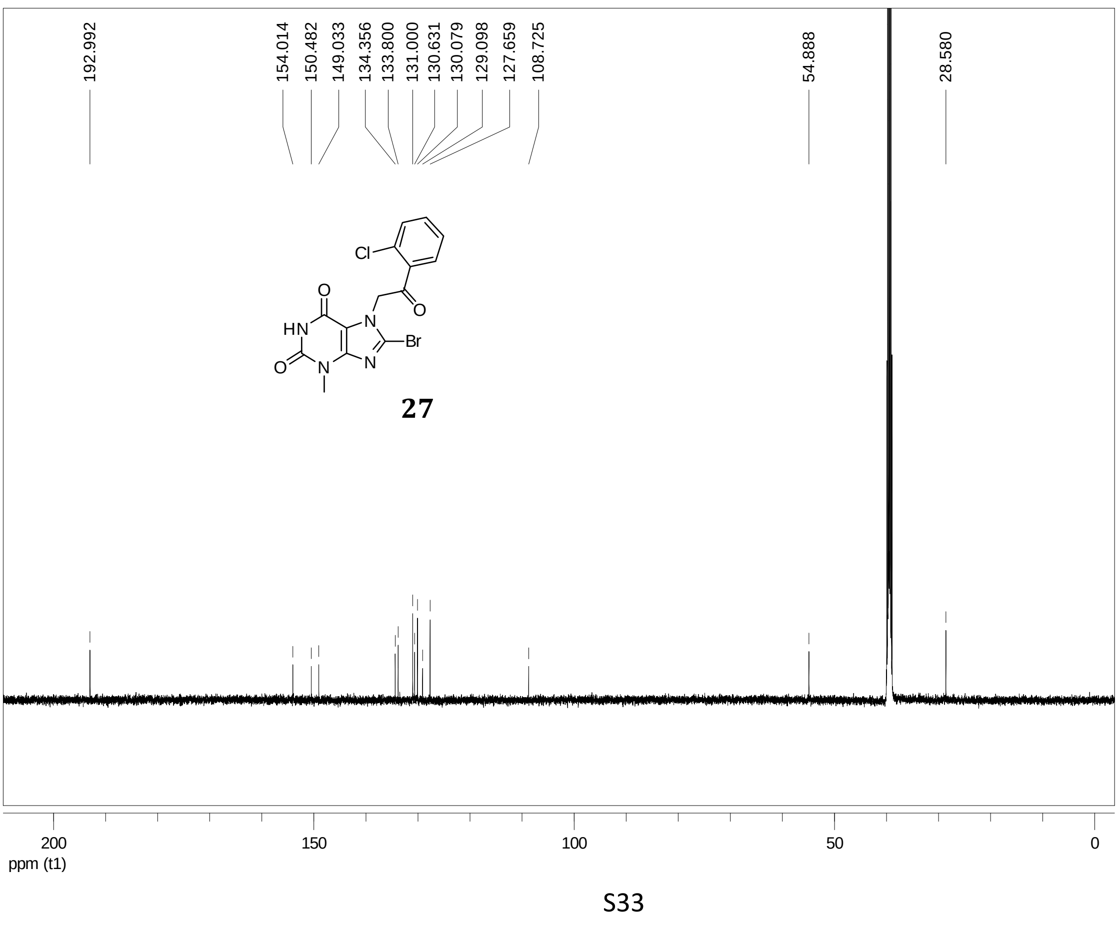

11.345
8.198
8.187
8.180
8.168
7.303
7.286
5.793
3.361
2.441
F
O
HN
O
N
N
N
Br
O
25
1.00
1.01
2.05
2.06
3.00
2.95
10.0
5.0
0.0
ppm (t1)

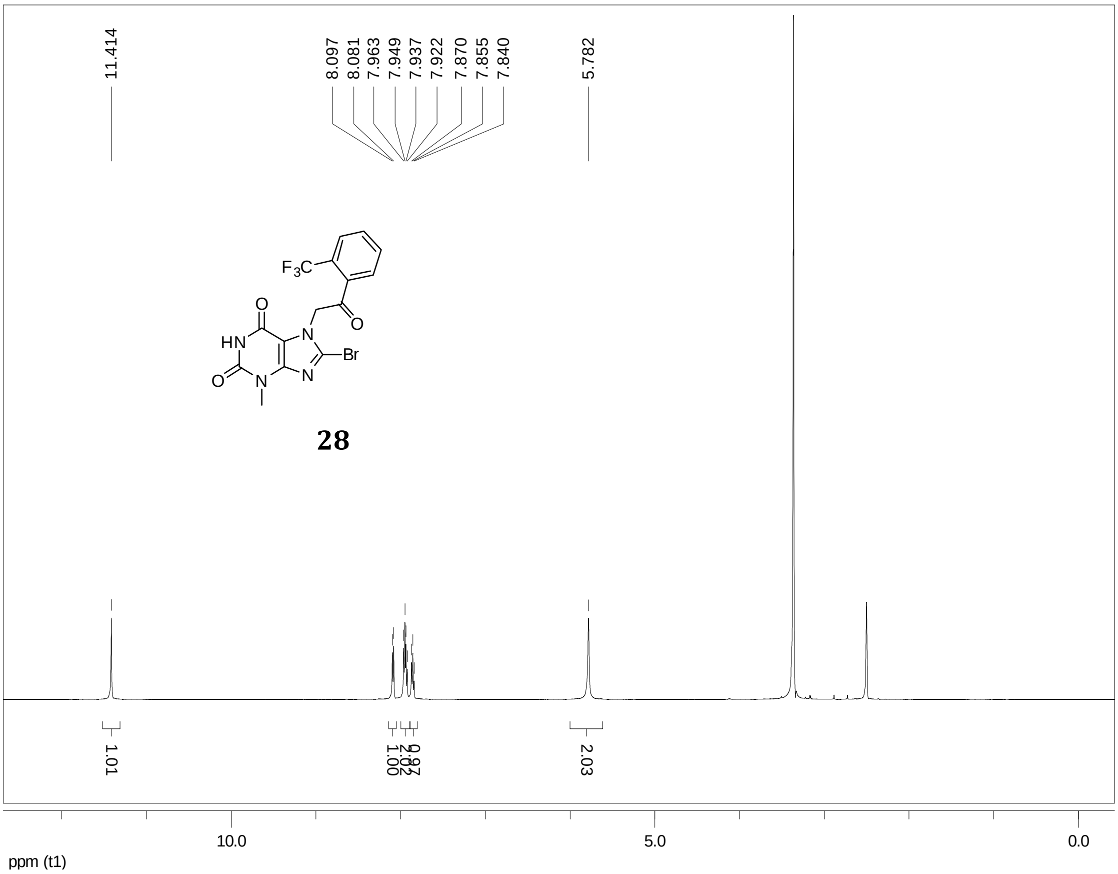

192.736
165.023
163.019
154.016
150.474
149.030
142.994
142.921
132.450
132.371
130.287
130.265
129.176
118.934
118.763
113.154
112.984
108.847
54.289
28.564
20.920
F
O
HN
O
N
N
N
Br
O
25
200
150
100
50
0
ppm (t1)

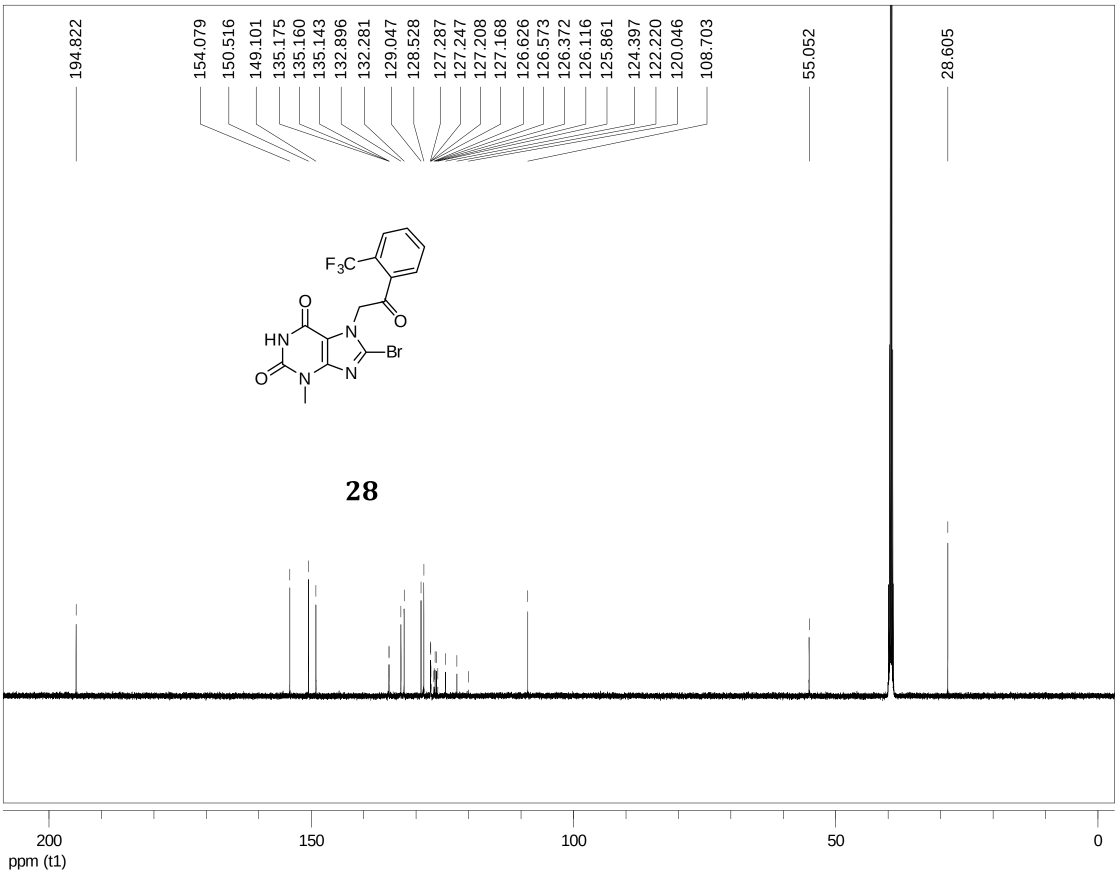

11.336
8.161
8.157
8.153
8.065
8.063
8.060
8.050
8.047
8.045
7.857
7.855
7.853
7.851
7.841
7.839
7.836
7.835
7.680
7.664
7.648
5.955
3.362
Cl
O
HN
N
Br
O
N
N
O
26
0.88
1.00
1.00
1.03
1.92
2.91
10.0
5.0
0.0
ppm (t1)

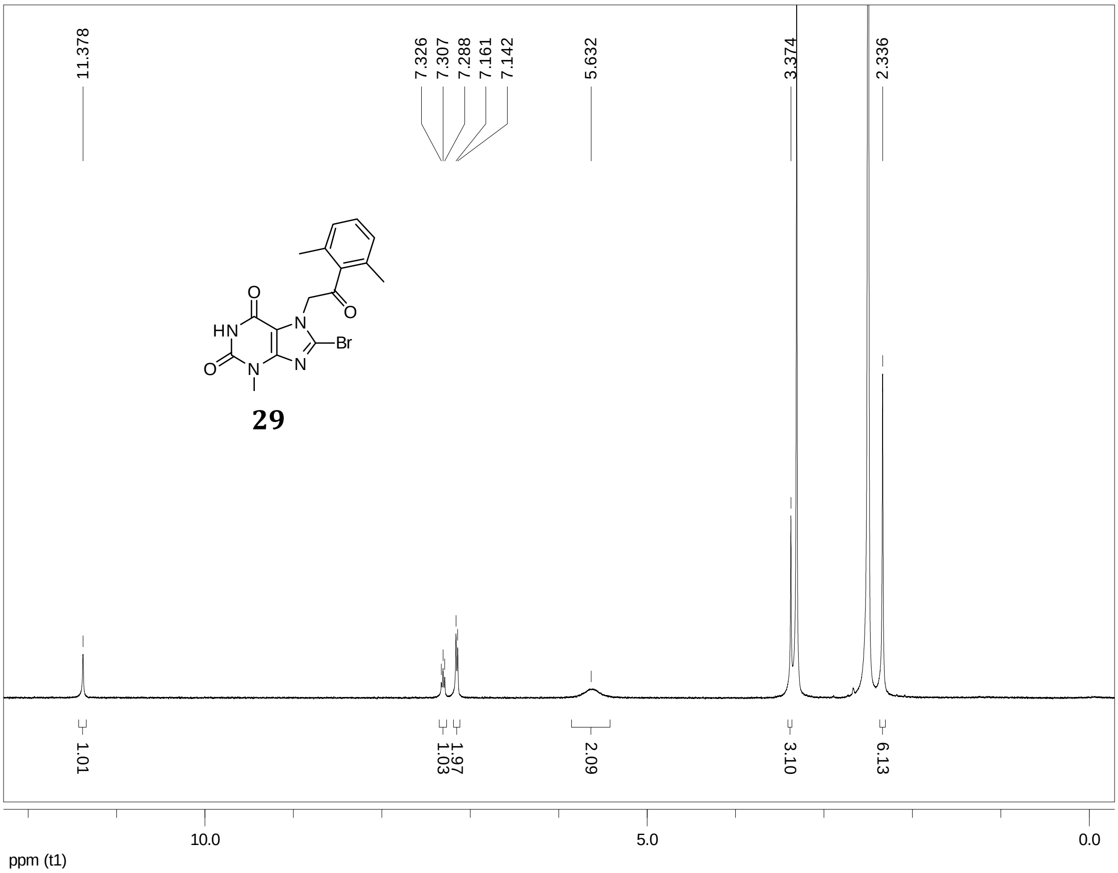

190.661
153.939
150.468
149.057
135.352
134.221
133.971
131.059
129.126
128.013
126.900
108.850
53.033
28.568
Cl
O
HN
N
Br
O
N
N
O
26
200
150
100
50
0
ppm (t1)


11.383
7.956 7.955 7.942 7.940 7.938 7.684 7.671 7.668 7.665 7.660 7.658 7.650 7.606 7.596 7.590 7.585 7.581 7.579 7.573 7.571 7.563 5.795
3.363
Cl
O
HN
N
Br
27
0.85
1.00
2.06
1.02
1.92
2.96
10.0
5.0
0.0
ppm (t1)

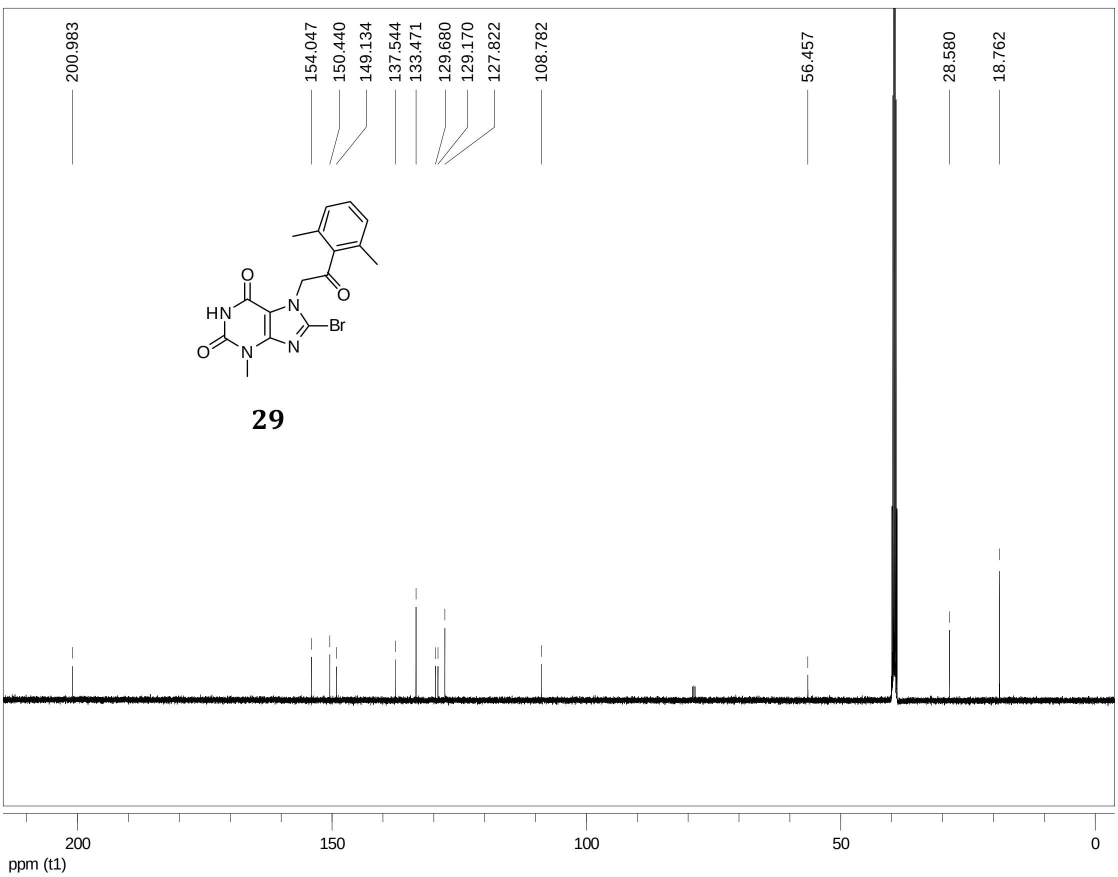

192.992
154.014 150.482 149.033 134.356 133.800 131.000 130.631 130.079 129.098 127.659 108.725
54.888
28.580
Cl
O
HN
N
Br
27
200
150
100
50
0
ppm (t1)


11.414
8.097
8.081
7.963
7.949
7.937
7.922
7.870
7.855
7.840
5.782
F3C
O
N
HN
O
N
Br
N
O
28
1.01
1.00
2.02
0.97
2.03
10.0
5.0
0.0
ppm (t1)

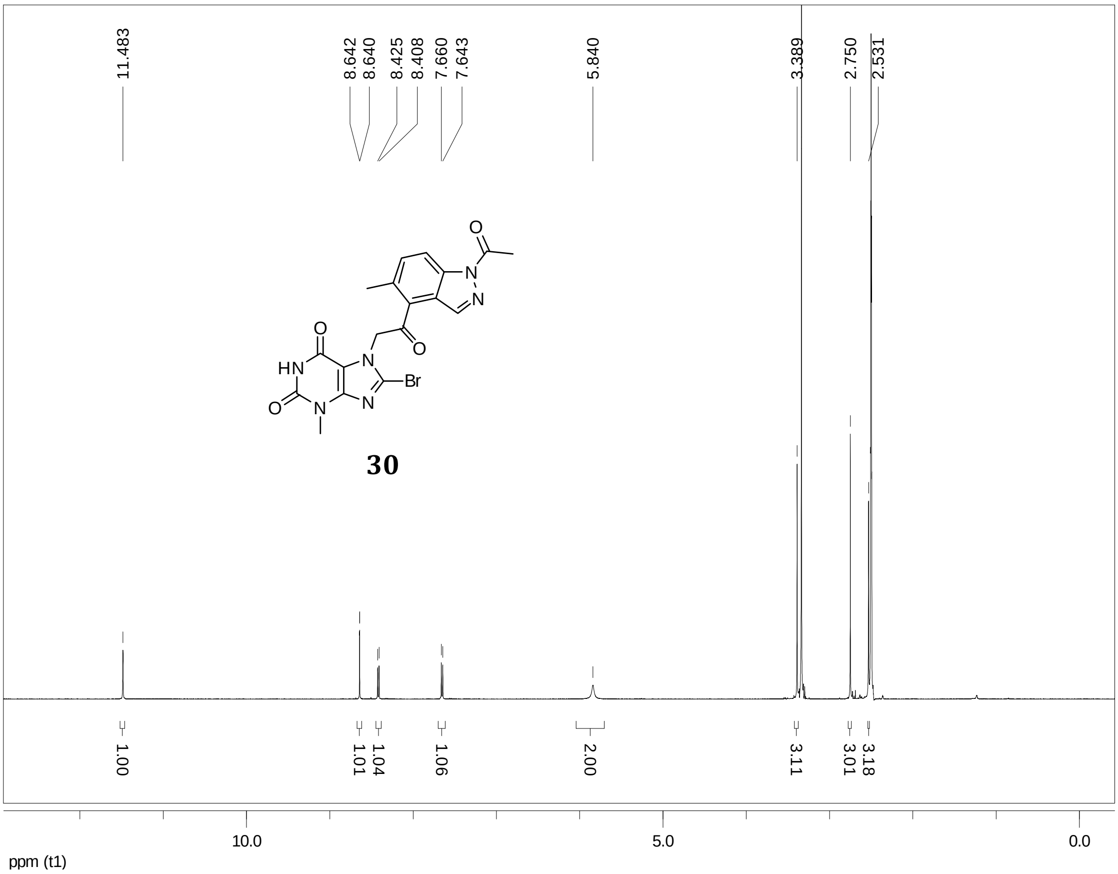

194.822
154.079
150.516
149.101
135.175
135.160
135.143
132.896
132.281
129.047
128.528
127.287
127.247
127.208
127.168
126.626
126.573
126.372
126.116
125.861
124.397
122.220
120.046
108.703
55.052
28.605
F3C
O
N
HN
O
N
Br
N
O
28
200
150
100
50
0
ppm (t1)

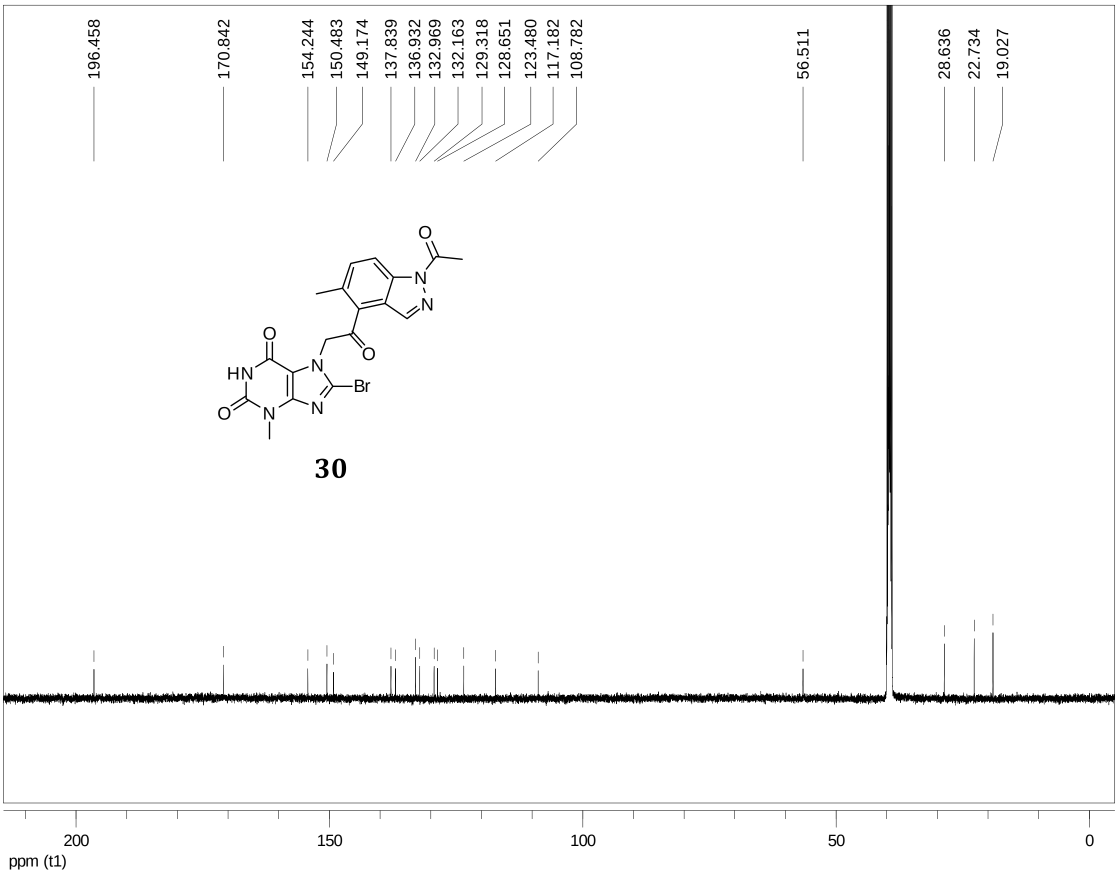


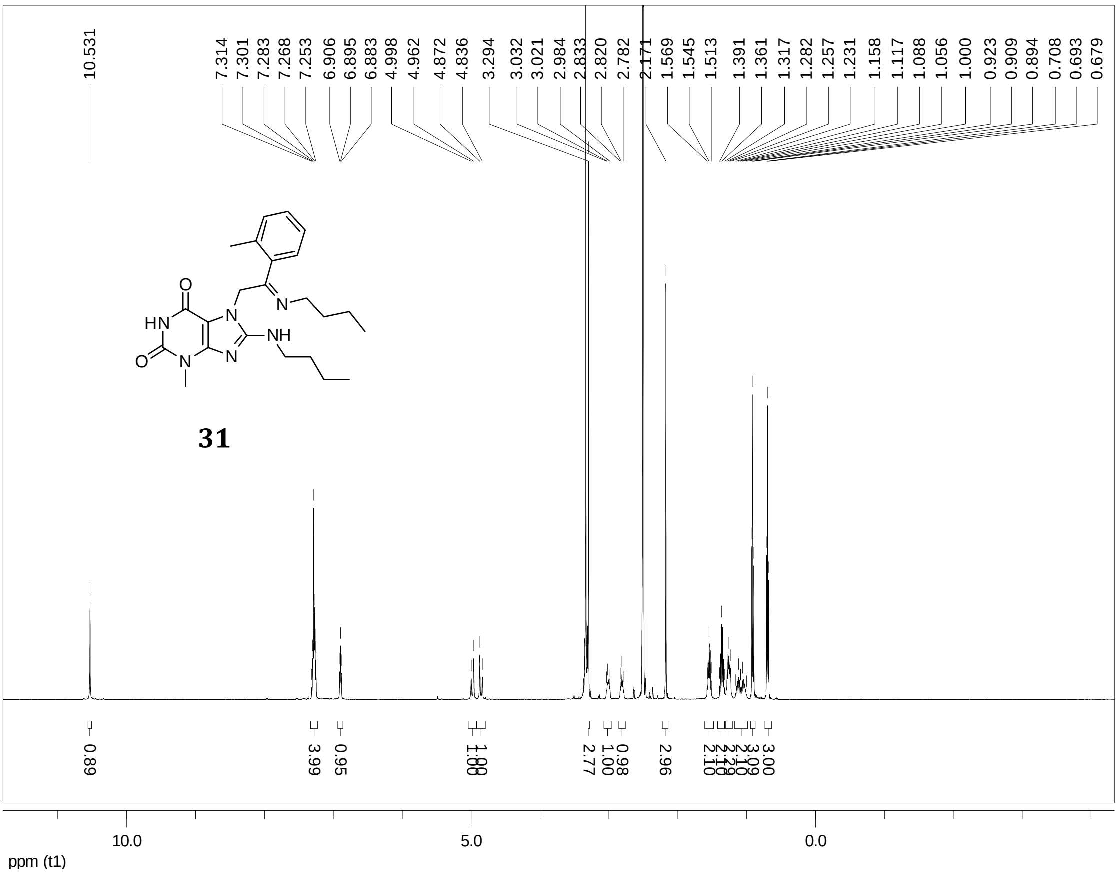
11.378
7.326
7.307
7.288
7.161
7.142
5.632
3.374
2.336
29
1.01
1.03
1.97
2.09
3.10
6.13
10.0
5.0
0.0
ppm (t1)

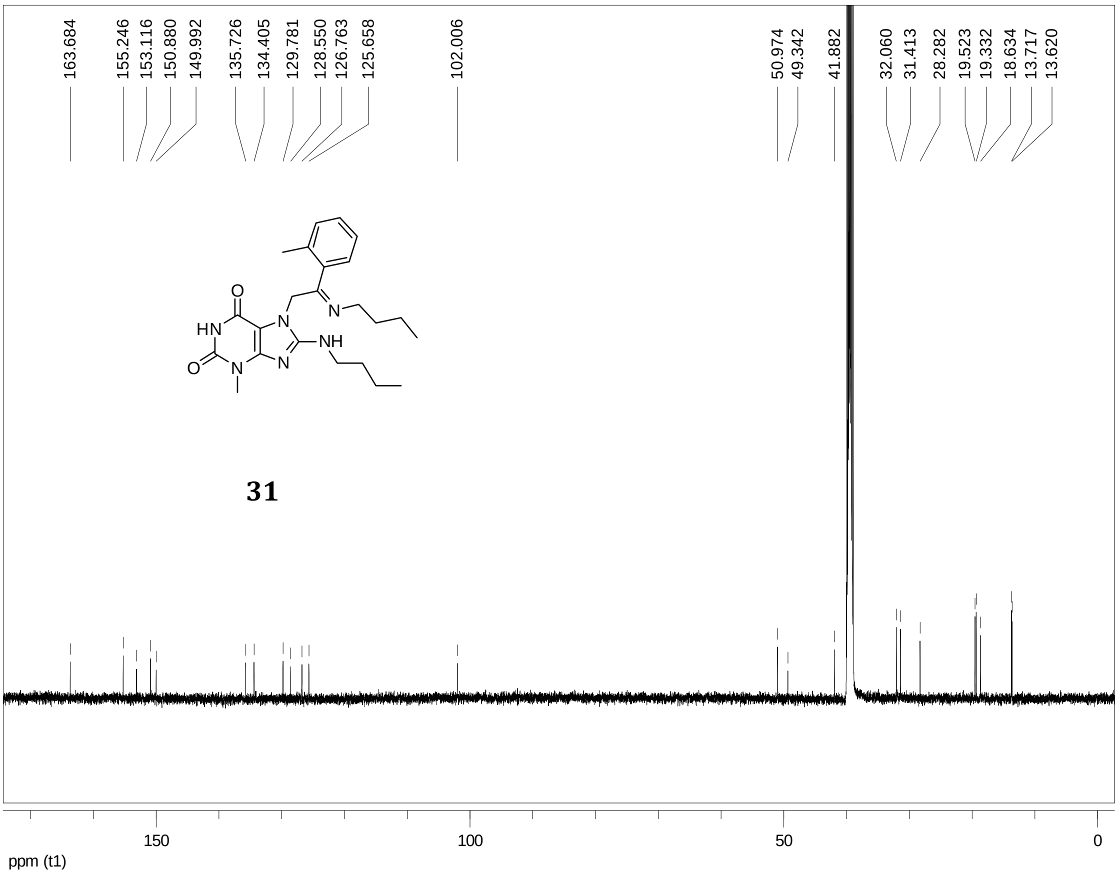


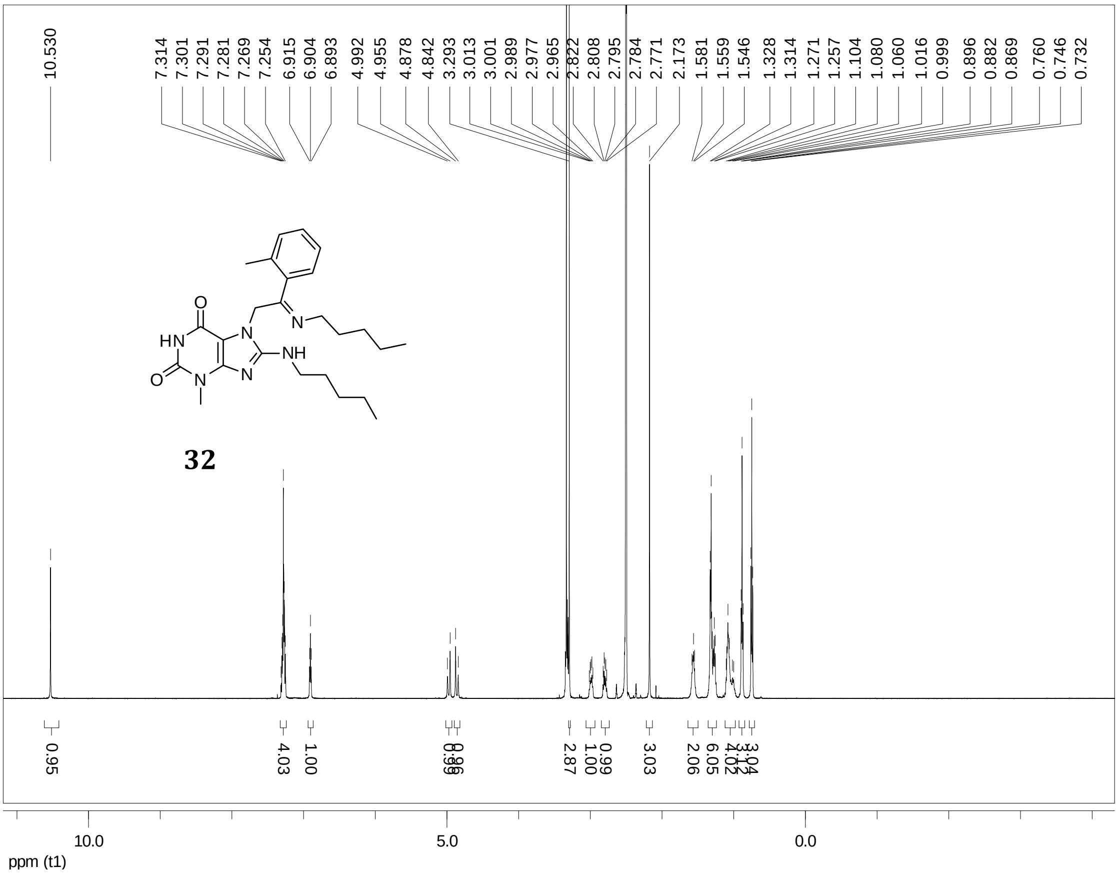
200.983
154.047
150.440
149.134
137.544
133.471
129.680
129.170
127.822
108.782
56.457
28.580
18.762
29
200
150
100
50
0
ppm (t1)

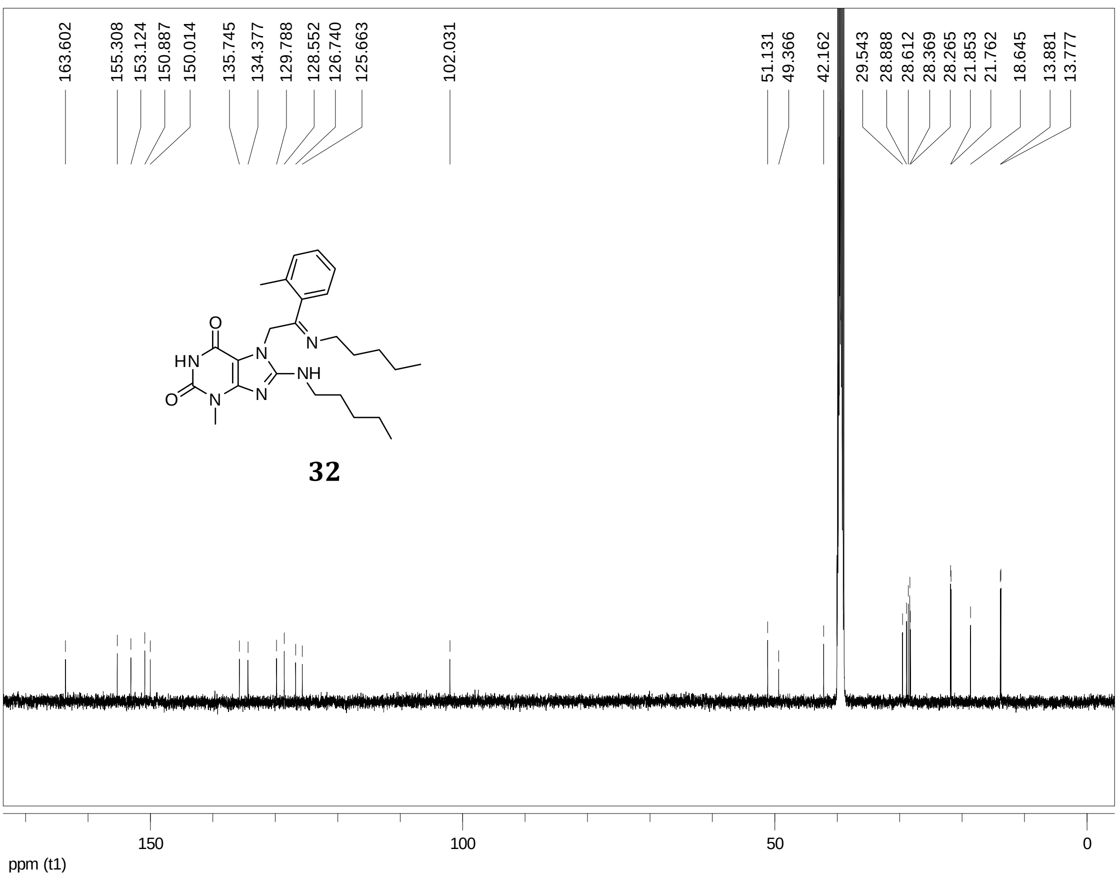

11.483
8.642
8.640
8.425
8.408
7.660
7.643
5.840
3.389
2.750
2.531
HN
O
N
N
N
O
Br
O
N
N
O
30
1.00
1.01
1.04
1.06
2.00
3.11
3.01
3.18
10.0
5.0
0.0
ppm (t1)

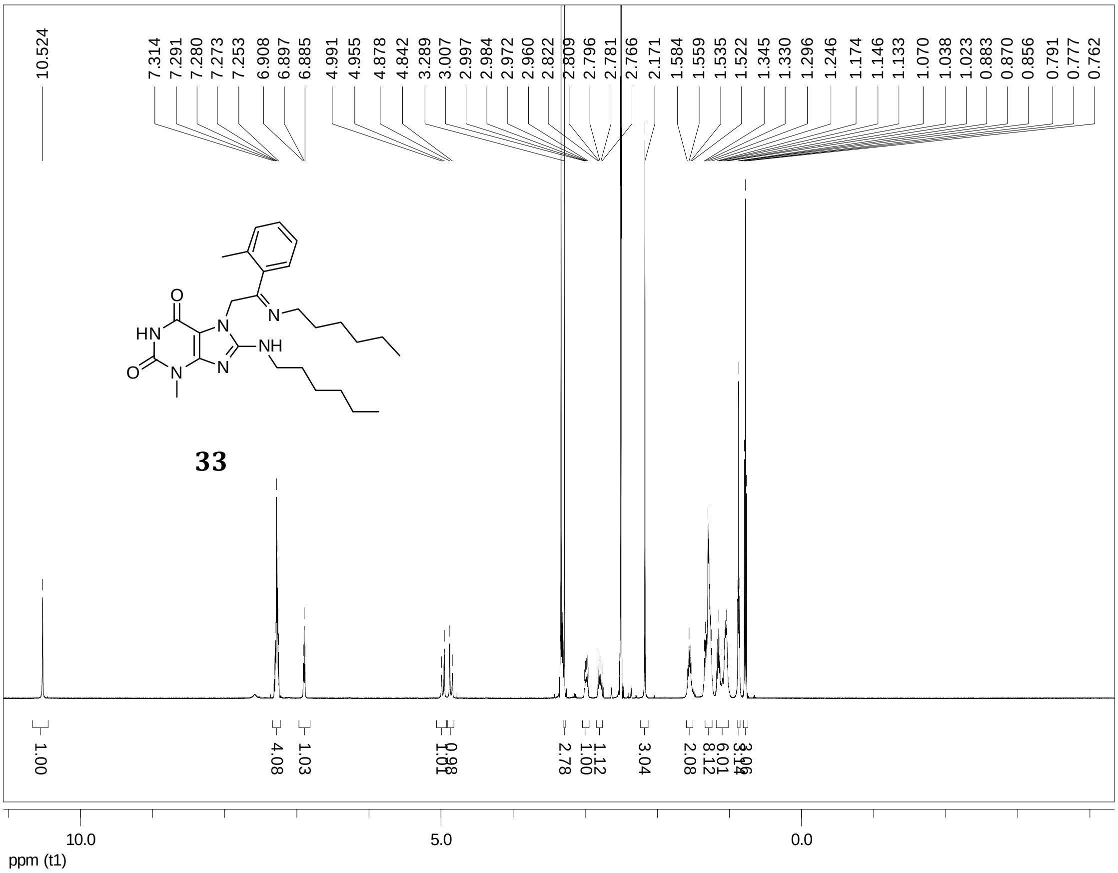

196.458
170.842
154.244
150.483
149.174
137.839
136.932
132.969
132.163
129.318
128.651
123.480
117.182
108.782
56.511
28.636
22.734
19.027
HN
O
N
N
N
O
Br
O
N
N
O
30
200
150
100
50
0
ppm (t1)

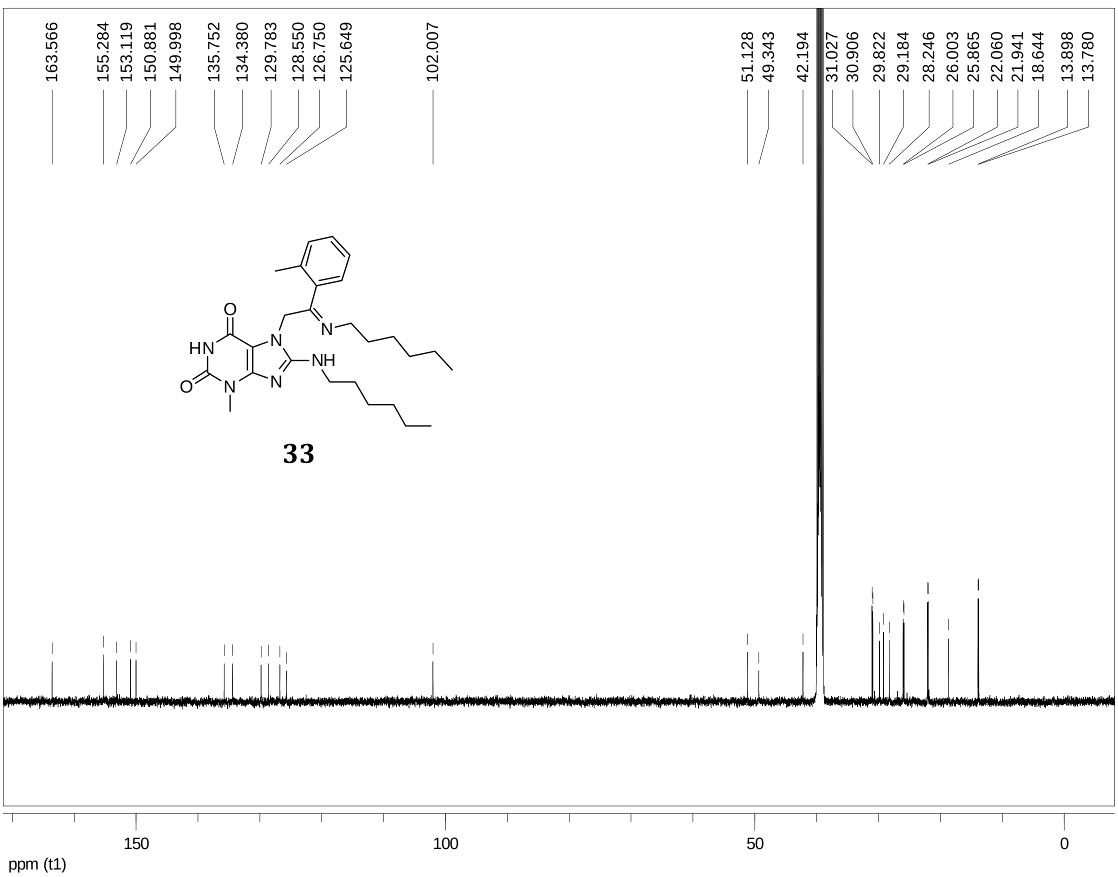

10.531
7.314 7.301 7.283 7.268 7.253 6.906 6.895 6.883 4.998 4.962 4.872 4.836 3.294 3.032 3.021 2.984 2.833 2.820 2.782 2.171 1.569 1.545 1.513 1.391 1.361 1.317 1.282 1.257 1.231 1.158 1.117 1.088 1.056 1.000 0.923 0.909 0.894 0.708 0.693 0.679
O
HN
N
O
N
N
N
NH
31
0.89 3.99 0.95 [illegible] 2.77 1.00 0.98 2.96 2.10 [illegible] 3.09 3.00
10.0
5.0
0.0
ppm (t1)

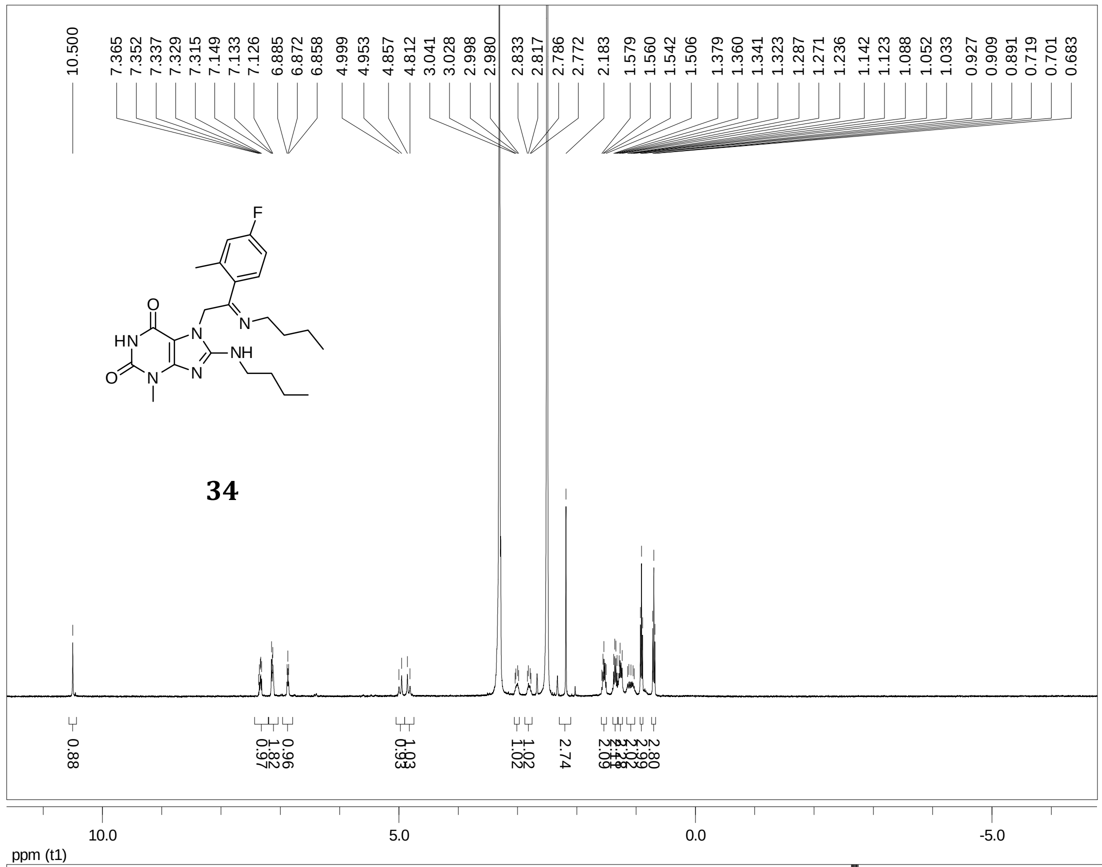

163.684 155.246 153.116 150.880 149.992 135.726 134.405 129.781 128.550 126.763 125.658 102.006 50.974 49.342 41.882 32.060 31.413 28.282 19.523 19.332 18.634 13.717 13.620
O
HN
N
O
N
N
N
NH
31
150
100
50
0
ppm (t1)


10.530
7.314
7.301
7.291
7.281
7.269
7.254
6.915
6.904
6.893
4.992
4.955
4.878
4.842
3.293
3.013
3.001
2.989
2.977
2.965
2.822
2.808
2.795
2.784
2.771
2.173
1.581
1.559
1.546
1.328
1.314
1.271
1.257
1.104
1.080
1.060
1.016
0.999
0.896
0.882
0.869
0.760
0.746
0.732
32
0.95
4.03
1.00
2.87
1.00
0.99
3.03
2.06
6.05
10.0
5.0
0.0
ppm (t1)

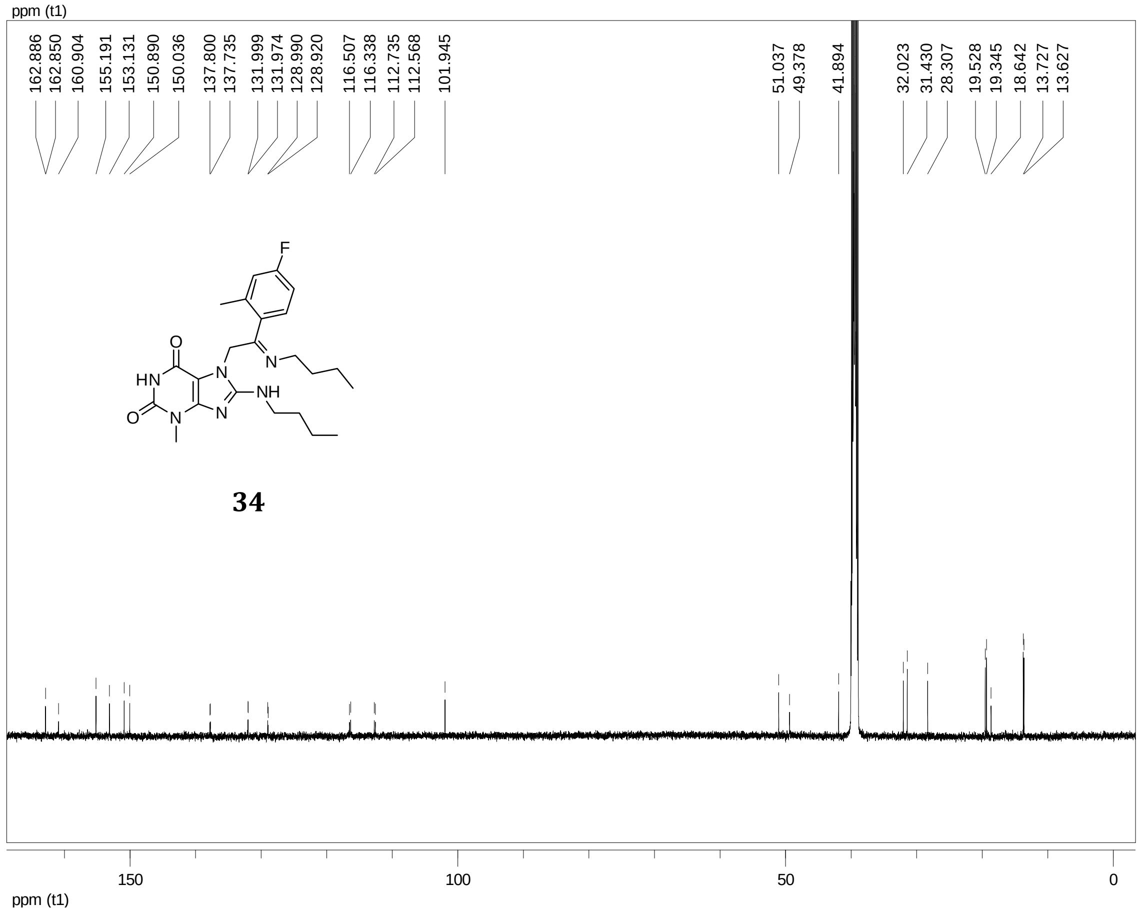

163.602
155.308
153.124
150.887
150.014
135.745
134.377
129.788
128.552
126.740
125.663
102.031
51.131
49.366
42.162
29.543
28.888
28.612
28.369
28.265
21.853
21.762
18.645
13.881
13.777
32
150
100
50
0
ppm (t1)


10.524
7.314
7.291
7.280
7.273
7.253
6.908
6.897
6.885
4.991
4.955
4.878
4.842
3.289
3.007
2.997
2.984
2.972
2.960
2.822
2.809
2.796
2.781
2.766
2.171
1.584
1.559
1.535
1.522
1.345
1.330
1.296
1.246
1.174
1.146
1.133
1.070
1.038
1.023
0.883
0.870
0.856
0.791
0.777
0.762
HN
O
N
N
NH
O
N
N
33
1.00
4.08
1.03
1.01
0.98
2.78
1.00
1.12
3.04
2.08
8.12
6.01
3.14
3.06
10.0
5.0
0.0
ppm (t1)

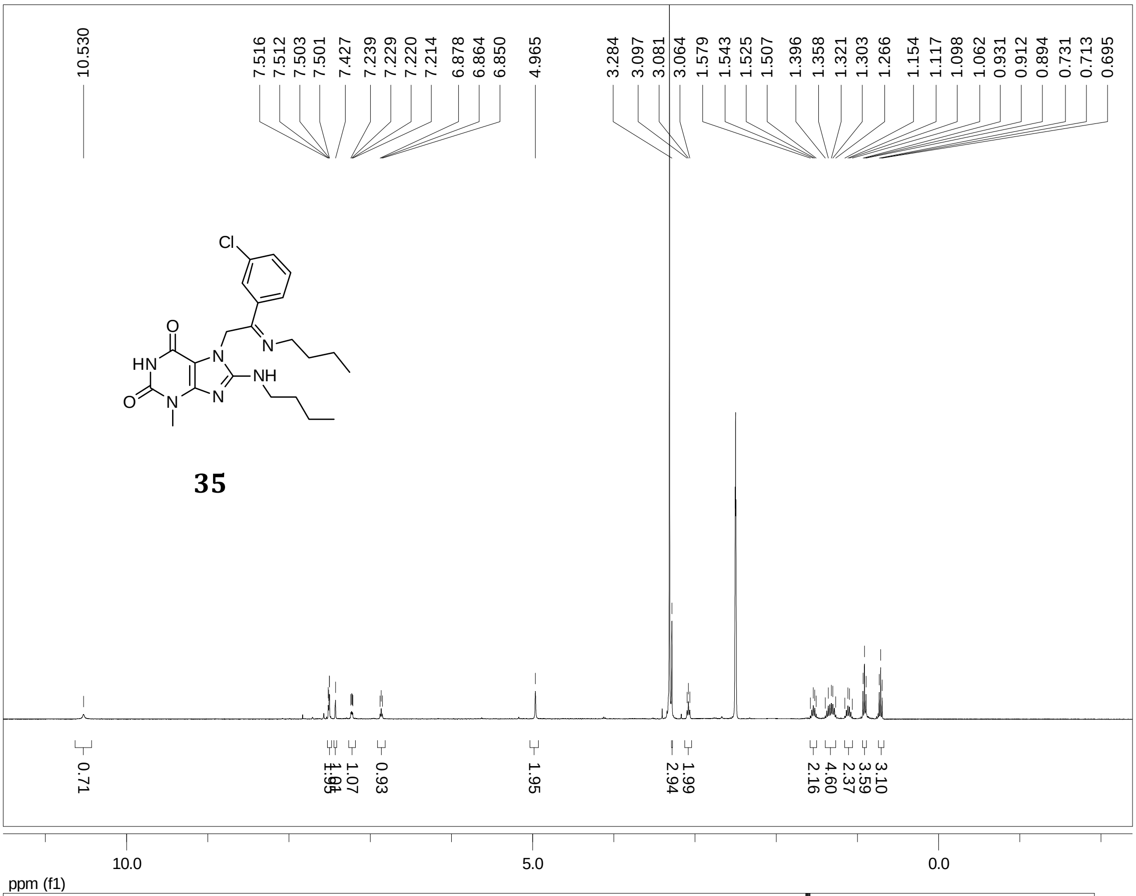

163.566
155.284
153.119
150.881
149.998
135.752
134.380
129.783
128.550
126.750
125.649
102.007
51.128
49.343
42.194
31.027
30.906
29.822
29.184
28.246
26.003
25.865
22.060
21.941
18.644
13.898
13.780
HN
O
N
N
NH
O
N
N
33
150
100
50
0
ppm (t1)

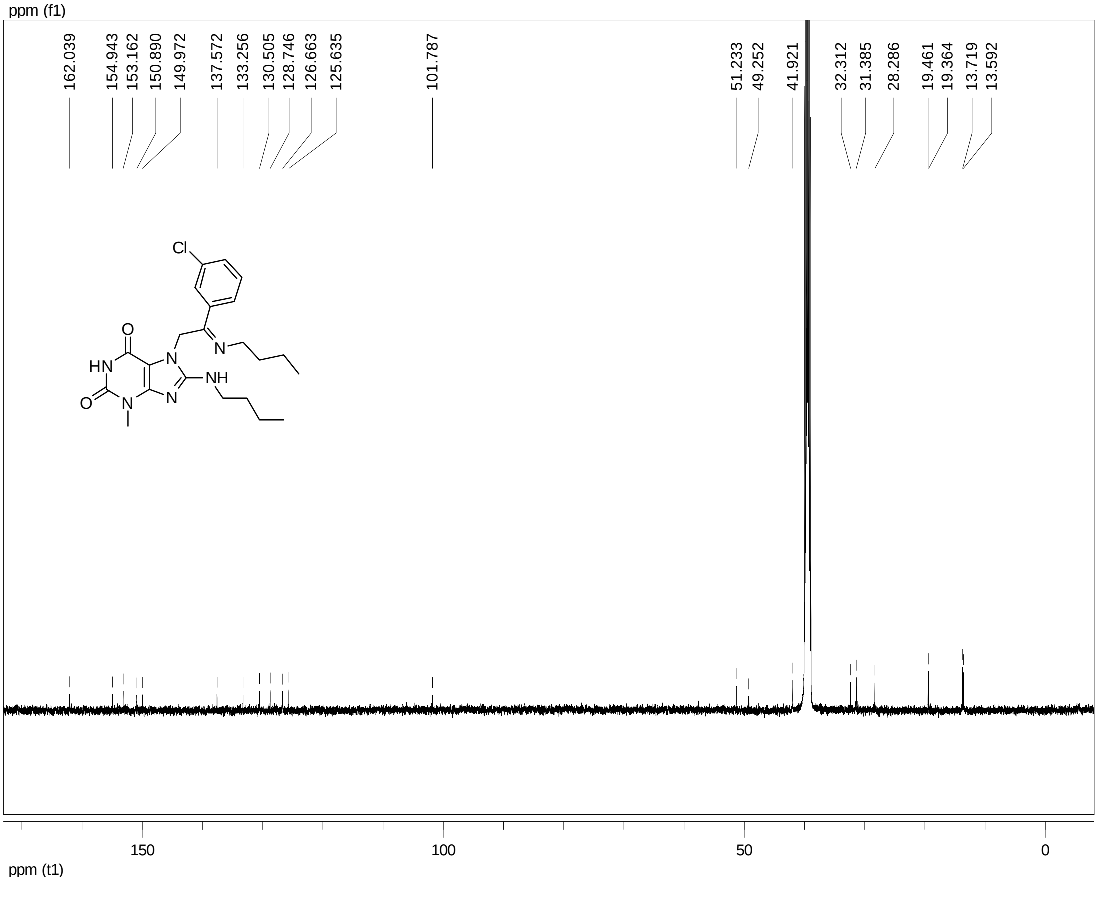


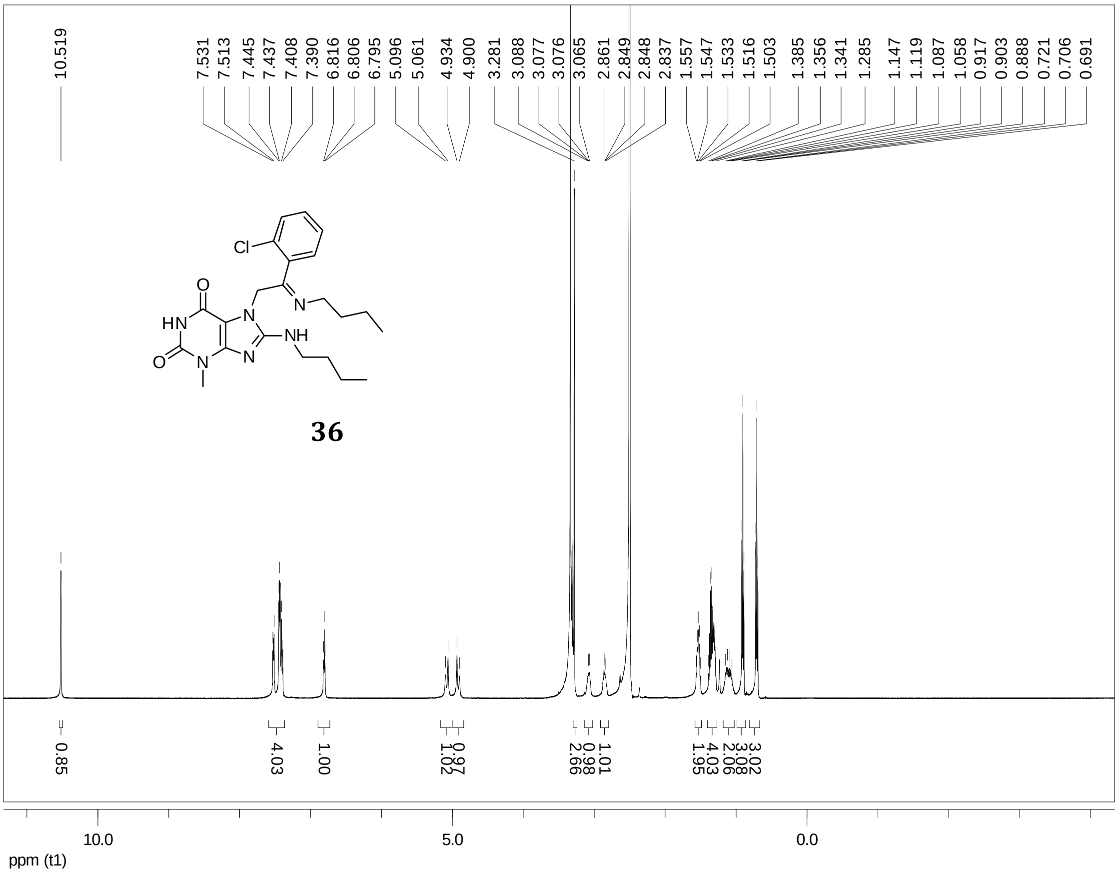
34

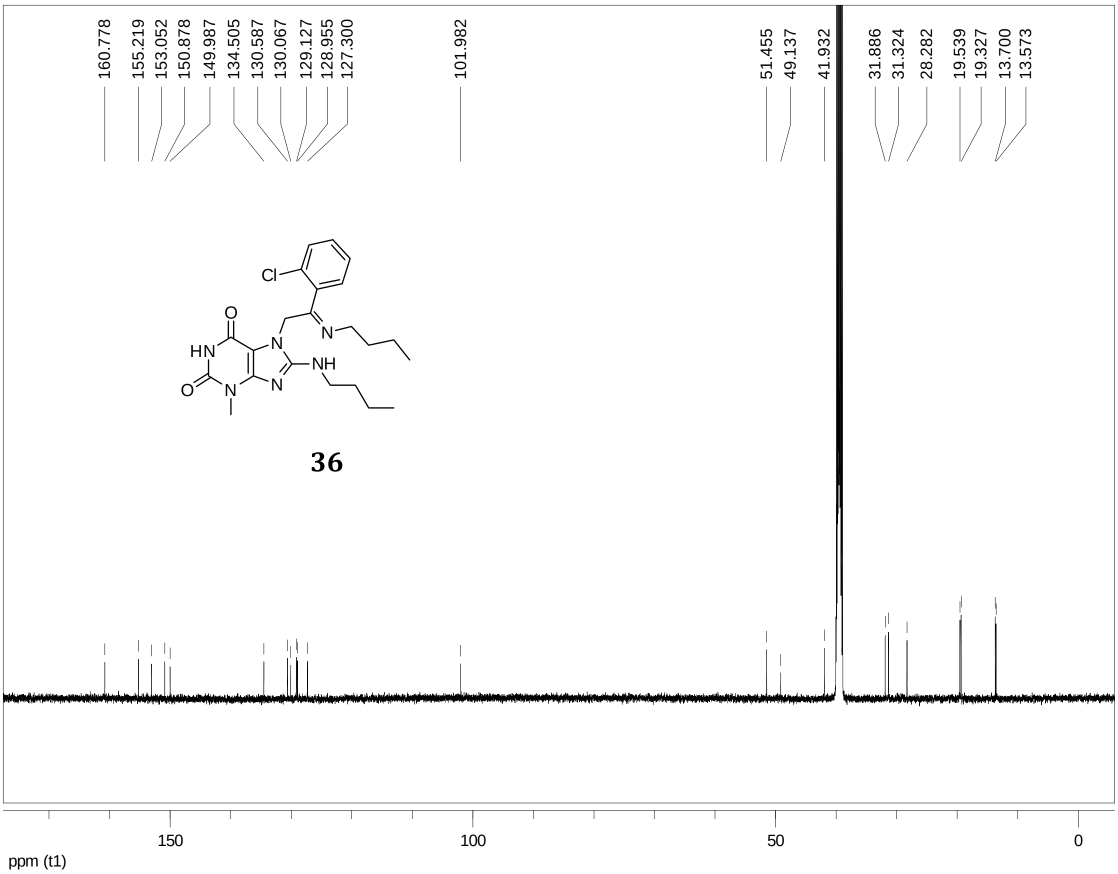


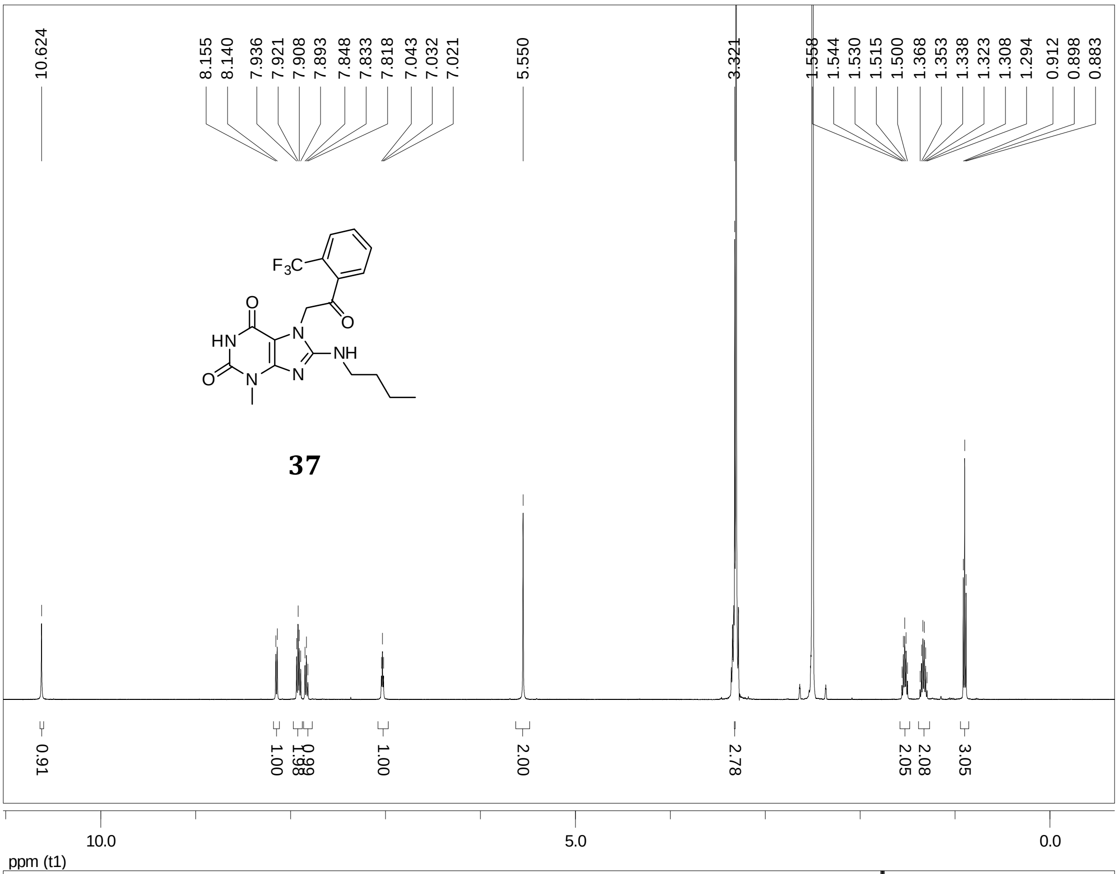
34

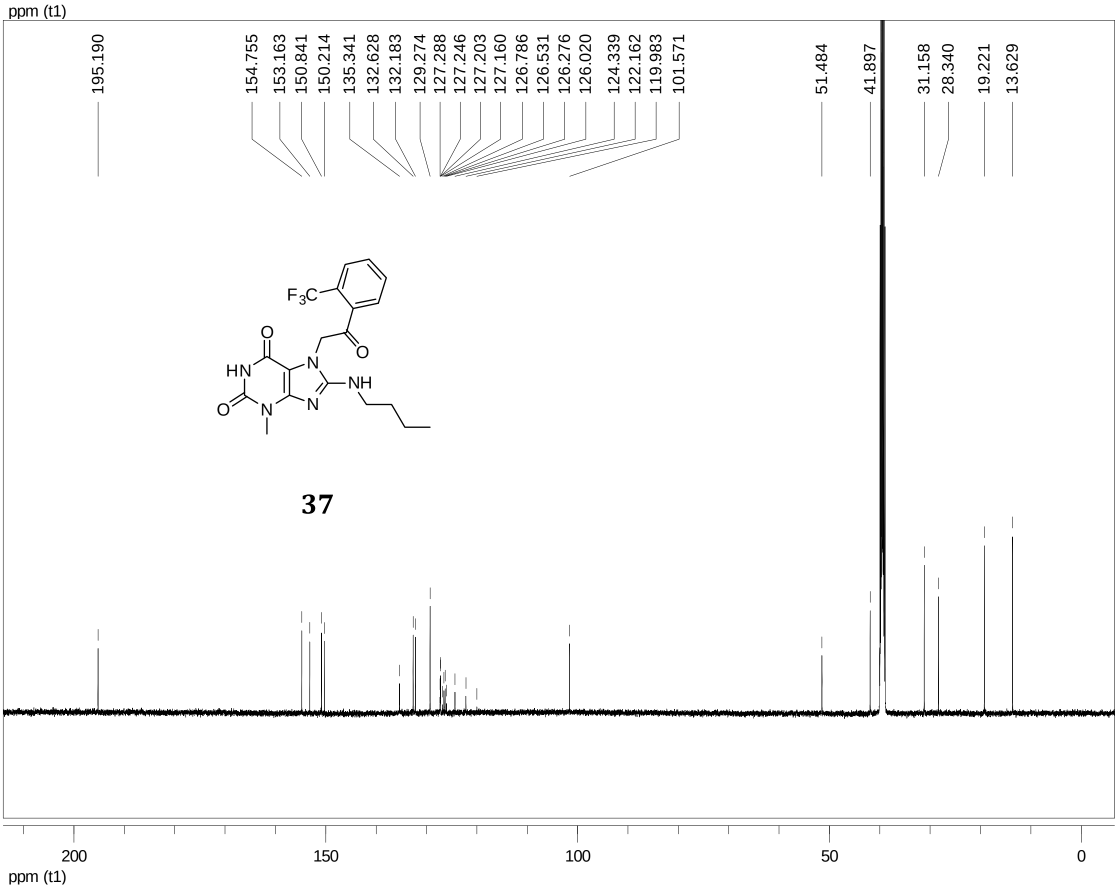

10.530
7.516
7.512
7.503
7.501
7.427
7.239
7.229
7.220
7.214
6.878
6.864
6.850
4.965
3.284
3.097
3.081
3.064
1.579
1.543
1.525
1.507
1.396
1.358
1.321
1.303
1.266
1.154
1.117
1.098
1.062
0.931
0.912
0.894
0.731
0.713
0.695
Cl
O
HN
N
N
N
NH
O
35
0.71
1.07
0.93
1.95
2.94
1.99
2.16
4.60
2.37
3.59
3.10
10.0
5.0
0.0
ppm (f1)

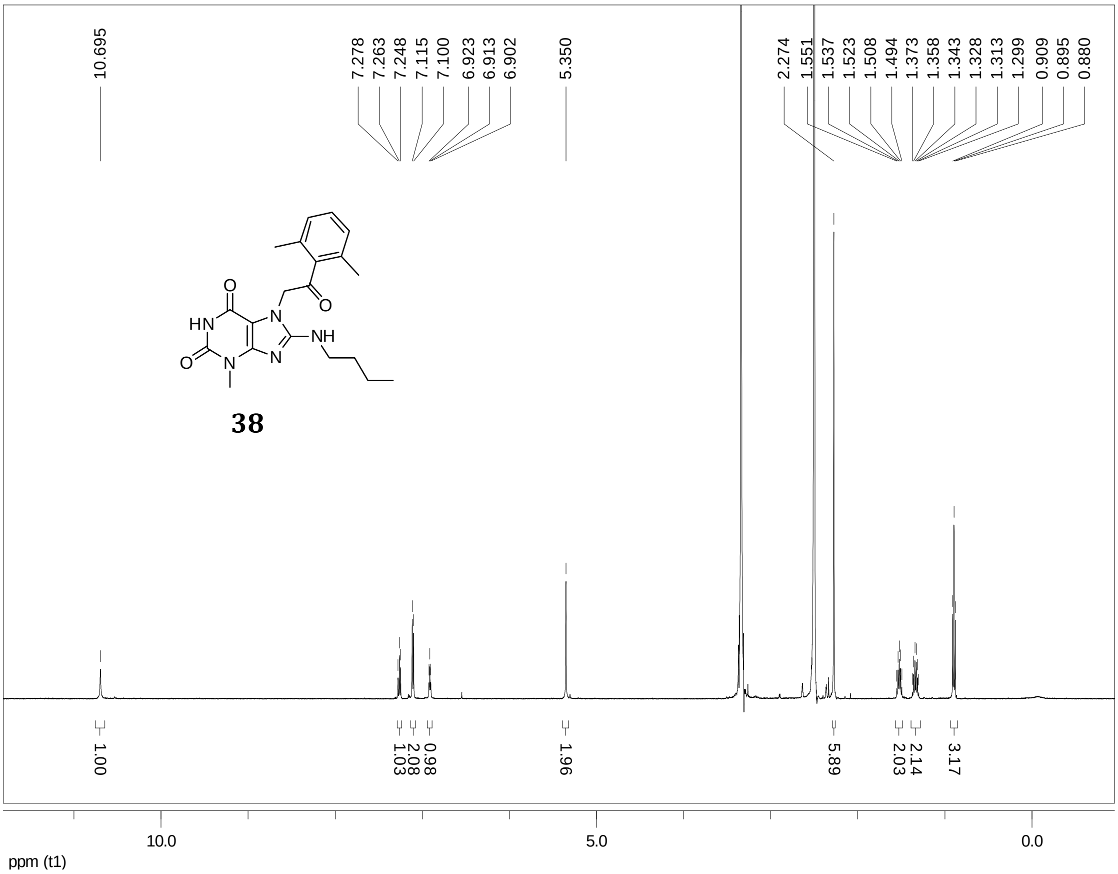

162.039
154.943
153.162
150.890
149.972
137.572
133.256
130.505
128.746
126.663
125.635
101.787
51.233
49.252
41.921
32.312
31.385
28.286
19.461
19.364
13.719
13.592
Cl
O
HN
N
N
N
NH
O
150
100
50
0
ppm (t1)

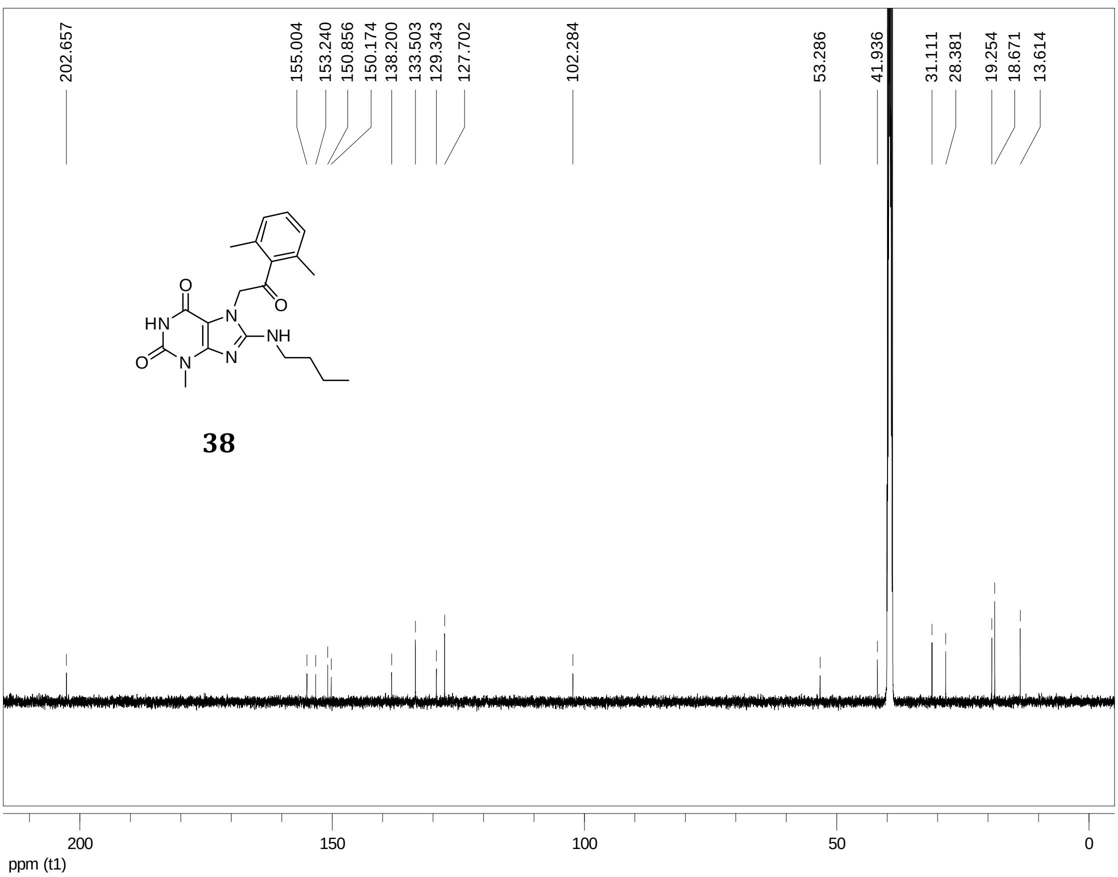

10.519
7.531
7.513
7.445
7.437
7.408
7.390
6.816
6.806
6.795
5.096
5.061
4.934
4.900
3.281
3.088
3.077
3.076
3.065
2.861
2.849
2.848
2.837
1.557
1.547
1.533
1.516
1.503
1.385
1.356
1.341
1.285
1.147
1.119
1.087
1.058
0.917
0.903
0.888
0.721
0.706
0.691
Cl
O
HN
N
N
NH
N
O
N
36
0.85
4.03
1.00
1.02
0.97
2.66
0.98
1.01
1.95
4.03
2.06
3.08
3.02
10.0
5.0
0.0
ppm (t1)

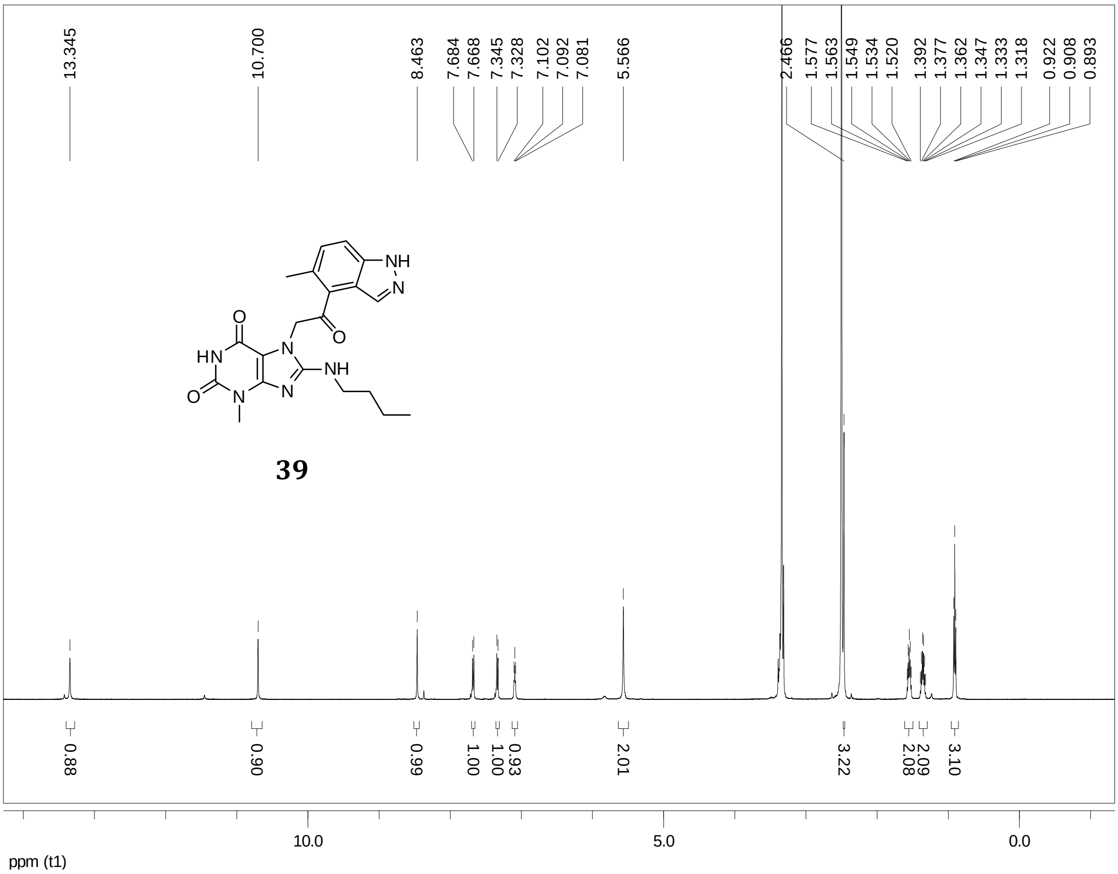

160.778
155.219
153.052
150.878
149.987
134.505
130.587
130.067
129.127
128.955
127.300
101.982
51.455
49.137
41.932
31.886
31.324
28.282
19.539
19.327
13.700
13.573
Cl
O
HN
N
N
NH
N
O
N
36
150
100
50
0
ppm (t1)

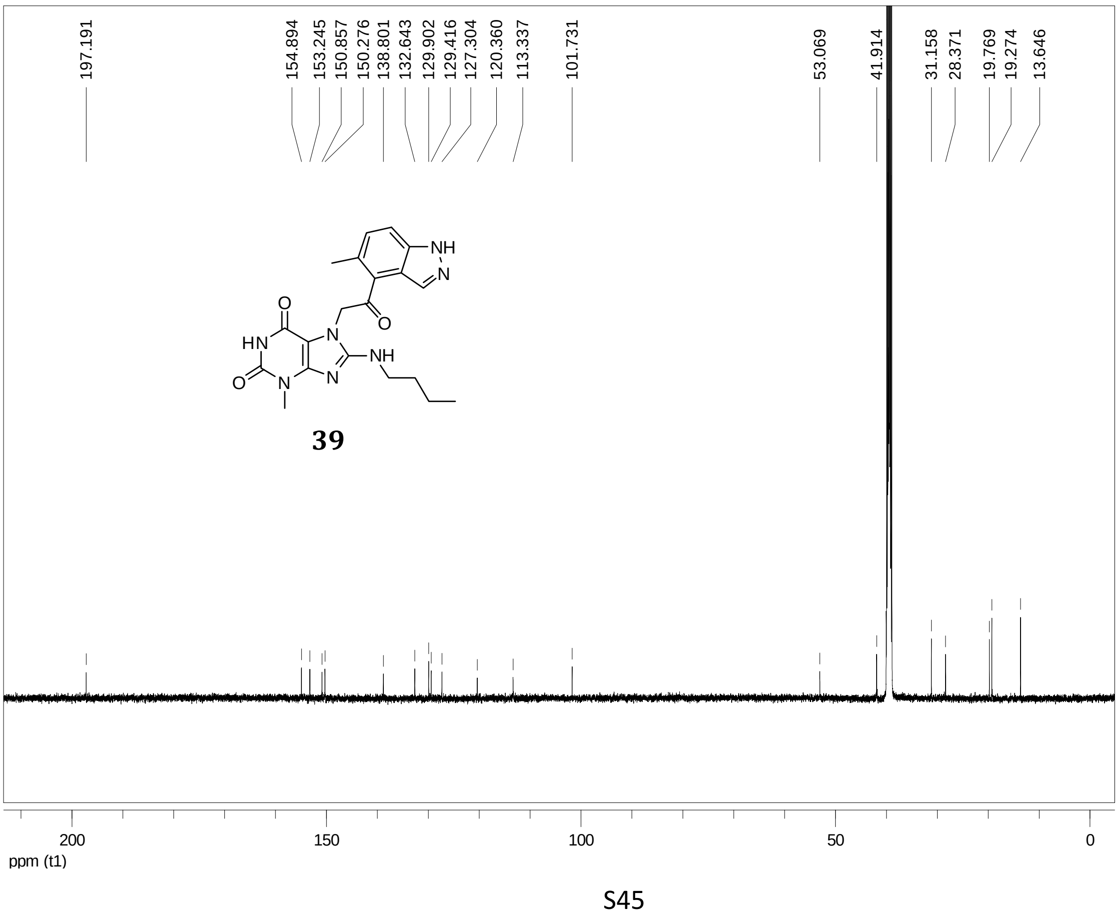

10.624
8.155 8.140 7.936 7.921 7.908 7.893 7.848 7.833 7.818 7.043 7.032 7.021
5.550
3.321
1.558 1.544 1.530 1.515 1.500 1.368 1.353 1.338 1.323 1.308 1.294 0.912 0.898 0.883
F3C
HN
O
N
NH
37
0.91 1.00 1.98 0.99 1.00 2.00 2.78 2.05 2.08 3.05
10.0
5.0
0.0
ppm (t1)

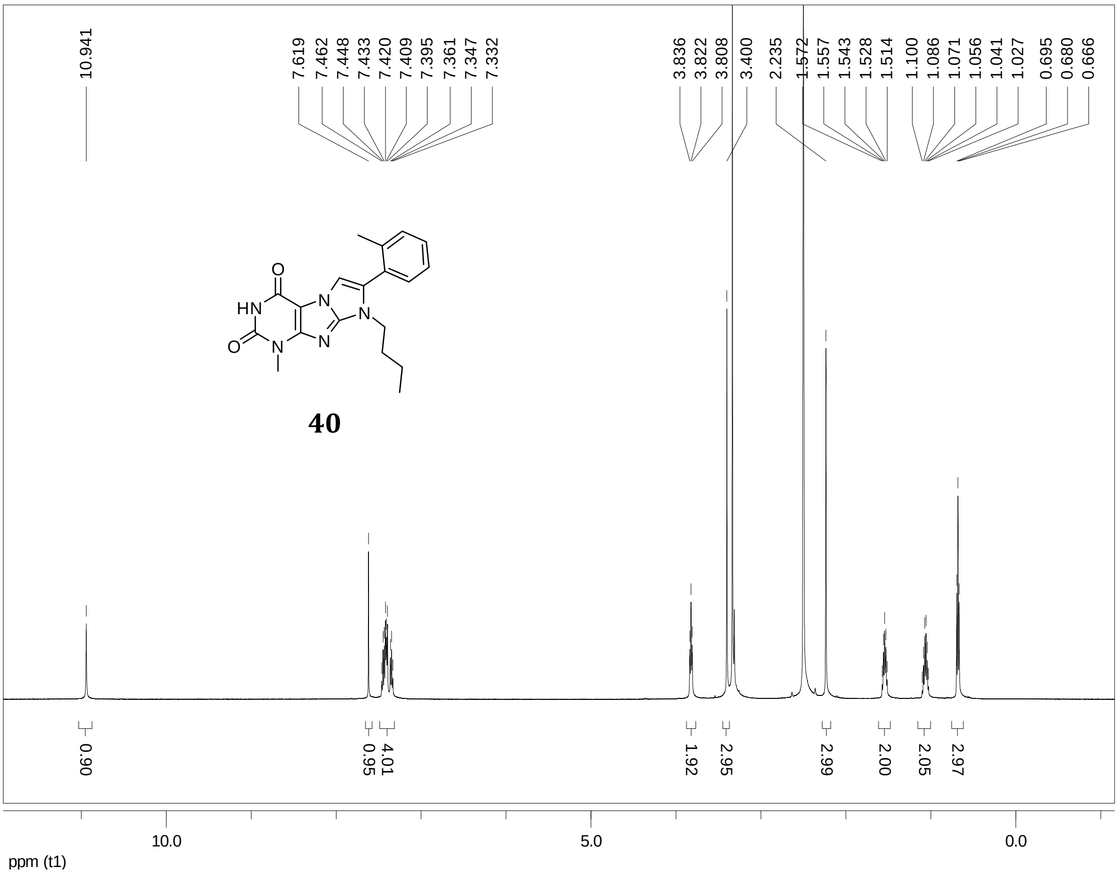

195.190
154.755 153.163 150.841 150.214 135.341 132.628 132.183 129.274 127.288 127.246 127.203 127.160 126.786 126.531 126.276 126.020 124.339 122.162 119.983 101.571
51.484 41.897
31.158 28.340 19.221 13.629
F3C
HN
O
N
NH
37
200
150
100
50
0
ppm (t1)

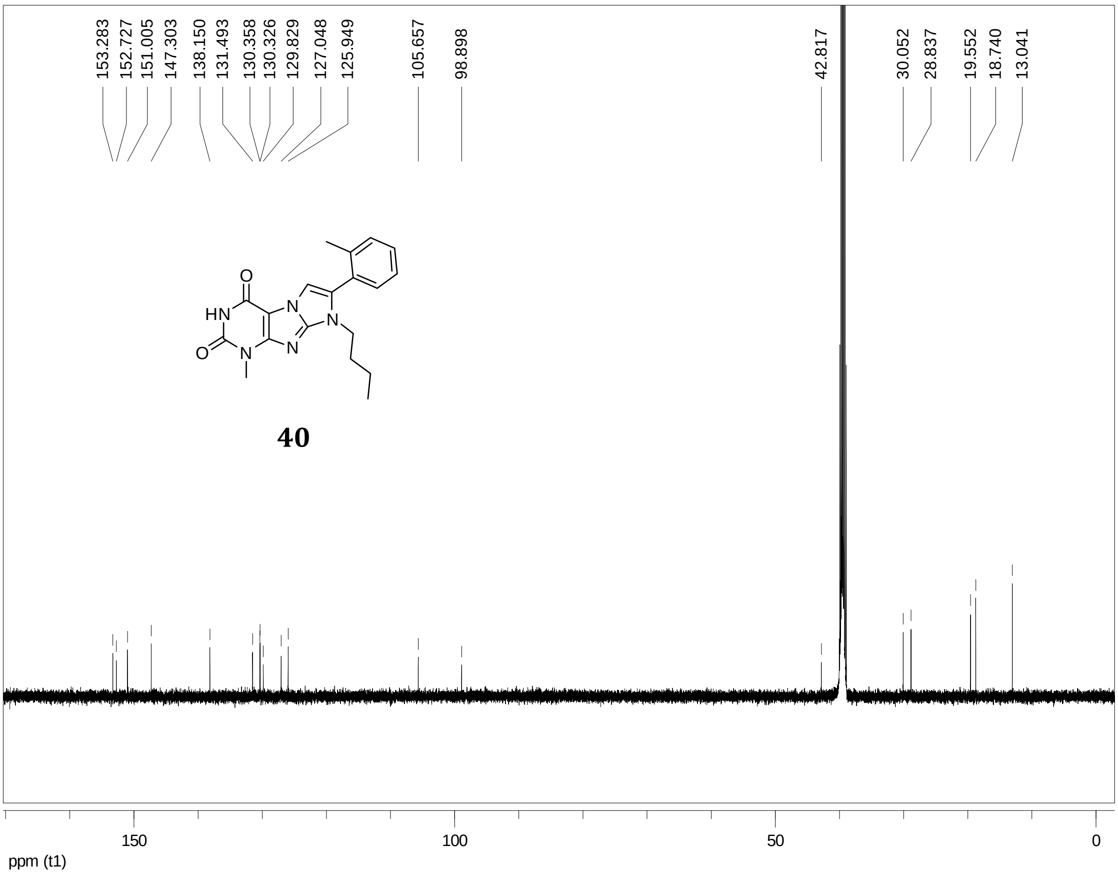

10.695
7.278 7.263 7.248 7.115 7.100 6.923 6.913 6.902
5.350
2.274 1.551 1.537 1.523 1.508 1.494 1.373 1.358 1.343 1.328 1.313 1.299 0.909 0.895 0.880
HN
O
N
NH
38
1.00
1.03 2.08 0.98
1.96
5.89
2.03 2.14
3.17
10.0
5.0
0.0
ppm (t1)

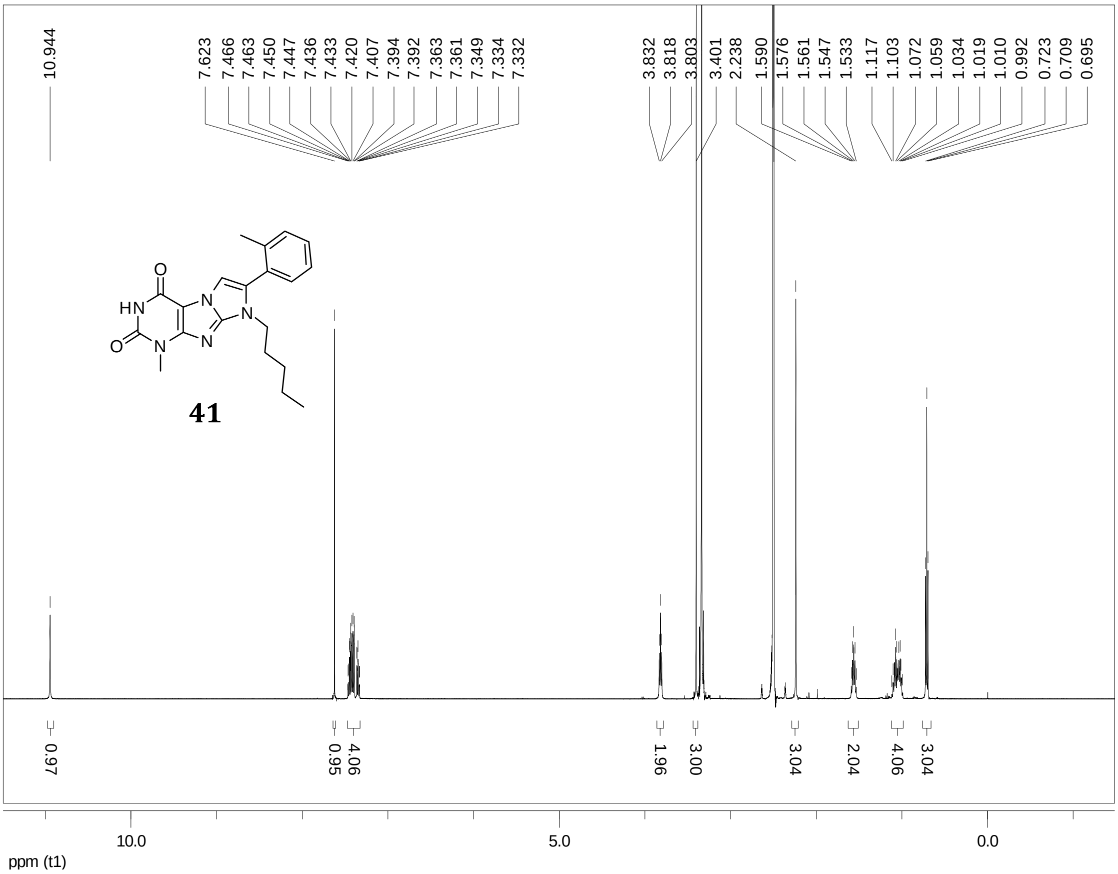

202.657
155.004 153.240 150.856 150.174 138.200 133.503 129.343 127.702
102.284
53.286
41.936
31.111 28.381 19.254 18.671 13.614
HN
O
N
NH
38
200
150
100
50
0
ppm (t1)


13.345
10.700
8.463
7.684
7.668
7.345
7.328
7.102
7.092
7.081
5.566
2.466
1.577
1.563
1.549
1.534
1.520
1.392
1.377
1.362
1.347
1.333
1.318
0.922
0.908
0.893
39
0.88
0.90
0.99
1.00
1.00
0.93
2.01
3.22
2.08
2.09
3.10
10.0
5.0
0.0
ppm (t1)


197.191
154.894
153.245
150.857
150.276
138.801
132.643
129.902
129.416
127.304
120.360
113.337
101.731
53.069
41.914
31.158
28.371
19.769
19.274
13.646
39
200
150
100
50
0
ppm (t1)

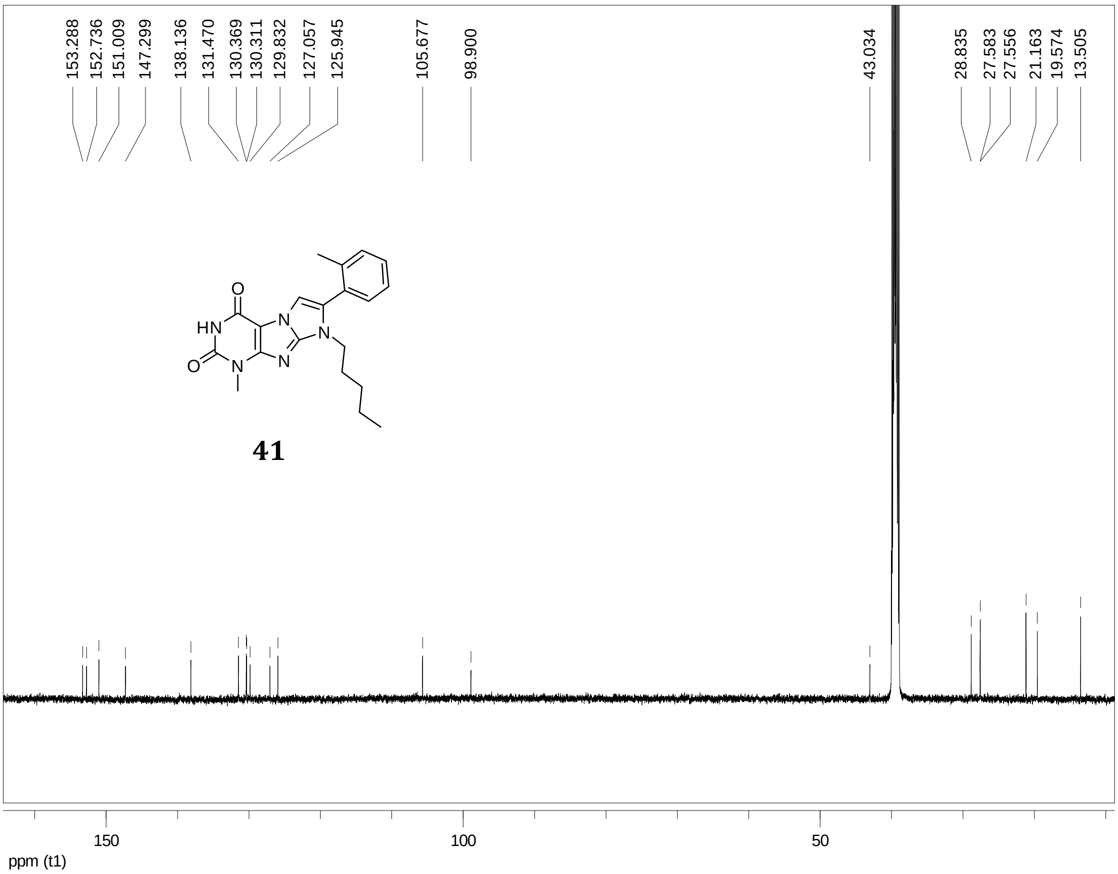

10.941
7.619
7.462
7.448
7.433
7.420
7.409
7.395
7.361
7.347
7.332
3.836
3.822
3.808
3.400
2.235
1.572
1.557
1.543
1.528
1.514
1.100
1.086
1.071
1.056
1.041
1.027
0.695
0.680
0.666
HN
O
N
N
N
O
N
40
0.90
0.95
4.01
1.92
2.95
2.99
2.00
2.05
2.97
10.0
5.0
0.0
ppm (t1)


153.283
152.727
151.005
147.303
138.150
131.493
130.358
130.326
129.829
127.048
125.949
105.657
98.898
42.817
30.052
28.837
19.552
18.740
13.041
HN
O
N
N
N
O
N
40
150
100
50
0
ppm (t1)



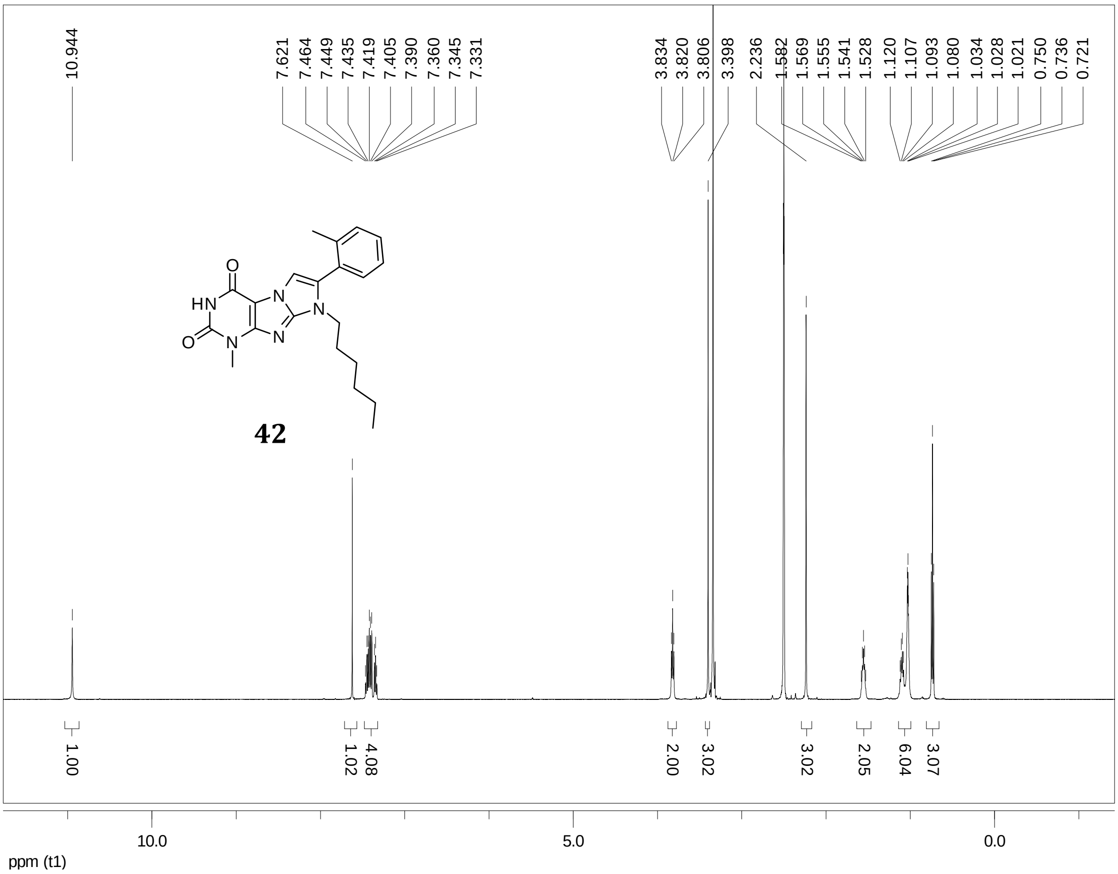
10.944
7.623
7.466
7.463
7.450
7.447
7.436
7.433
7.420
7.407
7.394
7.392
7.363
7.361
7.349
7.334
7.332
3.832
3.818
3.803
3.401
2.238
1.590
1.576
1.561
1.547
1.533
1.117
1.103
1.072
1.059
1.034
1.019
1.010
0.992
0.723
0.709
0.695
HN
O
N
N
N
N
O
0.97
0.95
4.06
1.96
3.00
3.04
2.04
4.06
3.04
10.0
5.0
0.0
ppm (t1)

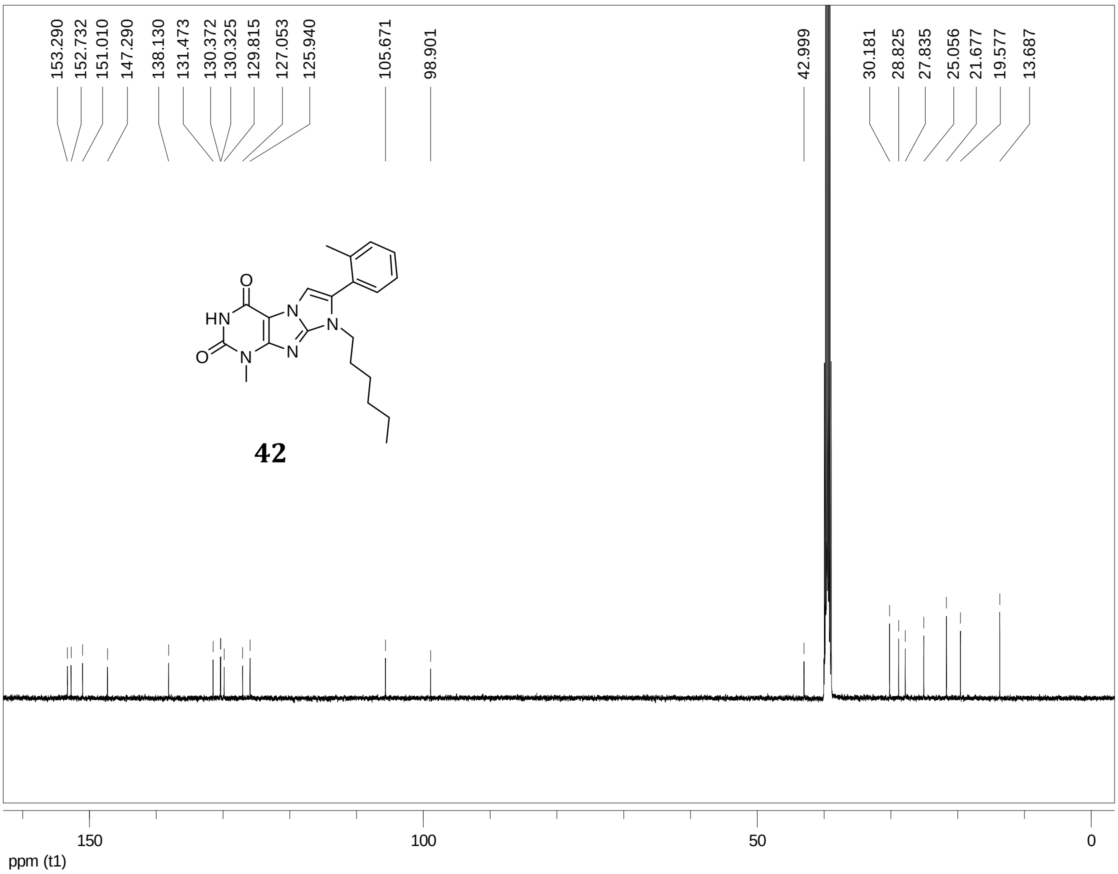
41

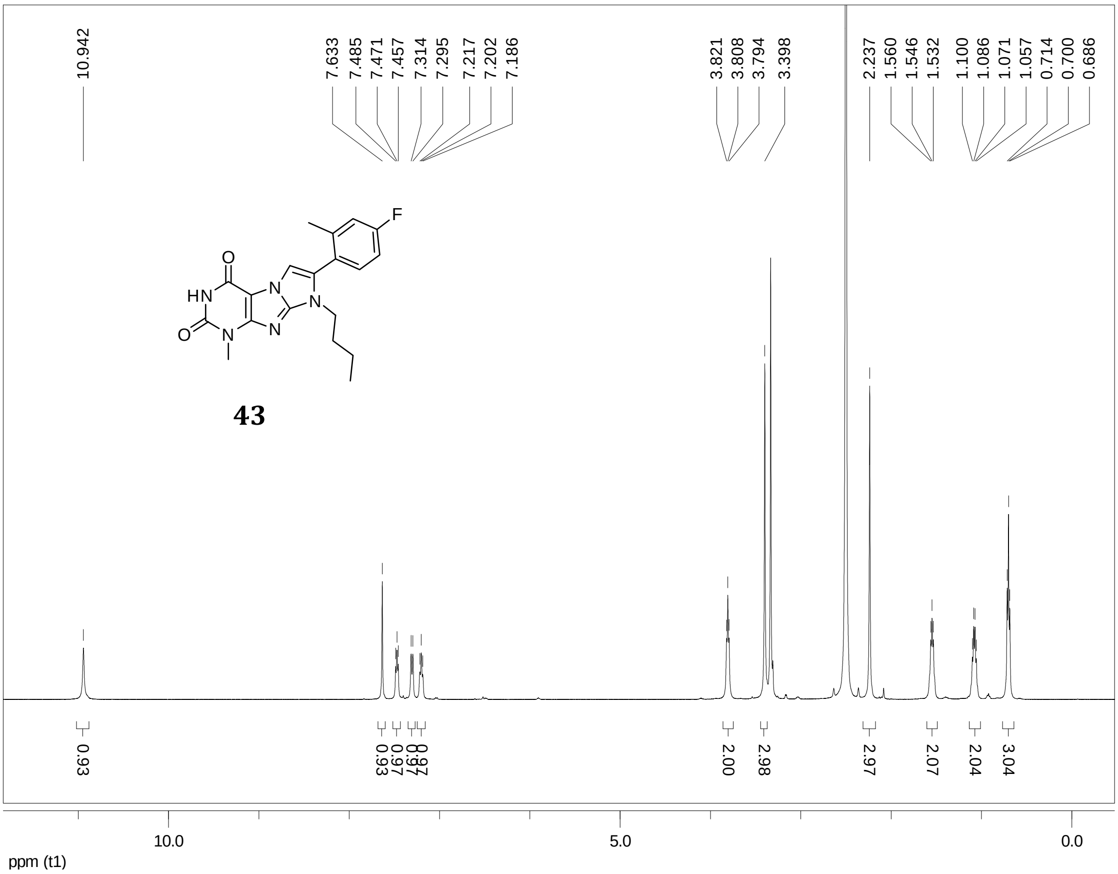


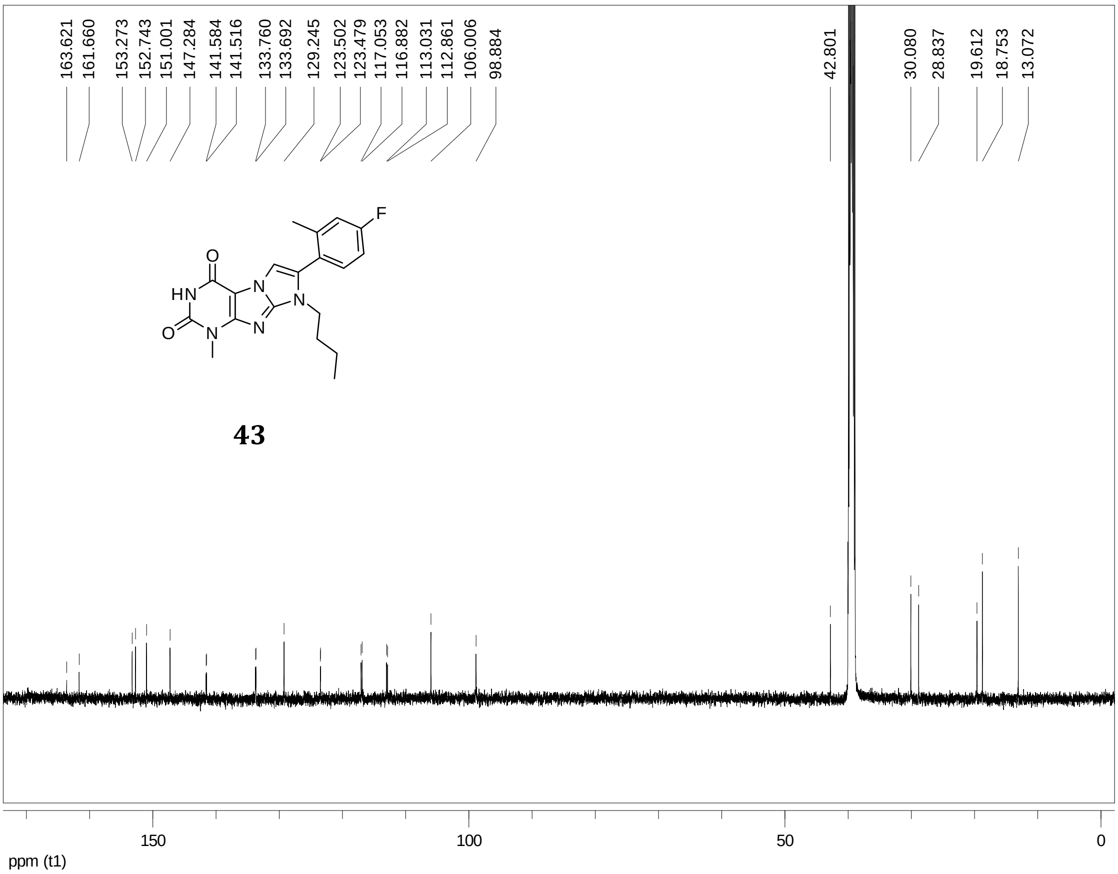
153.288
152.736
151.009
147.299
138.136
131.470
130.369
130.311
129.832
127.057
125.945
105.677
98.900
43.034
28.835
27.583
27.556
21.163
19.574
13.505
HN
O
N
N
N
N
O
150
100
50
ppm (t1)

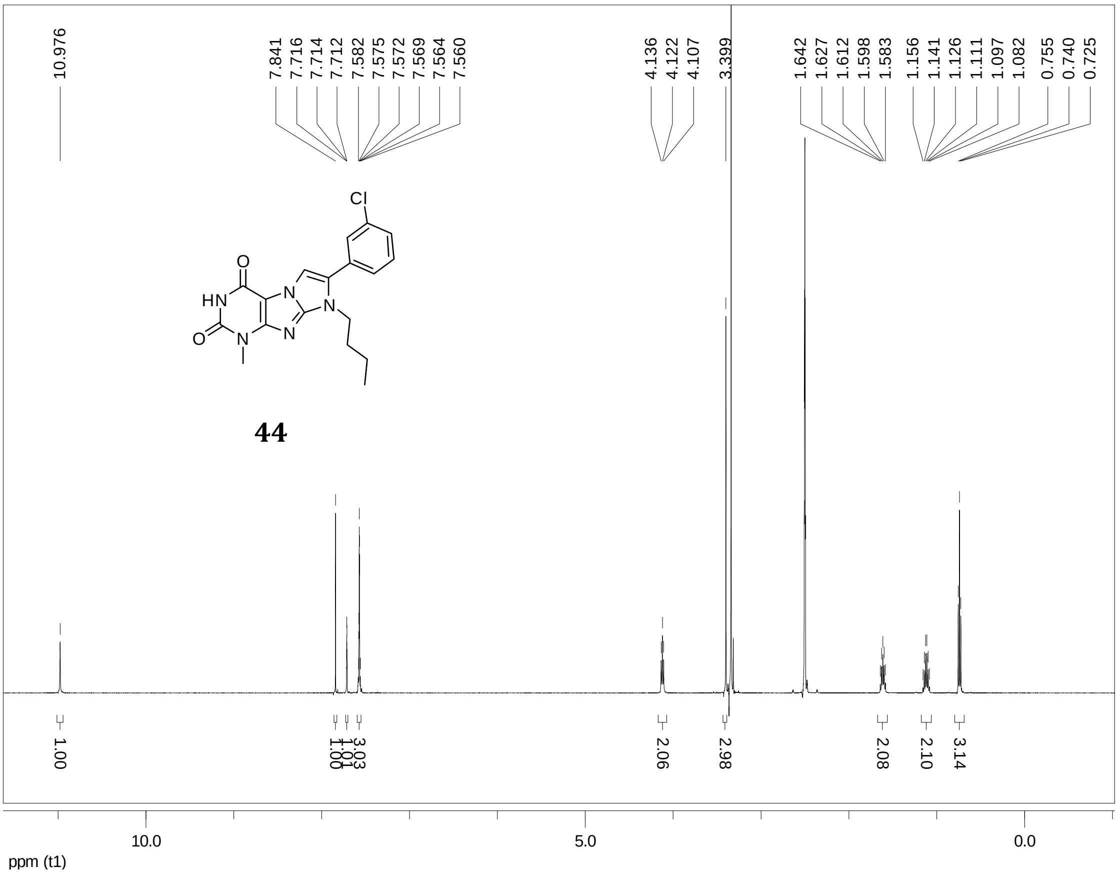
41

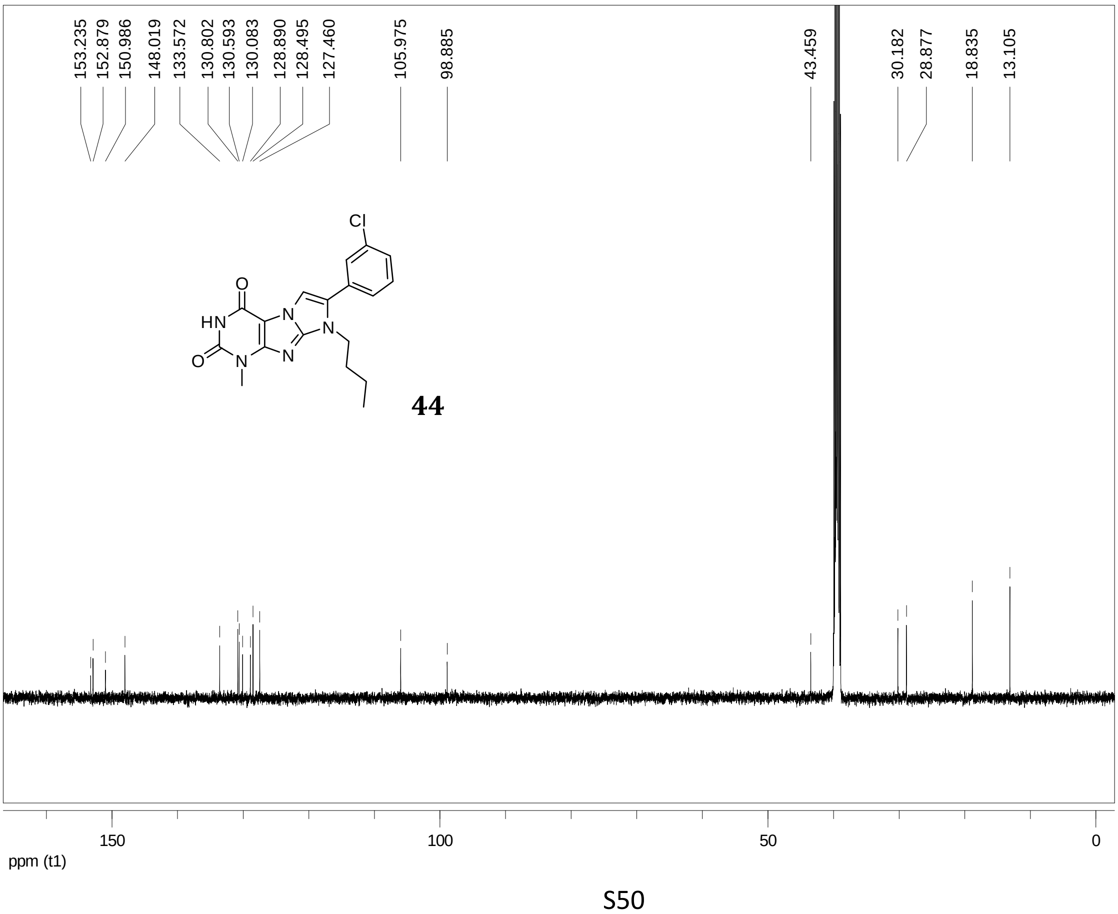

10.944
7.621 7.464 7.449 7.435 7.419 7.405 7.390 7.360 7.345 7.331
3.834 3.820 3.806 3.398 2.236 1.582 1.569 1.555 1.541 1.528 1.120 1.107 1.093 1.080 1.034 1.028 1.021 0.750 0.736 0.721
HN
O
N
42
1.00 1.02 4.08 2.00 3.02 3.02 2.05 6.04 3.07
10.0
5.0
0.0
ppm (t1)

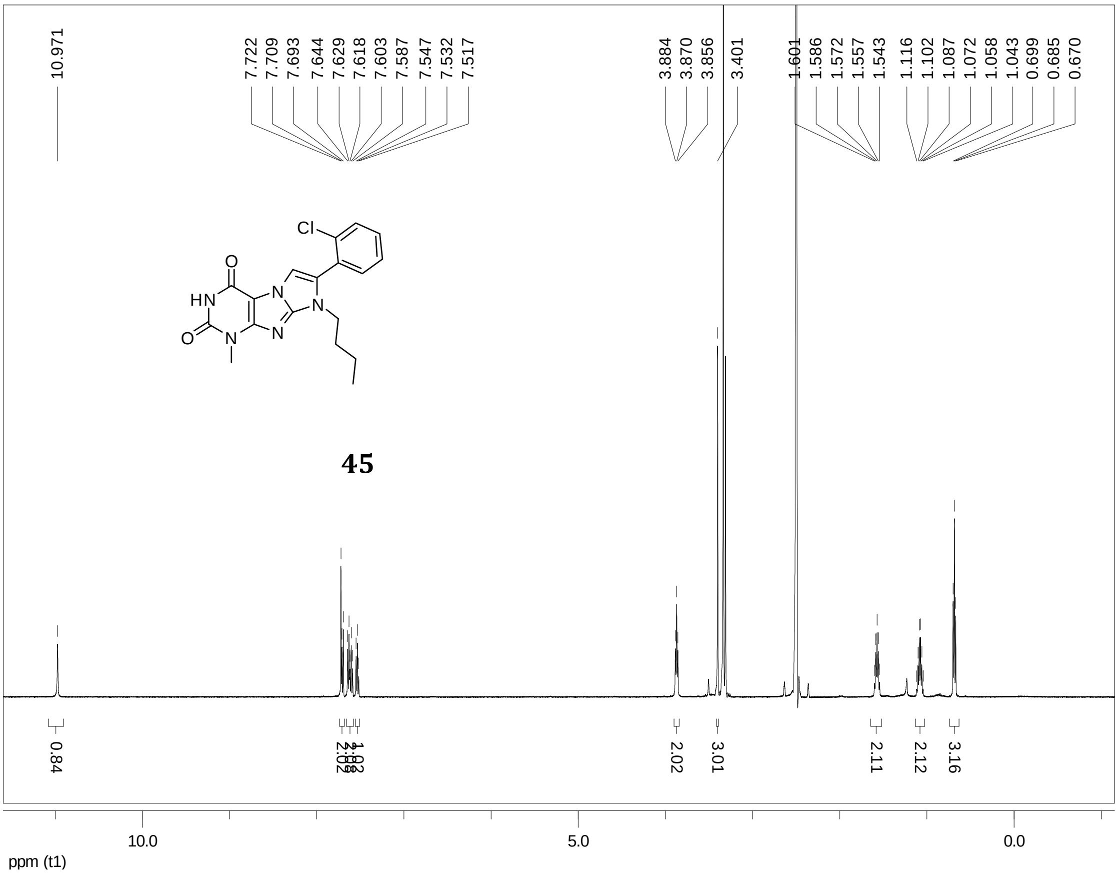

153.290 152.732 151.010 147.290 138.130 131.473 130.372 130.325 129.815 127.053 125.940
105.671
98.901
42.999
30.181 28.825 27.835 25.056 21.677 19.577 13.687
HN
O
N
42
150
100
50
0
ppm (t1)

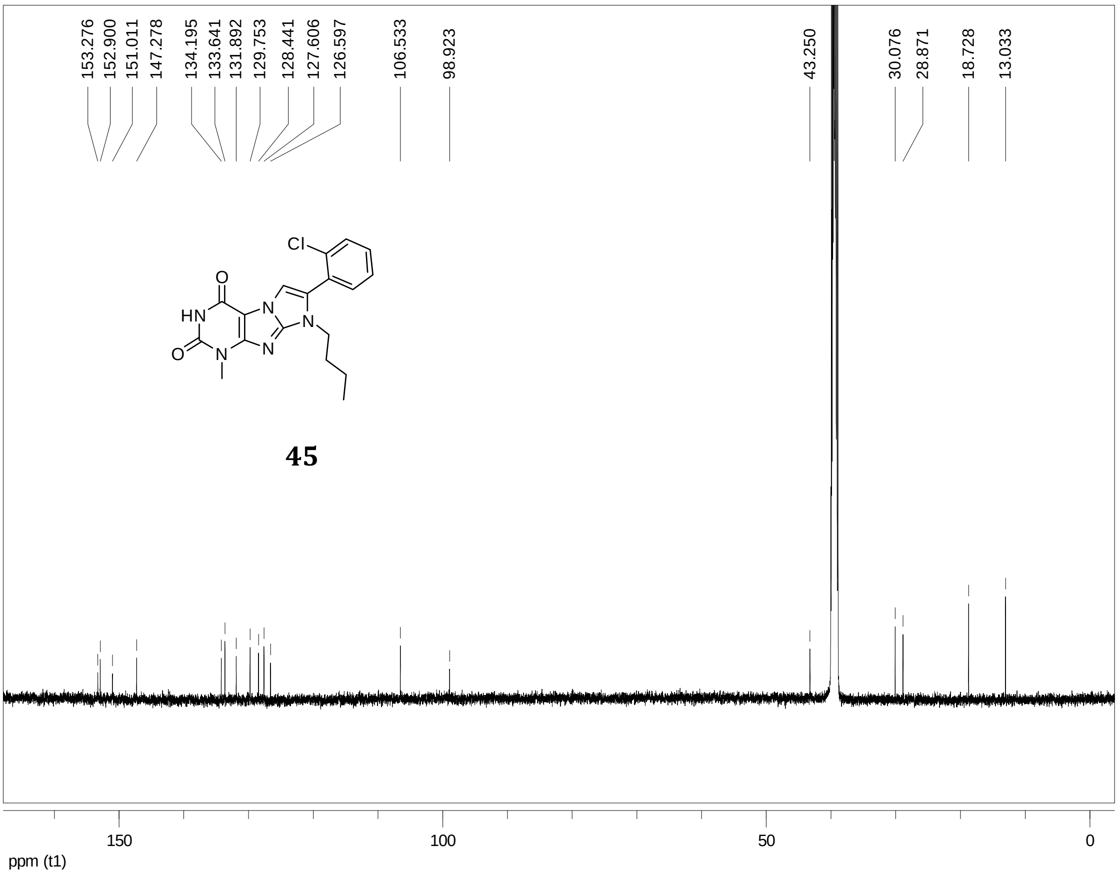

10.942
7.633
7.485
7.471
7.457
7.314
7.295
7.217
7.202
7.186
3.821
3.808
3.794
3.398
2.237
1.560
1.546
1.532
1.100
1.086
1.071
1.057
0.714
0.700
0.686
O
HN
O
N
N
N
N
F
43
0.93
0.93
0.97
0.97
0.97
2.00
2.98
2.97
2.07
2.04
3.04
10.0
5.0
0.0
ppm (t1)

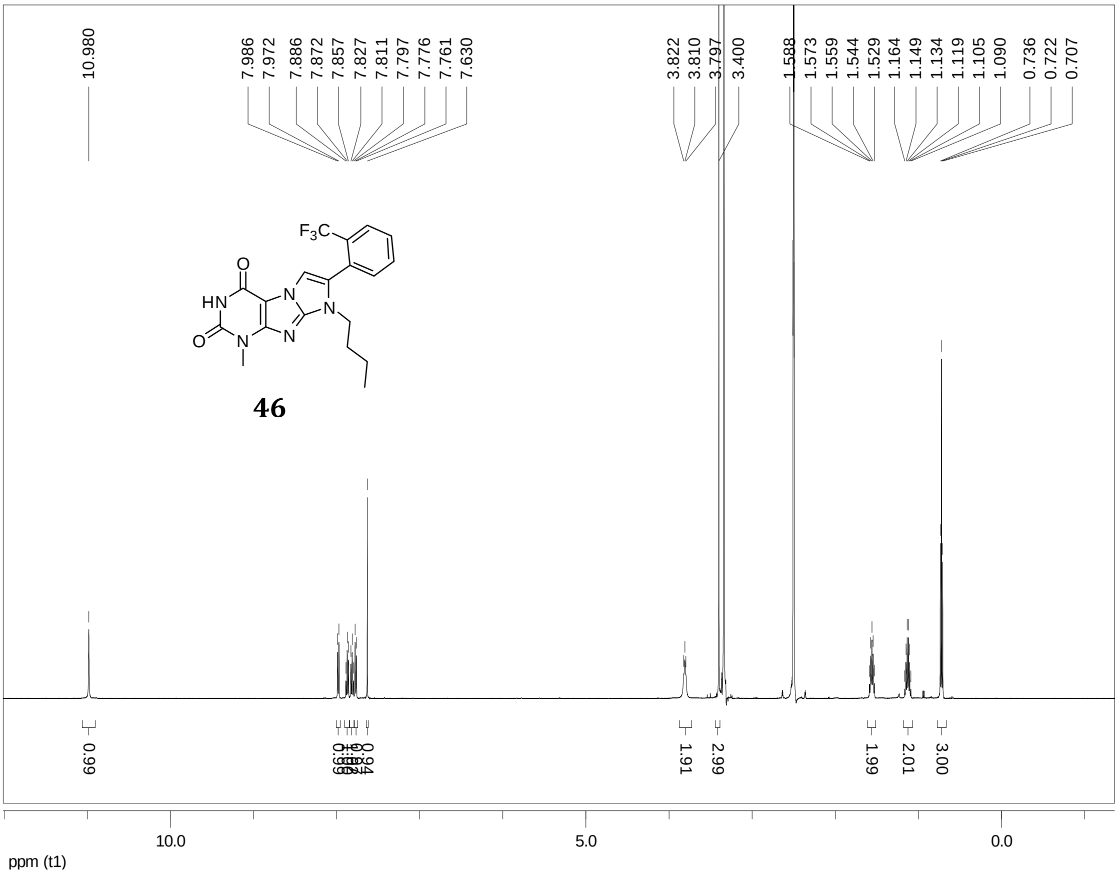

163.621
161.660
153.273
152.743
151.001
147.284
141.584
141.516
133.760
133.692
129.245
123.502
123.479
117.053
116.882
113.031
112.861
106.006
98.884
42.801
30.080
28.837
19.612
18.753
13.072
O
HN
O
N
N
N
N
F
43
150
100
50
0
ppm (t1)

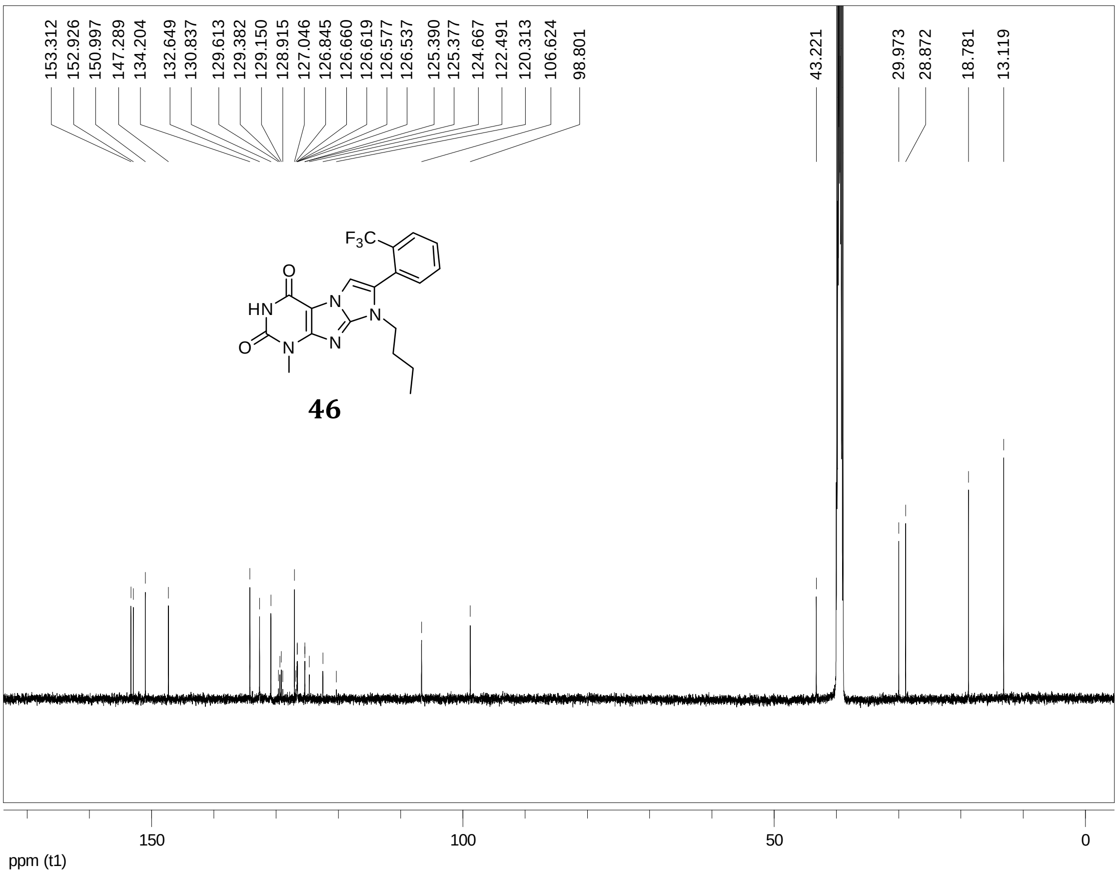

10.976
7.841
7.716
7.714
7.712
7.582
7.575
7.572
7.569
7.564
7.560
4.136
4.122
4.107
3.399
1.642
1.627
1.612
1.598
1.583
1.156
1.141
1.126
1.111
1.097
1.082
0.755
0.740
0.725
Cl
O
HN
N
O
N
N
N
44
1.00
1.00
1.01
3.03
2.06
2.98
2.08
2.10
3.14
10.0
5.0
0.0
ppm (t1)

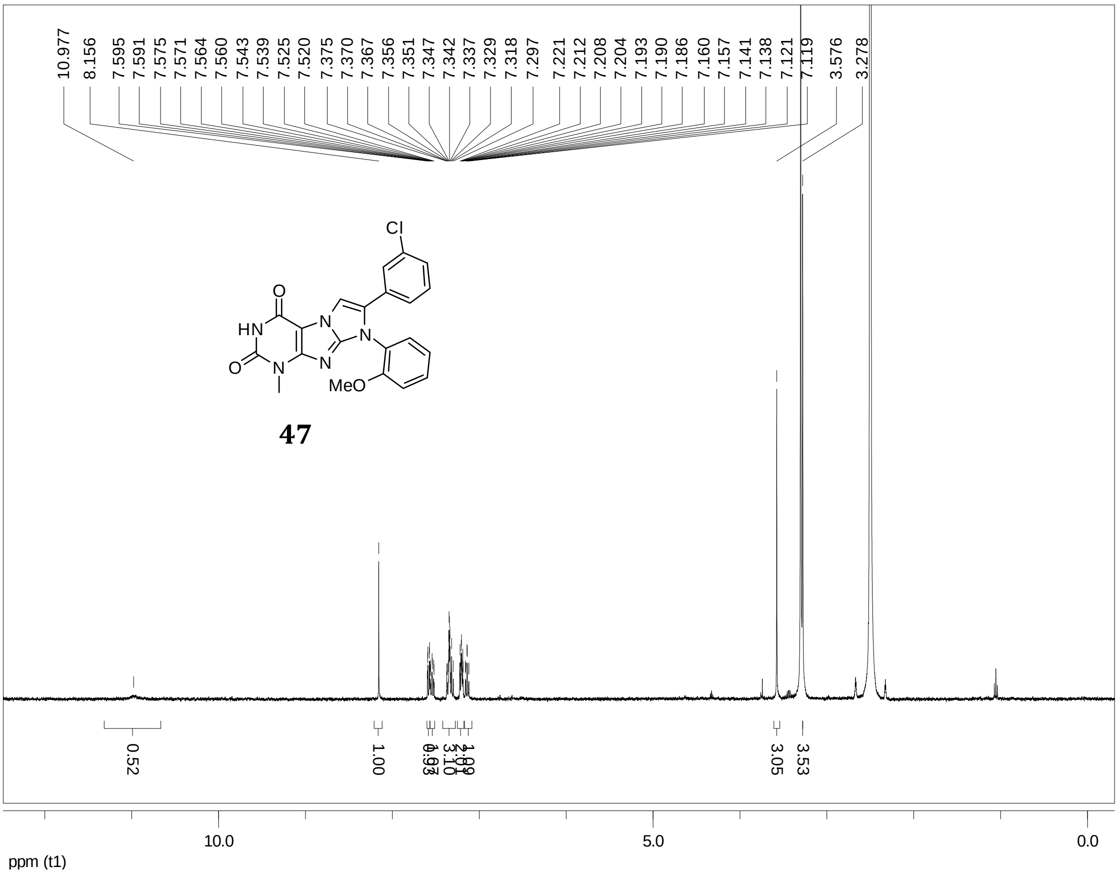

153.235
152.879
150.986
148.019
133.572
130.802
130.593
130.083
128.890
128.495
127.460
105.975
98.885
43.459
30.182
28.877
18.835
13.105
Cl
O
HN
N
O
N
N
N
44
150
100
50
0
ppm (t1)


10.971
7.722
7.709
7.693
7.644
7.629
7.618
7.603
7.587
7.547
7.532
7.517
3.884
3.870
3.856
3.401
1.601
1.586
1.572
1.557
1.543
1.116
1.102
1.087
1.072
1.058
1.043
0.699
0.685
0.670
Cl
O
HN
N
N
N
O
N
45
0.84
2.02
3.01
2.11
2.12
3.16
10.0
5.0
0.0
ppm (t1)

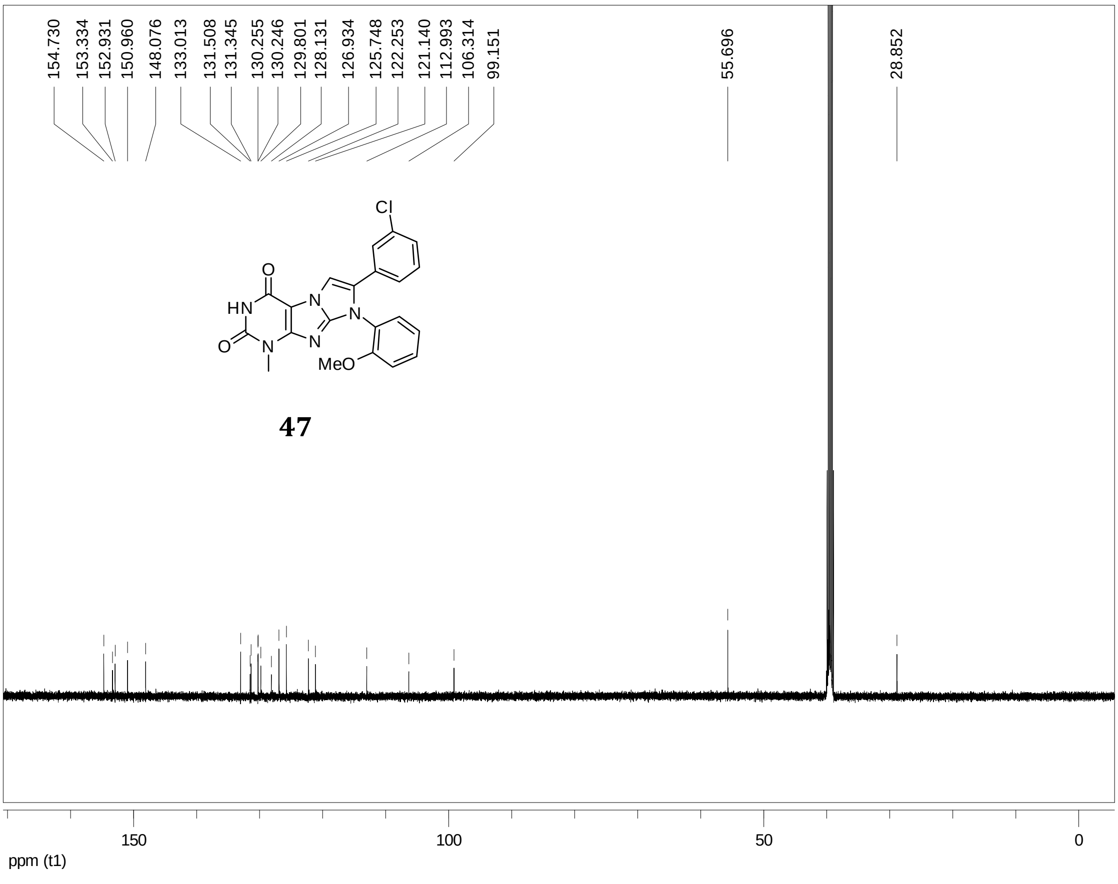

153.276
152.900
151.011
147.278
134.195
133.641
131.892
129.753
128.441
127.606
126.597
106.533
98.923
43.250
30.076
28.871
18.728
13.033
Cl
O
HN
N
N
N
O
N
45
150
100
50
0
ppm (t1)


10.980
7.986 7.972 7.886 7.872 7.857 7.827 7.811 7.797 7.776 7.761 7.630
3.822 3.810 3.797 3.400
1.588 1.573 1.559 1.544 1.529 1.164 1.149 1.134 1.119 1.105 1.090 0.736 0.722 0.707
F_3C
HN
O
N
46
0.99
1.91
2.99
1.99
2.01
3.00
10.0
5.0
0.0
ppm (t1)

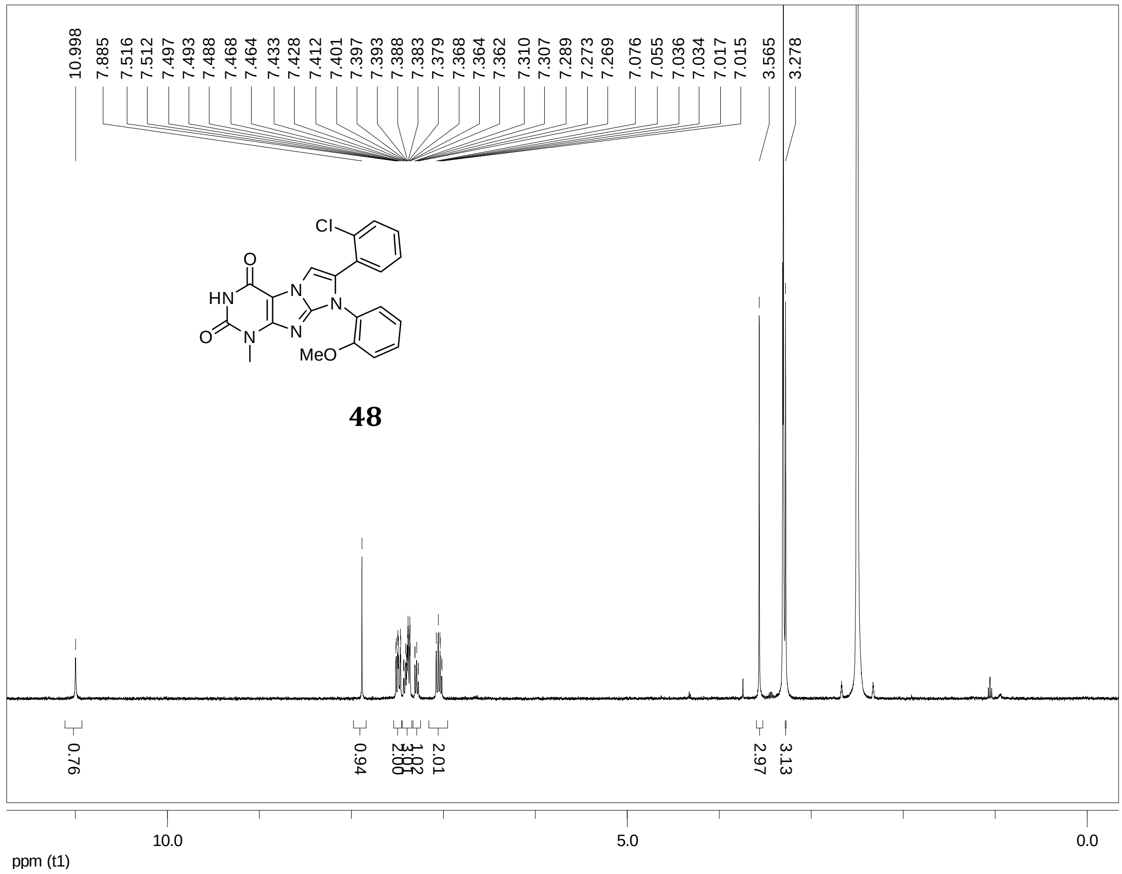

153.312 152.926 150.997 147.289 134.204 132.649 130.837 129.613 129.382 129.150 128.915 127.046 126.845 126.660 126.619 126.577 126.537 125.390 125.377 124.667 122.491 120.313 106.624 98.801
43.221
29.973 28.872 18.781 13.119
F_3C
HN
O
N
46
150
100
50
0
ppm (t1)

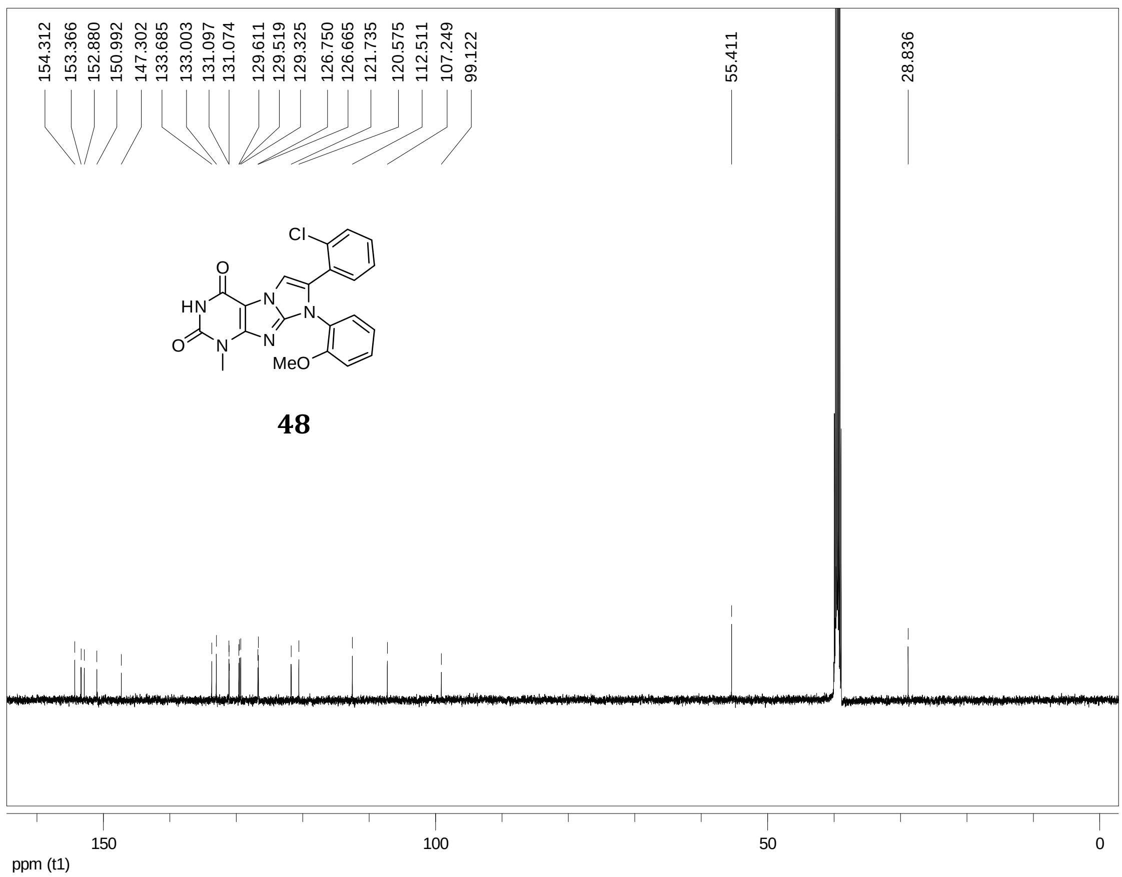


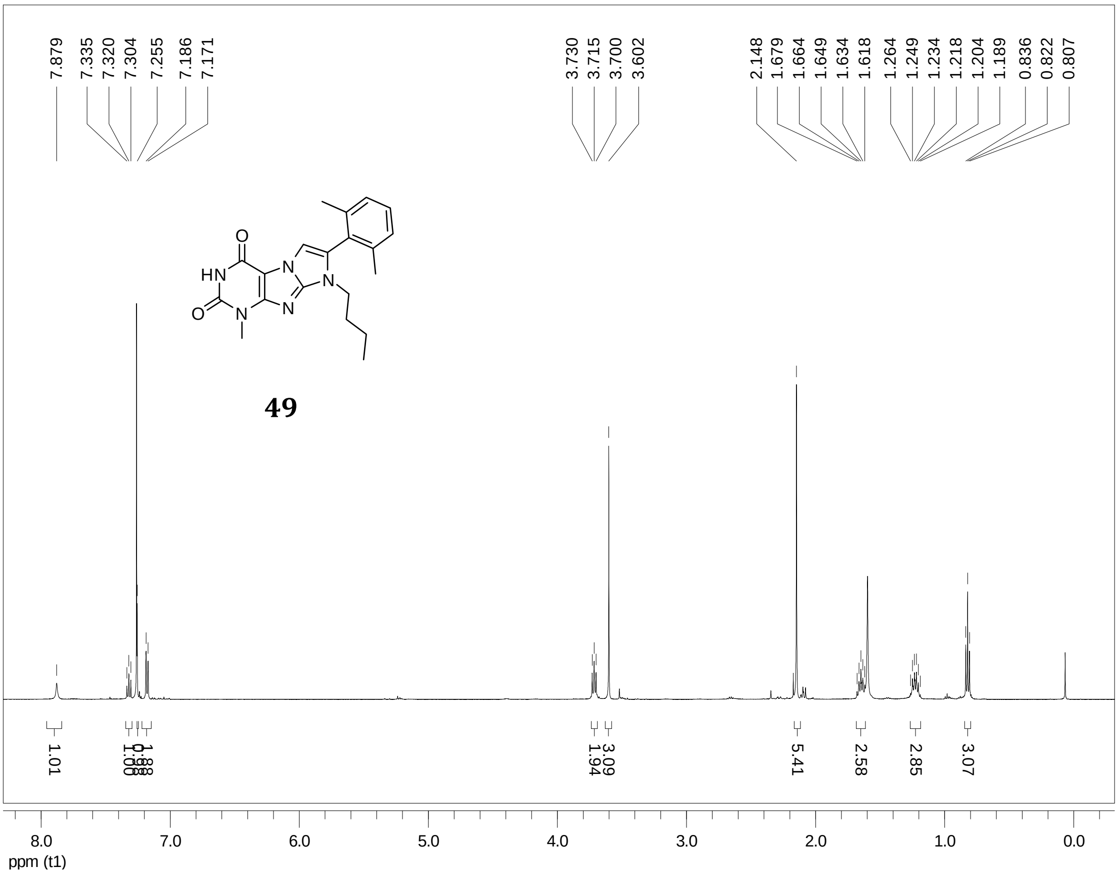
47



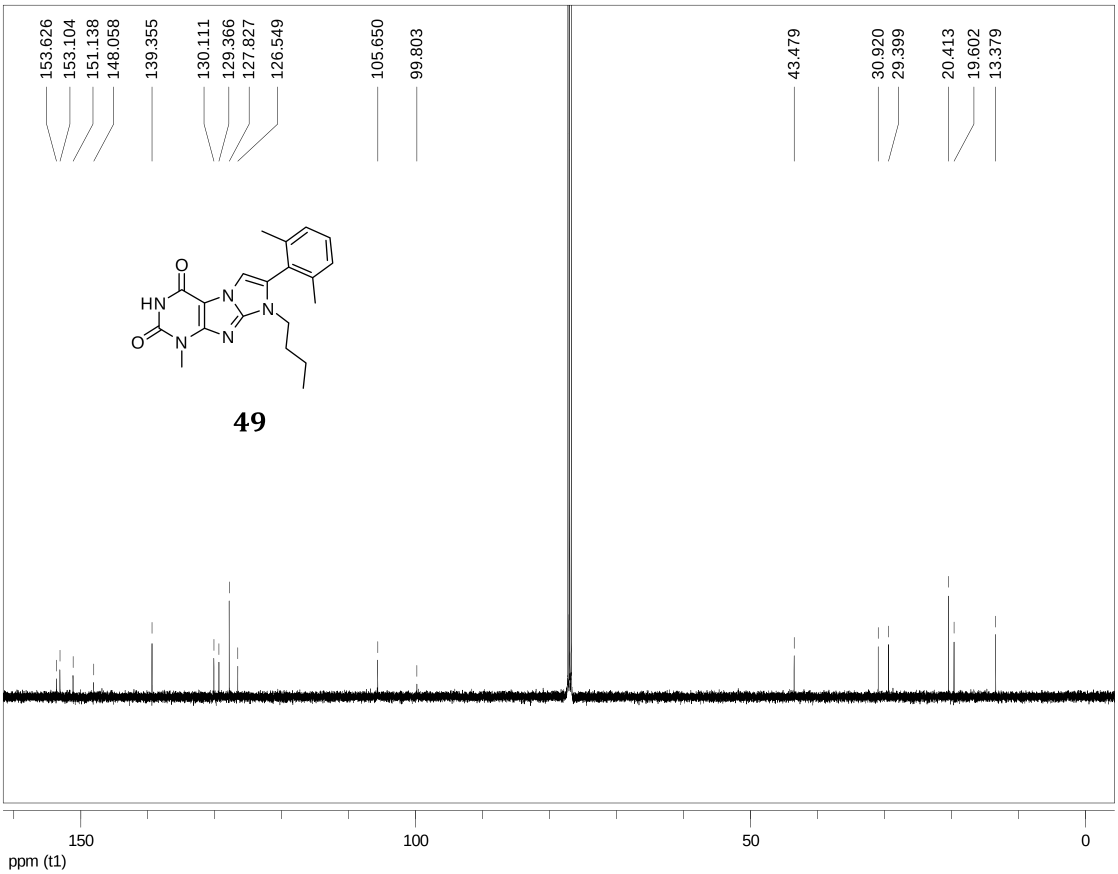
47



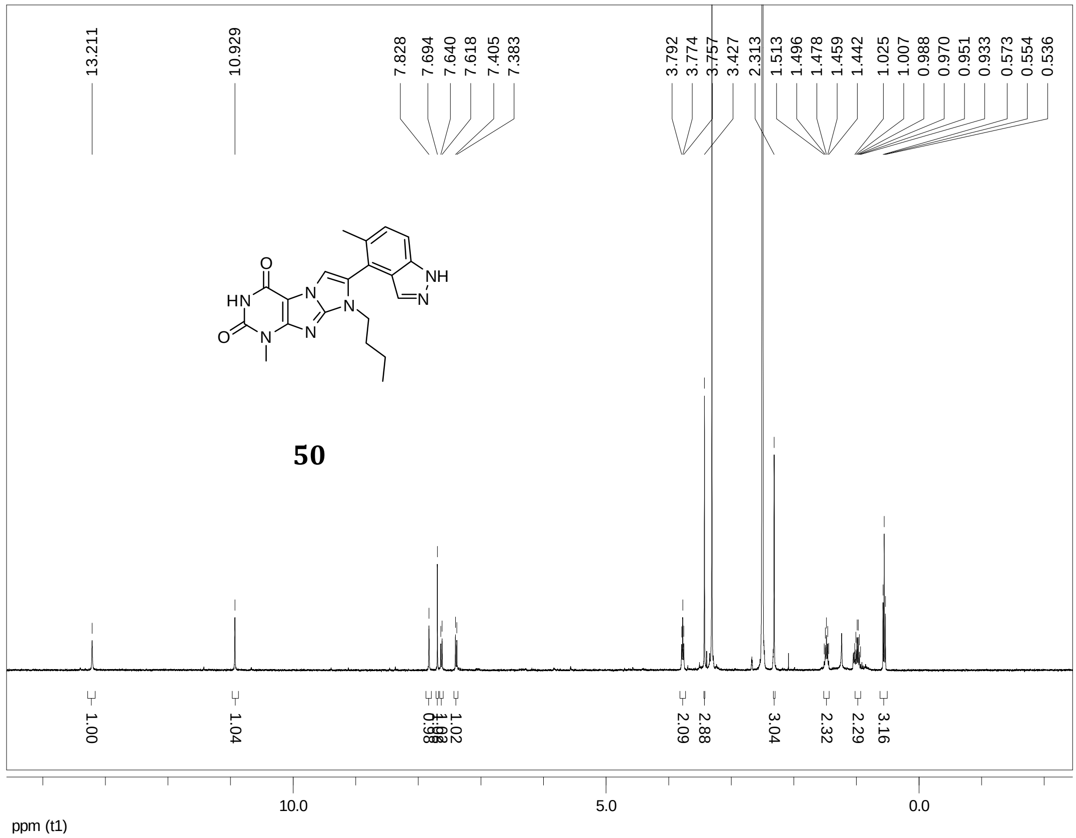


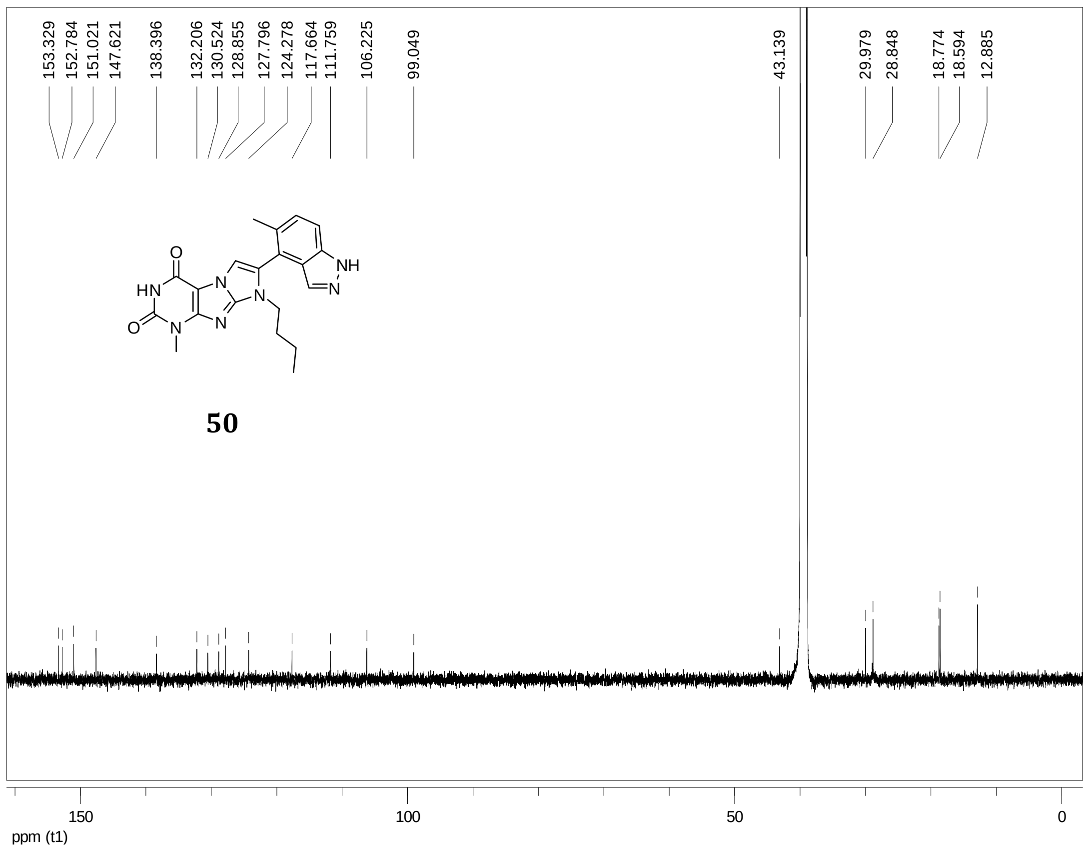

7.879
7.335
7.320
7.304
7.255
7.186
7.171
3.730
3.715
3.700
3.602
2.148
1.679
1.664
1.649
1.634
1.618
1.264
1.249
1.234
1.218
1.204
1.189
0.836
0.822
0.807
HN
O
N
N
N
N
O
1.01
1.94
3.09
5.41
2.58
2.85
3.07
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

49

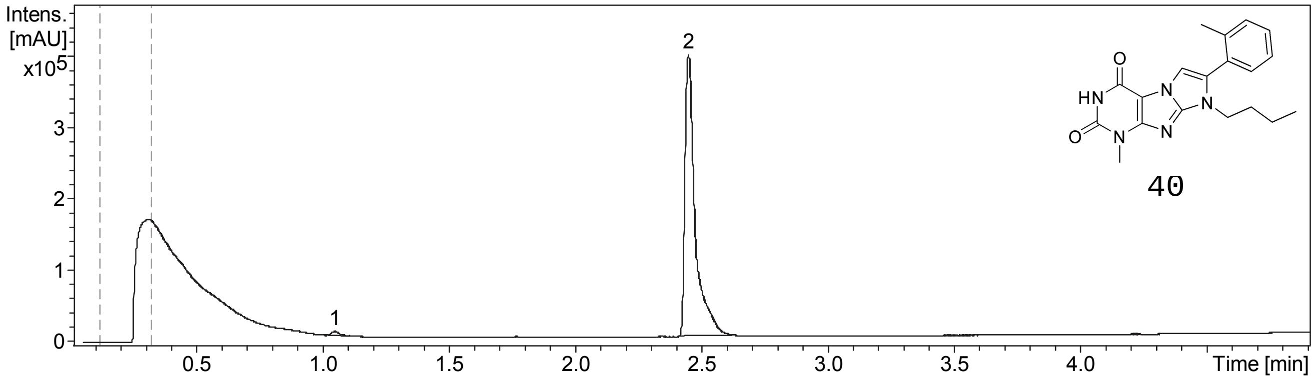

153.626
153.104
151.138
148.058
139.355
130.111
129.366
127.827
126.549
105.650
99.803
43.479
30.920
29.399
20.413
19.602
13.379
HN
O
N
N
N
N
O
150
100
50
0
ppm (t1)

49

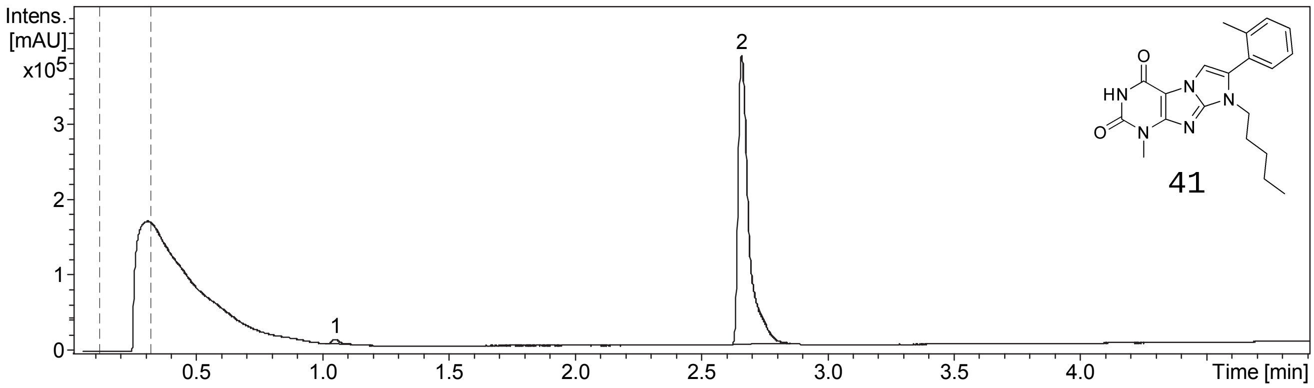




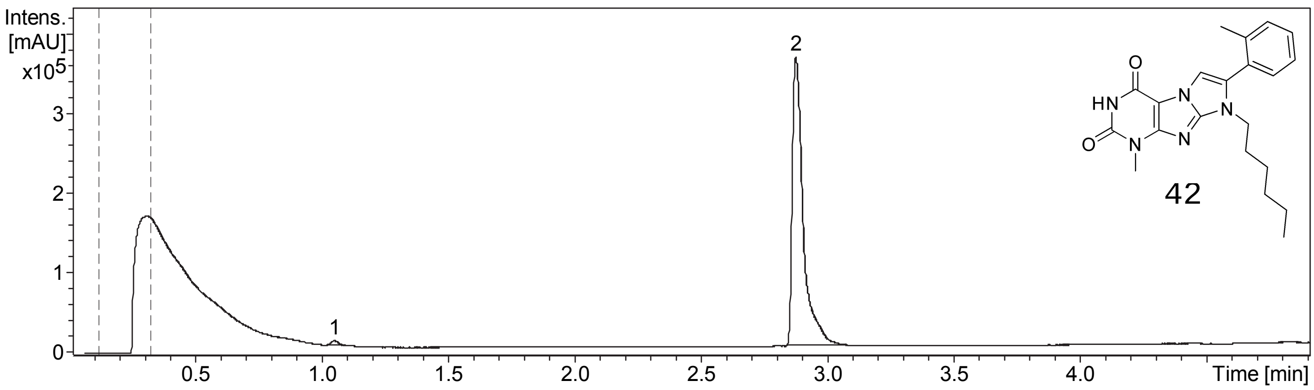
HPLC Traces of tested compounds



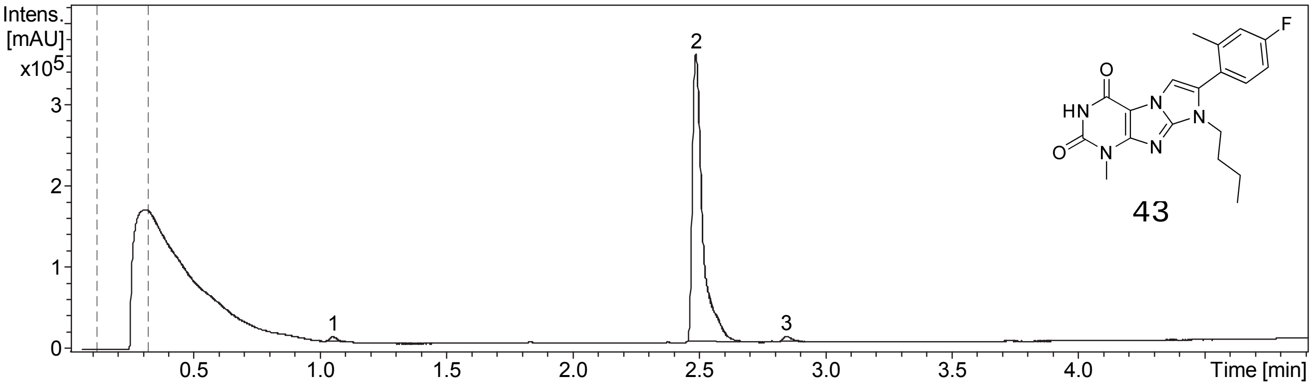
#	RT [min]	Area	FWHM [min]	Area Frac. %
1	1.05	13780		1.2
2	2.45	1118262	0.04	98.8
n.a.	2.47	n.a.	n.a.	n.a.



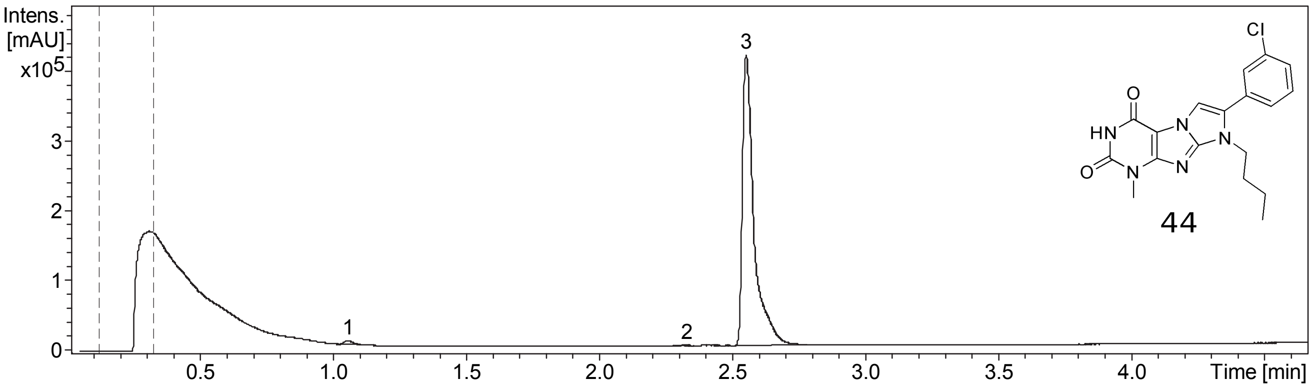
#	RT [min]	Area	FWHM [min]	Area Frac. %
1	1.05	13746		1.2
2	2.66	1130637	0.04	98.8
n.a.	2.72	n.a.	n.a.	n.a.



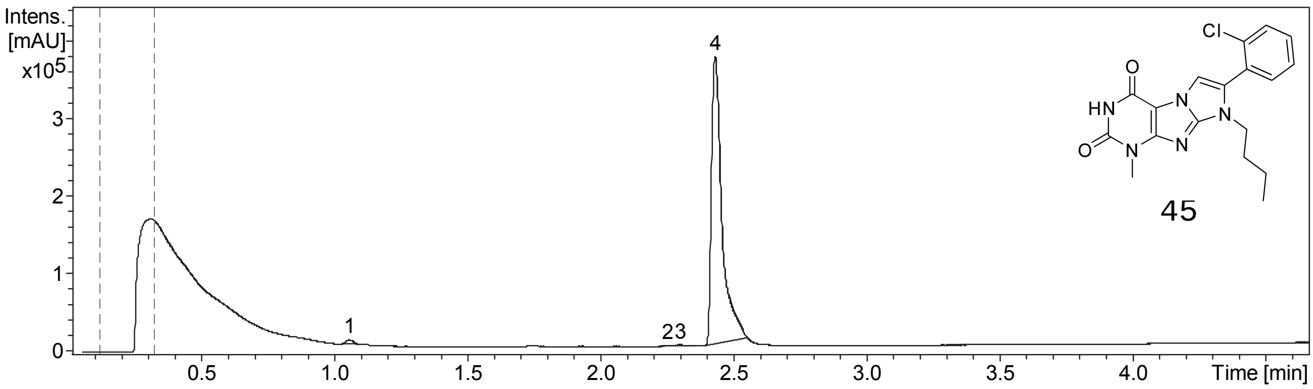
#	RT [min]	Area	FWHM [min]	Area Frac. %
1	1.05	11304	0.02	1.0
2	2.87	1080157	0.04	99.0
n.a.	2.92	n.a.	n.a.	n.a.



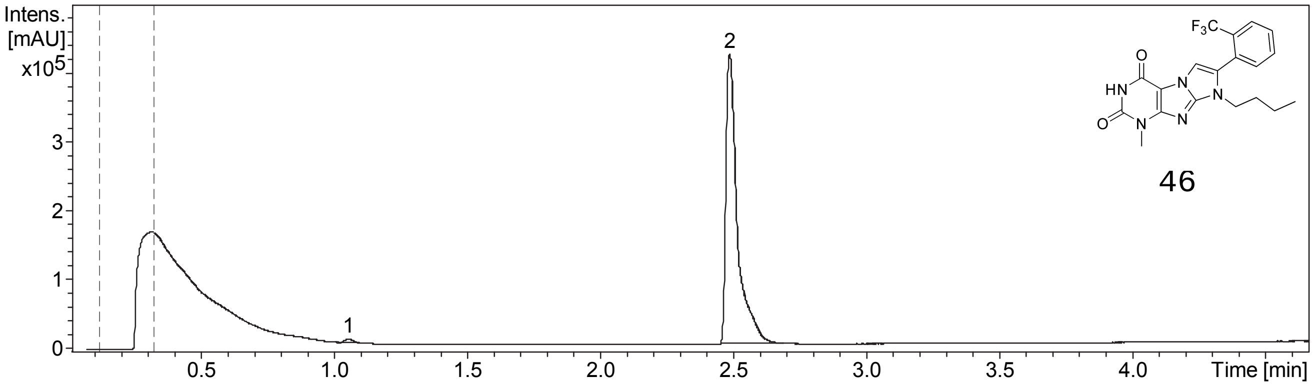
#	RT [min]	Area	FWHM [min]	Area Frac. %
1	1.05	10938	0.03	1.1
2	2.49	991323	0.04	97.4
3	2.84	15711		1.5
n.a.	2.53	n.a.	n.a.	n.a.



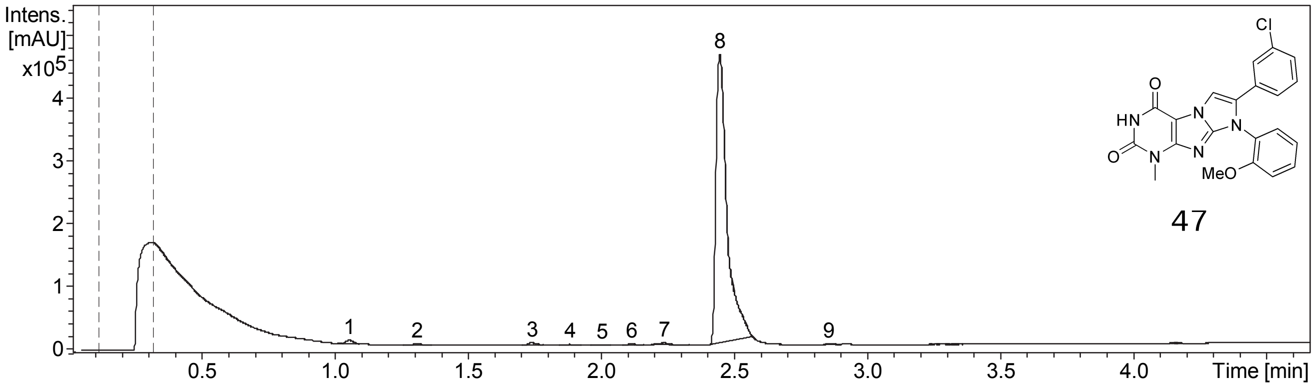
#	RT [min]	Area	FWHM [min]	Area Frac. %
1	1.05	12056.5		0.9
2	2.33	3207.2		0.3
3	2.55	1258883.7	0.04	98.8
n.a.	2.60	n.a.	n.a.	n.a.



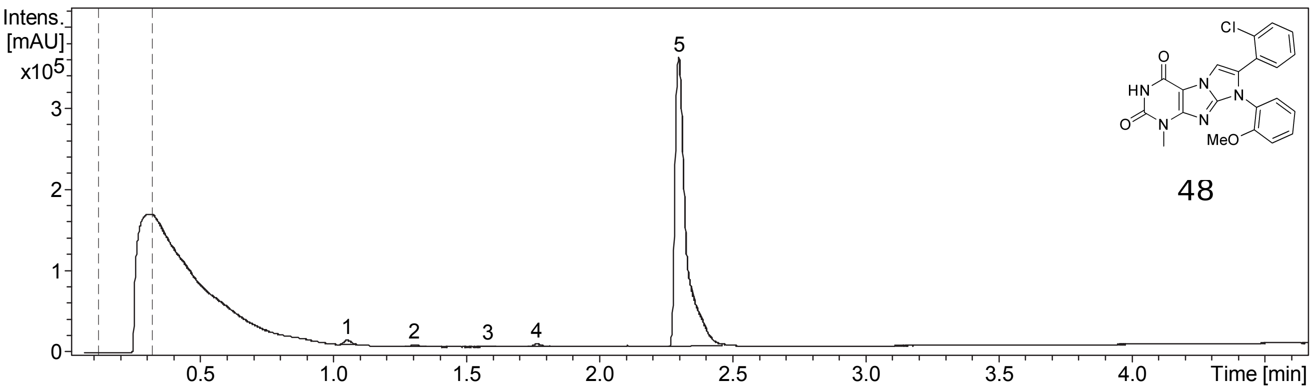
#	RT [min]	Area	FWHM [min]	Area Frac. %
1	1.05	11134.1	0.03	1.1
2	2.25	2524.2		0.2
3	2.30	3449.4		0.3
4	2.43	1020709.6	0.04	98.4
n.a.	2.46	n.a.	n.a.	n.a.



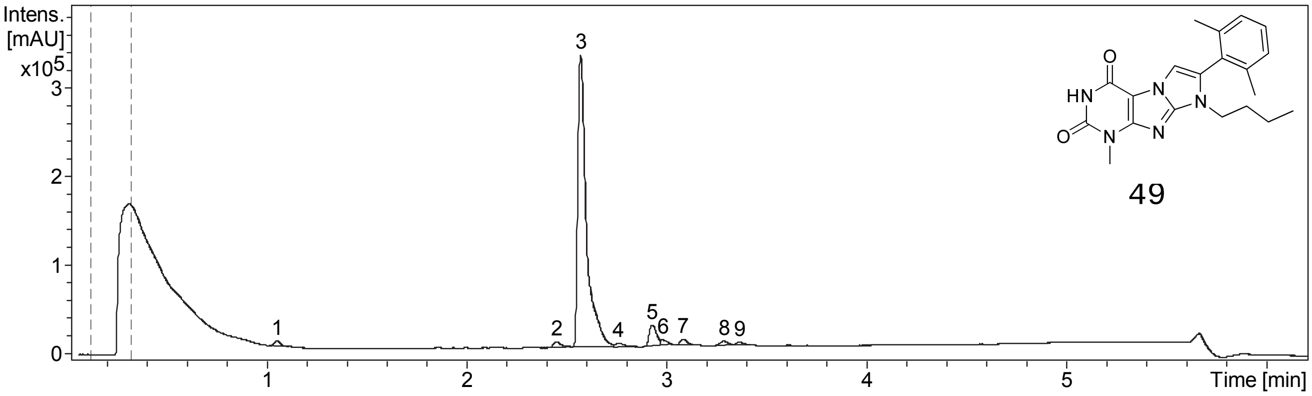
#	RT [min]	Area	FWHM [min]	Area Frac. %
1	1.05	10533		0.8
2	2.48	1257846	0.04	99.2
n.a.	2.51	n.a.	n.a.	n.a.



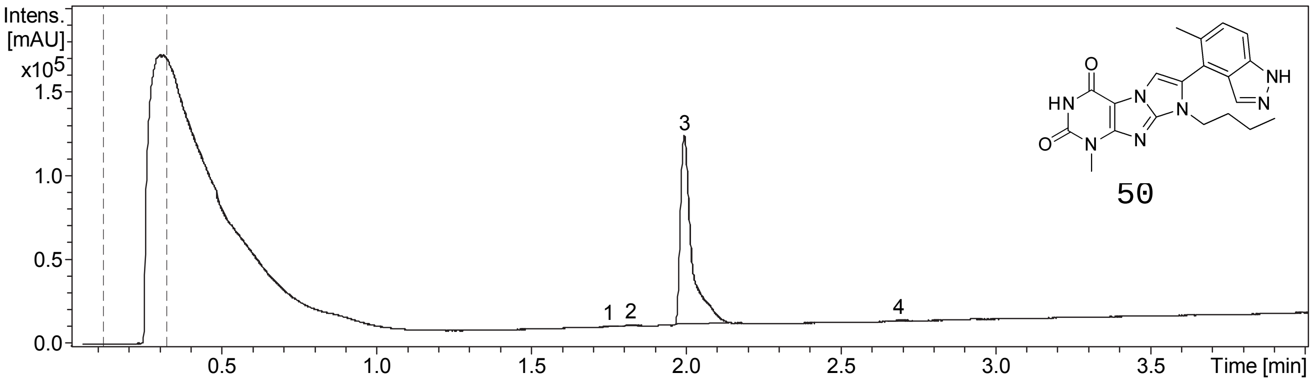
#	RT [min]	Area	FWHM [min]	Area Frac. %
1	1.05	12380.2		0.9
2	1.31	7299.6		0.5
3	1.74	8465.3		0.6
4	1.88	3174.4		0.2
5	2.00	2067.3		0.1
6	2.11	4854.6		0.3
7	2.23	12131.9		0.9
8	2.44	1338824.7	0.04	96.3
9	2.85	1091.3		0.1
n.a.	2.50	n.a.	n.a.	n.a.



#	RT [min]	Area	FWHM [min]	Area Frac. %
1	1.05	10648.66	0.03	1.0
2	1.30	3513.64		0.3
3	1.58	957.91		0.1
4	1.76	6103.18		0.6
5	2.30	1035999.49	0.04	98.0
n.a.	2.32	n.a.	n.a.	n.a.



#	RT [min]	Area	FWHM [min]	Area Frac. %
1	1.05	12520.3		1.1
2	2.45	17708.0	0.02	1.5
3	2.57	997652.5	0.04	86.7
4	2.76	15065.5		1.3
5	2.92	59780.1	0.04	5.2
6	2.98	12859.2	0.03	1.1
7	3.08	15046.6	0.04	1.3
8	3.28	12579.1	0.04	1.1
9	3.36	7012.8		0.6
n.a.	2.55	n.a.	n.a.	n.a.



#	RT [min]	Area	FWHM [min]	Area Frac. %
1	1.75	447.43		0.2
2	1.82	1343.04		0.5
3	1.99	292278.84	0.03	98.7
4	2.69	2103.76		0.7
n.a.	2.03	n.a.	n.a.	n.a.

- Composite Omit Map of Ligand 3