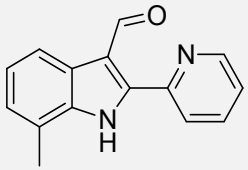
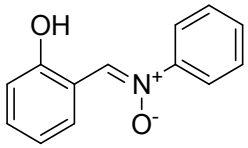
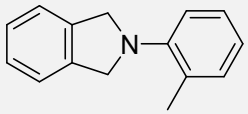
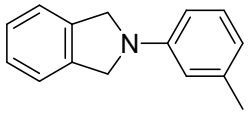
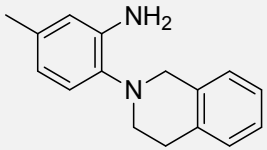
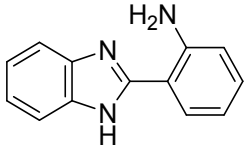
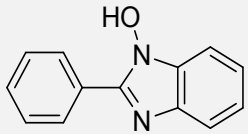
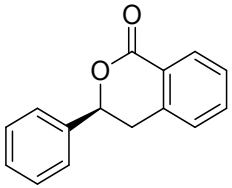
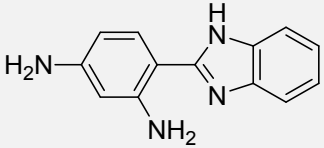
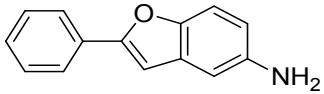
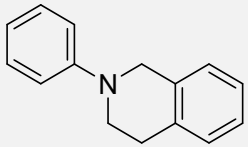
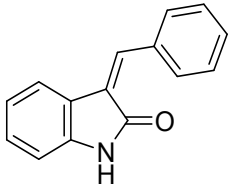
Electronic Supplementary Material (ESI) for MedChemComm.

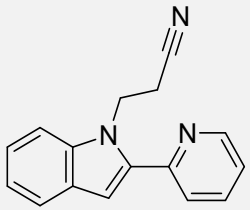
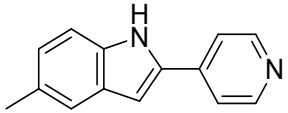
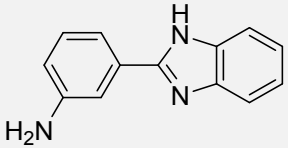
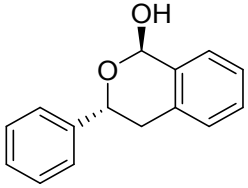
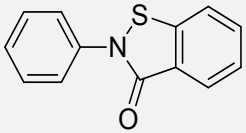
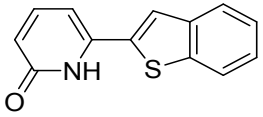
Towards Identifying Potent New Hits for Glioblastoma

*Chris Sherer, Saurabh Prabhu, David Adams, Joseph Hayes, Farzana Rowther, Ibrahim Tolaymat, Tracy Warr and Timothy J. Snape**

Analogues of compound 1 found as part of the similarity search

Compound numbering	Structure	ZINC Identifier	Similarity	Shape	Electronic	Isomers and pseudoisomers	Different core	Very different	No relevant functional group
		ZINC45235565	0.765	0.633	0.898				×
		ZINC00159358	0.766	0.660	0.873			×	
		ZINC01025941	0.766	0.607	0.925				×
		ZINC02144604	0.766	0.607	0.926				×
		ZINC37401152	0.766	0.603	0.930		×		
		ZINC00144326	0.767	0.639	0.895		×		

Compound numbering	Structure	ZINC Identifier	Similarity	Shape	Electronic	Isomers and pseudoisomers	Different core	Very different	No relevant functional group
		ZINC01391331	0.767	0.617	0.918		×		
		ZINC00397633	0.767	0.595	0.940				×
		ZINC00236875	0.768	0.611	0.924		×		
		ZINC02538818	0.768	0.617	0.919		×		
		ZINC71711321	0.768	0.617	0.919				×
		ZINC13403054	0.768	0.645	0.890				×

Compound numbering	Structure	ZINC Identifier	Similarity	Shape	Electronic	Isomers and pseudoisomers	Different core	Very different	No relevant functional group
		ZINC13194625	0.768	0.638	0.898				×
		ZINC00507751	0.769	0.616	0.921				×
		ZINC00122913	0.769	0.618	0.919		×		
		ZINC03847971	0.769	0.591	0.947				×
		ZINC00478097	0.769	0.601	0.937				×
		ZINC65339301	0.769	0.600	0.938		×		

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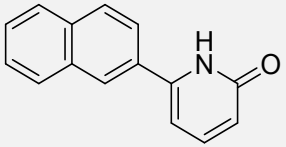
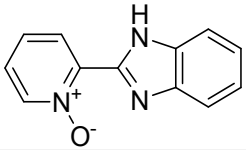
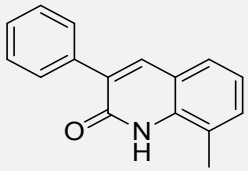
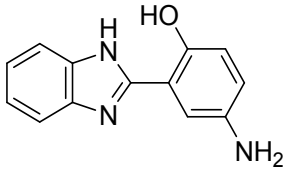
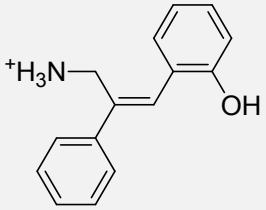
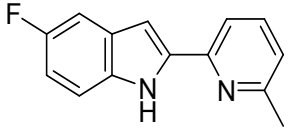
		ZINC65339268	0.769	0.624	0.914		×		
		ZINC46085466	0.770	0.598	0.941				×
		ZINC32099770	0.770	0.641	0.899		×		
		ZINC00246170	0.770	0.618	0.921		×		
		ZINC01716698	0.770	0.670	0.870			×	
		ZINC95835619	0.770	0.638	0.902				×

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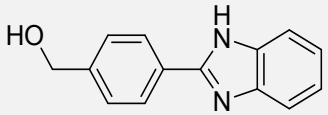
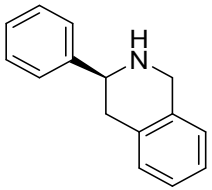
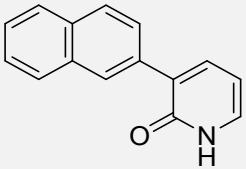
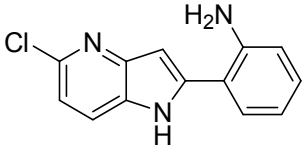
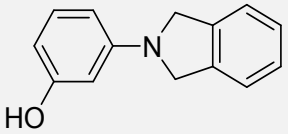
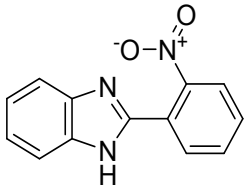
		ZINC79387317	0.770	0.618	0.923				×
		ZINC23625305	0.771	0.599	0.942				×
		ZINC65339264	0.771	0.600	0.942		×		
		ZINC40450030	0.771	0.618	0.924		×		
		ZINC00056346	0.771	0.593	0.949		×		
		ZINC00188622	0.771	0.645	0.897				×

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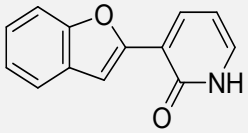
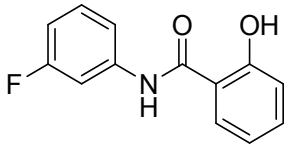
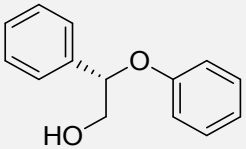
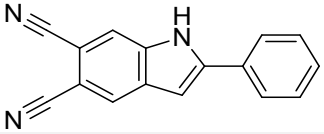
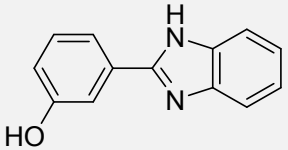
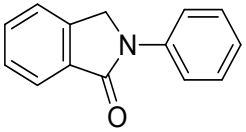
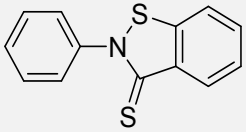
		ZINC65490232	0.771	0.601	0.941		×		
		ZINC06567825	0.771	0.575	0.968			×	
		ZINC04824058	0.772	0.622	0.921				×
		ZINC66091588	0.772	0.636	0.908				×
		ZINC03881190	0.772	0.623	0.920		×		
		ZINC00364176	0.772	0.606	0.939				×
		ZINC00329431	0.772	0.607	0.937				×

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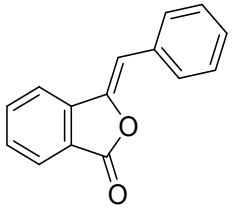
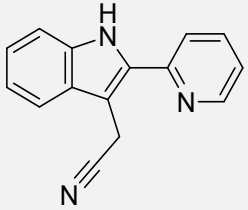
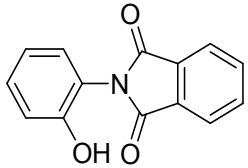
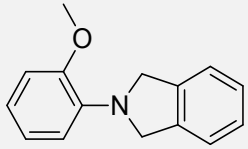
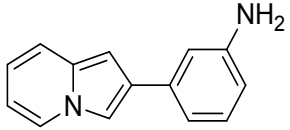
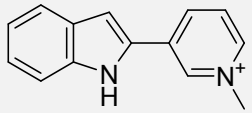
		ZINC00080737	0.772	0.682	0.863				×
		ZINC13284363	0.773	0.628	0.918				×
21		ZINC00148440	0.775	0.609	0.941		×		
		ZINC00559647	0.776	0.624	0.928				×
		ZINC12350724	0.777	0.611	0.943		×		
		ZINC00393231	0.777	0.665	0.889				×

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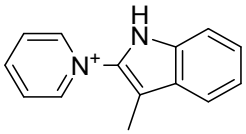
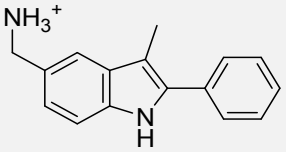
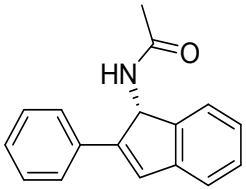
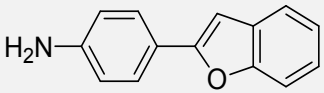
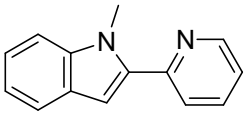
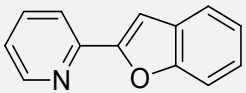
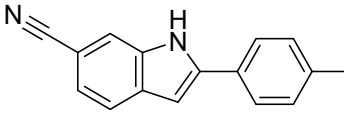
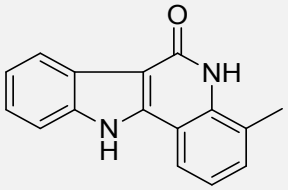
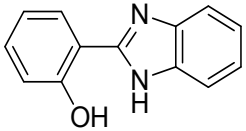
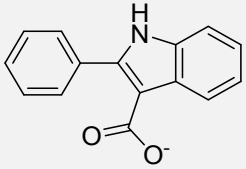
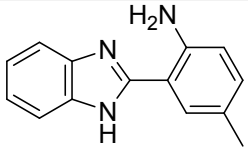
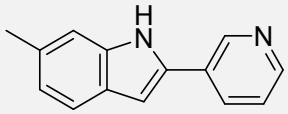
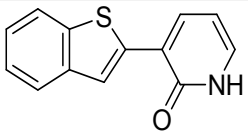
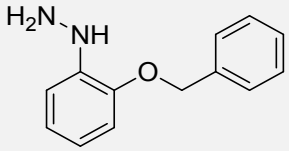
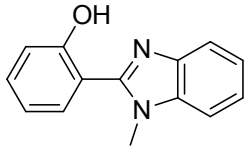
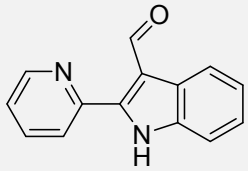
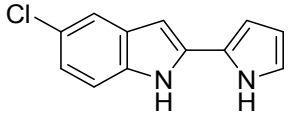
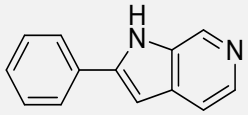
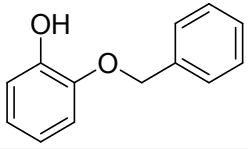
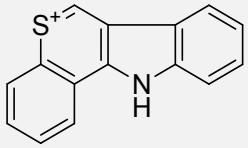
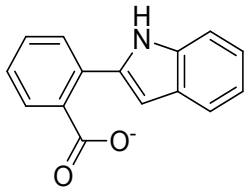
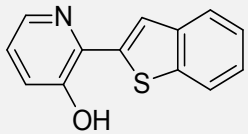
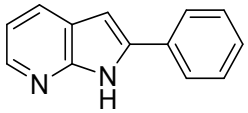
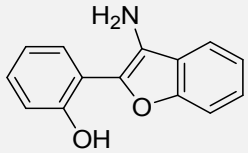
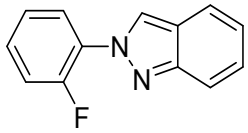
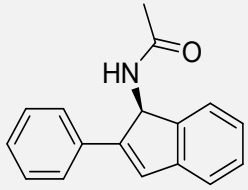
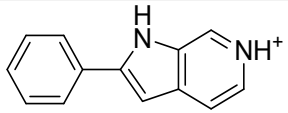
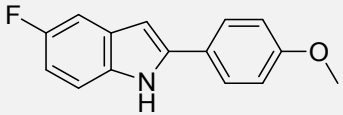
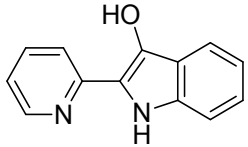
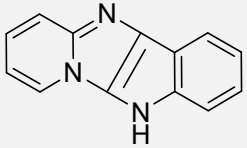
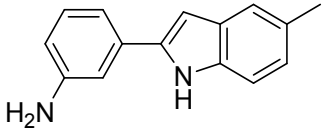
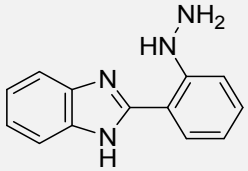
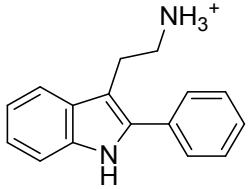
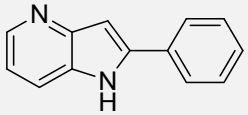
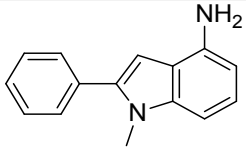
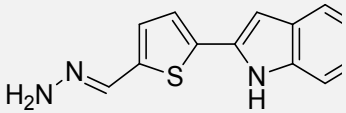
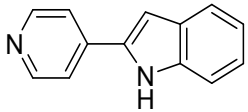
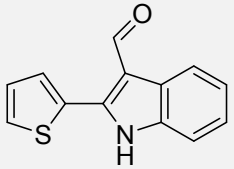
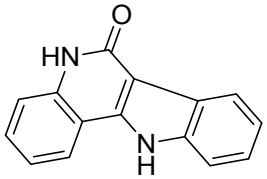
		ZINC01705340	0.778	0.646	0.909				×
		ZINC14001405	0.778	0.676	0.881				×
		ZINC05480960	0.778	0.609	0.947				×
		ZINC00122320	0.778	0.638	0.918		×		
		ZINC34268568	0.778	0.635	0.922				×
		ZINC15084532	0.779	0.616	0.941				×
		ZINC39232949	0.779	0.650	0.908				×

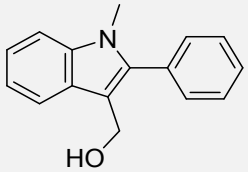
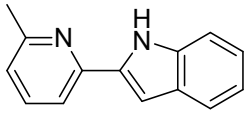
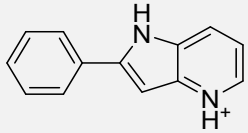
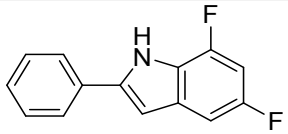
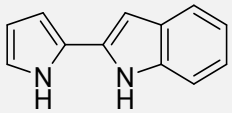
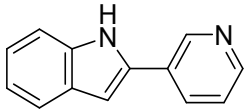
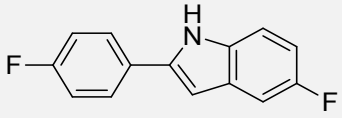
Compound numbering	Structure	ZINC Identifier	Similarity	Shape	Electronic	Isomers and pseudoisomers	Different core	Very different	No relevant functional group
		ZINC04086135	0.779	0.658	0.901	×			
22		ZINC00166610	0.779	0.665	0.893		×		
		ZINC05775431	0.779	0.695	0.864				×
		ZINC19486558	0.780	0.615	0.945		×		
		ZINC00050693	0.781	0.642	0.920				×
		ZINC38918044	0.782	0.597	0.967		×		

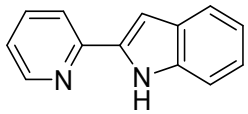
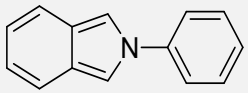
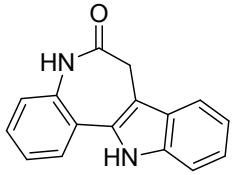
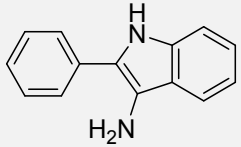
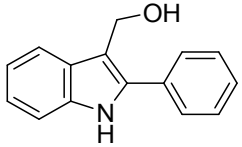
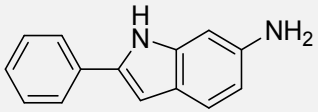
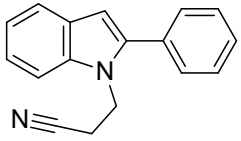
Compound numbering	Structure	ZINC Identifier	Similarity	Shape	Electronic	Isomers and pseudoisomers	Different core	Very different	No relevant functional group
		ZINC02505847	0.783	0.623	0.943			×	
		ZINC05837089	0.783	0.666	0.901		×		
		ZINC02534051	0.784	0.653	0.915				×
		ZINC66055026	0.784	0.625	0.942				×
		ZINC22015465	0.784	0.629	0.940				×
23		ZINC00406909	0.785	0.649	0.920			×	
		ZINC05105345	0.785	0.674	0.895				×

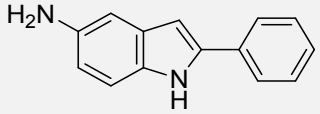
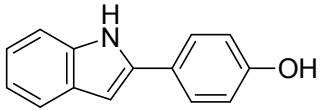
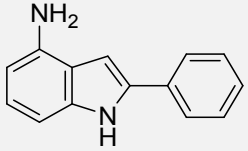
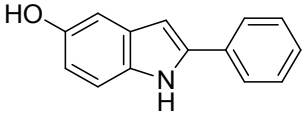
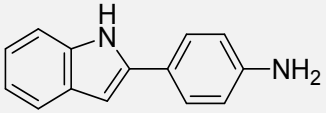
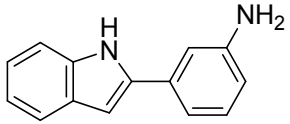
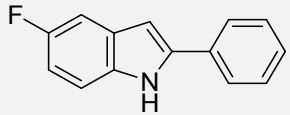
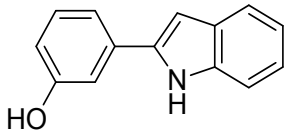
Compound numbering	Structure	ZINC Identifier	Similarity	Shape	Electronic	Isomers and pseudoisomers	Different core	Very different	No relevant functional group
		ZINC00103501	0.786	0.706	0.866				×
		ZINC65339297	0.786	0.603	0.970		×		
		ZINC32233020	0.787	0.635	0.940				×
		ZINC39119558	0.788	0.650	0.925		×		
		ZINC33884628	0.788	0.608	0.967				×
		ZINC05480972	0.789	0.629	0.948				×
		ZINC22015465	0.789	0.645	0.933				×

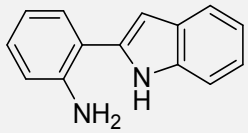
Compound numbering	Structure	ZINC Identifier	Similarity	Shape	Electronic	Isomers and pseudoisomers	Different core	Very different	No relevant functional group
		ZINC01518176	0.789	0.652	0.926				×
		ZINC03845012	0.790	0.635	0.946		×		
		ZINC05117514	0.792	0.593	0.991				×
		ZINC00501252	0.792	0.681	0.903	×			
		ZINC13285077	0.792	0.639	0.945		×		
		ZINC15445928	0.793	0.693	0.893				×

Compound numbering	Structure	ZINC Identifier	Similarity	Shape	Electronic	Isomers and pseudoisomers	Different core	Very different	No relevant functional group
		ZINC40448330	0.793	0.645	0.942				×
		ZINC35325036	0.794	0.684	0.903	×			
		ZINC05777096	0.794	0.642	0.947				×
		ZINC01519035	0.794	0.646	0.942				×
		ZINC19724840	0.795	0.647	0.942				×
		ZINC03944854	0.796	0.674	0.918	×			

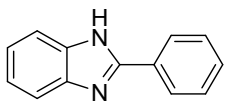
Compound numbering	Structure	ZINC Identifier	Similarity	Shape	Electronic	Isomers and pseudoisomers	Different core	Very different	No relevant functional group
		ZINC08707999	0.797	0.689	0.904				×
		ZINC95831280	0.797	0.671	0.923				×
		ZINC40448330	0.798	0.663	0.932				×
		ZINC01516739	0.798	0.673	0.923				×
		ZINC98233994	0.799	0.658	0.939				×
		ZINC00050695	0.799	0.657	0.941				×
		ZINC01518212	0.800	0.654	0.946				×

Compound numbering	Structure	ZINC Identifier	Similarity	Shape	Electronic	Isomers and pseudoisomers	Different core	Very different	No relevant functional group
		ZINC00050716	0.801	0.659	0.942				×
		ZINC39241206	0.806	0.616	0.996				×
		ZINC01626613	0.808	0.718	0.898	×			
		ZINC03844886	0.810	0.699	0.921	×			
2		ZINC08752894	0.812	0.706	0.919				×
		ZINC34543816	0.818	0.691	0.945	×			
		ZINC02495043	0.820	0.693	0.946				×

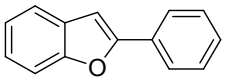
Compound numbering	Structure	ZINC Identifier	Similarity	Shape	Electronic	Isomers and pseudoisomers	Different core	Very different	No relevant functional group
		ZINC33978742	0.820	0.672	0.968	×			
		ZINC37632465	0.821	0.698	0.944	×			
		ZINC35325033	0.822	0.699	0.945	×			
		ZINC89203406	0.823	0.701	0.945	×			
		ZINC01708901	0.825	0.703	0.946	×			
		ZINC01663940	0.826	0.708	0.945	×			
		ZINC01518159	0.828	0.713	0.944				×
		ZINC12356961	0.835	0.725	0.944	×			

Compound numbering	Structure	ZINC Identifier	Similarity	Shape	Electronic	Isomers and pseudoisomers	Different core	Very different	No relevant functional group
		ZINC000154770	0.874	0.752	0.996	×			

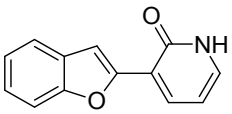
The 14 different cores identified during the similarity search



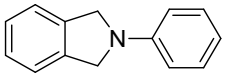
11 Occurrences
Benzimidazole



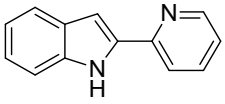
3 Occurrences
2-Phenylbenzofuran



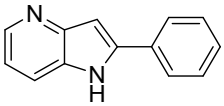
2 Occurrences
2-(3-(2-Pyridonyl))benzofuran



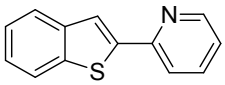
1 Occurrence
2-Phenylisoindoline



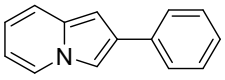
1 Occurrence
2-(2-Pyridyl)indole



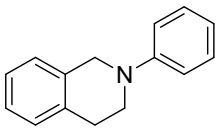
1 Occurrence
2-Phenyl-4-azaindole



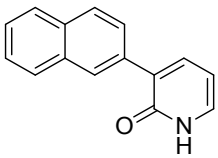
1 Occurrence
2-(2-Pyridyl)benzothiophene



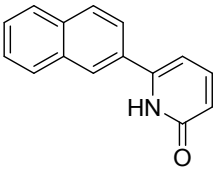
1 Occurrence
2-Phenylindolizine



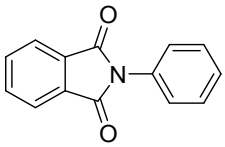
1 Occurrence
2-Phenyltetrahydroisoquinoline



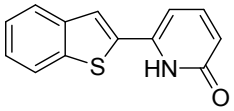
1 Occurrence
2-(3-(2-Pyridonyl))naphthalene



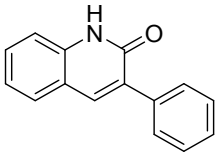
1 Occurrence
2-(6-(2-Pyridonyl))naphthalene



1 Occurrence
2-Phenylphthalimide



1 Occurrence
2-(6-(2-Pyridonyl))benzothiophene



1 Occurrence
3-Phenyl-2(1H)-quinolinone

Time-course study

To investigate the possibility of the *O*-protected heptanoyl analogue being used as a prodrug for **1**, time course assays for both **1** and its *O*-heptanoyl analogue **27** were carried out using the MTS assay. The results from these assays, which were carried out on the primary glioblastoma culture BTNW911 and the short-term human glioma cell line IN859, are shown in Figure 1. This data shows that **1** has rapid initial activity against both cell lines, whereas **27** reduced cell viability much more gradually. Importantly, both compounds tend towards the same activity over time. This would agree with the hypothesis that the heptanoyl group can be cleaved off to produce **1**, as the activity of compound **27** is equal to that of compound **1**, yet it takes time for the enzymatic cleavage to occur.

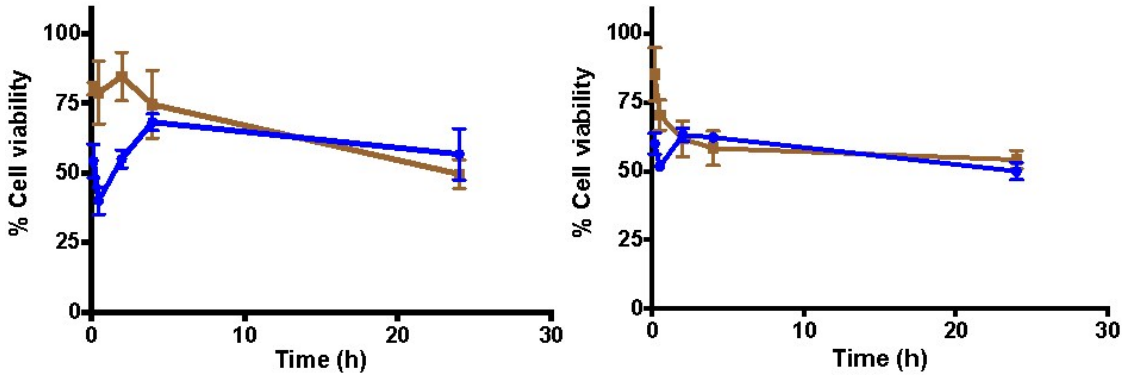
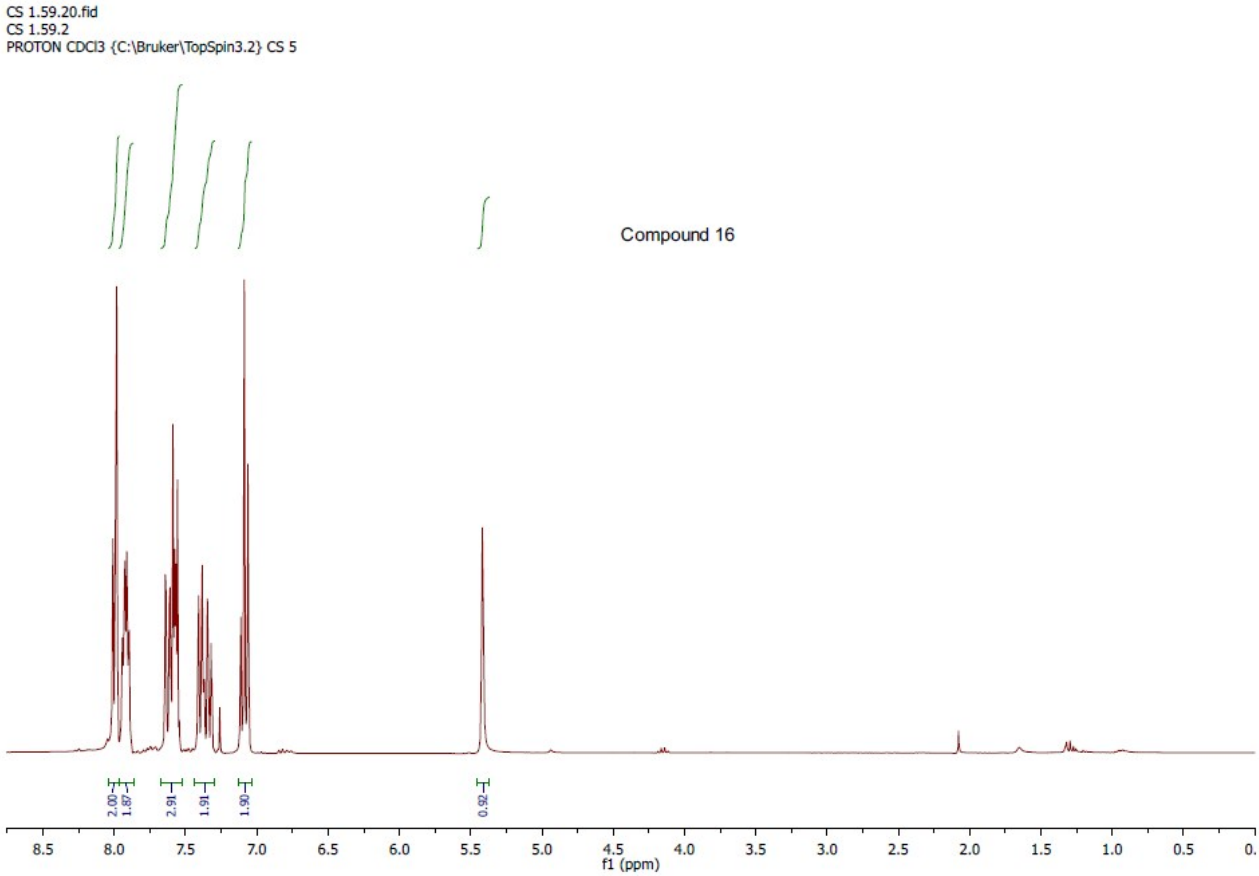
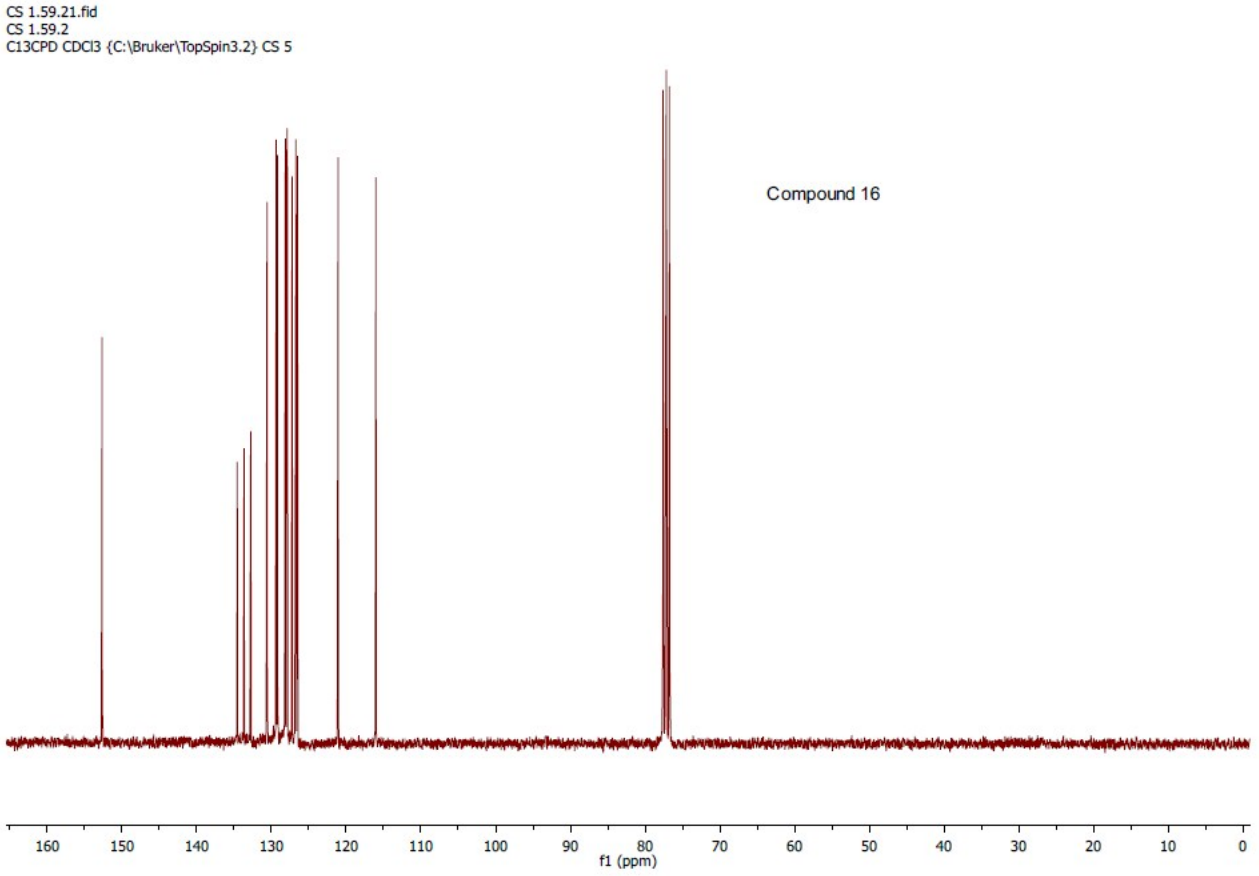
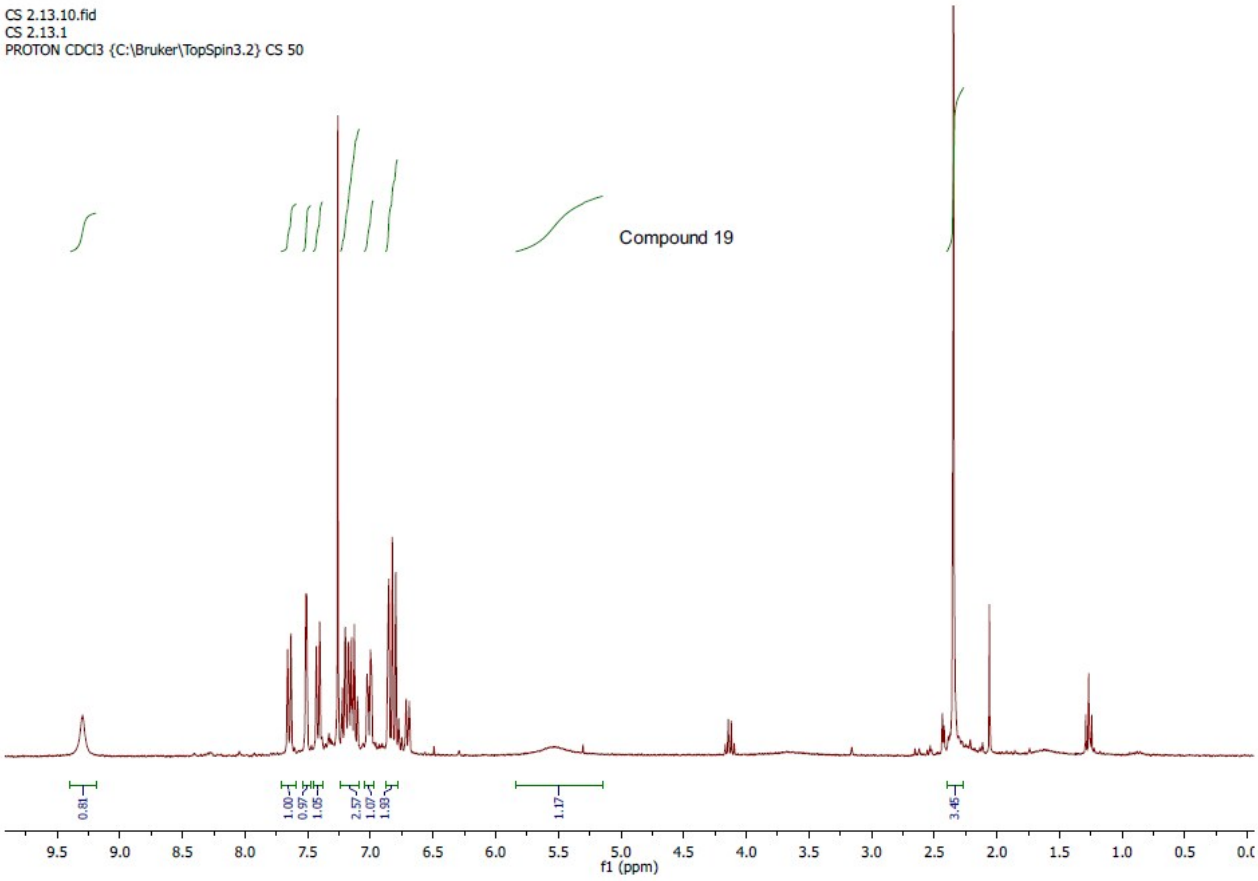


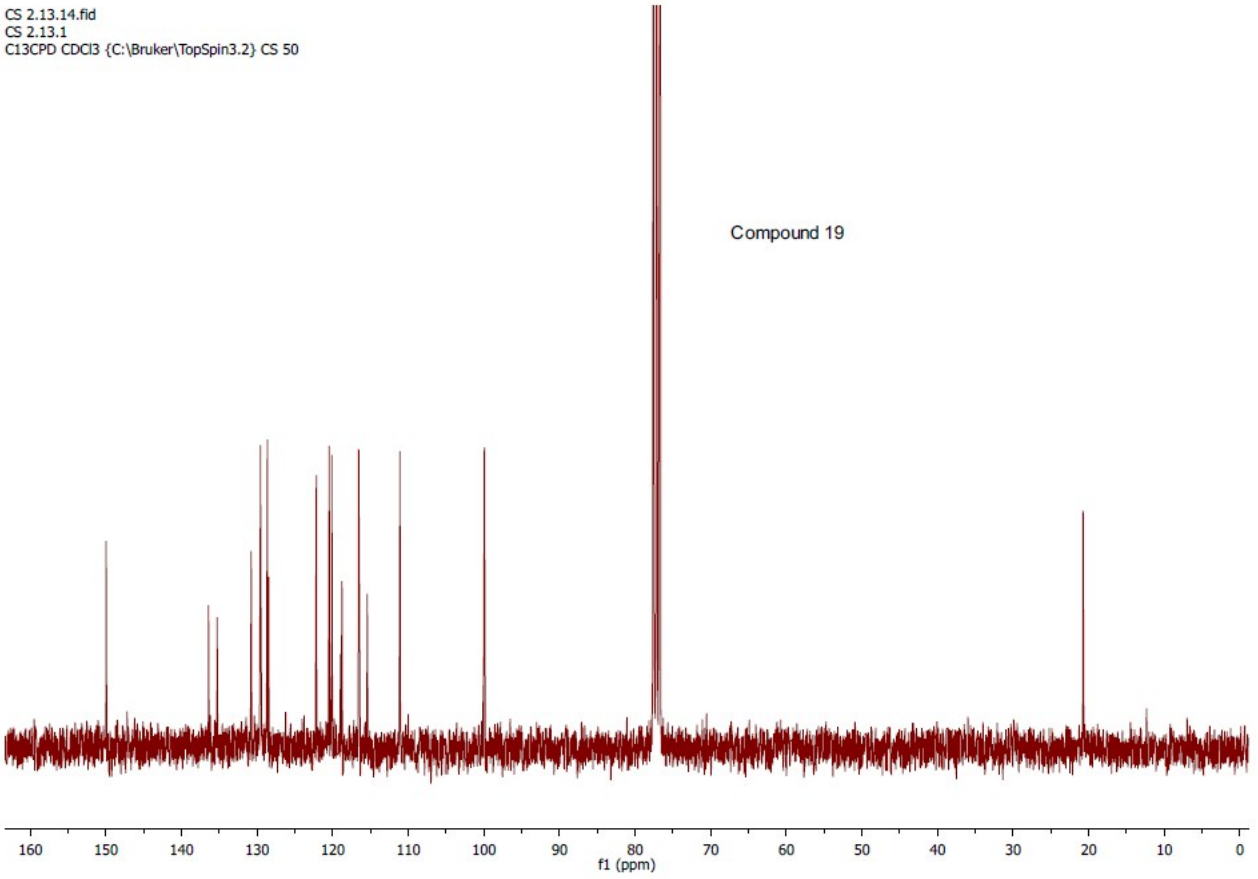
*Figure 1 - Time course graphs comparing the activity of **1** (blue) against compound **27** (brown) against BTNW911 (left) and IN859 (right) cell cultures.*

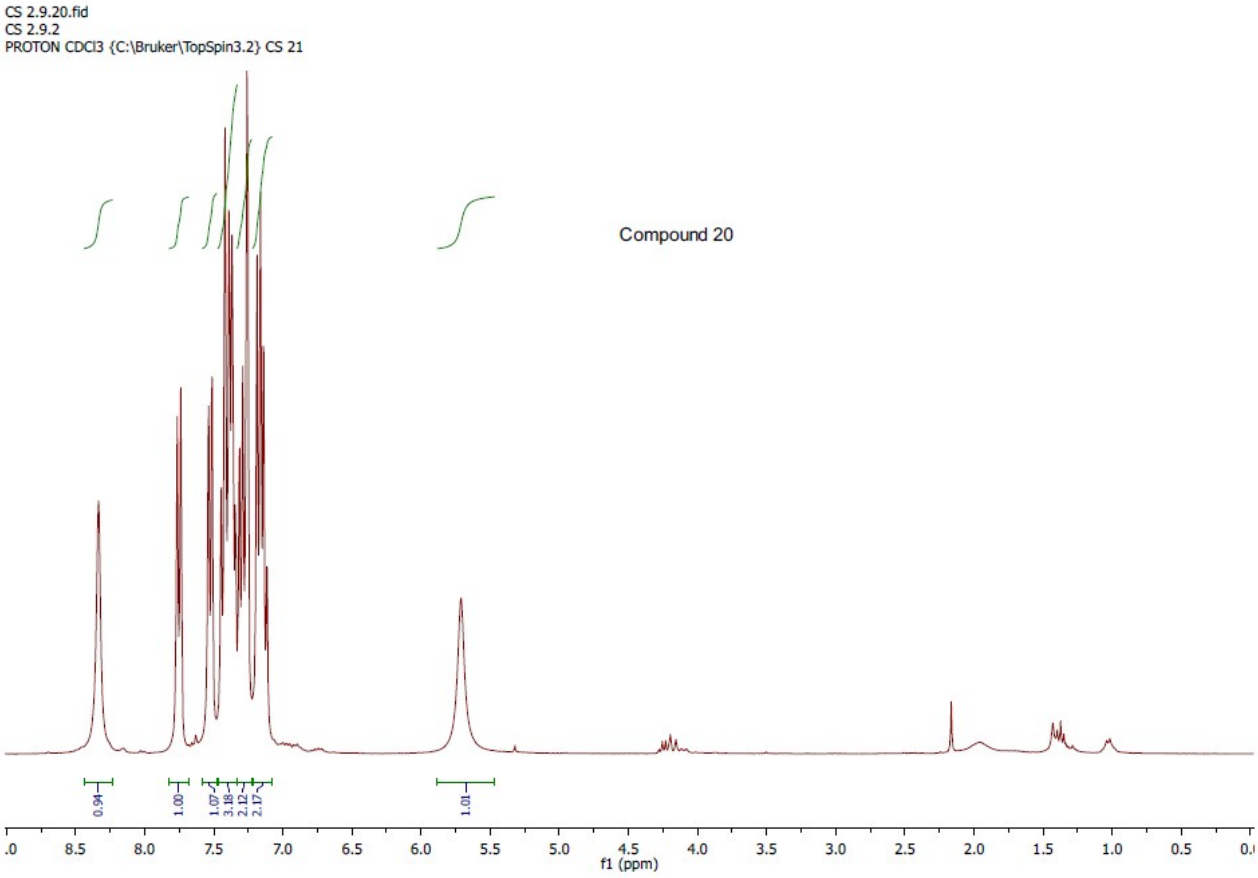
NMR Spectra

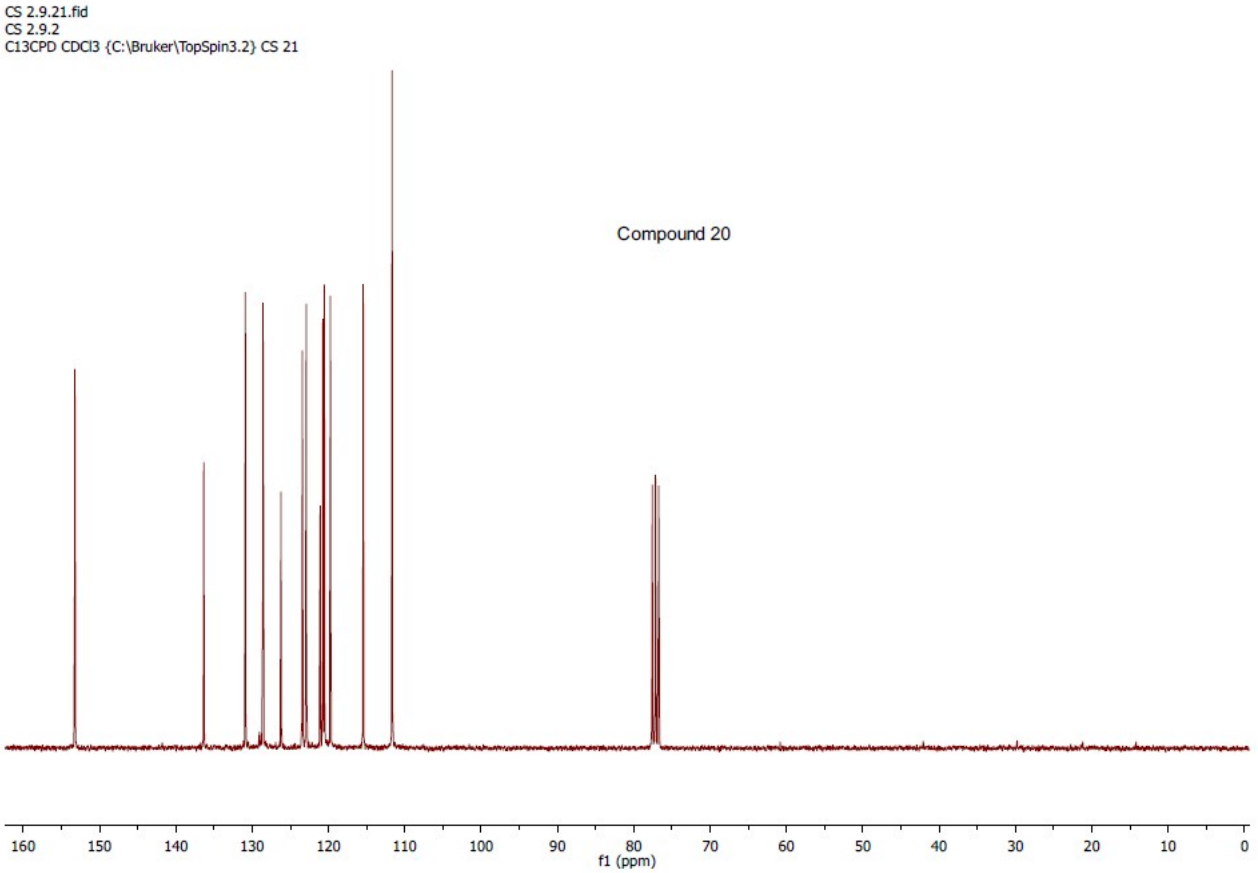

CS 1.59.20.fid
CS 1.59.2
PROTON CDCl3 {C:\Bruker\TopSpin3.2} CS 5
Compound 16
2.00
1.87
2.91
1.91
1.90
0.92
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


CS 1.59.21.fid
CS 1.59.2
C13CPD CDCl3 {C:\Bruker\TopSpin3.2} CS 5
Compound 16
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

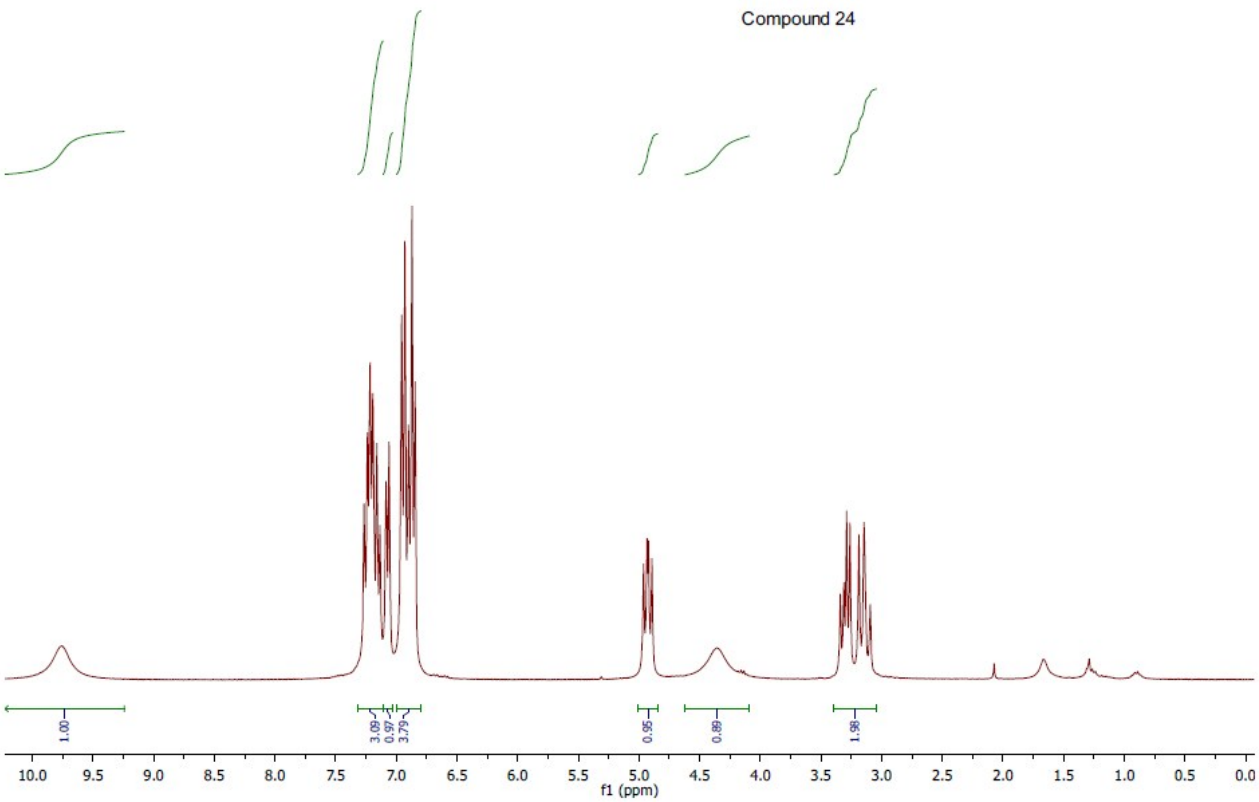

CS 2.13.10.fid
CS 2.13.1
PROTON CDCl3 {C:\Bruker\TopSpin3.2} CS 50
Compound 19
0.81
1.00
0.97
1.05
2.57
1.07
1.93
1.17
3.46
f1 (ppm)


CS 2.13.14.fid
CS 2.13.1
C13CPD CDCl3 {C:\Bruker\TopSpin3.2} CS 50
Compound 19
f1 (ppm)

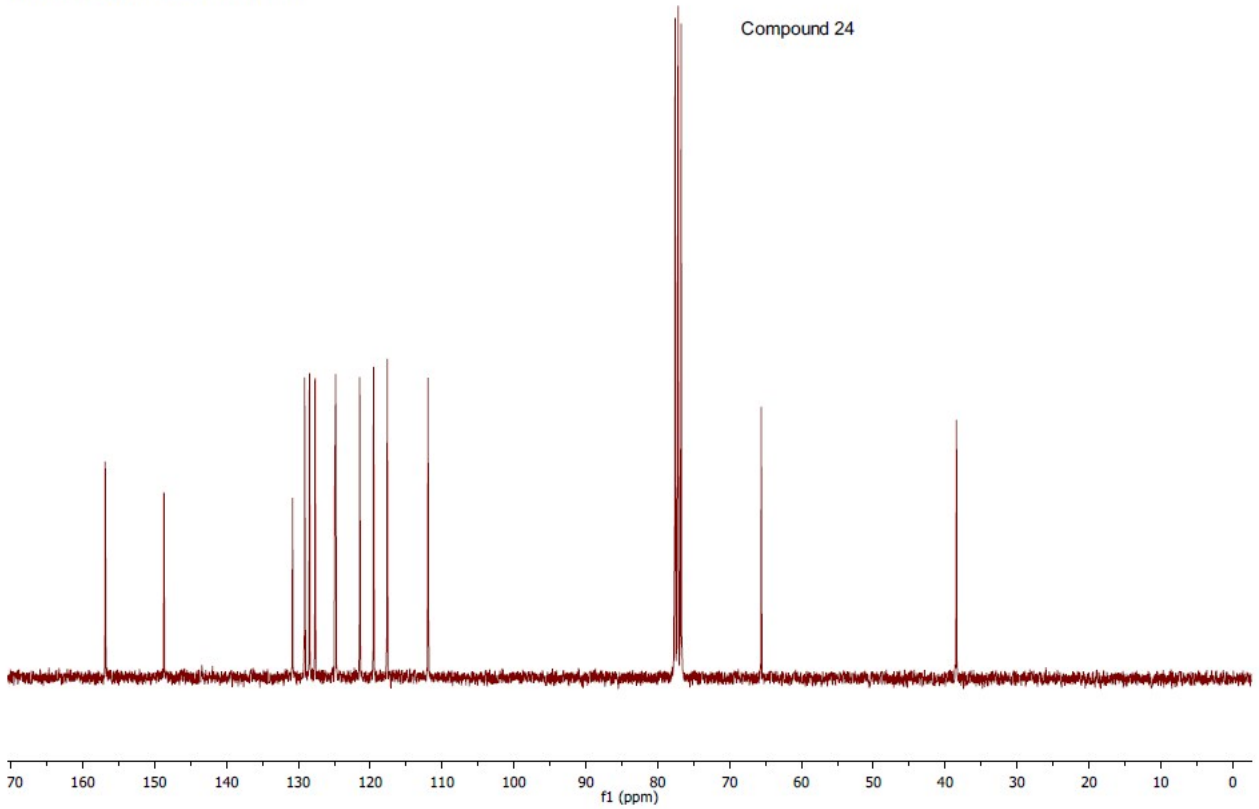

CS 2.9.20.fid
CS 2.9.2
PROTON CDCl3 {C:\Bruker\TopSpin3.2} CS 21
Compound 20
0.94
1.00
1.07
3.18
2.12
2.17
1.01
f1 (ppm)

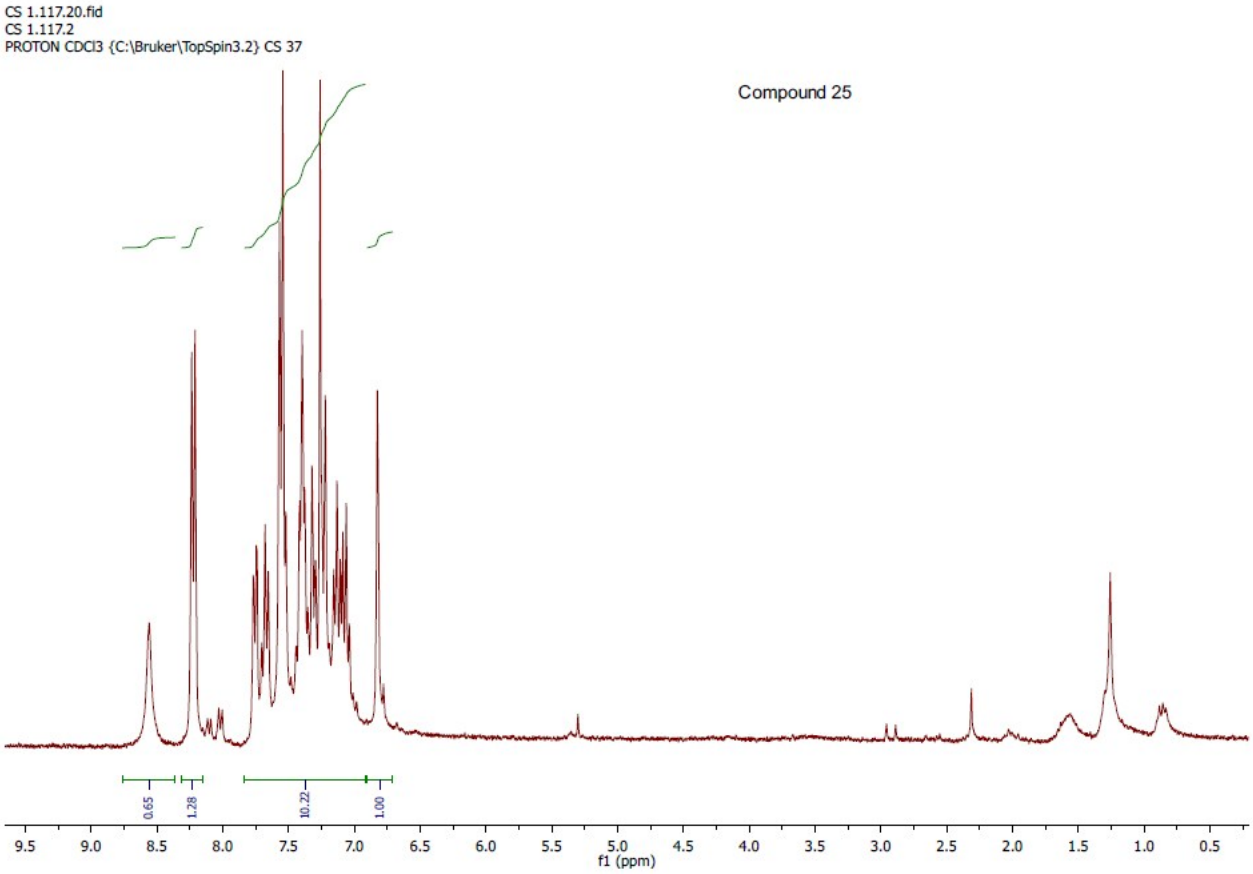

CS 2.9.21.fid
CS 2.9.2
C13CPD CDCl3 {C:\Bruker\TopSpin3.2} CS 21
Compound 20
f1 (ppm)

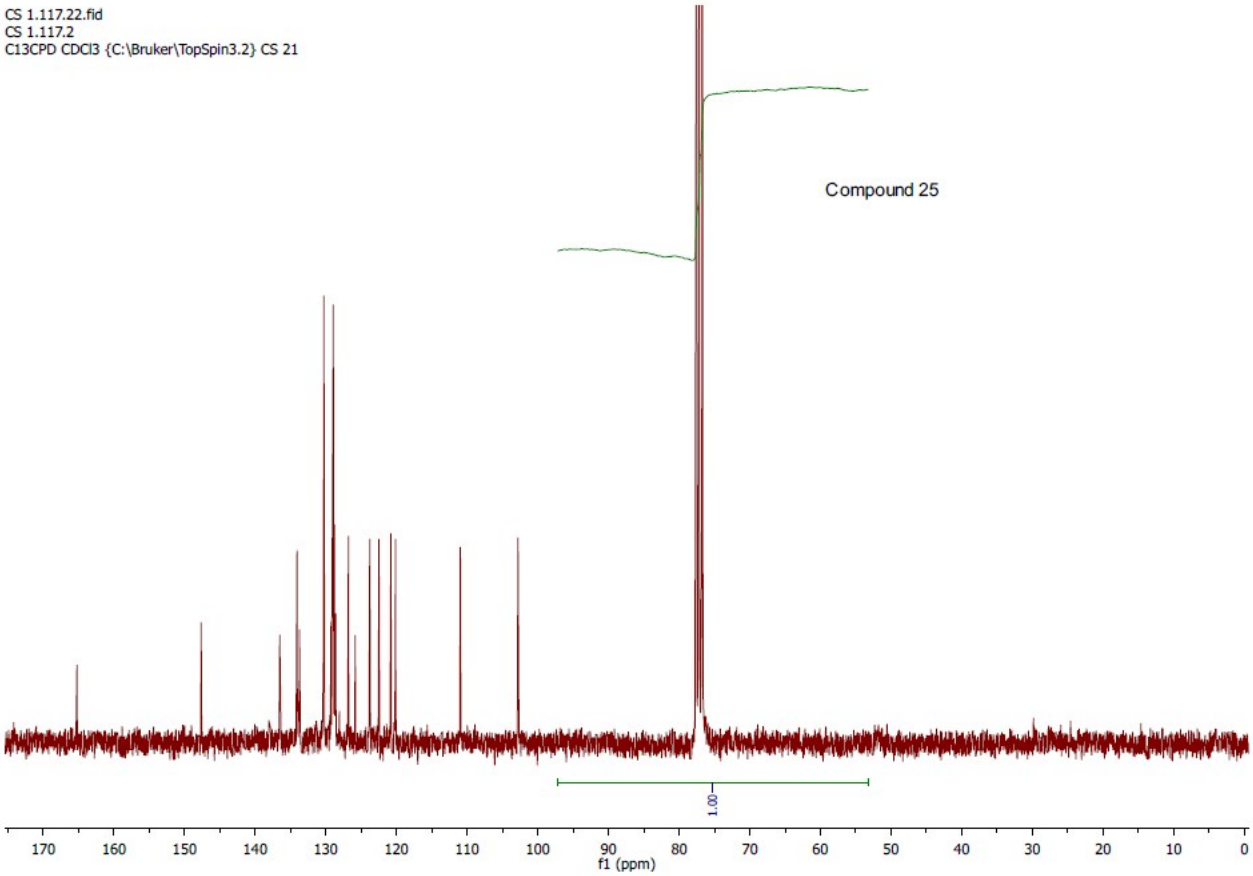
CS 2.12.20.fid
CS 2.12.2
PROTON CDCl3 {C:\Bruker\TopSpin3.2} CS 17

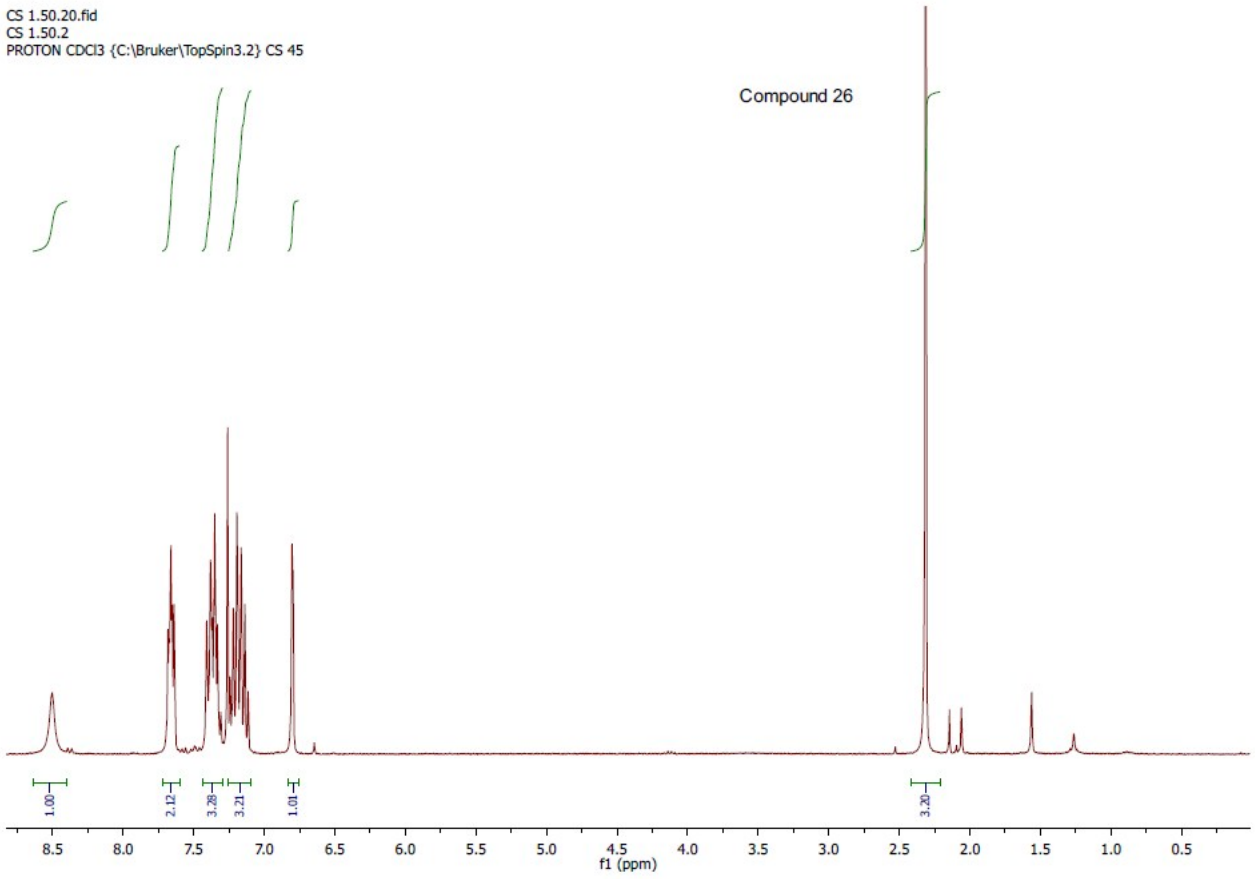


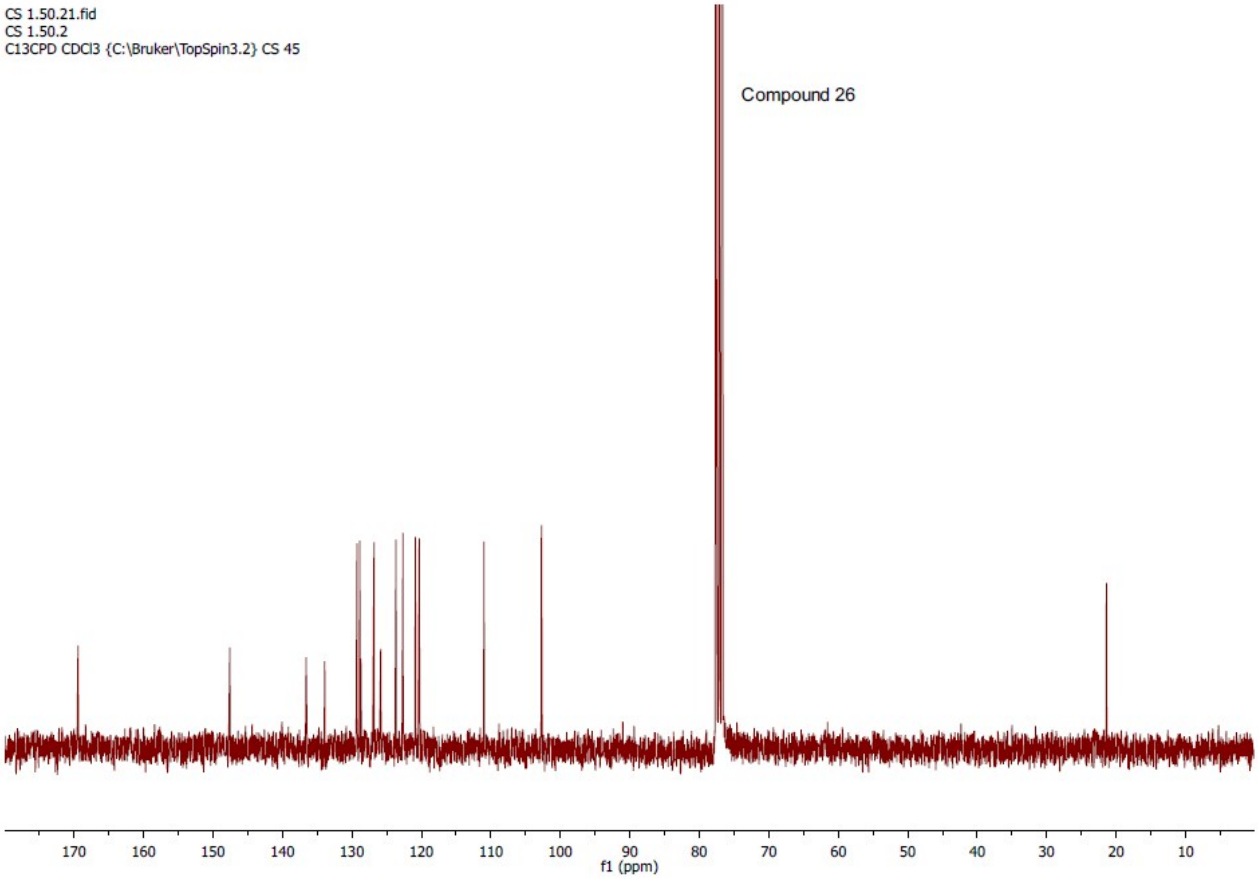
CS 2.12.21.fid
CS 2.12.2
C13CPD CDCl3 {C:\Bruker\TopSpin3.2} CS 17

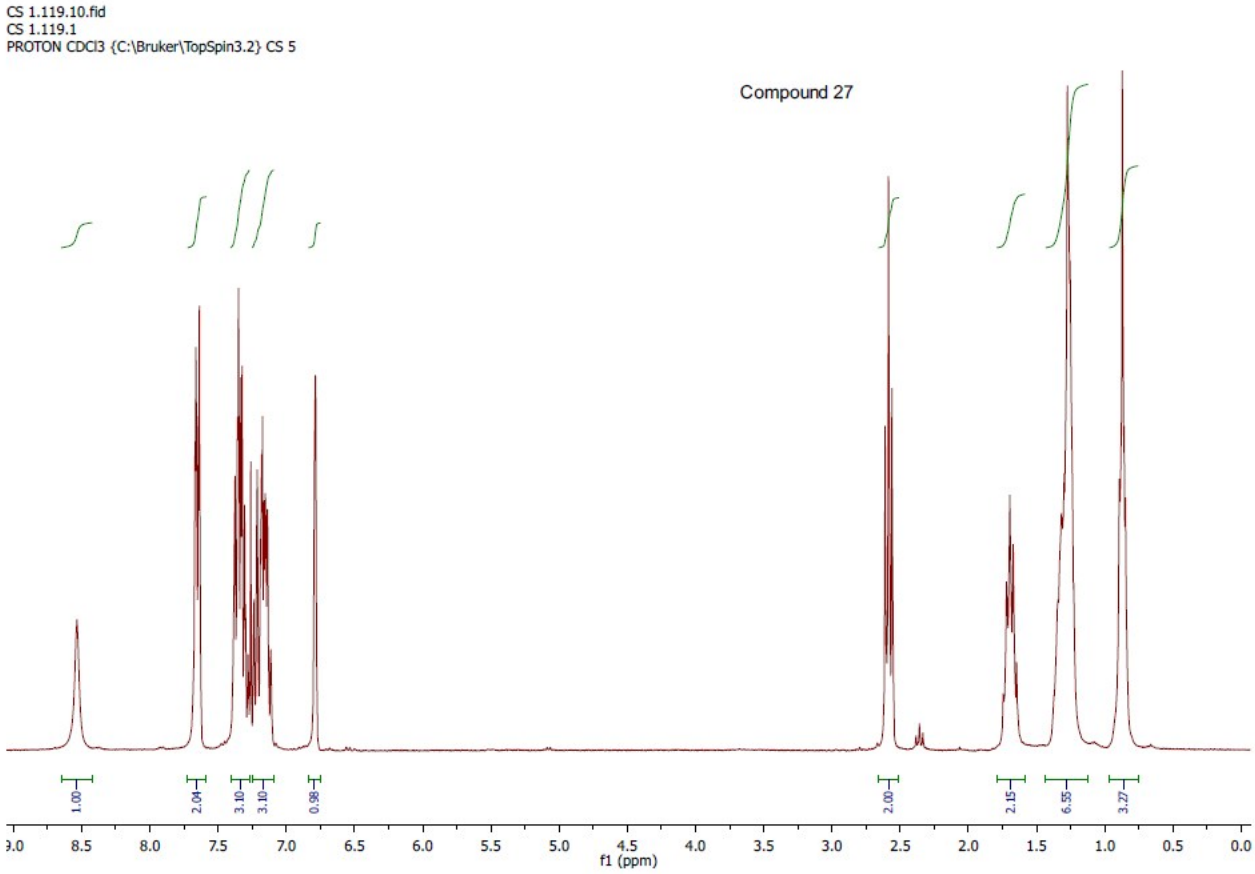



CS 1.117.20.fid
CS 1.117.2
PROTON CDCl3 {C:\Bruker\TopSpin3.2} CS 37
Compound 25
0.65
1.28
10.22
1.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


CS 1.117.22.fid
CS 1.117.2
C13CPD CDCl3 {C:\Bruker\TopSpin3.2} CS 21
Compound 25
1.00
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


CS 1.50.20.fid
CS 1.50.2
PROTON CDCl3 {C:\Bruker\TopSpin3.2} CS 45
Compound 26
1.00
2.12
3.28
3.21
1.01
3.20
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


CS 1.50.21.fid
CS 1.50.2
C13CPD CDCl3 {C:\Bruker\TopSpin3.2} CS 45
Compound 26
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


CS 1.119.10.fid
CS 1.119.1
PROTON CDCl3 {C:\Bruker\TopSpin3.2} CS 5
Compound 27
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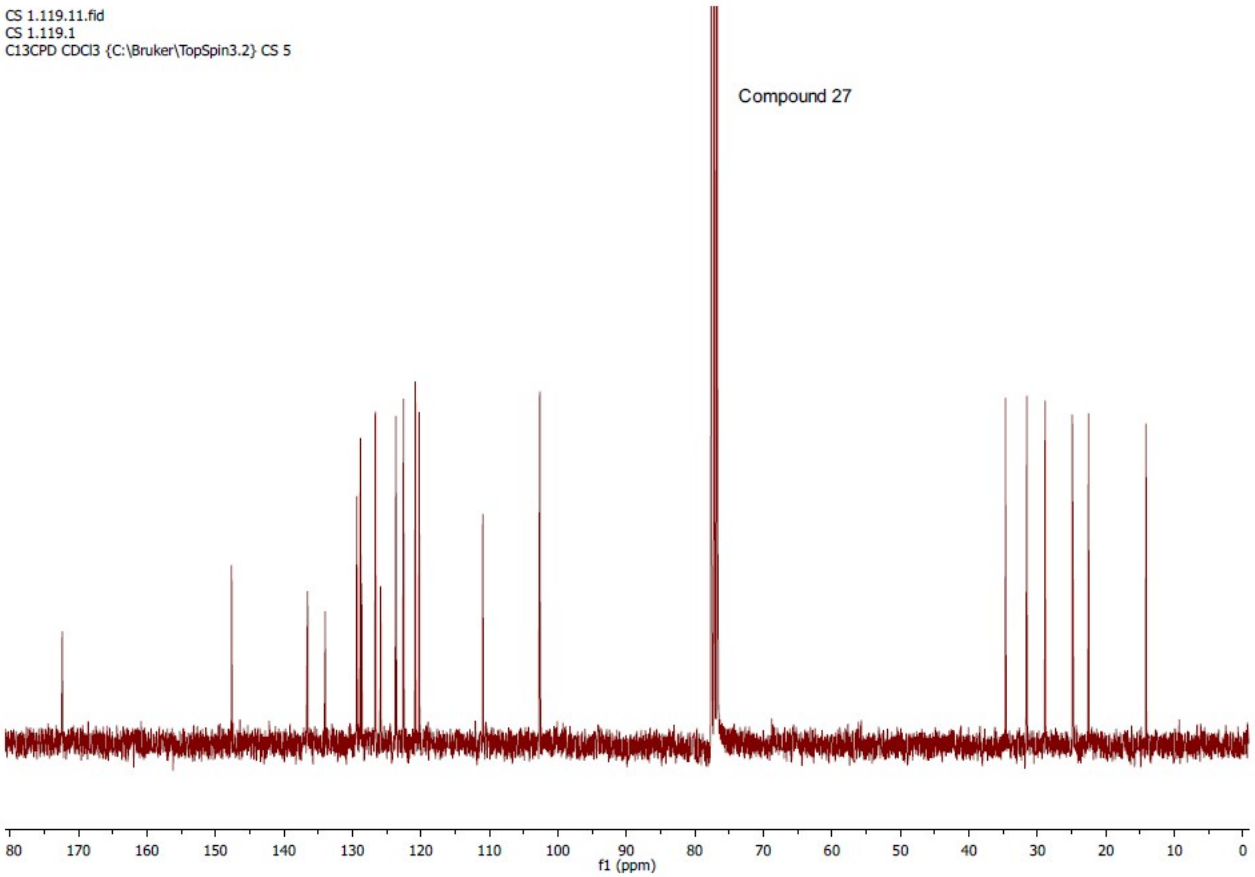
2.04
3.10
3.10
0.98
2.00
2.15
6.55
3.27
f1 (ppm)


CS 1.119.11.fid
CS 1.119.1
C13CPD CDCl3 {C:\Bruker\TopSpin3.2} CS 5
Compound 27
f1 (ppm)