

# Design, Synthesis and Biological Evaluation of Biphenylglyoxamide-based Small Molecular Antimicrobial Peptide Mimics as Antibacterial Agents

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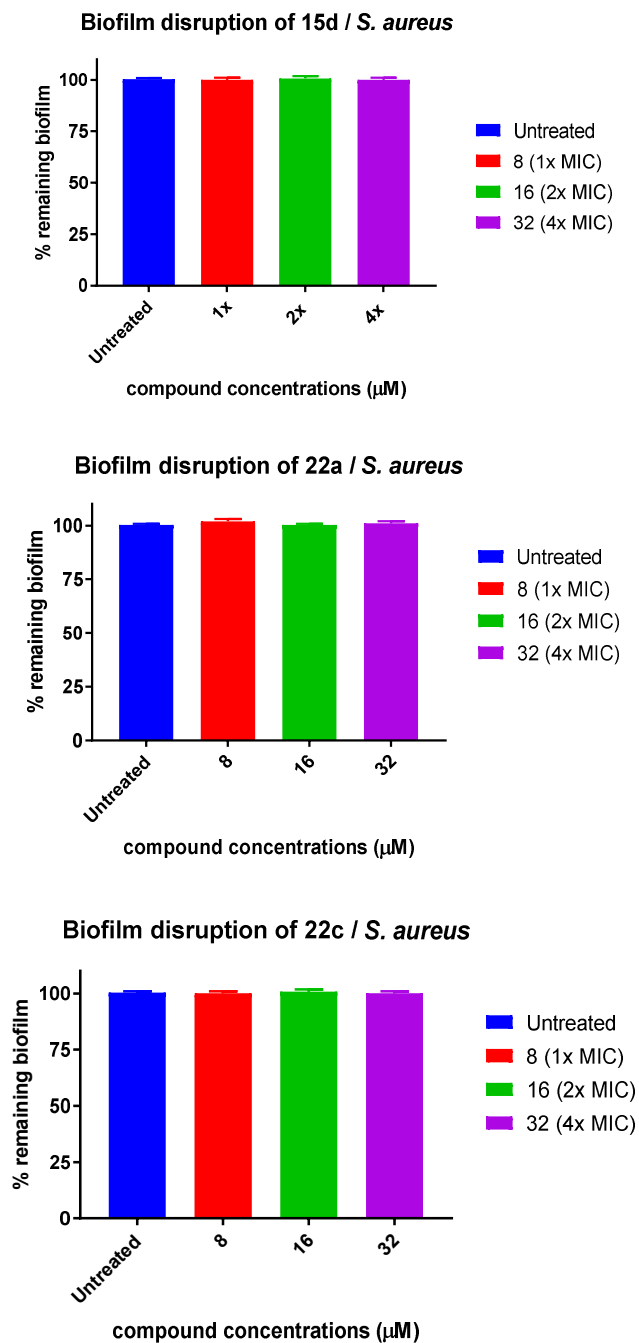
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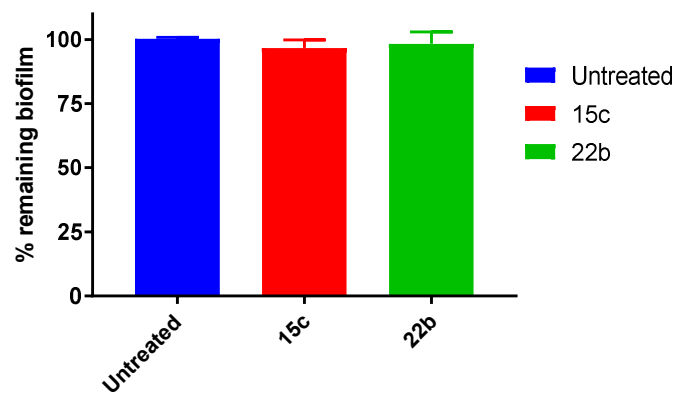
( <i>E</i> )-1- <i>tert</i> -Butyl- <i>N</i> -( <i>N'</i> -(( <i>tert</i> -butyloxidanyl)carbonyl)- <i>N</i> -(3-(2-(4-(octylsulfonamido)-[1,1'-biphenyl]-3-yl)-2-oxoacetamido)propyl)carbamimidoyl)-1-oxidanecarboxamide ( <b>21a</b> ).....	42
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## Supplementary figures for the antibiofilm activity of compounds 15c-15d, 22a-22d



**Figure S1.** Percentage of remaining *S. aureus* biofilms after 24 h treatment with compounds **15d** (top), **22a** (middle) or **22c** (bottom) at 1x, 2x and 4x of their MIC. Error bars represent the standard error of triplicates (n = 3).

### Biofilm disruption of 15c and 22b / *E. coli*

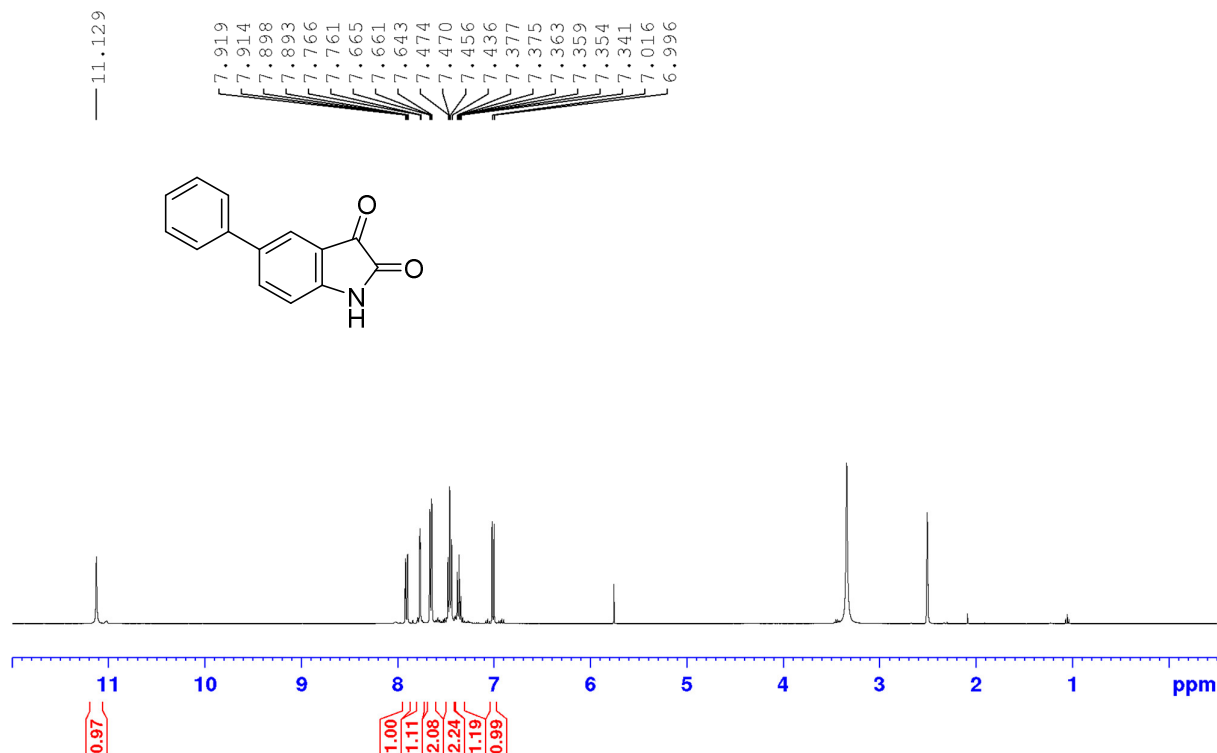


**Figure S2.** Percentage of remaining *E. coli* biofilms after 24 h treatment with compounds **15c** or **22c** at 4× of their MIC (64  $\mu$ M). Error bars represent the standard error of triplicates (n = 3).

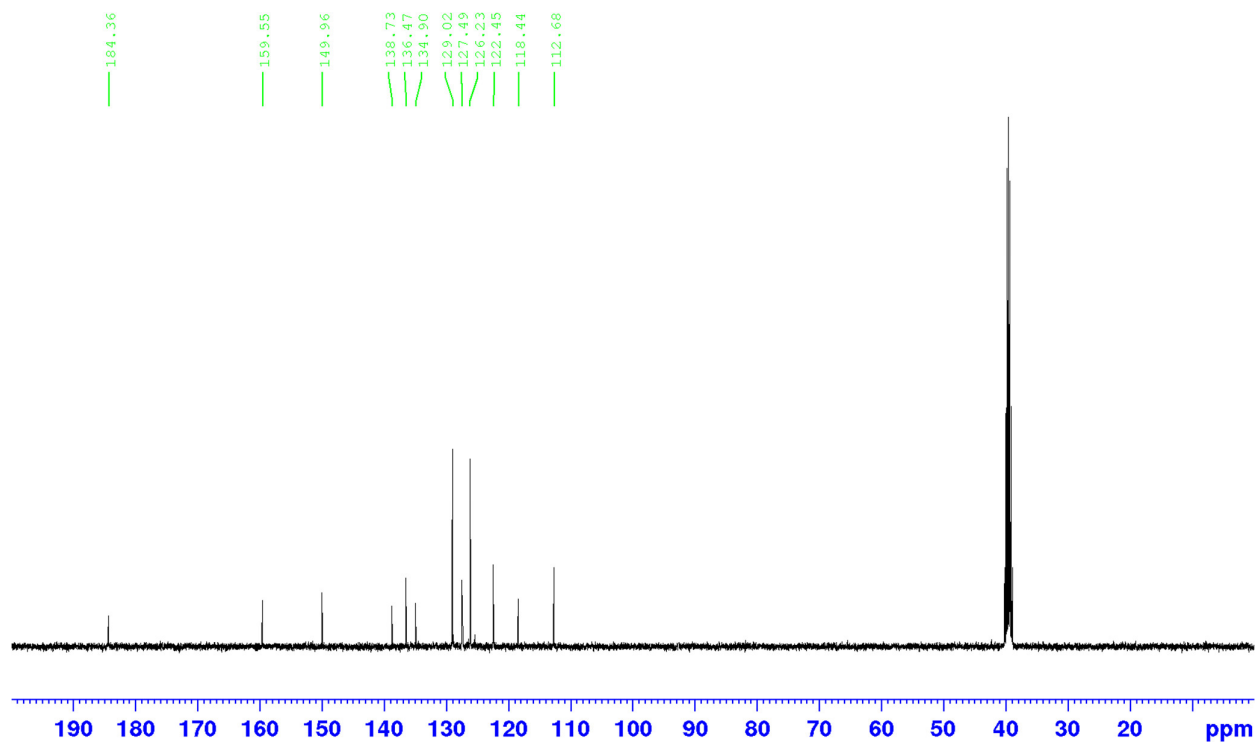
# $^1\text{H}$ NMR and $^{13}\text{C}$ NMR spectra of synthesized compounds

5-Phenylindoline-2,3-dione (**7a**)

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):

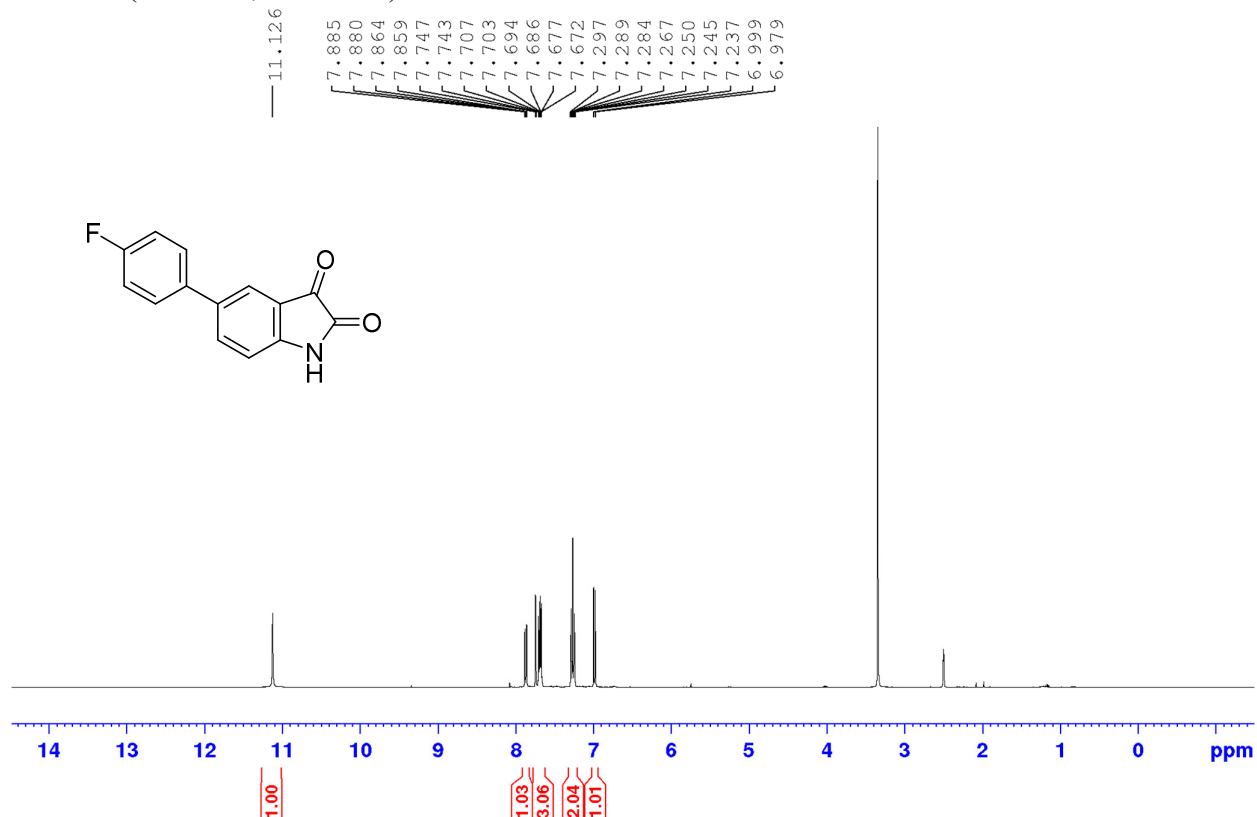


$^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):

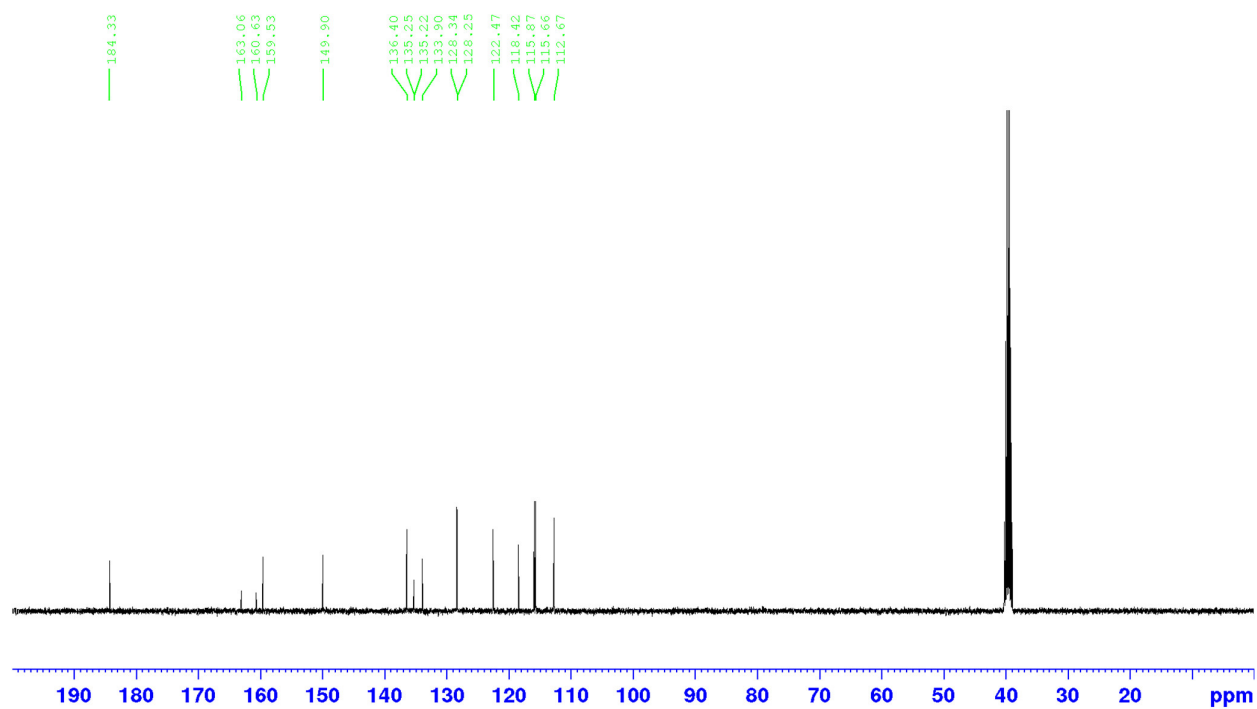


5-(4-Fluorophenyl)indoline-2,3-dione (**7b**)

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):

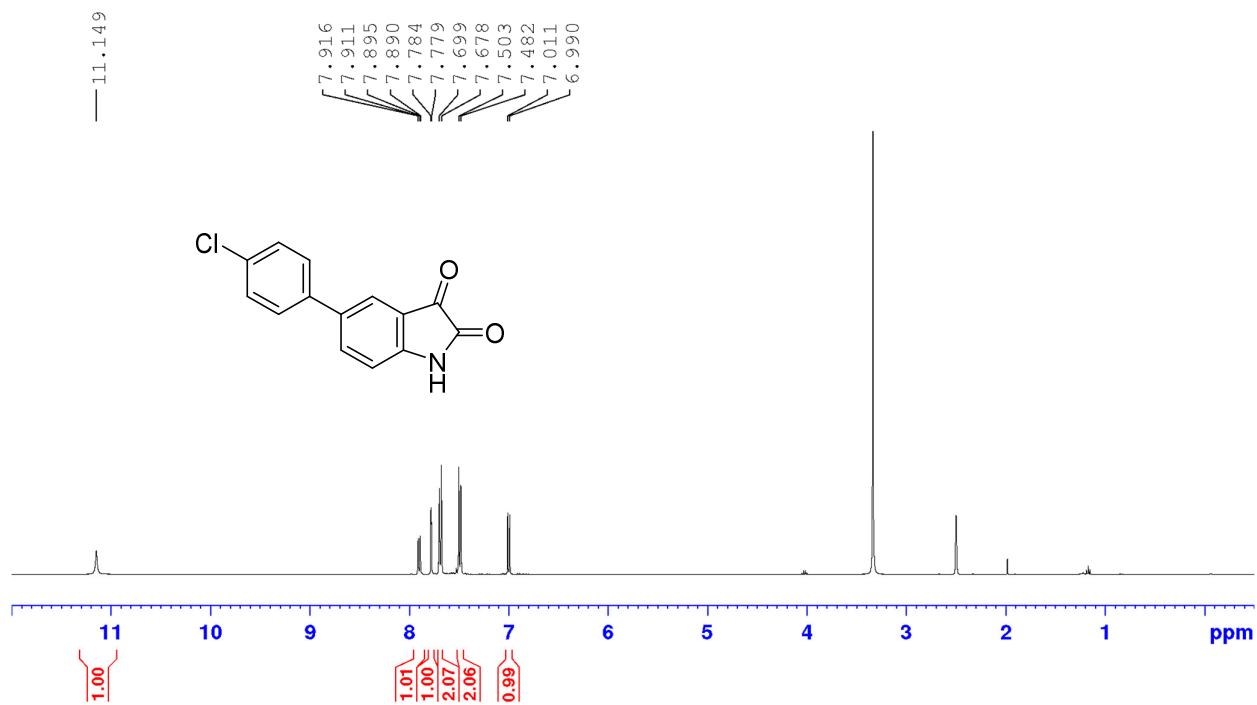


$^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):

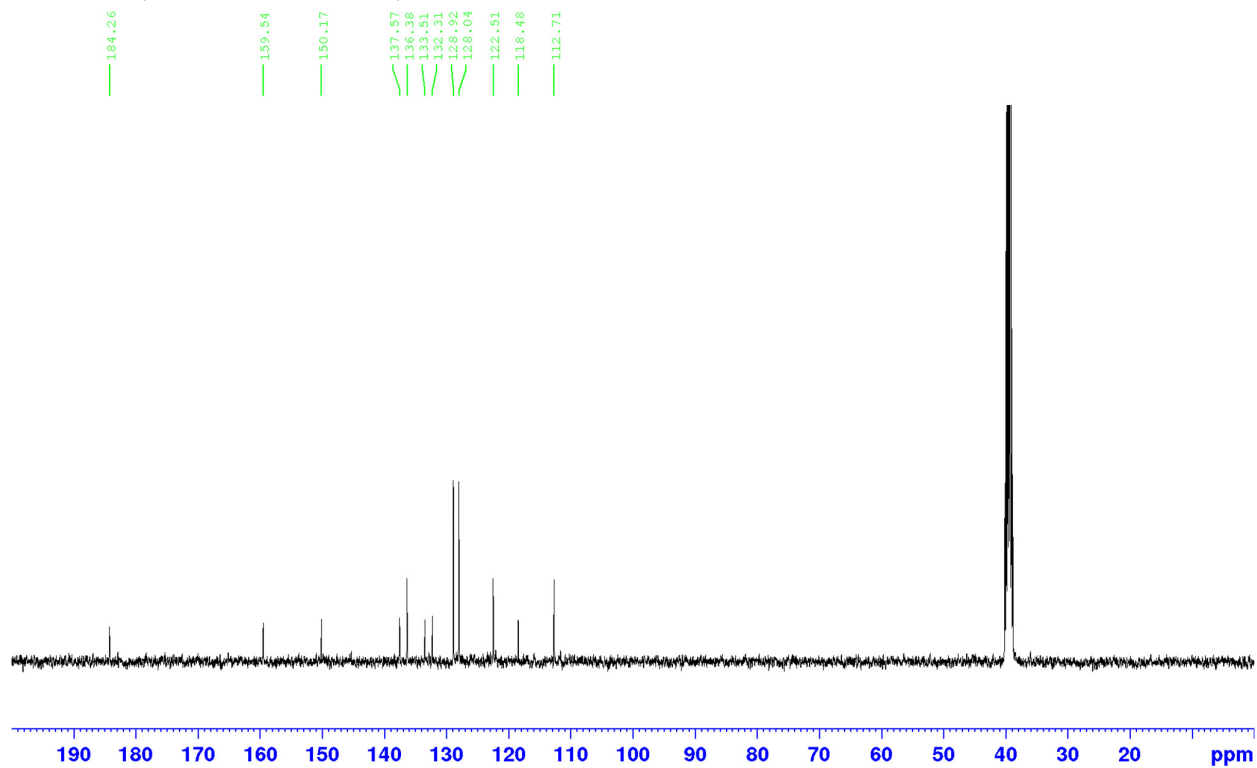


5-(4-Chlorophenyl)indoline-2,3-dione (**7c**)

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):



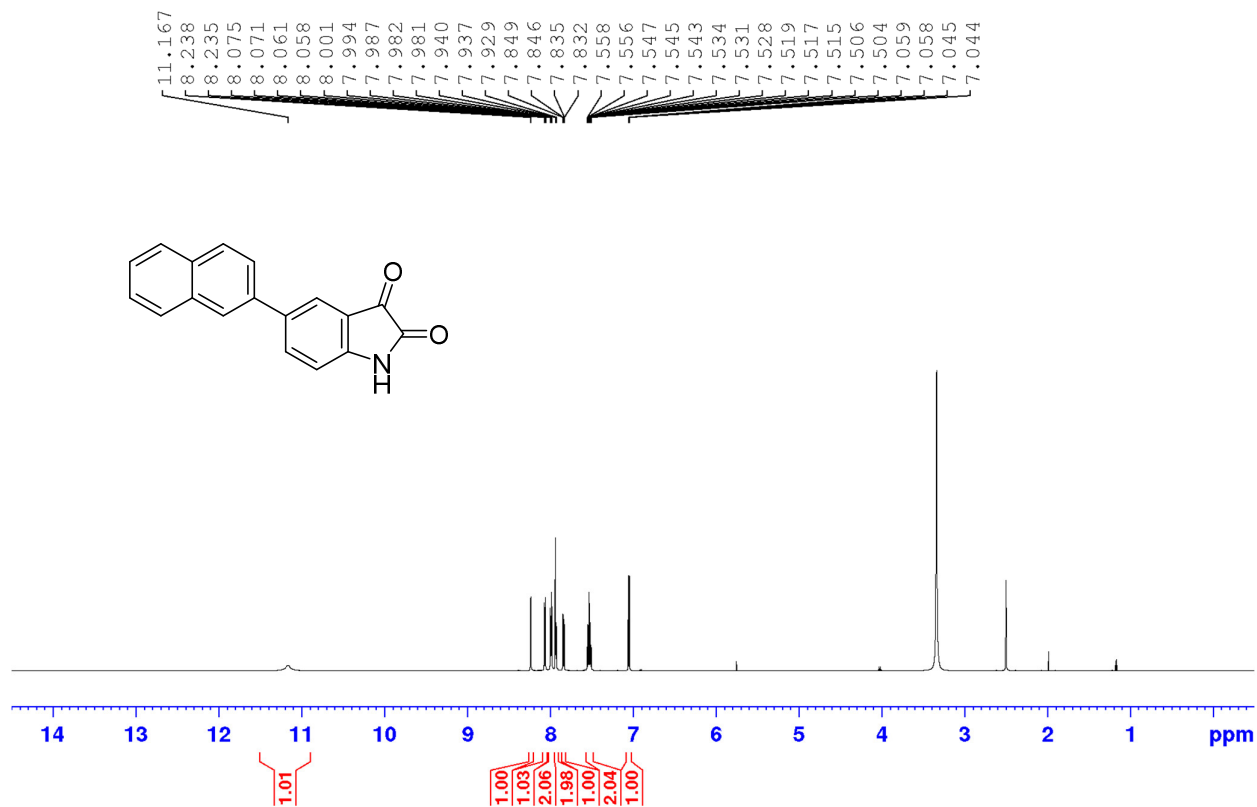
$^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):



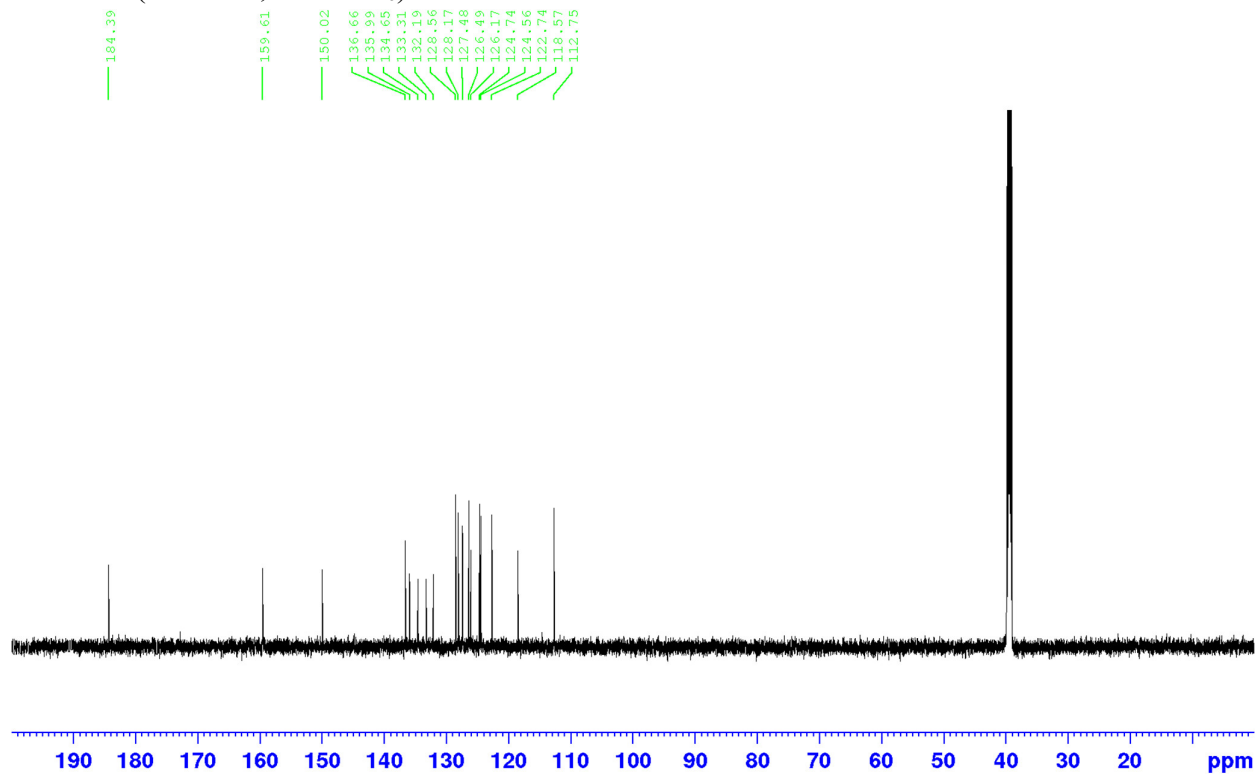


5-(Naphthalen-2-yl)indoline-2,3-dione (**7d**)

$^1\text{H}$  NMR (600 MHz,  $\text{DMSO-}d_6$ ):

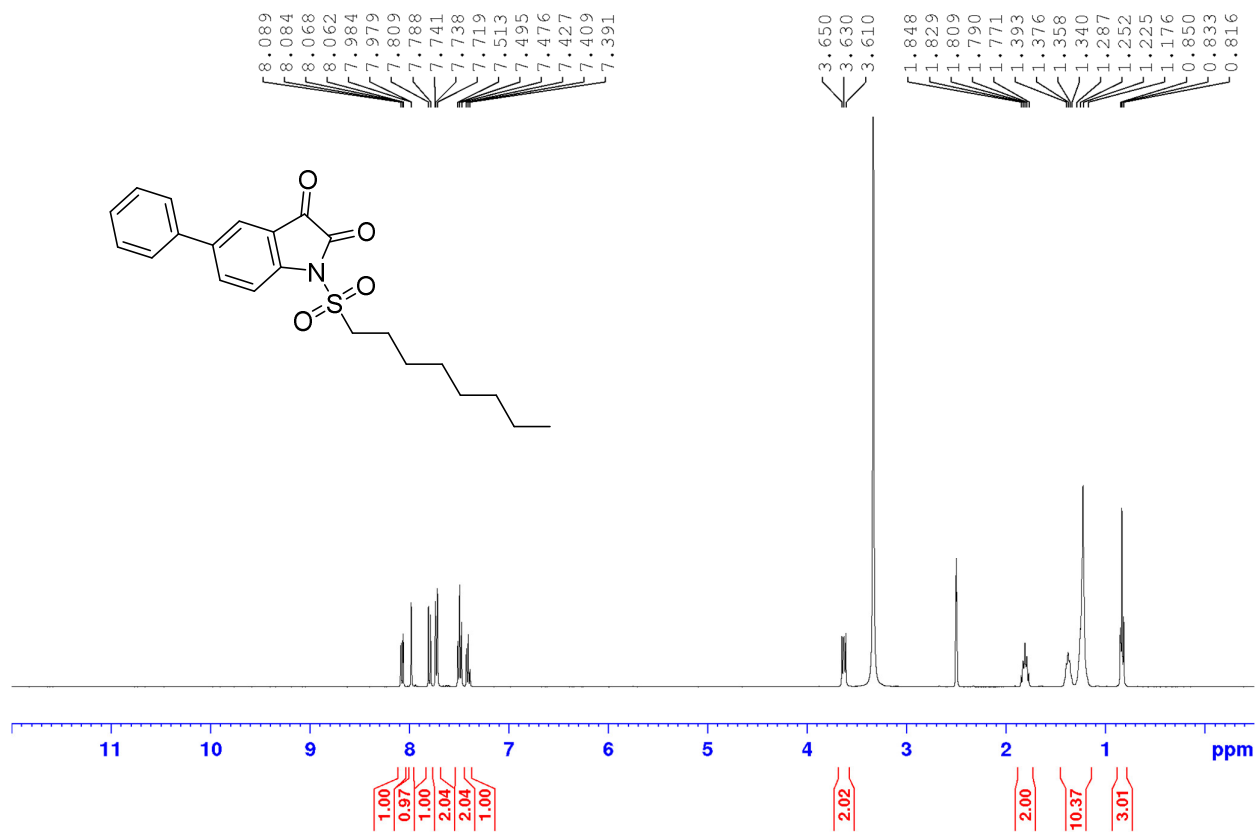


$^{13}\text{C}$  NMR (150 MHz,  $\text{DMSO-}d_6$ ):

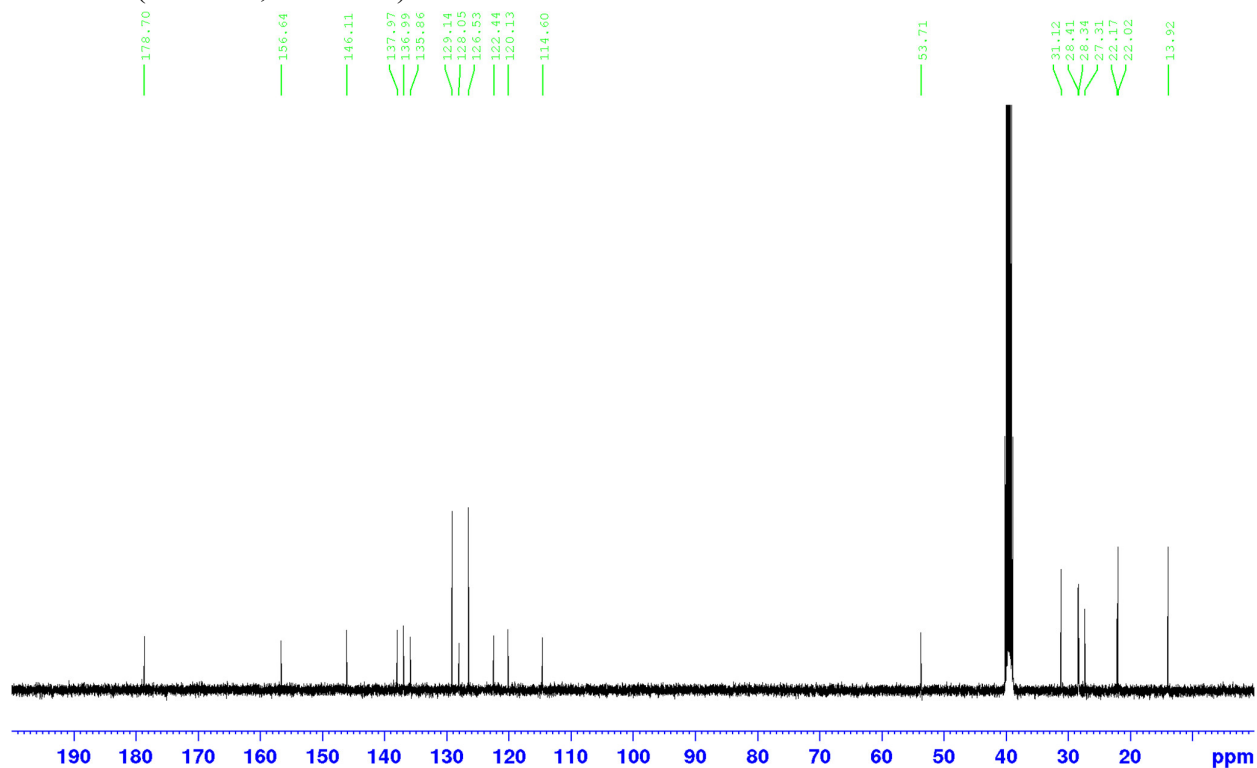


1-(Octylsulfonyl)-5-phenylindoline-2,3-dione (**8a**)

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):

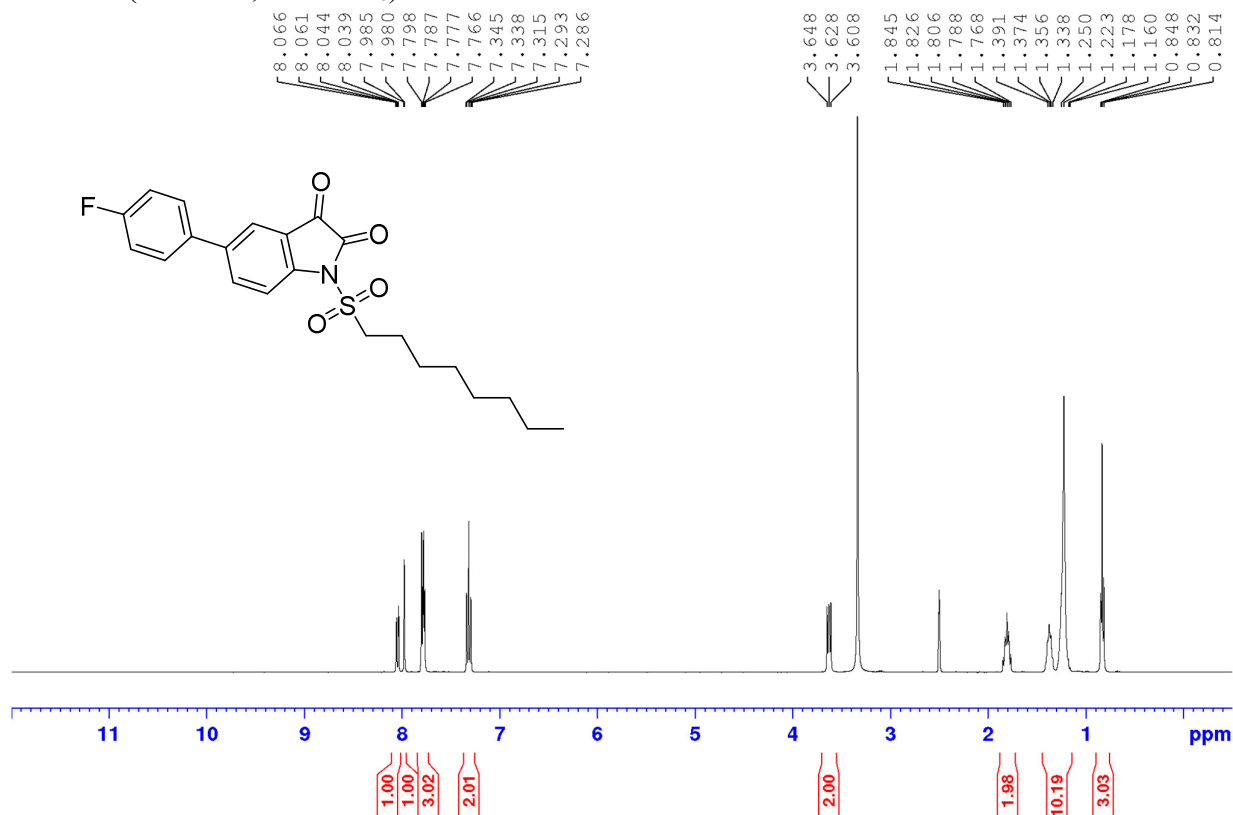


$^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):

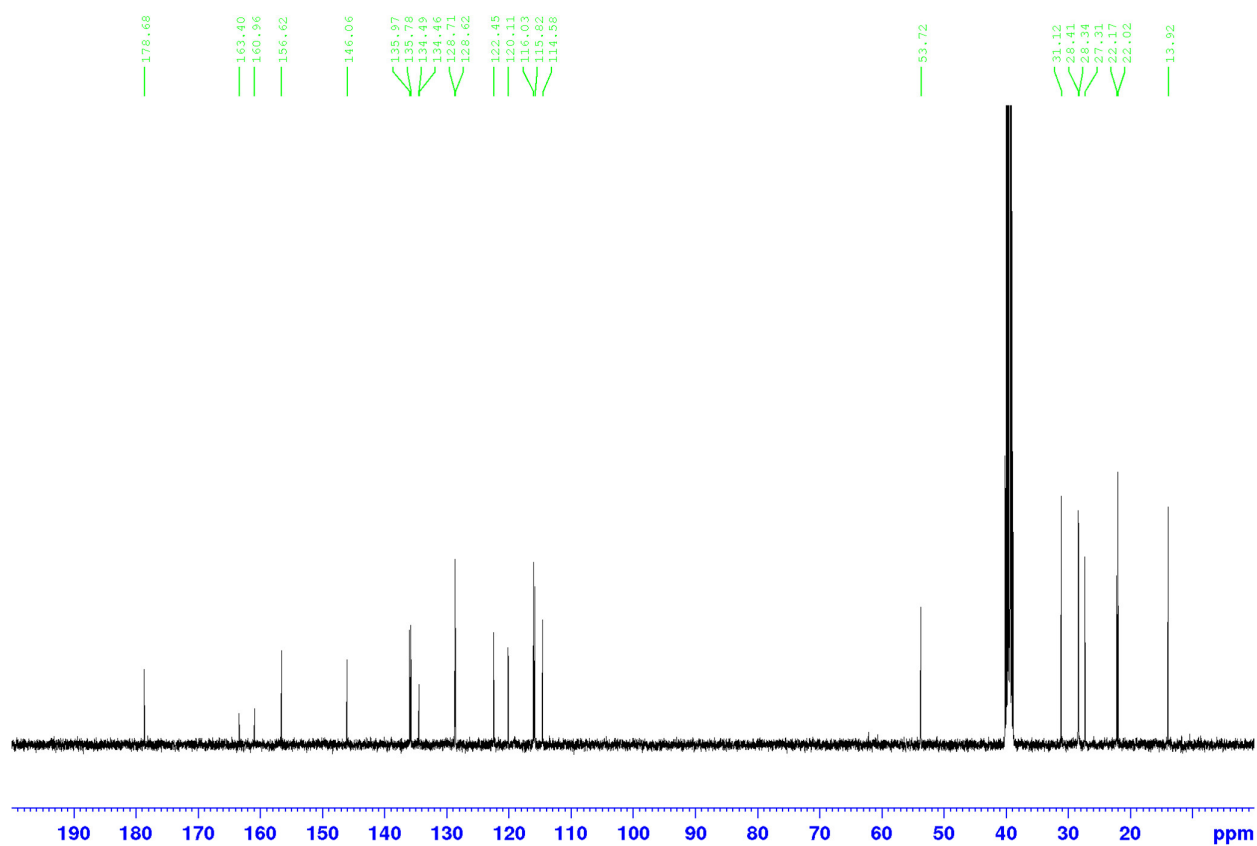


# 5-(4-Fluorophenyl)-1-(octylsulfonyl)indoline-2,3-dione (**8b**)

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):

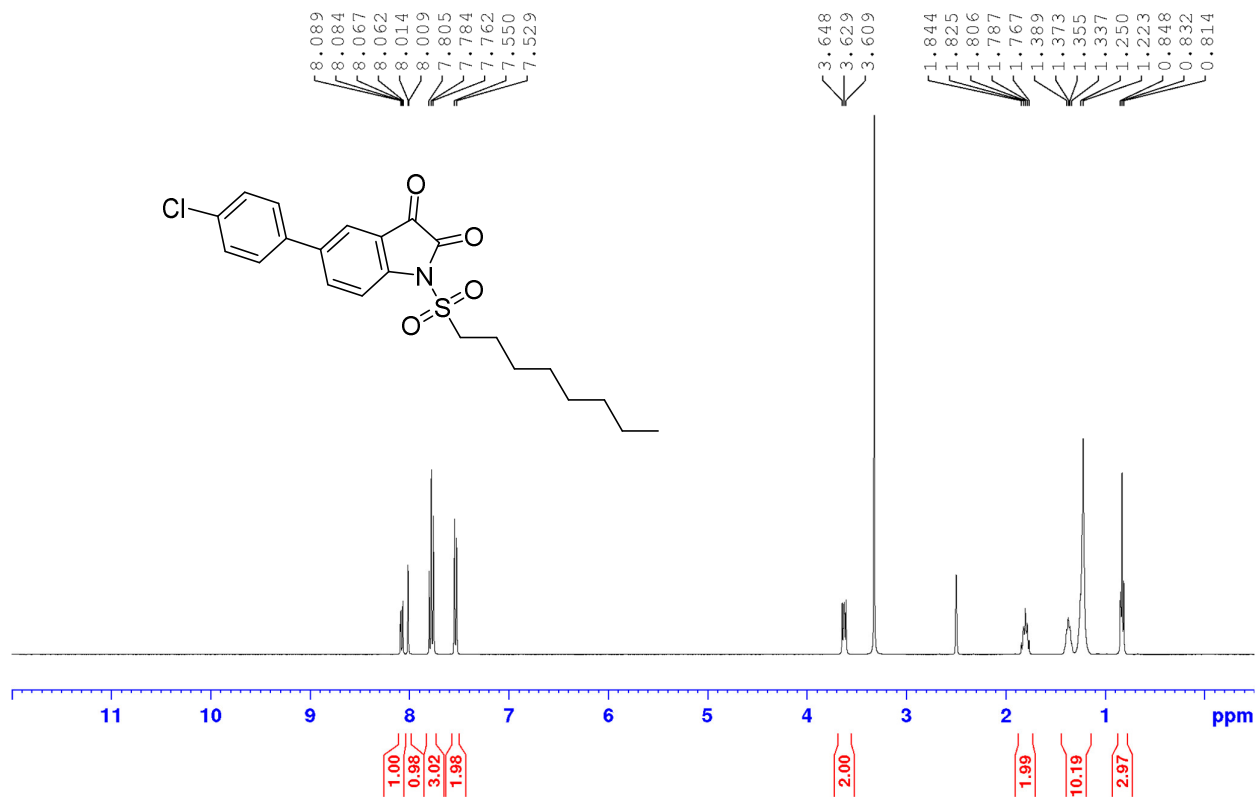


<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):

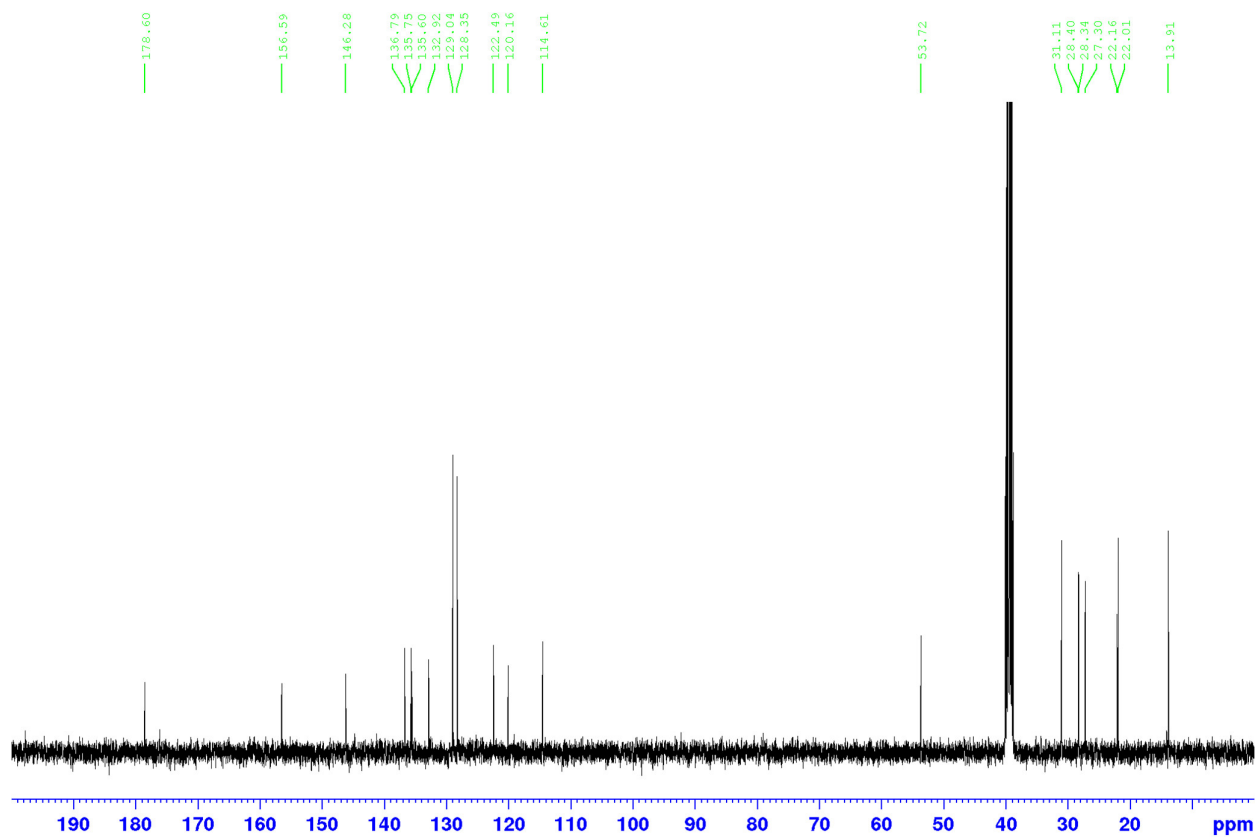


5-(4-Chlorophenyl)-1-(octylsulfonyl)indoline-2,3-dione (**8c**)

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):

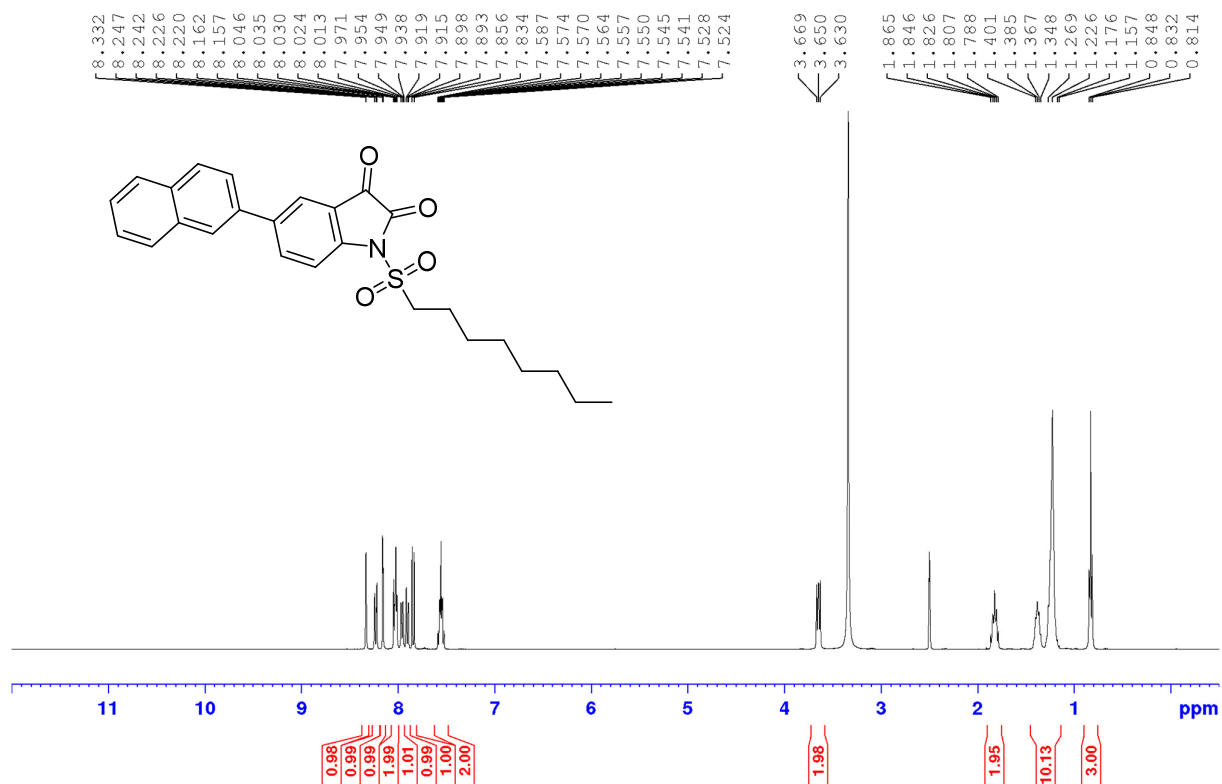


$^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ ):

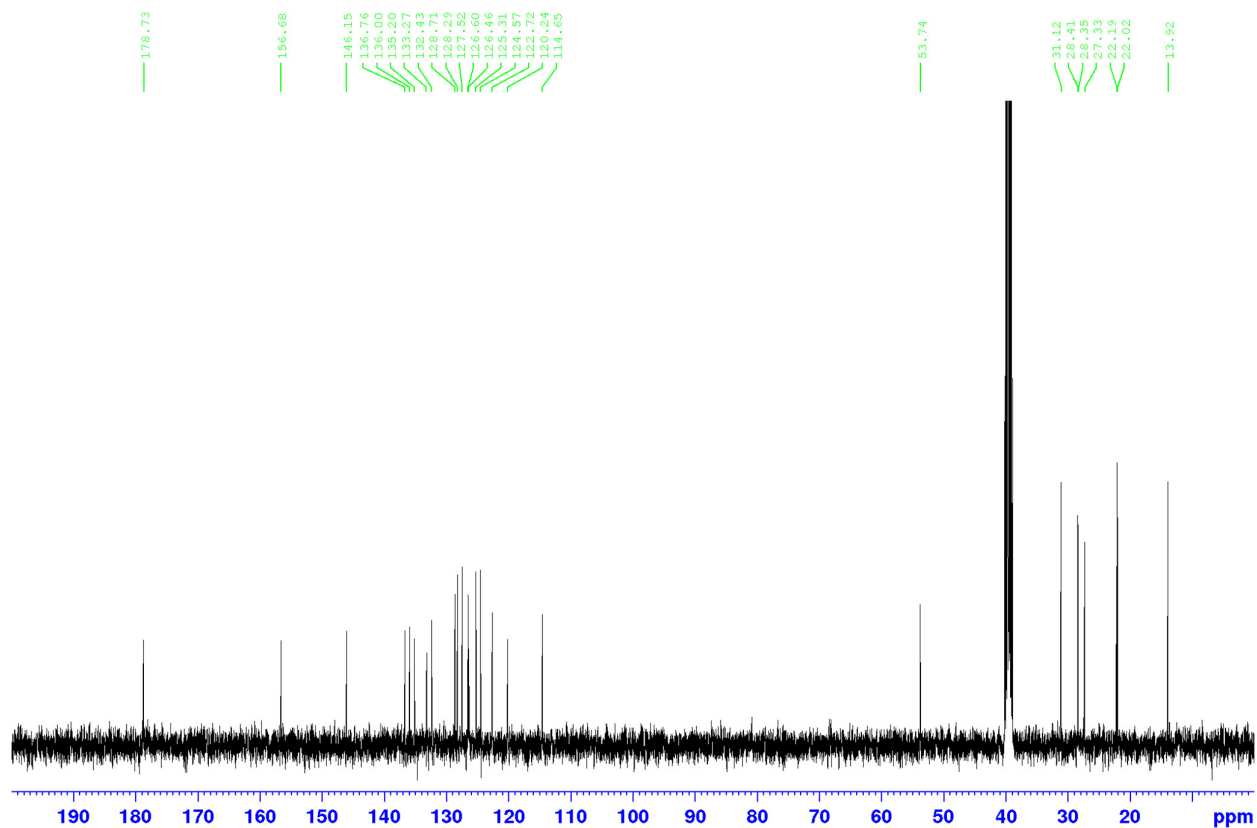


5-(Naphthalen-2-yl)-1-(octylsulfonyl)indoline-2,3-dione (**8d**)

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):

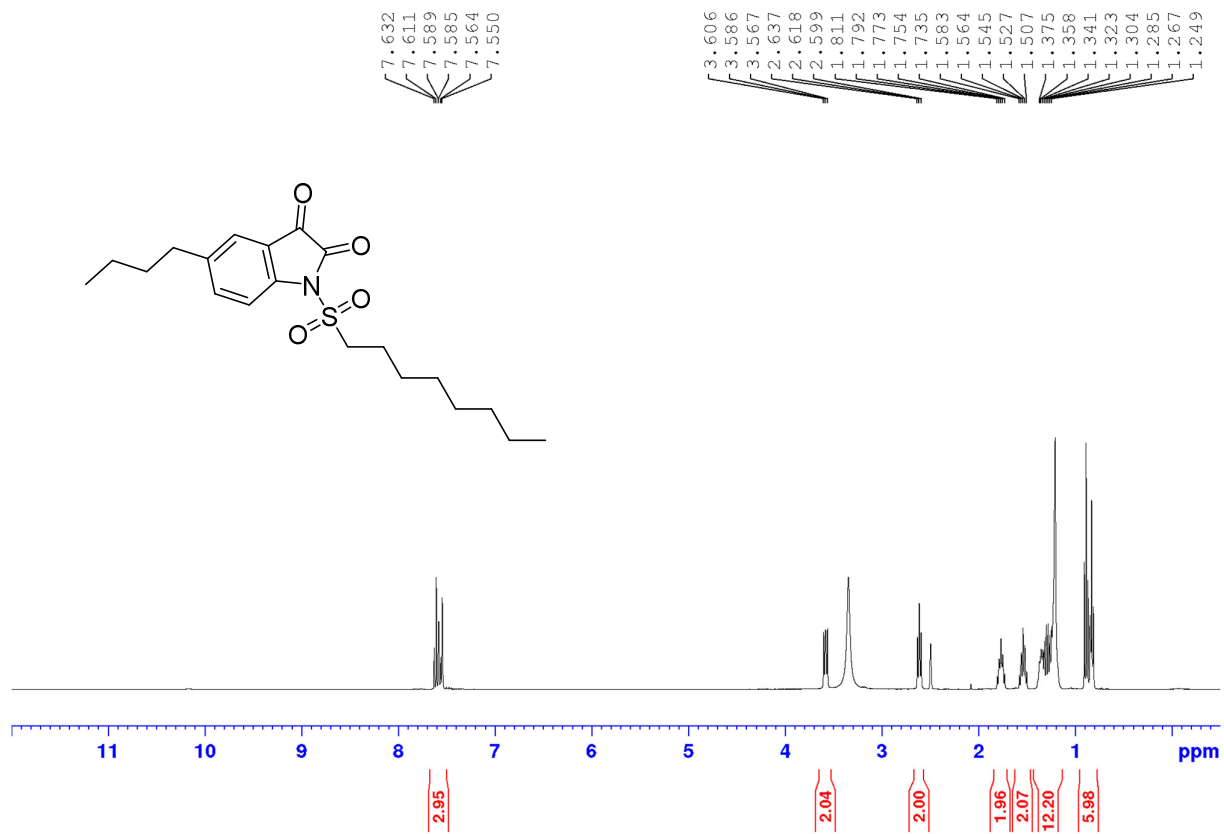


$^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):

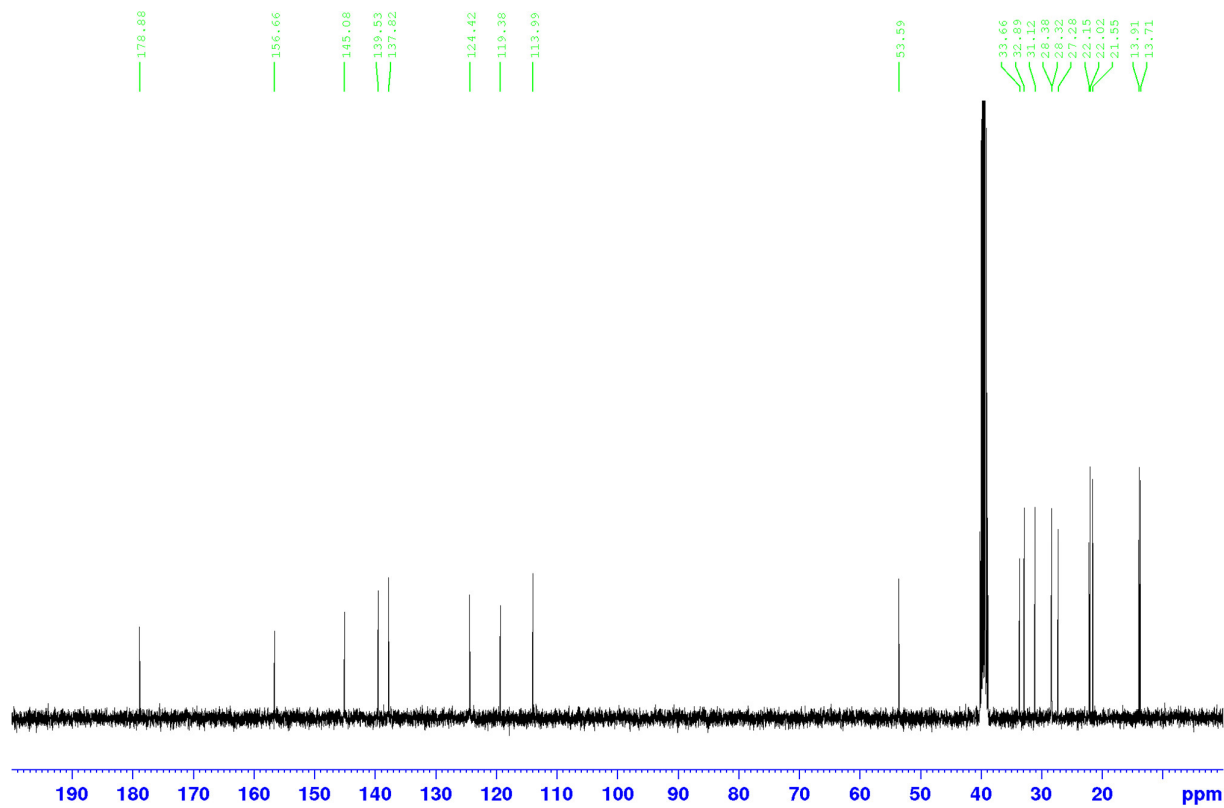


5-Butyl-1-(octylsulfonyl)indoline-2,3-dione (**8e**)

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):



$^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):

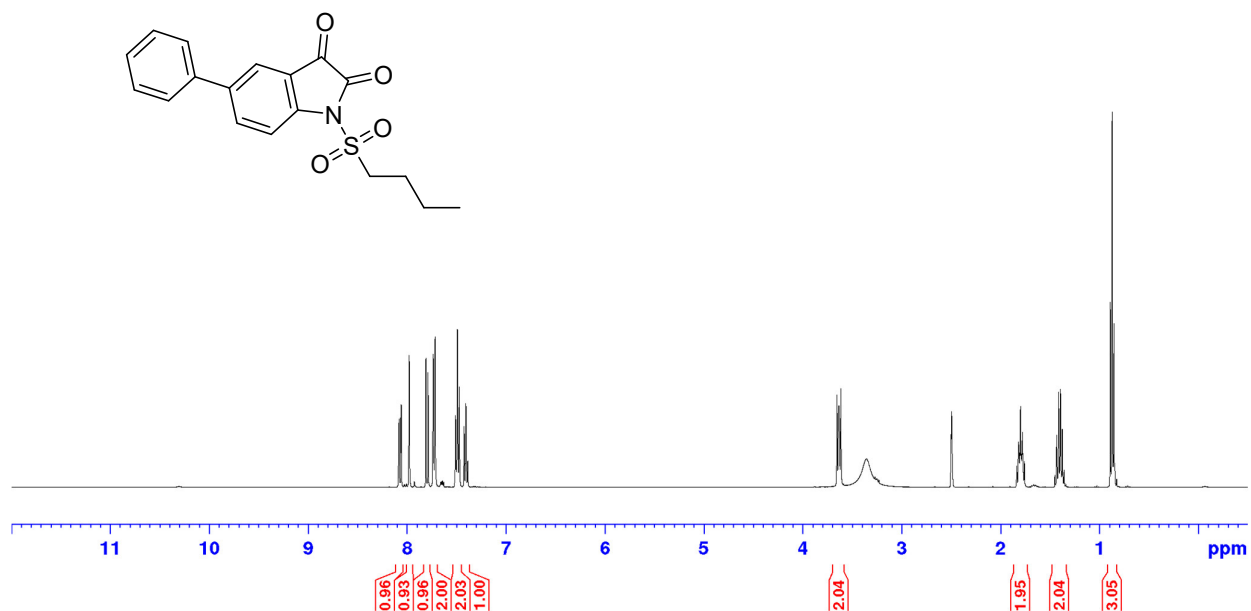


# 1-(Butylsulfonyl)-5-phenylindoline-2,3-dione (**9a**)

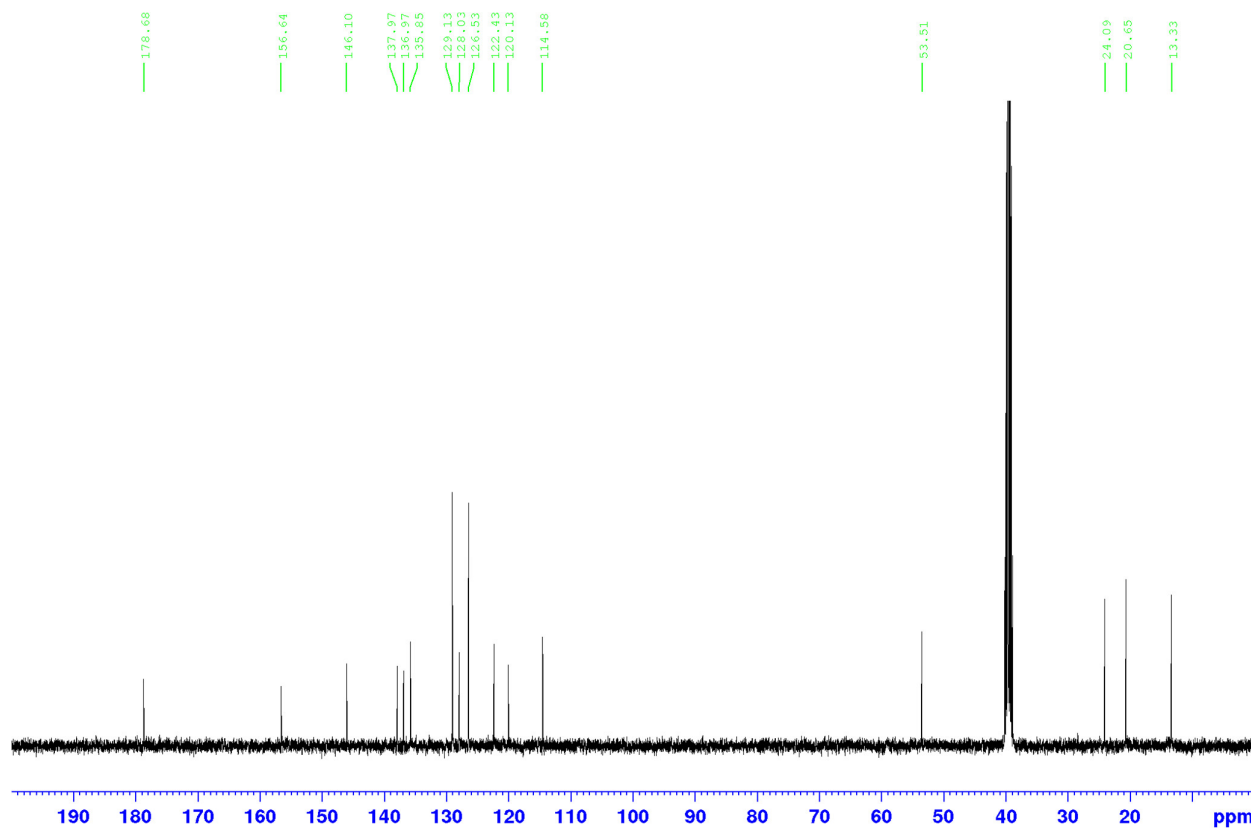
$^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):

8.090  
8.085  
8.068  
8.063  
7.985  
7.980  
7.814  
7.792  
7.743  
7.739  
7.721  
7.514  
7.496  
7.476  
7.428  
7.409  
7.404  
7.391

3.659  
3.639  
3.619  
1.842  
1.823  
1.810  
1.803  
1.795  
1.785  
1.780  
1.765  
1.456  
1.437  
1.418  
1.400  
1.381  
1.363  
0.896  
0.877  
0.859

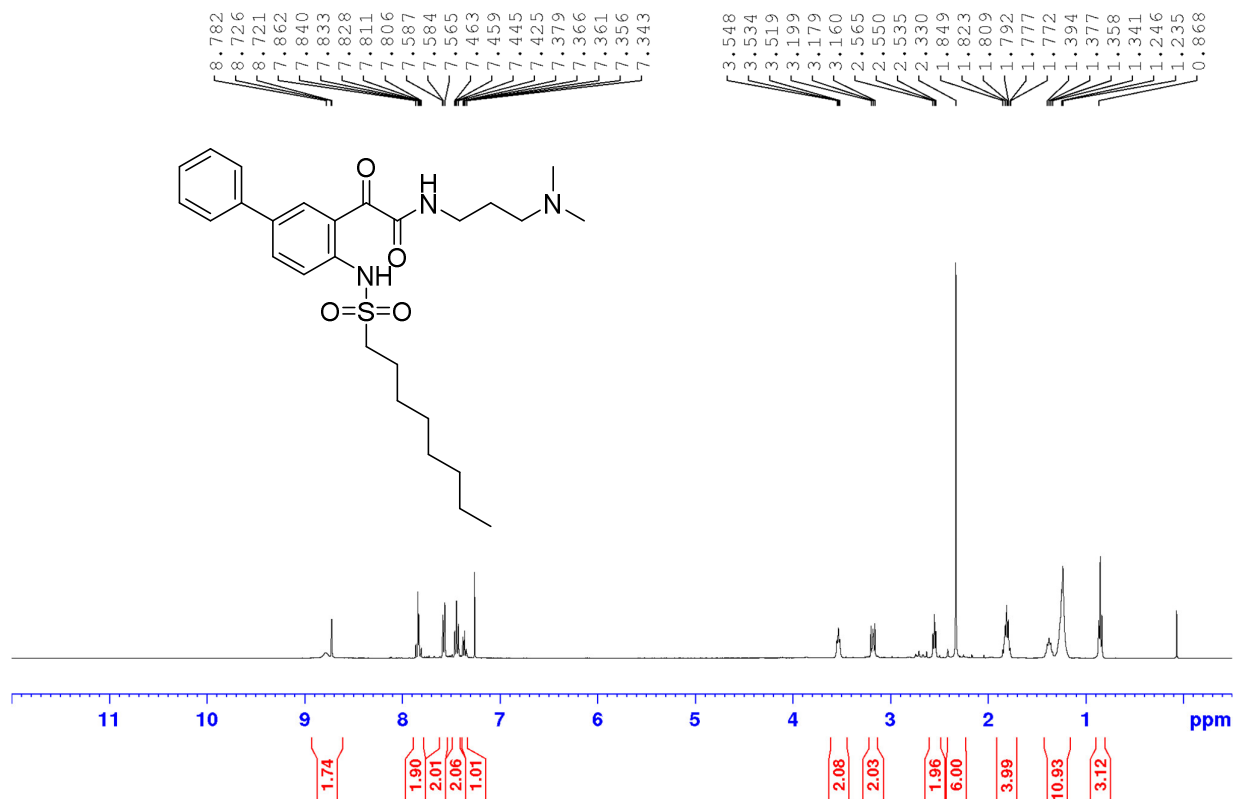


$^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):

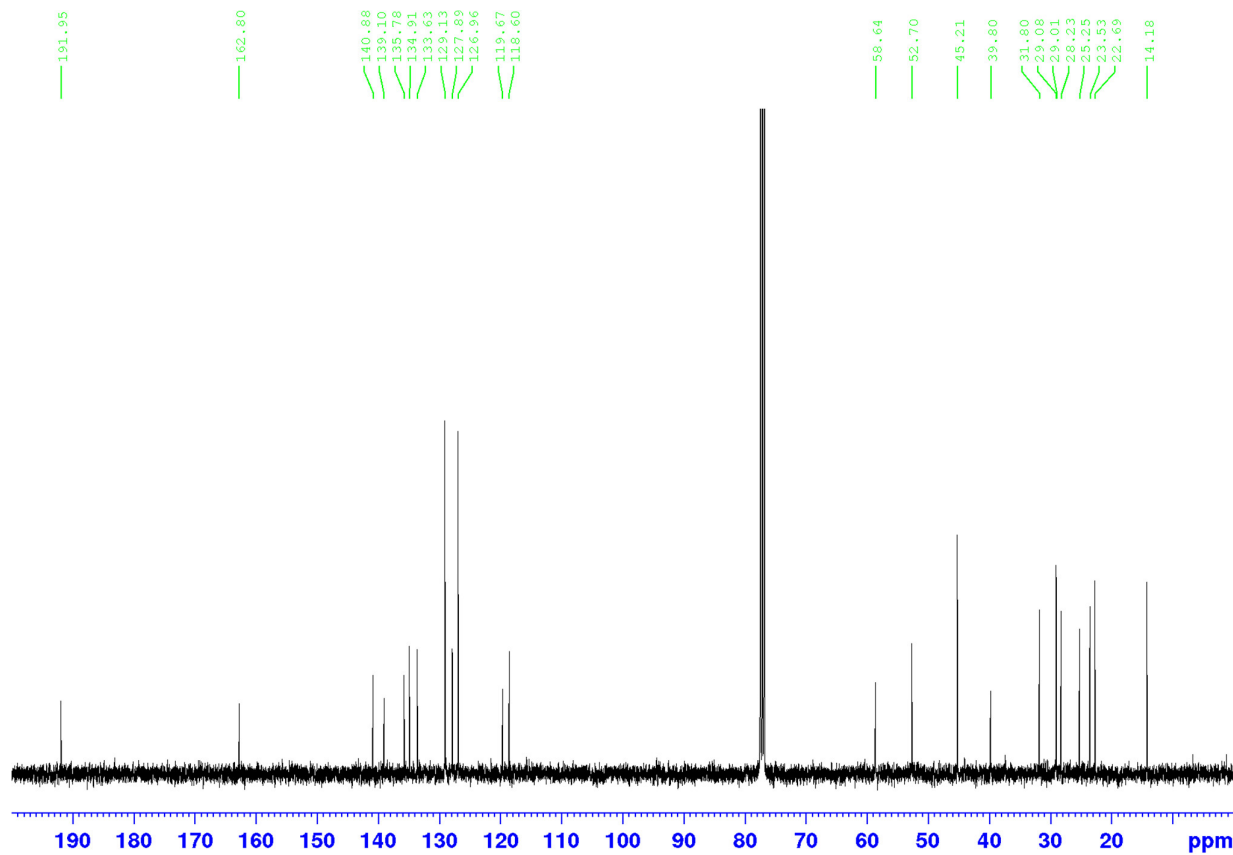


*N*-(3-(Dimethylamino)propyl)-2-(4-(octylsulfonamido)-[1,1'-biphenyl]-3-yl)-2-oxoacetamide (**11a**)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):



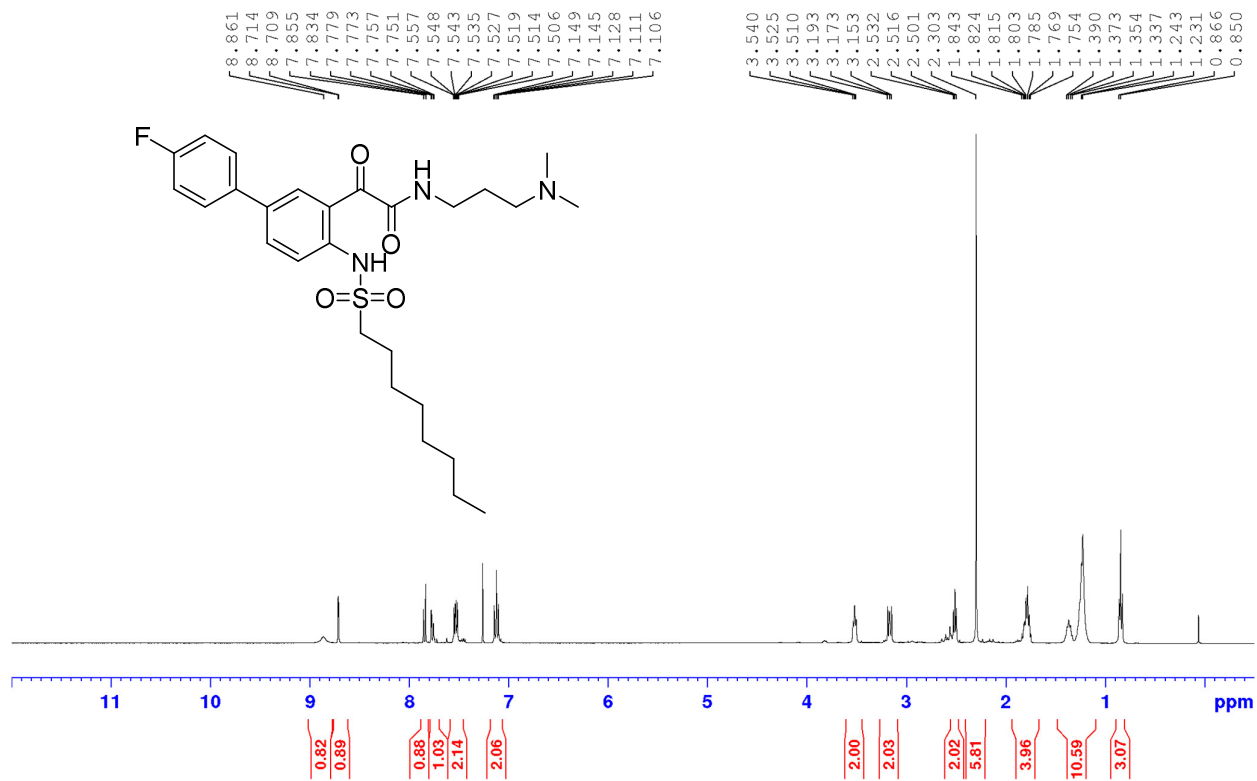
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):



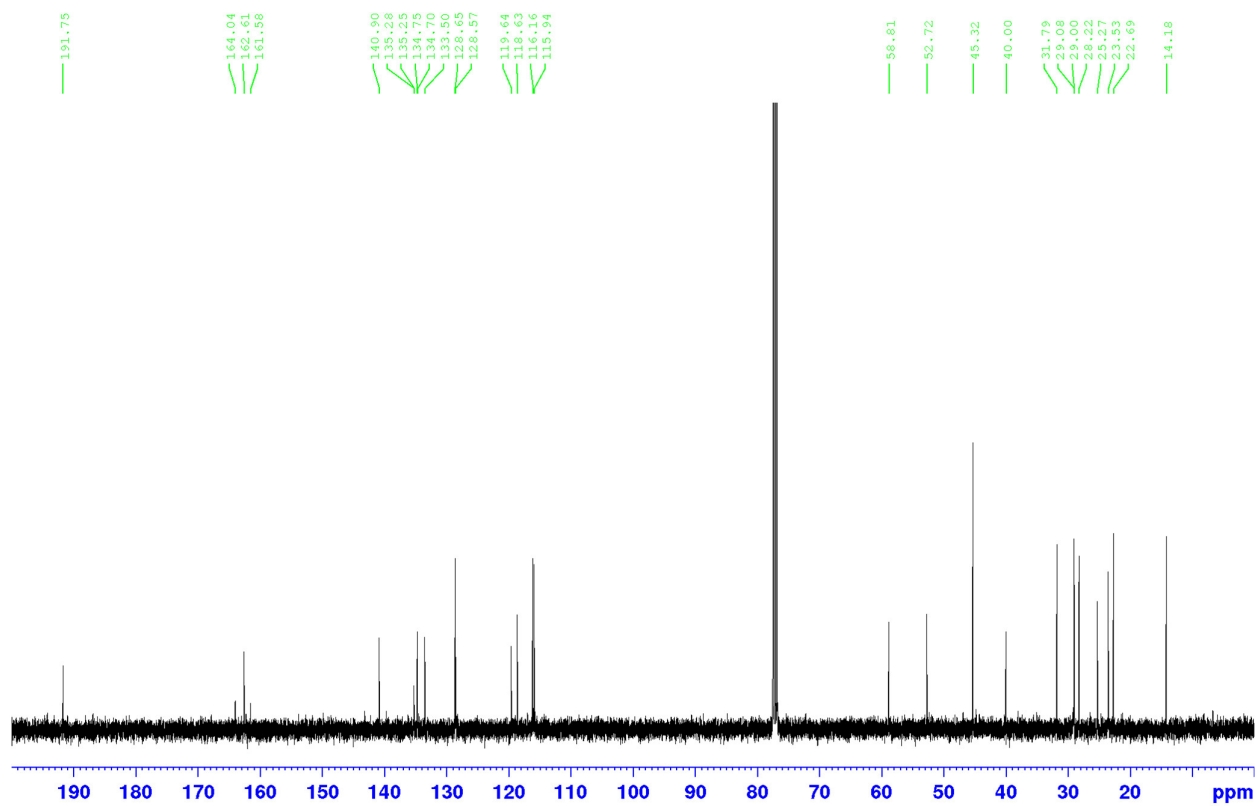


*N*-(3-(Dimethylamino)propyl)-2-(4'-fluoro-4-(octylsulfonamido)-[1,1'-biphenyl]-3-yl)-2-oxoacetamide (**11b**)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):

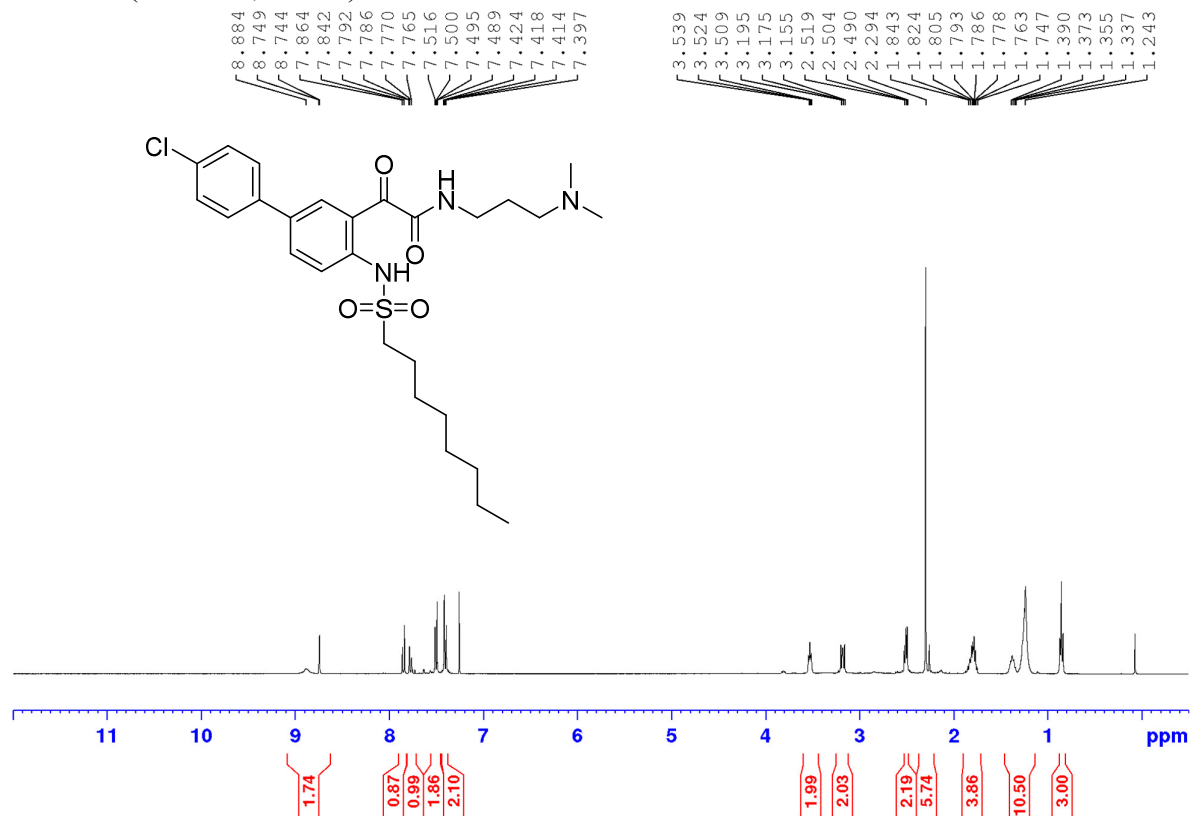


$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):

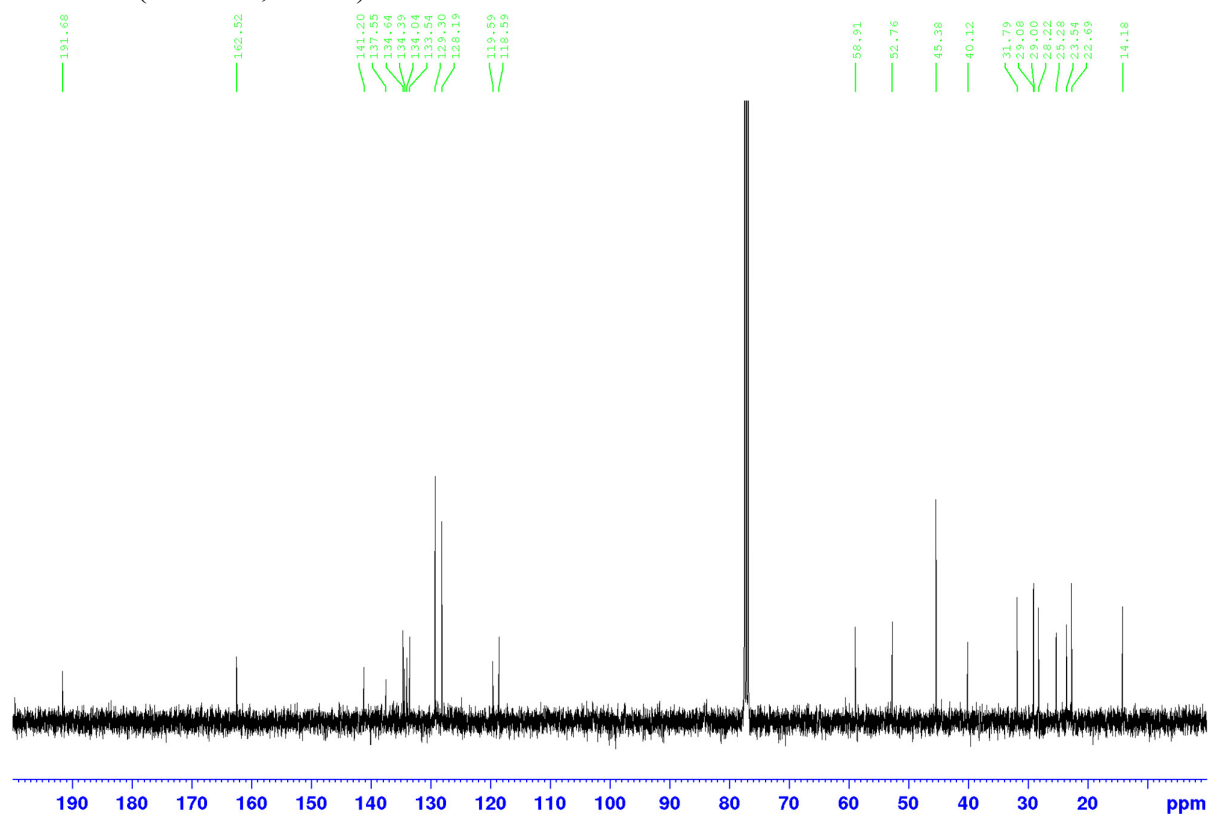


2-(4'-Chloro-4-(octylsulfonamido)-[1,1'-biphenyl]-3-yl)-N-(3-(dimethylamino)propyl)-2-oxoacetamide (11c)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):

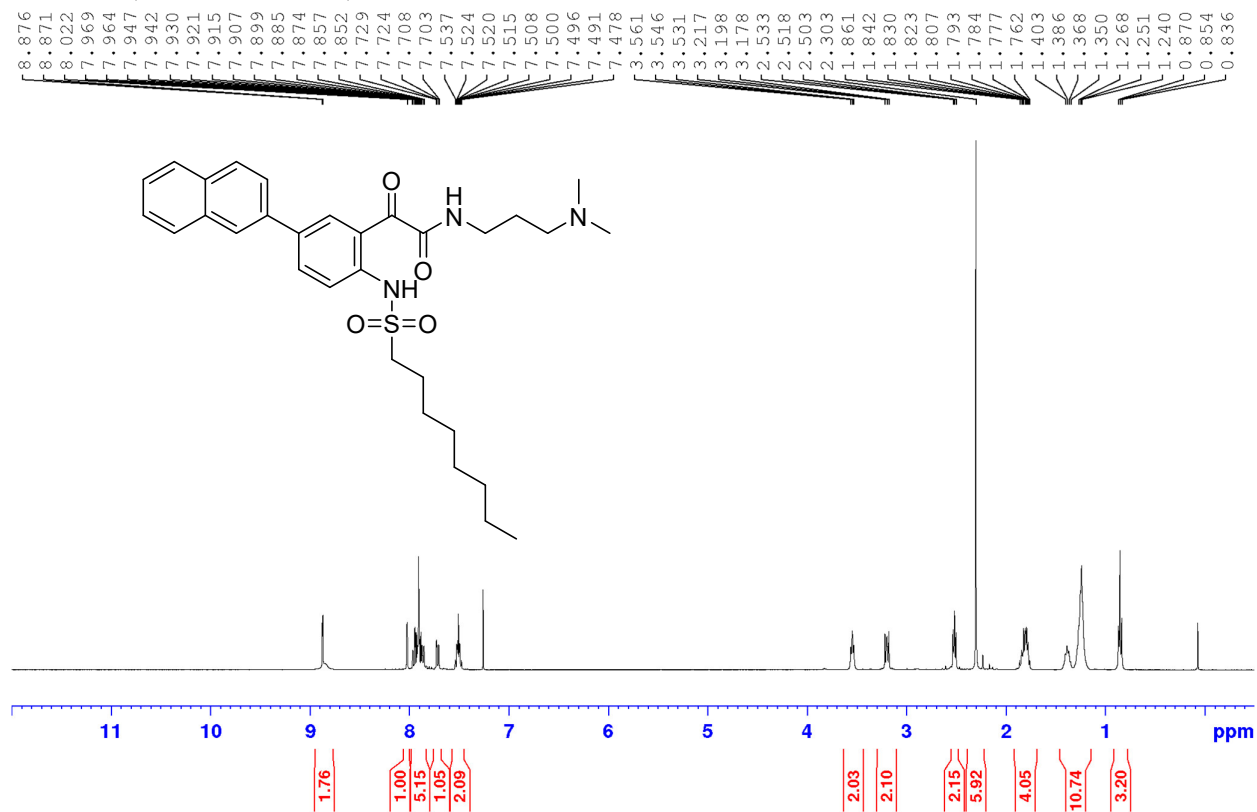


$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):

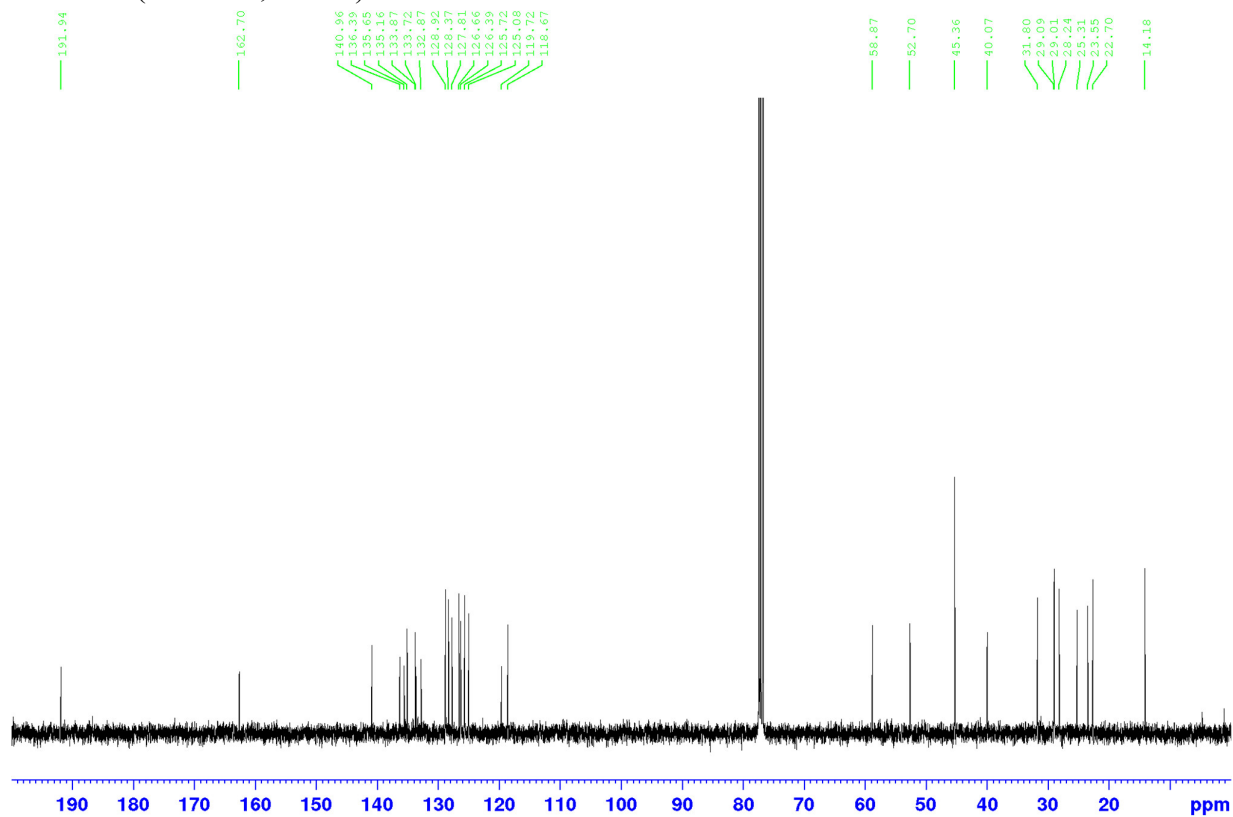


*N*-(3-(Dimethylamino)propyl)-2-(5-(naphthalen-2-yl)-2-(octylsulfonamido)phenyl)-2-oxoacetamide  
**(11d)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):



<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):

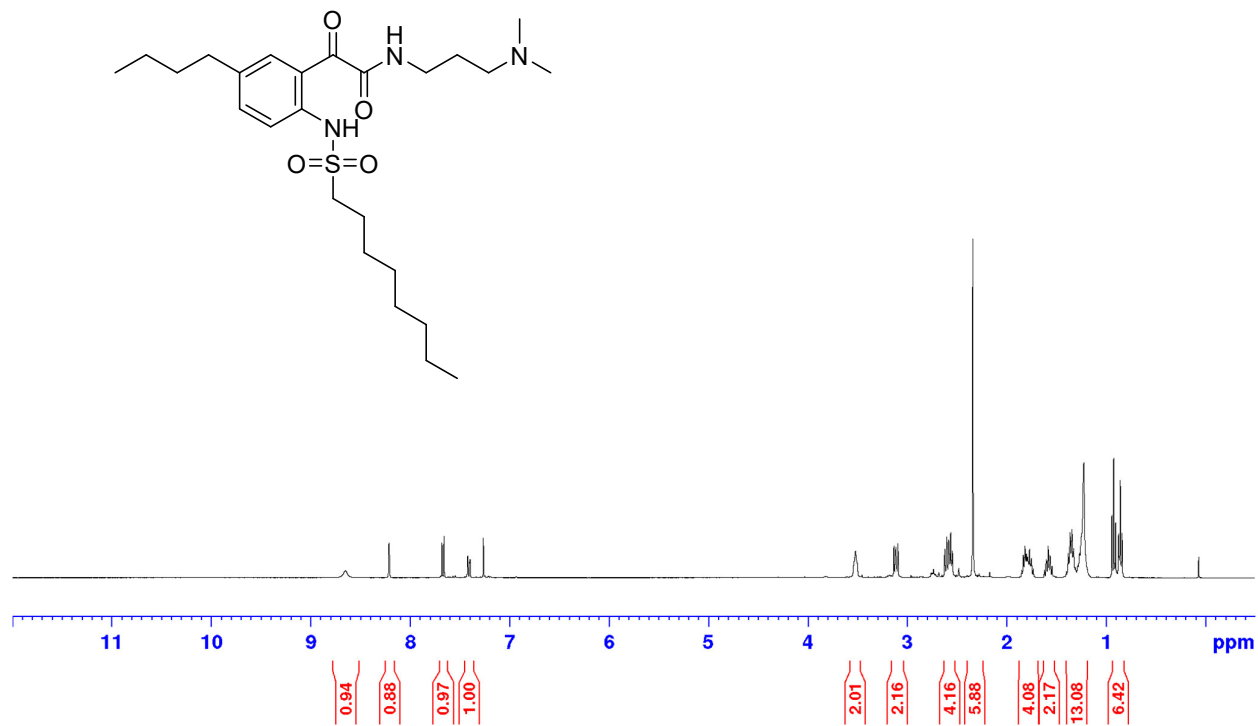


2-(5-Butyl-2-(octylsulfonamido)phenyl)-N-(3-(dimethylamino)propyl)-2-oxoacetamide (**11e**)

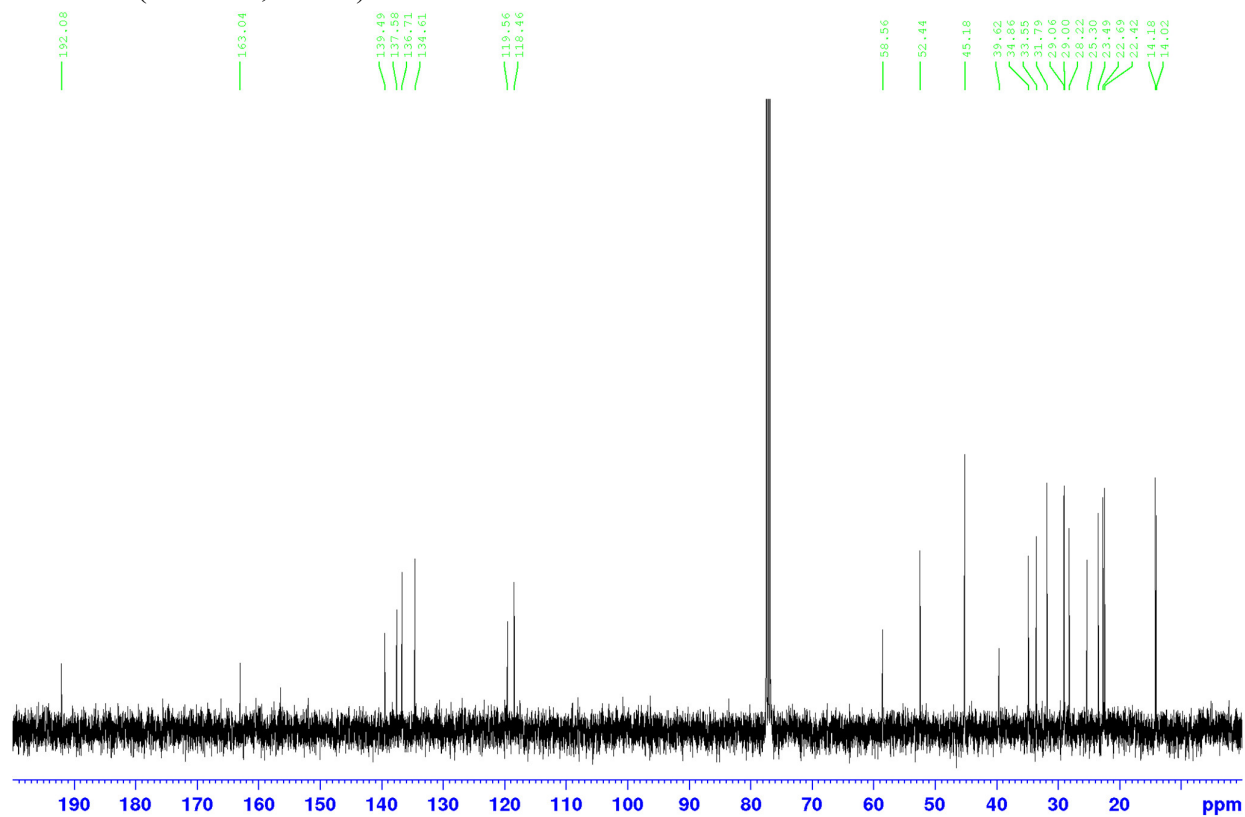
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):

8.649  
8.211  
8.206  
7.677  
7.655  
7.419  
7.414  
7.398  
7.393

3.522  
3.129  
3.110  
3.090  
2.618  
2.599  
2.579  
2.558  
2.543  
2.336  
1.827  
1.812  
1.797  
1.785  
1.774  
1.766  
1.758  
1.747  
1.727  
1.616  
1.598  
1.578  
1.559  
1.540  
1.395  
1.376  
1.358

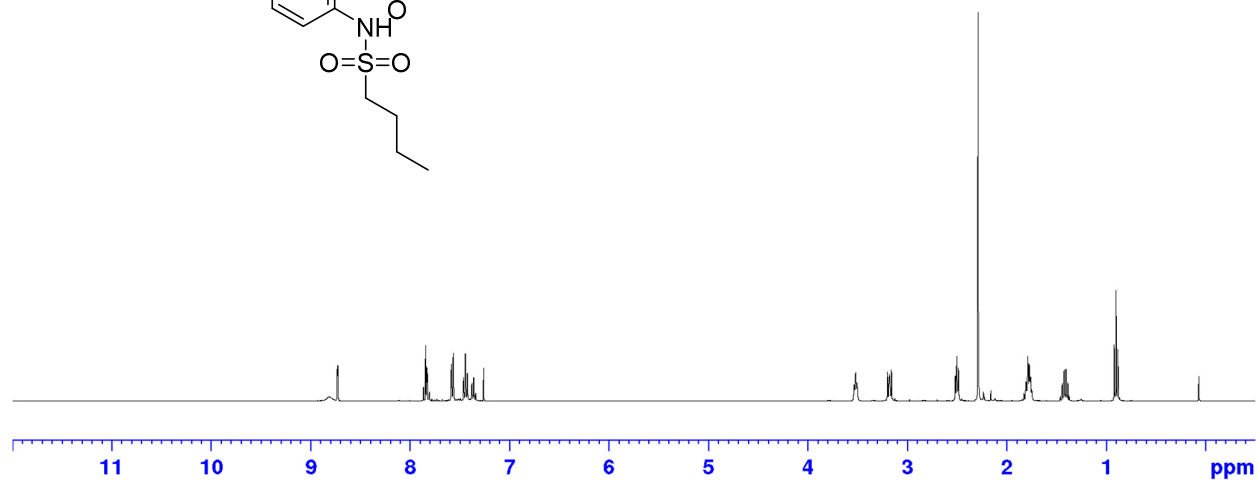
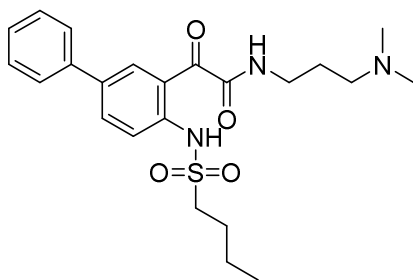
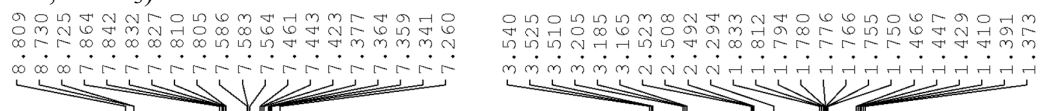


$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):

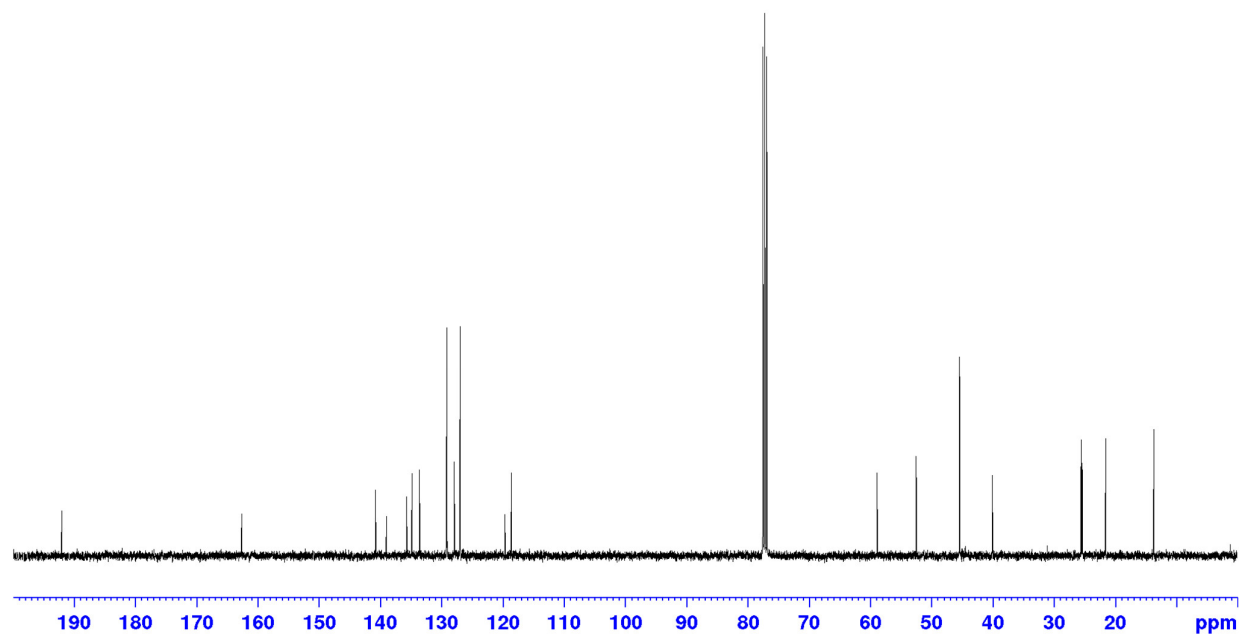


2-(4-(Butylsulfonamido)-[1,1'-biphenyl]-3-yl)-N-(3-(dimethylamino)propyl)-2-oxoacetamide (**12a**)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):

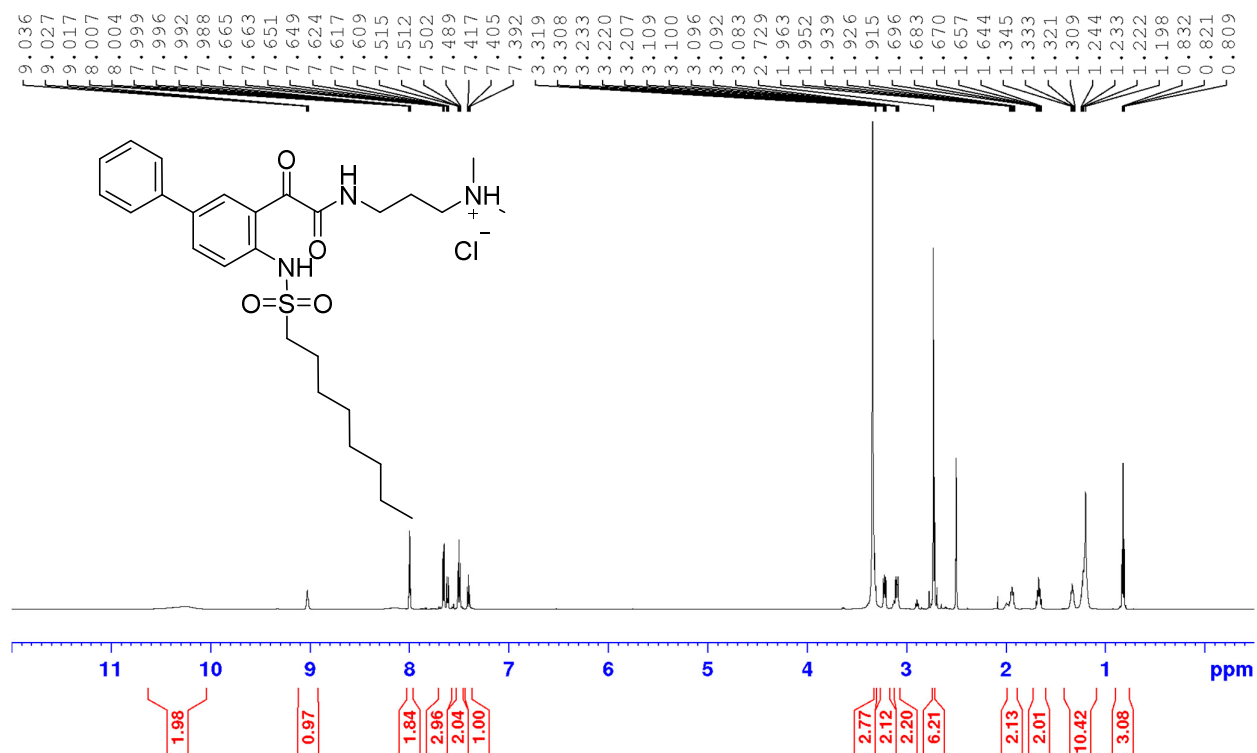


$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):

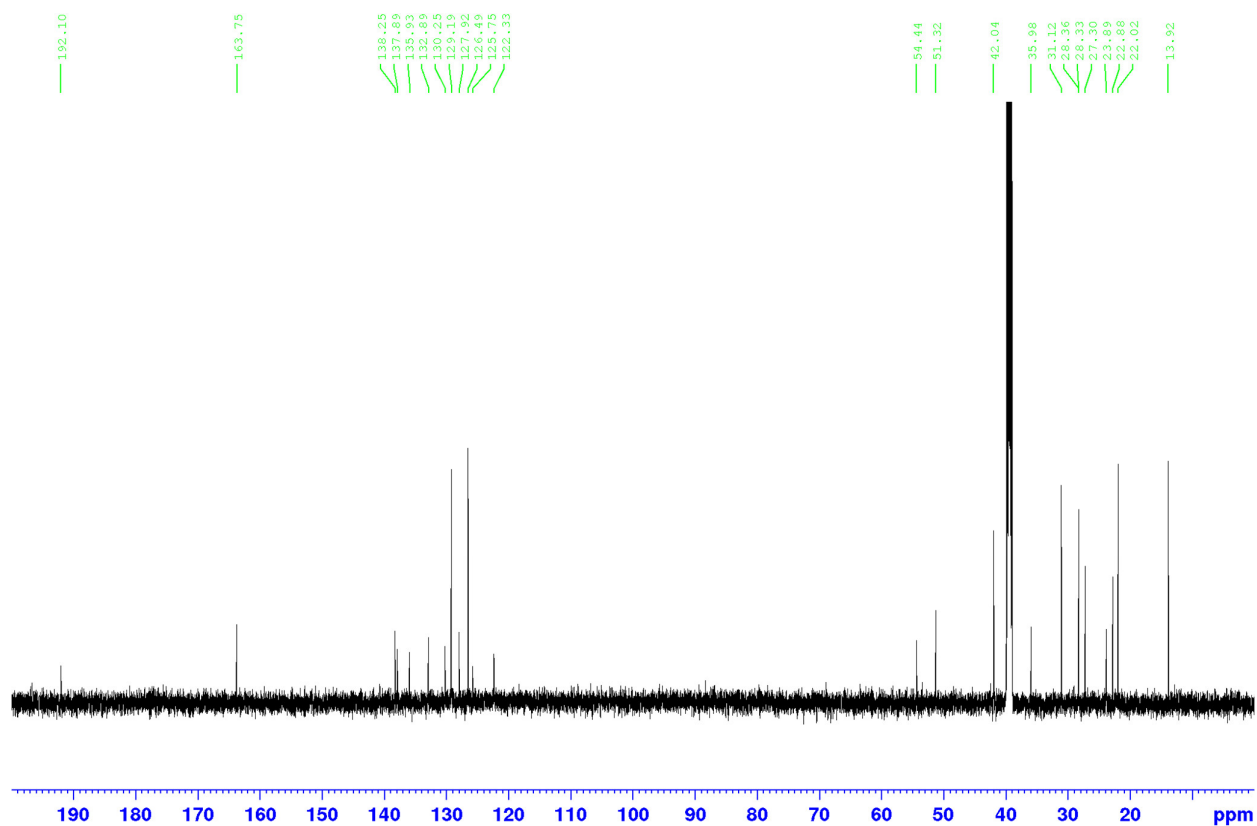


*N,N*-Dimethyl-3-(2-(4-(octylsulfonamido)-[1,1'-biphenyl]-3-yl)-2-oxoacetamido)propan-1-aminium chloride (**13a**)

<sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>):

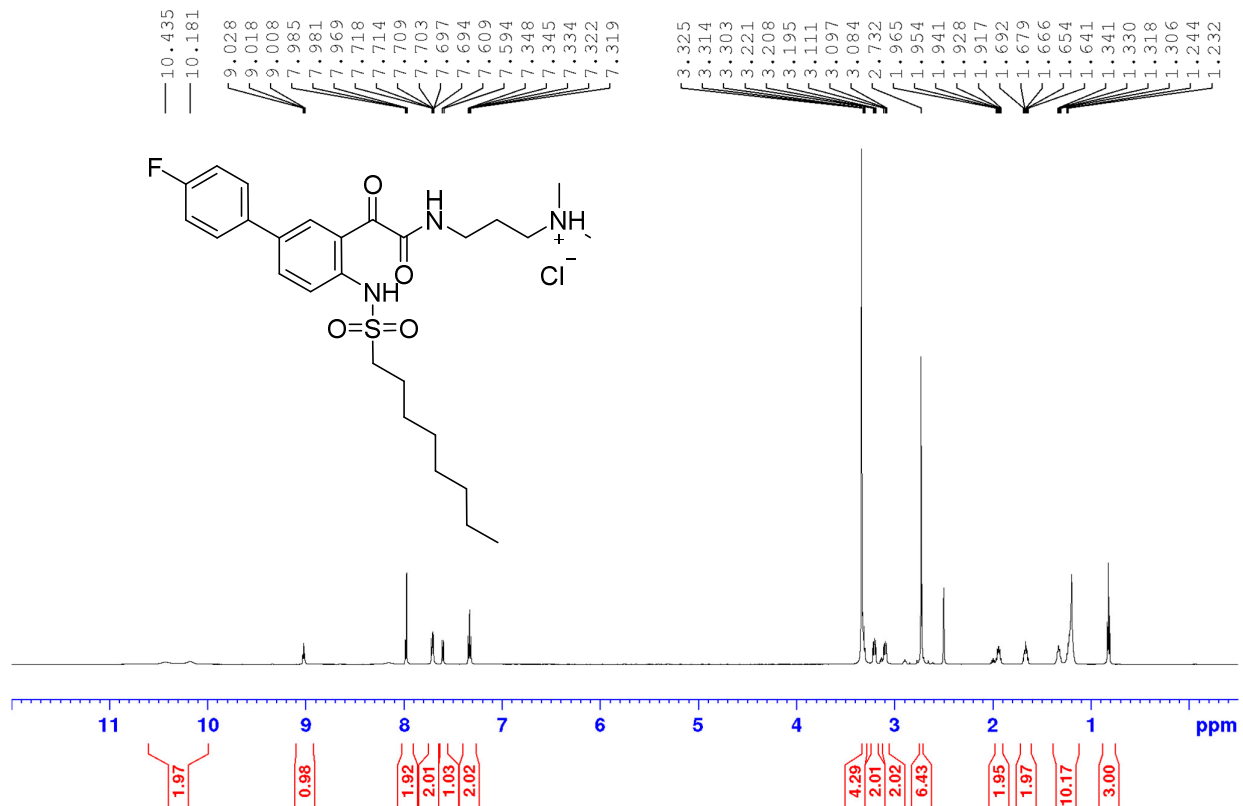


<sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>):

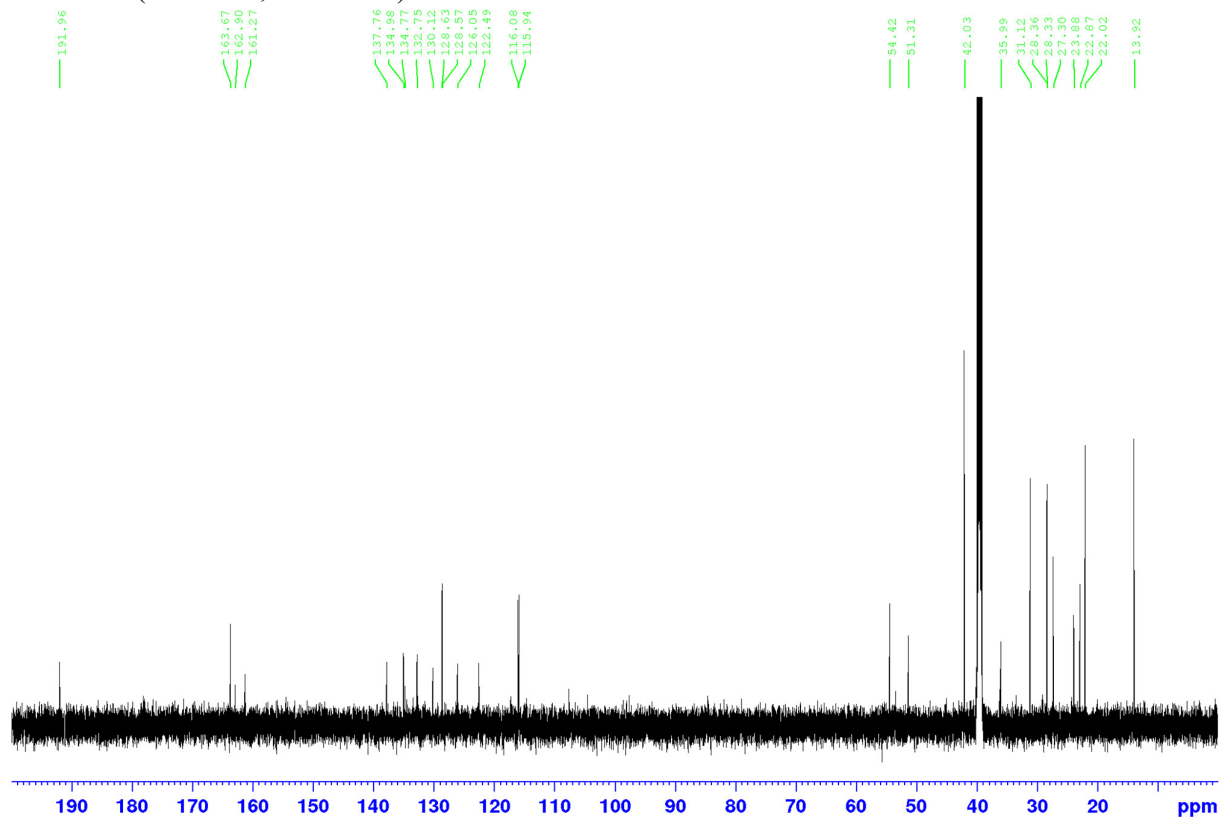


3-(2-(4'-Fluoro-4-(octylsulfonamido)-[1,1'-biphenyl]-3-yl)-2-oxoacetamido)-*N,N*-dimethylpropan-1-aminium chloride (**13b**)

<sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>):

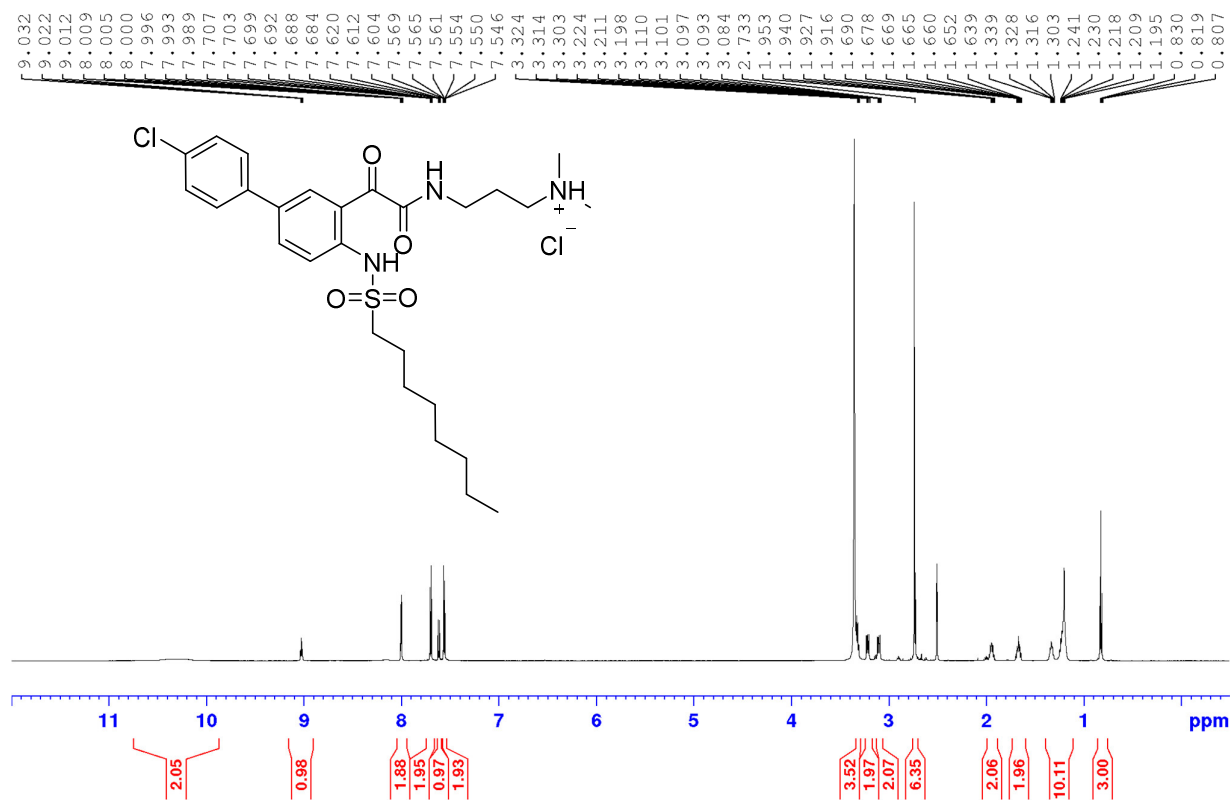


<sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>):

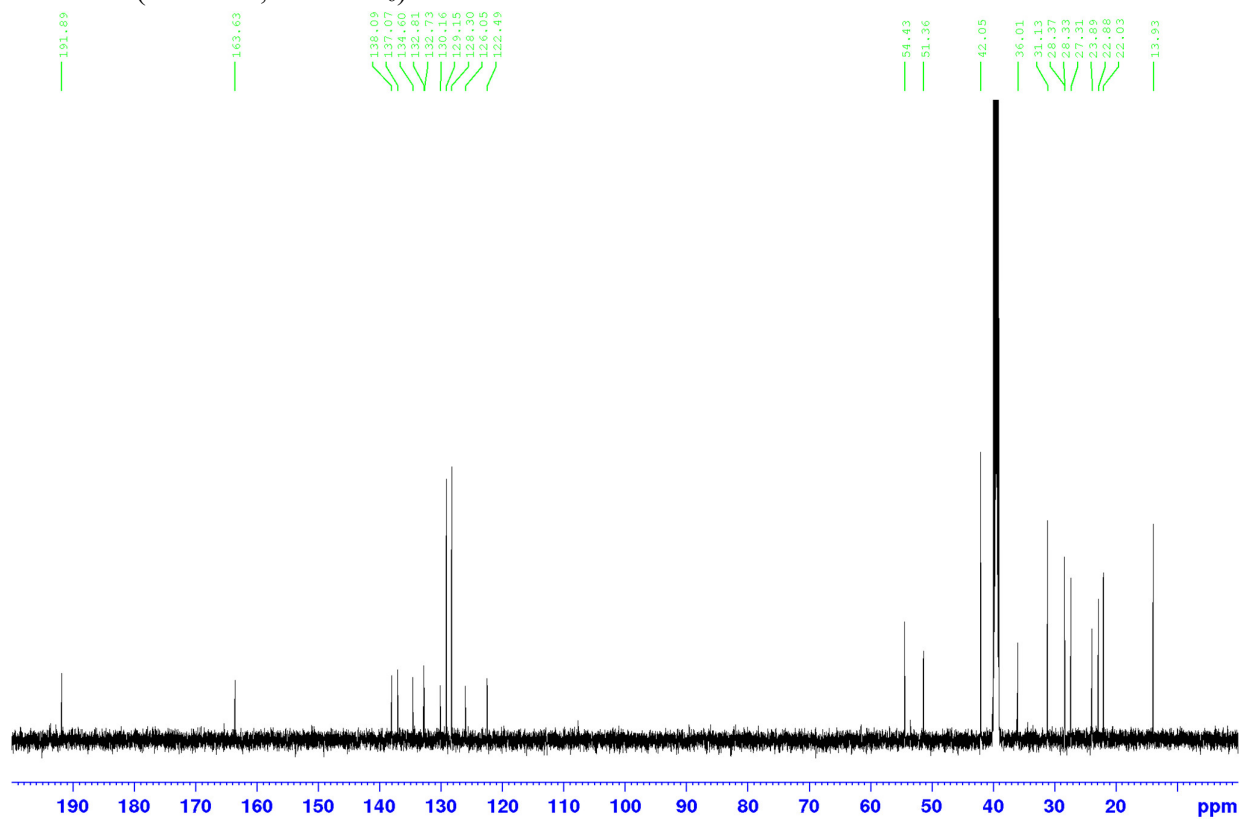


3-(2-(4'-Chloro-4-(octylsulfonamido)-[1,1'-biphenyl]-3-yl)-2-oxoacetamido)-*N,N*-dimethylpropan-1-aminium chloride (**13c**)

$^1\text{H}$  NMR (600 MHz,  $\text{DMSO-}d_6$ ):



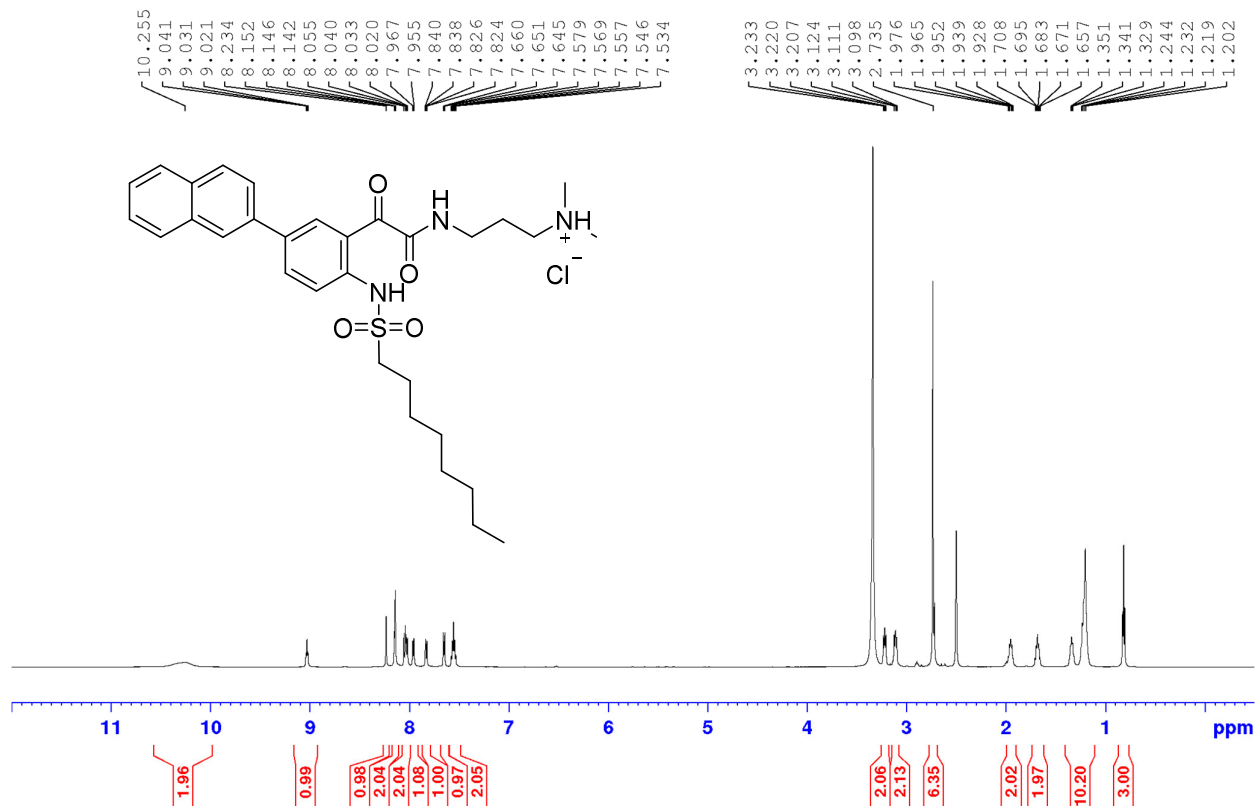
$^{13}\text{C}$  NMR (150 MHz,  $\text{DMSO-}d_6$ ):



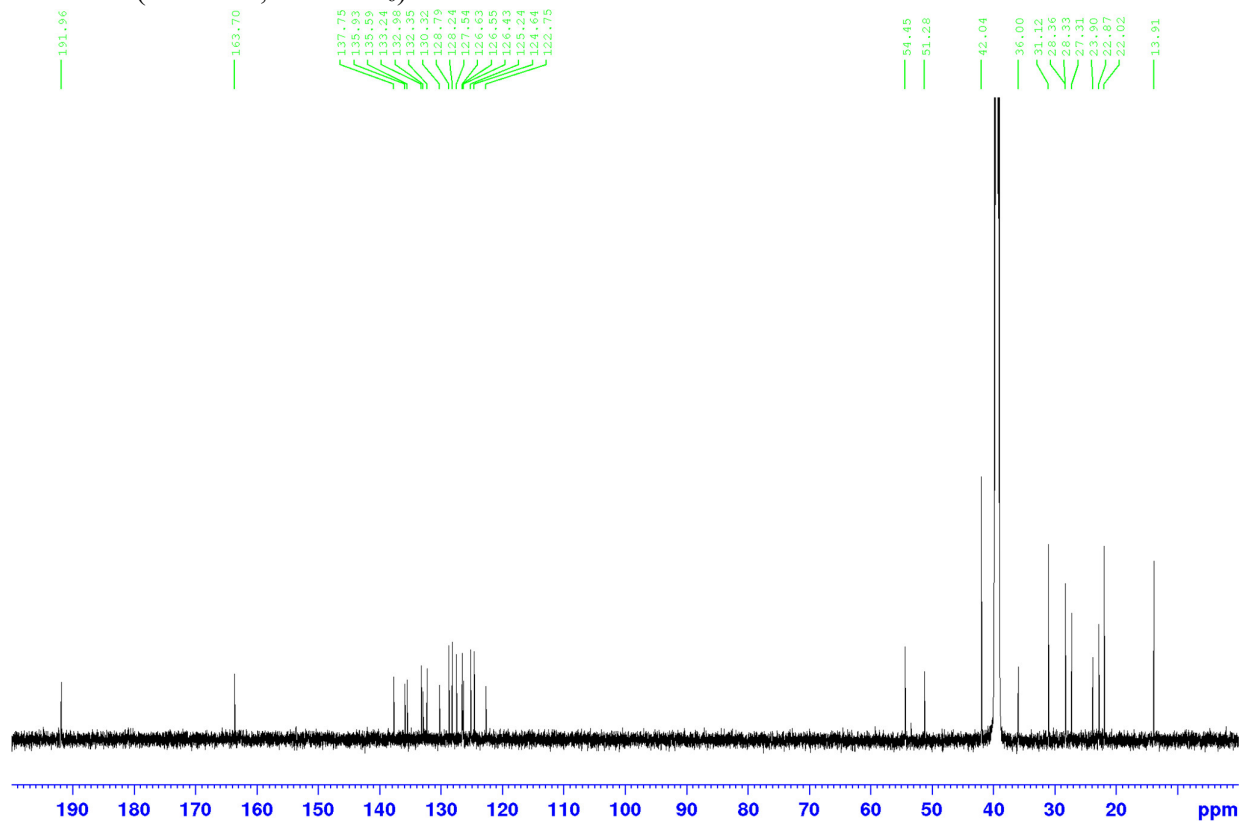


*N,N*-Dimethyl-3-(2-(5-(naphthalen-2-yl)-2-(octylsulfonamido)phenyl)-2-oxoacetamido)propan-1-aminium chloride (**13d**)

<sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>):

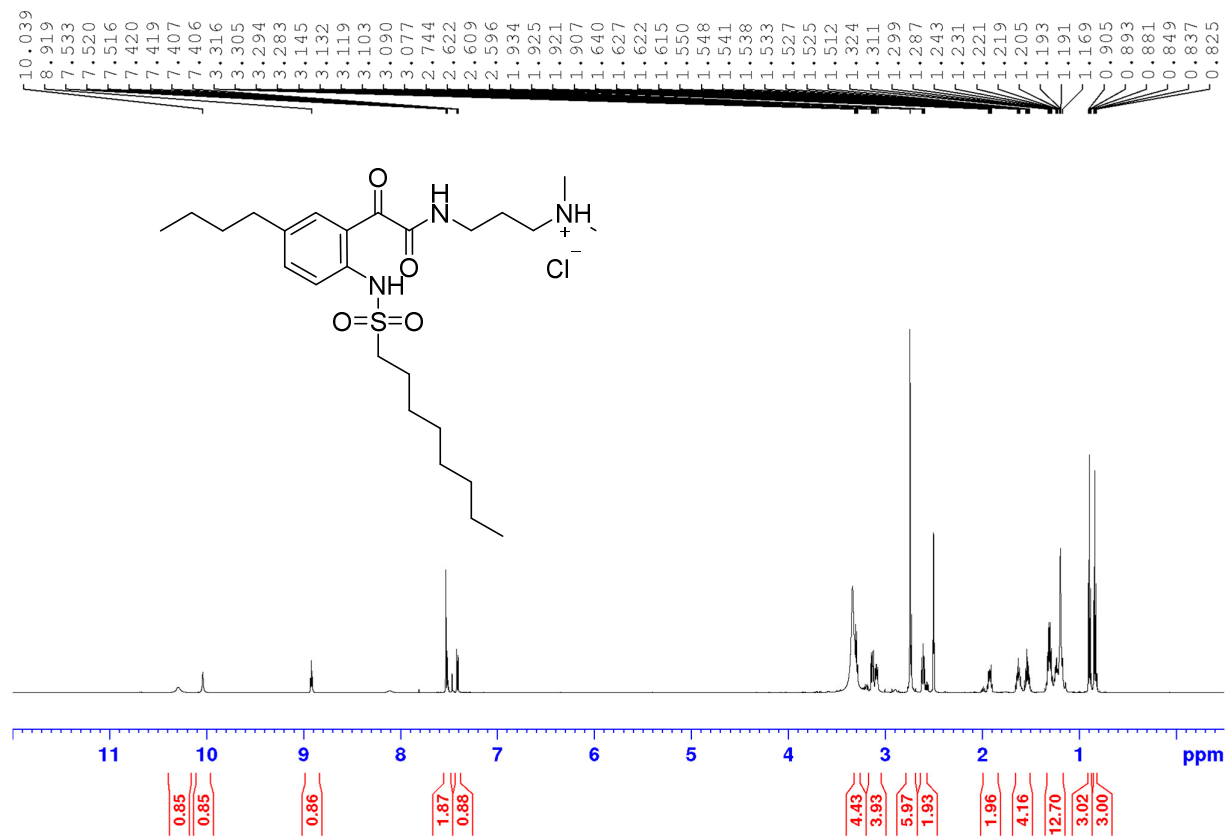


<sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>):

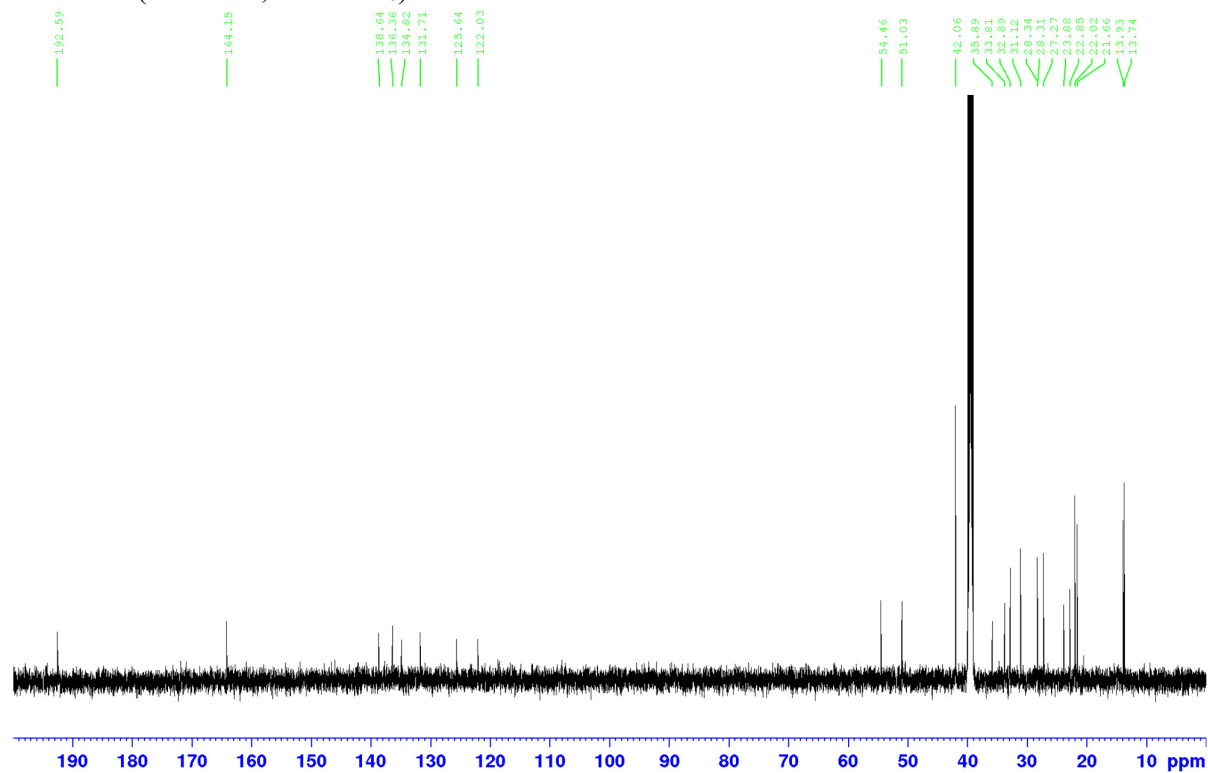


3-(2-(5-Butyl-2-(octylsulfonamido)phenyl)-2-oxoacetamido)-*N,N*-dimethylpropan-1-aminium chloride (13e)

$^1\text{H}$  NMR (600 MHz,  $\text{DMSO-}d_6$ ):

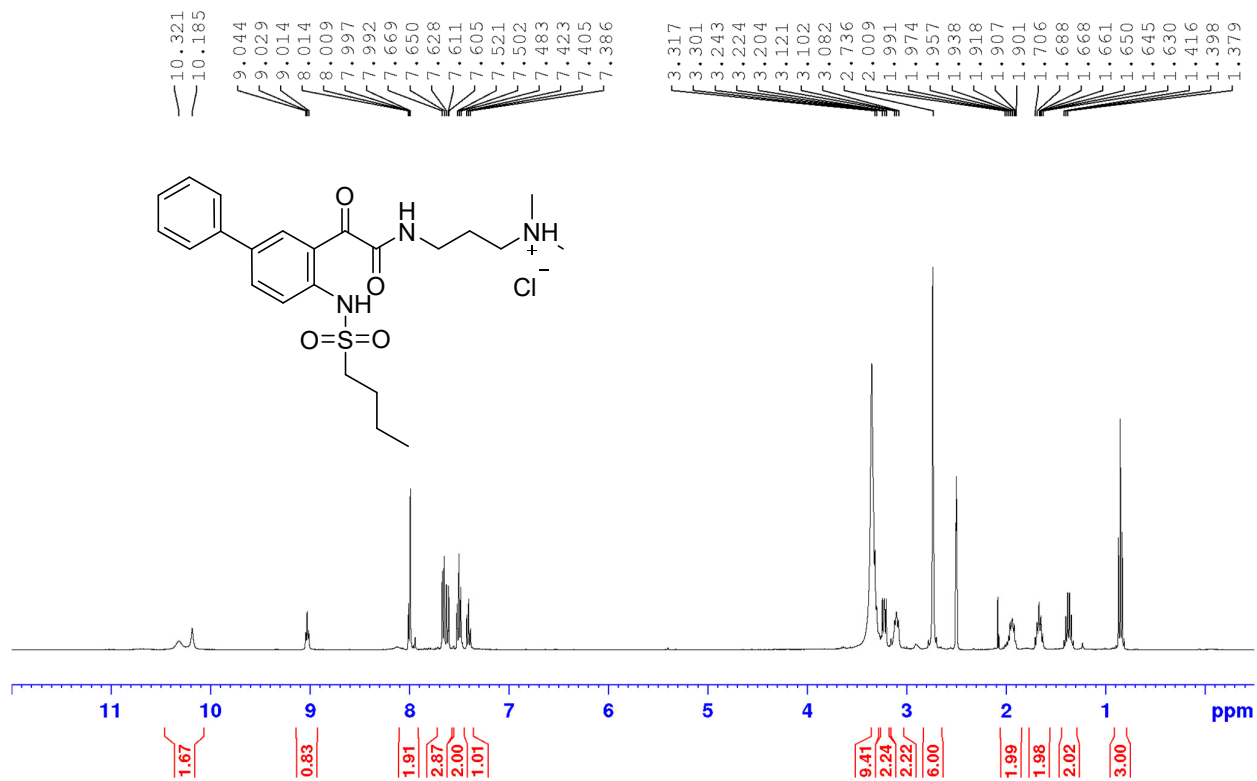


$^{13}\text{C}$  NMR (150 MHz,  $\text{DMSO-}d_6$ ):

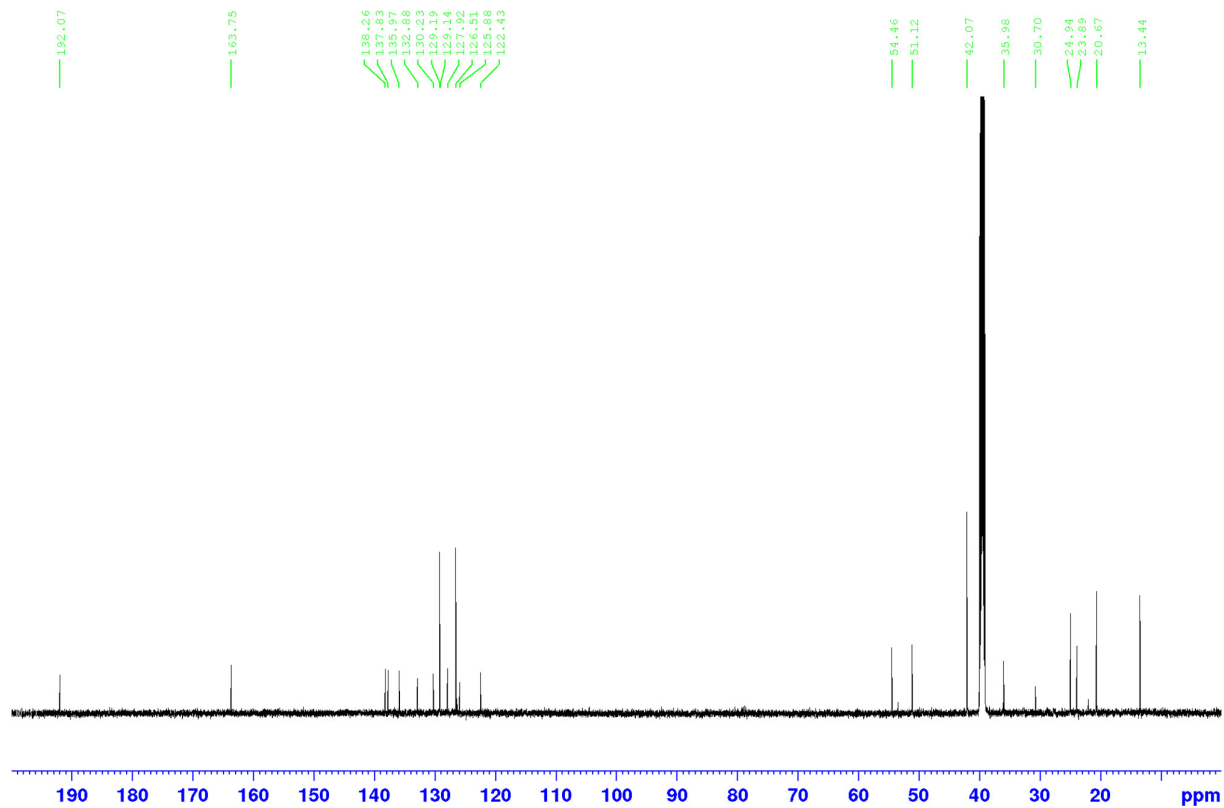


3-(2-(4-(Butylsulfonamido)-[1,1'-biphenyl]-3-yl)-2-oxoacetamido)-*N,N*-dimethylpropan-1-aminium chloride (**14a**)

$^1\text{H}$  NMR (600 MHz,  $\text{DMSO-}d_6$ ):

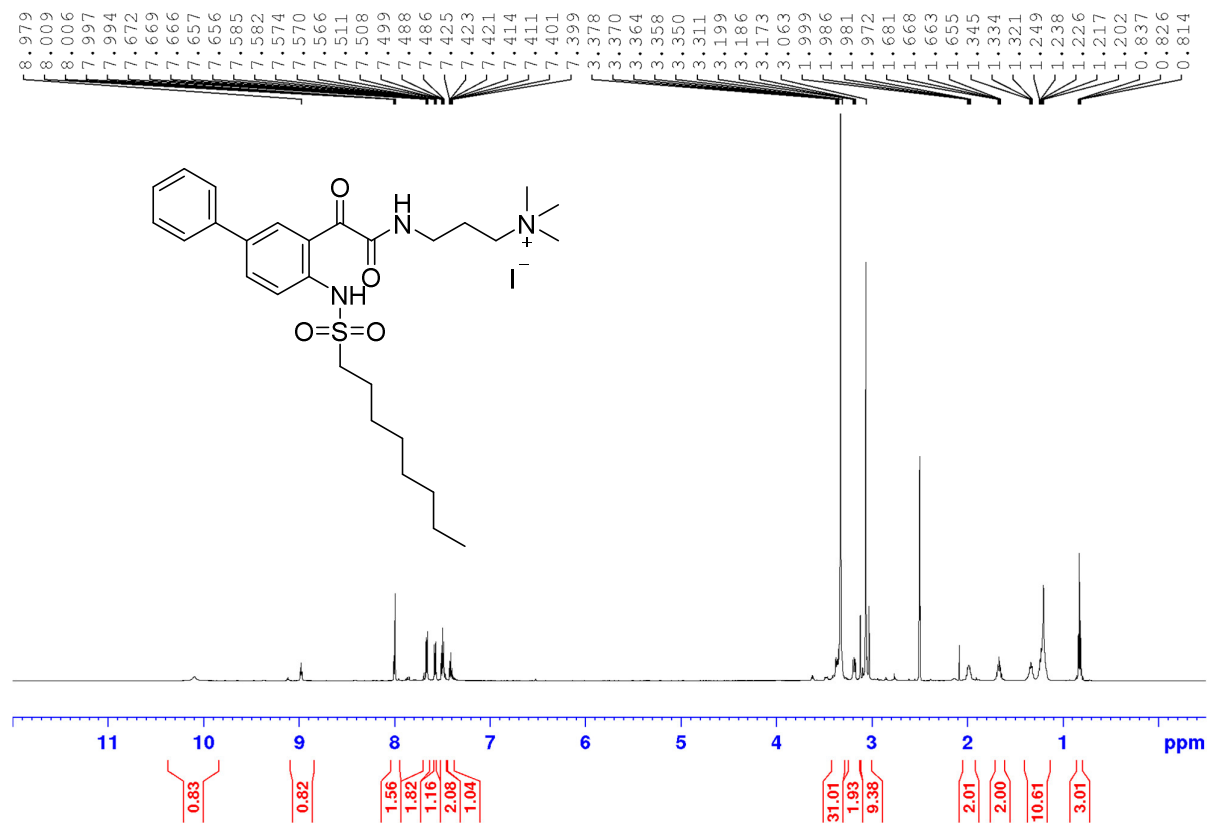


$^{13}\text{C}$  NMR (150 MHz,  $\text{DMSO-}d_6$ ):

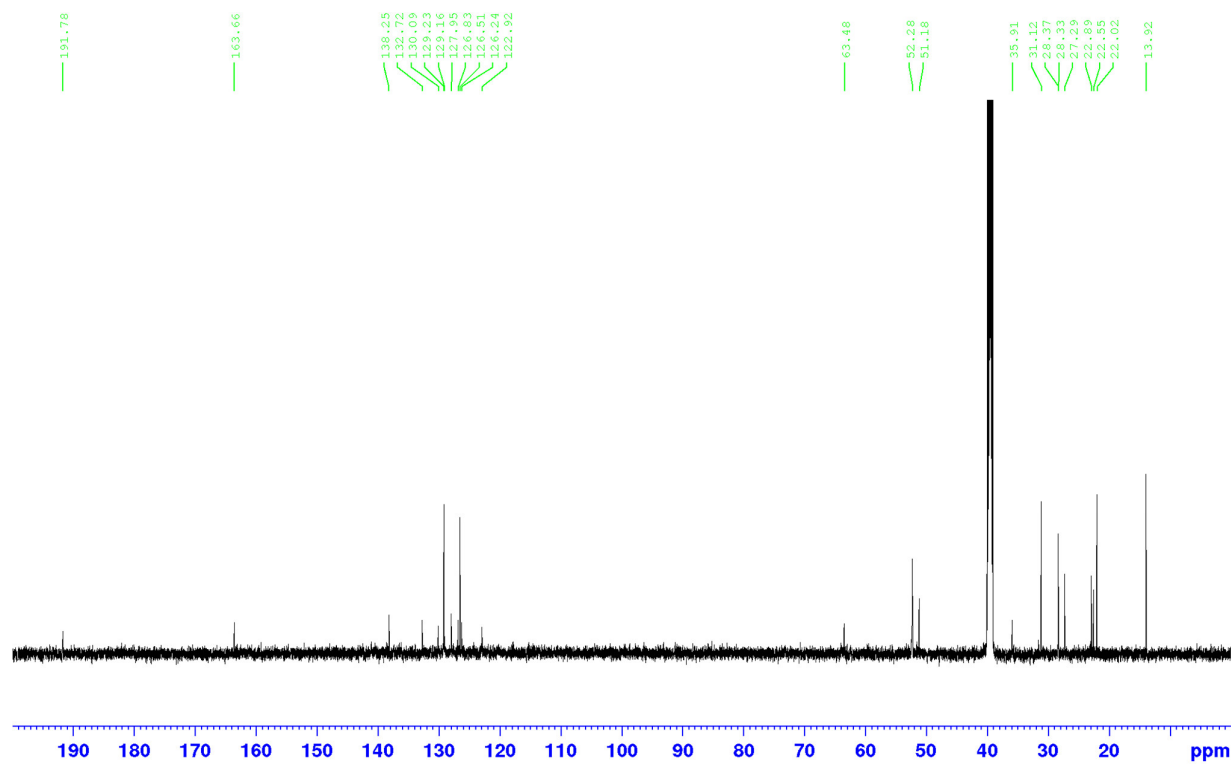


*N,N,N*-Trimethyl-3-(2-(4-(octylsulfonamido)-[1,1'-biphenyl]-3-yl)-2-oxoacetamido)propan-1-aminium iodide (**15a**)

$^1\text{H}$  NMR (600 MHz,  $\text{DMSO-}d_6$ ):

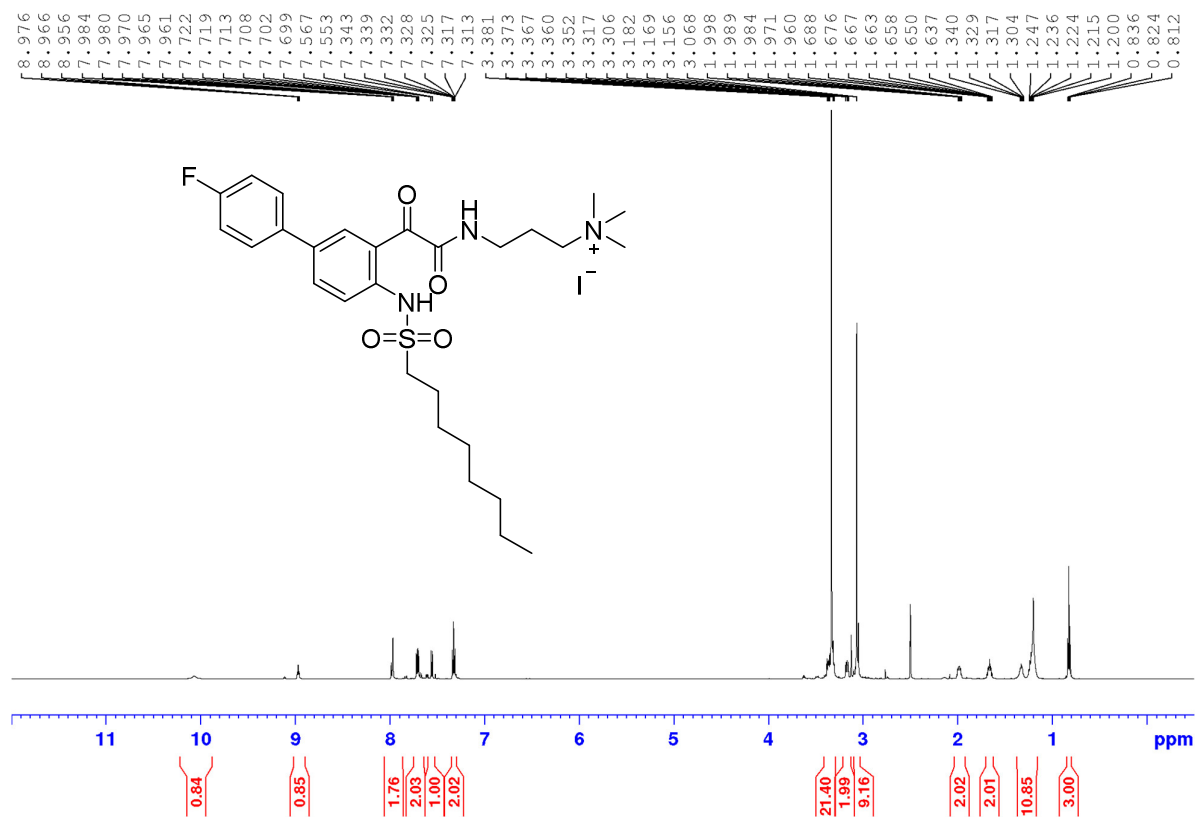


$^{13}\text{C}$  NMR (150 MHz,  $\text{DMSO-}d_6$ ):

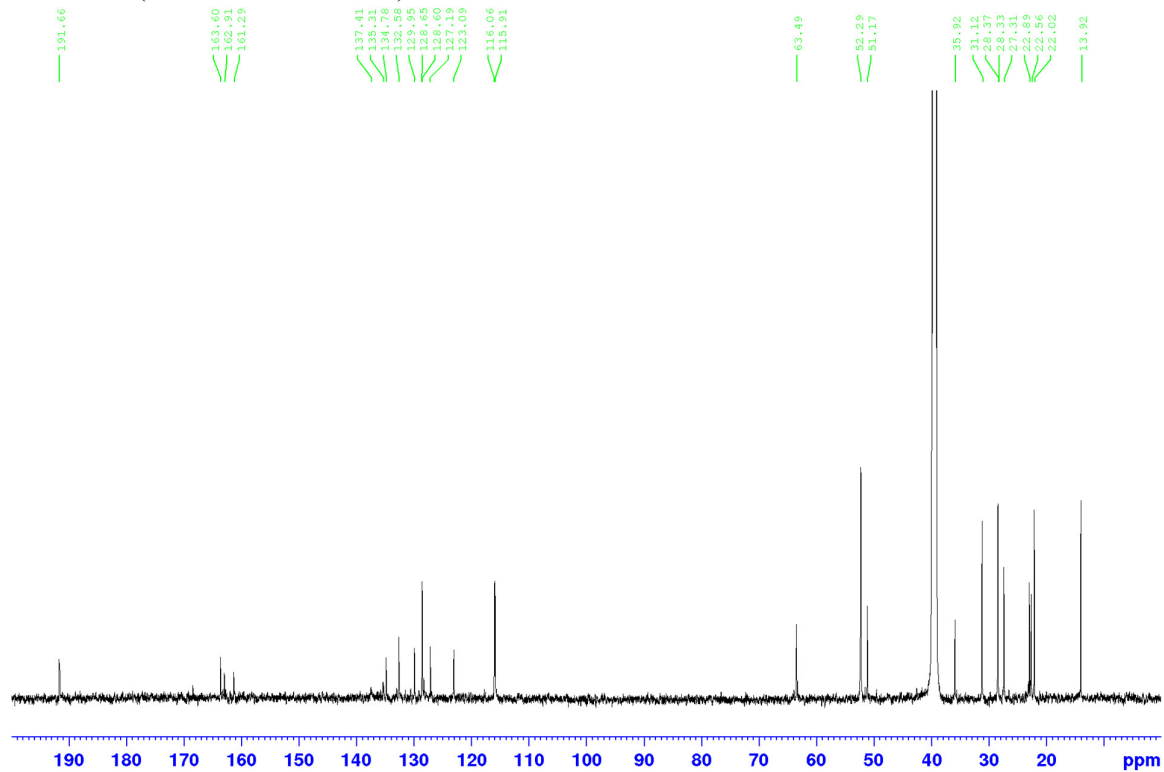


3-(2-(4'-Fluoro-4-(octylsulfonamido)-[1,1'-biphenyl]-3-yl)-2-oxoacetamido)-*N,N,N*-trimethylpropan-1-aminium iodide (**15b**)

$^1\text{H}$  NMR (600 MHz,  $\text{DMSO-}d_6$ ):

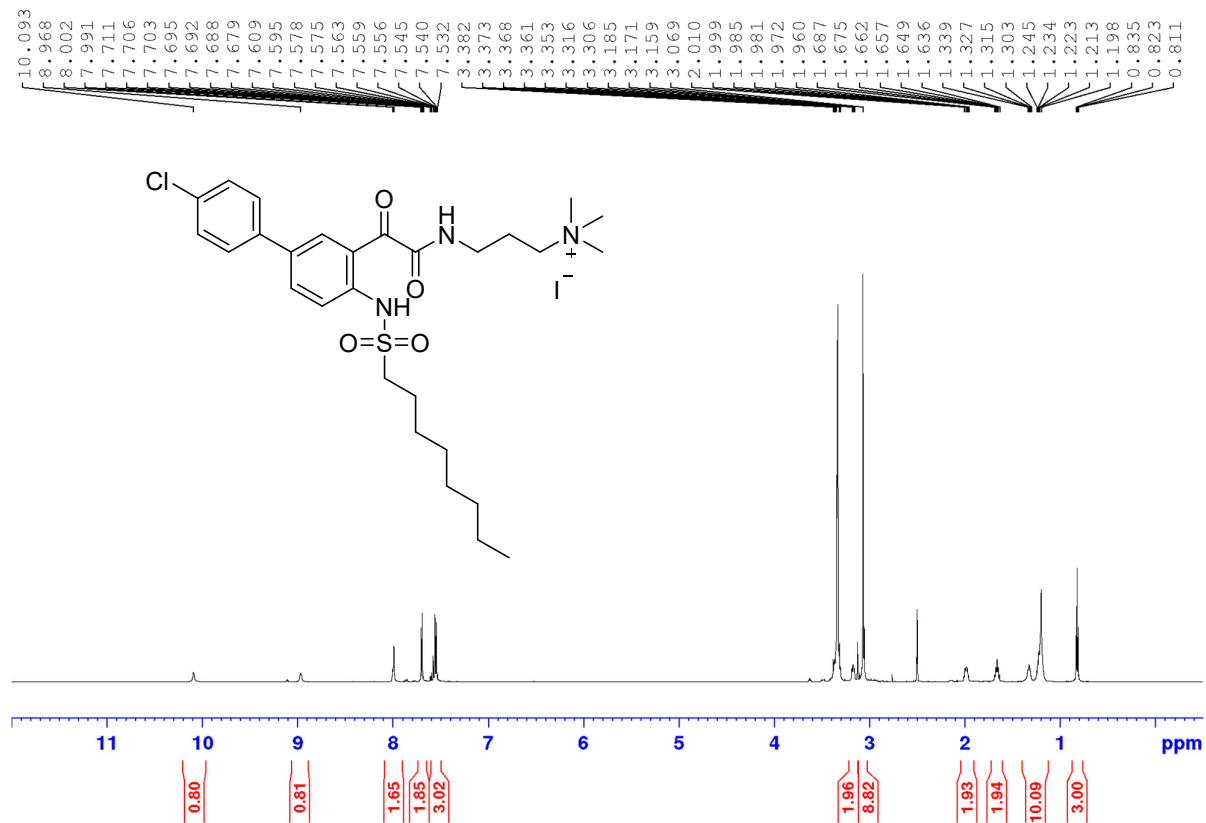


$^{13}\text{C}$  NMR (150 MHz,  $\text{DMSO-}d_6$ ):

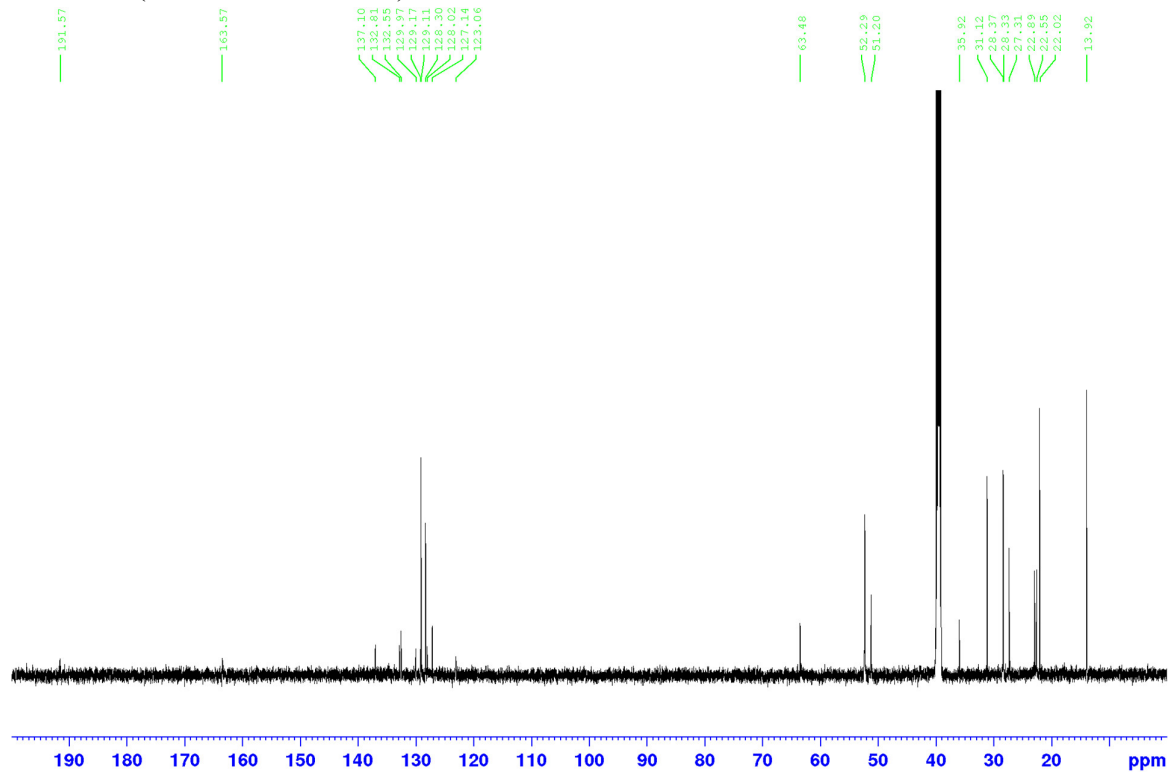


3-(2-(4'-Chloro-4-(octylsulfonamido)-[1,1'-biphenyl]-3-yl)-2-oxoacetamido)-*N,N,N*-trimethylpropan-1-aminium iodide (**15c**)

$^1\text{H}$  NMR (600 MHz,  $\text{DMSO-}d_6$ ):

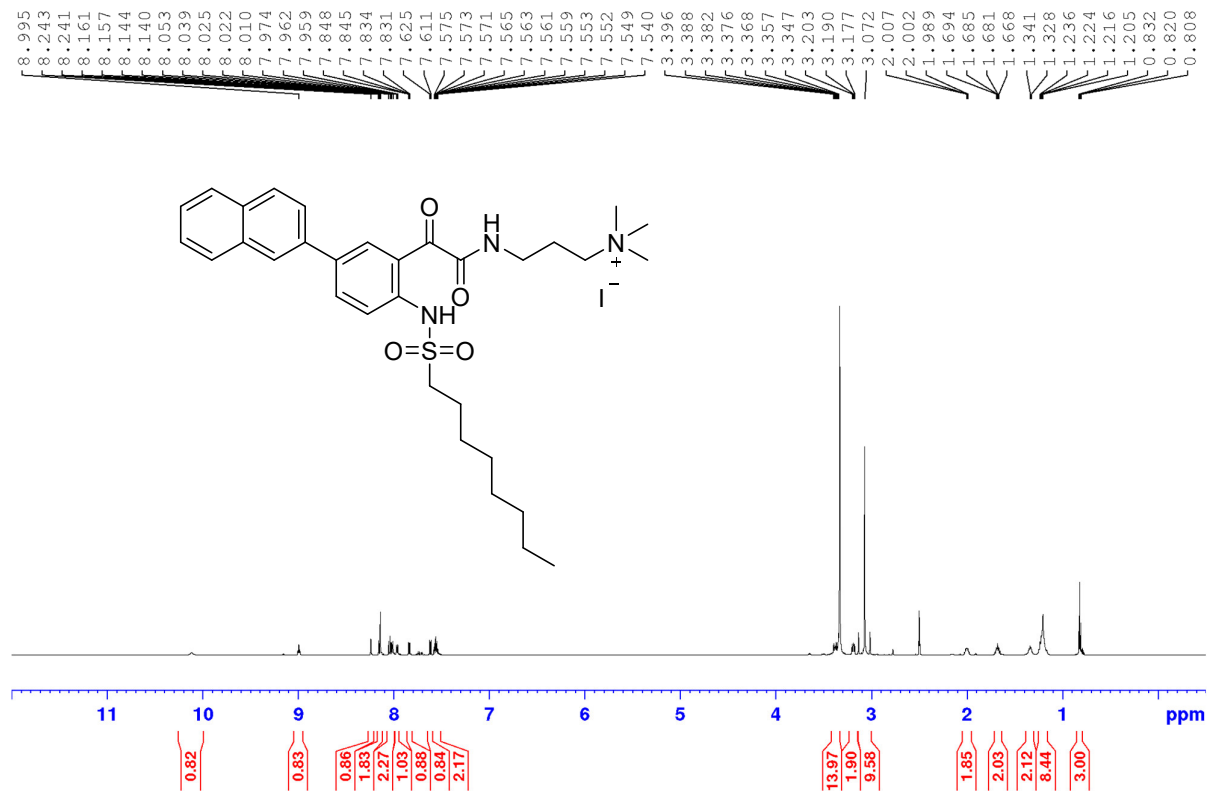


$^{13}\text{C}$  NMR (150 MHz,  $\text{DMSO-}d_6$ ):

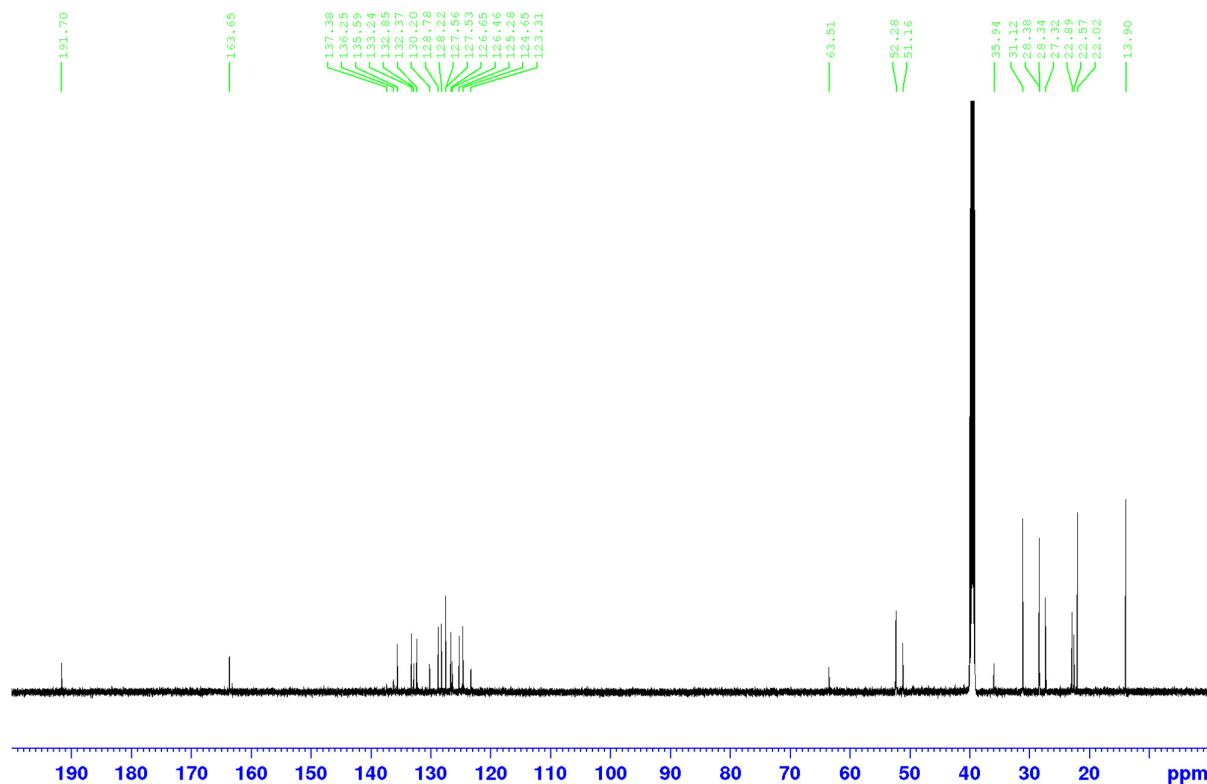


*N,N,N*-Trimethyl-3-(2-(5-(naphthalen-2-yl)-2-(octylsulfonamido)phenyl)-2-oxoacetamido)propan-1-aminium iodide (**15d**)

$^1\text{H}$  NMR (600 MHz,  $\text{DMSO-}d_6$ ):

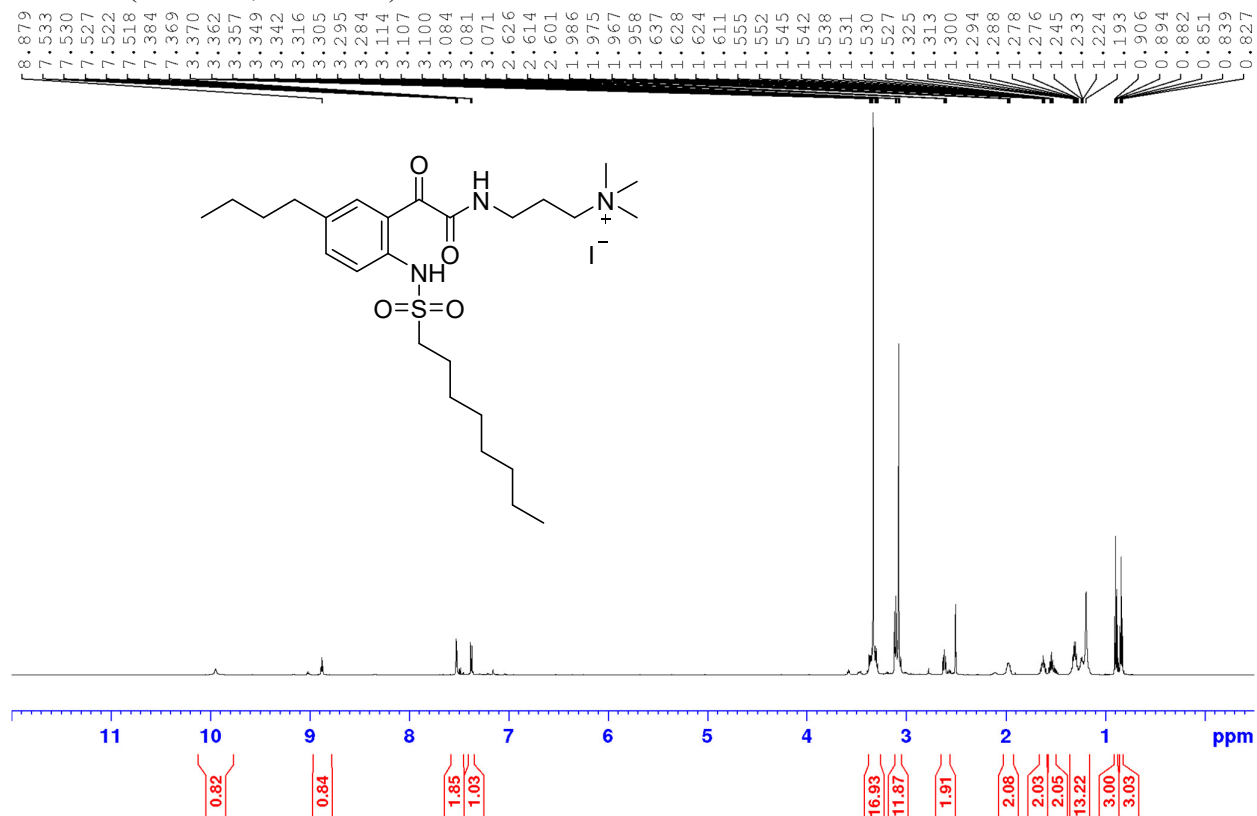


$^{13}\text{C}$  NMR (150 MHz,  $\text{DMSO-}d_6$ ):

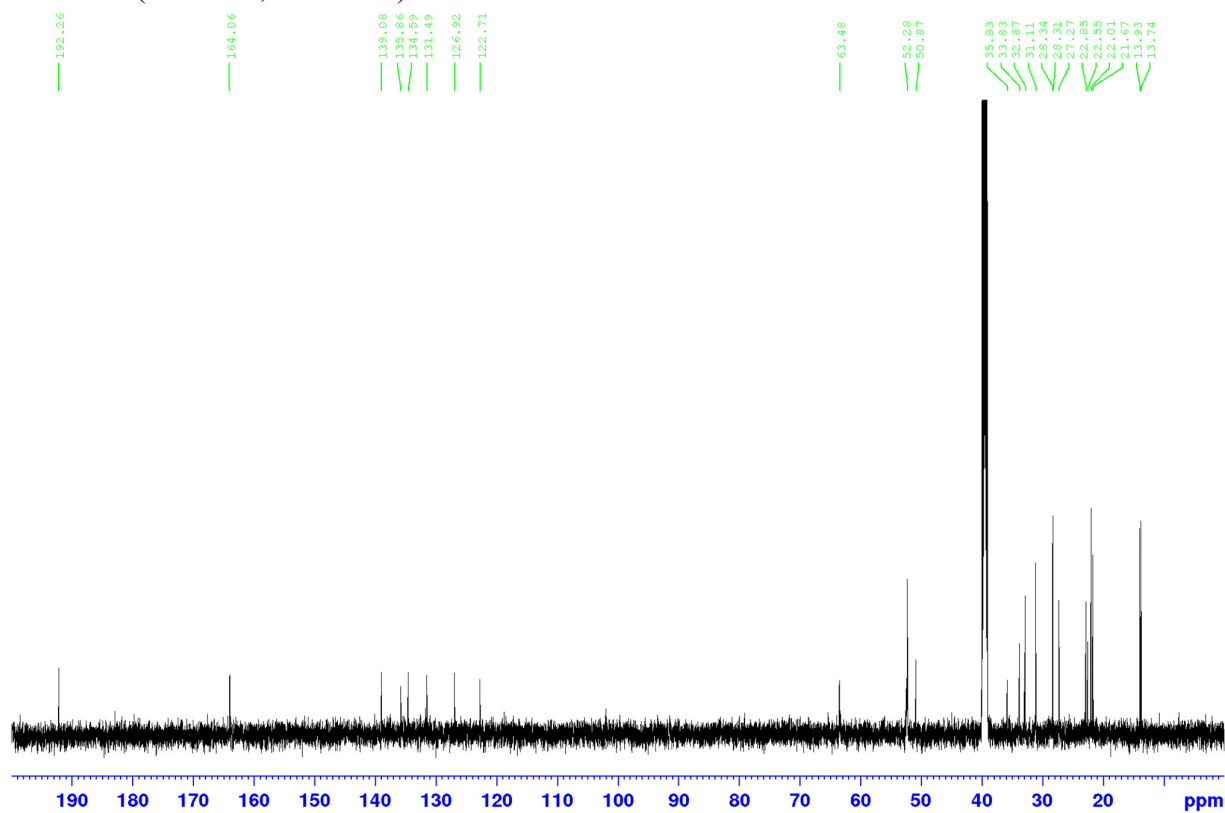


3-(2-(5-Butyl-2-(octylsulfonamido)phenyl)-2-oxoacetamido)-*N,N,N*-trimethylpropan-1-aminium iodide (**15e**)

<sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>):



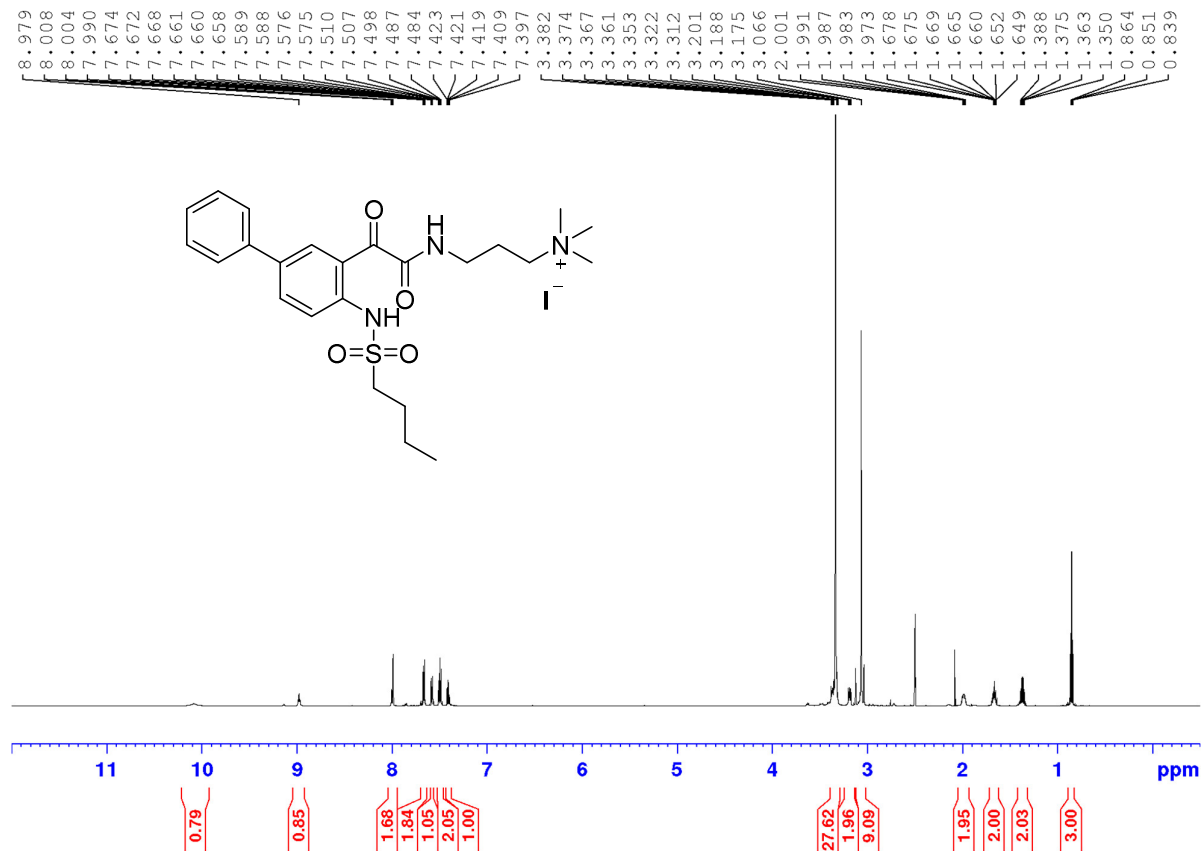
<sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>):



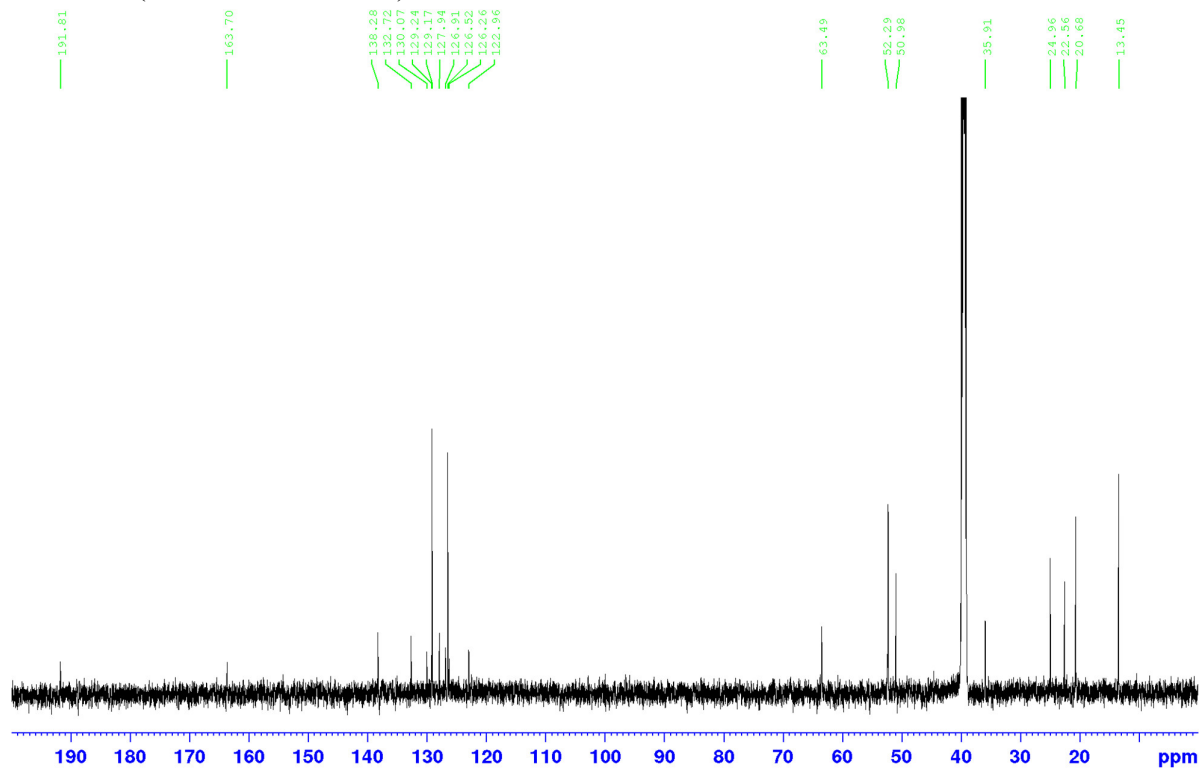


3-(2-(4-(Butylsulfonamido)-[1,1'-biphenyl]-3-yl)-2-oxoacetamido)-*N,N,N*-trimethylpropan-1-aminium iodide (**16a**)

<sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>):

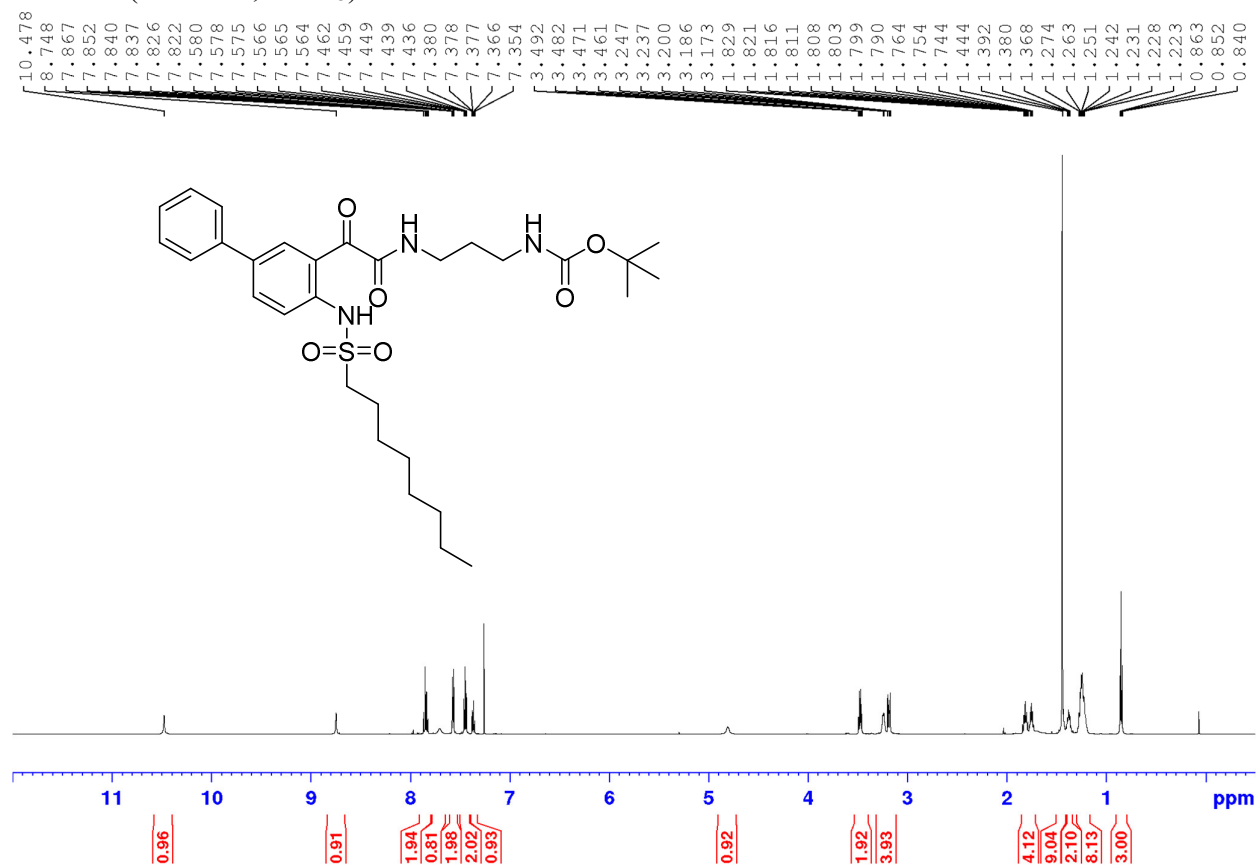


<sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>):

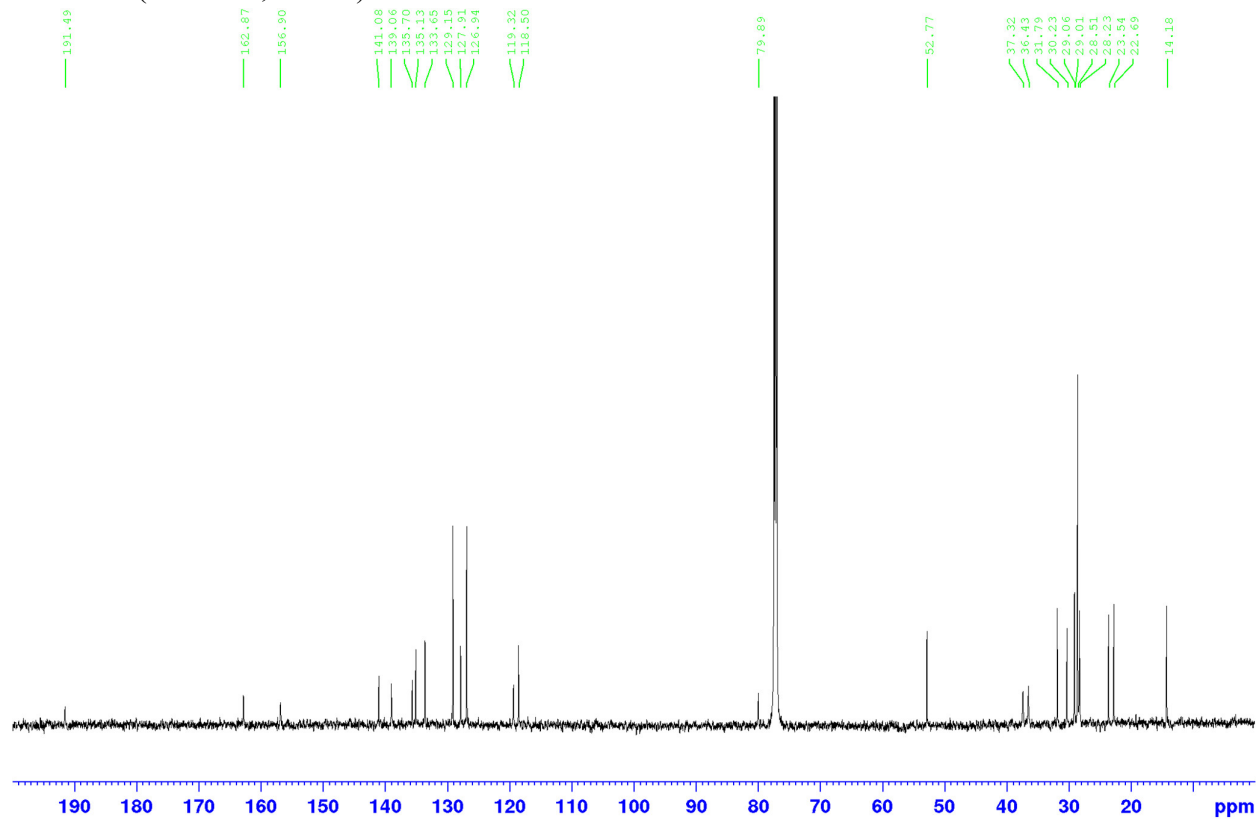


*tert*-Butyl (3-(2-(4-(octylsulfonamido)-[1,1'-biphenyl]-3-yl)-2-oxoacetamido)propyl)carbamate (**18a**)

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):

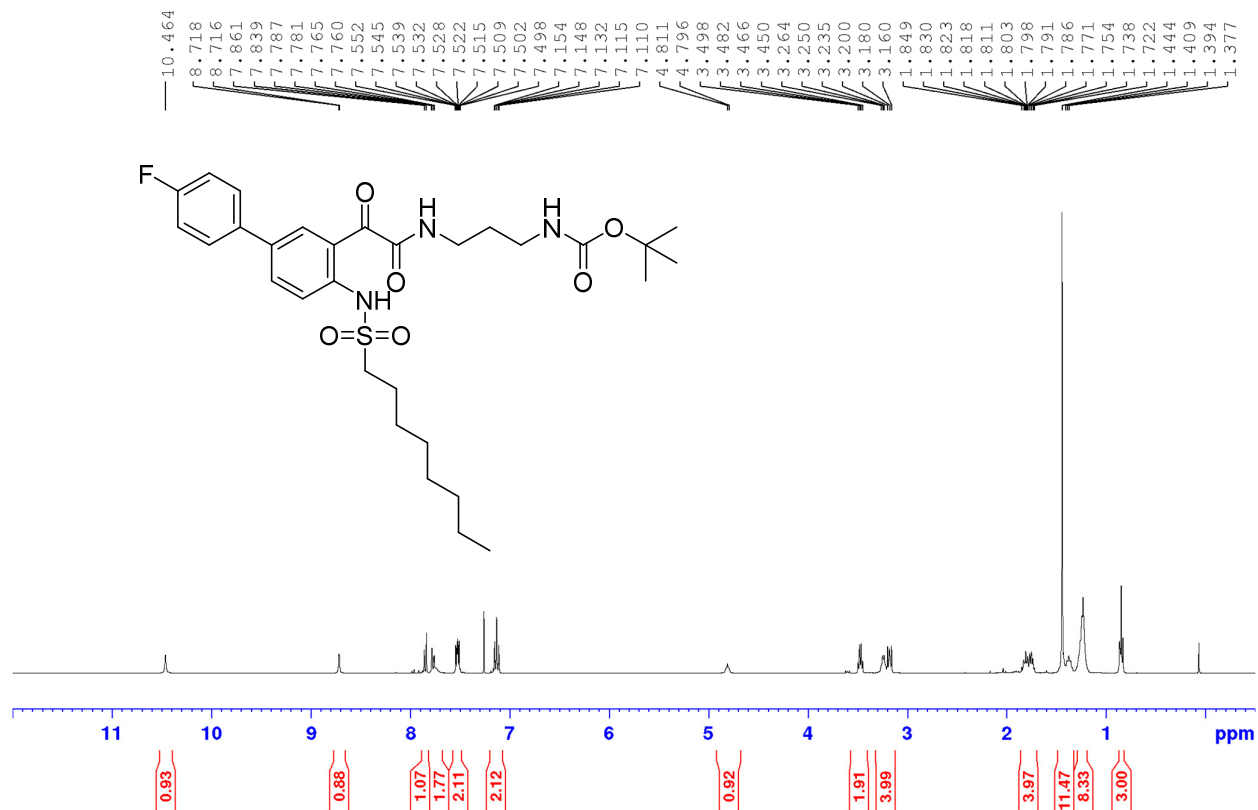


<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):

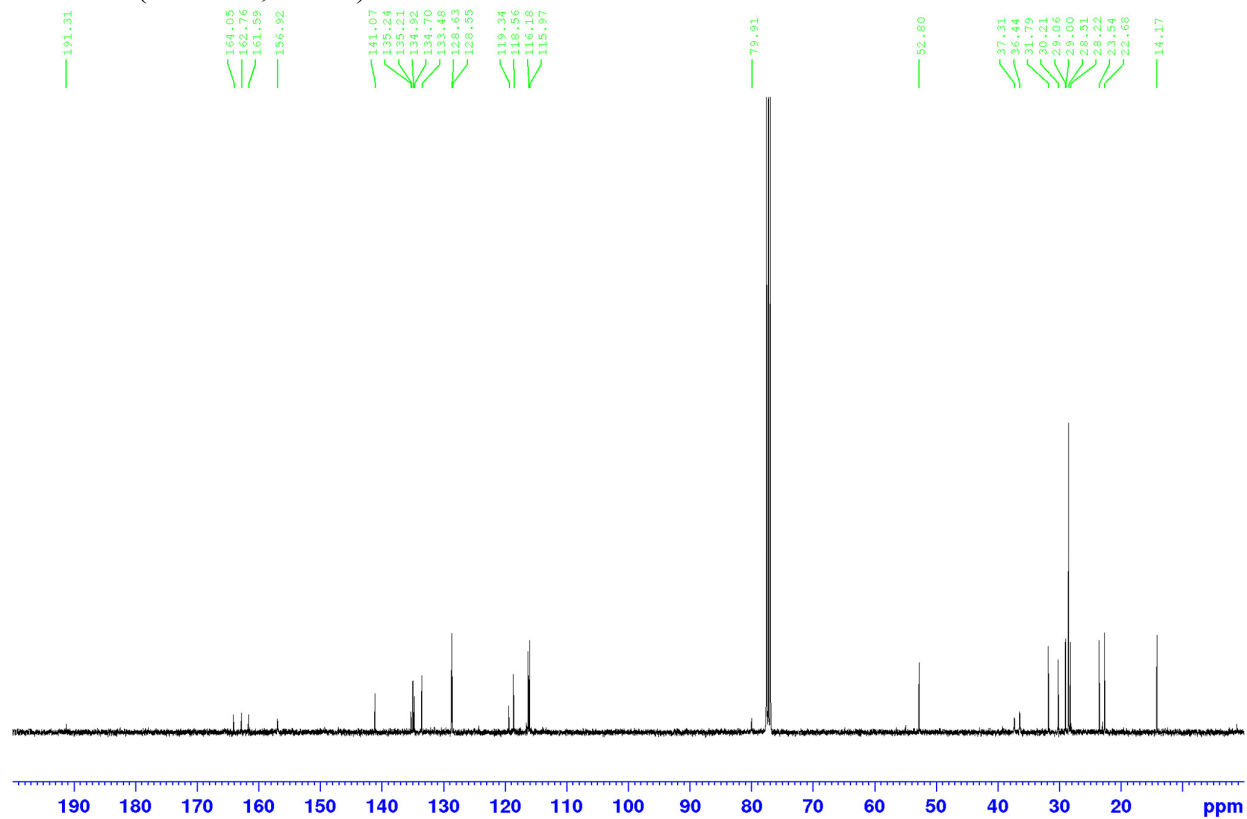


*tert*-Butyl (3-(2-(4'-fluoro-4-(octylsulfonamido)-[1,1'-biphenyl]-3-yl)-2-oxoacetamido)propyl) carbamate (**18b**)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):

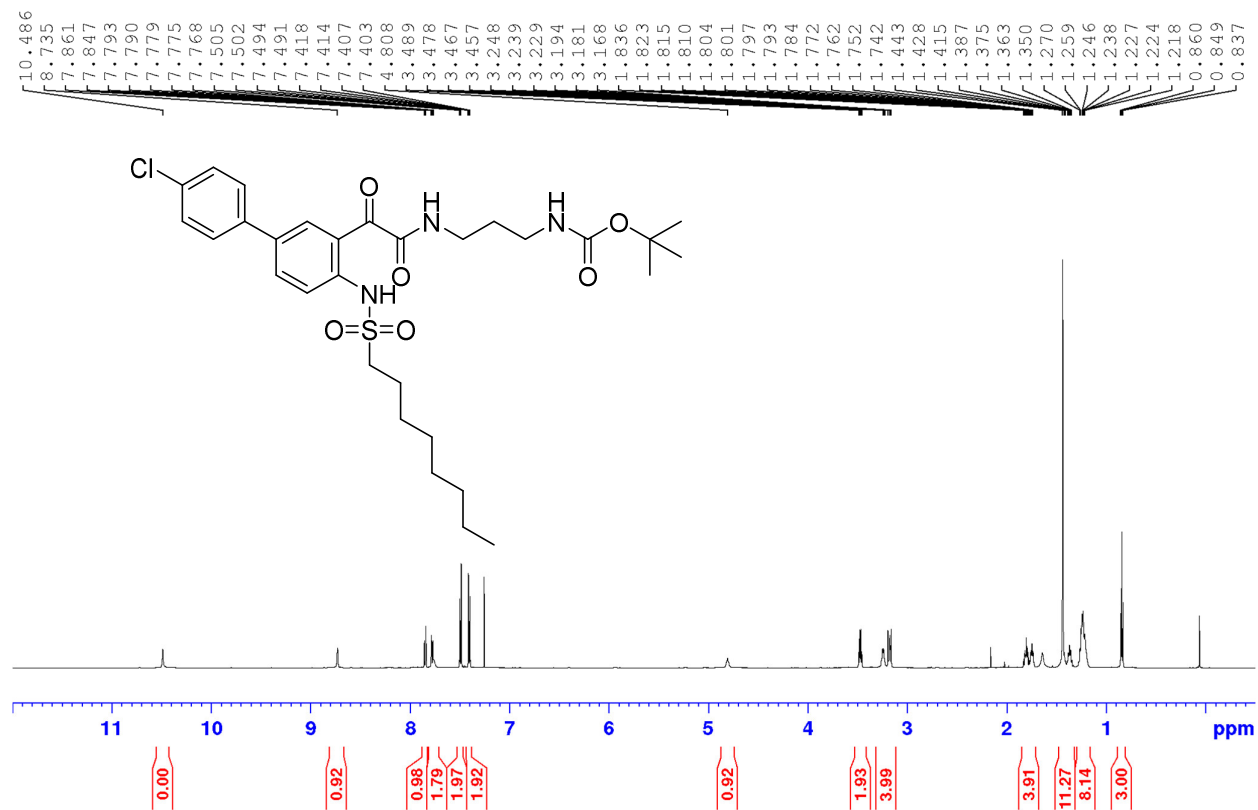


$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):

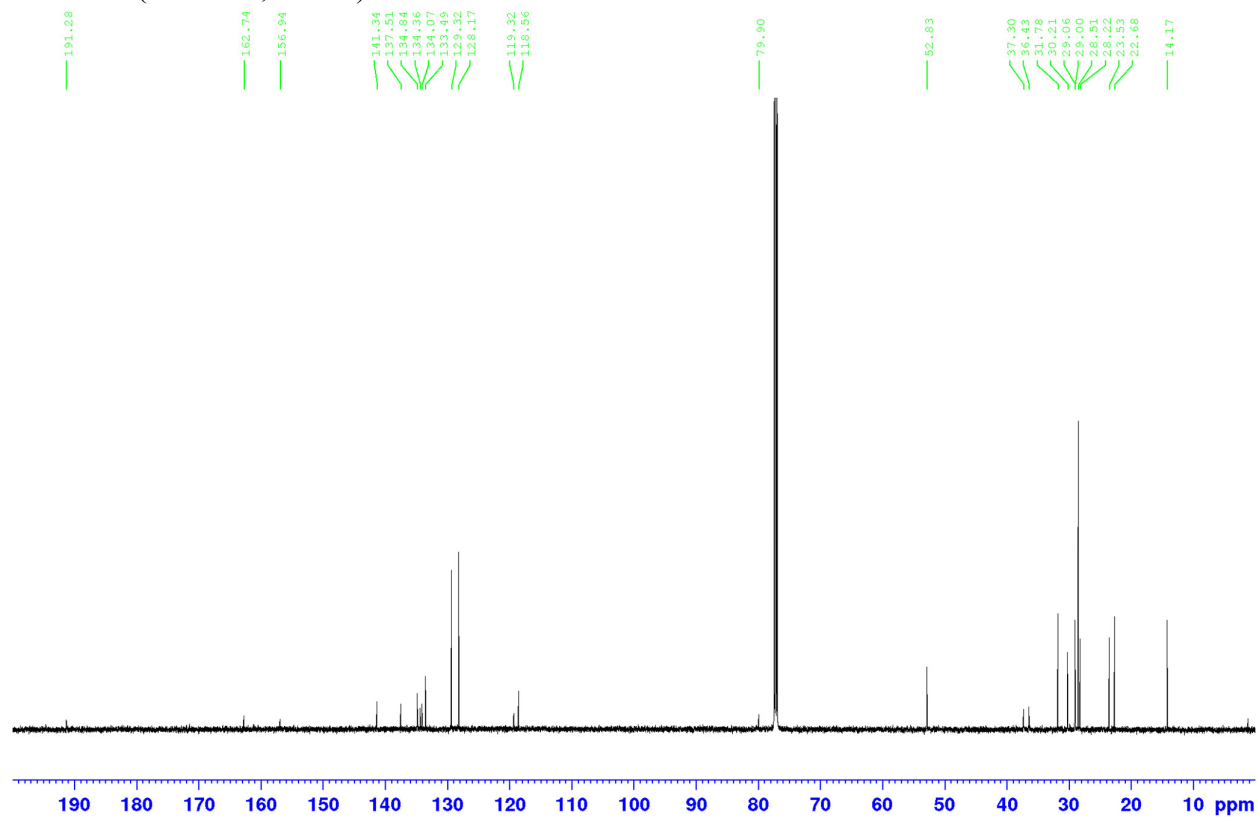


*tert*-Butyl (3-(2-(4'-Chloro-4-(octylsulfonamido)-[1,1'-biphenyl]-3-yl)-2-oxoacetamido)propyl) carbamate (**18c**)

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):

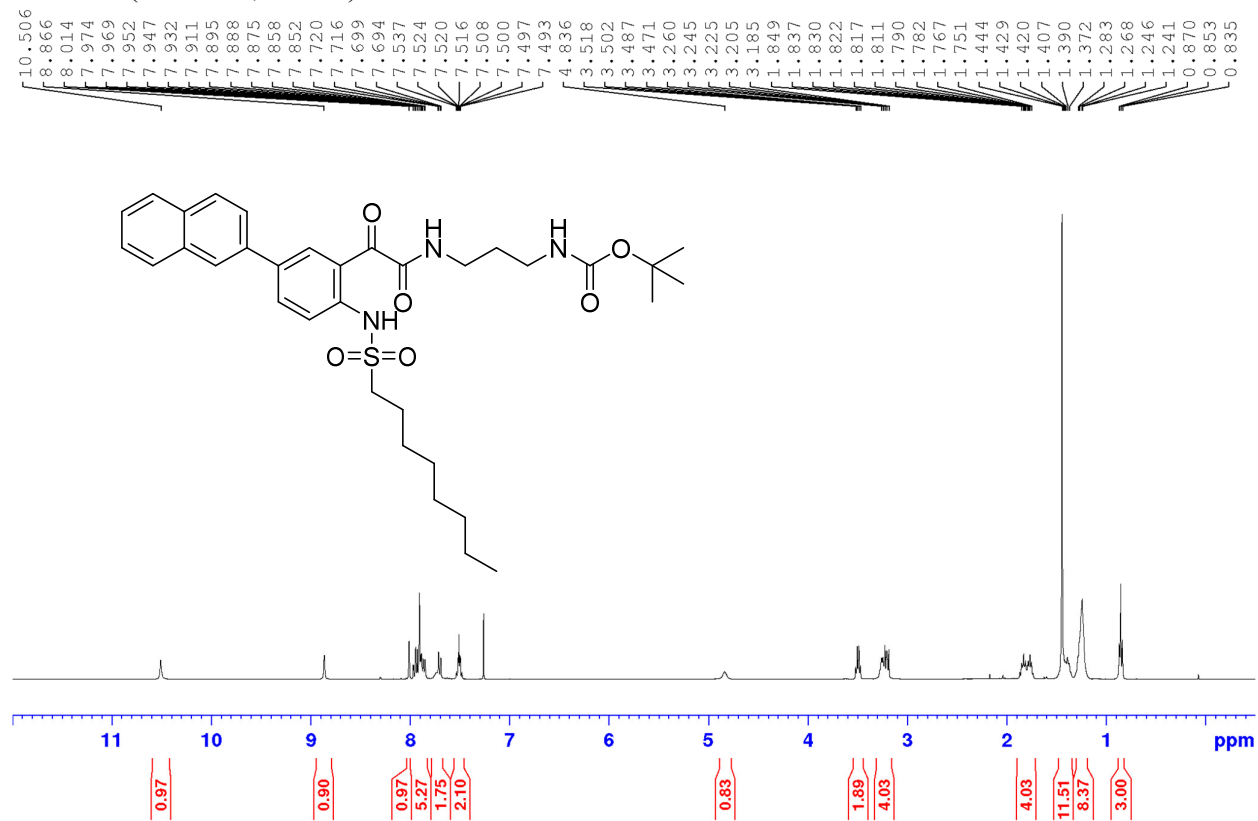


<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):

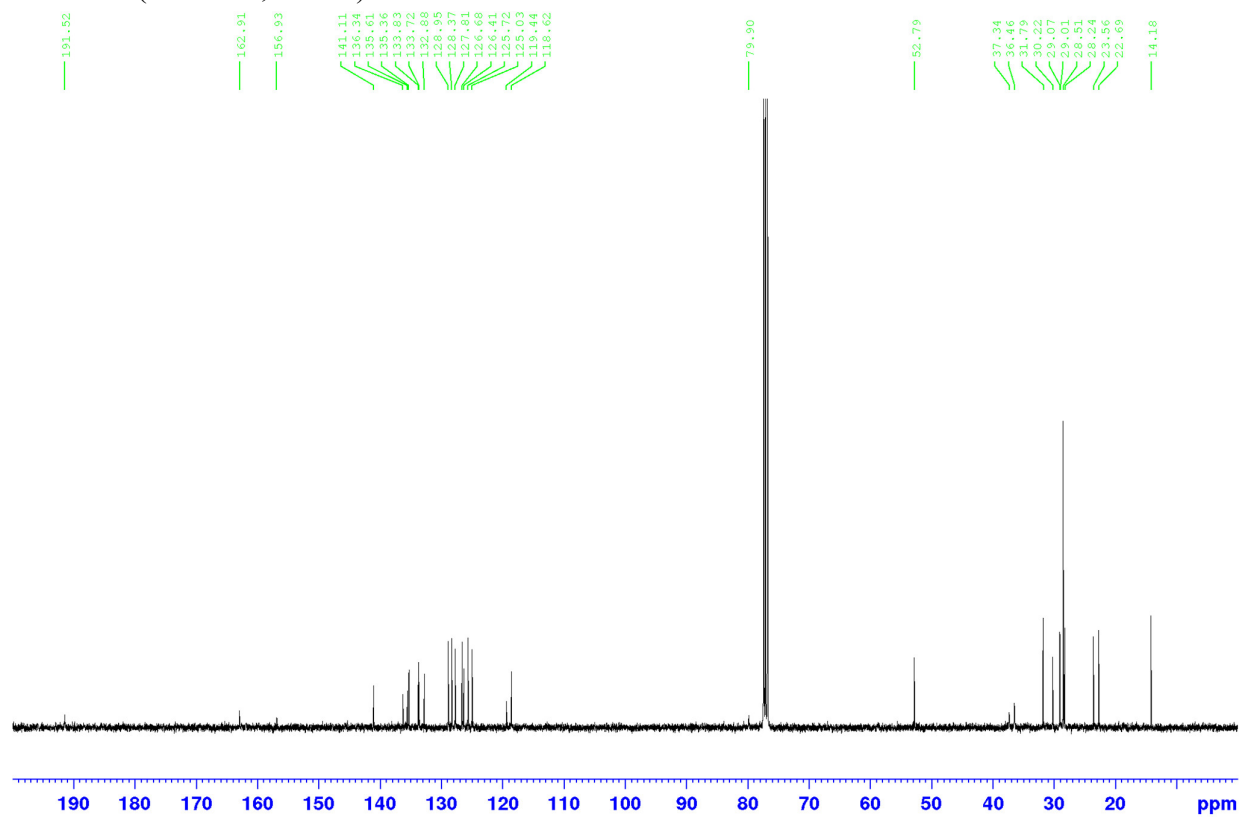


*tert*-Butyl (3-(2-(5-(naphthalen-2-yl)-2-(octylsulfonamido)phenyl)-2-oxoacetamido)propyl) carbamate (18d)

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):

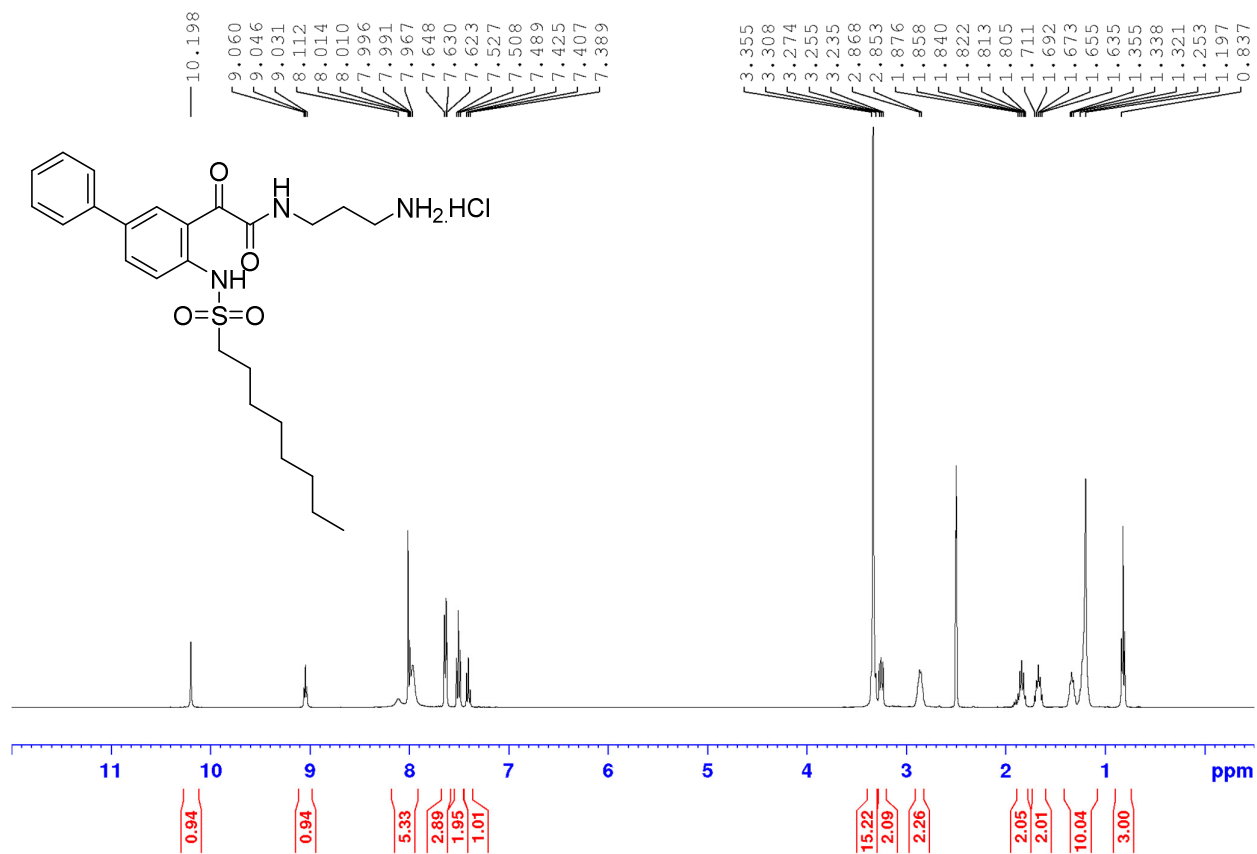


<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):

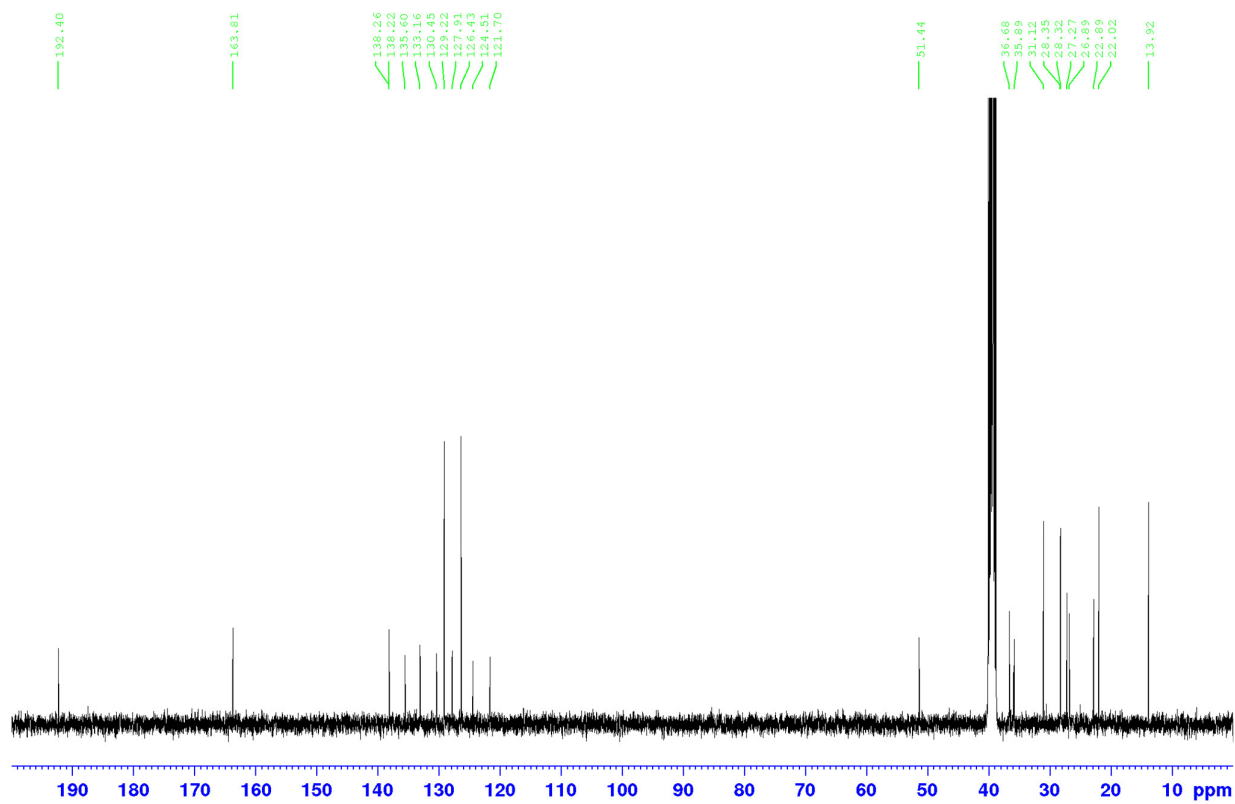


*N*-(3-Aminopropyl)-2-(4-(octylsulfonamido)-[1,1'-biphenyl]-3-yl)-2-oxoacetamide hydrochloride (**19a**)

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):

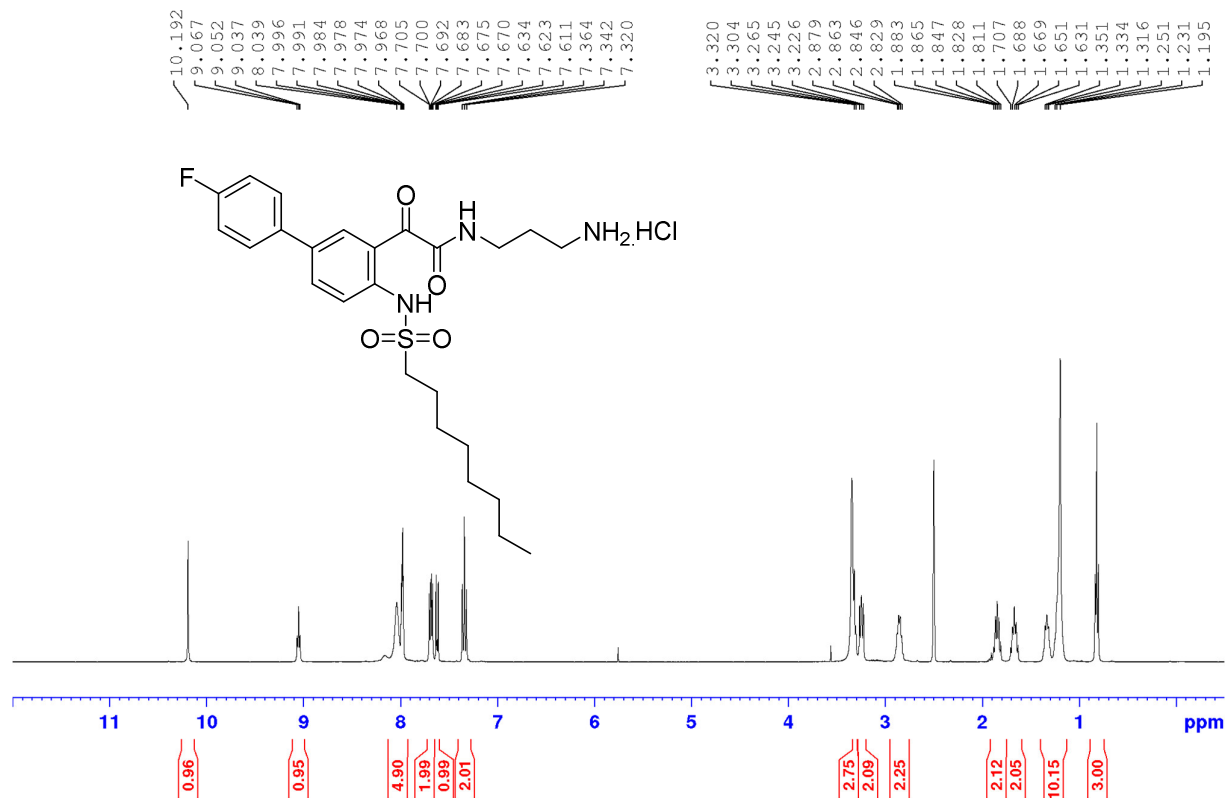


<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):

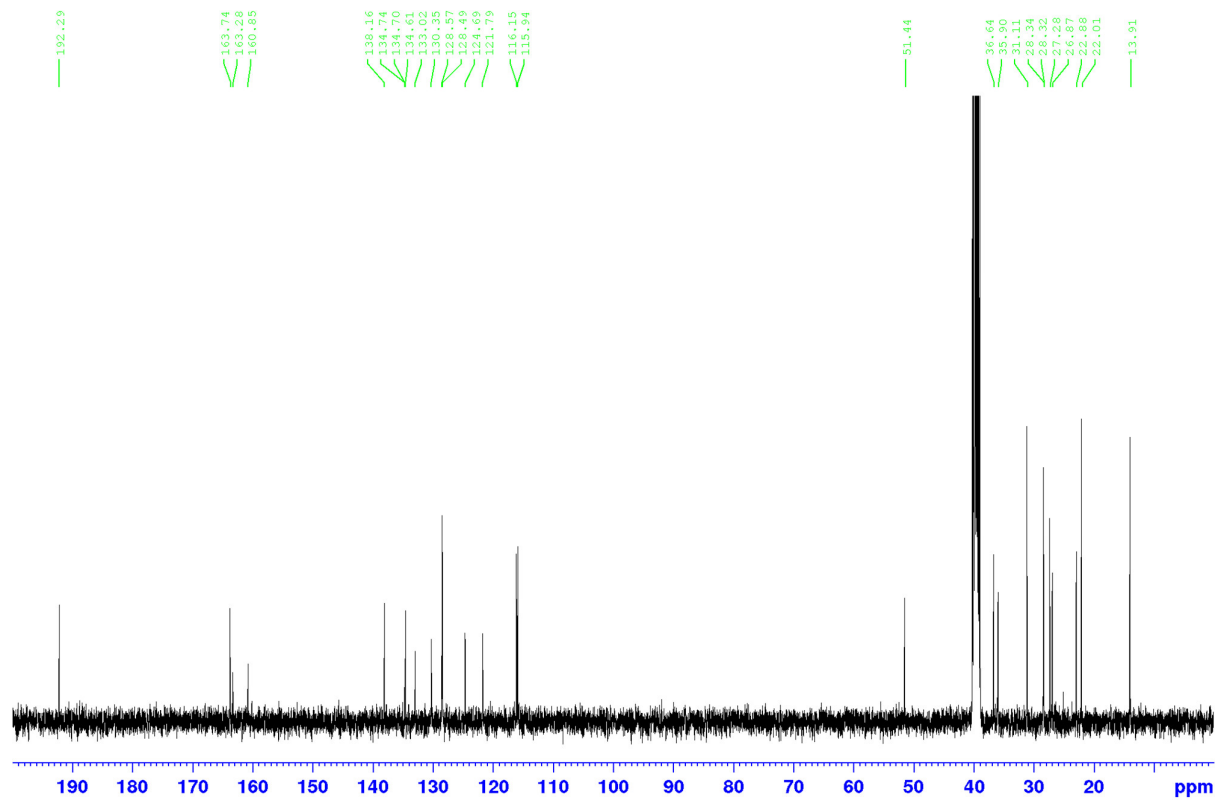


*N*-(3-Aminopropyl)-2-(4'-fluoro-4-(octylsulfonamido)-[1,1'-biphenyl]-3-yl)-2-oxoacetamide hydrochloride (**19b**)

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):

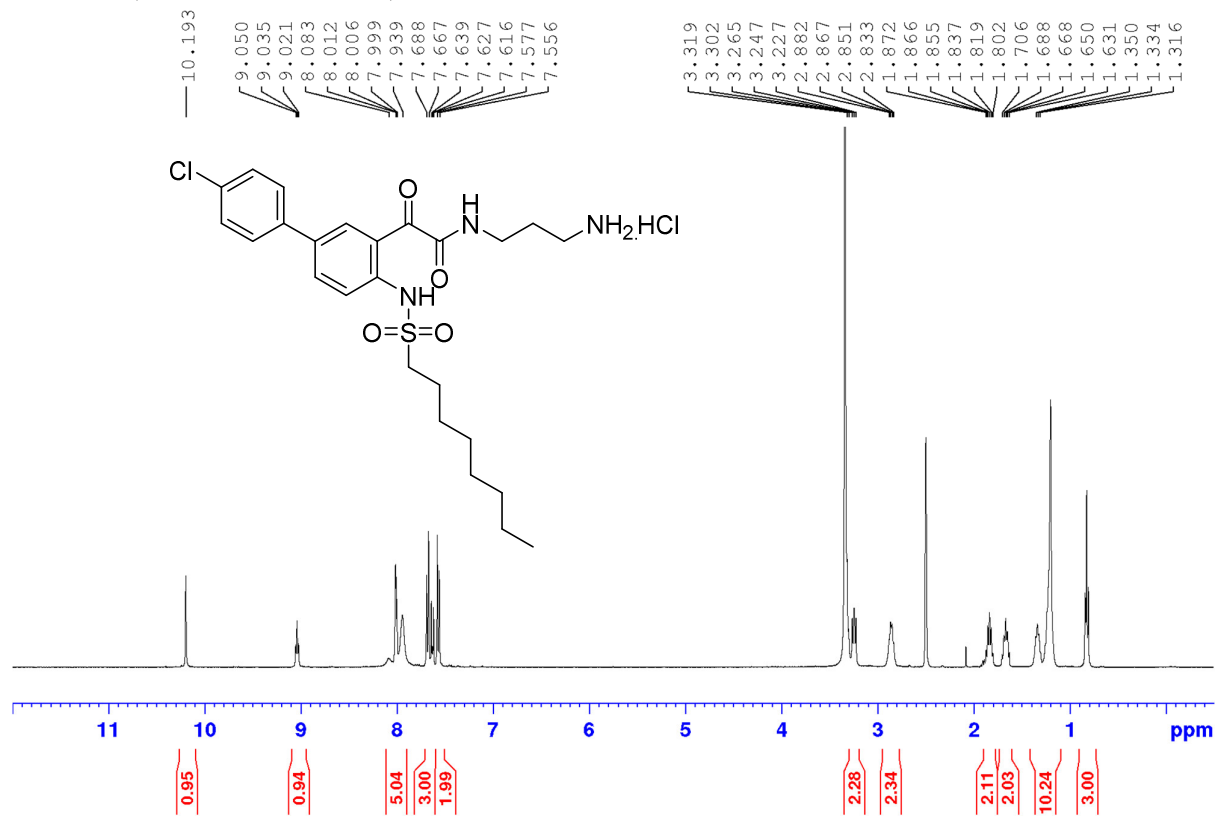


<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):

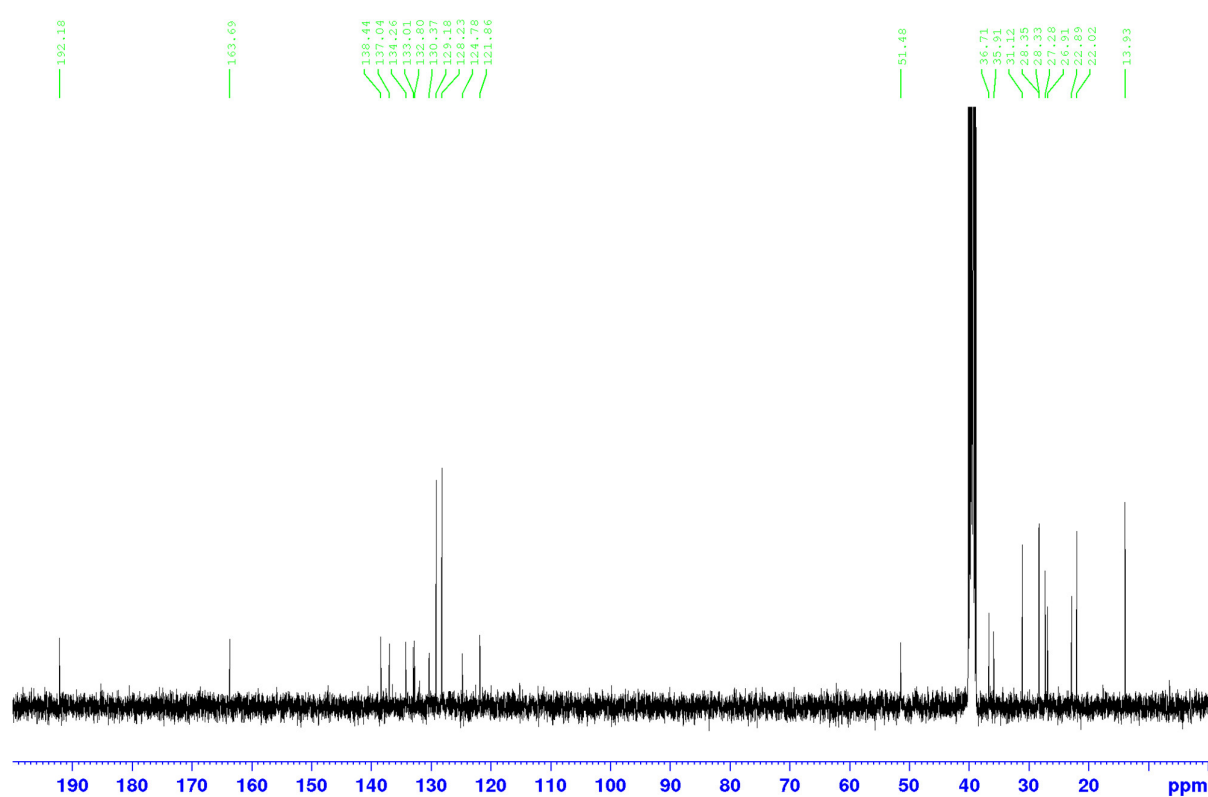


*N*-(3-Aminopropyl)-2-(4'-chloro-4-(octylsulfonamido)-[1,1'-biphenyl]-3-yl)-2-oxoacetamide hydrochloride (**19c**)

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):



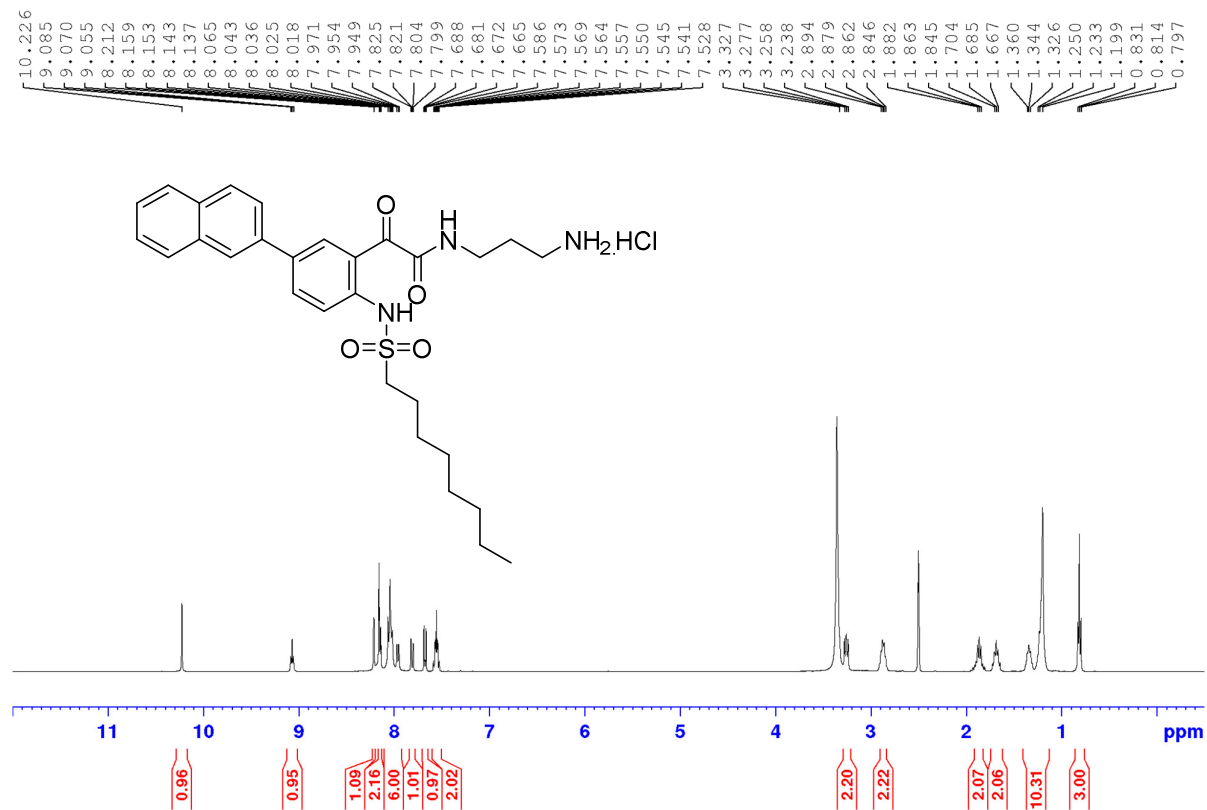
$^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):



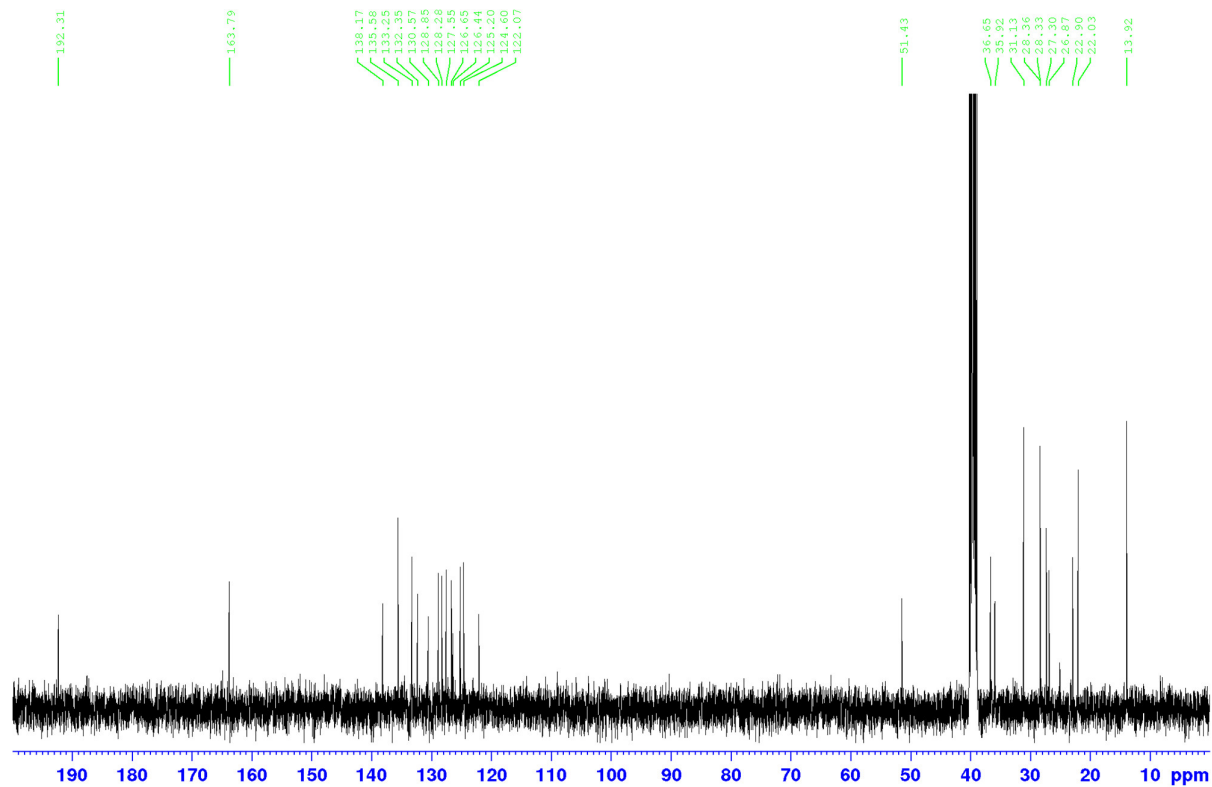


*N*-(3-Aminopropyl)-2-(5-(naphthalen-2-yl)-2-(octylsulfonamido)phenyl)-2-oxoacetamide hydrochloride (**19d**)

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):

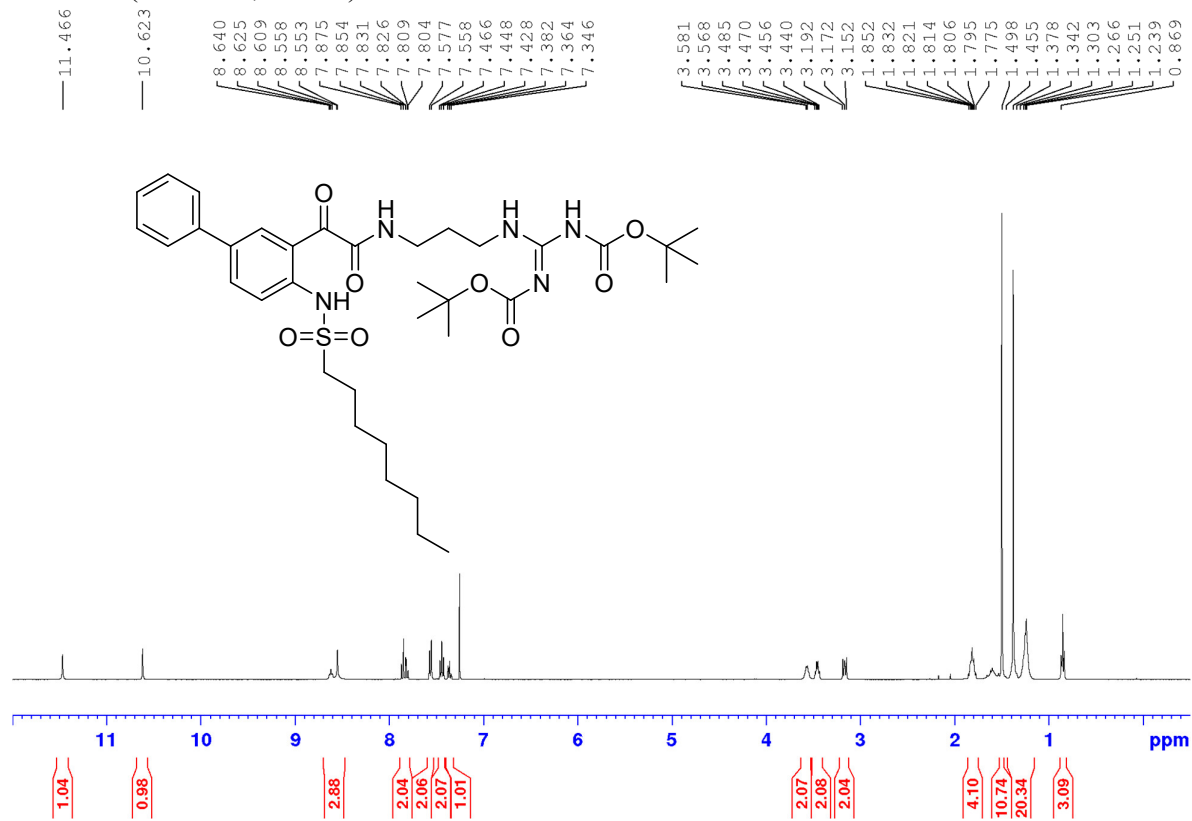


<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):

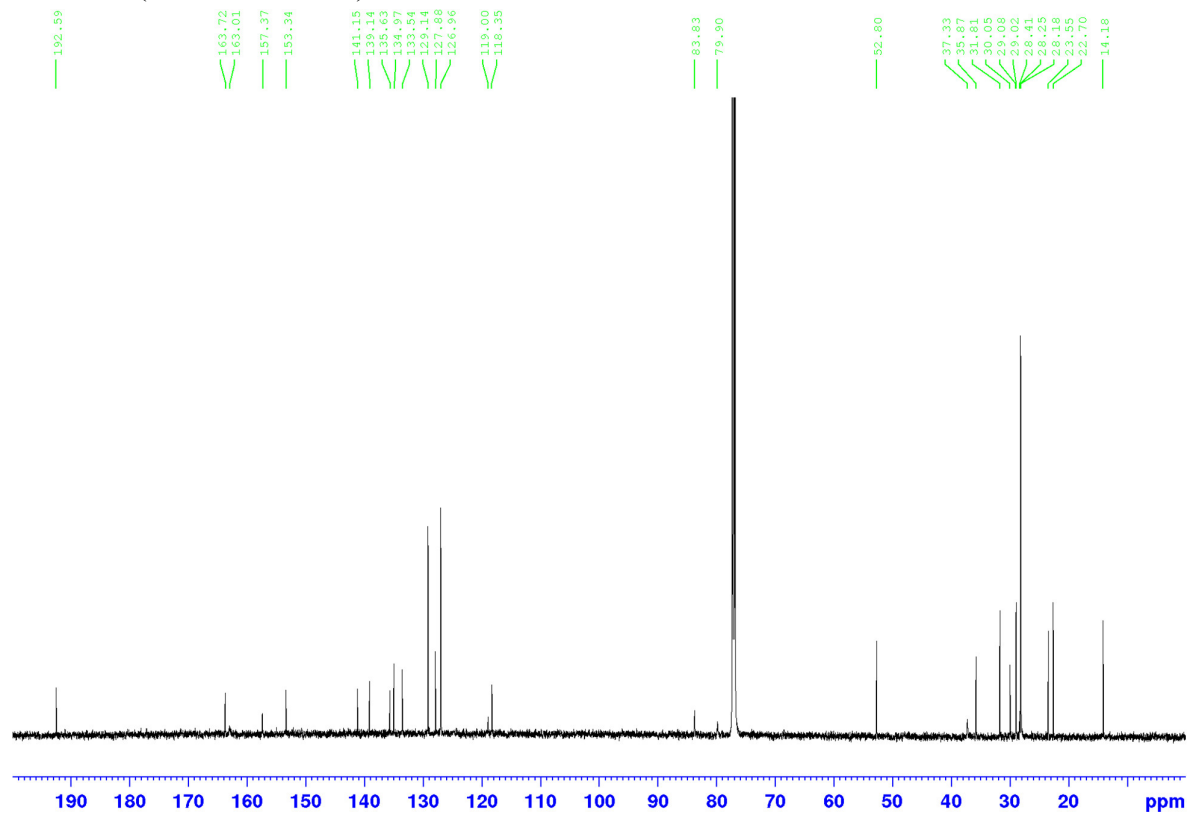


(*E*)-1-*tert*-Butyl-*N*-(*N'*-((*tert*-butyloxidanyl)carbonyl)-*N*-(3-(2-(4-(octylsulfonamido)-[1,1'-biphenyl]-3-yl)-2-oxoacetamido)propyl)carbamimidoyl)-1-oxidanecarboxamide (**21a**)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):

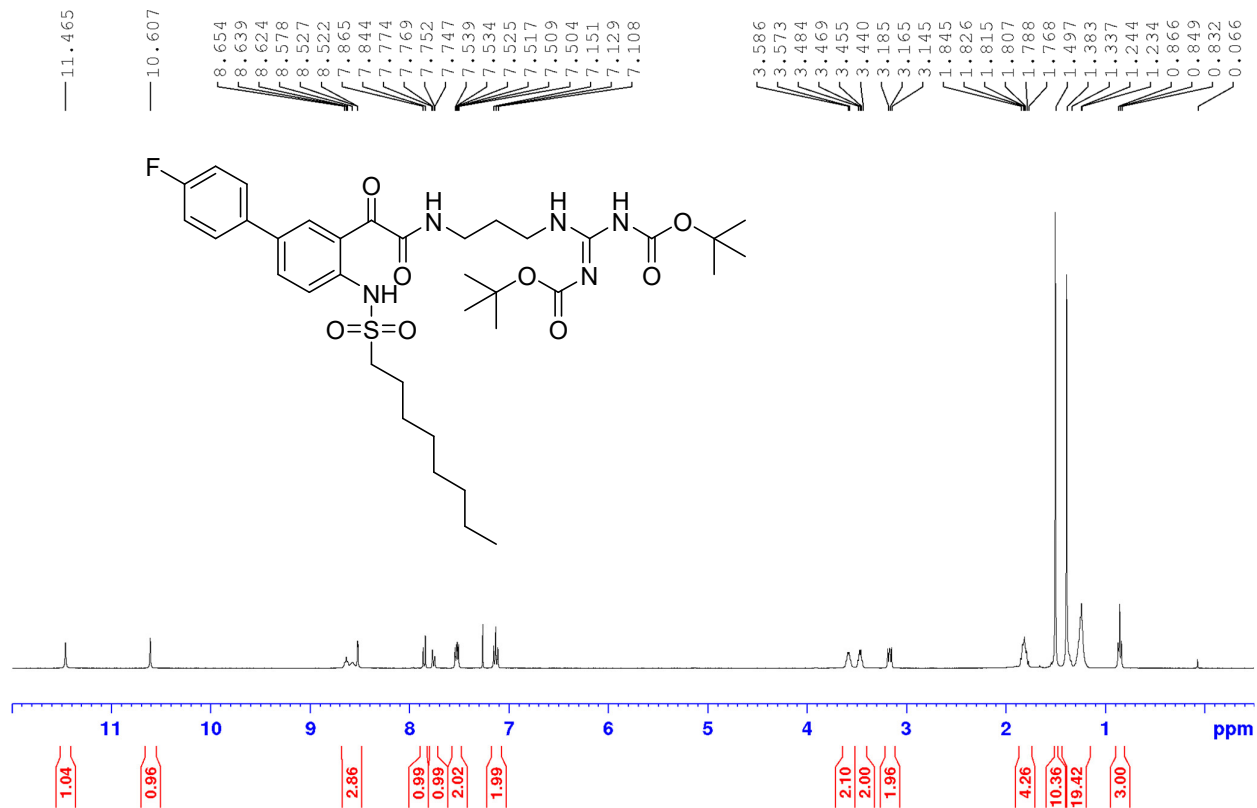


$^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):

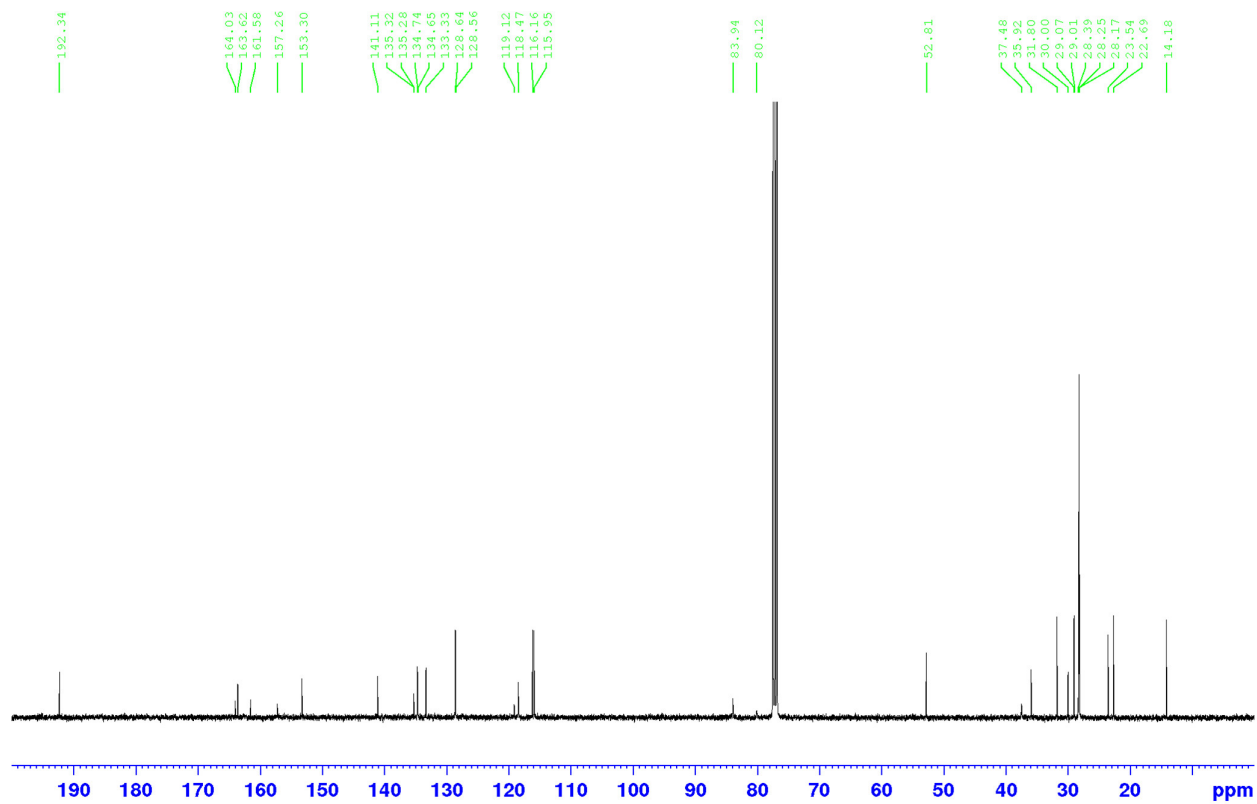


(*E*)-1-*tert*-Butyl-*N*-(*N'*-((*tert*-butyloxidanyl)carbonyl)-*N*-(3-(2-(4'-fluoro-4-(octylsulfonamido)-[1,1'-biphenyl]-3-yl)-2-oxoacetamido)propyl)carbamidoyl)-1-oxidanecarboxamide (**21b**)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):

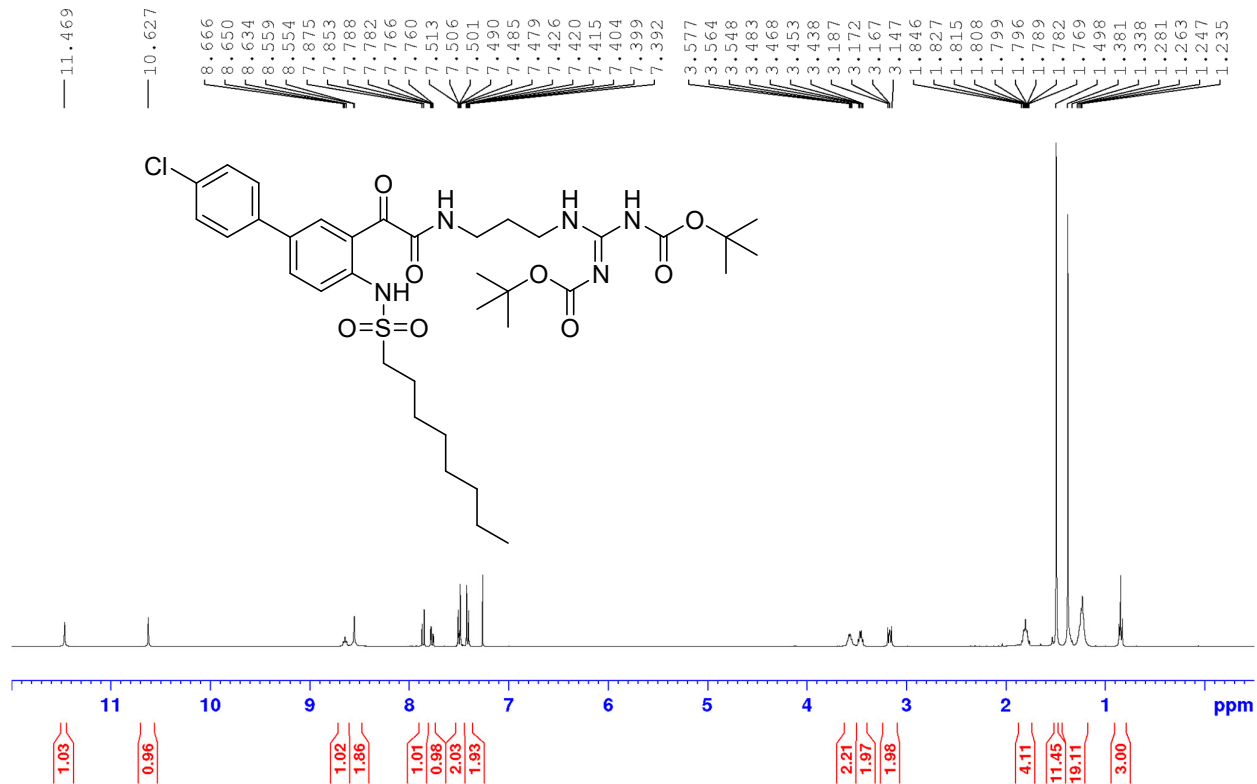


$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):

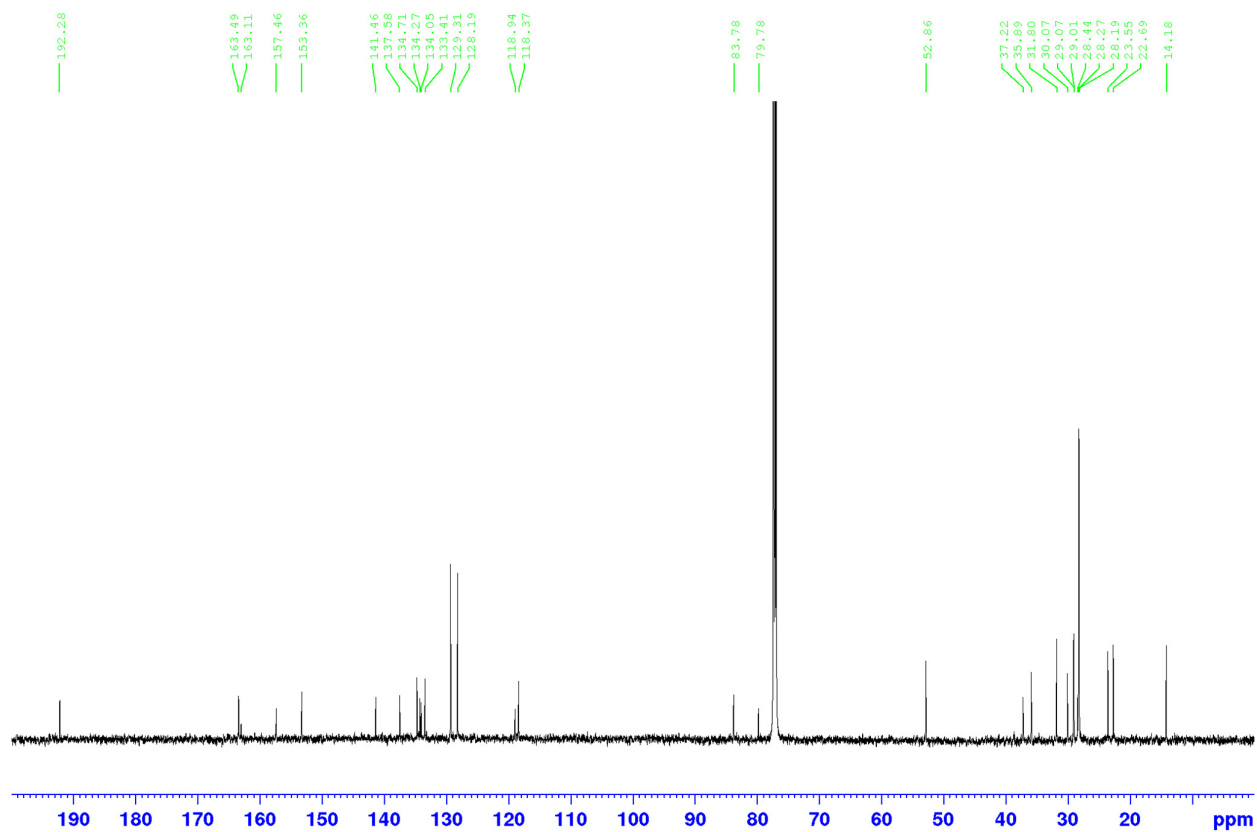


(*E*)-1-*tert*-Butyl-*N*-(*N'*-((*tert*-butyloxidanyl)carbonyl)-*N*-(3-(2-(4'-chloro-4-(octylsulfonamido)-[1,1'-biphenyl]-3-yl)-2-oxoacetamido)propyl)carbamimidoyl)-1-oxidanecarboxamide (**21c**)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):

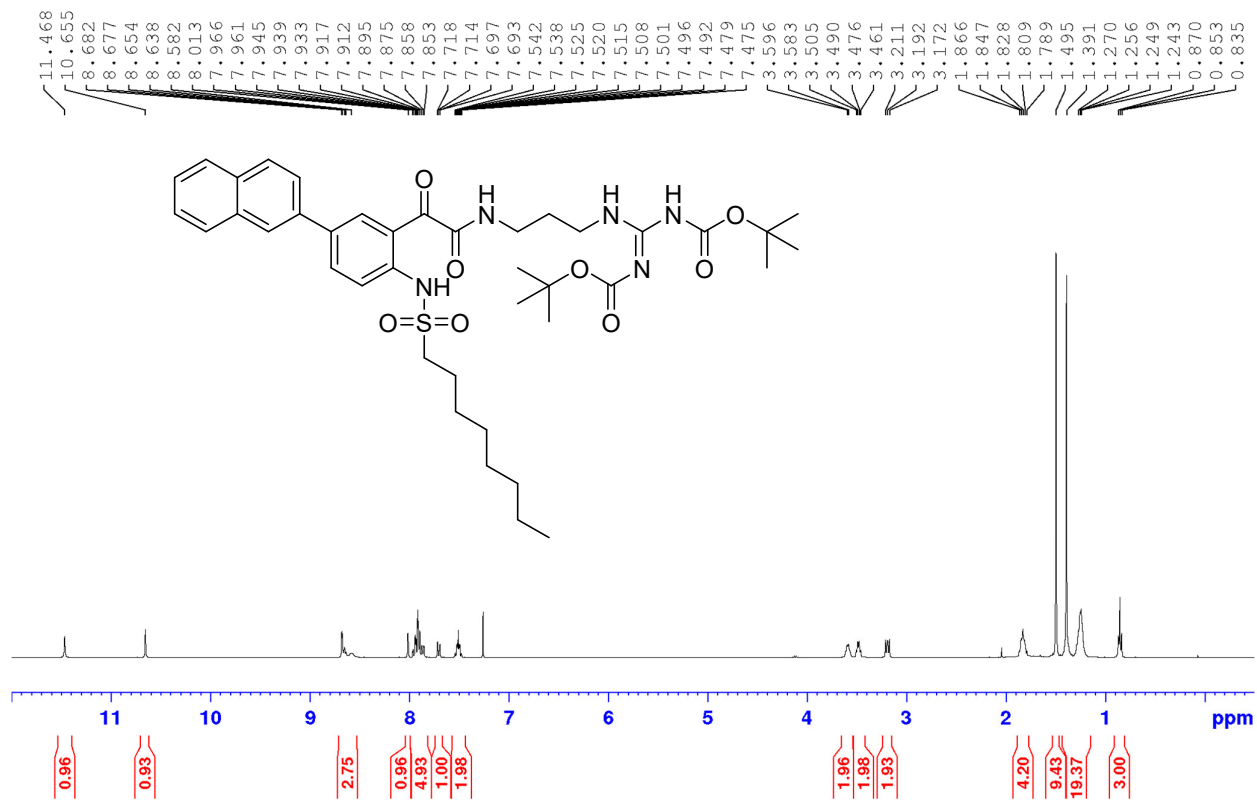


$^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):

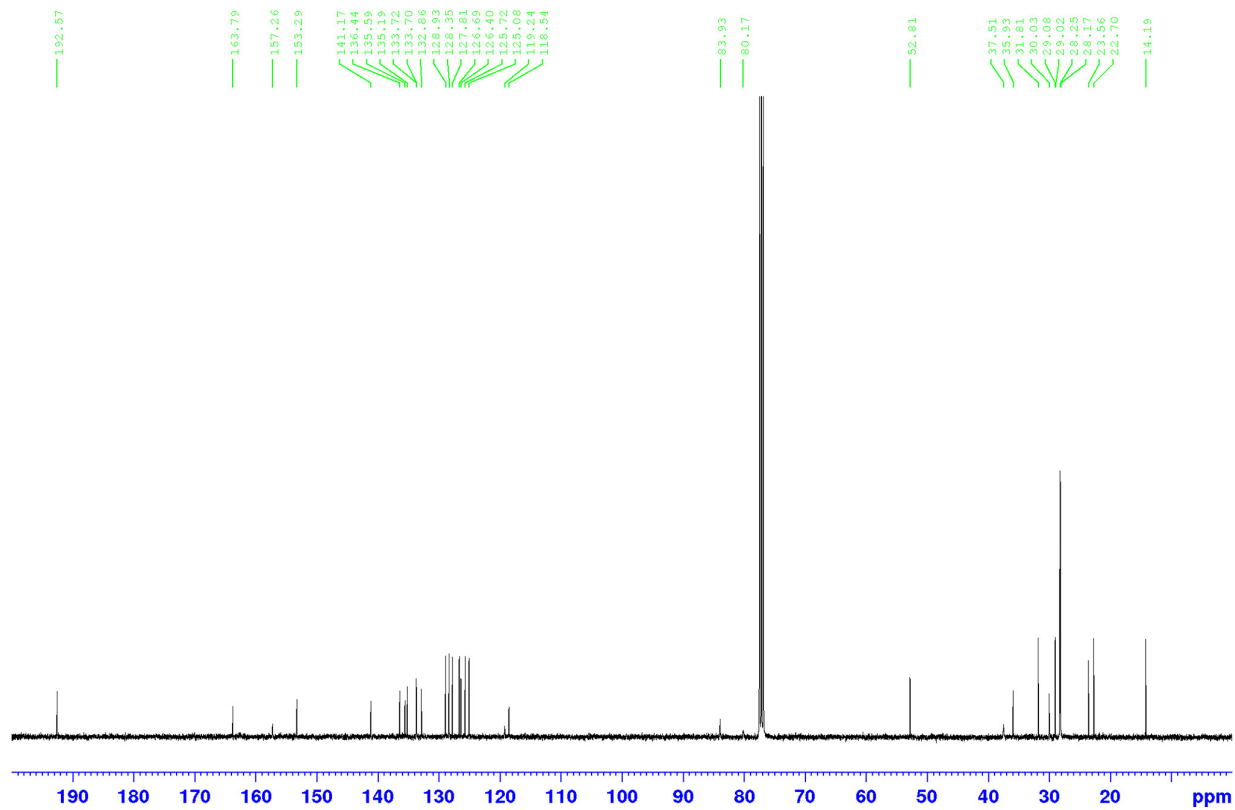


(*E*)-1-*tert*-Butyl-*N*-(*N'*-((*tert*-butyloxidanyl)carbonyl)-*N*-(3-(2-(5-(naphthalen-2-yl)-2-(octylsulfonamido)phenyl)-2-oxoacetamido)propyl)carbamimidoyl)-1-oxidanecarboxamide (**21d**)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):

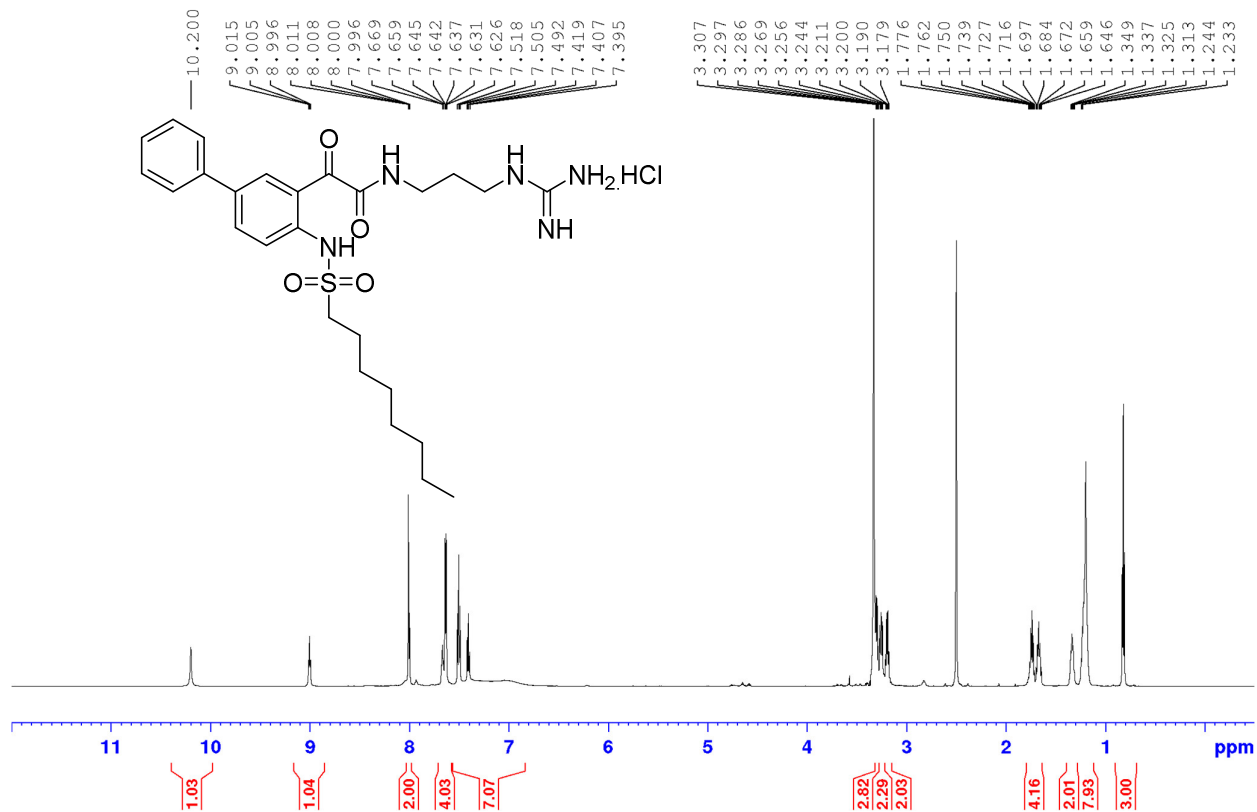


$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):

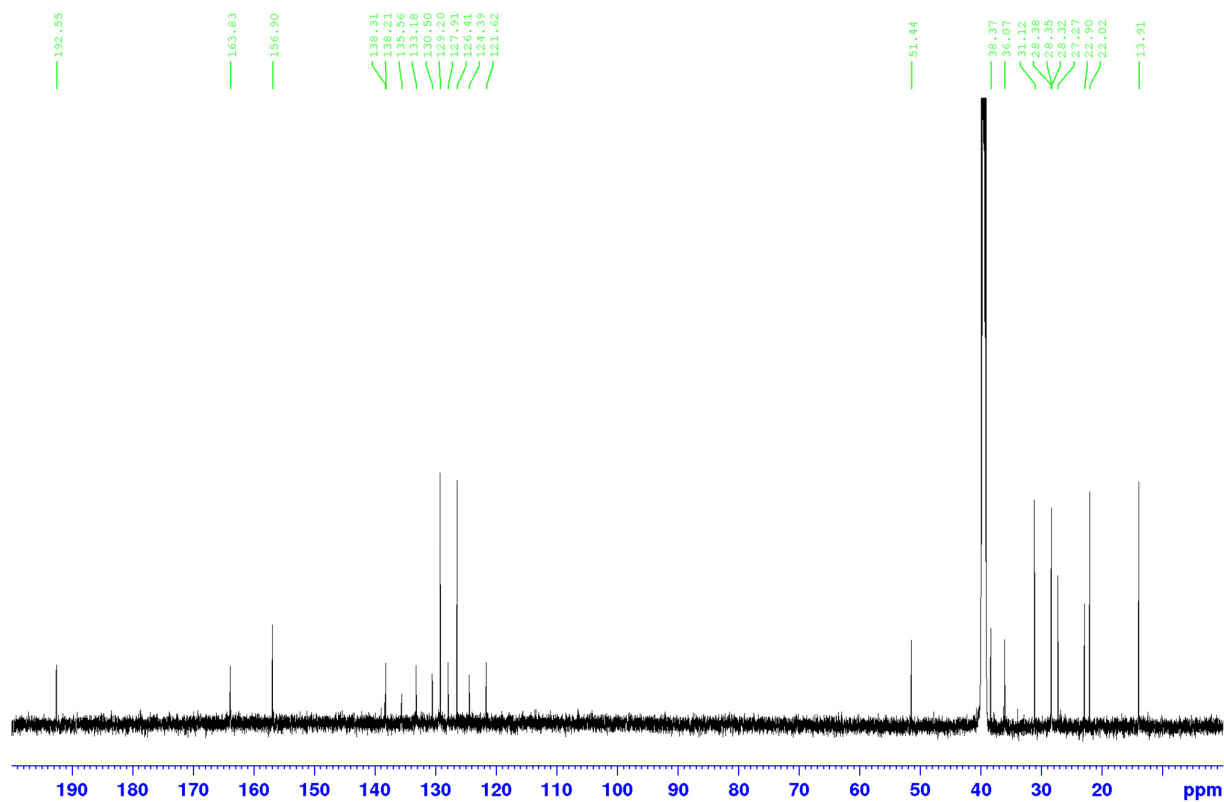


*N*-(3-Guanidinopropyl)-2-(4-(octylsulfonamido)-[1,1'-biphenyl]-3-yl)-2-oxoacetamide hydrochloride (**22a**)

<sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>):

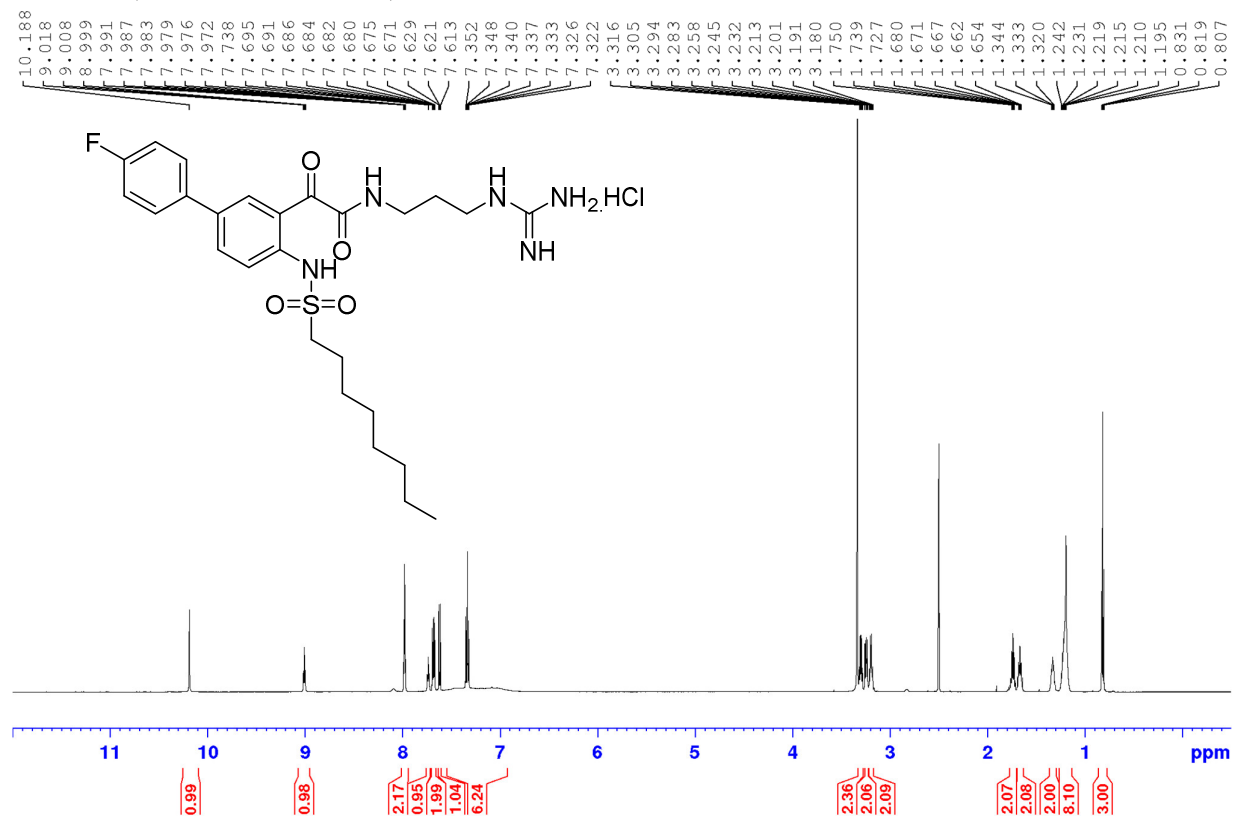


<sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>):

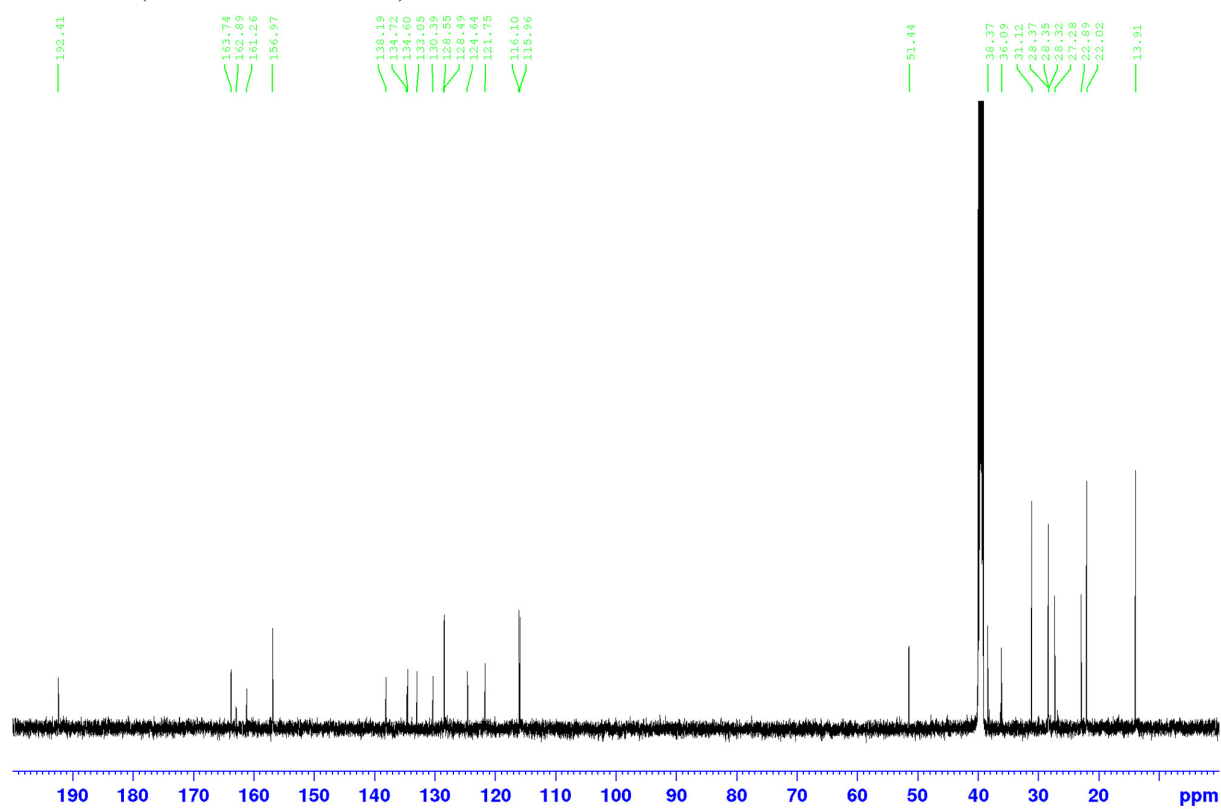


2-(4'-Fluoro-4-(octylsulfonamido)-[1,1'-biphenyl]-3-yl)-N-(3-guanidinopropyl)-2-oxoacetamide hydrochloride (**22b**)

$^1\text{H}$  NMR (600 MHz,  $\text{DMSO-}d_6$ ):

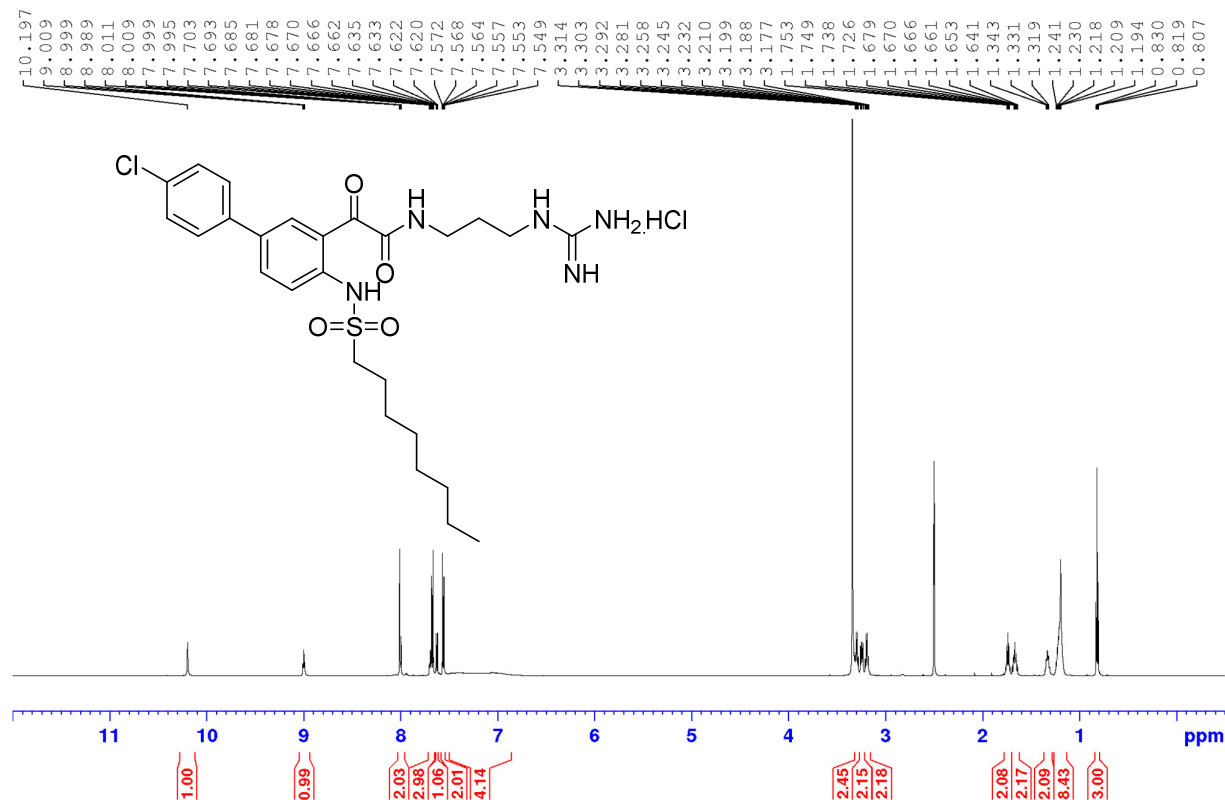


$^{13}\text{C}$  NMR (150 MHz,  $\text{DMSO-}d_6$ ):

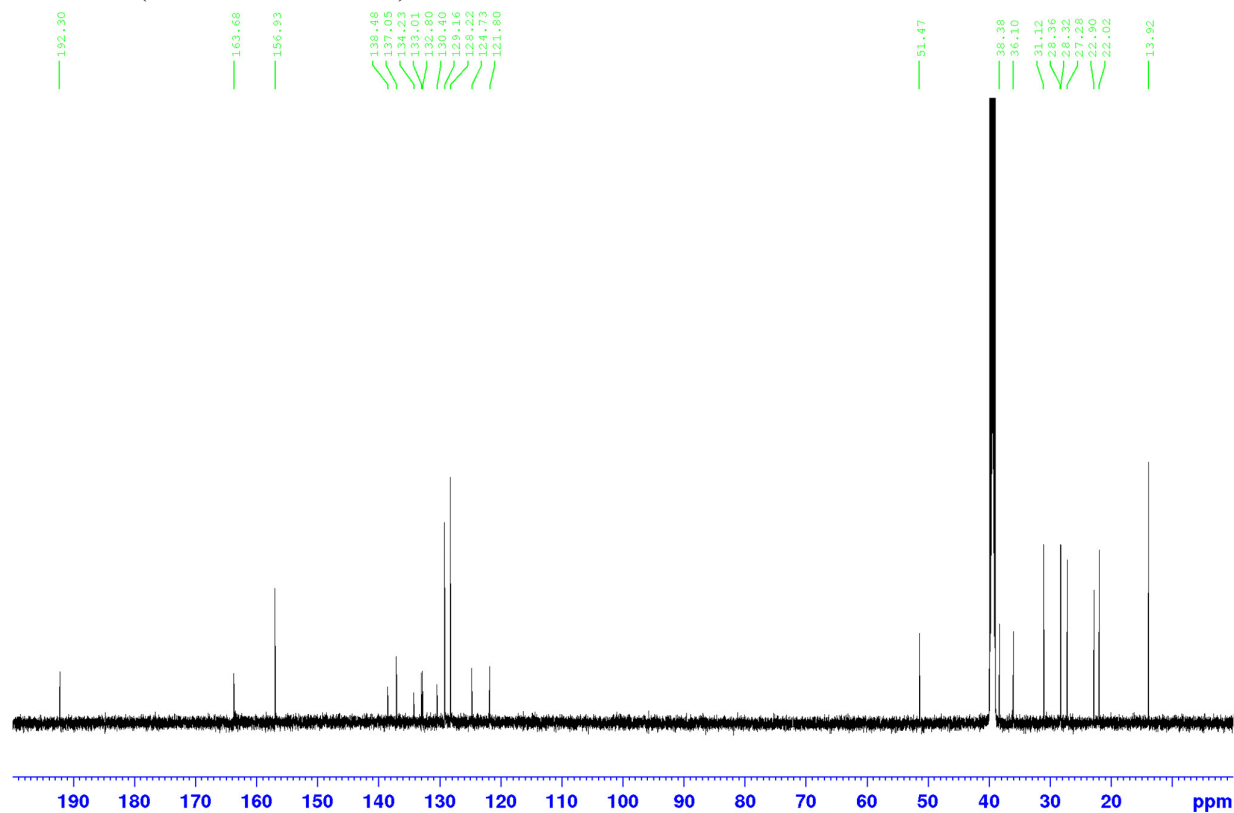


2-(4'-Chloro-4-(octylsulfonamido)-[1,1'-biphenyl]-3-yl)-*N*-(3-guanidinopropyl)-2-oxoacetamide hydrochloride (**22c**)

<sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>):



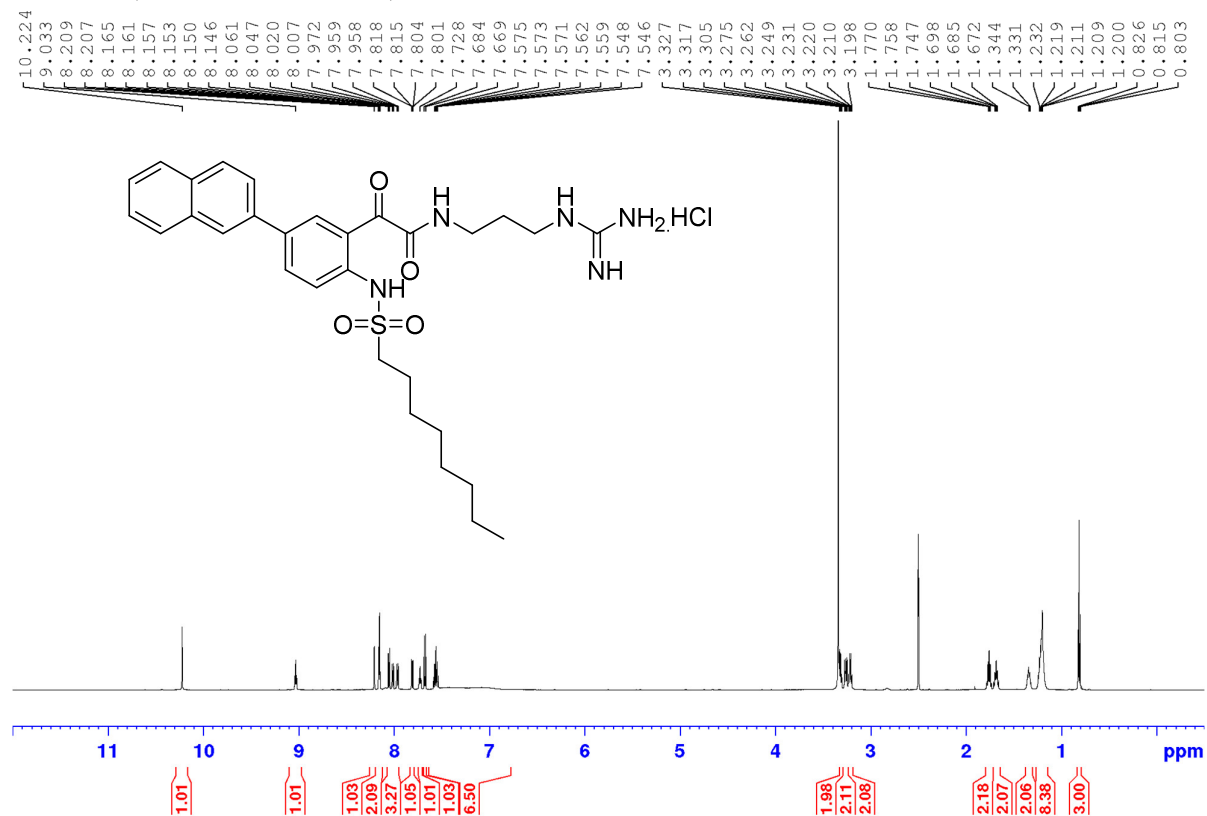
<sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>):



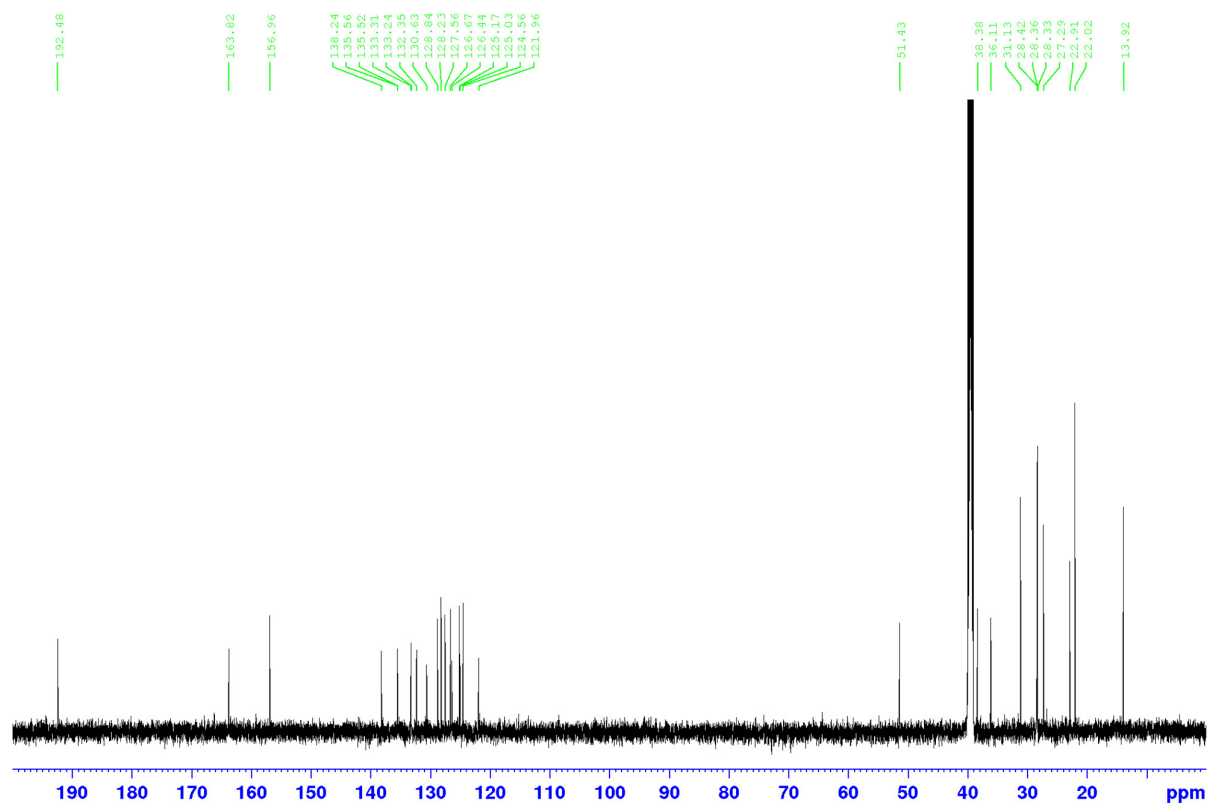


*N*-(3-Guanidinopropyl)-2-(5-(naphthalen-2-yl)-2-(octylsulfonamido)phenyl)-2-oxoacetamide hydrochloride (**22d**)

<sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>):

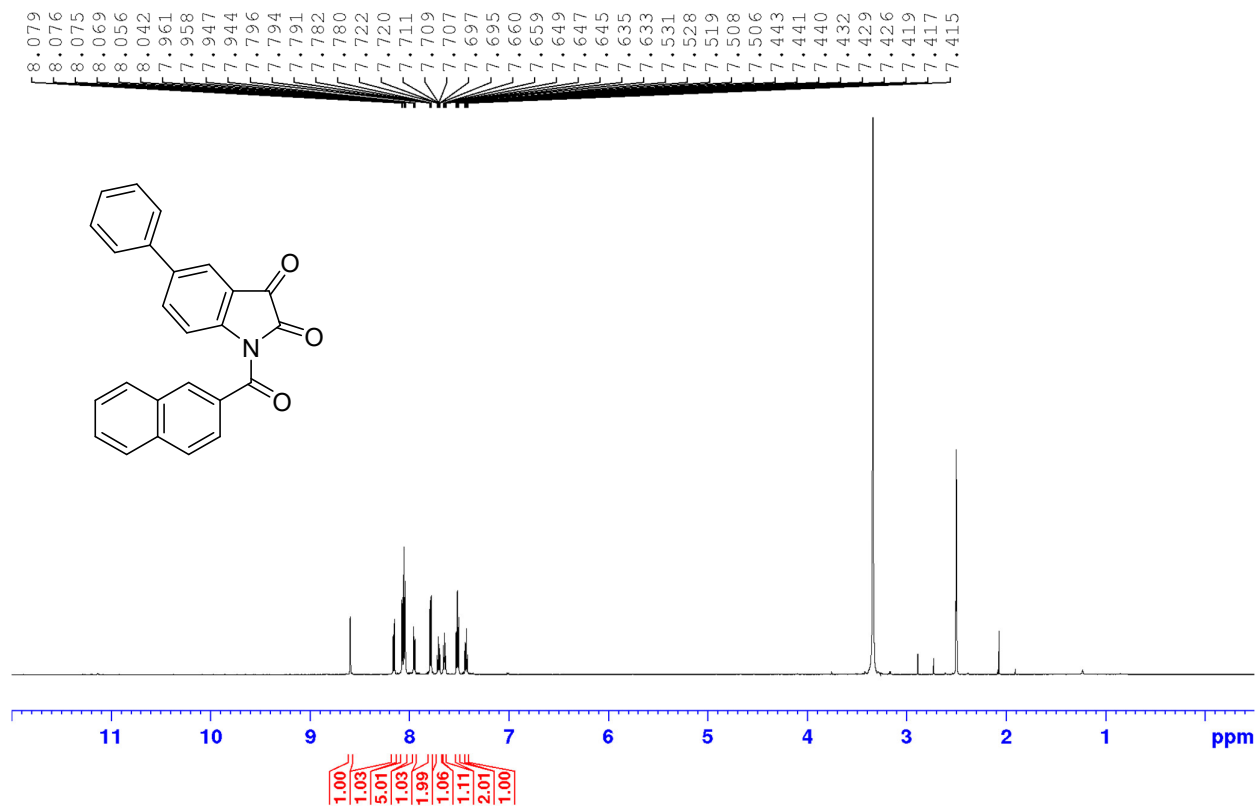


<sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>):

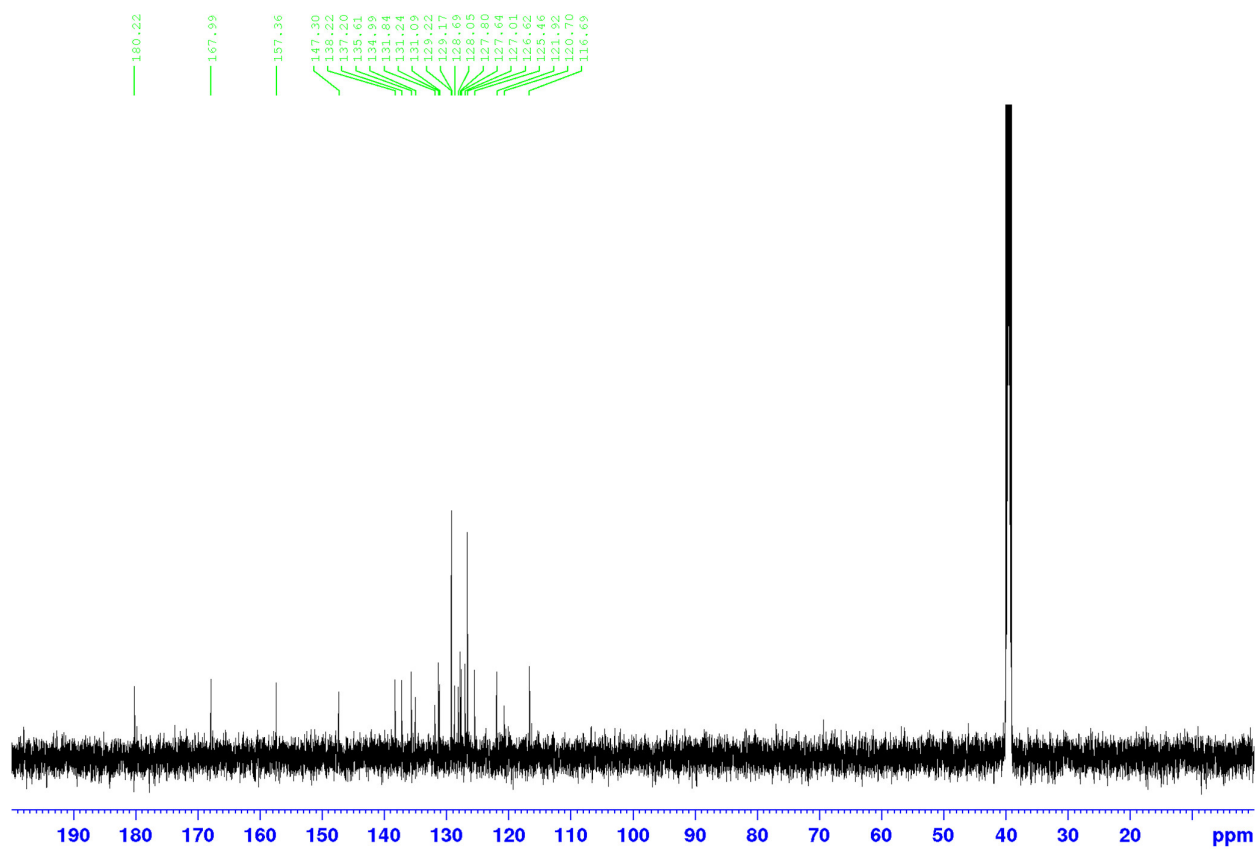


# 1-(2-Naphthoyl)-5-phenylindoline-2,3-dione (24)

<sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>):

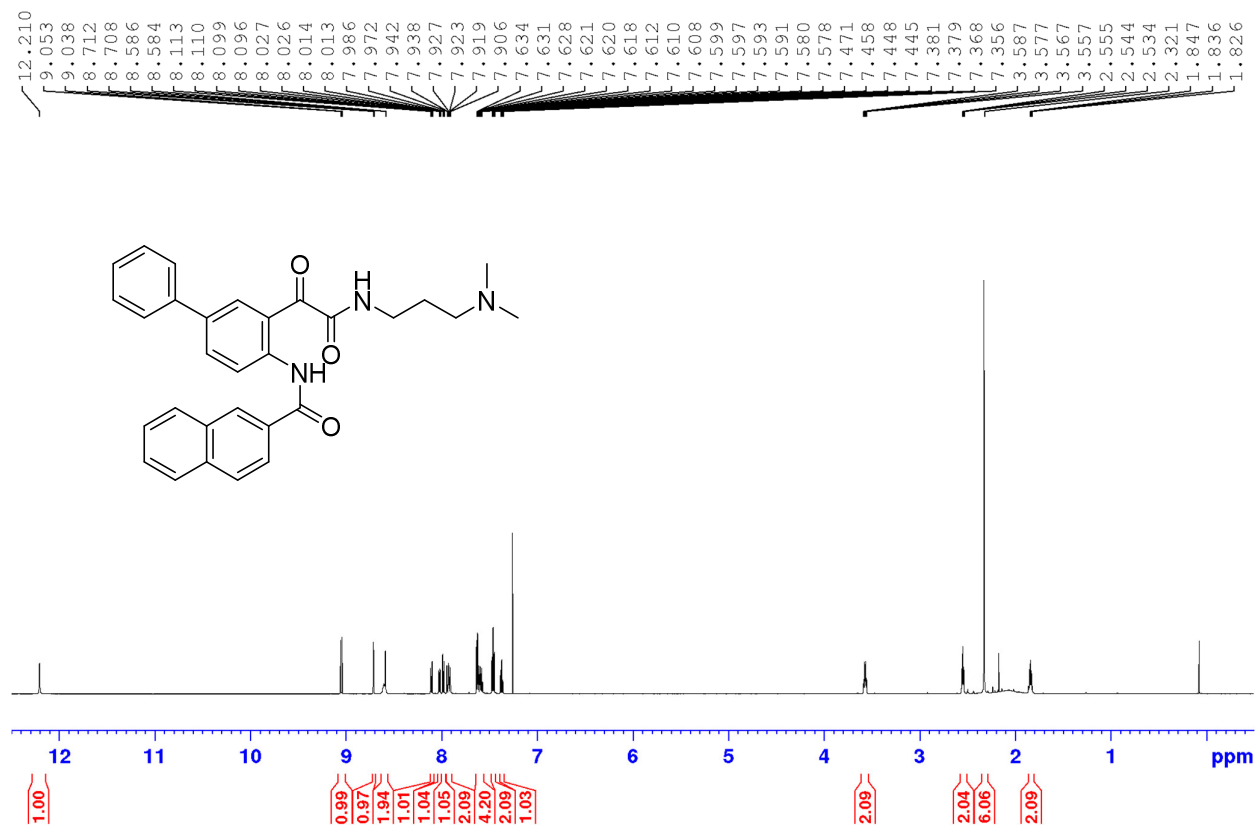


<sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>):

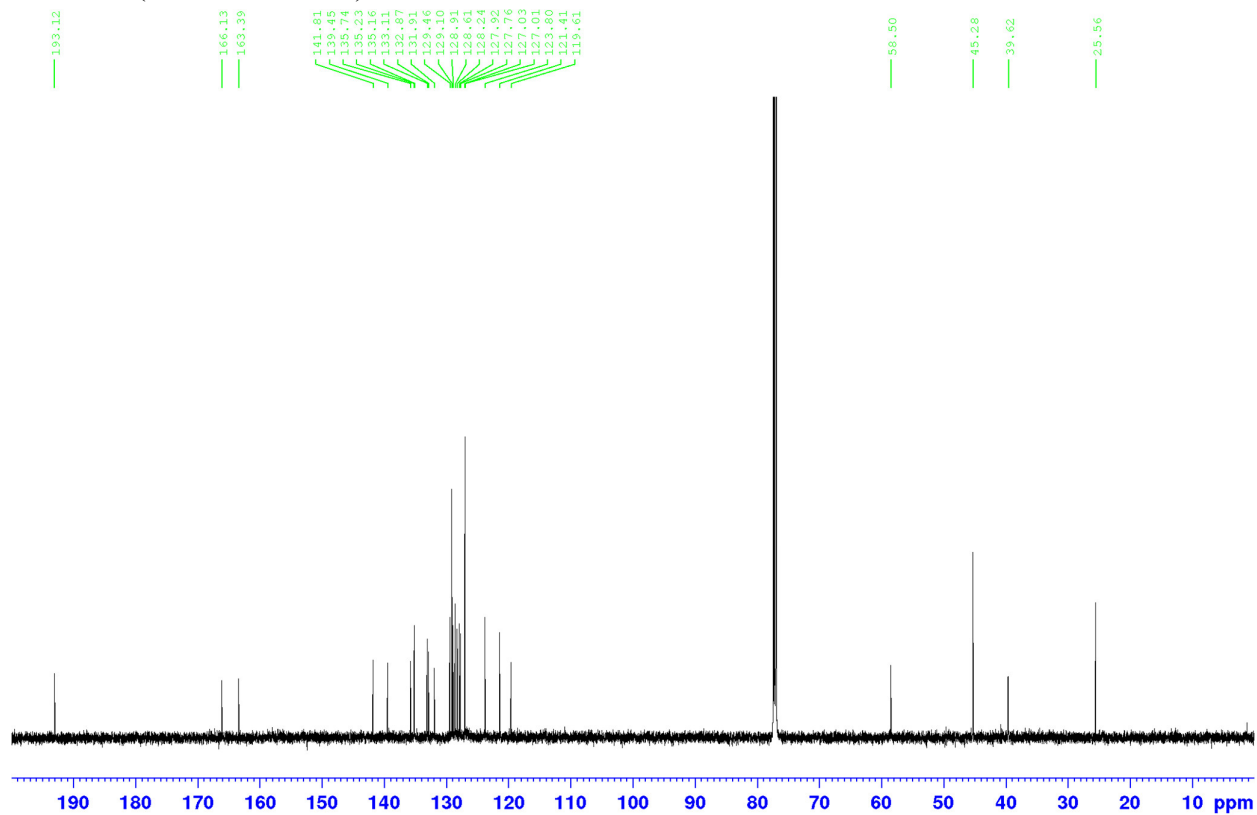


*N*-(3-(2-((3-(Dimethylamino)propyl)amino)-2-oxoacetyl)-[1,1'-biphenyl]-4-yl)-2-naphthamide (**25**)

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):

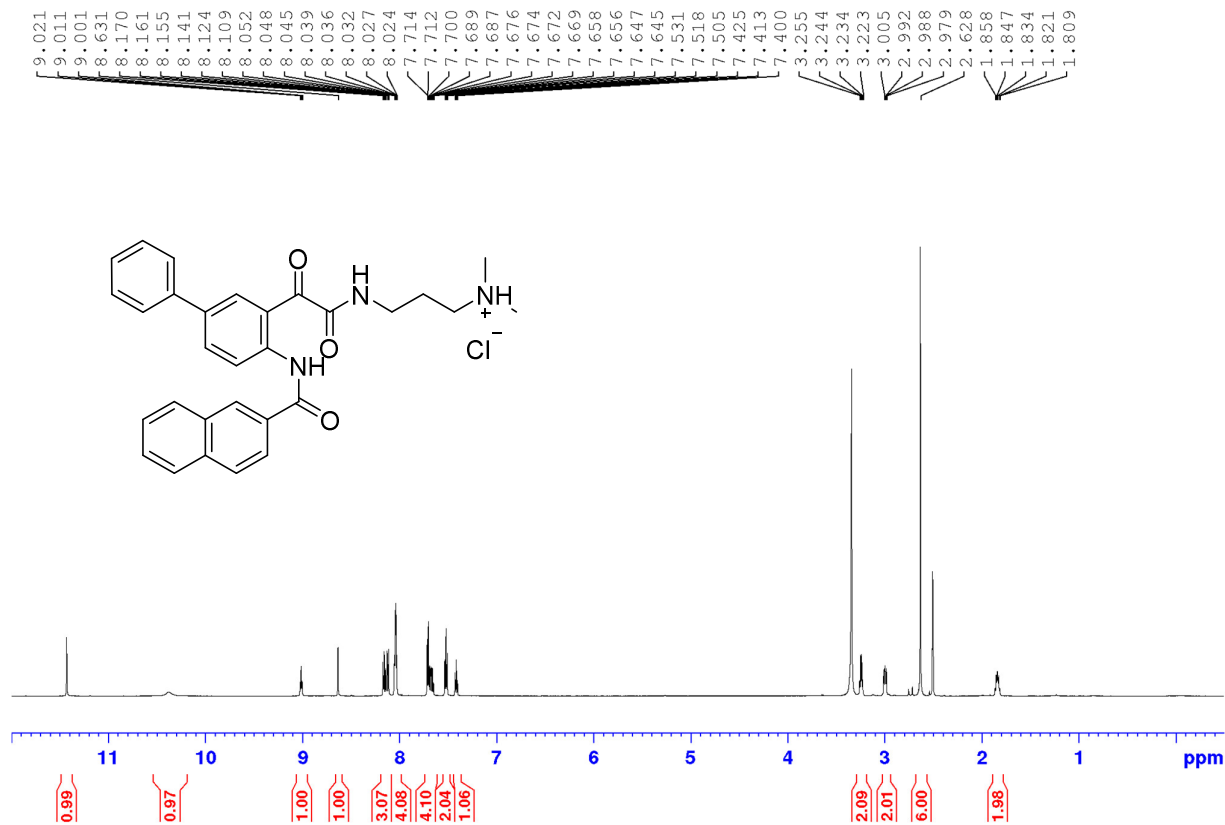


<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):

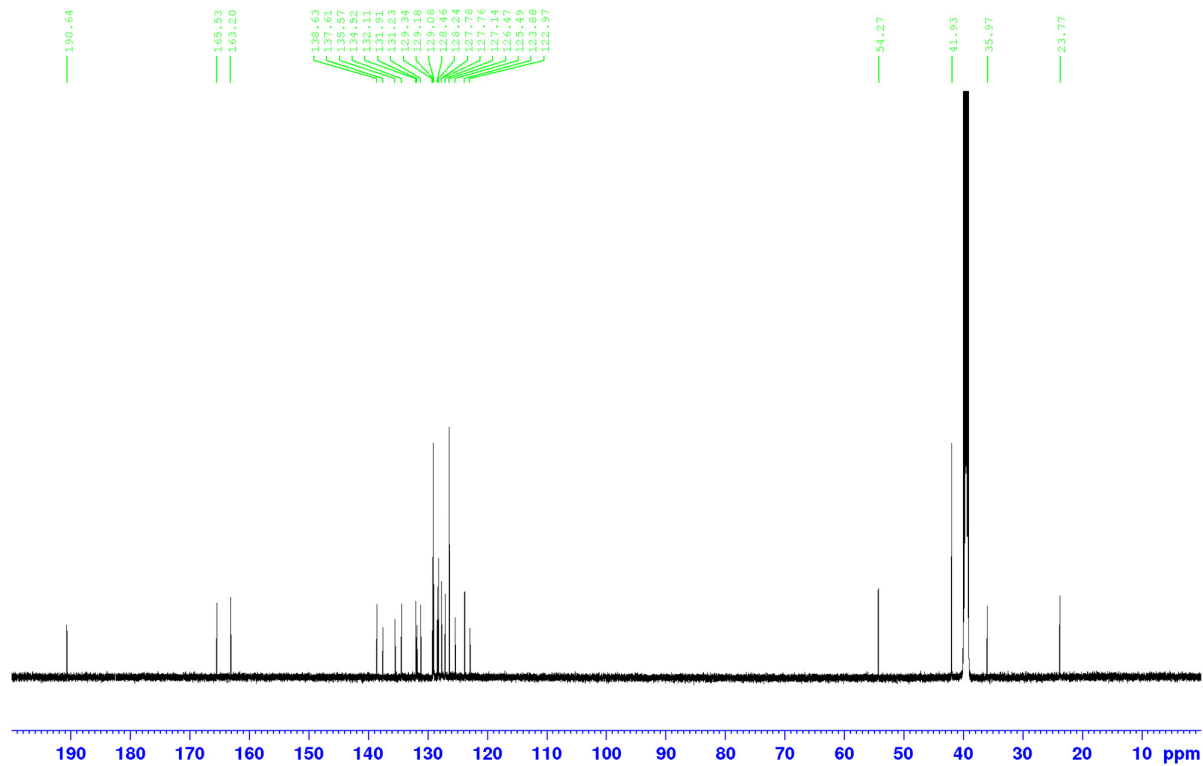


3-(2-(4-(2-Naphthamido)-[1,1'-biphenyl]-3-yl)-2-oxoacetamido)-*N,N*-dimethylpropan-1-aminium chloride (**26**)

$^1\text{H}$  NMR (600 MHz,  $\text{DMSO-}d_6$ ):

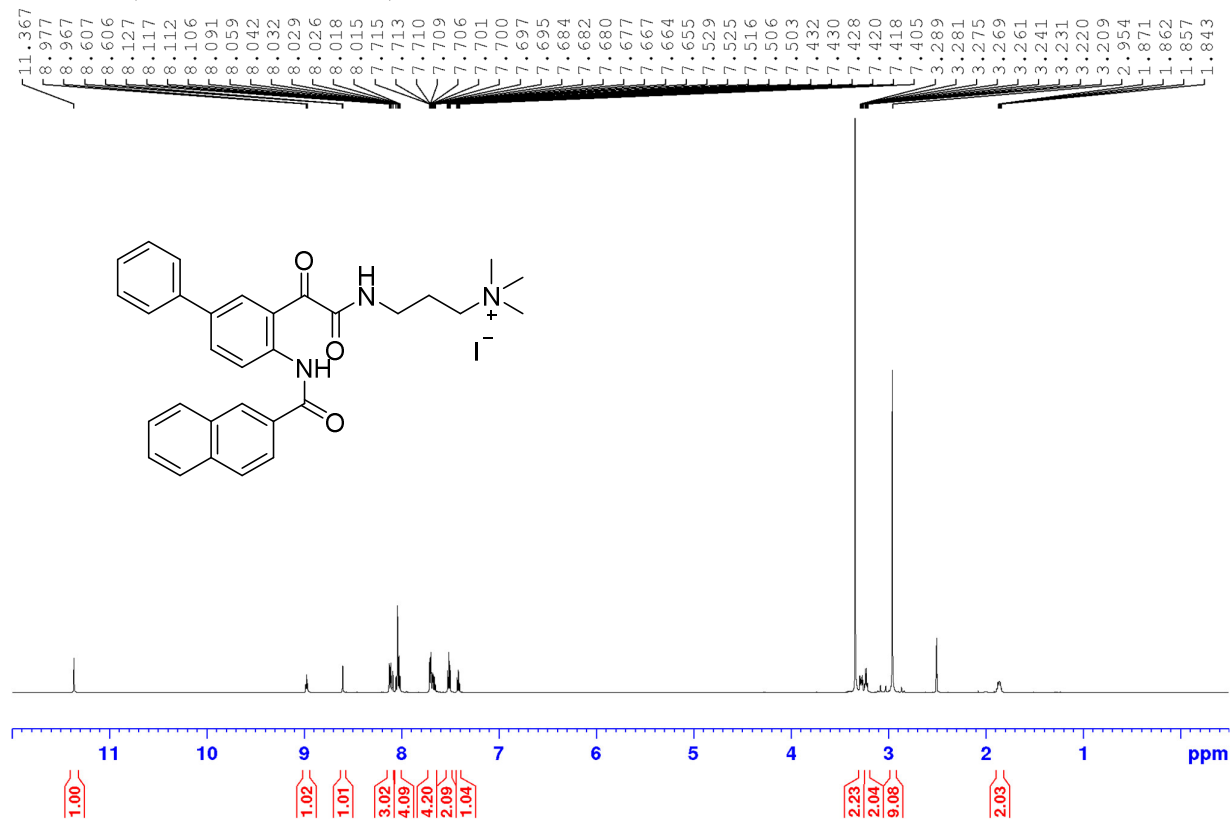


$^{13}\text{C}$  NMR (150 MHz,  $\text{DMSO-}d_6$ ):



3-(2-(4-(2-Naphthamido)-[1,1'-biphenyl]-3-yl)-2-oxoacetamido)-*N,N,N*-trimethylpropan-1-aminium iodide (**27**)

$^1\text{H}$  NMR (600 MHz,  $\text{DMSO-}d_6$ ):



$^{13}\text{C}$  NMR (150 MHz,  $\text{DMSO-}d_6$ ):

