universität wien

# DIPLOMARBEIT / DIPLOMA THESIS

Titel der Diplomarbeit / Title of the Diploma Thesis

## „Synthesis of Taurine Derivates“

verfasst von/ submitted by

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angestrebter akademischer Grad / in partial fulfilment of the requirements for the degree of

Magistra der Pharmazie (Mag. pharm.)

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# Acknowledgment

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Additionally, I would also like to acknowledge the experts who were involved in my work for this research project: Mag. pharm. Philipp Schreppel, Mag. pharm. Michael Hintersteininger and Dipl.-Ing. (FH) Mario Gabriel.
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Finally, I must express my very profound gratitude to my parents and my colleagues for providing me with unfailing support and continuous encouragement throughout my years of study and through the process of researching and writing this thesis. This accomplishment would not have been possible without them.

# Abstract (English/German)

The main objective of this diploma thesis was to synthesize taurine derivates, by adding lipophilic remnants. A better penetration through the blood brain barrier and inhibition of NKCC1 was to be expected. By blocking this co-transporter, the intracellular high chlorid ($Cl^-$) concentration would be lowered and would lead to a reduction of neonatal epileptic seizures when the $GABA_A$ ion channel opens.

In total, 11 compounds were synthesized. Compounds **1 – 6** were generated from sodium 2-bromoethanesulfonate with different lipophilic remnants, while the compounds **7 – 11** were synthesized from aminoethansulfonic acid *via* reductive amination.

Das Hauptziel dieser Diplomarbeit war es, Taurinderivate mit lipophilen Resten zu synthetisieren. Dies würde voraussichtlich zu einem besseren Überwinden der Blut-Hirn-Schranke führen und eine Hemmung des NKCC1 bewirken. Durch Blockierung dieses Co-Transporters würde die intrazelluläre hohe Chlorid (Cl-) -Konzentration gesenkt werden, zur Öffnung des $GABA_A$-Ionenkanals und könnte dadurch zu einer Verringerung von epileptischen Anfällen bei neonataler Epilepsie führen.

Insgesamt wurden 11 Verbindungen synthetisiert. Ausgangsstruktur für die Verbindungen **1 – 6** war Natrium 2-Bromethansulfonat, das mit verschiedenen Resten substituiert wurde, während die Verbindungen **7 – 11** ausgehend von Aminoethansulfonsäure mittels reduktiver Aminierung synthetisiert wurden.

# Table of Contents

# 1 Introduction

## 1.1 Epilepsy

Epilepsy is a complex disease with many different characteristics that exclude a unique mechanism. One method to understand more about these mechanisms is to reduce the characteristics of epilepsy to the main components: “seizures, epileptogenesis and the state of recurrent unprovoked seizures that defines epilepsy itself”. The disease is defined by spontaneous seizures. The definition for „seizure“ is a period of synchronous, abnormal excitation of the neurons which can last seconds or minutes, but can also linger in case of status epilepticus. There are many reasons that can lead to seizures and often they appear quite different. One of the most common principles is that seizures can be caused by an imbalance between excitation and inhibition. Research into seizures has concentrated on mechanisms concerning synaptic transmission, “because of its critical role in maintaining the balance between excitation and inhibition”. As research has identified the molecular mechanisms of synaptic transmission, it has gained the understanding that defects in every respective step can lead to spontaneous seizures. Glutamatergic and γ-aminobutyric acid (GABA)-ergic transmission are the main excitatory and inhibitory transmitters of the nervous system (Scharfman, 2007).

By now there is evidence that there are many differences in the pathophysiology between the mature and the immature brain, which leads to different consequences of seizures.

Even though the vulnerability of the immature brain is less than the mature brain to seizure-induced cell death, seizures can lead to irreversible alterations in neuronal connectivity. The main physiologic characteristic of epileptic seizures is hyperexcitability of CNS neurons. A seizure starts, when a huge amount of neurons synchronously depolarize and cause action potentials, which is called “paroxysmal depolarizing shift” (PDS), the hallmark in the epileptic focus. In the PDS, the cell membrane undergoes a high-voltage (approximately 10–15 mV) and long (100–200 ms) depolarization, which is longer than the normal excitatory postsynaptic potential (EPSP) (duration: 10-16 ms). This has the effect of causing a series of action potentials that are conducted along the axon of the neuron, which is marked as a spike in the EEG. Afterwards, the hyperpolarization starts, which has the main function to limit the duration of interictal paroxysms. This hyperpolarization is caused by different ionic channels, including GABA and $Ca^{2+}$-activated $K^{+}$ channels. (Holmes et al., 2001)

## 1.2 Neonatal seizures

The definition of neonatal seizures is “abnormal, stereotyped, paroxysmal alterations in neurological function (motor, behavioral, and autonomic)”. According to US population-based studies reporting an incidence of seizures of 1.8 to 5 out of every 1000 live births, the risk of seizures during the neonatal period is the highest. There are differences in “terms of etiology, semiology, electroencephalographic features, treatment options and treatment responses”, between neonatal seizures and seizures affecting other age groups. Over 90% of neonatal seizures are caused by “hypoxic–ischemic encephalopathy (HIE), cerebral vascular ischemia and hemorrhage, cerebral malformation, and infections”. From all the causes of neonatal seizures the most common one is HIE, with an incidence of 1 to 2 per 1000 live births. (Shetty, 2015)

## 1.3 GABA

In the central nervous system the most common inhibitory neurotransmitter is gamma-aminobutyric acid (GABA). It is responsible for limiting the excitability of neurons in every areas in the brain. An excessive function of GABA can lead to “sedation, amnesia and ataxia”.

In the presynaptic neurons the synthesis of GABA takes place, which is then stored in the synaptic vesicle. L-glutamic acid decarboxylase, an enzyme that promotes the synthesis of GABA is relevant for the rate-limiting step in the process. During the neuronal activation, the vesicle releases GABA into the synapse, where it can bind on postsynaptic receptors, or diffuse into the extracellular space and activate extrasynaptic receptors on postsynaptic neurons.

There are different types of GABA receptors but there are two main type. The first one is the fast-acting ionotropic $GABA_A$, which consists of five protein subunits arranged around a central pore. By activating the receptor, chloride ions flow into the cell, which leads to a hyperpolarization. This receptor is the predominant type of GABA in the brain.

The second type is the slow-acting metabolic $GABA_B$, which is a G-protein-linked receptor, linked by intracellular signal transduction cascades to calcium and potassium channels. As the first type, this receptor also causes a hyperpolarization by increasing the potassium current and decreasing the voltage-dependent calcium current. (Nutt, 2006)

## 1.4 Chloride homeostasis

During the early brain development the main reason for changed function of GABA are changes in the $Cl^-$ homeostasis. GABA is the main inhibitory neurotransmitter, which causes a hyperpolarization and inhibits neuronal excitability. The inhibitory effect is created by the $Cl^-$-permeable $GABA_A$ receptor-channels, causing $Cl^-$ influx down the electrochemical gradient and hyperpolarizing the membrane. But when the intracellular $Cl^-$ concentration is high, the equilibrium potential for $Cl^-$ can be positive in comparison to the membrane potential. So, GABA can depolarize the membrane potential over the threshold of action potential generation. In contrast to adult neurons, which hyperpolarize as a response to $GABA_AR$ activation by GABA, in immature neurons it induces depolarization and can be excitatory. GABAergic excitation-inhibition switches are caused by changes in $Cl^-$ gradients, which are controlled by cation- $Cl^-$ co-transporters. Through the $Na^+$-$K^+$-$2Cl^-$ co-transporter (NKCC1), the intracellular $Cl^-$ concentration in neuronal precursors and immature neurons increases and this leads to depolarizing (excitatory) actions of GABA in the developing brain. The upregulation of the $Cl^-$ extruder $KCC_2$, which is a $K^+$-$Cl^-$ co-transporter causes a low $[Cl^-]_i$ levels and hyperpolarization. (Watanabe et al., 2015)

## 1.5 Current standard therapy of neonatal seizures

Phenobarbital is still the first line treatment for neonatal seizures, despite the evidence that it is ineffective in many babies. Seizures are “associated with underlying conditions like brain hemorrhage, stroke, meningitis and hypoxic ischemic encephalopathy”.

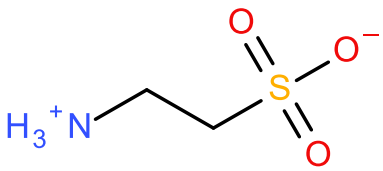
According to recent studies, seizures in the newborn are often clinically silent (or “electrographic”) and their severity in the sick baby is often underestimated. For diagnosing electrographic seizures the use of an EEG is needed. The video-EEG is the most useful technique for “identifying, classifying and quantifying neonatal seizures”. Most current therapy is often ineffective in inhibiting abnormal electrical activity, which was shown by the EEG monitoring.

Phenobarbital is a sedative and a powerful anticonvulsant. However, studies have shown that babies who had been treated with phenobarbital are more susceptible to electrographic seizures. The effect of this drug is sedating the babies and inhibiting clinical manifestations of seizures, nevertheless it has little effect on the electrographic discharge. Whether neonatal

seizures, especially electrographic seizures, are themselves harmful is not yet known. (Boylan et al., 2002)

## 1.6 Taurine

**Scheme 1: Taurine**




**Taurine**

2-Aminoethane-sulfonic acid, also called taurine is an organic osmolyte, which is important in cell volume regulation, also provides a substrate for the formation of bile salts and has the function of modulating the intracellular free calcium concentration. This substance is the most common amino acid in the brain and spinal cord, leukocytes, heart and muscle cells and the retina. It was first found and isolated from the bile of the ox (*Bos taurus*) and that is why 2-aminoethane-sulfonic acid is also called taurine.

The chemical structure of taurine reveals that the carboxyl group, which is typical for amino acids is missing, but instead it contains a sulfonate group.

Taurine is indispensable for our body, because there is more and more evidence showing that a lack of taurine leads to a wide range of "pathological conditions, including severe cardiomyopathy, renal dysfunction, pancreatic β cell malfunction, and loss of retinal photoreceptors". (Ripps et al., 2012)

# 2 Objective

The objective of this thesis was to synthesize derivates of taurine with lipophilic remnants. The administration of these derivates can be considered as a potential treatment option for neonatal seizures. So they should be able to penetrate the blood-brain-barrier and inhibit NKCC1, which leads to lower intracellular chloride concentration in the brain cells and should reduces epileptic seizures.

# 3 Synthesis of Taurine Derivates

**Scheme 2: Synthesis overview**

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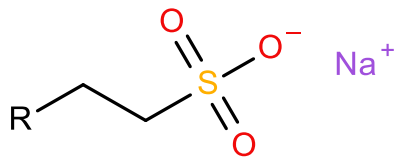
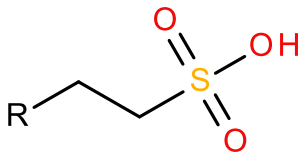



**(1 – 6)**




**(7 – 11)**

## 3.1 Compounds **1 – 6**

**Scheme 3:** Compounds **1 – 6**

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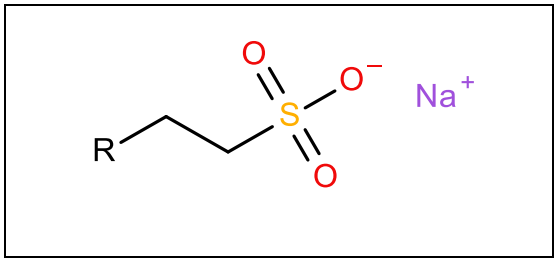
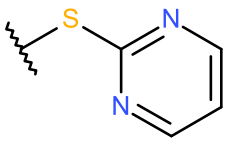
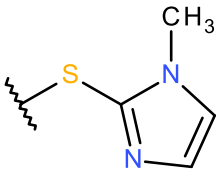
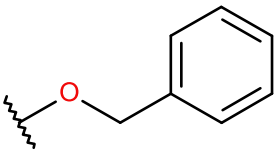
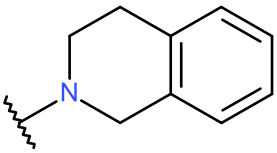
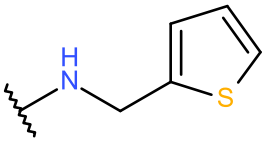
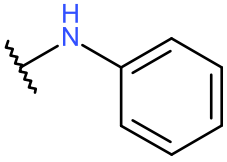



| Compound | R |
|---|---|
| **Compound 1** |  |
| **Compound 2** |  |
| **Compound 3** |  |
| **Compound 4** |  |
| **Compound 5** |  |
| **Compound 6** |  |

The objective was to synthesize taurine derivates by adding lipophilic remnants to the structure. The first two compounds were formed in the same way *via* nucleophilic substitution by adding THF, metallic sodium and the respective reagent to sodium 2-bromoethansulfonate. The only difference was that for compound **1** 1,4-dioxane was also added, because of solubility issues.

Afterwards the suspension was stirred for 24 hours at 60°C and then evaporated under reduced pressure. Then the product was recrystallized from absolute ethanol und dried under vacuum.

Compounds **3-6** worked similarly, except that another solvent was used and metallic sodium was omitted. Instead of THF, methanol was added.

## 3.2 Compounds **7 – 11**

**Scheme 4:** Compounds **7 – 11**

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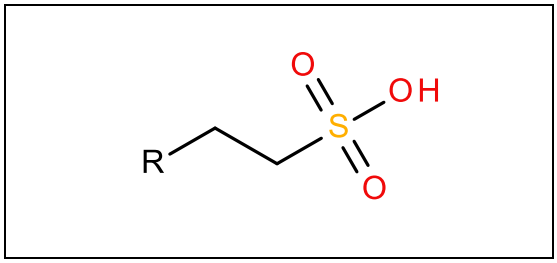
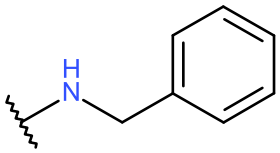
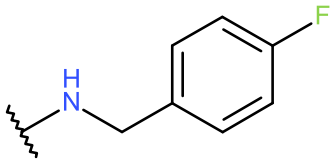
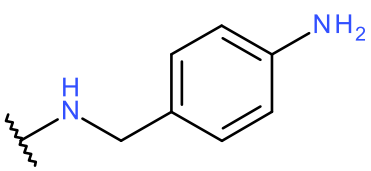
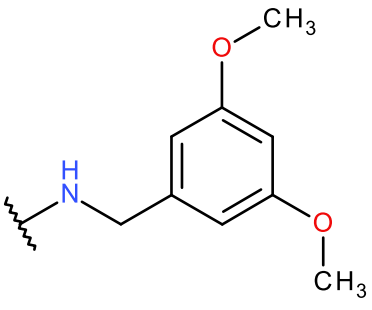
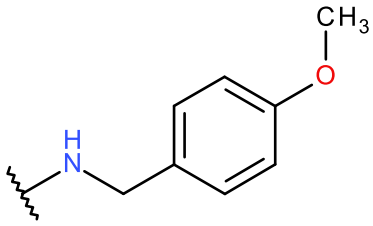



| Compound | R |
|---|---|
| **Compound 7** |  |
| **Compound 8** |  |
| **Compound 9** |  |
| **Compound 10** |  |

| | |
|---|---|
| **Compound 11** |  |

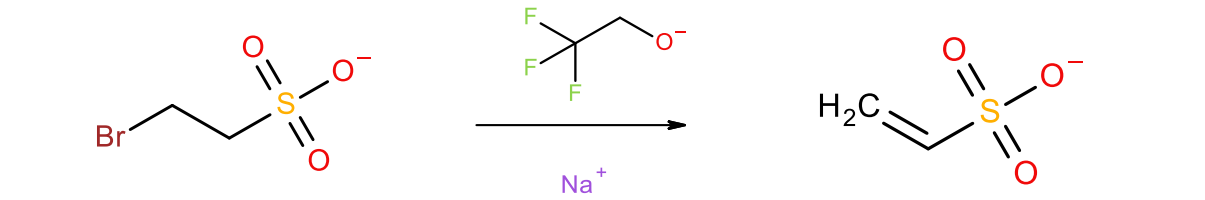
All five compounds were synthesized in the exact same way *via* reductive amination. Therefore NaOH, MeOH, the respective reagent and aminoethansulfonic acid were combined. This solution was stirred for 45 minutes at room temperature prior to cooling in an ice bath. Then $NaBH_4$ was added to reduce the intermediate Schiff base that was formed in the step before. Half an hour later, the solution was acidified with acetic acid to pH 3-5 to yield the respective product, which was filtered off and washed with EtOH and dried under vacuum

# 4 Discussion

The goal of this thesis was to synthesize taurine derivatives by adding lipophilic remnants. Those should penetrate the BBB, inhibit NKCC1 and effectively treat neonatal seizures.

Nevertheless, some problems during the work occurred.

**Scheme 5:**



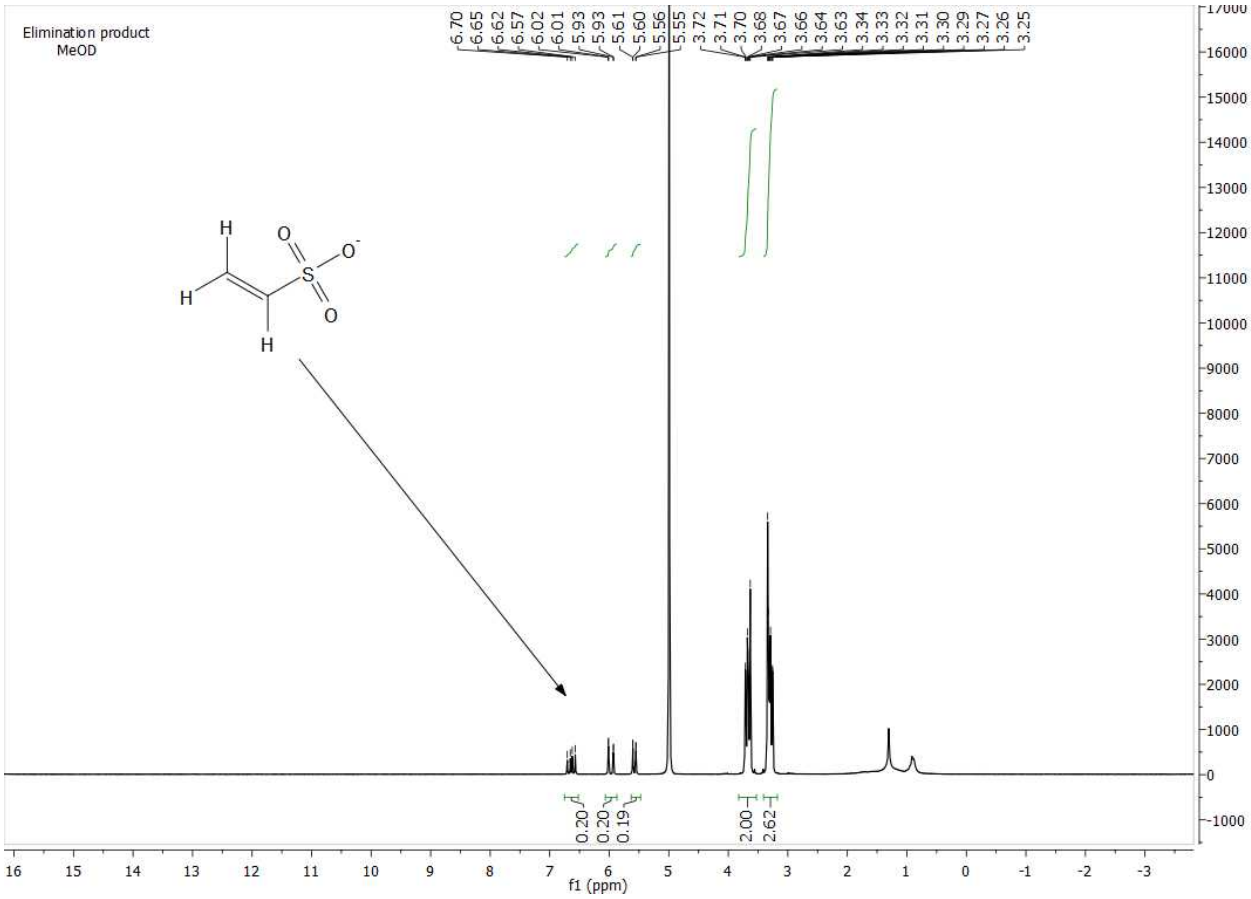

Scheme 5 shows the main problem and that was the elimination product that was generated during the synthesis. In the first try sodium 2-bromeethanesulfonate, 2,2,2-trifluoroethanol and metallic sodium were added. The solution was stirred for 24 hours at 75°C. After 24 hours, the mixture was evaporated under reduced pressure. Afterwards the product was recrystallized from absolute ethanol und dried under vacuum. The final product was a mixture of the elimination product and the starting compound.

The next step was changing the order of the reagents. So at first 2,2,2-trifluoroethanol and metallic sodium were added. After 10 minutes sodium 2-bromeethanesulfonate was added. The order of the following steps remained the same. Like before, the end product was a mixture of the elimination product and the starting compound. Another idea was changing the temperatures. Instead of stirring the mixture for 24 hours at 75°C, an ice bath was used. In this case, a mixture of two components, the elimination product and the sodium 2-bromeethanesulfonate was the result. So a certain temperature is necessary for the synthesis and therefore the mixture was stirred for 3 days at room temperatures. Nevertheless, only the mixture of the two compounds has resulted.

To see how long it takes to get to the elimination product sodium 2-bromeethanesulfonate was solved in methanol-$d_4$. The solution was stirred for 24 hours at room temperatures. After

15 minutes, the first sample was taken. By proton NMR, after 15 minutes the elimination product was observed. Five additional measurements were carried out. After 24 hours, the elimination product could be detected.

**Scheme 6:**




In the future additional experiments have to be conducted to receive the desired compound.

# 5 Experimental Section

## 5.1 General Methods

All chemicals and solvents were purchased from commercial suppliers (Sigma Aldrich, Merck, Apollo Scientific, abcr and TCI Europe) at analytical grade.

To monitor reactions *via* thin layer chromatography, silica gel $F_{254}$ coated aluminium sheets from Merck were used.

As a stationary phase for column chromatography silica gel 60 70-230 mesh ASTM from Merck was used.

Melting points were taken on a ThermoGalen Kofler hot stage microscope.

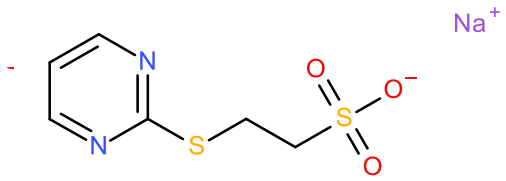
$^{1}H$- and $^{13}C$-NMR spectra were recorded on a Brucker Advance (200 and 50 MHz respectively) and chemical shifts are reported in ppm relatively to the solvent residual line or tetramethylsilane as internal standard.

Mass spectra were recorded on a Shimadzu (GC-17A; MS-QP5050A) spectrometer. The peak intensity is specified in per cent relative to the biggest signal in the spectrum.

High-resolution mass spectra were recorded on a MALDI-q/q-TOF-spectrometer (Bruker maxis HD) by Dr. Judith Wackerlig at the University of Vienna.

## 5.2 Compound **1**: Sodium 2-pyrimidin-2-ylsulfanylethanesulfonate

**Scheme 7:** Compound **1**



**Compound 1**

| | |
|---|---|
| Molecular formula: | $C_6H_7N_2NaO_3S_2$ |
| Molecular weight: | 242.25 g/mol |
| Melting point: | > 300 °C |

To 2 mmol (211 mg) of sodium 2-bromoethanesulfonate (TAU2), tetrahydrofuran (8 mL), 1,4-dioxane (4 mL), metallic sodium (catalytic amount) and 4 mmol of 2-mercaptopyrimidin (448 mg) were added. The suspension was stirred for 24 hours at 60°C. After the reaction was completed, the solvent was evaporated under reduced pressure. Afterwards, the product was recrystallized from absolute ethanol and dried under vacuum to yield 36 mg of yellow crystals (7.4% yield).

$^1$H NMR (200 MHz, Methanol-$d_4$) δ 8.57 (d, $J$ = 4.9 Hz, 2H), 7.14 (t, $J$ = 4.9 Hz, 1H), 3.56 – 3.44 (m, 2H), 3.28 – 3.14 (m, 2H).

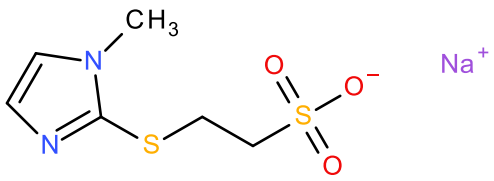
$^{13}$C NMR (50 MHz, Methanol-$d_4$) δ 157.4, 116.8, 51.0, 25.5. (1 Cq not detectable)

**HRMS–Analys**

| Meas.m/z | Formular | m/z | err [ppm] |
|---|---|---|---|
| 264.9694 | $C_6H_7N_2Na_2O_3S_2$ | 264.9688 | -2.2 |

## 5.3 Compound **2:** Sodium 2-(1-methylimidazol-2-yl)sulfanylethanesulfonate

**Scheme 8:** Compound **2**




**Compound 2**

| | |
|---|---|
| Molecular formula: | $C_6H_9N_2NaO_3S_2$ |
| Molecular weight: | 244.27 g/mol |
| Melting point: | > 300 °C |

To 1 mmol (211 mg) of sodium 2-bromoethanesulfonate, tetrahydrofuran (4 mL), metallic sodium (catalytic amount) and 2 mmol of 2-mercapto-1-methylimidazole (228 mg) were added. The suspension was stirred for 24 hours at 60°C. After the reaction was completed, the mixture was evaporated under reduced pressure. Afterwards, the product was recrystallized from absolute ethanol. The precipitate was filtered off and dried under vacuum to yield 20 mg of white crystals (8.2% yield).

$^{1}$H NMR (200 MHz, DMSO-$d_6$) δ 7.80 – 7.72 (m, 2H), 3.79 (s, 3H), 3.41 – 3.26 (m, 2H), 2.80 – 2.66 (m, 2H).

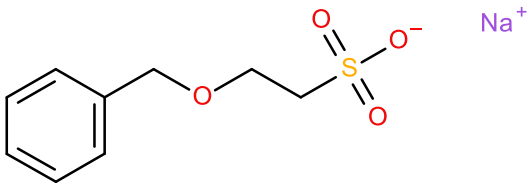
$^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 140.5, 125.2, 121.2, 51.2, 35.1, 31.2.

**HRMS–Analysis**

| Meas.m/z | Formula | m/z | err [ppm] |
|---|---|---|---|
| 245.0026 | $C_6H_{10}N_2NaO_3S_2$ | 245.0025 | -0.4 |

## 5.4 Compound **3**: Sodium 2-benzyloxyethanesulfonate

**Scheme 9:** Compound **3**




**Compound 3**

| | |
|---|---|
| Molecular formula: | $C_9H_{11}NaO_4S$ |
| Molecular weight: | 238.24 g/mol |
| Melting point: | > 300 °C |

To 1 mmol (211 mg) of sodium 2-bromoethanesulfonate, benzyl alcohol (1 mL) and metallic sodium (catalytic amount) were added. The solution was stirred for 24 hours at 75°C. After the reaction was completed, the mixture was evaporated under reduced pressure. Afterwards the product was recrystallized from absolute ethanol and dried under vacuum to yield 105 mg of white crystals (44.1% yield).

$^{1}$H-NMR (200 MHz, Methanol-$d_4$) δ 7.51 – 7.12 (m, 5H), 4.54 (s, 2H), 3.87 (t, $J$ = 7.3 Hz, 2H), 3.13 (t, $J$ = 7.3 Hz, 2H).

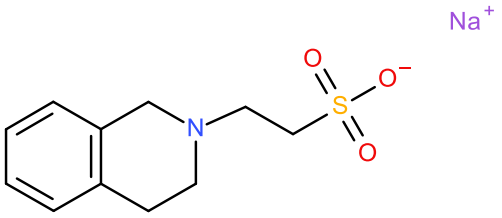
$^{13}$C-NMR (50 MHz, Methanol-$d_4$) δ 139.5, 129.3, 128.9, 128.7, 74.0, 66.9, 52.3.

**HRMS–Analysis**

| Meas.m/z | Formula | m/z | err [ppm] |
|---|---|---|---|
| 261.0173 | $C_9H_{11}Na_2O_4S$ | 261.0168 | -2.1 |

## 5.5 Compound **4:** Sodium 2-(3,4-dihydro-1H-isoquinolin-2-yl)ethanesulfonate

**Scheme 10:** Compound **4**




**Compound 4**

| | |
|---|---|
| Molecular formula: | $C_{11}H_{14}NNaO_3S$ |
| Molecular weight: | 263.29 g/mol |
| Melting point: | > 300 °C |

To 1 mmol (211 mg) of sodium 2-bromoethanesulfonate, 1 mL of 1,2,3,4-tetrahydroisoquinoline and also 2 mL methanol were added. The solution was stirred for 24 hours at 75°C. After the reaction was completed, the solvent was evaporated under reduced pressure. Afterwards, the product was recrystallized from absolute ethanol. The precipitate was filtered off and dried under vacuum to yield 140 mg of white crystals (53.2% yield).

$^{1}$H-NMR (200 MHz, $D_2O$) δ 7.40 – 7.04 (m, 4H), 3.73 (s, 2H), 3.36 – 3.18 (m, 2H), 3.14 – 2.74 (m, 6H).

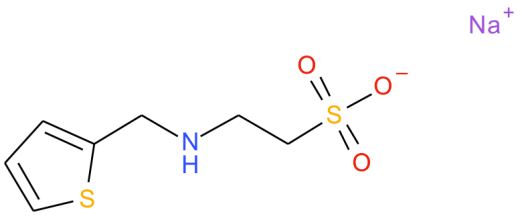
$^{13}$C-NMR (50 MHz, $D_2O$) δ 133.8, 133.6, 128.7, 126.7, 126.0, 54.5, 51.8, 49.8, 47.8, 27.6.

**HRMS–Analysis**

| Meas.m/z | Formula | m/z | err [ppm] |
|---|---|---|---|
| 264.0670 | $C_{11}H_{15}NNaO_3S$ | 264.0665 | -1.9 |

## 5.6 Compound **5:** Sodium 2-(2-thienylmethylamino)ethanesulfonate

**Scheme 11:** Compound **5**




**Compound 5**

| | |
|---|---|
| Molecular formula: | $C_7H_{10}NNaO_3S_2$ |
| Molecular weight: | 243.28 g/mol |
| Melting point: | > 300 °C |

To 2 mmol (211 mg) of sodium 2-bromoethanesulfonate, 2 mL of thiophenemethylamin and also 2 mL methanol were added. The solution was stirred for 24 hours at 75°C. After the reaction was completed, the solvent was evaporated under reduced pressure. Afterwards, the product was recrystallized from absolute ethanol. The precipitate was filtered off and dried under vacuum to yield 158 mg of white crystals (32.5% yield).

$^{1}$H NMR (200 MHz, DMSO-$d_6$) δ 7.46 – 7.24 (m, 1H), 6.94 (d, $J$ = 3.4 Hz, 2H), 3.84 (s, 2H), 2.78 (m, $J$ = 6.5 Hz, 2H), 2.59 (m, $J$ = 6.5 Hz, 2H).

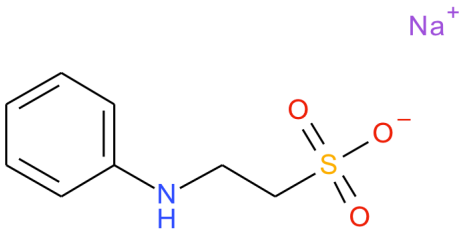
$^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 133.8, 118.2, 117.5, 116.2, 41.9, 38.9, 35.9.

**HRMS–Analysis**

| Meas.m/z | Formula | m/z | err [ppm] |
|---|---|---|---|
| 244.0075 | $C_7H_{11}NNaO_3S_2$ | 244.0073 | -1.0 |

## 5.7 Compound **6:** Sodium 2-benzyoxyethanesulfonate

**Scheme 12:** Compound **6**




**Compound 6**

| | |
|---|---|
| Molecular formula: | $C_8H_{10}NNaO_3S$ |
| Molecular weight: | 223.23 g/mol |
| Melting point: | > 300 °C |

To 2 mmol (211 mg) of sodium 2-bromoethanesulfonate, 2 mL of anilin and 2 mL methanol were added. The solution was stirred for 24 hours at 75°C. After the reaction was completed, the solvent was evaporated under reduced pressure. Afterwards, the product was recrystallized from absolute ethanol. The precipitate was filtered off and dried under vacuum to yield 246 mg of white powder (55.2% yield).

$^{1}$H NMR (200 MHz, Methanol-$d_4$) δ 7.24 – 7.01 (m, 2H), 6.76 – 6.56 (m, 3H), 3.54 (t, $J$ = 6.9 Hz, 2H), 3.06 (t, $J$ = 6.9 Hz, 2H).

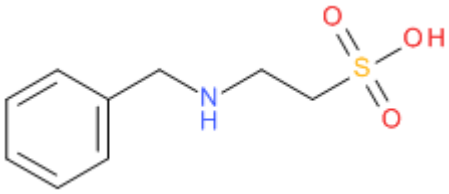
$^{13}$C NMR (50 MHz, Methanol-$d_4$) δ 149.5, 130.1, 118.6, 114.4, 51.2, 40.9.

**HRMS–Analysis**

| Meas.m/z | Formula | m/z | err [ppm] |
|---|---|---|---|
| 246.0172 | $C_8H_{10}NNa_2O_3S$ | 246.0171 | -0.3 |

## 5.8 Compound **7:** 2-(Benzylamino)ethanesulfonic acid

**Scheme 13:** Compound **7**




**Compound 7**

| | |
|---|---|
| Molecular formula: | $C_9H_{13}NO_3S$ |
| Molecular weight: | 215.27 g/mol |
| Melting point: | 203 °C – 215 °C (decomposition) |

To a solution of 1 mmol NaOH (40 mg) in 4 ml MeOH, 1 mmol benzaldehyde (0.1 mL) and 1 mmol aminoethanesulfonic acid (125 mg) were added. The solution was stirred for 45 minutes at room temperature prior to cooling in an ice bath. Then 1.05 mmol $NaBH_4$ (40 mg) were added. After 30 hours the solution was acidified with acetic acid (2N) to pH 3-5. The resulting product was filtered off and washed with ethanol, and dried under vacuum to yield 104 mg of a white powder (48.3% yield).

$^1$H NMR (200 MHz, DMSO-$d_6$) δ 8.63 (br s, 1H), 7.56 – 7.28 (m, 5H), 4.20 (s, 2H), 3.17 (t, $J$ = 6.9 Hz, 2H), 2.82 (t, $J$ = 6.9 Hz, 2H).

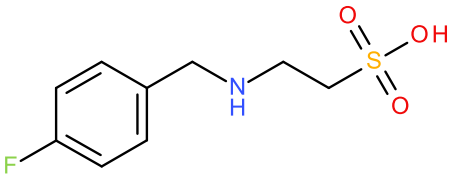
$^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 132.0, 129.8, 129.0, 128.8, 49.8, 46.6, 43.4

**HRMS–Analysis**

| Meas.m/z | Formula | m/z | err [ppm] |
|---|---|---|---|
| 238.0509 | $C_9H_{13}NNaO_3S$ | 238.0508 | -0.3 |

## 5.9 Compound **8**: 2-(4-Fluorophenyl)methylamino)ethanesulfonic acid

**Scheme 14:** Compound **8**




**Compound 8**

| | |
|---|---|
| Molecular formula: | $C_9H_{12}FNO_3S$ |
| Molecular weight: | 233.26 g/mol |
| Melting point: | 223 °C – 242 °C (decomposition) |

To a solution of 1 mmol NaOH (40 mg) in 4 ml MeOH, 1 mmol 4-fluorobenzaldehyde (0.1 mL) and 1 mmol aminoethanesulfonic acid (125 mg) were added. The solution was stirred for 45 minutes at room temperature prior to cooling in an ice bath. Then 1.05 mmol $NaBH_4$ (40 mg) were added. After 30 hours the solution was acidified with acetic acid (2N) to pH 3-5. The resulting product was filtered off und washed with ethanol, and dried under vacuum to yield 105 mg of a white powder (45.0% yield).

$^1$H NMR (200 MHz, DMSO-$d_6$) δ 8.61 (br s, 1H), 7.63 – 7.46 (m, 2H), 7.39 – 7.19 (m, 2H), 4.19 (s, 2H), 3.15 (t, $J$ = 6.9 Hz, 3H), 2.82 (t, $J$ = 6.9 Hz, 1H).

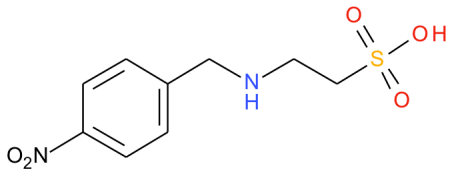
$^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 162.4 (d, $J$ = 245.5 Hz), 132.3 (d, $J$ = 6.9 Hz), 128.4 (d, $J$ = 3.1 Hz), 115.7 (d, $J$ = 21.6 Hz), 49.0, 46.6, 43.3.

**HRMS–Analysis**

| Meas.m/z | Formula | m/z | err [ppm] |
|---|---|---|---|
| 256.0415 | $C_9H_{12}FNNaO_3S$ | 256.0414 | -0.4 |

## 5.10 Compound **9**: 2-(4-Nitrophenyl)methylamino) ethanesulfonic acid

**Scheme 15:** Compound **9**




**Compound 9**

| | |
|---|---|
| Molecular formula: | $C_9H_{12}N_2O_5S$ |
| Molecular weight: | 260.27 g/mol |
| Melting point: | 268 °C – 281 °C (decomposition) |

To a solution of 1 mmol NaOH (40 mg) in 4 mL MeOH, 1 mmol p-nitrobenzaldehyde (0.1 mL) and 1 mmol aminoethanesulfonic acid (125 mg) were added. The solution was stirred for 45 minutes at room temperature prior to cooling in an ice bath. Then 1.05 mmol $NaBH_4$ (40 mg) were added. After 30 hours the solution was acidified with acetic acid (2N) to pH 3-5. The resulting product was filtered off und washed with ethanol, and dried under vacuum to yield 177 mg of a yellow powder (68.0% yield).

$^1$H NMR (200 MHz, DMSO-$d_6$) δ 8.88 (br s, 1H), 8.31 (A-part of AB-system, $J_{AB}$ = 8.7 Hz, 2H), 7.77 (B-part of AB system, $J_{AB}$ = 8.7 Hz, 2H), 4.36 (s, 2H), 3.21 (t, $J$ = 6.9 Hz, 2H), 2.86 (t, $J$ = 6.9 Hz, 2H).

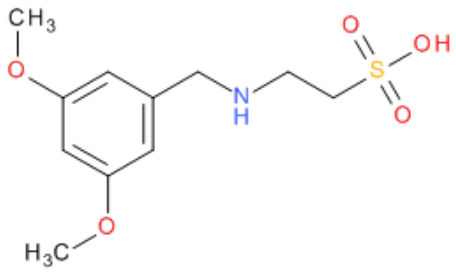
$^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 147.8, 139.4, 131.2, 123.8, 48.9, 46.6, 43.7.

**HRMS–Analysis**

| Meas.m/z | Formula | m/z | err [ppm] |
|---|---|---|---|
| 283.0364 | $C_9H_{12}N_2NaO_5S$ | 283.0359 | -1.8 |

## 5.11 Compound **10**: 2-[(3,5-Dimethoxyphenyl)methylamino]ethanesulfonic acid

**Scheme 16:** Compound **10**



**Compound 10**

| | |
|---|---|
| Molecular formula: | $C_{11}H_{17}NO_5S$ |
| Molecular weight: | 275.32 g/mol |
| Melting point: | 224 °C – 231 °C |

To a solution of 1 mmol NaOH (39 mg) in 4 mL MeOH, 1 mmol 3,5-dimethoxybenzaldehyde (0.1 mL) and 1 mmol aminoethanesulfonic acid (125 mg) were added. The solution was stirred for 45 minutes at room temperature prior to cooling in an ice bath. Then 1.05 mmol $NaBH_4$ (40 mg) were added. After 30 hours the solution was acidified with acetic acid (2N) to pH 3-5. The resulting product was filtered off und washed with ethanol, and dried under vacuum to yield 199 mg of a white powder (72.3% yield).

$^1$H NMR (200 MHz, DMSO-$d_6$) δ 8.69 (br s, 1H), 6.68 (d, $J$ = 2.2 Hz, 2H), 6.53 (t, $J$ = 2.2 Hz, 1H), 4.12 (s, 2H), 3.76 (s, 6H), 3.15 (t, $J$ = 6.8 Hz, 2H), 2.82 (t, $J$ = 6.8 Hz, 2H).

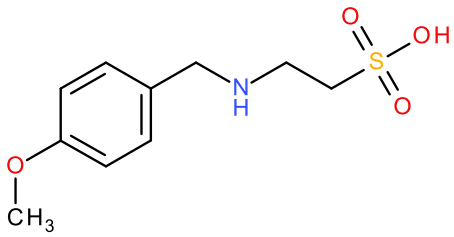
$^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 160.6, 134.0, 107.6, 100.5, 55.3, 49.8, 46.6, 43.3.

**HRMS–Analysis**

| **Meas.m/z** | **Formula** | **m/z** | **err [ppm]** |
|---|---|---|---|
| 298.0724 | $C_{11}H_{17}NNaO_5S$ | 298.0720 | -1,6 |

## 5.12 Compound **11:** 2-[(4-Methoxyphenyl)methylamino]ethanesulfonic acid

**Scheme 17:** Compound **11**




**Compound 11**

| | |
|---|---|
| Molecular formula: | $C_{10}H_{15}NO_4S$ |
| Molecular weight: | 245.30 g/mol |
| Melting point: | 249°-256° |

To a solution of 1 mmol NaOH (40 mg) in 4 mL MeOH, 1 mmol anisaldehyde (0.1 mL) and 1 mmol aminoethanesulfonic acid were added. The solution was stirred for 45 minutes at room temperature prior to cooling in an ice bath. Then 1.05 mmol $NaBH_4$ (40 mg) were added. After 30 hours the solution was acidified with acetic acid (2N) to pH 3-5. The resulting product was filtered off und washed with ethanol, and dried under vacuum to yield 156 mg of a white powder (63.6% yield).

$^1$H NMR (200 MHz, DMSO-$d_6$) δ 8.27 (br s, 1H), 7.41 (A-part of AB-system, $J_{AB}$ = 8.6 Hz, 2H), 6.99 (B-part of AB system, $J_{AB}$ = 8,6 Hz, 2H), 4.11 (s, 2H), 3.77 (s, 3H), 3.13 (t, $J$ = 6.9 Hz, 2H) 2.81 (t, $J$ = 6.9 Hz, 2H).

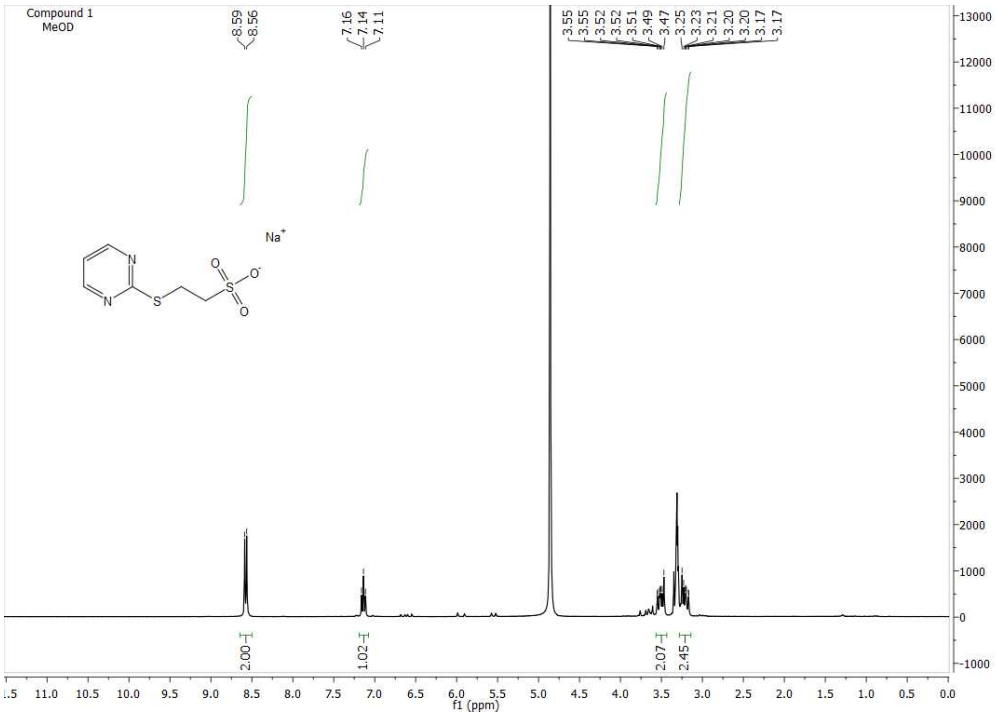
$^{13}$C NMR (50 MHz, DMSO-$d_6$) δ 159.7, 131.4, 123.9, 114.1, 55.2, 49.4, 46.7, 43.1.

**HRMS–Analysis**

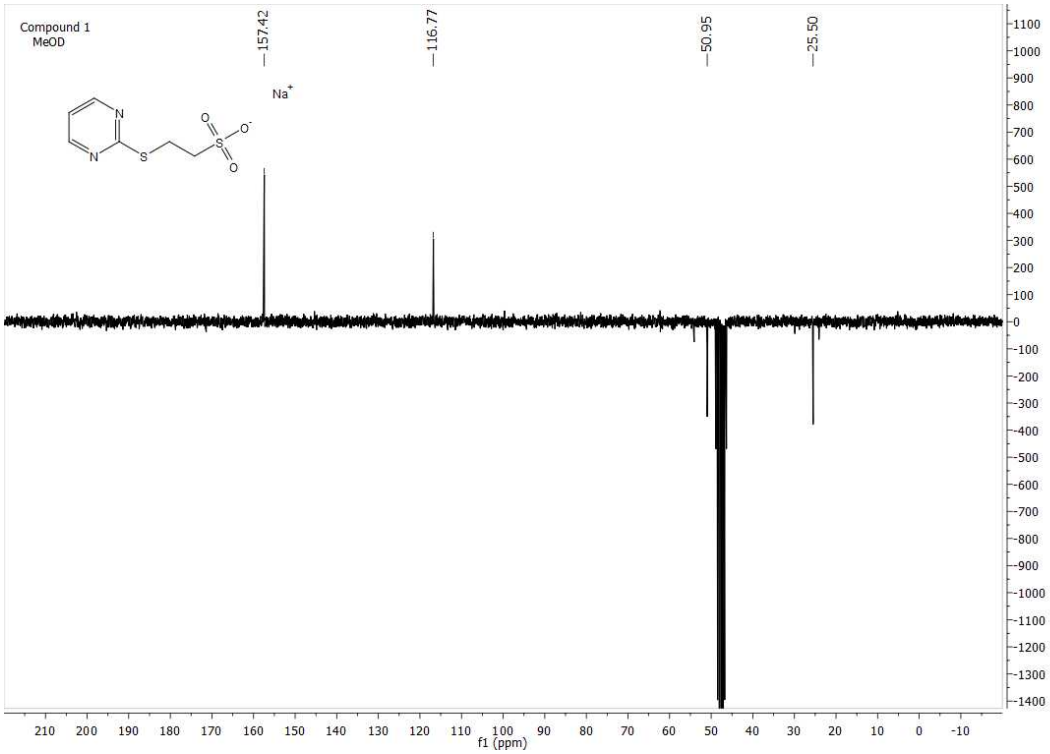
| **Meas.m/z** | **Formel** | **m/z** | **err [ppm]** |
|---|---|---|---|
| 268.0618 | $C_{10}H_{15}NNaO_4S$ | 268.0614 | -1.3 |

# 6 Analytics

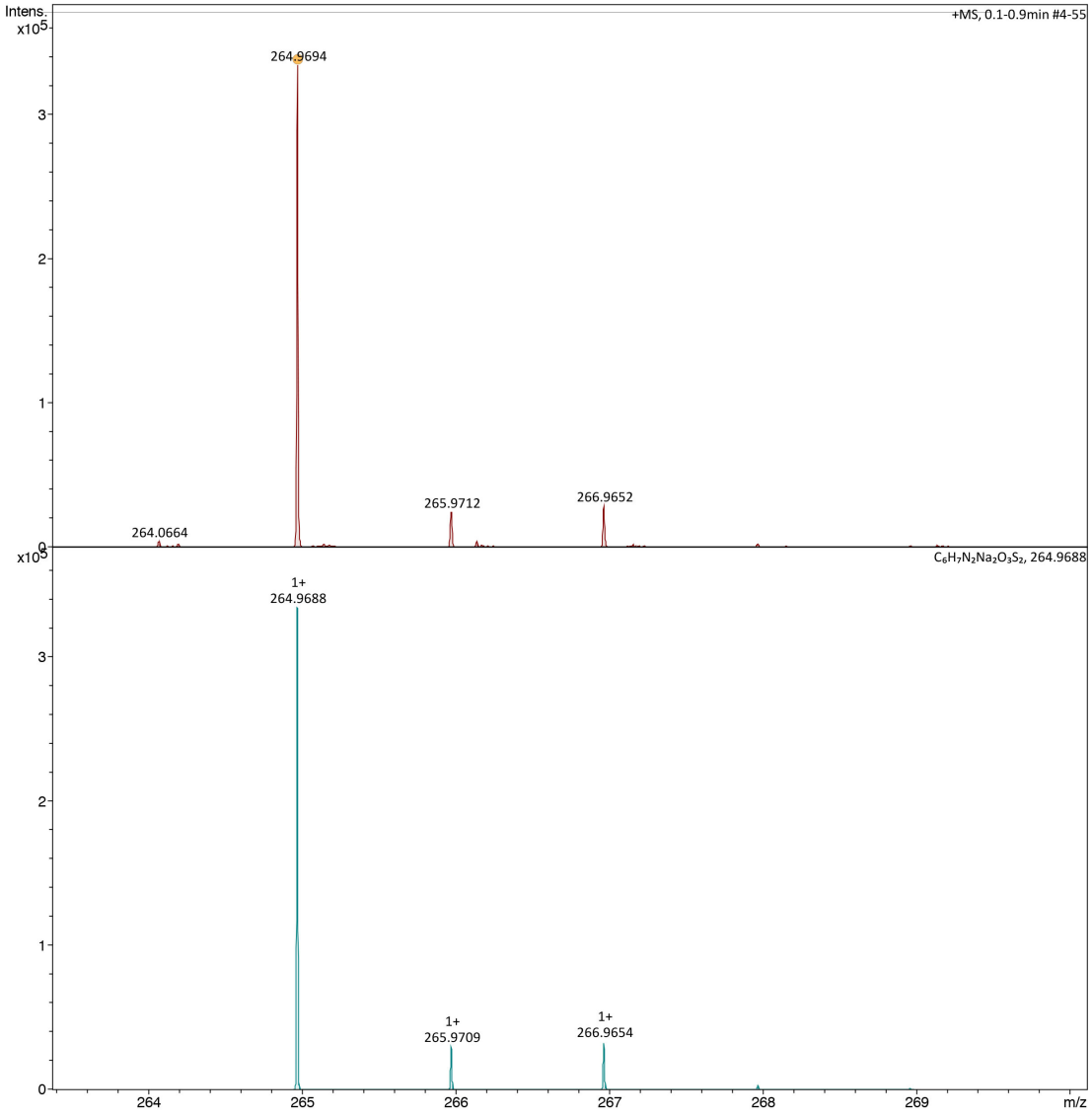
Compound **1** $^{1}$H NMR (Methanol-$d_4$)



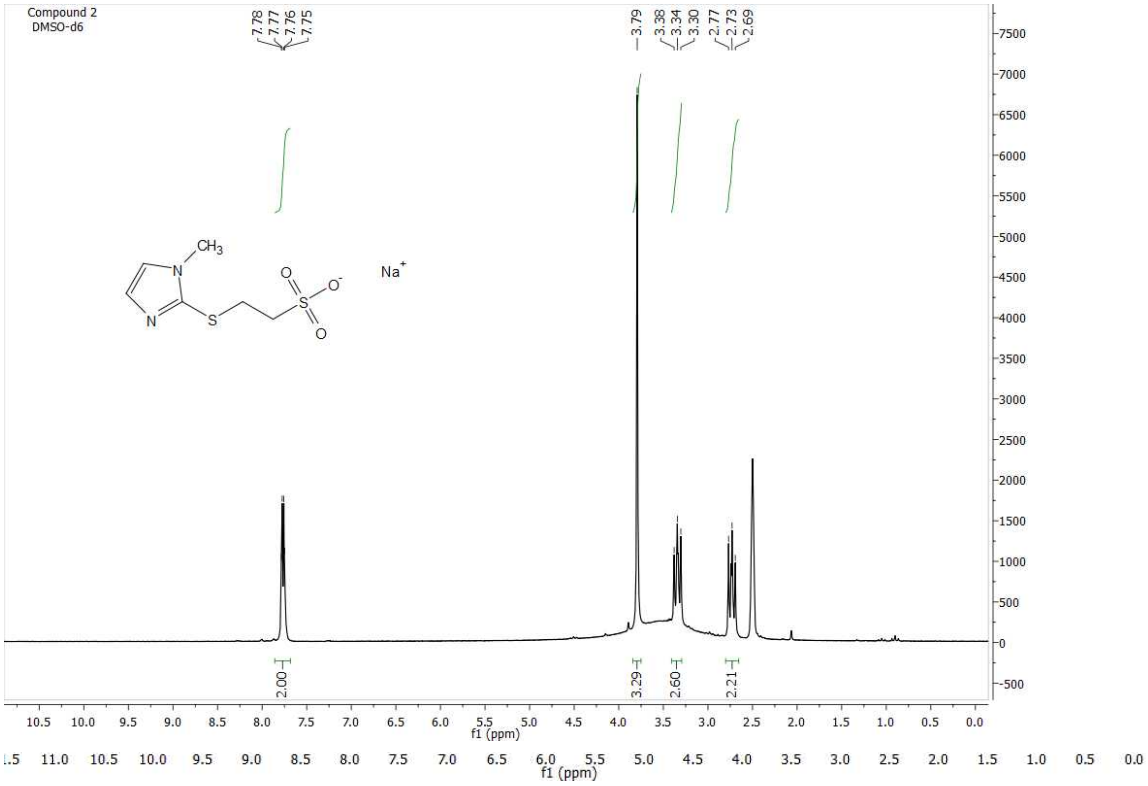

Compound **1** $^{13}$C NMR (Methanol-$d_4$)



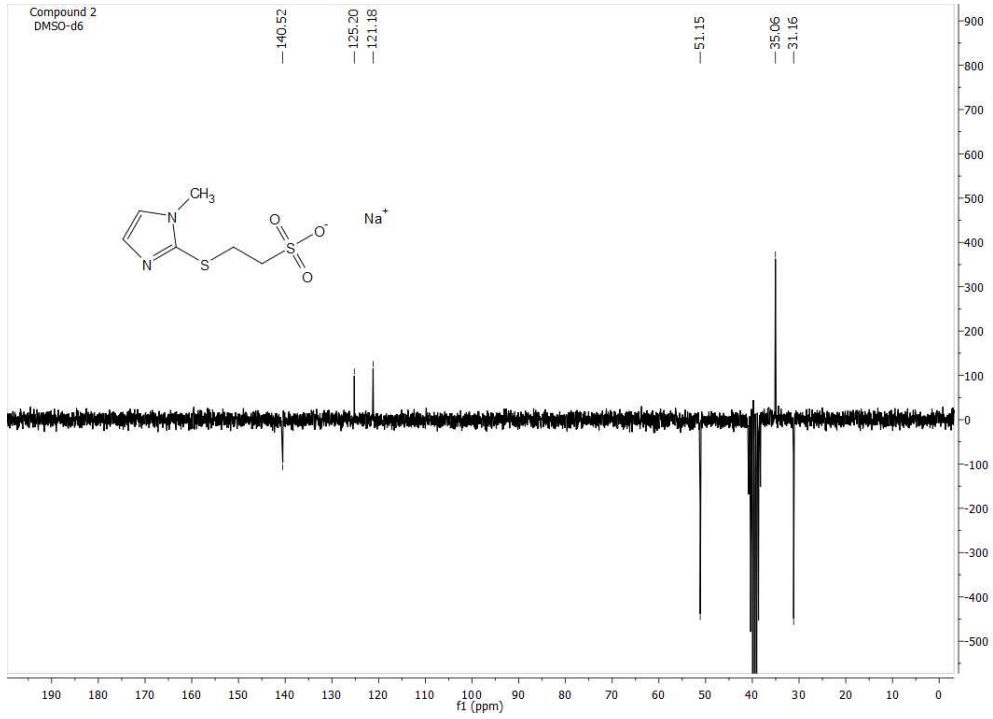
Compound **1** HRMS



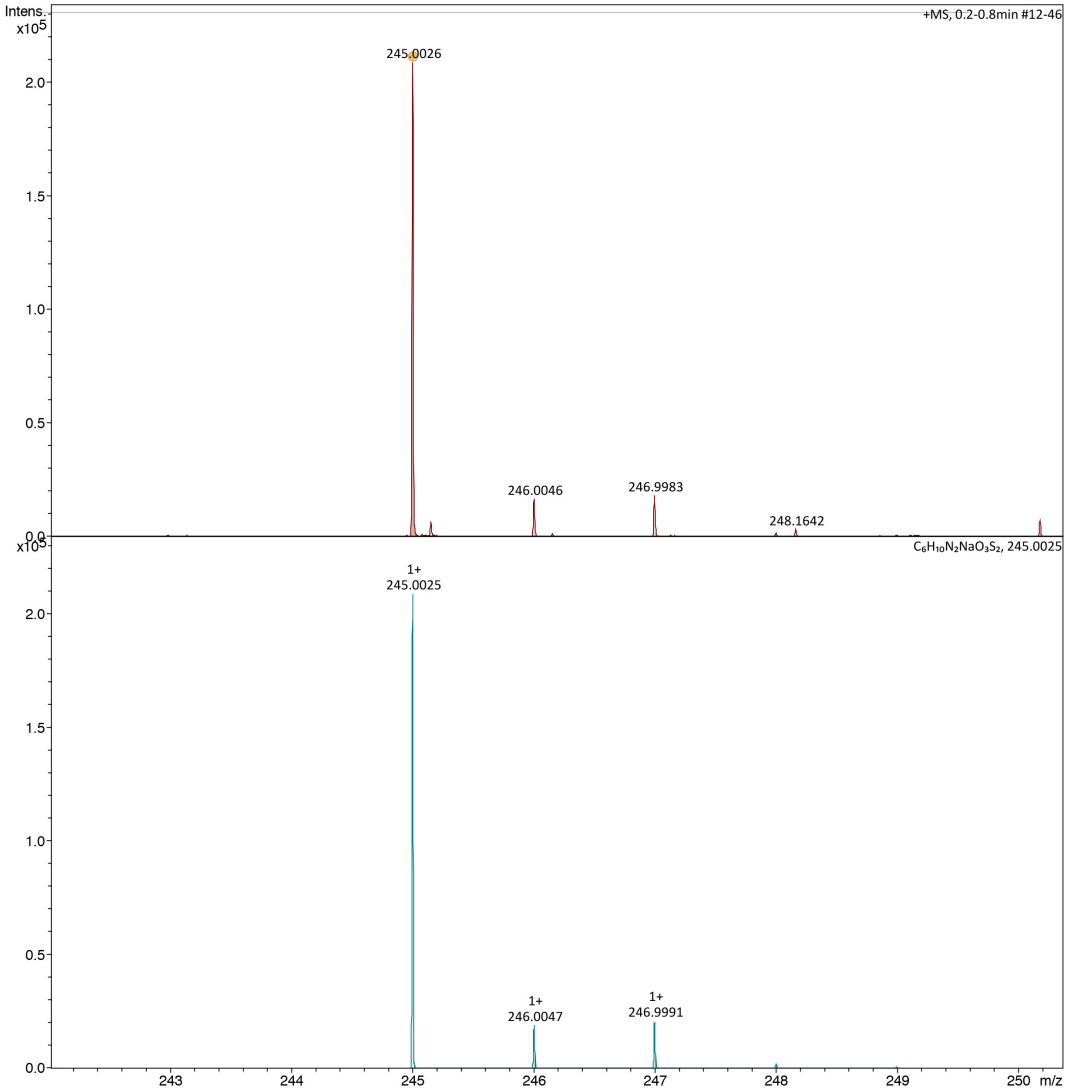
Compound **2** $^{1}$H NMR (DMSO-$d_6$)



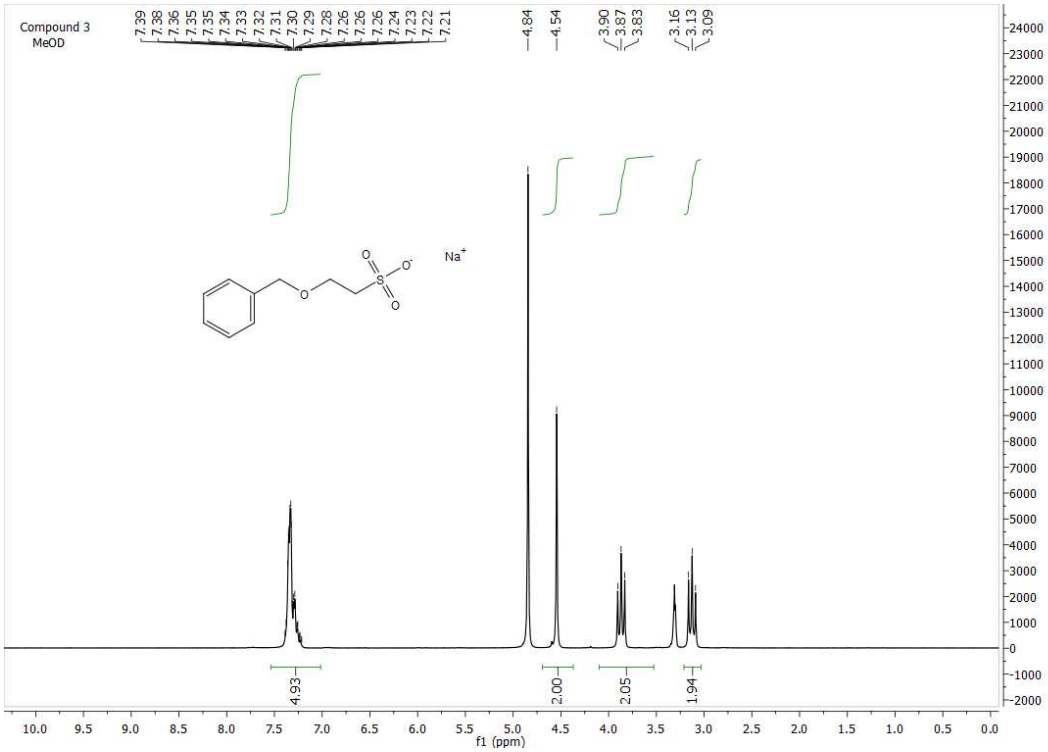

Compound **2** $^{13}$C NMR (DMSO-$d_6$)



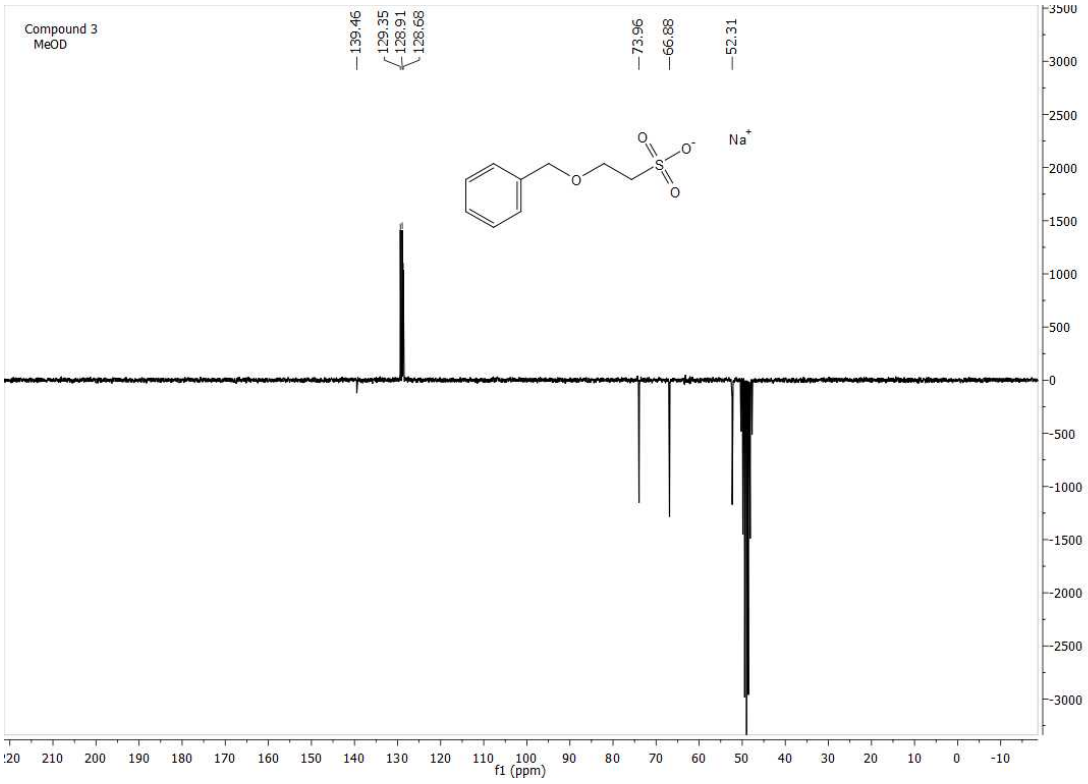
Compound **2** HRMS



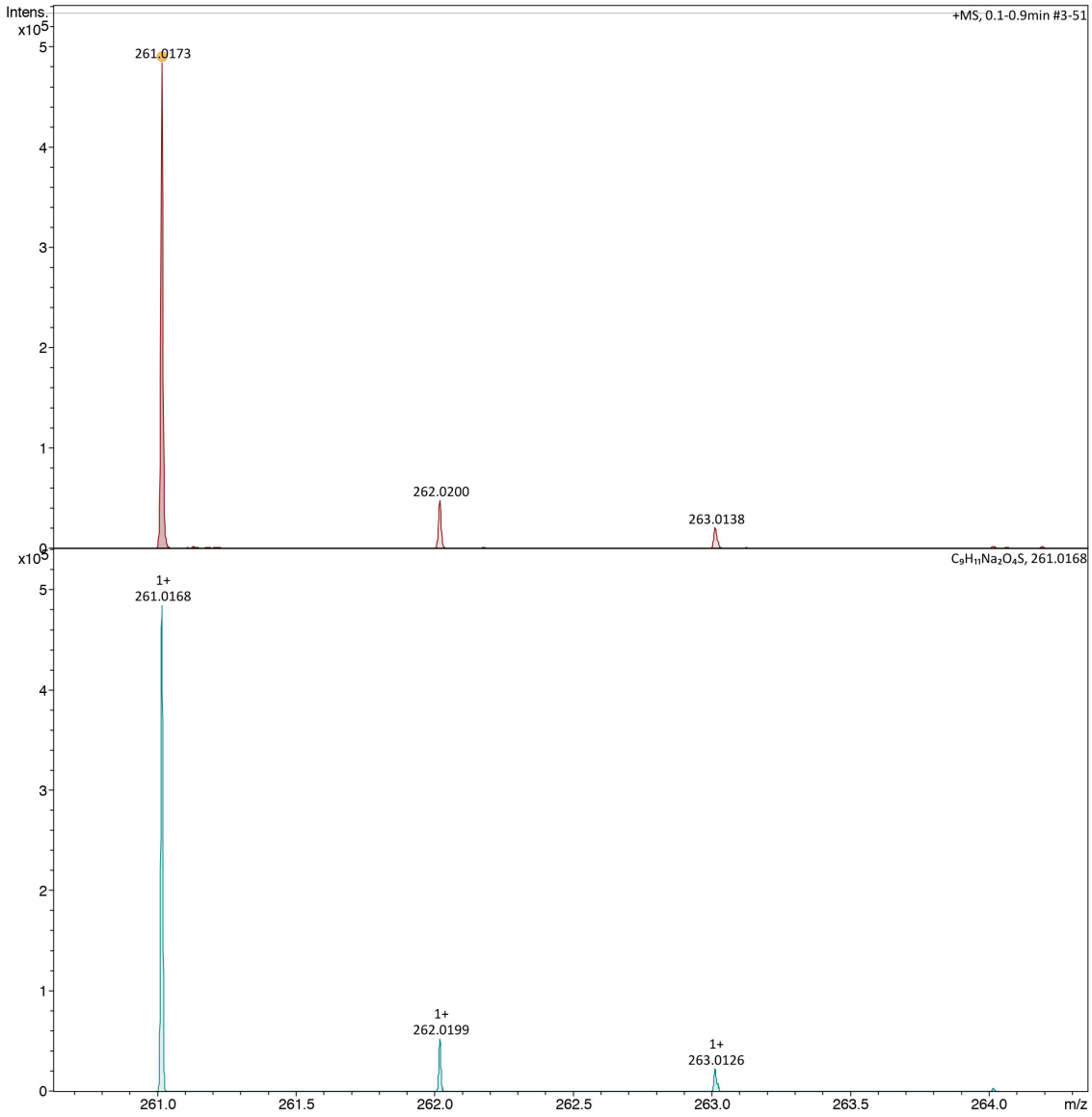
Compound **3** $^{1}$H NMR (Methanol-$d_4$)



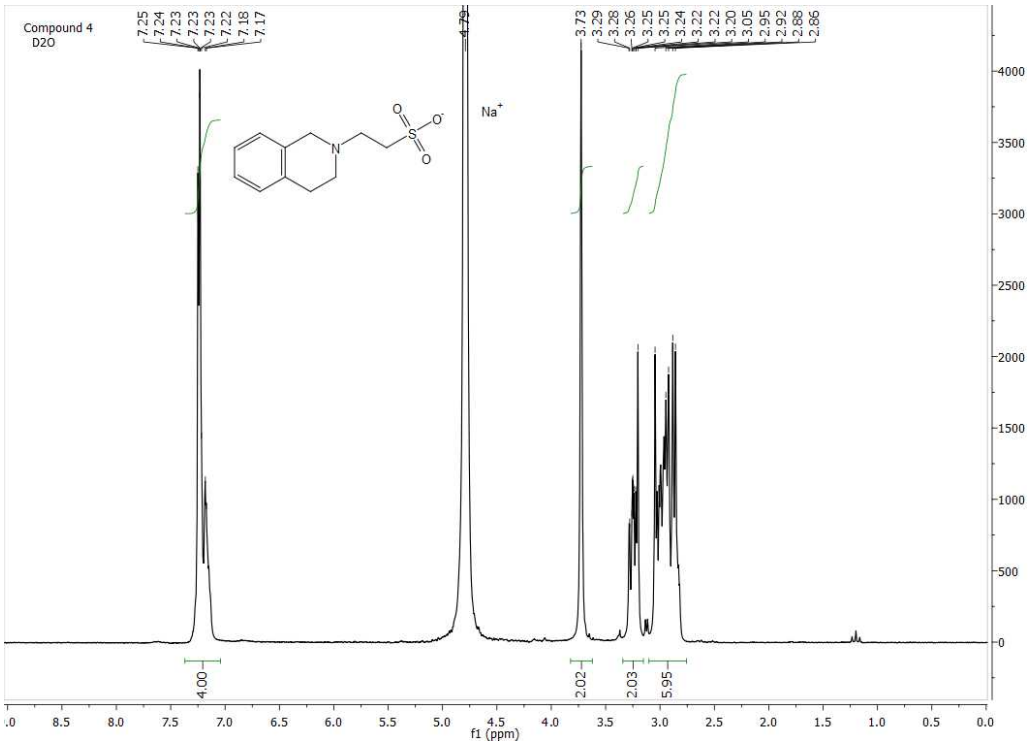

Compound **3** $^{13}$C NMR (Methanol-$d_4$)



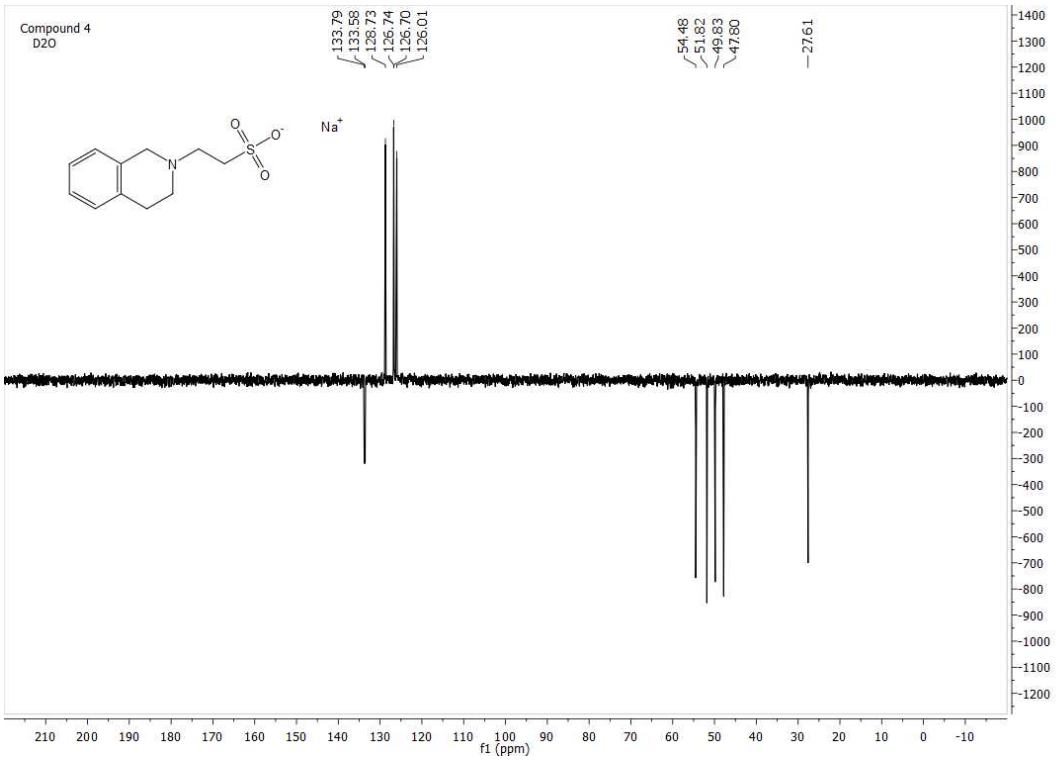
Compound **3** HRMS



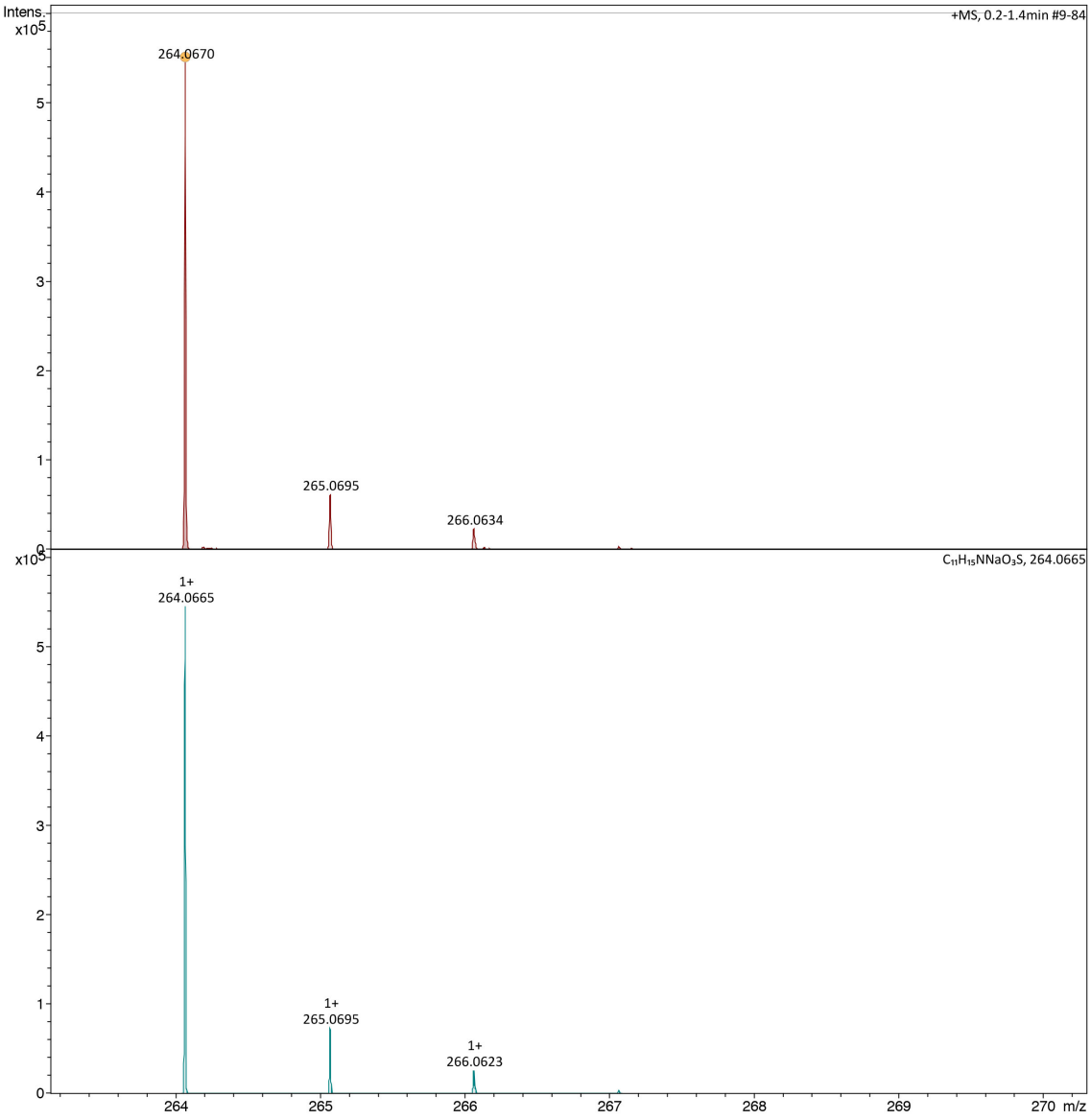
Compound **4** $^{1}H$ NMR ($D_2O$)



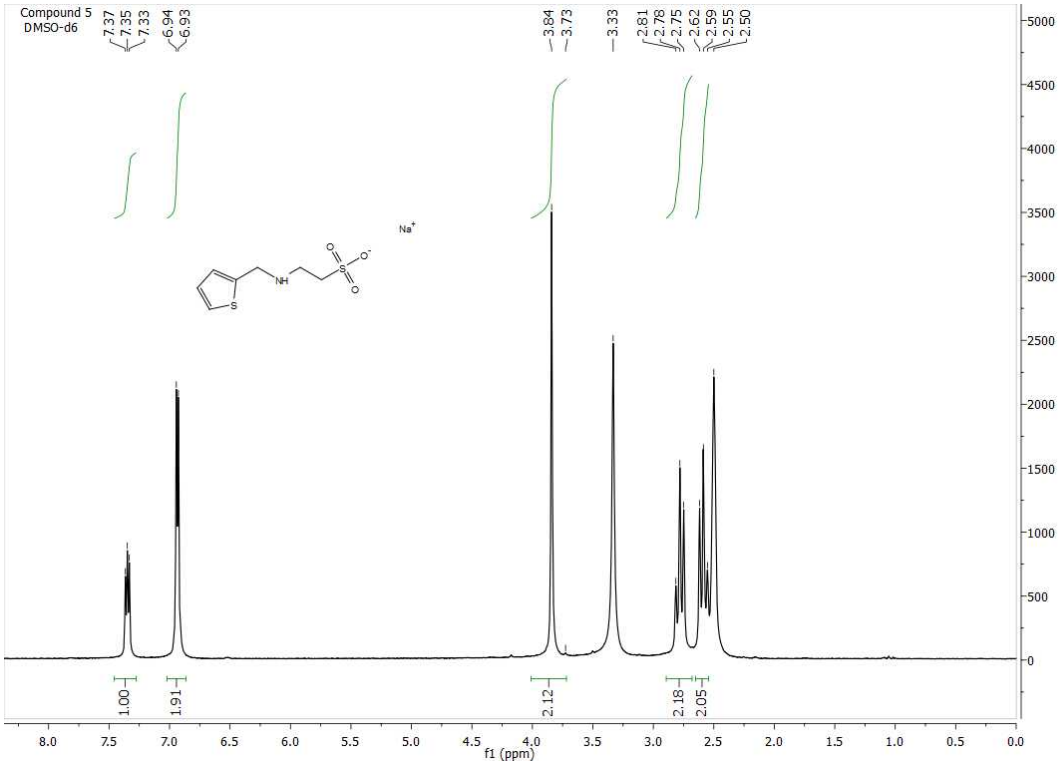

Compound **4** $^{13}C$ NMR ($D_2O$)



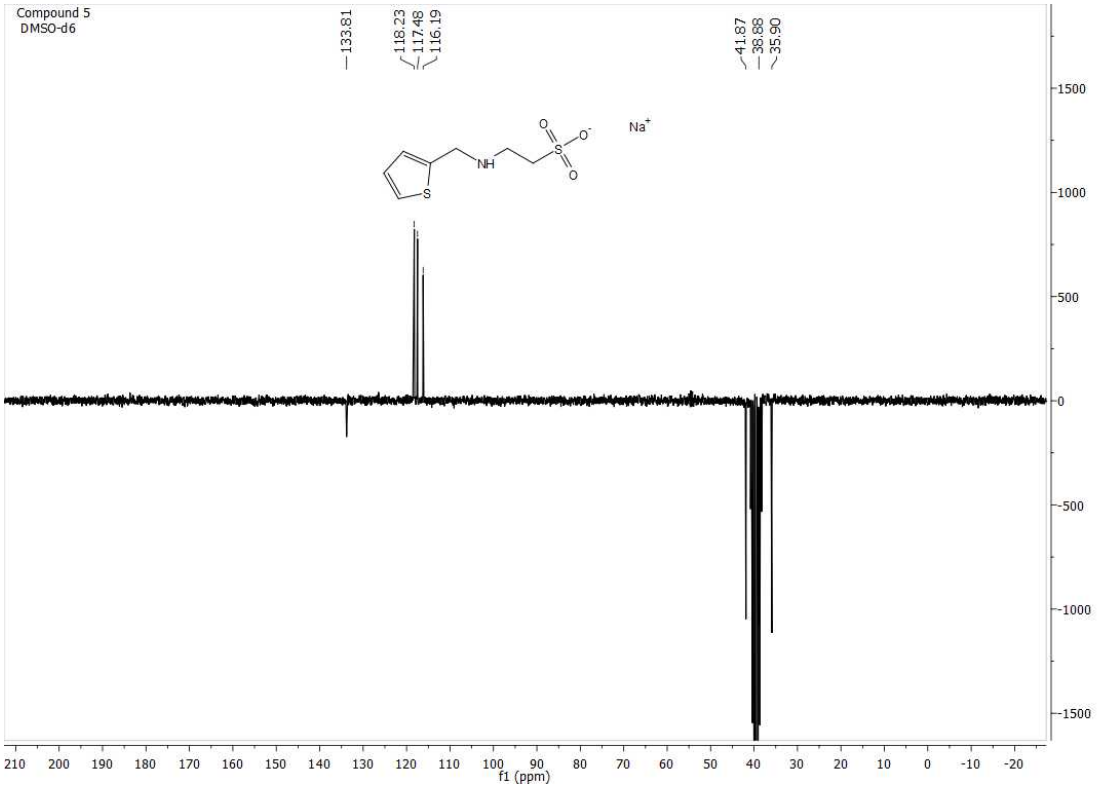
Compound **4** HRMS



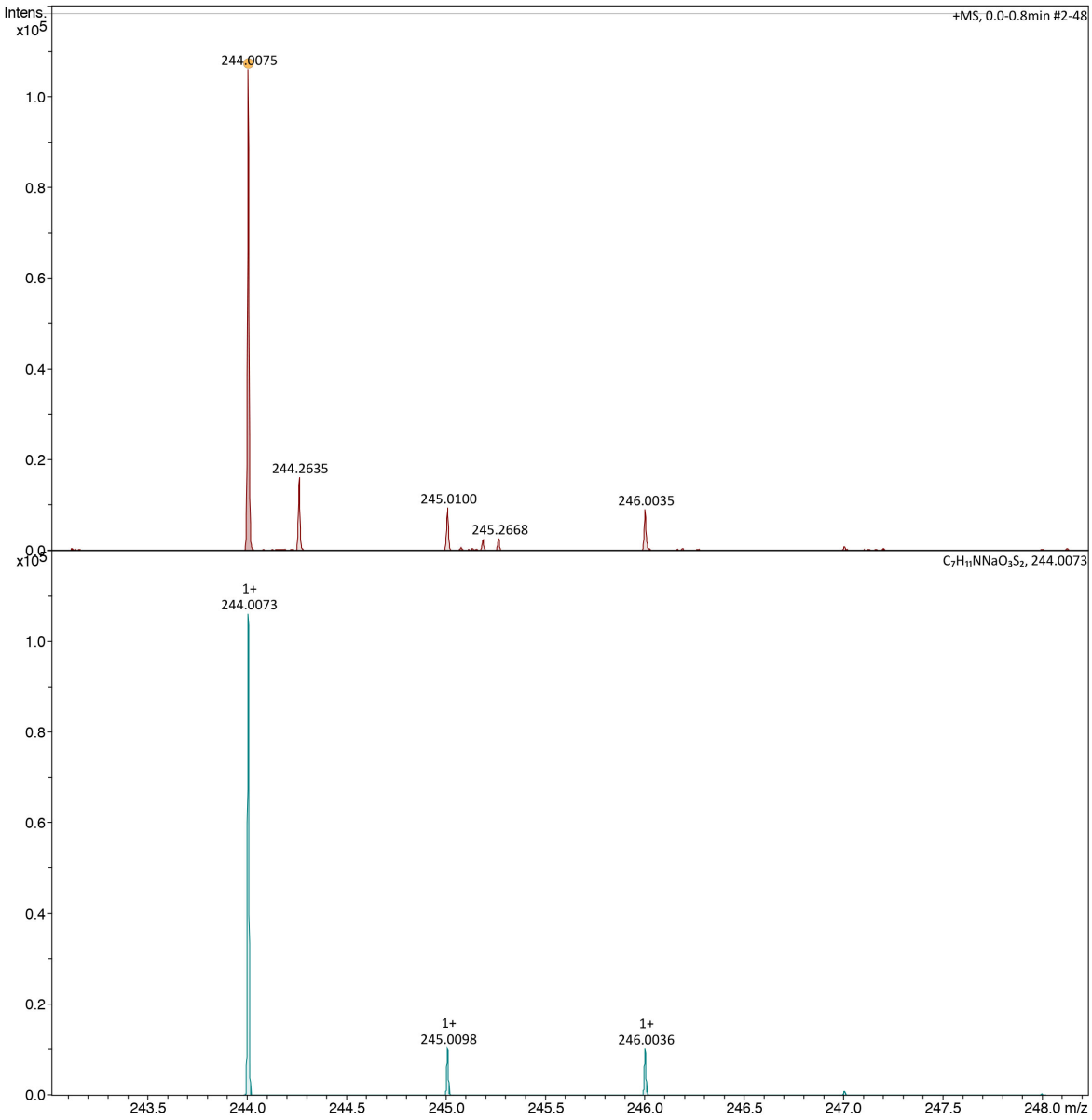
Compound **5** $^{1}$H NMR (DMSO-$d_6$)



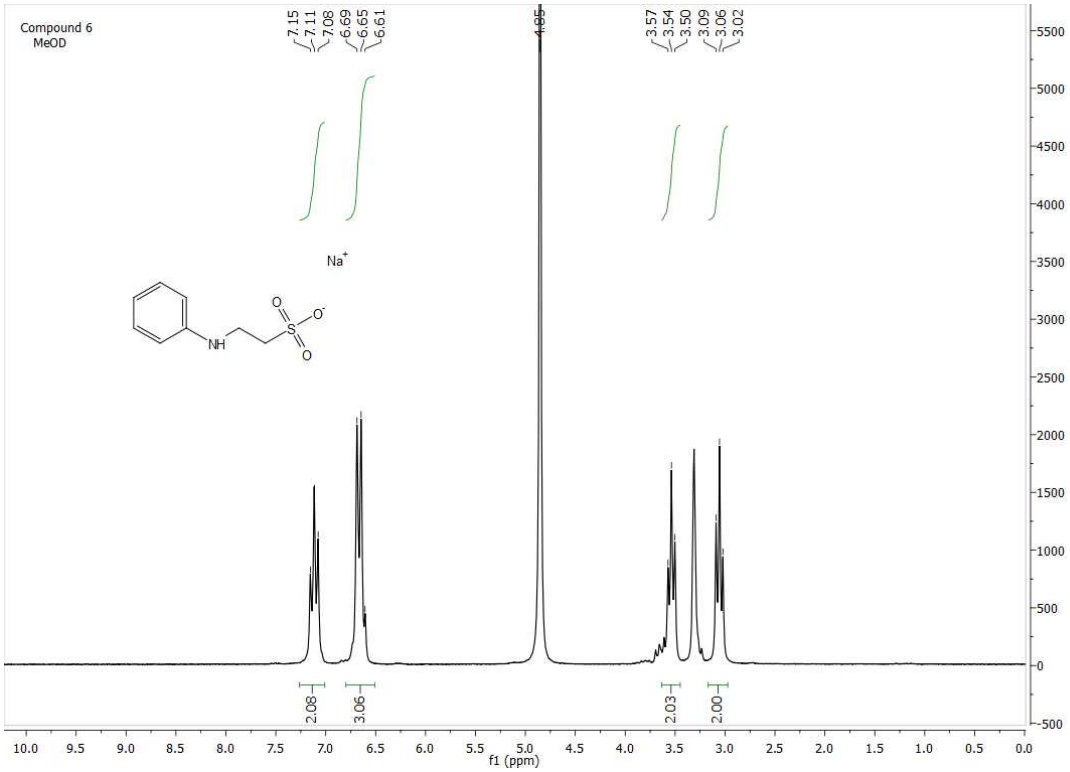

Compound **5** $^{13}$C NMR (DMSO-$d_6$)



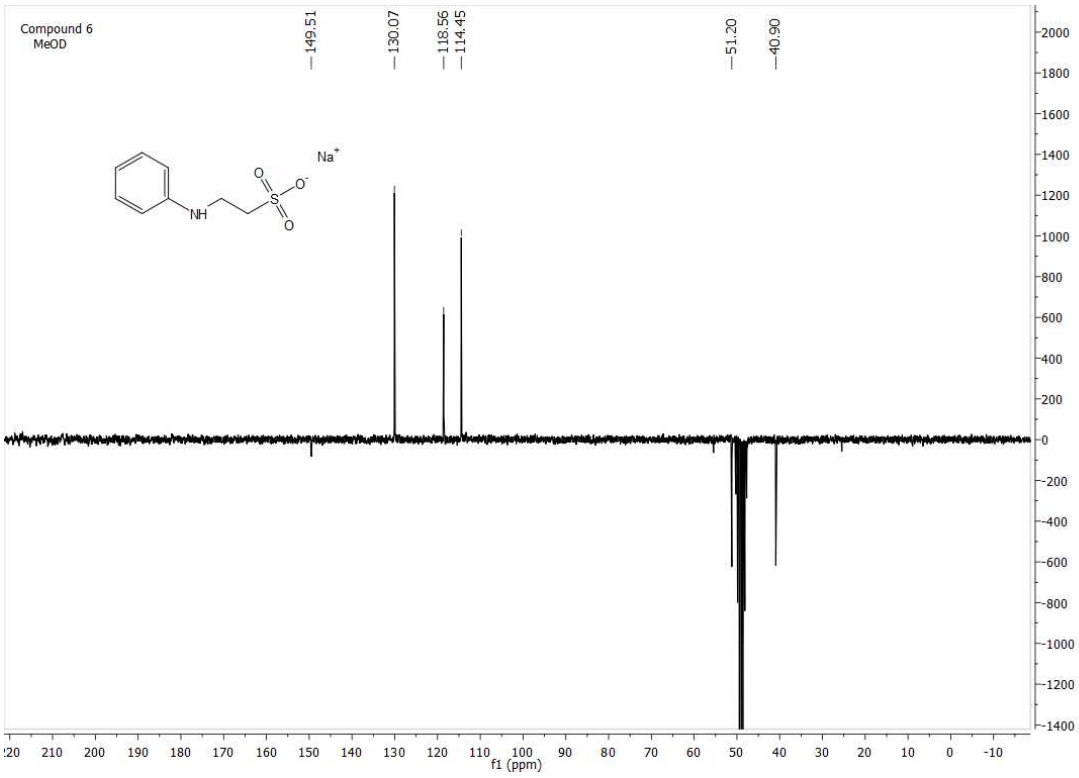
Compound **5** HRMS



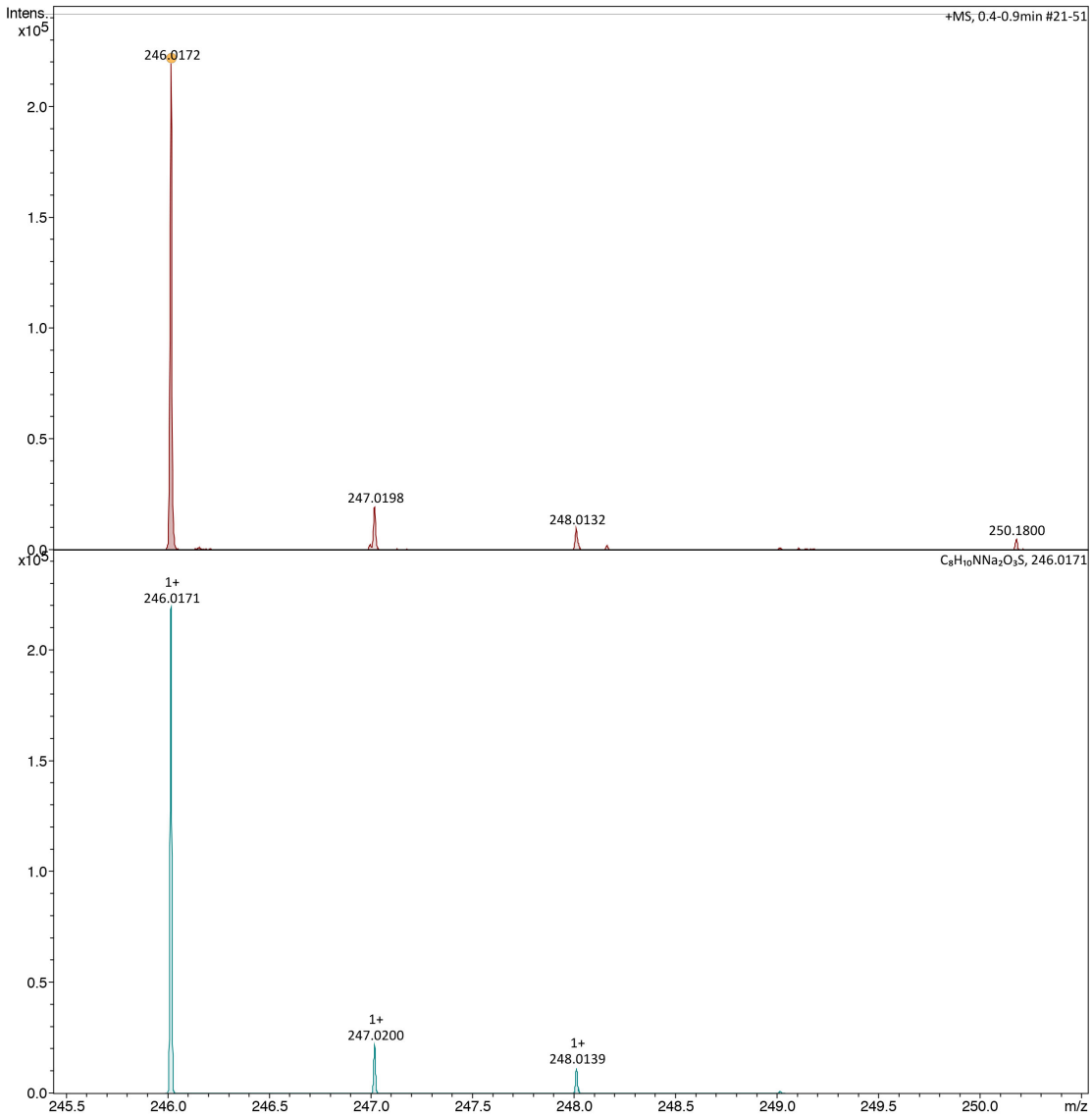
Compound **6** $^{1}$H NMR (Methanol-$d_4$)



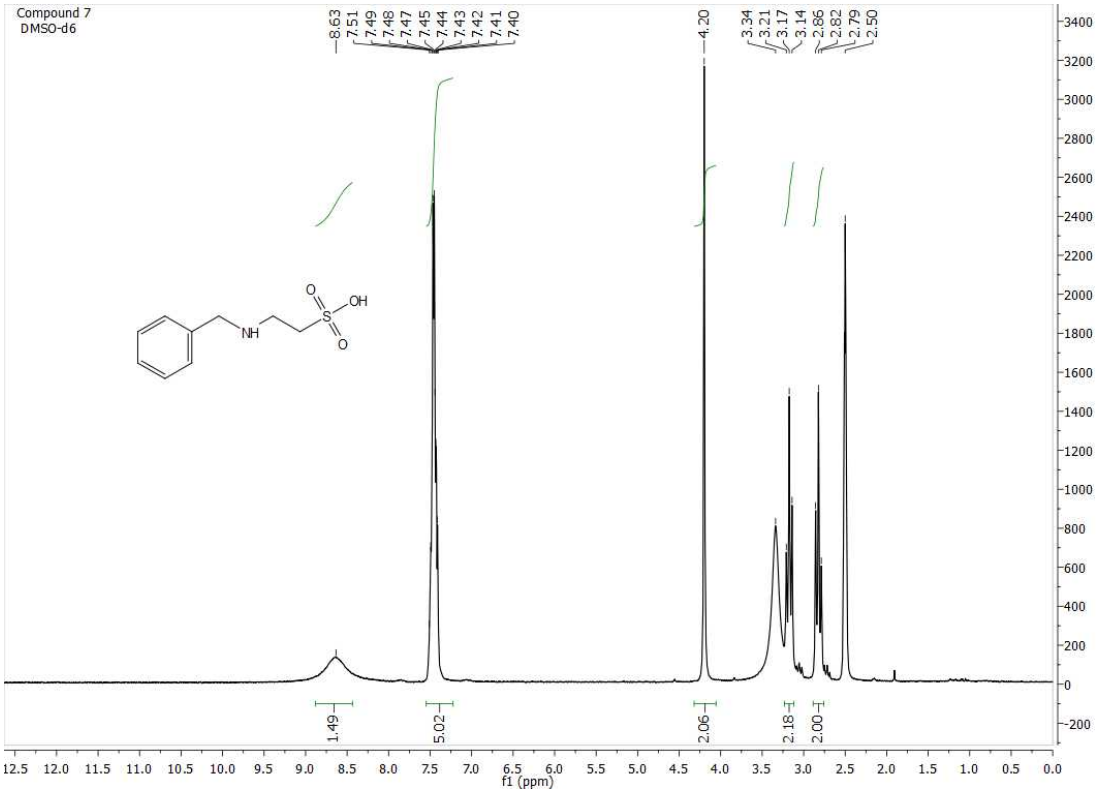

Compound **6** $^{13}$C NMR (Methanol-$d_4$)



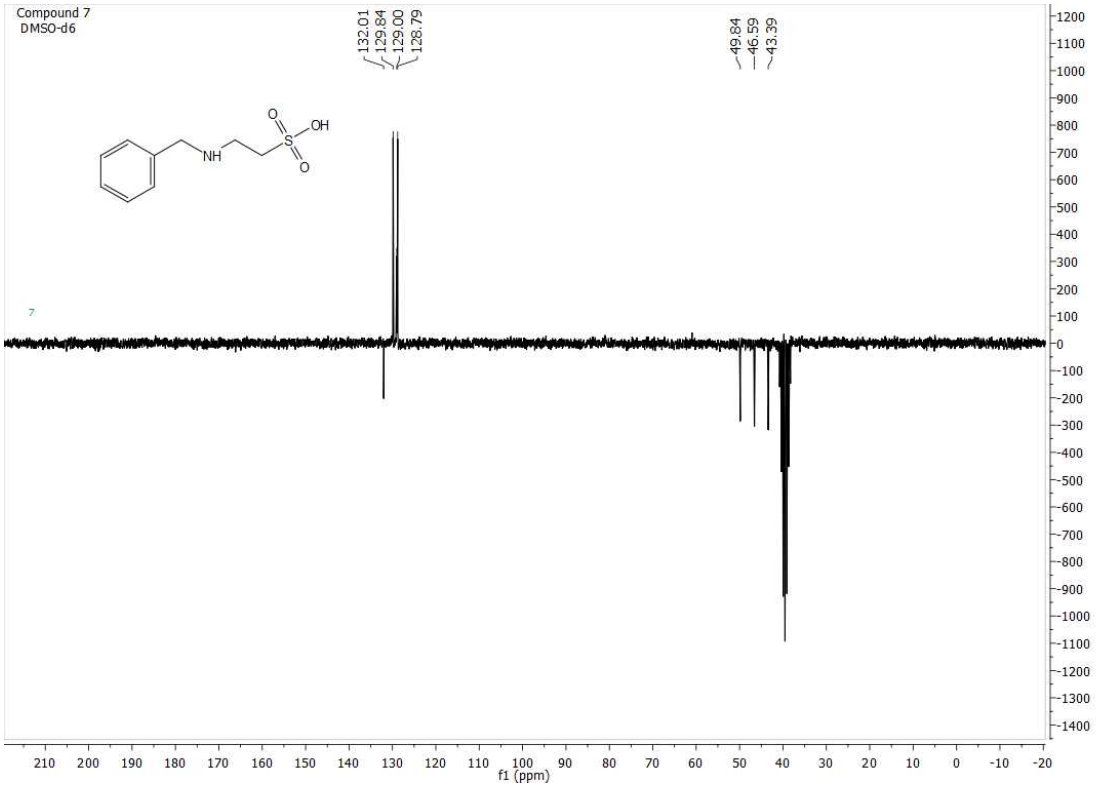
Compound **6** HRMS



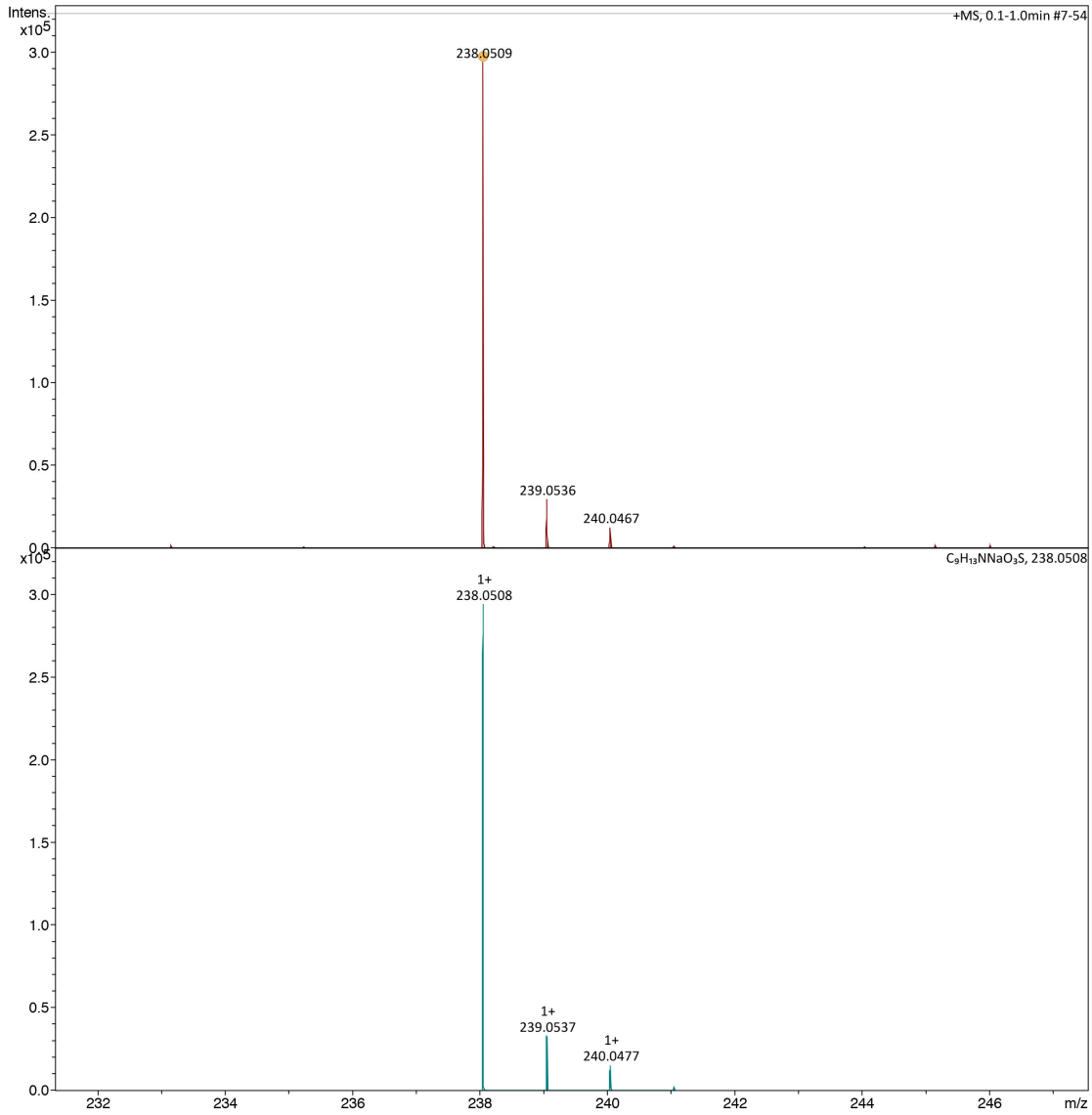
Compound **7** $^{1}$H NMR (DMSO-$d_6$)



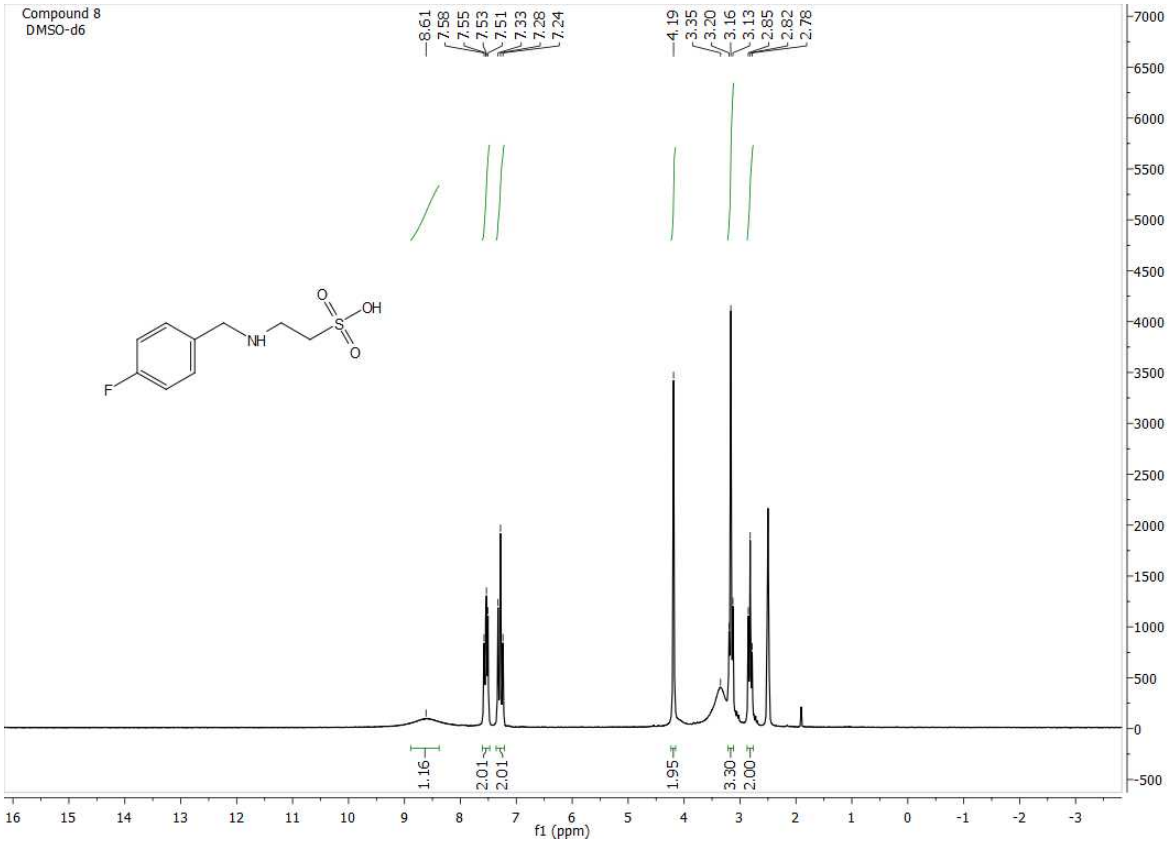

Compound **7** $^{13}$C NMR (DMSO-$d_6$)



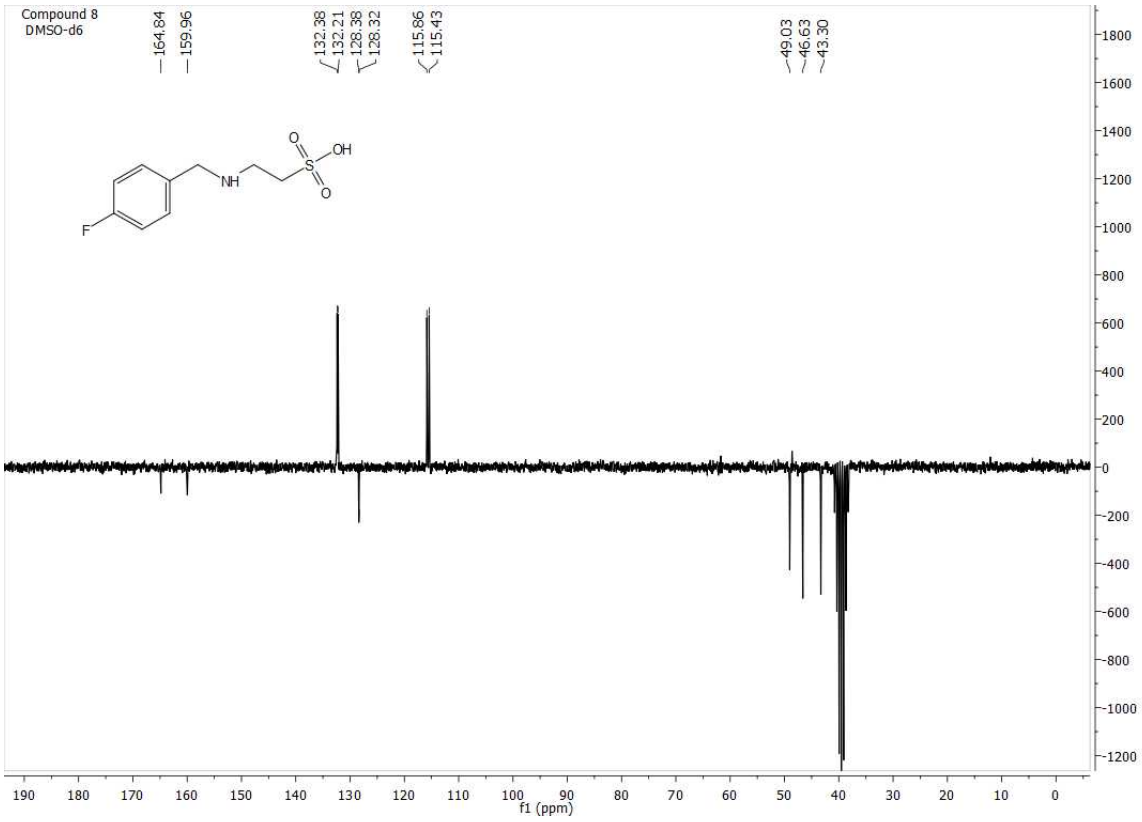
Compound **7** HRMS



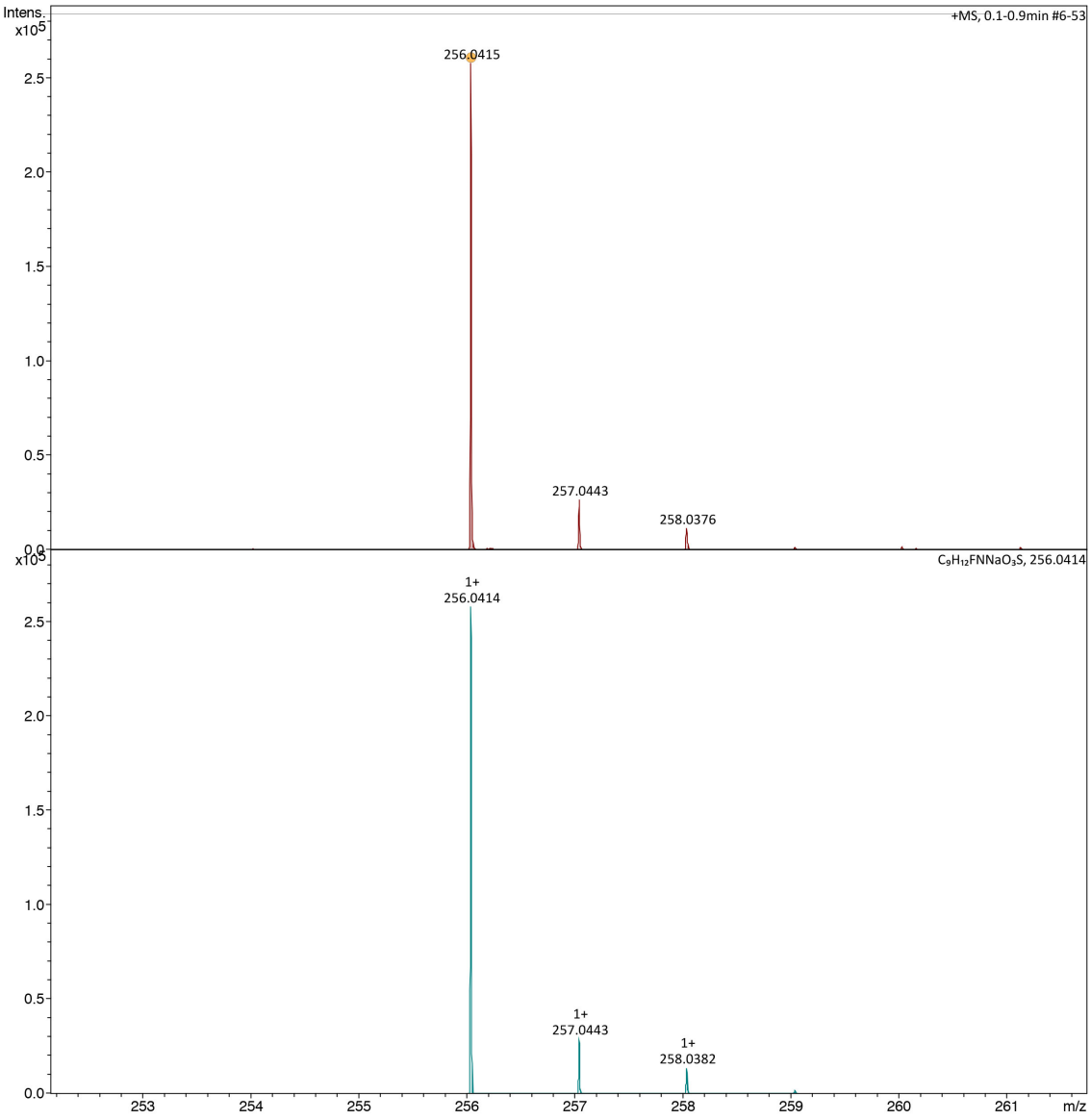
Compound **8** $^{1}$H NMR (DMSO-$d_6$)



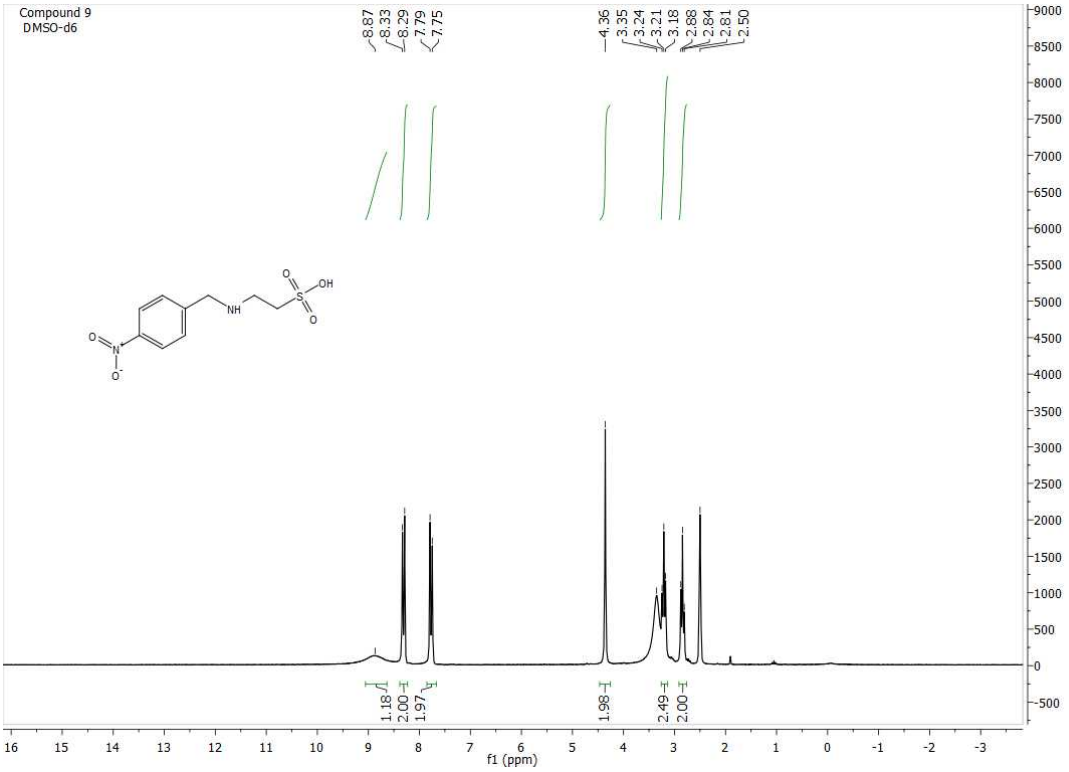

Compound **8** $^{13}$C NMR (DMSO-$d_6$)



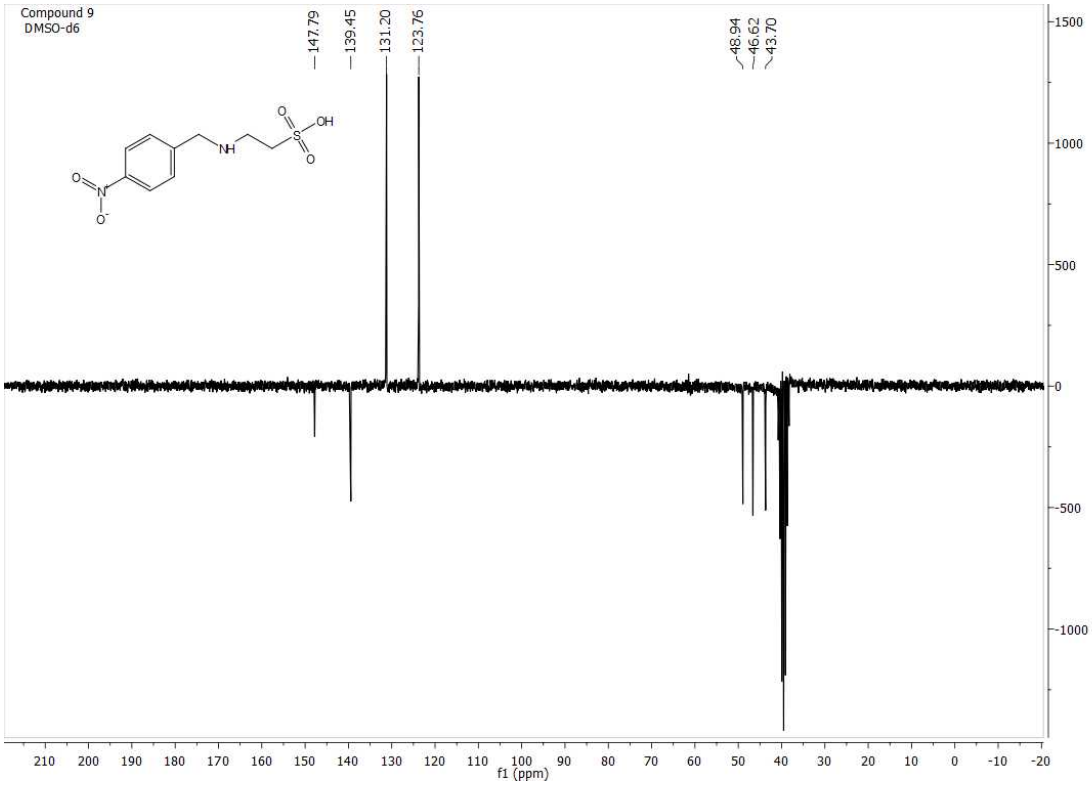
Compound **8** HRMS



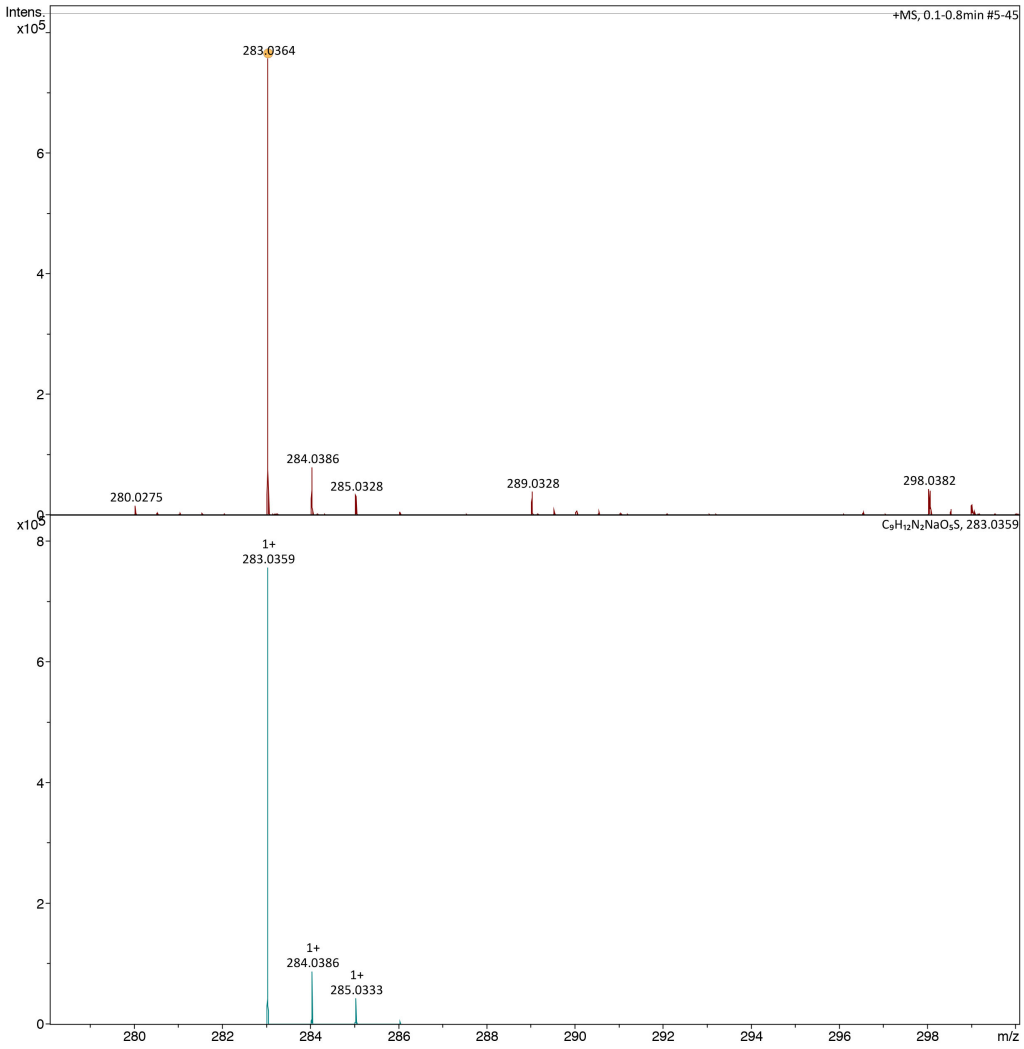
Compound **9** $^{1}$H NMR (DMSO-$d_6$)



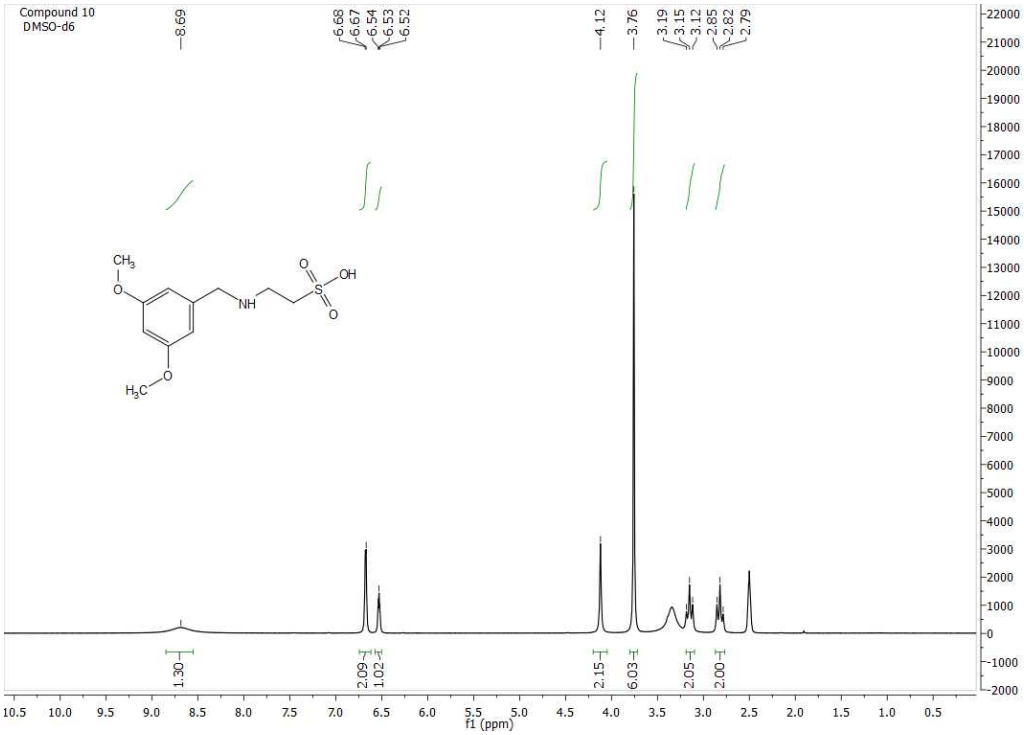

Compound **9** $^{13}$C NMR (DMSO-$d_6$)



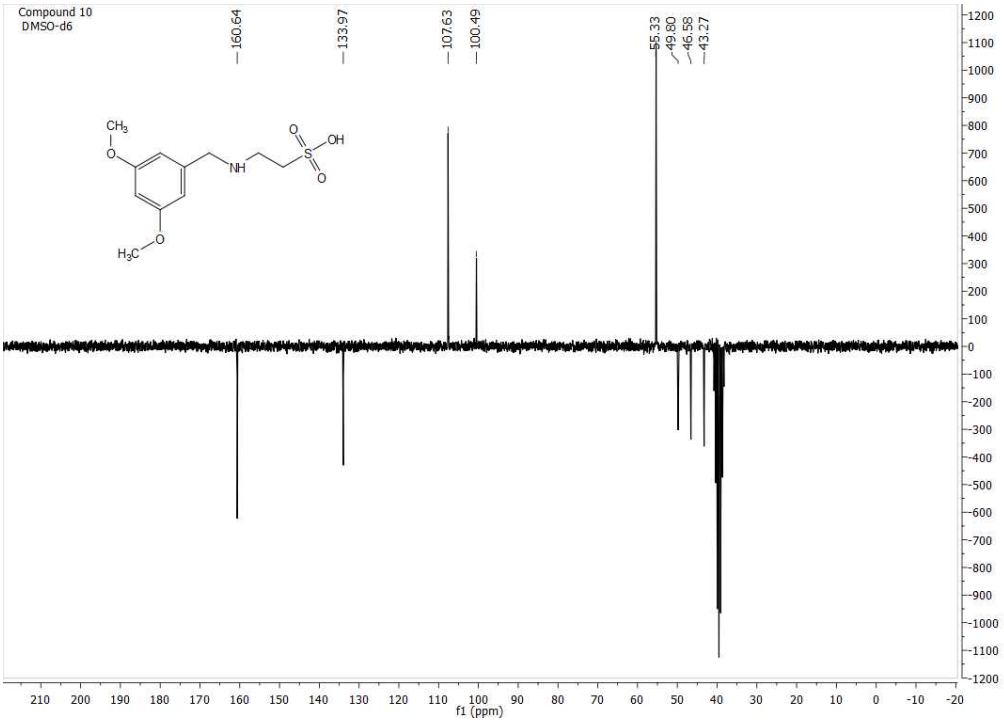
Compound **9** HRMS



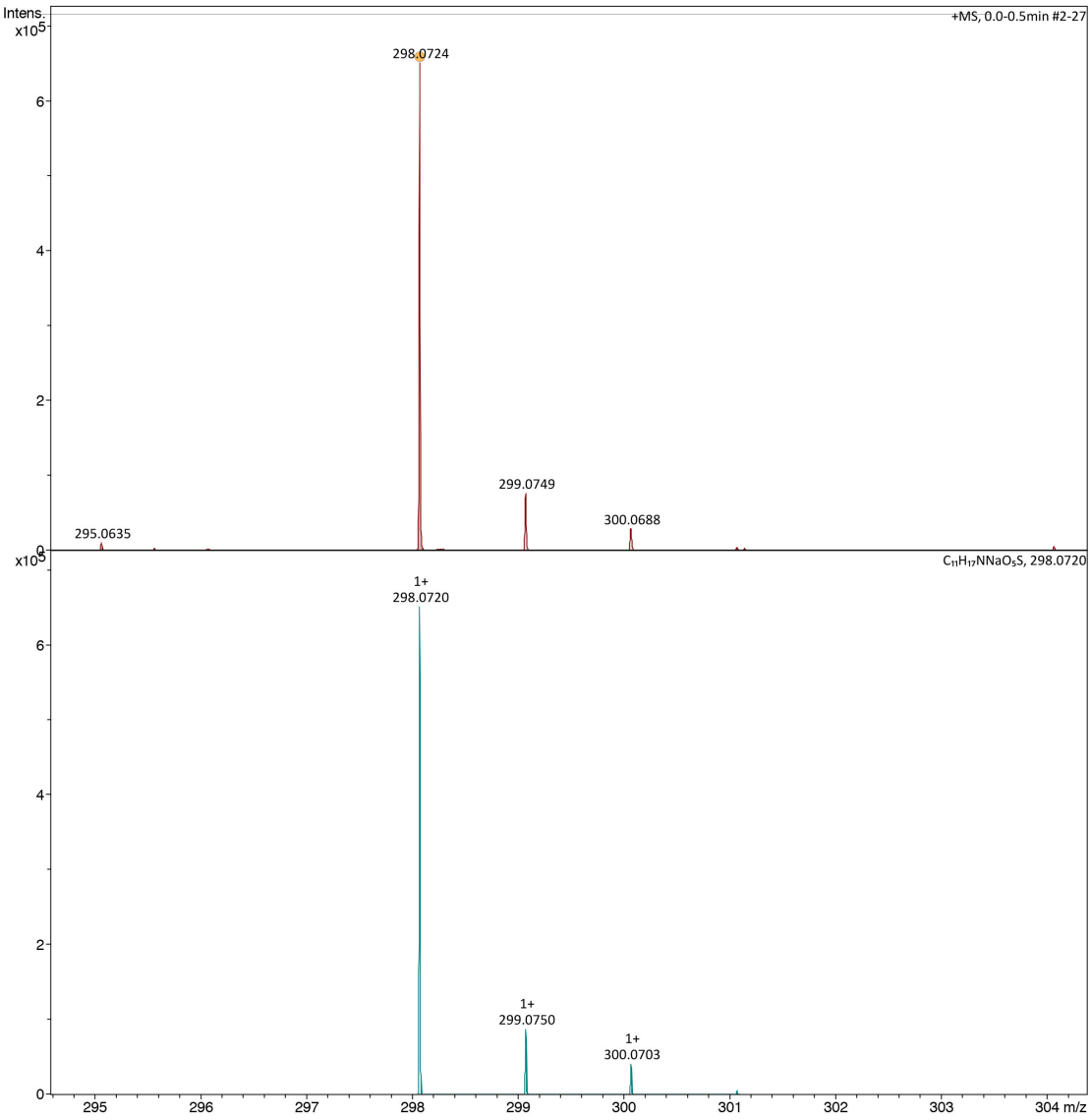
Compound **10** $^{1}$H NMR (DMSO-$d_6$)



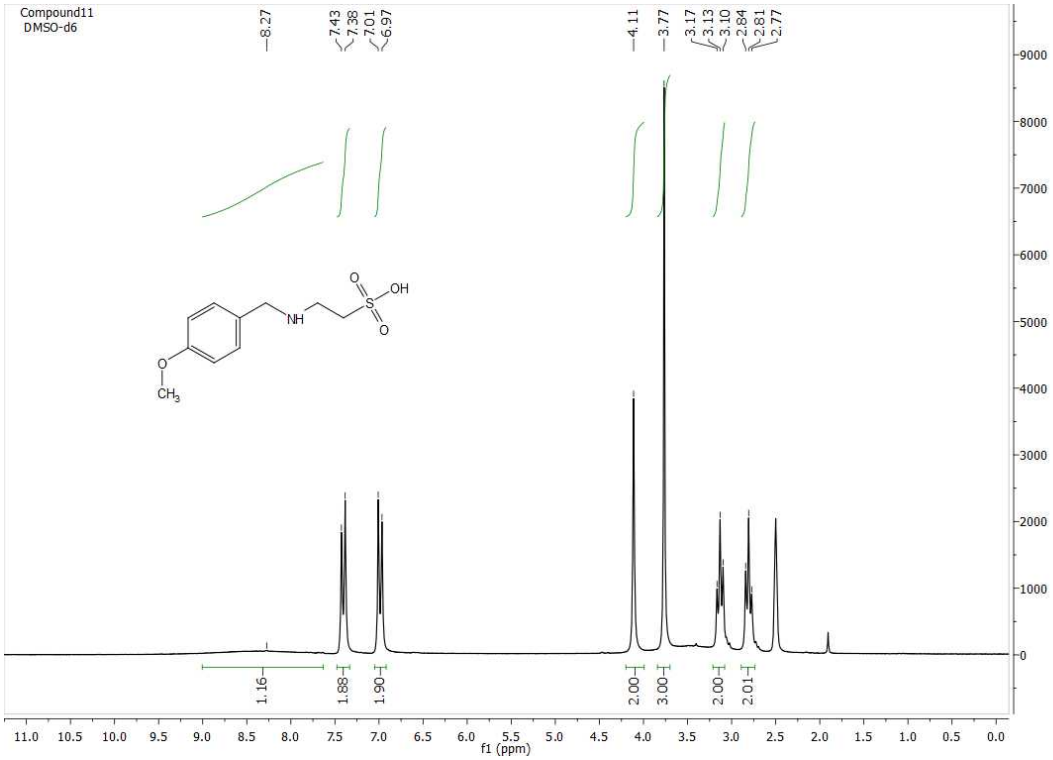

Compound **10** $^{13}$C NMR (DMSO-$d_6$)



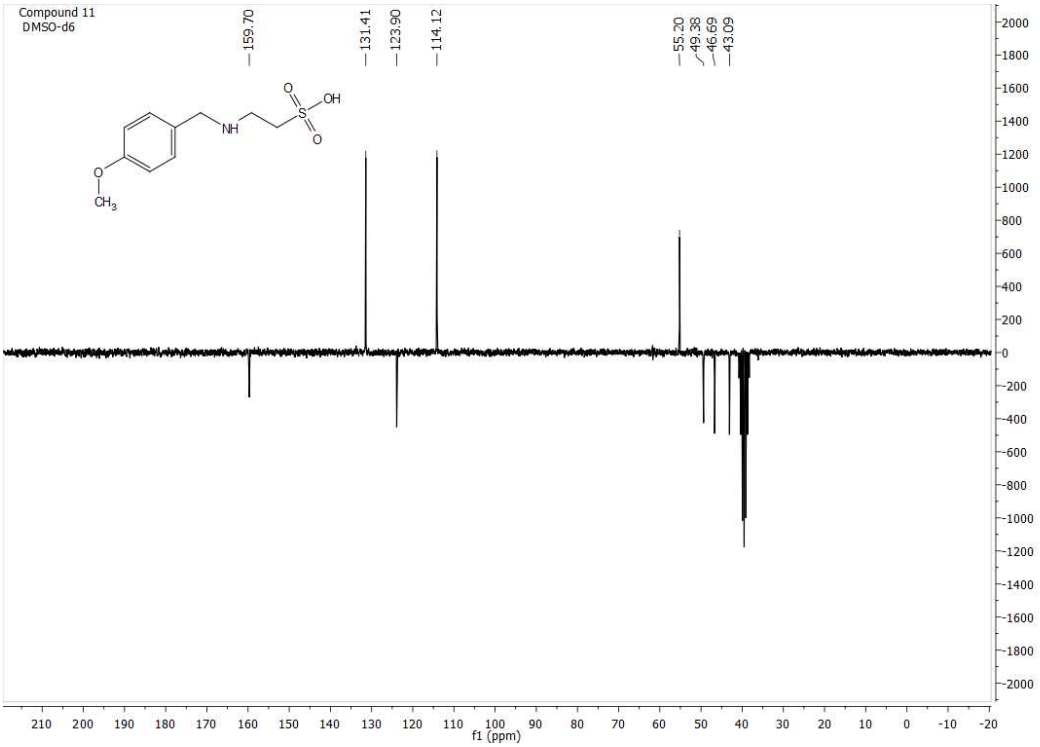
Compound **10** HRMS



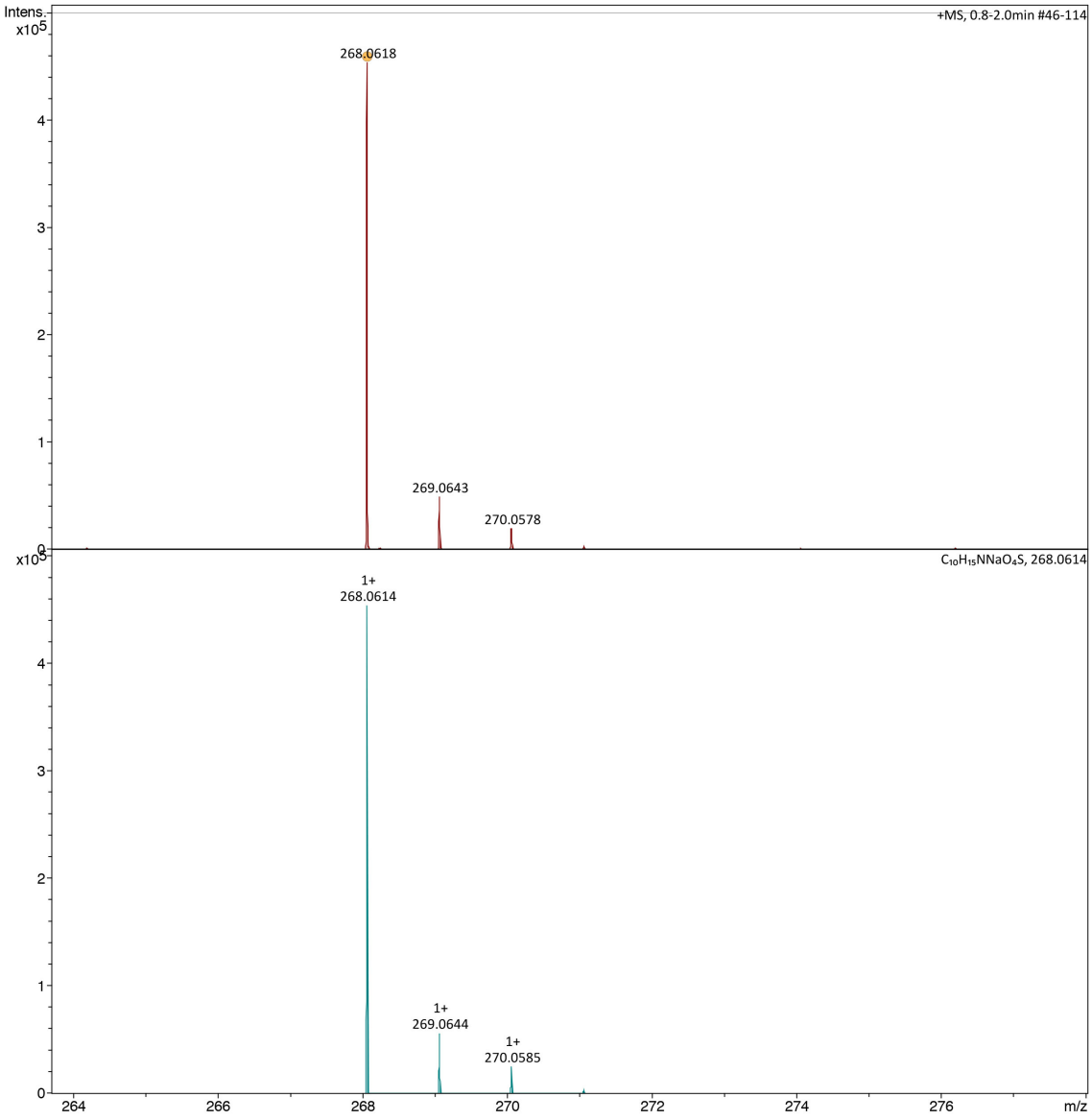
Compound **11** $^{1}$H NMR (DMSO-$d_6$)




Compound **11** $^{13}$C NMR (DMSO-$d_6$)



Compound **11** HRMS



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