

Sulfamoyl [^{18}F]Fluorides: Novel Radiosynthesis Methods and Evaluation of their Potential for PET Imaging



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Abstract

Positron emission tomography (PET) is a non-invasive imaging modality that enables the visualization of physiological and pathological processes by tracking the *in vivo* biodistribution of probes labeled with β^+ -emitting radionuclides. As such, the success of PET imaging critically depends on the availability of suitable radiotracers. Nowadays, hybrid methods that combine morphological imaging techniques like computed tomography (CT) or magnetic resonance imaging (MRI) with PET are widely used in nuclear medicine for routine clinical diagnostics. Due to the significantly increasing importance, especially in the fields of oncological (re)staging, theranostics and neurology, continuous scientific efforts are devoted to the development of new PET imaging agents. Fluorine-18 is the most widely used PET radionuclide due to its accessibility and favorable decay properties. However, conventional ^{18}F -labeling strategies involving C–F bond formation can be synthetically challenging and often require harsh reaction conditions that are incompatible with sensitive biomolecules. As a result, heteroatom-based labeling approaches have emerged as an attractive alternative. In this context, the radiofluorination of fluorosulfates via isotopic exchange reactions based on sulfur-fluoride exchange (SuFEx) click chemistry has sparked significant interest due to its operational simplicity and mild reaction conditions. However, several studies have demonstrated significant *in vivo* defluorination of [^{18}F]fluorosulfate-based tracers, posing a critical barrier to clinical translation. To address this limitation, the present work explored sulfamoyl [^{18}F]fluorides (SAFs) as a potentially more stable class of [^{18}F]fluorosulfuryl-based building blocks for PET radiochemistry. For this purpose, the work was divided into three interconnected subprojects.

In the first subproject, a chromatography-free synthetic protocol for the preparation of the solid fluorosulfurylating agent desmethyl SuFEx-IT, which avoids the need of SO_2F_2 , was developed. This method enabled hectogram-scale production of the reagent in 85% overall yield over 3 steps using inexpensive starting materials. Subsequent application of desmethyl SuFEx-IT as FO_2S -donor provided access to a wide range of fluorosulfates and SAFs in high to excellent yields.

In the second subproject, the SuFEx-based isotopic exchange radiolabeling strategy was adapted for SAF precursors and the stability of [^{18}F]SAFs was evaluated *in vitro* and *in vivo*. Application of a base-free protocol previously developed for the radiofluorination of fluorosulfates enabled efficient ^{18}F -incorporation within minutes at temperatures as low as 40 °C using nanomolar precursor amounts. Radiochemical conversions (RCCs) exceeding 80% were

achieved for indole-derived SAFs, which displayed the highest reactivity. In contrast, aliphatic SAFs showed reduced labeling efficiency. Stability assessments of selected [^{18}F]SAFs revealed high *in vitro* stability across a wide pH range and in human serum. Additionally, *in vivo* imaging in mice demonstrated minimal defluorination of a *N,O*-protected N_{in} -[^{18}F]SAF-functionalized tryptophan, while the corresponding free amino acid, H-Trp([^{18}F]SO $_2$ F)-OH, showed diminished stability, likely due to an altered excretion pathway. The corresponding dihydrotryptophan analogs displayed substantially improved metabolic stability, indicating structural avenues for optimization.

In the third subproject, an alternative no-carrier-added approach for the radiosynthesis of aliphatic [^{18}F]SAFs from imidazolium and dimethylaminopyridinium salt precursors was developed to overcome limitations in labeling aliphatic SAFs via isotopic exchange. Both leaving groups enabled highly efficient radiolabeling under “minimalist green” conditions, achieving RCCs exceeding 90% across a broad range of substrates. The method was successfully applied for the radiofluorination of various cyclic and acyclic secondary amine-based scaffolds and tolerated common protecting groups. Moreover, automated synthesis of an ^{18}F -fluorosulfonylated amoxapine derivative demonstrated the clinical translatability of the method. Finally, *in vivo* evaluation of an ^{18}F -fluorosulfonylated piperidyl-based artificial amino acid in a subcutaneous glioma mouse model confirmed the superior metabolic stability of aliphatic [^{18}F]SAFs, with negligible defluorination observed. In an orthotopic glioblastoma rat model, the tracer also showed a better tumor-to-background ratio than [^{18}F]FET, the current “gold standard” for glioma imaging.

Taken together, these findings establish [^{18}F]SAFs as hydrolytically and metabolically stable, synthetically accessible structural motifs for the development of PET-tracers, offering a promising platform for future applications in molecular imaging.

Kurzzusammenfassung

Die Positronen-Emissions-Tomographie (PET) ist ein nicht-invasives bildgebendes Verfahren für die Visualisierung (patho)physiologischer Prozesse, das auf der Verwendung von mit einem β^+ -emittierenden Radionuklid (PET-Nuklid) markierten molekularen Sonden (Radiotracer) beruht. Der Erfolg der PET-Bildgebung hängt daher entscheidend von der Entwicklung und Verfügbarkeit geeigneter Radiotracer ab. Heutzutage werden in der Nuklearmedizin für die routinemäßige klinische Diagnostik häufig Hybridverfahren eingesetzt, die morphologische Bildgebungsverfahren wie Computertomographie (CT) oder Magnetresonanztomographie (MRT) mit der PET-Bildgebung kombinieren. Aufgrund der deutlich zunehmenden Bedeutung, insbesondere in den Bereichen des onkologischen (Re-)Stagings, der Theranostik und der Neurologie, werden kontinuierlich wissenschaftliche Anstrengungen zur Entwicklung neuer PET-Sonden unternommen. Fluor-18 ist aufgrund seiner Verfügbarkeit und seiner günstigen Zerfallseigenschaften das am häufigsten verwendete PET-Nuklid. Konventionelle ^{18}F -Markierungsstrategien, die auf der Bildung von C–F-Bindungen basieren, können jedoch synthetisch anspruchsvoll sein und erfordern oft harsche Reaktionsbedingungen, die mit empfindlichen Biomolekülen nicht kompatibel sind. Daher haben sich Markierungsmethoden auf Grundlage von C–Heteroatom-Bindungen als vielversprechende Alternative etabliert. In diesem Zusammenhang hat die Radiofluorierung von aromatischen Fluorsulfaten durch $^{19}\text{F}/^{18}\text{F}$ -Isotopenaustausch mittels Schwefel-Fluorid-Austausch-Klickchemie (sulfur fluoride exchange; SuFEx) aufgrund ihrer einfachen Handhabung und milden Reaktionsbedingungen großes Interesse geweckt. Mehrere Studien haben jedoch eine signifikante *in vivo*-Defluorierung von ^{18}F -Fluorsulfat-basierten Tracern gezeigt, was ein entscheidendes Hindernis für die Translation in die Klinik darstellt. Vor dem Hintergrund dieser Problematik wurden in der vorliegenden Arbeit ^{18}F -Sulfamoylfluoride (^{18}F -SAFs) als potenziell stabilere ^{18}F -fluorsulfuryl-basierte Verbindungen hergestellt und evaluiert. Zu diesem Zweck wurde die Arbeit in drei miteinander verbundene Teilprojekte unterteilt.

Im ersten Teilprojekt wurde ein Chromatographie-freies Syntheseverfahren zur Produktion des Fluorsulfurylierungsreagenz Desmethyl-SuFEx-IT entwickelt, das den Einsatz von SO_2F_2 überflüssig macht. Dieses Verfahren ermöglichte die Synthese des Reagenzes im Hektogramm-Maßstab in drei Schritten mit einer Gesamtausbeute von 85% unter Verwendung kostengünstiger Ausgangsstoffe. Die anschließende Anwendung von Desmethyl-SuFEx-IT als FO_2S -Donor ermöglichte den Zugang zu einer breiten Auswahl von Fluorsulfaten und Sulfamoylfluoriden in hohen bis ausgezeichneten Ausbeuten.

Im zweiten Teilprojekt wurde die SuFEx-basierte Radiomarkierungsstrategie mittels Isotopenaustausch für die Markierung von SAFs angepasst und die Stabilität der so erhaltenen [^{18}F]SAFs *in vitro* und *in vivo* untersucht. Die Anwendung eines zuvor für die Radiofluorierung von Fluorsulfaten entwickelten basenfreien Protokolls ermöglichte eine effiziente ^{18}F -Fluorierung innerhalb von Minuten bei Temperaturen von nur 40 °C unter Verwendung von nanomolaren Vorläufermengen. Für Indol-basierte SAFs, welche die höchste Reaktivität zeigten, wurden radiochemische Umsätze (RCUs) von über 80% erreicht. Im Gegensatz dazu zeigten aliphatische SAFs eine verringerte Markierungseffizienz. Stabilitätsuntersuchungen ausgewählter [^{18}F]SAFs ergaben eine hohe *in vitro*-Stabilität in wässrigen Lösungen über einen breiten pH-Bereich sowie in humanem Blutserum. Darüber hinaus zeigten *in vivo*-Bildgebungsstudien in Mäusen nur minimale Defluorierung eines *N,O*-geschützten N_{in} -[^{18}F]SAF-funktionalisierten Tryptophan-Derivats, während die entsprechende freie Aminosäure (H-Trp([^{18}F]SO₂F)-OH) eine verminderte Stabilität aufwies, wahrscheinlich aufgrund einer geänderten Ausscheidungsroute. Die entsprechenden Dihydrotryptophan-Analoga zeigten eine deutlich verbesserte metabolische Stabilität, was die Möglichkeit zur Stabilitätsverbesserung über strukturelle Optimierungen nahelegt.

Im dritten Teilprojekt wurde eine alternative Markierungsmethode ohne Zusatz von Träger für die Radiosynthese von aliphatischen [^{18}F]SAFs aus Imidazolium- und Dimethylaminopyridiniumsalz-Vorläufern entwickelt. Ziel war dabei, die niedrigen molaren Aktivitäten von mittels Isotopenaustausch produzierten aliphatischen [^{18}F]SAFs zu vermeiden. Beide Abgangsgruppen ermöglichten eine hocheffiziente Radiomarkierung unter „grünen minimalistischen“ Bedingungen, mit RCUs von über 90% über einen breiten Substratbereich. Die Methode wurde erfolgreich für die Radiofluorierung verschiedener zyklischer und azyklischer von sekundären Aminen abgeleiteten Verbindungen angewendet, wobei auch gängige Schutzgruppen toleriert wurden. Darüber hinaus bestätigte die automatisierte Synthese eines *N*- ^{18}F -fluorsulfurylierten Amoxapin-Derivats die Eignung der Methode für die Herstellung von Tracern für die klinische Anwendung. Schließlich konnte durch *in vivo*-Untersuchung einer ^{18}F -fluorsulfurylierten Piperidyl-basierten künstlichen Aminosäure in einem subkutanen Gliom-Xenograft Modell die überlegene metabolische Stabilität von aliphatischen [^{18}F]SAFs belegt werden. In einem orthotopen Glioblastom-Modell zeigte der Tracer zudem ein besseres Tumor-zu-Hintergrund-Verhältnis als [^{18}F]FET, der derzeitige „Goldstandard“ für die Gliom-Bildgebung.

Zusammengenommen belegen diese Ergebnisse, dass synthetisch zugängliche *N,N*-dialkyl und *N*-aryl-*N*-alkyl-substituierte [^{18}F]SAFs aufgrund ihrer hydrolytischen und metabolischen Stabilität für die Verwendung als PET-Tracer gut geeignet sind.

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1 Introduction

1.1 Tracer Principle

The radiotracer principle, first described by *George de Hevesy* – widely regarded as the "father of nuclear medicine" – is the underlying concept for medical nuclear imaging. The principle asserts that radiolabeled compounds administered in trace quantities can participate in biological processes without altering them, enabling non-invasive imaging of physiological and pathological processes. This is made possible by the exceptional sensitivity of radioactivity detection techniques, which can detect minute quantities of radioactive substances that do not perturb biological systems. *De Hevesy's* pioneering work included the first application of a radiotracer in an animal, using bismuth-210 to track the distribution of antisyphilitic drugs in rabbits.^[1] For his contributions, he was awarded the Nobel Prize in Chemistry in 1943. These early discoveries laid the groundwork for the evolution of nuclear medicine, where the precise tracing of molecular pathways via imaging techniques like positron emission tomography (PET) or single photon emission computed tomography (SPECT) remains central to diagnostics, therapy monitoring, and follow-up control today.

1.2 Positron Emission Tomography

Positron emission tomography (PET) is a nuclear imaging modality that is based on the use of radiolabeled molecular probes, known as PET tracers. These tracers typically consist of a pharmacophore moiety that interacts with a specific biological target or physiological process, and a positron-emitting radionuclide that enables their non-invasive tracing via detection of the radiation. The radionuclide can either be attached to the targeting moiety/ligand via a covalent bond (with or without linker) or indirectly through a bifunctional chelator, which is usually attached via a linker.

Following administration to the patient, the tracer preferentially accumulates in the target tissues, where β^+ -decay of the incorporated radionuclide results in emission of a positron and an electron neutrino. The positron travels a short distance (typically a few millimeters) through adjacent tissues, losing its nuclide-dependent kinetic energy via scattering with surrounding matter until it encounters an electron, its antiparticle. In accordance with *Einstein's* mass-energy equivalence principle, the subsequent matter-antimatter annihilation results in the emission of two gamma photons, each with an energy of 511 keV, emitted at an angle of approximately 180° to each other. In over 40% of cases, this annihilation is preceded by transient formation of

an exotic bound state of the positron with the electron known as positronium – an analog to the hydrogen atom in which the positron replaces the proton.^[2] Positronium can exist in either of two spin configurations: parallel (*ortho*-positronium, *o*-Ps) and antiparallel (*para*-positronium, *p*-Ps). While the *p*-Ps state has a very short lifetime (~ 125 picoseconds in vacuum and liquids)^[3] and decays via two-photon annihilation, the *o*-Ps configuration is longer-lived (~ 142 ns in vacuum and ~ 1.8 ns in liquids)^[2a, 4] and typically undergoes three-photon decay in vacuum. However, in biological tissues, the probability of direct *o*-Ps decay is less than 0.5%^[5], since interaction with radicals such as molecular oxygen (O_2) induces spin conversion to the *p*-Ps state.^[6] In addition, *o*-Ps may undergo "pick-off annihilation" with an external electron from the surrounding medium, resulting in two-photon emission indistinguishable from *p*-Ps decay or direct annihilation.^[2a]

The PET scanner, composed of a circular array of detectors surrounding the subject, registers only coincident photon pairs within a timeframe of a few nanoseconds. The line connecting two opposing detector subunits that record a photon pair are defined as a "line of response" (LOR). By collecting and processing millions of LORs registered during the PET scan, a three-dimensional image of radioactivity distribution within the patient can be reconstructed (Fig. 1).

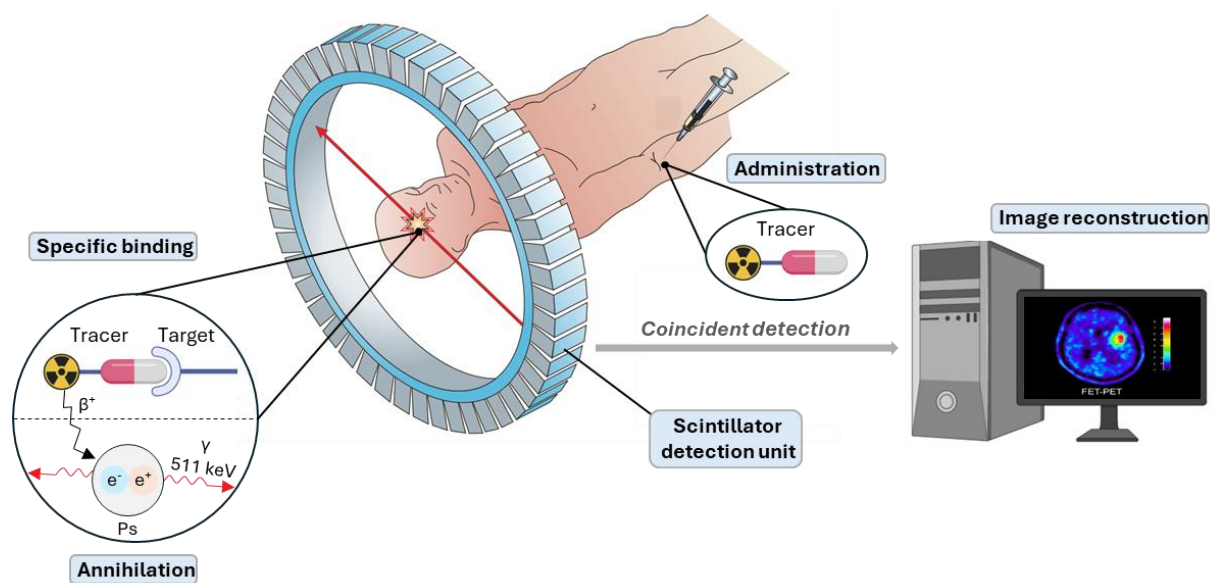


Figure 1: Schematic illustration of the PET principle adapted from West et al. ^[7] using BioRender.

1.3 Fluorine-18 as a PET Nuclide

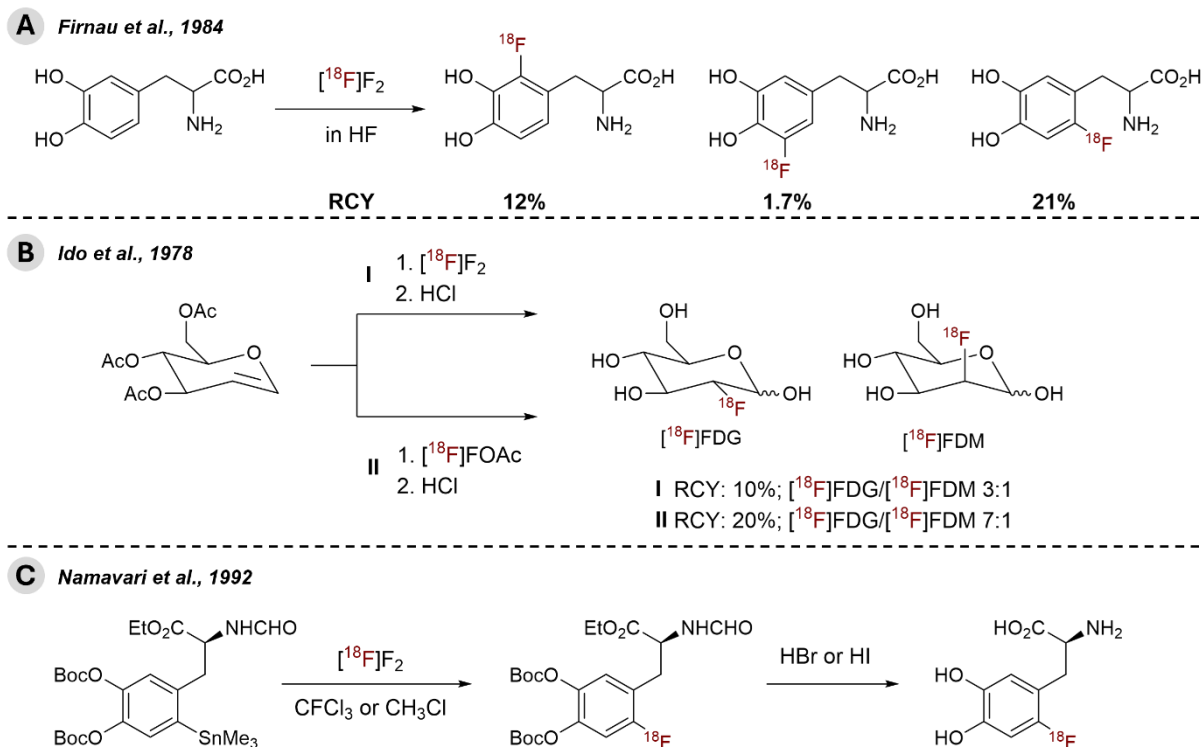
Since carbon, nitrogen, and oxygen are the most abundant elements in organic compounds, the corresponding β^+ -emitting isotopes (^{11}C , ^{13}N , and ^{15}O) have the advantage that they can often be incorporated into pharmacophores without structural modification. However, their extremely short half-lives (Table 1) impose stringent logistical constraints on radiotracer synthesis, purification and application, limiting their practical utility and restricting their use to institutes with radionuclide production infrastructures. In contrast, fluorine-18 has a half-life of 109.7 minutes, which is sufficiently long to allow for complex, multi-step radiosyntheses and comprehensive imaging studies. In addition, the longer half-life supports centralized production and distribution of radiotracers according to a satellite concept, enabling supply of clinics without their own production facilities. Although naturally occurring organofluorine compounds are rare, fluorination is a well-established method in medicinal chemistry to modulate pharmacokinetics of drug candidates. Therefore it is not surprising that fluorine is present in approximately 20% of all approved drugs.^[8] Due to its steric similarity to hydrogen and its electronic resemblance to hydroxyl groups, fluorine serves as an effective bioisostere.^[9] Furthermore, [^{18}F]fluoride is easily accessible in > 200 GBq amounts at medical cyclotrons via high yielding $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ nuclear reaction. Finally, fluorine-18 exhibits a high positron emission branching ratio (96.9%) and a low maximum positron energy (635 keV), limiting the positron range in tissues and improving the spatial resolution compared to most other PET isotopes (Table 1).^[10] Taken together, this combination of accessibility, favorable decay properties and synthetic versatility has established fluorine-18 as the PET radionuclide of choice for both clinical and research applications.

Table 1: Overview of common PET radionuclides, their main production routes and half-lives.^[11]

Nuclide	β^+ -decay	Max β^+ energy (MeV)	Half-Life	mean β^+ range (mm in H_2O)	Production
^{18}F (F^-)	96.8%	0.634	109.7 min	0.66	$^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$
^{18}F (F_2)	96.8%	0.634	109.7 min	0.66	$^{20}\text{Ne}(\text{d},\alpha)^{18}\text{F}$
^{11}C	99.8%	0.960	20.4 min	1.27	$^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$
^{13}N	99.8%	1.20	10.0 min	1.73	$^{16}\text{O}(\text{p},\alpha)^{13}\text{N}$
^{15}O	99.9%	1.73	2.0 min	2.97	$^{14}\text{N}(\text{d},\text{n})^{15}\text{O}$
^{64}Cu	17.5%	0.653	12.7 h	0.56	$^{64}\text{Ni}(\text{p},\text{n})^{64}\text{Cu}$
^{68}Ga	88.9%	1.90	67.6 min	3.56	$^{68}\text{Ge}/^{68}\text{Ga}$ gen.
^{89}Zr	22.8%	0.902	78.4 h	1.27	$^{89}\text{Y}(\text{p},\text{n})^{89}\text{Zr}$

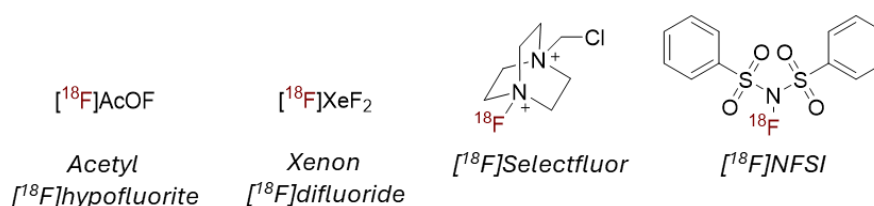
1.4 Electrophilic Radiofluorination

Fluorine-18 can be produced in two distinct chemical forms: electrophilic [^{18}F] F_2 and nucleophilic [^{18}F]fluoride ([^{18}F] F^-). Electrophilic [^{18}F] F_2 is typically obtained by gas target irradiation using the $^{20}\text{Ne}(\text{d},\alpha)^{18}\text{F}$ or $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ nuclear reaction. To reduce adsorption of highly reactive atomic fluorine-18 onto the target surfaces, the addition of toxic and corrosive carrier F_2 to the target gas is required. As a result, this route yields carrier-added (c.a.) [^{18}F] F_2 with relatively low molar activity (typically around 100 MBq/ μmol).^[12] High molar activity is essential to avoid pharmacological and/or toxicological effects of the radiotracer. Moreover, insufficient molar activity can significantly impair imaging sensitivity when targeting low-abundance targets like neuroreceptors. In addition to these limitations, electrophilic radiofluorination is inherently constrained by a maximum theoretical radiochemical yield (RCY) of 50%, since each [^{18}F] F_2 molecule contains only one fluorine-18 atom. The use of [^{18}F] F_2 is further complicated by its high chemical reactivity, which often results in poor regio- and/or chemoselectivity.^[13] Despite these drawbacks, electrophilic radiofluorination has historically played a critical role in PET tracer development. Notably, early radiosyntheses of some of the most clinically important ^{18}F -labeled radiopharmaceuticals, such as 2-[^{18}F]fluoro-2-deoxy-D-glucose (2-[^{18}F]FDG) for imaging glucose metabolism^[14] and 6-[^{18}F]fluoro-3,4-dihydroxy-L-phenylalanine (6-[^{18}F]FDOPA) for imaging the dopaminergic system^[15], relied on electrophilic methods. Scheme 1A and 1B illustrate the challenges of regio- and stereoselectivity posed by electrophilic [^{18}F] F_2 , as encountered in early production routes for 2-[^{18}F]FDG^[16] and 6-[^{18}F]FDOPA^[17].



Scheme 1: **A** Seminal radiosynthesis of 6- $[^{18}\text{F}]\text{FDOPA}$ using $[^{18}\text{F}]\text{F}_2$.^[17] **B** Early syntheses of 2- $[^{18}\text{F}]\text{FDG}$ using $[^{18}\text{F}]\text{F}_2$ or $[^{18}\text{F}]\text{FOAc}$.^[16] **C** Preparation of 6- $[^{18}\text{F}]\text{FDOPA}$ via electrophilic $[^{18}\text{F}]\text{fluorodestannylation}$.^[18]

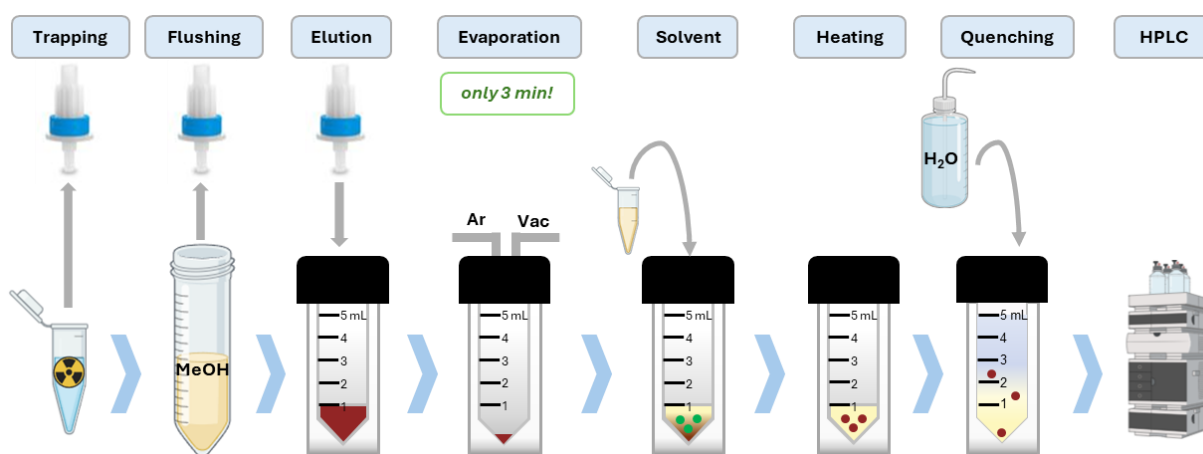
Substantial improvements in regioselectivity have since been achieved through aromatic $[^{18}\text{F}]\text{fluorodemetalation}$ of group IV metalloarenes (Si, Ge, Sn).^[19] This approach has proven effective for the radiosynthesis of 6- $[^{18}\text{F}]\text{FDOPA}$ ^[18] and is still applied for its routine production according to European Pharmacopeia specifications due to its reliability (Scheme 1C).^[20] Another approach to improve selectivity is the conversion of $[^{18}\text{F}]\text{F}_2$ into less reactive, ^{18}F -labeled electrophilic fluorination reagents. A representative selection of such reagents is depicted in Scheme 2.^[13]



Scheme 2: Selected examples of electrophilic radiofluorination reagents.^[13]

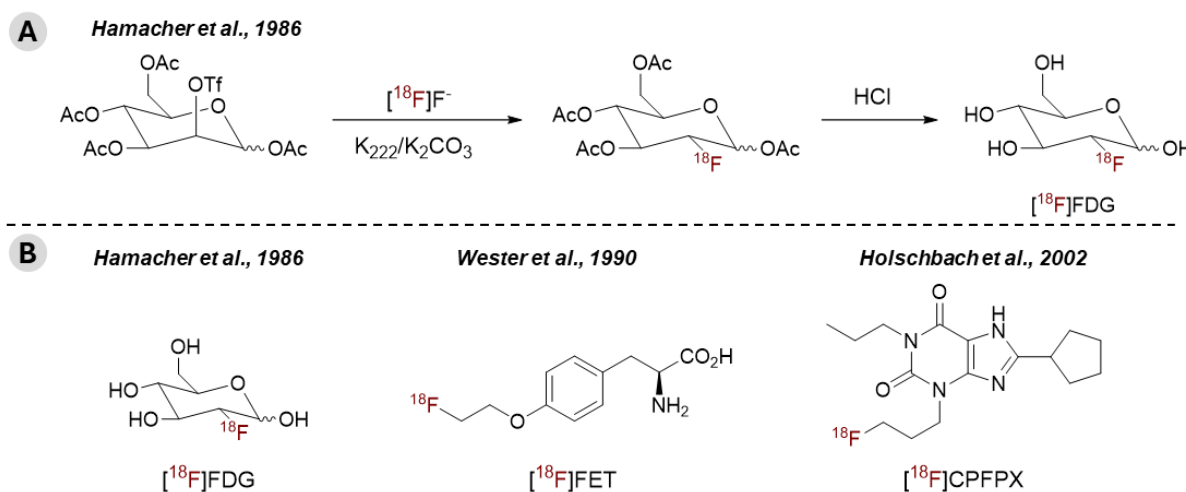
1.5 Nucleophilic Radiofluorination

In contrast to electrophilic $[^{18}\text{F}]\text{F}_2$, nucleophilic $[^{18}\text{F}]\text{F}^-$ can be produced in no-carrier-added (n.c.a.) form by irradiation of enriched $[^{18}\text{O}]\text{H}_2\text{O}$ using the $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ nuclear reaction. In medical cyclotrons $[^{18}\text{F}]\text{F}^-$ can be obtained in high activity amounts of up to 300 GBq^[21] and molar activities of about 600 GBq μmol^{-1} .^[12] However, due to its high charge density, the resulting aqueous $[^{18}\text{F}]\text{F}^-$ is strongly hydrated and readily protonated to form $[^{18}\text{F}]\text{HF}$, which significantly diminishes its nucleophilicity. To circumvent this, aqueous $[^{18}\text{F}]\text{F}^-$ must undergo a series of preprocessing steps before it can be used for nucleophilic radiolabeling reactions. Conventionally, the irradiated target water is initially passed through an anion exchange cartridge to trap $[^{18}\text{F}]\text{F}^-$ and remove most of the $[^{18}\text{O}]\text{H}_2\text{O}$. The $[^{18}\text{F}]\text{F}^-$ is then eluted with an aqueous solution of a basic salt (e.g. $\text{K}_2\text{CO}_3/\text{KHCO}_3$ or Cs_2CO_3) to prevent formation of $[^{18}\text{F}]\text{HF}$ usually in combination with a phase-transfer catalyst (e.g., Kryptofix[®] 2.2.2 or tetraalkylammonium salts). Subsequent repetitive azeotropic drying with acetonitrile removes residual water. The “naked” $[^{18}\text{F}]\text{F}^-$ species thus obtained is usually resolubilized in polar aprotic solvents containing the precursor and the reaction mixture is heated for a short period of time to afford the desired ^{18}F -labeled compound.^[10, 21] To avoid the time-consuming azeotropic drying steps, several approaches including the “minimalist” protocol developed by Richarz *et al.* were established (Scheme 3). In this method, the $[^{18}\text{F}]\text{F}^-$ is trapped on an anion exchange cartridge, the cartridge is flushed with an alcohol to remove residual water, and $[^{18}\text{F}]\text{F}^-$ is directly eluted with an alcoholic solution of a suitable onium salt precursor (e.g., sulfonium, iodonium, or ammonium salts). This strategy eliminates the need for azeotropic drying, addition of base or other additives, and enables efficient labeling of aliphatic and aromatic compounds.^[22]



Scheme 3: Schematic illustration of the “minimalist” approach as described by Richarz *et al.*^[22] Made with BioRender.

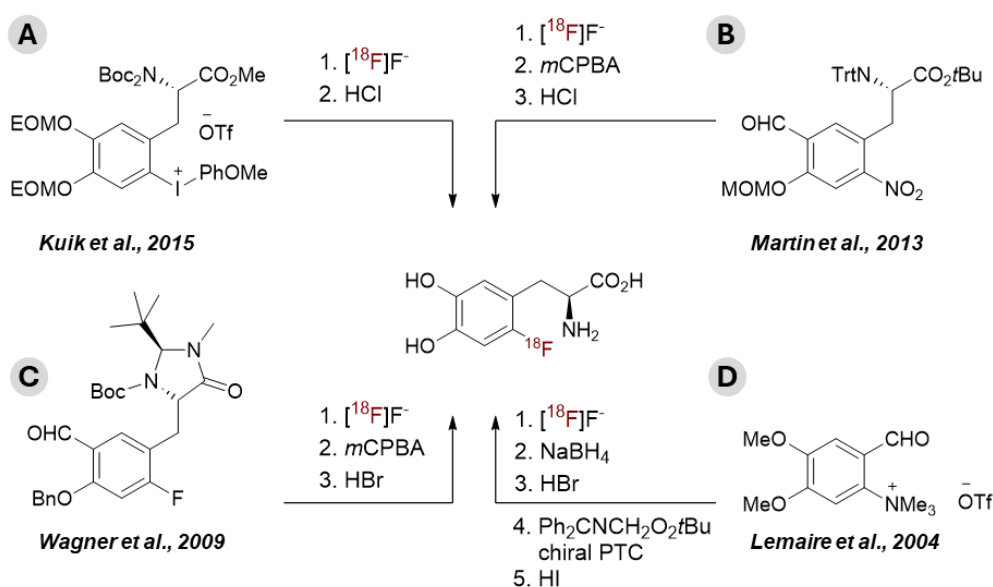
Regarding the substrates, nucleophilic radiofluorination reactions can be divided into aromatic and aliphatic substitutions. Aliphatic substitutions are usually more efficient and represent the predominant route for clinical radiotracer production. Suitable leaving groups for aliphatic nucleophilic radiofluorination include halides (Cl, Br, I) and sulfonates (e.g., mesylate, tosylate, nosylate or triflate), with the latter being favored due to their superior reactivity. Aliphatic substitutions can proceed via S_N1 or S_N2 mechanisms.^[10, 21] S_N2 radiofluorination is usually preferred as it enables to obtain stereochemically pure products. This is exemplified by the synthesis of [^{18}F]FDG from a tetraacetyl triflate precursor (Scheme 4A), which undergoes inversion of the stereocenter at the C-2 position (Walden inversion).^[23] To avoid interference from acidic, sensitive or nucleophilic functional groups present in the precursor, appropriate protection strategies are often required (e.g. acetyl protection of hydroxyl groups in Scheme 4A). The choice of the reaction solvent is another important consideration, with most aliphatic radiofluorinations being performed in polar aprotic solvents like MeCN, DMF, or DMSO at elevated temperatures (80–100 °C). However, effective S_N2 ^{18}F -labeling has also been demonstrated in tertiary alcohols.^[10]



Scheme 4: **A** Preparation of [^{18}F]FDG from an acetyl-protected triflate precursor via nucleophilic aliphatic substitution (S_N2) with [^{18}F]fluoride with Walden inversion.^[23] **B** Selection of ^{18}F -labeled radiotracers that are commonly prepared via nucleophilic aliphatic radiofluorination.^[23-24]

The most common route for preparation of [^{18}F]fluoroarenes is nucleophilic aromatic substitution ($S_N\text{Ar}$), which can proceed either via a stepwise addition-elimination mechanism with intermediate Meisenheimer complex formation, via a concerted reaction or a mixture of both cases.^[25] In the case of applying conventional leaving group like nitro- (NO_2), tetramethyl ammonium ($^+\text{NMe}_3$), or halides (Cl, Br, I, F), efficient $S_N\text{Ar}$ radiofluorination typically requires an electron-withdrawing group positioned *ortho* or *para* to the leaving group. Owing to this limitation several PET-tracers should be prepared via multistep production protocols. Onium

salts like iodonium or sulfonium are also used as leaving groups for S_NAr labeling enabling ¹⁸F-fluorination of electron neutral and even electron rich (hetero)aromatics. Aromatic substitution reactions are typically conducted at elevated temperatures. Accordingly, high-boiling polar aprotic solvents such as DMSO, DMF, or DMA are commonly used.^[10] Various approaches for the preparation of 6-[¹⁸F]FDOPA by nucleophilic aromatic ¹⁸F-substitution exemplify the versatility of this methodology (Scheme 5).

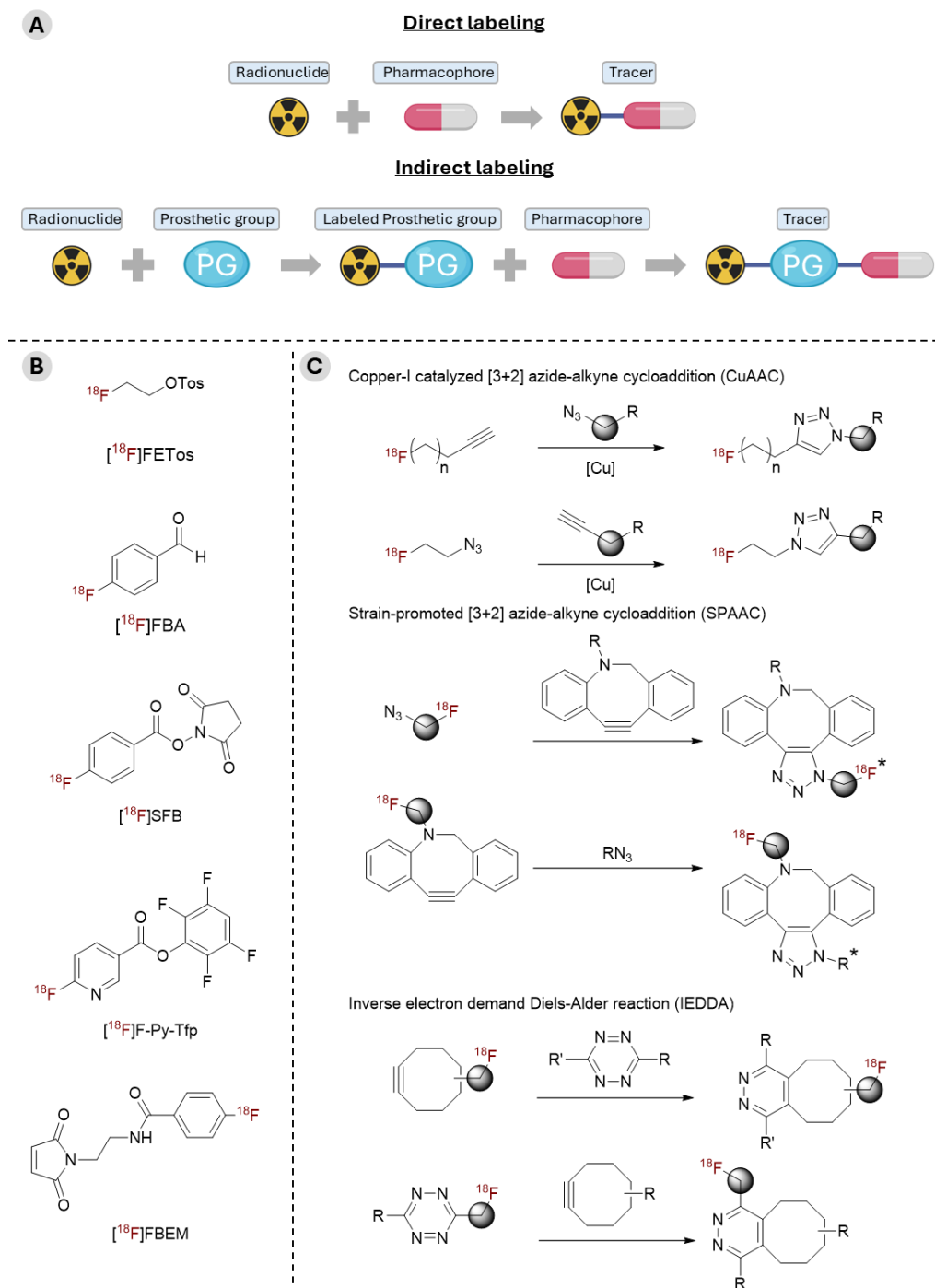


Scheme 5: Overview of nucleophilic aromatic substitution reactions for the preparation of 6-[¹⁸F]FDOPA. Simplified reaction conditions are given for the preparation from an iodonium salt precursor (A),^[26] a precursor with nitro- or trimethylammonium leaving group (B^[27] and D^[28]) or a fluorinated precursor for radiolabeling via isotopic exchange (C).^[29]

1.6 Prosthetic Groups for Radiolabeling

The application of direct ¹⁸F-labeling methods to sensitive biomolecules like peptides, proteins, or antibodies is often complicated by the harsh reaction conditions required (e.g., high temperatures, strong bases and/or organic solvents), which may compromise their structural integrity. In such cases, indirect radiofluorination applying labeled prosthetic groups (PGs) offers a valuable alternative.^[30] This strategy involves the initial ¹⁸F-fluorination of a small molecule bearing a reactive functional group, which can then be conjugated with the biomolecule of interest (Scheme 6A). Conjugation is typically performed under mild aqueous conditions, thereby preserving the pharmacophore's structure and function. The most common PGs for functionalization of nucleophilic sites are summarized in scheme 6B. In recent years, the emergence of “click chemistry” reactions has further expanded the toolkit for indirect ¹⁸F-labeling (Scheme 6C). Notable examples include Cu-catalyzed (CuAAC) and strain-promoted azide-alkyne cycloadditions (SPAAC), and the inverse electron demand Diels-Alder reaction (IEDDA). These reactions are characterized by extraordinary efficiency and mild

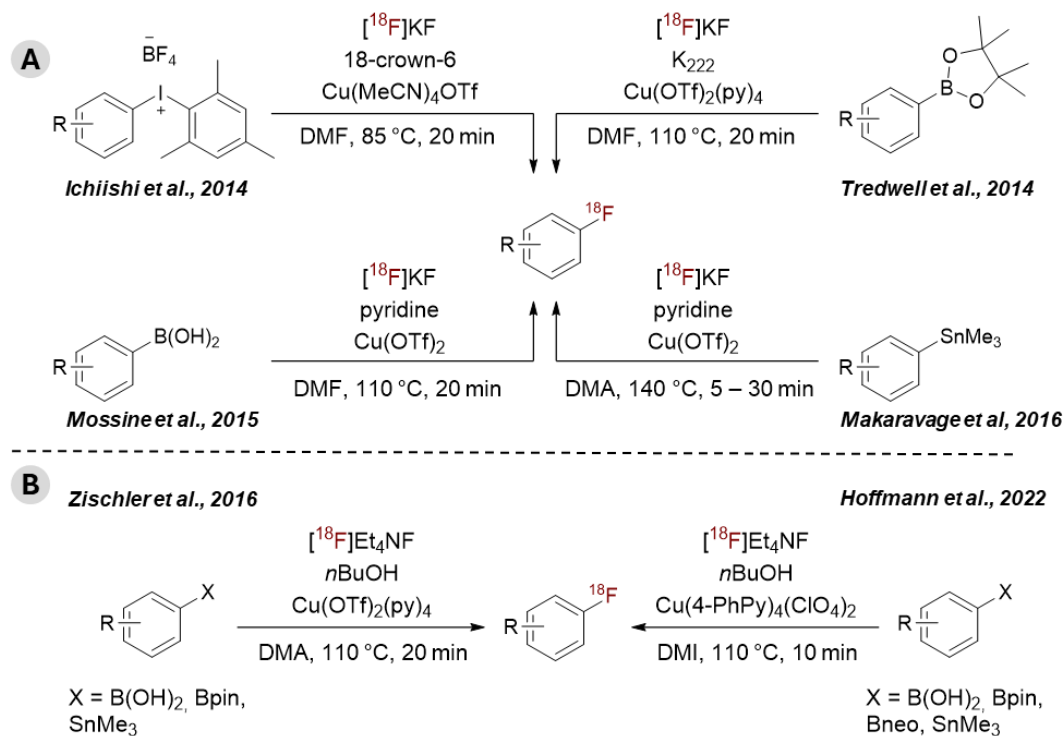
reaction conditions making them ideally suited for late-stage bioconjugation of ^{18}F -labeled PGs to complex biomolecules.



*Scheme 6: A Schematic representation of direct and indirect radiolabeling approaches. B Overview of common prosthetic groups for indirect radiofluorination.^[30-31] Abbreviations: $[^{18}\text{F}]\text{FETos}$, $[^{18}\text{F}]\text{fluoroethyl tosylate}$; $[^{18}\text{F}]\text{FBA}$, 4- $[^{18}\text{F}]\text{fluorobenzaldehyde}$; $[^{18}\text{F}]\text{SFB}$, N-succinimidyl 4- $[^{18}\text{F}]\text{fluorobenzoate}$; $[^{18}\text{F}]\text{FPy-TFP}$, 6- $[^{18}\text{F}]\text{fluoronicotinyl-2,3,5,6-tetrafluorophenyl ester}$; $[^{18}\text{F}]\text{FBEM}$, N-[2-(4- $[^{18}\text{F}]\text{fluorobenzamido})\text{ethyl}]\text{maleimide}$. C General overview on cycloaddition reactions for indirect radiofluorination.^[30] * One of two possible regioisomers is shown.*

1.7 Copper-mediated Radiofluorination

Copper-mediated radiofluorination (CMRF) of iodonium salts and arylboronic acid pinacol esters was independently introduced by *Ichiishi et al.*^[32] and *Tredwell et al.*^[33] in 2014 (Scheme 7A). The CMRF has significantly expanded the toolkit of ^{18}F -labeling radiochemistry, because it provides a one-step access to a wide range of ^{18}F -labeled (heteroarenes)arenes independent on their electronic properties.



Scheme 7: **A** Overview of seminal CMRF developments.^[32–35] **B** Relevant contributions to CMRF from INM-5 and IREMB.^[36–37]

As already mentioned, the method enabled efficient ^{18}F -incorporation into electron-rich, electron-neutral, and electron-deficient arenes using the established $\text{K}_{222}/[^{18}\text{F}]\text{KF}$ system, typically affording good radiochemical conversion across a wide substrate scope. In 2015, the methodology was extended to free arylboronic acids,^[34] and in 2016 to arylstannanes^[35] (Scheme 7A). A subsequent work from *Zischler et al.* revealed a beneficial effect of alcoholic co-solvents on the efficiency of copper-mediated radiofluorination (Scheme 7B). The “alcohol-enhanced” radiolabeling protocol based on this observation allowed high-yielding preparation of ^{18}F -labeled (hetero)arenes without any evaporation steps. The procedure demonstrated marked tolerance to different functional groups enabling radiolabeling of unprotected phenols, anilines and indoles.^[36] More recently, the introduction of next-generation copper mediators has further optimized the CMRF protocol (Scheme 7B), enabling efficient ^{18}F -labeling of a

broad range of boronic and stannyl substrates also at lower temperatures (60–90 °C) and with minimal precursor loadings (2.5 μmol).^[37]

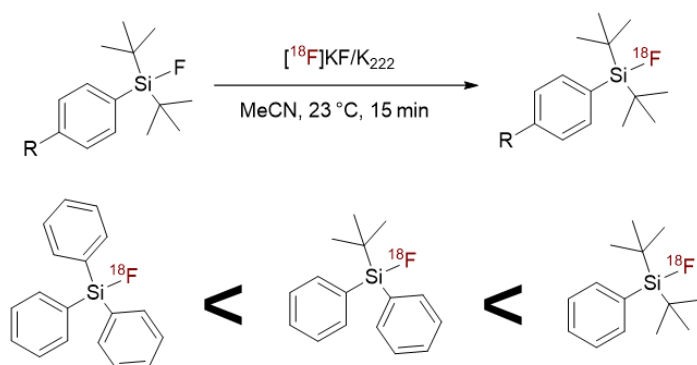
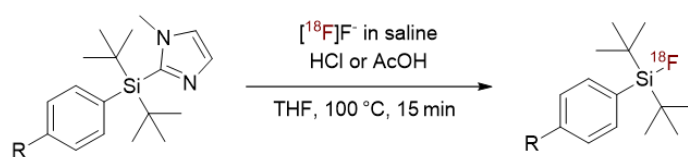
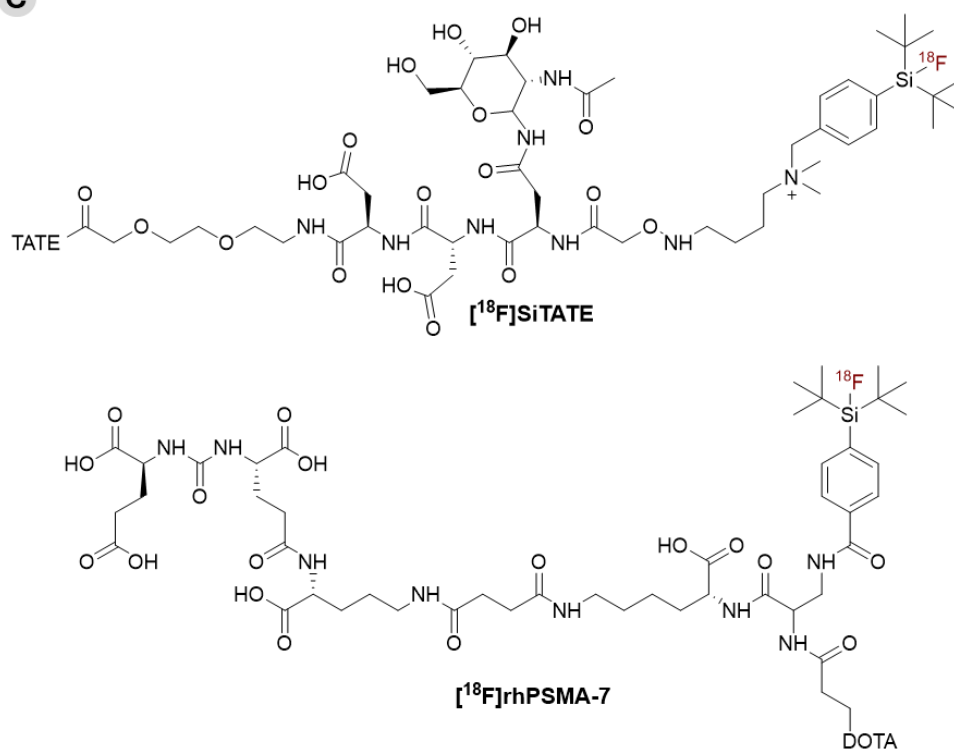
Due to its extreme versatility, CMRF has emerged as a valuable platform for the development of novel PET tracers, as well as for the streamlined production of established radiopharmaceuticals.

1.8 Radiofluorinations Based on Heteroatom–Fluorine Bond Formation

Conventional ^{18}F -labeling strategies rely on the formation of carbon-fluorine (C–F) bonds. As outlined in sections 1.4, 1.5 and 1.7, this is typically achieved through nucleophilic ($\text{S}_{\text{N}}2/\text{S}_{\text{N}}\text{Ar}$) or electrophilic substitution ($\text{S}_{\text{E}}\text{Ar}$) reactions, or via umpolung strategies mediated by transition metals.^[10, 38] However, these methods often require elaborate precursor synthesis and harsh reaction conditions that are incompatible with sensitive substrates like peptides, proteins, or antibodies.^[11] Indirect labeling strategies (section 1.6) can mitigate these limitations, but are often more time-consuming and less efficient. An alternative approach involves the formation of heteroatom-fluorine bonds, such as B–F, Al–F, Si–F, S–F, and P–F bonds. These bonds show similar or even higher dissociation energies than C–F bonds (C–F: 536 kJ mol^{-1} ; B–F: 766 kJ mol^{-1} ; Al–F: 664 kJ mol^{-1} ; Si–F: 540 kJ mol^{-1} , P–F: 439 kJ mol^{-1} , S–F: 343 kJ mol^{-1}),^[39] suggesting a suitable thermodynamic stability. In addition, their formation often proceeds under milder conditions than C–F bond formation, making them attractive for direct labeling of sensitive biomolecules.^[11] Nevertheless, depending on the chemical environment and metabolic pathways involved, heteroatom- ^{18}F -labeled compounds can be more susceptible to *in vivo* defluorination than tracers labeled via C–F bond formation. A key challenge in this domain is therefore to balance *in vivo* stability with sufficient reactivity to enable efficient ^{18}F -incorporation under mild conditions.^[40]

1.8.1 Silicium

The first investigation of silicon-fluorine (Si–F) bond formation for radiolabeling was conducted by *Rosenthal* in 1985, who reported the production of [^{18}F]fluorotrimethylsilane from the corresponding chloro analog. However, the compound suffered from rapid *in vivo* defluorination, leading to pronounced bone uptake of free [^{18}F]F $^-$. Subsequent studies addressed this limitation by introducing sterically demanding substituents such as *tert*-butyl or phenyl groups. These modifications provided steric shielding, significantly enhancing the stability of the Si– ^{18}F bond.^[41] Building on these findings, *Schirrmacher* and co-workers developed the concept of silicon-based fluoride acceptors (SiFAs), in which two *tert*-butyl substituents at the silicon center of aryl silane prevents hydrolysis and provides functionalization capability for bioconjugation (Scheme 8A).^[41a] While such substituents improve S–F bond stability, they also increase the overall lipophilicity, which can negatively impact the pharmacokinetic profile of radiotracers. One approach to address this limitation and improve the biodistribution of radiotracers based on Si– ^{18}F bonds is the introduction of hydrophilic linkers like polyethylene glycol. Another class of silicon-based fluoride acceptors bearing an *N*-methyl imidazole leaving group was reported by *Tisseraud et al*.^[42] (Scheme 8B). Functionalization with these motifs enabled efficient radiofluorination of peptides and nucleosides in aqueous media. More recently, isotopic exchange strategies have emerged as the preferred method for SiFA radiolabeling, as they can be performed under mild reaction conditions and simplify purification.^[43] SiFA building blocks have since been applied for the radiolabeling of a variety of biomolecules, including peptides,^[44] affibodies,^[45] and small molecules,^[46] demonstrating their utility in the synthesis of metabolically stable PET tracers. Clinically relevant applications include the preparation of [^{18}F]SiTATE for imaging somatostatin receptor-positive neuroendocrine tumors and [^{18}F]rhPSMA-7/-7.3 for prostate cancer imaging, respectively (Scheme 8C).^[47]

A Schirmacher et al., 2006**B** Tisseraud et al., 2018**C**

Scheme 8: **A** Hydrolytic stability of different sterically hindered fluorosilanes.^[41a] **B** Typical conditions for radiolabeling via SiFA-based isotopic exchange.^[43] **C** Clinically applied tracers [¹⁸F]SiTATE and [¹⁸F]rhPSMA-7/-7.3.^[47]

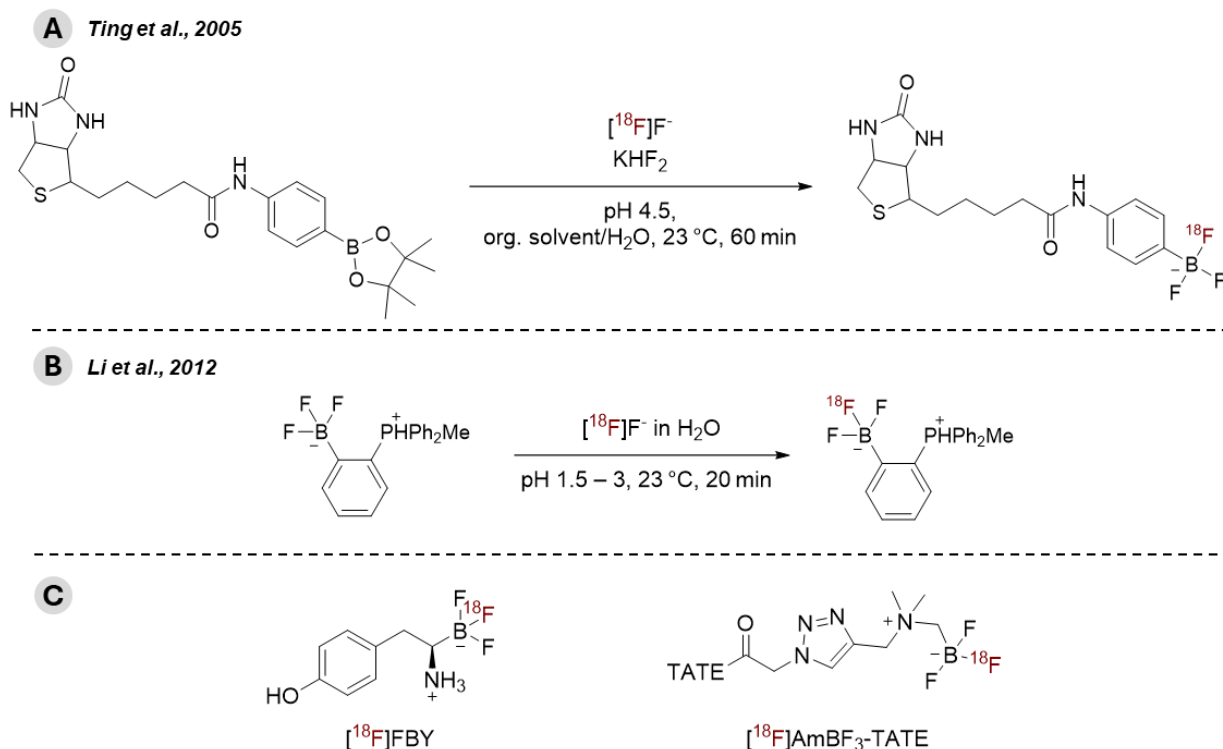
1.8.2 Boron

Boron was among the first heteroatoms explored as [^{18}F] F^- acceptor, with initial methods reported as early as the 1960s.^[48] However, practical application of boron-based ^{18}F -labeling methods remained limited to the preparation of [^{18}F] BF_4^- until 2005, when *Ting et al.* demonstrated that biotinylated aryl boronic esters could be efficiently radiolabeled in aqueous media under mild conditions and without the need for azeotropic drying. However, this approach utilized KHF_2 as a carrier to improve the reaction efficiency (Scheme 9A), severely limiting the achievable molar activity. Nevertheless, the resulting [^{18}F]trifluoroborates showed promising stability in blood serum, which encouraged their further development as PET imaging agents.^[49]

Subsequent studies identified key structural determinants of $\text{B}-^{18}\text{F}$ bond stability. Similar to [^{18}F]fluorosilanes, the hydrolytic stability of aryltrifluoroborates was found to be strongly influenced by the electronic and steric properties of substituents on the aromatic ring. *Perrin and co-workers* demonstrated that electron-withdrawing groups, particularly in *ortho*-position, significantly extend $\text{B}-\text{F}$ bond half-lives by providing both electronic stabilization and steric shielding of the boron center.^[50] The same group also showed the stabilizing effect of using nitrogenous heteroaryl compounds.^[51] Stability was further improved by introducing zwitterionic motifs such as phosphonium^[52] or ammonium^[53] moieties, which confer intramolecular electrostatic stabilization (Scheme 9B).^[52]

Generally, [^{18}F]fluoroborates can be synthesized from boronic acids or esters under acidic conditions (pH 2–3). In addition, isotopic exchange methods employing $^{19}\text{F}/^{18}\text{F}$ substitution have been shown to be particularly effective. *Gabbai et al.* demonstrated that efficient radiolabeling can be achieved within 20 minutes at room temperature by mixing aqueous [^{18}F] F^- with the trifluoroborate precursor in a mildly acidic acetonitrile-water mixture (<15% v/v MeCN, pH 1.5–3.0). Notably, higher pH values were found to substantially diminish the labeling efficiency.^[52]

Clinically relevant applications of boron-based ^{18}F -labeling methods have since emerged. A somatostatin (Tyr_3 -octreotate, TATE) analog bearing a [^{18}F] BF_3^- group (Scheme 9C) has progressed into clinical trials for neuroendocrine tumor (NET) imaging.^[54] Additionally, [^{18}F]trifluoroborate-labeled boramino acids (Scheme 9C) have been assessed in first-in-human studies to probe L-type amino acid transporter 1 (LAT1) expression in glioma patients,^[55] further demonstrating the translational potential of this class of radiotracers.

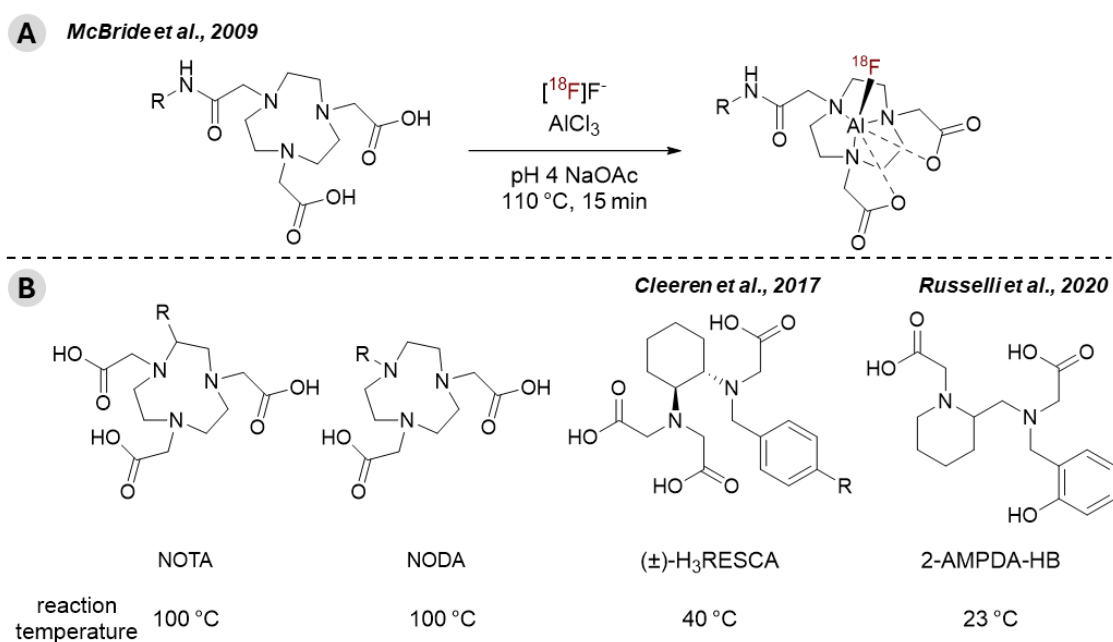


Scheme 9: **A** ^{18}F -labeling of biotinylated aryl boronic esters.^[49] **B** Isotopic exchange reaction on zwitterionic stabilized trifluoroborate.^[52] **C** Trifluoroborate-based tracers currently under investigation in clinical trials.^[54-55]

1.8.3 Aluminum

Radiolabeling via aluminum-fluoride ($\text{Al}[^{18}\text{F}]\text{F}$) complexes was pioneered by *McBride et al.* in 2009. In their seminal work, the authors demonstrated that $\text{Al}[^{18}\text{F}]\text{F}$ could be efficiently coordinated to a diethylenetriaminopentaacetic acid (DTPA)-modified peptide. However, the resulting complexes exhibited insufficient stability in aqueous media and serum, which was attributed to a low affinity of the DTPA chelator for aluminum. In contrast, the corresponding 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA) complex was significantly more stable, albeit at the expense of reduced radiolabeling yields (Scheme 10A).^[56] Therefore, subsequent investigations focused on the evaluation and optimization of alternative, macrocyclic chelators. Among these, the pentadentate analog NODA was identified as particularly promising, offering improved radiochemical yields and *in vivo* stability by leaving one coordination site on the aluminum ion available for fluoride.^[57] Due to their commercial availability, NOTA and NODA (Scheme 10B) remain the most widely used chelators for development of $\text{Al}[^{18}\text{F}]\text{F}$ -based radiopharmaceutical. Standard $\text{Al}[^{18}\text{F}]\text{F}$ -labeling protocols for NOTA- or NODA-conjugated precursors employ mildly acidic conditions (pH $\sim$ 4–5, NaOAc buffer) to prevent formation of HF (pH <4) or $\text{Al}(\text{OH})_3$ (pH >5). Radiolabeling is typically conducted at elevated temperatures ($\sim$ 100 °C), which is compatible with small molecules and peptides but limits the applicability for direct labeling of thermolabile biomolecules.^[58]

To overcome these limitations, efforts were directed toward the development of novel chelators with improved labeling efficiency under milder conditions. *Cleeren et al.* introduced acyclic chelators designed to lower the activation energy of complex formation through replacement of a nitrogen donor with an oxygen atom, thereby enhancing aluminum coordination without compromising complex stability. These chelators enabled efficient $\text{Al}[^{18}\text{F}]\text{F}$ -labeling at reduced temperatures (as low as 40°C) and in high yields of over 90%. However, stability of such conjugates was insufficient.^[59] Further refinement led to the development of conformationally constrained chelators such as $(\pm)\text{-H}_3\text{RESCA}$ (Scheme 10B), which enabled efficient $\text{Al}[^{18}\text{F}]\text{F}$ -labeling at room temperature. This advancement allowed for direct labeling of sensitive biomolecules, including human serum albumin and HER2-targeting affibodies.^[60] Similarly, *Russelli et al.* developed a series of acyclic chelators, among which the $\text{Al}[^{18}\text{F}]\text{F}$ -2-AMDA-HB complex demonstrated the highest *in vivo* stability, as evidenced by minimal bone uptake of radioactivity.^[61]



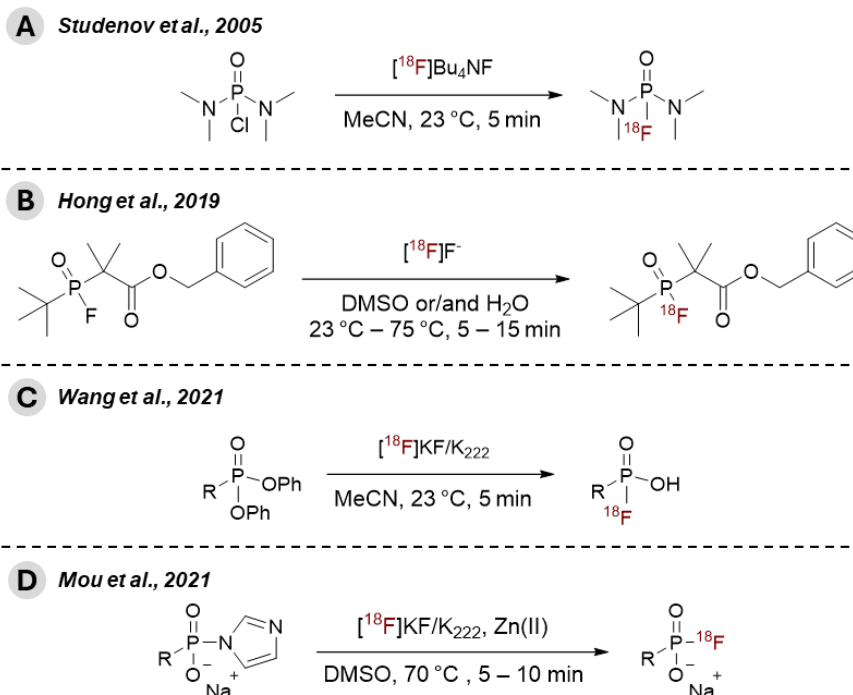
Scheme 10: A Labeling conditions for preparation of $\text{Al}[^{18}\text{F}]\text{F}$ -NOTA complex in the seminal publication by McBride et al.^[56] *B* Selection of ligands for $\text{Al}[^{18}\text{F}]\text{F}$ -labeling. Standard ligands NOTA and NODA and optimized ligands $(\pm)\text{-H}_3\text{RESCA}$ and 2-AMPA-HB for labeling of biomolecules.^[56, 60-61]

Generally, $\text{Al}[^{18}\text{F}]\text{F}$ chelation represents a promising strategy for PET tracer development, especially in the context of theranostic concept. Thus, the use of chelators that can accommodate both, $\text{Al}[^{18}\text{F}]\text{F}$ and a therapeutic radiometal like ^{67}Cu , would allow for preparation of diagnostic and therapeutic agents from a common precursor. Additionally, the introduction of a hydrophilic chelator influences favorably the pharmacokinetic behavior of the resulting radiotracers. Not surprisingly, a variety of $\text{Al}[^{18}\text{F}]\text{F}$ -based radiotracers to visualize

targets like prostate specific membrane antigen (PSMA)^[62], fibroblast activation protein (FAP)^[63] or somatostatin receptors (SSTR) are currently under clinical investigation.^[64]

1.8.4 Phosphorus

Compared to other heteroatom-based radiolabeling strategies, methods involving the formation of phosphorus–fluorine (P–F) bonds have remained relatively underexplored until very recently. The first report on this approach was published by *Studenov et al.* in 2005, who described the synthesis of an ¹⁸F-labeled analog of the pesticide Dimefox via substitution of the corresponding chloride (Scheme 11A). While this method afforded high radiochemical yields, the resulting labeled compound exhibited limited stability in aqueous media.^[65] Subsequent work by *Hong et al.* revealed that [¹⁸F]fluorophosphines can also be prepared via isotopic exchange, analogous to the SiFA strategy (Scheme 11B). In addition, the hydrolytic stability could be significantly improved by incorporating bulky substituents. *In vivo* evaluation of [¹⁸F]fluorophosphine-labeled peptides and human serum albumin conjugates showed promising stability profiles, with negligible bone uptake indicating minimal defluorination.^[66] To overcome the inherently low molar activity associated with isotopic exchange methods, an alternative approach involving nucleophilic substitution on phosphonates has been investigated (Scheme 11C). This approach benefits from the remarkably high reactivity of phosphonate electrophiles toward [¹⁸F]F[−], enabling efficient radiolabeling of sensitive biomolecules at room temperature.^[67] Alternatively, imidazole-based leaving groups have been used for n.c.a. preparation of ¹⁸F-labeled organofluorophosphates (Scheme 11D).^[68] Recent advances in the field of P–¹⁸F-based labeling include the synthesis of structurally exotic [¹⁸F]fluorothiophosphates^[69] and the development of protocols for late-stage radiofluorination of alkyl phosphonates via electrophilic activation^[70]. While these developments underscore continued progress in the field of phosphorus-based ¹⁸F-labeling, no radiotracers prepared using these methods have yet advanced into clinical evaluation.



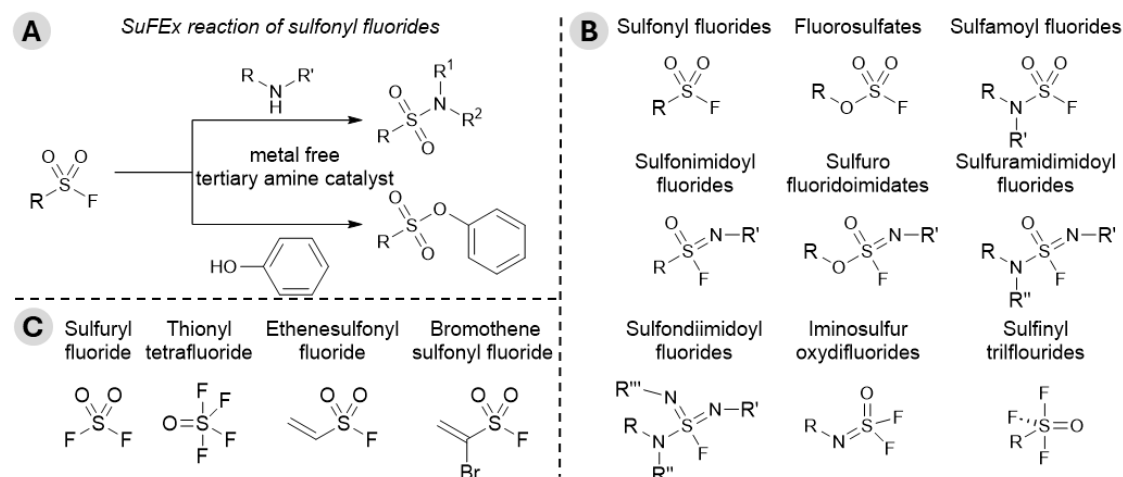
Scheme 11: **A** Seminal work on P–¹⁸F bond formation.^[65] **B** Preparation of [¹⁸F]fluorophosphines via isotopic exchange.^[66] **C** Preparation of [¹⁸F]fluorophosphonates via nucleophilic substitution.^[67] **D** Preparation of [¹⁸F]organofluorophosphates using an imidazole leaving group.^[68]

1.9 Labeling Strategies Based on S^{VI}–¹⁸F Bond Formation

1.9.1 The S^{VI}–F bond beyond its use in radiochemistry

Since the introduction of sulfur(VI) fluoride exchange (SuFEx) as a new class of "click chemistry" reactions (CC) by *Sharpless* and co-workers in 2014, considerable efforts have been devoted to exploiting the exceptional properties of sulfur–fluorine (S^{VI}–F) functionalities. The immense potential of this reaction class for CC derives from the optimal balance between stability and reactivity inherent to sulfur(VI) fluorides. On the one hand, the S^{VI}–F bond exhibits exceptional stability under harsh conditions, markedly superior to its S–Cl counterpart. At the same time, these compounds can be selectively activated to undergo controlled nucleophilic substitution via the SuFEx reaction (Scheme 12A).^[71] This dual nature of high kinetic inertness coupled with tunable reactivity makes S^{VI}–F motifs ideal candidates for diverse applications. Another major advantage of SuFEx-able moieties is that S^{VI}–F functional groups (Scheme 12B), especially with a fluorosulfonyl (–SO₂F) functionality, can be readily introduced into various molecular scaffolds using well-established synthetic protocols and commercially available reagents (Scheme 12C). As such, S^{VI}–F-containing structures have found utility across a wide array of applications, such as synthetic chemistry, material science and medicinal chemistry. Among these, sulfonyl fluorides (C–SO₂F) have been intensively studied as

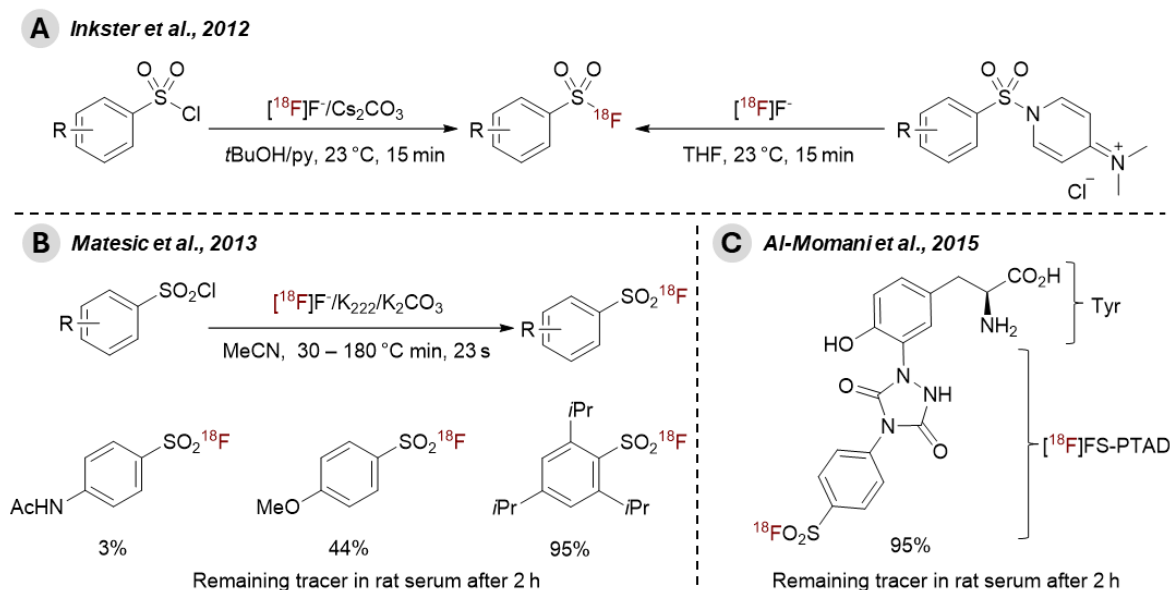
warheads for targeted covalent inhibition (TCI)^[72] and are emerging as promising candidates for the development of therapeutic agents.^[73]



Scheme 12: **A** Common SuFEx-able functional groups.^[74] **B** Reagent for introduction of SuFEx-Hubs **C** General SuFEx reaction of a sulfonyl fluoride.^[71]

1.9.2 Sulfonyl fluorides

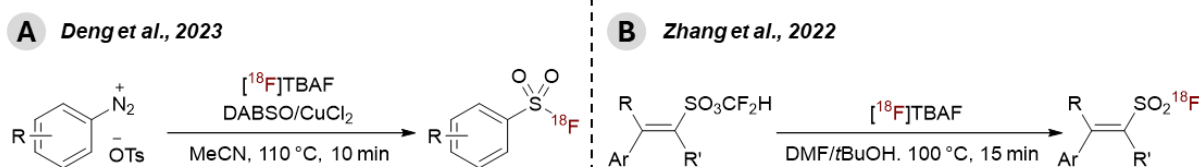
Sulfonyl [^{18}F]fluorides were the first radiolabeled FO_2S -functionalized compounds studied in the context of their suitability as PET-tracers. The first radiolabeled sulfonyl fluoride was reported as early as in 1975, when *de Kleijn* and colleagues prepared tosyl [^{18}F]fluoride from tosyl chloride in aqueous solution.^[75] However, interest in such radiolabeled compounds did not re-emerge until more than three decades later. In 2012, *Inkster et al.* proposed aryl sulfonyl [^{18}F]fluorides as potential PGs for indirect radiofluorination.^[76] In their study, bifunctional sulfonyl [^{18}F]fluorides were prepared from sulfonyl chloride or dimethylaminopyridinium (DMAP)-based precursors (Scheme 13A). While the most sterically hindered variant showed high stability in phosphate buffered saline (PBS) and was successfully conjugated to an analog of the neuropeptide bombesin, the labeled peptide conjugate exhibited rapid defluorination in mouse serum, precluding further *in vivo* studies.^[76] In 2013, *Matesic et al.* prepared a series of 12 aryl sulfonyl fluorides via microfluidic reactions from the corresponding sulfonyl chlorides and conducted structure-stability studies with selected substrates in PBS and rat serum (Scheme 13B). While electron-withdrawing groups facilitated hydrolysis of the fluorosulfonyl moiety, electron-donating groups were found to have a stabilizing effect, although the resulting compounds were still susceptible to defluorination in rat serum. In contrast, *ortho*-substitution with sterically demanding triisopropyl groups significantly improved serum stability, indicating that steric hindrance may be more important than electronic properties.^[77] These findings were recently corroborated in a broader *in vitro* stability study with non-labelled sulfonyl fluorides by the same group.^[78]



Scheme 13: **A** Preparation of sulfonyl [^{18}F]fluorides by Inkster et al.^[76] **B** Synthesis of sulfonyl [^{18}F]fluorides and influence of different functional groups on serum stability.^[77] **C** Tyrosine derivative functionalized with a sulfonyl [^{18}F]fluoride-based prosthetic group.^[79]

Another [^{18}F]fluorosulfonyl-based PG for tyrosine-selective labeling of peptide and proteins was introduced by *Al-Momani* and co-workers (Scheme 13C). Notably, both the PG and its tyrosine conjugates were reported to be stable in rat serum despite lacking steric shielding.^[79] However, follow-up validation studies have not yet been published. An interesting approach to exploit the apparent hydrolytic lability of sulfonyl [^{18}F]fluorides was introduced by *Zhang et al.* After observing stability issues during investigation of the Michael-acceptor [^{18}F]ethenesulfonyl fluoride ([^{18}F]ESF) as potential PG,^[80] the authors proposed that [^{18}F]ESF could be repurposed as a transportable source of reactive [^{18}F]F⁻ (Scheme 15B). This concept could enable decentralized radiolabeling with minimal infrastructure, offering practical advantages for satellite concepts.^[81]

An alternative labeling strategy for the preparation of sulfonyl [^{18}F]fluorides without the need for sulfonyl chlorides was reported by *Deng et al.* The group used arenediazonium tosylates in the presence of DABSO and a copper mediator to prepare a wide range of structurally diverse sulfonyl [^{18}F]fluorides (Scheme 14A). This method was also applied to prepare a maleimide-derived PG that could be conjugated to a carcinoembryonic antigen targeting antibody and bovine serum albumin. However, no stability data for the resulting conjugates were reported.^[82]

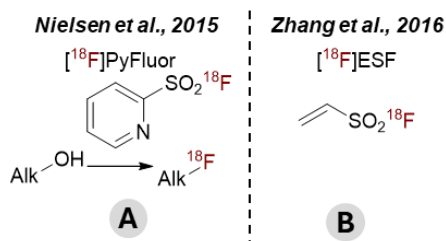


Scheme 14: Preparation of sulfonyl [^{18}F]fluorides from diazonium salts^[82] (A) and difluoromethyl sulfonic esters (B).^[83]

Zhang *et al.* reported an unconventional synthetic pathway to access alkenyl sulfonyl [^{18}F]fluorides via ^{18}F -fluorination of difluoromethyl sulfonic esters, affording high RCC across a wide substrate scope (Scheme 14B).^[83]

Despite these developments, the inherent hydrolytic lability of sulfonyl [^{18}F]fluorides has prevented their progression into preclinical *in vivo* studies. As such, their utility as PET labeling motifs remains uncertain and will likely depend on further improvements in stability.

However, beyond their use as PET labeling motifs, sulfonyl [^{18}F]fluorides have also been employed in ancillary radiochemical applications. For example, [^{18}F]PyFluor has been developed as a deoxyfluorination agent (Scheme 15A)^[84] and the formation of tosyl [^{18}F]fluoride from tosyl chloride has been used as a quantitative tool to determine the molar activity of [^{18}F]F⁻.^[85]

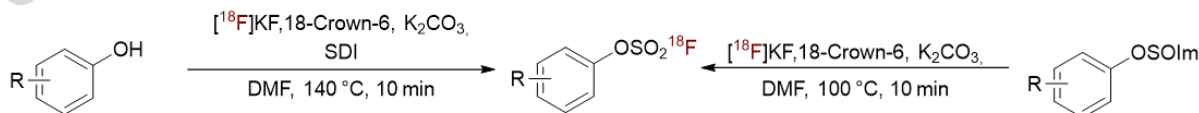
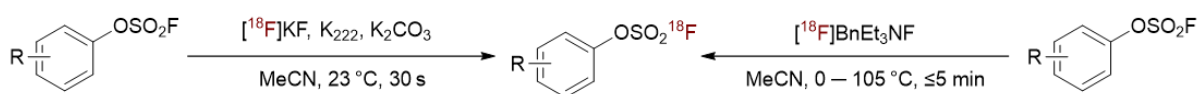


Scheme 15: Deoxyfluorination agent [^{18}F]PyFluor (A) and prosthetic group [^{18}F]ESF (B).

1.9.3 Fluorosulfates

^{18}F -Labeled fluorosulfates are a more recently explored class of $\text{S}^{\text{VI}}\text{-}^{18}\text{F}$ compounds. The first successful preparation of a $[\text{}^{18}\text{F}]\text{FO}_2\text{SO}$ -group was reported by *Khoshnevisan et al.* in 2017. The authors prepared the $[\text{}^{18}\text{F}]$ fluorosulfate anion from a SO_3 -pyridine adduct and evaluated its suitability as a Na/I symporter (NIS) PET imaging agent. The tracer was obtained in 31% RCY after the isolation by solid phase extraction (SPE) and exhibited high stability in acidic media and human serum (RCP of >95% after 4 h). In addition, $[\text{}^{18}\text{F}]\text{FSO}_3^-$ showed NIS-specific uptake *in vitro* and *in vivo*. However, progressive accumulation of radioactivity in bones, likely due to *in vivo* defluorination, may limit its utility despite potential for NIS imaging.

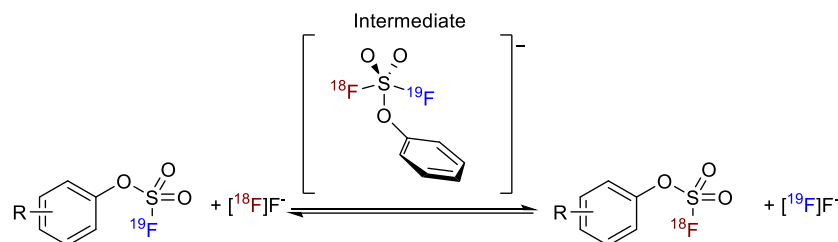
In 2020, *Kwon et al.* introduced the first method for preparation of aryl $[\text{}^{18}\text{F}]$ fluorosulfates (Scheme 16A).^[86] The authors described the preparation of 43 (hetero)aryl substrates from sulfonyl imidazole precursors. Alternatively, the compounds were also accessible via a one-pot reaction from the corresponding phenols by *in situ* generation of imidazoles using inductive heating in an *Anton Paar*[®] induction reactor, delivering an average RCC of 53%. Both procedures were successfully automated, enabling the preparation of 4-acetamidophenyl $[\text{}^{18}\text{F}]$ fluorosulfate in AYs of 9–22% and molar activities of 42–55 $\text{GBq } \mu\text{mol}^{-1}$.

A *Kwon et al., 2017***B** *Zheng et al., 2021**Walter et al., 2022*

Scheme 16: **A** Preparation of $[\text{}^{18}\text{F}]$ fluorosulfates from sulfonyl imidazoles according to *Kwon et al.*^[86] **B** Seminal^[87] and optimized approach for the synthesis of $[\text{}^{18}\text{F}]$ fluorosulfates via SuFEx $^{18}\text{F}/^{19}\text{F}$ -isotopic exchange.^[88]

Another interesting approach based on SuFEx chemistry was published by *Zheng et al.* in 2021. The group reported the automated radiosynthesis of 25 functionally diverse aryl $[\text{}^{18}\text{F}]$ fluorosulfates using a SuFEx-based $^{18}\text{F}/^{19}\text{F}$ -isotopic exchange reaction (Scheme 16B) that proceeds via a pentacoordinated intermediate (Scheme 17). The products were obtained in RCCs between 83–100% (however see below) and high molar activities (up to 280 $\text{GBq } \mu\text{mol}^{-1}$) at ambient temperature within only 30 s and could be isolated simply by SPE. An ^{18}F -fluorosulfurylated analog of the anticancer drug Olaparib (Scheme 18A) was produced using the procedure and evaluated in immunocompromised mice bearing human breast cancer

(MCF-7) xenografts. High accumulation of radioactivity in the spine observed in these experiments was attributed by the authors to poly (ADP-ribose) polymerase 1 (PARP1) expression in bone marrow rather than *in vivo* defluorination. To further confirm metabolic stability of the [^{18}F]fluorosulfate moiety, ^{18}F -fluorosulfurylated derivatives of *S*-TPMBU and Fulvestrant (Scheme 18A) were evaluated in healthy mice, which reportedly revealed no radioactivity accumulation in the bones, although the corresponding quantitative data were not provided.^[87]



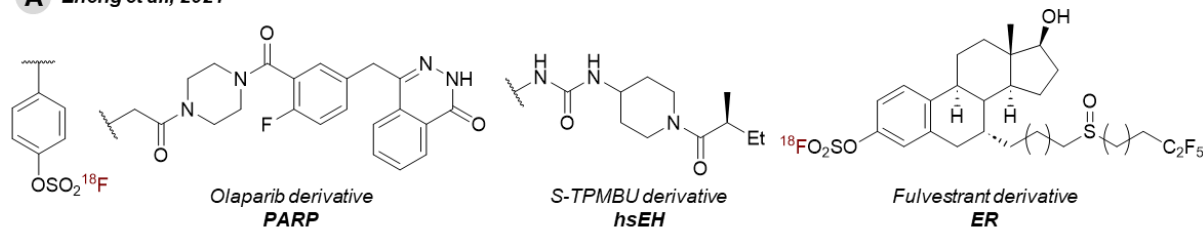
Scheme 17: Isotopic exchange via 5 membered intermediate as proposed by Zheng *et al.*^[87]

In 2022, *Walter et al.* introduced an optimized protocol for the SuFEx-based preparation of [^{18}F]fluorosulfates using base-free [^{18}F]F⁻ elution with ammonium salts, thereby omitting the need for the conventional [^{18}F]KF/K₂CO₃/K₂₂₂ complex (Scheme 16B).^[88] A key motivation for this refinement was the discovery that the RCCs reported for the original protocol had been overestimated, due to strong retention of [^{18}F]F⁻ on the SunFire C₁₈ column used for radio-HPLC analysis. The refined protocol enabled efficient ^{18}F -fluorination of low nanomolar amounts of 29 fluorosulfurylated phenols, including structurally complex biomolecules and pharmaceuticals. Furthermore, the new protocol was applied to prepare several [^{18}F]fluorosulfate-based tracer candidates for imaging of fibroblast activation protein (FAP), LAT1 and translocator protein (TSPO) (Scheme 18B). Among these, the [^{18}F]FET derivative H-Tyr([^{18}F]SO₂F)-OMe enabled clear tumor visualization in rats bearing orthotopic U87 MG glioblastoma xenografts. Similarly, a ^{18}F -fluorosulfurylated analog of DPA-714 reliably visualized neuroinflammation in a rat stroke model. However, in both cases, gradual accumulation of radioactivity in the bones over time took place, indicating *in vivo* defluorination. Even more pronounced signs of defluorination were observed for an electron-deficient derivative of the FAP-targeting compound UAMC1110, highlighting the need for further structural optimization to enhance *in vivo* stability.

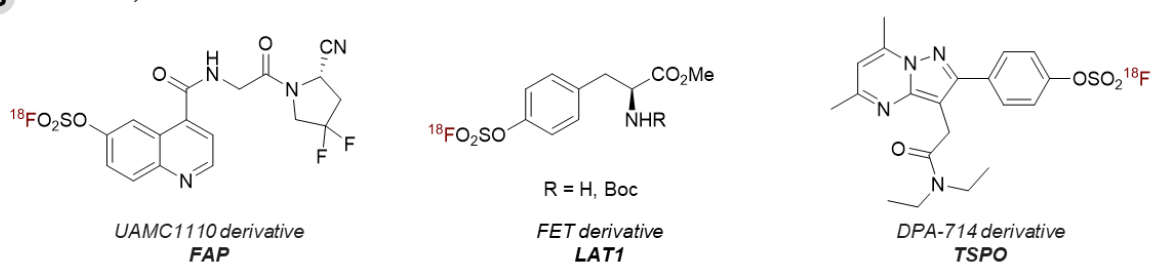
In the same year, six ^{18}F -fluorosulfurylated analogues of the FDA approved β -amyloid (A β)-targeting tracers [^{18}F]BAY-94-9172, [^{18}F]AV-45, and [^{18}F]GE-067 were evaluated (Scheme 18C).^[89] All of these tracer candidates could be prepared within 30 min in sufficient

RCP (>95%), and good isolated yields (AY: 14–27%) and molar activities (A_m : 44–109 GBq/ μ mol). *In vivo* biodistribution studies in healthy mice revealed effective penetration of the blood brain barrier (BBB). In addition, *in vitro* autoradiography using brain sections from Alzheimer's disease (AD) patients and healthy human subjects demonstrated high-affinity, A β -selective binding of two candidates. However, strong *in vivo* defluorination manifested in accumulation of radioactivity in bones was observed for all tracers.

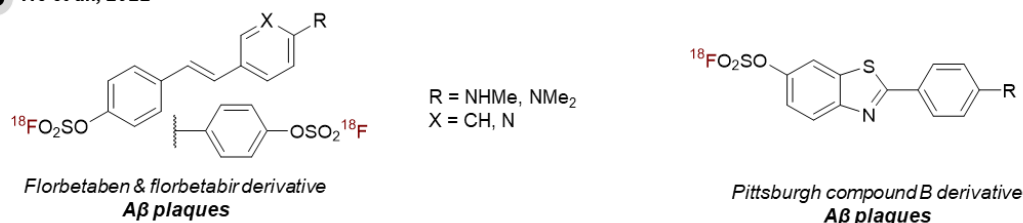
A Zheng et al., 2021



B Walter et al., 2022



C He et al., 2022

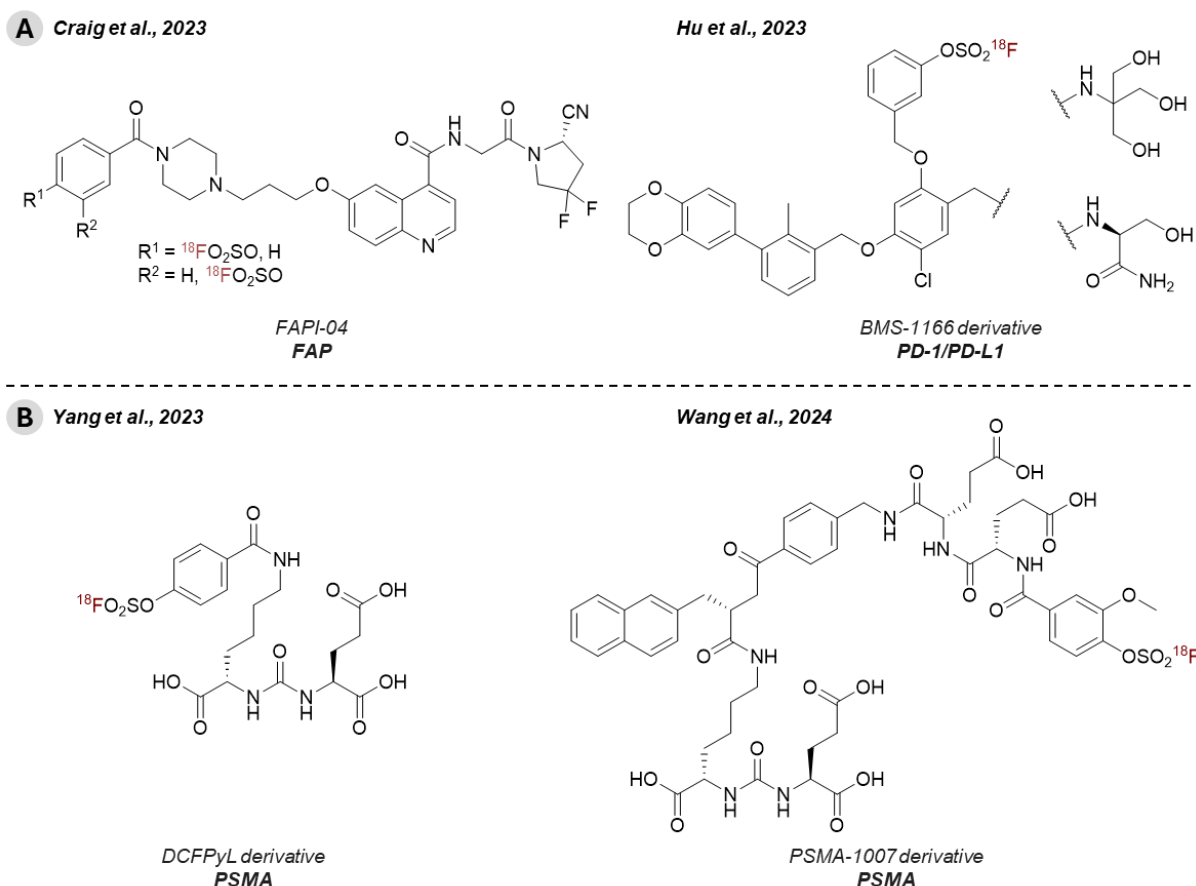


Scheme 18: **A** [^{18}F]Fluorosulfate-based tracer candidates prepared by Zheng et al. **B** [^{18}F]Fluorosulfate-based tracers targeting FAP, LAT1 or TSPO produced by Walter et al.^[88] **C** [^{18}F]Fluorosulfate-based tracers for imaging of A β plaques published by He et al.^[89]

One year after the study by Walter and co-workers^[88] two alternative FAP-targeting tracers were evaluated by Craig et al.^[90] In this case, the [^{18}F]FO₂SO moiety was not directly attached to the quinoline core of the UAMC1110 scaffold but instead a linker was used (FAPI-04, Scheme 19A). Both tracers were obtained in high AYs (43–54%), RCPs (>99%) and A_m (22–52 GBq/ μ mol). Unfortunately, they also suffered from significant degradation in human blood serum and in healthy mice.

Hu et al. prepared and evaluated two ^{18}F -fluorosulfurylated radiotracers based on a phoxymethyl-biphenyl scaffold for imaging of programmed cell death protein ligand 1 (PD-L1) expression in tumors (Scheme 19A).^[91] The compounds were successfully labeled by

SuFEx isotopic exchange (RCY: ~30%, RCP: >98%, A_m : 13–14 GBq/ μ mol). *In vitro* binding studies confirmed high-affinity of the tris(hydroxymethyl)aminomethane (TRIS)-functionalized tracer to PD-L1 and μ PET imaging in murine melanoma (B16-F10) tumor bearing mice revealed rapid tumoral tracer accumulation. However, both tracers exhibited high uptake in abdominal organs, likely attributable to their high lipophilicity, and significant radioactivity accumulation in bone, indicative of *in vivo* defluorination.

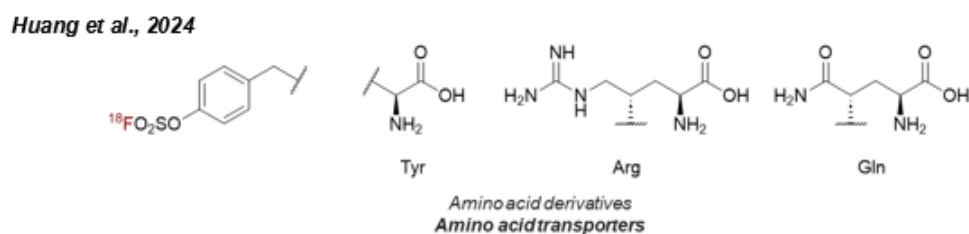


Scheme 19: **A** FAP- and PD-L1-targeting [^{18}F]fluorosulfate-based tracers investigated by Craig et al.^[90] and Hu et al.^[91], respectively. **B** PSMA-targeting [^{18}F]fluorosulfate-based tracers prepared by Yang et al.^[92] and Wang et al.^[93]

Yang et al. described the automated synthesis of an ^{18}F -fluorosulfurated PSMA-targeting tracer candidate derived from DCFPyL (Scheme 19B) on a cassette-based GE FASTlab™ module, which afforded the radioligand in AYs of 25% and molar activities of 0.13 GBq μmol^{-1} after 70 min. *In vitro* and *in vivo* studies revealed high uptake by PSMA-positive cancer cells and significant tumoral accumulation in PSMA-positive prostate carcinoma (LNCaP) xenografts. Interestingly, biodistribution studies in healthy mice also revealed low skeletal radioactivity uptake, which did not interfere with tumor visualization. However, the corresponding quantitative data were not provided^[92], and studies with the same tracer performed by another group indicated significant radioactivity accumulation in the bones after 120 min.^[94]

Two other [^{18}F]FO₂SO-based ligands for prostate cancer imaging derived from PSMA-1007 were investigated by *Wang et al.* (Scheme 19B). The tracers were obtained in 95% RCP but no yields were reported. *In vivo* studies in nude mice with human prostate carcinoma (22Rv1) xenografts demonstrated tumor uptake for both tracers, with the methoxy-substituted derivate showing a slightly better *in vivo* performance. However, besides slow blood clearance and high renal uptake, pronounced bone uptake of radioactivity was also observed for these tracers.^[93]

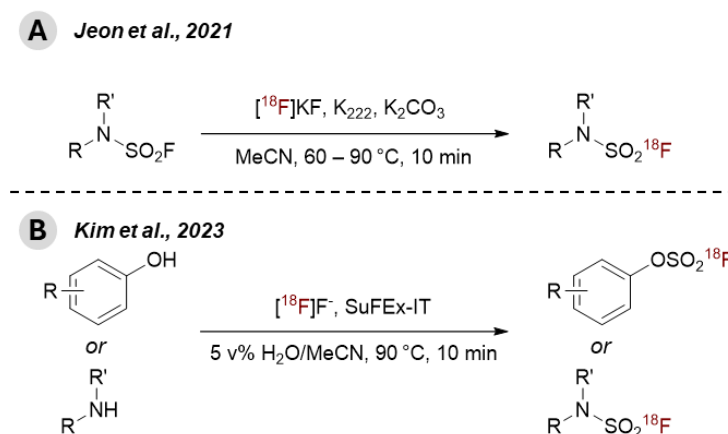
The SuFEx labeling approach has also been applied for the preparation of ^{18}F -labeled amino acids. Specifically, ^{18}F -fluorosulfurylated derivatives of glutamine (Gln), arginine (Arg) and tyrosine (Tyr) were prepared in RCYs of ~10 % and RCPs of >95% (Scheme 20). The tyrosine derivative could be directly labeled without protection groups and was successfully used for visualization of human breast cancer (MCF-7), human prostate carcinoma (22Rv1) and human glioblastoma (U87 MG) xenografts. The arginine and glutamine derivatives showed low tumoral uptake in the MCF-7 xenograft model. However, significant tumor uptake was observed in the prostate carcinoma and glioblastoma models. Notably, the authors observed surprisingly low radioactivity uptake in the bones, indicating high stability of ^{18}F -fluorosulfurylated amino acids against *in vivo* defluorination.^[95] However, this observation contradicts unpublished results from our own group, which show clear signs of defluorination for the same tyrosine-based tracer candidate.



Scheme 20: Amino acid derived [^{18}F]fluorosulfate-based tracers investigated by Huang et al.^[95]

1.9.4 Sulfamoyl Fluorides

In contrast to sulfonyl [^{18}F]fluorides and [^{18}F]fluorosulfates, sulfamoyl [^{18}F]fluorides have been barely investigated as scaffolds for PET tracer development. The first preparation of sulfamoyl [^{18}F]fluorides was reported in 2021 by *Jeon* and colleagues.^[96] Just one month after the seminal work on SuFEx isotopic exchange by *Zheng et al.*, the authors described the successful application of this approach for the preparation of 30 primary and secondary sulfamoyl [^{18}F]fluorides (Scheme 21A). RCCs between 50–97% were achieved using the [^{18}F]KF/K₂CO₃/K₂₂₂ complex, 0.5–20 μmol of precursor and inductive heating in an *Anton Paar*[®] reactor. The group erroneously claimed molar activities of up to 55.7 GBq μmol^{-1} for the automated synthesis of an amoxapine derivative on a GE TRACERlab[™] FX_{FN} module. However, an inconsistency arises from their reported use of 1.7 GBq [^{18}F]F[−] to label 5 μmol of precursor, which would result in a maximum molar activity of 0.34 GBq μmol^{-1} .

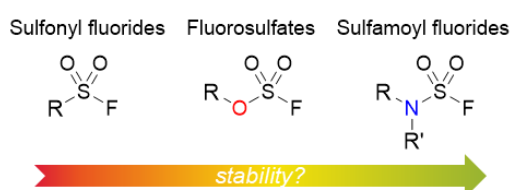


Scheme 21: **A** Preparation of sulfamoyl [^{18}F]fluorides via SuFEx-based isotopic exchange. **B** Preparation of sulfamoyl [^{18}F]fluorides and [^{18}F]fluorosulfates using SuFEx-IT.^[97]

The same group reported an alternative approach for preparation of sulfamoyl [^{18}F]fluorides and [^{18}F]fluorosulfates from the corresponding amines and phenols using the fluorosulfurylation agent SuFEx-imidazolium triflate (SuFEx-IT, Scheme 21B).^[97] In this approach, a solution of SuFEx-IT was passed through a standard Waters Sep-Pak[®] quaternary methyl ammonium (QMA) cartridge containing trapped [^{18}F]F[−] to generate a [^{18}F]FO₂S-species on-cartridge. The resulting stock solution was then used to label a series of primary or secondary amines and phenols in 95% MeCN, affording moderate to good RCCs (20–82% and 20–85%, respectively). The method was also successfully automated on a GE TRACERlab[™] FX_{FN} module, enabling the production of ^{18}F -fluorosulfurylated derivatives of propofol (AY: 17%) and triclosan (AY: 35%). Again, relatively high molar activities of 36–42 GBq μmol^{-1} were

reported despite the use of 20 μmol of SuFEx-IT precursor, which casts doubt on the accuracy of these values.

Thus, several studies investigating functional groups for targeted covalent inhibition have shown that sulfamoyl fluorides possess notably low intrinsic reactivity, rendering them unsuitable for such applications.^[98] This low reactivity has likely contributed to the comparatively limited scientific exploration of sulfamoyl fluorides relative to sulfonyl fluorides and fluorosulfates. Nevertheless, the inherent inertness of sulfamoyl fluorides could also confer increased *in vivo* stability and thus prove advantageous for radiotracer development (Scheme 22).



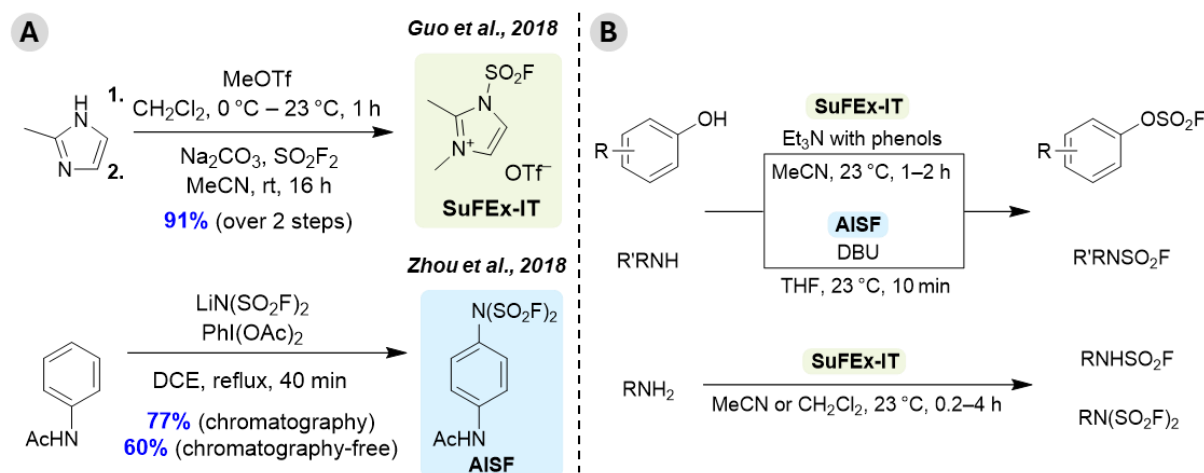
Scheme 22: Stability tendencies of compounds containing a FO_2S -group described in the literature.^[99] Primary sulfamoyl fluorides (NHSO_2F) are excluded as they readily undergo HF elimination via formation of highly reactive azasulfene intermediates.^[74c, 100]

1.10 Methods and Reagents for the Preparation of Aryl Fluorosulfates and Sulfamoyl Fluorides

The prototypical SuFEx hub for introduction of FO_2S -groups into phenols or secondary amines is gaseous sulfuryl fluoride (SO_2F_2), which is typically obtained from pressurized lecture bottles. While SO_2F_2 displays ideal reactivity for the fluorosulfurylation of phenols, it reacts sluggishly with secondary amines and has proven to be unsuitable for conversion of primary amines into the corresponding sulfamoyl fluorides. Moreover, despite the apparent simplicity of SO_2F_2 -based fluorosulfurylation protocols, their routine use is hampered by the neurotoxicity of SO_2F_2 , which has led to several fatalities beyond laboratory settings.^[101] As a consequence, the availability of SO_2F_2 is often restricted by regulatory measures, and the requirement for specialized equipment to handle toxic gases has further impeded its adoption as a SuFEx hub.

To overcome these challenges, Guo and co-workers developed the fluorosulfonyl imidazolium triflate salt SuFEx-IT as a solid, bench-stable equivalent to SO_2F_2 (Scheme 23A), greatly improving access to SuFExable compounds.^[102] Thus, using SuFEx-IT as an FO_2S -donor, the group could prepare a wide range of aryl fluorosulfates and sulfamoyl fluorides from the corresponding phenols and amines (Scheme 23B). Notably, SuFEx-IT exhibited better reactivity and/or chemoselectivity than SO_2F_2 and enabled fluorosulfurylation of primary amines, providing access to the corresponding sulfamoyl fluorides and

bis(fluorosulfonyl)imides. In addition, SuFEx-IT proved to be stable for several months when stored at 4 °C or in a desiccator, and could be synthesized on a multigram scale in two steps from 2-methylimidazole via fluorosulfonylation with SO₂F₂ followed by quaternization of the resulting intermediate with methyl triflate (MeOTf) (Scheme 23A).



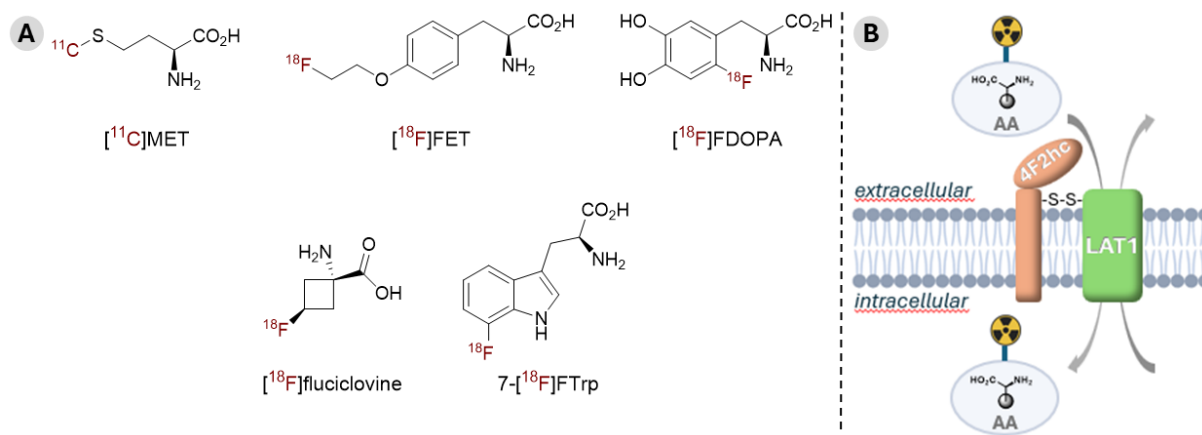
Scheme 23: **A** Preparation of SuFEx-IT^[102] and AISF.^[103] **B** Reaction conditions for preparation of aryl fluorosulfates and sulfamoyl fluorides using SuFEx-IT^[102] or AISF.^[103]

Another solid and bench-stable SuFEx hub developed by Zhou *et al.* is [4-(acetylamino)phenyl]imidodisulfonyl difluoride (AISF).^[103] This FO₂S-donor could be prepared in a single step by oxidative C-H functionalization of acetanilide with bis(fluorosulfonyl)imide (Scheme 23A). The authors demonstrated the utility of AISF for the synthesis of various aryl fluorosulfates and sulfamoyl fluorides (Scheme 23B). Noteworthy mono- or bi-functionalization of primary amines with the FO₂S-moiety using this reagent proved challenging, indicating an inferior reactivity compared to SuFEx-IT.^[74c]

1.11 Amino Acid Tracers for Neurooncological and Neurodegenerative Imaging

Amino acid (AA)-based tracers are routinely employed for PET imaging of primary brain tumors and cerebral metastases, with [^{18}F]FET, [^{11}C]methyl-L-methionine ([^{11}C]Met), and 6-[^{18}F]FDOPA (Scheme 24A) being the most frequently used probes.^[104] These tracers are substrates of LAT1 (Scheme 24B) and/or other amino acid transporters, which are present in the BBB and overexpressed in most brain tumors.^[105] Historically, [^{11}C]Met was the tracer of choice in early PET studies, but the short half-life of carbon-11 (20 min) imposes significant logistical constraints, leading to its gradual replacement by [^{18}F]FET.^[106] After uptake into the brain and neoplastic tissue mediated by LAT1 or other amino acid transporters, [^{18}F]FET is not metabolized.^[107] In contrast, [^{11}C]Met is incorporated into proteins and participates in other metabolic processes or degradation pathways.^[108] [^{18}F]FDOPA is primarily used to assess the density of presynaptic dopaminergic neurons in patients with Parkinson's disease (PD) but can also be employed for imaging cerebral and neuroendocrine tumors.^[15] However, its physiological accumulation in the dopaminergic striatum can complicate tumor delineation, limiting its utility for imaging tumors in these brain regions.^[109] Another promising synthetic amino acid analog is *anti*-1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid ([^{18}F]fluciclovine, Scheme 24A), which has gained clinical traction for imaging both primary and metastatic brain tumors. Originally approved for detecting recurrent prostate cancer,^[110] [^{18}F]fluciclovine was later granted orphan drug status in the United States for glioma imaging.^[111] Although tumor uptake of [^{18}F]fluciclovine is partly mediated by LAT1, it predominantly depends on another neutral amino acid transporter, the neutral alanine, serine, cysteine transporter 2 (ASCT2).^[112] Notably, [^{18}F]fluciclovine exhibits significantly higher tumor-to-background contrast than traditional AA-based tracers, largely due to its limited permeability across the intact BBB.^[113] A particularly promising AA-based tracer for imaging of neurological diseases is 7-[^{18}F]fluorotryptophan (7-[^{18}F]FTrp, Scheme 24A), a substrate for different tryptophan (Trp) metabolic pathways.^[114] Since alterations of Trp-metabolism have been implicated in several pathological processes,^[115] visualization of these pathways could provide valuable diagnostic insights. For example, in neurodegenerative diseases like AD and PD, serotonin synthesis is often markedly downregulated, while metabolism of Trp via the kynurenine pathway is increased.^[116] The suitability of 7-[^{18}F]FTrp for visualizing such changes was demonstrated in a 6-hydroxydopamine (6-OHDA)-induced mouse model of PD.^[117] This study showed increased 7-[^{18}F]FTrp uptake at the injection site, indicative of kynurenine pathway activation due to neuroinflammation, while uptake in the dorsal hippocampus was decreased and inversely correlated to dopamine depletion severity, indicating

reduced serotonin synthesis. As a substrate of LAT1 and other amino acid transporters, 7- ^{18}F FTrp is also suitable for brain tumor imaging, underscoring its potential as a broadly applicable PET neurotracer.



Scheme 24: A Overview of the most commonly used amino acid-based tracers for neurooncological and neurodegenerative imaging. B Visualization of heterodimeric LAT1 amino acid transporter and its dimerization partner 4F2hc, which is essential for its translocation and stability. Created with BioRender and freely adapted from Newstead.^[118]

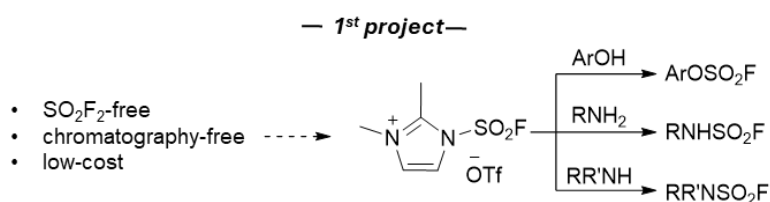
2 Motivation

Recent introduction of a radiolabeling method for the preparation of [^{18}F]fluorosulfates via isotopic exchange based on SuFEx click chemistry has garnered significant interest, offering a straightforward and versatile approach for the development of new PET tracers. This method is particularly attractive due to its operational simplicity and mild reaction conditions, making it suitable for labeling sensitive biomolecules.

However, several follow-up studies have demonstrated that *in vivo* defluorination is a recurring issue for [^{18}F]fluorosulfate-based tracers, potentially hindering their clinical translation. To address this limitation, alternative fluorosulfonyl-containing compound classes are currently under investigation. Among them, sulfamoyl fluorides have emerged as promising candidates that likely offer improved metabolic stability.

Therefore, the overarching objective of this thesis was to assess the potential of sulfamoyl fluorides for application in PET radiochemistry. This objective was addressed by three interconnected subprojects:

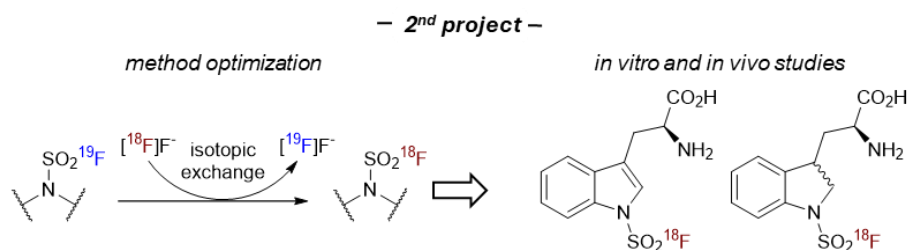
The first subproject aimed to improve access to sulfamoyl fluoride precursors by establishing a cost-effective and straightforward synthetic route to the fluorosulfonylating agent SuFEx-IT. The published process for preparation of this reagent relies on the use of sulfonyl fluoride (SO_2F_2), which is difficult to acquire and highly toxic. Therefore, the goal was to design a synthesis that is scalable, avoids chromatographic purification, and utilizes safe and inexpensive starting materials (Scheme 25).



Scheme 25: 1st project | Alternative synthetic route to the fluorosulfonylation agent SuFEx-IT.

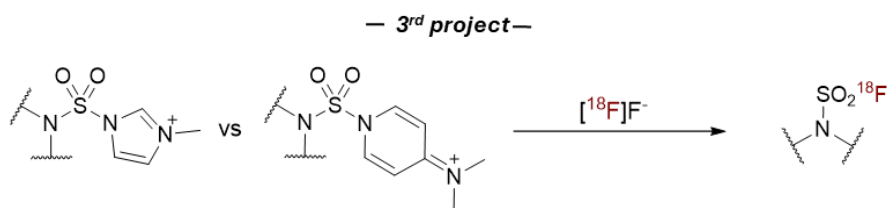
The second subproject focused on the development of a robust ^{18}F -labeling SuFEx-based protocol for the preparation of sulfamoyl [^{18}F]fluorides using low precursor amounts and mild reaction conditions. The optimization strategy focused on systematically varying key parameters, including reaction time, temperature, elution salt, and particularly the precursor amount in relation to different sulfamoyl substrates. After preparation, the hydrolytic stability

and *in vivo* biodistribution of the novel compounds should be evaluated *in vivo* by PET imaging experiments (Scheme 26).



Scheme 26: 2nd project | SuFEx-based preparation of sulfamoyl [¹⁸F]fluorides and first *in vivo* assessment.

The third subproject sought to develop a non-isotopic exchange labeling strategy that provides access to n.c.a. ¹⁸F-labelled aliphatic sulfamoyl fluorides in high molar activities. For this purpose, imidazolium- and dimethylaminopyridinium-based leaving groups should be investigated (Scheme 27). The project aimed to develop an efficient and operationally simple method for synthesizing sulfamoyl [¹⁸F]fluorides with higher molar activities than existing SuFEx-based labeling approaches.



Scheme 27: 3rd project | No carrier added preparation of sulfamoyl [¹⁸F]fluorides using onium salts.

3 Results

3.1 Publication | Desmethyl SuFEx-IT: SO₂F₂-Free Synthesis and Evaluation as a Fluorosulfonylating Agent

Abstract

Access to SuFExable compounds was remarkably simplified by introduction of the solid FO₂S-donor SuFEx-IT. However, the published process for preparation of this reagent relies on the use of sulfuryl fluoride (SO₂F₂), which is difficult to obtain and highly toxic. Herein, we disclose a simple protocol for SO₂F₂-free, hectogram-scale preparation of the analogous desmethyl SuFEx-IT from inexpensive starting materials. The reagent was prepared in a high (85%) total yield and without chromatographic purification steps. In addition, we demonstrate the utility of desmethyl SuFEx-IT by successful preparation of a series of fluorosulfates and sulfamoyl fluorides in high to excellent yields. As such, our work recognizes desmethyl SuFEx-IT as a valuable alternative to common FO₂S-donors and enables cost-efficient access to substrates for SuFEx click chemistry.

The concept for the following publication was developed by Prof. Dr. B. D. Zlatopolskiy, J. Bertram and Prof. Dr. B. Neumaier. The organic syntheses were carried out by J. Bertram and Prof. Dr. B. D. Zlatopolskiy. The manuscript was jointly authored by J. Bertram, Dr. F. Neumaier, Prof. Dr. B. D. Zlatopolskiy and Prof. Dr. B. Neumaier.

Desmethyl SuFEx-IT: SO₂F₂-Free Synthesis and Evaluation as a Fluorosulfurylating Agent

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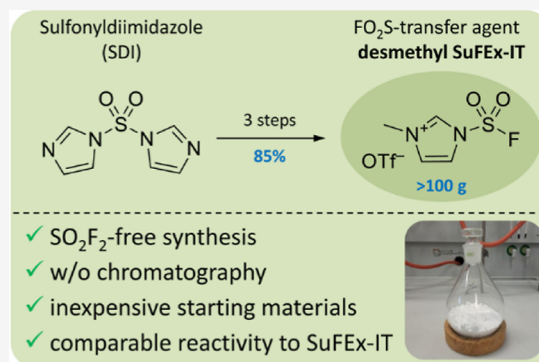


Article Recommendations



Supporting Information

ABSTRACT: Access to SuFExable compounds was remarkably simplified by introduction of the solid FO₂S-donor SuFEx-IT. However, the published process for preparation of this reagent relies on the use of sulfonyl fluoride (SO₂F₂), which is difficult to obtain and highly toxic. Herein, we disclose a simple protocol for SO₂F₂-free, hectogram-scale preparation of the analogous desmethyl SuFEx-IT from inexpensive starting materials. The reagent was prepared in a high (85%) total yield and without chromatographic purification steps. In addition, we demonstrate the utility of desmethyl SuFEx-IT by successful preparation of a series of fluorosulfates and sulfamoyl fluorides in high to excellent yields. As such, our work recognizes desmethyl SuFEx-IT as a valuable alternative to common FO₂S-donors and enables cost-efficient access to substrates for SuFEx click chemistry.



INTRODUCTION

The unique chemistry of the fluorosulfonyl (FO₂S-) group has intrigued researchers since the early 20th century.^{1,2} Introduction of sulfur(VI)-fluoride exchange (SuFEx) as a new class of click reactions in 2014³ fostered scientific efforts by chemists from all over the world to exploit the exceptional properties of this functional group. The S^{VI}-F bond in the FO₂S-group is generally highly stable and can tolerate unusually harsh conditions. However, it demonstrates a latent reactivity with various nucleophiles that can be triggered under specific conditions. In addition, the facile introduction of the FO₂S-group into target molecules using SuFEx hub-reagents has rendered FO₂S-substituted compounds valuable building blocks across diverse applications in organic synthesis, material sciences, drug discovery, and even radiochemistry.⁴

The prototypical SuFEx hub for introduction of FO₂S-groups into phenols or secondary amines is gaseous sulfonyl fluoride (SO₂F₂), which is typically obtained from pressurized lecture bottles. However, while SO₂F₂ shows ideal reactivity for fluorosulfurylation of phenols, it exhibits sluggish reactivity with secondary amines and has proven to be unsuitable for conversion of primary amines to the corresponding sulfamoyl fluorides. Moreover, despite the apparent simplicity of SO₂F₂-based fluorosulfurylation methods, their routine application is hampered by the neurotoxic nature of SO₂F₂, which has led to several fatalities beyond laboratory environments.^{5,6} As a consequence, the availability of SO₂F₂ is often restricted by regulations, and the need for specialized equipment to handle toxic gases has further impeded broad adoption of this reagent as a SuFEx hub.

To overcome these limitations, de Borggraeve and co-workers introduced a fluorosulfurylation method based on *ex situ* generation of SO₂F₂ from 1,1'-sulfonyldiimidazole (SDI) in a two-chamber reactor.⁷ Although this method simplifies conversion of phenols into the corresponding aryl fluorosulfates, the requirement for specialized glassware, limited scalability, and the formation of HF gas as a side product represent obvious disadvantages.

Accordingly, development of a fluorosulfonyl imidazolium triflate salt (termed SuFEx-IT) as a solid equivalent for SO₂F₂ by Guo and co-workers greatly improved access to SuFExable compounds.⁸ Thus, using SuFEx-IT as a FO₂S-donor, the group was able to prepare a wide range of fluorosulfates and sulfamoyl fluorides from the corresponding alcohols and amines. Remarkably, SuFEx-IT showed better reactivity/chemoselectivity than SO₂F₂ and enabled fluorosulfurylation of primary amines, providing access to the corresponding sulfamoyl fluorides and bis(fluorosulfonyl)imides (Scheme 1). In addition, SuFEx-IT proved to be sufficiently stable for several months when stored at 4 °C or in a desiccator and could be synthesized on a multigram scale in two steps from 2-methylimidazole via fluorosulfurylation with SO₂F₂ followed by quaternization of the

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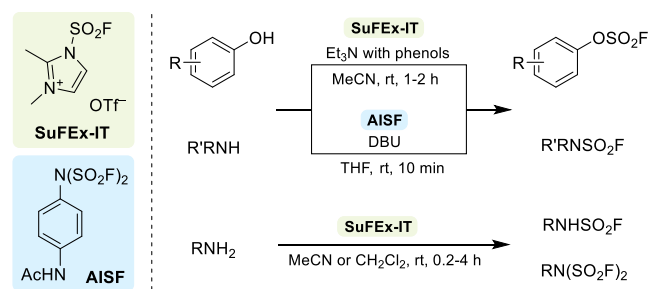
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Accepted: February 9, 2024

Published: February 22, 2024



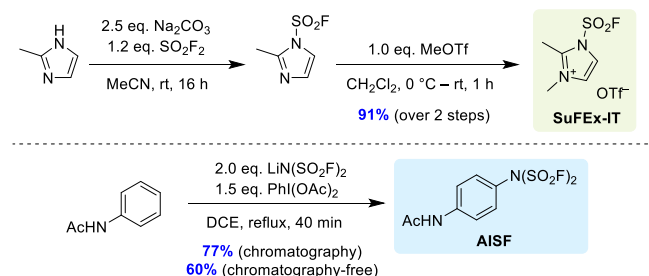
Scheme 1. Preparation of Fluorosulfates and Sulfamoyl Fluorides with SuFEx-IT⁸ and AISF⁹



resulting intermediate with methyl triflate (MeOTf) (Scheme 2).

Another solid and bench-stable SuFEx hub developed by Zhou et al. is [4-(acetylamino)phenyl]imidodisulfuryl difluoride (AISF).⁹ This FO₂S-donor could be prepared in a single step by oxidative C–H functionalization of acetanilide with bis-(fluorosulfonyl)imide (Scheme 2). In addition, the authors demonstrated the utility of AISF for the synthesis of various aryl fluorosulfates and sulfamoyl fluorides. However, mono- or bifunctionalization of primary amines with the FO₂S-moiety using this reagent has proven to be challenging, indicating an inferior reactivity compared to SuFEx-IT.¹⁰

Scheme 2. Literature Procedures for the Preparation of SuFEx-IT⁸ and AISF⁹



As such, SuFEx-IT remains the most widely used reagent for facile production of sulfamoyl fluorides or fluorosulfates for SuFEx click chemistry. Nevertheless, the reagent is rather expensive and its preparation still relies on the use of toxic and hardly available SO₂F₂, which is associated with the aforementioned handling and regulatory issues.

For our ongoing studies on the use of SuFEx ¹⁸F-fluorination¹¹ for the preparation of PET-tracers,¹² a series of aryl fluorosulfates and sulfamoyl fluorides had to be prepared. Therefore, the aim of the present work was to simplify access to SuFEx-IT or alternative solid fluorosulfurylating agents by development of a simple and efficient production route that utilizes inexpensive starting materials and obviates the need for SO₂F₂.

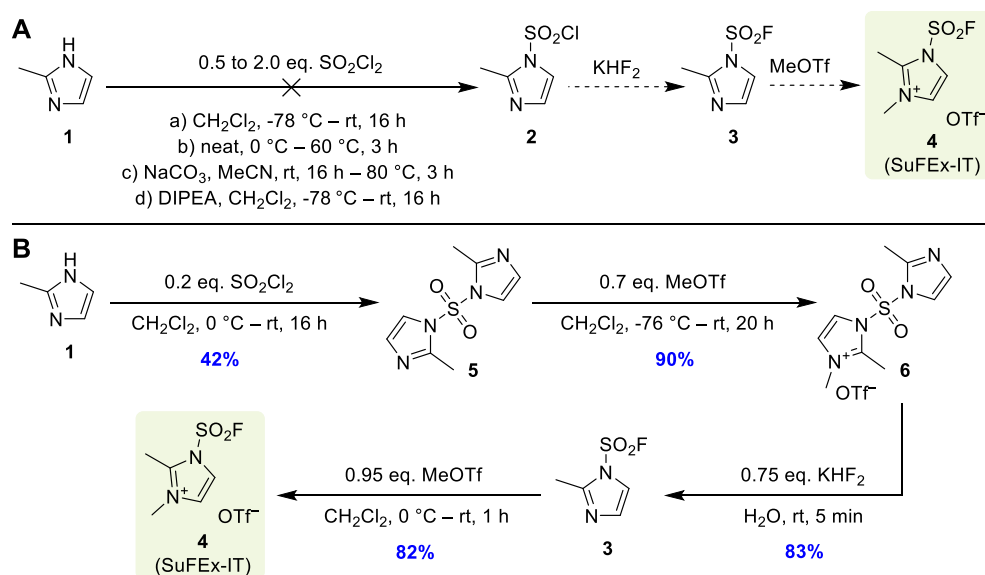
RESULTS AND DISCUSSION

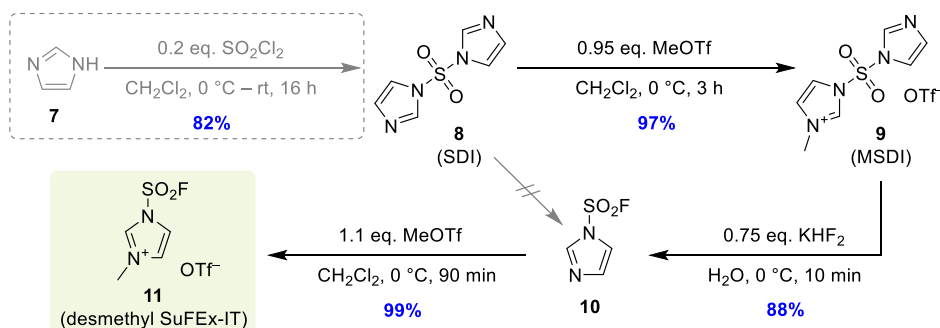
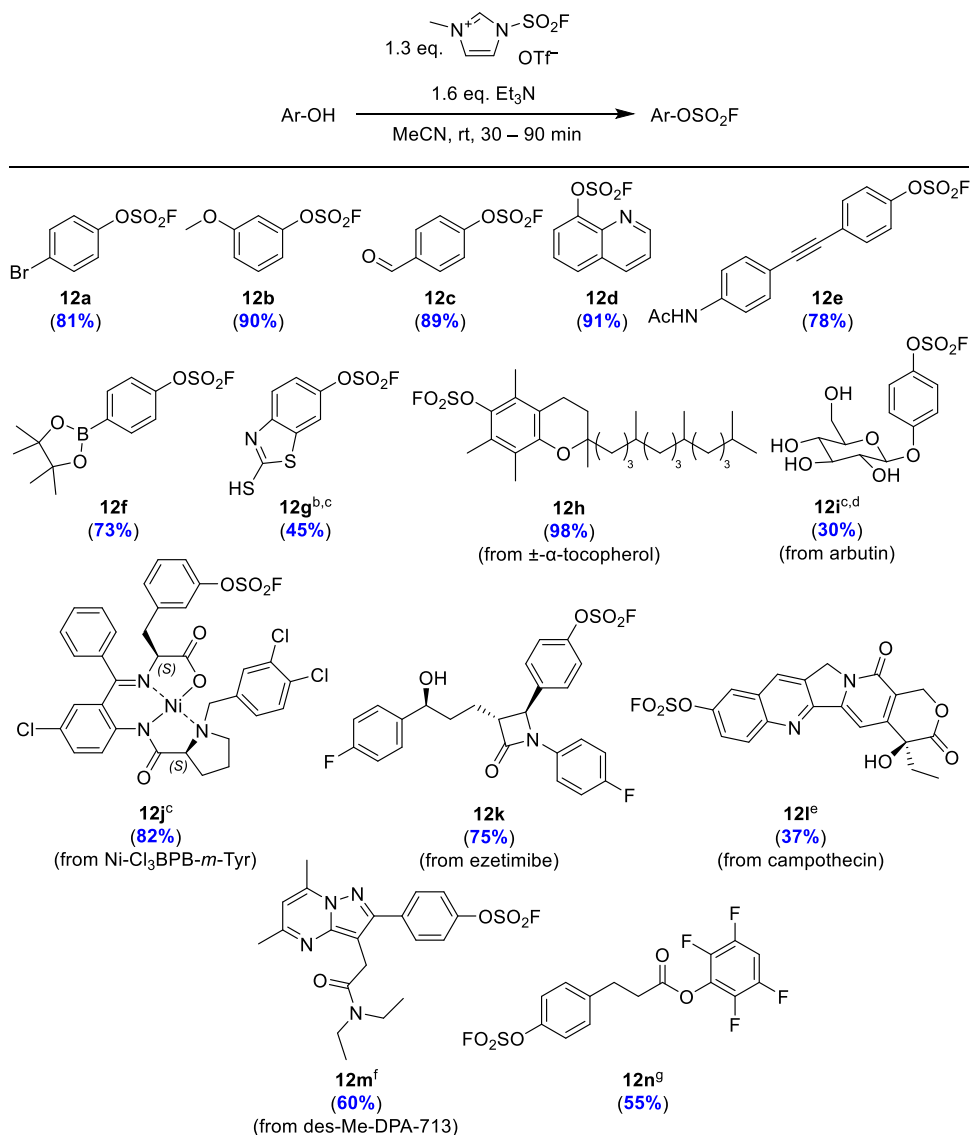
Initially, we hypothesized that application of sulfuryl chloride (SO₂Cl₂) as an inexpensive and liquid substitute for SO₂F₂ could be used to improve the synthesis of SuFEx-IT (4). In particular, it was envisioned that reaction of 2-methylimidazole (1) with SO₂Cl₂ should afford the corresponding sulfamoyl chloride 2, which could in turn be converted to sulfamoyl fluoride 3 using an adequate fluoride source (Scheme 3A). However, no formation of the desired sulfamoyl chloride was observed under various reaction conditions (see a–d in Scheme 3A). Therefore, this approach was abandoned.

Next, we turned our attention to the imidazolium salt 6 as an alternative precursor for sulfamoyl fluoride 3 (Scheme 3B). This compound bears the quaternized imidazolium moiety that serves as the leaving group in SuFEx-IT and could be prepared from 1 via 1,1'-sulfonylbis(2-methylimidazole) (5) using procedures described in the literature. To our delight, fluorination of 6 in aqueous solution proceeded efficiently and afforded sulfamoyl fluoride 3 in 83% yield. Subsequent methylation of 3 with MeOTf yielded the desired SuFEx-IT on a 3 g scale. However, a moderate overall yield of 26% (which was mainly attributable to the rather inefficient preparation of 5) limited the practical utility of this production route.

Therefore, our interest shifted to desmethyl SuFEx-IT (11), which should represent a more accessible alternative to

Scheme 3. Attempted Preparation of SuFEx-IT via Sulfamoyl Chloride 2 (A) and SO₂F₂-Free Synthesis of SuFEx-IT (B)



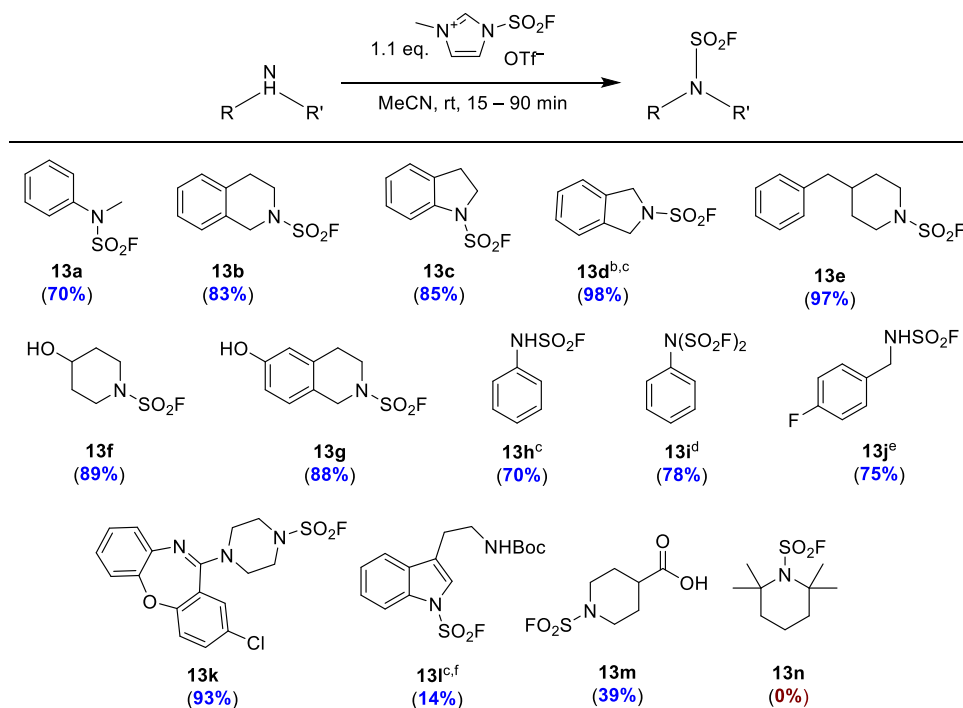
Scheme 4. SO₂F₂-Free Synthesis of Desmethyl SuFEx-IT (11)Scheme 5. Synthesis of Fluorosulfates from the Corresponding Phenols Using Desmethyl SuFEx-IT (11) as a FO₂S-Donor^a

^aIndicated yields refer to isolated products. ^bEt₃N (2.6 equiv). ^cAdditional Et₃N (1.0 equiv) and **11** (1.0 equiv) after 1 h. ^dIn DMF. ^eEt₃N (6.4 equiv) and **11** (5.2 equiv). ^fIn DMF/MeCN (1:1). ^gGram scale, **11** (1.4 equiv) and Et₃N (1.7 equiv), 16 h.

SuFExIT. Although the preparation of **11** has been described in the patent literature,¹³ neither its suitability as a FO₂S-transfer agent nor its storage stability have been evaluated so far. In addition, the reported procedure for preparation of desmethyl

SuFEx-IT is essentially the same as for the production SuFEx-IT and thus suffers from the same drawbacks.

When the above synthetic strategy was applied to this target compound (Scheme 4), the first step could be omitted by directly starting from inexpensive SDI (**8**; available from

Scheme 6. Synthesis of Sulfamoyl Fluorides from the Corresponding Amines Using Desmethyl SuFEx-IT (11) as a FO₂S-Donor^a

^aIndicated yields refer to isolated products. ^b11 (1.6 equiv) and Et₃N (1.0 equiv). ^cIn CH₂Cl₂. ^d11 (2.5 equiv) and Et₃N (0.5 equiv; added after 10 min), 10 min at 0 °C, then 30 min at rt. ^e11 (1.05 equiv). ^fDBU (2.2 equiv).

numerous providers for 0.5–1 €/g in 25–500 g packages). Alternatively, decagram quantities of **8**⁷ could be easily prepared from imidazole (**7**) and SO₂Cl₂ in >80% yield. Subsequent quaternization of **8** with MeOTf provided the corresponding monomethylated sulfonyldiimidazolium salt (MSDI, **9**),¹⁴ which precipitated from the solution and could be readily isolated in 97% yield after a total reaction time of 3 h. Thereafter, **9** was dissolved in ice-cooled water and treated with KHF₂ to produce sulfamoyl fluoride **10**¹⁵ within 10 min. Purification of the crude product by distillation afforded **10** in 88% yield when the reaction was performed on a decagram scale (we efficiently prepared up to ~60 g product). On a smaller scale, the yield was ~10% lower, presumably due to increased loss of the volatile product (see the Supporting Information). Finally, methylation of **10** with MeOTf provided, after simple crystallization, desmethyl SuFEx-IT (**11**) as a colorless solid in almost quantitative yields. This route enabled preparation of **11** on a hectogram scale in 85% total yield and without any chromatographic purifications within 2 days. Attempts to further shorten the procedure by direct fluorination of SDI were unsuccessful due to low conversion of **8** to **10**.

Next, we investigated the reactivity and chemoselectivity of desmethyl SuFEx-IT as a FO₂S-donor by preparation of several fluorosulfates and sulfamoyl fluorides. The results confirmed that **11** reacts readily with various simple phenols to form the corresponding fluorosulfates **12a–e** in yields of 78–91% within 30–90 min (Scheme 5). The reaction was unaffected by the presence of electron-withdrawing or electron-donating groups. Substrates containing a Bpin or unprotected thiol group could also be fluorosulfurated in 73 and 45% yields, respectively (Scheme 5, **12f** and **12g**, respectively). In addition, reaction of desmethyl SuFEx-IT with more complex and/or sensitive substrates like $\pm$ - α -tocopherol (vitamin D), the skin-lightening glycoside arbutin, the Ni-complex Ni-Cl₃BPB-*m*-Tyr, the

cholesterol lowering drug ezetimibe, the topoisomerase inhibitor camptothecin or the precursor for the ¹¹C-labeled TSPO-specific ligand [¹¹C]DPA-713¹⁶ afforded the desired fluorosulfurated products in 30–98% yields (Scheme 5, **12h–m**). Scalability of the procedure was confirmed by the preparation of base sensitive active ester **12n** on a gram scale in 55% yield.

Fluorosulfurylation of both aliphatic and aromatic secondary amines with **11** afforded the corresponding sulfamoyl fluorides **13a–g** in good to excellent yields (Scheme 6). Noteworthy, 4-hydroxypiperidine and 6-hydroxy-1,2,3,4-tetrahydroisoquinoline were mono-fluorosulfurated at the nitrogen with excellent selectivity to furnish the corresponding sulfamoyl fluorides as single products in 88–89% yields (Scheme 6, **13f** and **13g**). The observed chemoselectivity for fluorosulfurylation of the secondary amino over the hydroxy groups in these substrates can most likely be attributed to its higher nucleophilicity. **11** was also successfully applied for the mono- and bi-fluorosulfurylation of aniline and mono-fluorosulfurylation of 4-fluorobenzylamine (Scheme 6, **13h–j**). A fluorosulfurated derivative of the antidepressant amoxapine was prepared in 93% yield (Scheme 6, **13k**). Fluorosulfurylation of an indole nitrogen, e.g., in *N*_α-Boc-protected tryptamine, was also possible. In this case, application of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base was necessary to prepare the desired product in a fair yield (Scheme 6, **13l**). Notably, the preparation of *N*-fluorosulfurated indoles using SuFEx-IT or AISF has not been described so far. Finally, desmethyl SuFEx-IT enabled installation of a FO₂S group in the presence of an unprotected carboxylic acid function, as exemplified by transformation of the GABA_A receptor partial agonist isonipecotic acid into the corresponding sulfamoyl fluoride in 39% yield (Scheme 6, **13m**). Generally, desmethyl SuFEx-IT demonstrated a reactivity comparable to that of SuFEx-IT.⁸ Thus, fluorosulfurylation of

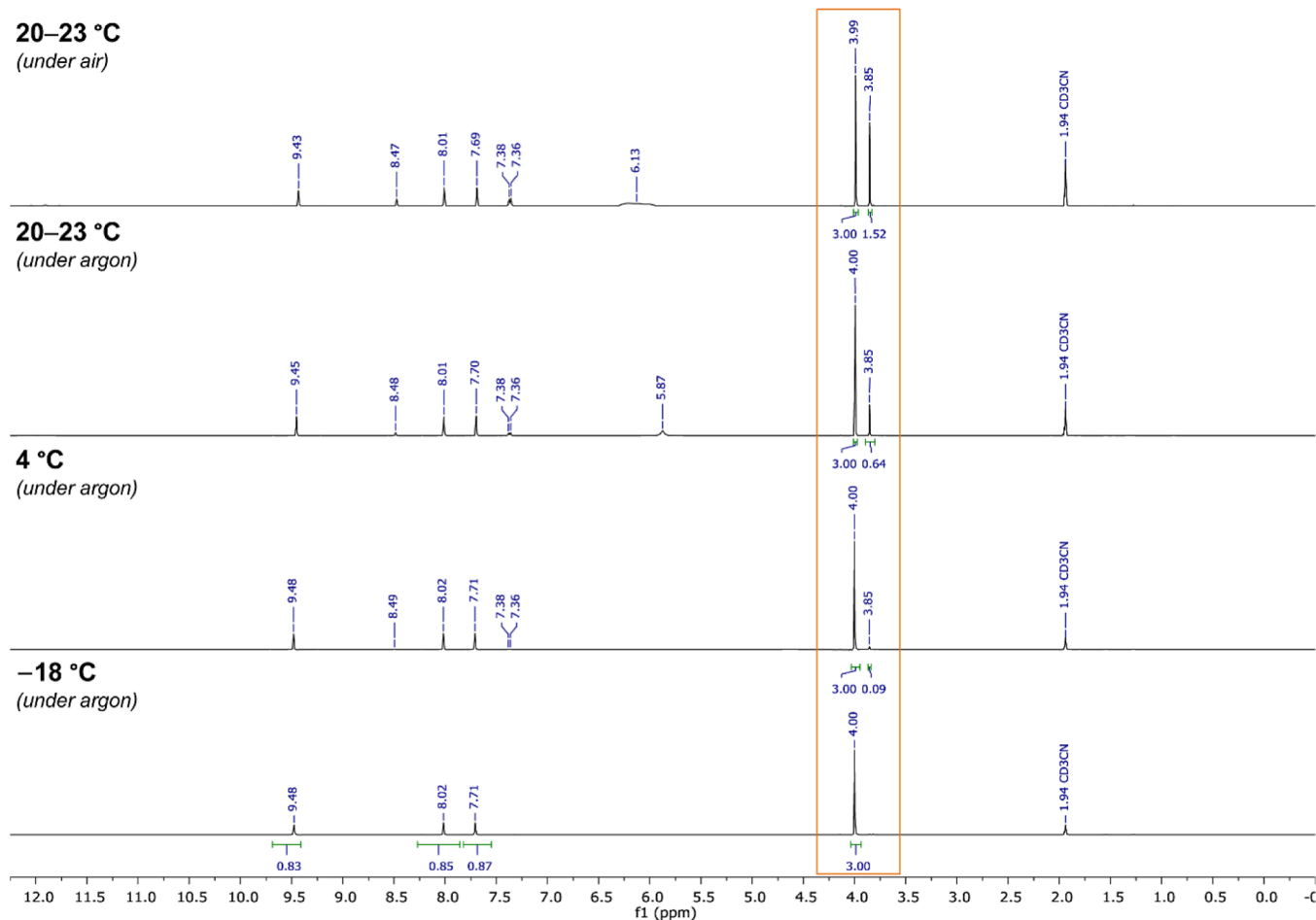


Figure 1. ^1H NMR of desmethyl SuFEx-IT (**11**) after storage for 288 days at the indicated temperatures under air or argon.

sterically hindered 2,2,6,6-tetramethylpiperidine, which could not be fluorosulfurylated using SuFEx-It, AISF, or SO_2F_2 , was also impossible using desmethyl SuFEx-IT (Scheme 6, **13n**).

Finally, the long-term stability of **11** during storage under different conditions was investigated by nuclear magnetic resonance (NMR) analysis (Figure 1). Bench storage under air for 288 days at ambient temperature (20–23 °C) resulted in decomposition by 34%, which could be reduced to 18% by storing the compound under argon. In contrast, minimal (<3%) or no signs of decomposition were observed after 288 days at 4 °C or –18 °C under argon, respectively, demonstrating an excellent shelf life of **11** under these conditions.

CONCLUSIONS

We have developed a convenient three-step procedure for the SO_2F_2 -free, hectogram-scale preparation of desmethyl SuFEx-IT. This process affords the compound in 85% total yield from inexpensive starting materials without chromatographic purification steps within only 2 days. The utility of the reagent was demonstrated by the preparation of a series of fluorosulfates and sulfamoyl fluorides in good to excellent yields. Furthermore, desmethyl SuFEx-IT could be applied for *N*-selective mono-fluorosulfurylation of secondary amines containing aliphatic or aromatic hydroxyl groups. As such, our results identify desmethyl SuFEx-IT as a valuable alternative to common FO_2S -donors, which offers safe and cost-efficient access to substrates for SuFEx click chemistry.

EXPERIMENTAL SECTION

Unless noted otherwise, all chemicals and solvents were purchased from VWR International GmbH (Darmstadt, Germany), Sigma-Aldrich Chemie GmbH (Steinheim, Germany), ABCR GmbH (Karlsruhe, Germany), Apollo Scientific Ltd. (Bredbury, United Kingdom) or BLD Pharmatech GmbH (Kaiserslautern, Germany) and used without further purification.

If not stated otherwise, all reactions were carried out with magnetic stirring. Organic extracts were dried over anhydrous MgSO_4 . Air- or moisture-sensitive reagents were handled under argon (>99.999%, Air Liquide GmbH, Düsseldorf, Germany). CH_2Cl_2 [HPLC grade (GC: 99.8%), <0.01% H_2O] was stored under argon and was used with moisture sensitive reagents (like MeOTf or SO_2Cl_2). Solutions were concentrated under reduced pressure (1–900 mbar) at 40–50 °C using a rotary evaporator (Heidolph GmbH & Co. KG, Schwabach, Germany).

Nuclear Magnetic Resonance Spectroscopy. NMR spectra were measured at ambient temperature in deuteriochloroform (CDCl_3), trideuteroacetonitrile (CD_3CN), hexadeuterodimethyl sulfoxide [$(\text{CD}_3)_2\text{SO}$] or octadeuterotetrahydrofuran ($\text{THF}-d_8$) as indicated using a Bruker Ascend 400 (^1H : 400 MHz; $^{13}\text{C}\{^1\text{H}\}$: 101 MHz; ^{19}F : 376 MHz; Bruker Biospin GmbH, Rheinstetten, Germany). The measured chemical shifts are reported in δ [ppm] relative to residual peaks of nondeuterated solvents. Higher order NMR spectra were approximately interpreted as first-order spectra if possible. The observed signal multiplicities are characterized as follows: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, sep = septet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublets of doublets, dt = doublet of triplets, ddt = doublet of doublets of triplets, td = triplet of doublets, tt = triplet of triplets, qd = quartet of doublets, and pt = pentet of triplets. Coupling constants *J* are reported in hertz (Hz).

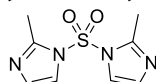
Mass Spectrometry. Low-resolution electrospray ionization mass spectrometry (LR-ESI-MS) was performed with an MSQ Plus™ mass spectrometer (Thermo Electron Corporation, San Jose, USA). High-resolution electrospray ionization mass spectrometry (HR-ESI-MS) was performed with an LTQ XL Orbitrap mass spectrometer (Thermo Fisher Scientific Inc., Bremen, Germany). Low-resolution electron ionization mass spectrometry (LR-EI-MS) was performed with an ISQ EC Single Quadrupole mass spectrometer (Thermo Fisher Scientific Inc., Bremen, Germany). High-resolution electron ionization mass spectrometry (HR-EI-MS) was performed with an Exactive GC Orbitrap mass spectrometer (Thermo Fisher Scientific Inc., Bremen, Germany).

Column Chromatography. Manual column chromatography was performed with silica gel, 60 Å, 230–400 mesh particle size from VWR International GmbH (Darmstadt, Germany) or silica gel (w/0.1% Ca), 60 Å, 230–400 mesh particle size from Sigma-Aldrich GmbH (Steinheim, Germany). Automated column chromatography was performed on a Büchi Pure C-815 flash system (Büchi Labortechnik GmbH, Essen, Germany) using Reveleris C₁₈ reversed phase cartridges (Büchi Labortechnik GmbH, Essen, Germany).

Thin-Layer Chromatography. Thin-layer chromatography (TLC) was performed using aluminum sheets coated with silica gel 0.25 mm SIL G/UV 254 (Merck KGaA, Darmstadt, Germany). Chromatograms were inspected under UV light ($\lambda = 254$ nm) and/or stained with phosphomolybdic acid (4% in EtOH), ninhydrin (0.5% in 1-butanol), or potassium permanganate solution (0.75% KMnO₄, 5% K₂CO₃, and 0.07% NaOH in H₂O).

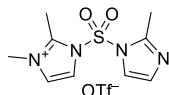
Elemental Analysis. Elemental analyses were conducted by HEKAtech GmbH (Wegberg, Germany).

Chemistry. 1,1'-Sulfonylbis(2-methyl-1H-imidazole) (5).¹⁴



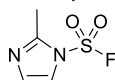
A solution of SO₂Cl₂ (29.99 g, 222 mmol, 1.0 equiv) in CH₂Cl₂ (20 mL) was added over 30 min to an ice-cooled suspension of 2-methylimidazole (82.1 g, 1.00 mol, 4.5 equiv) in CH₂Cl₂. The reaction mixture was stirred overnight under argon, after which H₂O (350 mL) was added and the aqueous phase was extracted with CH₂Cl₂ (2 × 100 mL). The combined organic phases were washed with brine, dried, and the solvent was removed under reduced pressure. The residue was recrystallized from *i*PrOH to afford the title compound 5 (21.0 g, 93.0 mmol, 42%) as an off-white solid. Molecular formula (molecular mass): C₈H₁₀N₄O₂S (226.25 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 7.37 (s, 2H), 6.94 (s, 2H), 2.51 (s, 6H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 146.1, 128.6, 120.1, 15.1. HR-ESI-MS *m/z*: [M + H]⁺ calcd for C₈H₁₁N₄O₂S 227.0597; found, 227.0598.

2,3-Dimethyl-1-[(2-methyl-1H-imidazole-1-yl)sulfonyl]-1H-imidazole-3-ium Trifluoromethanesulfonate (6).^{14,17}



A solution of MeOTf (2.00 mL, 17.7 mmol, 0.7 equiv) in CH₂Cl₂ (20 mL) was added over 3.5 h to a cooled solution (−78 °C) of 5 (5.72 g, 25.3 mmol, 1.0 equiv) in CH₂Cl₂ (200 mL) and the reaction mixture was allowed to warm to ambient temperature within 16 h. The resulting precipitate was filtered under argon and washed with ice-cold CH₂Cl₂ to afford the title compound 6 (6.21 g, 15.9 mmol, 90%) as a colorless solid. Molecular formula (molecular mass): C₁₀H₁₃F₃N₄O₂S₂ (390.35 g/mol). ¹H NMR (400 MHz, CD₃CN): δ 7.89 (d, *J* = 2.5 Hz, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.48 (d, *J* = 2.5 Hz, 1H), 7.03 (d, *J* = 2.0 Hz, 1H), 3.75 (s, 3H), 2.76 (s, 3H), 2.56 (s, 3H). ¹³C{¹H} NMR (101 MHz, CD₃CN): δ 148.0, 130.0, 124.7, 121.9, 121.6, 37.0, 15.7, 12.6. ¹⁹F NMR (376 MHz, CD₃CN): δ −79.29.

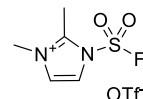
2-Methyl-1H-imidazole-1-sulfonyl Fluoride (3).⁸



4.5 M KHF₂* (5.56 mL, 25.0 mmol, 0.75 equiv) was added to a solution of 6 (13.0 g, 33.3 mmol, 1.0 equiv) in H₂O (20 mL, HPLC grade) and the mixture was stirred for 5 min. The aqueous solution was extracted with Et₂O (3 × 10 mL) and the combined organic phases were dried, filtered, and concentrated under reduced pressure at room temperature (due to the volatility of the product, the pressure was kept above 300 mbar). The raw product was purified by Kugelrohr distillation with acetone/dry ice-cooling of the receiver bulb to afford the title compound 3 (4.53 g, 27.6 mmol, 83%) as a colorless liquid. Molecular formula (molecular mass): C₄H₅FN₂O₂S (164.15 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 7.33 (d, *J* = 1.9 Hz, 1H), 6.99 (d, *J* = 1.9 Hz, 1H), 2.66 (s, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 146.9, 129.1, 120.1, 15.1. ¹⁹F NMR (376 MHz, CDCl₃): δ 58.16. LR-EI-MS *m/z*: [M]⁺ calcd for C₄H₅FN₂O₂S 164.01; found, 164.00.

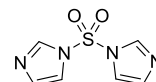
* Safety Precaution: it is strongly recommended to ensure the availability of 2.5% calcium gluconate gel as a safety measure when handling KHF₂.

1-(Fluorosulfonyl)-2,3-dimethyl-1H-imidazole-3-ium Trifluoromethanesulfonate (SuFEx-IT, 4).⁸



MeOTf (1.31 mL, 11.6 mmol, 0.95 equiv) was added dropwise under argon to an ice-cooled solution of 3 (2.00 g, 12.2 mmol, 1.00 equiv) in CH₂Cl₂. The reaction mixture was allowed to warm to ambient temperature and stirred for 1 h. The solution was then concentrated under reduced pressure, *t*BuOMe (30 mL) was added and solidification of the residual oil was induced by addition of a seed crystal and ultrasonication. The resulting solid was crushed with a spatula, filtered off, and washed with *t*BuOMe (30 mL) to afford SuFEx-IT (3.29 g, 10.0 mmol, 82%) as a colorless solid. Molecular formula (molecular mass): C₆H₈F₄N₂O₂S₂ (328.25 g/mol). ¹H NMR (400 MHz, CD₃CN): δ 7.88 (d, *J* = 2.5 Hz, 1H), 7.57 (d, *J* = 2.5 Hz, 1H), 3.86 (s, 3H), 2.86 (s, 3H). ¹³C{¹H} NMR (101 MHz, CD₃CN): δ 151.3, 125.5, 122.2, 122.0 (q, *J* = 320.1 Hz), 37.6, 12.9. ¹⁹F NMR (376 MHz, CD₃CN): δ 60.13, −79.34.

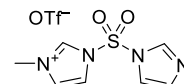
1,1'-Sulfonyldiimidazole (SDI, 8).⁷



SO₂Cl₂ (19.4 mL, 240 mmol, 1.0 equiv) in CH₂Cl₂ (20 mL) was added dropwise to an ice-cooled solution of imidazole (75.0 g, 1.10 mol, 4.6 equiv) in CH₂Cl₂ (450 mL). The yellow suspension was stirred overnight and filtered on the next day. The solvent was removed and the crude product was recrystallized from *i*PrOH to afford the title compound 8 (38.97 g, 197 mmol, 82%) as a colorless solid. Molecular formula (molecular mass): C₆H₆N₄O₂S (198.20 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 8.09–7.96 (m, 1H), 7.32–7.27 (m, 1H), 7.19–7.09 (m, 1H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 136.6*, 132.5, 117.5. LR-ESI-MS *m/z*: [M + H]⁺ calcd for C₆H₇N₄O₂S 199.03; found, 199.20.

* Note that phase inversion of the C-2 signal in the APT spectrum of imidazole derivatives has been described in the literature as a “regular feature” of these compounds (for details see¹⁸). HSQC data further confirmed the corresponding ¹J_{CH}-coupling at C-2 (see the Supporting Information).

3-(Imidazole-1-sulfonyl)-1-methyl-3H-imidazole-1-ium Trifluoromethanesulfonate (MSDI, 9).¹⁴

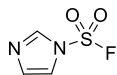


A solution of MeOTf (54.3 mL, 480 mmol, 0.95 equiv) in CH₂Cl₂ (80 mL) was added dropwise over the course of 30 min to an ice-cooled solution of SDI (100.0 g, 505 mmol, 1.0 equiv) in CH₂Cl₂ (1.5 L). The reaction mixture was stirred for 2.5 h in an ice bath, during which a colorless precipitate formed. The precipitate was allowed to settle, the supernatant solvent was decanted, and the precipitate was washed with

CH_2Cl_2 (3×300 mL). The residual solvent was removed under reduced pressure to afford the title compound **9** (169.5 g, 467 mmol, 97%) as a colorless solid. Molecular formula (molecular mass): $\text{C}_8\text{H}_9\text{F}_3\text{N}_4\text{O}_5\text{S}_2$ (362.30 g/mol). ^1H NMR (400 MHz, CD_3CN): δ 9.37 (s, 1H), 8.27 (s, 1H), 7.93 (s, 1H), 7.68 (s, 1H), 7.55 (s, 1H), 7.23 (s, 1H), 3.90 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CD_3CN): δ 139.7, 138.9, 133.6, 127.3, 121.5, 119.7, 38.2. ^{19}F NMR (376 MHz, CD_3CN): δ -79.33.

* Note that phase inversion of the C-2 signal in the APT spectrum of imidazole derivatives has been described in the literature as a “regular feature” of these compounds (for details see¹⁸).

1H-Imidazole-1-sulfonyl Fluoride (**10**).¹³

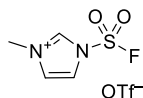


4.5 M KHF_2 (100 mL, 341 mmol, 0.75 equiv) was added slowly to an ice-cooled solution of MSDI (164.6 g, 454 mmol, 1.0 equiv) in H_2O (1 L, HPLC grade), and the reaction mixture was stirred for 10 min. The resulting emulsion was extracted with Et_2O (5×200 mL), the combined organic phases were dried, and the solvent was removed under reduced pressure (due to the volatility of the title compound, the pressure was held above 400 mbar at 40 °C). The colorless liquid raw material thus obtained was purified by distillation (80 °C, 20 mbar, collecting flask cooled in an ice bath) to afford title compound **10** (60.1 g, 400 mmol, 88%) as a colorless liquid which crystallized on storage in the fridge. The compound should be stored at ≤ -18 °C to avoid formation of SDI over time. Molecular formula (molecular mass): $\text{C}_3\text{H}_3\text{FN}_2\text{O}_2\text{S}$ (150.13 g/mol). ^1H NMR (400 MHz, CDCl_3): δ 8.05 (s, 1H), 7.42 (pt, $J = 1.7$ Hz), 7.24 (dd, $J = 1.7, 0.6$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 137.2, 132.4, 118.4. ^{19}F NMR (376 MHz, CDCl_3): δ 59.59. HR-EI-MS m/z : $[\text{M}]^{+}$ calcd for $\text{C}_3\text{H}_3\text{FN}_2\text{O}_2\text{S}$ 149.9894; found, 149.9893.

* Safety Precaution: it is strongly recommended to ensure the availability of 2.5% calcium gluconate gel as a safety measure when handling KHF_2 .

** Note that phase inversion of the C-2 signal in the APT spectrum of imidazole derivatives has been described in the literature as a “regular feature” of these compounds (for details see¹⁸).

1-(Fluorosulfonyl)-3-methyl-1H-imidazole Trifluoromethanesulfonate (Desmethyl SuFEx-IT, **11**).¹³



MeOTf (46.5 mL, 411 mmol, 1.1 equiv) was added dropwise over the course of 15 min to an ice-cooled solution of **10** (56.1 g, 374 mmol, 1.0 equiv) in anhydrous Et_2O (750 mL), and the reaction mixture was stirred for 90 min. The resulting precipitate was allowed to settle, the supernatant solvent was decanted, and the precipitate was washed with Et_2O (3×300 mL). The residual solvent was removed under reduced pressure and the residue dried under high vacuum overnight to afford title compound **11** (116.2 g, 370 mmol, 99%) as a colorless solid. Molecular formula (molecular mass): $\text{C}_5\text{H}_6\text{F}_4\text{N}_2\text{O}_5\text{S}_2$ (314.23 g/mol). ^1H NMR (400 MHz, CD_3CN): δ 9.50 (s, 1H), 8.02 (pt, $J = 2.0$ Hz, 1H), 7.72 (pt, $J = 2.0$ Hz, 1H), 4.01 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CD_3CN): δ 141.2, 127.7, 122.8, 122.0 (q, $J = 320.1$ Hz), 38.6. ^{19}F NMR (376 MHz, CD_3CN): δ 59.89, -79.38. LR-ESI-MS m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_5\text{H}_6\text{F}_4\text{N}_2\text{O}_5\text{S}_2$ 314.97; found, 315.06. Elemental analysis: Calcd for $\text{C}_5\text{H}_6\text{F}_4\text{N}_2\text{O}_5\text{S}_2$: C, 19.11%; H, 1.92%; N, 8.92%; S, 20.41%. Found: C, 19.06 $\pm$ 0.02%; H, 1.95 $\pm$ 0.03%; N, 8.47 $\pm$ 0.06%; S, 20.52 $\pm$ 0.08% ($n = 2$).

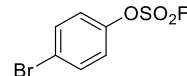
* Note that phase inversion of the C-2 signal in the APT spectrum of imidazole derivatives has been described in the literature as a “regular feature” of these compounds (for details see¹⁸).

General Procedure for Preparation of Fluorosulfates (GP1). **11** (1.3 equiv) was added to a solution of the phenol substrate (1.0 equiv) and Et_3N (1.6 equiv) in MeCN (2–5 mL), and the mixture was stirred until TLC showed full conversion (30–90 min). The products were

purified by dry load column chromatography or filtration over a silica plug with an appropriate solvent unless stated otherwise.

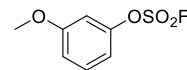
General Procedure for Preparation of Sulfamoyl Fluorides (GP2). **11** (1.1 equiv) was added to a solution of the amine substrate (1.0 equiv) in MeCN (2–5 mL), and the mixture was stirred until TLC or HPLC showed full conversion (15–90 min). The products were purified by dry load column chromatography or filtration over a silica plug with an appropriate solvent unless stated otherwise.

4-Bromophenyl Sulfurofluoride (**12a**).¹⁹



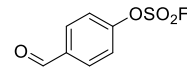
12a (119 mg, 467 μmol , 81%, colorless liquid) was prepared according to GP1 from 4-bromophenol (100 mg, 578 μmol) and purified by column chromatography ($R_f = 0.38$, n -hexane). Molecular formula (molecular mass): $\text{C}_6\text{H}_4\text{BrFO}_3\text{S}$ (255.06 g/mol). ^1H NMR (400 MHz, CDCl_3): δ 7.64–7.58 (m, 2H), 7.28–7.20 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 149.1, 133.7, 122.8, 122.5. ^{19}F NMR (376 MHz, CDCl_3): δ 37.80. HR-EI-MS m/z : $[\text{M}]^{+}$ calcd for $\text{C}_6\text{H}_4\text{BrFO}_3\text{S}$ 253.9043; found, 253.9039. HR-EI-MS m/z : $[\text{M}]^{+}$ calcd for $\text{C}_6\text{H}_4\text{BrFO}_3\text{S}$ 255.9023; found, 255.9018.

3-Methoxyphenyl Sulfurofluoride (**12b**).¹²



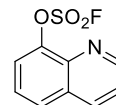
12b (170 mg, 824 μmol , 90%, colorless liquid) was prepared according to GP1 from 3-methoxyphenol (113 mg, 910 μmol) and purified by filtration over a silica plug ($R_f = 0.47$, $\text{EtOAc}:\text{n-hexane} = 1:8$). Molecular formula (molecular mass): $\text{C}_7\text{H}_7\text{FO}_4\text{S}$ (206.19 g/mol). ^1H NMR (400 MHz, CDCl_3): δ 7.37 (t, $J = 8.3$ Hz, 1H), 6.94 (td, $J = 7.3, 6.3, 1.7$ Hz, 2H), 6.87 (d, $J = 2.2$ Hz, 1H), 3.84 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 161.1, 150.9, 130.8, 114.5, 112.8, 107.1, 55.8. ^{19}F NMR (376 MHz, CDCl_3): δ 37.70. HR-EI-MS m/z : $[\text{M}]^{+}$ calcd for $\text{C}_7\text{H}_7\text{FO}_4\text{S}$ 206.0044; found, 206.0038.

4-Formylphenyl Sulfurofluoride (**12c**).²⁰



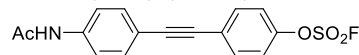
12c (149 mg, 730 μmol , 89%, colorless liquid) was prepared according to GP1 from 4-hydroxybenzaldehyde (100 mg, 819 μmol) and purified by column chromatography ($R_f = 0.21$, $\text{EtOAc}:\text{n-hexane} = 1:6$). Molecular formula (molecular mass): $\text{C}_7\text{H}_5\text{FO}_4\text{S}$ (204.17 g/mol). ^1H NMR (400 MHz, CDCl_3): δ 10.06 (s, 1H), 8.06–8.00 (m, 2H), 7.57–7.48 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 190.2, 153.7, 136.3, 132.0, 121.9. ^{19}F NMR (376 MHz, CDCl_3): δ 39.11. HR-EI-MS m/z : $[\text{M}]^{+}$ calcd for $\text{C}_7\text{H}_5\text{FO}_4\text{S}$ 203.9887; found, 203.9885.

Quinolin-8-yl Sulfurofluoride (**12d**).¹²



12d (142 mg, 627 μmol , 91%, pale yellow solid) was prepared according to GP1 from 8-hydroxyquinoline (100 mg, 689 μmol) and purified by column chromatography ($R_f = 0.33$, $\text{EtOAc}:\text{n-hexane} = 1:6$). Molecular formula (molecular mass): $\text{C}_9\text{H}_6\text{FNO}_3\text{S}$ (227.21 g/mol). ^1H NMR (400 MHz, CDCl_3): δ 9.06 (dd, $J = 4.2, 1.6$ Hz, 1H), 8.24 (dd, $J = 8.4, 1.6$ Hz, 1H), 7.90 (dd, $J = 8.4, 1.1$ Hz, 1H), 7.75 (dt, $J = 7.7, 1.1$ Hz, 1H), 7.66–7.47 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 152.0, 146.0, 140.5, 136.1, 130.1, 128.8, 126.0, 122.8, 121.5. ^{19}F NMR (376 MHz, CDCl_3): δ 40.66. HR-EI-MS m/z : $[\text{M}]^{+}$ calcd for $\text{C}_9\text{H}_6\text{FNO}_3\text{S}$ 227.0047; found, 227.0041.

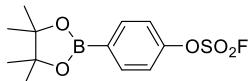
4-[(4-Acetamidophenyl)ethynyl]phenyl Sulfurofluoride (**12e**).



12e (65.0 mg, 195 μmol , 78%, yellow solid) was prepared according to GP1 from N -{4-[(4-hydroxyphenyl)ethynyl]phenyl}acetamide (62.8 mg, 250 μmol) and purified by column chromatography ($R_f = 0.19$, $\text{EtOAc}:\text{n-hexane} = 1:1$). Molecular formula (molecular mass):

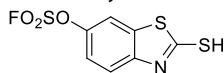
$C_{16}H_{12}FNO_4S$ (333.33 g/mol). 1H NMR (400 MHz, THF- d_8): δ 9.22 (s, 1H), 7.72–7.57 (m, 4H), 7.52–7.45 (m, 2H), 7.45–7.38 (m, 2H), 2.04 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, THF- d_8): δ 168.6, 150.5, 141.6, 134.3, 133.0, 125.7, 122.2, 119.5, 117.6, 92.3, 87.2, 24.2. ^{19}F NMR (376 MHz, THF- d_8): δ 36.77. HR-ESI-MS m/z : $[M]^{+}$ calcd for $C_{16}H_{12}FNO_4S$ 333.0466; found, 333.0467.

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl Sulfurofluoridate (12f).



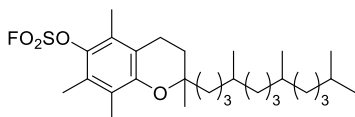
12f (100 mg, 330 μ mol, 73%, pale yellow solid) was prepared according to GP1 from 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (100 mg, 454 μ mol). The reaction mixture was extracted with *n*-pentane (4×10 mL) and the collected phases were filtered over a silica plug (R_f = 0.43, *n*-pentane). Molecular formula (molecular mass): $C_{12}H_{16}BFO_5S$ (302.12 g/mol). 1H NMR (400 MHz, $CDCl_3$): δ 7.96–7.88 (m, 2H), 7.37–7.30 (m, 2H), 1.35 (s, 12H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 152.3, 137.2, 120.2, 84.5, 25.0. C-B was not observed. ^{19}F NMR (376 MHz, $CDCl_3$): δ 38.11. HR-ESI-MS m/z : $[M]^{+}$ calcd for $C_{12}H_{16}BFO_5S$ 302.0790; found, 302.0794; $[M-CH_3]^{+}$ calcd for $C_{11}H_{13}BFO_5S$ 287.0555; found, 287.0556.

2-Mercaptobenzo[d]thiazol-6-yl Sulfurofluoridate (12g).



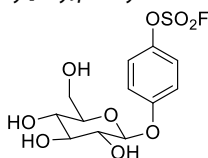
12g (64.9 mg, 245 μ mol, 45%, colorless solid) was prepared according to a modification of GP1 as follows. 2-Mercaptobenzo[d]thiazol-6-ol (100 mg, 546 μ mol) was dissolved (under argon) in a solution of Et_3N (197 μ L, 1.42 mmol, 2.6 equiv) in MeCN (3 mL) before **11** was added. After 1 h, a second portion of **11** and Et_3N (1 equiv of each) was added and the reaction mixture was left to stand for another 30 min before it was diluted with CH_2Cl_2 (20 mL) and washed with 0.1 M HCl (2×10 mL). The organic phase was dried and **12g** was isolated by dry load filtration over a silica plug (R_f = 0.34, EtOAc:*n*-hexane = 1:3). Molecular formula (molecular mass): $C_7H_4FNO_3S_3$ (265.29 g/mol). 1H NMR [400 MHz, (CD_3) $_2$ SO]: δ 14.01 (s, 1H), 8.07 (s, 1H), 7.62 (dd, J = 8.9, 2.1 Hz, 1H), 7.41 (d, J = 8.9 Hz, 1H). $^{13}C\{^1H\}$ NMR [101 MHz, (CD_3) $_2$ SO]: δ 191.2, 145.9, 141.5, 131.0, 120.4, 115.1, 113.5. ^{19}F NMR [376 MHz, (CD_3) $_2$ SO]: δ 38.34. HR-ESI-MS m/z : $[M]^{+}$ calcd for $C_7H_4FNO_3S_3$ 264.9332; found, 264.9332.

$\pm$ - α -Tocopherol-Derived Sulfurofluoridate (12h).¹²



12h (256 mg, 499 μ mol, 98%, colorless oil) was prepared according to GP1 from $\pm$ - α -tocopherol (220 mg, 511 μ mol) and purified by filtration over a silica plug (R_f = 0.79, EtOAc:*n*-hexane = 1:9). Molecular formula (molecular mass): $C_{29}H_{49}FO_4S$ (512.77 g/mol). Mixture of diastereomers. Inequivalent signals of diastereomers in the $^{13}C\{^1H\}$ NMR spectrum are separated by forward slash symbols. 1H NMR (400 MHz, $CDCl_3$): δ 2.60 (t, J = 6.8 Hz, 2H), 2.23 (s, 3H), 2.20 (s, 3H), 2.10 (s, 3H), 1.89–1.72 (m, 2H), 1.61–1.06 (m, 25H), 0.94–0.77 (m, 12H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 151.2, 142.0, 127.6, 126.2, 124.5, 118.6, 75.9, 40.1/40.0, 39.5, 37.7/37.62, 37.60/37.54, 37.49/37.4, 33.0/32.9, 32.83/32.81, 31.0, 30.9, 28.1, 25.0, 24.6, 24.0, 22.9/22.8, 21.1, 20.8, 19.9/19.83, 19.82/19.7, 13.7, 12.9, 12.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ 41.37. HR-ESI-MS m/z : $[M]^{+}$ calcd for $C_{29}H_{49}FO_4S$ 512.3330; found, 512.3330.

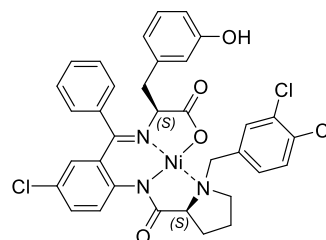
4-((2S,3R,4S,5S,6R)-3,4,5-Trihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yl)oxyphenyl Sulfurofluoridate (12i).



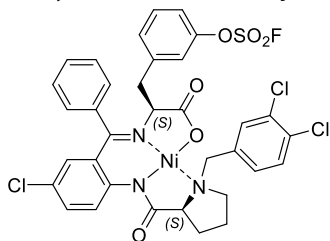
12i (39.5 mg, 111 μ mol, 30%, colorless solid) was prepared according to a modification of GP1 from arbutin (100 mg, 367 μ mol) as follows.

11 was added to a solution of the starting material and Et_3N in DMF (3 mL) and the reaction mixture was left to stand for 1 h before another portion of Et_3N and **11** (1 equiv of each) was added. The crude material obtained was purified by RP chromatography. Conditions: column: FlashPure Select C_{18} 12 g (Büchi Labortechnik GmbH, Essen, Germany); eluent: 0–5 min: 10% MeCN, 5–20 min: 10 $\rightarrow$ 20% MeCN, 20–25 min: 20 $\rightarrow$ 100% MeCN; flow rate: 20 mL/min; detection: UV, λ = 210 and 220 nm. Molecular formula (molecular mass): $C_{12}H_{15}FO_9S$ (354.30 g/mol). 1H NMR (400 MHz, CD_3OD): δ 7.37 (d, J = 9.1 Hz, 2H), 7.28–7.18 (m, 2H), 5.04–4.92 (m, 1H), 3.90 (dd, J = 12.1, 2.0 Hz, 1H), 3.70 (dd, J = 12.1, 5.7 Hz, 1H), 3.55–3.33 (m, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, CD_3OD): δ 158.8, 146.2, 123.1, 119.3, 102.3, 78.3, 77.9, 74.8, 71.3, 62.4. ^{19}F NMR (376 MHz, CD_3OD): δ 34.55. HR-ESI-MS m/z : $[M + Na]^{+}$ calcd for $C_{12}H_{15}FO_9SNa$ 377.03130; found, 377.03180.

(S,S)-Ni-Cl₃BPB-m-Tyr Sulfurofluoridate (12j). (S,S)-Ni-Cl₃BPB-m-Tyr.

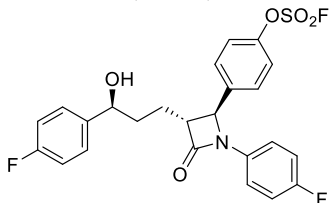


A solution of (S)-N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)pyrrolidine-2-carboxamide²¹ (8.1 g, 16.6 mmol), racemic *m*-Tyr (5.89 g, 32.5 mmol), $Ni(OAc)_2 \cdot 4H_2O$ (8.09 g, 32.5 mmol), and K_2CO_3 (20.4 g, 147.75 mmol) in anhydrous MeOH (400 mL) was stirred at 60 $^{\circ}C$ for 24 h and at ambient temperature for 72 h. The reaction mixture was poured into an ice-cold solution of AcOH (50 mL) in H_2O (3 L) and the resulting suspension was allowed to stand at ambient temperature for 24 h, after which a fine red precipitate had formed. The precipitate was collected by filtration, washed with H_2O (3×100 mL), air-dried, and dissolved in EtOAc (200 mL). The resulting solution was washed with H_2O (3×50 mL) and brine (2×50 mL), dried, and concentrated under reduced pressure. The residue was triturated with Et_2O to give a red precipitate, which was recrystallized from EtOAc/hexane to afford a first crop of the title compound as a red solid. The combined mother liquors (from trituration with Et_2O and recrystallization) were concentrated under reduced pressure and the residue was purified by column chromatography (R_f = 0.25; $CHCl_3$:acetone = 5:1; broad spot) followed by recrystallization from EtOAc/hexane to afford a second crop of the title compound (total: 10.35 g, 88%) as a red solid. Molecular formula (molecular mass): $C_{34}H_{28}Cl_3N_3NiO_4$ (707.66 g/mol). 1H NMR (400 MHz, $CDCl_3$): δ 8.90 (s, 1H), 8.30 (br s, 1H), 8.09 (d, J = 8.9 Hz, 1H), 7.81–7.41 (m, 4H), 7.40–7.20 (m, 3H), 7.10 (d, J = 8.5 Hz, 1H), 6.91 (dd, J = 22.3, 6.9 Hz, 2H), 6.80–6.70 (m, 1H), 6.69–6.53 (m, 2H), 4.29 (s, 1H), 4.13 (d, J = 12.4 Hz, 1H), 3.33–3.16 (m, 1H), 3.09 (d, J = 11.6 Hz, 2H), 2.96 (d, J = 12.4 Hz, 1H), 2.67 (d, J = 8.8 Hz, 1H), 2.45–2.19 (m, 3H), 2.17–1.83 (m, 2H). $^{13}C\{^1H\}$ -NMR (101 MHz, $CDCl_3$): δ 180.2, 179.1, 171.0, 157.7, 140.9, 136.8, 135.0, 133.8, 133.44, 133.36, 133.3, 132.6, 132.5, 131.1, 130.5, 130.2, 129.9, 129.6, 129.4, 127.8, 127.4, 127.2, 126.0, 124.0, 122.2, 117.7, 115.3, 71.7, 71.6, 63.5, 58.8, 39.2, 30.9, 23.1. *ortho*- and *meta*-Carbons of the phenyl substituent are not equivalent owing to hindered rotation. HR-ESI-MS m/z : $[M + K]^{+}$ calcd for $C_{34}H_{28}Cl_3N_3NiO_4K$ 744.01387; found, 744.01305; $[M + Na]^{+}$ calcd for $C_{34}H_{28}Cl_3N_3NiO_4Na$ 728.04024; found, 728.03911; $[M + H]^{+}$ calcd for $C_{34}H_{29}Cl_3N_3NiO_4$ 706.05836; found, 706.05716. Correct isotopic pattern.

(S,S)-Ni-Cl₃BPB-*m*-Tyr Sulfurofluoridate (**12j**).

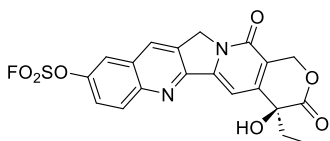
12j (90.8 mg, 115 μ mol, 82%, red solid) was prepared according to a modification of GP1 from *(S,S)*-Ni-Cl₃BPB-*m*-Tyr (100 mg, 141 μ mol) as follows. **11** was added to a solution of the starting material and Et₃N in MeCN (10 mL) and the reaction mixture was left to stand for 1 h before a second portion of **11** and Et₃N (1 equiv of each) was added. TLC showed incomplete conversion of the starting material after 16 h. The crude material was purified by dry load column chromatography (R_f = 0.18, CH₂Cl₂:MeOH = 40:1). Molecular formula (molecular mass): C₃₄H₂₇Cl₃FN₃NiO₆S (789.71 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 8.90 (d, J = 2.0 Hz, 1H), 8.17 (d, J = 9.3 Hz, 1H), 7.70–7.56 (m, 3H), 7.53–7.43 (m, 2H), 7.40–7.30 (m, 3H), 7.16–7.10 (m, 2H), 7.00–6.95 (m, 1H), 6.82 (d, J = 7.7 Hz, 1H), 6.62 (d, J = 2.6 Hz, 1H), 4.28–4.17 (m, 2H), 3.25 (dd, J = 10.6, 6.5 Hz, 2H), 3.16–3.05 (m, 2H), 2.97 (dd, J = 13.8, 6.4 Hz, 1H), 2.70–2.55 (m, 1H), 2.53–2.31 (m, 2H), 2.03–1.88 (m, 2H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 180.1, 177.6, 171.4, 150.5, 141.2, 139.0, 135.0, 133.8, 133.6, 133.5, 133.1, 132.9, 132.5, 131.2, 130.7, 130.61, 130.56, 129.90, 129.86, 129.5, 127.5, 127.4, 127.1, 126.0, 124.1, 122.8, 120.1, 71.4, 71.2, 63.3, 58.6, 40.0, 31.0, 23.4. *Ortho*- and *meta*-carbons of the phenyl substituent are not equivalent owing to hindered rotation. ¹⁹F NMR (376 MHz, CDCl₃): δ 38.15. HR-ESI-MS m/z : [M + Na]⁺ calcd for C₃₄H₂₇Cl₃FN₃NiO₆Na 809.99158; found, 809.99107. Correct isotopic pattern.

4-[(2*S*,3*R*)-1-(4-Fluorophenyl)-3-[(*S*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxazetidin-2-yl]phenyl Sulfurofluoridate (**12k**).¹²



12k (90 mg, 183 μ mol, 75%, colorless solid) was prepared according to GP 1 from ezetimibe (100 mg, 244 μ mol) and purified by column chromatography (R_f = 0.32, EtOAc:*n*-hexane = 1:2). Molecular formula (molecular mass): C₂₄H₂₀F₃NO₅S (491.48 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 7.49–7.40 (m, 2H), 7.36 (d, J = 8.5 Hz, 2H), 7.33–7.26 (m, 2H), 7.19 (ddt, J = 8.0, 5.6, 2.8 Hz, 2H), 7.08–6.90 (m, 4H), 4.72 (t, J = 5.8 Hz, 1H), 4.68 (d, J = 2.4 Hz, 1H), 3.07 (td, J = 7.5, 2.4 Hz, 1H), 2.25 (s, 1H), 2.12–1.84 (m, 4H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 167.0, 162.4 (d, J = 245.8 Hz), 159.3 (d, J = 244.2 Hz), 150.0, 140.0 (d, J = 3.0 Hz), 138.7, 133.6 (d, J = 2.7 Hz), 128.0, 127.5 (d, J = 8.2 Hz), 122.1, 118.4 (d, J = 7.9 Hz), 116.2 (d, J = 22.7 Hz), 115.6 (d, J = 21.4 Hz), 73.3, 60.8, 60.5, 36.7, 25.3. ¹⁹F NMR (376 MHz, CDCl₃): δ 38.03, –114.62, –117.30. HR-ESI-MS m/z : [M + Na]⁺ calcd for C₂₄H₂₀F₃NO₅Na 514.09065; found, 514.09065.

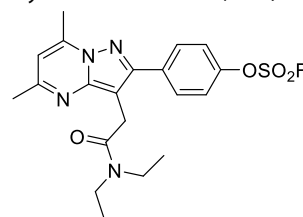
(*S*)-4-Ethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-9-yl Sulfurofluoridate (**12l**).⁸



12l (68.9 mg, 154 μ mol, 37%, green-yellow solid) was prepared according to GP1 from 10-hydroxycamptothecin (150 mg, 412 μ mol) using increased amounts of **11** (5.2 equiv) and Et₃N (6.4 equiv) and purified by column chromatography (R_f = 0.14, EtOAc:*n*-hexane = 2:1).

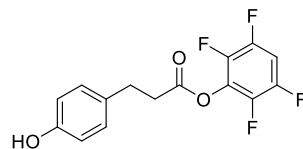
Molecular formula (molecular mass): C₂₀H₁₅FN₂O₇S (446.41 g/mol). ¹H NMR [400 MHz, (CD₃)₂SO]: δ 8.81 (s, 1H), 8.50 (s, 1H), 8.42–8.30 (m, 1H), 8.13–7.97 (m, 1H), 7.37 (d, J = 2.9 Hz, 1H), 6.56 (s, 1H), 5.44 (s, 2H), 5.32 (s, 2H), 1.87 (sep, J = 7.1 Hz, 2H), 0.88 (t, J = 7.3 Hz, 3H). ¹³C{¹H} NMR [101 MHz, (CD₃)₂SO]: δ 172.4, 156.7, 154.3, 149.9, 147.5, 146.9, 144.9, 132.2, 132.0, 131.4, 128.2, 123.7, 120.1, 119.8, 97.3, 72.3, 65.2, 50.3, 30.3, 7.8. ¹⁹F NMR [376 MHz, (CD₃)₂SO]: δ 39.33. HR-ESI-MS m/z : [M + H]⁺ calcd for C₂₀H₁₆FN₂O₇S 447.06568; found, 447.06623; [M + Na]⁺ calcd for C₂₀H₁₅FN₂O₇Na 469.04762; found, 469.04838.

4-[3-[2-(Diethylamino)-2-oxoethyl]-5,7-dimethylpyrazolo[1,5-*a*]pyrimidin-2-yl]phenyl Sulfurofluoridate (**12m**).¹²



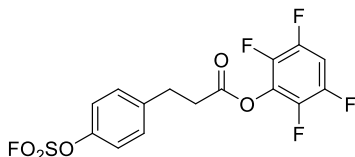
12m (73.9 mg, 170 μ mol, 60%, colorless solid) was prepared according to GP1 from *N,N*-diethyl-2-[2-(4-hydroxyphenyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidin-3-yl]-acetamide (des-Me-DPA-713) (100 mg, 284 μ mol; prepared as described in²²) and purified by column chromatography (R_f = 0.26, CHCl₃:acetone = 5:1). The reaction was conducted in a mixture of DMF/MeCN (1:1, 6 mL). Molecular formula (molecular mass): C₂₀H₂₃FN₄O₄S (434.49 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 8.04 (d, J = 8.9 Hz, 2H), 7.42 (d, J = 8.1 Hz, 2H), 6.56 (s, 1H), 3.93 (s, 2H), 3.56 (q, J = 7.1 Hz, 2H), 3.40 (q, J = 7.1 Hz, 2H), 2.74 (s, 3H), 2.55 (s, 3H), 1.25 (t, J = 7.1 Hz, 4H), 1.10 (t, J = 7.1 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 170.0, 158.1, 153.4, 150.1, 147.8, 145.0, 134.8, 130.9, 121.1, 109.0, 101.7, 42.6, 40.9, 27.9, 24.8, 17.0, 14.6, 13.2. ¹⁹F NMR (376 MHz, CDCl₃): δ 37.66. HR-ESI-MS m/z : [M + Na]⁺ calcd for C₂₀H₂₃FN₄O₄Na 457.13163; found, 457.13162; [M + H]⁺ calcd for C₂₀H₂₄FN₄O₄S 435.14968; found, 435.14983.

2,3,5,6-Tetrafluorophenyl 3-[4-[(fluorosulfonyl)oxy]phenyl]-propanoate (**12n**). 2,3,5,6-Tetrafluorophenyl 3-(4-Hydroxyphenyl)-propanoate.²³



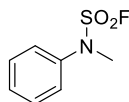
N-[3-(Dimethylamino)propyl]-*N'*-ethylcarbodiimide hydrochloride (1.2 g, 6.28 mmol, 1.04 equiv) was added to an ice-cold solution of (4-hydroxyphenyl)propionic acid (1.00 g, 6.02 mmol, 1.0 equiv) and 2,3,5,6-tetrafluorophenol (1.1 g, 6.02 mmol, 1.0 equiv) in CH₂Cl₂ (20 mL) and the reaction mixture was stirred for 15 min. The cooling bath was removed and the mixture was stirred for another 16 h. The mixture was then concentrated under reduced pressure and the residue was taken up into Et₂O and H₂O (50 mL of each). The organic phase was separated, washed with H₂O (3 $\times$ 20 mL) and brine (2 $\times$ 20 mL), dried, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (R_f = 0.15, EtOAc:*n*-hexane = 1:2.3) to afford the title compound (1.44 g, 4.83 mmol, 76%) as a colorless liquid. Molecular formula (molecular mass): C₁₅H₁₀F₄O₃ (314.24 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 7.16–7.08 (m, 2H), 7.04–6.93 (m, 1H), 6.82–6.73 (m, 2H), 4.87 (d, J = 27.4 Hz, 1H), 3.09–2.86 (m, 4H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 169.0, 154.4, 146.1 (ddd, J = 240.5, 7.1, 4.0 Hz), 142.3–139.2 (m), 131.8, 129.6, 115.6, 103.3 (t, J = 22.8 Hz), 35.5, 30.0. C_{Ar}-O was not observed. ¹⁹F NMR (376 MHz, CDCl₃): δ –139.02 (dd, J = 21.8, 9.8 Hz), –152.84 (dd, J = 21.8, 9.8 Hz). LR-ESI-MS m/z : [M + NH₄]⁺ calcd for C₁₅H₁₄NF₄O₃ 332.09; found, 332.22.

2,3,5,6-Tetrafluorophenyl 3-[4-[(Fluorosulfonyl)oxy]phenyl]propanoate (**12n**).



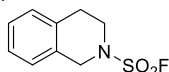
12n was prepared according to a modification of GP1 as follows. **11** (2.02 g, 6.40 mmol, 1.4 equiv) was added to a solution of 2,3,5,6-tetrafluorophenyl (4-hydroxyphenyl)propanoate (1.44 g, 4.58 mmol) and Et₃N (1.09 mL, 0.79 g, 7.82 mmol, 1.7 equiv) in MeCN (20 mL) and the reaction mixture was vigorously stirred for 16 h. The mixture was then concentrated under reduced pressure, the residue was taken up into Et₂O and H₂O (50 mL of each), and the insoluble tar and aqueous fraction were discarded. The organic phase was washed with H₂O (3 × 20 mL) and brine (2 × 20 mL), dried, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (*R_f* = 0.52, EtOAc:*n*-hexane = 1:15) to afford, after low-temperature (−20 °C) recrystallization from pentane, **12n** (0.99 g, 2.50 mmol, 55%) as a colorless solid. Molecular formula (molecular mass): C₁₅H₉F₅O₅S (396.28 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 7.40–7.34 (m, 2H), 7.34–7.28 (m, 2H), 7.00 (tt, *J* = 9.9, 7.1 Hz, 1H), 3.14 (t, *J* = 7.4 Hz, 2H), 3.05–2.98 (m, 2H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 168.4, 149.0, 146.2 (ddd, *J* = 250.5, 7.0, 4.0 Hz), 142.1–139.0 (m), 130.4, 121.3, 103.5 (t, *J* = 22.8 Hz), 34.8, 30.1. C_{ar}-O was not observed. ¹⁹F NMR (376 MHz, CDCl₃): δ 37.42, −138.79 (dd, *J* = 21.7, 9.8 Hz), −152.93 (dd, *J* = 21.7, 9.8 Hz). Elemental analysis: Calcd for C₁₅H₉F₅O₅S: C, 45.46%; H, 2.29%; S, 8.09%. Found: C, 45.85 ± 0.02%; H, 2.31 ± 0.04%; S, 8.16 ± 0.00% (*n* = 2).

Methyl(phenyl)sulfamoyl Fluoride (**13a**).⁸



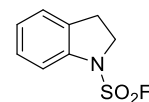
13a (247 mg, 1.31 mmol, 70%, yellow oil) was prepared according to GP2 from *N*-methylaniline (200 mg, 1.87 mmol). After HPLC indicated full conversion, the reaction solvent was removed and the residue was taken up into CH₂Cl₂. The organic phase was washed with H₂O, dried, and the solvent was removed. The crude material thus obtained was purified by RP chromatography. Conditions: column: FlashPure Select C₁₈ 12 g (Büchi Labortechnik GmbH, Essen, Germany); eluent: 0–15 min: 40% MeCN, 15–17 min: 40 → 80% MeCN, 17–22 min: 80 → 100% MeCN; flow rate: 20 mL/min; detection: UV, λ = 210, 220, 254, 280 nm. Molecular formula (molecular mass): C₇H₈FNO₂S (189.20 g/mol). ¹H NMR (400 MHz, CDCl₃): δ = 7.50–7.33 (m, 5H), 3.44 (d, *J* = 2.2 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 140.0, 130.0, 129.1, 126.7, 40.8. ¹⁹F NMR (376 MHz, CDCl₃): δ 42.33. HR-EI-MS *m/z*: [M]⁺⁺ calcd for C₇H₈FNO₂S 189.0254; found, 189.0254.

1,2,3,4-Tetrahydroisoquinoline-2-sulfonyl Fluoride (**13b**).²⁴



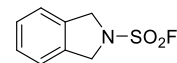
13b (200 mg, 929 μmol, 83%, pale rose solid) was prepared according to GP2 from 1,2,3,4-tetrahydroisoquinoline (150 mg, 1.23 mmol). After TLC indicated full conversion, the reaction solvent was removed, the residue was dissolved in Et₂O and the organic phase was washed with H₂O. After removal of the solvent, no further purification was required. Molecular formula (molecular mass): C₉H₁₀FNO₂S (215.24 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 7.31–7.24 (m, 2H), 7.24–7.18 (m, 1H), 7.17–7.10 (m, 1H), 4.67 (s, 2H), 3.78 (td, *J* = 6.0, 1.9 Hz, 2H), 3.05 (t, *J* = 6.0 Hz, 2H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 132.6, 130.4, 129.2, 127.6, 127.0, 126.3, 48.3, 45.1, 28.1. ¹⁹F NMR (376 MHz, CDCl₃): δ 40.96. HR-EI-MS *m/z*: [M]⁺⁺ calcd for C₉H₁₀FNO₂S 215.0411; found, 215.0407.

Indoline-1-sulfonyl Fluoride (**13c**).²⁴



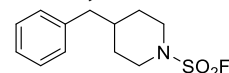
13c (143 mg, 711 μmol, 85%, pale rose solid) was prepared according to GP2 from indoline (100 mg, 839 μmol) and purified by filtration over a silica plug (*R_f* = 0.45, EtOAc:*n*-hexane = 1:6). Molecular formula (molecular mass): C₈H₈FNO₂S (201.22 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 7.54–7.37 (m, 1H), 7.30–7.19 (m, 2H), 7.17–7.05 (m, 1H), 4.14 (td, *J* = 8.4, 2.5 Hz, 2H), 3.21 (t, *J* = 8.4 Hz, 2H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 139.9, 131.0, 128.3, 125.6, 125.3, 114.7, 51.7, 28.1. ¹⁹F NMR (376 MHz, CDCl₃): δ 39.12. HR-EI-MS *m/z*: [M]⁺⁺ calcd for C₈H₈FNO₂S 201.0254; found, 201.0252.

Isoindoline-2-sulfonyl Fluoride (**13d**).



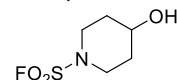
11 (488 mg, 1.55 mmol, 1.6 equiv) was added to a suspension of isoindoline × HCl (150 mg, 0.96 mmol) in CH₂Cl₂ (4 mL) followed by dropwise addition of Et₃N (134 μL, 0.96 mmol, 1.0 equiv). After TLC indicated full conversion, the reaction mixture was filtered over a plug of silica. The crude product was purified by column chromatography (*R_f* = 0.43, EtOAc:*n*-hexane = 1:10) to afford the title compound **13d** (191 mg, 0.95 mmol, 98%) as a colorless solid. Molecular formula (molecular mass): C₈H₈FNO₂S (201.22 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 7.42–7.32 (m, 2H), 7.31–7.26 (m, 2H), 4.86 (d, *J* = 2.4 Hz, 4H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 134.8, 128.5, 122.9, 55.0. ¹⁹F NMR (376 MHz, CDCl₃): δ 37.93. HR-EI-MS *m/z*: [M]⁺⁺ calcd for C₈H₈FNO₂S 201.0254; found, 201.0251.

4-Benzylpiperidine-1-sulfonyl Fluoride (**13e**).⁸



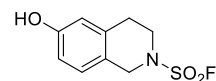
13e (285 mg, 1.11 mmol, 97%, colorless solid) was prepared according to GP2 from 4-benzylpiperidine (200 mg, 1.14 mmol). After TLC indicated full conversion, the reaction mixture was diluted with Et₂O (10 mL) and washed with H₂O (10 mL) and brine (10 mL). The organic phase was dried and concentrated under reduced pressure and the product was purified by filtration over a silica plug (*R_f* = 0.42, EtOAc:*n*-hexane = 1:6). Molecular formula (molecular mass): C₁₂H₁₆FNO₂S (257.32 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 7.37–7.27 (m, 2H), 7.25–7.19 (m, 1H), 7.17–7.09 (m, 2H), 3.91 (dt, *J* = 12.7, 2.3 Hz, 2H), 2.94 (tt, *J* = 12.7, 3.0 Hz, 2H), 2.59 (d, *J* = 7.0 Hz, 2H), 1.84–1.61 (m, 3H), 1.39 (qd, *J* = 12.8, 4.2 Hz, 2H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 139.4, 129.2, 128.6, 126.4, 47.6, 42.7, 37.2, 30.8. ¹⁹F NMR (376 MHz, CDCl₃): δ 40.17. HR-EI-MS *m/z*: [M]⁺⁺ calcd for C₁₂H₁₆FNO₂S 257.0880; found, 257.0878.

4-Hydroxypiperidyl-1-sulfonyl Fluoride (**13f**).



13f (160 mg, 876 μmol, 89%, colorless solid) was prepared according to GP2 from 4-hydroxypiperidine (100 mg, 989 μmol) and purified by filtration over a silica plug (*R_f* = 0.46, EtOAc:*n*-hexane = 2:1). Molecular formula (molecular mass): C₅H₁₀FNO₃S (183.20 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 4.19–3.88 (m, 1H), 3.87–3.61 (m, 2H), 3.55–3.25 (m, 2H), 2.12–1.90 (m, 2H), 1.78–1.65 (m, 2H), 1.76 (br s, 1H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 65.0, 44.1, 32.6. ¹⁹F NMR (376 MHz, CDCl₃): δ 41.07. HR-EI-MS *m/z*: [M-H₂O]⁺⁺ calcd for C₅H₉FNO₃S 165.0254; found, 165.0253.

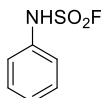
6-Hydroxy-1,2,3,4-tetrahydroisoquinoline-2-sulfonyl Fluoride (**13g**).



13g (205 mg, 887 μmol, 88%, colorless oil) was prepared according to GP2 from 1,2,3,4-tetrahydroisoquinolin-6-ol (150 mg, 1.01 mmol) and

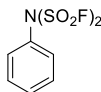
purified by filtration over a silica plug ($R_f = 0.37$, EtOAc:*n*-hexane = 1:2). Molecular formula (molecular mass): $C_9H_{10}FNO_3S$ (231.24 g/mol). 1H NMR (400 MHz, $CDCl_3$): δ 6.97 (d, $J = 8.4$ Hz, 1H), 6.72 (dd, $J = 8.3, 2.6$ Hz, 1H), 6.65 (d, $J = 2.6$ Hz, 1H), 4.97 (s, 1H), 4.56 (s, 2H), 3.71 (td, $J = 6.1, 1.9$ Hz, 2H), 2.95 (t, $J = 6.1$ Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 154.9, 134.2, 127.6, 122.6, 115.4, 114.5, 47.9, 44.9, 28.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ 41.05. HR-ESI-MS m/z : $[M]^+$ calcd for $C_9H_{10}FNO_3S$ 231.0360; found, 231.0361.

Phenylsulfamoyl Fluoride (13h).⁸



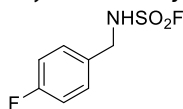
A solution of aniline (147 μ L, 1.61 mmol) in CH_2Cl_2 (1.5 mL) was added to an ice-cooled suspension of **11** (556 mg, 1.77 mmol, 1.1 equiv) in CH_2Cl_2 (4 mL). After TLC indicated full conversion, CH_2Cl_2 (10 mL) was added and the solution was washed with 0.1 M HCl (3×10 mL) and brine (20 mL). The organic phase was dried and the solvent was removed under reduced pressure to afford the title compound **13h** (196 mg, 1.12 mmol, 70%) as a pale red liquid. Molecular formula (molecular mass): $C_6H_6FNO_2S$ (175.18 g/mol). 1H NMR (400 MHz, $CDCl_3$): δ 7.42 (ddd, $J = 8.0, 6.2, 1.8$ Hz, 2H), 7.36–7.24 (m, 3H), 7.16 (br s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 134.0, 129.9, 127.6, 123.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ 50.90. HR-ESI-MS m/z : $[M]^+$ calcd for $C_6H_6FNO_2S$ 175.0098; found, 175.0096.

Phenyliminodisulfonyl Difluoride (13i).⁸



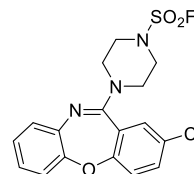
11 (1.26 g, 4.03 mmol, 2.5 equiv) was added to an ice-cooled solution of aniline (147 μ L, 1.61 mmol) in MeCN (4 mL). The mixture was stirred for 10 min before Et_3N (112 μ L, 805 μ mol, 0.5 equiv) was added. After TLC indicated full conversion, silica was added, the solvent was removed, and the residue was filtered over a plug of silica ($R_f = 0.50$, EtOAc:*n*-hexane = 1:10) to afford the title compound **13i** (322 mg, 1.26 mmol, 78%) as a colorless solid. Molecular formula (molecular mass): $C_6H_5F_2NO_4S_2$ (257.23 g/mol). 1H NMR (400 MHz, $CDCl_3$): δ 7.69–7.54 (m, 3H), 7.54–7.47 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 133.2, 132.5, 130.9, 129.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ 56.32. HR-ESI-MS m/z : $[M]^+$ calcd for $C_6H_5F_2NO_4S_2$ 256.9623; found, 256.9621.

(4-Fluorobenzyl)sulfamoyl Fluoride (13j).²⁵



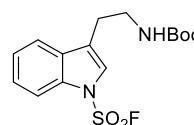
11 (0.68 g, 2.10 mmol, 1.05 equiv) was added to a solution of 4-fluorobenzylamine (0.228 mL, 0.25 g, 2.0 mmol) in MeCN (2 mL). An exothermic reaction was observed. The reaction mixture was stirred for 40 min and taken up into Et_2O/H_2O (30 mL of each). The organic layer was separated, washed with H_2O (3×20 mL) and brine (2×10 mL), dried, and successively concentrated under atmospheric pressure and at 750 mbar. The crude product was purified by fast column chromatography ($R_f = 0.38$, CH_2Cl_2 :*n*-pentane = 1:1; **13j** is not completely stable on silica). The product containing fractions were pooled and concentrated under atmospheric pressure to afford, after drying at 100 mbar and ambient temperature, **13j** (0.31 g, 75%, 1.5 mmol) as a volatile colorless liquid. Molecular formula (molecular mass): $C_7H_7F_2NO_2S$ (207.19 g/mol). 1H NMR (400 MHz, $CDCl_3$): δ 7.32 (ddd, $J = 8.1, 5.0, 2.5$ Hz, 2H), 7.11–7.04 (m, 2H), 5.37–5.11 (br s, 1H), 4.42 (d, $J = 5.9$ Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 163.1 (d, $J = 248.2$ Hz), 130.8 (dd, $J = 2.9, 1.1$ Hz), 130.2 (d, $J = 8.5$ Hz), 116.3 (d, $J = 21.8$ Hz), 48.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ 51.25, –112.67. LR-ESI-MS m/z : $[M-H]^-$ calcd for $C_7H_7F_2NO_2S$ 206.01; found, 206.06. HR-ESI-MS m/z : $[M]^+$ calcd for $C_7H_7F_2NO_2S$ 207.0160; found, 207.0159.

4-(2-Chlorodibenzo[b,f][1,4]oxazepin-11-yl)piperazine-1-sulfonyl Fluoride (13k).⁸



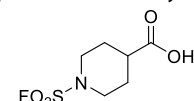
13k (235 mg, 594 μ mol, 93%, colorless solid) was prepared according to GP2 from amoxapine (200 mg, 637 μ mol) and purified by filtration over a silica plug ($R_f = 0.38$, EtOAc:*n*-hexane = 1:4). Molecular formula (molecular mass): $C_{17}H_{15}ClFN_3O_3S$ (395.83 g/mol). 1H NMR (400 MHz, $CDCl_3$): δ 7.44 (dd, $J = 8.7, 2.6$ Hz, 1H), 7.31 (d, $J = 2.6$ Hz, 1H), 7.22 (d, $J = 8.7$ Hz, 1H), 7.19–7.08 (m, 3H), 7.08–7.02 (m, 1H), 3.62 (d, $J = 35.1$ Hz, 8H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 159.6, 158.4, 151.8, 139.5, 133.3, 130.8, 128.7, 127.3, 126.1, 125.6, 124.5, 123.1, 120.4, 46.7, 46.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ 39.17. HR-ESI-MS m/z : $[M + H]^+$ calcd for $C_{17}H_{16}ClFN_3O_3S$ 396.0579; found, 396.0578.

tert-Butyl {2-[1-(Fluorosulfonyl)-1H-indol-3-yl]ethyl}carbamate (13l).



11 (531 mg, 1.69 mmol, 1.1 equiv) was added to a solution of *tert*-butyl [2-(1H-indol-3-yl)ethyl]carbamate (400 mg, 1.54 mmol) and DBU (505 μ L, 3.38 mmol, 2.2 equiv) in CH_2Cl_2 . Conversion of the starting material was monitored by HPLC. After 1 h, a second portion of **11** (241 mg, 768 μ mol, 0.5 equiv) was added, but no further conversion was observed after another 2 h. Therefore, silica was added, the solvent was removed, and the residue was purified by column chromatography with solid loading ($R_f = 0.26$, EtOAc:*n*-hexane = 1:4) to afford the title compound **13l** (72.0 mg, 210 μ mol, 14%) as a colorless solid. Molecular formula (molecular mass): $C_{15}H_{19}FN_2O_4S$ (342.39 g/mol). 1H NMR (400 MHz, $CDCl_3$): δ 8.02–7.78 (m, 1H), 7.63 (d, $J = 7.6$ Hz, 1H), 7.53–7.31 (m, 2H), 7.28–7.23 (m, 1H), 4.67 (s, 1H), 3.47 (q, $J = 6.7$ Hz, 2H), 2.93 (t, $J = 6.7$ Hz, 2H), 1.44 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 156.0, 135.4, 130.8, 126.2, 124.8, 123.0, 122.2, 120.2, 113.9, 79.7, 39.9, 28.5, 25.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ 53.90. HR-ESI-MS m/z : $[M + Na]^+$ calcd for $C_{15}H_{19}FN_2O_4SNa$ 365.0942; found, 365.0948.

1-(Fluorosulfonyl)piperidine-4-carboxylic Acid (13m).



13m (62.6 mg, 298 μ mol, 39%, colorless solid) was prepared according to GP2 from isonipecotic acid (100 mg, 774 μ mol) and purified by column chromatography ($R_f = 0.21$, CH_2Cl_2 :MeOH = 30:1). Molecular formula (molecular mass): $C_6H_{10}FNO_4S$ (211.21 g/mol). 1H NMR (400 MHz, CD_3OD): δ 3.93–3.74 (m, 2H), 3.26–3.11 (m, 2H), 2.65–2.47 (m, 1H), 2.14–1.97 (m, 2H), 1.90–1.68 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, CD_3OD): δ 177.2, 47.6, 40.5, 28.2. ^{19}F NMR (376 MHz, CD_3OD): δ 38.16. HR-ESI-MS m/z : $[M-CO_2H]^+$ calcd for $C_5H_9FNO_3S$ 166.0333; found, 166.0332.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its [Supporting Information](#).

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.3c02643>.

Appearance and preparation of 1*H*-imidazole-1-sulfonyl fluoride (10) and desmethyl SuFEx-IT (11) and NMR-spectra for all prepared compounds (PDF)

fluoromethanesulfonate; THF-*d*₈, octadeuterotetrahydrofuran; TLC, thin-layer chromatography; LR-EI-MS, low-resolution electron ionization mass spectrometry

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ABBREVIATIONS

AISF, [4-(acetylamino)phenyl]imidodisulfonyl difluoride; (CD₃)₂SO, hexadeuterodimethyl sulfoxide; CD₃CN, trideuterioacetonitrile; CDCl₃, deuteriochloroform; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; desmethyl SuFEx-IT, 1-(fluorosulfonyl)-3-methyl-1*H*-imidazole trifluoromethanesulfonate; FO₂S-, fluorosulfonyl; HR-EI-MS, high-resolution electron ionization mass spectrometry; HR-ESI-MS, high-resolution electrospray ionization mass spectrometry; LR-EI-MS, low-resolution electron ionization mass spectrometry; LR-ESI-MS, low-resolution electrospray ionization mass spectrometry; MeOTf, methyl triflate; MS, mass spectrometry; MSDI, 3-(imidazole-1-sulfonyl)-1-methyl-3*H*-imidazole-1-ium trifluoromethanesulfonate; NMR, nuclear magnetic resonance; SDI, 1,1'-sulfonyldiimidazole; SO₂Cl₂, sulfonyl chloride; SO₂F₂, sulfonyl fluoride; SuFEx, sulfur(VI)-fluoride exchange; SuFEx-IT, 1-(fluorosulfonyl)-2,3-dimethyl-1*H*-imidazole-3-ium tri-

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3.2 Manuscript 1 | Arylsulfamoyl [^{18}F]fluorides: Preparation via Base-free SuFEx ^{18}F -Fluorination and Assessment of their Applicability as Potential PET Tracers

Abstract

N-Aryl sulfamoyl fluorides (ASAFs) often exhibit high hydrolytic stability and are widely used in chemical biology and drug design. Despite this, the suitability of [^{18}F]ASAFs as PET-tracers has not yet been assessed. A series of [^{18}F]ASAFs was efficiently produced via a base-free sulfur(VI) fluoride exchange (SuFEx) protocol using nanomolar precursor amounts enabling access to radiolabeled compounds with high molar activities. ^{18}F -Labeled ASAFs demonstrated a high stability over a wide pH range and in human serum. *In vivo* evaluation of a $N_{\text{in}}\text{-}[^{18}\text{F}]\text{SAF}$ -functionalized Boc-Trp-OMe in healthy mice confirmed high metabolic stability and minimal defluorination. $N_{\text{in}}\text{-}[^{18}\text{F}]\text{SAF}$ -substituted Trp and 2,3-dihydro-Trps were produced and studied *in vitro* in U87 MG glioblastoma cells. All three radiofluorinated amino acids demonstrated significantly higher cellular accumulation (up to 2–3 fold after 40 min incubation) compared to [^{18}F]FET. The cellular uptake of novel tracers was significantly reduced by the suppression of amino acid transport system L. $N_{\text{in}}\text{-}[^{18}\text{F}]\text{SAF}$ -substituted Trp enabled clear delineation of glioma in the subcutaneous mouse model. This probe, however, suffered from rapid defluorination in the glioma xenograft bearing mice. In contrast, the corresponding (*S,S*)-2,3-dihydro derivative was completely stable toward *in vivo* defluorination, suggesting that stability issues can be addressed by structural adjustment. Taken together, our findings demonstrate that appropriate ^{18}F -labeled *N*-alkyl-*N*-aryl sulfamoyl fluorides fulfill all necessary requirements and could be applied as PET tracers for *in vivo* imaging.

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Arylsulfamoyl [^{18}F]Fluorides: Preparation via Base-free SuFEx ^{18}F -Fluorination and Assessment of their Applicability as Potential PET Tracers

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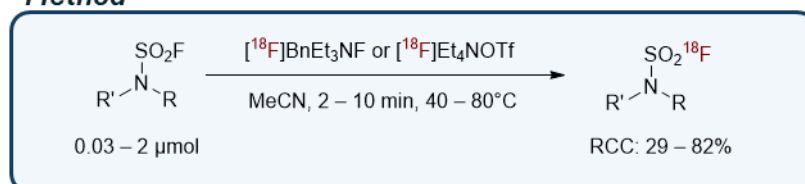
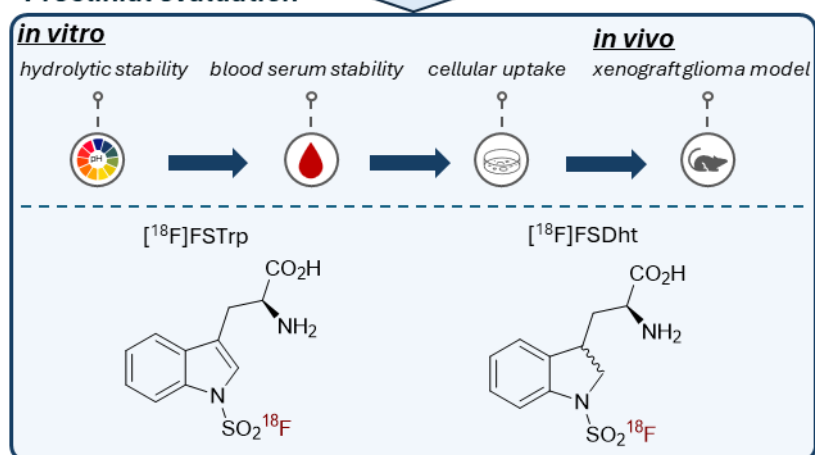
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KEYWORDS: SuFEx, fluorosulfurylation, FO₂S-donor, fluorosulfate, sulfamoyl fluoride

GRAPHICAL ABSTRACT

Method**Preclinical evaluation****Summary**

- ✓ Simple SuFEx-based ^{18}F -labeling method
- ✓ Base-free & nanomolar precursor amount
- ✓ First *in vivo* evaluation of ^{18}F -labelled sulfamoyl fluorides
- ✓ Demonstrating promising stability

1. INTRODUCTION

Positron emission tomography (PET) is a non-invasive imaging modality that enables quantitative visualization of physiological and pathological processes by tracing the biodistribution of radiolabeled molecular probes labeled with a β^+ -emitter. Fluorine-18 (^{18}F) is the most widely used PET radionuclide in clinical and preclinical settings. This preference can be attributed to its ready accessibility in the form of [^{18}F]fluoride ([^{18}F]F $^-$) from [^{18}O]H $_2\text{O}$ via the high-yielding $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ nuclear reaction as well as favorable nuclear properties, which include a half-life (110 min) compatible with complex radiosyntheses, centralized production and longitudinal measurements, and also a low maximum positron energy ($E_{\text{max}} = 635 \text{ keV}$) that translates into high spatial resolution. The continued demand for efficient and reliable ^{18}F -labeling methods has resulted in significant methodological advances, such as the introduction of copper-mediated radiofluorination^[1] or minimalist labeling strategies based on onium salt precursors.^[2] However, direct C– ^{18}F bond formation remains synthetically challenging and is often not suitable for radiolabeling of sensitive substrates. These limitations have spurred growing interest in alternative ^{18}F -labeling strategies involving heteroatom-fluorine bond formation^[3]. In this context, sulfur(VI)-fluoride exchange (SuFEx) chemistry^[4] represents a particularly promising approach due to the high intrinsic stability of the S $^{\text{VI}}$ –F bond. However, its application in radiochemistry remained limited to metabolically unstable aryl sulfonyl [^{18}F]fluorides until 2021, when Zheng et al. reported a SuFEx-based isotopic exchange reaction for the preparation of aryl [^{18}F]fluorosulfates (Scheme 1).^[5] This method enabled rapid radiofluorination of 25 structurally diverse aryl fluorosulfates at ambient temperature, achieving radiochemical conversions (RCC) of 83–100% and molar activities of up to 280 GBq μmol^{-1} . In addition, *in vivo* imaging with an ^{18}F -fluorosulfurylated olaparib analogue in tumor-bearing mice confirmed the potential of this functional group for PET tracer development.

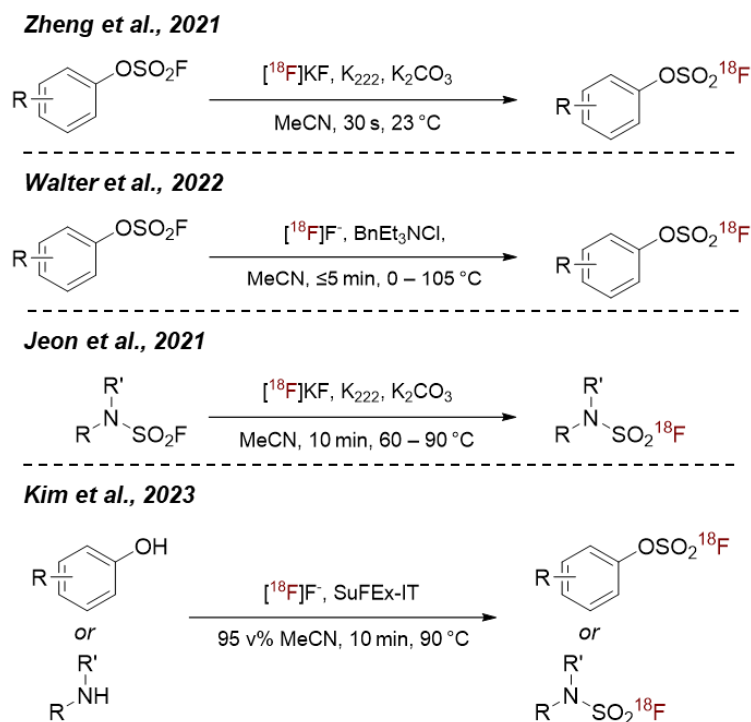
Nevertheless, the original method based on [^{18}F]KF/K $_2\text{CO}_3$ /K $_{222}$ showed limited robustness and reproducibility. To address this issue, a base-free [^{18}F]fluoride elution strategy using quaternary ammonium salts (Scheme 1) was developed, which enabled efficient ^{18}F -fluorination of diverse phenolic substrates, including complex biomolecules and tracer candidates^[6]. Despite promising preliminary imaging results, *in vivo* stability of the [^{18}F]fluorosulfate moiety proved to be in many cases insufficient, corroborating recent reports that aryl [^{18}F]fluorosulfates undergo considerable defluorination in human serum and healthy mice.^[7]

Owing to their documented superior hydrolytic and thermal resistance, sulfamoyl [^{18}F]fluorides (SAFs) could represent a potentially more stable alternative to aryl

[^{18}F]fluorosulfates.^[4, 8] Jeon et al. recently reported a $^{18}\text{F}/^{19}\text{F}$ -SuFEx-based approach for the radiofluorination of SAFs with [^{18}F]KF/ $\text{K}_2\text{CO}_3/\text{K}_{222}$ under inductive heating (Scheme 1), achieving RCCs of 50–97% across more than 30 SAF derivatives.^[9] Subsequently, the same group introduced a complementary strategy involving *in situ* generation of ^{18}F -labeled fluorosulfates or SAFs from the corresponding phenols and amines using the radiolabeled FSO_2 -transfer agent [^{18}F]SuFEx-IT (Scheme 1).^[10]

However, despite these advances, no *in vitro* or *in vivo* investigations of ^{18}F -labeled SAFs have been reported to date. Therefore, the aim of the present work was to evaluate the chemical and metabolic stability of this functional group and to evaluate its utility for PET-tracer development. Furthermore, we envisioned that application of our base-free SuFEx radiofluorination protocol to SAFs could reduce the required precursor amounts compared to previously reported methods, which use high precursor loadings (up to 20 μmol).

Scheme 1. Existing radiolabeling protocols for the preparation of ^{18}F -labeled sulfamoyl fluorides and fluorosulfates.^[5-6, 9-10]



2. RESULTS AND DISCUSSION

To evaluate the applicability of our base-free SuFEx labeling strategy to sulfamoyl fluorides (SAFs), we initially employed Boc-Trp-OMe and Boc-Trp-O*t*Bu-derived SAFs (**1** and **2**) as model substrates. Efficient ^{18}F -labeling was achieved within 2 min at moderate temperatures (40 °C to 60 °C) under conventional heating, yielding RCCs exceeding 80% (Fig. 1A–C). Furthermore, the amount of the elution salt BnEt₃NCl could be reduced from initial 10 to 2 μmol , although this reduction compromised labeling reliability (Fig. 1D). We further evaluated three alternative elution salts previously found to be effective in fluorosulfate labeling.^[6] While use of Et₄NOTf yielded RCCs comparable to BnEt₃NCl, use of Et₄NOH or Bu₄NClO₄ resulted in reduced (by ~10%) or highly inconsistent conversions, respectively (Fig. 1D).

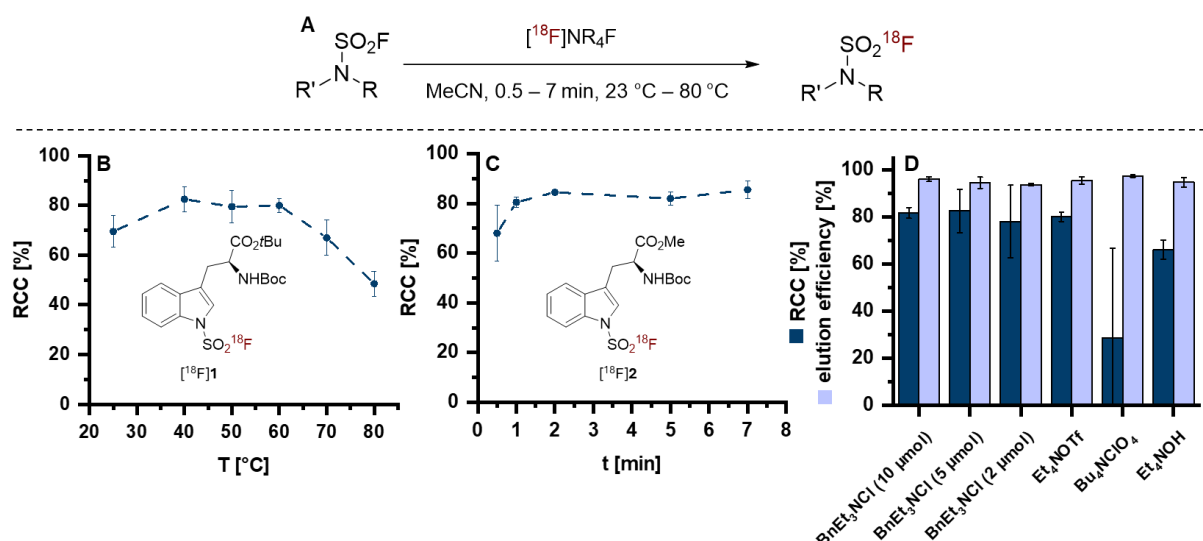
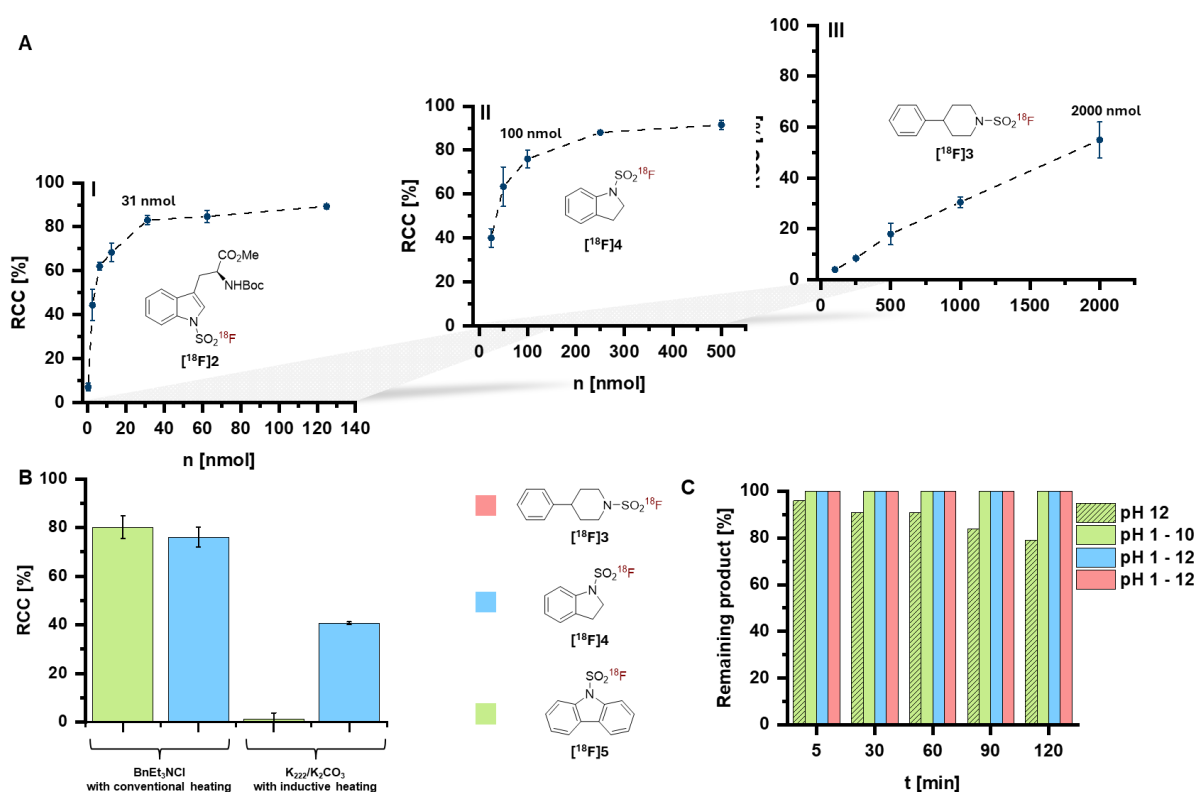


Figure 1. A General labeling conditions evaluated for preparation of ^{18}F **1** and ^{18}F **2**. B Dependency of RCC on temperature for labeling of **1**. The methyl ester **2** showed significant hydrolysis at higher temperatures. Thus *tert*-butyl ester **1** was used for temperature dependency. C Dependency of RCC on time for labeling of **2**. D Dependency of RCC for labeling of **2** on different elution salts and concentrations. Conditions: 40 °C, 5 min, 1 mL MeCN, 10 μmol elution salt (if not stated otherwise) in MeOH.

Next, we sought to determine the minimal precursor amount required to achieve high ^{18}F -labeling conversions, as this parameter directly impacts the attainable molar activity (A_m) in isotopic exchange-based labeling reactions. Boc-Trp(^{18}F SO₂F)-OMe (^{18}F **2**) was prepared in high RCCs (>80%) using as little as 31 nmol precursor (Fig. 2A I). The indoline derivative ^{18}F **4** could be prepared from 100 nmol precursor, although elevated temperatures (80 °C) and longer reaction times (10 min) were required to maintain high RCCs (Fig. 2A II). In contrast,

labeling of the phenylpiperidyl sulfamoyl fluoride (**3**) necessitated precursor amounts $\geq 2 \mu\text{mol}$ to achieve RCCs above 50% (Fig. 2A III). This relatively poor reactivity resulted in low molar activities and could limit the practical utility of $^{18}\text{F}/^{19}\text{F}$ -SuFEx protocols for the preparation of aliphatic ^{18}F SAFs as probes for *in vivo* imaging.

Figure 2. **A** Dependency of RCC on precursor amount for three different substrates (^{18}F **2**, ^{18}F **3** and ^{18}F **4**). Conditions: **I** 40 °C, 5 min, 1 mL MeCN; **II** 80 °C, 10 min, 1 mL MeCN; **III** 80 °C, 10 min, 1 mL MeCN. **B** Comparison of the $\text{K}_{222}/\text{K}_2\text{CO}_3$ -based labeling approach under conductive heating (conditions: 100 nmol precursor, 2 mL MeCN; ^{18}F **4** and ^{18}F **5** 60 °C, 10 min) with the base-free approach using conventional heating (conditions: 100 nmol precursor, 2 mL MeCN; ^{18}F **5**: 40 °C, 3 min and ^{18}F **4**: 80 °C, 10 min). **C** Hydrolytic stability of ^{18}F **3–5** at different pH values (1–12) for 2 h.



Additionally, we benchmarked our base-free protocol against a conventional $\text{K}_{222}/\text{K}_2\text{CO}_3$ -based method employing a conductively heated reactor (Monowave 50, Anton Paar) as reported by Jeon *et al.*^[9] For the indoline derivative ^{18}F **4**, RCCs under base-free conditions were nearly two-fold higher (Fig. 2B). Even more strikingly, the carbazole derivative **5**, which was essentially non-reactive under basic conditions, was labeled in high efficiency RCCs of ~80% using BnEt_3NCl , underscoring the broader substrate scope of the base-free approach (Fig. 2B).

Next, we studied the hydrolytic stability of ^{18}F **3–5**. Thus, as summarized in Fig. 2C, while ^{18}F **3** and ^{18}F **4** remained stable across a broad pH range (pH 1–12) ^{18}F **5** was only stable up to pH 10. However, it showed signs of mild degradation under strongly basic conditions (pH 12; 21% defluorination after 120 min). Notably however, all three compounds exhibited excellent

stability in phosphate buffered saline (PBS, pH 7.4), with no signs of defluorination for up to 2 h.

To further validate the radiofluorination protocol, we applied it to a broader scope of SAF substrates (Fig. 3). Labeling of indole-derived SAFs like **2**, **5** and **6** consistently afforded the highest RCCs (71–83%) using minimal precursor amounts (~30 nmol) and mild reaction conditions (40 °C), confirming the beneficial influence of the electron-rich indole scaffold. This trend was not influenced by incorporating electron withdrawing (**7**) or donating group (**8**) on the indole moiety. *N*-Alkyl-*N*-aryl SAFs (**4**, **9**, **13** and **14**) required moderately elevated temperatures (80–90 °C) and reaction times of 10 min, along with slightly higher precursor loadings (100 nmol), to achieve moderate to high RCCs (38–76%). For labeling of substrates with electron donating groups in *para*-position (**10**, **11**) higher temperature (100 °C) were needed, while labeling of electron-deficient **12** required lower temperatures to avoid decomposition and side-product formation. In contrast, *N*-imidazolyl SAF, Boc-His(SO₂F)-OMe (**15**), was effectively labeled at ambient temperature within only 1 min.

In line with prior observations, aliphatic SAFs like **3** and **16** proved to be less reactive, requiring precursor amounts in the micromolar range to achieve meaningful RCCs. Attempts to label the (fluorosulfonyl)(phenyl)sulfamoyl fluoride (**17**), which contains a bis-SO₂F-substituted amino group were unsuccessful under a variety of reactions conditions, with chromatographic analysis indicating complete hydrolysis of the precursor. Similarly, its monosubstituted analog already showed degradation prior to use. These findings are consistent with the reported susceptibility of *N*-monosubstituted SAFs to hydrolysis,^[4] suggesting that such substrates are unsuitable for PET tracer development.

Figure 3. Substrate scope of the base-free SuFEx radiolabeling protocol with indicated reaction conditions using BnEt_3NCl (10 μmol) in MeOH (1 mL) for elution. All radiolabeling reactions were conducted at least in triplicate.

indole SAFs

$[^{18}\text{F}]6$

$[^{18}\text{F}]7$

$[^{18}\text{F}]8$

$[^{18}\text{F}]5$

$[^{18}\text{F}]2$

n [nmol]	30			
RCC [%]	71 $\pm$ 5	85 $\pm$ 2	81 $\pm$ 7	77 $\pm$ 4
conditions	60 $^{\circ}\text{C}$, 2 min	40 $^{\circ}\text{C}$, 2 min		

N-alkyl-N-aryl SAFs

$[^{18}\text{F}]9$

$[^{18}\text{F}]10$

$[^{18}\text{F}]11$

$[^{18}\text{F}]12$

n [nmol]	100			
RCC [%]	38 $\pm$ 16	61 $\pm$ 13	62 $\pm$ 8	22 $\pm$ 1
conditions	80 $^{\circ}\text{C}$, 10 min	100 $^{\circ}\text{C}$, 10 min		50 $^{\circ}\text{C}$, 5 min

cyclic N-alkyl-N-aryl SAFs

$[^{18}\text{F}]13$

$[^{18}\text{F}]4$

(S,R)- $[^{18}\text{F}]14$

(S,S)- $[^{18}\text{F}]14$

N-imidazolyl SAF

$[^{18}\text{F}]15$

n [nmol]	100			
RCC [%]	71 $\pm$ 5	76 $\pm$ 4	69 $\pm$ 11	76 $\pm$ 16
conditions	80 $^{\circ}\text{C}$, 10 min		90 $^{\circ}\text{C}$, 10 min	23 $^{\circ}\text{C}$, 1 min

aliphatic SAFs

$[^{18}\text{F}]16$

$[^{18}\text{F}]3$

$[^{18}\text{F}]17$

N-aryl bis-SAF

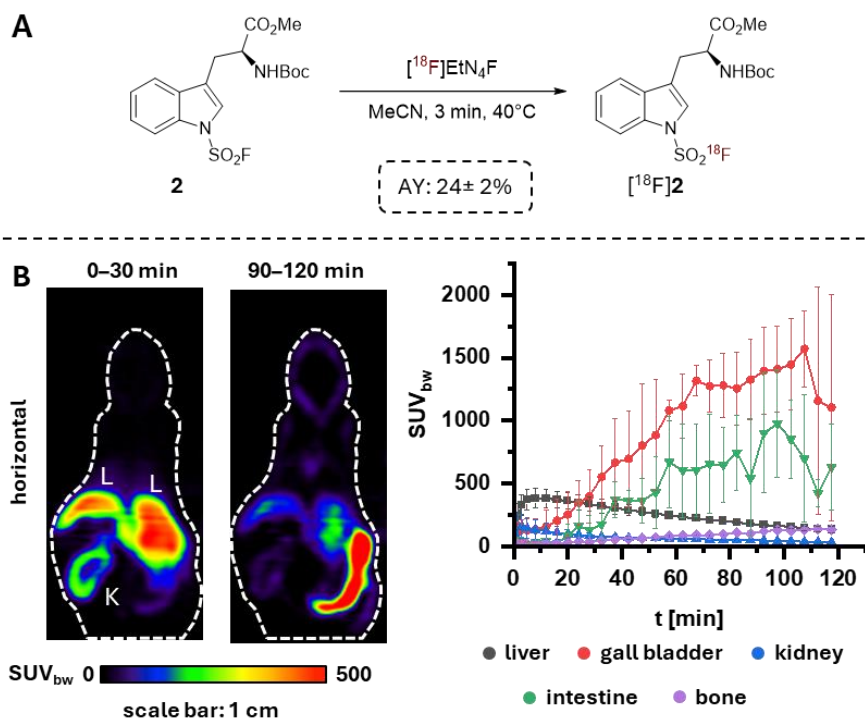
n [nmol]	2000		100 – 1000	
RCC [%]	29 $\pm$ 1		55 $\pm$ 7	
conditions	80 $^{\circ}\text{C}$, 10 min		23 $^{\circ}\text{C}$ – 85 $^{\circ}\text{C}$	

We excluded *N*-alkyl and monosubstituted SAFs from the following feasibility study owing to the inaccessibility with high molar activity and pronounced lability, respectively, and concentrated our efforts on the evaluation of *N*-aryl substituted SAFs (ASAFs).

To assess the *in vivo* stability of radiolabeled ASAFs, we selected Boc-Trp([^{18}F]SO₂F)-OMe ([^{18}F]2) as a representative model compound. The tracer was prepared in an activity yield (AY; non-decay-corrected) of 24 $\pm$ 2% and radiochemical purity of 99%, after isolation by solid-phase extraction (SPE) and formulation of an injectable solution within a total production time of 50 minutes (Fig. 4A). Preclinical PET imaging in healthy mice demonstrated pronounced accumulation of [^{18}F]2 in the liver (maximum SUV_{bw} 381 $\pm$ 79, 0–30 min p.i.) gall bladder (maximum SUV_{bw} 1571 $\pm$ 301, 90–120 min p.i.) and intestine (maximum SUV_{bw} 975 $\pm$ 429, 90–120 min p.i.), consistent with hepatobiliary clearance of the highly lipophilic [^{18}F]2 (Fig.

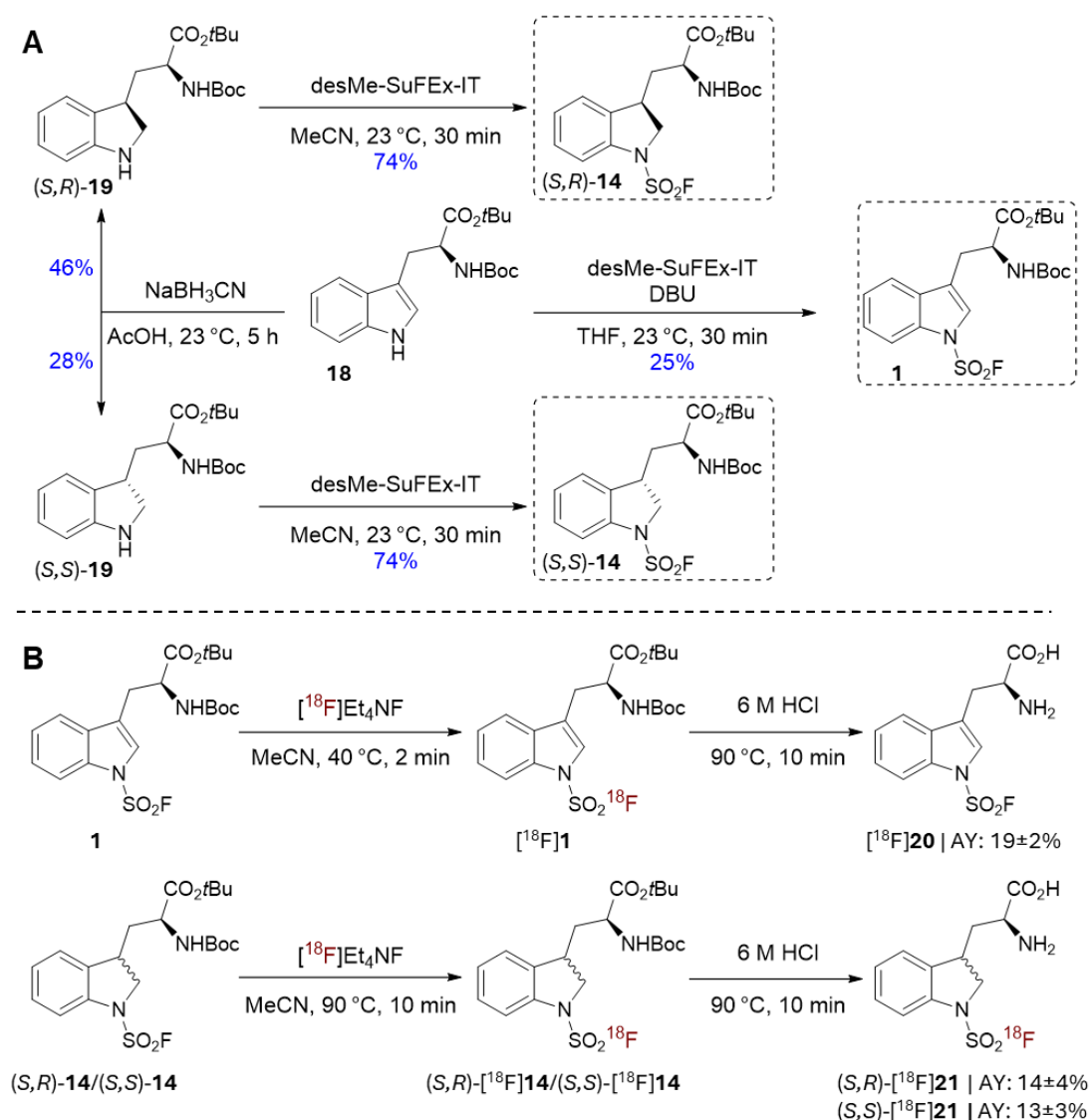
4B). Importantly, bone uptake of radioactivity remained low throughout the whole observation period (maximum SUV_{bw} 133 ± 11 , 90–120 min p.i.), indicating a high *in vivo* stability of [^{18}F]2 against defluorination.

Figure 4 **A** Synthesis of Boc-Trp([^{18}F]SO $_2$ F)-OMe ([^{18}F]2). **B** *In vivo* evaluation of [^{18}F]2 by μ PET imaging in healthy mice ($n = 3$). Shown are representative PET images (summed over the indicated 30 min time frames) of two individual mice in horizontal orientation.



Encouraged by the favorable *in vivo* stability, we next aimed to demonstrate the applicability of the methodology towards the preparation of clinically relevant PET tracers. Radiolabeled amino acids serve as valuable tools for visualizing the upregulation of amino acid transporters in various tumors, particularly within the central nervous system. Among these, *O*-(2-[^{18}F]fluoroethyl)tyrosine ([^{18}F]FET) is routinely used for brain tumor imaging due to its selective tumor uptake via L-type amino acid transporter 1 (LAT1). With the goal of developing alternative LAT1-targeting tracers, we prepared three radiolabeled ASAF substituted amino acids. To this end, Boc-Trp-OH was converted to *tert*-butyl ester **18**,^[11] which was subsequently *N*_{in}-fluorosulfonylated using desmethyl SuFEx-IT^[12], affording **1** in 13% overall yield. For preparation of the 2,3-dihydrotryptophan-derived precursors, (*S,S*)- and (*S,R*)-**14**, Boc-Trp-*Ot*Bu was first reduced with NaBH $_3$ CN and the diastereoisomers were separated by column chromatography. Subsequent *N*-fluorosulfonylation with desmethyl SuFEx-IT furnished the desired precursors, (*S,S*)- and (*S,R*)-**14**, in a total yield of 17% and 10%, respectively (Scheme 2A).

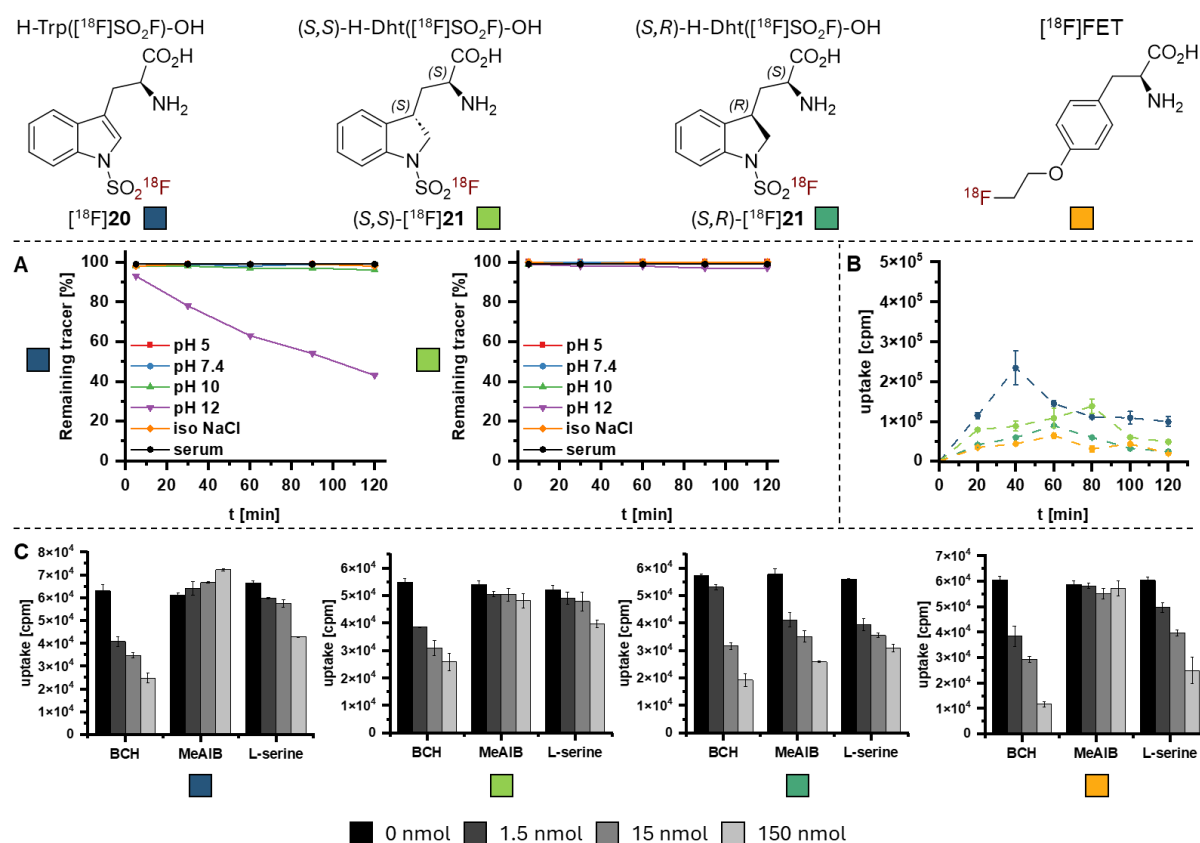
Scheme 2: A Preparation of radiolabeling precursors **1**, (*S,R*)-**14** and (*S,S*)-**14**. **B** Radiosynthesis of amino acid tracers [^{18}F]**20** and (*S,R*)-[^{18}F]**21**, (*S,S*)-[^{18}F]**21**.



Next, $N_{\text{in}}\text{-}[^{18}\text{F}]\text{fluorosulfonyl-tryptophan}$ ($\text{H-Trp}([^{18}\text{F}]\text{SO}_2\text{F})\text{-OH}$; [^{18}F]**20**) was prepared by isotopic exchange on precursor **1**, purified by SPE, and formulated as an injectable solution, which afforded the tracer in AYs of 19±2% within 55 min (Scheme 2B). The diastereomers of $N_1\text{-}[^{18}\text{F}]\text{fluorosulfonyl-2,3-dihydrotryptophan}$ {(*S,S*)-H-Dht($[^{18}\text{F}]\text{SO}_2\text{F})\text{-OH}$; (*S,S*)-[^{18}F]**21**, and (*S,R*)-H-Dht($[^{18}\text{F}]\text{SO}_2\text{F})\text{-OH}$; (*S,R*)-[^{18}F]**21**} were prepared from (*S,S*)- and (*S,R*)-**14** using analogous conditions and obtained in AYs of 13±3% {(*S,S*)-[^{18}F]**21**} and 14±4% {(*S,R*)-[^{18}F]**21**} within 70 min (Scheme 2B). All three tracer candidates were obtained in a high radiochemical purity (RCP >98%).

Consequently, the hydrolytic stability and cellular uptake of the candidate probes were examined *in vitro*. [^{18}F]**20** exhibited a high stability over pH 5–10 (<4% defluorination, 2 h) but significant (>50%, 2 h) defluorination at pH 12 (Fig. 5A, left panel). (*S,S*)-[^{18}F]**21** remained completely intact over pH 5–10 and showed negligible defluorination (3%) at pH 12 (Fig. 6A, right panel). Both compounds demonstrated excellent stability in human serum, with no defluorination detected over a period of 2 h.

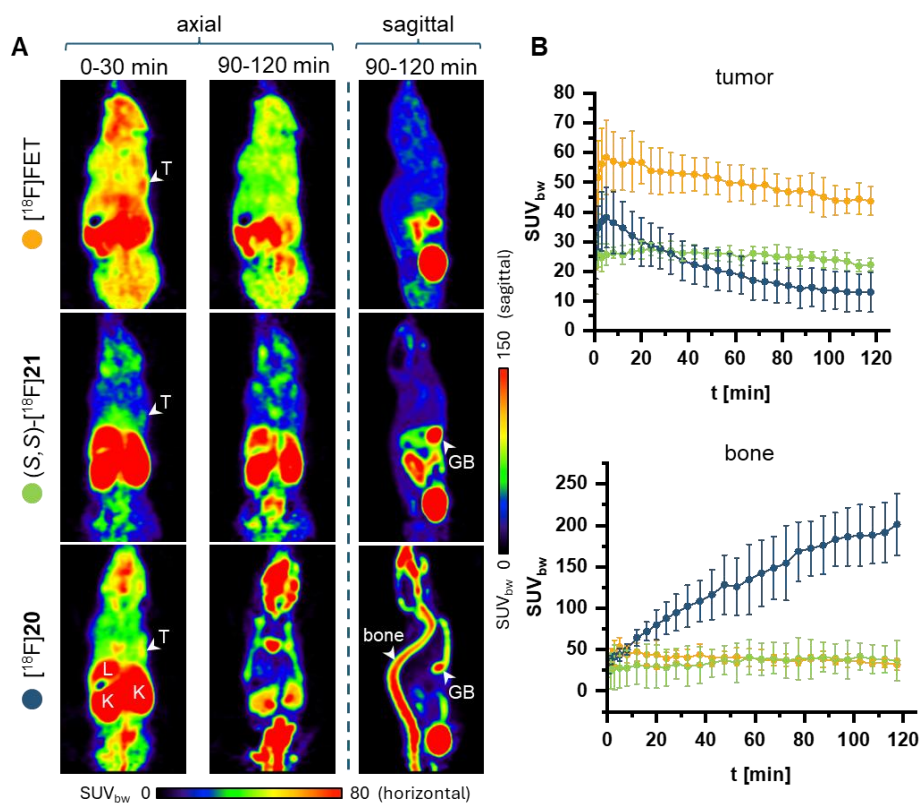
Figure 5. Hydrolytic stability and cellular uptake of ASAF-based tracer candidates. **A** Hydrolytic stability of [^{18}F]**20** (left) and (*S,S*)-[^{18}F]**21** (right) at different pH values (1–12) over 2 h. **B** Uptake of [^{18}F]**20**, (*S,S*)- and (*S,R*)-[^{18}F]**21** in comparison to [^{18}F]FET by human U87 MG glioblastoma cells. Uptake was quantified after incubation of the cells with 150 kBq of the different radiolabeled probes for up to 2 h. **C** Effect of different amino acid transport inhibitors on the uptake of (from left to right) [^{18}F]**21**, (*S,S*)- and (*S,R*)-[^{18}F]**21** and [^{18}F]FET by U87 MG glioblastoma cells. Uptake was quantified after incubation of the cells with 150 kBq of the tracers for 1 h in the presence of the indicated inhibitor concentrations. The inhibitors used were 2-aminobicyclo[2.2.1]heptane-2-carboxylic acid (BCH) for system L, L-serine for system ASC, and α -(methylamino)isobutyric acid (MeAIB) for system A.



Next, cellular uptake of the candidate tracers by U87 MG glioblastoma cells was compared to that of the established tracer [^{18}F]FET. H-Dht([^{18}F]SO₂F)-OH exhibited approximately two-fold higher cellular accumulation than [^{18}F]FET after 60 min of incubation, with the *S,S*-diastereomer showing slightly superior uptake (Fig. 5B). Strikingly, H-Trp([^{18}F]SO₂F)-OH ([^{18}F]**20**) revealed even a three-fold increase in uptake relative to [^{18}F]FET (Fig. 5B),

highlighting its potential for brain tumor imaging. To elucidate the amino acid transport systems mediating tracer uptake, we performed competitive inhibition assays with U87 MG cells (Fig. 5C). Inhibition of system L with 2-aminobicyclo[2.2.1]heptane-2-carboxylic acid (BCH) significantly reduced cellular accumulation of all three candidate probes in a concentration-dependent manner. Inhibition of system ASC with L-serine also reduced tracer accumulation, although the effect was less pronounced and only reached statistical significance at higher inhibitor concentrations. Interestingly, inhibition of system A with α -(methylamino)isobutyric acid (MeAIB) significantly reduced uptake of only (*S,R*)-[^{18}F]21, suggesting an influence of the distant stereocenter on the interaction with amino acid transporters.

Figure 6: **A** Comparison of *in vivo* tumor uptake of [^{18}F]20, (*S,S*)-[^{18}F]21 and [^{18}F]FET in a subcutaneous U87 MG glioblastoma mouse model. Representative vertical PET images (summed over the indicated 30 min time frames) of a tumor-bearing mouse measured (on different days) with [^{18}F]FET (top), (*S,S*)-[^{18}F]21 (middle) and [^{18}F]20 (bottom). **B** Comparison of mean time-activity curves ($n = 3$) for tumoral and bone accumulation of radioactivity in measurements with [^{18}F]20 (blue), (*S,S*)-[^{18}F]21 (green) and [^{18}F]FET (orange).



Finally, (*S,S*)-H-Dht([^{18}F]SO₂F)-OH and H-Trp([^{18}F]SO₂F)-OH were evaluated by *in vivo* PET imaging in a subcutaneous tumor xenograft mouse model based on the same U87 MG cell line as used for the uptake studies. As illustrated in Fig. 6A/B, both tracers enabled visualization of the tumors within 30 min, although tumor uptake was lower than for the reference tracer [^{18}F]FET. Notably, high skeletal accumulation of radioactivity was observed for [^{18}F]20 after

120 min p.i., indicative of significant *in vivo* defluorination (maximum SUV_{bw} 201 ± 37 , 90–120 min p.i., Fig. 6B). In contrast, (*S,S*)-[^{18}F]**21** showed substantially lower bone uptake, suggesting superior *in vivo* stability of this tracer (maximum SUV_{bw} 42 ± 16 , 120 min p.i., Fig. 6B). These findings imply that, in contrast to (*S,S*)-[^{18}F]**21**, H-Trp([^{18}F]SO₂F)-OH may be covalently captured by some protein(s) either as a suicide substrate or as an inhibitor. However, *N*-alkyl-*N*-aryl substituted SAF [^{18}F]**21** appears to confer sufficient metabolic stability for potential PET tracer applications, warranting further exploration of this structural motif in future radiopharmaceutical development.

3. CONCLUSION

In this study, we successfully adapted a base-free SuFEx radiofluorination strategy to *N*-aryl substituted sulfamoyl fluorides (ASAFs) and demonstrated its utility for PET tracer development. Importantly, the presence of a *N*-aryl substituent enhanced labeling efficiency, likely by facilitating the formation of a five-membered transition state, as previously proposed. The optimized protocol enabled efficient ^{18}F -fluorination under mild conditions across a structurally diverse set of ASAF substrates, with high radiochemical conversions achieved using minimal precursor amounts.

Stability assessments revealed that most ^{18}F -labeled ASAF compounds display excellent resistance to hydrolytic degradation over a broad pH range. *In vivo* evaluation of the protected amino acid derivative [^{18}F]**2** confirmed high metabolic stability, with negligible defluorination in healthy mice. However, PET imaging with the deprotected analog [^{18}F]**20** in glioma models revealed substantial bone uptake of radioactivity, suggesting that *N*-indolyl substituted ASAFs may be prone to metabolic cleavage. By contrast, the *N*-alkyl-*N*-aryl substituted dihydro-analog (*S,S*)-[^{18}F]**21**, demonstrated markedly improved *in vivo* stability and remains a promising candidate for further developments. In addition, both tracers achieved clear tumor visualization *in vivo*, validating the general suitability of amino acid derivatives with a SAF motif for oncological imaging.

Taken together, these results establish secondary *N*-aryl sulfamoyl fluorides as a robust and tunable alternative to fluorosulfates for PET radiochemistry. Future studies will aim to further broaden the structural repertoire of SAF-based probes and optimize their metabolic stability to enhance the translational potential for molecular imaging applications.

4. EXPERIMENTAL SECTION

4.1 Organic Chemistry – Materials and Methods

4.1.1 General

Unless noted otherwise, all chemicals and solvents were purchased from VWR International GmbH (Darmstadt, Germany), Sigma-Aldrich Chemie GmbH (Steinheim, Germany), ABCR GmbH (Karlsruhe, Germany), Apollo Scientific Ltd. (Bredbury, United Kingdom), Alfa Aesar GmbH (Karlsruhe, Germany) or BLD Pharmatech GmbH (Kaiserslautern, Germany) and used without further purification.

All reactions were carried out with magnetic stirring (unless noted otherwise) and organic extracts were dried over anhydrous MgSO_4 . Air- or moisture-sensitive reagents and reaction mixtures were handled under argon (>99.999%, Air Liquide GmbH, Düsseldorf, Germany). Solutions were concentrated under reduced pressure (1–900 mbar) at 40–50 °C using a rotary evaporator (Heidolph GmbH & Co. KG, Schwabach, Germany).

4.1.2 Nuclear magnetic resonance (NMR) spectroscopy

NMR-spectra were measured at ambient temperature in deuteriochloroform (CDCl_3), tetradeuteromethanol (CD_3OD) or trideuteroacetonitrile (CD_3CN) as indicated, using a Bruker Ascend™ 400 (^1H : 400 MHz; ^{13}C : 101 MHz; ^{19}F : 376 MHz; Bruker Biospin GmbH, Rheinstetten, Germany). The measured chemical shifts are reported in δ [ppm] relative to residual peaks of non-deuterated solvents. Higher order NMR spectra were approximately interpreted as first-order spectra if possible. The observed signal multiplicities are characterized as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, tt = triplet of triplets and qd = quartet of doublets. Coupling constants J are reported in hertz (Hz).

4.1.3 Mass spectrometry (MS)

Low resolution electrospray ionization mass spectrometry (LR-ESI-MS) was performed with an MSQ Plus™ mass spectrometer (Thermo Electron Corporation, San Jose, USA). High resolution electrospray ionization mass spectrometry (HR-ESI-MS) was performed with an LTQ XL™ Orbitrap™ (Thermo Fisher Scientific Inc., Bremen, Germany). High resolution electron ionization mass spectrometry (HR-EI-MS) and high resolution positive chemical ionization (HR-PCI-MS) was performed with an Exactive™ GC Orbitrap™ (Thermo Fisher Scientific Inc., Bremen, Germany).

4.1.4 Column chromatography

Manual column chromatography was performed with silica gel, 60 Å, 230–400 mesh particle size from VWR International GmbH (Darmstadt, Germany) or silica gel (w/0.1% Ca), 60 Å, 230–400 mesh particle size from Sigma-Aldrich GmbH (Steinheim, Germany). Automated column chromatography was performed on a Büchi Pure C-815 flash system (Büchi Labortechnik GmbH, Essen, Germany) using Reveleris™ C₁₈ reversed phase cartridges (Büchi Labortechnik GmbH, Essen, Germany).

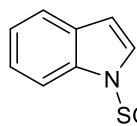
4.1.5 Thin layer chromatography (TLC)

TLC was performed using aluminum sheets coated with silica gel 0.25 mm SIL G/UV 254 (Merck KGaA, Darmstadt, Germany). Chromatograms were inspected under UV light ($\lambda = 254$ nm) and/or stained with phosphomolybdic acid (4% in EtOH), ninhydrin (0.5% in 1-butanol) or potassium permanganate solution (0.75% KMnO₄, 5% K₂CO₃ and 0.07% NaOH in H₂O).

4.1.6 Chemistry

1',1-Sulfonyldiimidazole (SDI), indoline-1-sulfonyl fluoride (**4**), methyl(phenyl)sulfamoyl fluoride (**9**), 1,2,3,4-tetrahydroisoquinoline-2-sulfonyl fluoride (**16**) and phenyliminodisulfonyl difluoride (**17**) were prepared as described previously.^[12]

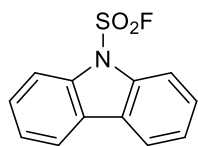
Preparation of 1*H*-indole-1-sulfonyl fluoride (**6**)



A two-chamber system with argon atmosphere was used for the reaction. Chamber A was loaded with SDI (3.38 g, 17.0 mmol, 8.0 eq.) and KF (2.47 g, 42.6 mmol, 20.0 eq), while chamber B was loaded with a solution of indole (250 mg, 2.13 mmol, 1.0 eq) and DIPEA (1.09 mL, 6.39 mmol, 3.0 eq.) in MeCN (5 mL) and cooled to -40°C (CO₂ in MeCN). TFA (15 mL) was then cautiously added to chamber A and the resulting gas was bubbled (via a cannula) through the solution in chamber B. After a few minutes, the cannula was removed from the solution to avoid suck-back into chamber A. The reaction mixture in chamber B was stirred for 12 h, diluted with CH₂Cl₂ (40 mL), and washed with H₂O (2×20 mL) and brine (20 mL). The organic phase was dried and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane:EtOAc /8:1, TLC: $R_f = 0.63$) to afford the title compound as a colorless oil (307 mg, 1.54 mmol, 72%). C₈H₆FNO₂S (199.20 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 7.91 (d, $J = 9.0$ Hz, 1H), 7.64 (d, $J = 7.9$ Hz, 1H), 7.47–7.41 (m, 2H), 7.41–7.35 (m, 1H), 6.81 (d, $J = 4.4$ Hz, 1H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 134.97, 130.47, 126.22, 125.98, 124.94, 122.07, 113.68, 111.13. ¹⁹F

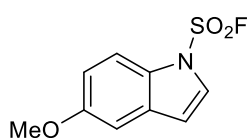
NMR (376 MHz, CDCl₃): δ 54.31. HR-EI-MS m/z : [M]⁺⁺ Calcd for C₈H₆FNO₂S 199.0098; Found: 199.0095.

Preparation of 9H-carbazole-9-sulfonyl fluoride (5)



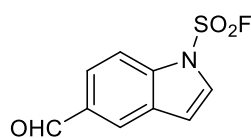
DBU (522 μ L, 533 mg, 3.50 mmol, 2.2 eq.) was added to a solution of carbazole (266 mg, 1.59 mmol, 1.0 eq.) and [4-(acetylamino)phenyl]imidodisulfuryl difluoride (AISF, 600 mg, 1.91 mmol, 1.2 eq.)^[13] in THF (10 mL) and the reaction mixture was stirred for 2 h. Afterwards, more AISF (0.4 g, 1.27 mmol, 0.8 eq.) and DBU (348 μ L, 355 mg, 2.33 mmol, 1.47 eq.) was added and stirring was continued for a further 2 h. Thereafter, the reaction mixture was diluted with Et₂O (40 mL) and washed with 0.5 M NaHSO₄ (3 $\times$ 10 mL) and brine (2 $\times$ 10 mL). The organic phase was dried and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane:EtOAc/14:1, TLC: R_f = 0.28) to afford the title compound as a colorless solid (348 mg, 1.40 mmol, 88%) C₁₂H₈FNO₂S (249.26 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 8.07 (d, J = 8.3 Hz, 2H), 8.02 (dd, 2H), 7.55 (td, J = 8.4, 7.9, 1.4 Hz, 2H), 7.49 (td, J = 7.5, 0.9 Hz, 2H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 137.55, 128.19, 126.42, 125.41, 120.55, 114.95. ¹⁹F NMR (376 MHz, CDCl₃): δ 52.32. HR-EI-MS m/z : [M]⁺⁺ Calcd for C₁₂H₈FNO₂S 249.0254; Found: 249.0252.

Preparation of 5-methoxy-1H-indole-1-sulfonyl fluoride (7)



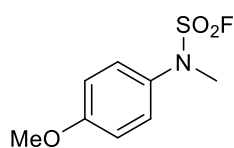
Desmethyl SuFEx-IT (587 mg, 1.87 mmol, 1.1 eq) was added to a solution of 5-methoxy-1H-indole (250 mg, 1.70 mmol, 1.0 eq.) and DBU (254 μ L, 1.70 mmol, 1.0 eq.) in MeCN (10 mL) and the resulting mixture was stirred for 2 h. Additional portions of desmethyl SuFEx-IT (2.67 g, 8.50 mmol, 5.0 eq) and DBU (1.27 mL, 8.50 mmol, 1.0 eq) were added and the mixture as stirred for 1. The solvent was removed under reduced pressure, the residue was taken up in CH₂Cl₂ (~10 mL) and the solution was filtered through a silica plug. The plug was washed with CH₂Cl₂ and the solvent was removed under reduced pressure again. The crude product was purified by column chromatography (*n*-hexane:EtOAc/20:1, TLC: R_f = 0.25) to afford the title compound as a colorless solid (211 mg, 918 μ mol, 54%). C₉H₈FNO₃S (229.23 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 7.78 (d, J = 9.0 Hz, 1H), 7.39 (d, J = 3.8 Hz, 1H), 7.08 (d, J = 2.5 Hz, 1H), 7.03 (dd, J = 9.0, 2.5 Hz, 1H), 6.73 (d, J = 3.8 Hz, 1H), 3.87 (s, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 157.54, 131.57, 129.46, 126.89, 114.71, 114.46, 111.25, 104.56, 55.88. ¹⁹F NMR (376 MHz, CDCl₃): δ 53.75. HR-EI-MS m/z : [M]⁺⁺ Calcd for C₉H₈FNO₃S 229.0203; Found: 229.0201.

Preparation of 5-formyl-1*H*-indole-1-sulfonyl fluoride (**8**)



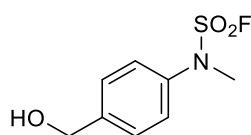
Desmethyl SuFEx-IT (2.71 g, 8.61 mmol, 5.0 eq) was added to a solution of 5-formyl-1*H*-indole (250 mg, 1.72 mmol, 1.0 eq.) and DBU (1.29 mL, 8.61 mmol, 5.0 eq.) in MeCN (10 mL) and the resulting mixture was stirred for 2 h. The solvent was removed under reduced pressure, the residue was taken up in CH₂Cl₂ (~10 mL) and the solution was filtered through a silica plug. The plug was washed with CH₂Cl₂ and the solvent was removed under reduced pressure again. The crude product was purified by column chromatography (*n*-hexane:EtOAc/5:1, TLC: *R_f* = 0.29) to afford the title compound as a colorless solid (100 mg, 440 μmol, 26%). C₉H₆FNO₃S (227.21 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 10.11 (s, 1H), 8.19 (dd, *J* = 1.5, 0.7 Hz, 1H), 8.04 (d, *J* = 8.6 Hz, 1H), 7.98 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.55 (d, *J* = 3.8 Hz, 1H), 6.94 (dd, *J* = 3.8, 0.7 Hz, 1H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 191.47, 138.15, 133.63, 130.79, 127.93, 126.89, 124.74, 114.26, 111.30. ¹⁹F NMR (376 MHz, CDCl₃): δ 55.87. HR-ESI-MS *m/z*: [M+H]⁺ Calcd for C₉H₇FNO₃S 242.02817; Found: 242.02839.

Preparation of (4-methoxyphenyl)(methyl)sulfamoyl fluoride (**10**)



Desmethyl SuFEx-IT (630 mg, 2.00 mmol, 1.1 eq) was added to a solution of 4-methoxy-*N*-methylaniline (250 mg, 1.82 mmol, 1.0 eq.) in MeCN (3 mL) and the resulting mixture was stirred for 1 h. The solvent was removed under reduced pressure and the crude product was purified by dry-loaded column chromatography (*n*-hexane:EtOAc/10:1, TLC: *R_f* = 0.21) to afford the title compound as a yellow liquid (353 mg, 1.62 mmol, 88%). C₈H₁₀FNO₃S (219.23 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 7.39 – 7.28 (m, 2H), 7.00 – 6.86 (m, 2H), 3.82 (s, 3H), 3.40 (s, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 159.99, 132.53, 128.22, 115.10, 55.68, 41.10. ¹⁹F NMR (376 MHz, CDCl₃): δ 41.28. HR-EI-MS *m/z*: [M]⁺ Calcd for C₈H₁₀FNO₃S 219.0359; Found: 219.0358.

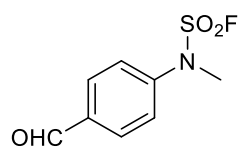
Preparation of (4-(hydroxymethyl)phenyl)(methyl)sulfamoyl fluoride (**11**)



Desmethyl SuFEx-IT (3.15 g, 10.0 mmol, 1.1 eq) was added to a solution of (4-(methylamino)phenyl)methanol (1.25 g, 9.11 mmol, 1.0 eq.) in MeCN (10 mL) and the resulting mixture was stirred for 1 h. The solvent was removed under reduced pressure and the crude product was purified by dry-loaded column chromatography (*n*-hexane:EtOAc/2:1, TLC: *R_f* = 0.15) to afford the title compound as a green oil (1.28 g, 5.84 mmol, 64%). C₈H₁₀FNO₃S (219.23 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 7.48 – 7.40 (m, 2H), 7.40 – 7.35 (m, 2H), 4.71 (s, 2H), 3.42 (s, 3H), 1.95 (s, 1H). ¹³C{¹H} NMR

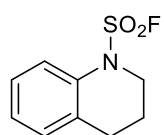
(101 MHz, CDCl₃): δ 142.04, 139.13, 128.25, 126.85; 64.51, 40.80. ¹⁹F NMR (376 MHz, CDCl₃): δ 42.31. HR-ESI-MS m/z : [M+Na]⁺ Calcd for C₈H₁₀FNO₃SNa 242.02576; Found: 242.02586.

Preparation of (4-formylphenyl)(methyl)sulfamoyl fluoride (**12**)



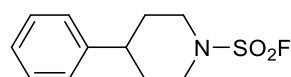
Desmethyl SuFEx-IT (640 mg, 2.04 mmol, 1.1 eq) was added to a solution of 4-(methylamino)benzaldehyde (250 mg, 1.85 mmol, 1.0 eq.) and DBU (276 μ L, 1.85 mmol, 1.0 eq.) in MeCN (2 mL) and the resulting mixture was stirred for 2 h. Additional portions of desmethyl SuFEx-IT (1.74 g, 5.55 mmol, 3.0 eq) and DBU (555 μ L, 3.70 mmol, 2.0 eq) were added and the mixture as stirred for 1. The solvent was removed under reduced pressure, the residue was taken up in CH₂Cl₂ (~5 mL) and the solution was filtered through a silica plug. The plug was washed with CH₂Cl₂ and the solvent was removed under reduced pressure again. The crude product was purified by column chromatography (*n*-hexane:EtOAc/2:1, TLC: R_f = 0.38) to afford the title compound as an orange solid (38 mg, 175 μ mol, 9%). C₈H₈FNO₃S (217.21 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 10.04 (s, 1H), 8.14 – 7.83 (m, 2H), 7.67 – 7.44 (m, 2H), 3.50 (s, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 190.79, 144.93, 136.05, 131.17, 126.73, 40.39. ¹⁹F NMR (376 MHz, CDCl₃): δ 44.16. HR-EI-MS m/z : [M]⁺ Calcd for C₈H₈FNO₃S 217.0197; Found: 217.0203.

Preparation of 3,4-dihydroquinoline-1(2*H*)-sulfonyl fluoride (**13**)



Desmethyl SuFEx-IT (389 mg, 1.24 mmol, 1.1 eq) was added to a solution of 1,2,3,4-tetrahydroquinoline (150 mg, 1.13 mmol, 1.0 eq.) in MeCN (3 mL) and the resulting mixture was stirred for 1 h. The solvent was removed under reduced pressure and the crude product was purified by dry-loaded column chromatography (*n*-hexane:EtOAc/20:1, TLC: R_f = 0.29) to afford the title compound as a colorless solid (207 mg, 962 μ mol, 85%). C₈H₁₀FNO₃S (215.24 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 7.52 (d, J = 8.0 Hz, 1H), 7.26 – 7.09 (m, 3H), 3.97 – 3.81 (m, 2H), 2.91 (t, J = 6.8 Hz, 2H), 2.15 – 2.09 (m, 2H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 135.31, 130.72, 129.67, 126.95, 126.52, 124.20, 48.59, 26.23, 22.24. ¹⁹F NMR (376 MHz, CDCl₃): δ 49.47. HR-EI-MS m/z : [M]⁺ Calcd for C₉H₁₀FNO₂S 215.0411; Found: 215.0406.

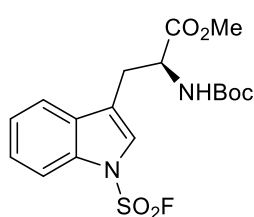
Preparation of 4-phenylpiperidine-1-sulfonyl fluoride (**3**)



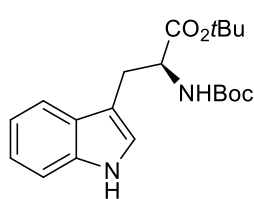
DBU (510 μ L, 3.41 mmol, 2.2 eq.) was slowly added to a solution of 4-phenylpiperidine (250 mg, 1.55 mmol, 1.0 eq.) and AISF (585 mg,

1.86 mmol, 1.2 eq.) in THF (10 mL) and the mixture was stirred for 30 min. The reaction mixture was diluted with EtOAc (40 mL) and washed with 0.5 M NaHSO₄ (2×10 mL) and brine (10 mL). The organic phase was dried and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane:EtOAc/14:1, TLC: *R*_f = 0.28) to afford the title compound as a colorless solid (298 mg, 1.22 mmol, 79%). C₁₁H₁₄FNO₂S (243.30 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 7.42–7.30 (m, 2H), 7.30–7.18 (m, 3H), 4.16–3.97 (m, 2H), 3.13 (tt, *J* = 12.7, 3.1 Hz, 2H), 2.69 (tt, *J* = 12.0, 3.8 Hz, 1H), 2.08–1.80 (m, 4H). ¹³C {¹H} NMR (101 MHz, CDCl₃): δ 144.26, 128.90, 127.04, 126.79, 48.03, 41.59, 32.09. ¹⁹F NMR (376 MHz, CDCl₃): δ 40.43. HR-EI-MS *m/z*: [M]⁺ Calcd for C₁₁H₁₄FNO₂S 243.07238; Found: 243.07227.

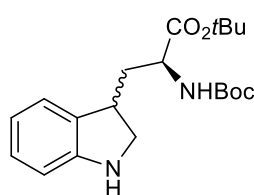
Preparation of methyl *N*_α-(*tert*-butoxycarbonyl)-1-(fluorosulfonyl)-L-tryptophan (**2**)



A two-chamber system was used for the reaction. Chamber A was loaded with SDI (3.98 g, 20.1 mmol, 16.0 eq.) and KF (2.92 g, 50.2 mmol, 40.0 eq.), while chamber B was loaded with a solution of Boc-Trp-OMe (400 mg, 1.26 mmol, 1.0 eq) and DIPEA (641 μL, 3.77 mmol, 3.0 eq.) in MeCN (5 mL) and cooled to –40 °C (dry ice in MeCN). TFA (20 mL) was then cautiously added to chamber A and the resulting SO₂F₂ gas was bubbled (via a cannula) through the solution in chamber B. After a few minutes the cannula was removed from the solution to avoid suck-back into chamber A. The reaction mixture in chamber B was stirred for 12 h, diluted with CH₂Cl₂ (40 mL), and washed with H₂O (2×20 mL) and brine (20 mL). The organic phase was dried and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane:EtOAc/4:1, TLC: *R*_f = 0.39) to afford the title compound as a colorless solid (256 mg, 640 μmol, 51%). C₁₇H₂₁FN₂O₆S (400.42 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 7.88 (d, *J* = 8.1 Hz, 1H), 7.62–7.56 (m, 1H), 7.47–7.41 (m, 1H), 7.41–7.36 (m, 1H), 7.24 (s, 1H), 5.16 (d, *J* = 7.2 Hz, 1H), 4.78–4.59 (m, 1H), 3.71 (s, 3H), 3.34–3.13 (m, 2H), 1.43 (s, 9H). ¹³C {¹H} NMR (101 MHz, CDCl₃): δ 172.00, 155.16, 135.14, 130.82, 126.25, 124.88, 123.87, 120.15, 119.76, 113.85, 80.45, 53.38, 52.68, 28.39, 28.08. ¹⁹F NMR (376 MHz, CDCl₃): δ 54.06. HR-ESI-MS *m/z*: [M+Na]⁺ Calcd for C₁₇H₂₁FN₂O₆SNa 423.09966; Found: 423.09974.

Preparation of *tert*-butyl (*tert*-butoxycarbonyl)-L-tryptophan (**18**)

*t*BuBr (16.7 mL, 147.9 mmol, 10.0 eq.) was added dropwise to a suspension of Boc-Trp-OH (4.51 g, 14.8 mmol, 1.0 eq.), K₂CO₃ (10.2 g, 73.9 mmol, 5.0 eq.) and BnEt₃NCl (3.37 g, 14.8 mmol, 1.0 eq.) in DMA (20 mL), and the mixture was refluxed for 2.5 h at 55 °C. The reaction mixture was diluted with H₂O (40 mL) and extracted with EtOAc (3×25 mL). The organic phase was washed with H₂O (10×25 mL) and brine (2×25 mL), dried, and concentrated under reduced pressure. The residue was recrystallized from Et₂O/*n*-hexane to afford the title compound as a colorless solid (2.66 g, 7.39 mmol, 50%). C₂₀H₂₈N₂O₄ (360.45 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 8.32 (s, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.35–7.29 (m, 1H), 7.28–7.21 (m, 1H), 7.17–7.09 (m, 1H), 5.21 (d, *J* = 7.9 Hz, 1H), 4.68 (q, *J* = 5.8 Hz, 1H), 3.39 (tt, *J* = 15.0, 7.4 Hz, 2H), 1.56 (s, 8H), 1.51 (s, 9H). ¹³C {¹H} NMR (101 MHz, CDCl₃): δ 171.59, 155.42, 136.18, 128.06, 122.78, 122.17, 119.56, 119.21, 111.17, 110.76, 81.91, 79.70, 54.84, 28.47, 28.13, 28.07. HR-ESI-MS *m/z*: [M+H]⁺ Calcd for C₂₀H₂₉N₂O₄ 361.21218; Found: 361.21252.

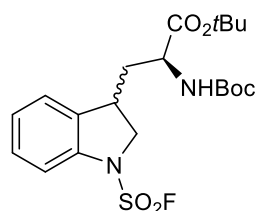
Preparation of *tert*-butyl (*S,S*)- and (*S,R*)-2-[(*tert*-butoxycarbonyl)amino]-3-(indolin-3-yl)propanoate ((*S,R*)-**19** and (*S,S*)-**19**)

NaBH₃CN (1.57 g, 25.3 mmol, 3.0 eq.) was added to an ice-cooled solution of Boc-Trp-*O**t*Bu (3.04 g, 8.43 mmol, 1.0 eq.) in AcOH (40 mL). Additional portions of NaBH₃CN (8×1.05 g 16.6 mmol, 2.0 eq) were added at hourly intervals until HPLC indicated full conversion. The reaction mixture was then diluted with H₂O (100 mL) and the pH was adjusted to 10 using 1 M NaOH. The resulting solution was extracted with CH₂Cl₂ (2×200 mL), the organic phase was washed with brine (150 mL), dried and concentrated under reduced pressure. The residue was purified and the diastereomers separated by three consecutive column chromatography runs (*n*-hexane:EtOAc/3:1, TLC: (*S,R*)-**19**: *R*_f = 0.22 / (*S,S*)-**19**: *R*_f = 0.17). The diastereomers were obtained as colorless oils ((*S,R*)-**19**: 729 mg, 2.01 mmol, 46%; (*S,S*)-**19**: 431 mg, 1.19 mmol, 28%). C₂₀H₃₀N₂O₄ (362.47 g/mol). (*S,R*)-**19**: ¹H NMR (400 MHz, CDCl₃): δ 7.07 (d, *J* = 7.3 Hz, 1H), 7.04 (t, *J* = 7.7 Hz, 1H), 6.72 (t, *J* = 7.4 Hz, 1H), 6.64 (d, *J* = 7.7 Hz, 1H), 5.10 (d, *J* = 8.1 Hz, 1H), 4.29 (td, *J* = 9.0, 4.2 Hz, 1H), 3.95–3.46 (m, 2H), 3.44–3.19 (m, 2H), 2.18–1.91 (m, 2H), 1.46 (s, 9H), 1.45 (s, 9H). ¹³C {¹H} NMR (101 MHz, CDCl₃): δ 172.11, 155.66, 151.46, 132.16, 127.92, 123.83, 118.78, 109.72, 82.23, 79.92, 53.29, 52.75, 38.82, 38.08, 28.45, 28.14. HR-ESI-MS *m/z*: [M+H]⁺ Calcd for C₂₀H₃₁N₂O₄ 363.22783; Found: 363.22767. (*S,S*)-**19**: ¹H

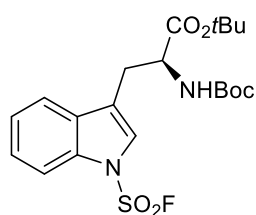
NMR (400 MHz, CDCl₃): δ 7.14 (d, J = 7.1 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 6.73 (td, J = 7.4, 0.9 Hz, 1H), 6.65 (d, J = 7.7 Hz, 1H), 5.09 (d, J = 7.9 Hz, 1H), 4.44–4.02 (m, 1H), 3.75 (t, J = 8.6 Hz, 2H), 3.45–3.33 (m, 1H), 3.28 (t, J = 8.0 Hz, 1H), 2.38–2.13 (m, 1H), 1.93–1.78 (m, 1H), 1.47 (s, 9H), 1.45 (s, 9H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 172.11, 155.35, 151.26, 132.11, 127.90, 124.09, 118.90, 109.74, 82.28, 79.94, 53.76, 53.11, 39.12, 37.97, 28.47, 28.16. HR-ESI-MS m/z : [M+H]⁺ Calcd for C₂₀H₃₁N₂O₄ 363.22783; Found: 363.22814.

* The stereoconfiguration of the diastereomers was determined by comparing the corresponding ¹H-NMR spectra with literature data for enantiomers of Boc-Dht-OMe.^[14]

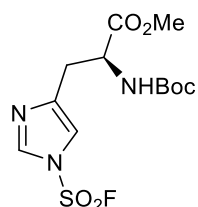
Preparation of *tert*-butyl (*S,S*)- and (*S,R*)-2-[(*tert*-butoxycarbonyl)amino]-3-(1-(fluorosulfonyl)indolin-3-yl)propanoate ((*S,R*)-**14** and (*S,S*)-**14**)



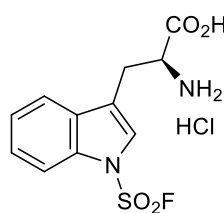
Desmethyl SuFEx-IT (292 mg, 929 μ mol, 1.1 eq.) was added to a solution of (*S,S*)-**19** (324 mg, 893 μ mol, 1.0 eq.) in MeCN (5 mL). The reaction mixture was stirred for 35 min and then concentrated under reduced pressure. The residue was taken up into EtOAc (20 mL) and the resulting solution was washed with H₂O (20 mL). The organic phase was dried and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane:EtOAc/8:1, TLC: (*S,S*)-**14**: R_f = 0.17) to afford (*S,S*)-**14** as a colorless solid (275 mg, 618 μ mol, 74%). Using this procedure (*S,R*)-**14** was also prepared as a colorless solid in 74% yield (*n*-hexane:EtOAc/8:1, TLC: (*S,R*)-**14**: R_f = 0.21). C₂₀H₂₉FN₂O₆S (444.52 g/mol). (*S,S*)-**14**: ¹H NMR (400 MHz, CDCl₃): δ 7.46 (d, J = 8.1 Hz, 1H), 7.27 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 7.4 Hz, 1H), 7.14 (t, J = 7.4 Hz, 1H), 5.22 (d, J = 7.2 Hz, 1H), 4.49–4.05 (m, 2H), 4.05–3.84 (m, 1H), 3.62–3.41 (m, 1H), 2.19–2.03 (m, 1H), 2.02–1.93 (m, 1H), 1.48 (s, 9H), 1.46 (s, 9H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 171.28, 155.75, 139.78, 134.33, 128.83, 125.39, 124.73, 114.93, 83.01, 80.38, 57.28, 52.46, 38.99, 37.33, 28.42, 28.13. ¹⁹F NMR (376 MHz, CDCl₃): δ 39.61. HR-ESI-MS m/z : [M+Na]⁺ Calcd for C₂₀H₂₉FN₂O₆SN_a 467.16226; Found: 467.16223. (*S,R*)-**14**: ¹H NMR (400 MHz, CDCl₃): δ 7.45 (d, J = 8.1 Hz, 1H), 7.38–7.23 (m, 2H), 7.16 (td, J = 7.5, 0.9 Hz, 1H), 5.17 (d, J = 7.5 Hz, 1H), 4.44–4.04 (m, 2H), 3.95–3.84 (m, 1H), 3.69–3.45 (m, 1H), 2.47–2.19 (m, 1H), 1.97–1.79 (m, 1H), 1.48 (s, 9H), 1.47 (s, 9H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 171.31, 155.49, 139.51, 134.26, 128.84, 125.51, 125.09, 114.83, 83.08, 80.45, 57.71, 52.93, 38.46, 37.56, 28.45, 28.14. ¹⁹F NMR (376 MHz, CDCl₃): δ 39.38. HR-ESI-MS m/z : [M+Na]⁺ Calcd for C₂₀H₂₉FN₂O₆SN_a 467.16226; Found: 467.16232.

Preparation of *tert*-butyl N_{α} -(*tert*-butoxycarbonyl)-1-(fluorosulfonyl)-L-tryptophan (**1**)

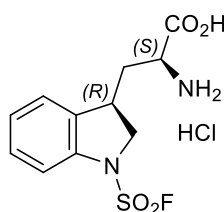
Desmethyl SuFEx-IT (144 mg, 458 μ mol, 1.1 eq) was added to a solution of Boc-Trp-*O*tBu (150 mg, 416 μ mol, 1.0 eq.) and DBU (62 μ L, 416 μ mol, 1.0 eq.) in MeCN (1 mL) and the resulting mixture was stirred for 1 h. Additional three portions of desmethyl SuFEx-IT (1.1 eq) and DBU (1.0 eq) were added at hourly intervals until TLC indicated full conversion. The solvent was removed under reduced pressure, the residue was taken up in CH₂Cl₂ (~10 mL) and the solution was filtered through a silica plug. The plug was washed with *n*-hexane:EtOAc (2:1) and the solvent was removed under reduced pressure again. The residue was purified by column chromatography (*n*-hexane:EtOAc/4:1, TLC: R_f = 0.61) to afford the title compound as a colorless solid (102 mg, 231 μ mol, 55%). C₂₀H₂₇FN₂O₆S (442.50 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 7.88 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.53 – 7.34 (m, 2H), 7.26 (s, 1H, overlap with residual solvent), 5.17 (d, J = 7.0 Hz, 1H), 4.56 (q, J = 6.1 Hz, 1H), 3.40 – 2.94 (m, 2H), 1.44 (s, 9H), 1.39 (s, 9H). ¹³C {¹H} NMR (101 MHz, CDCl₃): δ 170.60, 155.23, 135.06, 131.08, 126.17, 124.82, 123.79, 120.52, 120.22, 113.75, 82.91, 80.19, 53.87, 28.43, 28.18, 28.04. ¹⁹F NMR (376 MHz, CDCl₃): δ 54.00. HR-ESI-MS m/z : [M+Na]⁺ Calcd for C₂₀H₂₇FN₂O₆SNa 465.14661; Found: 465.14699.

Preparation of methyl N_{α} -(*tert*-butoxycarbonyl)- N_{im} -(fluorosulfonyl)-L-histidinate (**15**)

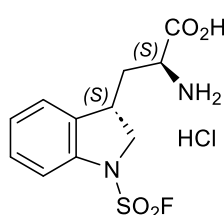
DBU (522 μ L, 3.50 mmol, 2.2 eq.) was added to a solution of Boc-His-OMe (428 mg, 1.59 mmol, 1.0 eq.) and AISF (600 mg, 1.91 mmol, 1.2 eq.) in THF (10 mL) and the reaction mixture was stirred for 2 h. Afterwards, the reaction mixture was diluted with Et₂O (40 mL) and washed with 0.5 M NaHSO₄ (3 $\times$ 10 mL) and brine (2 $\times$ 10 mL). The organic phase was dried and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane:EtOAc/1:1, TLC: R_f = 0.75) and low temperature crystallization (–25 $^{\circ}$ C) from Et₂O/pentane to afford the title compound as a colorless solid (316 mg, 899 μ mol, 57%). C₁₂H₁₈FN₃O₆S (351.35 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 7.96 (s, 1H), 7.20 (s, 1H), 5.45 (d, J = 7.5 Hz, 1H), 4.74–4.39 (m, 1H), 3.75 (s, 3H), 3.25–2.93 (m, 2H), 1.43 (s, 9H). ¹³C {¹H} NMR (101 MHz, CDCl₃): δ 171.97, 155.41, 141.58, 137.00, 115.50, 80.32, 52.70, 52.67, 30.68, 28.40. ¹⁹F NMR (376 MHz, CDCl₃): δ 59.36. HR-EI-MS m/z : [M-Boc]⁺ Calcd for C₇H₉FN₃O₄S 250.0298; Found: 250.0290.

Preparation of 1-(fluorosulfonyl)-L-tryptophan hydrochloride (**20**×HCl)

Boc-Trp(SO₂F)-OtBu (65 mg, 147 μmol, 1.0 eq.) was added to 4 M HCl in dioxan (500 μL) and the resulting mixture was stirred at 60 °C until TLC indicated full conversion (~2 h). The solvent was then removed under reduced pressure, the residue was washed with Et₂O/*n*-pentane (1:1, 2×5 mL), and remaining solvent was removed under reduced pressure to afford the title compound as a colorless solid (46 mg, 143 μmol, 97%). C₁₁H₁₂ClFN₂O₄S (322.74 g/mol). ¹H NMR (400 MHz, CD₃OD): δ 7.89 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 7.4 Hz, 1H), 7.62 (s, 1H), 7.57 – 7.42 (m, 2H), 4.39 (t, *J* = 6.4 Hz, 1H), 3.57 – 3.34 (m, 2H). ¹³C{¹H} NMR (101 MHz, CD₃OD): δ 169.66, 135.17, 129.97, 126.16, 124.82, 119.84, 117.72, 113.17, 51.98, 25.37. ¹⁹F NMR (376 MHz, CD₃OD): δ 51.68. HR-ESI-MS *m/z*: [M+H]⁺ Calcd for C₁₁H₁₂FN₂O₄S 287.04963; Found: 287.04977.

Preparation of (*S,R*)-2-amino-3-[1-(fluorosulfonyl)indolin-3-yl]propanoic acid hydrochloride ((*S,R*)-**21**×HCl)

(*S,R*)-**14** (50 mg, 112 μmol, 1.0 eq.) was dissolved in 4 M HCl in dioxan (500 μL) and the resulting mixture was stirred at 60 °C in a closed reaction vessel until TLC analysis indicated full conversion (3 h). The solvent was then removed under reduced pressure, the residue was washed with Et₂O (2×2 mL) and dried under reduced pressure to afford the title compound as a colorless solid (33 mg, 102 μmol, 91%) C₁₁H₁₄ClFN₂O₄S (324.75 g/mol). ¹H NMR (400 MHz, CD₃OD): δ 7.45 (dd, *J* = 7.5, 5.2 Hz, 2H), 7.35 (t, *J* = 8.1 Hz, 1H), 7.29 – 7.18 (m, 1H), 4.47 – 4.30 (m, 1H), 4.12 (t, *J* = 7.2 Hz, 1H), 4.00 (dd, *J* = 12.4, 4.7 Hz, 1H), 3.82 – 3.68 (m, 1H), 2.35 – 2.15 (m, 2H). ¹³C{¹H} NMR (101 MHz, CD₃OD): δ 171.37, 140.77, 134.96, 130.13, 126.74, 126.53, 115.74, 58.36, 52.17, 38.26, 37.09. ¹⁹F NMR (376 MHz, CD₃OD): δ 36.65. HR-ESI-MS *m/z*: [M+H]⁺ Calcd for C₁₁H₁₄FN₂O₄S 289.06528; Found: 289.06535.

Preparation of (*S,S*)-2-amino-3-[(1-(fluorosulfonyl)indolin-3-yl]propanoic acid hydrochloride ((*S,S*)-**21** ×HCl)

Acetyl chloride (2.8 mL, 40 mmol) was added slowly to an ice-cooled solution of (*S,S*)-**14** (47 mg, 106 μmol, 1.0 eq) in 1,2-dichloroethane (5.5 mL) and MeOH (1.6 mL, 40 mmol). The flask was closed with a screw cap and the reaction mixture was stirred until TLC indicated full conversion (~2.5 h). The solvent was then removed under reduced pressure to afford the title compound as

a colorless solid (31 mg, 96 μ mol, 91%) that could be used without further purification. $C_{11}H_{14}ClFN_2O_4S$ (324.75 g/mol) 1H NMR (400 MHz, CD_3OD): δ 7.48–7.38 (m, 2H), 7.39–7.30 (m, 1H), 7.23 (td, $J = 7.5, 1.0$ Hz, 1H), 4.49–4.29 (m, 1H), 4.26–4.10 (m, 1H), 4.10–3.96 (m, 1H), 3.93–3.72 (m, 1H), 2.57–2.38 (m, 1H), 2.19–2.04 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, CD_3OD): δ 171.31, 140.62, 135.09, 130.02, 126.79, 126.04, 115.62, 57.78, 51.99, 37.97, 36.46. ^{19}F NMR (376 MHz, CD_3OD): δ 36.54. HR-ESI-MS m/z : $[M+H]^+$ Calcd for $C_{11}H_{14}FN_2O_4S$ 289.06528; Found: 289.06533.

4.2 Radiochemistry – Materials and Methods

4.2.1 General

[^{18}F]Fluoride ($[^{18}\text{F}]\text{F}^-$) was produced via the $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ reaction by bombardment of enriched [^{18}O]H $_2$ O with 17 MeV protons in a BC1710 cyclotron (The Japan Steel Works, Tokyo, Japan) or a GE PETtrace (GE Healthcare, Chicago, USA), located at the INM-5 (Forschungszentrum Jülich GmbH). Radioactivity was measured using a CRC-120 Radioisotope Calibrator[®] from Capintec, Inc. (Florham Park, Netherlands) or a Curiementor 2 (PTW, Freiburg, Germany). The following cartridges were used for radiosyntheses and solid phase extractions (SPE): Sep-Pak[®] Plus Light QMA Carbonate cartridges (130 mg sorbent per cartridge, preconditioned with 1 mL H $_2$ O) from Waters GmbH (Eschborn, Germany) and StrataTM-X 33 μm Polymeric RP cartridges [30 mg sorbent, preconditioned with EtOH (2 mL) and H $_2$ O (10 mL)] from Phenomenex (Aschaffenburg, Germany).

Identity of radiolabeled products was confirmed by co-injection of the non-radioactive reference compounds. Radiochemical yields (RCY) corrected for decay to the start of synthesis and/or activity yields (AY, non-decay-corrected) are provided for analytically pure radiolabeled compounds. Radiochemical conversions (RCC) were determined by HPLC analysis after dilution of the reaction mixtures with H $_2$ O. The identity of radiolabeled products was confirmed by co-injection of the non-radioactive reference compounds if the amount of unlabeled precursor was insufficient for reliable detection. The decay corrected product peak areas in the chromatograms were compared to the peak area obtained by post-column injection (p.c.i.).^[15] HPLC analyses were carried out on a Dionex Ultimate[®] 3000 System with Ultimate[®] 3000 RS Variable Wavelength Detector or Ultimate[®] 3000 Diode Array Detector, coupled in series with a Berthold LB500 NaI detector. Two Rheodyne 6 port injection valves equipped with equal sample loops were installed before and behind the column. The UV and radioactivity detectors were coupled in series, giving a time delay of 0.1–0.2 min (depending on flow rate) between the corresponding responses. Columns and methods are given for each chromatogram (see SI). All radiosyntheses were carried out according to the radiation protection rules of our institute using appropriate personal protective equipment and shielding. Unless noted otherwise, 5 mL screw top V-Vials[®] (20–400 thread, 20 mm $\times$ 65 mm) were used for all radiosyntheses. Prior to their first use and after every 10–15 reactions, the vials were (re)siliconized to minimize adsorption of [^{18}F]F $^-$ to the vessel walls. To this end, the vials were incubated for 10 min with a solution of SiCl $_2$ Me $_2$ (5v%) in CH $_2$ Cl $_2$. Following incubation, the vials were sequentially rinsed with EtOAc, CH $_2$ Cl $_2$, acetone, H $_2$ O, acetone and MeOH. During the water and acetone

rinsing steps, mechanical assistance with a lint-free paper towel was applied to enhance cleaning efficiency. Finally, the vials were dried at 90 °C for 10 min prior to (re)use.

4.2.2 General SuFEx radiolabeling protocol GP 1

1. Aqueous [^{18}F] F^- (10–30 MBq) was loaded (from the male side) onto a Sep-Pak® Plus Light QMA Carbonate cartridge (130 mg sorbent, preconditioned with H_2O (1 mL)).
2. The cartridge was washed (from the male side) with MeOH (2 mL) to remove residual water.
3. [^{18}F] F^- was eluted (from the female side) with a solution of BnEt_3NCl or Et_4NOTf (10 μmol) in MeOH (1 mL).
4. The MeOH was evaporated at 80–90 °C under dynamic vacuum (~400 mbar) and in a stream of argon for 3–5 min. Complete removal of MeOH was verified by visual inspection (throughout drying is essential and should not be guided by time alone).
5. After equilibration of the reaction vessel to the desired temperature (~3 min), a solution of the precursor (30–1000 nmol, depending on the substrate) in MeCN (1 mL) was added.
6. The reaction was allowed to proceed for 1–10 min at 23–80 °C, depending on the specific substrate.
7. The reaction was quenched by addition of H_2O (~2–4 mL) and the RCC was determined by radio-HPLC.

4.2.3 Preparation of [^{18}F]**4** and [^{18}F]**5** using $\text{K}_{222}/\text{K}_2\text{CO}_3$ and application of inductive heating

[^{18}F]**4** and [^{18}F]**5** were additionally prepared using a modified version of the $\text{K}_{222}/\text{K}_2\text{CO}_3$ -based protocol with inductive heating, adapted from Jeon *et al.* to avoid labeling with aliquots.^[9] Aqueous [^{18}F] F^- was loaded (from the male side) onto a Sep-Pak® Plus Light QMA Carbonate cartridge (130 mg sorbent, preconditioned with 10 mL H_2O). The trapped [^{18}F] F^- was then eluted with a solution of K_{222} (3.76 mg, 9.99 μmol) and K_2CO_3 (0.69 mg, 5.0 μmol) in MeCN: H_2O (96:4, 1.2 mL) into a borosilicate glass vessel equipped with a silicone/PTFE septum cap (Anton Paar GmbH, Austria). The solvent was removed at 110 °C under dynamic vacuum (~400 mbar) and in a stream of argon for 10–12 min. After cooling for 3 min, the dried [^{18}F] F^- complex was redissolved in MeCN (1 mL), and a solution of the precursor (100 nmol) in MeCN (1 mL) was added. The reaction was performed in a conductively heated synthesis reactor (Monowave 50, Anton Paar GmbH, Austria). After 10 min at 60 °C, the reaction was quenched by addition of H_2O :MeCN (1:1, 2 mL) and the RCC was determined by radio-HPLC.

For comparison, labeling with our base-free protocol according to GP1 was performed using identical precursor amounts (100 nmol) and solvent volumes (2 mL). [^{18}F]**5** was labeled at 40 °C for 3 min, and [^{18}F]**4** was labeled at 80 °C for 10 min.

4.2.4 Preparation of Boc-Trp([^{18}F]SO₂F)-OMe [^{18}F]**2**

The general radiolabeling protocol GP1 was followed up to step 4.

5. After equilibration of the reactor to 40 °C, a solution of precursor **2** (30 nmol) in MeCN (1 mL) was added.
6. The reaction mixture was incubated at 40 °C for 3 min.
7. The reaction was quenched by addition of H₂O (~9 mL) and the RCC was determined by radio-HPLC.
8. The crude reaction mixture was loaded (from the female side) onto a StrataTM-X RP (30 mg) cartridge.
9. The cartridge was dried with air (50 mL syringe) and the product was eluted with EtOH (1 mL).
10. The EtOH was removed under dynamic vacuum (~400 mbar) in a stream of argon.
11. The tracer was reconstituted in 1% Tween 80 solution (200 μL).

4.2.5 Preparation of H-Trp([^{18}F]SO₂F)-OH ([^{18}F]**20**), (*S,S*)-H-Dht([^{18}F]SO₂F)-OH ((*S,S*)-**21**) and *S,R*-H-Dht([^{18}F]SO₂F)-OH ((*S,R*)-**21**)

The general radiolabeling protocol GP1 was followed up to step 4.

5. After equilibration of the reactor to the target temperature (50 °C for [^{18}F]**1**; 80 °C for [^{18}F]**14**), a solution of the precursor (**1**: 30 nmol*; **14**: 100 nmol*) in MeCN (1 mL) was added.
6. The reaction mixture was incubated for 3 min at 50 °C (**1**) or 10 min at 90 °C (**14**).
7. The reaction was quenched by addition of H₂O (~9 mL) and the RCC was determined by radio-HPLC.
8. The crude reaction mixture was loaded (from the female side) onto a StrataTM-X RP (30 mg) cartridge.
9. The cartridge was dried with air (50 mL syringe) and the product was eluted with acetone (500 μL).
10. The acetone was removed under dynamic vacuum (~400 mbar) in a stream of argon.
11. The residue was treated with 6 M HCl (100 μL) and heated at 90 °C for 10 min to cleave the protecting groups.

12. HCl was removed under dynamic vacuum (~400 mbar) in a stream of argon at 90 °C for 5–10 min using a N₂-cooled trap.

13. The tracer was reconstituted in isotonic NaCl solution or 0.1 M NaOAc buffer (pH 5.3)**.

* In radiosyntheses of probes for the *in vivo* experiments, 100 nmol of **1** and 200 nmol of (*S,S*)-**14** were used.

** For *in vivo* studies, formulation in 0.1 M NaOAc buffer was preferred over isotonic NaCl to maintain an acceptable pH for injection (4.5–8.5, per European Pharmacopeia for [¹⁸F]FET). In small formulation volumes (e.g., 500 µL), residual HCl occasionally reduced the pH to <3 if isotonic NaCl was used.

4.2.6 Preparation of [¹⁸F]FET

[¹⁸F]FET was produced at the cyclotron facility of INM-5 (Forschungszentrum, Jülich) as described previously.^[16]

4.3 Preclinical evaluation

4.3.1 pH Stability Tests

[¹⁸F]**3**, [¹⁸F]**4** and [¹⁸F]**5** were prepared according to GP1 (using 50 nmol of precursor), the reaction mixtures were diluted with H₂O (9 mL), and the crude products were loaded (from the female side) onto StrataTM-X RP cartridges (30 mg). The cartridges were washed (from the female side) with H₂O (10 mL) and dried with air (50 mL syringe). The radiolabeled products were then eluted with MeCN (500 µL), followed by addition of H₂O (500 µL). [¹⁸F]**20** and (*S,S*)- [¹⁸F]**21** were prepared as described in section 4.2.4.

For stability testing, an aliquot (~ 1–2 MBq, 100 µL) of each radiotracer was mixed with an equal volume (100 µL) of aqueous buffer solution at a defined pH (**Table S1**). At predetermined time points (5, 30, 60, 90, and 120 min), small aliquots (2.5 µL) of each solution were collected and spotted on a TLC plate. The non-radioactive reference compounds were spotted on a separate lane. The TLC plates were air-dried and developed using an appropriate mobile phase. After development, UV-active spots of the reference compounds, along with the origin and solvent front at both edges of the TLC plate, were spiked with a diluted radioactive solution to aid alignment. The TLC plates were then analyzed using a phosphor imager (BAS 5000, Fuji Pharma, Japan) and phosphor imaging plates (Fuji Pharma, Japan). Radiolabeled compounds were identified by comparing their migration distances with those of the non-radioactive reference compounds. pH values of the buffer solutions were measured using a model 766 pH

meter (Knick, Berlin, Germany) equipped with an Inlab® Micro electrode (Mettler Toledo, Columbus, USA). See SI for details.

4.3.2 *In Vitro* Analysis of H-Trp([¹⁸F]SO₂F)-OH ([¹⁸F]**20**) and (S,S)-H-Dht([¹⁸F]SO₂F)-OH ((S,S)-[¹⁸F]**21**) in Human Blood Plasma

The *in vitro* stability of H-Trp([¹⁸F]SO₂F)-OH ([¹⁸F]**20**) and (S,S)-H-Dht([¹⁸F]SO₂F)-OH ((S,S)-[¹⁸F]**21**) was assessed in human plasma obtained by centrifugation (300 rcf) of fresh, heparinized or citrated blood. For each tracer, 500 µL of plasma was prewarmed in a 2 mL Eppendorf vial at 37 °C for 5 min using a thermoshaker. A solution of the radiotracer in isotonic NaCl (~10 µL, approximately 0.5–1 MBq) was then added, and the mixture was further shaken at 37 °C. Aliquots (80 µL) of the mixtures were removed at 5, 30, 60, 90, and 120 min. To determine the recovery rate, 1 µL of each aliquot was immediately spotted on a paper strip (back-side coated with a polymer layer), while 60 µL were transferred into an Eppendorf vial containing 120 µL of MeCN for precipitation of plasma proteins. The vials were vigorously vortexed for 2 min and centrifuged at 20000 rcf for 2 min, after which the supernatant was spotted on a TLC plate (three lanes, 2 µL per time-point). The non-radioactive reference compounds were spotted on a separate lane. The TLC plates were air-dried and developed using *n*-butanol/H₂O/AcOH (5:1:1) as the mobile phase. After development, the UV-active spots of the reference compounds, the origin, and the solvent front at both edges of the TLC plate were spiked with a diluted radioactive solution to aid alignment. The TLC plates and the paper strips with untreated plasma samples were simultaneously scanned using a phosphor imager (BAS 5000, Fuji Pharma, Japan) and phosphor imaging plates (Fuji Pharma, Japan). Radioactivity recovery for the precipitation step was calculated by comparing the activity of the untreated plasma samples (paper strips) and the supernatant after protein precipitation, taking into account the dilution factor. H-Trp([¹⁸F]SO₂F)-OH ([¹⁸F]**20**) and (S,S)-H-Dht([¹⁸F]SO₂F)-OH ((S,S)-[¹⁸F]**21**) were identified by comparing their migration distance with those of the non-radioactive reference compounds.

4.3.3 Cell Culture

Human U87 MG glioblastoma cells were purchased from the American Type Culture Collection (ATCC) and cultured under normal growth conditions (37 °C and 5% CO₂) in minimum essential medium GlutaMAX (MEM, Gibco 41090 028, Fisher Scientific GmbH, Schwerte, Germany) supplemented with 10% fetal bovine serum (FBS, Sigma-Aldrich F2442, Merck KGaA, Darmstadt, Germany), 1% penicillin/streptomycin (Gibco 115140 122), and. The

cells were grown in cell-culture dishes (ThermoFisher 150350, F 100mm) with 9 mL culture medium and routinely passaged every 4–5 days after they had reached 80–90% confluency. For the cellular uptake and inhibition studies, cells were seeded into 12-well plates (2×10^5 cells in 1 mL medium/well) 48 h before the start of the experiments.

4.3.4 Cellular Uptake Experiments

Two hours before the start of the experiments, the culture medium was carefully aspirated, the cells were washed with phosphate-buffered saline (PBS, 1 mL, Gibco 10 010 023), and a dye exclusion test with trypan blue (Sigma-Aldrich T 8154) was performed to determine cell viability and the exact cell count (cell viability was always >95%). The tracer solutions were prepared in FBS- and amino acid-free Dulbecco's Phosphate-Buffered Saline (DPBS) at a concentration of 150 kBq/mL. DPBS was removed from the wells, and the tracer solution was added (1 mL/well). The cells were then incubated with the tracer solution at 37 °C for 60 min, washed twice with ice-cold PBS (1 mL), trypsinized, and harvested. The accumulated radioactivity was measured on an automatic gamma counter (Perkin Elmer, 1480 Automatic Gamma Counter, Shelton, USA). Each experiment was conducted at least in triplicate.

4.3.5 Cellular inhibition studies

For the inhibition experiments, U87 MG cells were used and cultured as described above. The following inhibitors, obtained from Sigma-Aldrich, were used: 2-(methylamino)-2-methylpropionic acid (MeAIB) for system A, L-serine for system ASC, and 2-aminobicyclo[2,2,1]heptane-2-carboxylic acid (BCH) for system L transporters. The inhibitors were diluted with DPBS to give the desired final concentrations (1.5 nM, 15 nM, or 150 nM) and added together with the tracer. After incubation for 60 min at 37 °C, the cells were processed, and the uptake of radioactivity measured, as described in section 4.3.4.

4.3.6 *In vivo* experiments

All experiments were carried out in accordance with the EU directive 2010/63/EU for animal experiments and the German Animal Welfare Act (TierSchG, 2006) and were approved by the regional authorities (State Office for Nature, Environment and Consumer Protection of North-Rhine Westphalia [LANUV NRW], Dept. Animal Welfare, license number: 81-02.04.2023.A034).

4.3.7 μ PET with Boc-Trp(^{18}F)SO₂F)-OMe (^{18}F)2 in Healthy Mice

Four healthy male C57BL/6 mice (35–40 g) were anesthetized with isoflurane (5% for induction, 2% for maintenance) in O₂/air (3:7), and a catheter for tracer injection was inserted into the lateral tail vein. Mice were placed on an animal holder (Medres, Cologne, Germany) and fixed with a tooth bar in a respiratory mask. Body temperature was maintained at 37 °C by continuous warm water flow through the wall of the animal bed. Eyes were protected from drying with Bepanthen eye and nose ointment (Bayer, Leverkusen, Germany). A dynamic PET scan in list mode was conducted using a Focus 220 micro PET scanner (CTI-Siemens, Erlangen, Germany) with a resolution at the center of field of view of 1.4 mm. Data acquisition started with intravenous injection of Boc-Trp(^{18}F)SO₂F)-OMe (^{18}F)2, 30 MBq in 125 μL) and ended after 120 min. This was followed by a 10 min transmission scan using a ^{57}Co point source for attenuation correction. After the scan was finished, the catheter was removed and the mice were allowed to recover in their home cages. After Fourier rebinning, data were reconstructed in two ways: 4 $\times$ 30 min frames for visual display and 28 frames (2 $\times$ 1 min, 2 $\times$ 2 min, 6 $\times$ 4 min, 18 $\times$ 5 min) for time-activity curves. An iterative OSEM3D/MAP algorithm with attenuation and decay correction was used. The resulting voxel sizes were 0.47 mm $\times$ 0.47 mm $\times$ 0.80 mm. All further analyses were performed with the software VINCI 5.24 (Max Planck Institute for Metabolism Research, Cologne, Germany). Standardized uptake values based on body weight (SUV_{bw}) were determined according to the following equation: SUV_{bw} = radioactivity [Bq/g] $\times$ body weight [g] $\times$ 100 / injected dose [Bq].

4.3.8 Subcutaneous glioma model

For subcutaneous tumor xenografts, a suspension of U87 MG tumor cells (1 $\times$ 10⁷ in 75 μL matrigel; n = 5) was injected subcutaneously in the scruff of the neck near the right shoulder of the mice. After 2 weeks the mice developed palpable tumors of about 0.5–1 cm³. PET scans were performed as described above with a scan time of 120 min after tracer injection (11.2 – 16.7 MBq in 125 μL i.v.). All PET images were normalized to the injected dose per kg body weight. Summed PET images over 0–120 min post injection were used for determining mean and maximum SUV_{bw} values for the tumor, muscle (thigh), kidneys, liver, intestine, and bone. The resulting voxel sizes were 0.47 mm $\times$ 0.47 mm $\times$ 0.80 mm. The tumor volume was determined using the well-defined tumor VOI. Multi-frame files (2 $\times$ 1 min, 2 $\times$ 2 min, 6 $\times$ 4 min, 6 $\times$ 5 min) were used to generate the TACs by placing VOIs on the tumor, liver, and intestine. After completion of the measurements, the tumor-bearing mice were sacrificed by cervical dislocation under deep isoflurane anesthesia.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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ABBREVIATIONS

[¹⁸ F]F ⁻	[¹⁸ F]fluoride
[¹⁸ F]FET	<i>O</i> -(2-[¹⁸ F]fluoroethyl)tyrosine
A _m	molar activity
ASAFs	aromatic sulfamoyl fluorides
ASC	alanine/serine/cysteine transporter
AY	activity yield
BCH	2-aminobicyclo[2,2,1]heptane-2-carboxylic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-en
desMe-SuFEx-IT	1-(fluorosulfonyl)-3-methyl-1 <i>H</i> -imidazole trifluoromethanesulfonate
HPLC	high-performance liquid chromatography
iso NaCl	isotonic saline
LAT1	L-type amino acid transporter
MeAIB	α-(methylamino)isobutyric acid
PBS	phosphate buffered saline
PET	positron emission tomography
QMA	quaternary methyl ammonium
RCC	radiochemical conversion
RCP	radiochemical purity
SAF	sulfamoyl fluoride
SPE	solid phase extraction
SuFEx	sulfur fluoride exchange
SUV _{bw}	standardized uptake value normalized by body weight
TBRs	target-to-background ratios
Tf	triflate
U87 MG	Uppsala 87 malignant glioma
VOI	volume of interest M

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3.3 Manuscript 2 | Aliphatic Sulfamoyl [^{18}F]Fluorides: Preparation via “Minimalist Green” Radiofluorination and Initial Biological Assessment

Abstract

Aliphatic sulfamoyl fluorides (AlSAFs) have found applications in material science and drug development. However, their radiofluorinated counterparts are so far seldom used in PET chemistry, mainly due to the lack of routes for production of [^{18}F]AlSAFs in high molar activities. Here, we introduce a "minimalist green" protocol for the efficient preparation of no-carrier-added (n.c.a.) [^{18}F]AlSAFs from imidazolium salt precursors. Radiolabeling proceeds in EtOH without the need for additives or evaporation steps, and delivers high radiochemical conversions using minimal precursor amounts. The operational simplicity of the novel labeling protocol facilitates automation, supporting production of [^{18}F]AlSAFs for preclinical and clinical studies. Furthermore, preliminary biological evaluation of an [^{18}F]AlSAF-functionalized amino acid demonstrated negligible *in vivo* defluorination, underscoring the excellent metabolic stability of [^{18}F]AlSAFs. These results establish [^{18}F]AlSAFs as robust and translationally viable scaffolds for PET tracer development that are easily accessible via the sustainable "minimalist green" approach.

The concept for the following manuscript was developed by Prof. Dr. B. D. Zlatopolskiy, J. Bertram and Prof. Dr. B. Neumaier. The organic precursor and reference compound syntheses were carried out by J. Bertram, C. Weisselberg and Prof. Dr. B. D. Zlatopolskiy. Radiosyntheses were carried out by J. Bertram. Automation of radiosynthesis was assisted by D. Antuganov. Preclinical biological investigations were carried out by Prof. Dr. H. Endepols, O. Gokhadze, Q. Wang and L. Vieth. The manuscript was jointly authored by J. Bertram, Dr. F. Neumaier, Prof. Dr. B. D. Zlatopolskiy, Prof. Dr. H. Endepols, and Prof. Dr. B. Neumaier.

Aliphatic Sulfamoyl [^{18}F]Fluorides ([^{18}F]AlSAFs): Preparation via “Minimalist Green” Radiofluorination and Initial Biological Assessment

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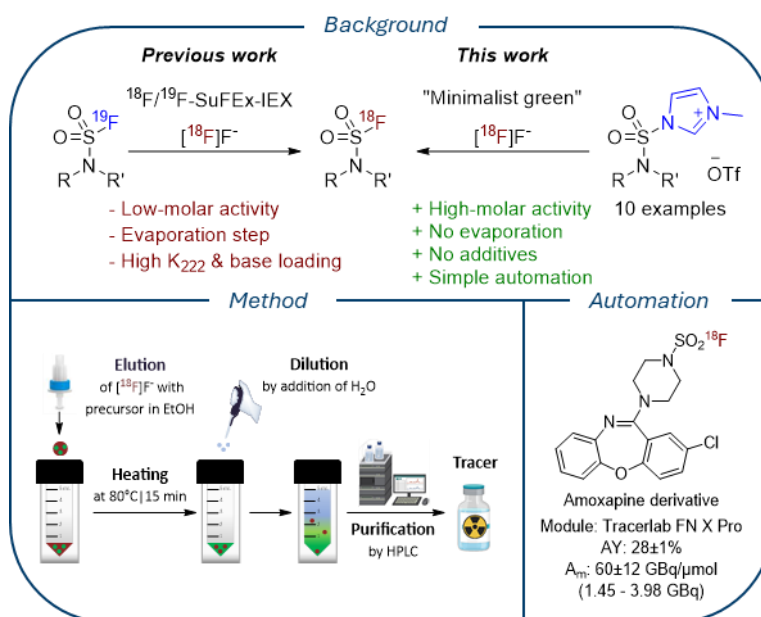
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KEYWORDS: minimalist labeling, fluorosulfate, sulfamoyl fluoride, radiofluorination

GRAPHICAL ABSTRACT



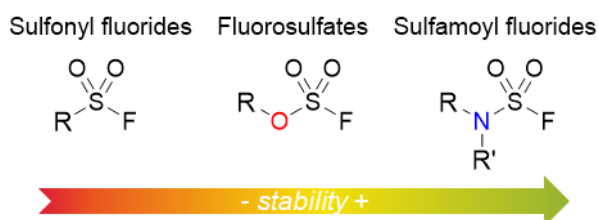
1. INTRODUCTION

Positron emission tomography (PET) is a powerful molecular imaging technique that enables non-invasive assessment of biological processes *in vivo*. The success of PET imaging critically depends on the availability of radiotracers that integrate a biologically active targeting moiety with a positron-emitting radionuclide. Among the available PET radionuclides, fluorine-18 (^{18}F) has become the most widely used isotope in clinical and research settings, primarily due to its ready availability in the form of [^{18}F]fluoride, its favorable half-life (109.8 min), and its low maximal positron energy ($E_{\text{max}} = 635 \text{ keV}$).

While direct C- ^{18}F bond formation has traditionally been the cornerstone for production of ^{18}F -labeled PET tracers, significant attention has also been devoted to heteroatom-based labeling strategies that could address limitations in functional group tolerance, synthetic accessibility, and/or reaction conditions.^[1] In this context, compounds containing a fluorosulfonyl group ($-\text{SO}_2\text{F}$, Fig. 1) have attracted particular interest due to their potential to combine synthetic tractability with hydrolytic stability. Among these, sulfonyl fluorides (CSO_2F), fluorosulfates (OSO_2F) and sulfamoyl fluorides (NSO_2F) have emerged as the most promising candidates that can be radiofluorinated via the hallex reaction or ultra-fast isotopic exchange using sulfur(VI) fluoride exchange (SuFEx) chemistry.^[2] Unfortunately, ^{18}F -labeled sulfonyl fluorides suffer from virtually instant *in vitro*^[3] and *in vivo*^[4] defluorination. The *in vivo* stability of fluorosulfate-based tracers has proven to be highly structure-dependent, with promising imaging results in some cases but significant *in vivo* defluorination in others.^[2a, 5] Sulfamoyl fluorides (SAFs), while less extensively explored, could offer a potentially more stable alternative. In a recent study, we demonstrated that aromatic SAFs (ArSAFs) can be efficiently labeled via SuFEx-based isotopic exchange, but fair *in vivo* stability remained a concern for certain structural motifs. In contrast, aliphatic sulfamoyl fluorides (AlSAFs) were characterized by notably reduced reactivity, a property that may confer enhanced *in vivo* stability. Interestingly, this limited reactivity has also been documented in medicinal chemistry studies, where AlSAFs were considered too inert for covalent inhibitor development.^[6] Although this inertness could prove advantageous for PET tracer development, AlSAFs have remained largely unexplored in PET radiochemistry, mainly due to their poor reactivity under isotopic exchange conditions. This necessitates very high precursor loadings and leads to significant non-radioactive (^{19}F -containing) carrier in the final product, reducing the achievable molar activities. High carrier content can impair the quality of PET images and/or cause undesirable effects in patients, impeding the clinical application of [^{18}F]AlSAFs prepared by isotopic exchange.

Therefore, the aim of this work was to develop a general protocol for production of no-carrier-added (n.c.a.) [^{18}F]AISAFs from sulfamoyl imidazolium precursors as a viable alternative to the established isotopic exchange approach and to assess their *in vivo* stability and imaging performance in a glioblastoma xenograft model. To meet these objectives, we adapted the "minimalist green" labeling protocol that employs EtOH as an environmentally benign and non-toxic solvent, eliminates the need for azeotropic drying or additives, and minimizes precursor quantities.^[7] This streamlined and easy-to-automate method reduces waste and simplifies the radiosynthesis while offering improved molar activities, providing a sustainable and operationally efficient route to [^{18}F]AISAFs.

Figure 1. Chemical structures of sulfonyl fluorides, fluorosulfates and sulfamoyl fluorides.



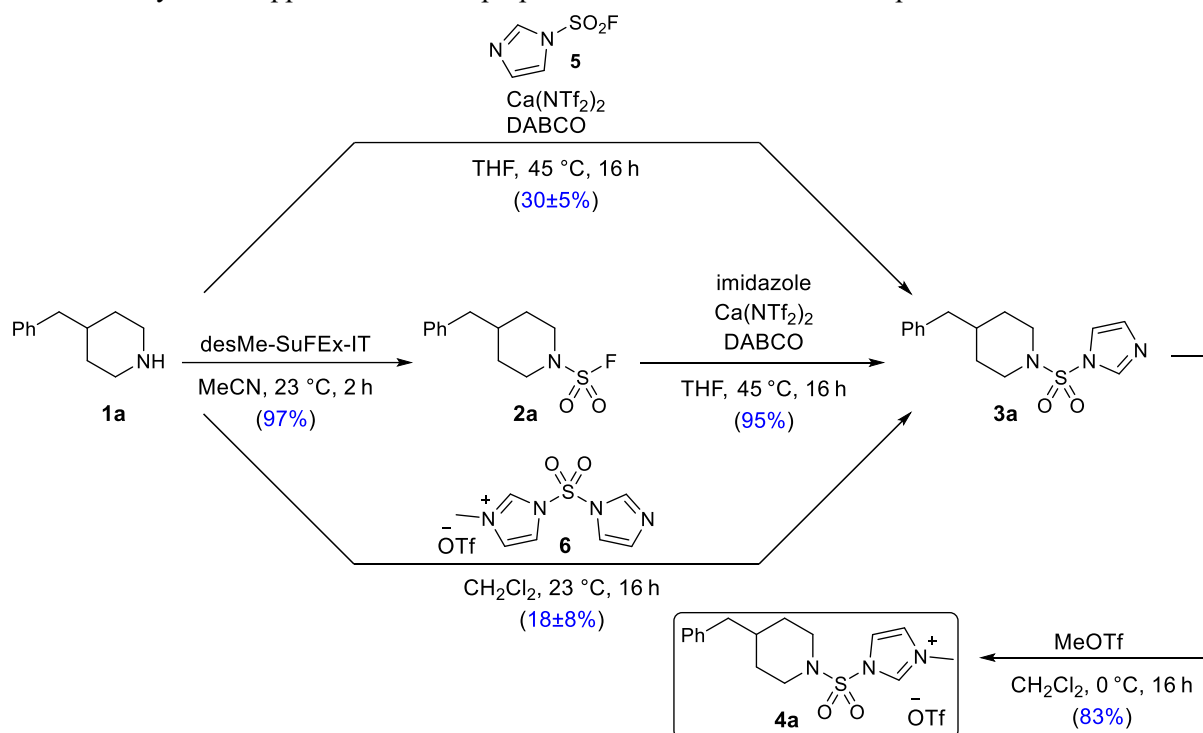
2. RESULTS AND DISCUSSION

Sulfonyl imidazoles have been widely used for the preparation of FO₂S-functionalized compounds^[8], including [^{18}F]fluorosulfates^[9]. In addition, imidazole leaving groups have proven effective for the synthesis of ^{18}F -labeled phosphorofluoridates, phosphonofluoric acids, and fluorosilanes.^{[10],[11]} Notably, *N*-methylation of sulfonyl imidazoles yields imidazolium salts with enhanced reactivity^[12], and the feasibility of fluorinating such compounds has been exemplified by the generation of sulfonyl fluoride from the fluorosulfonylating agent SuFEx-IT.^[13] Based on these precedents, we hypothesized that sulfamoyl imidazolium salts could serve as effective precursors for the n.c.a. preparation of [^{18}F]AISAFs.

To test this hypothesis, we selected 4-benzyl piperidyl sulfamoyl imidazolium salt **4a** as a model substrate for radiolabeling (Scheme 1). Initial efforts focused on preparation of the intermediate sulfonyl imidazole **3a** from the corresponding amine **1a** using mono-methylated sulfonyldiimidazole (**6**, MSDI) according to a published protocol^[12]. However, this approach afforded **3a** in <20% yields, which could not be further improved through optimization of the reaction conditions (see SI). We therefore pursued an alternative strategy involving conversion of amine **1a** into the corresponding sulfamoyl fluoride **2a** using desmethyl-SuFEx-IT^[14]. This approach not only improved overall accessibility, but also furnished the reference compound

2a. Subsequent transformation of **2a** into sulfonyl imidazole **3a** was achieved in excellent yields by adapting a protocol by Mahapatra *et al.*^[15] based on SuFEx activation with $\text{Ca}(\text{NTf}_2)_2$. Methylation of **3a** proceeded smoothly, affording the desired sulfamoyl imidazolium salt **4a** in an overall yield of 76% over three steps (Scheme 1). Attempts to bypass intermediate **2a** by direct conversion of amine **1a** into **3a** using sulfamoyl fluoride **5** afforded the desired intermediate in fair yields of $30\pm 5\%$. The precursor demonstrated excellent stability during storage at -18°C , with no signs of degradation observed for up to 1 year (see SI).

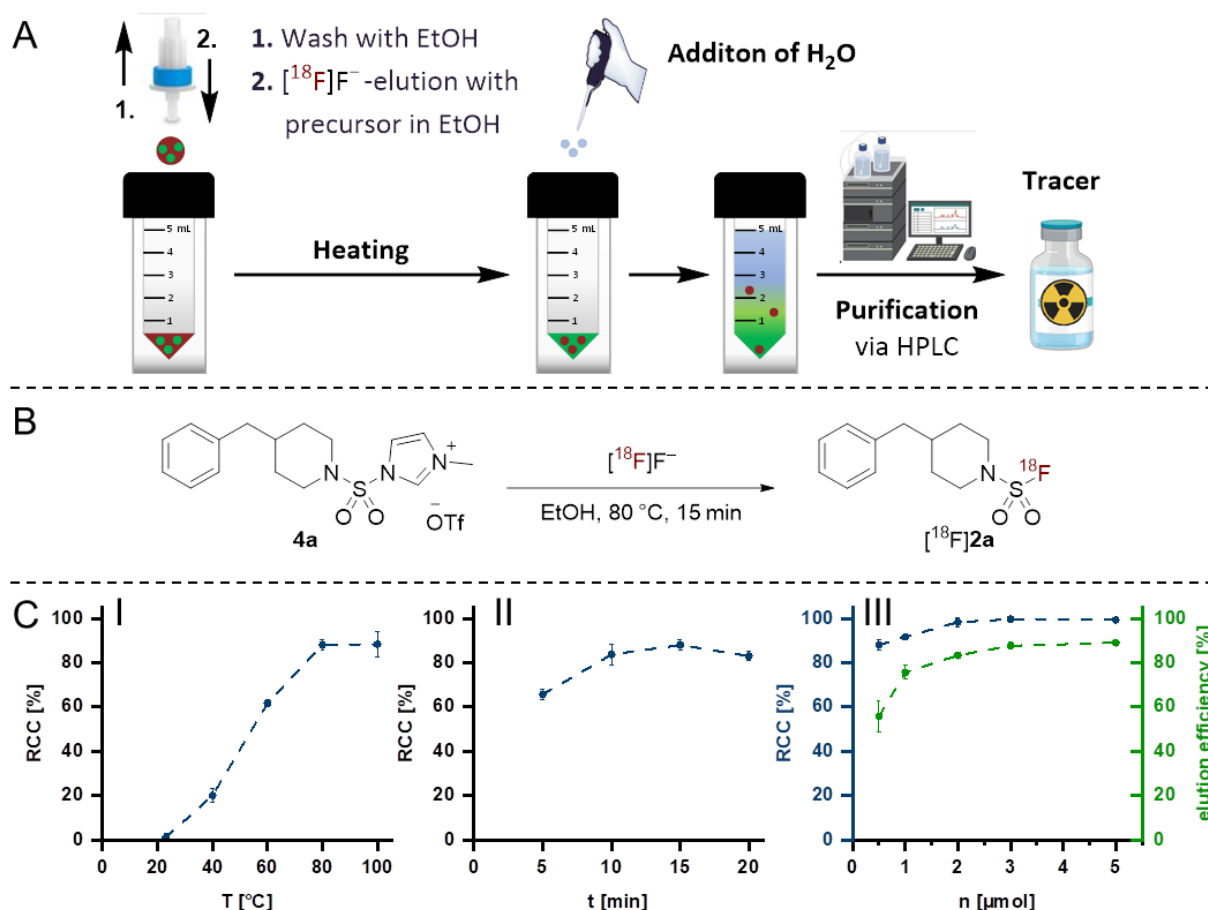
Scheme 1. Synthetic approaches for the preparation of imidazolium triflate precursors.



With the sulfamoyl imidazolium salt **4a** in hand, we next sought to identify a suitable labeling protocol. Given its exceptional simplicity, operational efficiency and sustainable nature, we selected the "minimalist green" approach previously developed in our group for the ^{18}F -labeling of strongly activated (hetero)aryl *N,N,N*-methylammonium and DABCO salts (Fig. 2A).^[7] In this method, ^{18}F fluoride ($^{18}\text{F}\text{F}^-$) is trapped on a anion exchange resin and the resin is washed with EtOH. $^{18}\text{F}\text{F}^-$ is then directly eluted with a solution of the corresponding onium salt precursor ($8\text{--}17\ \mu\text{mol}$) in EtOH and the resulting ethanolic solution of ^{18}F fluoride salts is heated at 150°C for 10–20 min to afford the corresponding radiolabeled (hetero)aromatics. This protocol proved compatible with imidazolium salt **4a**, affording the corresponding ^{18}F -labeled sulfamoyl fluoride ^{18}F **2a** in excellent radiochemical conversions (RCCs, Fig. 2B). Thus, optimization studies revealed that radiofluorination of only $0.5\ \mu\text{mol}$ precursor at temperatures as low as 80°C for 10–15 min resulted in RCCs exceeding 80% (Fig. 2C). Further increases in

temperature or reaction time did not significantly improve the RCCs, indicating that the reaction had reached a plateau.

Figure 2. Preparation of [^{18}F]AISAFs. **A** Schematic depiction of the "minimalist green" radiofluorination approach. **B** Optimization of the reaction conditions for preparation of [^{18}F]AISAFs. Conditions: **I** 0.5 μmol **4a**, 15 min. **II** 0.5 μmol **4a**, 80 $^{\circ}\text{C}$. **III** **4a**, 80 $^{\circ}\text{C}$, 15 min. EtOH (1 mL) and Sep-PakTM Plus Light QMA Carbonate cartridges (130 mg) were used in all cases. Experiments were conducted at least in triplicate. RCCs were determined by radio-HPLC.



Despite these promising RCCs, [^{18}F] F^- recoveries from standard Sep-PakTM Plus Light QMA Carbonate cartridges remained moderate at low precursor loadings (see III in Fig. 2C). In an attempt to improve [^{18}F] F^- recovery without increasing precursor amounts, we explored several modifications (Tab. 1). Co-elution with Et_4NOTf (entry 2) enhanced [^{18}F] F^- release from the cartridge, but no product formation was observed, presumably due to precursor hydrolysis under the more basic conditions (owing to the presence of $(\text{Et}_4\text{N})_2\text{CO}_3$ resulting from anion metathesis on the resin). Substitution of EtOH with MeOH (entry 3) increased [^{18}F] F^- recovery by almost 30%, but also led to a notable drop in RCCs. Other modifications, including the use of cartridges with reduced amounts of silica- or polystyrene-based sorbents (entries 4–6) or alternative counter ions like chloride (entry 7) or triflate (entries 8–9), failed to enhance [^{18}F] F^-

recovery or compromised the labeling outcome. Consequently, no further optimization was pursued. Ultimately, a precursor loading of just 1 μmol (470 μg) afforded high [^{18}F]F $^-$ recoveries of $76\pm3\%$ and excellent RCCs of $92\pm2\%$, demonstrating the suitability of the "minimalist green" protocol for efficient and reproducible radiosynthesis of [^{18}F]AISAfS.

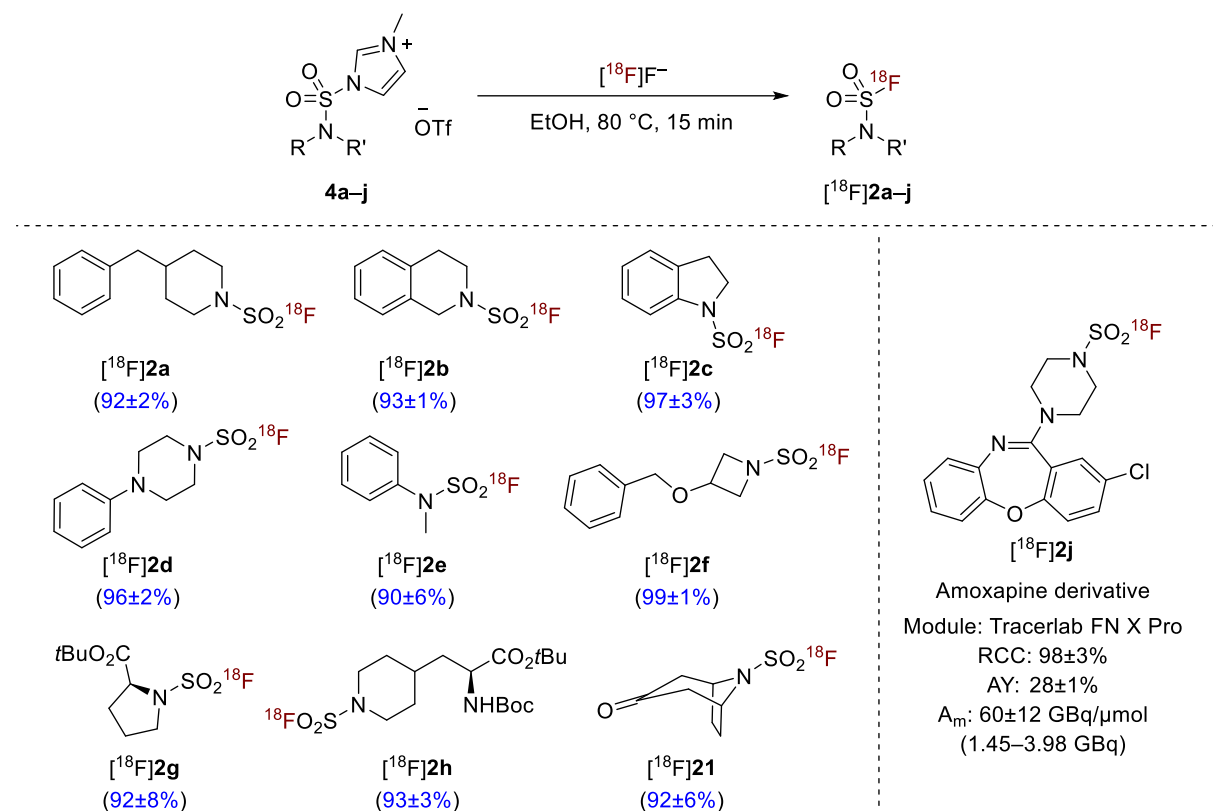
Table 1. Optimization studies to increase [^{18}F]F $^-$ recovery at low precursor loadings. 0.5 μmol **4a**

Entry	Solvent	Cartridge	Co-eluent	[^{18}F]F $^-$ recovery [%]	RCC [%]
1	EtOH	QMA-HCO $_3$ (130 mg)	-	$56\pm7\%$	$88\pm3\%$
2	EtOH	QMA-HCO $_3$ (130 mg)	Et $_4$ NOTf ^a	$91\pm4\%$	0%
3	MeOH	QMA-HCO $_3$ (130 mg)	-	$83\pm8\%$	$12\pm11\%$
4	EtOH	QMA-HCO $_3$ (46 mg)	-	$60\pm1\%$	$80\pm8\%$
5	EtOH	PS-HCO $_3$ (45 mg)	-	$55\pm3\%$	$88\pm4\%$
6	EtOH	PS-HCO $_3$ (30 mg)	-	$57\pm9\%$	$69\pm18\%$
7	EtOH	QMA-Cl (130 mg)	-	$24\pm2\%$	$48\pm1\%$
8	EtOH	QMA-OTf (130 mg) ^b	-	$31\pm2\%$	$56\pm13\%$
9	EtOH	QMA-OTf (130 mg) ^b	Et $_4$ NOTf ^a	$72\pm2\%$	$19\pm1\%$

^a 10 μmol . ^b QMA-OTf cartridges were prepared by preconditioning Sep-PakTM Plus Light QMA Carbonate cartridges (130 mg) with 0.1 M Et $_4$ NOTf (10 mL).

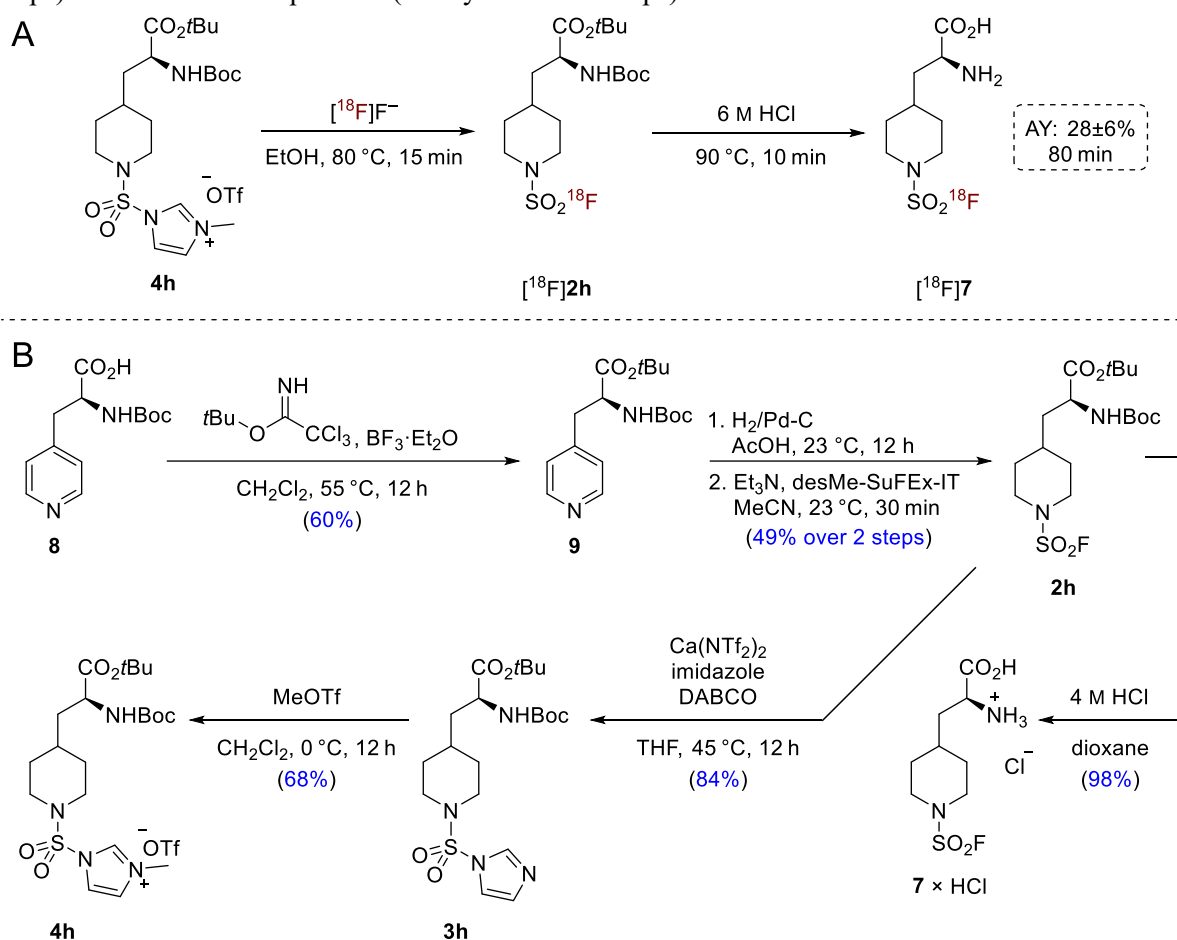
Following optimization of the radiolabeling procedure, we evaluated the substrate scope of the method using a series of ten structurally diverse imidazolium salt precursors (**4a–j**). As summarized in Scheme 2, all of these compounds were successfully converted to the corresponding [^{18}F]AISAfS, with RCCs of $>90\%$ in all cases. Notably, sulfamoyl-functionalized piperidyl and piperazyl derivatives bearing six-membered rings (**2a** and **2d**), as well as the indoline derivative **2c** with a five-membered pyrrolidine ring, were labeled in almost quantitative RCCs of 92–97%. High RCCs were also achieved for more strained systems, including the four-membered azetidine derivative [^{18}F]**2f** and the bicyclic tropinone derivative [^{18}F]**2i**. Moreover, the methyl aniline derivative **2e**, which lacks a cyclic aliphatic moiety, was successfully labeled, demonstrating the method's tolerance for acyclic substrates. *N*-Boc- and *O*-*t*Bu protecting groups commonly used in peptide and small molecule synthesis were also well tolerated, as exemplified by high RCCs for the amino acid derivatives [^{18}F]**2g** and [^{18}F]**2h**. Finally, the reaction could be readily automated on a Tracerlab FN X Pro module, enabling preparation of an ^{18}F -fluorosulfurylated derivative of the antidepressant amoxapine ([^{18}F]**2j**) in activity yields (AYs) of $28\pm1\%$ and molar activities of $60\pm12\text{ GBq}/\mu\text{mol}$ (1.45–3.98 GBq starting activity) within ~ 55 min. Taken together, these results underscore the broad applicability and functional group tolerance of the "minimalist green" protocol for n.c.a. [^{18}F]AISAf synthesis.

Scheme 2. Substrate scope of the "minimalist green" labeling protocol for the preparation of [^{18}F]AISAFs. Conditions: 1 μmol precursor, 80 $^{\circ}\text{C}$, 15 min, EtOH (1 mL), Sep-PakTM Plus Light QMA Carbonate cartridges (130 mg). Also shown are results for the automated radiosynthesis of ^{18}F -fluorosulfurylated amoxapine derivative [^{18}F]2j.



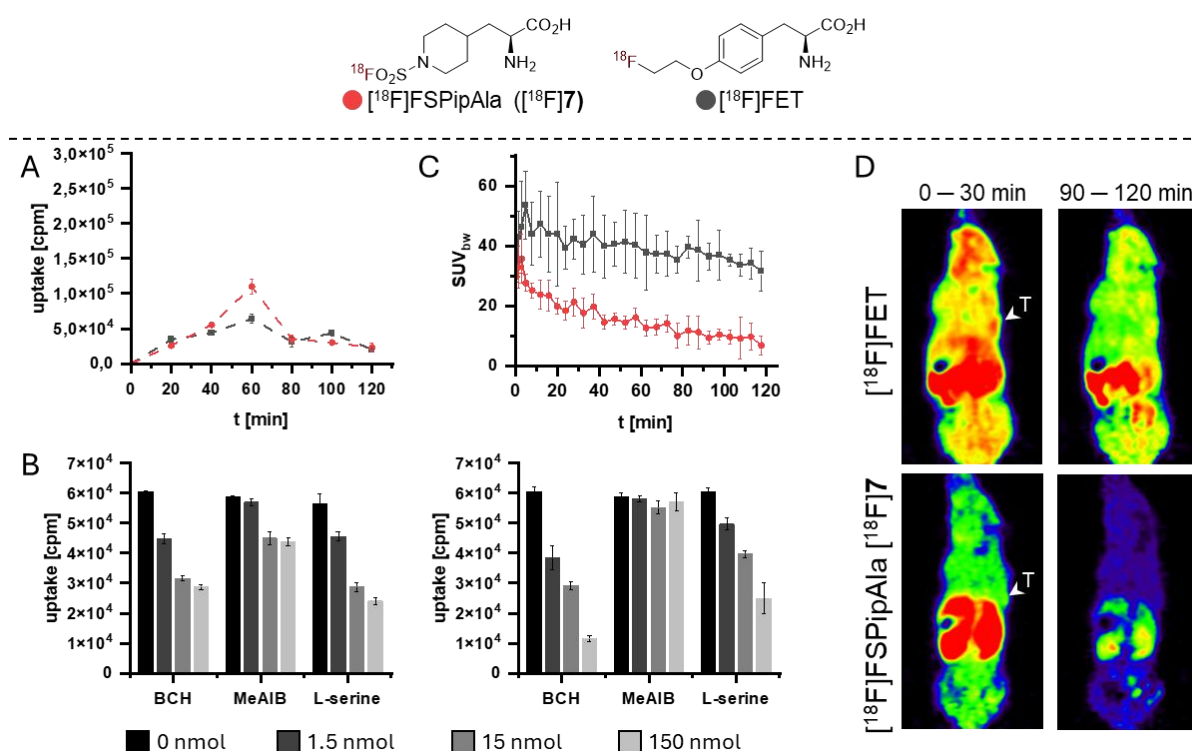
To assess the suitability of [^{18}F]AISAFs as PET tracers, we next prepared the radiolabeled amino acid [^{18}F]fluorosulfuryl piperidyl alanine (H-PipAla([^{18}F]SO₂F)-OH, [^{18}F]7) and evaluated its *in vitro* and *in vivo* properties. [^{18}F]7 was produced by "minimalist green" radiofluorination of the respective *N*-Boc- and *O*-*t*Bu-protected imidazolium precursor **4h**, followed by HPLC purification and acidic deprotection (6 M HCl at 90 $^{\circ}\text{C}$ for 10 min) of the resulting intermediate [^{18}F]2h (Scheme 3A). Finally, evaporation and formulation in 0.1 M NaOAc buffer afforded the desired tracer as a ready-to-inject solution in AYs of 28±6% within 80 min. Precursor **4h** was synthesized from commercially available Boc-2-(4-pyridyl)Ala-OH (**8**), as summarized in Scheme 3B. Briefly, esterification of **8** using *tert*-butyl trichloroacetamidate with catalytic amounts of BF₃·Et₂O afforded intermediate **9**, which was subjected to hydrogenation with H₂ on Pd/C to yield Boc-2-(4-piperidyl)Ala-*Ot*Bu (**10**). Subsequent fluorosulfonylation of **10** with desmethyl SuFEx-IT under standard conditions furnished the protected intermediate **2h**. One portion of **2h** was deprotected to afford the reference compound **7** in 29% yield over four steps. Another portion was converted to imidazolium salt **4h** using the two-step sequence described above, furnishing the radiolabeling precursor in 17% yield over five steps.

Scheme 3. A Radiosynthesis of [^{18}F]7. **B** Preparation of imidazolium precursor **4h** (17% yield over 5 steps) and reference compound **7** (29% yield over 3 steps).



The cellular uptake of [^{18}F]7 by U87 MG glioblastoma cells was evaluated in comparison to the clinically used tumor imaging agent *O*-(2-[^{18}F]fluoroethyl)tyrosine ([^{18}F]FET) as reference tracer. As illustrated in Fig. 3A, [^{18}F]7 exhibited substantial cellular accumulation, comparable to that of [^{18}F]FET, supporting its potential utility for tumor imaging. In addition, competitive inhibition assays revealed a similar inhibition profile for [^{18}F]7 and [^{18}F]FET, with inhibition of system L significantly reducing uptake of both compounds in a concentration-dependent manner (Fig. 3B). Inhibition of system ASC also reduced accumulation of both tracers, albeit to a lesser extent, indicating that both transport systems directly or indirectly contribute to cellular uptake of these probes.

Figure 3. **A** Uptake of [^{18}F]7 and [^{18}F]FET by human U87 MG glioblastoma cells. Uptake was quantified after incubation of the cells with 150 kBq of the different probes for up to 2 h. **B** Effect of different amino acid transporter inhibitors on the uptake of [^{18}F]7 (left) and [^{18}F]FET (right) by U87 MG glioblastoma cells. Uptake was quantified after incubation of the cells with 150 kBq of the probes for 1 h in the presence of the indicated inhibitor concentrations. The inhibitors used were 2-aminobicyclo[2,2,1]heptane-2-carboxylic acid (BCH) for system L, L-serine for system ASC, and α -(methylamino)isobutyric acid (MeAIB) for system A. **C** Comparison of mean time-activity curves ($n = 3$) for bone accumulation of radioactivity in measurements with [^{18}F]7 or [^{18}F]FET performed in a subcutaneous U87 MG glioblastoma mouse model. **D** Comparison of *in vivo* tumor uptake of [^{18}F]7 and [^{18}F]FET in a subcutaneous U87 MG glioblastoma mouse model. Representative vertical PET images (summed over the indicated 30 min time frames) of a tumor-bearing mouse measured (on different days) with [^{18}F]FET (top) and [^{18}F]7 (bottom).



Encouraged by these *in vitro* findings, we also examined the *in vivo* biodistribution of [^{18}F]7 in a subcutaneous U87 MG glioblastoma xenograft mouse model. Mice bearing small peripheral tumors (0.5–1.0 cm³) were intentionally selected, as such lesions are challenging to detect with radiolabeled amino acids due to their relatively high uptake in surrounding non-target tissues. As shown in Fig. 3D, [^{18}F]7 exhibited lower absolute tumor uptake than [^{18}F]FET. However, background uptake of the novel tracer was also lower, resulting in comparable target-to-background ratios (TBRs) and limited tumor visualization for both tracers (see SI for TACs). Notably, [^{18}F]7 showed faster clearance from non-target tissues, which could prove advantageous for imaging larger peripheral tumors. Elimination of both radiolabeled amino acids was predominantly via the urinary route. Importantly, very low bone uptake of radioactivity was observed for [^{18}F]7 (maximum SUV_{bw} 35±8, 0–30 min p.i.),

indicating minimal *in vivo* defluorination (Fig 3C). High metabolic stability is a critical prerequisite for the practical application of PET tracers, as radiolabeled metabolites may accumulate in non-target tissues and compromise image quality. Accordingly, the high resistance of [^{18}F]7 to *in vivo* defluorination underscores the potential of [^{18}F]AlSAFs as metabolically stable scaffolds for PET tracer development.

3. CONCLUSION

In summary, we have developed a sustainable, efficient and high-yielding method for the preparation of ^{18}F -labeled aliphatic sulfamoyl fluorides ([^{18}F]AlSAFs) by "minimalist green" radiofluorination of sulfamoyl imidazolium precursors. This approach enables rapid production of n.c.a. [^{18}F]AlSAFs in RCCs exceeding 90% across a broad substrate scope. The method is compatible with a range of cyclic and acyclic secondary amine scaffolds and tolerates common protecting groups, demonstrating its versatility for tracer development. Automated synthesis of an ^{18}F -fluorosulfurylated amoxapine derivative further highlights the potential for clinical translation of this methodology. Finally, *in vivo* evaluation of an [^{18}F]AlSAF-substituted amino acid confirmed the high metabolic stability of aliphatic sulfamoyl [^{18}F]fluorides, evidenced by negligible *in vivo* defluorination. These results establish [^{18}F]AlSAFs as chemically robust, synthetically accessible structural motifs for the development of PET tracers, offering a promising platform for future applications in molecular imaging.

4. EXPERIMENTAL SECTION

4.1 Organic Chemistry – Materials and Methods

4.1.1 General

Unless noted otherwise, all chemicals and solvents were purchased from VWR International GmbH (Darmstadt, Germany), Sigma-Aldrich Chemie GmbH (Steinheim, Germany), ABCR GmbH (Karlsruhe, Germany), Apollo Scientific Ltd. (Bredbury, United Kingdom), Alfa Aesar GmbH (Karlsruhe, Germany), or BLD Pharmatech GmbH (Kaiserslautern, Germany) and used without further purification.

All reactions were carried out with magnetic stirring (unless noted otherwise) and organic extracts were dried over anhydrous MgSO_4 . Air- or moisture-sensitive reagents were handled under argon (>99.999%, Air Liquide GmbH, Düsseldorf, Germany). Solutions were concentrated under reduced pressure (1–900 mbar) at 40–50 °C using a rotary evaporator (Heidolph GmbH & Co. KG, Schwabach, Germany).

4.1.2 Nuclear magnetic resonance (NMR) spectroscopy

NMR spectra were measured at ambient temperature in deuteriochloroform (CDCl_3), trideuteroacetonitrile (CD_3CN), or tetradeuteromethanol (CD_3OD) as indicated, using a Bruker Ascend™ 400 (^1H : 400 MHz; $^{13}\text{C}\{^1\text{H}\}$: 101 MHz; ^{19}F : 376 MHz; Bruker Biospin GmbH, Rheinstetten, Germany). The measured chemical shifts are reported in δ [ppm] relative to residual peaks of non-deuterated solvents. Higher order NMR spectra were approximately interpreted as first-order spectra if possible. The observed signal multiplicities are characterized as follows: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, and td = triplet of doublets. Coupling constants J are reported in hertz (Hz).

4.1.3 Mass spectrometry (MS)

Low resolution electrospray ionization mass spectrometry (LR-ESI-MS) was performed with an MSQ Plus™ mass spectrometer (Thermo Electron Corporation, San Jose, USA). High resolution electrospray ionization mass spectrometry (HR-ESI-MS) was performed with an LTQ XL™ Orbitrap™ (Thermo Fisher Scientific Inc., Bremen, Germany). High resolution electron ionization mass spectrometry (HR-EI-MS) and high resolution positive chemical ionization mass spectrometry (HR-PCI-MS) were performed with an Exactive™ GC Orbitrap™ (Thermo Fisher Scientific Inc., Bremen, Germany).

4.1.4 Column chromatography

Manual column chromatography was performed with silica gel, 60 Å, 230–400 mesh particle size from VWR International GmbH (Darmstadt, Germany) or silica gel (w/0.1% Ca), 60 Å, 230–400 mesh particle size from Sigma-Aldrich GmbH (Steinheim, Germany). Automated column chromatography was performed on a Büchi Pure C-815 flash system (Büchi Labortechnik GmbH, Essen, Germany) using Reveleris™ C₁₈ reversed phase cartridges (Büchi Labortechnik GmbH, Essen, Germany).

4.1.5 Thin layer chromatography (TLC)

TLC was performed using aluminum sheets coated with silica gel 0.25 mm SIL G/UV 254 (Merck KGaA, Darmstadt, Germany). Chromatograms were inspected under UV light ($\lambda = 254$ nm) and/or stained with phosphomolybdic acid (4% in EtOH), ninhydrin (0.5% in 1-butanol) or potassium permanganate solution (0.75% KMnO₄, 5% K₂CO₃ and 0.07% NaOH in H₂O).

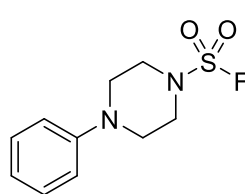
4.1.6 Chemistry

4.1.6.1 Preparation of sulfamoyl fluorides

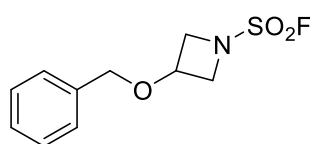
Methyl(phenyl)sulfamoyl fluoride (**2e**), 1,2,3,4-tetrahydroisoquinoline-2-sulfonyl fluoride (**2b**), indoline-1-sulfonyl fluoride (**2c**), 4-benzylpiperidine-1-sulfonyl fluoride (**2a**), 4-(2-chlorodibenzo[b,f][1,4]oxazepin-11-yl)piperazine-1-sulfonyl fluoride (**2j**), 3-(imidazole-1-sulfonyl)-1-methyl-3*H*-imidazole-1-ium trifluoromethanesulfonate (MSDI), and 1*H*-imidazole-1-sulfonyl fluoride were prepared as described by Bertram *et al.*^[14]

General procedure for the preparation of sulfamoyl fluorides (**GP1**)

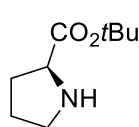
Desmethyl SuFEx-IT (1.1 eq.) was added to a solution of the amine substrate (1.0 eq.) in MeCN (2–5 mL), and the mixture was stirred until TLC or HPLC indicated full conversion (15–90 min). Unless noted otherwise, the products were purified by dry load column chromatography or filtration over a silica plug with an appropriate solvent.

4-Phenylpiperazine-1-sulfonyl fluoride (**2d**)

2d (212 mg, 868 μ mol, 94%, colorless solid) was prepared according to GP1 from 4-phenylpiperazine (150 mg, 925 μ mol) and purified by column chromatography (*n*-hexane EtOAc: = 10:1, TLC: R_f = 0.26). Molecular formula (molecular mass): C₁₀H₁₃FN₂O₂S (244.28 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 7.40 – 7.27 (m, 2H), 7.01 – 6.90 (m, 3H), 3.67 – 3.57 (m, 4H), 3.38 – 3.24 (m, 4H). ¹³C {¹H} NMR (101 MHz, CDCl₃): δ 150.50, 129.53, 121.54, 117.34, 48.97, 47.14. ¹⁹F NMR (376 MHz, CDCl₃): δ 39.13. HR-EI-MS m/z : [M]⁺ calcd for C₁₀H₁₃FN₂O₂S 244.06763; found, 244.0678.

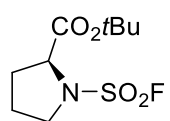
3-(Benzyloxy)azetidine-1-sulfonyl fluoride (**2f**)

2f (267 mg, 1.09 mmol, 87%, colorless liquid) was prepared according to GP1 from 3-(benzyloxy)azetidine hydrochloride (250 mg, 1.25 mmol) in the presence of Et₃N (190 μ L, 139 mg, 1.38 mmol, 1.1 eq.) and purified by filtration over a silica plug (*n*-hexane EtOAc: = 10:1, R_f = 0.21). Molecular formula (molecular mass): C₁₀H₁₂FNO₃S (245.27 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 7.60 – 7.28 (m, 5H), 4.50 (s, 2H), 4.45 – 4.37 (m, 1H), 4.24 – 4.17 (m, 2H), 4.11 – 4.04 (m, 2H). ¹³C {¹H} NMR (101 MHz, CDCl₃): δ 136.50, 128.88, 128.65, 128.22, 72.02, 66.26, 60.37. ¹⁹F NMR (376 MHz, CDCl₃): δ 29.27. HR-ESI-MS m/z : [M+Na]⁺ calcd for C₁₀H₁₂FNO₃SNa 268.04141; found, 268.04163.

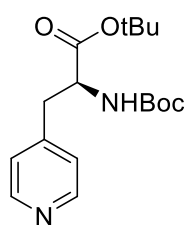
tert-Butyl L-prolinate (**10**)^[16]

HClO₄ (5 ml) was added dropwise to a solution of L-proline (4.00 g, 34.7 mmol, 1.0 eq.) in *t*BuOAc (74 mL, 0.50 mol), and the mixture was stirred for 24 h. A second portion of HClO₄ (7 mL) was then added and the mixture was stirred for another 5 h. The reaction mixture was quenched with NaHCO₃ and brought to pH 6 before the solvent was removed under reduced pressure. The residue was taken up into 27% NH₃ solution and extracted with Et₂O (3 $\times$ 20 mL). The organic phase was dried, concentrated under reduced pressure and the residue was purified by bulb-to-bulb distillation to afford **10** (1.10 g, 6.42 mmol, 19%) as a colorless liquid. Molecular formula (molecular mass): C₉H₁₇NO₂ (171.24 g/mol). ¹H NMR (300 MHz, CDCl₃): δ 3.68 – 3.54 (m, 1H), 3.14 – 2.97 (m, 1H), 2.93 – 2.81 (m, 1H), 2.16 – 1.99 (m, 1H), 1.85 – 1.62 (m, 3H), 1.44 (s, 9H).*

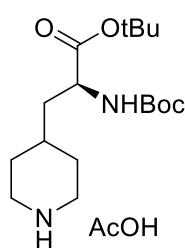
* ¹H NMR spectrum in accordance with the literature.^[16]

tert-Butyl (fluorosulfonyl)-L-prolinate (**2g**)

2g (359 mg, 1.41 mmol, 81%, colorless oil) was prepared according to GP1 from *tert*-butyl L-prolinate (300 mg, 1.75 mmol) and purified by filtration over a silica plug (*n*-hexane:EtOAc= 10:1, TLC: R_f = 0.18). Molecular formula (molecular mass): $C_9H_{16}FNO_4S$ (253.29 g/mol). 1H NMR (400 MHz, $CDCl_3$): δ 4.41 – 4.26 (m, 1H), 3.80 – 3.50 (m, 2H), 2.39 – 2.21 (m, 1H), 2.18 – 1.97 (m, 3H), 1.48 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 169.58, 82.83, 62.64, 49.89, 31.03, 27.99, 24.55. ^{19}F NMR (376 MHz, $CDCl_3$): δ 44.83. HR-ESI-MS m/z : $[M+Na]^{+}$ calcd for $C_9H_{16}FNO_4SNa$ 276.06763; found, 276.06782.

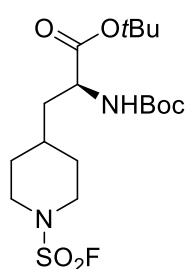
tert-Butyl (*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-(pyridin-4-yl)propanoate (**9**)

tert-Butyl 2,2,2-trichloroacetimidate (1.64 g, 7.52 mmol, 4.0 eq.) was added (under argon) to a solution of (*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-(pyridin-4-yl)propanoic acid (500 mg, 1.88 mmol, 1.0 eq.) in dry CH_2Cl_2 and the mixture was stirred for 12 h at 55 °C. Since TLC indicated incomplete conversion, the mixture was cooled to 0 °C and a drop of $BF_3 \cdot Et_2O$ was added. After gradual warming of the reaction mixture to ambient temperature and stirring for 16 h, TLC indicated full conversion. The flask was then cooled to –18 °C, a mixture of CH_2Cl_2/n -pentane (1:1, –18 °C) was added, and the resulting precipitate was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was taken up into Et_2O . The organic phase was successively washed with saturated $NaHCO_3$ ($\times 1$), H_2O ($\times 1$) and brine ($\times 2$), before it was dried and concentrated under reduced pressure. The residue was treated with *n*-pentane, the resulting precipitate was removed by filtration, and the filtrate was concentrated under reduced pressure. Any residual volatiles were then removed by bulb-to-bulb distillation (120 °C, 1 mbar), and the remaining brown oil was purified by column chromatography (*n*-hexane:EtOAc = 1.5:1, TLC R_f = 0.13) to afford **9** (361 mg, 1.12 mmol, 60%) as a colorless oil. Molecular formula (molecular mass): $C_{17}H_{26}N_2O_4$ (322.41 g/mol). 1H NMR (400 MHz, $CDCl_3$): δ 8.50 (d, J = 4.7 Hz, 2H), 7.12 (d, J = 4.8 Hz, 2H), 5.08 (d, J = 6.5 Hz, 1H), 4.48 (d, J = 6.4 Hz, 1H), 3.17 – 2.88 (m, 2H), 1.41 (s, 9H), 1.39 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): 170.46, 155.11, 149.71, 146.00, 124.98, 82.79, 80.11, 54.24, 38.16, 28.41, 28.07. HR-ESI-MS m/z : $[M+H]^+$ calcd for $C_{17}H_{27}N_2O_4$; 323.19650 found, 323.19650; $[M+Na]^+$ calcd for $C_{17}H_{26}N_2O_4Na$; 345.17848 found, 345.17839.

tert-Butyl (S)-2-[(*tert*-butoxycarbonyl)amino]-3-(piperidin-4-yl)propanoyl acetate (**11**)

A dried flask containing 5% Pd/C (5 wt.%, 132 mg, 124 μ mol, 0.2 eq.) was evacuated and flushed with argon ($\times 2$). AcOH (5 mL) and **9** were added and the flask was evacuated (100 mbar) and purged with argon ($\times 3$), followed by attachment of a H₂-filled balloon. The flask was again evacuated and purged with H₂ ($\times 3$), and the mixture was stirred under H₂-atmosphere for 22 h. The

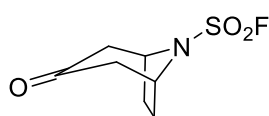
catalyst was then removed by filtration through a glass frit and the filter cake was washed with MeOH. The combined filtrate and washings were concentrated under reduced pressure and residual volatiles were removed by successive co-evaporation with toluene and EtOAc to afford raw **11** (240 mg, 618 μ mol, raw yield: 99%) as a colorless oil, which was used for the next step without further purification. Molecular formula (molecular mass): C₁₉H₃₆N₂O₆ (388.50 g/mol). HR-ESI-MS m/z : [M+H]⁺ calcd for C₁₇H₃₃N₂O₄ 329.24348; found, 329.24351; [M+Na]⁺ calcd for C₁₇H₃₂N₂O₄Na 351.22543; found, 351.22559.

tert-Butyl (S)-2-[(*tert*-butoxycarbonyl)amino]-3-[1-(fluorosulfonyl)piperidin-4-yl]propanoate (**2h**)

2h (125 mg, 304 μ mol, 49%, colorless oil) was prepared according to GP1 from **11** (240 mg, 618 μ mol) in the presence of Et₃N (137 μ L, 100 mg, 989 μ mol) and purified by column chromatography (*n*-hexane:EtOAc: = 6:1, TLC: R_f = 0.15). Molecular formula (molecular mass): C₁₇H₃₁FN₂O₆S (410.50 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 4.98 (d, J = 8.2 Hz, 1H), 4.29 – 3.99 (m, 1H), 3.98 – 3.82 (m, 2H), 3.05 – 2.86 (m, 2H), 2.17 – 1.73 (m, 2H),

1.72 – 1.16 (m, 5H), 1.47 (s, 9H) 1.44 (s, 9H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 172.09, 155.61, 82.39, 80.10, 51.75; 47.60; 47.55*, 39.81, 31.92, 31.26; 30.45*; 28.45, 28.15. ¹⁹F NMR (376 MHz, CDCl₃): δ 40.23. HR-ESI-MS m/z : [M+Na]⁺ calcd for C₁₇H₃₁FN₂O₆SNa 433.1779067; found, 433.17802.

*Additional aliphatic ¹³C-Signals have been reported for similar piperidyl alanine derivatives.^[17]

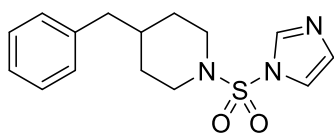
3-Oxo-8-azabicyclo[3.2.1]octane-8-sulfonyl fluoride (**2i**)

2i (287 mg, 1.39 mmol, 90%, colorless solid) was prepared according to GP1 from desmethyltropinone hydrochloride (250 mg, 1.55 mmol) in the presence of Et₃N (236 μ L, 172 mg, 1.70 mmol, 1.1 eq.) and purified by filtration over a silica plug (*n*-hexane:EtOAc = 5:1, TLC: R_f = 0.25). Molecular formula (molecular mass): C₇H₁₀FNO₃S (207.22 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 4.77 – 4.46 (m, 2H), 2.87 (dd, J = 16.9, 4.7 Hz, 2H), 2.52 – 2.42 (m, 2H), 2.37 – 2.25 (m, 2H), 1.90 – 1.76 (m, 2H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 204.57, 58.01, 48.85, 29.40. ¹⁹F NMR (376 MHz, CDCl₃): δ 48.69. HR-PCI-MS m/z : [M+H]⁺ calcd for C₇H₁₁FNO₃³²S 208.04382; found, 208.0435.

4.1.6.2 Preparation of sulfonyl imidazoles

General procedure for the preparation of sulfonyl imidazoles (**GP2**)

Sulfonyl imidazoles were prepared following a modified procedure by Mahapatra *et al.*^[15] A solution of the corresponding sulfamoyl fluoride (1.0 eq.), imidazole (1.3 eq.), DABCO (1.5 eq.) and Ca(NTf₂)₂ (1.3 eq.) in dry THF (0.5 M) was stirred at 40 °C until TLC indicated full conversion (~ 12 h). The solvent was removed under reduced pressure and the residue was taken up into EtOAc. The organic phase was washed with sat. NH₄Cl or 0.1 M NaHCO₃ ($\times$ 2), dried and concentrated under reduced pressure. Unless noted otherwise, the crude products were purified by column chromatography with dry loading using an alumina plug to retain residual HN(Tf)₂ (see SI, Fig.S1). Complete removal of NTf₂ was confirmed by ¹⁹F-NMR experiments.

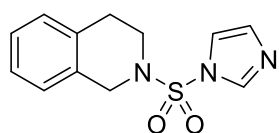
1-[(1*H*-Imidazol-1-yl)sulfonyl]-4-benzylpiperidine (**3a**)

3a (170 mg, 556 μ mol, 95%, colorless solid) was prepared according to GP2 from **2a** (150 mg, 583 μ mol) and purified by RP chromatography. Conditions: column: FlashPure Select C₁₈ 4 g (Büchi Labortechnik GmbH, Essen, Germany); eluent: 0–27 min: 35 $\rightarrow$ 60% MeCN, 27–32 min: 60 $\rightarrow$ 90% MeCN, 32–37 min: 90% MeCN, 37–41 min: 90 $\rightarrow$ 100% MeCN; flow-rate: 15 mL/min; detection: UV, λ = 210, 220, 254, 280 nm. (*n*-hexane:EtOAc = 1:1, TLC: R_f = 0.31). Molecular formula (molecular mass): C₁₅H₁₉N₃O₂S (305.40 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 7.88 (s, 1H), 7.32 – 7.03 (m, 7H), 3.91 – 3.76 (m, 2H), 2.52 (d, J = 7.1 Hz, 2H), 2.47 (td, J = 12.2, 2.6 Hz, 2H), 1.72 (d, J = 13.8 Hz, 2H), 1.61 – 1.47 (m, 1H), 1.38 – 1.20 (m, 2H). ¹³C{¹H} NMR* (101 MHz, CDCl₃): δ 139.31, 130.53, 129.10, 128.71, 128.55, 126.42, 117.76, 47.01, 42.49, 36.93, 30.89. HR-ESI-MS m/z : [M+H]⁺ calcd for C₁₅H₂₀N₃O₂S

306.12707; found, 306.12692, $[M+Na]^+$ calcd for $C_{15}H_{19}N_3O_2SNa$ 328.10902; found, 328.10894.

* Note that phase inversion or lack of the C-2 signal of the imidazole moiety in the APT spectrum has been described in the literature as a “regular feature” of these compounds (for details see^[18]).

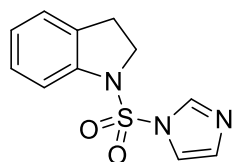
2-[(1*H*-Imidazol-1-yl)sulfonyl]-1,2,3,4-tetrahydroisoquinoline (**3b**)



3b (167 mg, 634 μ mol, 91%, colorless solid) was prepared according to GP2 from **2b** (150 mg, 697 μ mol). Column chromatography: *n*-hexane:EtOAc = 1.5:1, TLC: R_f = 0.21. Molecular formula (molecular mass): $C_{12}H_{13}N_3O_2S$ (263.32 g/mol). 1H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.29 – 7.24 (m, 1H), 7.23 – 7.16 (m, 2H), 7.15 – 7.01 (m, 3H), 4.43 (s, 2H), 3.54 (t, J = 6.0 Hz, 2H), 2.93 (t, J = 6.1 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 132.42, 130.88, 130.10, 129.05, 127.54, 127.00, 126.34, 117.63, 47.84, 44.41, 28.31.* HR-ESI-MS m/z : $[M+H]^+$ calcd for $C_{12}H_{14}N_3O_2S$ 264.08012; found, 264.08034.

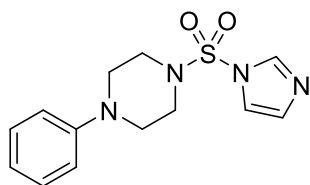
* Note that phase inversion or lack of the C-2 signal of the imidazole moiety in the APT spectrum has been described in the literature as a “regular feature” of these compounds (for details see^[18]).

1-[(1*H*-Imidazol-1-yl)sulfonyl]indoline (**3c**)



3c (91 mg, 365 μ mol, 86%, colorless solid) was prepared according to GP2 from **2c** (86 mg, 427 μ mol). Column chromatography: *n*-hexane:EtOAc = 2.5:1, TLC: R_f = 0.16. Molecular formula (molecular mass): $C_{11}H_{11}N_3O_2S$ (249.29 g/mol). 1H NMR (400 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.34 – 7.22 (m, 1H), 7.21 – 7.06 (m, 3H), 7.06 – 7.00 (m, 1H), 3.98 (t, J = 8.3 Hz, 2H), 2.98 (t, J = 8.3 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 139.78, 136.70, 131.84, 130.57, 128.31, 125.79, 125.72, 117.74, 115.53, 51.00, 27.94. HR-ESI-MS m/z : $[M+H]^+$ calcd for $C_{11}H_{12}N_3O_2S$ 250.06447; found, 250.06467, $[M+Na]^+$ calcd for $C_{11}H_{11}N_3O_2SNa$ 272.04641; found, 272.04682.

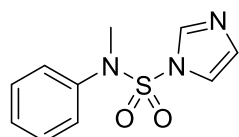
1-[(1*H*-Imidazol-1-yl)sulfonyl]-4-phenylpiperazine (**3d**)



3d (113 mg, 388 μ mol, 95%, colorless solid) was prepared according to GP2 from **2d** (100 mg, 409 μ mol). Column chromatography: CH_2Cl_2 :MeOH = 40:1, TLC: R_f = 0.22. Molecular

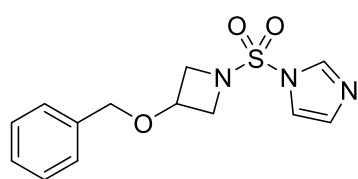
formula (molecular mass): C₁₃H₁₆N₄O₂S (292.36 g/mol). ¹H NMR (300 MHz, CDCl₃): δ 7.95 (s, 1H), 7.37 – 7.24 (m, 3H), 7.19 (s, 1H), 7.03 – 6.85 (m, 3H), 3.43 – 3.31 (m, 4H), 3.31 – 3.20 (m, 4H). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 150.34, 136.76, 130.91, 129.49, 121.60, 117.79, 117.35, 49.06, 46.57. HR-EI-MS *m/z*: [M]⁺ calcd for C₁₃H₁₆N₄O₂S 292.0989; found, 292.0990.

N-Methyl-*N*-phenyl-1*H*-imidazole-1-sulfonamide (**3e**)



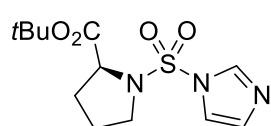
3e (115 mg, 483 μmol, 61%, colorless oil) was prepared according to GP2 from **2e** (150 mg, 793 μmol). Column chromatography: *n*-hexane:EtOAc = 1.5:1, TLC: *R_f* = 0.21. Molecular formula (molecular mass): C₁₀H₁₁N₃O₂S (237.28 g/mol). ¹H NMR (300 MHz, CDCl₃): δ 7.67 (s, 2H), 7.42 – 7.33 (m, 3H), 7.15 – 7.00 (m, 4H), 3.31 (s, 3H). ¹³C{¹H} NMR (75 MHz, CDCl₃): 139.53, 137.23, 130.44, 129.81, 129.18, 126.93, 118.20, 39.49. [M+H]⁺ calcd for C₁₀H₁₂N₃O₂S 238.06447; found, 238.06436.

1-[(1*H*-Imidazol-1-yl)sulfonyl]-3-(benzyloxy)azetidine (**3f**)



3f (120 mg, 409 μmol, 67%, colorless oil) was prepared according to GP2 from **2f** (150 mg, 612 μmol). Column chromatography: *n*-hexane:EtOAc = 1.5:1, *R_f* = 0.16. Molecular formula (molecular mass): C₁₃H₁₅N₃O₃S (293.34 g/mol). ¹H NMR (300 MHz, CDCl₃): δ 7.93 (s, 1H), 7.43 – 7.26 (m, 4H), 7.25 – 7.17 (m, 3H), 4.38 (s, 2H), 4.31 – 4.16 (m, 1H), 4.13 – 3.99 (m, 2H), 3.78 – 3.62 (m, 2H). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 137.21, 136.43, 130.75, 128.84, 128.63, 128.15, 118.50, 71.93, 65.68, 59.62. HR-ESI-MS *m/z*: [M+H]⁺ calcd for C₁₃H₁₆N₃O₃S 294.09069; found, 294.09077, [M+Na]⁺ calcd for C₁₃H₁₅N₃O₃SNa 316.07263; found, 316.07271.

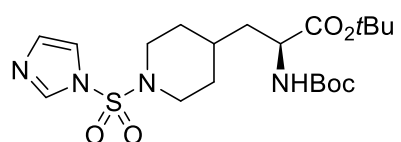
tert-Butyl [(1*H*-imidazol-1-yl)sulfonyl]-L-prolinate (**3g**)



3g (57 mg, 189 μmol, 67%, colorless oil) was prepared according to GP2 from **2g** (72 mg, 284 μmol). Column chromatography: *n*-hexane:EtOAc = 1.5:1, TLC: *R_f* = 0.24. Molecular formula (molecular mass): C₁₂H₁₉N₃O₄S (301.36 g/mol). ¹H NMR (300 MHz, CDCl₃): δ 7.95 (s, 1H), 7.40 – 7.30 (m, 1H), 7.19 – 7.08 (m, 1H), 4.23 (dd, *J* = 8.3, 3.3 Hz, 1H), 3.63 – 3.49 (m, 1H), 3.47 – 3.29 (m, 1H), 2.21 – 1.94 (m, 3H), 1.92 – 1.82 (m, 1H), 1.46 (s, 9H). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 169.97, 137.08, 130.60, 117.88, 82.82, 62.33, 49.12, 31.12, 28.01, 24.50. HR-ESI-

MS m/z : $[M+H]^+$ calcd for $C_{12}H_{20}N_3O_4S$ 302.11690; found, 302.11711, $[M+Na]^+$ calcd for $C_{12}H_{21}N_3O_4SNa$ 324.09885; found, 324.09904.

tert-Butyl (*S*)-3-{1-[(1*H*-imidazol-1-yl)sulfonyl]piperidin-4-yl}-2-[(*tert*-butoxycarbonyl)-amino]propanoate (**3h**)

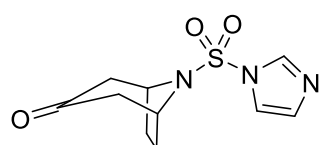


3h (77 mg, 169 μ mol, 84%, colorless solid) was prepared according to GP2 from **2h** (82 mg, 200 μ mol) and purified by RP column chromatography. Conditions: column: FlashPure

Select C_{18} 1 g (Büchi Labortechnik GmbH, Essen, Germany); eluent: 0–25 min: 15 $\rightarrow$ 60% MeCN, 25–30 min: 60 $\rightarrow$ 80% MeCN, 30–35 min: 80 $\rightarrow$ 100% MeCN, 35–40 min: 100% MeCN, flow-rate: 15 mL/min; detection: UV, λ = 210, 220, 254, 280 nm. (TLC: *n*-hexane:EtOAc = 1:1, R_f = 0.34). Molecular formula (molecular mass): $C_{20}H_{34}N_4O_6S$ (458.57 g/mol). 1H NMR (400 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.22 (s, 1H), 7.12 (s, 1H), 4.96 (d, J = 8.4 Hz, 1H), 4.26 – 3.91 (m, 1H), 3.89 – 3.75 (m, 2H), 2.58 – 2.36 (m, 2H), 1.97 (d, J = 12.7 Hz, 1H), 1.73 (d, J = 12.5 Hz, 1H), 1.67 – 1.53 (m, 1H), 1.52 – 1.56 (m, 1H), 1.42 (s, 9H), 1.39 (s, 9H), 1.36 – 1.15 (m, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 171.97, 155.56, 136.68, 130.54, 117.77, 82.29, 80.01, 51.68, 46.84, 39.49; 31.60, 31.30; 30.45, 28.38, 28.07. HR-ESI-MS m/z : $[M+H]^+$ calcd for $C_{20}H_{35}N_4O_6S$ 459.22718; found, 459.22705, $[M+Na]^+$ calcd for $C_{20}H_{34}N_4O_6SNa$ 481.20913; found, 481.20861.

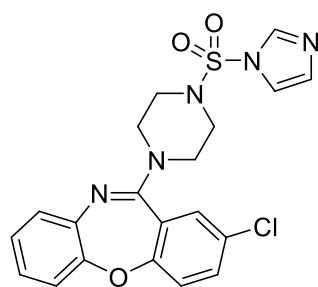
* Note that phase inversion or lack of the C-2 signal of the imidazole moiety in the APT spectrum has been described in the literature as a “regular feature” of these compounds (for details see^[18]). A signal was observed for C-2 in ^{13}C -standard spectrum.

8-[(1*H*-Imidazol-1-yl)sulfonyl]-8-azabicyclo[3.2.1]octan-3-one (**3i**)



3i (13 mg, 51 μ mol, 11%, colorless solid) was prepared according to GP2 from **2i** (100 mg, 483 μ mol) but the reaction was first stirred for 16 h at 40 $^{\circ}C$ and then for 12 h at 65 $^{\circ}C$. Column

chromatography: *n*-hexane:EtOAc = 1:1, TLC: R_f = 0.10. Molecular formula (molecular mass): $C_{10}H_{13}N_3O_3S$ (255.07 g/mol). 1H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.28 (s, 1H), 7.17 (s, 1H), 4.55 (s, 2H), 2.81 (dd, J = 16.7, 4.4 Hz, 2H), 2.43 (dd, J = 17.4, 1.6 Hz, 2H), 1.78 – 1.60 (m, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): 204.65, 137.03, 131.40, 117.80, 57.36, 49.73, 29.41. HR-PCI-MS m/z : $[M+H]^+$ calcd for $C_{10}H_{13}N_3O_3S$ 256.07504; found, 256.0746.

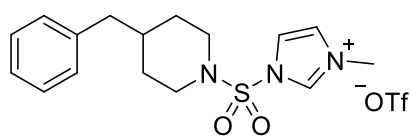
11-{4-[(1*H*-Imidazol-1-yl)sulfonyl]piperazin-1-yl}-2-chlorodibenzo[*b,f*][1,4]oxazepine (**3j**)

3j (161 mg, 362 μ mol, 96%, colorless solid) was prepared according to GP2 from **2j** (150 mg, 379 μ mol). Column chromatography: *n*-hexane:EtOAc = 3:1, TLC: R_f = 0.13. Molecular formula (molecular mass): C₂₀H₁₈ClN₅O₃S (443.91 g/mol). ¹H NMR (400 MHz, CD₃CN): δ 7.97 (s, 1H), 7.49 (dd, J = 8.7, 2.5 Hz, 1H), 7.41 (s, 1H), 7.35 (d, J = 2.5 Hz, 1H), 7.26 (d, J = 8.7 Hz, 1H), 7.12 (dd, J = 20.5, 5.2 Hz, 4H), 7.05 – 6.94 (m, 1H), 3.54 (s, 4H), 3.30 (s, 4H). ¹³C{¹H} NMR (101 MHz, CD₃CN) δ 160.34, 159.54, 152.69, 140.71, 137.81, 134.16, 131.48, 131.28, 129.90, 127.77, 126.93, 126.09, 125.39, 123.77, 121.21, 119.13, 118.32, 47.08, 46.97, 1.32. HR-ESI-MS m/z : [M+H]⁺ calcd for C₁₇H₁₅ClN₅O₃S 312.08982; found, 312.09003, [M+Na]⁺ calcd for C₁₇H₁₄ClN₅O₃SNa 376.05199; found, 376.05189.

4.1.6.3 Preparation of sulfonyl imidazolium salts

General procedure for preparation of sulfonyl imidazolium salts (**GP3**)

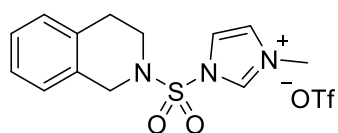
The corresponding sulfonyl imidazole (1.0 eq.) was dissolved in dry Et₂O (2–3 mL). If complete dissolution was not achieved, dry CH₂Cl₂ was added dropwise until a clear solution was obtained. The reaction mixture was cooled in an ice-bath and MeOTf (1.1 eq.) was slowly added. The mixture was stirred for 15–60 min until the formation of a precipitate was observed and TLC indicated complete conversion. The supernatant was decanted and the remaining residue was washed with Et₂O (3×5 mL) and dried under reduced pressure.

1-[(4-Benzyl)piperidin-1-yl)sulfonyl]-3-methyl-1*H*-imidazol-3-ium triflate (**4a**)

4a (114 mg, 243 μ mol, 82%, colorless solid) was prepared according to GP3 from **3a** (90 mg, 295 μ mol) but using CH₂Cl₂ as the only reaction solvent. Molecular formula (molecular mass): C₁₇H₂₂F₃N₃O₅S₂ (469.49 g/mol). ¹H NMR (400 MHz, CD₃CN): δ 8.94 (s, 1H), 7.66 (t, J = 2.0 Hz, 1H), 7.51 (t, J = 1.8 Hz, 1H), 7.43 – 7.24 (m, 2H), 7.24 – 6.93 (m, 3H), 4.07 – 3.78 (m, 2H), 3.88 (s, 3H), 2.88 (td, J = 12.4, 2.4 Hz, 2H), 2.56 (d, J = 6.9 Hz, 2H), 1.84 – 1.60 (m, 3H), 1.47 – 1.17 (m, 2H). ¹³C{¹H} NMR (101 MHz, CD₃CN): δ 140.70, 137.65, 130.00, 129.24, 127.03, 126.17, 121.28, 48.25, 42.40, 37.62, 36.88, 31.30.* ¹⁹F NMR (376 MHz, CD₃CN): δ -79.30. HR-ESI-MS m/z : [M-OTf]⁺ calcd for C₁₆H₂₂N₃O₂S 320.14272; found, 320.14241.

* ^{13}C -signal of trifluoromethanesulfonate could not be detected. Note that phase inversion or lack of the C-2 signal of the imidazole moiety in the APT spectrum has been described in the literature as a “regular feature” of these compounds (for details see^[18]).

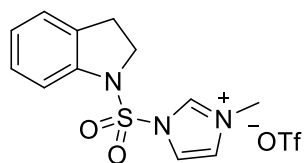
1-[(3,4-Dihydroisoquinolin-2(1*H*)-yl)sulfonyl]-3-methyl-1*H*-imidazol-3-ium triflate (**4b**)



4b (148 mg, 346 μmol , 91%, colorless solid) was prepared according to GP3 from **3b** (100 mg, 380 μmol). Molecular formula (molecular mass): $\text{C}_{14}\text{H}_{16}\text{F}_3\text{N}_3\text{O}_5\text{S}_2$ (427.41 g/mol). ^1H NMR (400 MHz, CD_3CN): δ 9.02 (s, 1H), 7.71 (t, $J = 1.9$ Hz, 1H), 7.48 (t, $J = 1.8$ Hz, 1H), 7.29 – 7.12 (m, 4H), 4.65 (s, 2H), 3.87 (s, 3H), 3.75 (t, $J = 6.1$ Hz, 2H), 2.98 (t, $J = 6.1$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CD_3CN): δ 137.93, 133.70, 130.84, 129.83, 128.47, 127.71, 127.25, 126.21, 121.28, 48.74, 45.93, 37.59, 28.49.* ^{19}F NMR (376 MHz, CD_3CN): δ -79.30. HR-ESI-MS m/z : $[\text{M}-\text{OTf}]^+$ calcd for $\text{C}_{13}\text{H}_{16}\text{N}_3\text{O}_2\text{S}$ 278.09577; found, 278.09589.

* ^{13}C -signal of trifluoromethanesulfonate could not be detected. Note that phase inversion or lack of the C-2 signal of the imidazole moiety in the APT spectrum has been described in the literature as a “regular feature” of these compounds (for details see^[18]).

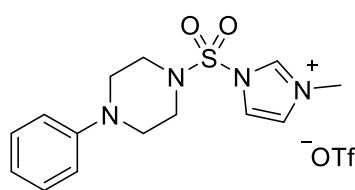
1-[(Indolin-1-yl)sulfonyl]-3-methyl-1*H*-imidazol-3-ium triflate (**4c**)



4c (81 mg, 196 μmol , 90%, colorless solid) was prepared according to GP3 from **3c** (54 mg, 217 μmol). Molecular formula (molecular mass): $\text{C}_{13}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_5\text{S}_2$ (413.39 g/mol). ^1H NMR (400 MHz, CD_3CN): δ 9.06 (s, 1H), 7.65 (t, $J = 2.0$ Hz, 1H), 7.56 (d, $J = 8.1$ Hz, 1H), 7.45 (t, $J = 1.9$ Hz, 1H), 7.37 – 7.29 (m, 2H), 7.25 – 7.16 (m, 1H), 4.20 (t, $J = 8.3$ Hz, 2H), 3.85 (s, 3H), 3.18 (t, $J = 8.3$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CD_3CN): δ 139.05, 133.70, 129.17, 127.22, 127.18, 126.28, 121.30, 115.36, 52.85, 37.64, 28.23.* ^{19}F NMR (376 MHz, CD_3CN): δ -79.32. HR-ESI-MS m/z : $[\text{M}-\text{OTf}]^+$ calcd for $\text{C}_{12}\text{H}_{14}\text{N}_3\text{O}_2\text{S}$ 264.08012; found, 264.07972.

* ^{13}C -signal of trifluoromethanesulfonate could not be detected. Note that phase inversion or lack of the C-2 signal of the imidazole moiety in the APT spectrum has been described in the literature as a “regular feature” of these compounds (for details see^[18]).

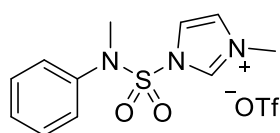
1-[(4-Phenyl)piperazin-1-yl)sulfonyl]-3-methyl-1*H*-imidazol-3-ium triflate (**4d**)



4d (69 mg, 151 μmol , 88%, colorless solid) was prepared according to GP3 from **3d** (50 mg, 171 μmol) but using 0.95 eq. of MeOTf. Molecular formula (molecular mass): $\text{C}_{15}\text{H}_{19}\text{F}_3\text{N}_4\text{O}_5\text{S}_2$ (456.46 g/mol). ^1H NMR (400 MHz, CD_3OD): δ 9.63 (s, 1H), 8.06 (s, 1H), 7.79 (s, 1H), 7.25 (t, $J = 8.0$ Hz, 2H), 6.97 (d, $J = 8.5$ Hz, 2H), 6.89 (t, $J = 7.3$ Hz, 1H), 4.01 (s, 3H), 3.61 – 3.59 (m, 4H), 3.35 – 3.28 [m, 4H (overlap with solvent signal)]. $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CD_3OD): δ 151.79, 139.16, 130.24, 126.60, 122.17, 121.91, 118.28, 50.03, 48.15, 37.40.* ^{19}F NMR (376 MHz, CD_3OD): δ 80.02. HR-ESI-MS m/z : $[\text{M-OTf}]^+$ calcd for $\text{C}_{14}\text{H}_{19}\text{N}_4\text{O}_2\text{S}$ 307.12232; found, 307.12276.

* ^{13}C -signal of trifluoromethanesulfonate could not be detected. Note that phase inversion or lack of the C-2 signal of the imidazole moiety in the APT spectrum has been described in the literature as a “regular feature” of these compounds (for details see^[18]).

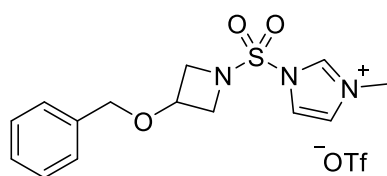
1-(*N*-Methyl-*N*-phenylsulfamoyl)-3-methyl-1*H*-imidazol-3-ium triflate (**4e**)



4e (72 mg, 179 μmol , 85%, colorless solid) was prepared according to GP3 from **3e** (50 mg, 211 μmol). Molecular formula (molecular mass): $\text{C}_{12}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_5\text{S}_2$ (401.38 g/mol). ^1H NMR (400 MHz, CD_3CN): δ 8.91 (s, 1H), 7.64 – 7.43 (m, 5H), 7.37 – 7.22 (m, 2H), 3.92 (s, 3H), 3.46 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CD_3CN): δ 139.25, 138.02, 131.11, 130.91, 128.11, 126.25, 121.75, 41.38, 37.74.* ^{19}F NMR (376 MHz, CD_3CN): δ -79.31. HR-ESI-MS m/z : $[\text{M-OTf}]^+$ calcd for $\text{C}_{11}\text{H}_{14}\text{N}_3\text{O}_2\text{S}$ 252.08012; found, 252.08007.

* ^{13}C -signal of trifluoromethanesulfonate could not be detected. Note that phase inversion of the C-2 signal of the imidazole moiety in the APT spectrum has been described in the literature as a “regular feature” of these compounds (for details see^[18]).

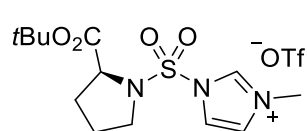
1-{[3-(Benzyloxy)azetidin-1-yl]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (**4f**)



4f (70 mg, 153 μmol , 90%, colorless solid) was prepared according to GP3 from **3f** (50 mg, 170 μmol). Molecular formula (molecular mass): $\text{C}_{15}\text{H}_{18}\text{F}_3\text{N}_3\text{O}_6\text{S}_2$ (457.44 g/mol). ^1H NMR (400 MHz, CD_3CN): δ 9.00 (s, 1H), 7.75 (t, $J = 2.0$ Hz, 1H), 7.53 (t, $J = 1.8$ Hz, 1H), 7.43 – 7.25 (m, 5H), 4.44 – 4.34 (m, 5H), 4.08 – 3.98 (m, 2H), 3.87 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CD_3CN): δ 138.17, 129.43, 129.00, 128.98, 126.21, 121.92, 71.78, 67.54, 61.76, 37.62.* ^{19}F NMR (376 MHz, CD_3CN): δ -79.29. HR-ESI-MS m/z : $[\text{M-OTf}]^+$ calcd for $\text{C}_{14}\text{H}_{18}\text{N}_3\text{O}_3\text{S}$ 308.10634; found, 308.10665.

* ^{13}C -signal of trifluoromethanesulfonate could not be detected. Note that phase inversion of the C-2 signal of the imidazole moiety in the APT spectrum has been described in the literature as a “regular feature” of these compounds (for details see^[18]).

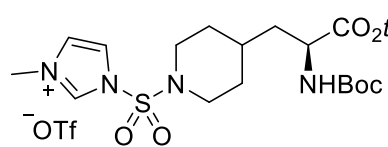
(*S*)-1-([2-(*tert*-Butoxycarbonyl)pyrrolidin-1-yl]sulfonyl)-3-methyl-1*H*-imidazol-3-ium triflate (**4g**)



4g (70 mg, 150 μmol , 90%, colorless solid) was prepared according to GP3 from **3g** (50 mg, 166 μmol). Molecular formula (molecular mass): $\text{C}_{14}\text{H}_{22}\text{F}_3\text{N}_3\text{O}_7\text{S}_2$ (465.46 g/mol). ^1H NMR (400 MHz, CD_3CN): δ 8.99 (s, 1H), 7.75 (t, $J = 1.9$ Hz, 1H), 7.51 (t, $J = 1.9$ Hz, 1H), 4.47 (dd, $J = 8.7, 3.3$ Hz, 1H), 3.91 (s, 3H), 3.72 – 3.63 (m, 1H), 3.59 – 3.49 (m, 1H), 2.36 – 2.24 (m, 1H), 2.13 – 2.06 (m, 1H), 2.04 – 1.96 (m, 2H), 1.46 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CD_3CN): δ 170.50, 138.15, 125.87, 121.49, 83.92, 64.29, 51.11, 37.58, 31.59, 27.96, 24.97.* ^{19}F NMR (376 MHz, CD_3CN): δ -79.31. HR-ESI-MS m/z : $[\text{M}-\text{OTf}]^+$ calcd for $\text{C}_{13}\text{H}_{22}\text{N}_3\text{O}_4\text{S}$ 316.13255; found, 316.13189.

* ^{13}C -signal of trifluoromethanesulfonate could not be detected. Note that phase inversion of the C-2 signal of the imidazole moiety in the APT spectrum has been described in the literature as a “regular feature” of these compounds (for details see^[18]).

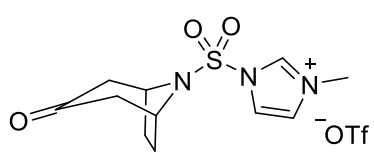
(*S*)-1-[(4-{3-(*tert*-Butoxy)-2-[(*tert*-butoxycarbonyl)amino]-3-oxopropyl}piperidin-1-yl)sulfonyl]-3-methyl-1*H*-imidazol-3-ium triflate (**4h**)



4h (36 mg, 58 μmol , 68%, colorless solid) was prepared according to GP3 from **3h** (39 mg, 84 μmol). Molecular formula (molecular mass): $\text{C}_{22}\text{H}_{37}\text{F}_3\text{N}_4\text{O}_9\text{S}_2$ (622.67 g/mol). ^1H NMR (400 MHz, CD_3CN): δ 8.93 (s, 1H), 7.67 (t, $J = 2.0$ Hz, 1H), 7.52 (t, $J = 2.0$ Hz, 1H), 5.49 (d, $J = 8.3$ Hz, 1H), 4.12 – 3.85 (m, 3H), 3.90 (s, 3H), 2.99 – 2.78 (m, 2H), 1.92 – 1.78 (m, 2H), 1.65 – 1.48 (m, 3H), 1.42 (s, 9H), 1.39 (s, 9H), 1.35 – 1.21 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CD_3CN): δ 172.86, 156.64, 137.66, 126.19, 121.36, 82.09, 79.87, 52.93; 48.17, 48.13; 38.32, 37.65, 31.90; 31.68, 30.84; 28.50, 28.10.* ^{19}F NMR (376 MHz, CD_3CN): δ -80.04. HR-ESI-MS m/z : $[\text{M}-\text{OTf}]^+$ calcd for $\text{C}_{21}\text{H}_{37}\text{N}_4\text{O}_6\text{S}$ 473.24283; found, 473.24226.

* ^{13}C -signal of trifluoromethanesulfonate could not be detected. Note that phase inversion of the C-2 signal of the imidazole moiety in the APT spectrum has been described in the literature as a “regular feature” of these compounds (for details see^[18]).

1-[(3-Oxo-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl]-3-methyl-1*H*-imidazol-3-ium triflate (**4i**)

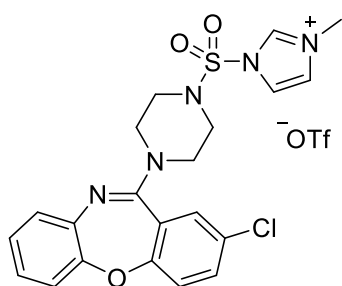


4i (18.9 mg, 45.1 μ mol, 92%, colorless solid) was prepared according to GP3 from **3i** (12.6 mg, 49.4 μ mol). Molecular formula (molecular mass): $C_{12}H_{16}F_3N_3O_6S_2$ (419.39 g/mol). 1H NMR (400 MHz, CD_3CN): δ 9.04 (s, 1H), 7.80 (s, 1H), 7.54 (s, 1H), 4.75 (s, 2H), 3.91 (s, 3H), 2.84 (dd, J = 16.9, 4.0 Hz, 2H), 2.44 (d, J = 16.9 Hz, 2H), 1.98 – 1.89 (m, 2H)**, 1.83 – 1.73 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, CD_3CN): δ 205.05, 138.15, 126.81, 120.91, 59.58, 49.76, 37.79, 29.72.* ^{19}F NMR (376 MHz, CD_3CN): δ -79.31. HR-ESI-MS m/z : $[M-OTf]^+$ calcd for $C_{11}H_{16}N_3O_3S$ 270.09069; found, 270.09094.

* ^{13}C -signal of trifluoromethanesulfonate could not be detected.

** overlap with solvent.

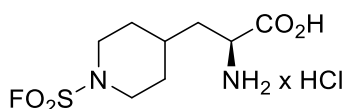
1-{[4-(2-Chlorodibenzo[b,f][1,4]oxazepin-11-yl)piperazin-1-yl]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (**4j**)



4j (36 mg, 60 μ mol, 53%, colorless solid) was prepared according to GP3 from **3j** (50 mg, 113 μ mol). Molecular formula (molecular mass): $C_{22}H_{21}ClF_3N_5O_6S_2$ (608.00 g/mol). 1H NMR (400 MHz, CD_3CN): δ 9.00 (s, 1H), 7.72 (t, J = 2.1 Hz, 1H), 7.60 – 7.47 (m, 2H), 7.38 (d, J = 2.6 Hz, 1H), 7.33 – 7.23 (m, 1H), 7.22 – 6.93 (m, 4H), 3.91 (s, 3H), 3.76 – 3.31 (m, 8H). $^{13}C\{^1H\}$ NMR (101 MHz, CD_3CN): δ 160.27, 159.19, 152.59, 140.57, 137.81, 134.23, 131.26, 129.79, 127.72, 126.92, 126.33, 126.16, 125.26, 123.81, 121.46, 121.19, 47.20, 46.87, 37.67.* ^{19}F NMR (376 MHz, CD_3CN): δ -79.30. HR-ESI-MS m/z : $[M-OTf]^+$ calcd for $C_{21}H_{21}ClN_5O_3S$ 458.10481; found, 458.10496.

* ^{13}C -signal of trifluoromethanesulfonate could not be detected.

(*S*)-2-Amino-3-[1-(fluorosulfonyl)piperidin-4-yl]propanoic acid hydrochloride (**7**)



2h (35.0 mg, 85.3 μ mol) was dissolved in 4 M HCl in dioxane (600 μ L) and the mixture was stirred for 2 h. A second portion of 4 M HCl in dioxane (200 μ L) was then added and the mixture was stirred at 60 $^{\circ}C$ until TLC indicated complete conversion ($\sim$ 2 h). The reaction mixture was concentrated under reduced pressure, the residue was washed with Et_2O (3×1 mL) and remaining solvent was removed under reduced pressure to afford **7** (24.3 mg, 83.6 μ mol, 98%) as a colorless solid. Molecular formula (molecular mass): $C_8H_{16}ClFN_2O_4S$ (290.73 g/mol). 1H

NMR (400 MHz, CD₃OD): δ 4.04 (t, J = 6.7 Hz, 1H), 3.97 – 3.84 (m, 2H), 3.17 – 2.99 (m, 2H), 2.03 – 1.86 (m, 3H), 1.84 – 1.68 (m, 2H), 1.46 – 1.30 (m, 2H). * ¹³C{¹H} NMR (101 MHz, CD₃OD): δ 172.02, 51.45, 49.00, 48.23, 37.91, 32.34, 31.70, 31.54. ¹⁹F NMR (376 MHz, CD₃OD): δ 37.94. HR-ESI-MS m/z : [M+H]⁺ calcd for C₈H₁₆FN₂O₄S 255.08093; found, 255.08110.

*Exchangeable protons of H₂N- and HO₂C-group were not detected.

4.2 Radiochemistry

4.2.1 General

[¹⁸F]Fluoride ([¹⁸F]F[−]) was produced via the ¹⁸O(p,n)¹⁸F reaction by bombardment of enriched [¹⁸O]H₂O with 17 MeV protons in a BC1710 cyclotron (The Japan Steel Works, Tokyo, Japan) or a GE PETtrace (GE Healthcare, Chicago, USA), both at the INM-5 (Forschungszentrum Jülich GmbH). Radioactivity was measured using a CRC-55tR Dose Calibrator from Capintec, Inc. (Florham Park, Netherlands) and/or a Curiementor 2 (PTW, Freiburg, Germany). The following cartridges were used for radiosyntheses and solid phase extractions (SPE): ¹⁸F separation cartridge PS-HCO₃[−] (45 mg or 30 mg sorbent, preconditioned with 1 mL H₂O) from Synthra (Hamburg, Germany), Sep-PakTM Plus Light QMA Carbonate cartridges (130 mg or 46 mg sorbent, preconditioned with 1 mL H₂O) from Waters GmbH (Eschborn, Germany), Sep-PakTM Plus Light QMA cartridges (130 mg sorbent, preconditioned with 1 mL H₂O) from Waters GmbH (Eschborn, Germany), StrataTM-X 33 μ m Polymeric RP cartridges (30 mg sorbent; preconditioned with 3 mL EtOH and 10 mL H₂O) from Phenomenex (Aschaffenburg, Germany), and Oasis[®] HLB 1cc extraction cartridges (10 mg sorbent, preconditioned with 3 mL EtOH and 10 mL H₂O) from Waters GmbH (Eschborn, Germany).

Identity of radiolabeled products was confirmed by co-injection of the non-radioactive reference compounds. Radiochemical yields (RCYs) corrected for decay to the start of synthesis and/or activity yields (AY; non-decay-corrected) are provided for analytically pure radiolabeled compounds. Radiochemical conversions (RCC) were determined by HPLC analysis after dilution of the reaction mixtures with H₂O. To this end, the decay-corrected product peak areas in the chromatograms were compared to the peak area obtained by a post-column injection (p.c.i.).^[19]

HPLC analyses were carried out on a Dionex Ultimate[®] 3000 System with Ultimate[®] 3000 RS Variable Wavelength Detector or Ultimate[®] 3000 Diode Array Detector coupled in series with a Berthold LB500 NaI detector. Two Rheodyne 6 port injection valves equipped with equal

sample loops were installed before and behind the column. The UV and radioactivity detectors were coupled in series, giving a time delay of 0.1–0.2 min (depending on flow-rate) between the corresponding responses. Columns and methods are given for each chromatogram (see SI). All radiosyntheses were carried out according to the radiation protection rules of our institute using appropriate personal protective equipment and shielding. Unless noted otherwise, 5 mL screw top V-Vials® (20–400 thread, 20×65 mm) were used for all radiosyntheses. Prior to their first use and after every 10–15 reactions, the vials were (re)siliconized to minimize adsorption of [^{18}F]F $^-$ to the vessel walls. To this end, the vials were incubated for 10 min with a solution of 5% SiCl $_2$ Me $_2$ in CH $_2$ Cl $_2$. Following incubation, the vials were sequentially rinsed with EtOAc, CH $_2$ Cl $_2$, acetone, H $_2$ O, acetone and MeOH. During the H $_2$ O and acetone rinsing steps, mechanical assistance with a lint-free paper towel was applied to enhance cleaning efficiency. Finally, the vials were dried at 90 °C for 10 min prior to (re)use.

4.2.2 General procedure for "minimalist green" radiofluorination of imidazolium salts (GP4)

1. Aqueous [^{18}F]F $^-$ (20–50 MBq) was loaded (from the male side) onto a Sep-Pak™ Plus Light QMA Carbonate cartridge (130 mg sorbent, preconditioned with 1 mL H $_2$ O).
2. The cartridge was washed (from the male side) with EtOH (2 mL) to remove residual H $_2$ O.
3. [^{18}F]F $^-$ was eluted (from the female to the male side) with a solution of the precursor (typically 1 μmol) in EtOH (1 mL).
4. The reaction mixture was incubated for 15 min at 80 °C.
5. The reaction was quenched with H $_2$ O (2–4 mL) and the RCC was determined by radio-HPLC.

4.2.3 Preparation of [^{18}F]7

[^{18}F]7 was prepared from **4h** (1 μmol) by following the general radiolabeling protocol GP4 up to step 5. The crude intermediate [^{18}F]2h was purified by semipreparative HPLC [column: Gemini C18 110A, 5 μm , 250×10 mm (Phenomenex, Aschaffenburg, Germany); eluent: 70% MeCN; flow-rate: 7.4 mL/min]. The collected product fraction was diluted with H $_2$ O (20 mL) and loaded onto a Strata™-X 33 μm Polymeric RP cartridge (30 mg). The cartridge was washed with H $_2$ O (3 mL) and the product was eluted with EtOH (1 mL). The EtOH was evaporated under dynamic vacuum (400 mbar) in a stream of argon at 90 °C for 5 min. The residue was treated with 6 M HCl (100 μL) and the mixture was heated at 90 °C for 10 min before the HCl was removed under dynamic vacuum at 90 °C for 5–10 min. The tracer was formulated in 0.1 M NaOAc buffer (500 μL , pH 5.3).

4.2.4 Automated preparation of [^{18}F]2j on a Tracerlab FX N Pro module

(for the corresponding flowchart see Fig. S2 in the Supporting Information)

Aqueous [^{18}F] F^- (1.45–3.98 GBq,) was loaded onto a Sep-PakTM Plus Light QMA Carbonate cartridge (130 mg sorbent, preconditioned with 1 mL H_2O) [TV→RV] and the cartridge was washed with EtOH (2 mL) [V1→RV]. [^{18}F] F^- was eluted from the cartridge with a solution of 4j (1 μmol) in EtOH (1 mL) [V3→R1]. The reaction mixture was stirred for 15 min at 80 °C, quenched with H_2O (4 mL) [V6→R1] and purified by semipreparative HPLC [column: Gemini C18 110A, 5 μm , 250×10 mm (Phenomenex, Aschaffenburg, Germany); eluent: 70% MeCN; flow-rate: 5 mL/min] [R1→HPLC]. The product fraction was diluted with H_2O (30 mL) [HPLC→DV2], loaded onto a HLB cartridge (10 mg) [DV2→Waste], and the cartridge was flushed with H_2O (3 mL) [V14→Waste]. The product was eluted with EtOH (1 mL) [V15→CV], and the eluate was diluted with H_2O (1 mL) [V16→CV] before it was analyzed for radiochemical purity, product identity and activity yield.

4.3. Preclinical evaluation

4.3.1 Cell culture

Human U87 MG glioblastoma cells were purchased from the American Type Culture Collection (ATCC) and cultured under normal growth conditions (37 °C and 5% CO_2) in minimum essential medium GlutaMAX (MEM, Gibco 41090 028, Fisher Scientific GmbH, Schwerte, Germany) supplemented with 10% fetal bovine serum (FBS, Sigma-Aldrich F2442, Merck KGaA, Darmstadt, Germany), 1% penicillin/streptomycin (Gibco 115140 122), and. The cells were grown in cell-culture dishes (ThermoFisher 150350, F 100 mm) with 9 mL culture medium and routinely passaged every 4–5 days after they had reached 80–90% confluency. For the cellular uptake and inhibition studies, cells were seeded into 12-well plates (2 × 10⁵ cells in 1 mL medium/well) 48 h before the start of the experiments.

4.3.2 Cellular uptake studies

Two hours before the start of the experiments, the culture medium was carefully aspirated, the cells were washed with phosphate-buffered saline (PBS, 1 mL, Gibco 10 010 023), and a dye exclusion test with trypan blue (Sigma-Aldrich T 8154) was performed to determine cell viability and the exact cell count (cell viability was always >95%). The tracer solutions were prepared in FBS- and amino acid-free Dulbecco's Phosphate-Buffered Saline (DPBS) at a

concentration of 150 kBq/mL. DPBS was removed from the wells, and the tracer solution was added (1 mL/well). The cells were then incubated with the tracer solution at 37 °C for 60 min, washed twice with ice-cold PBS (1 mL), trypsinized, and harvested. The accumulated radioactivity was measured on an automatic gamma counter (Perkin Elmer, 1480 Automatic Gamma Counter, Shelton, USA). Each experiment was conducted at least in triplicate.

4.3.3 Cellular inhibition studies

For the inhibition experiments, U87 MG cells were used and cultured as described above. The following inhibitors, obtained from Sigma-Aldrich, were used: 2-(methylamino)-2-methylpropionic acid (MeAIB) for system A, L-serine for system ASC, and 2-aminobicyclo[2,2,1]heptane-2-carboxylic acid (BCH) for system L transporters. The inhibitors were diluted with DPBS to give the desired final concentrations (1.5 nM, 15 nM, or 150 nM) and added together with the tracer. After incubation for 60 min at 37 °C, the cells were processed, and the uptake of radioactivity measured, as described above.

4.3.4 *In vivo* experiments in subcutaneous glioma model

All experiments were carried out in accordance with the EU directive 2010/63/EU for animal experiments and the German Animal Welfare Act (TierSchG, 2006) and were approved by the regional authorities (State Office for Nature, Environment and Consumer Protection of North-Rhine Westphalia [LANUV NRW], Dept. Animal Welfare, license number: 81-02.04.2023.A034).

For subcutaneous tumor xenografts, a suspension of U87 MG tumor cells (1×10^7 in 75 μ L matrigel; $n = 5$) was injected subcutaneously into the scruff of the neck near the right shoulder of the mice. After 2 weeks, the mice developed palpable tumors of about 0.5–1.0 cm³ and were used for the PET scans. To this end, the animals were anesthetized with isoflurane (5% for induction, 2% for maintenance) in O₂/air (3:7), and a catheter for tracer injection was inserted into the lateral tail vein. Mice were placed on an animal holder (Medres, Cologne, Germany) and fixed with a tooth bar in a respiratory mask. Body temperature was maintained at 37 °C by continuous warm water flow through the wall of the animal bed. Eyes were protected from drying with Bepanthen eye and nose ointment (Bayer, Leverkusen, Germany). A dynamic PET scan in list mode was conducted using a Focus 220 micro PET scanner (CTI-Siemens, Erlangen, Germany) with a resolution at the center of field of view of 1.4 mm. Data acquisition started with intravenous injection of H-PipAla([¹⁸F]SO₂F)-OH ([¹⁸F]7, 9–10.7 MBq in 125 μ L) and ended after 120 min. This was followed by a 10 min transmission scan using a ⁵⁷Co point source

for attenuation correction. After completion of the measurements, the tumor-bearing mice were sacrificed by cervical dislocation under deep isoflurane anesthesia. After Fourier rebinning, data were reconstructed in two ways: 4×30 min frames for visual display and 28 frames (2×1 min, 2×2 min, 6×4 min, 18×5 min) for time-activity curves. An iterative OSEM3D/MAP algorithm with attenuation and decay correction was used. The resulting voxel sizes were $0.47 \text{ mm} \times 0.47 \text{ mm} \times 0.80 \text{ mm}$. All further analyses were performed with the software VINCI 5.24 (Max Planck Institute for Metabolism Research, Cologne, Germany). The PET images were normalized by injected dose per kg body weight. Summed PET images over 0–120 min post injection were used for determining mean and maximum SUV_{bw} of the tumor, kidneys, liver, gall bladder and bone.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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ABBREVIATIONS

Abbreviations

[¹⁸ F]F ⁻	[¹⁸ F]fluoride
[¹⁸ F]FET	<i>O</i> -(2-[¹⁸ F]fluoroethyl)tyrosine
AlSAFs	aliphatic sulfamoyl fluorides
A _m	molar activity
ASC	alanine/serine/cysteine transporter
AY	activity yield
BCH	2-aminobicyclo[2,2,1]heptane-2-carboxylic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
desMe-SuFEx-IT	1-(fluorosulfonyl)-3-methyl-1 <i>H</i> -imidazole trifluoromethanesulfonate
HPLC	high-performance liquid chromatography
MeAIB	α-(methylamino)isobutyric acid
MSDI	mono-methylated sulfonyldiimidazole
n.c.a.	no carrier added
PET	positron emission tomography
QMA	quaternary methyl ammonium
RCC	radiochemical conversion
RCP	radiochemical purity
SAF	sulfamoyl fluoride
SuFEx	sulfur fluoride exchange
SUV _{bw}	standardized uptake value normalized by body weight
TBRs	target-to-background ratios
Tf	triflate
U87 MG	Uppsala 87 malignant glioma
VOI	volume of interest

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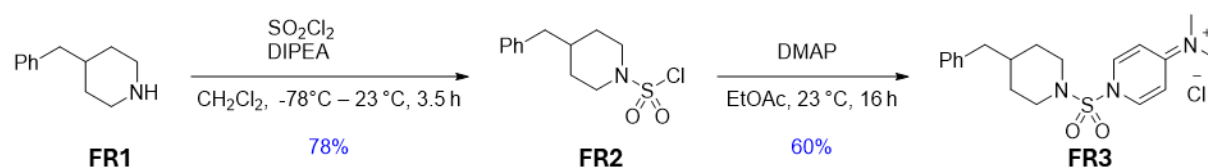
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4 Further Results

4.1 Dimethylaminopyridinium salts

As an alternative to the synthesis of aliphatic sulfamoyl [^{18}F]fluorides from imidazolium salts (manuscript 3), dimethylaminopyridinium (DMAP) salts were evaluated as potential radiolabeling precursors. While these compounds have been briefly mentioned in the literature (primarily in patents^[119]), they remain largely unexplored. Notably however, analogous sulfonyl DMAP salts have previously been employed for the preparation of sulfonyl [^{18}F]fluorides.^[76] To assess the suitability of sulfamoyl DMAP salts for ^{18}F -labeling, the model compound **FR3** was synthesized as shown in Scheme 28.



Scheme 28: 2 step synthesis of dimethylaminopyridinium salt **FR3**.

In the first step, 4-benzylpiperidine (**FR1**) was converted to the corresponding sulfamoyl chloride (**FR2**) in 78% yield. This intermediate was subsequently reacted with DMAP to afford the desired radiolabeling precursor **FR3**. Radiolabeling of **FR3** was performed using the “minimalist green” protocol (manuscript 2), and the performance under various reaction conditions was directly compared to that of the corresponding imidazolium salt.

As illustrated in Fig. 2A, at lower temperatures (60 – 80°C) the imidazolium salt consistently provided 10–30% greater RCCs, which may be advantageous for temperature-sensitive substrates. At temperatures above 80°C , the performance of the two leaving groups converged. However, the imidazolium salt also showed faster labeling kinetics at 80°C , reaching higher RCCs within the first 5 minutes before both compounds plateaued at approximately 85% RCC after 10 min (Fig. 2B I). Variations in precursor amount (0.5 – $5\ \mu\text{mol}$) had no notable effect, with RCCs exceeding 90% in all cases (Fig. 2B III). Similarly, [^{18}F]F $^-$ elution efficiencies from the QMA cartridge were comparable for both precursors (Fig. 2B IV).

In conclusion, both leaving groups exhibited comparable reactivity. However, the imidazolium precursor provided significantly higher RCCs at temperatures below 80°C . Furthermore imidazolium-based precursors were favored due to the milder reaction conditions required for preparation of the intermediate sulfamoyl fluorides. In contrast, preparation of DMAP salts proceeds through less stable sulfamoyl chloride intermediates and typically necessitates the use

of highly reactive sulfonyl chloride. Owing to these practical advantages, further investigations focused on the radiosynthesis of aliphatic sulfamoyl [^{18}F]fluorides from imidazolium salts.

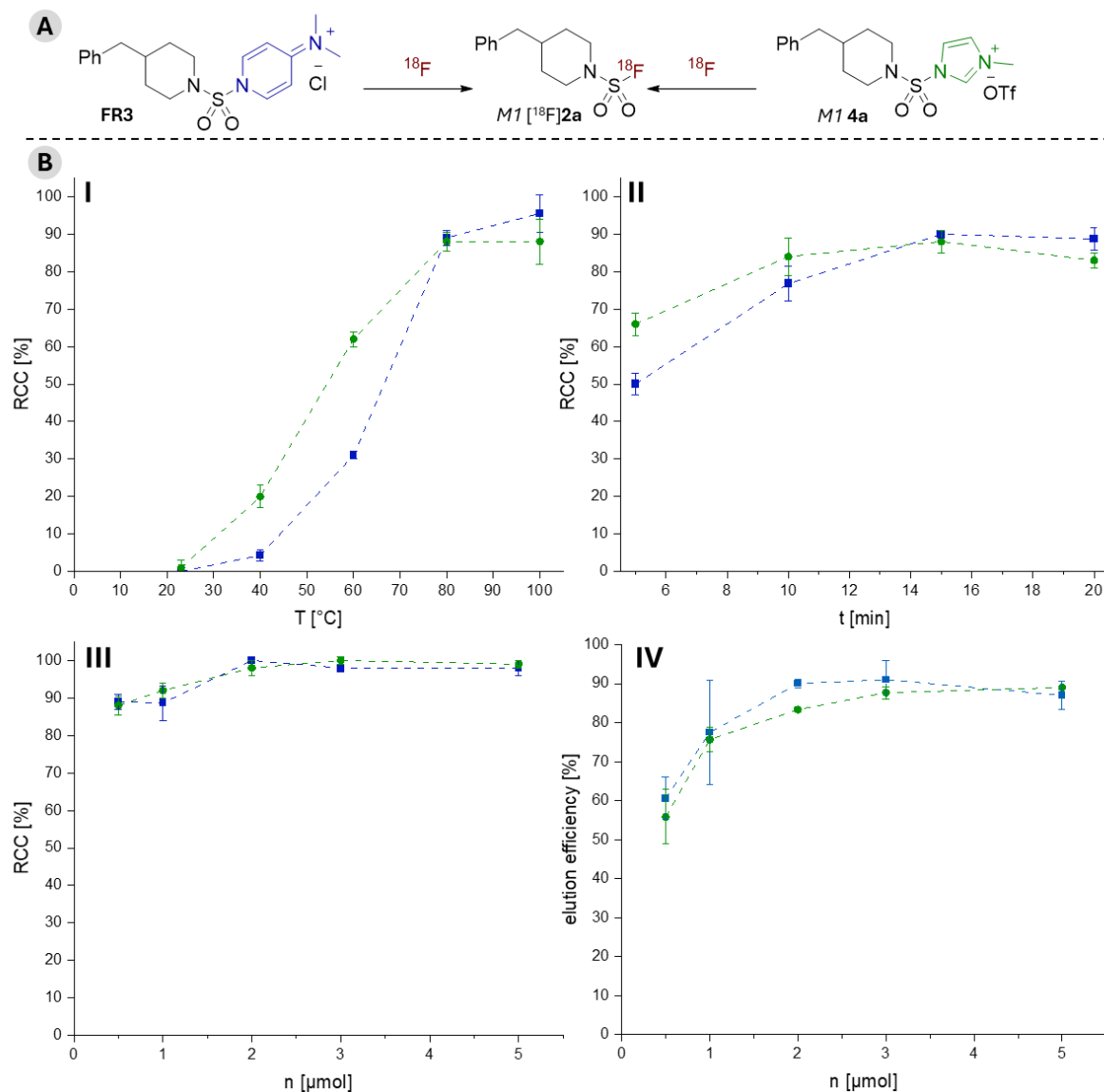
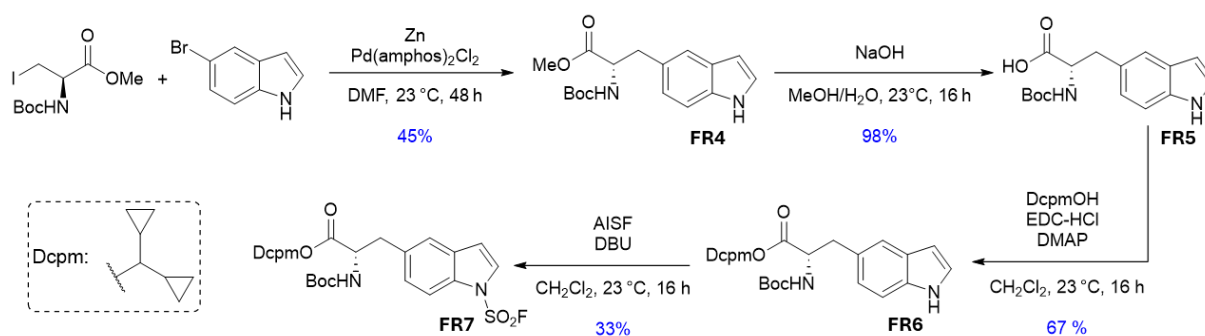


Figure 2: **A** Comparison of a DMAP (**FR3**) and an imidazolium salt (**M1 4a**) as precursors for radiolabeling. **B**; **I** Temperature-dependence of the RCCs. Conditions: 0.5 μmol precursor, 15 min, EtOH (1 mL). **II** Time-dependence of the RCCs. Conditions: 0.5 μmol precursor, 80 $^{\circ}\text{C}$, EtOH (1 mL). **III** Precursor amount-dependence of the RCCs. Conditions: 80 $^{\circ}\text{C}$, 15 min, EtOH (1 mL). **IV** Precursor amount-dependence of the [^{18}F]fluoride elution efficiency. Conditions: 80 $^{\circ}\text{C}$, 15 min, EtOH (1 mL).

4.2 Preparation and *in vivo* evaluation of H-5-*iso*-Trp(^{18}F)SO₂F)-OH

To mitigate the observed defluorination of H-Trp(^{18}F)SO₂F)-OH (*MI* [^{18}F]**20**) described in Manuscript 1, we explored structural modification on the indole scaffold. We hypothesized that shifting the Ala-residue from the third to the fifth position of the indole ring could alter the orientation of the tracer within potential protein binding pockets (e.g. LAT1). Such a modification was expected to reduce the likelihood of a productive alignment between the N_{in}-fluorosulfonyl substituent and nucleophilic residues (like Ser, Tyr, Cys and His) within the binding pocket. Based on this rationale, we designed the regioisomer H-5-*iso*-Trp(SO₂F)-OH (**FR8**) to attenuate tracer degradation via protein-mediated fluorine release. For preparation of the corresponding radiolabeling precursor, commercially available Boc-Ala(3-I)-OMe and 5-bromoindole were converted to Boc-5-*iso*-Trp-OMe (**FR4**) via Negishi cross-coupling.^[120] Subsequent saponification of **FR4** afforded the free acid **FR5**, which was esterified to obtain the dicyclopropylmethyl ester **FR6**. Finally, fluorosulfonylation of **FR6** with AISF afforded the desired radiolabeling precursor **FR7** in 10% overall yield over the 4 steps (Scheme 29).



Scheme 29: Synthetic route to Boc-5-*iso*-Trp(SO₂F)-ODcpm

The tracer H-5-*iso*-Trp(^{18}F)SO₂F)-OH (^{18}F **FR8**) was then prepared from **FR7** using the same SuFEx-based protocol as described for *MI* [^{18}F]**20** (AY: 19±7, Fig. 3A) and evaluated *in vivo* in healthy mice (Figure 3B). However, bone uptake of radioactivity remained comparable to that observed for the Trp-derivative *MI* [^{18}F]**20** (maximum SUV_{bw} 243±36, 90–120 min p.i.). These findings suggest that indole-based SAF analogues are intrinsically prone to undesired covalent interactions with nucleophilic protein side chains, rendering them susceptible to *in vivo* defluorination. Further structural modifications may therefore be required to attenuate the intrinsic reactivity and unlock the translational potential of this class of tracers.

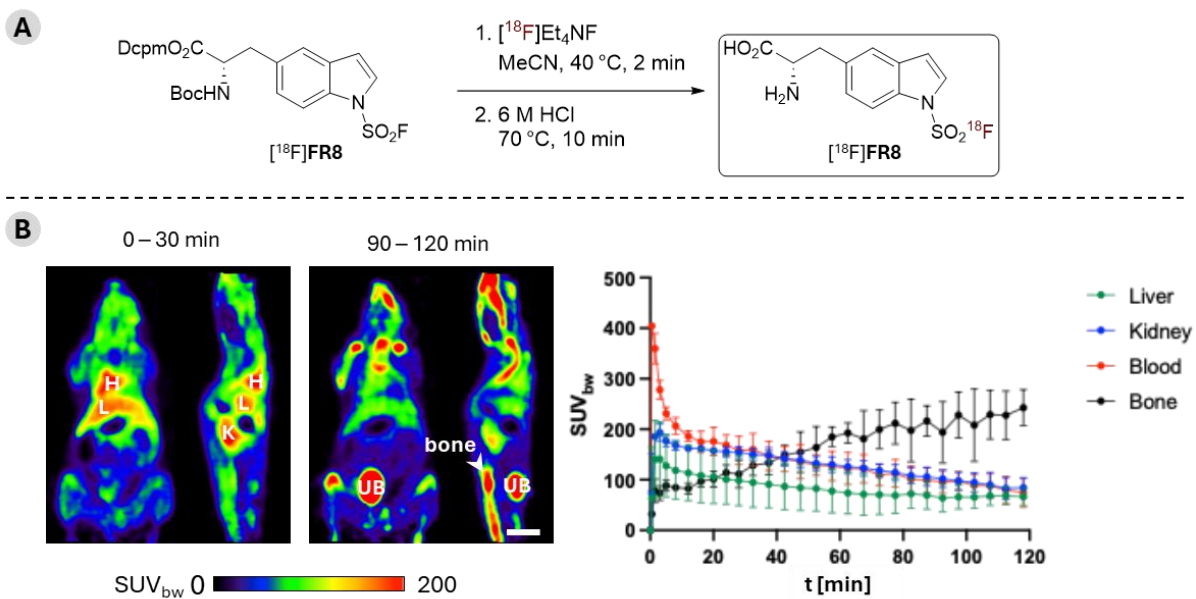


Figure 3: **A** Radiosynthesis of H -5- iso -Trp($[^{18}\text{F}]\text{SO}_2\text{F}$)-OH ($[^{18}\text{F}]\text{FR8}$). **B** In vivo evaluation of $[^{18}\text{F}]\text{FR8}$ by μPET imaging in healthy mice ($n = 4$). Shown are representative PET images (summed over the indicated 30 min time frames) of one mouse in horizontal and sagittal orientation.

4.3 Evaluation of H-PipAla(^{18}F)SO₂F)-OH in an orthotopic glioblastoma model

Due to the high stability of H-PipAla(^{18}F)SO₂F)-OH ($M2$ [^{18}F]7) observed in the subcutaneous tumor mouse model (see Manuscript 2), the tracer was further evaluated in an orthotopic glioblastoma rat model. This study was conducted in collaboration with Prof. Dr. Heike Endepols, Dr. Marco Timmer, Lukas Vieth and Otari Gokhadze. To this end, $M2$ [^{18}F]7 and the clinically established tracer [^{18}F]FET were compared in immunodeficient Rowett nude rats xenotransplanted with intracerebral U87 MG tumors.

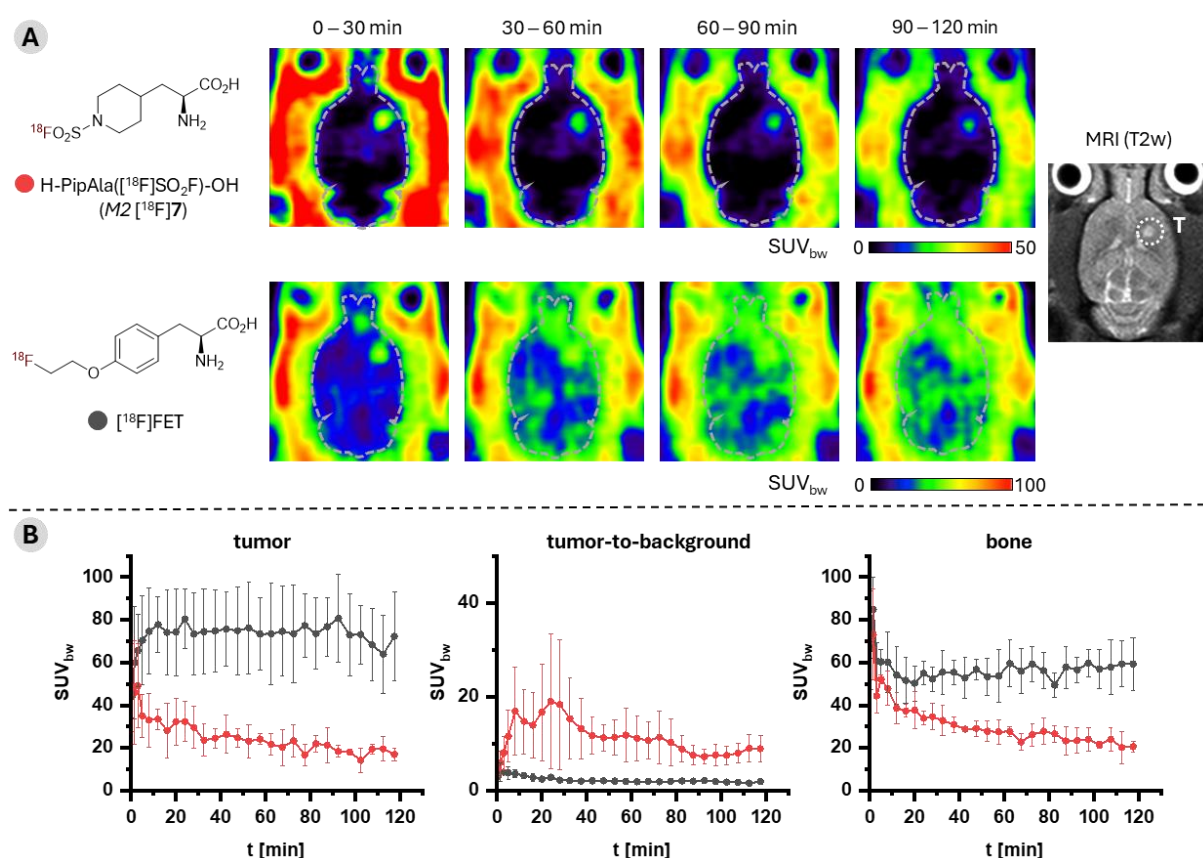


Figure 4: Comparison of in vivo tumor uptake of H-PipAla(^{18}F)SO₂F)-OH ($M2$ [^{18}F]7) and [^{18}F]FET in an orthotopic U87 MG glioblastoma rat model. **A** Representative horizontal PET images (summed over the indicated 30 min time frames) of the same tumor-bearing rat measured (on different days) with the two tracers. The outline of the brain is indicated by dashed lines. Also shown is a T2-weighted MRI of the animal, with the location of the intracerebral tumor indicated by a dashed circle. **B** Comparison of mean time-activity curves ($n = 3$) for tumor uptake, tumor-to-background ratios and bone accumulation of radioactivity in measurements with H-PipAla(^{18}F)SO₂F)-OH ($M2$ [^{18}F]7) and [^{18}F]FET.

Although absolute tumor uptake of H-PipAla(^{18}F)SO₂F)-OH ($M2$ [^{18}F]7, maximum SUV_{bw} of 49 ± 20 , 0–30 min p.i.) was lower than that of [^{18}F]FET (SUV_{bw} of 80 ± 14 , 0–30 min p.i.), the ALSAF-based tracer exhibited higher tumor-to-background ratios, enabling clear tumor delineation (Fig. 4). Notably, bone uptake of radioactivity in measurements with [^{18}F]7 (mean SUV_{bw} of 33 ± 13) was markedly lower than that in measurements with [^{18}F]FET (mean SUV_{bw} of 85 ± 6), further confirming the high metabolic stability of the tracer. Taken together, these

findings identify H-PipAla(^{18}F SO₂F)-OH as a promising candidate for glioma imaging, warranting further investigation in follow-up studies.

5 General Conclusion

Heteroatom–fluorine bond formation has emerged as a valuable strategy in PET radiochemistry, offering attractive alternatives to conventional labeling methods based on carbon–fluorine bonds. In this context, sulfur(VI)–fluoride compounds have attracted particular attention as potential scaffolds for radiotracer development. While the low hydrolytic stability of aryl sulfonyl [^{18}F]fluorides has rendered them unsuitable for imaging applications, recent introduction of a SuFEx-based isotopic exchange protocol for the preparation of aryl [^{18}F]fluorosulfates has sparked interest due to its operational simplicity and mild reaction conditions. However, subsequent studies revealed considerable *in vivo* defluorination of most [^{18}F]fluorosulfate-based tracers, which could impede their clinical translation. Given the susceptibility of aryl sulfonyl [^{18}F]fluorides and [^{18}F]fluorosulfates to defluorination, sulfamoyl [^{18}F]fluorides ([^{18}F]SAFs) were envisioned as a promising alternative. In particular, their lower intrinsic reactivity, which has been demonstrated in several studies on sulfur(VI)-based warheads for targeted covalent inhibition, could translate into superior metabolic stability in the context of PET tracer development. Accordingly, the overarching objective of this work was to evaluate the applicability of [^{18}F]SAFs as scaffolds for PET radiochemistry.

The first step toward this goal was to secure safe and cost-effective access to the corresponding SAF precursors. This was achieved by development of a straightforward and chromatography-free protocol for hectogram-scale preparation of the novel fluorosulfurylating agent desmethyl SuFEx-IT (publication), which was prepared in 85% total yield over 3 steps from inexpensive starting materials, circumventing the need for neurotoxic and difficult-to-obtain sulfuranyl fluoride (SO_2F_2). Although an analogous synthesis of SuFEx-IT was also feasible, it was hampered by low yields and limited availability of the corresponding 1,1'-sulfonylbis(2-methylimidazole) precursor. The utility of desmethyl SuFEx-IT was confirmed by successful preparation of a series of fluorosulfates and SAFs in moderate to excellent yields (14–98%), demonstrating its value as an easily accessible FO_2S -donor that provides cost-efficient access to substrates for SuFEx click chemistry.

With robust access to the radiolabeling precursors in hands, a SuFEx-based isotopic exchange protocol originally developed for the preparation of aryl [^{18}F]fluorosulfates was adapted for SAF radiolabeling (manuscript 1). This approach enabled the rapid and high-yielding ^{18}F -fluorination of SAFs under mild conditions using nanomolar precursor amounts, thereby increasing the achievable molar activity. Radiochemical conversions (RCCs) for indole-based

SAFs, which demonstrated the highest reactivity, exceeded 80% within minutes at temperatures as low as 40 °C. Aliphatic SAFs were less reactive but proved to exhibit increased hydrolytic stability. In addition, evaluation of a structurally diverse set of SAF substrates revealed that the presence of an aromatic system in close proximity to the SAF group improves both labeling efficiency and compound stability. Hydrolytic stability assays demonstrated that selected [^{18}F]SAFs are stable across a wide pH range and in human serum. *In vivo* evaluation of a protected [^{18}F]SAF-functionalized tryptophan analog confirmed high metabolic stability with minimal defluorination, while its deprotected counterpart exhibited reduced stability in a glioma model. In contrast, the corresponding dihydrotryptophan analogs showed improved resistance to defluorination, suggesting that stability issues can be mitigated by structural fine-tuning.

Finally, to address the limited labeling efficiency of aliphatic SAFs (AlSAFs) via isotopic exchange and capitalize on their enhanced hydrolytic stability, an alternative no-carrier-added approach for the preparation of [^{18}F]AlSAFs was developed (manuscript 2). For this purpose, imidazolium and dimethylaminopyridinium salts were investigated as potential precursors for radiofluorination by the “minimalist green” approach. Both classes exhibited comparable radiolabeling performance, but imidazolium-based precursors were preferred due to milder reaction conditions required for preparation of the intermediate sulfamoyl fluorides. Therefore, further investigations focused on the preparation of [^{18}F]AlSAFs by “minimalist green” radiofluorination of imidazolium salts. High RCCs exceeding 90% were consistently achieved across a broad range of substrates, including both cyclic and acyclic secondary amine scaffolds, with excellent tolerance for common protecting groups. Successful automated synthesis of an ^{18}F -fluorosulfurylated amoxapine derivative further demonstrated the potential of the protocol for clinical translation. In addition, *in vivo* evaluation of a ^{18}F -fluorosulfurylated 3-(4-piperidyl)alanine in a subcutaneous glioma mouse model confirmed the superior metabolic stability of [^{18}F]AlSAFs, with negligible defluorination observed. In an orthotopic glioblastoma rat model, the tracer also showed a better tumor-to-background ratio than [^{18}F]FET, the current “gold standard” for glioma imaging.

Taken together, this work establishes sulfamoyl [^{18}F]fluorides as chemically and metabolically robust, synthetically accessible structural motifs for PET radiochemistry offering a promising platform for future applications in molecular imaging.

Supporting Information

Supporting Information for

Desmethyl SuFEx-IT: SO₂F₂-free Synthesis and Evaluation as Fluorosulfonylating Agent

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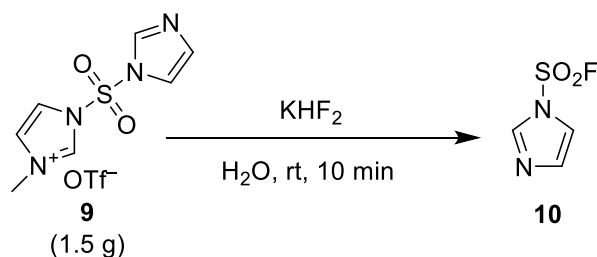
Appearance of 10 and desmethyl SuFEx-IT (11)



Figure S1: A) 1H-imidazole-1-sulfonyl fluoride (**10**). B) 116 g batch of desmethyl SuFEx-IT (**11**). C) Appearance of desmethyl SuFEx-IT after 162 days storage under different conditions: a) 23 °C under air, b) 23 °C under argon, c) 4 °C under argon, d) -18 °C under argon.

Production of 1H-imidazole-1-sulfonyl fluoride (**10**)

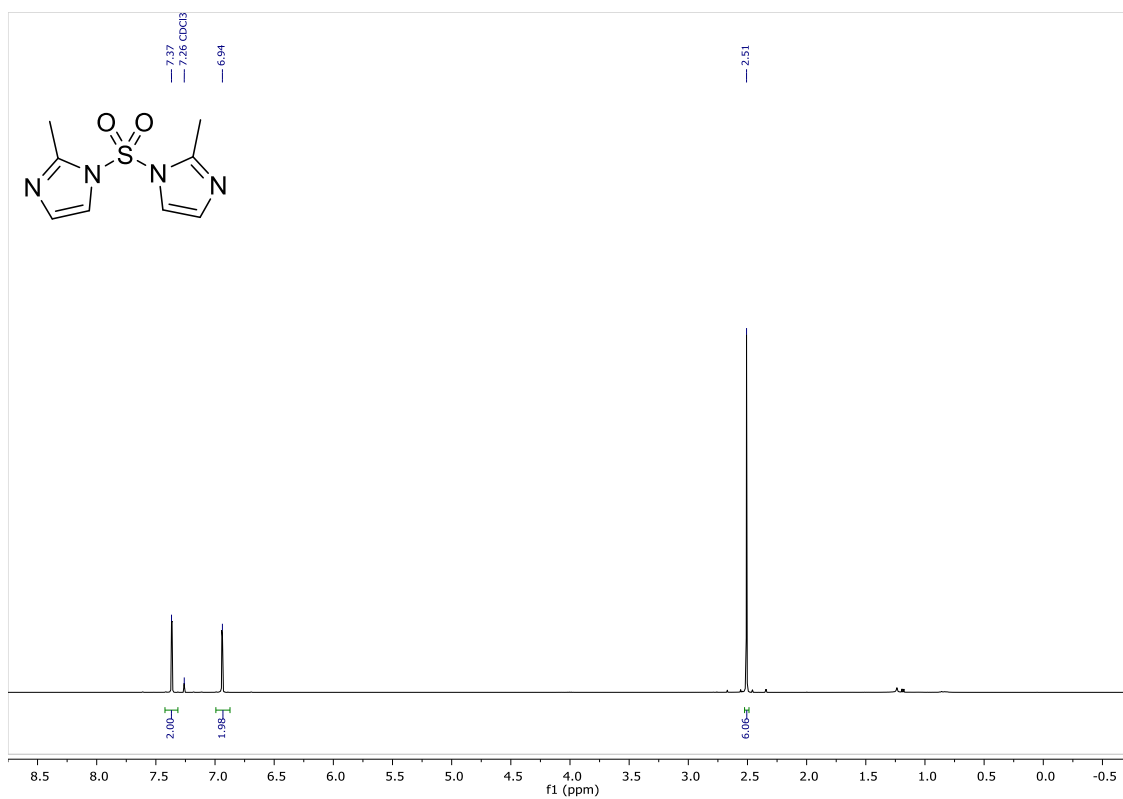
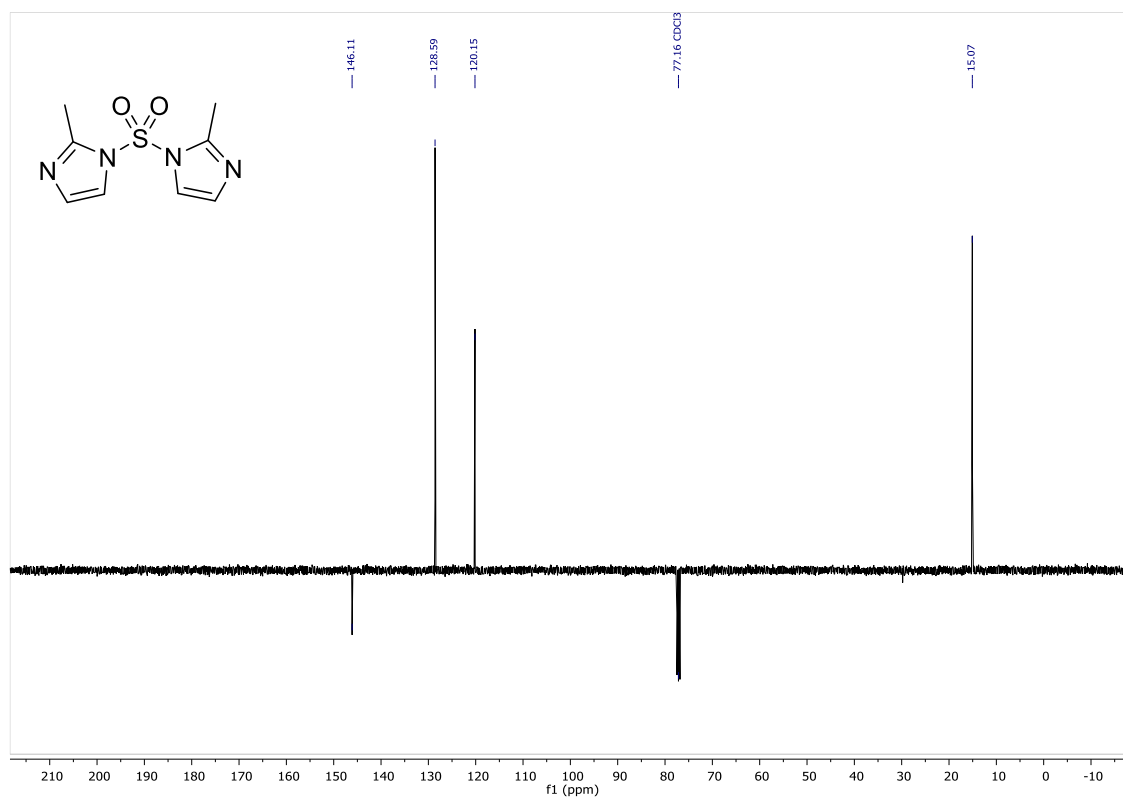
Table S1: Dependency of yield on the amount of KHF₂.

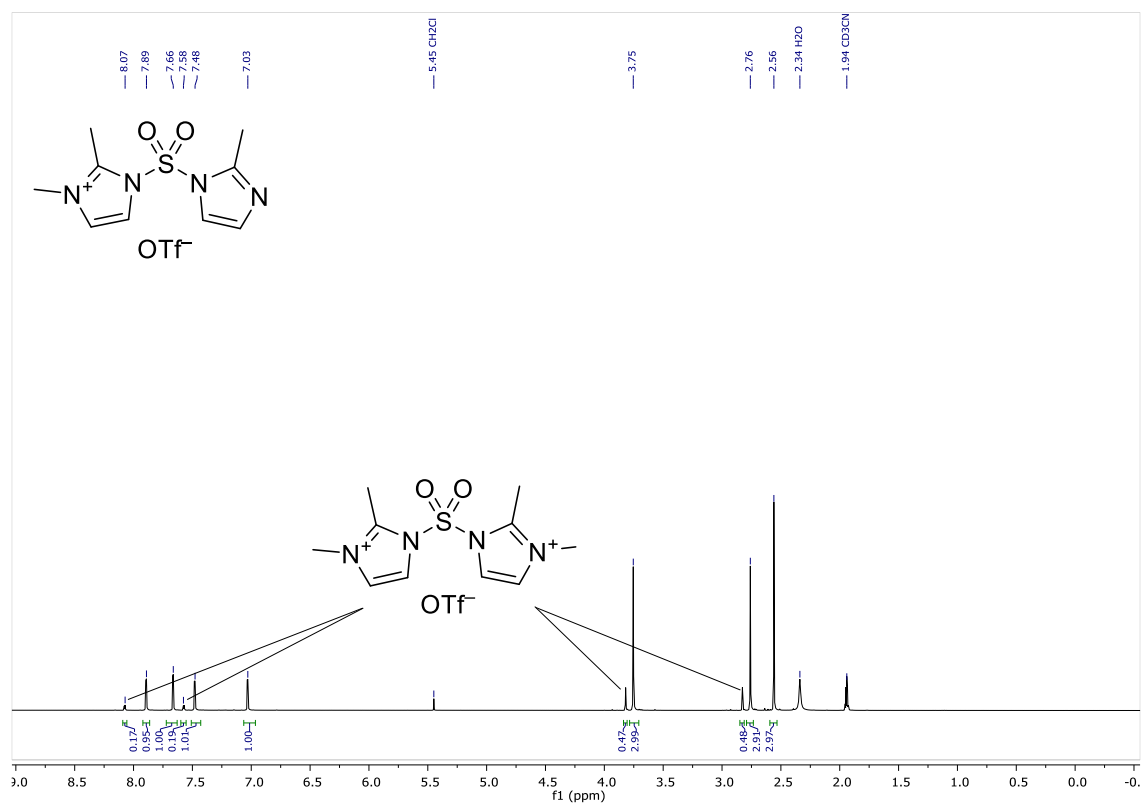
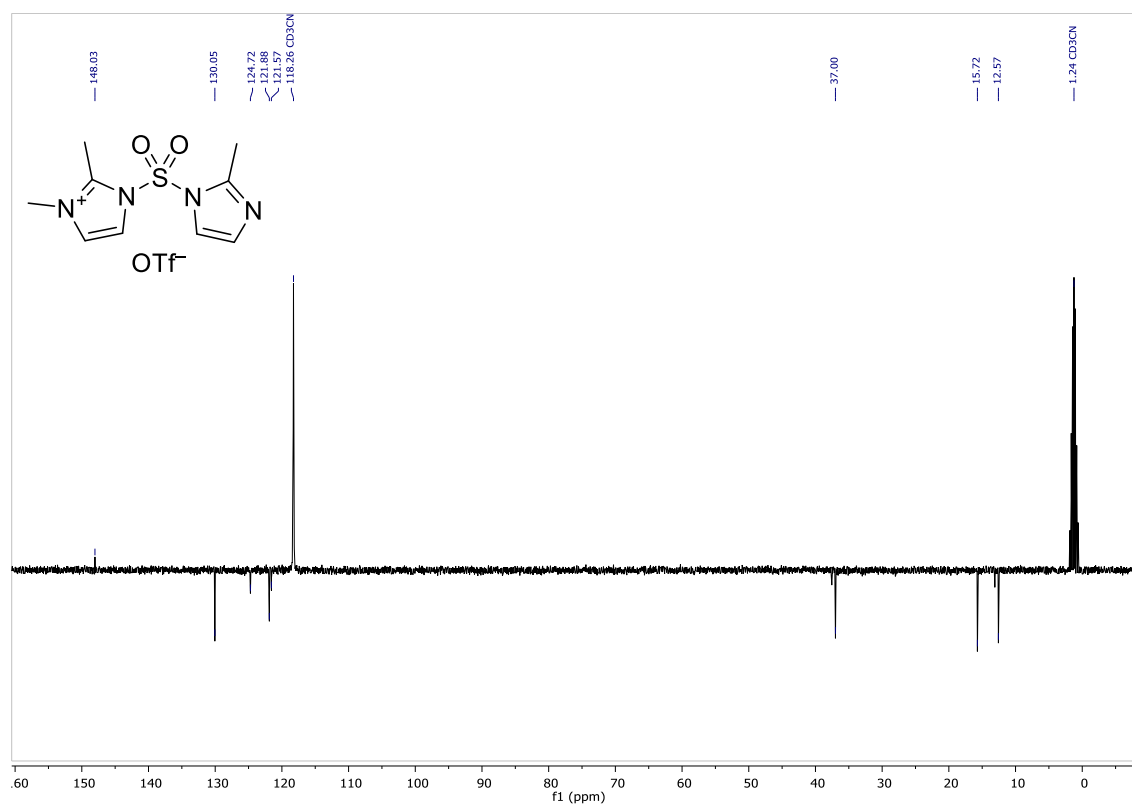


KHF ₂ [eq.]	0.50	0.75	1.00
Yield [%]	66	77 ^a	75

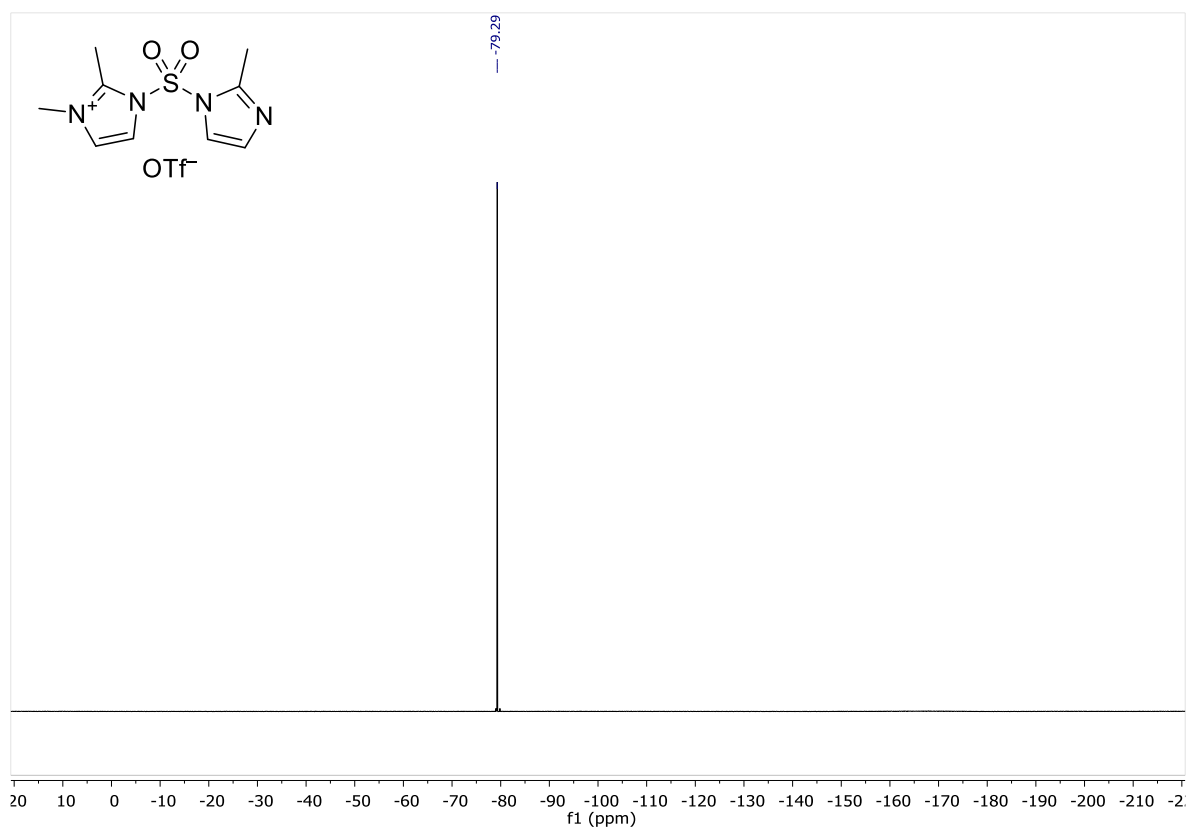
^a Note that a roughly 10% higher yield (88%) was obtained when the same reaction conditions were applied on a decagram scale, as described in the main text.

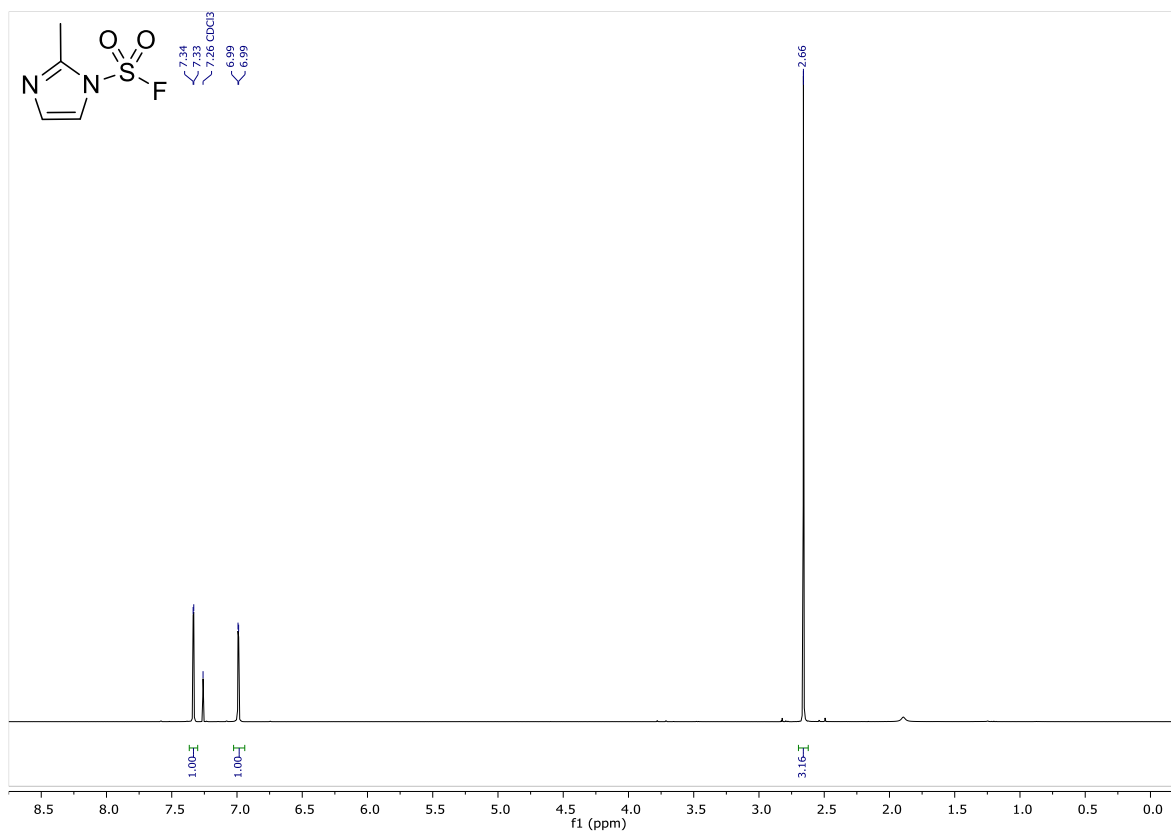
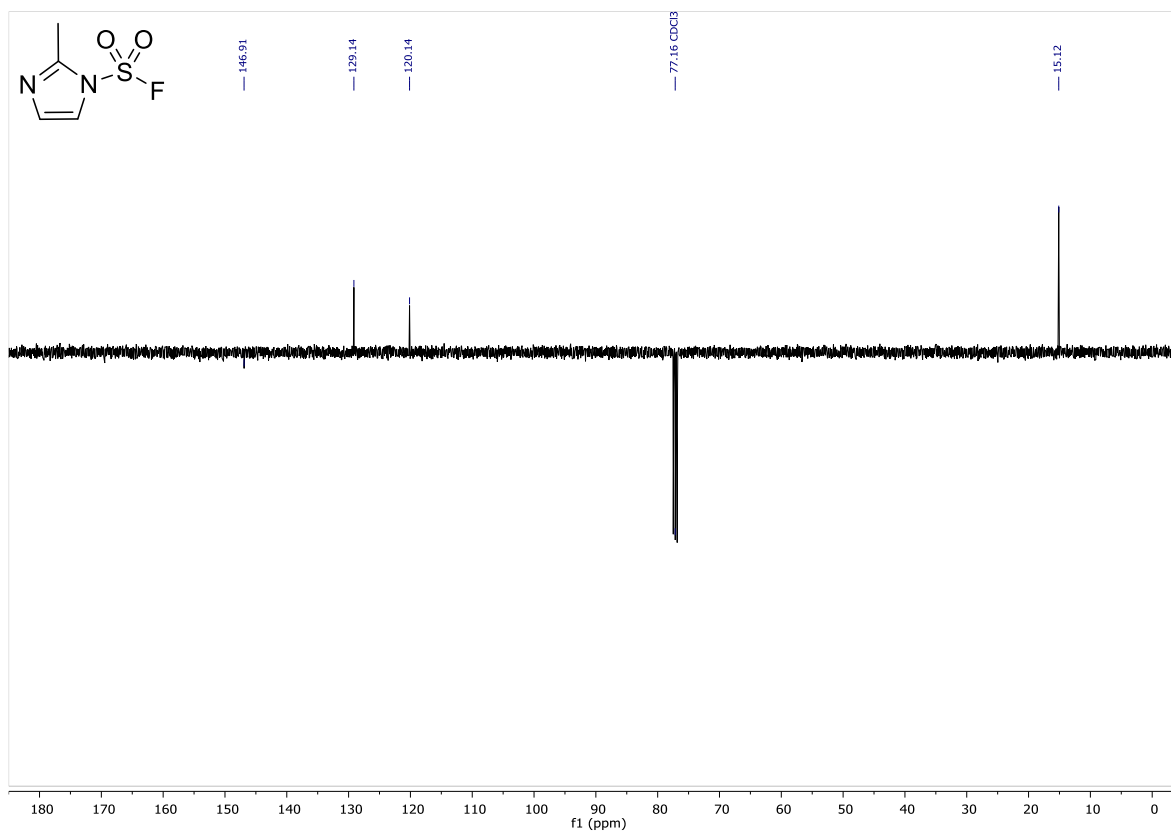
NMR Spectra

1,1'-Sulfonylbis(2-methyl-1*H*-imidazole) (**5**) ^1H NMR (400 MHz, CDCl_3) $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3)

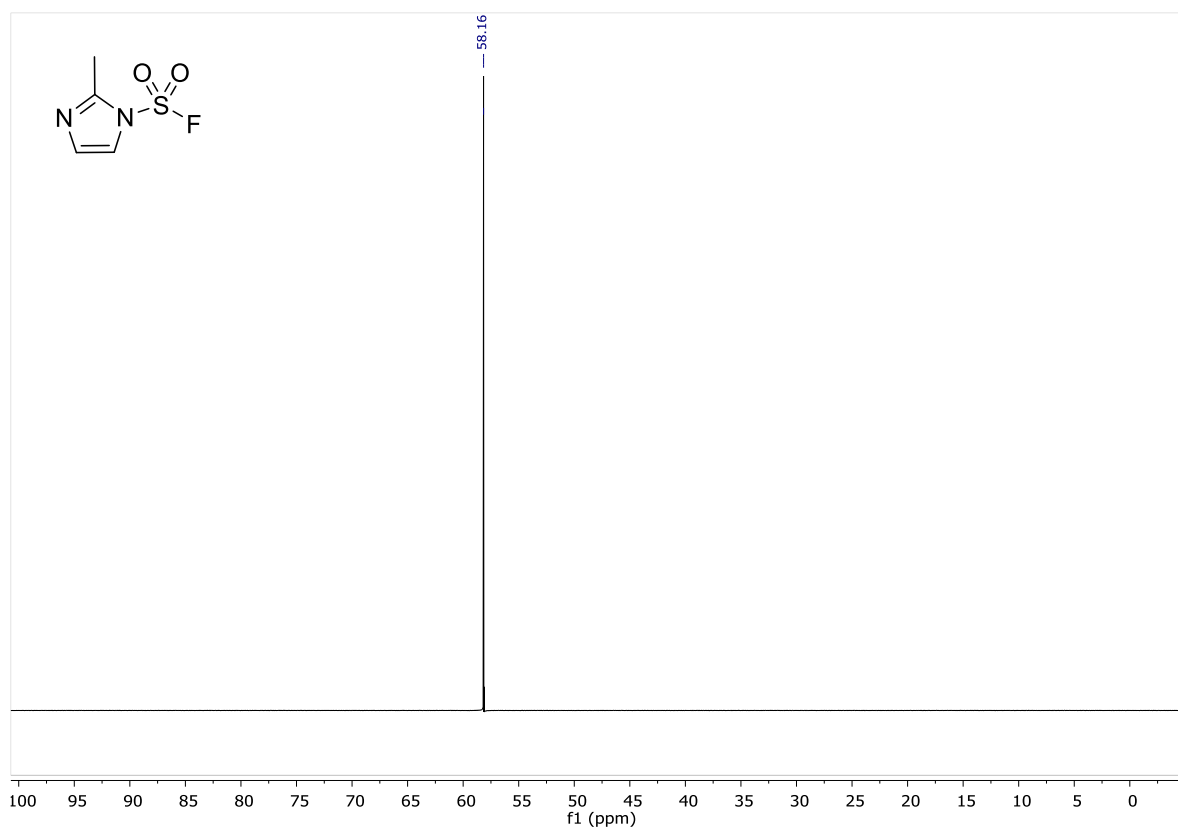
2,3-Dimethyl-1-[(2-methyl-1*H*-imidazol-1-yl)sulfonyl]-1*H*-imidazol-3-ium trifluoromethanesulfonate (6)¹H NMR (400 MHz, CD₃CN)¹³C{¹H} NMR (101 MHz, CD₃CN)

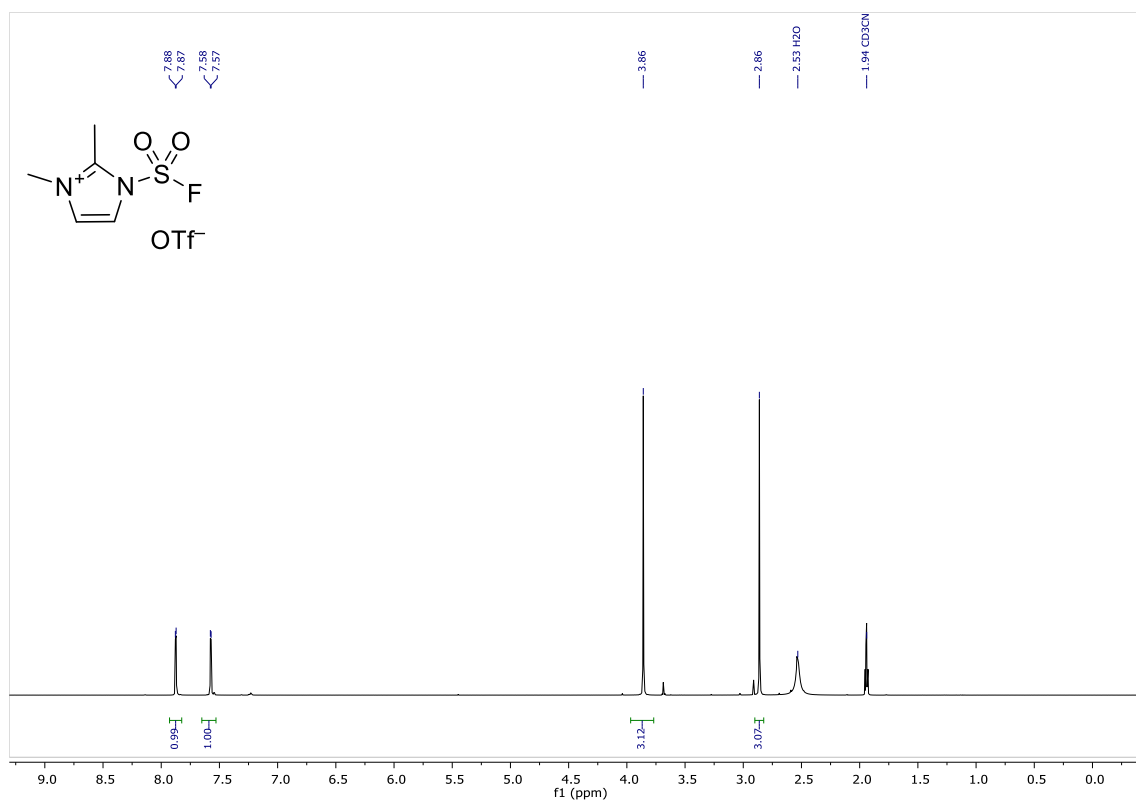
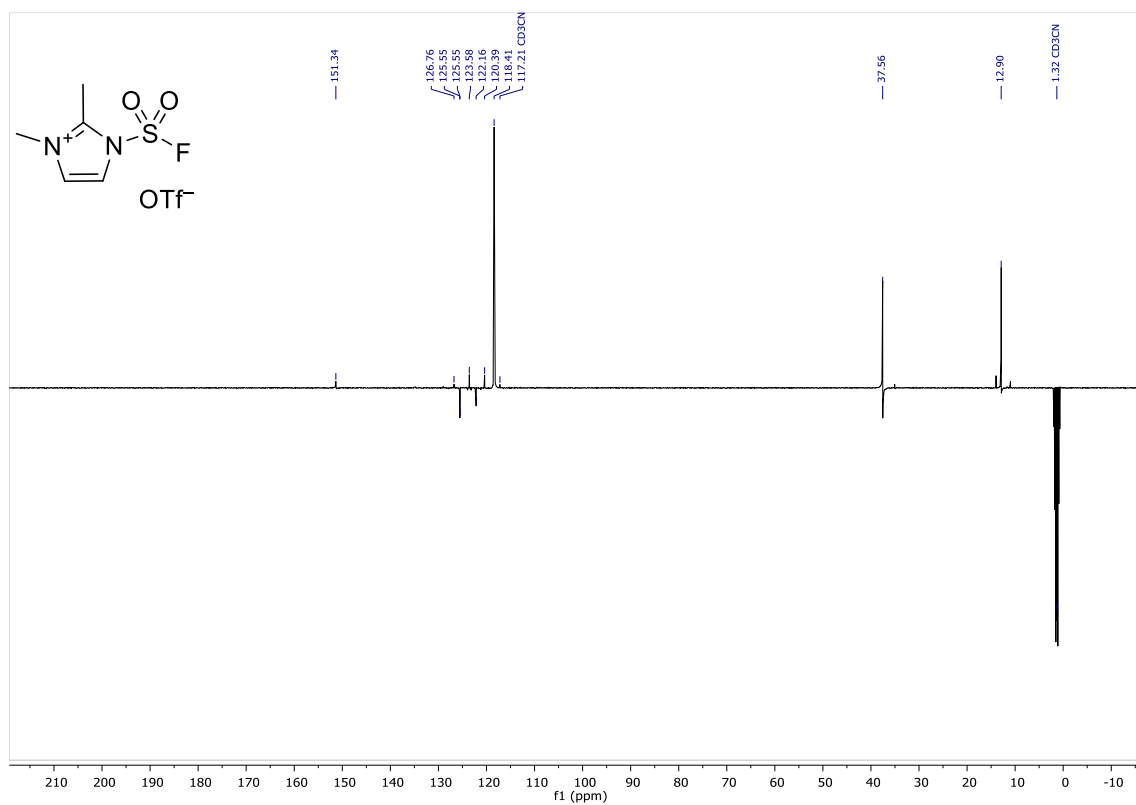
^{19}F NMR (376 MHz, CD_3CN)



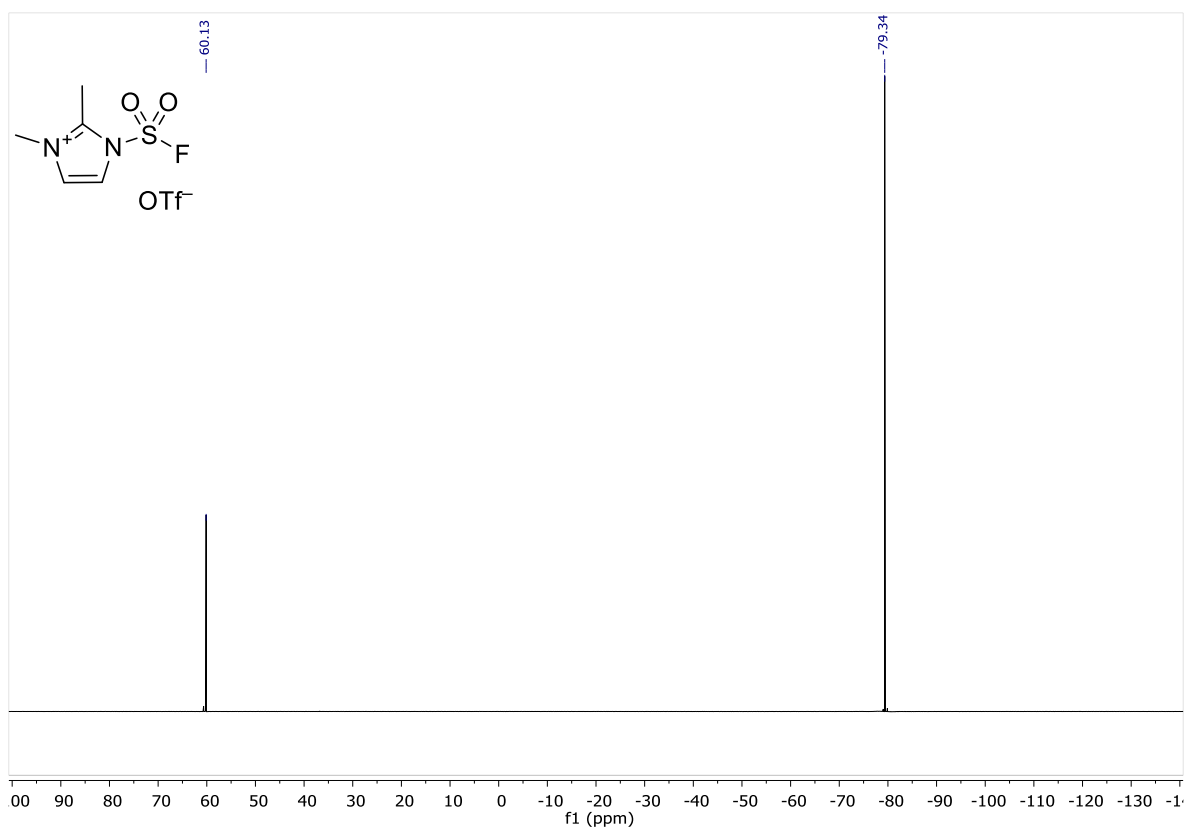
2-Methyl-1*H*-imidazole-1-sulfonyl fluoride (3)¹H NMR (400 MHz, CDCl₃)¹³C{¹H} NMR (101 MHz, CDCl₃)

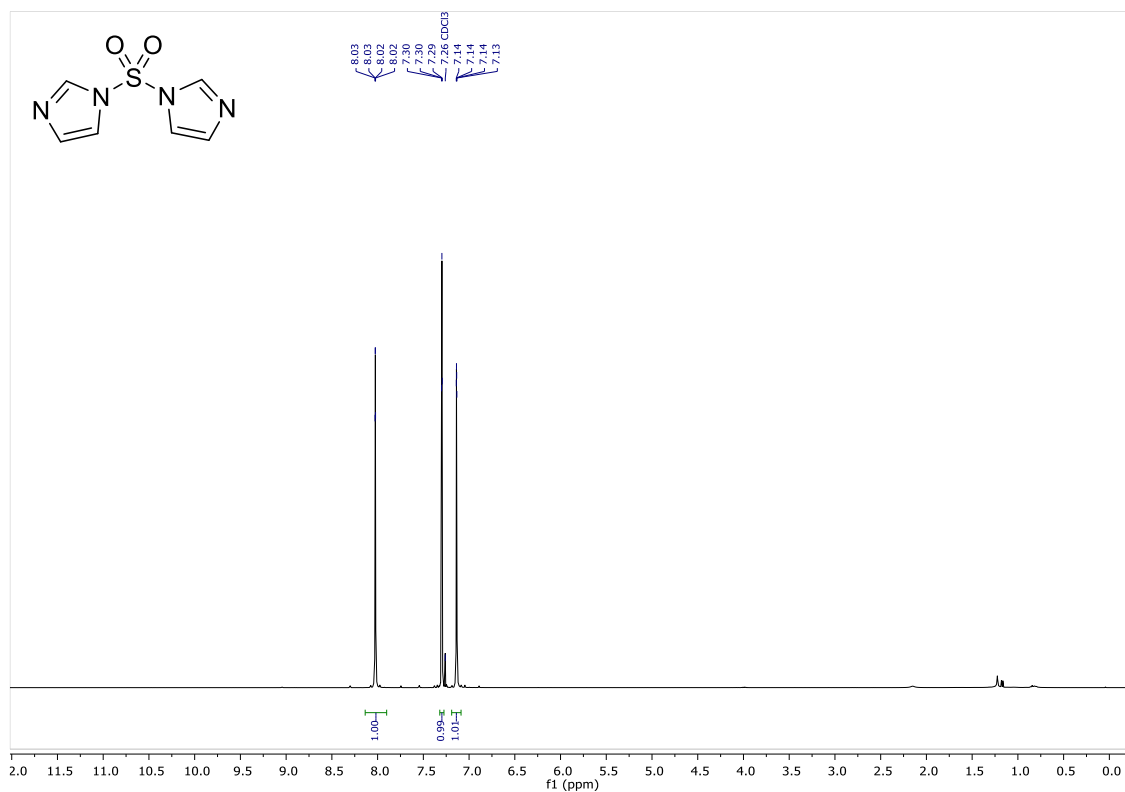
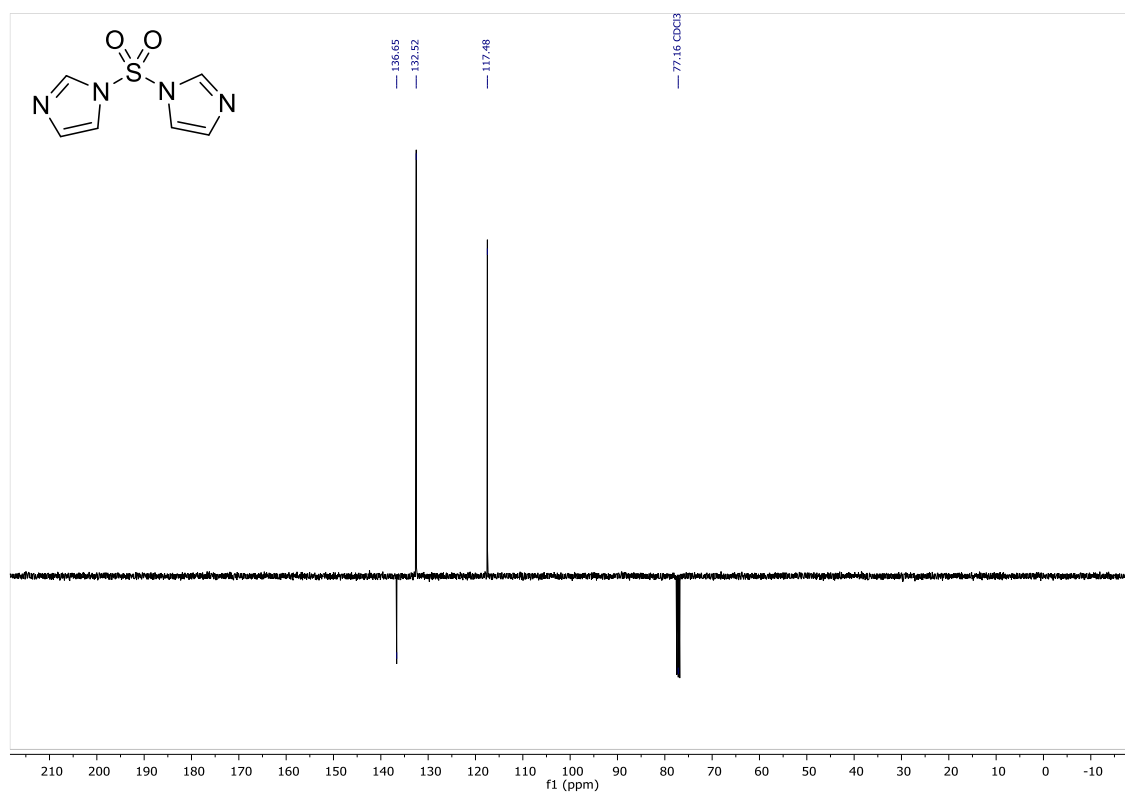
^{19}F NMR (376 MHz, CDCl_3)

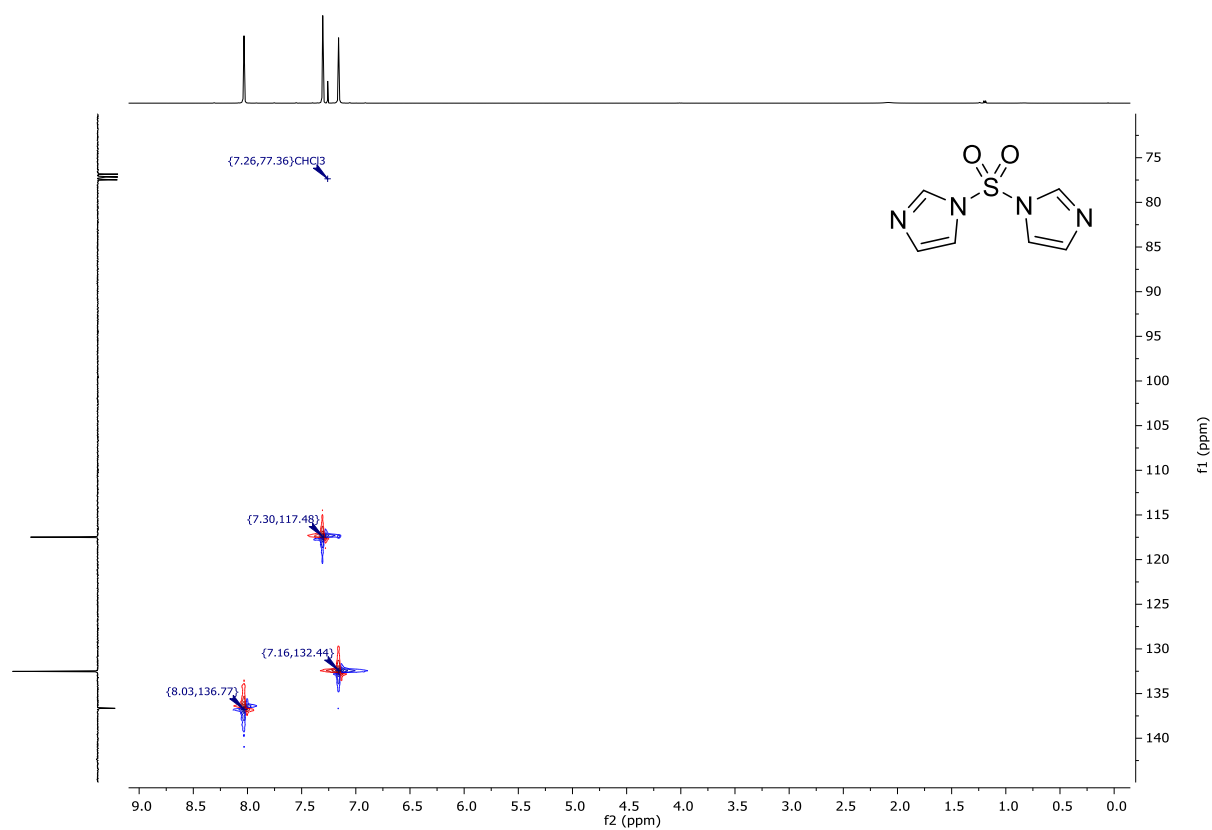


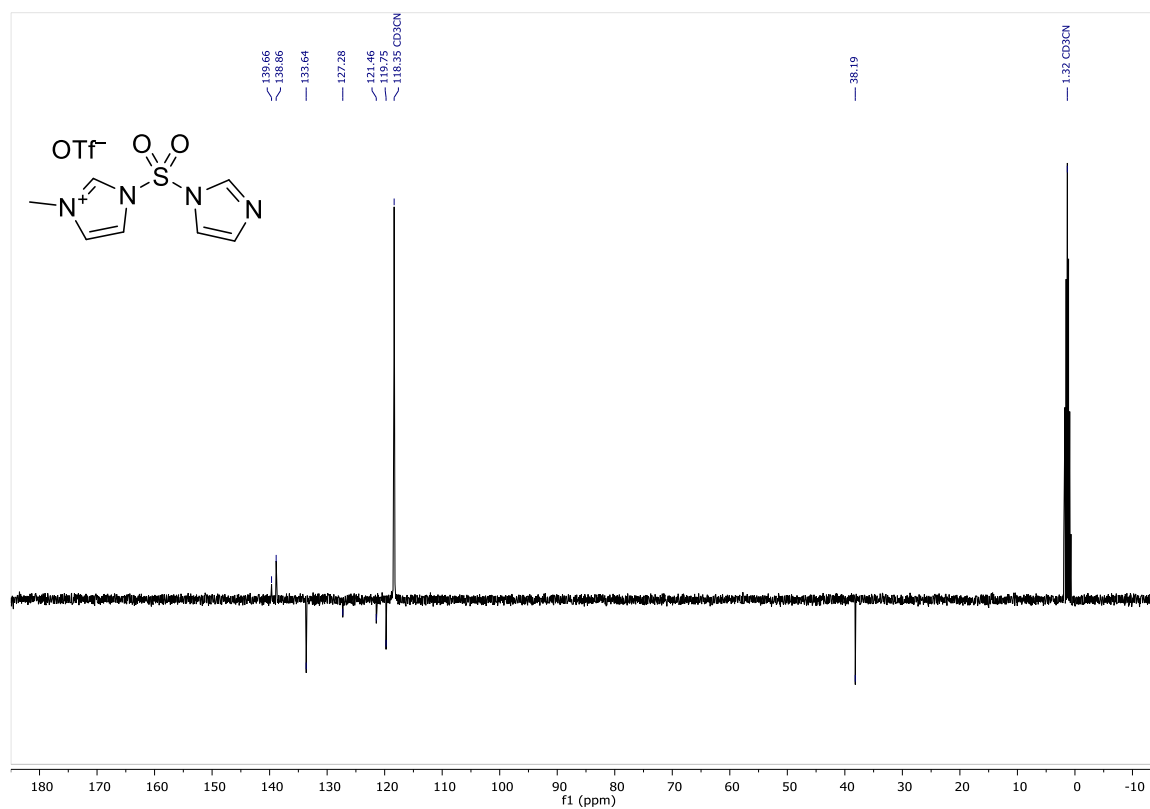
1-(Fluorosulfonyl)-2,3-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (SuFEx-IT, 4)¹H NMR (400 MHz, CD₃CN)¹³C{¹H} NMR (101 MHz, CD₃CN)

^{19}F NMR (376 MHz, CD_3CN)

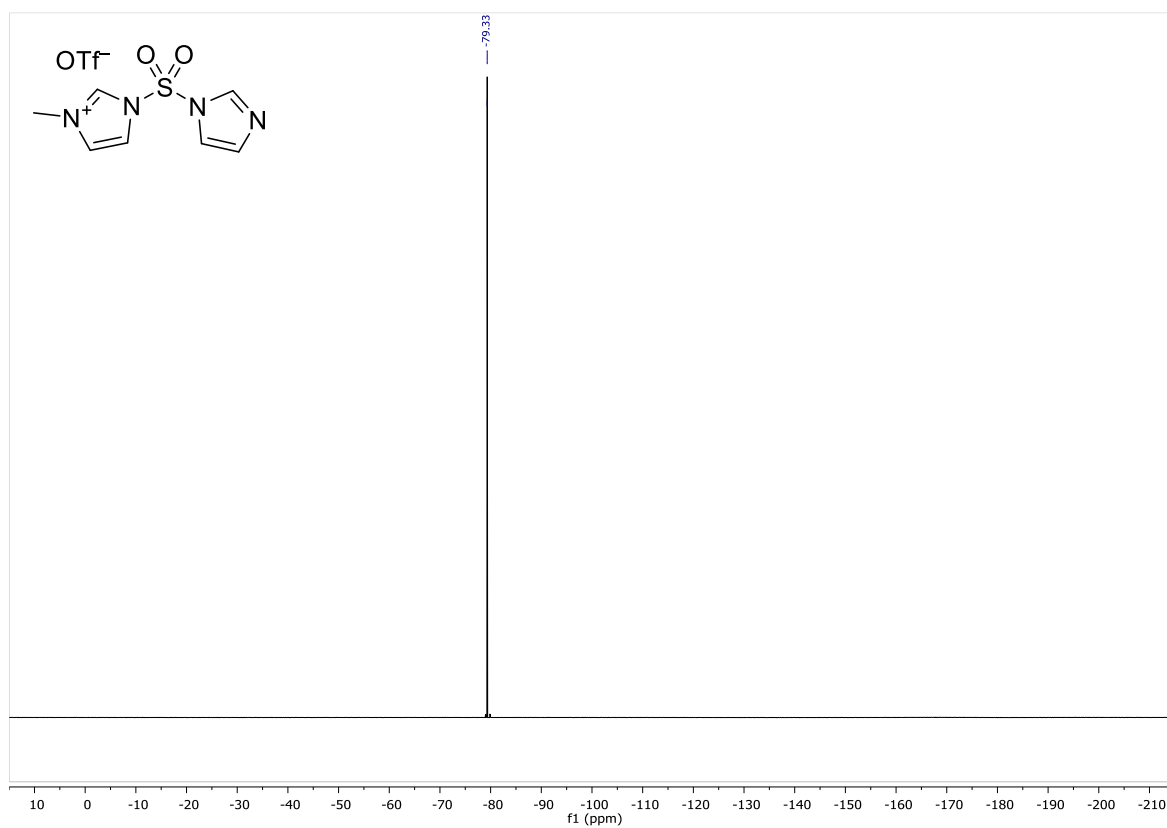


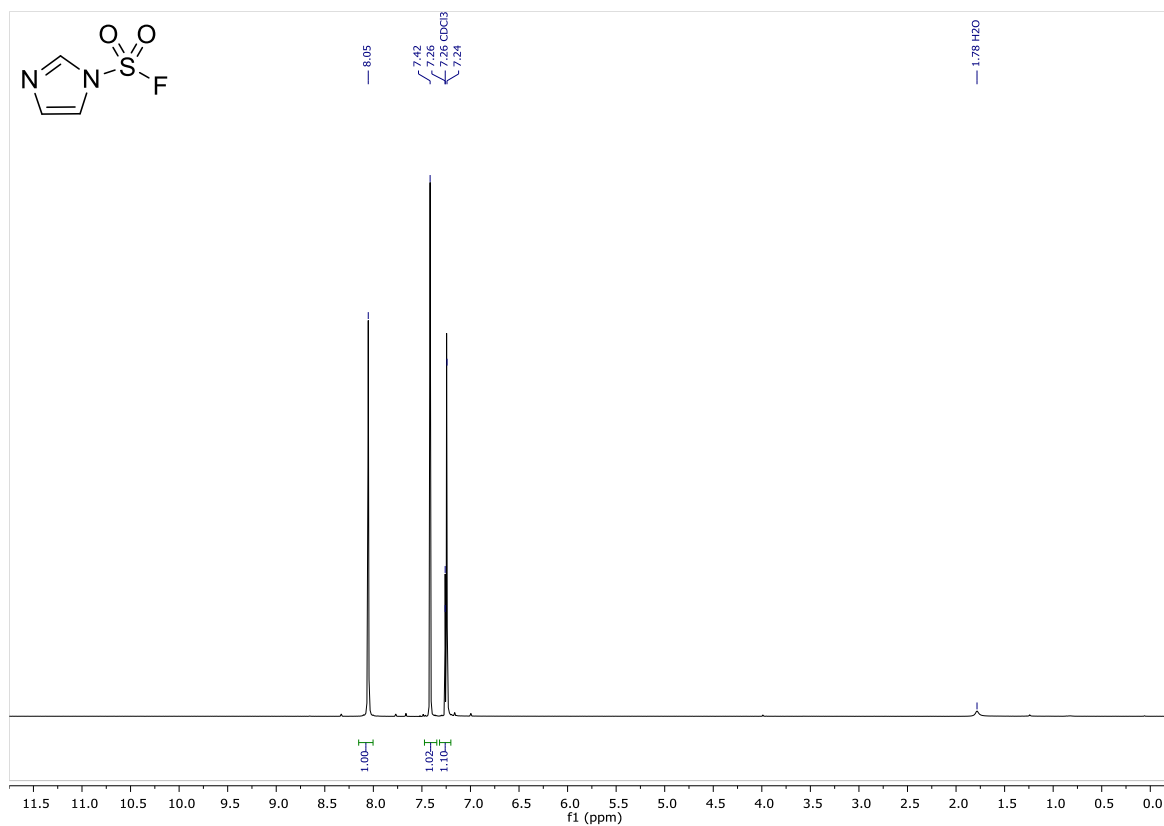
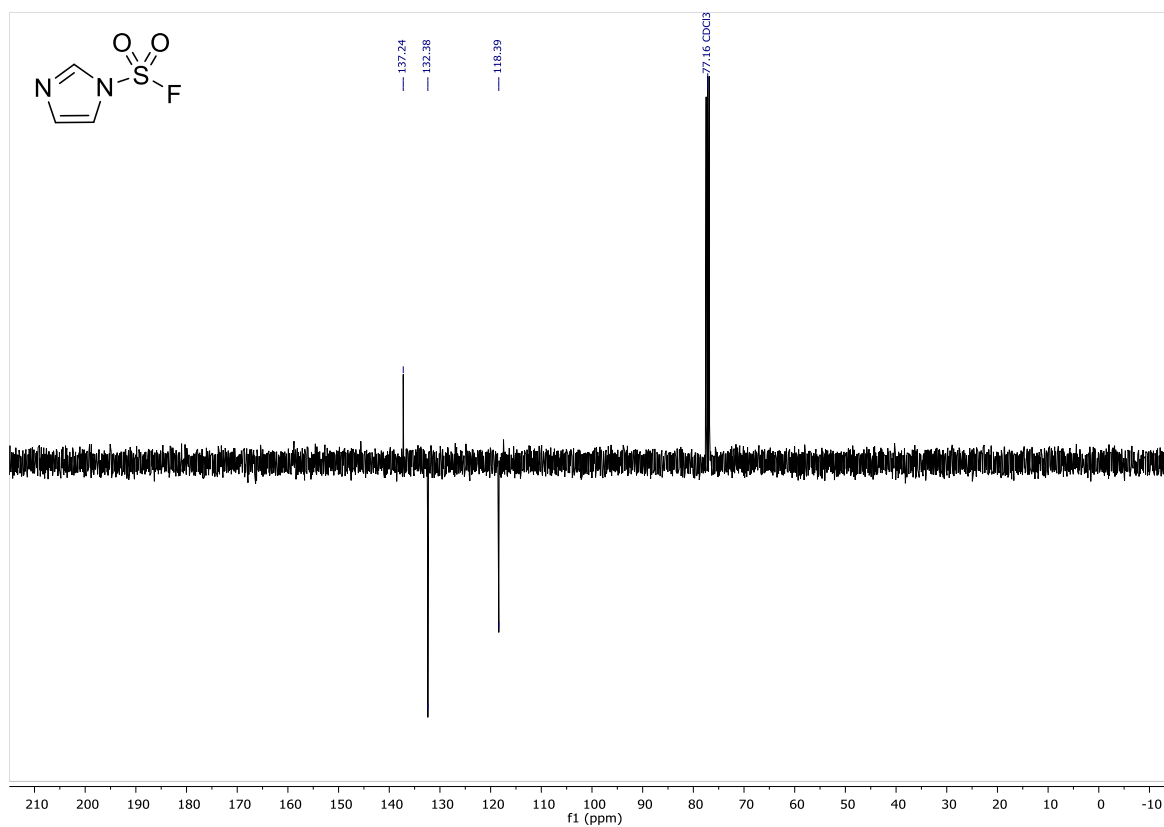
1,1'-Sulfonyldiimidazole (SDI, 8) ^1H NMR (400 MHz, CDCl_3) $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3)

HSQC NMR (400 MHz/101 MHz, CDCl₃)

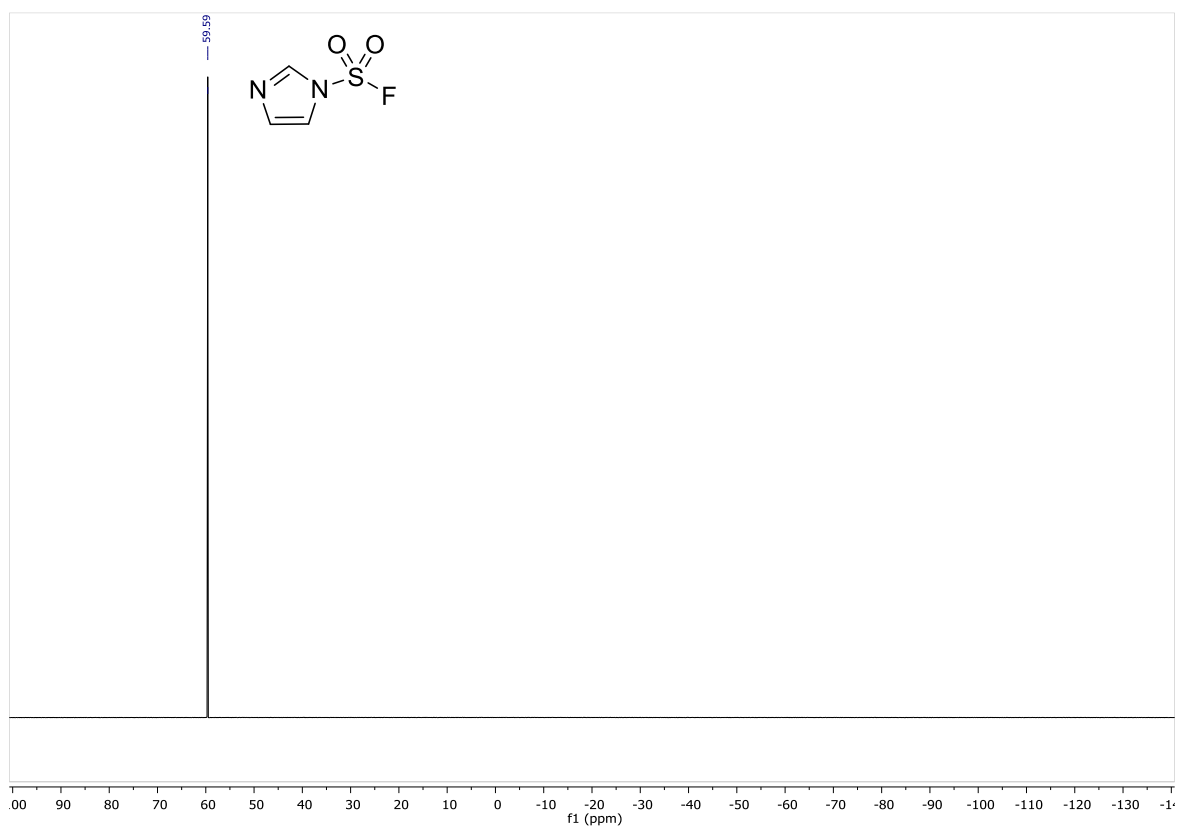
3-(Imidazole-1-sulfonyl)-1-methyl-3*H*-imidazol-1-ium trifluoromethanesulfonate (MSDI, 9) ^1H NMR (400 MHz, CD_3CN) $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CD_3CN)

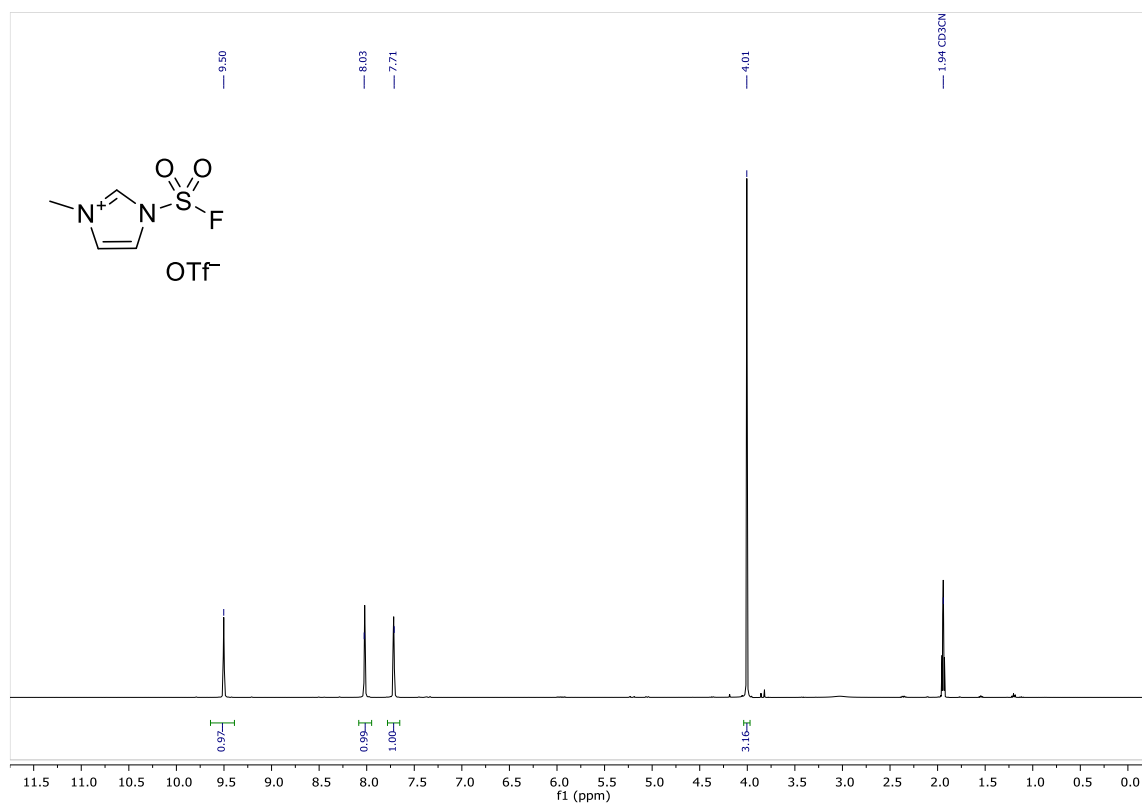
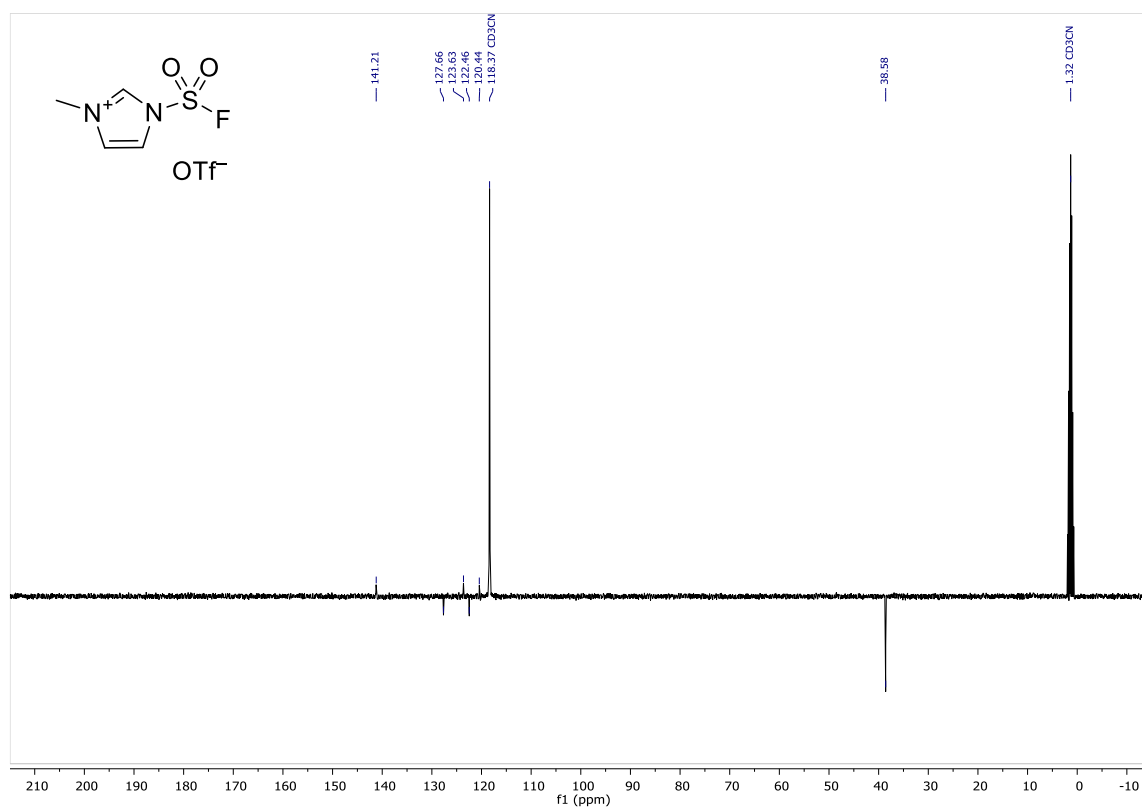
^{19}F NMR (376 MHz, CD_3CN)



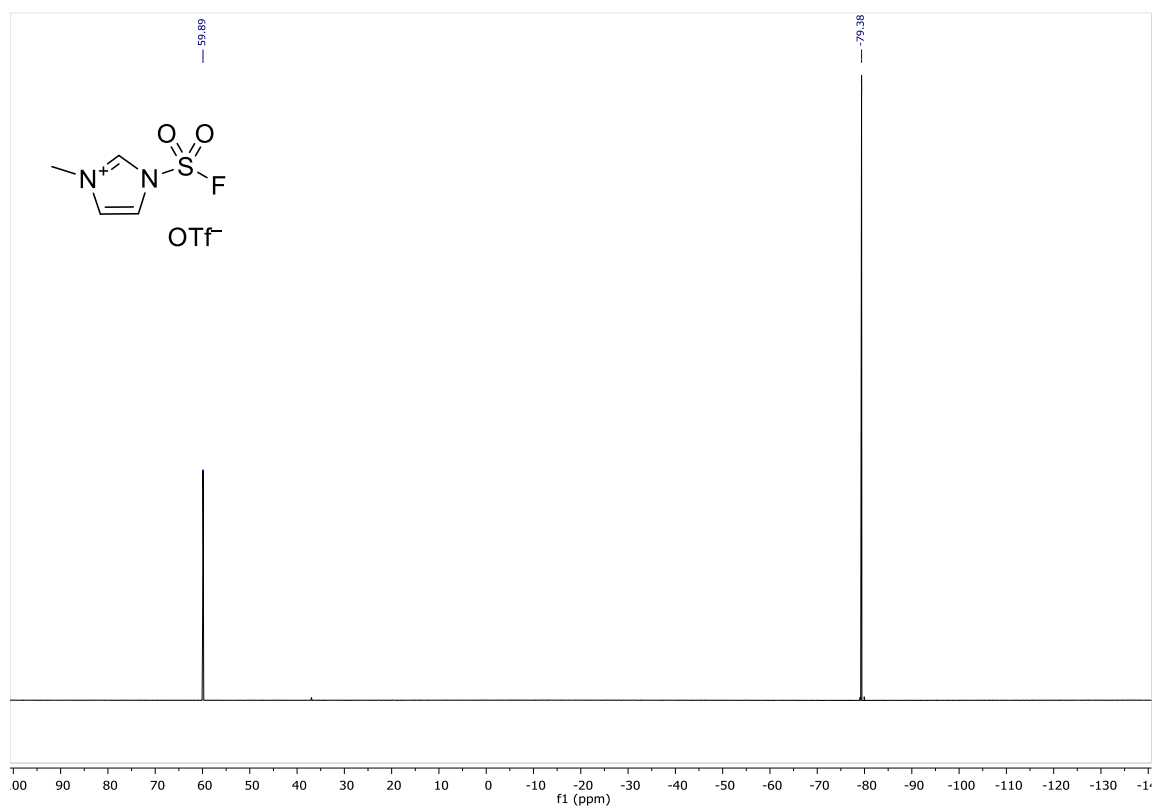
1*H*-Imidazole-1-sulfonyl fluoride (10)¹H NMR (400 MHz, CDCl₃)¹³C{¹H} NMR (101 MHz, CDCl₃)

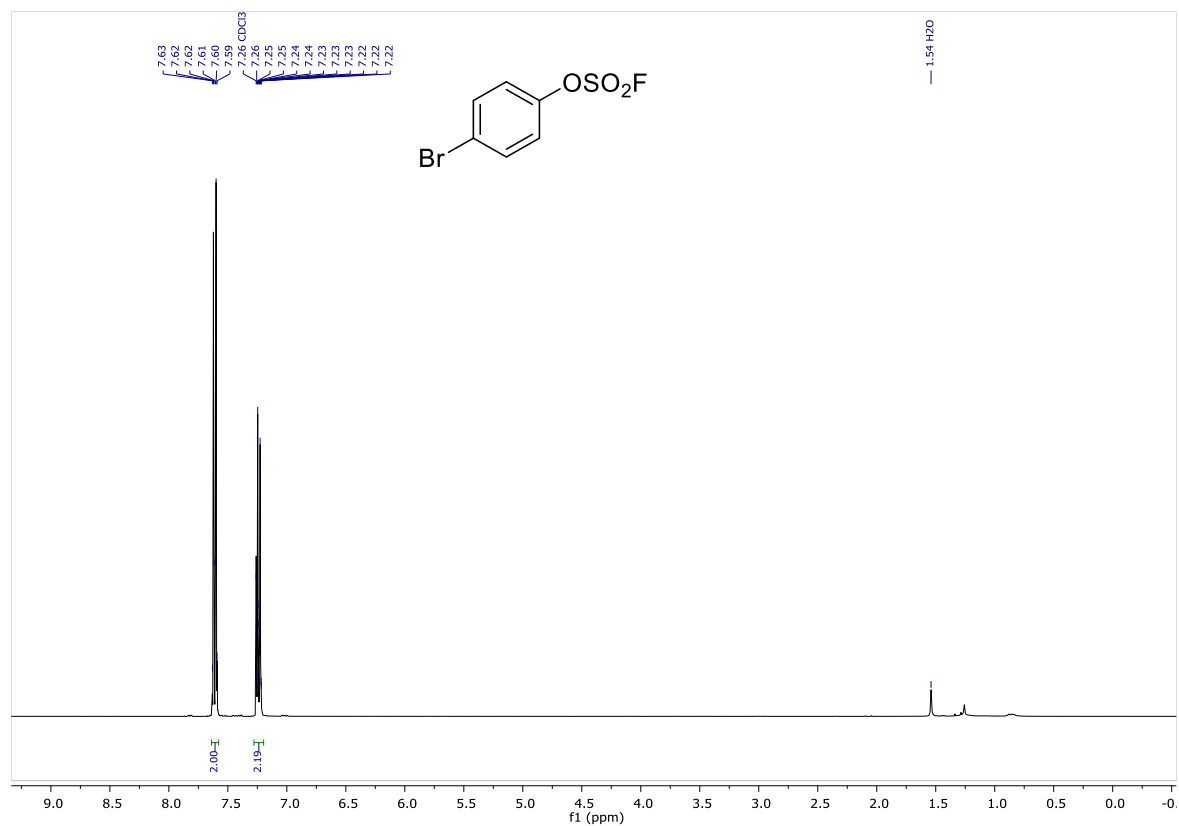
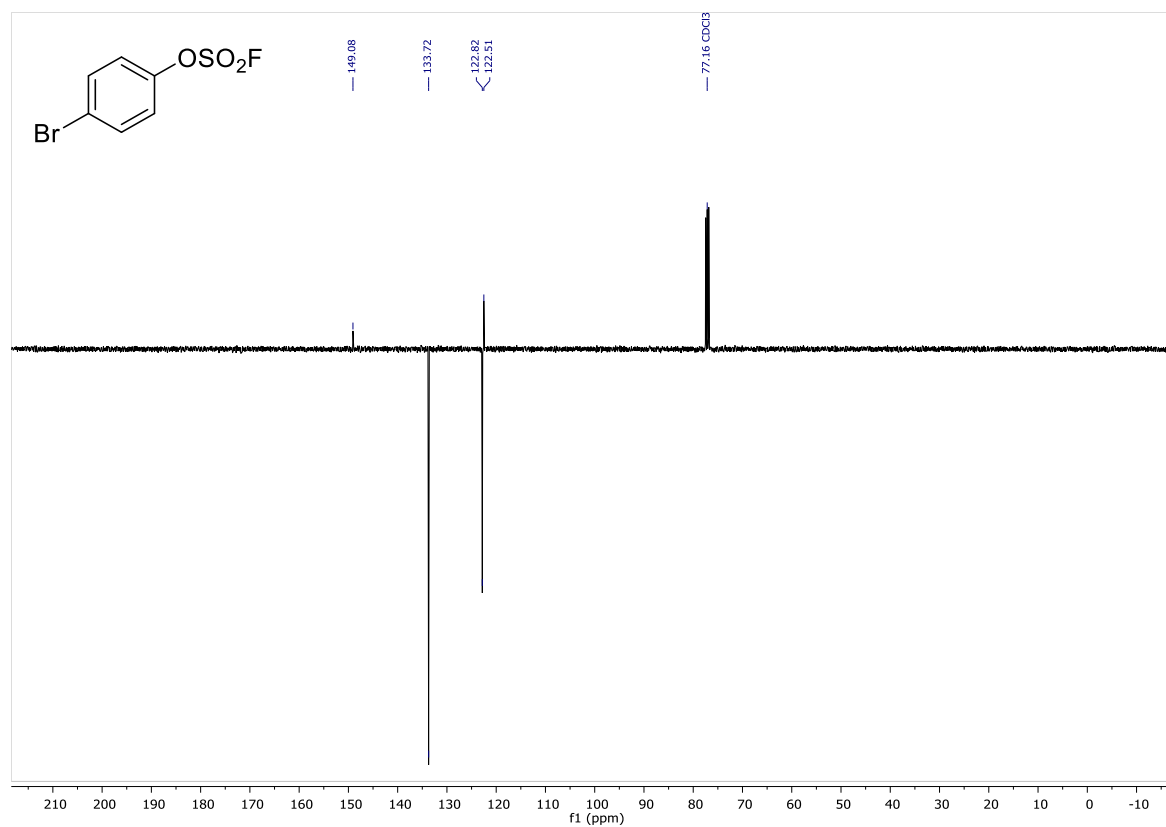
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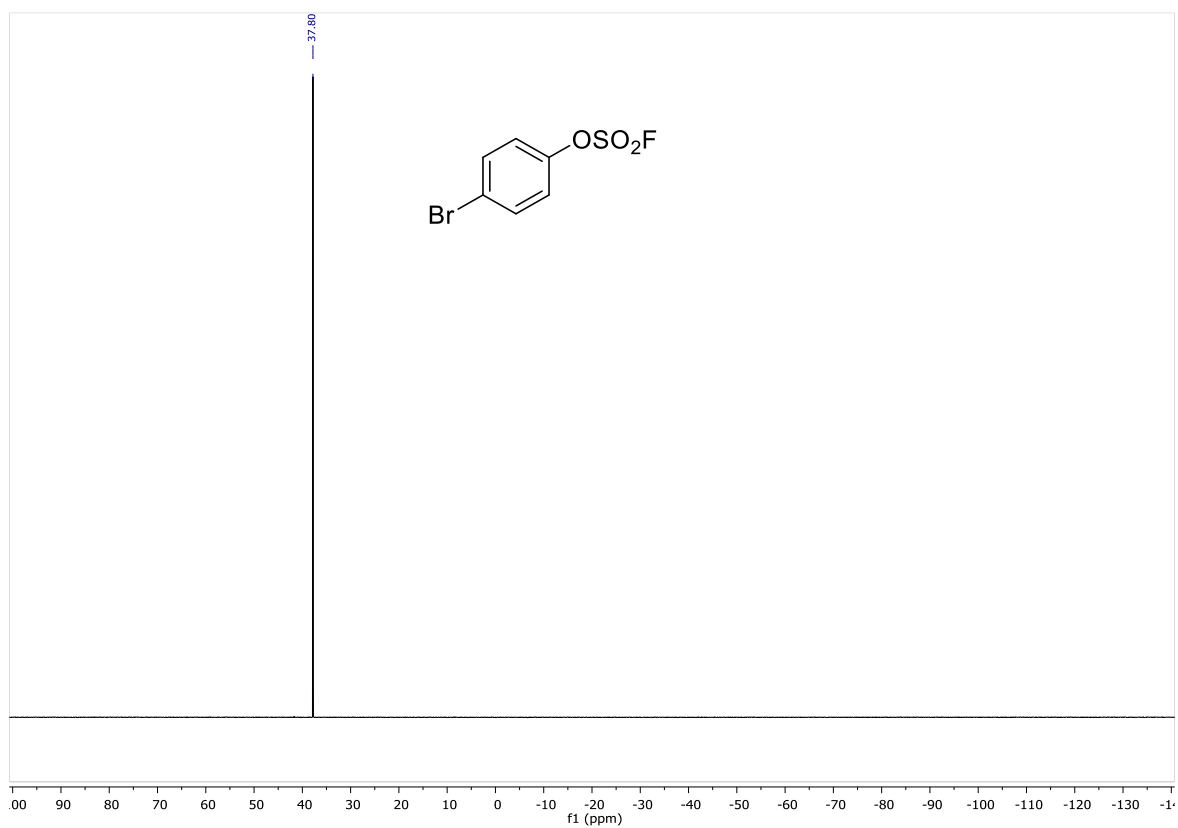
1-(Fluorosulfonyl)-3-methyl-1*H*-imidazole trifluoromethanesulfonate (desmethyl SuFEx-IT, 11) ^1H NMR (400 MHz, CD_3CN) $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CD_3CN)

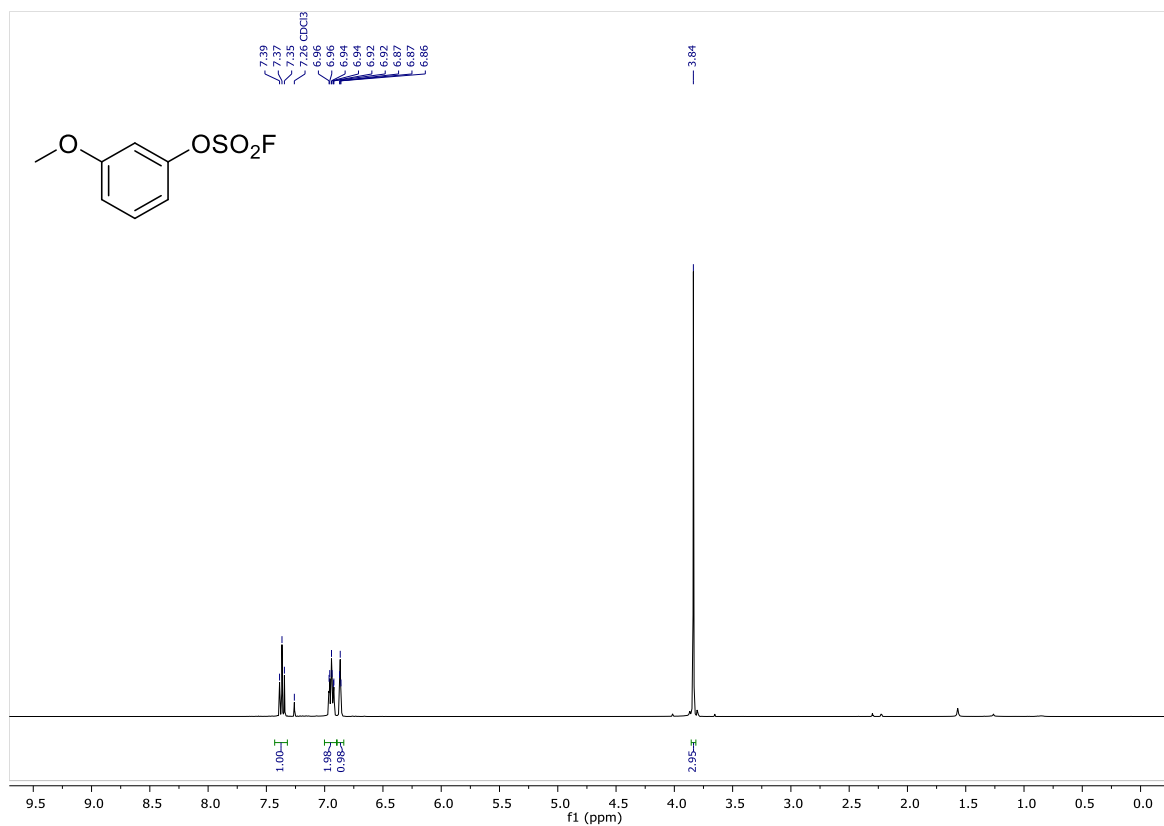
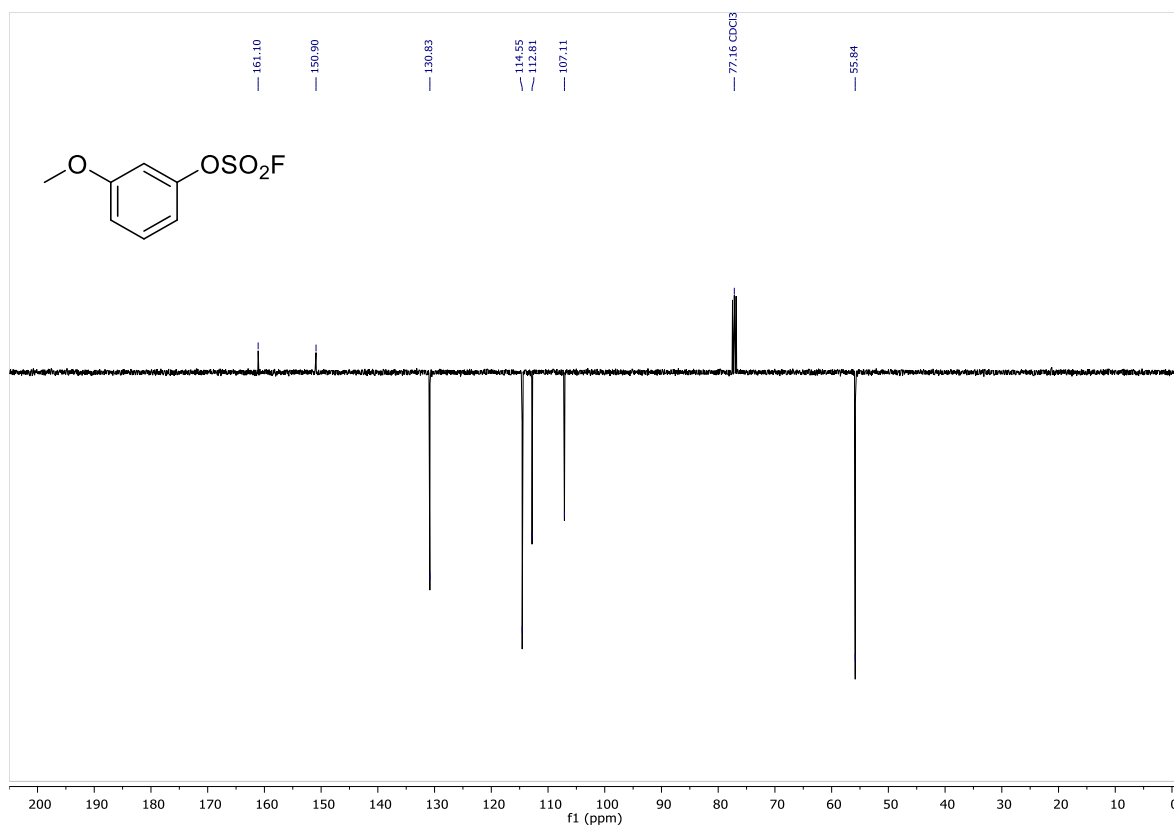
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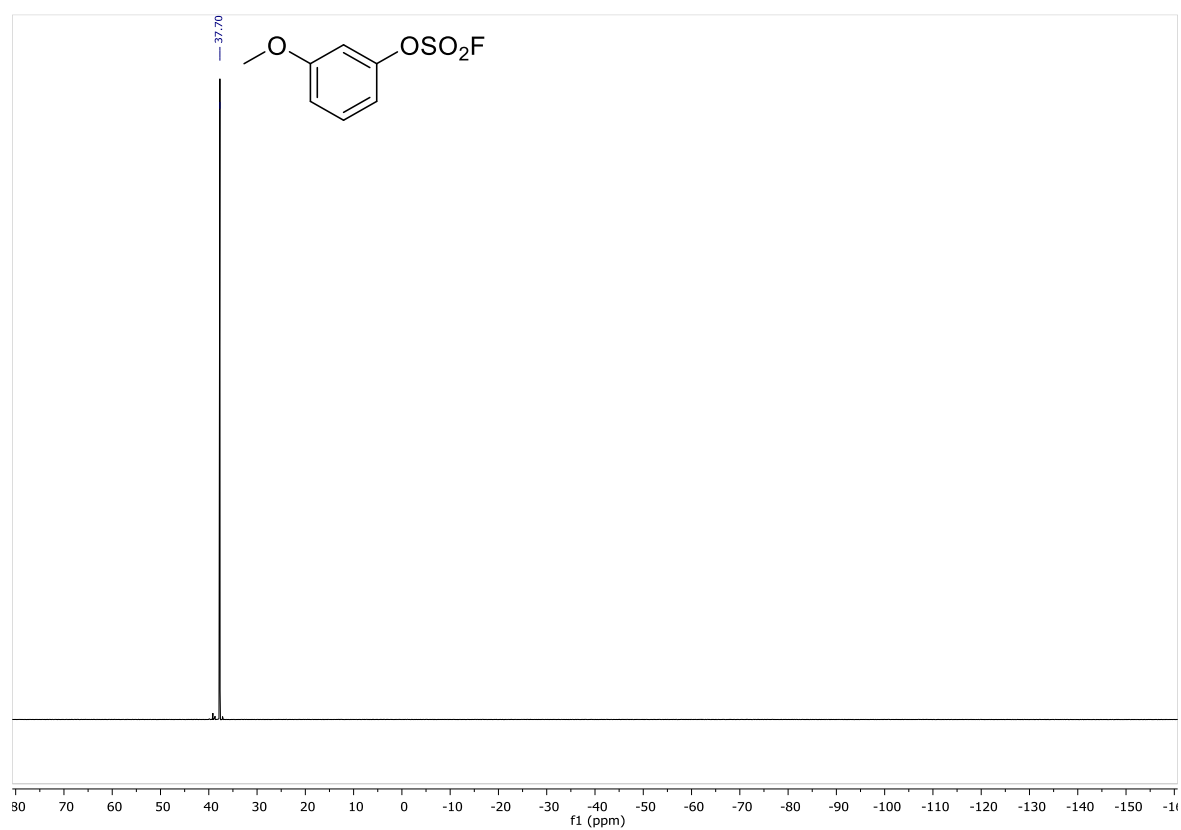
4-Bromophenyl sulfurofluoridate (12a) ^1H NMR (400 MHz, CDCl_3) $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3)

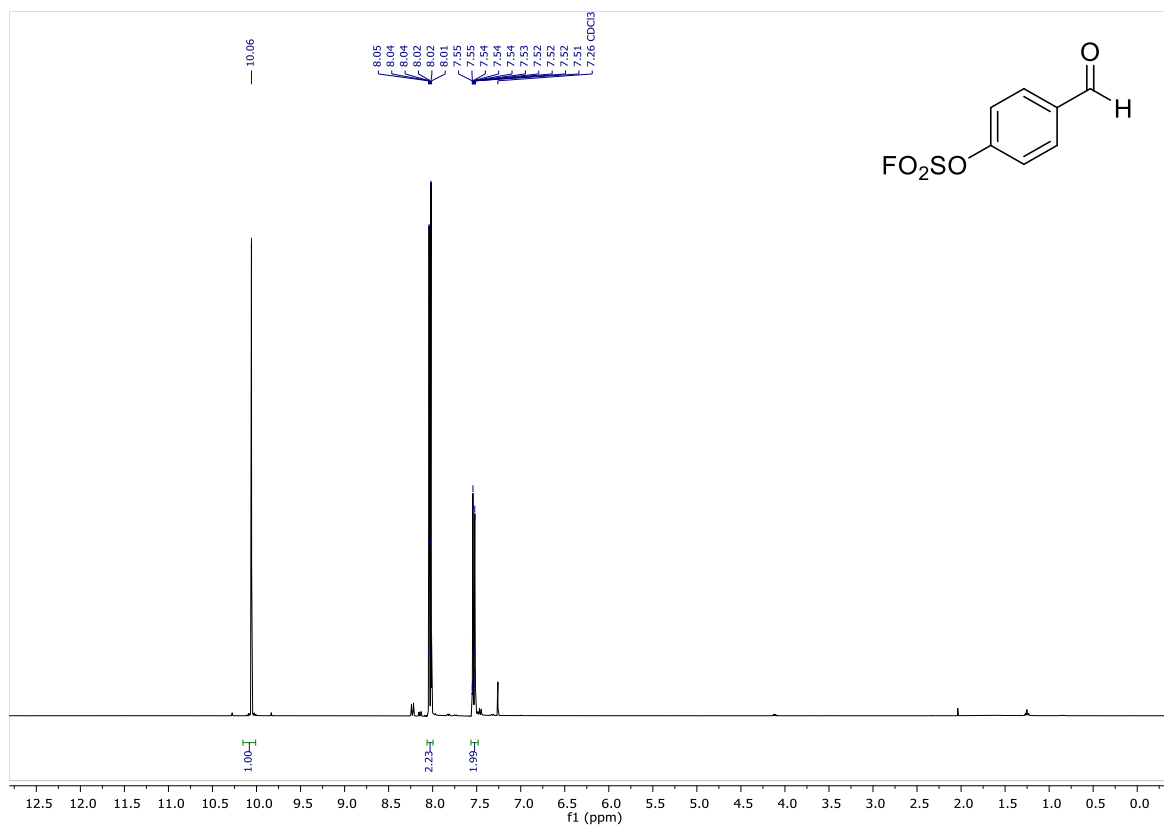
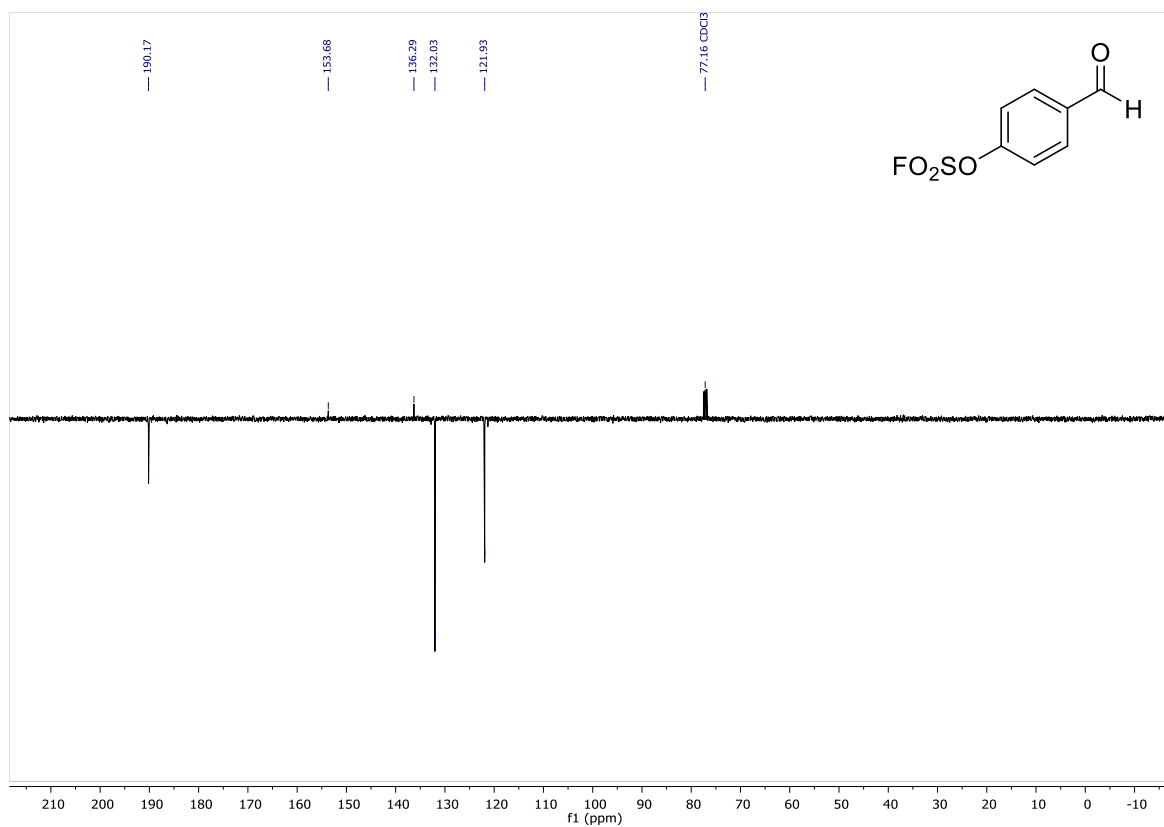
^{19}F NMR (376 MHz, CDCl_3)



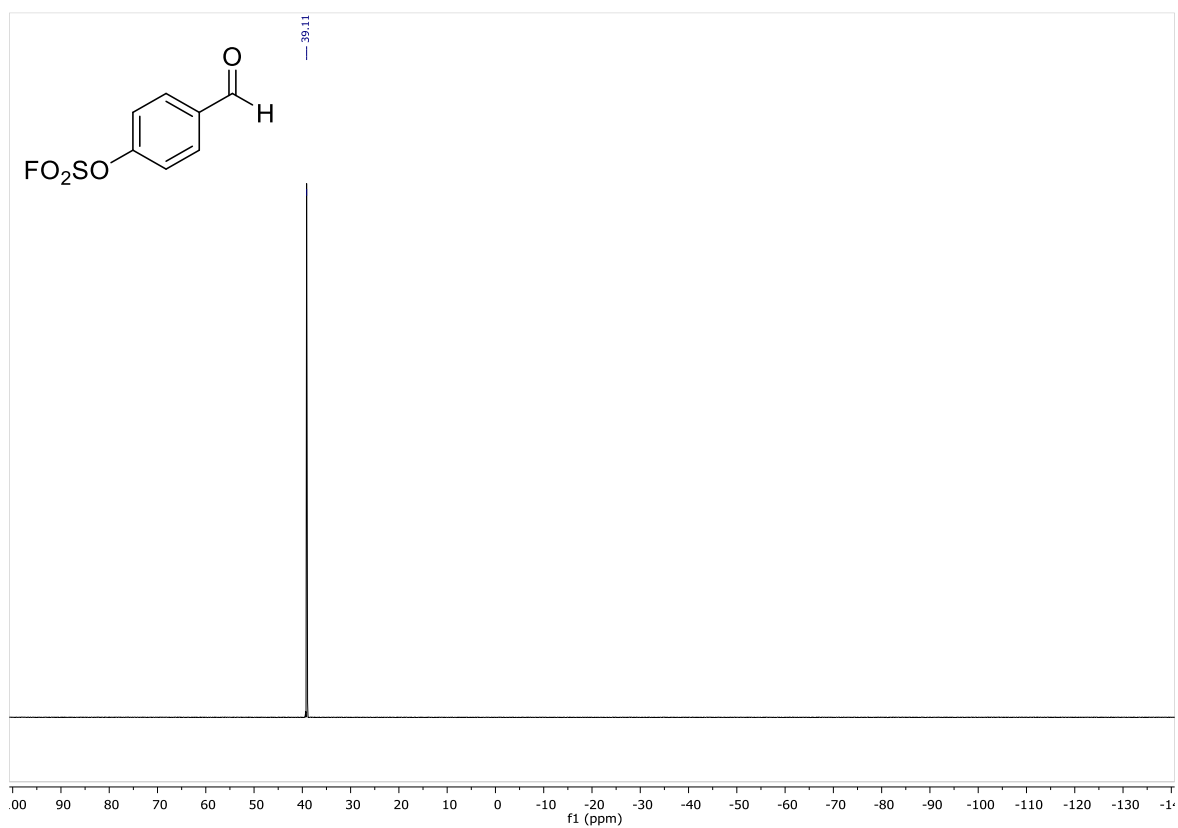
3-Methoxyphenyl sulfurofluoridate (12b) ^1H NMR (400 MHz, CDCl_3) $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3)

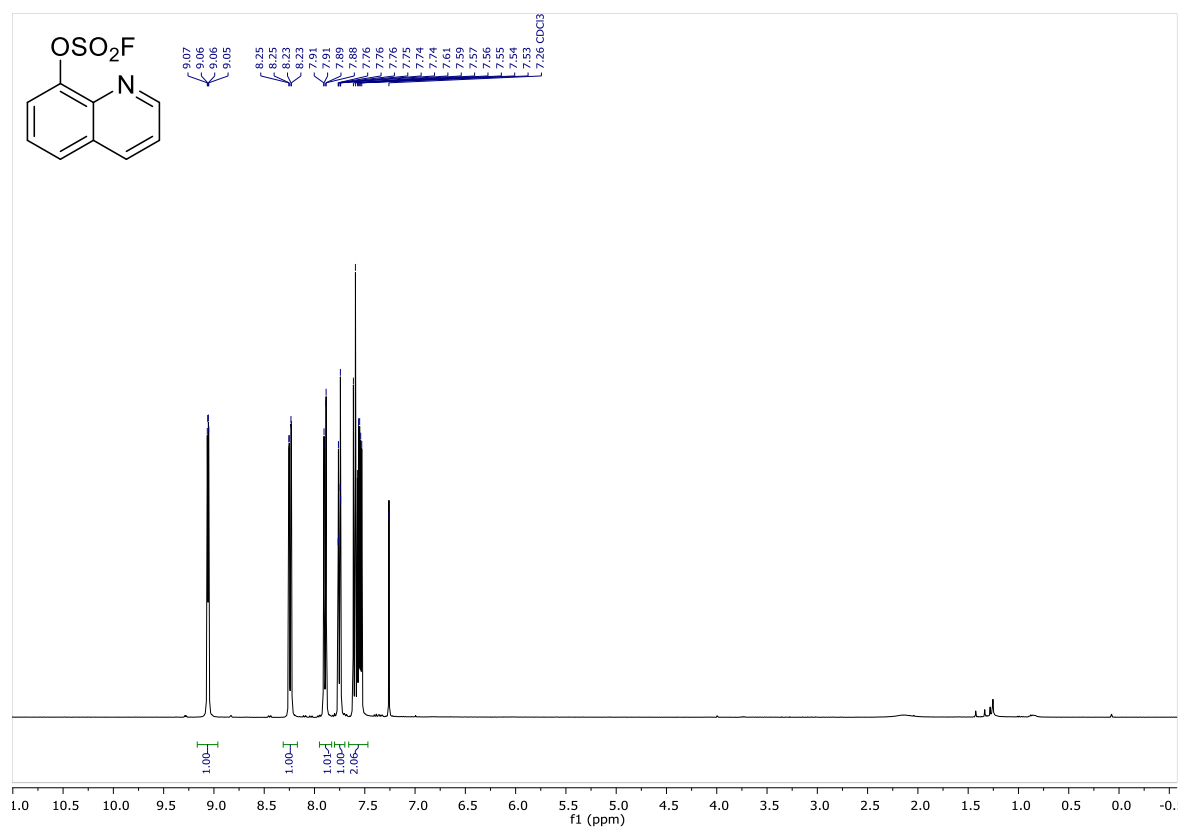
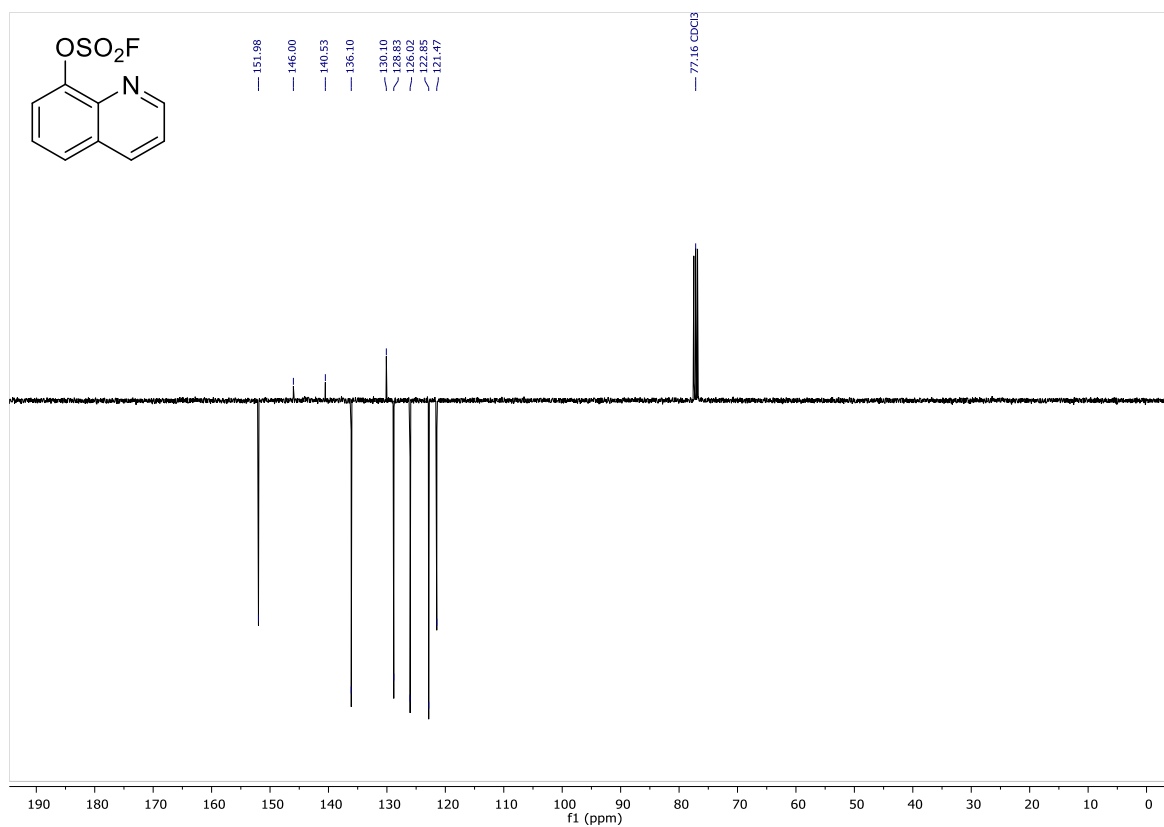
^{19}F NMR (376 MHz, CDCl_3)



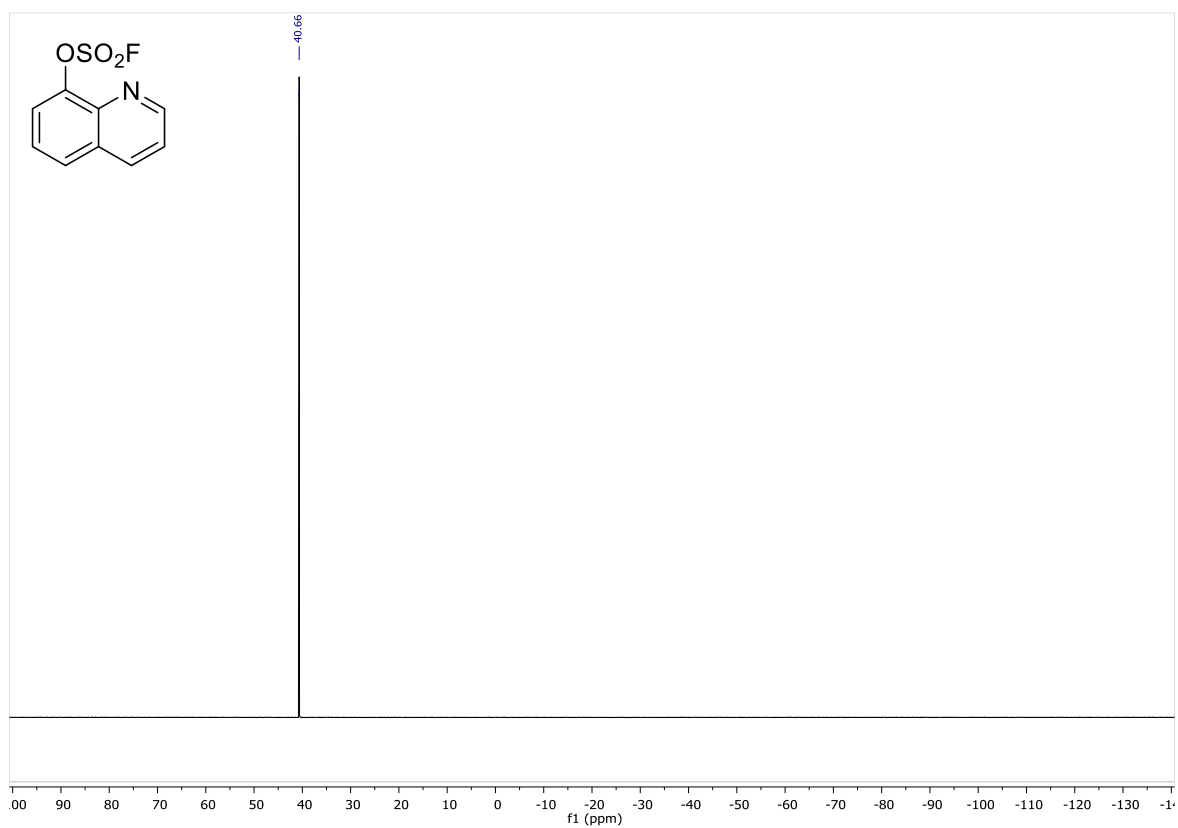
4-Formylphenyl sulfurofluoridate (12c) ^1H NMR (400 MHz, CDCl_3) $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3)

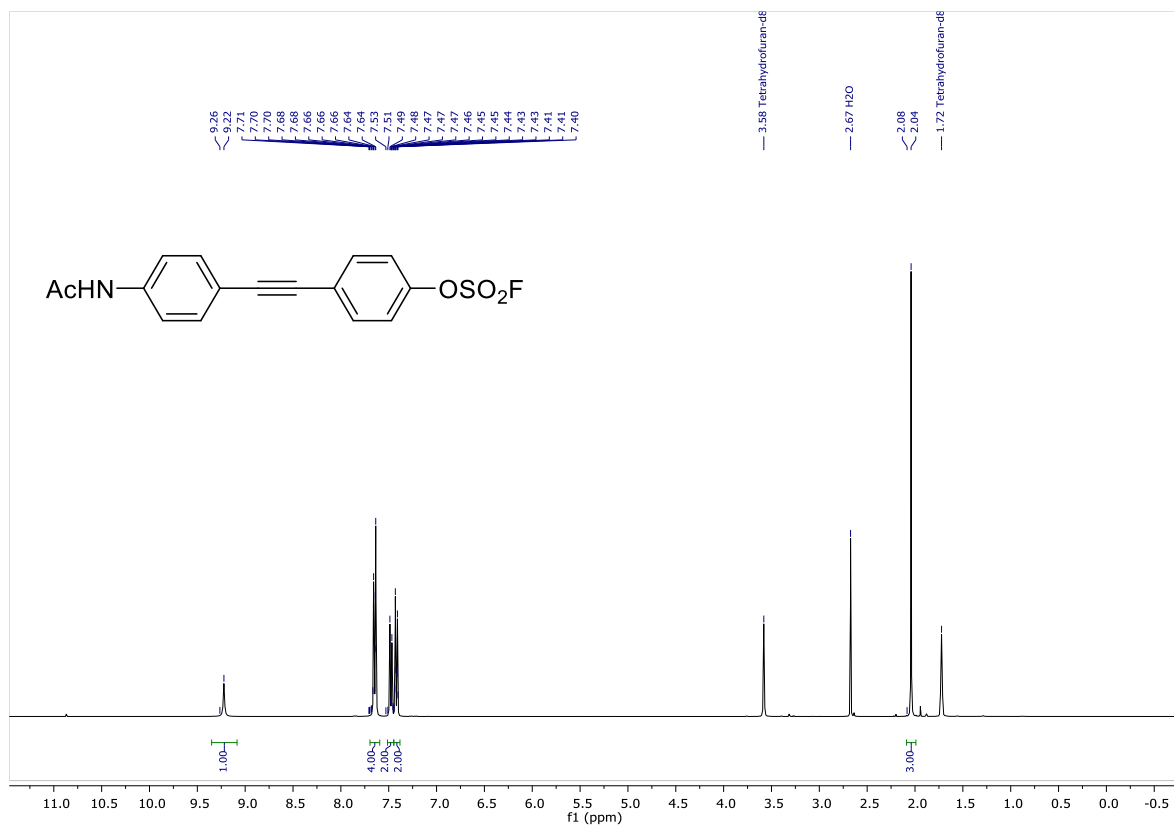
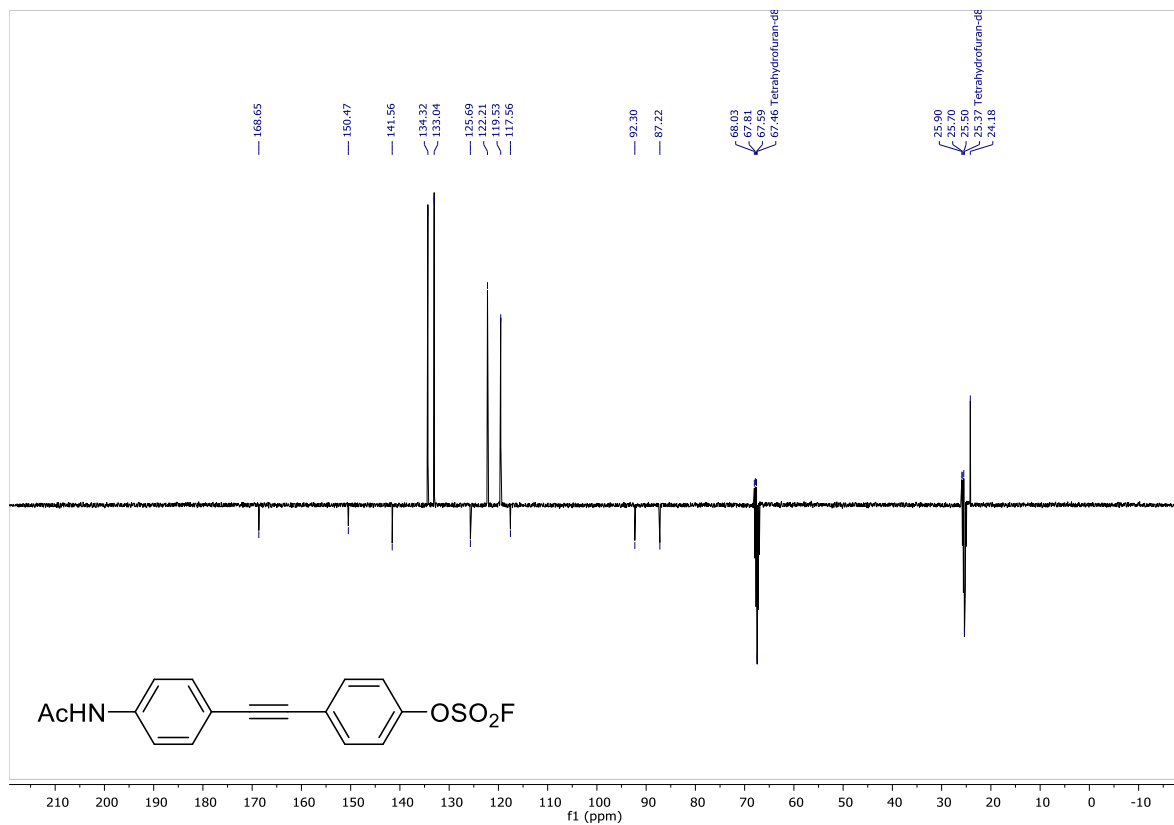
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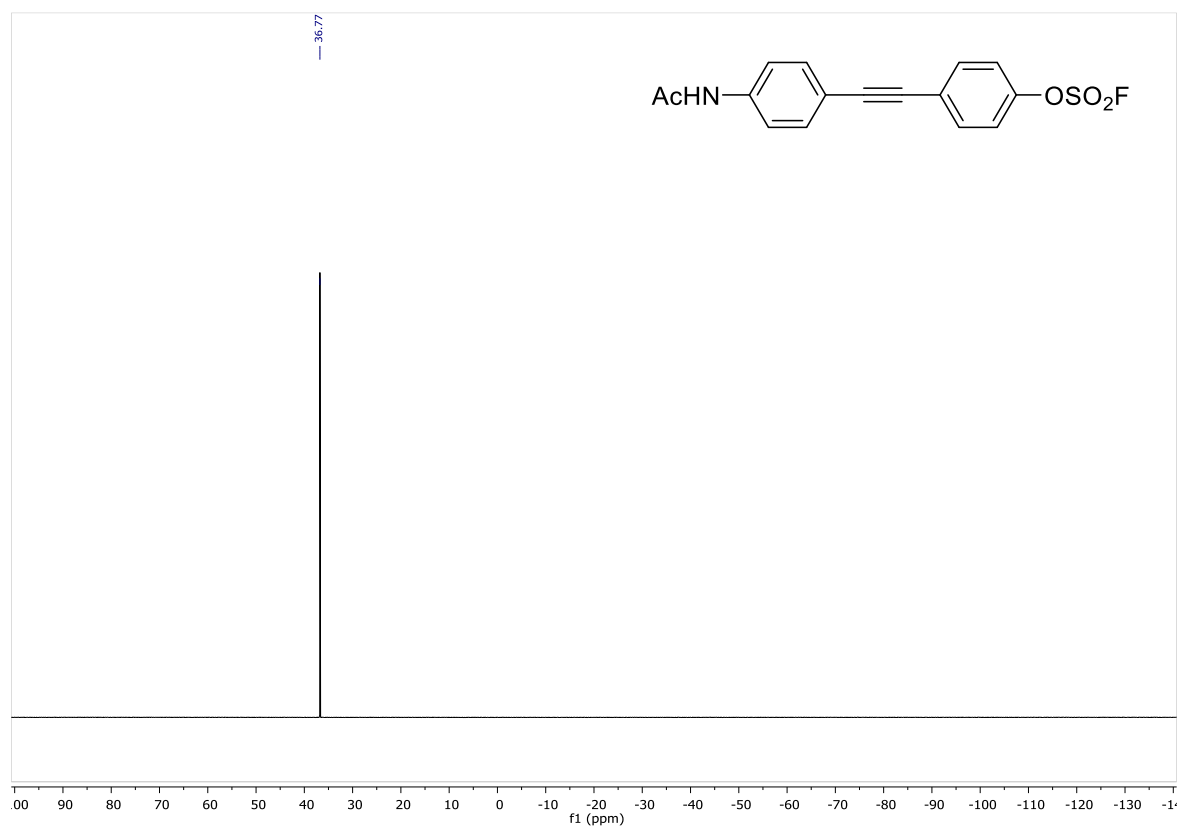
Quinolin-8-yl sulfurofluoridate (12d)¹H NMR (400 MHz, CDCl₃)¹³C{¹H} NMR (101 MHz, CDCl₃)

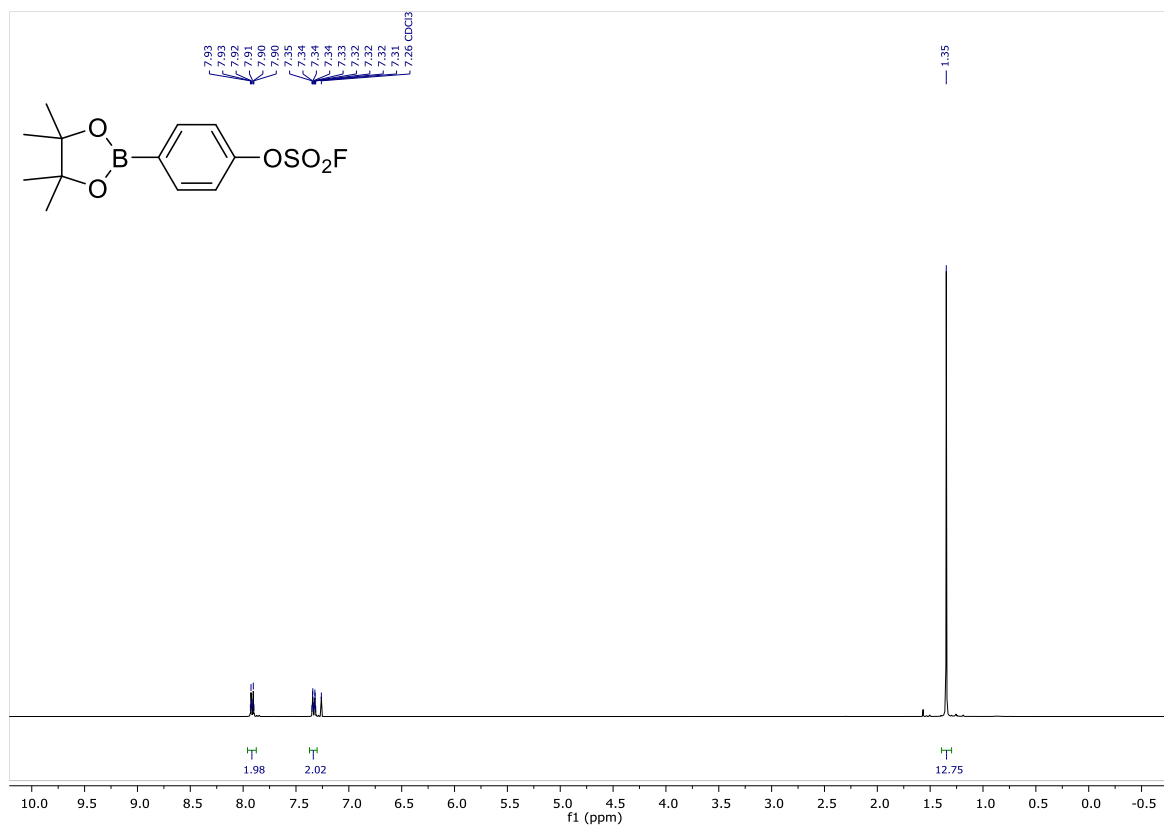
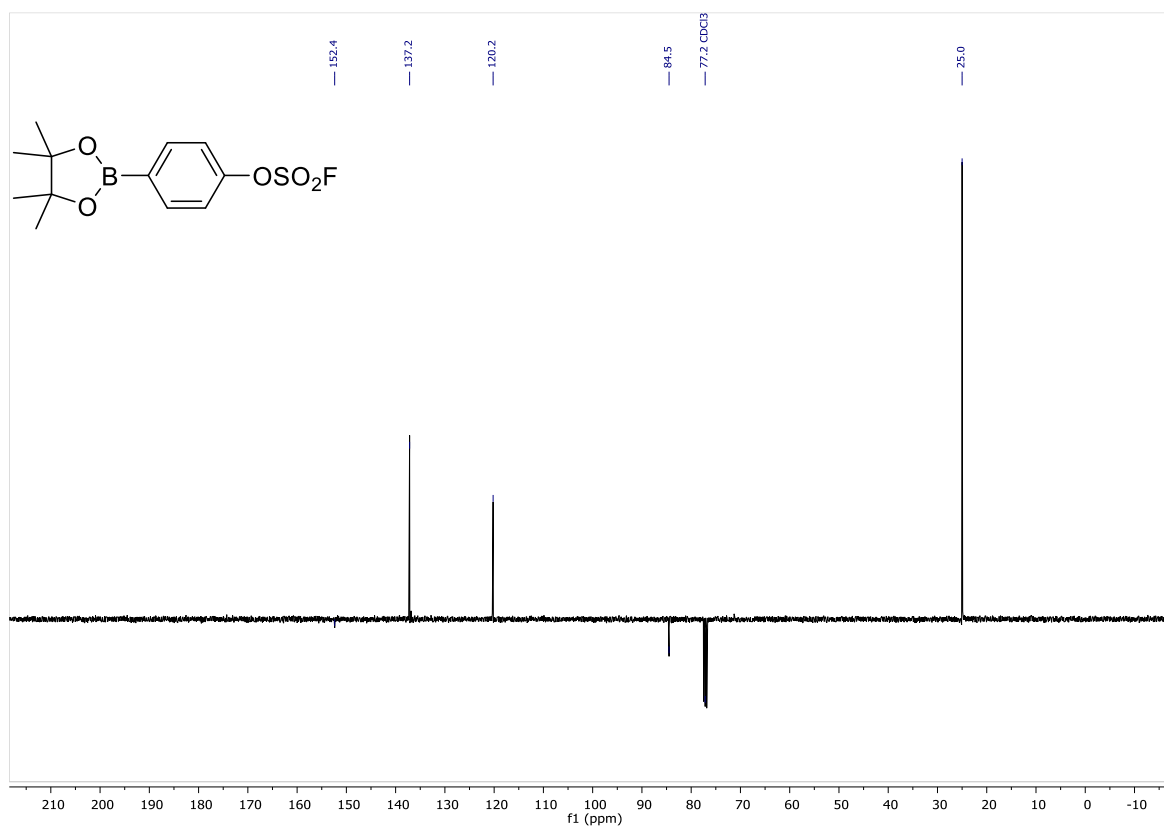
^{19}F NMR (376 MHz, CDCl_3)



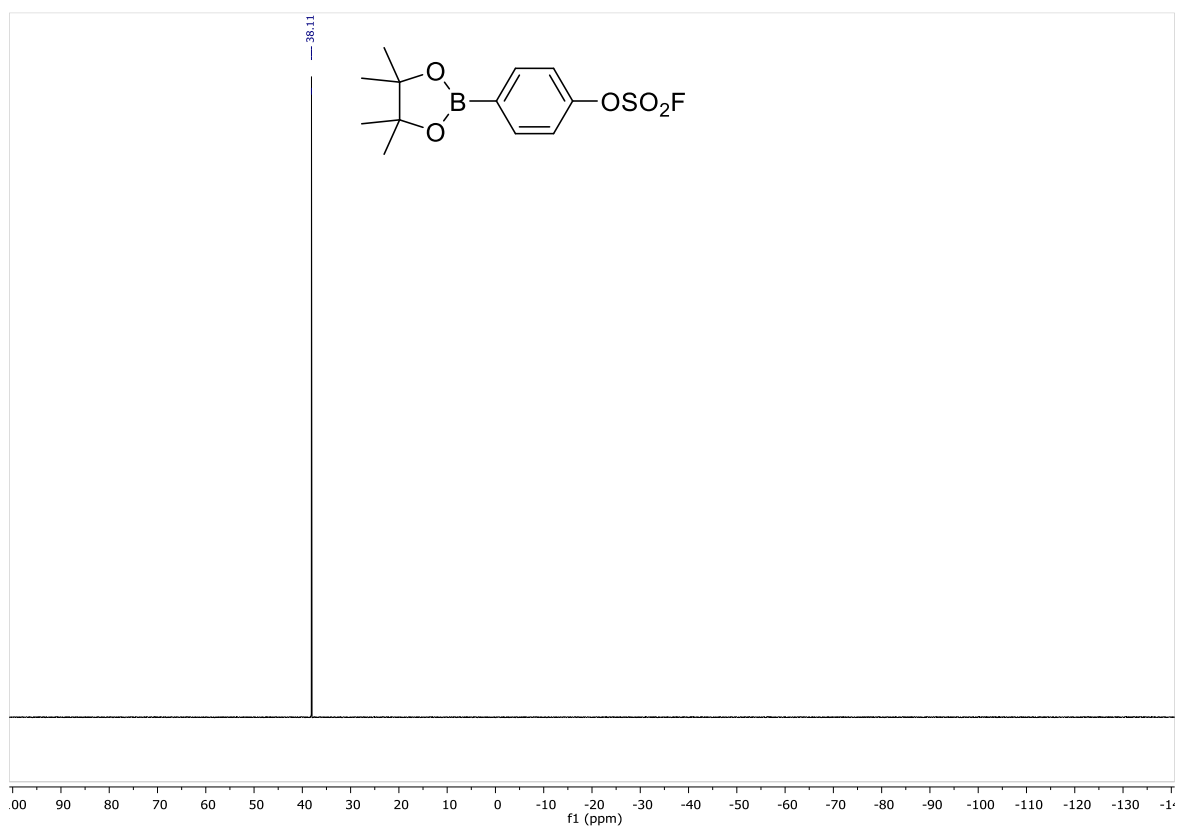
4-[(4-Acetamidophenyl)ethynyl]phenyl sulfurofluoridate (12e)¹H NMR (400 MHz, THF-d₈)¹³C{¹H} NMR (101 MHz, THF-d₈)

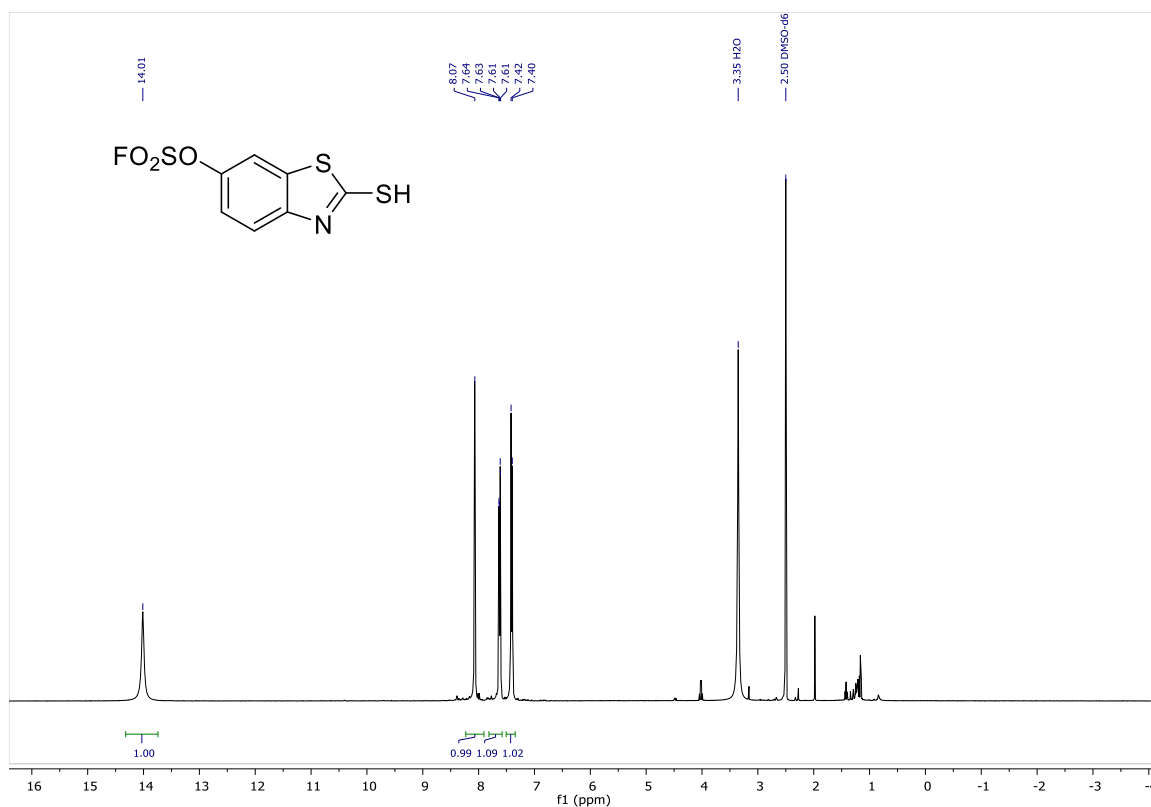
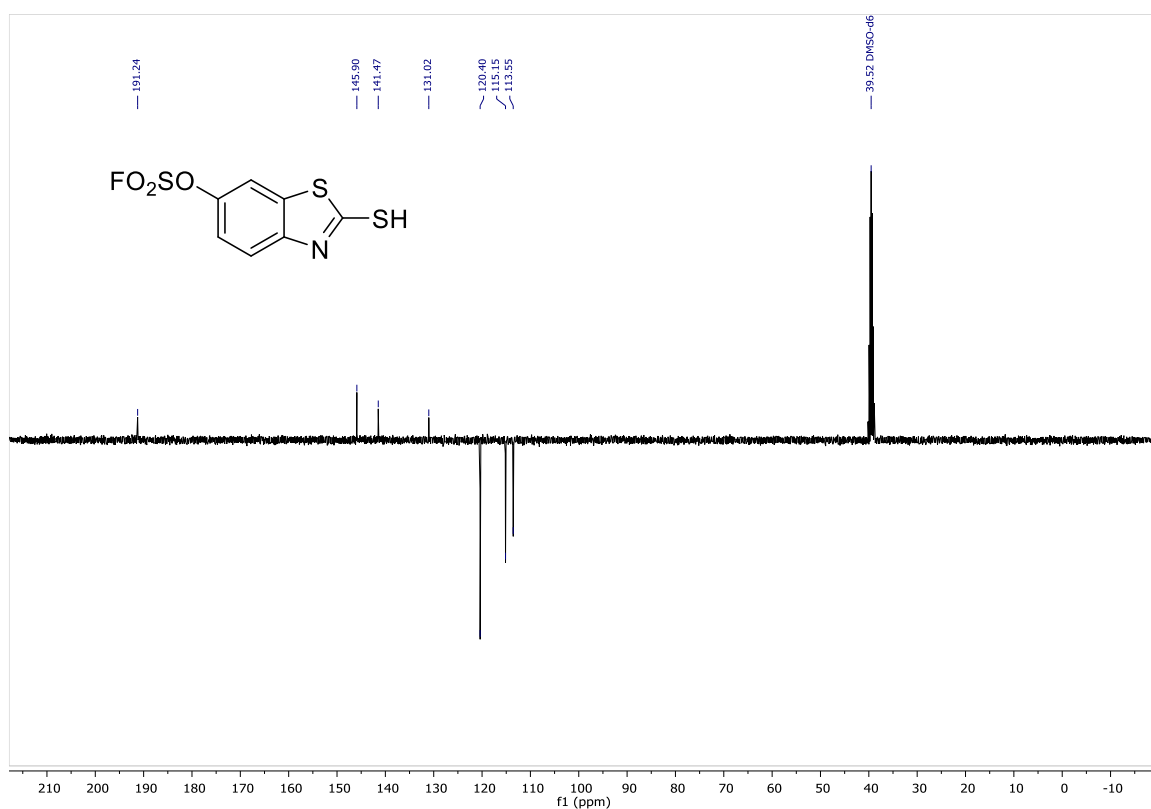
^{19}F NMR (376 MHz, THF-d₈)



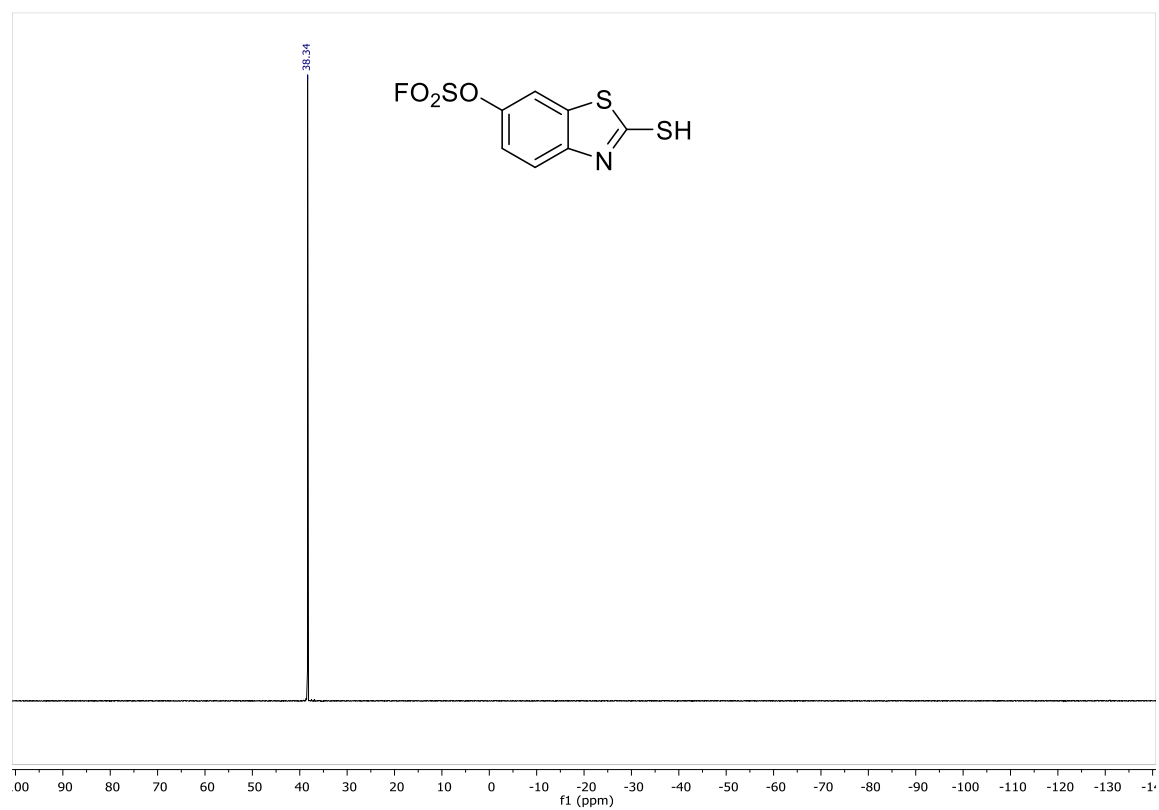
4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl sulfurofluoridate (12f) ^1H NMR (400 MHz, CDCl_3) $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3)

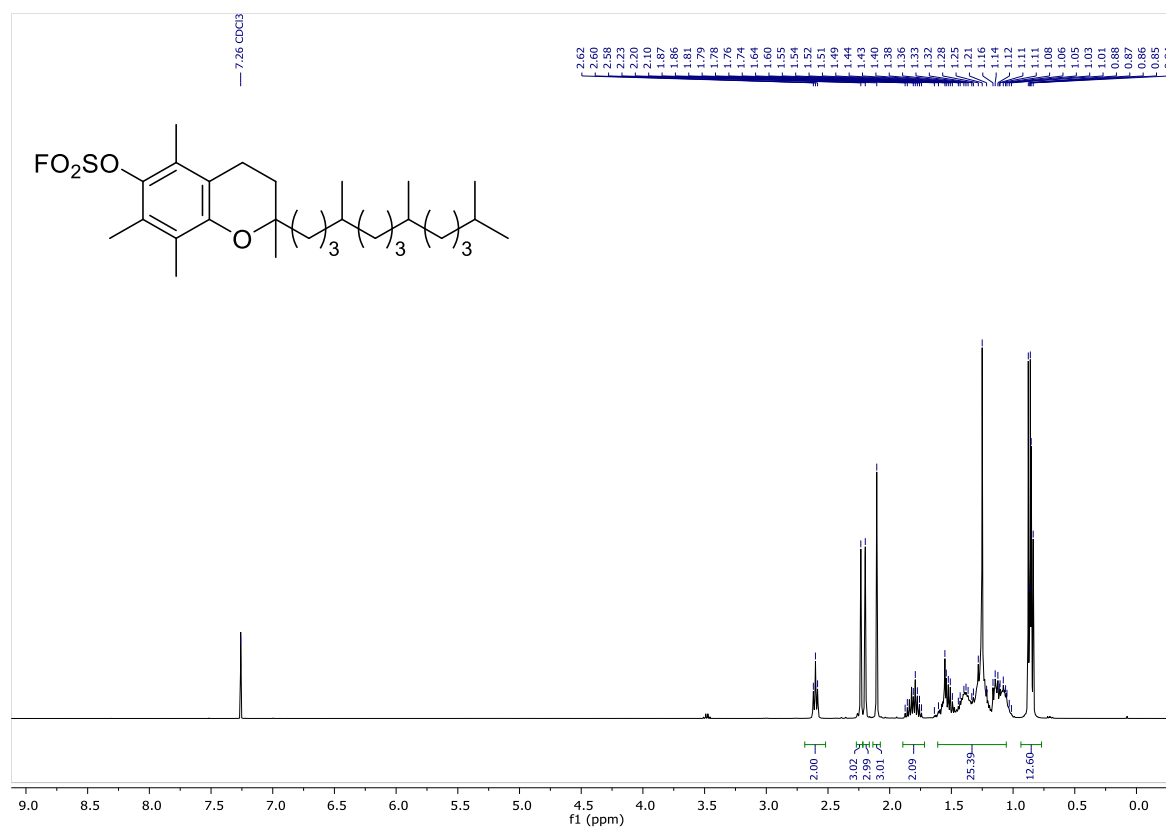
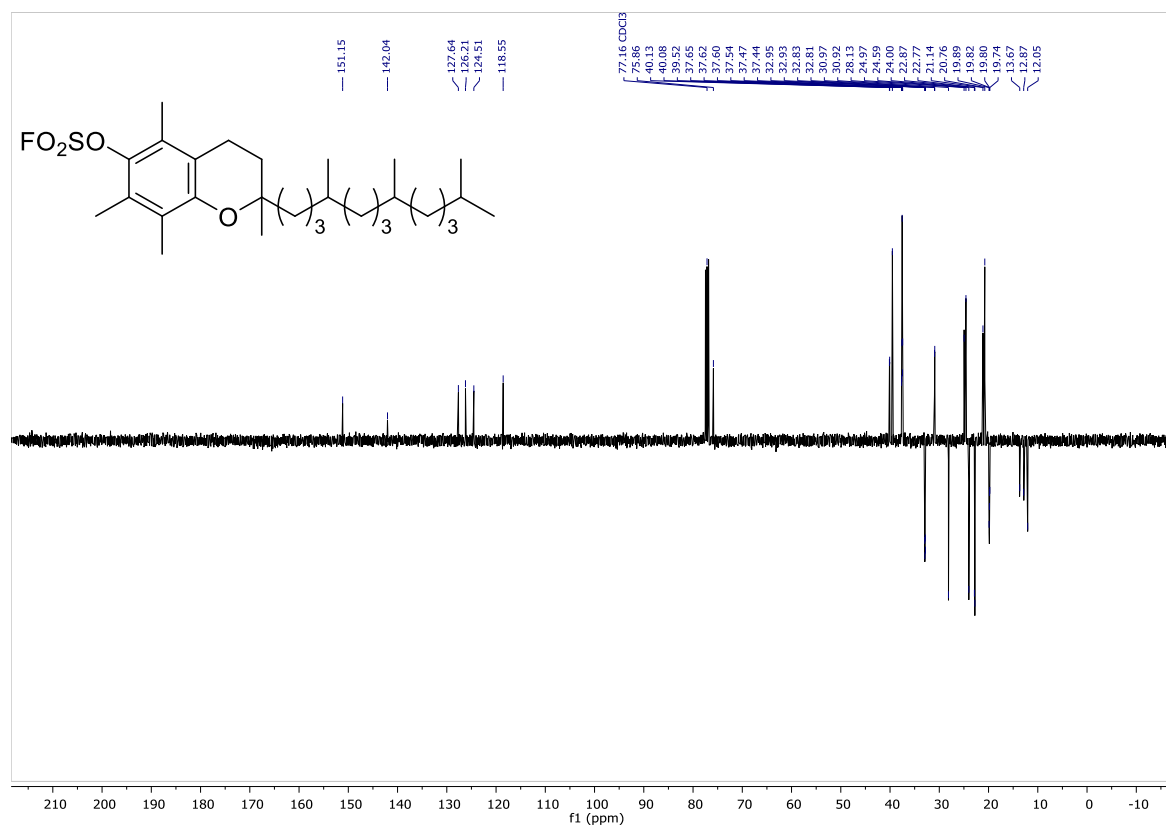
^{19}F NMR (376 MHz, CDCl_3)



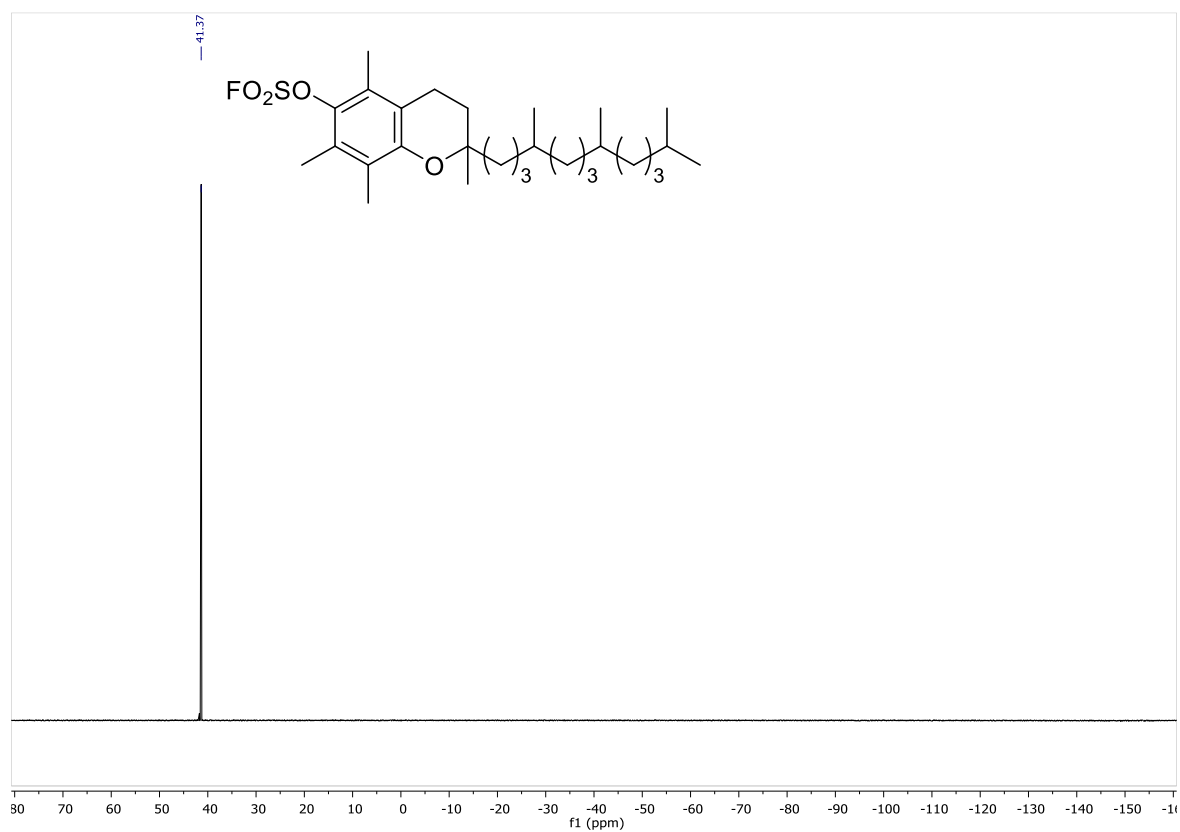
2-Mercaptobenzo[d]thiazol-6-yl sulfurofluoridate (12g) ^1H NMR [400 MHz, $(\text{CD}_3)_2\text{SO}$] $^{13}\text{C}\{^1\text{H}\}$ NMR [101 MHz, $(\text{CD}_3)_2\text{SO}$]

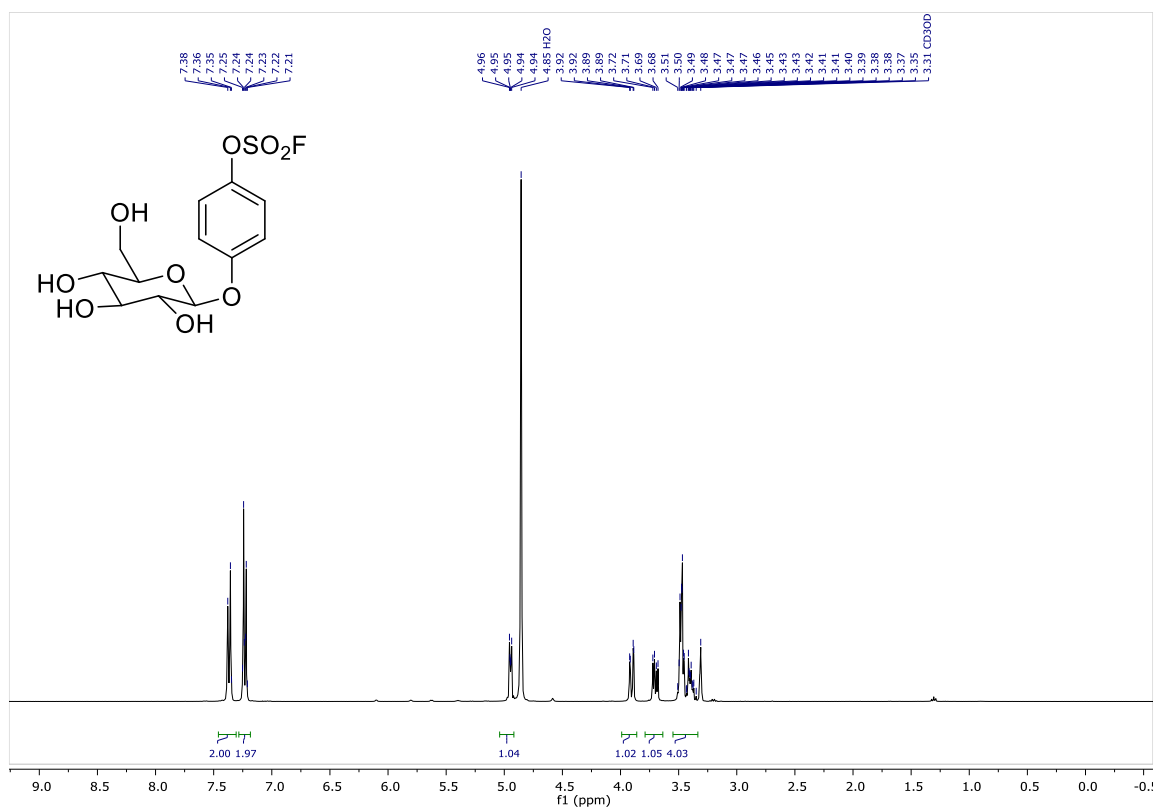
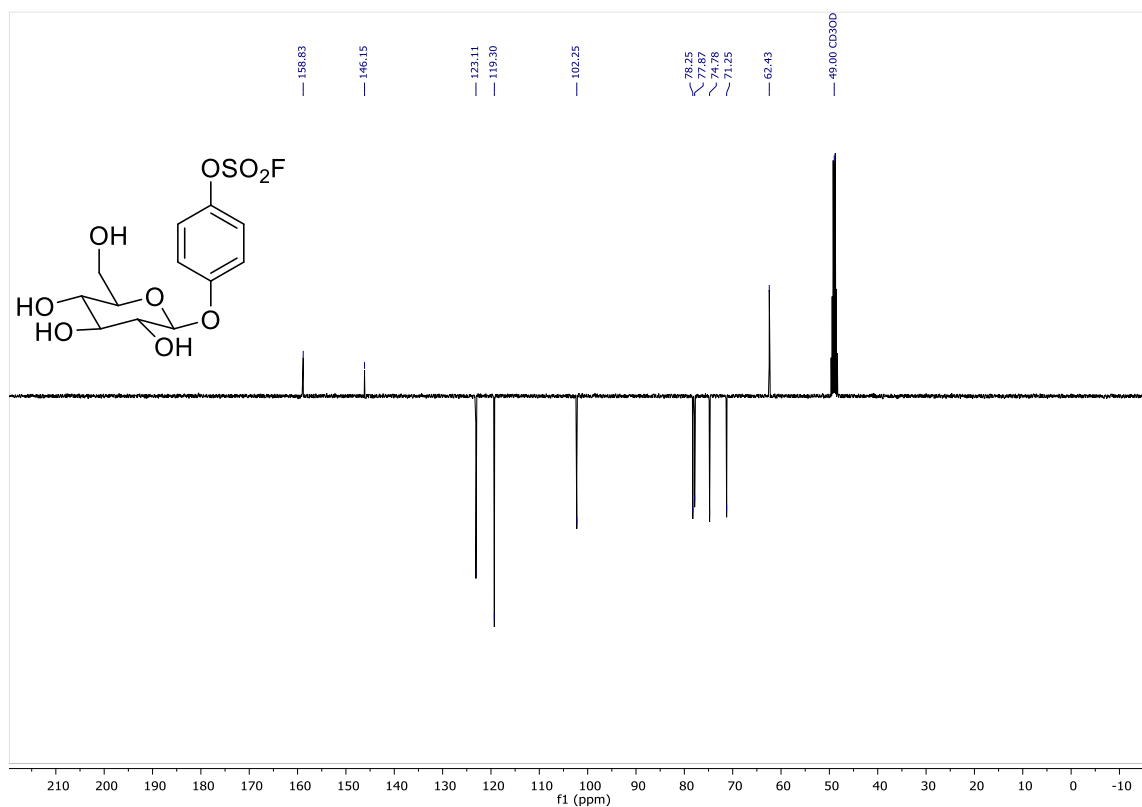
^{19}F NMR [376 MHz, $(\text{CD}_3)_2\text{SO}$]



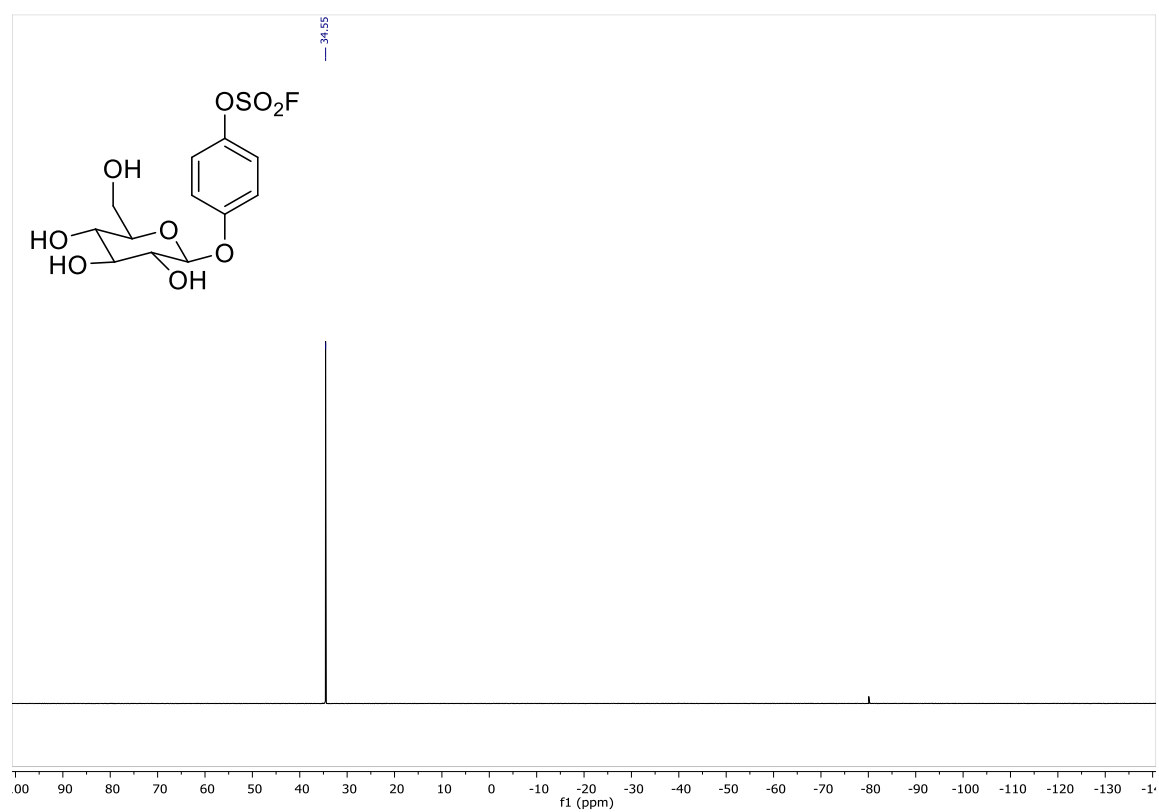
$\pm$ - α -Tocopherol-derived sulfurofluoridate (12h) ^1H NMR (400 MHz, CDCl_3) $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3)

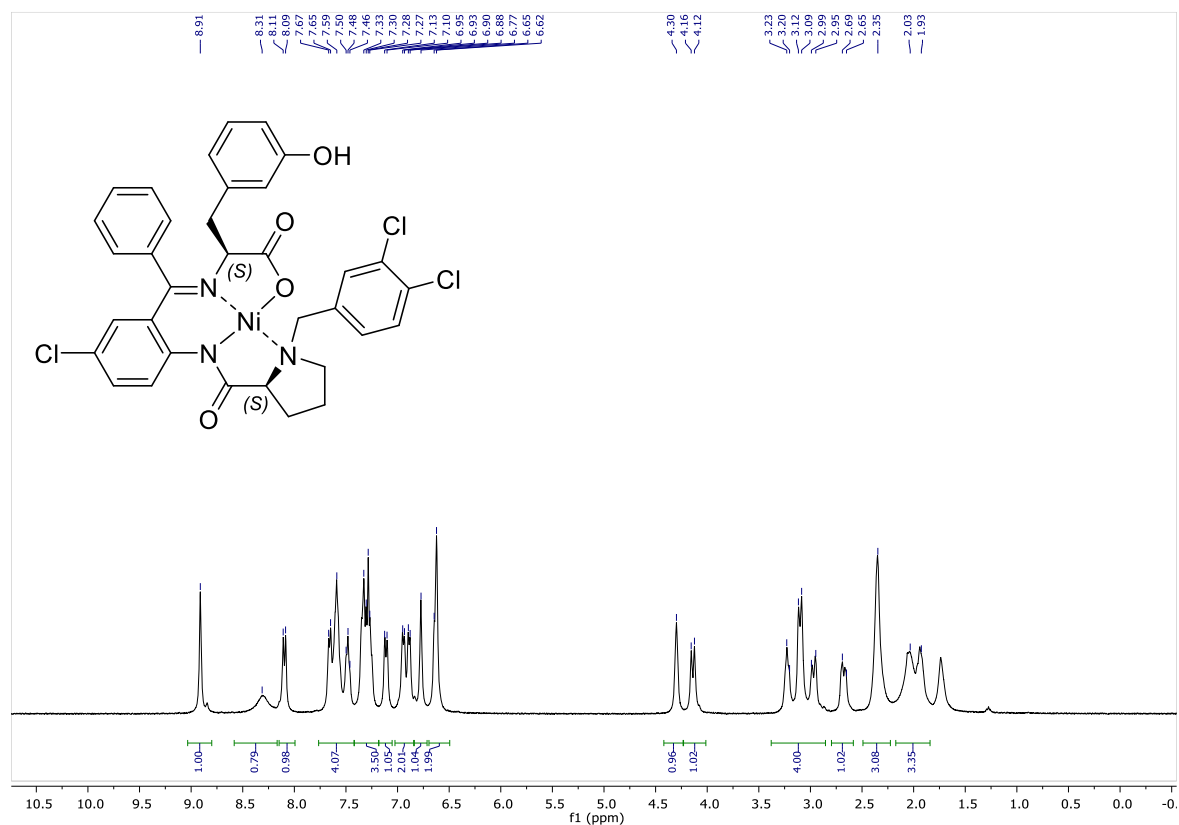
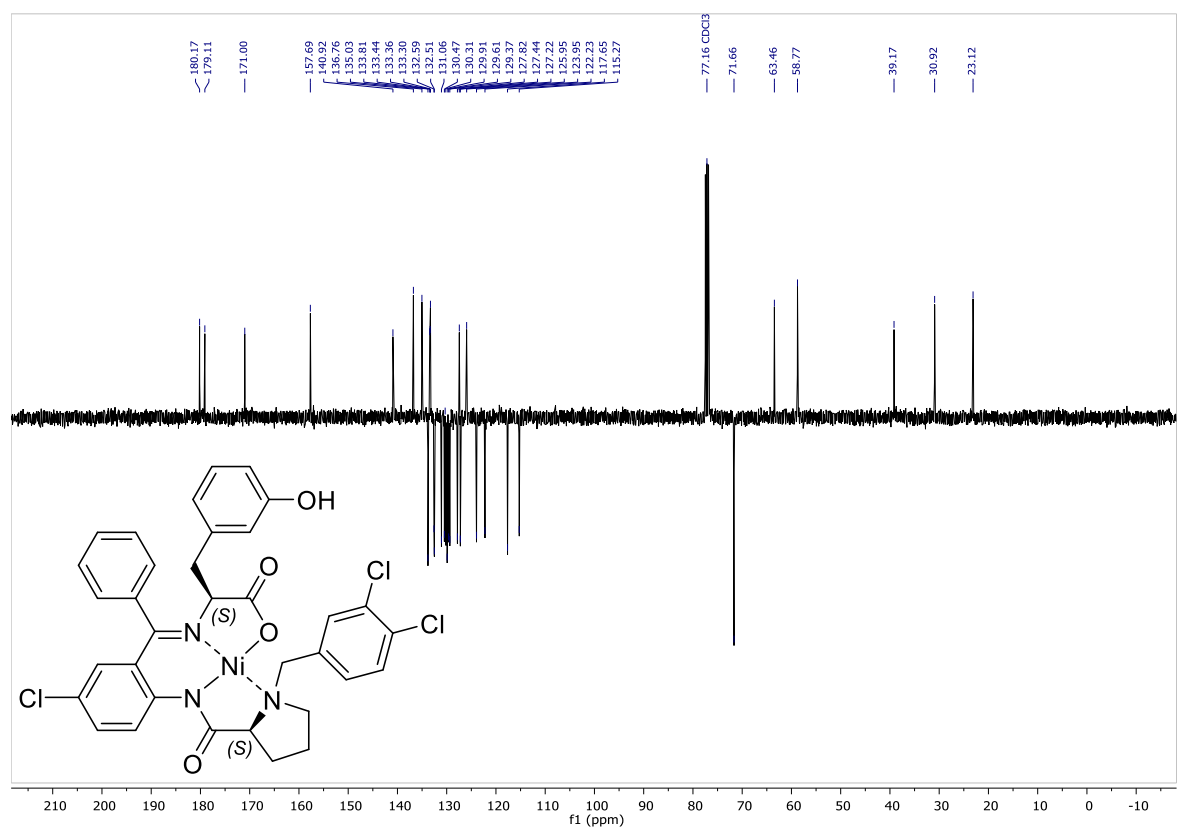
^{19}F NMR (376 MHz, CDCl_3)

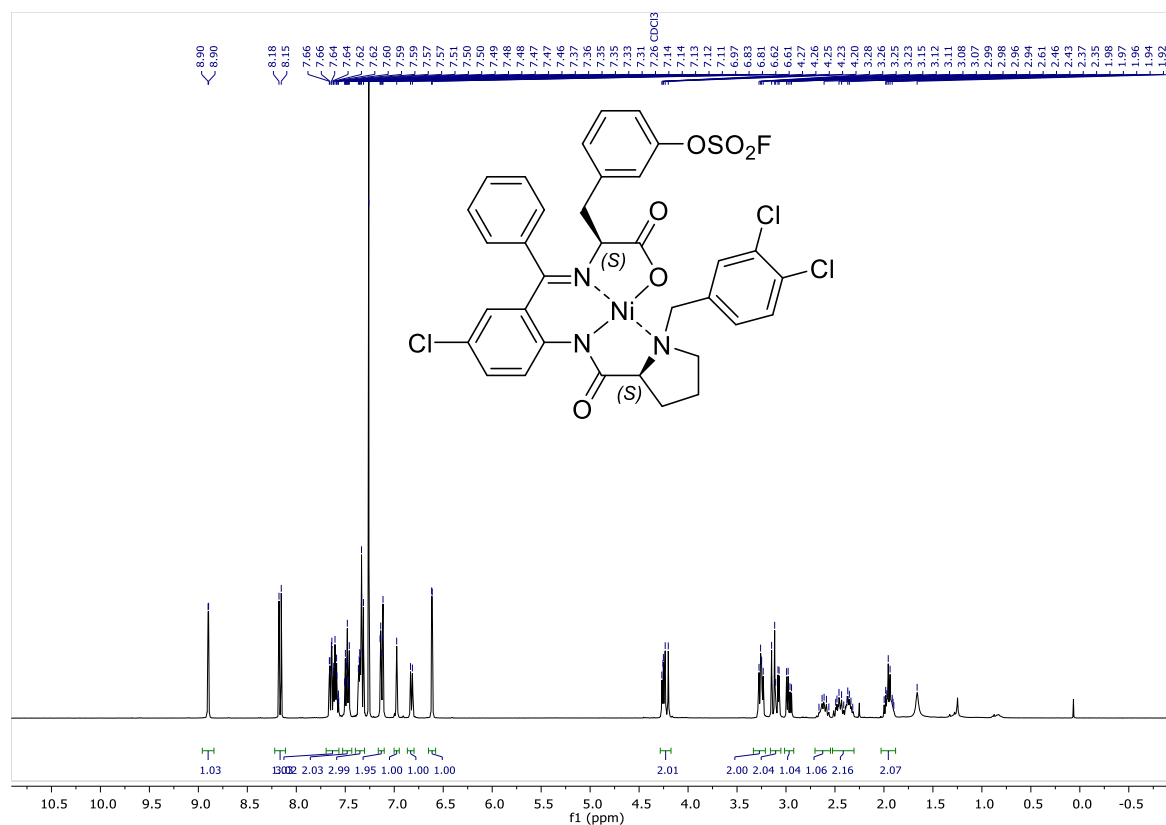
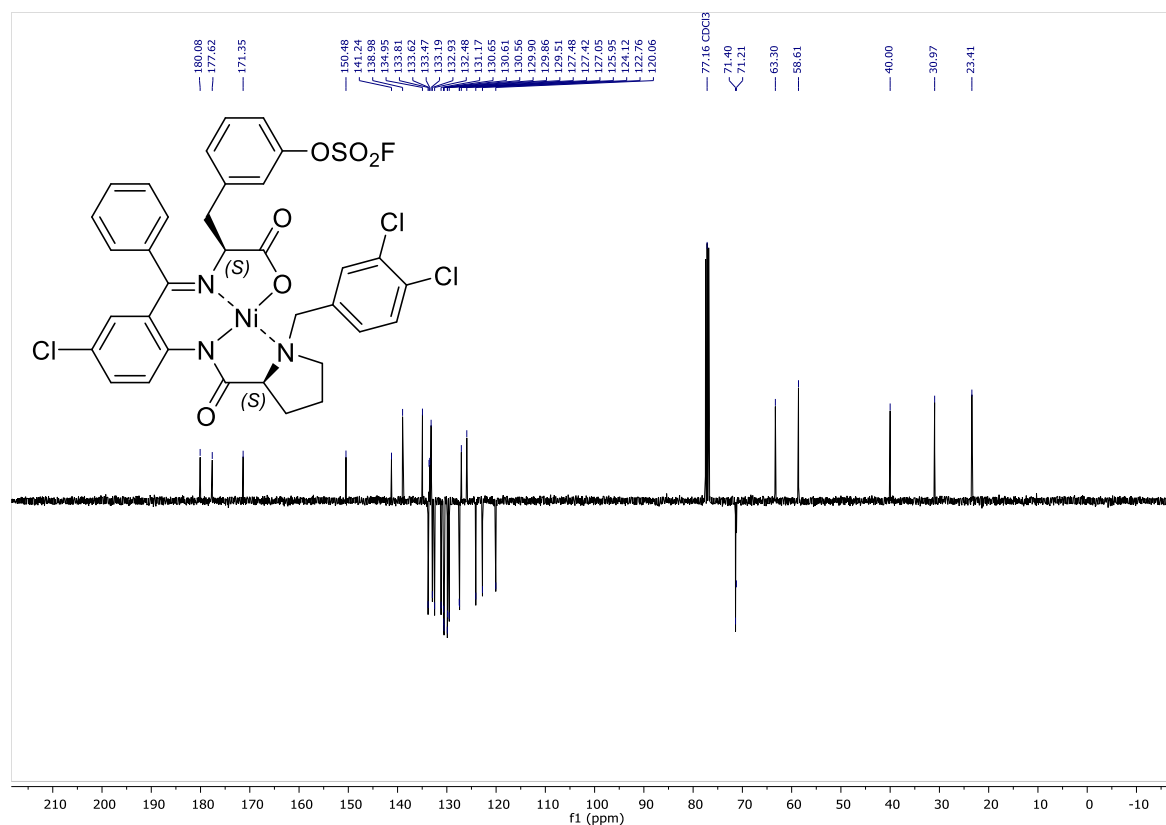


4-[[*(2S,3R,4S,5S,6R)*-3,4,5-Trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl]oxy]phenyl sulfurofluoridate (12i)¹H NMR (400 MHz, CD₃OD)¹³C{¹H} NMR (101 MHz, CD₃OD)

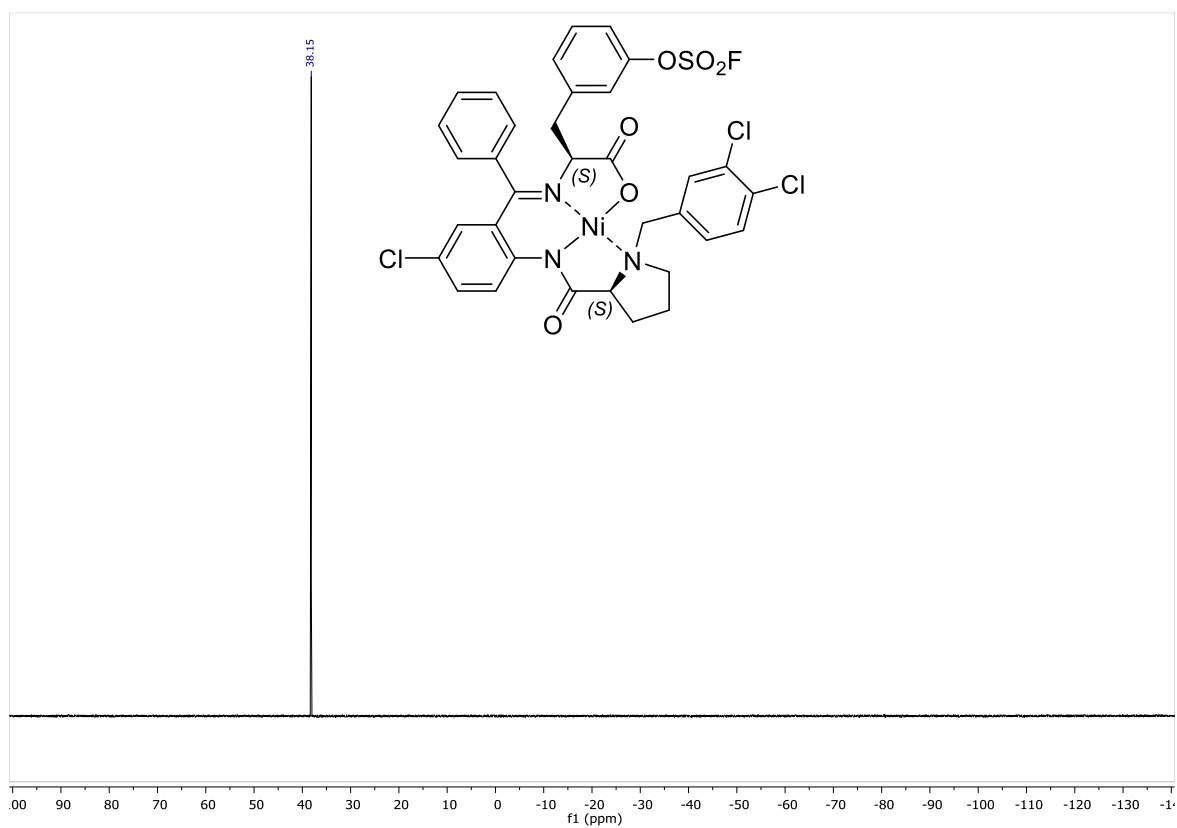
^{19}F NMR (376 MHz, CD_3OD)

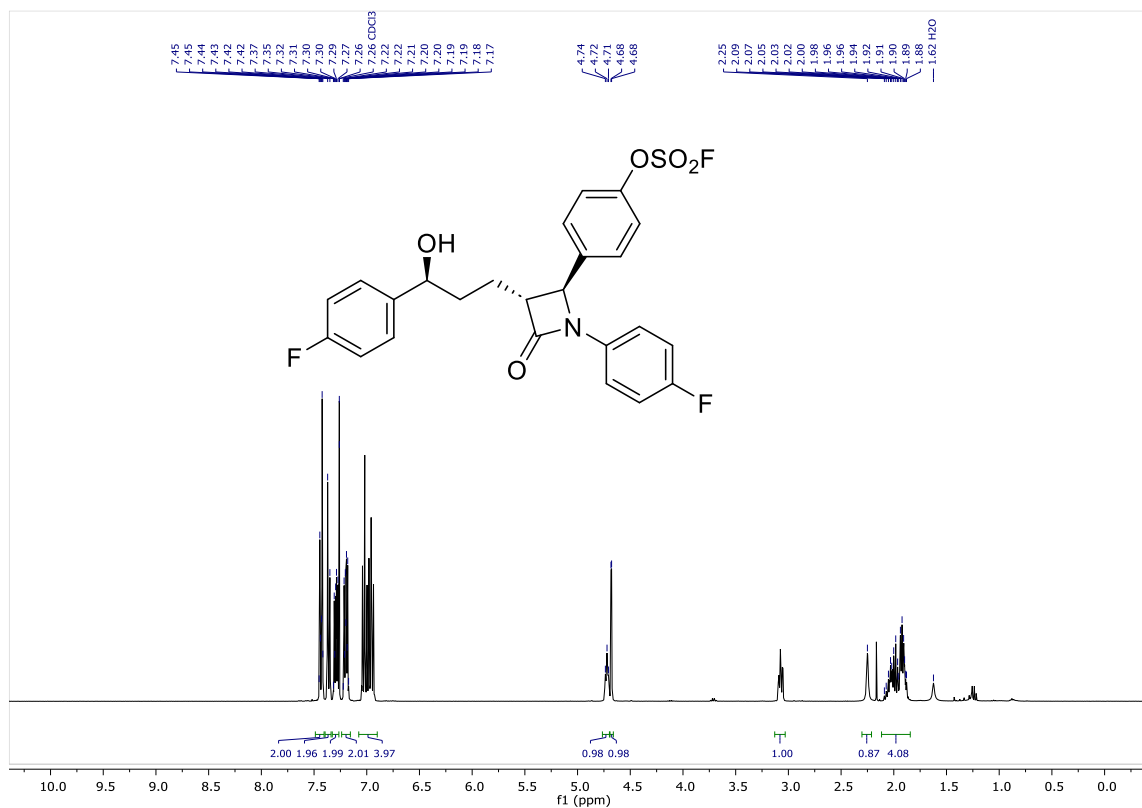
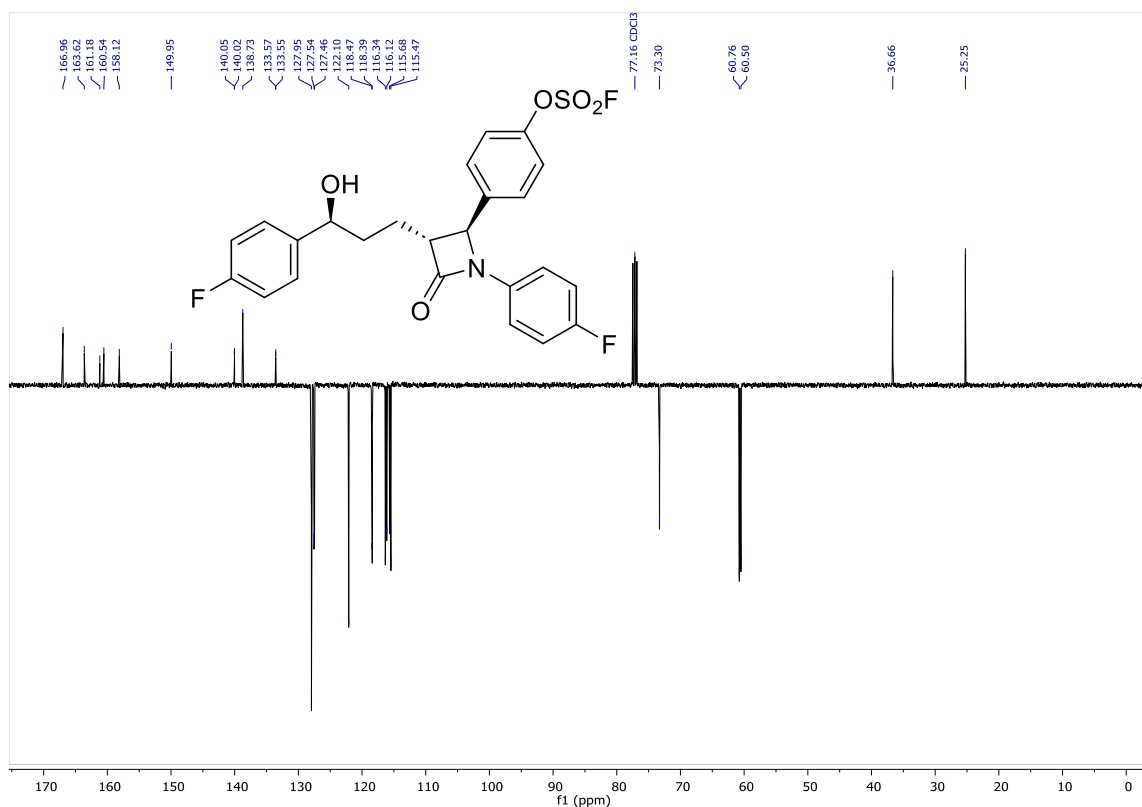


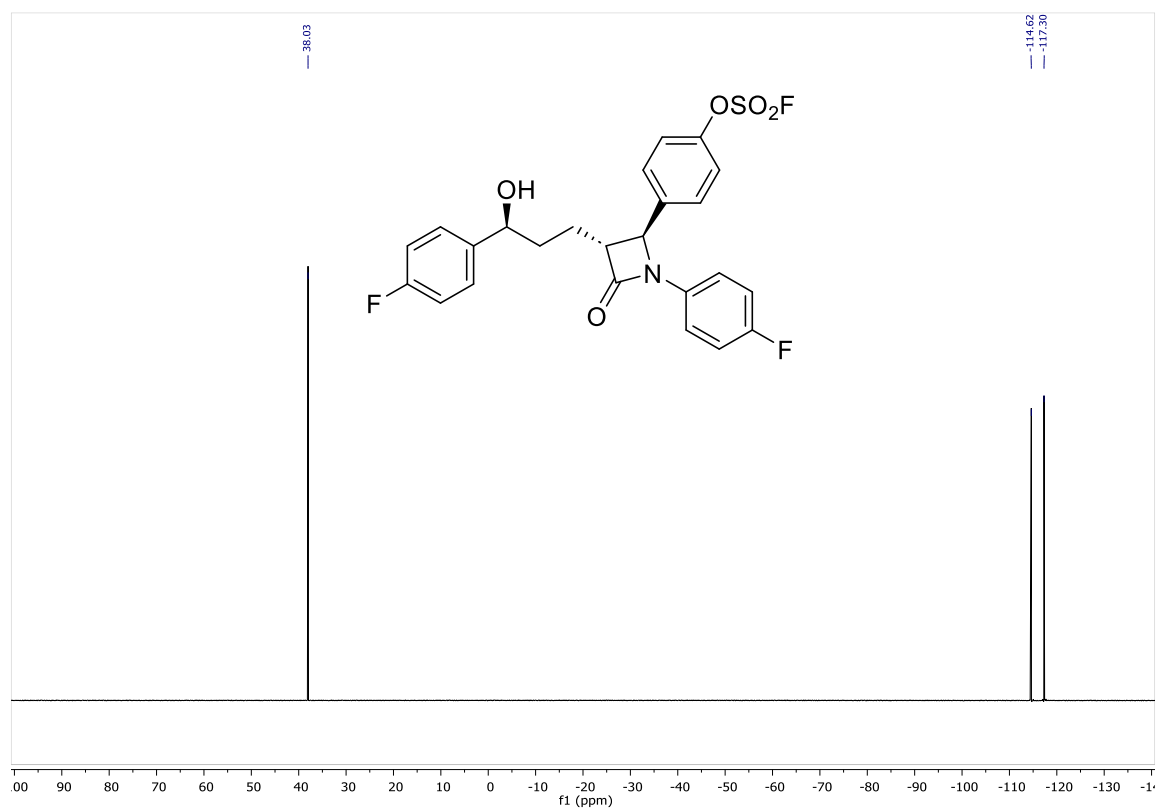
(*S,S*)-Ni-Cl₃BPB-*m*-Tyr¹H NMR (400 MHz, CDCl₃)¹³C{¹H} NMR (101 MHz, CDCl₃)

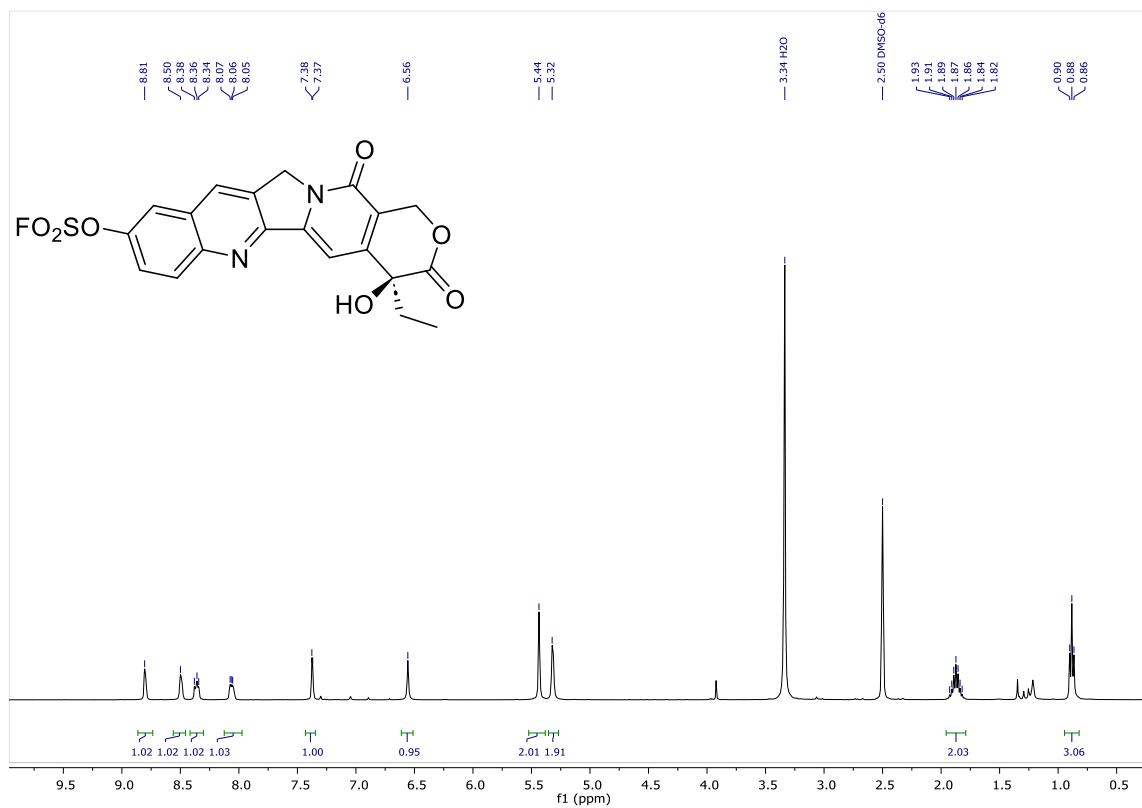
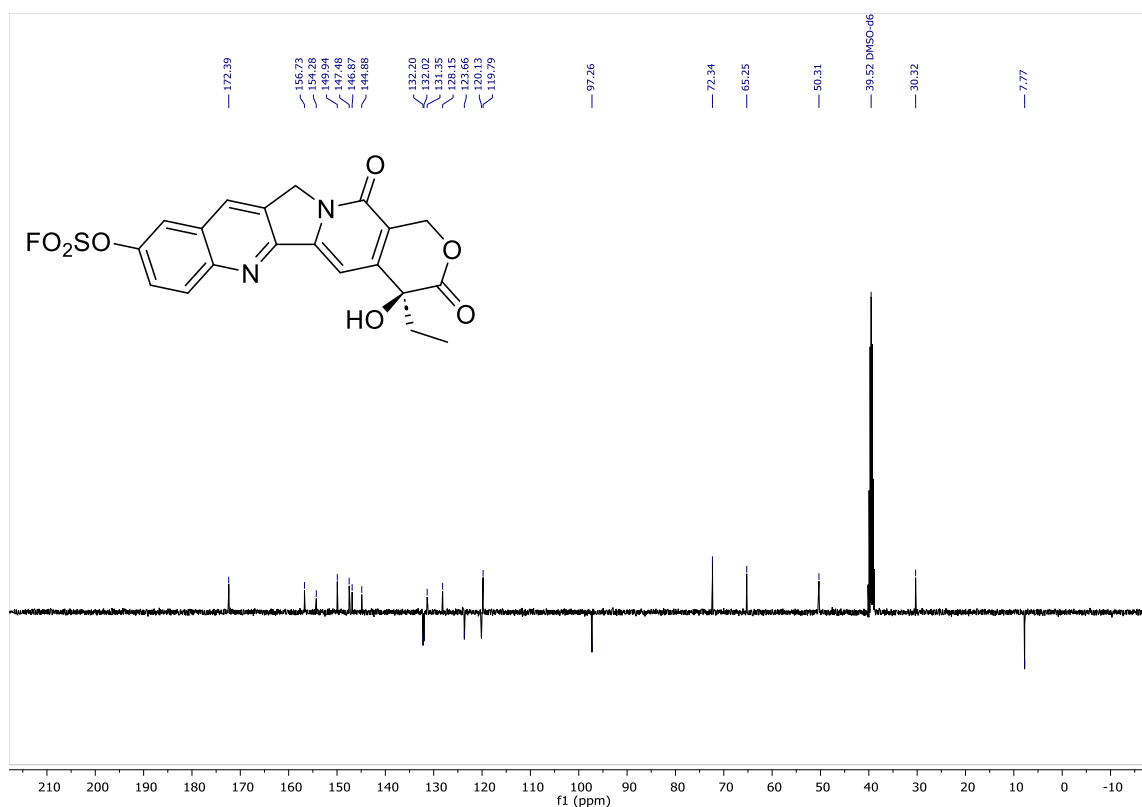
(*S,S*)-Ni-Cl₃BPB-*m*-Tyr sulfurofluoridate (12j)¹H NMR (400 MHz, CDCl₃)¹³C{¹H} NMR (101 MHz, CDCl₃)

^{19}F NMR (376 MHz, CDCl_3)

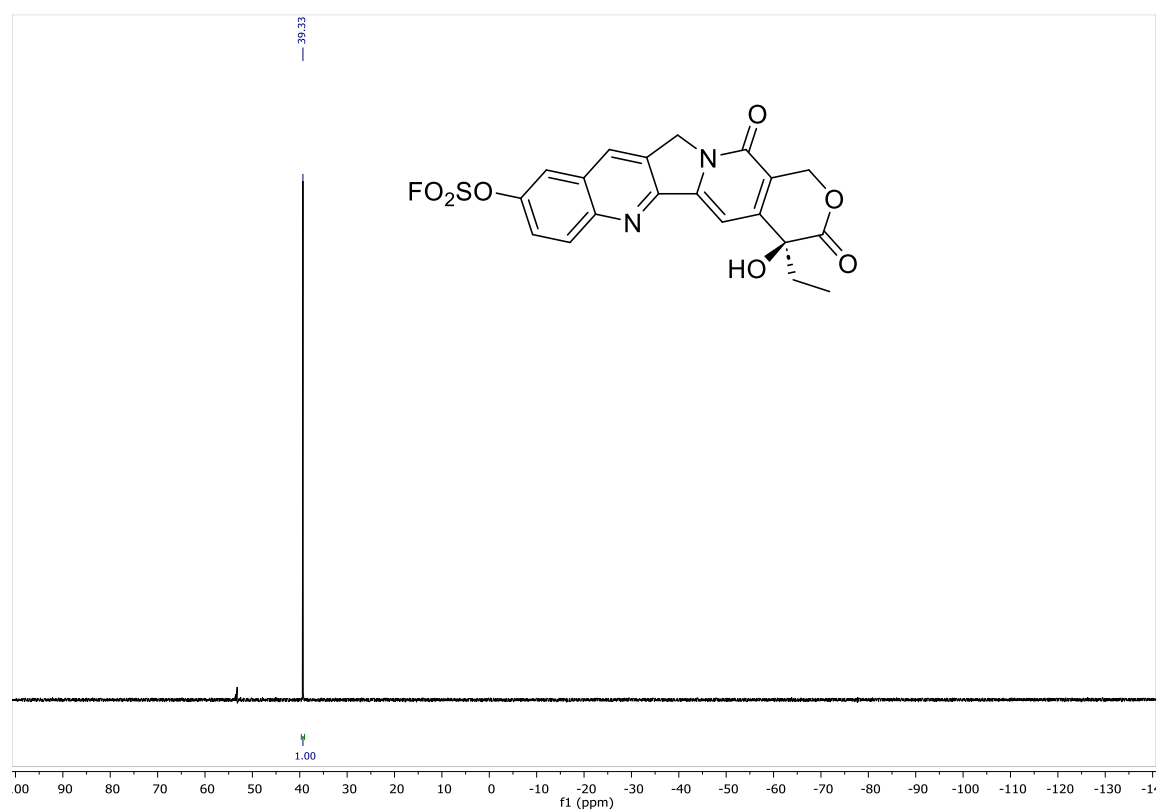


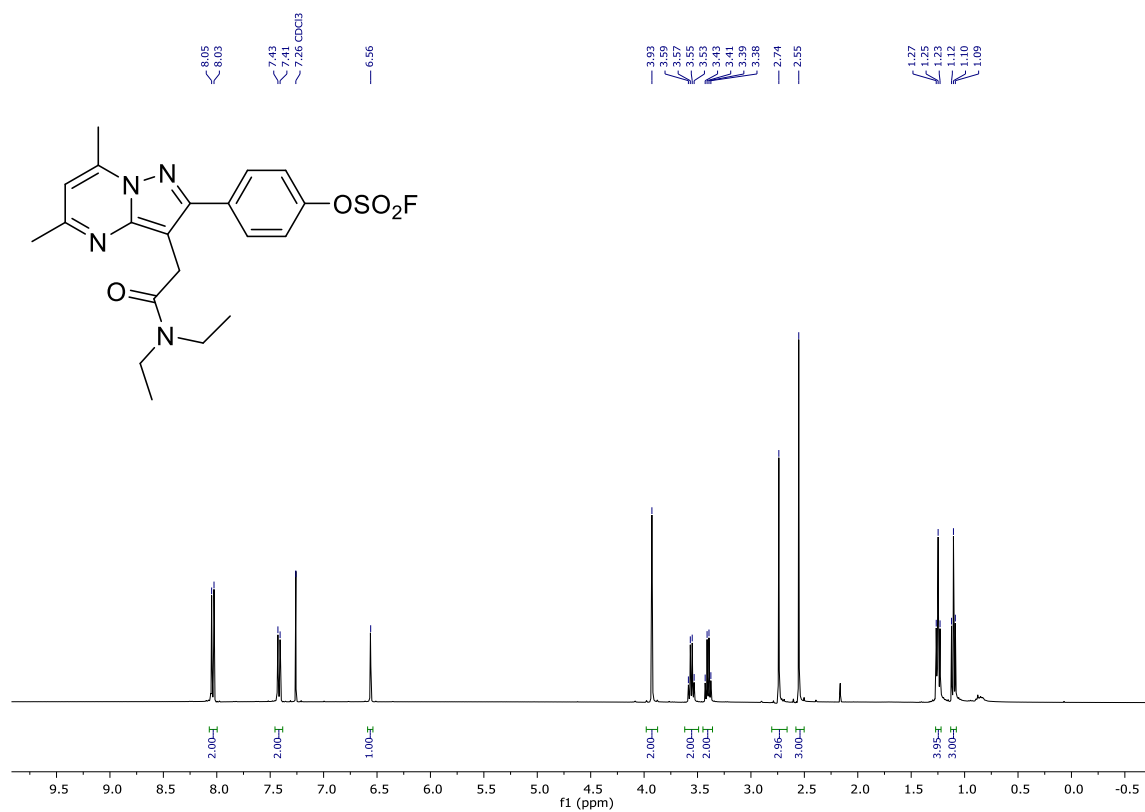
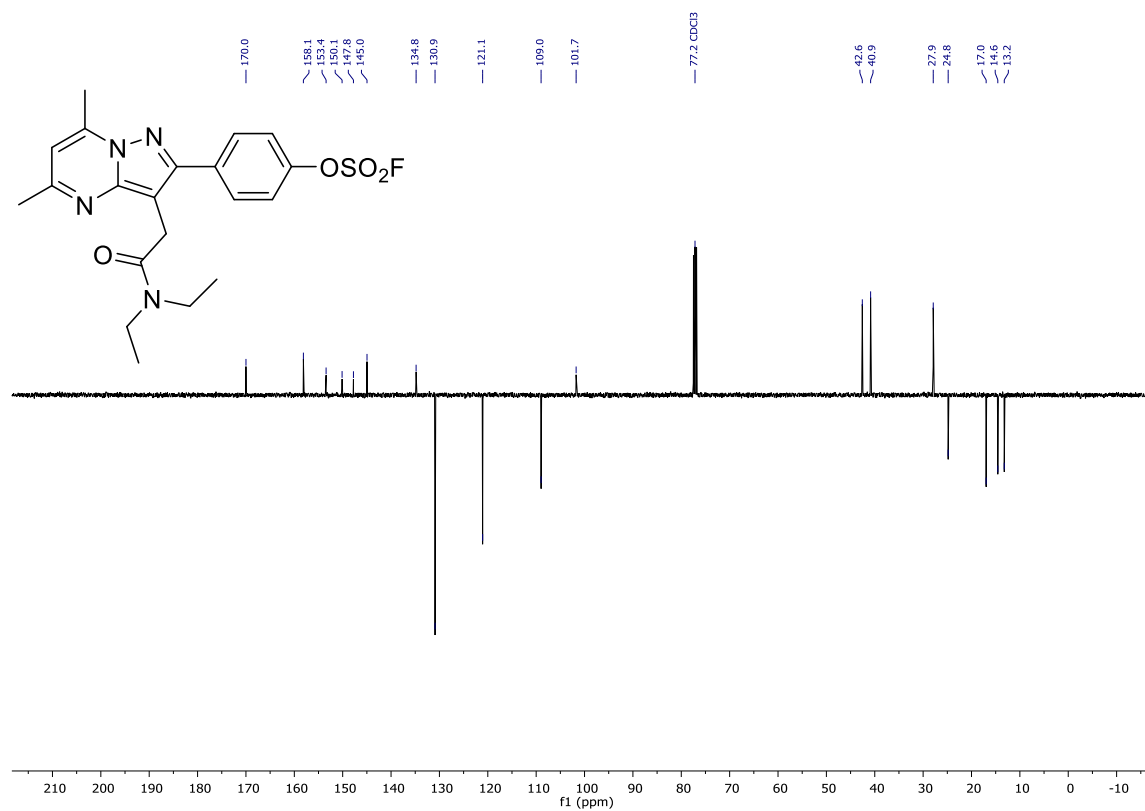
4-{(2*S*,3*R*)-1-(4-Fluorophenyl)-3-[(*S*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxoazetidin-2-yl}phenyl sulfurofluoridate (12k)¹H NMR (400 MHz, CDCl₃)¹³C{¹H} NMR (101 MHz, CDCl₃)

^{19}F NMR (376 MHz, CDCl_3)

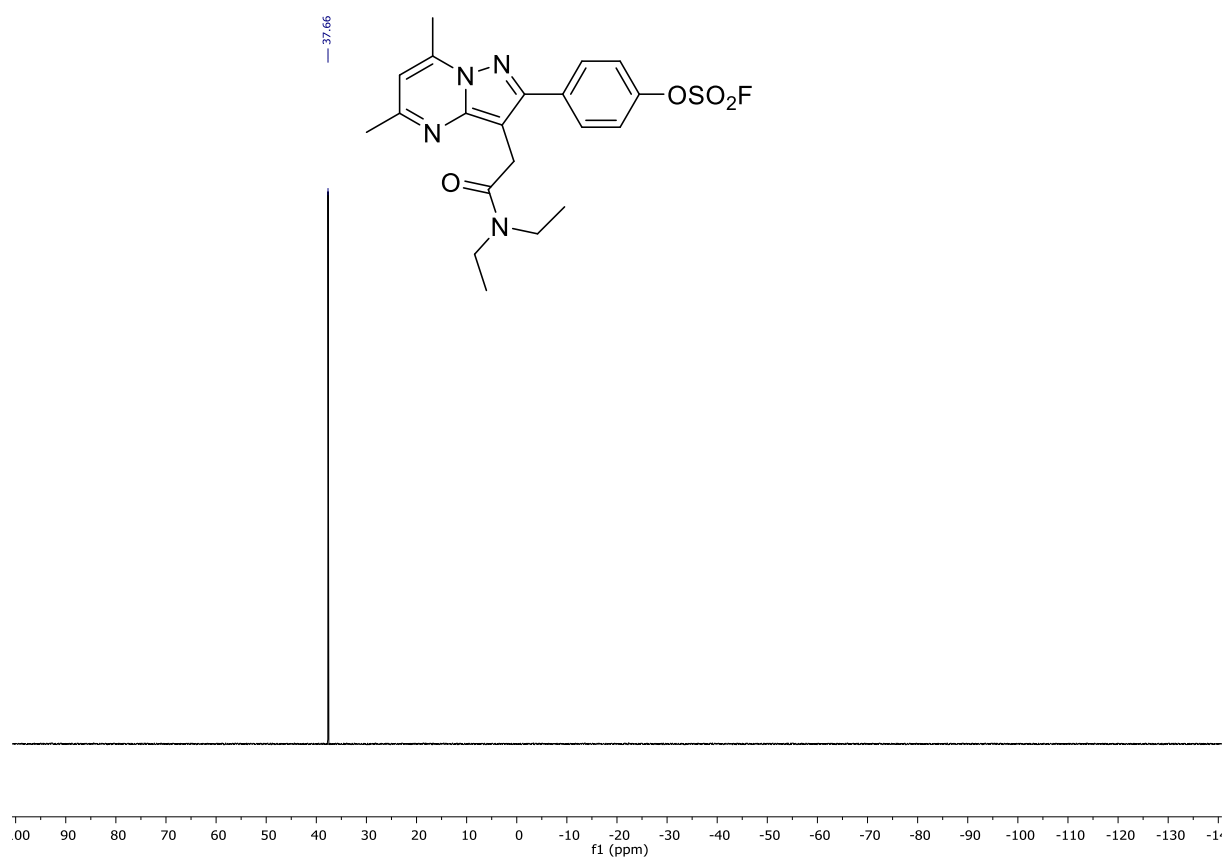
(S)-4-Ethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl sulfurofluoridate (12l)¹H NMR [400 MHz, (CD₃)₂SO]¹³C{¹H} NMR [101 MHz, (CD₃)₂SO]

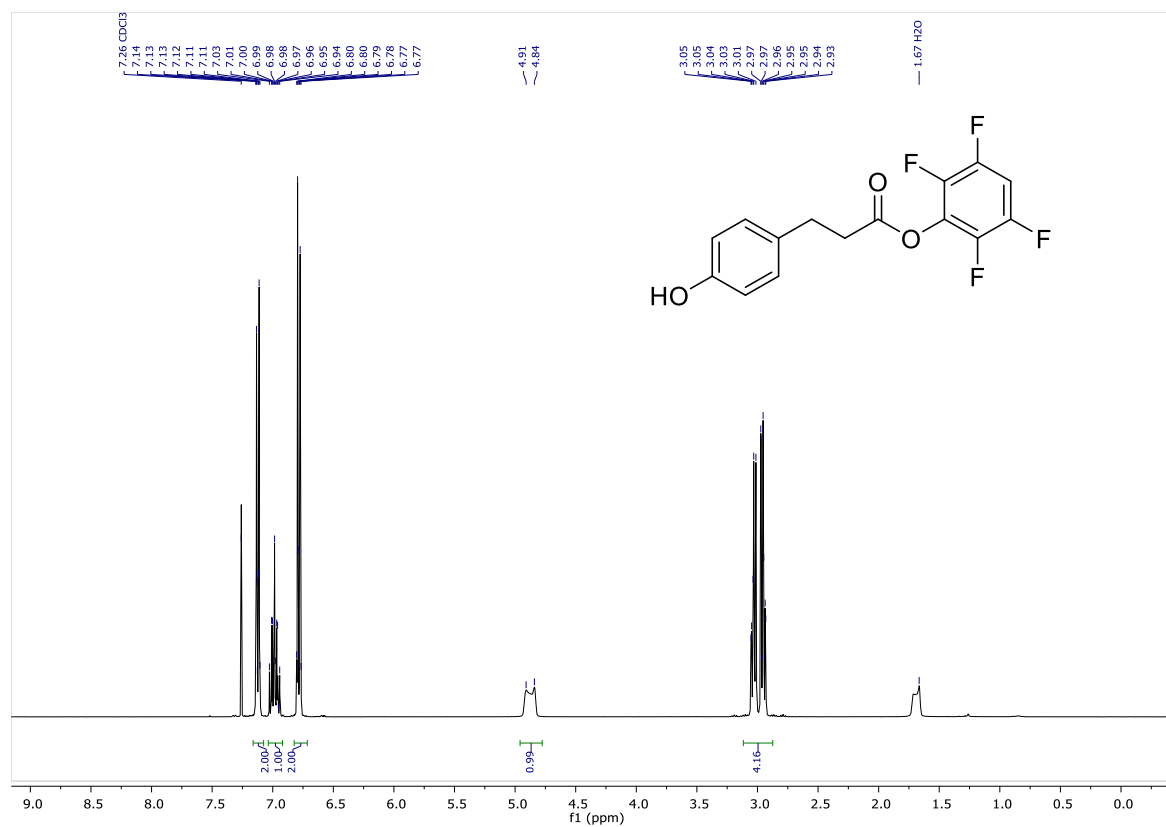
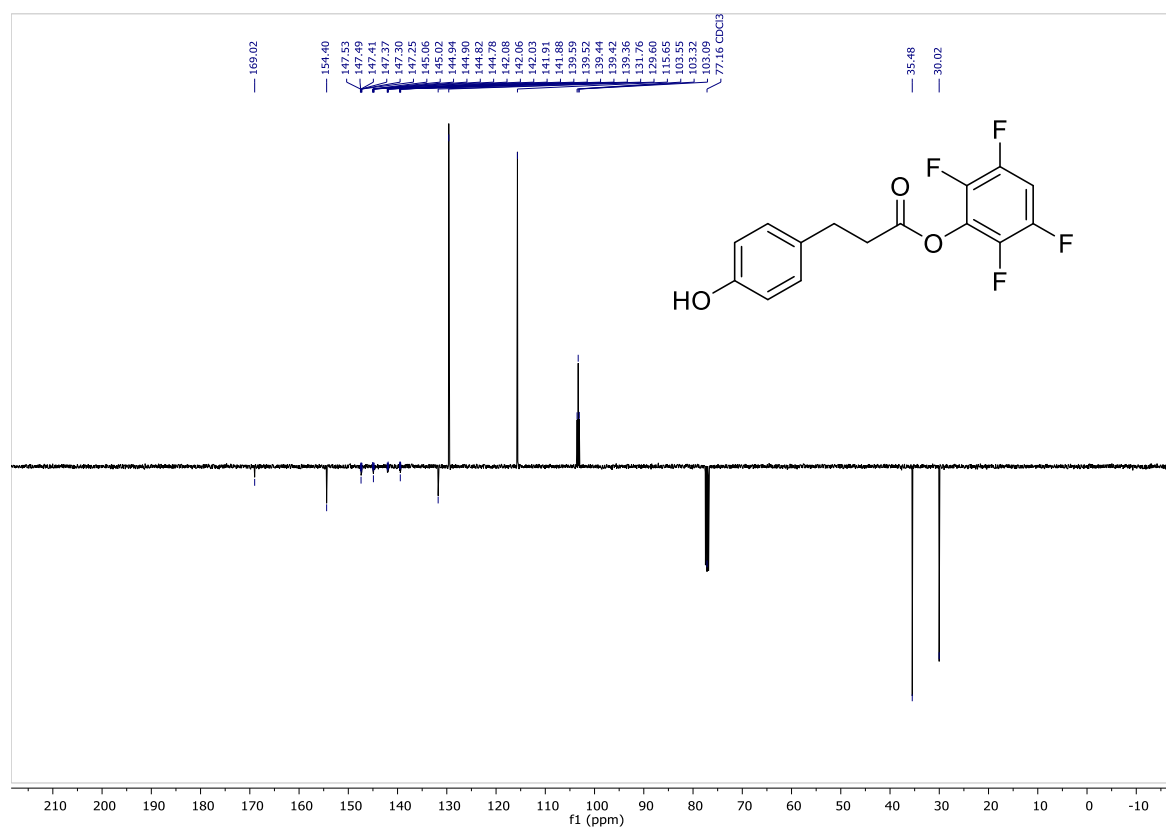
^{19}F NMR [376 MHz, $(\text{CD}_3)_2\text{SO}$]



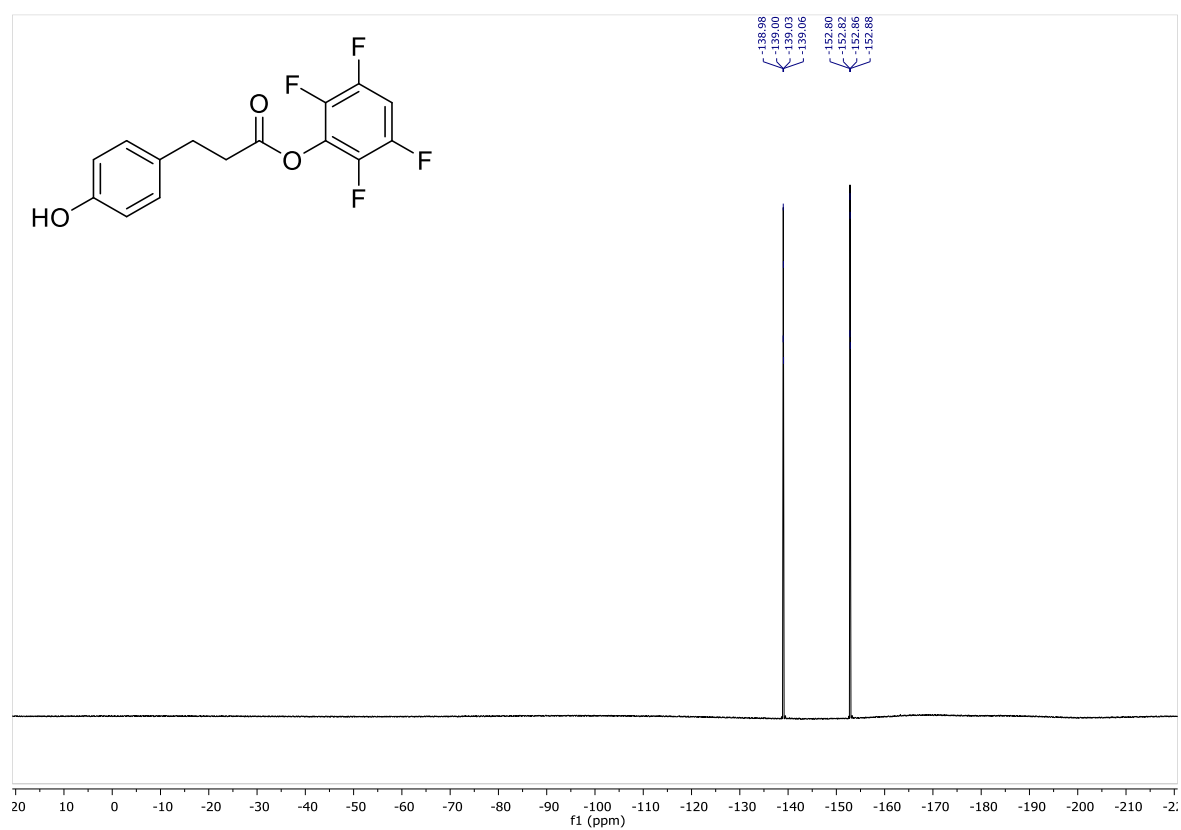
4-{3-[2-(Diethylamino)-2-oxoethyl]-5,7-dimethylpyrazolo[1,5-a]pyrimidin-2-yl}phenyl sulfurofluoridate (12m)¹H NMR (400 MHz, CDCl₃)¹³C {¹H} NMR (101 MHz, CDCl₃)

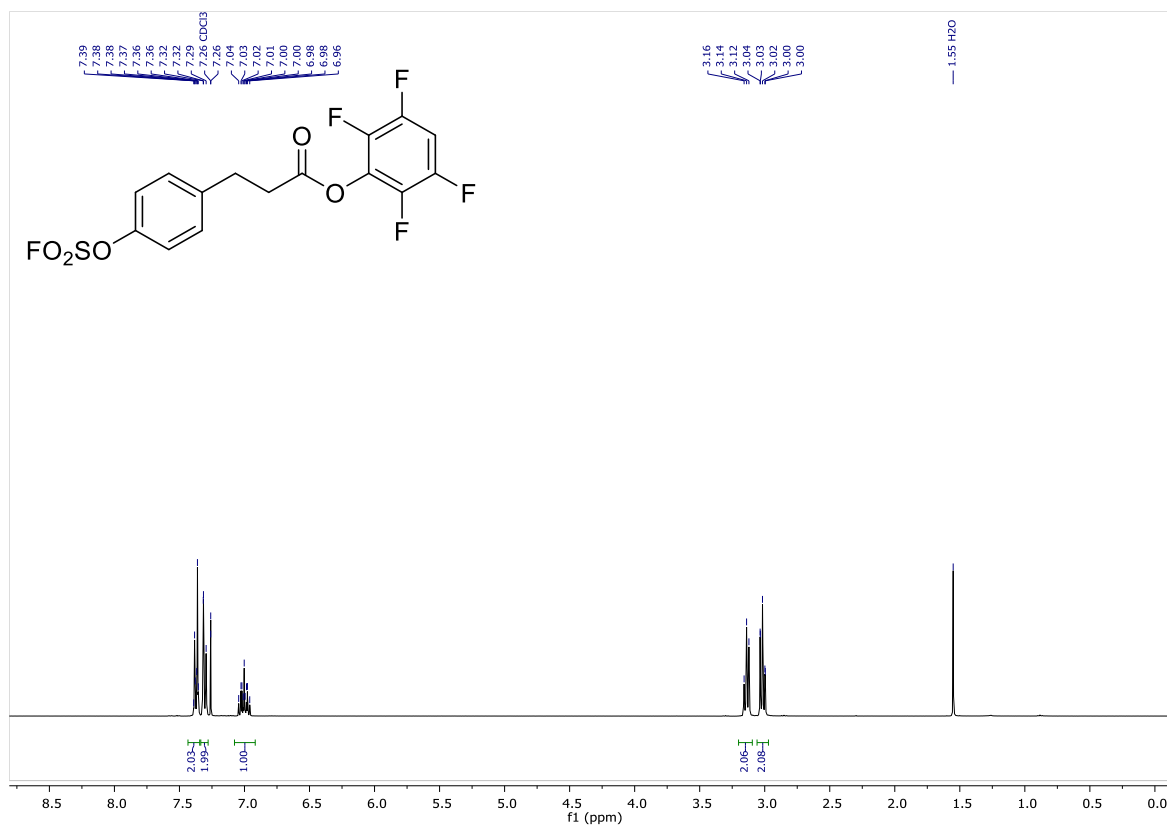
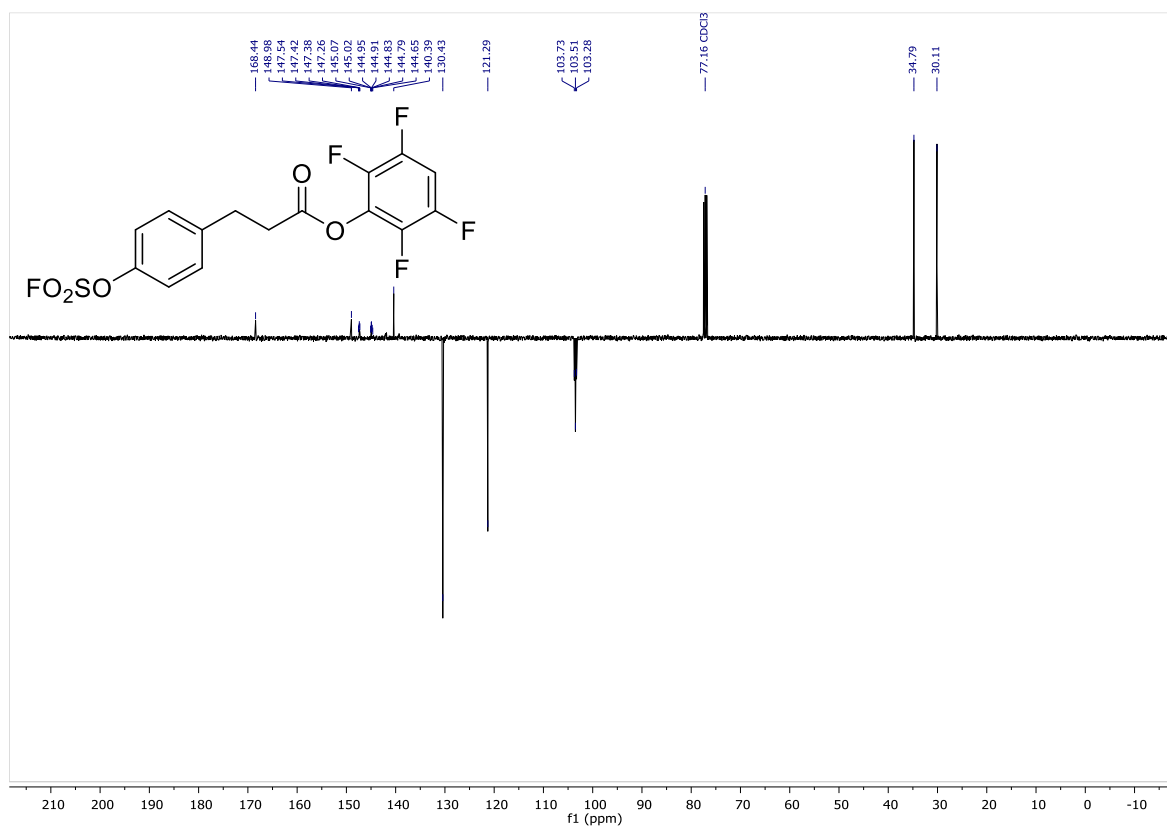
^{19}F NMR (376 MHz, CDCl_3)

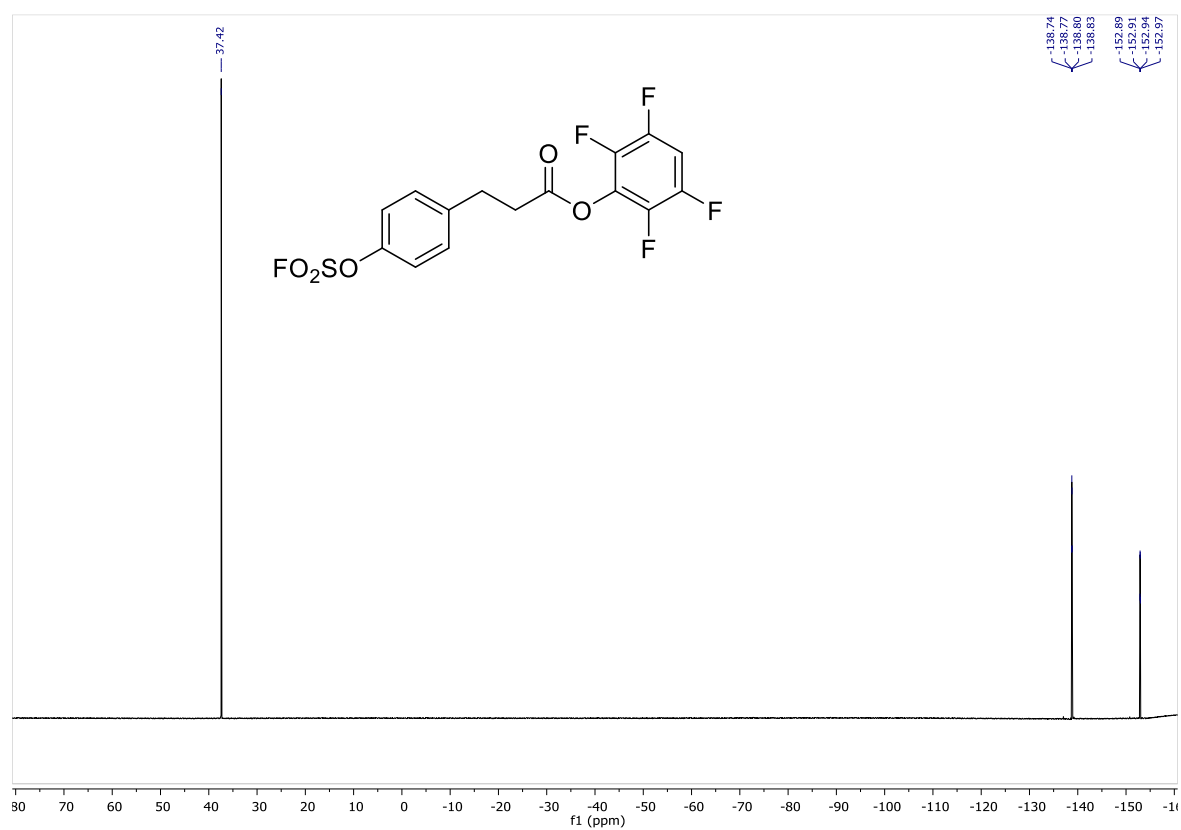


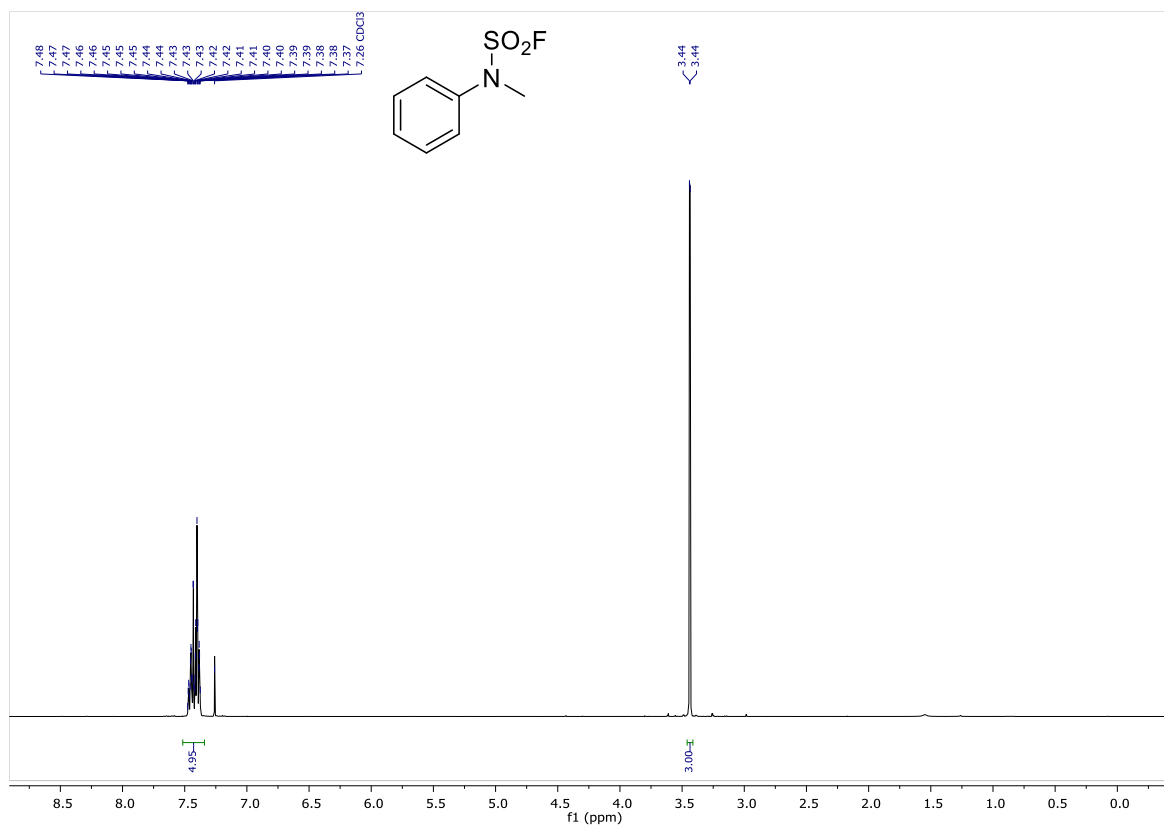
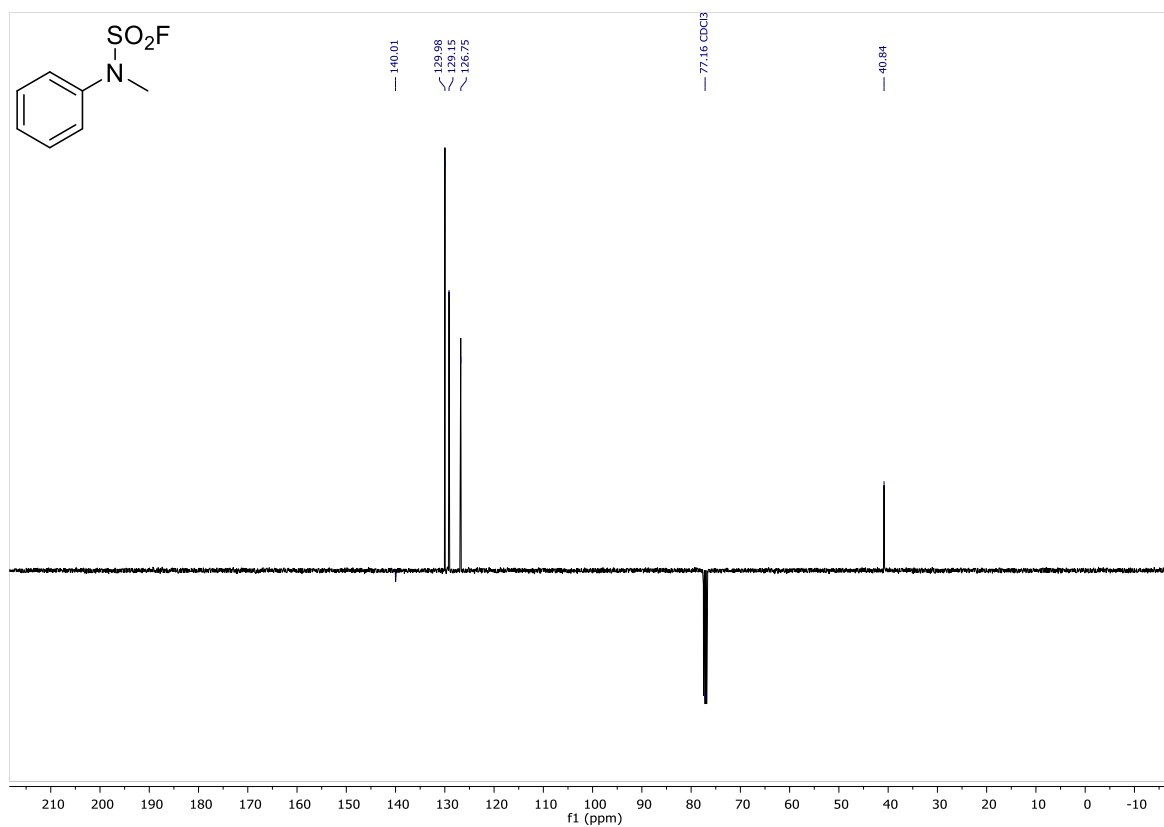
2,3,5,6-Tetrafluorophenyl 3-(4-hydroxyphenyl)propanoate ^1H NMR (400 MHz, CDCl_3) $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3)

^{19}F NMR (376 MHz, CDCl_3)

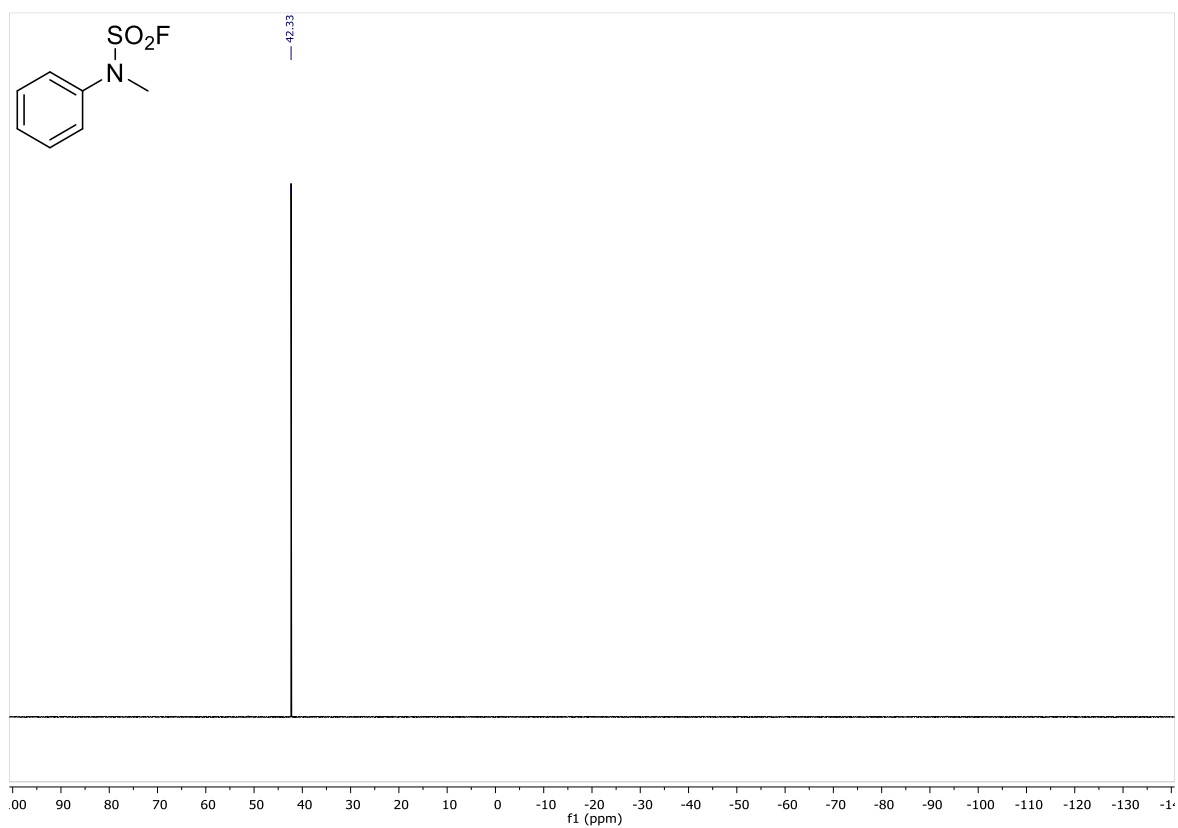


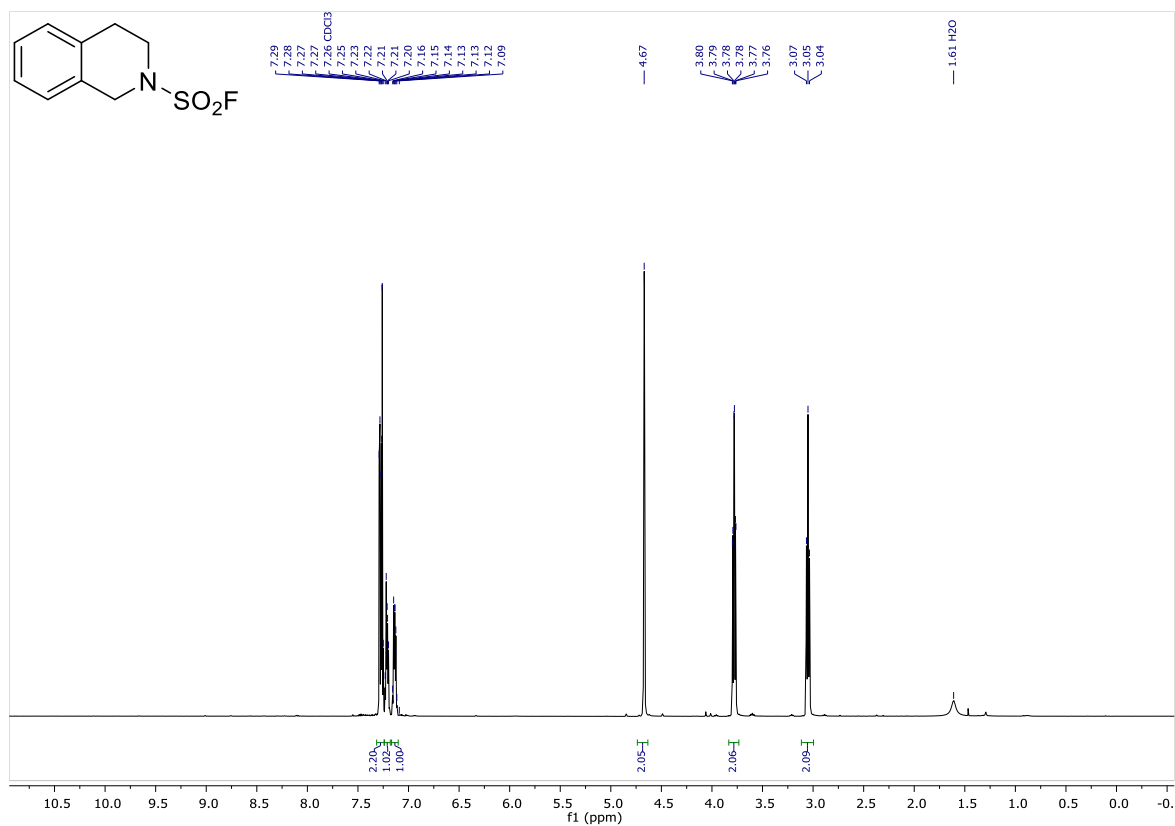
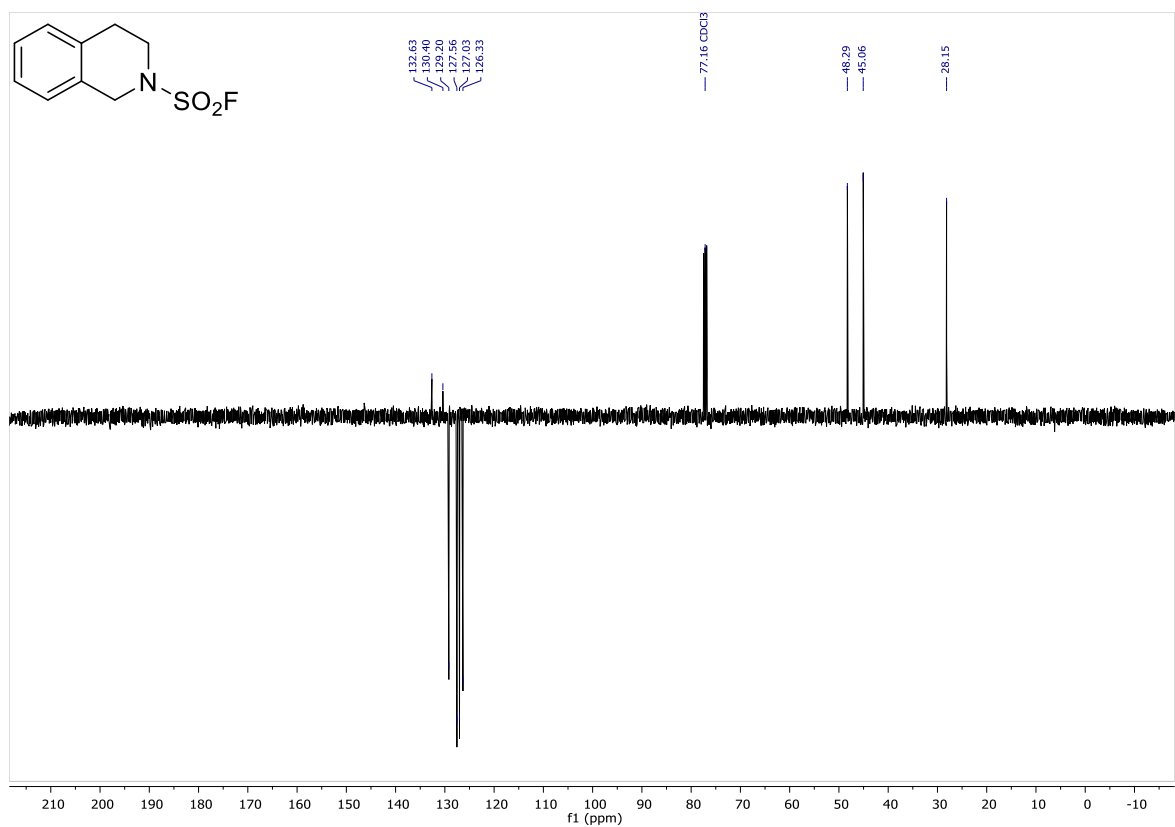
2,3,5,6-Tetrafluorophenyl 3-{4-[(fluorosulfonyl)oxy]phenyl}propanoate (12n)¹H NMR (400 MHz, CDCl₃)¹³C{¹H} NMR (101 MHz, CDCl₃)

^{19}F NMR (376 MHz, CDCl_3)

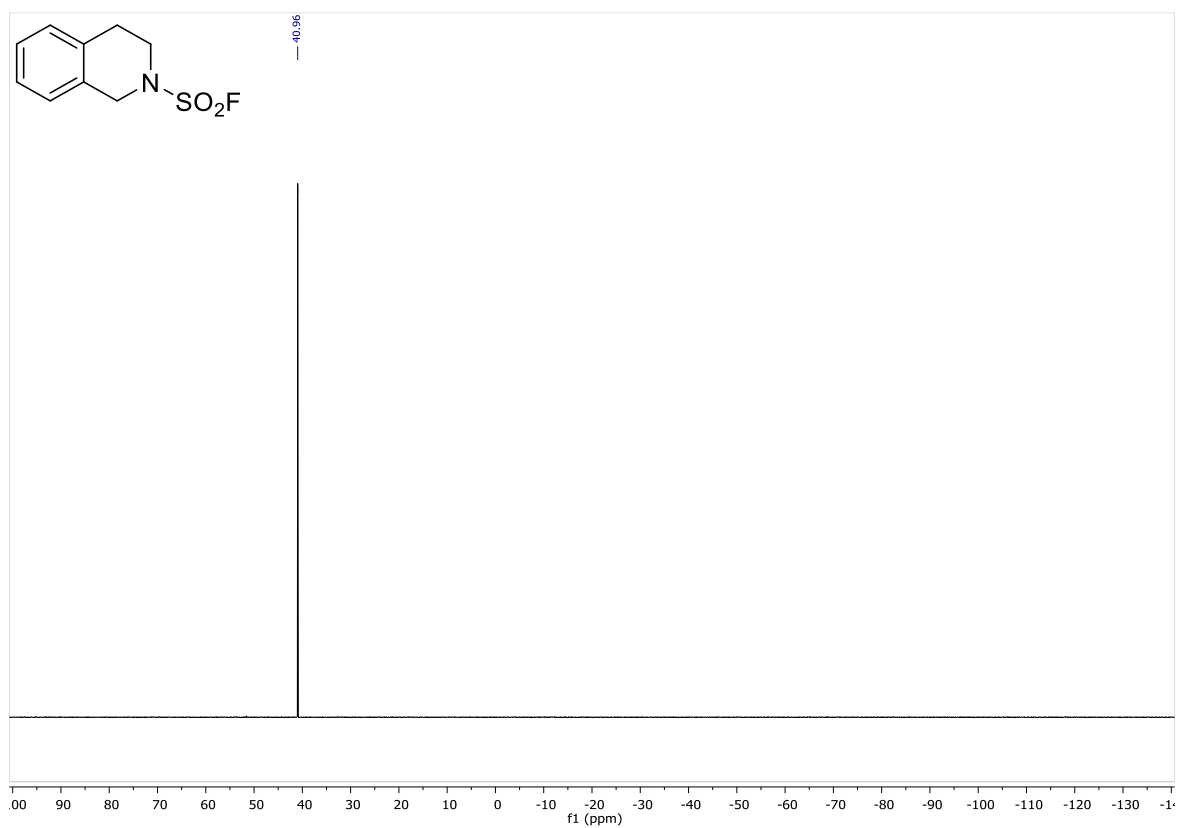
Methyl(phenyl)sulfamoyl fluoride (13a) ^1H NMR (400 MHz, CDCl_3) $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3)

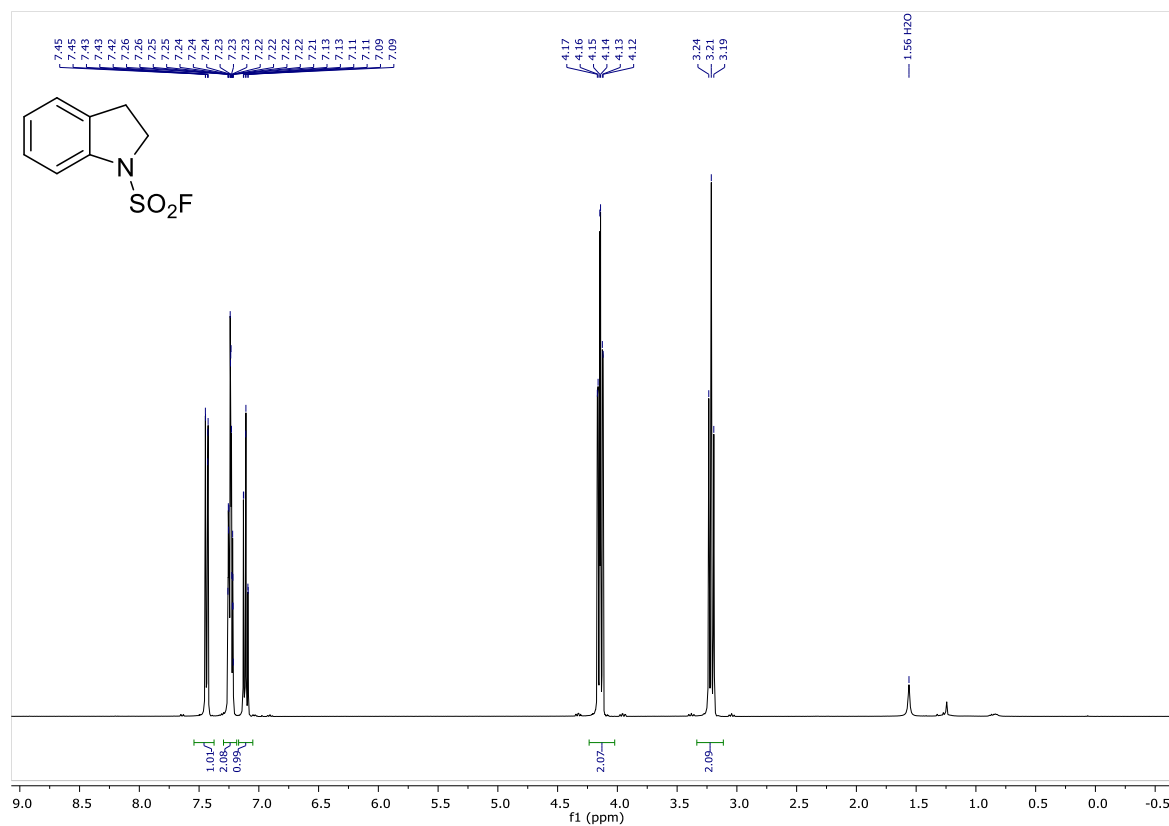
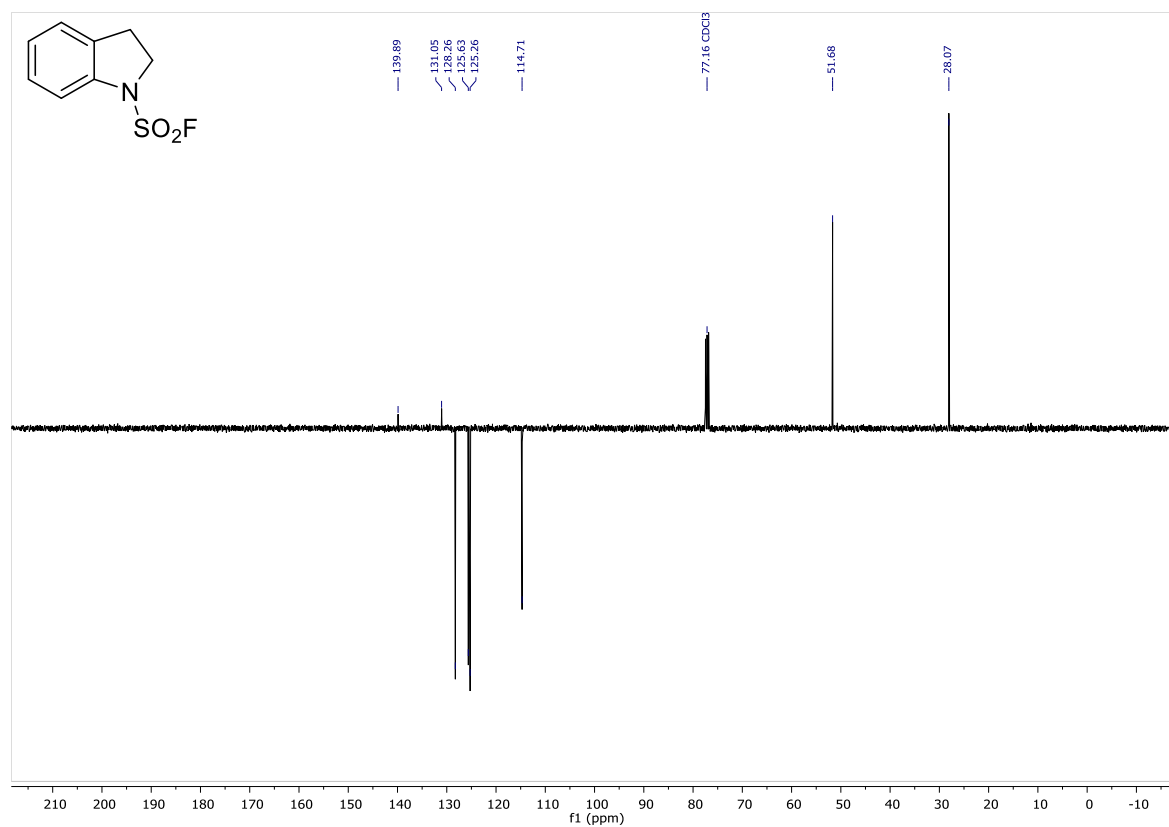
^{19}F NMR (376 MHz, CDCl_3)



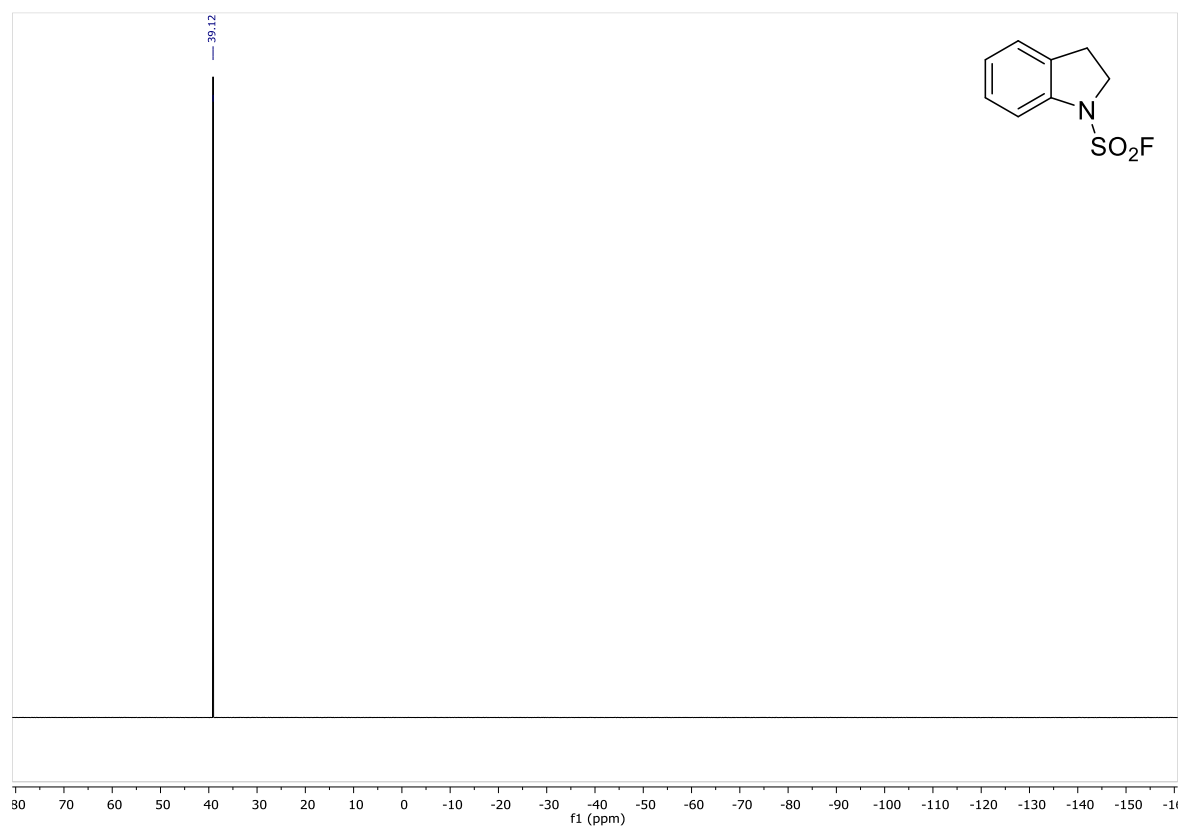
1,2,3,4-Tetrahydroisoquinoline-2-sulfonyl fluoride (13b) ^1H NMR (400 MHz, CDCl_3) $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3)

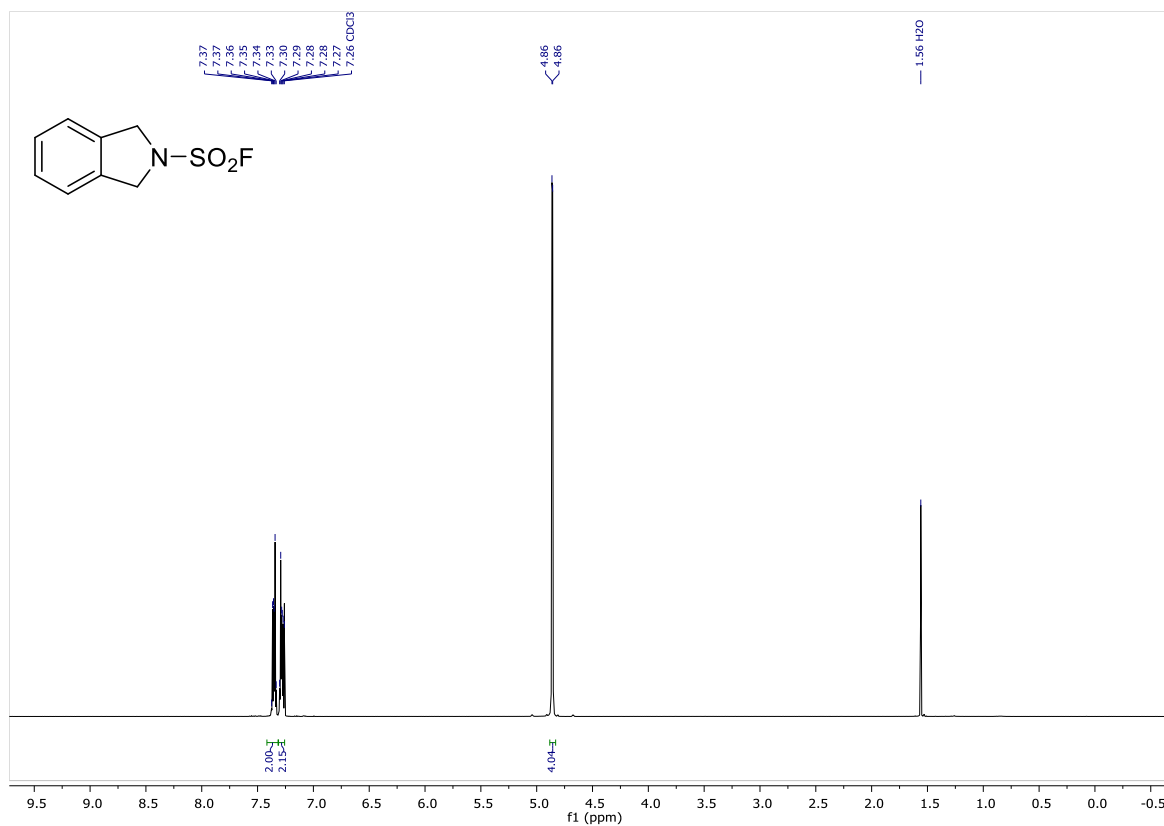
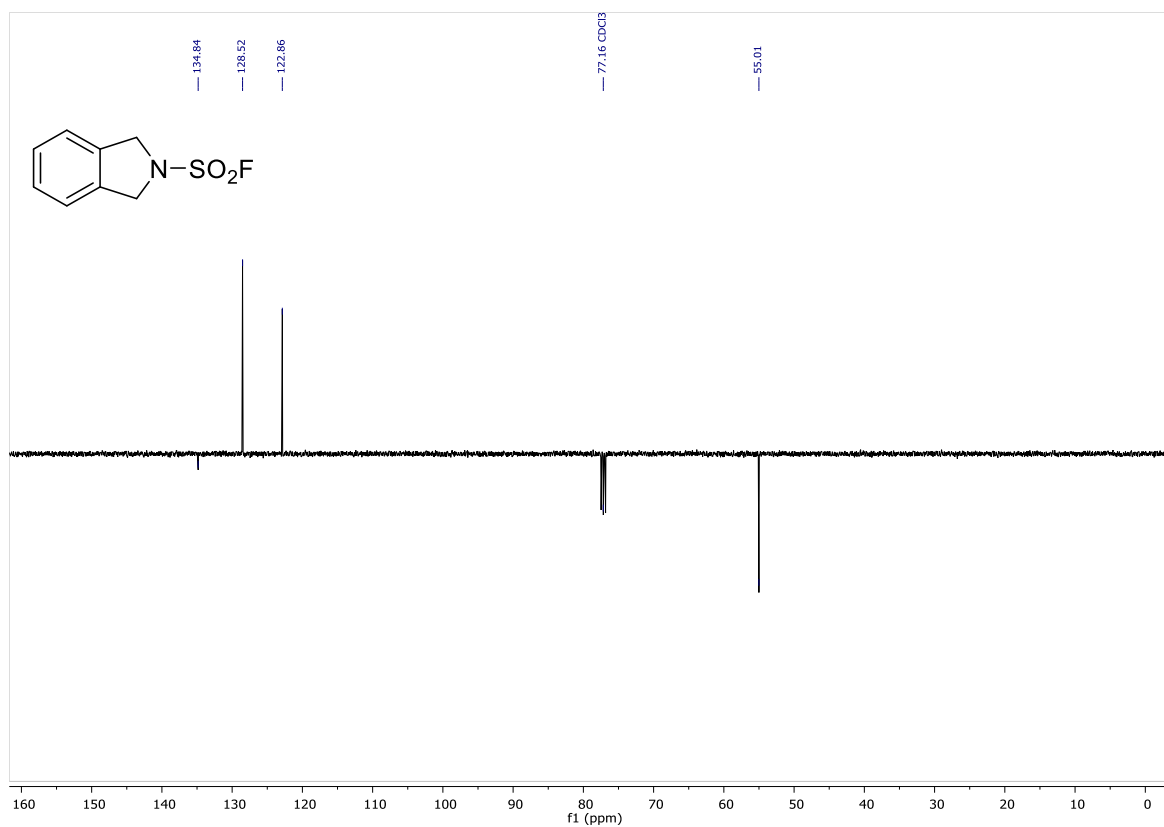
^{19}F NMR (376 MHz, CDCl_3)



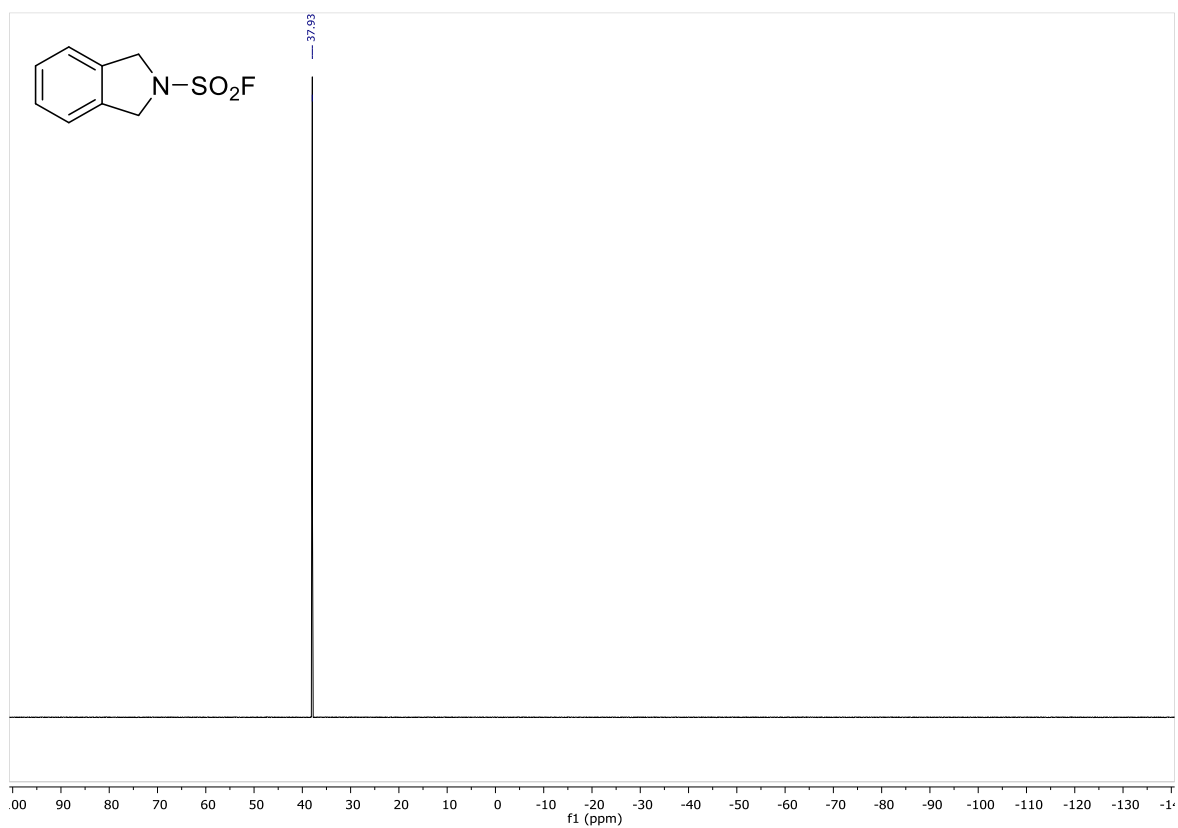
Indoline-1-sulfonyl fluoride (13c) ^1H NMR (400 MHz, CDCl_3) $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3)

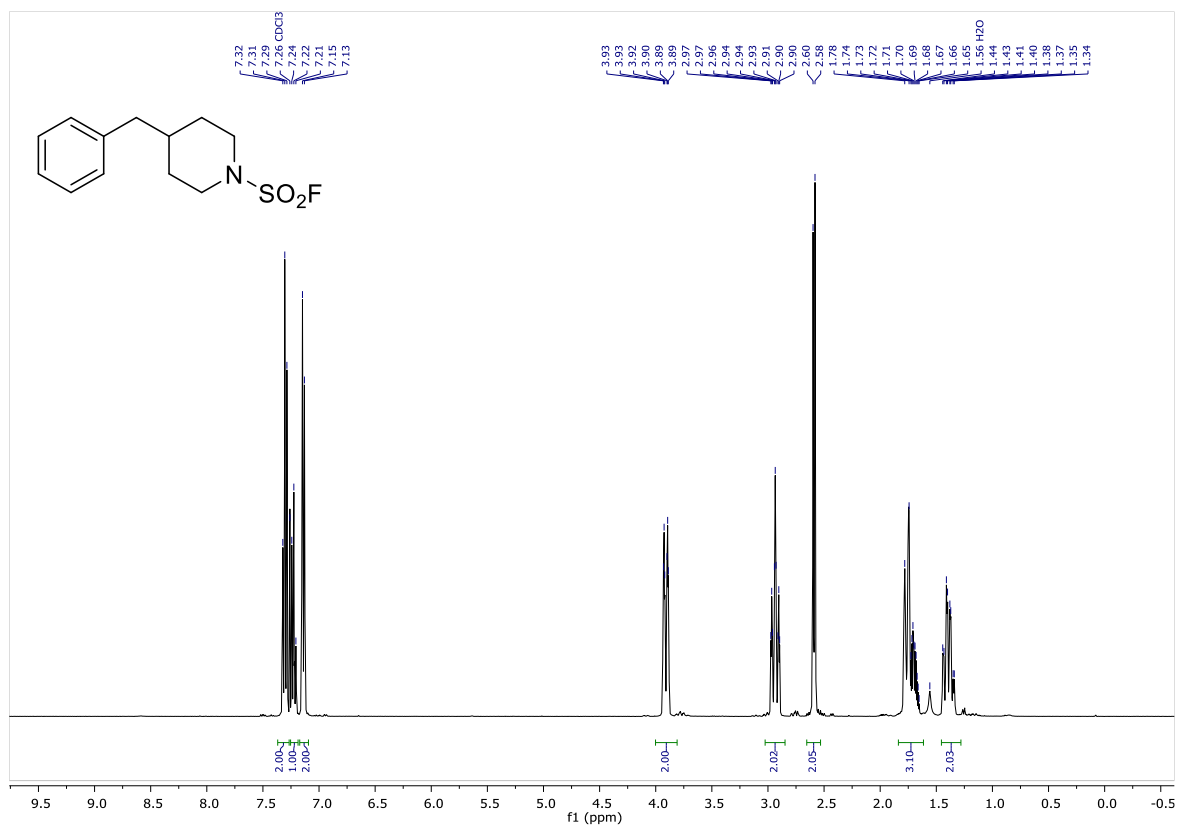
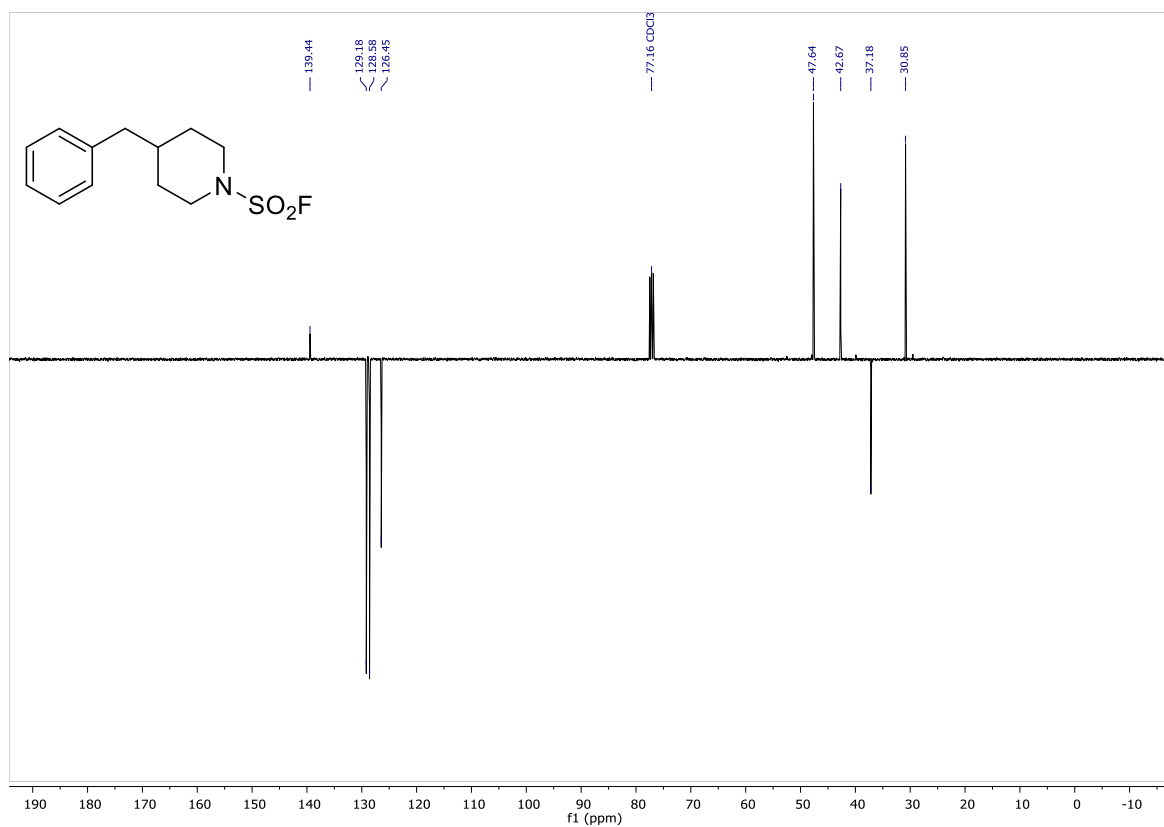
^{19}F NMR (376 MHz, CDCl_3)



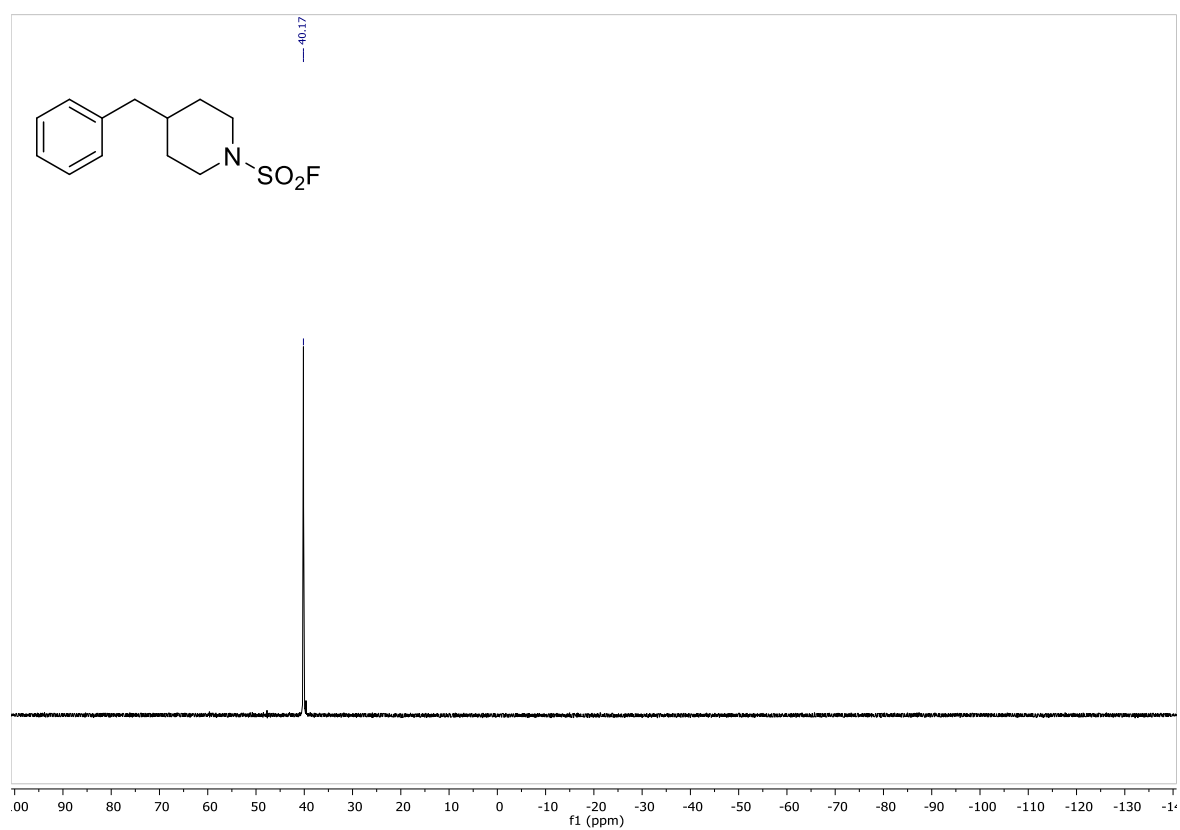
Isoindoline-2-sulfonyl fluoride (13d) ^1H NMR (400 MHz, CDCl_3) $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3)

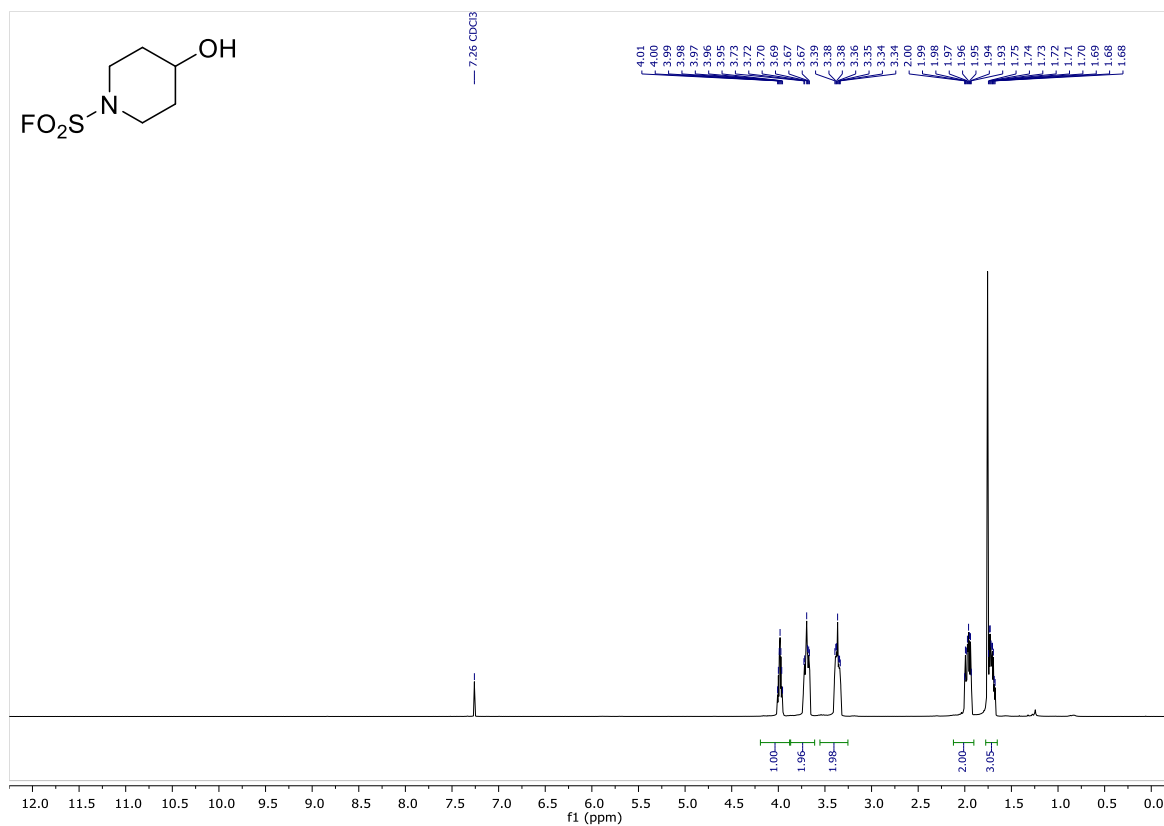
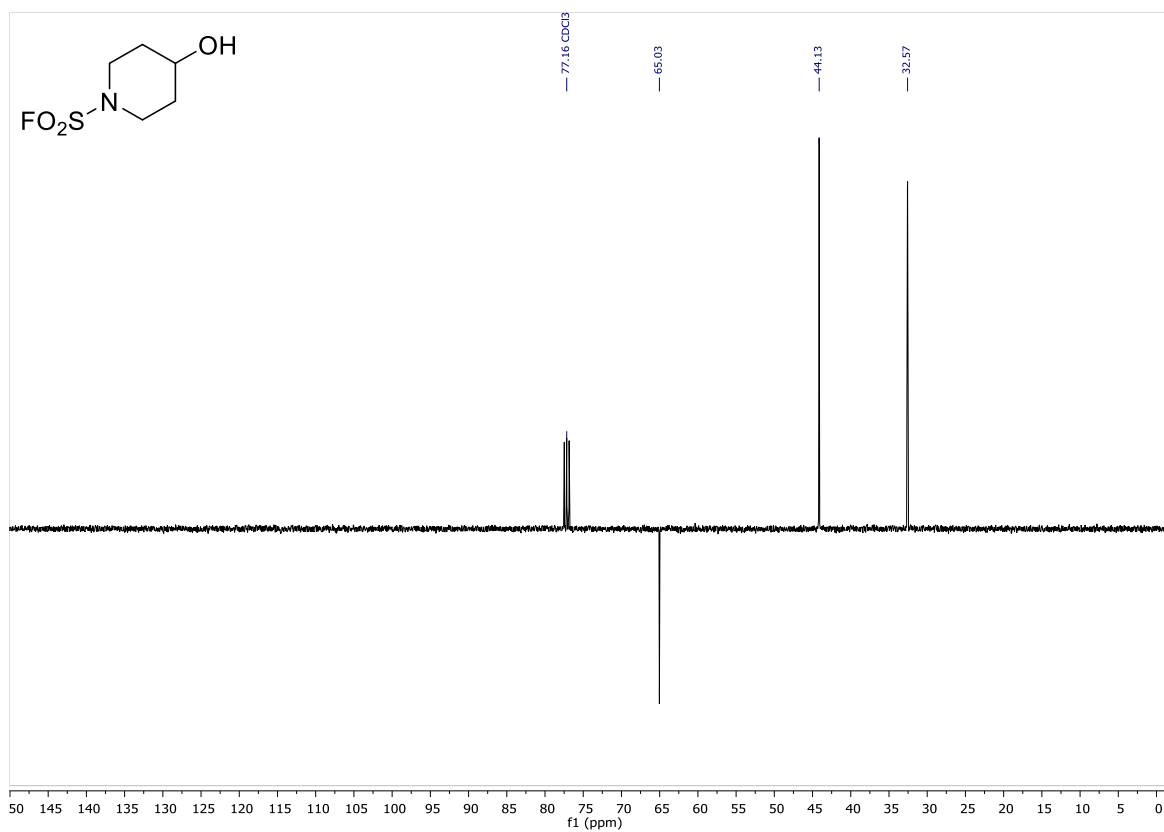
^{19}F NMR (376 MHz, CDCl_3)



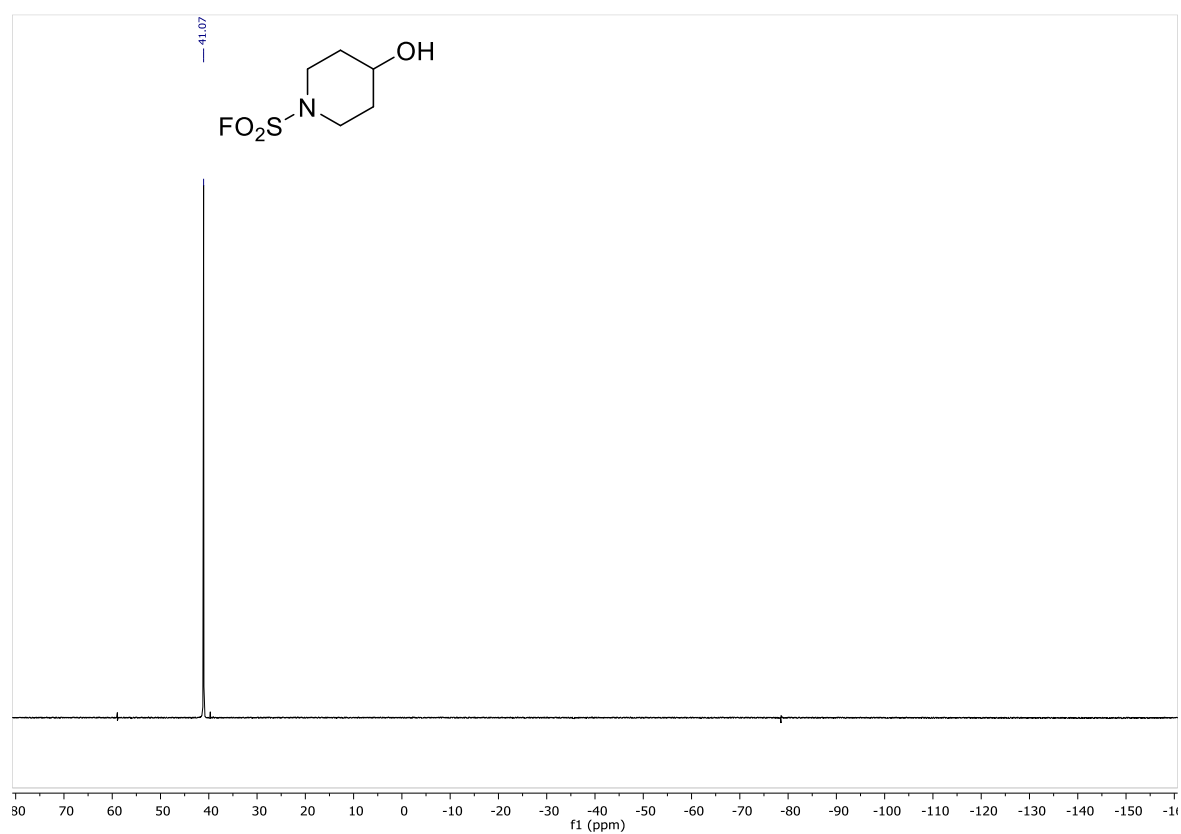
4-Benzylpiperidine-1-sulfonyl fluoride (13e) ^1H NMR (400 MHz, CDCl_3) $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3)

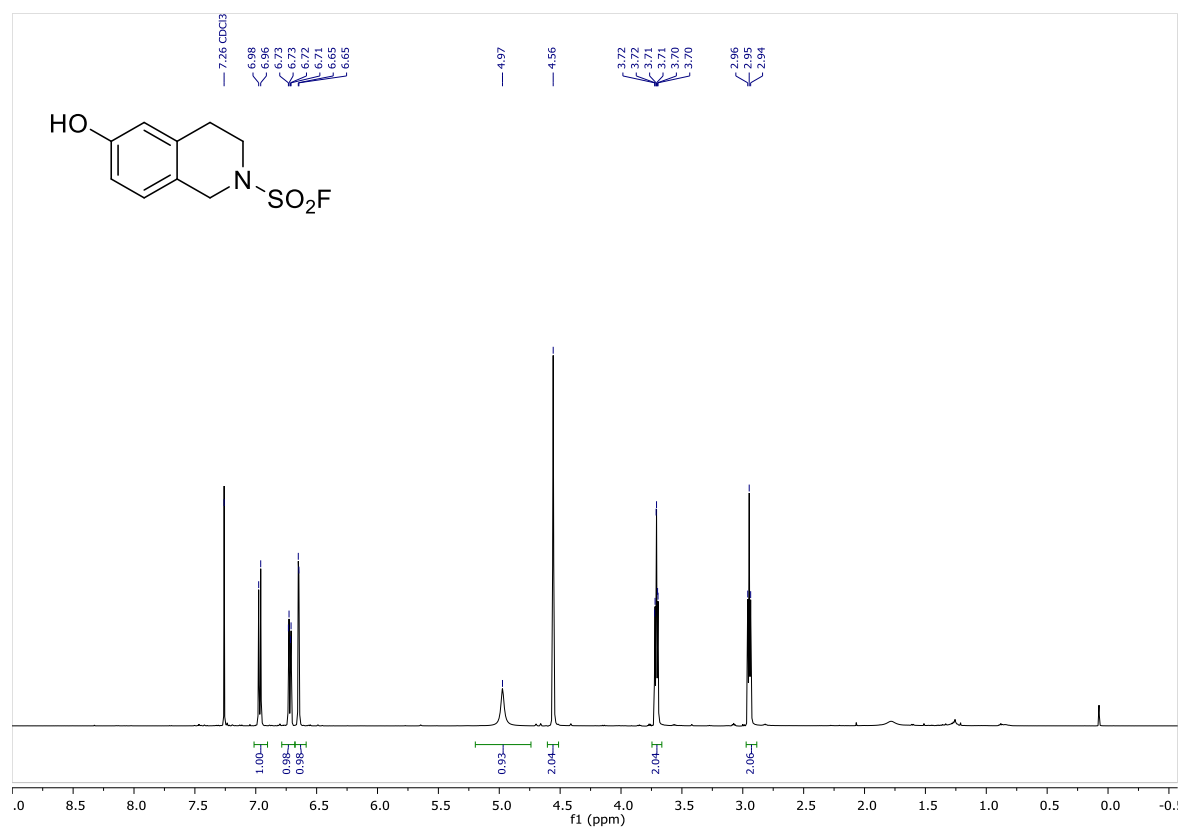
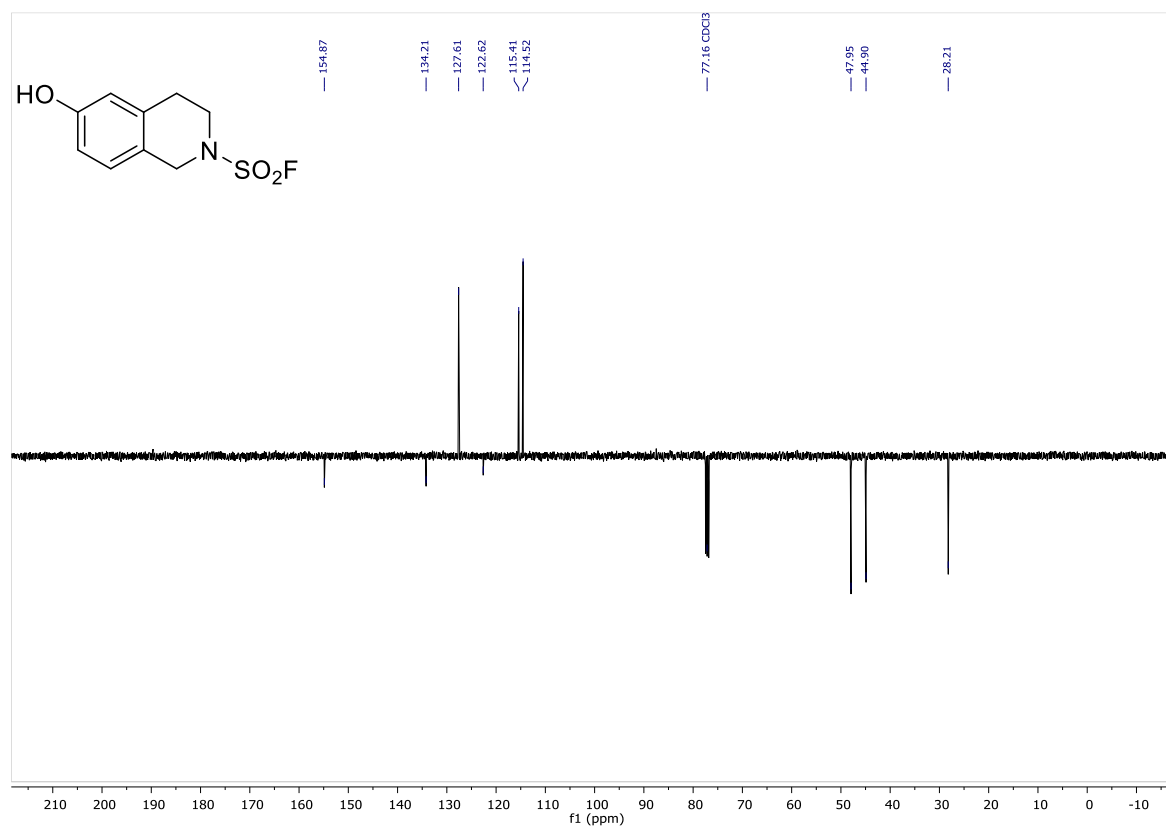
^{19}F NMR (376 MHz, CDCl_3)



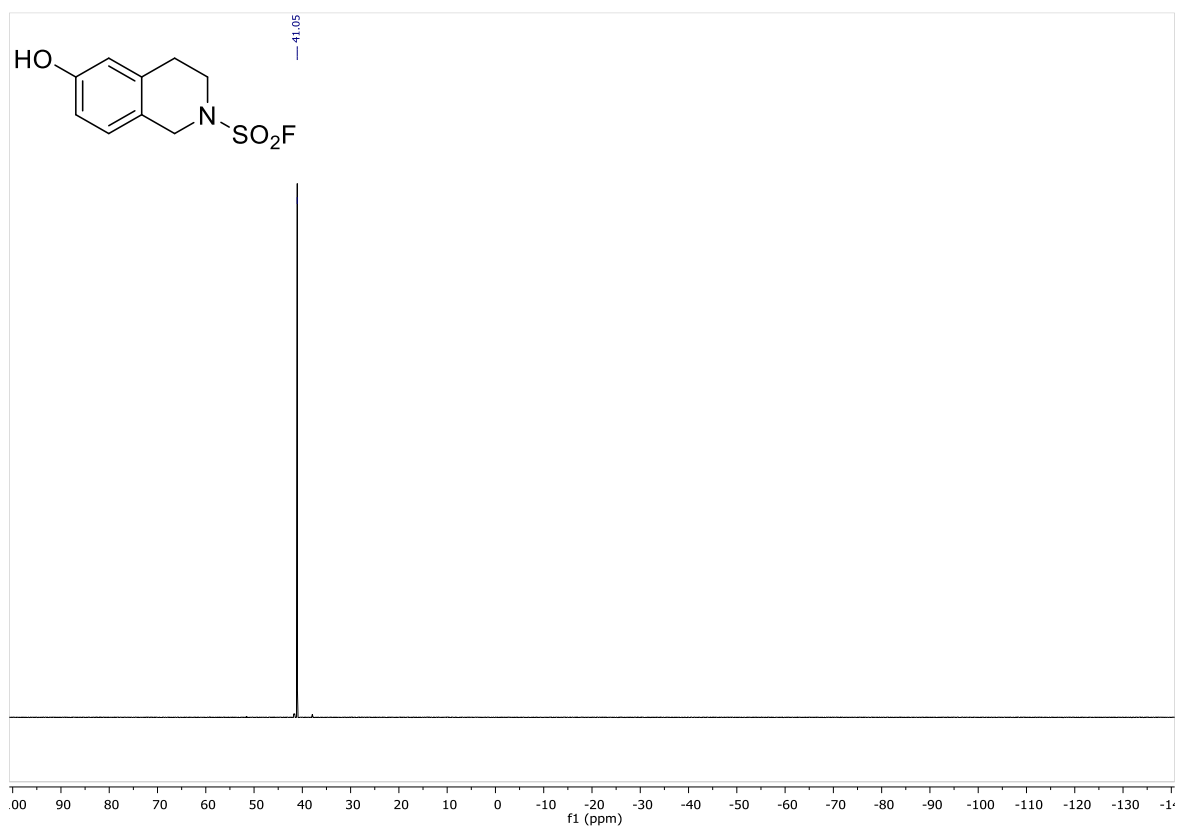
4-Hydroxypiperidyl-1-sulfonyl fluoride (13f) ^1H NMR (400 MHz, CDCl_3) $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3)

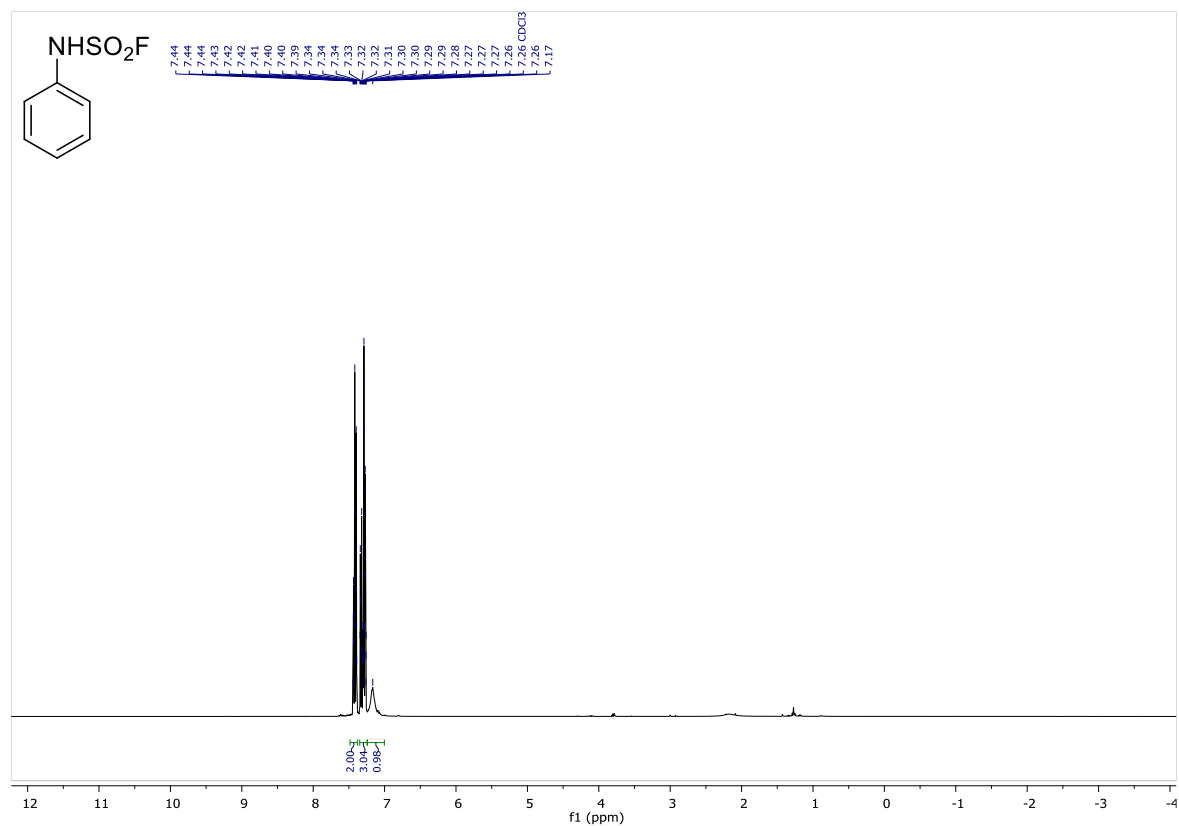
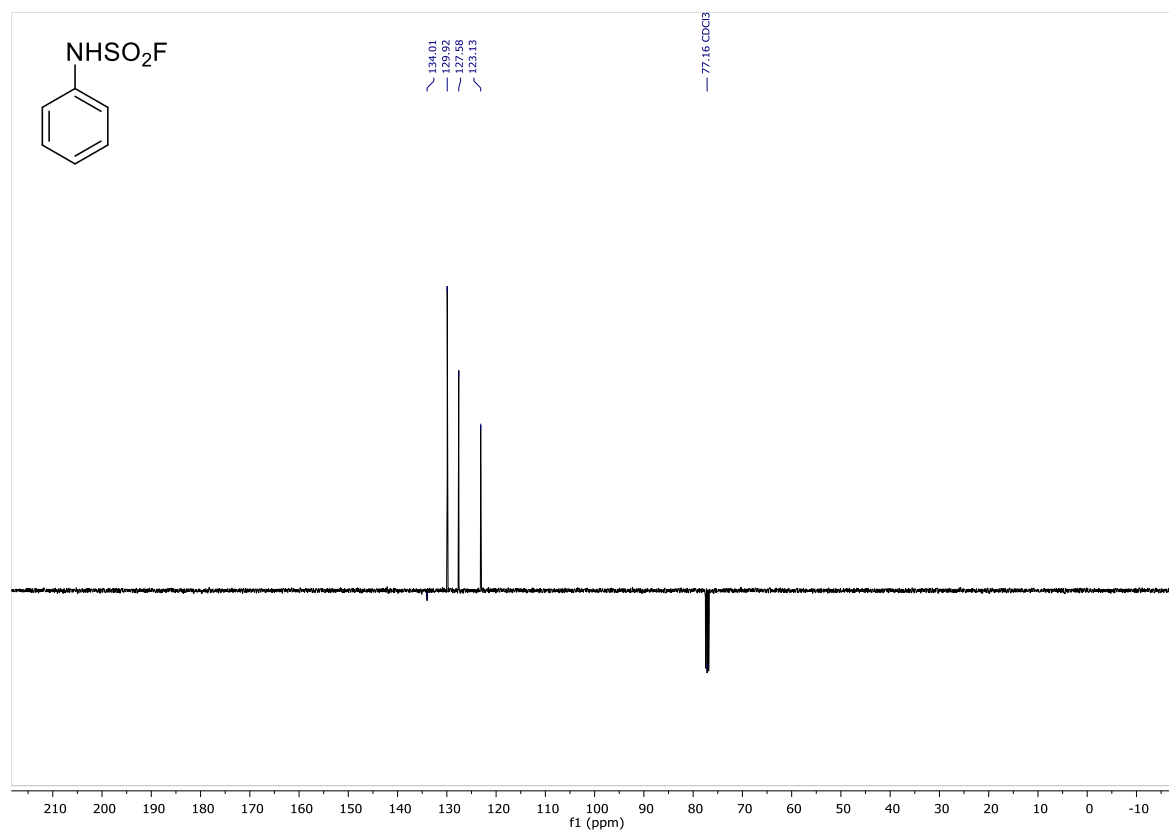
^{19}F NMR (376 MHz, CDCl_3)



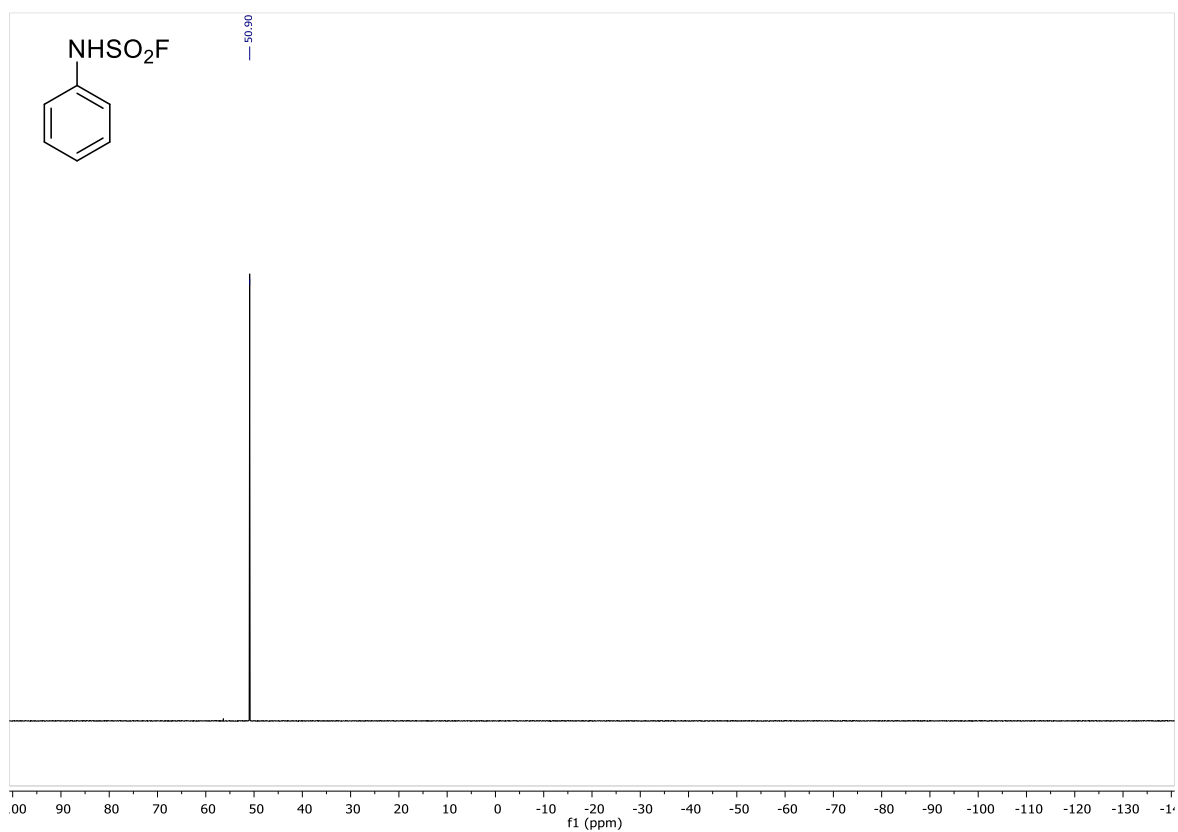
6-Hydroxy-1,2,3,4-tetrahydroisoquinoline-2-sulfonyl fluoride (13g) ^1H NMR (400 MHz, CDCl_3) $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3)

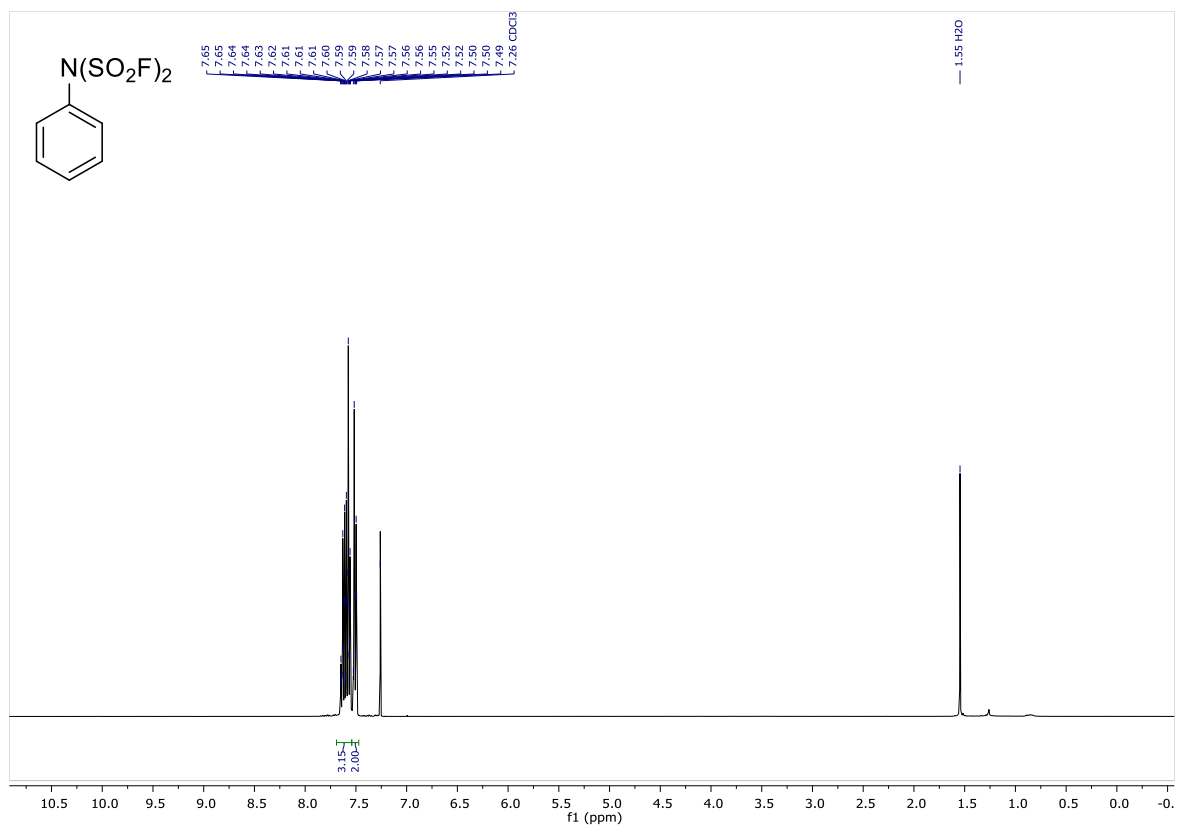
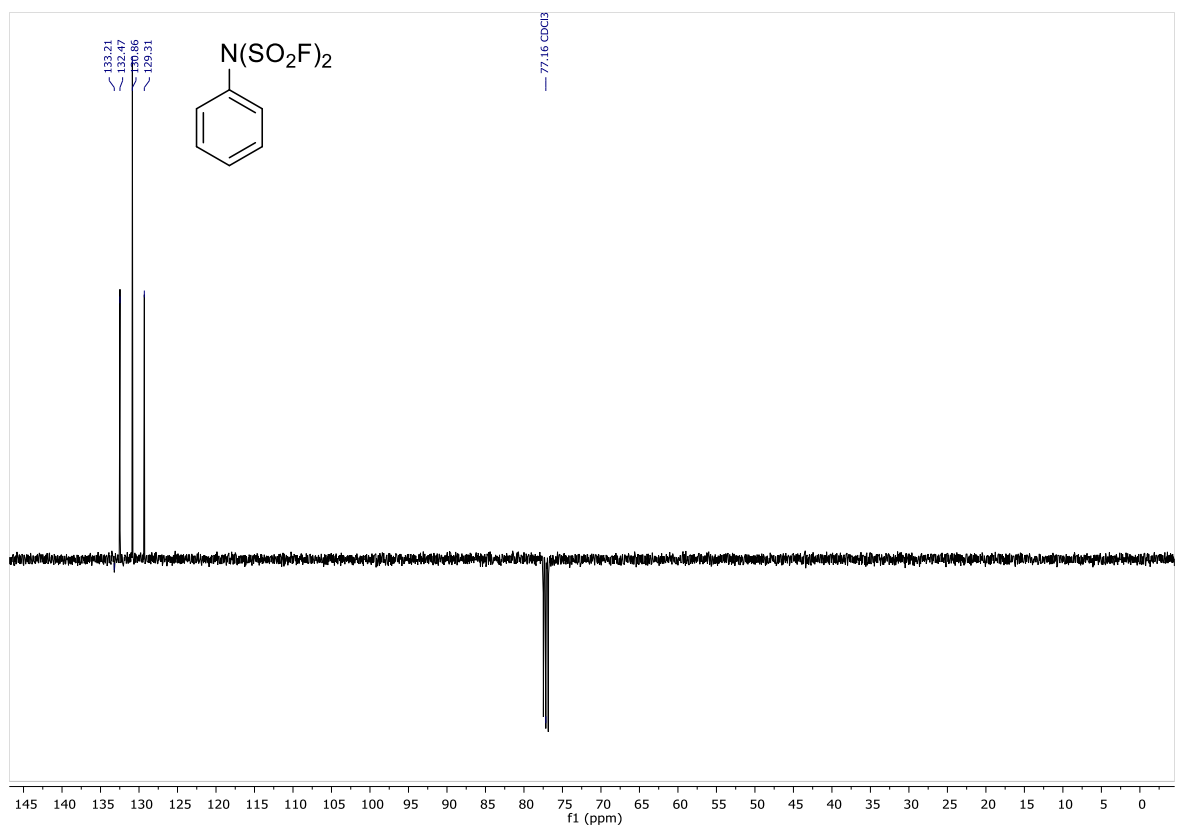
^{19}F NMR (376 MHz, CDCl_3)



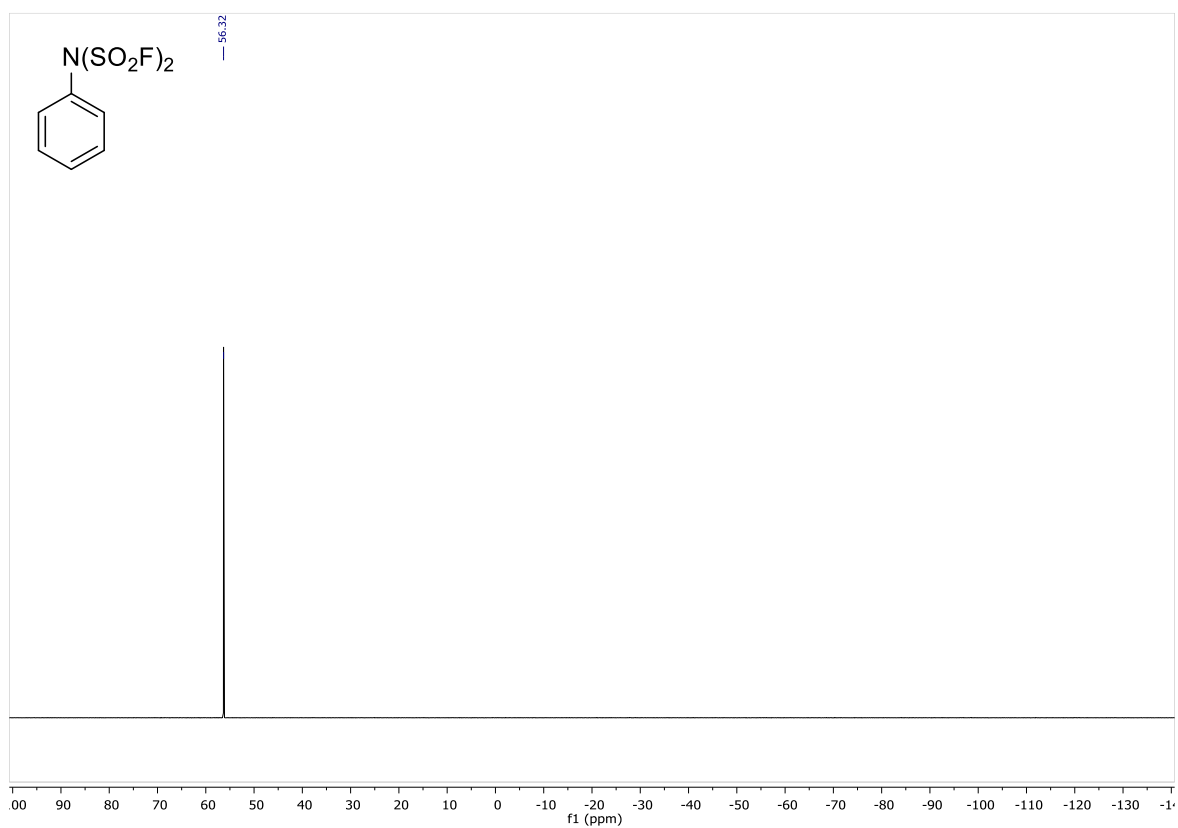
Phenylsulfamoyl fluoride (13h) ^1H NMR (400 MHz, CDCl_3) $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3)

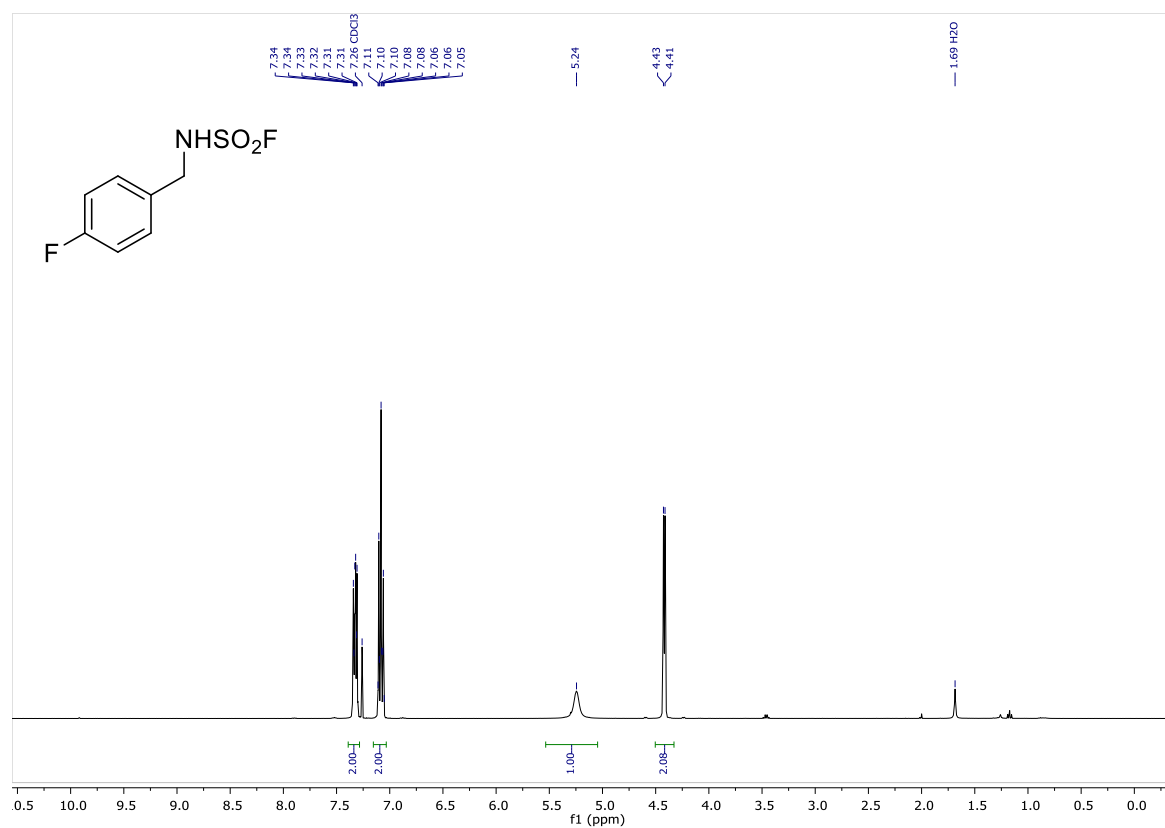
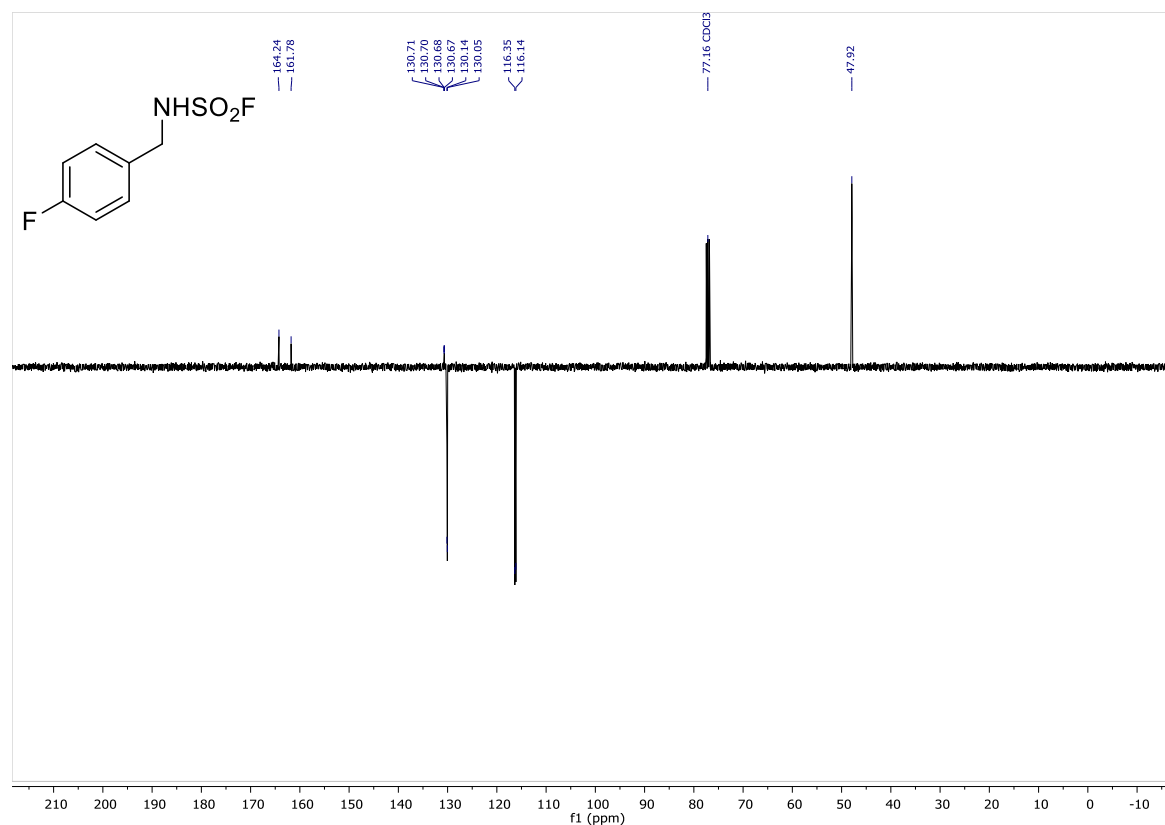
^{19}F NMR (376 MHz, CDCl_3)



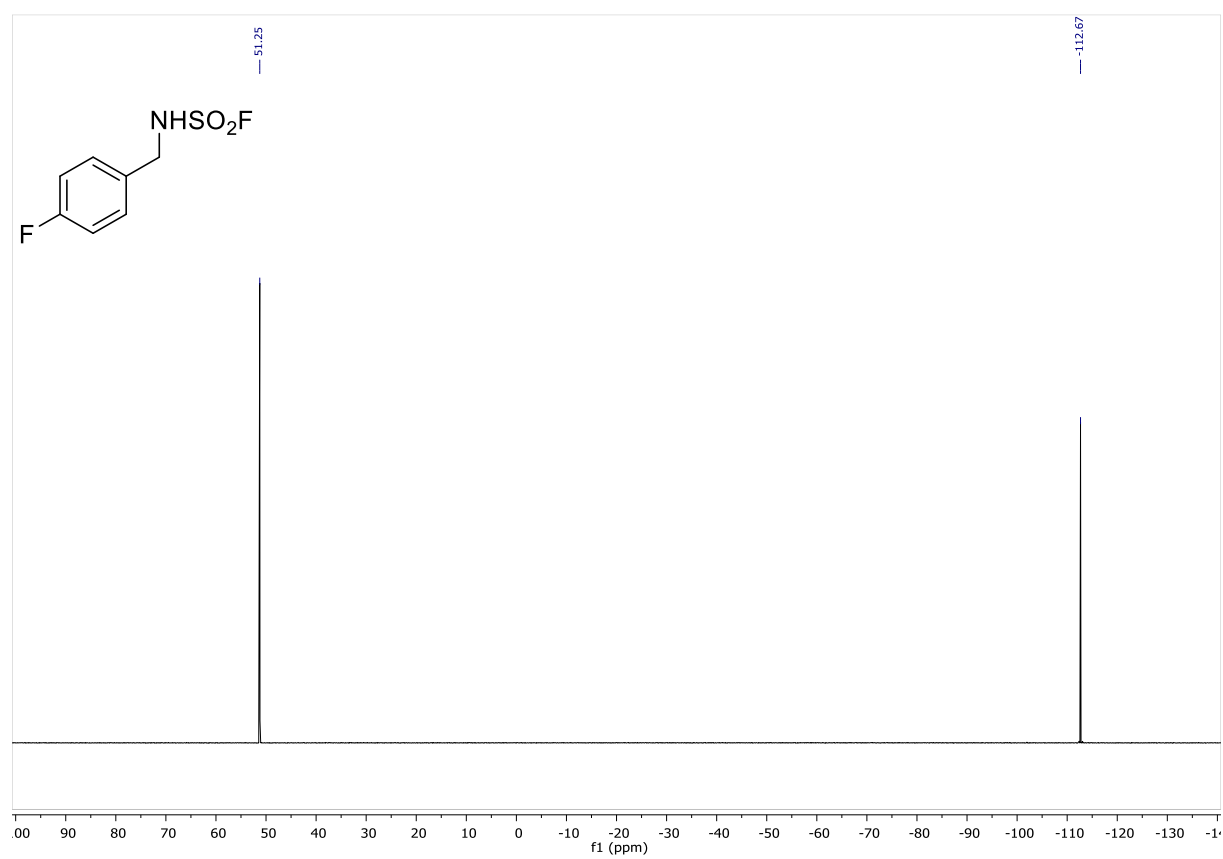
Phenyliminodisulfonyl difluoride (13i) ^1H NMR (400 MHz, CDCl_3) $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3)

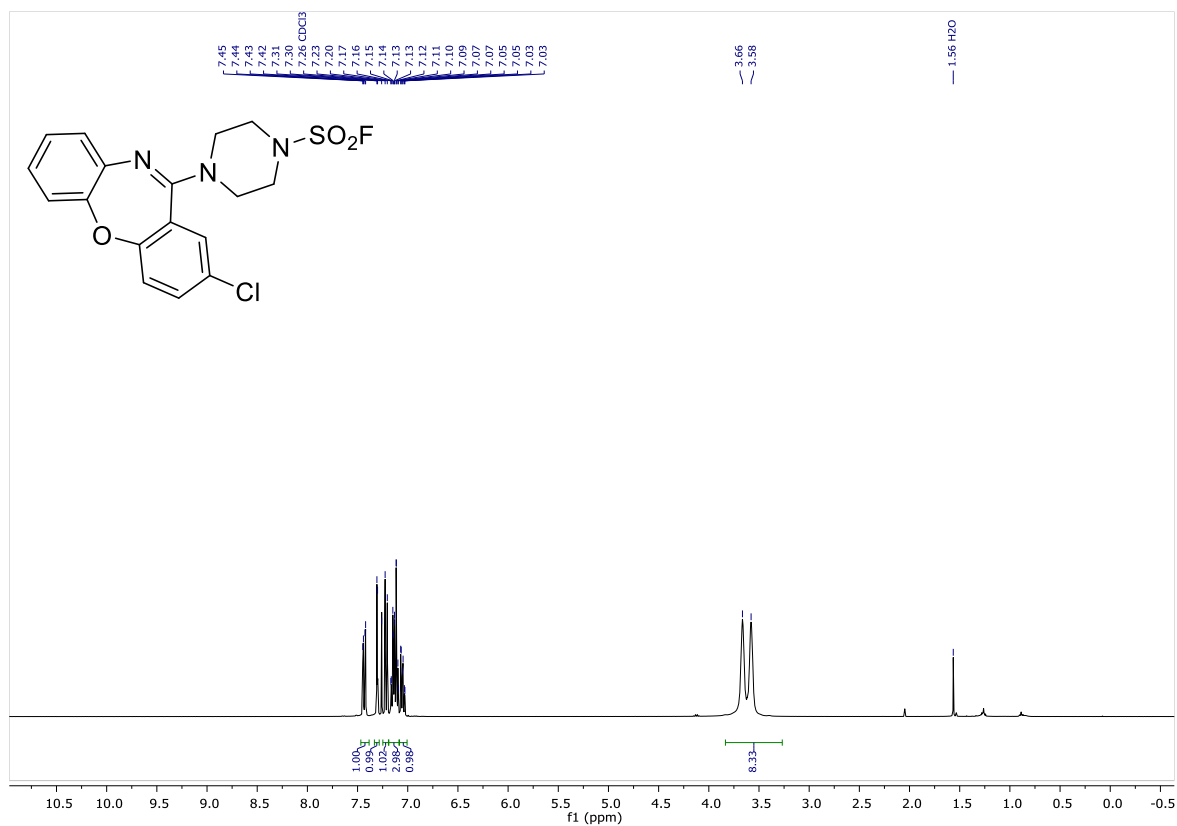
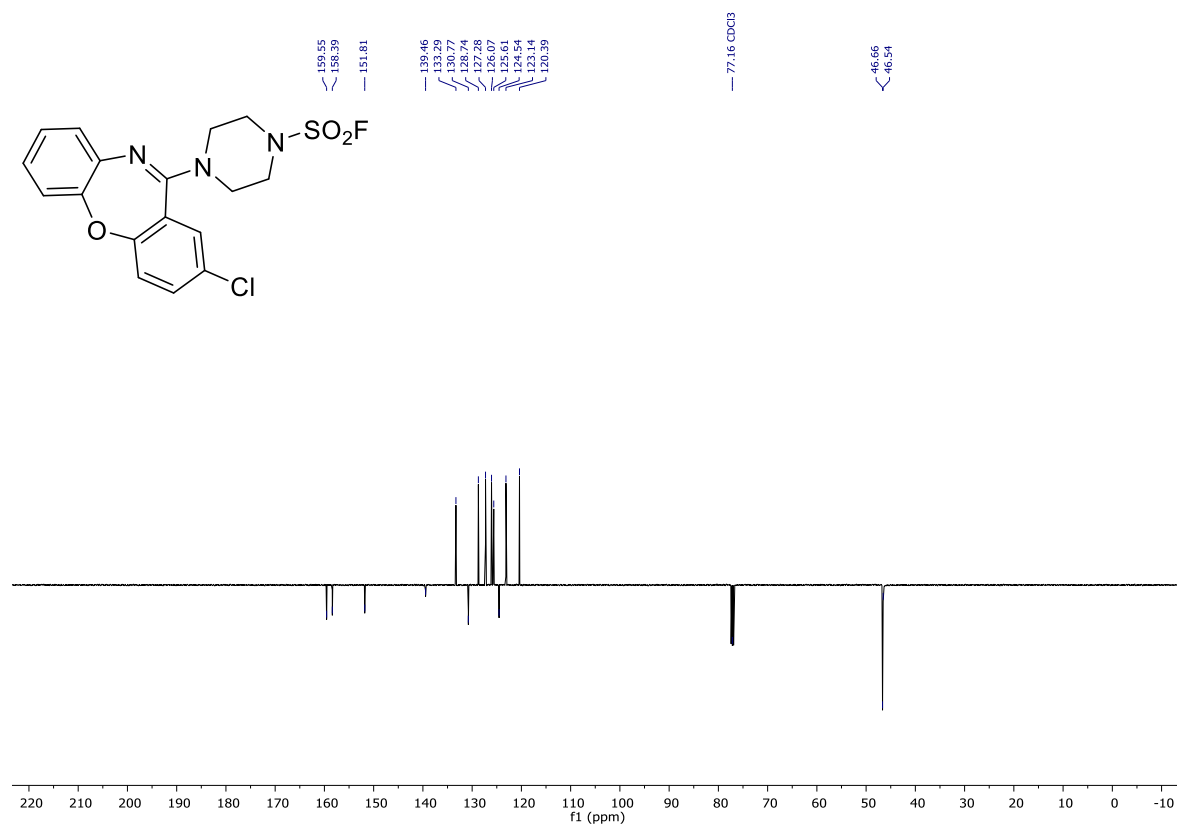
^{19}F NMR (376 MHz, CDCl_3)



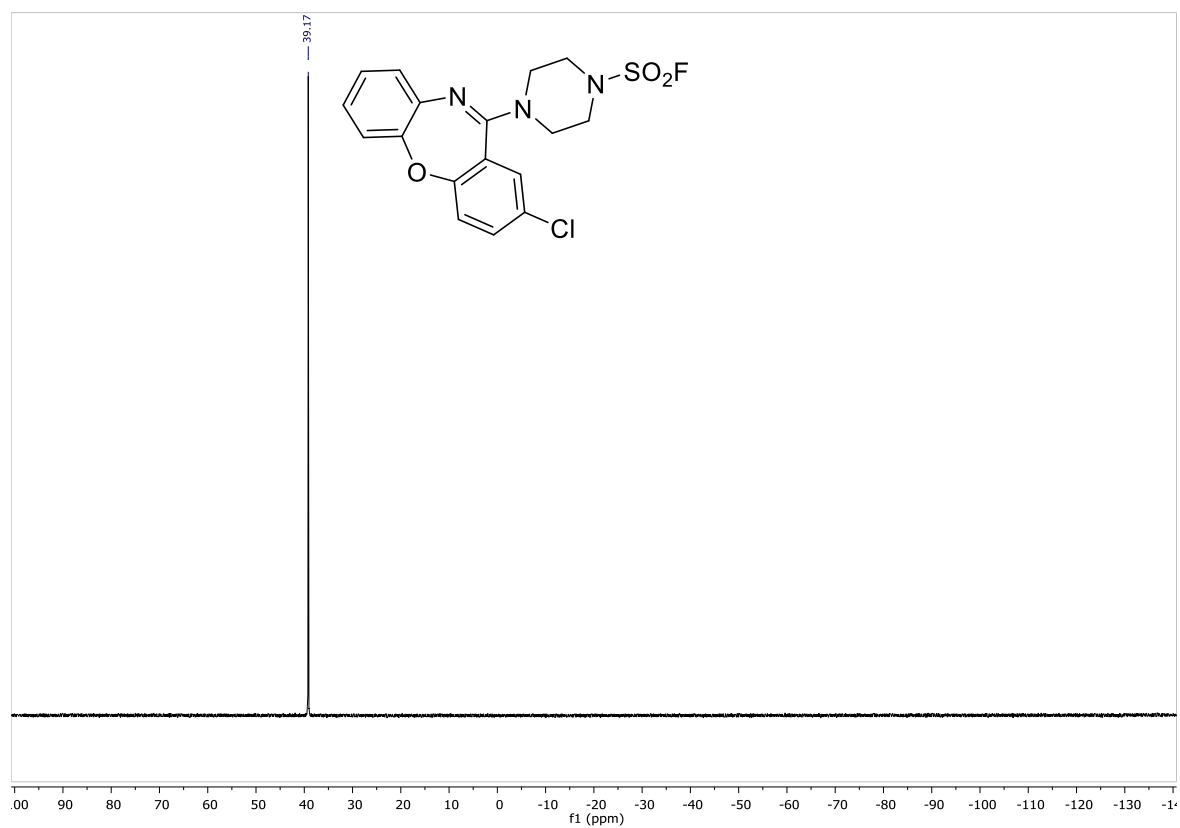
(4-Fluorobenzyl)sulfamoyl fluoride (13j)¹H NMR (400 MHz, CDCl₃)¹³C{¹H} NMR (101 MHz, CDCl₃)

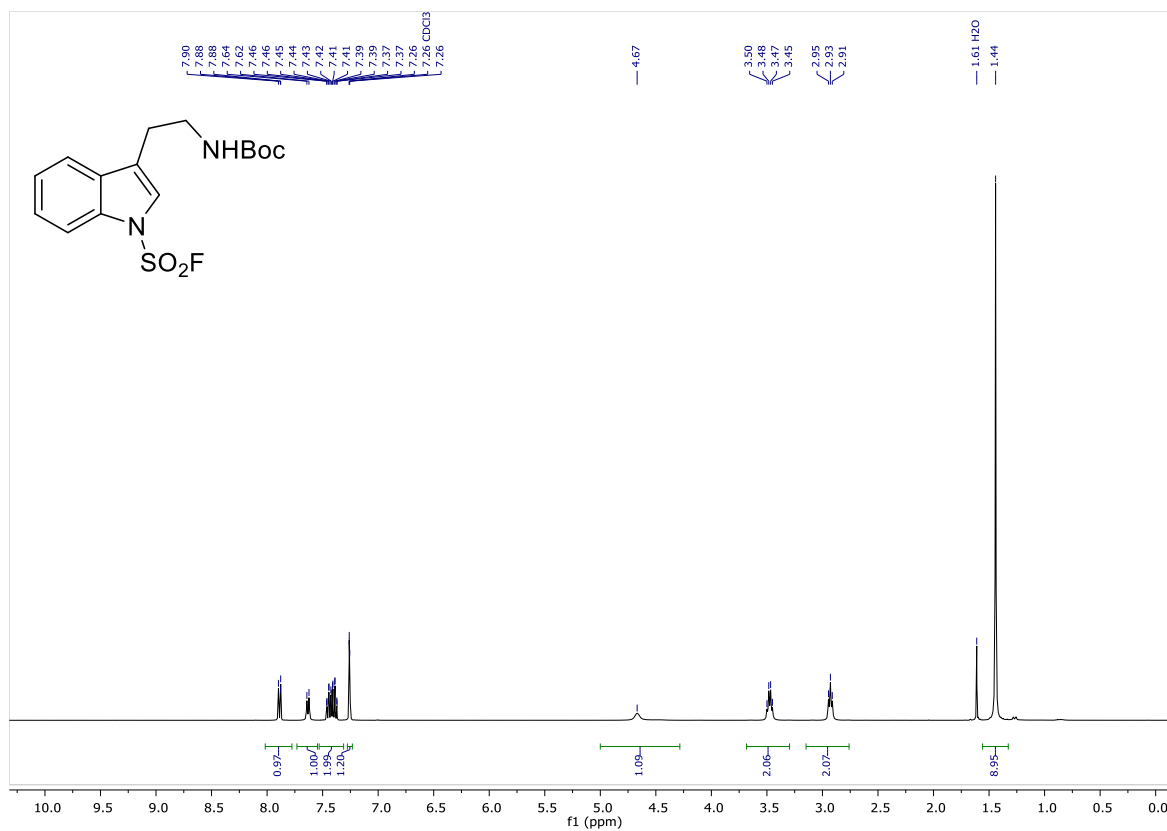
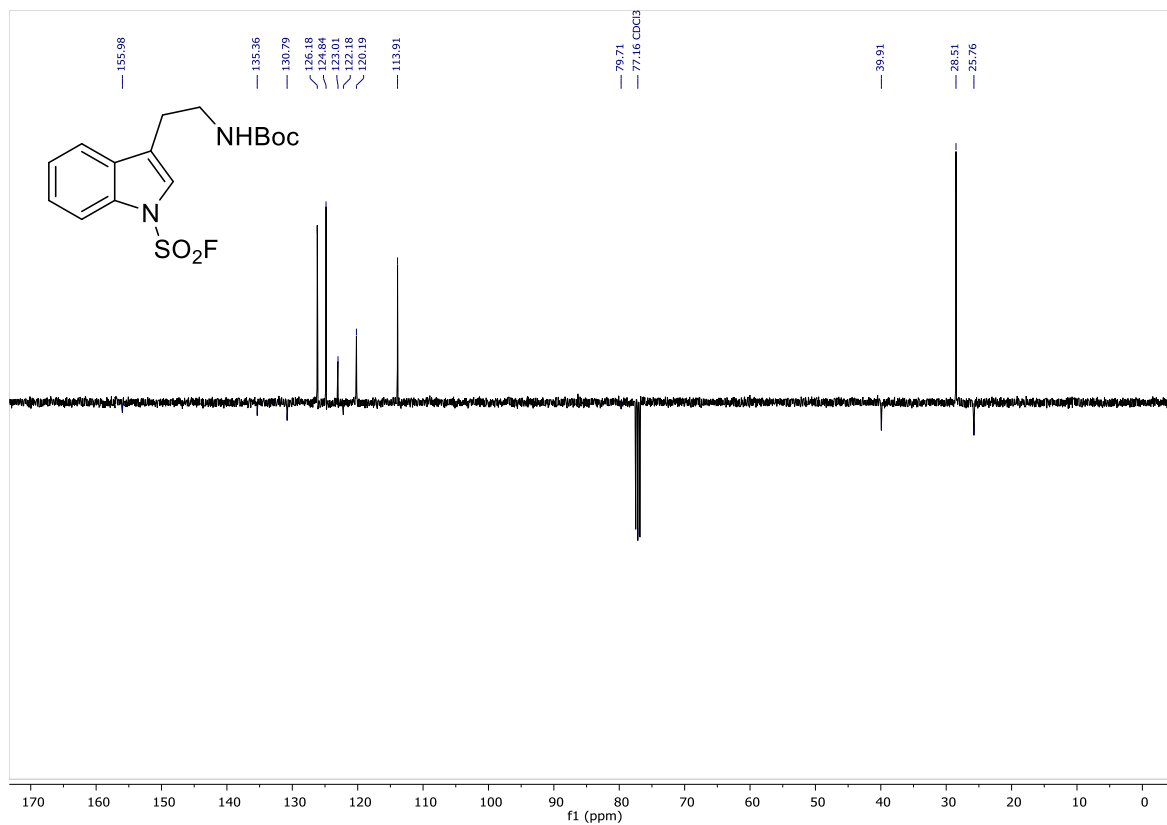
^{19}F NMR (376 MHz, CDCl_3)



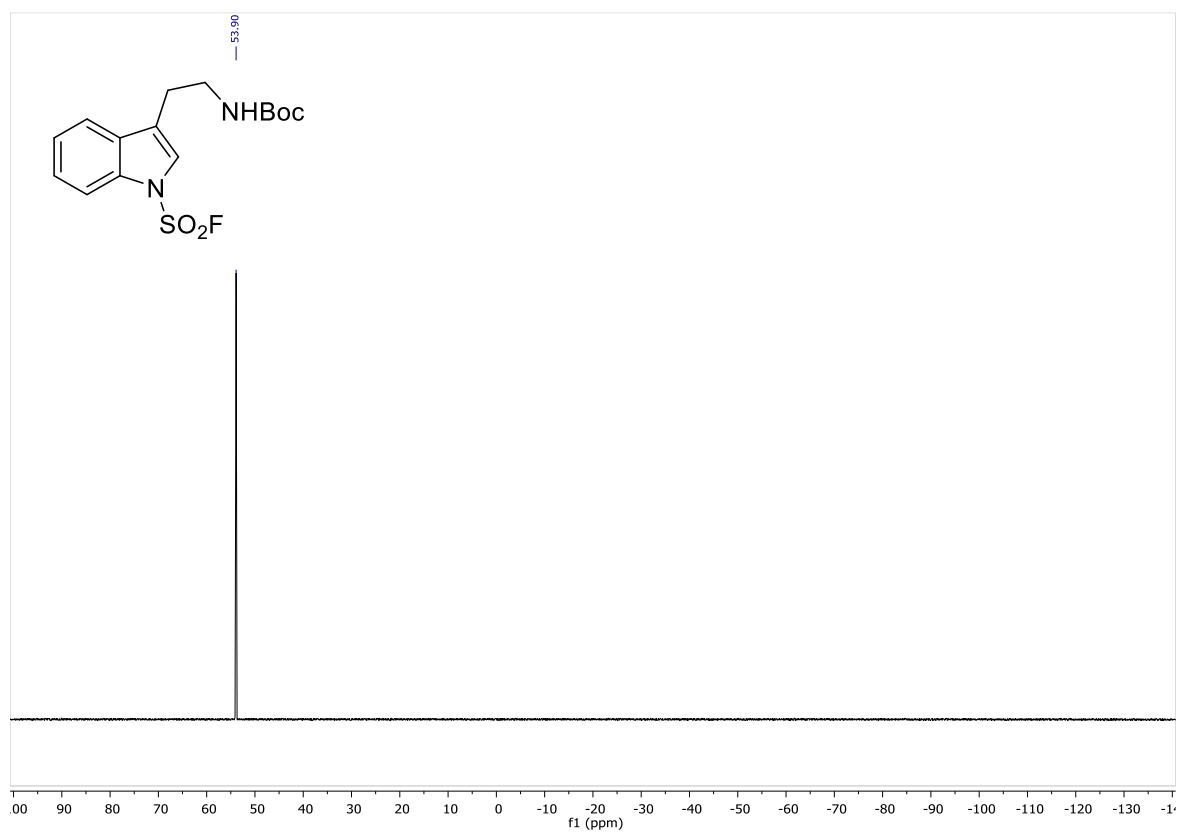
4-(2-Chlorodibenzo[b,f][1,4]oxazepin-11-yl)piperazine-1-sulfonyl fluoride (13k)¹H NMR (400 MHz, CDCl₃)¹³C {¹H} NMR (101 MHz, CDCl₃)

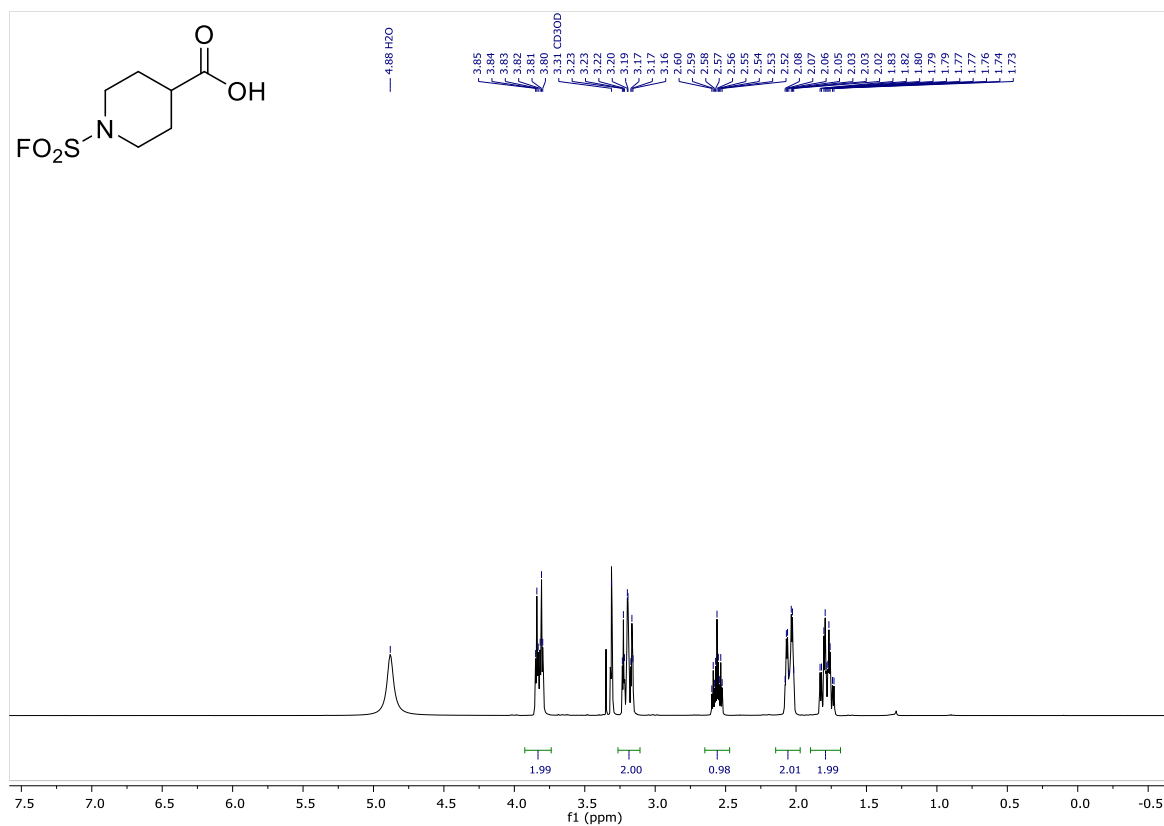
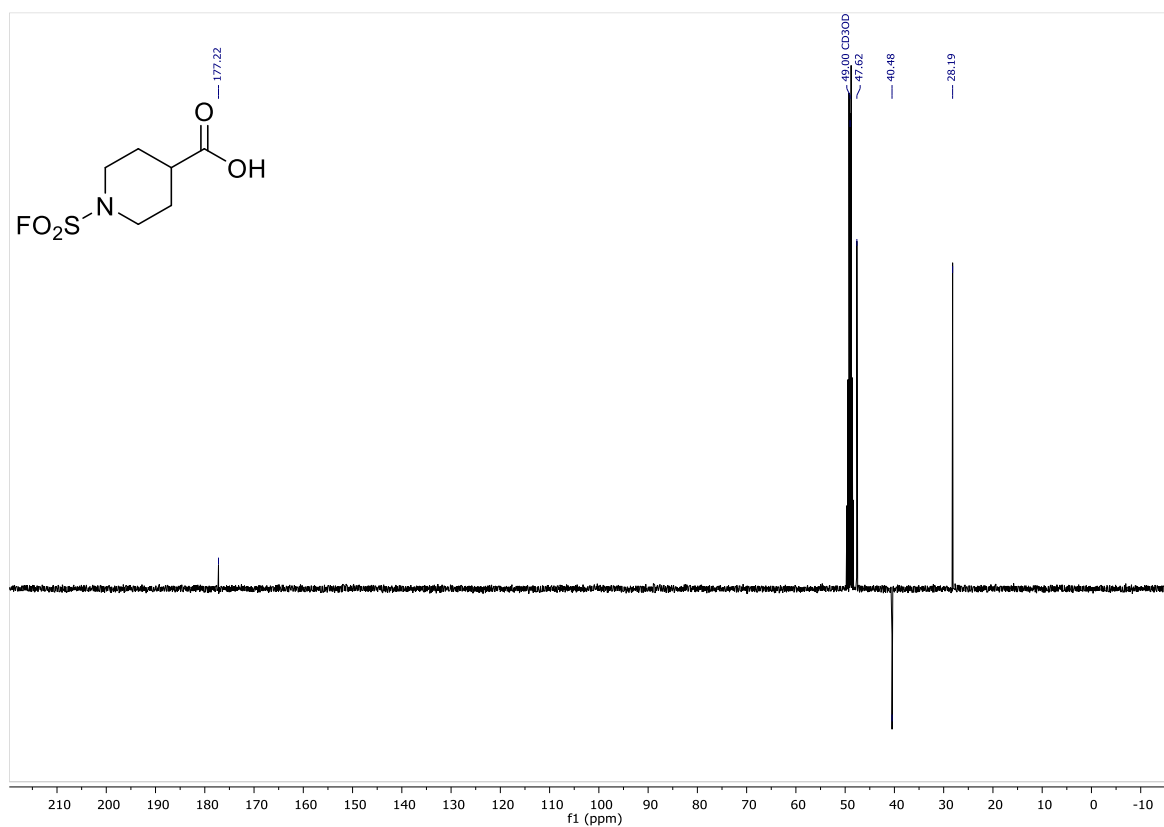
^{19}F NMR (376 MHz, CDCl_3)



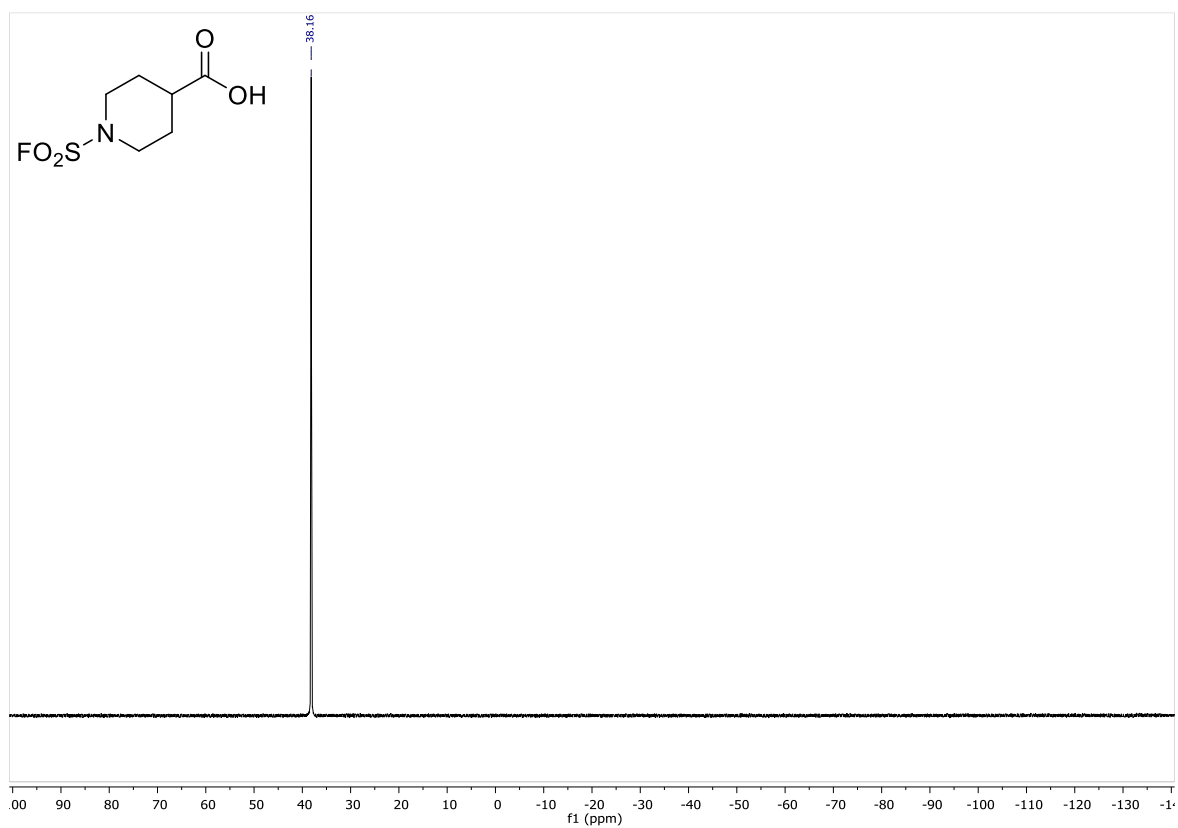
***tert*-Butyl {2-[1-(fluorosulfonyl)-1*H*-indol-3-yl]ethyl}carbamate (13l)**¹H NMR (400 MHz, CDCl₃)¹³C {¹H} NMR (101 MHz, CDCl₃)

^{19}F NMR (376 MHz, CDCl_3)



1-(Fluorosulfonyl)piperidine-4-carboxylic acid (13m) ^1H NMR (400 MHz, CD_3OD) $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CD_3OD)

^{19}F NMR (376 MHz, CD_3OD)



Supporting Information for

Arylsulfamoyl [^{18}F]Fluorides: Preparation via Base-free SuFEx ^{18}F -Fluorination and Assessment of their Applicability as Potential PET Tracers

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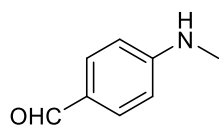
* correspondence: b.neumaier@fz-juelich.de

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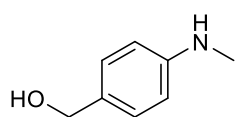
Further syntheses

Preparation of 4-(methylamino)benzaldehyde (S1)



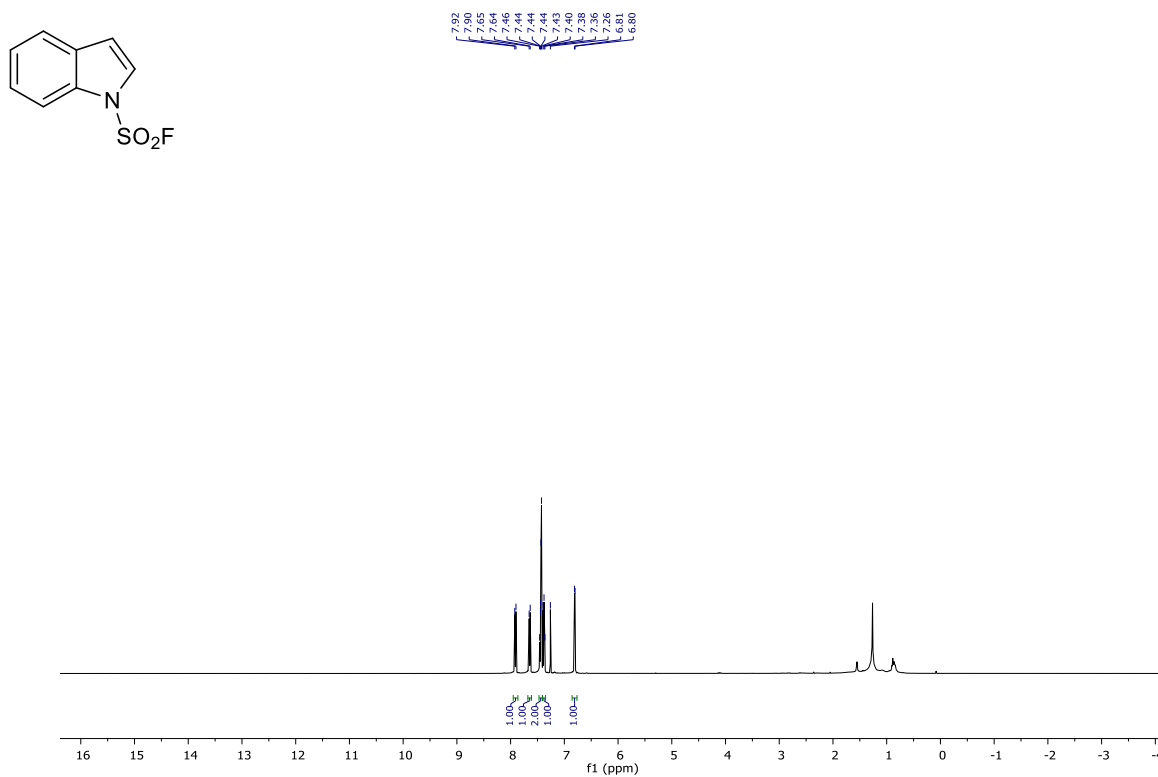
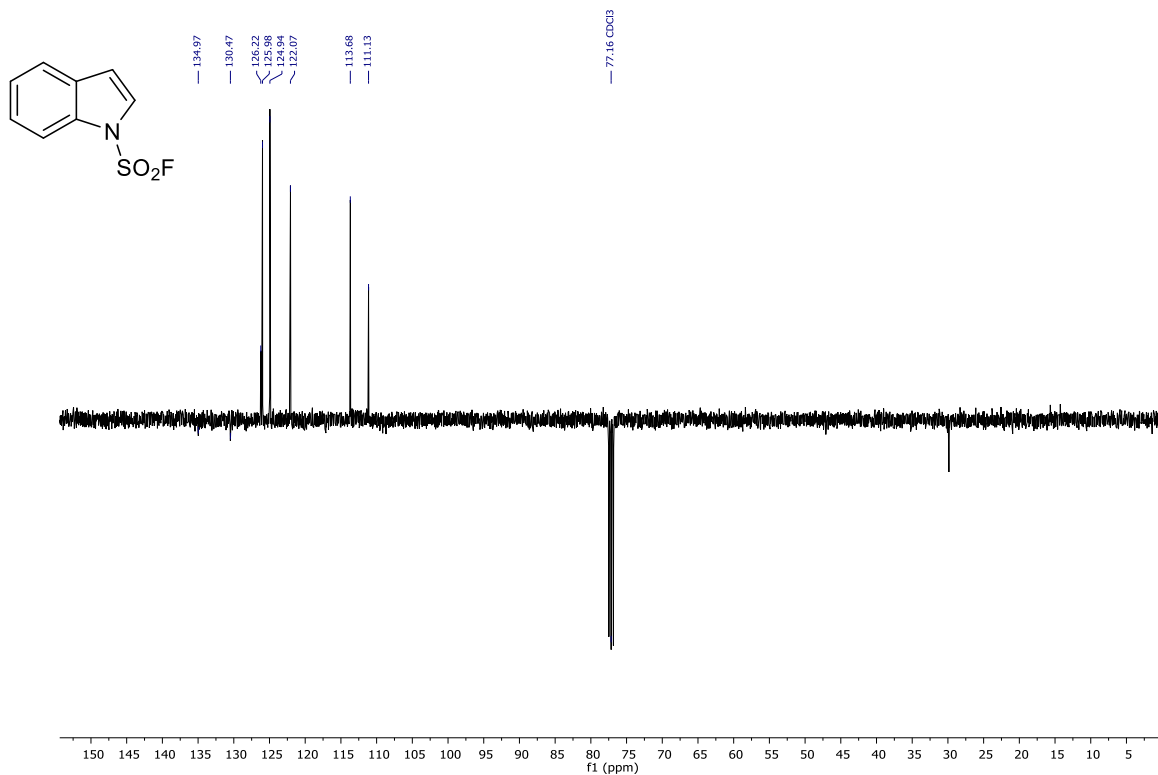
4-bromobenzaldehyde (9.25 g, 50.0 mmol, 1.0 eq.) and copper powder (159 mg, 2.5 mmol, 0.05 eq.) were added to a PTFE reaction flask and suspended in a solution of 40% MeNH₂ in H₂O (43.2 mL, 500 mmol, 10.0 eq.). The flask was placed in a high-pressure steel container and the reaction mixture was stirred for 48 h at 120 °C. After cooling to 23 °C, EtOAc (40 mL) was added and the aqueous phase was extracted with EtOAc (3×50 mL). The organic phase was dried and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (*n*-hexane:EtOAc/1:1.5, TLC: *R_f* = 0.48) to afford the title compound as a yellow solid (5.26 g, 38.9 mmol, 78%). C₈H₉NO (135.17 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 9.71 (s, 1H), 7.78 – 7.55 (m, 2H), 6.74 – 6.50 (m, 2H), 4.61 (bs, 1H), 2.90 (s, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 190.45, 154.42, 132.39, 126.36, 111.55, 30.08. ESI-MS *m/z*: [M+H]⁺ Calcd for C₈H₁₀NO 136.08; Found: 136.19.

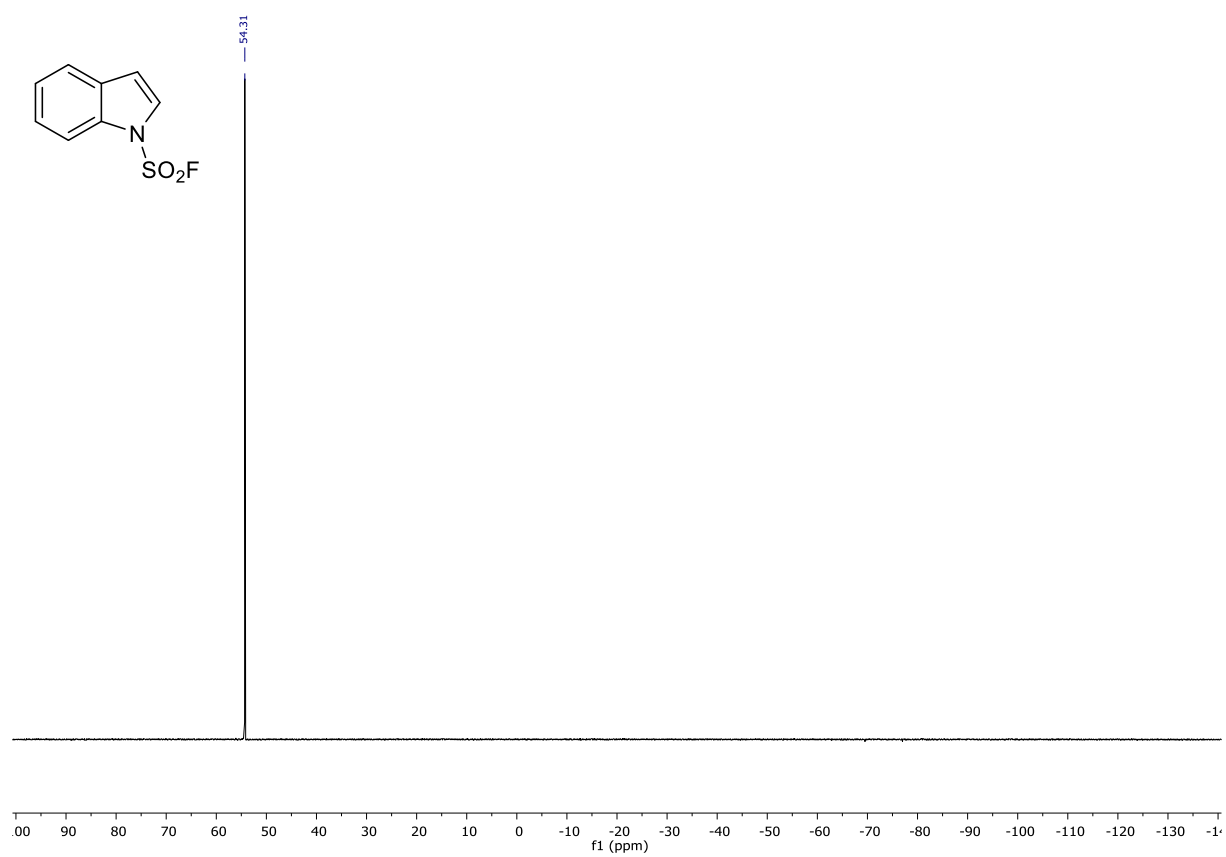
Preparation of (4-(methylamino)phenyl)methanol (S2)

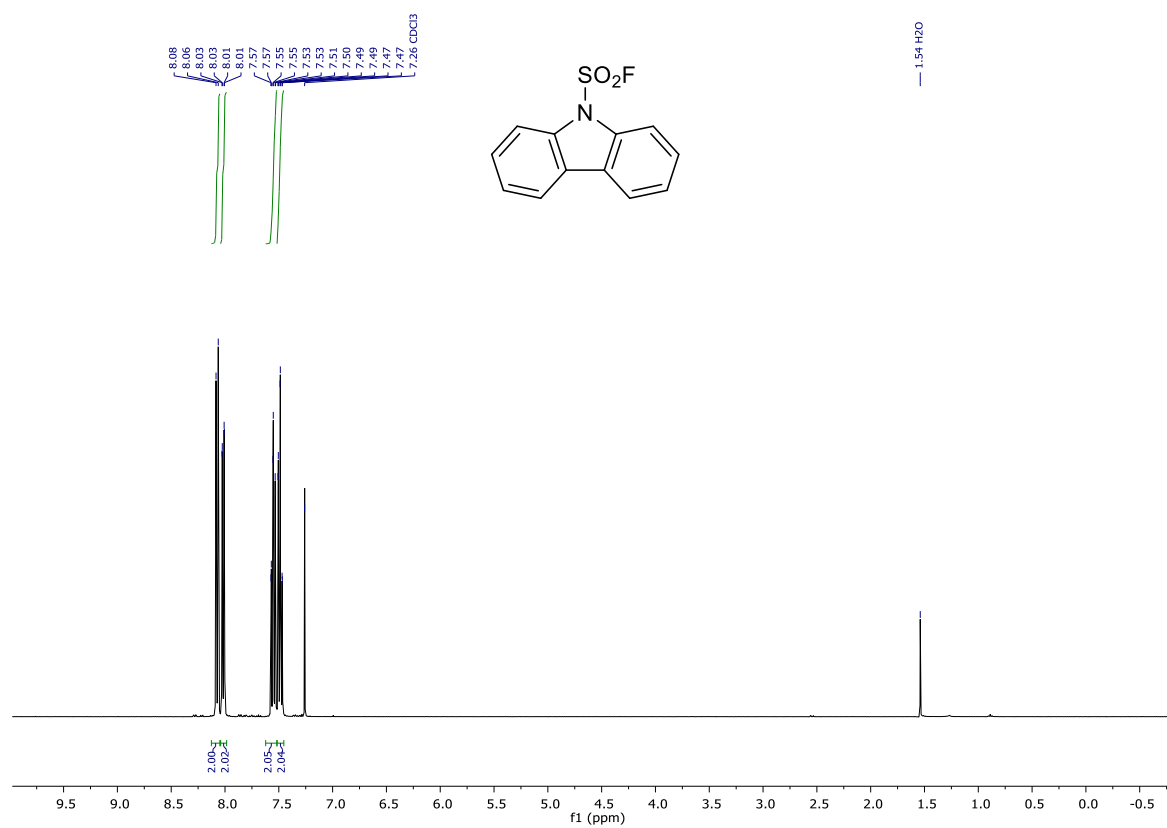
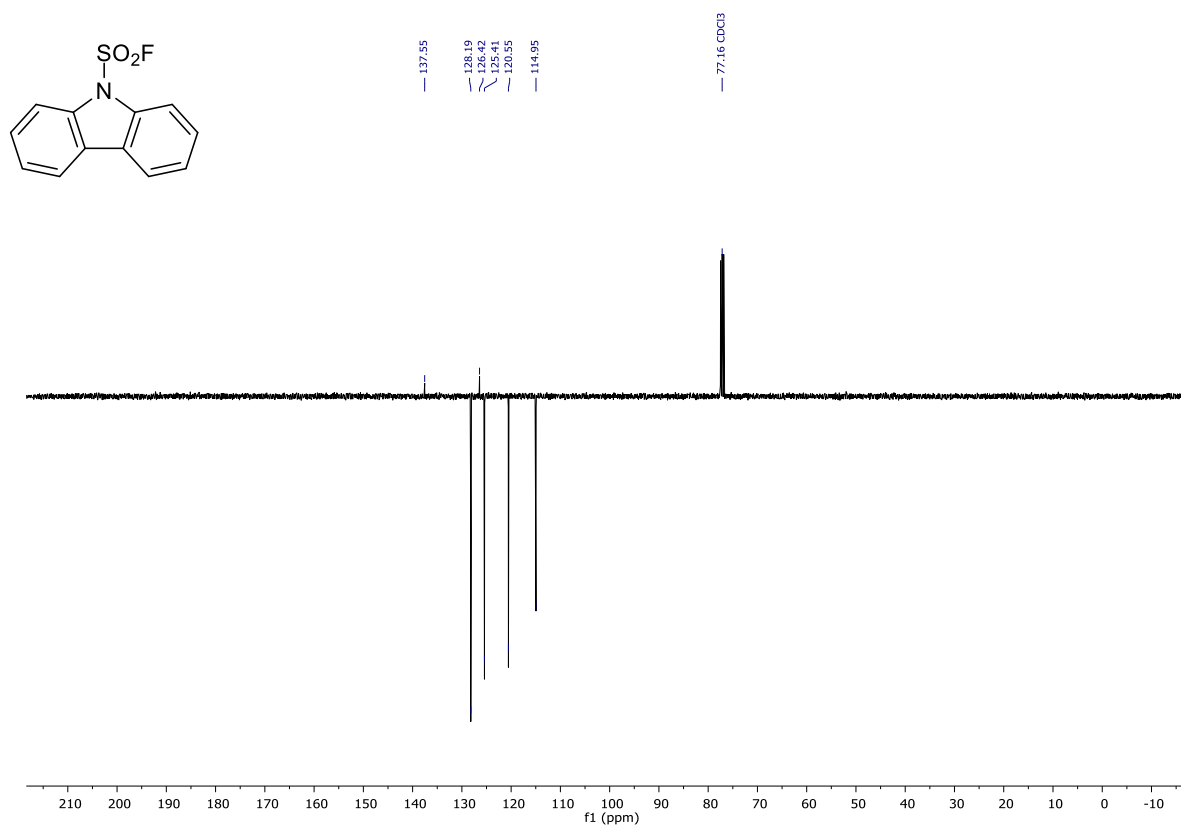


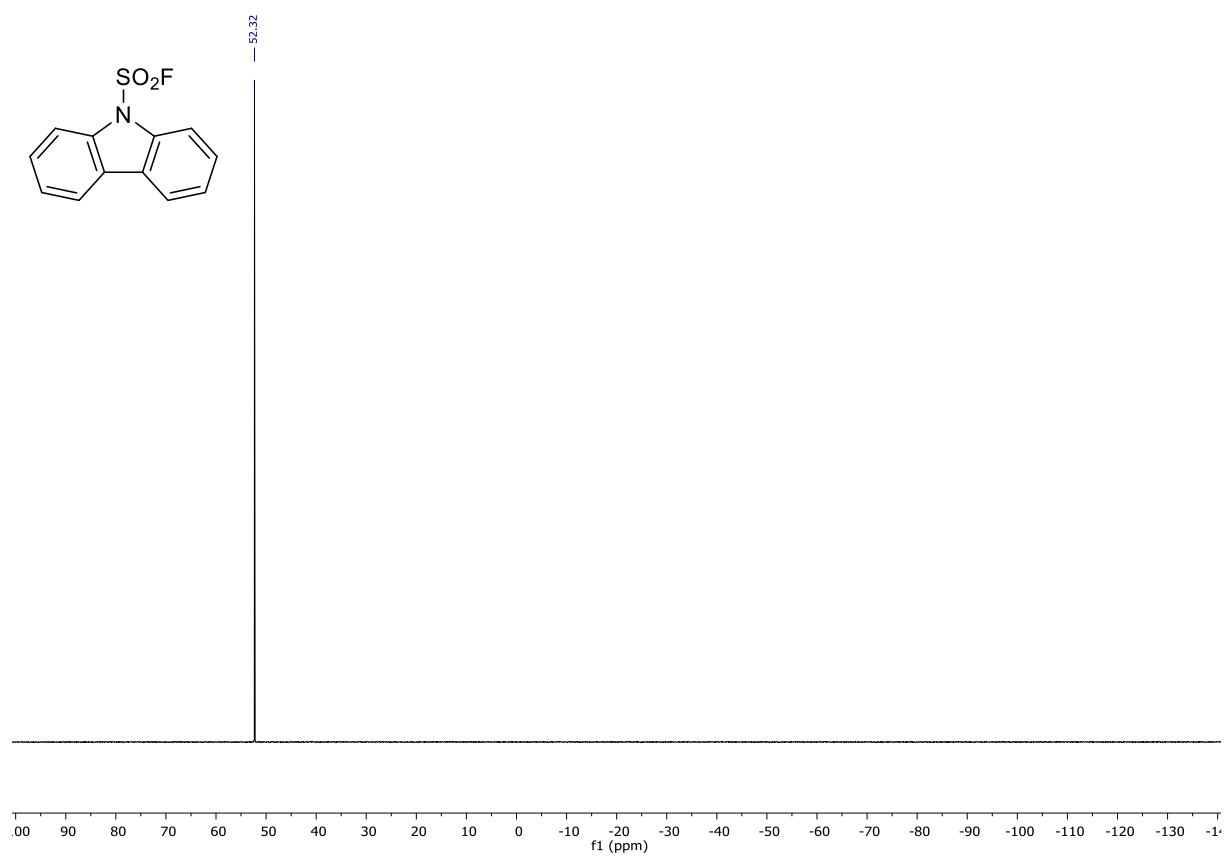
NaBH₄ (1.40 g, 37.0 mmol, 2.5 eq.) was added to an ice-cooled solution of 4-(methylamino)benzaldehyde (2.00 g, 14.8 mmol, 1.0 eq) in MeOH (50 mL) and the mixture was stirred for 3 h at 0 °C and 1 h at 23 °C. The solvent was removed under reduced pressure, the residue was taken up in H₂O (50 mL) and the aqueous phase was extracted with EtOAc (3×50 mL). The organic phase was dried and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (*n*-hexane:EtOAc/1:1, TLC: *R_f* = 0.32) to afford the title compound as a colorless solid (1.86 g, 13.6 mmol, 92%). C₈H₁₁NO (137.18 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 7.24 – 7.15 (m, 2H), 6.65 – 6.55 (m, 2H), 4.54 (s, 2H), 2.83 (s, 3H). (-OH was not detected) ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 149.16, 129.79, 128.90, 112.51, 65.47, 30.87. ESI-MS *m/z*: [M+H]⁺ Calcd for C₈H₁₂NO 138.09; Found: 138.19.

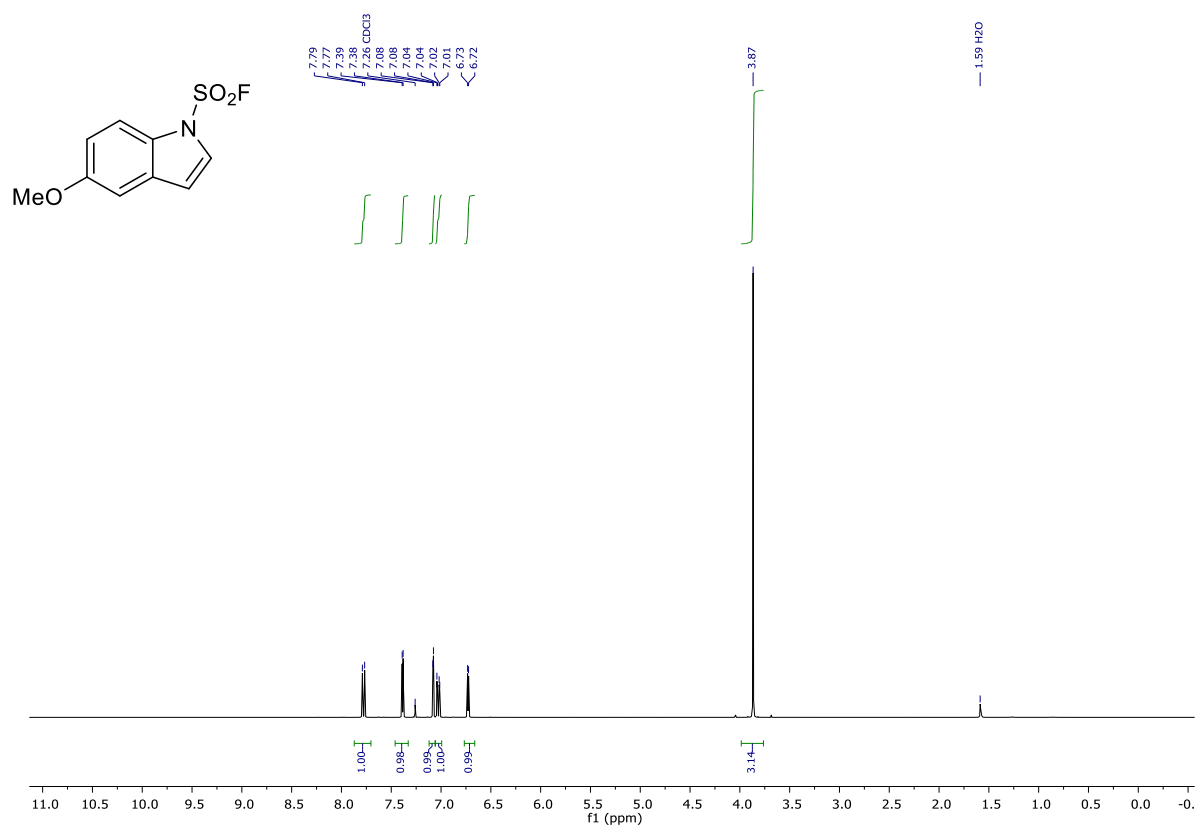
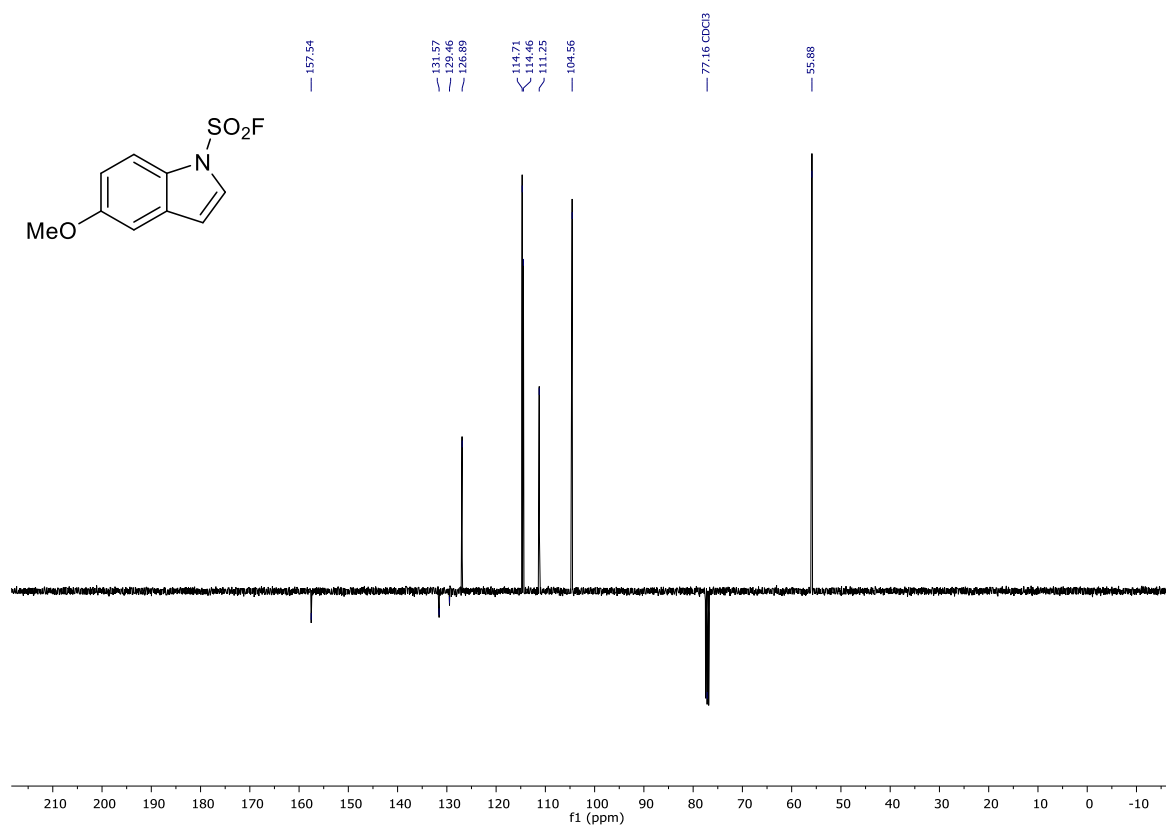
NMR spectra

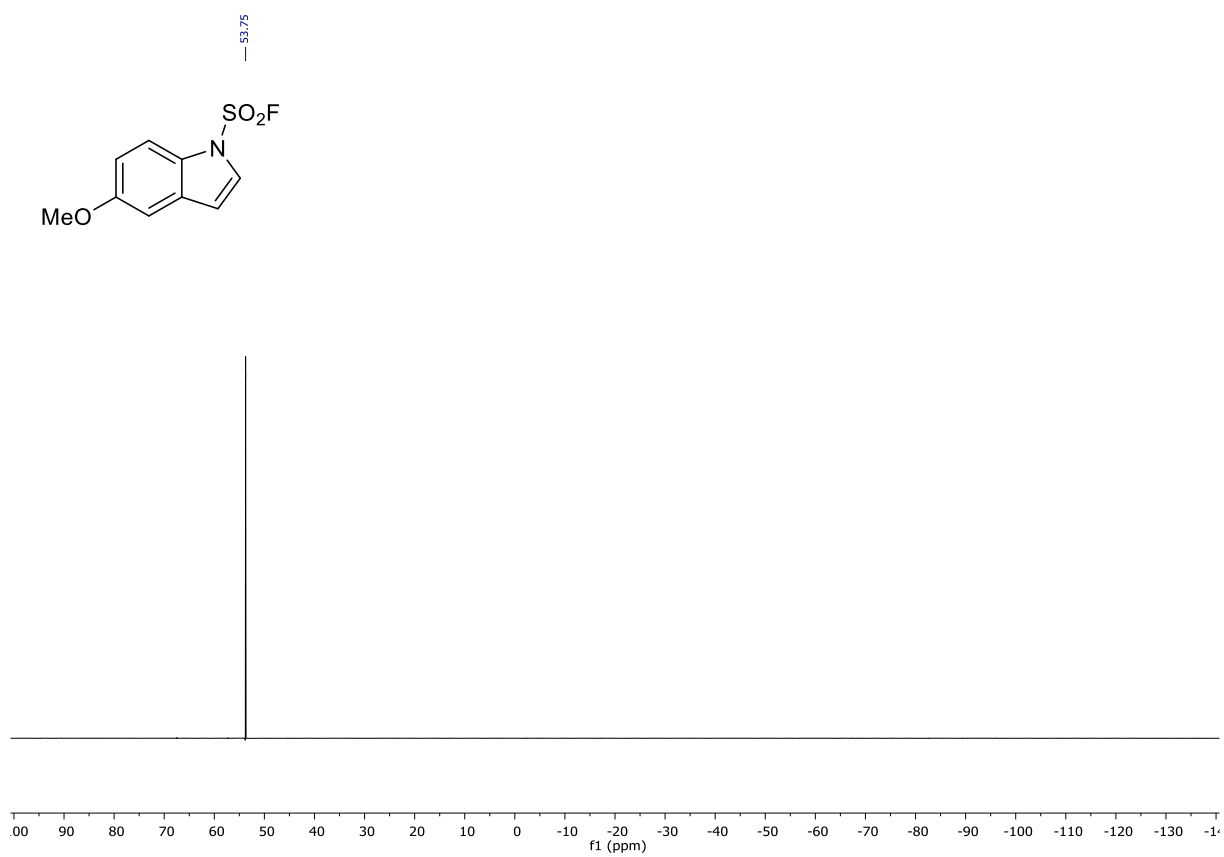
1*H*-Indole-1-sulfonyl fluoride (6)¹H NMR¹³C{¹H} NMR

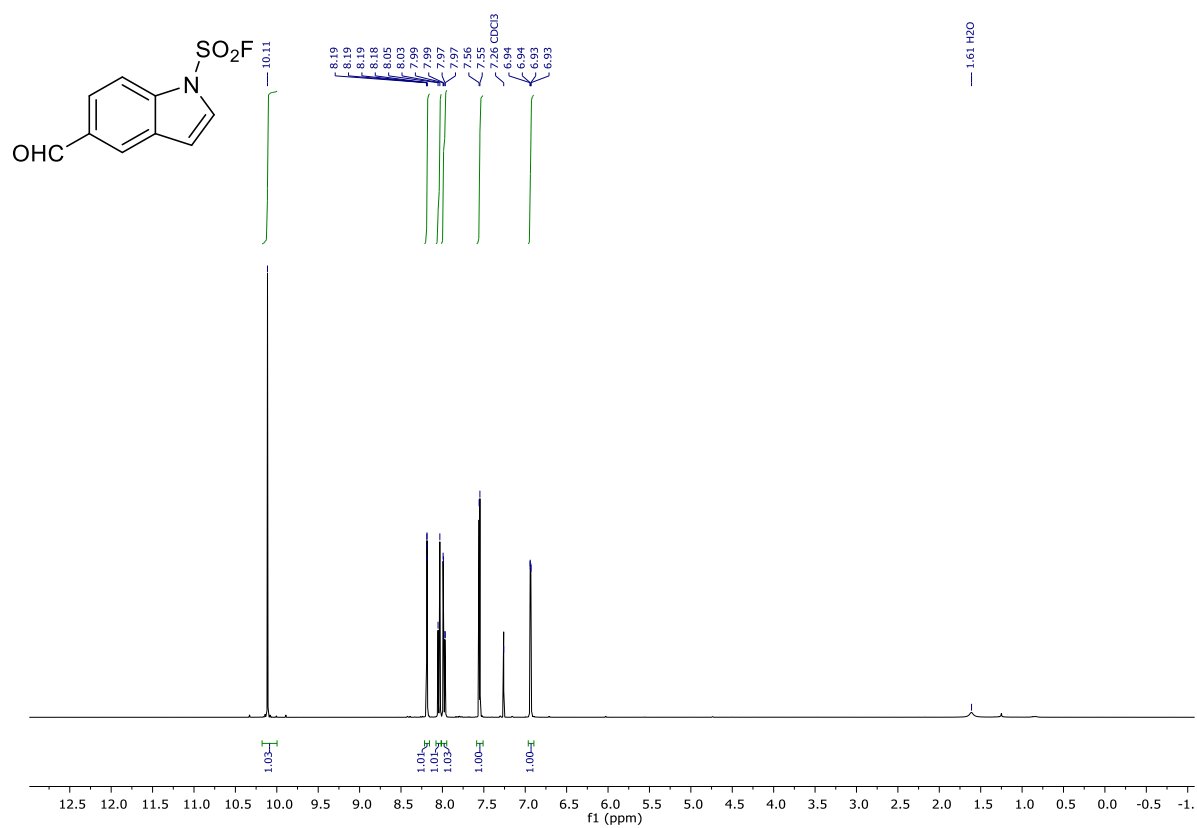
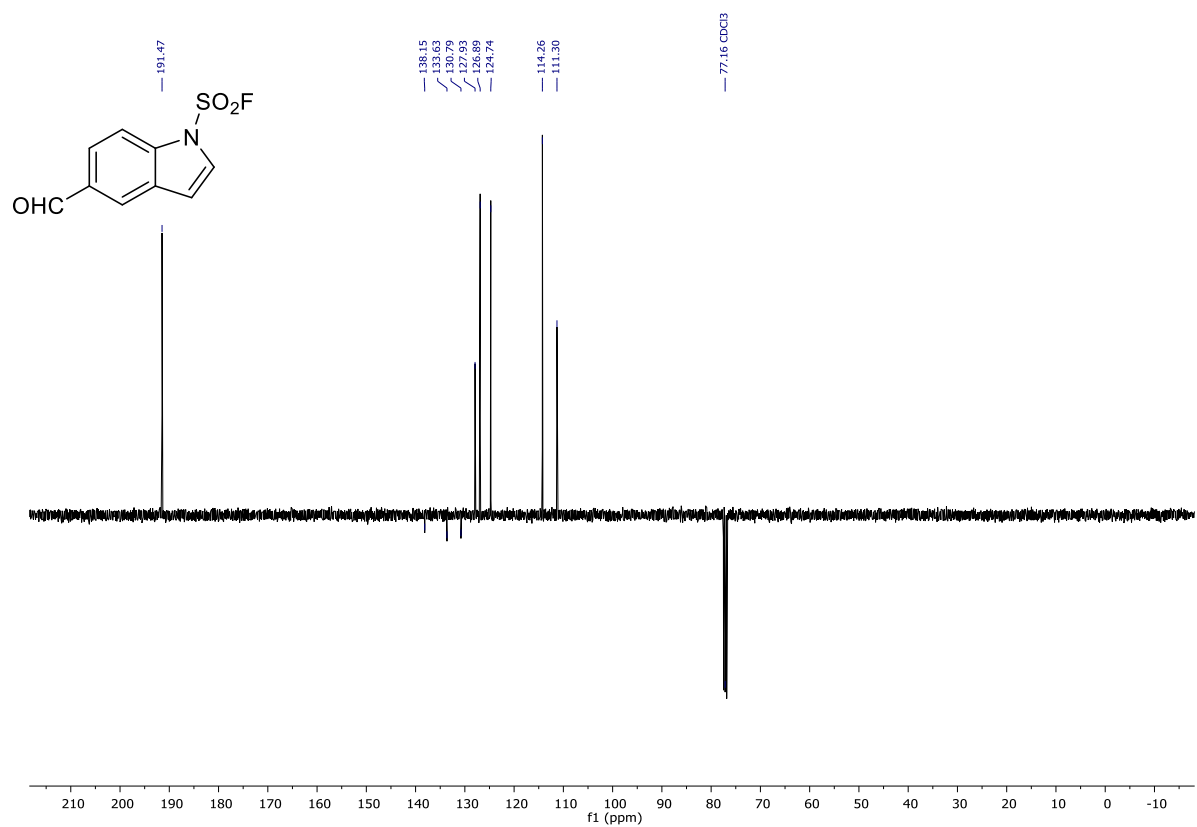
^{19}F NMR

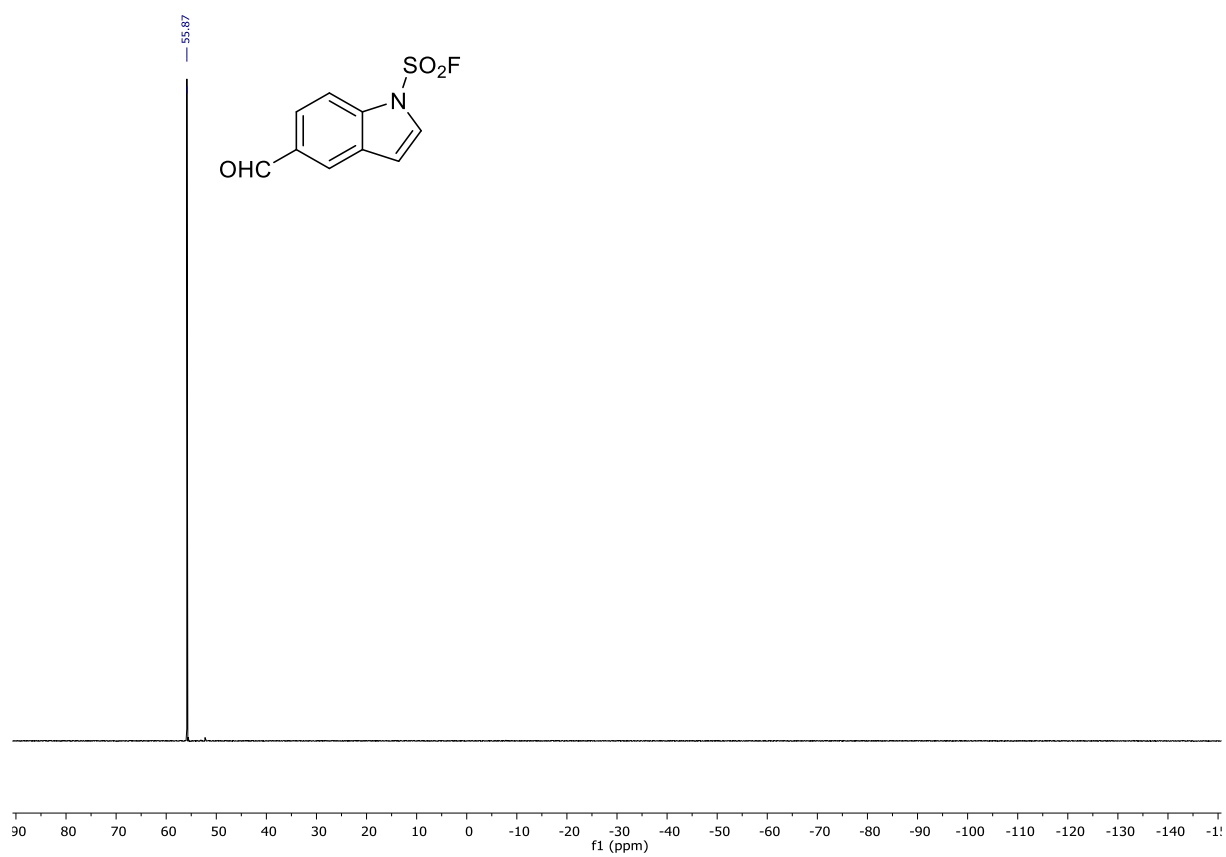
9*H*-Carbazole-9-sulfonyl fluoride (**5**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

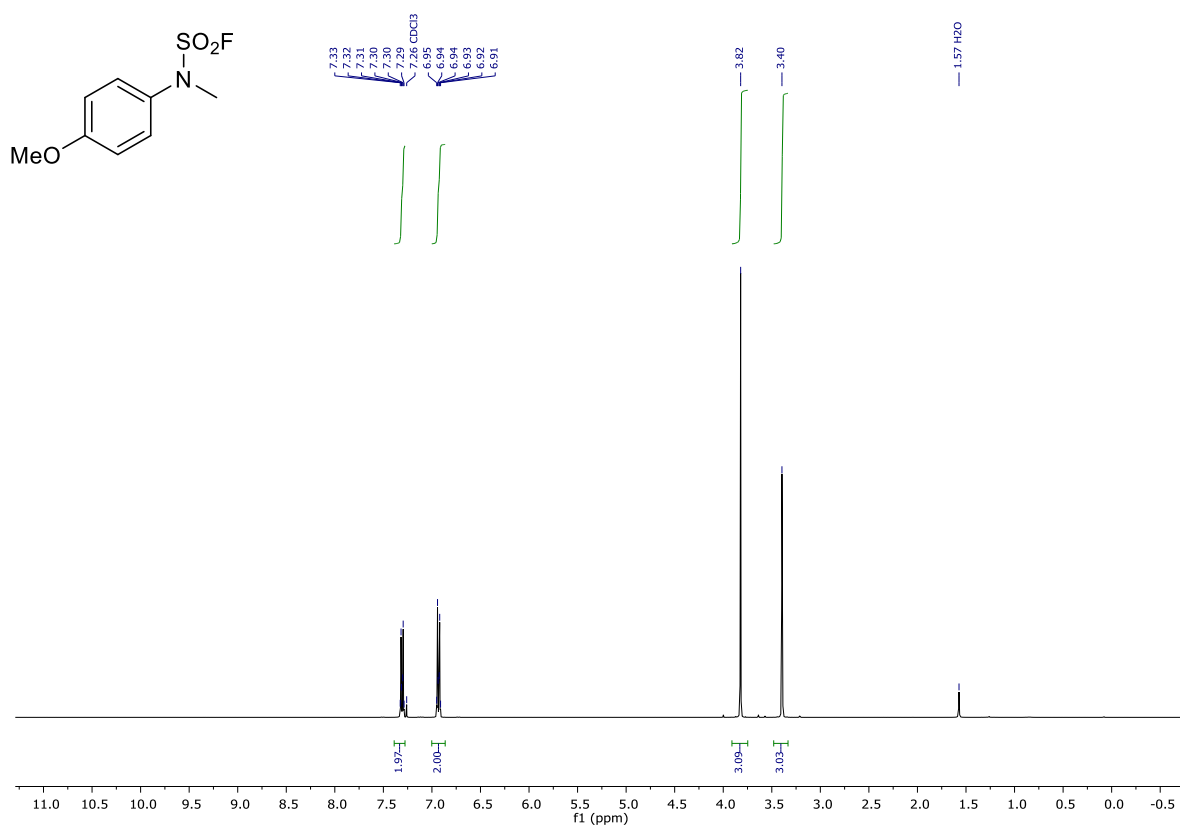
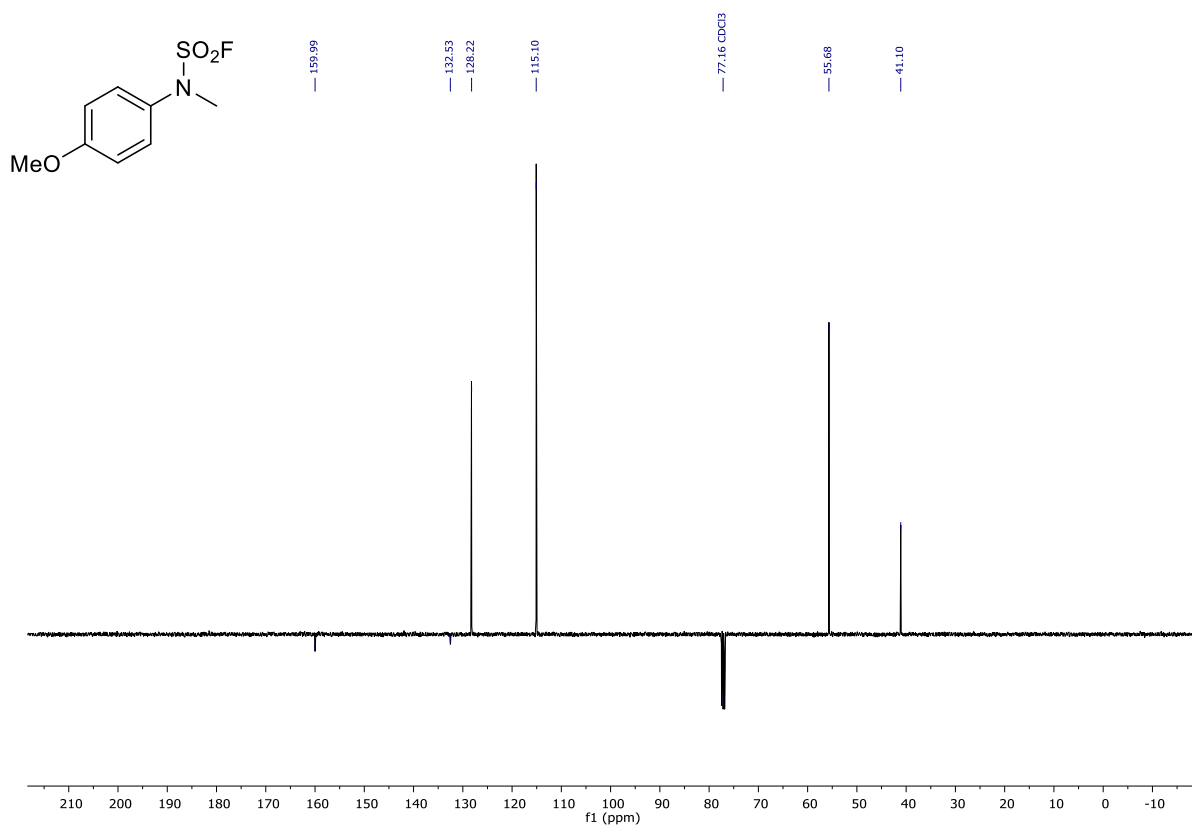
^{19}F NMR

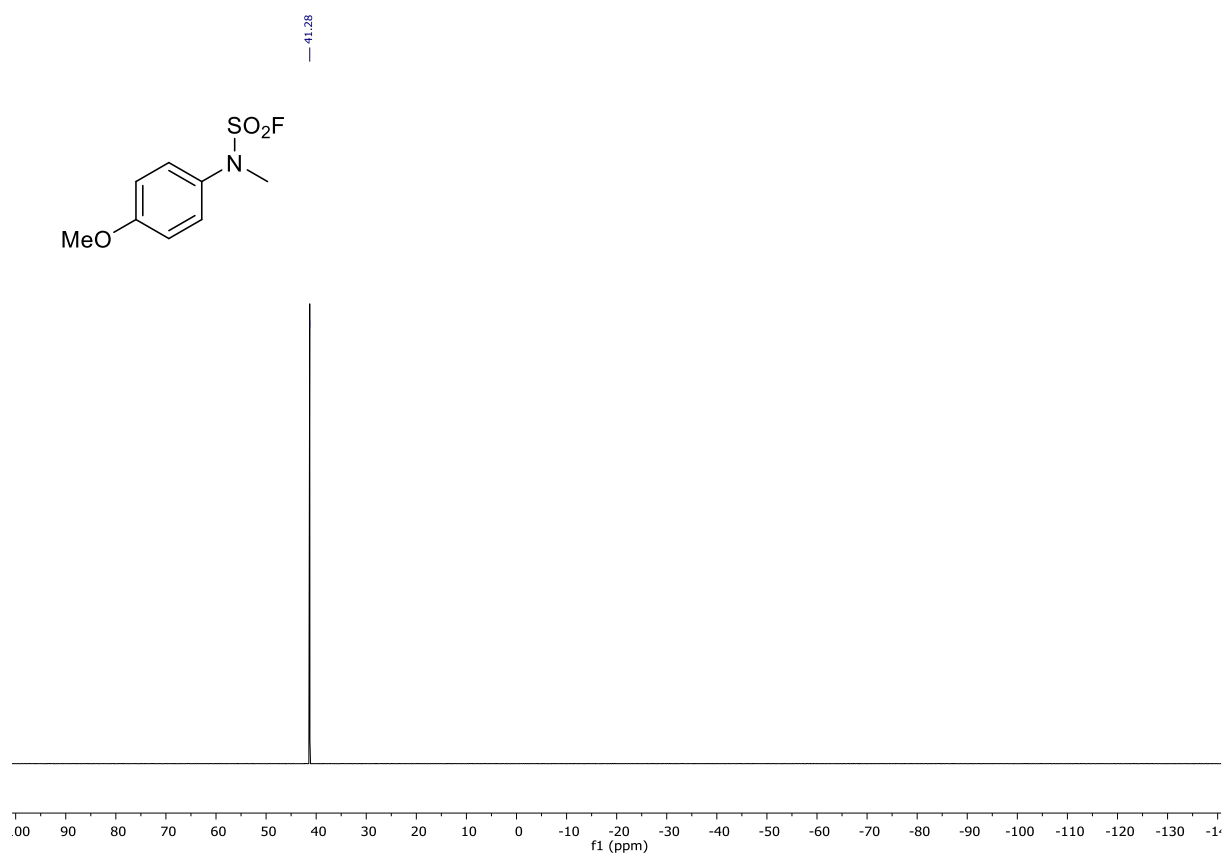
5-Methoxy-1*H*-indole-1-sulfonyl fluoride (7) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

^{19}F NMR

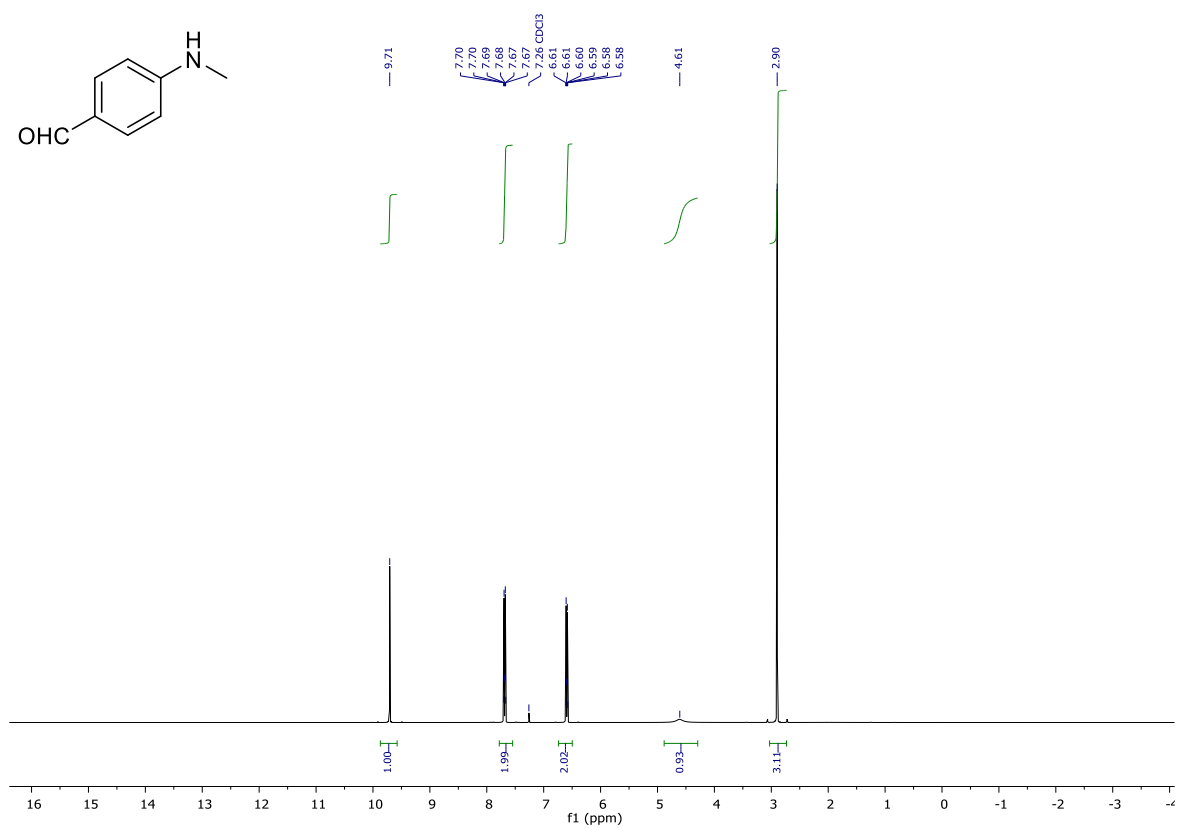
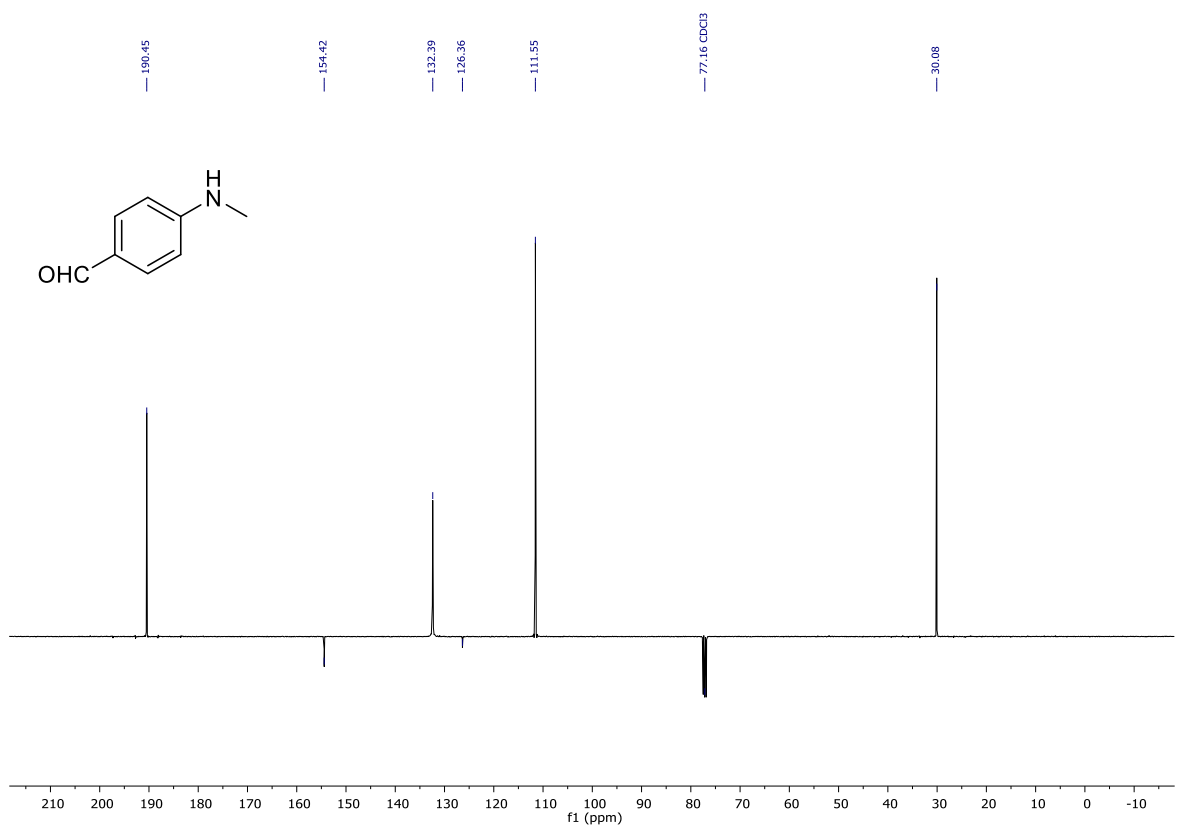
5-Formyl-1*H*-indole-1-sulfonyl fluoride (**8**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

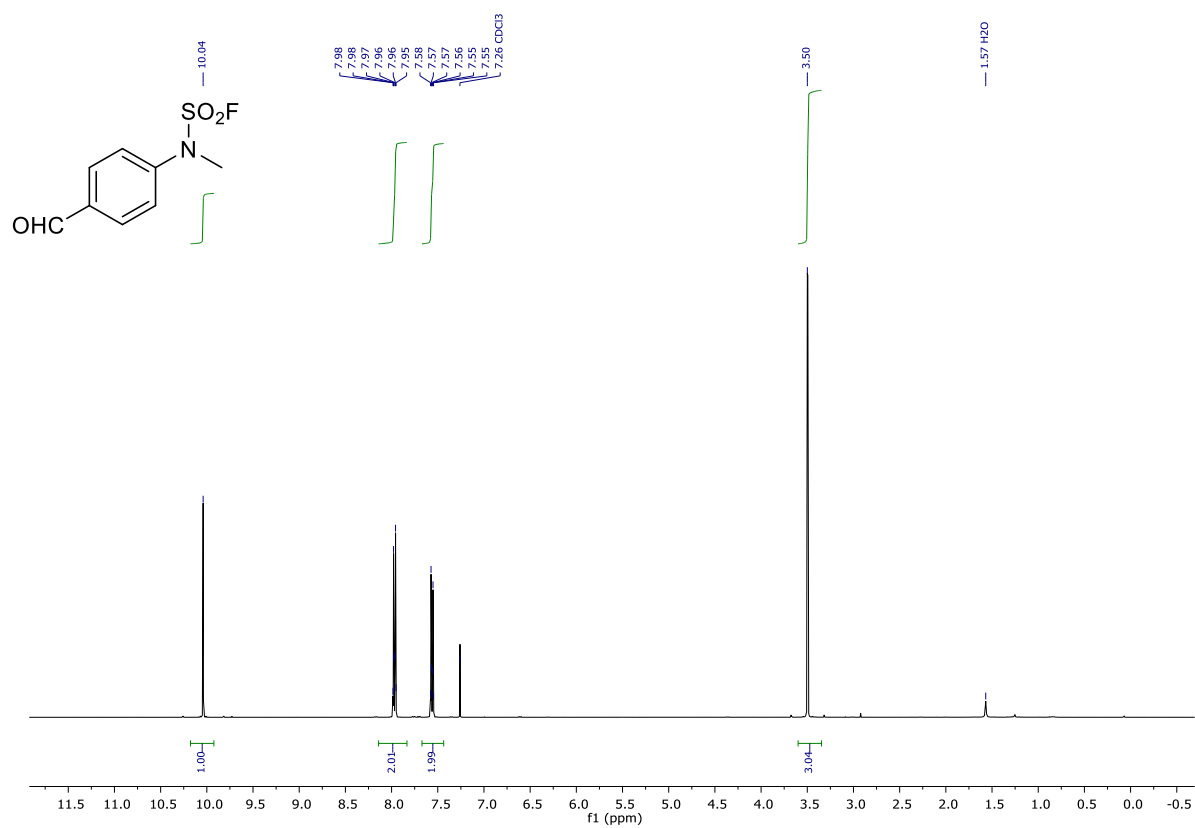
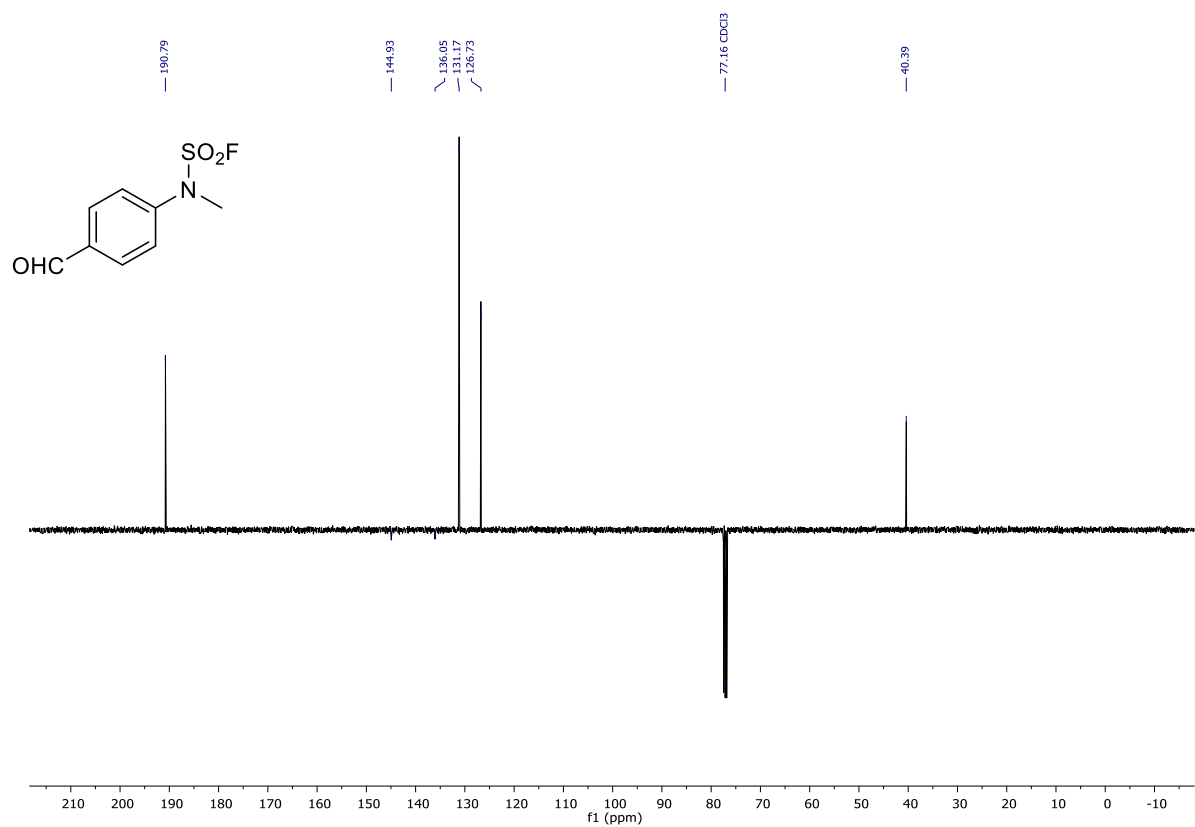
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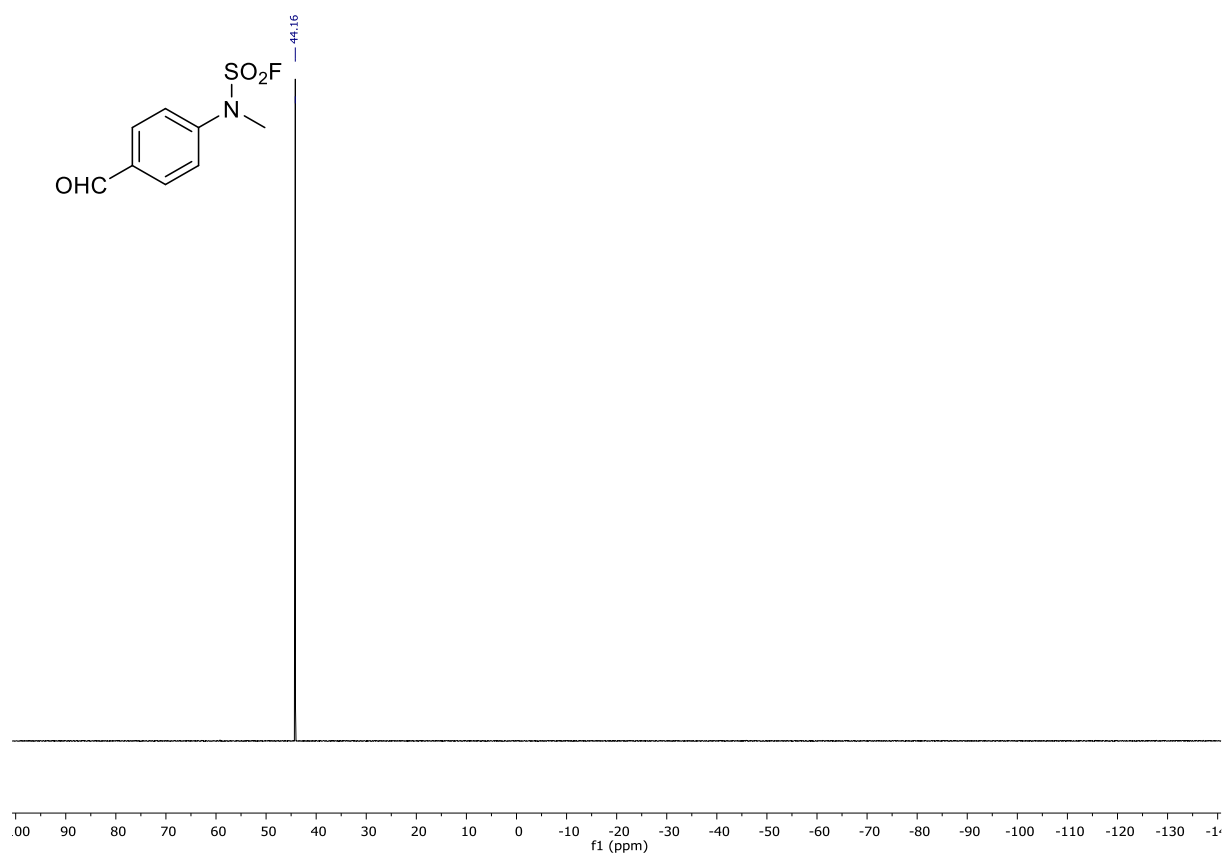
(4-Methoxyphenyl)(methyl)sulfamoyl fluoride (**10**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

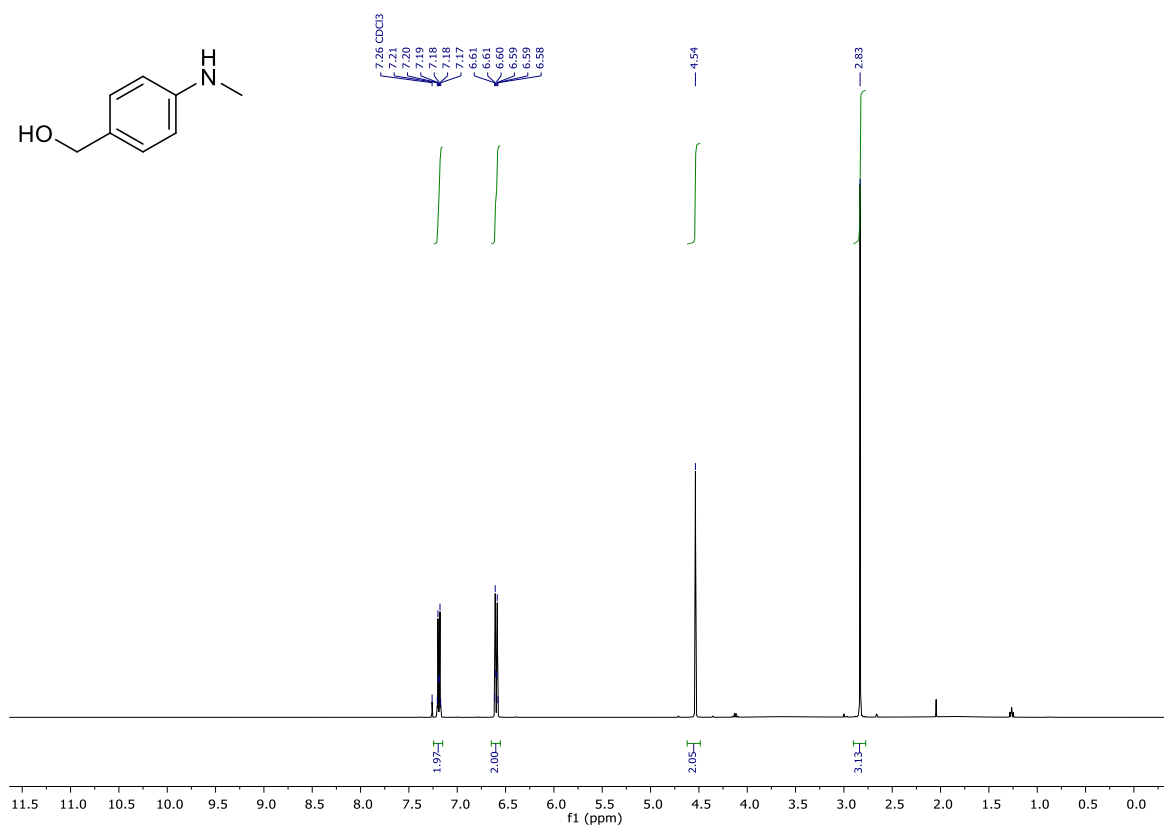
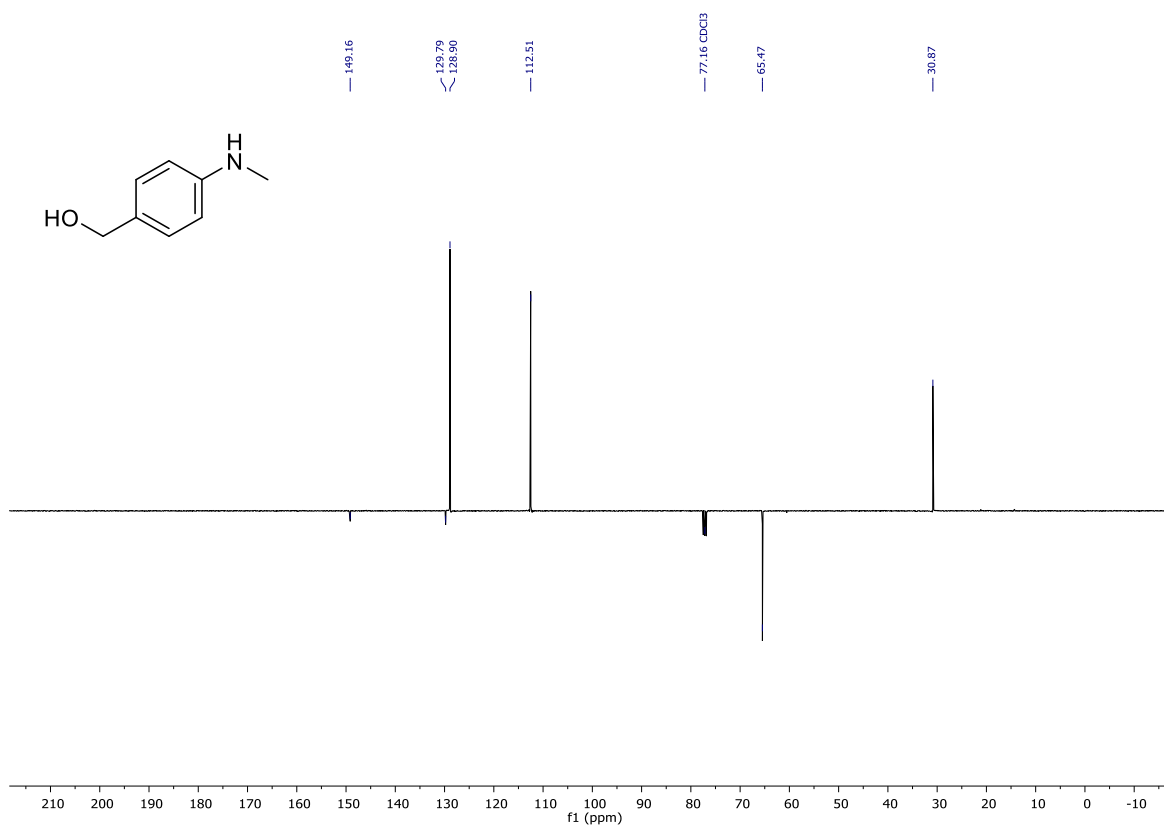
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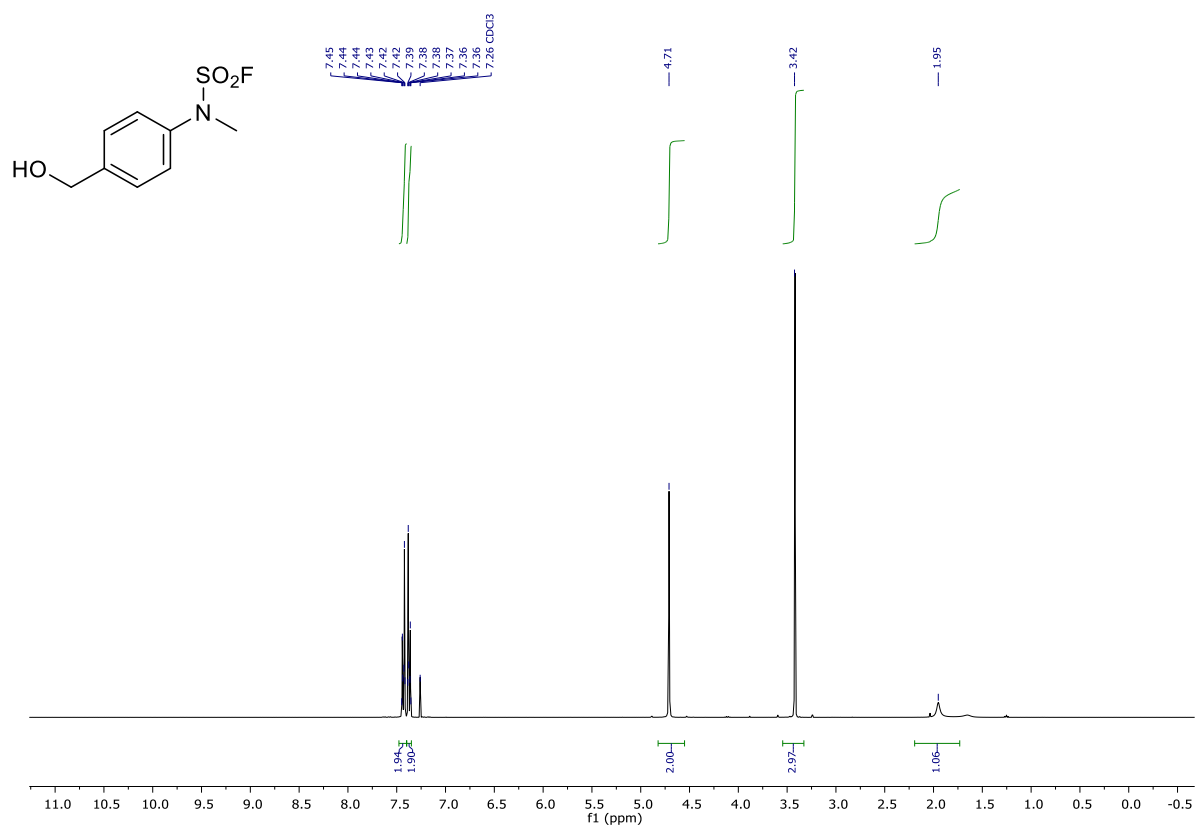
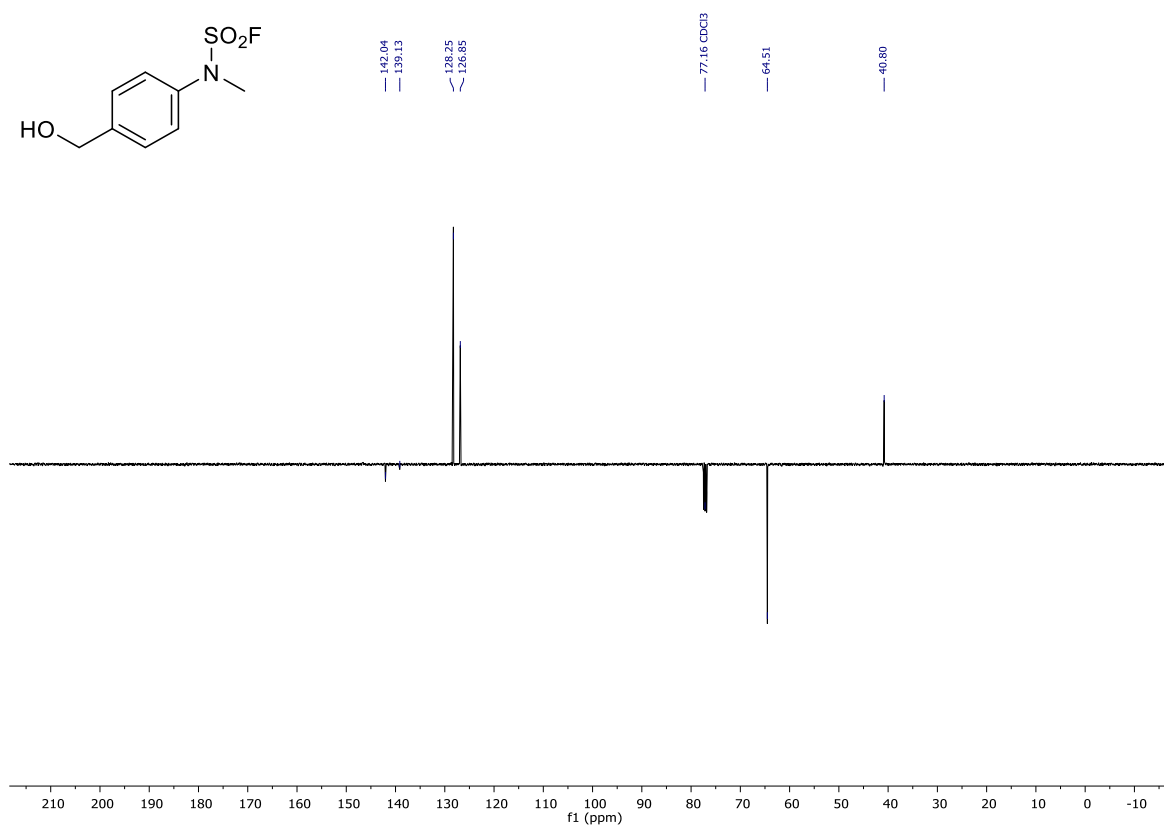
4-(Methylamino)benzaldehyde (S1)

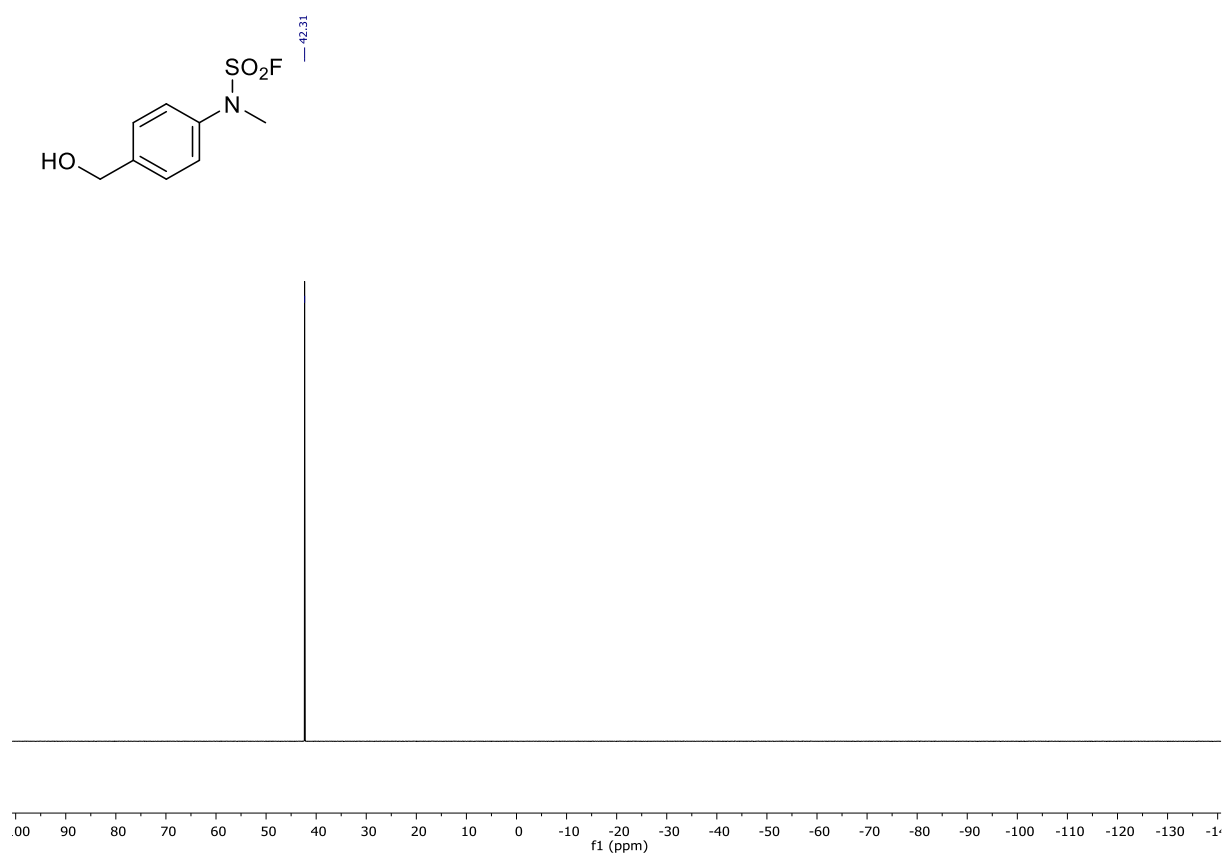
 ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

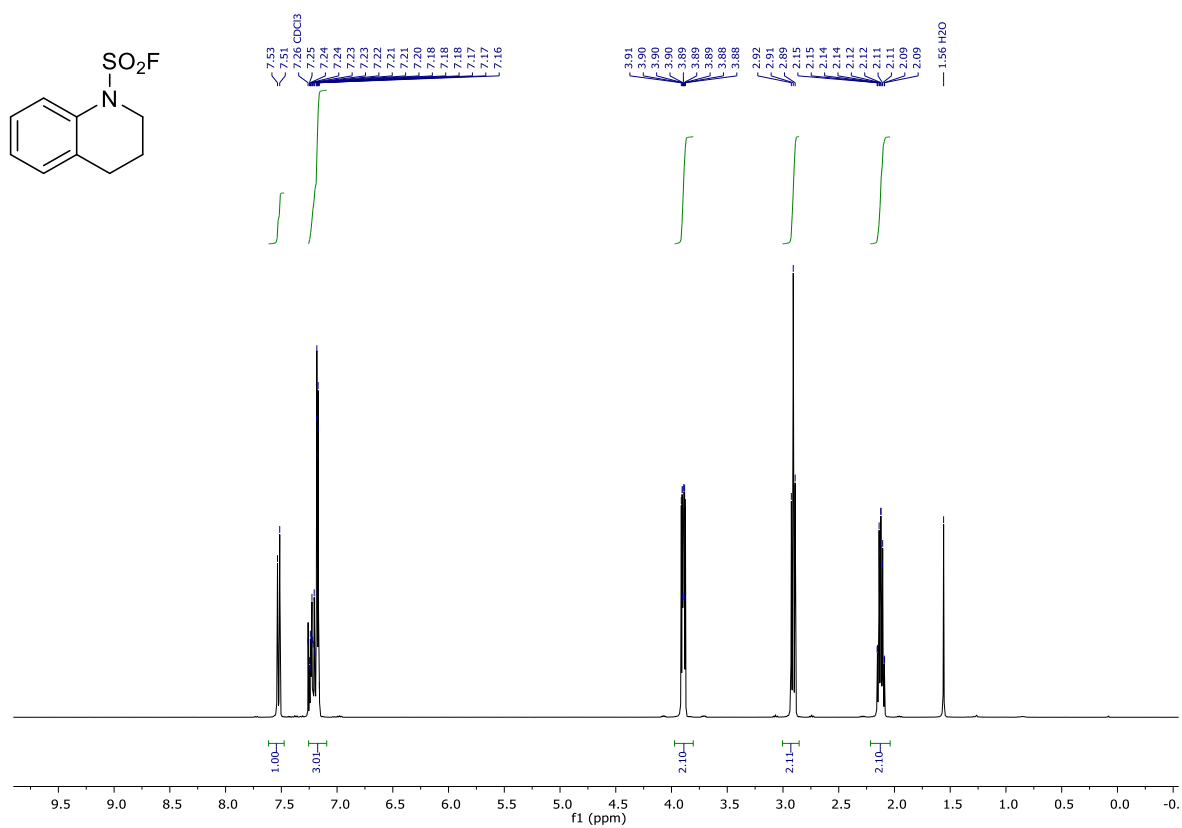
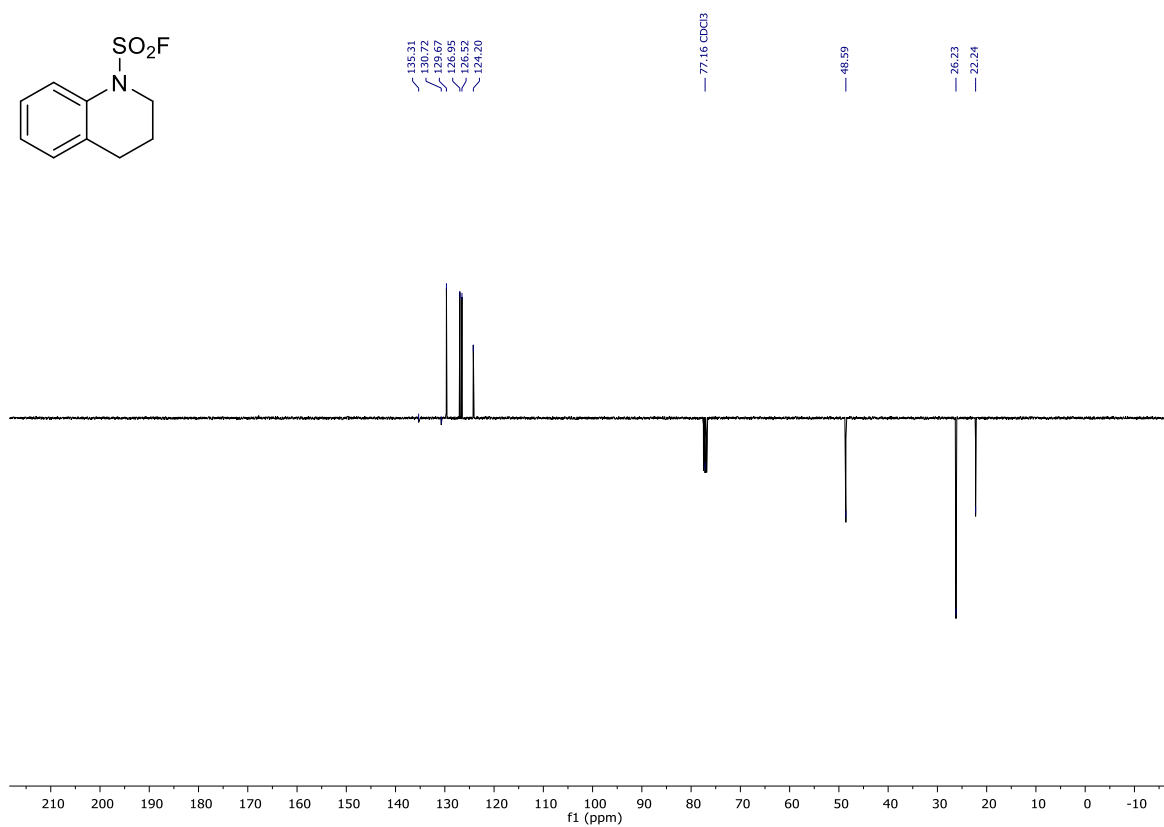
(4-Formylphenyl)(methyl)sulfamoyl fluoride (**12**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

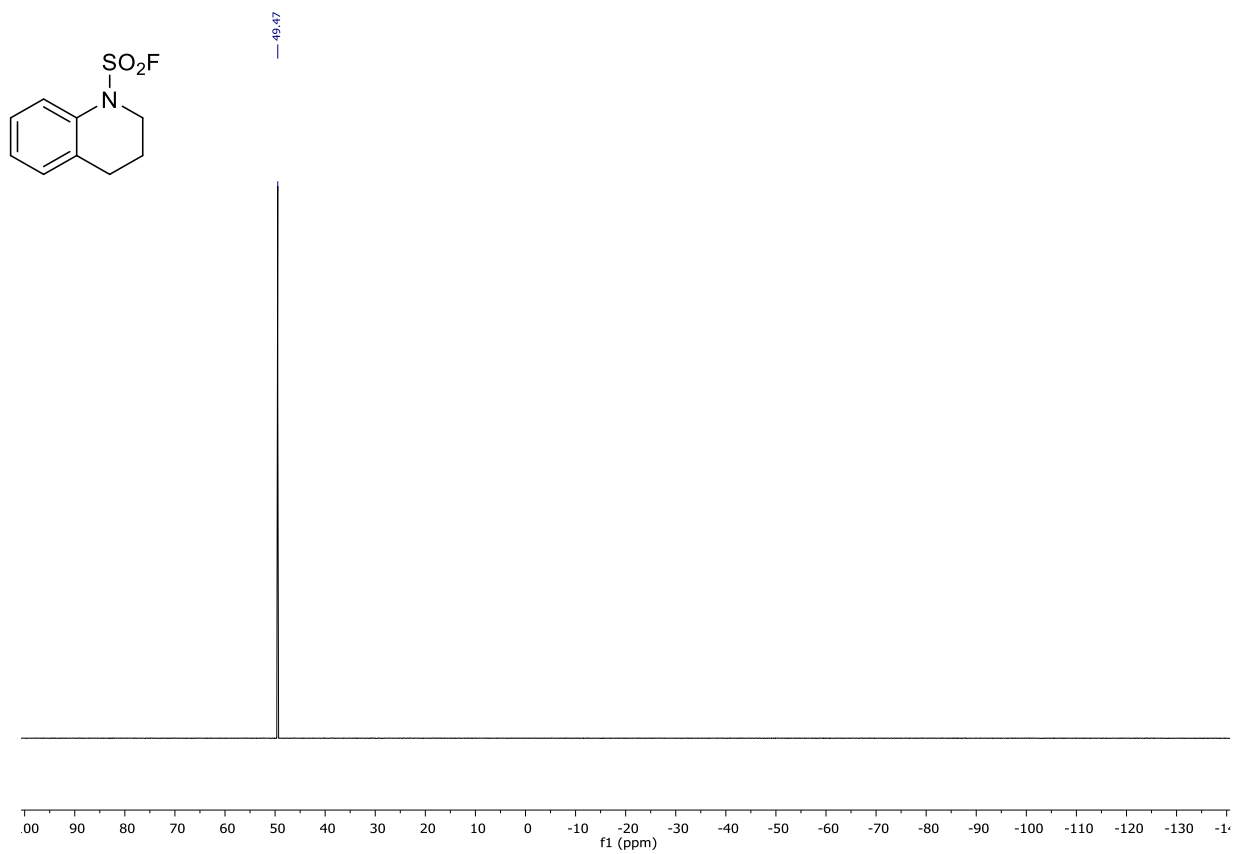
^{19}F NMR

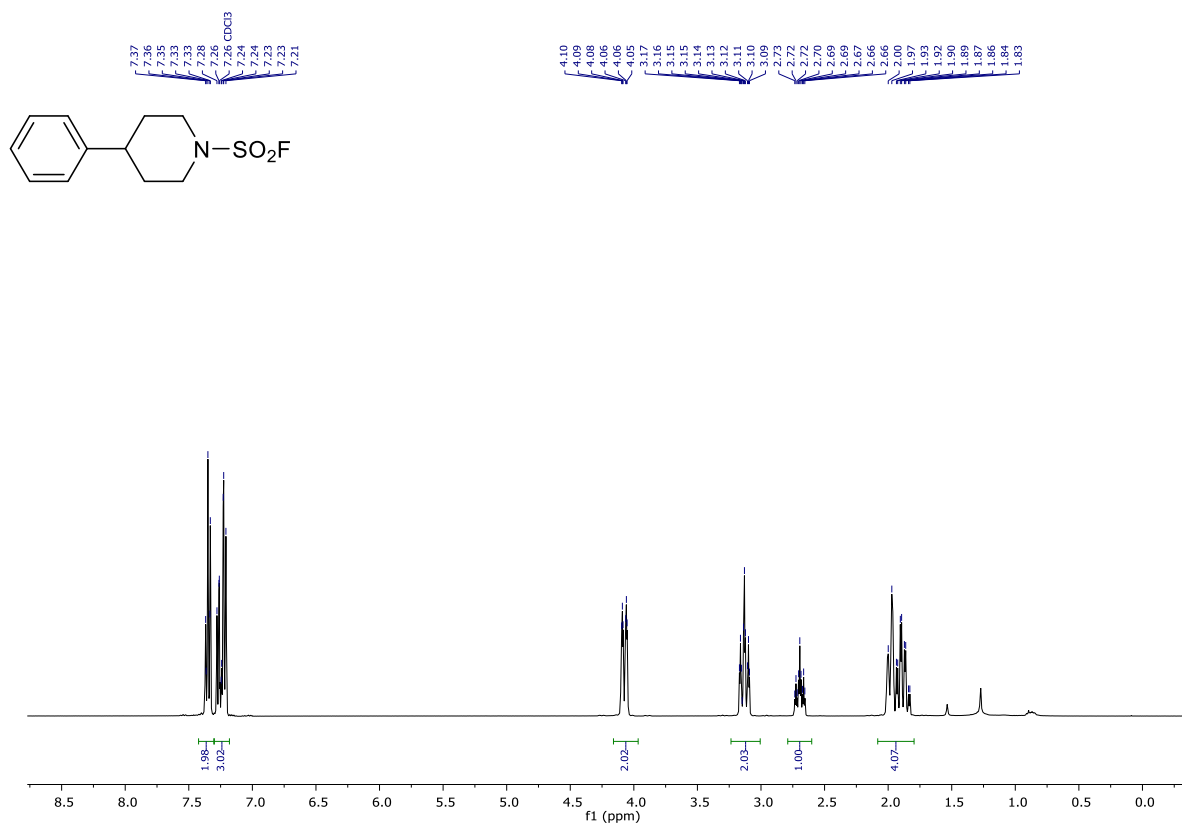
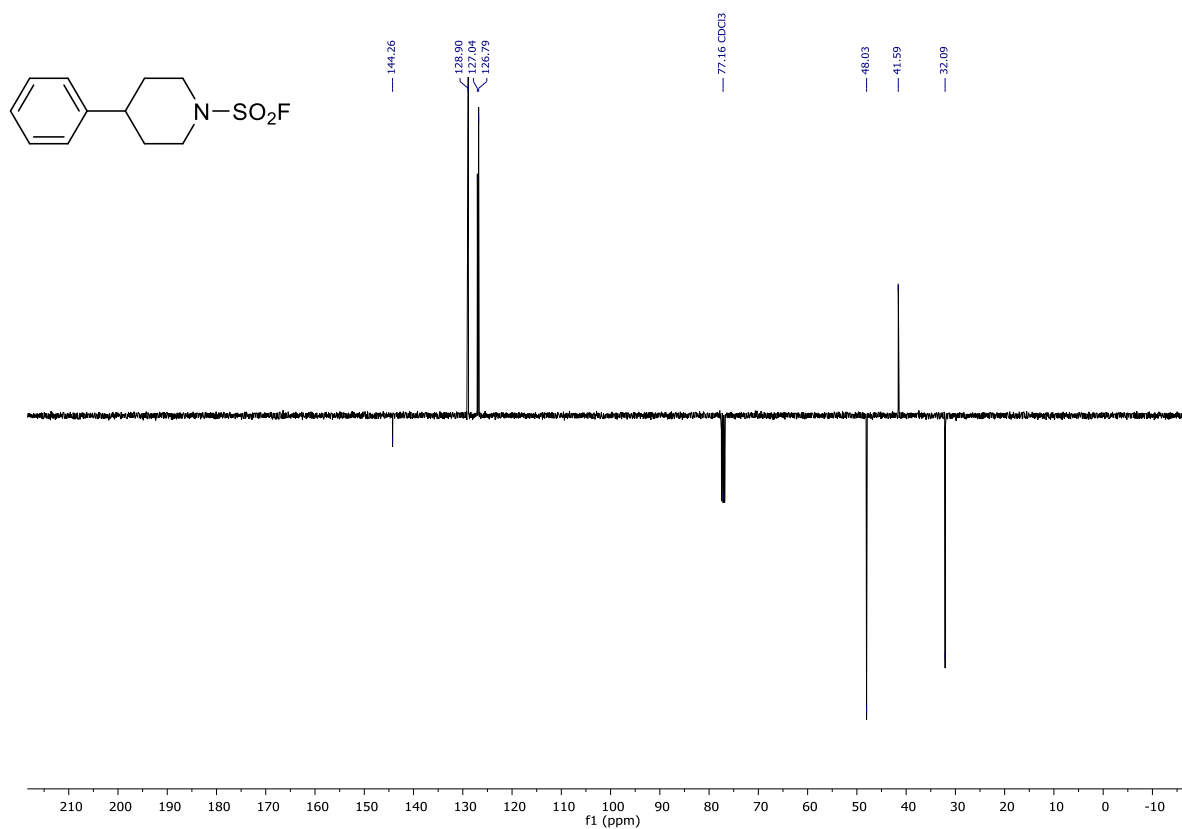
(4-(Methylamino)phenyl)methanol (**S2**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

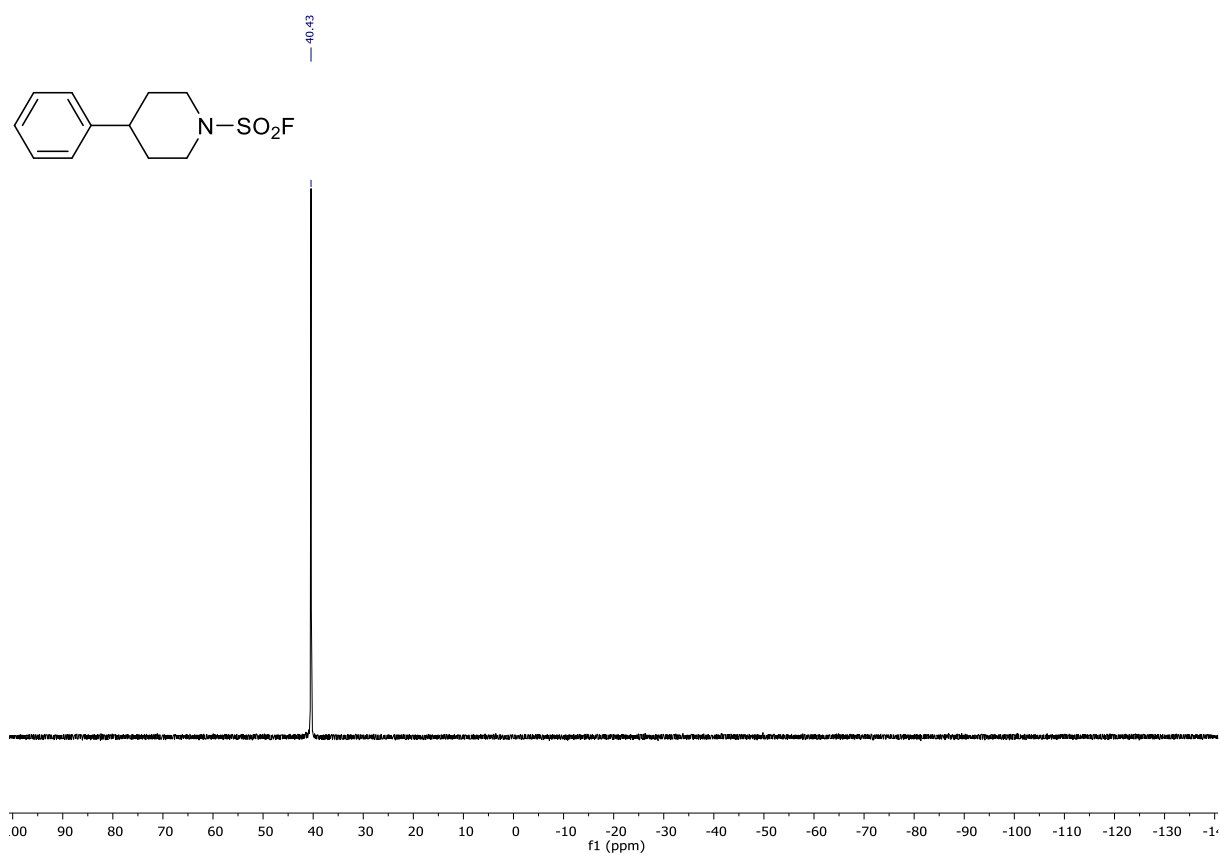
(4-(Hydroxymethyl)phenyl)(methyl)sulfamoyl fluoride (**11**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

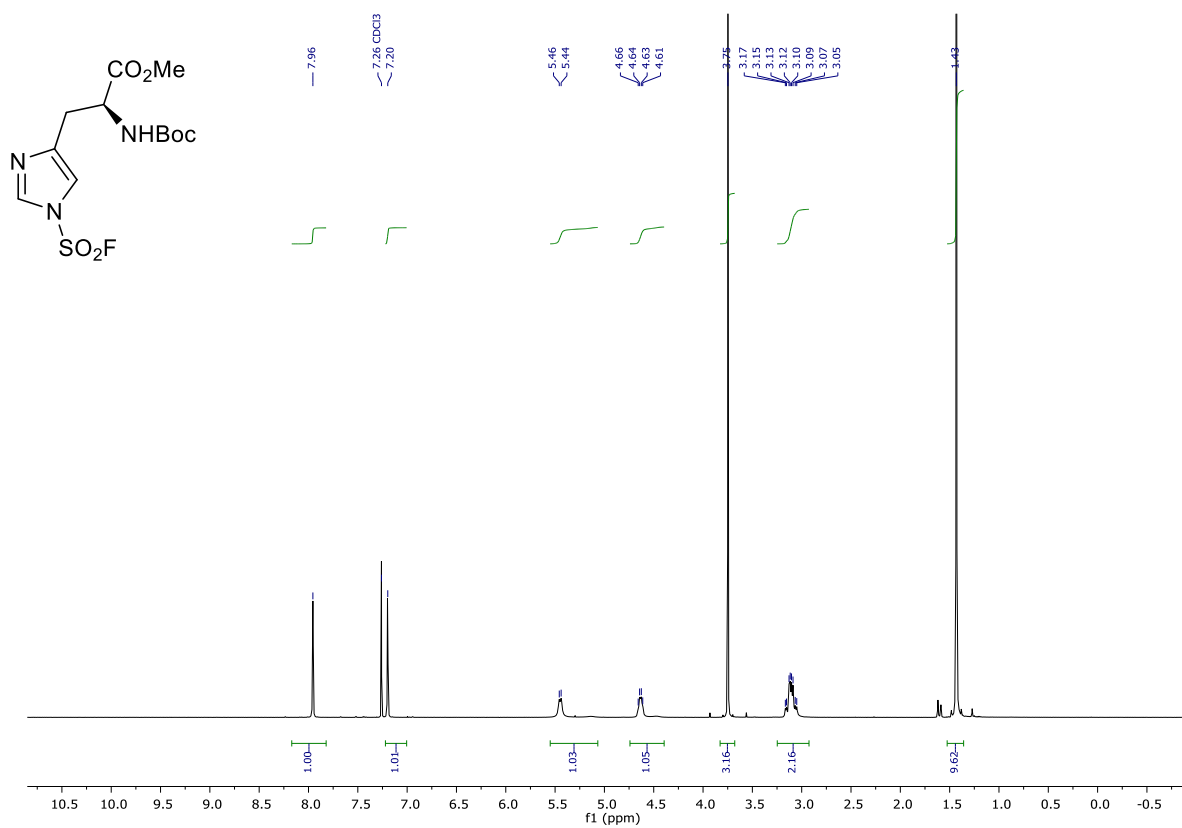
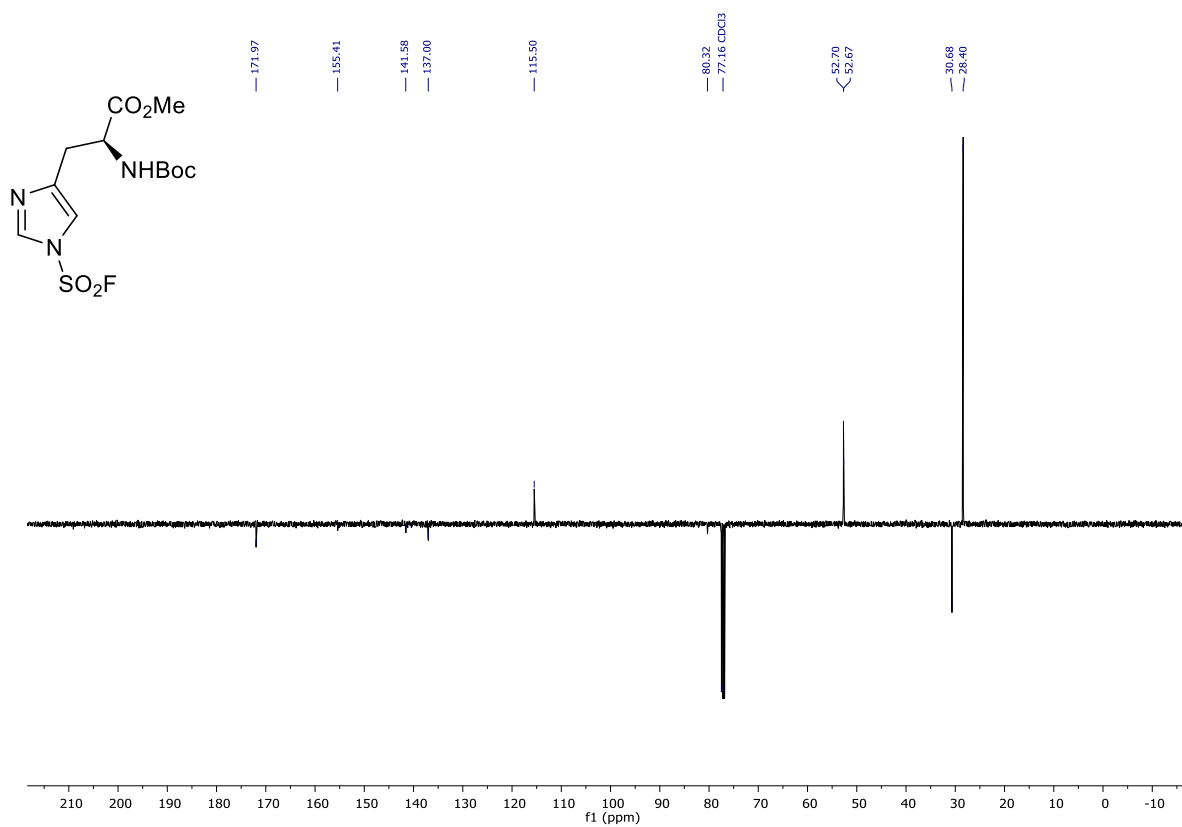
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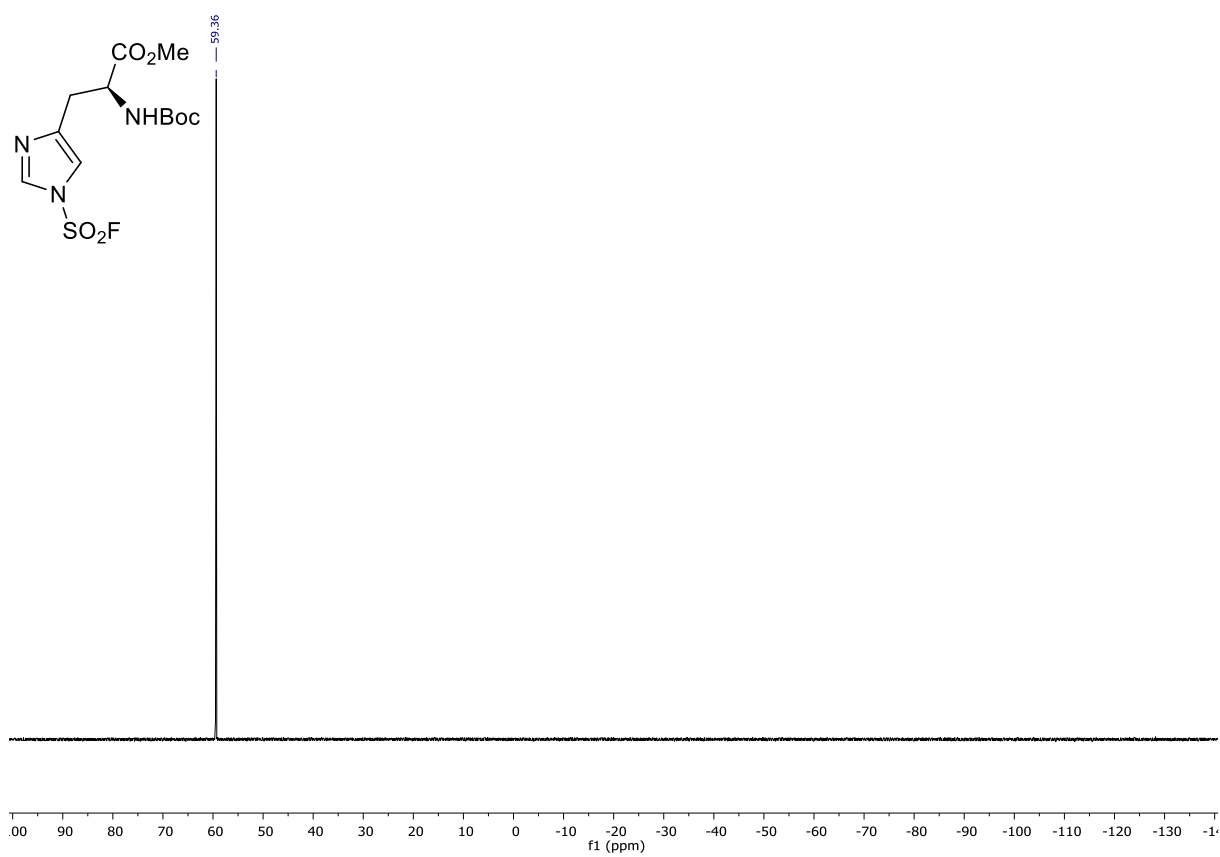
3,4-Dihydroquinoline-1(2*H*)-sulfonyl fluoride (**13**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

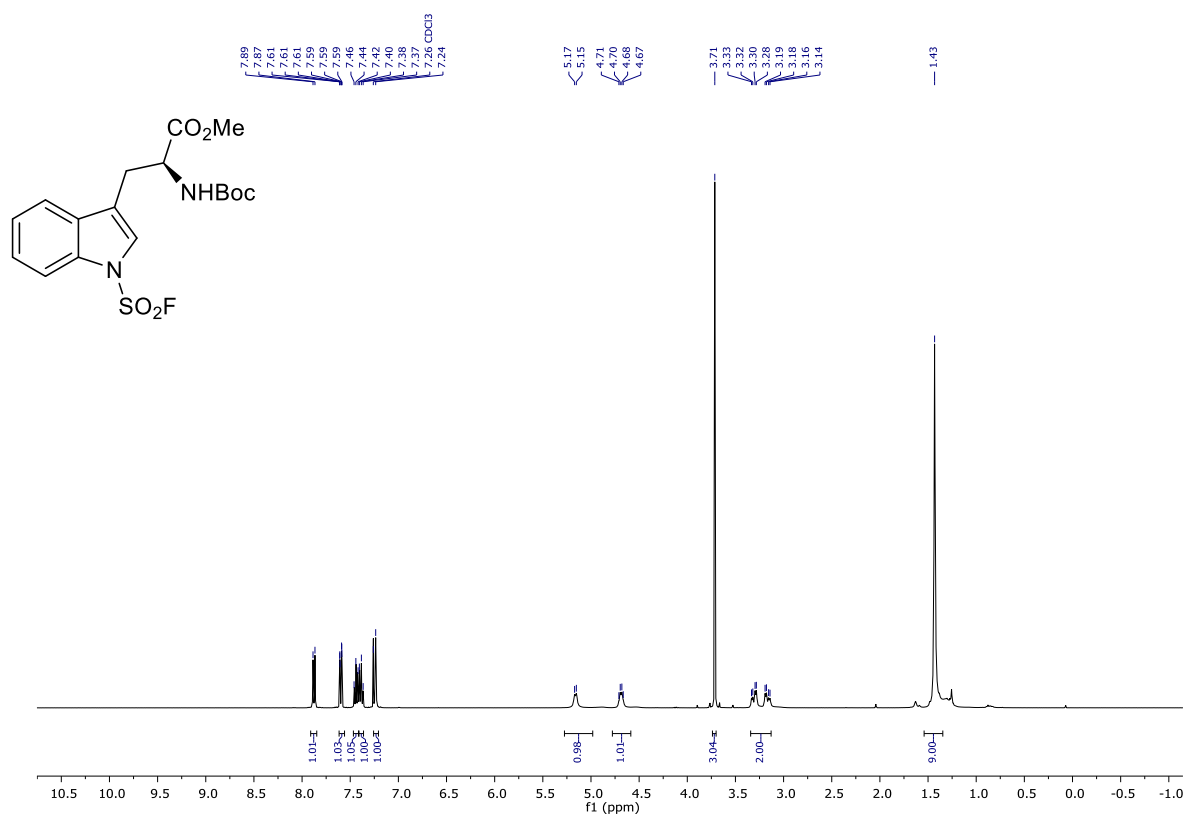
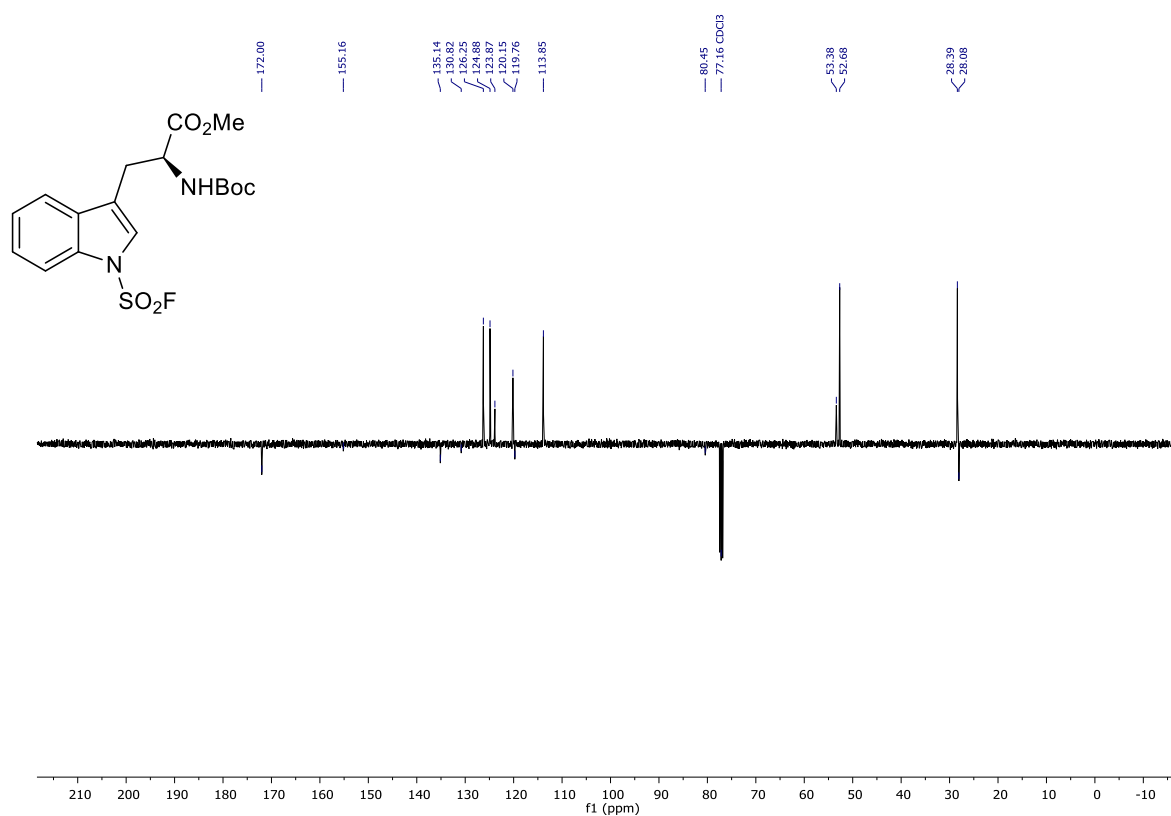
^{19}F NMR

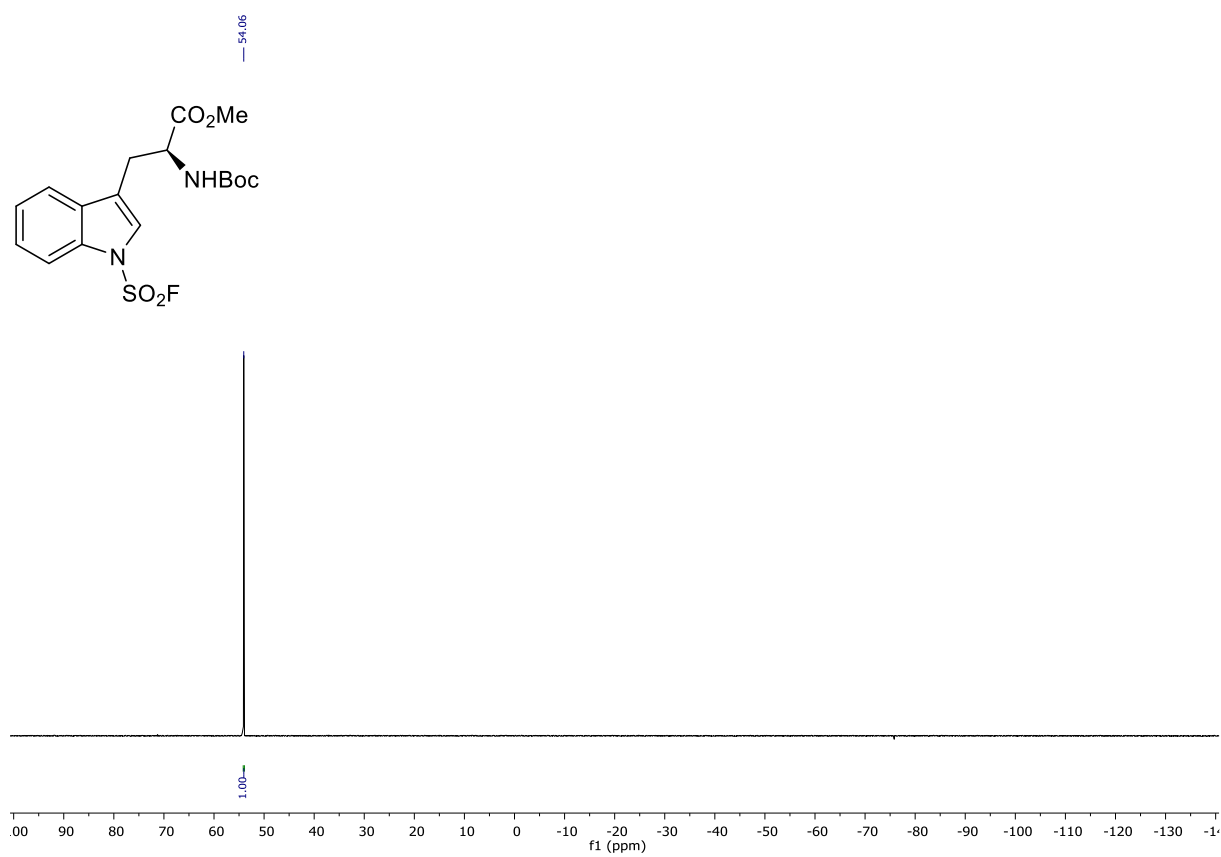
4-Phenylpiperidine-1-sulfonyl fluoride (**3**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

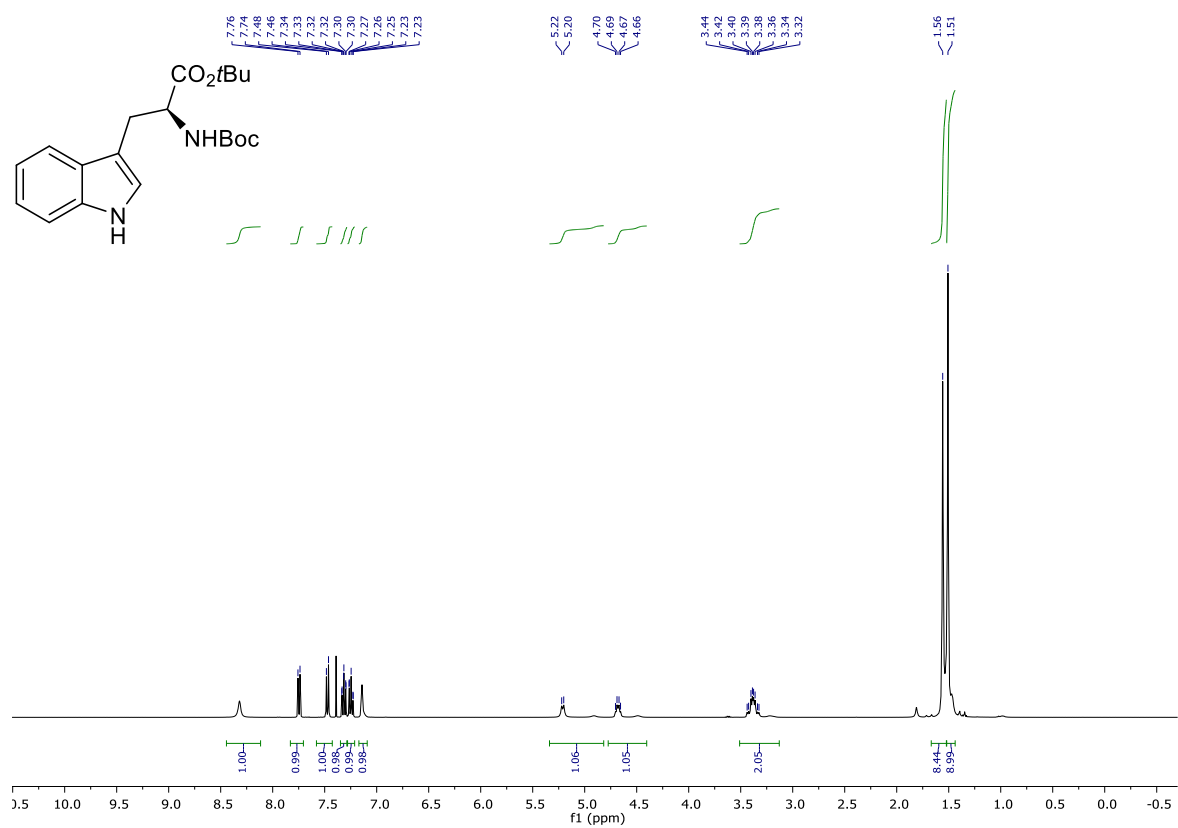
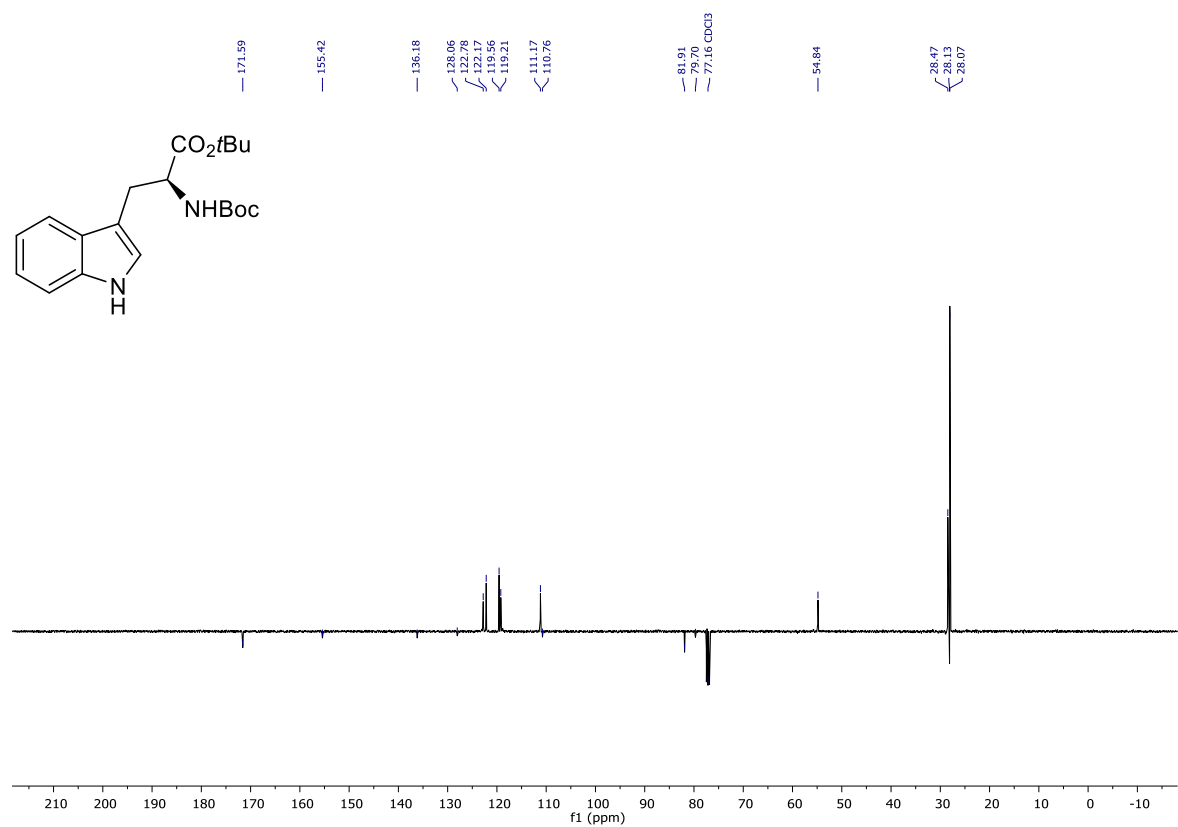
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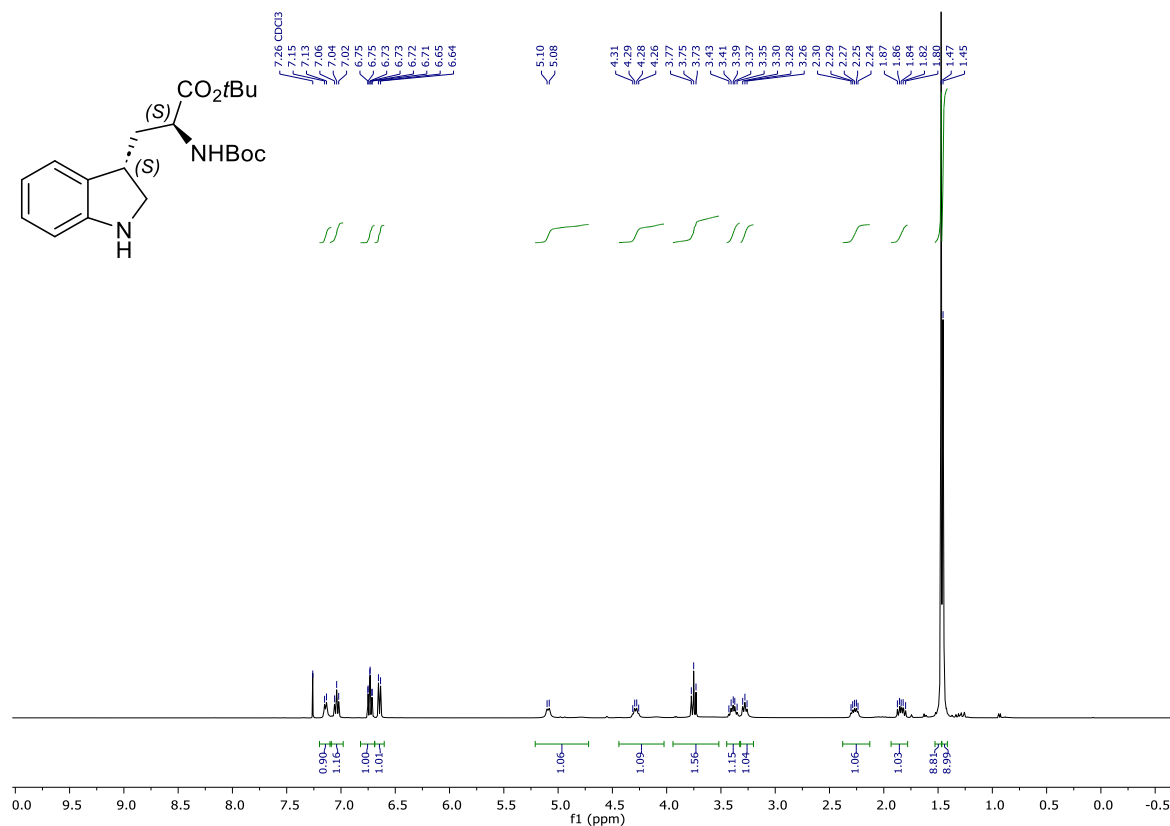
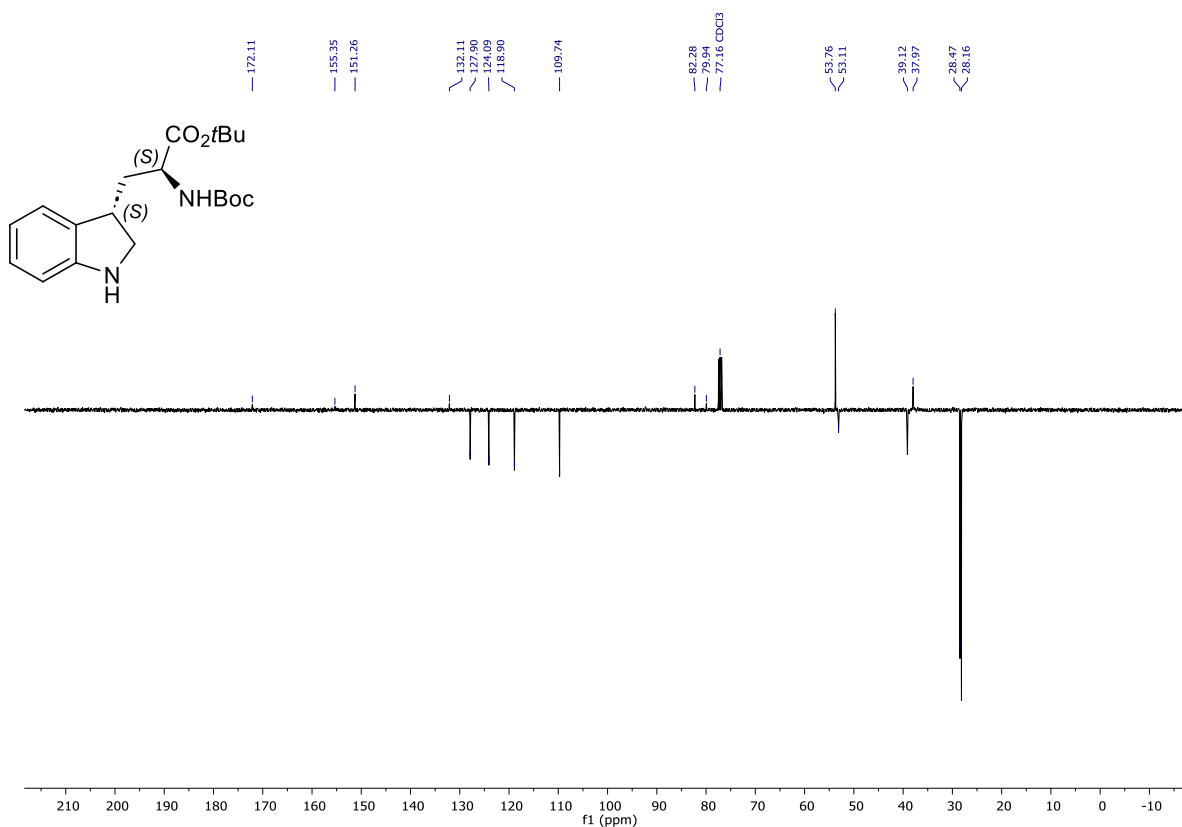
Methyl N_{α} -(*tert*-butoxycarbonyl)- N_{im} -(fluorosulfonyl)-L-histidinate (**15**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

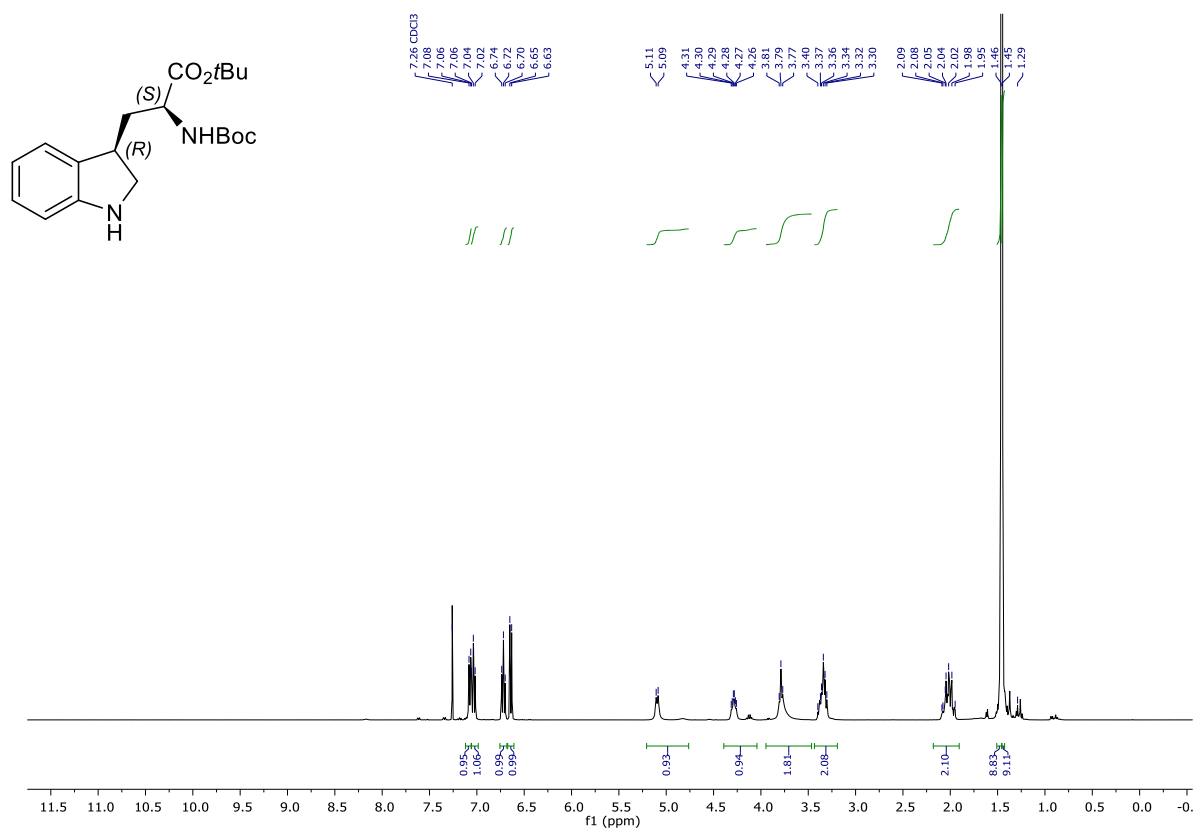
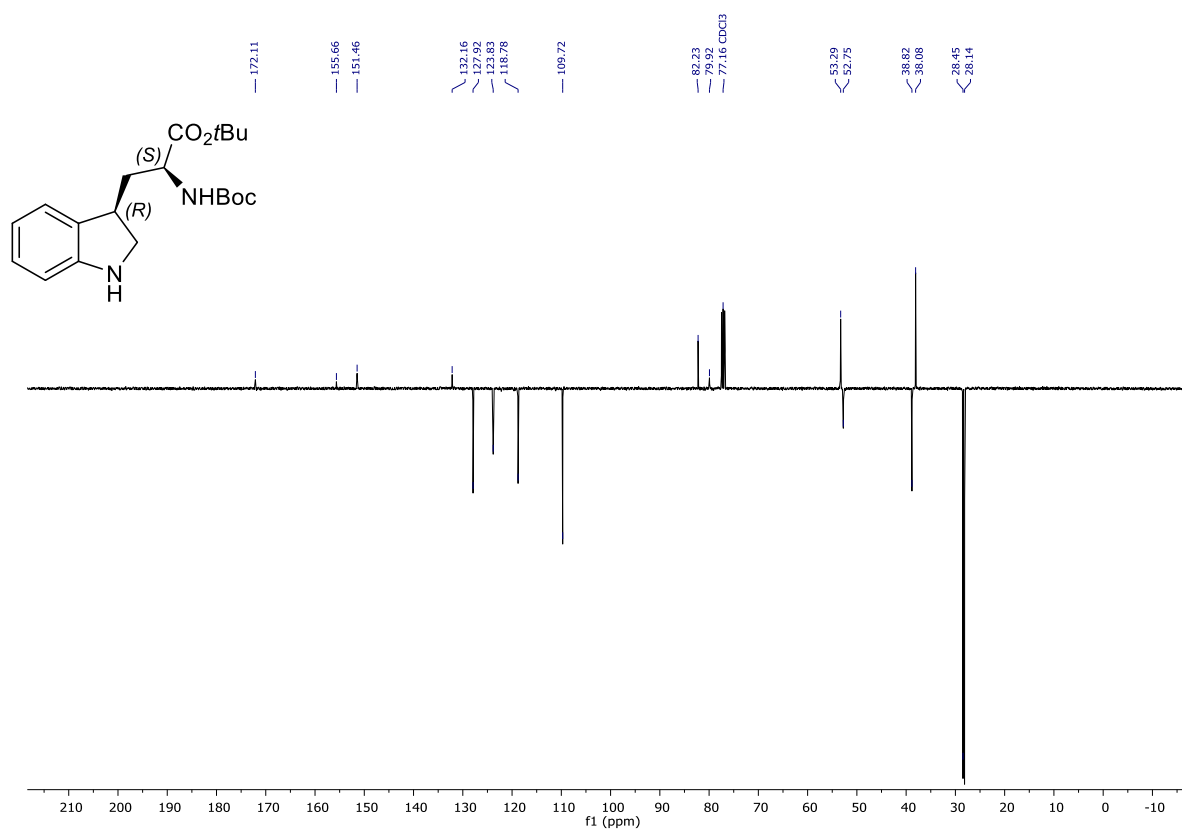
^{19}F NMR

Methyl *N*_α-(*tert*-butoxycarbonyl)-1-(fluorosulfonyl)-L-tryptophan (**2**)¹H NMR¹³C{¹H} NMR

^{19}F NMR

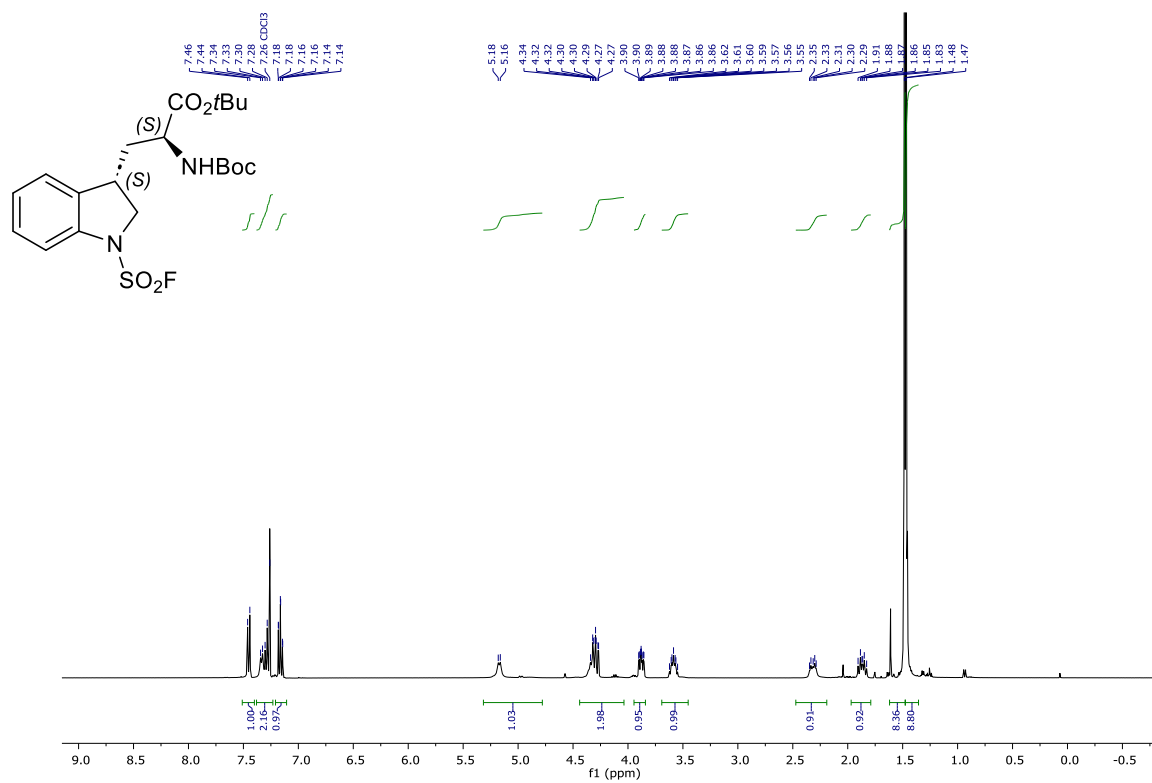
tert-Butyl (*tert*-butoxycarbonyl)-L-tryptophan (**18**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

tert-Butyl (S)-2-[(*tert*-butoxycarbonyl)amino]-3-[(S)-indolin-3-yl]propanoate [(S,S)-19] ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

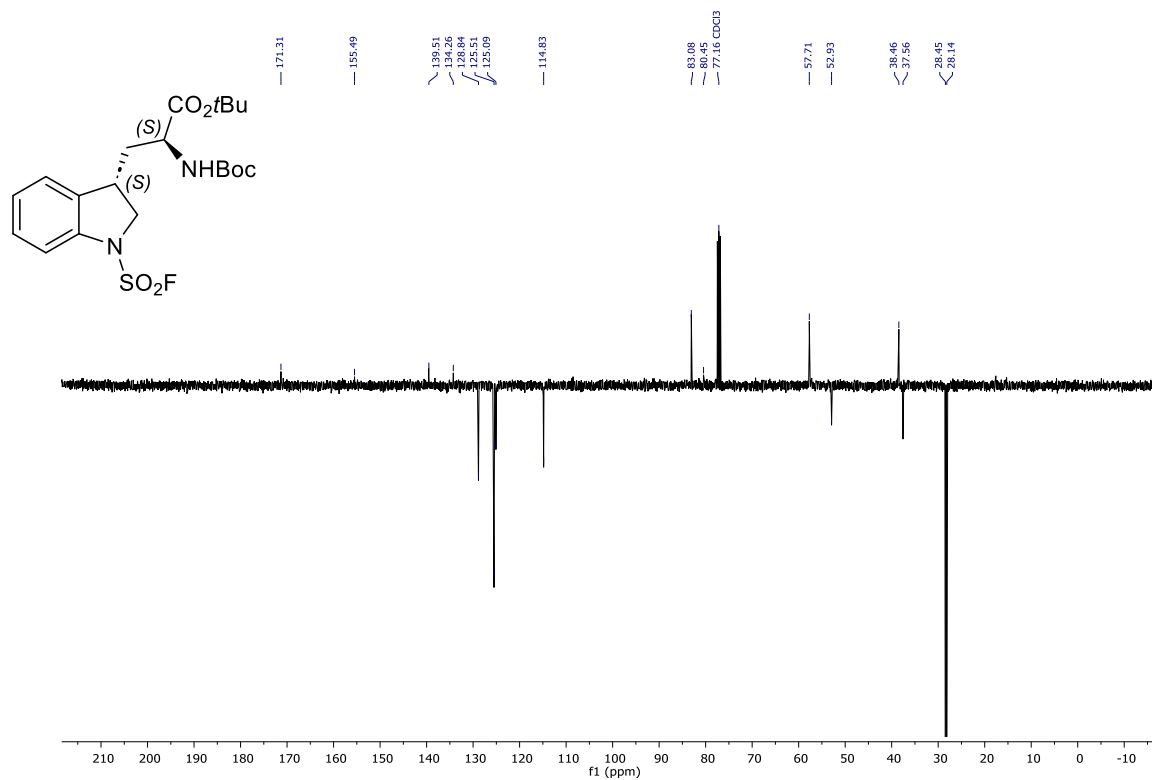
tert-Butyl (*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-[(*R*)-indolin-3-yl]propanoate [(*S,R*)-**19**] ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

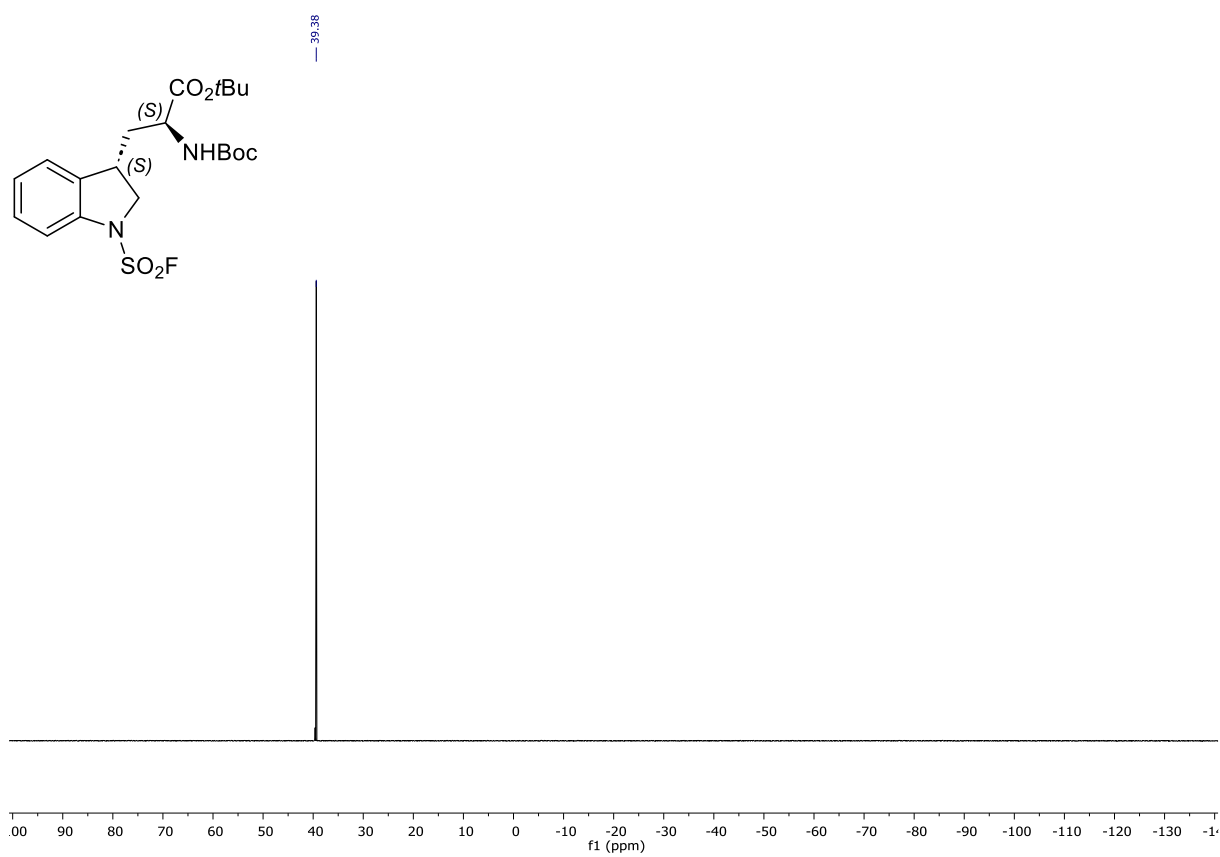
tert-Butyl (*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-[(*S*)-1-(fluorosulfonyl)indolin-3-yl]propanoate [(*S,S*)-14]

^1H NMR



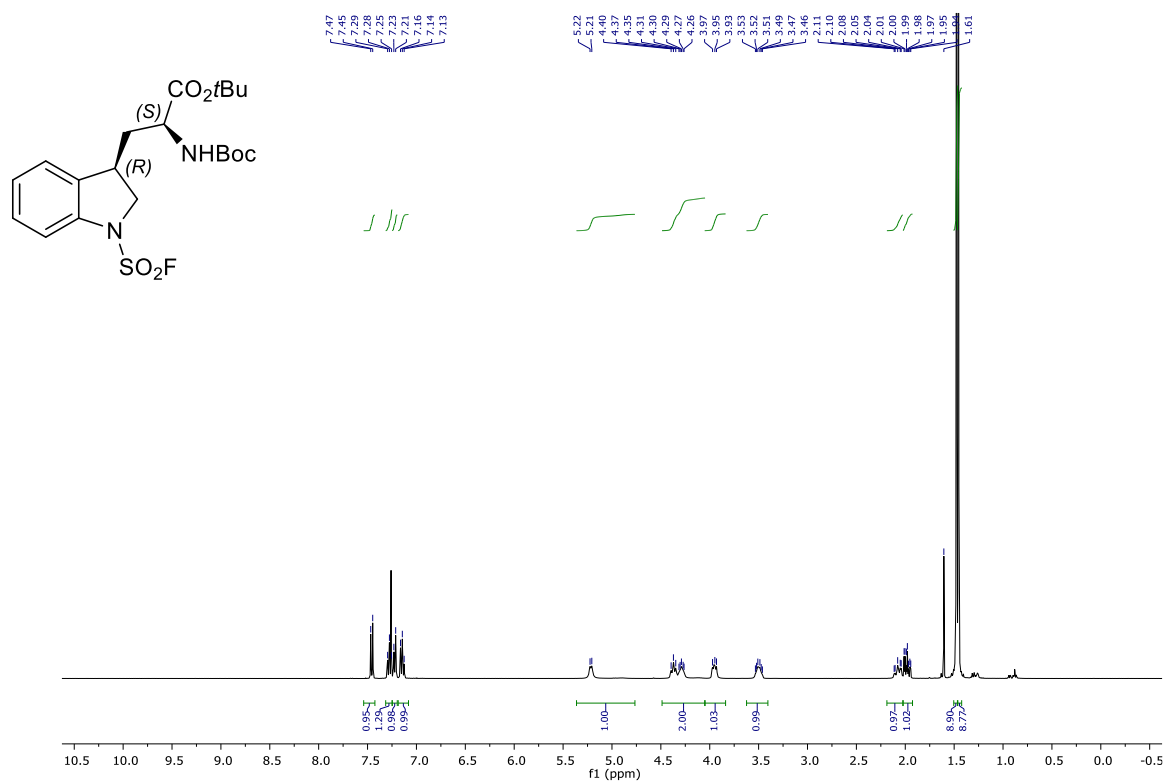
$^{13}\text{C}\{^1\text{H}\}$ NMR



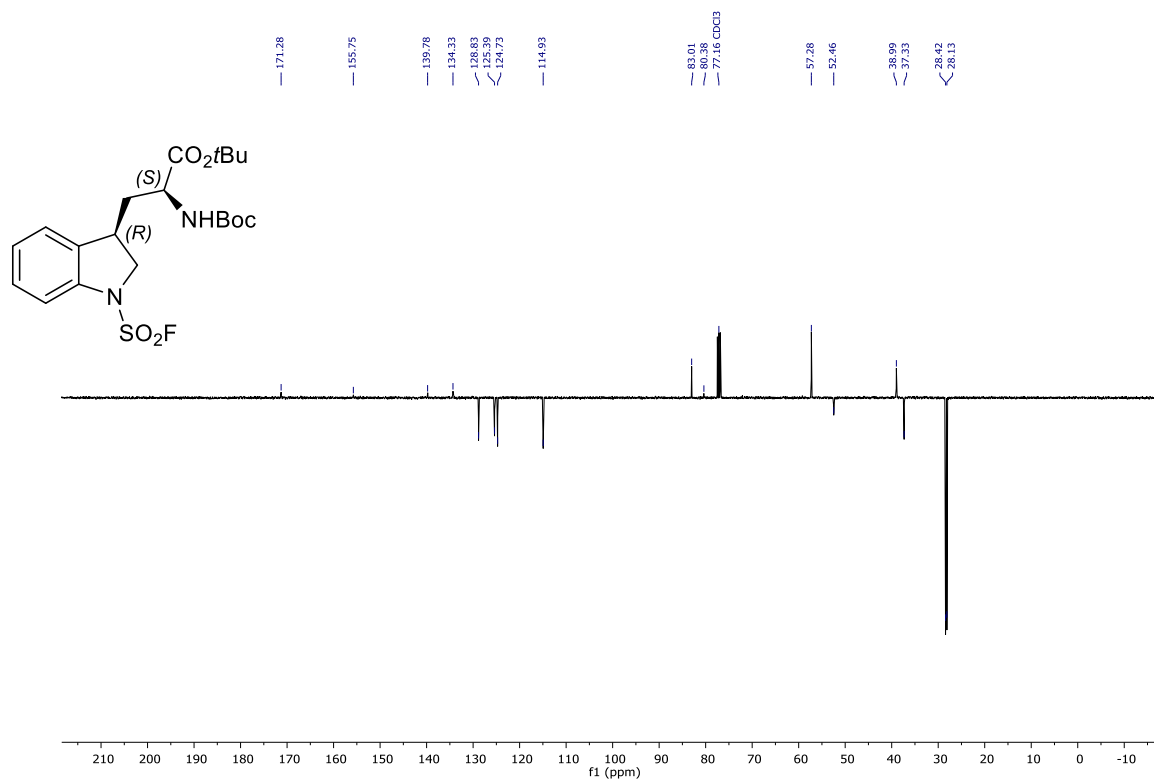
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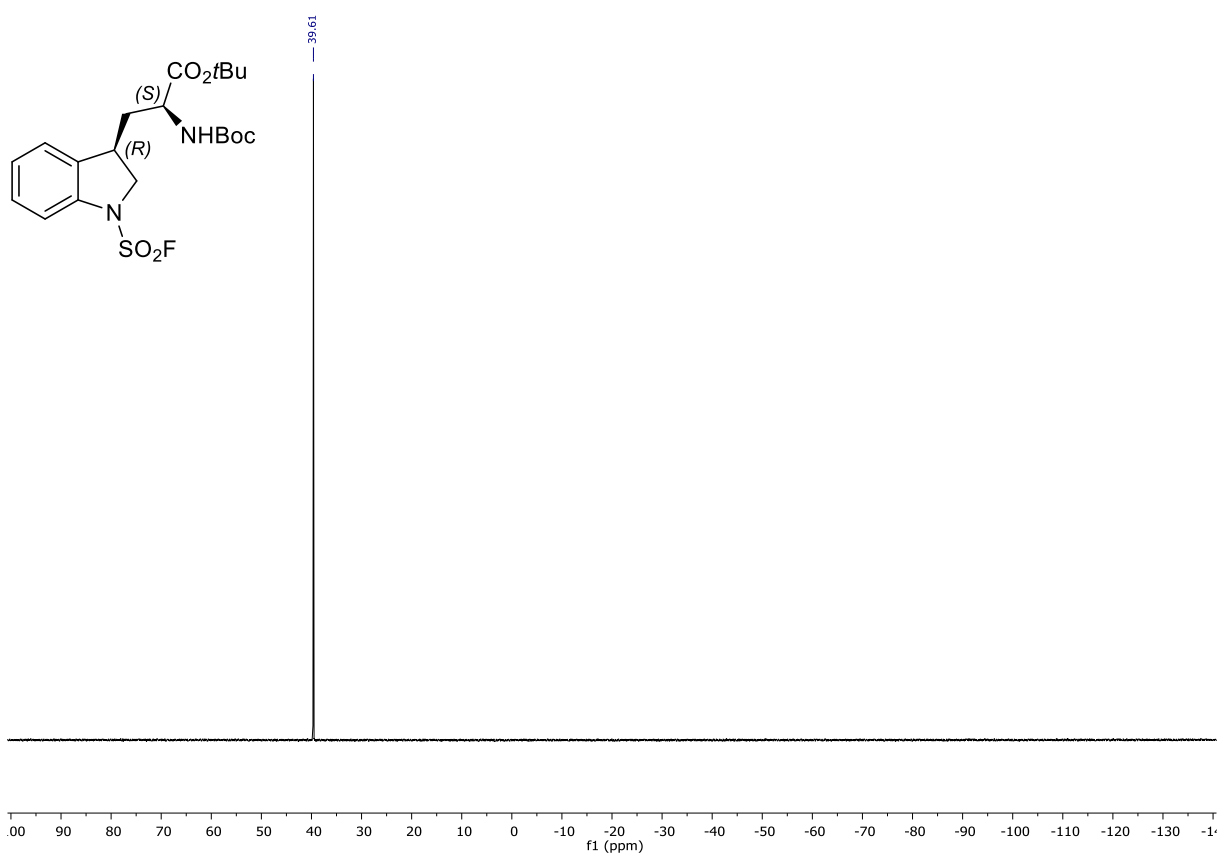
tert-Butyl (*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-[(*R*)-1-(fluorosulfonyl)indolin-3-yl]propanoate [(*S,R*)-**14**]

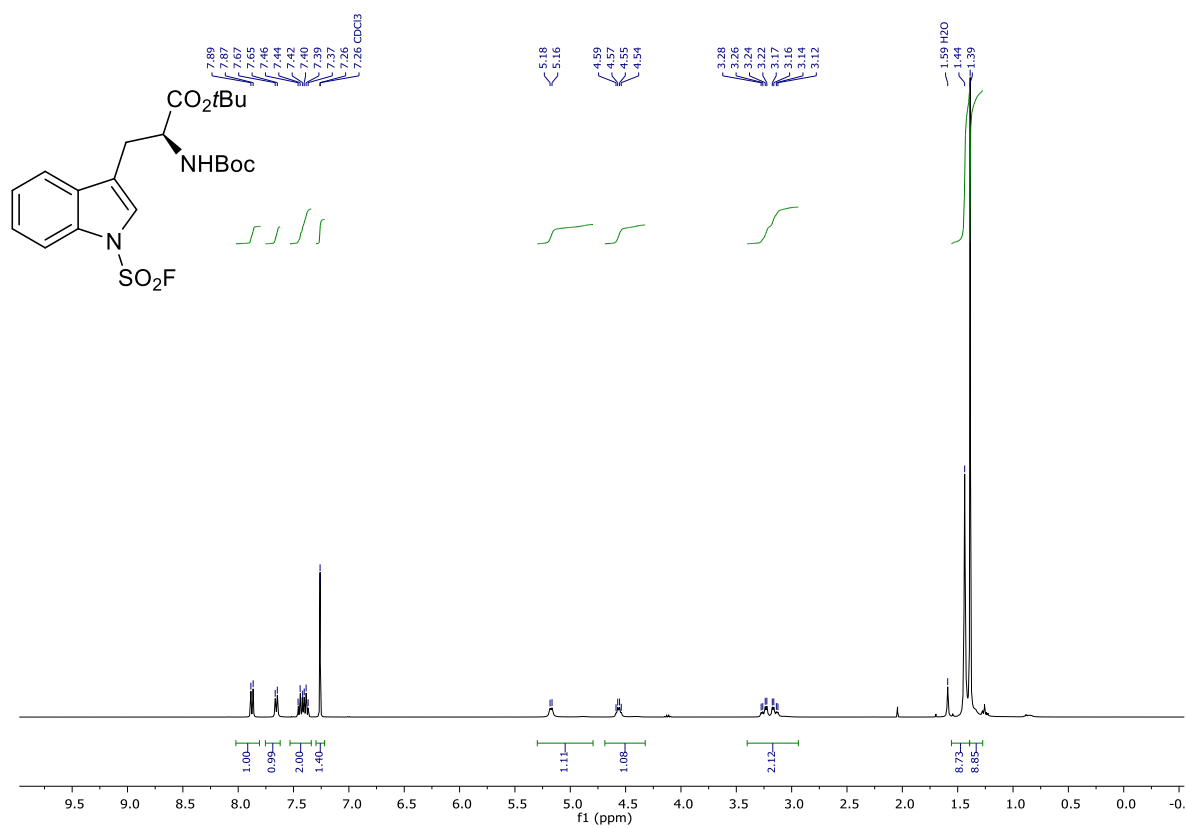
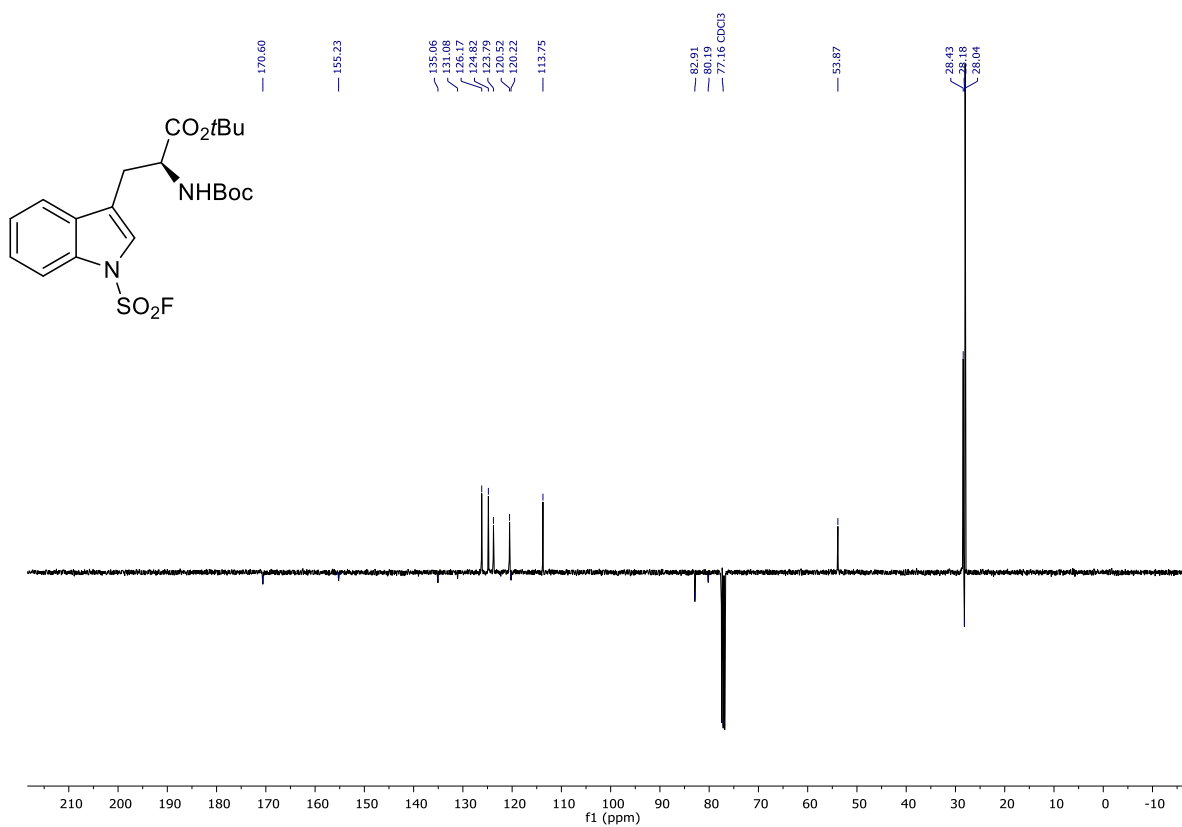
^1H NMR

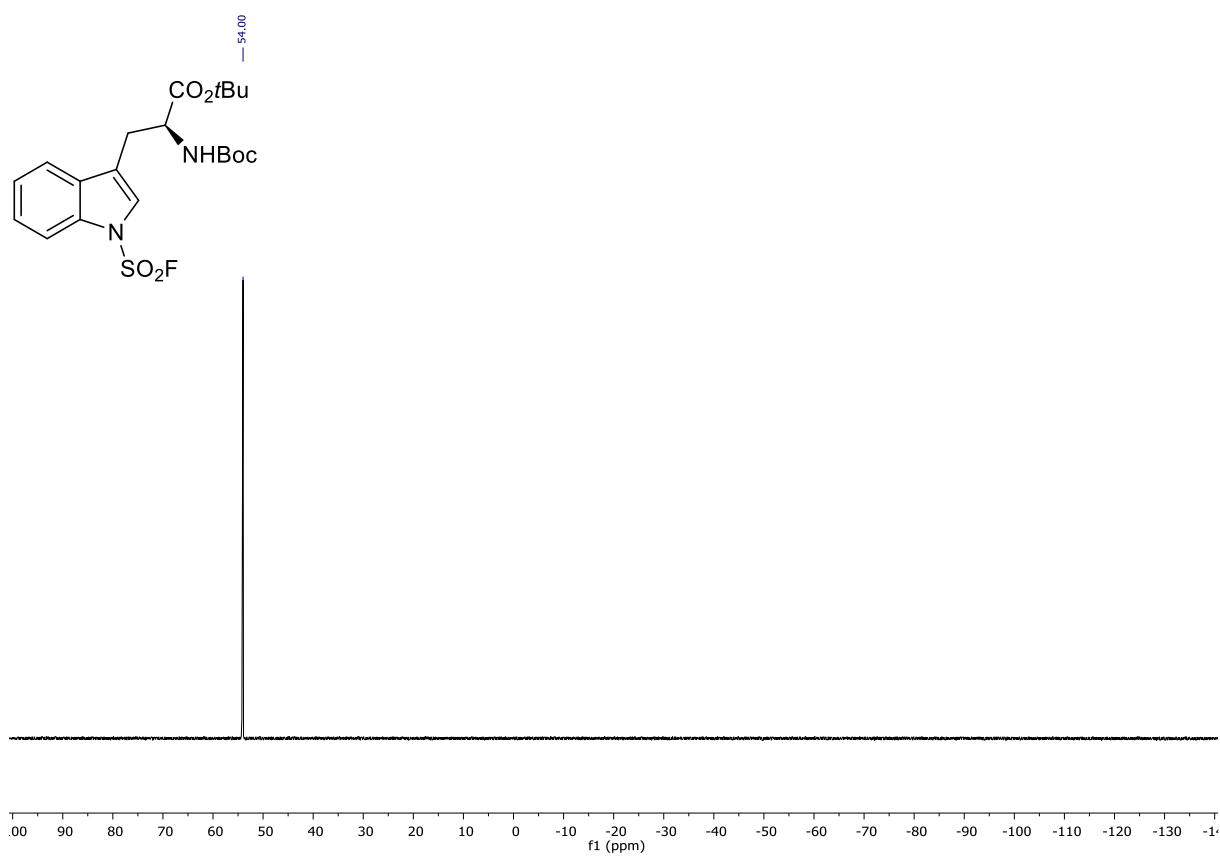


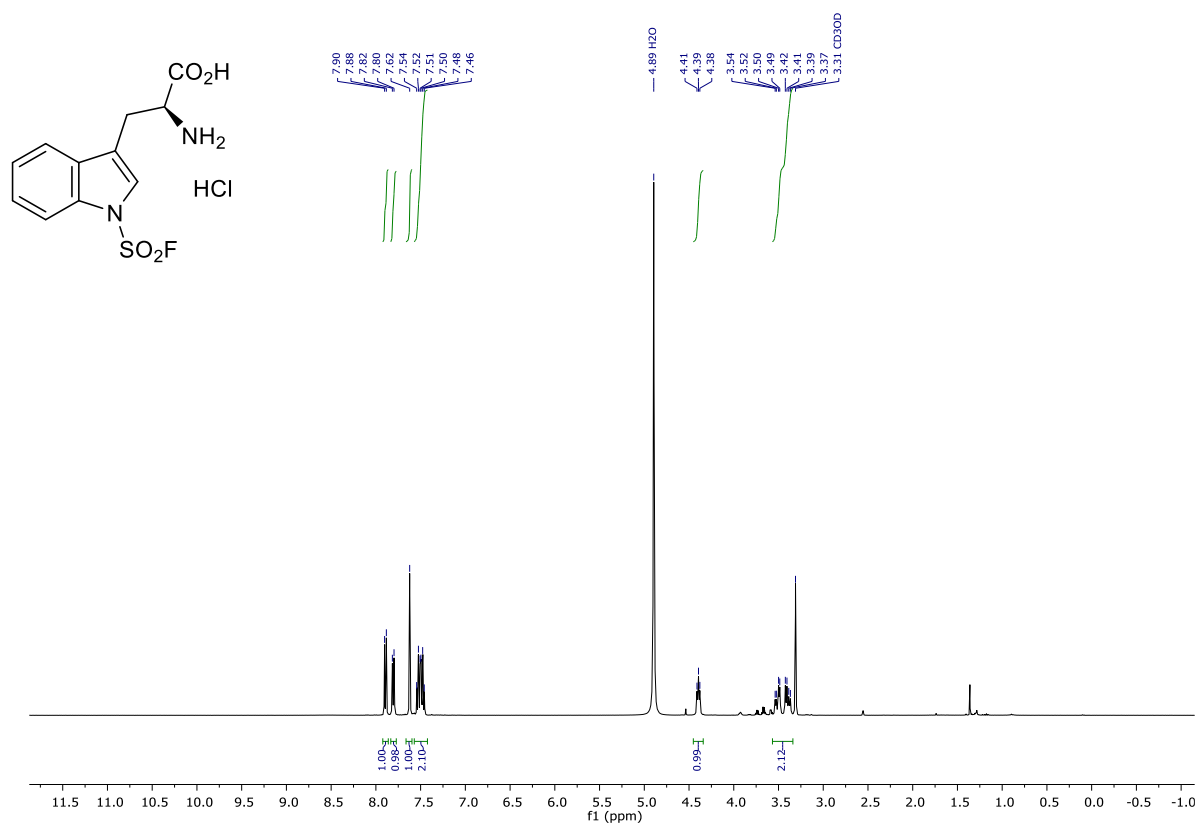
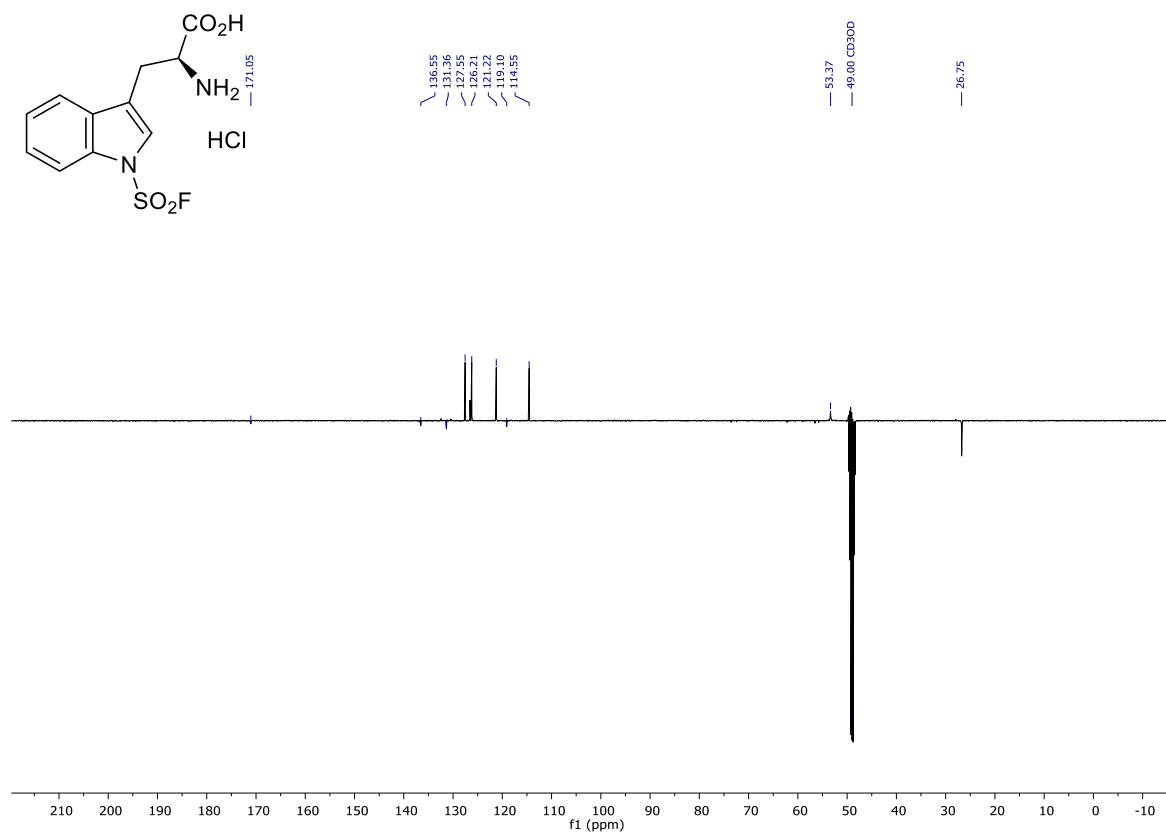
$^{13}\text{C}\{^1\text{H}\}$ NMR



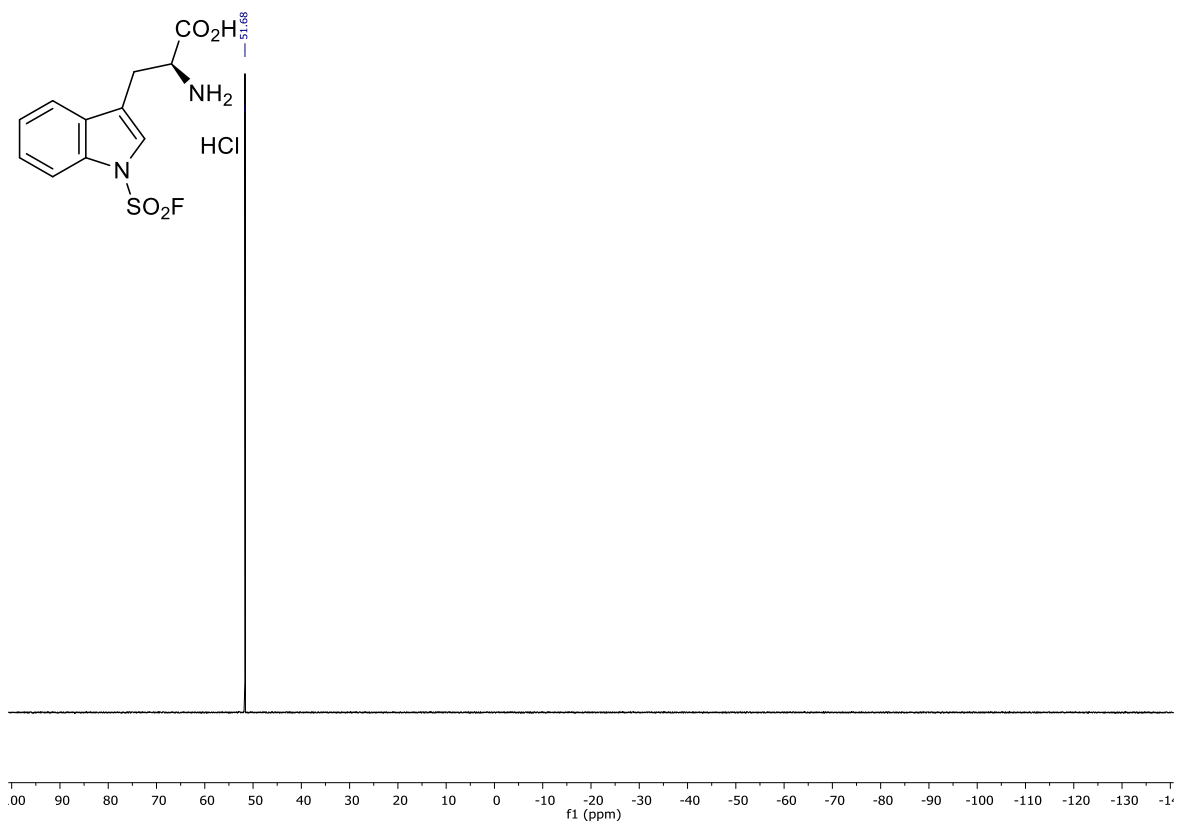
^{19}F NMR

N_{α} -(*tert*-Butoxycarbonyl)-1-(fluorosulfonyl)-L-tryptophan *tert*-butyl ester (**1**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

^{19}F NMR

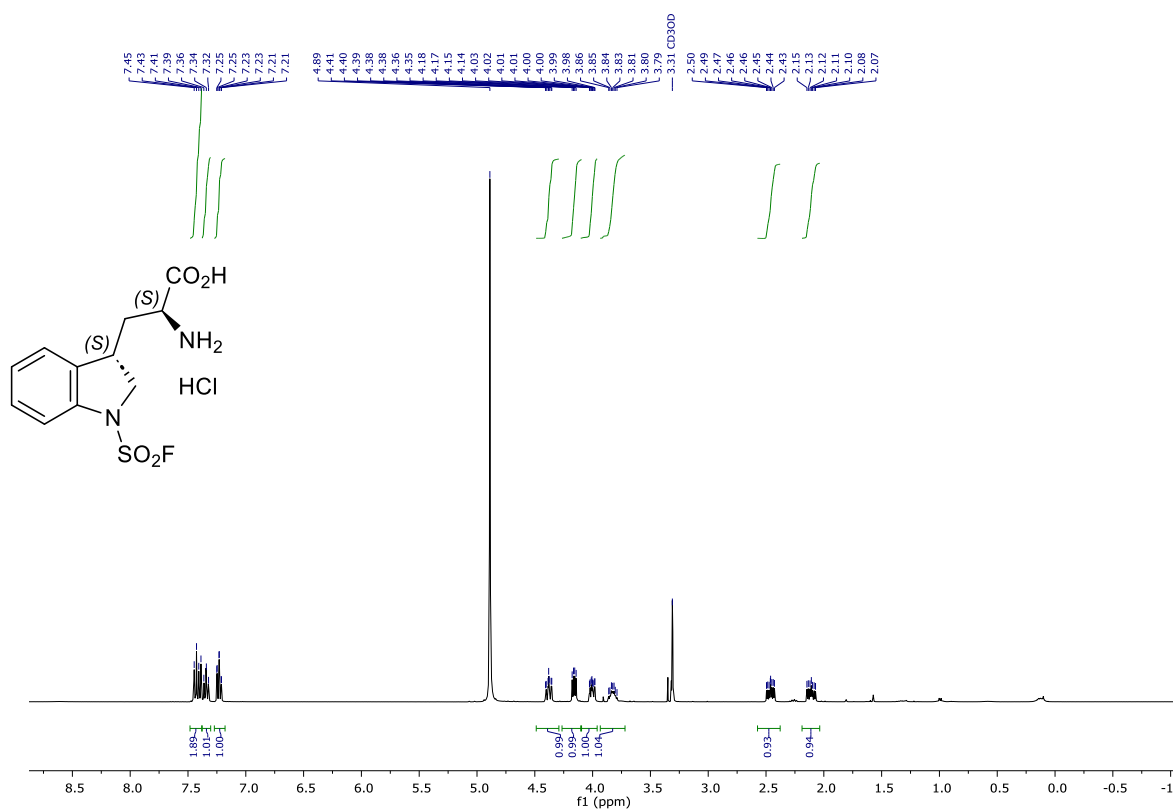
1-(Fluorosulfonyl)-L-tryptophan hydrochloride (**20**×HCl) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

¹⁹F NMR

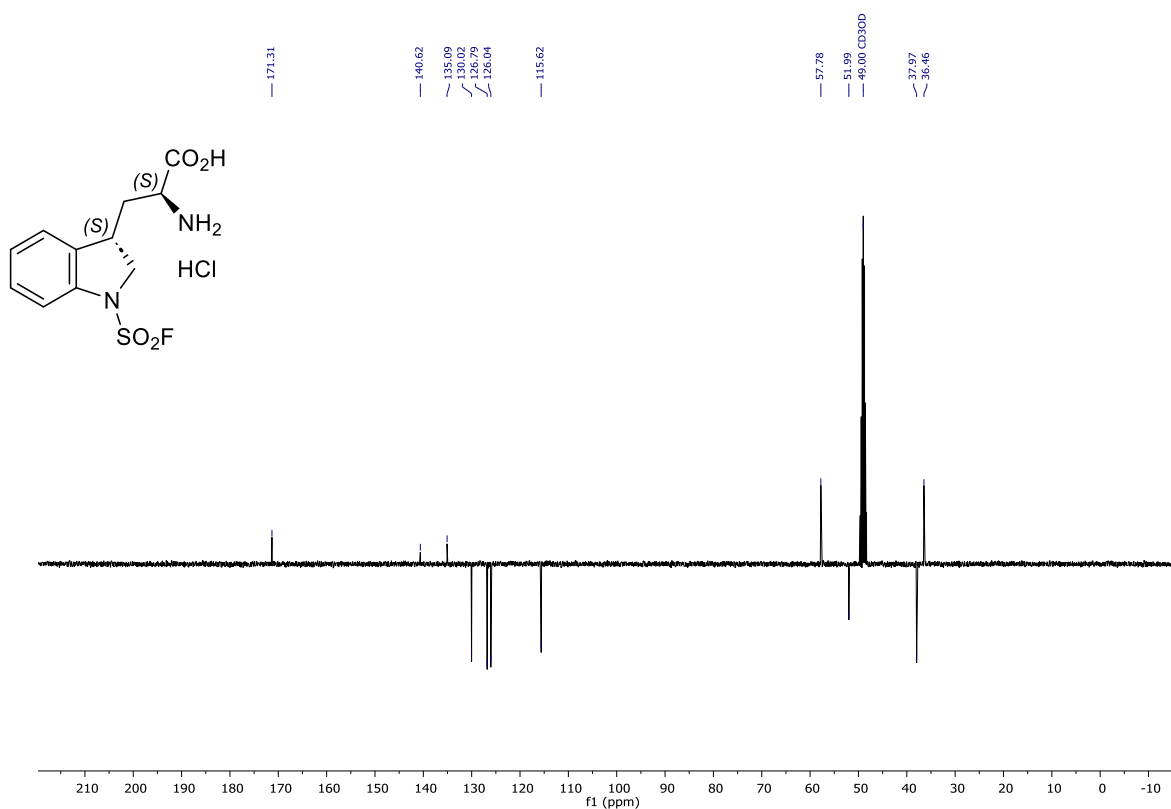


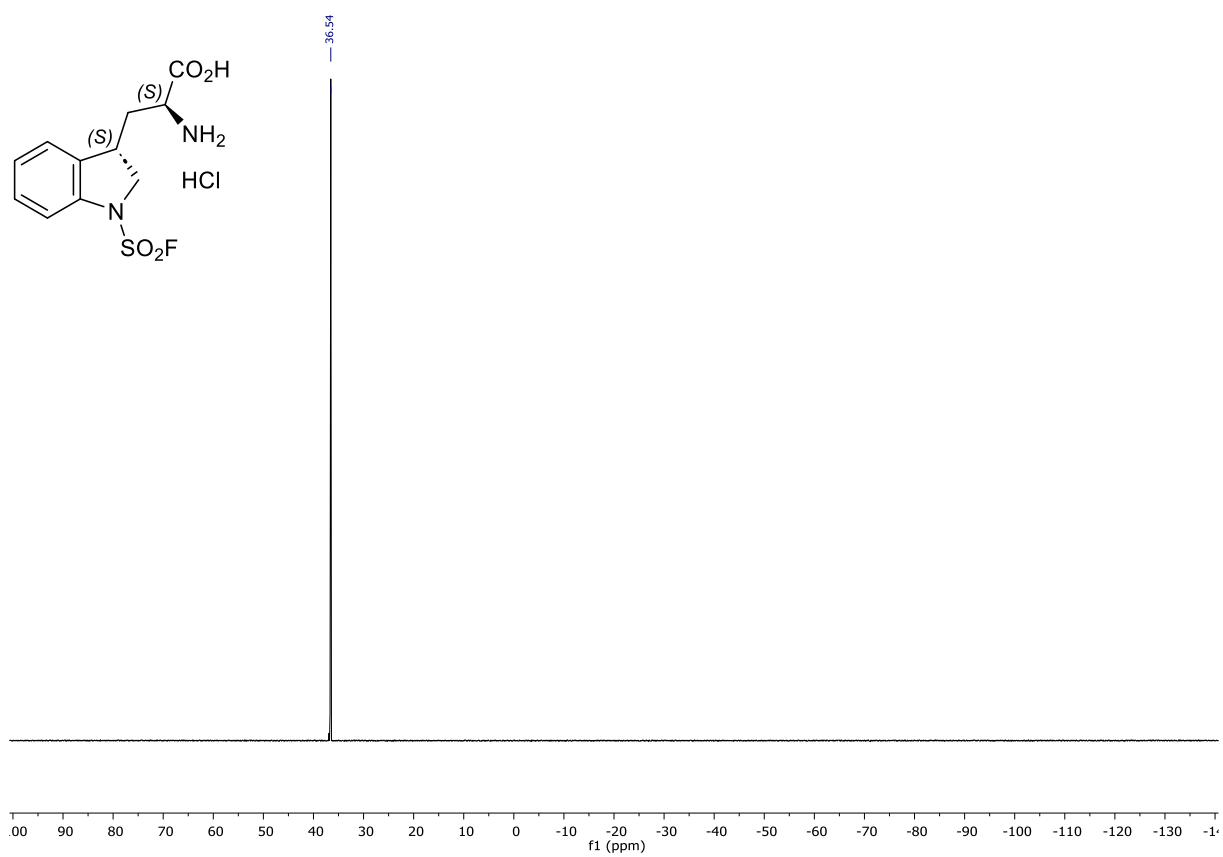
(*S*)-2-Amino-3-[(*S*)-1-(fluorosulfonyl)indolin-3-yl]propanoic acid hydrochloride [(*S,S*)-**21**×HCl]

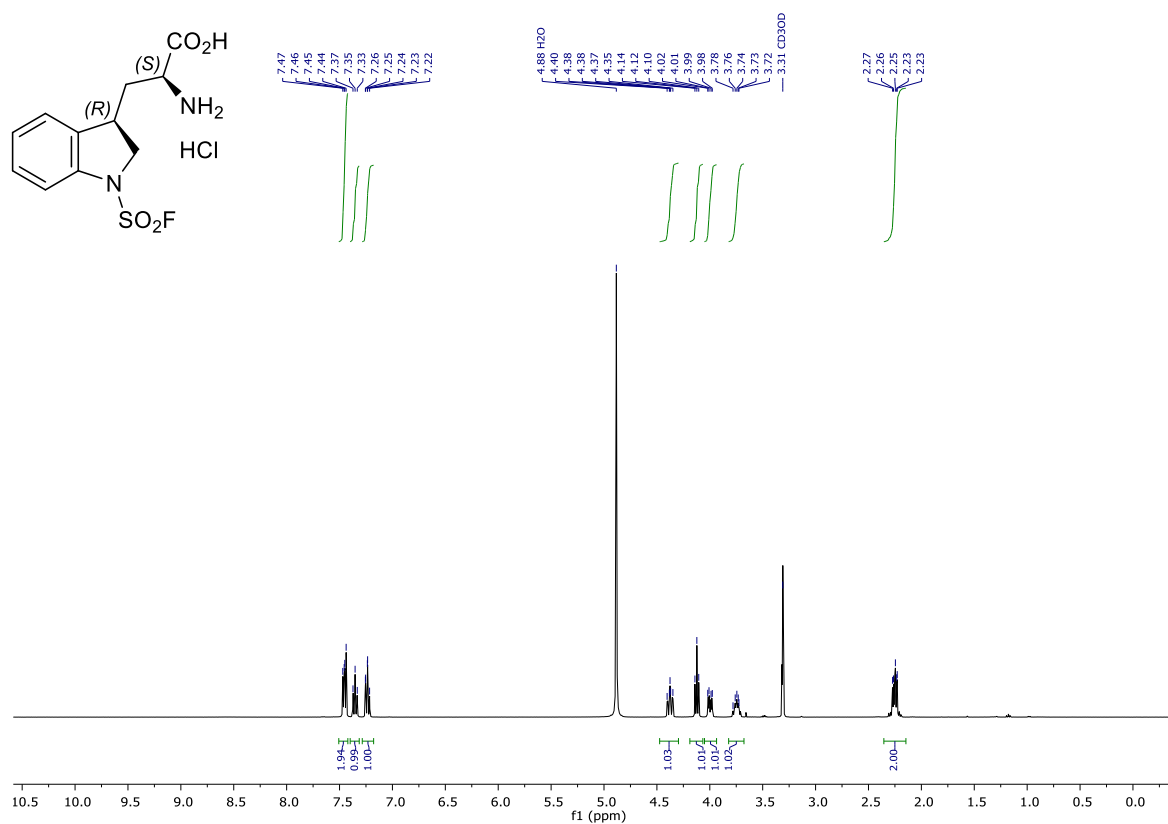
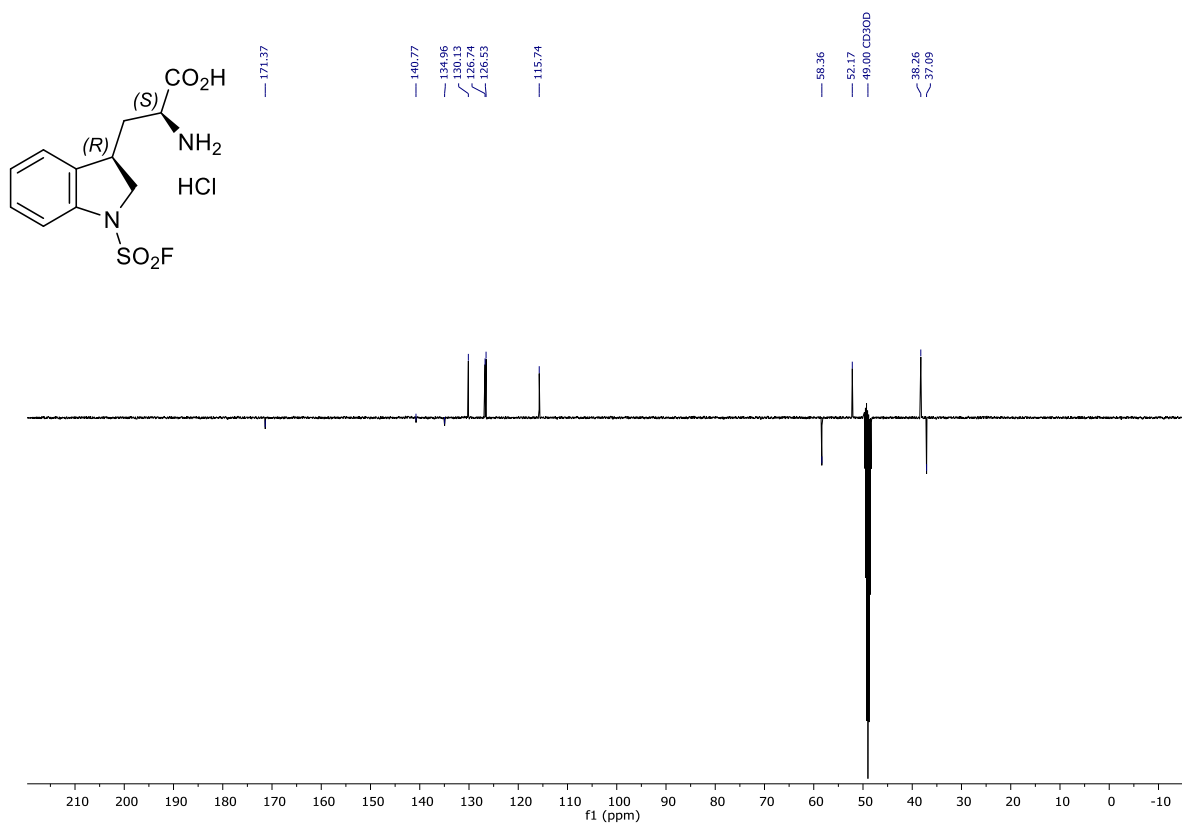
¹H NMR



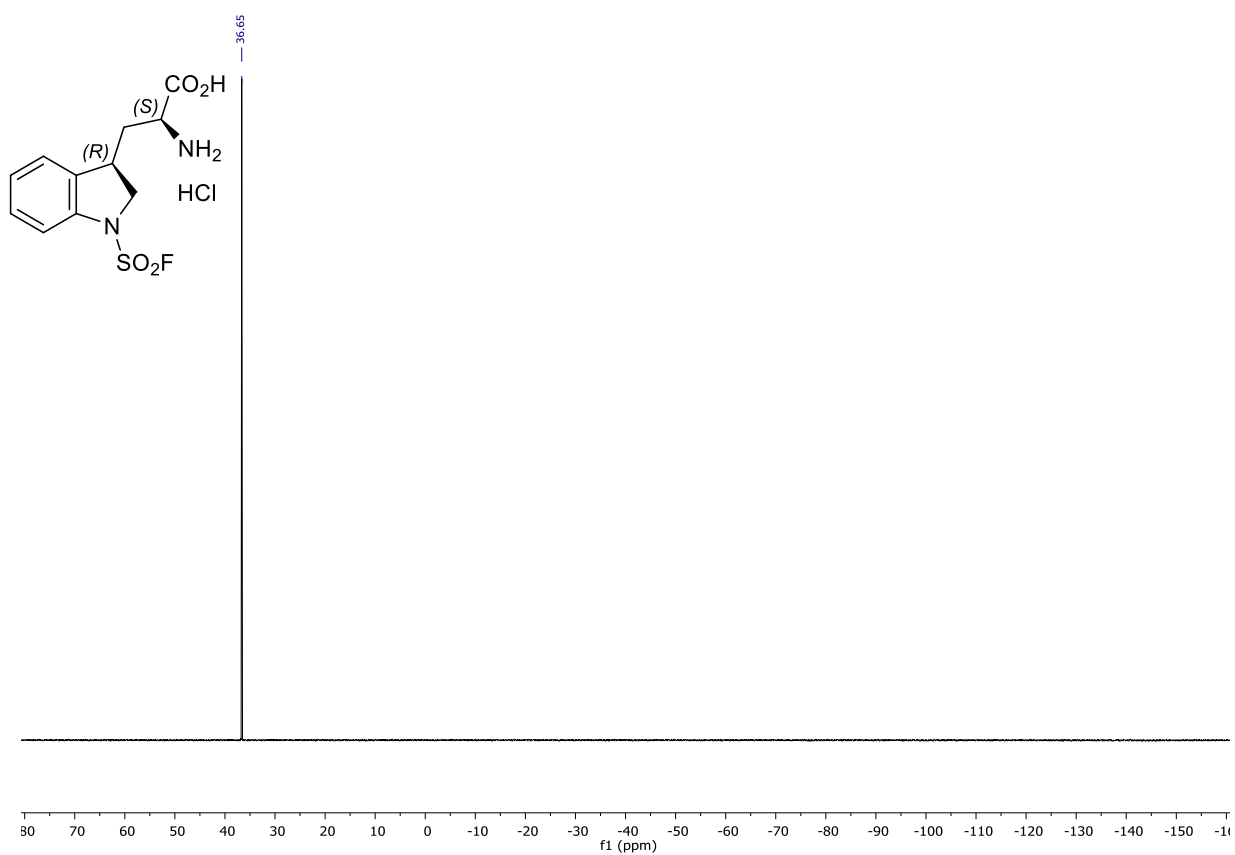
¹³C{¹H} NMR



^{19}F NMR

(S)-2-Amino-3-[(R)-1-(fluorosulfonyl)indolin-3-yl]propanoic acid (21**×HCl)****¹H NMR****¹³C{¹H} NMR**

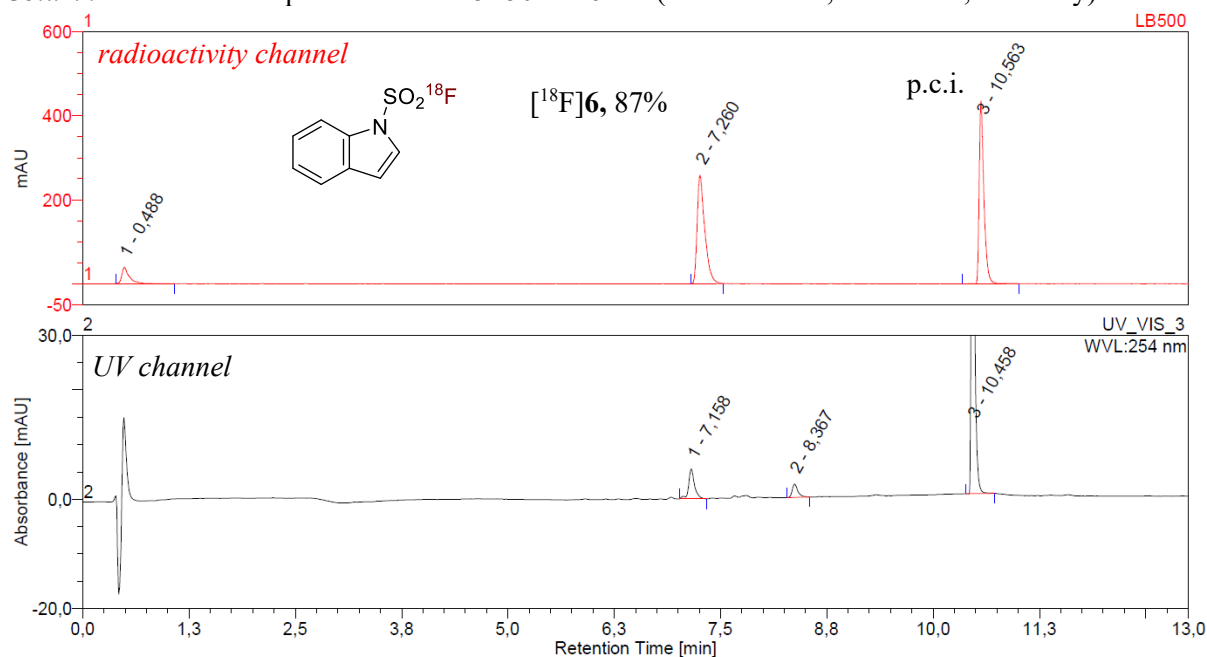
¹⁹F NMR



Chromatograms for determination of RCCs

1*H*-Indole-1-sulfonyl [¹⁸F]fluoride ([¹⁸F]6)

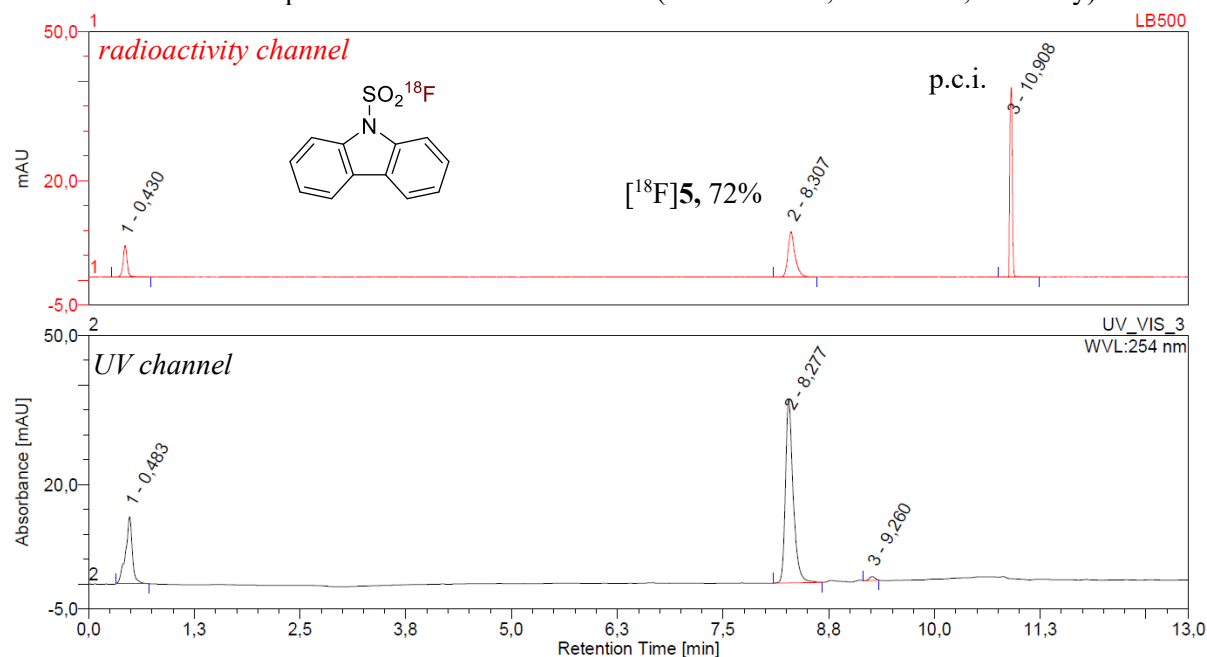
Column: Chromolith® SpeedROD RP-18e 50 × 4.6mm (Merck KGaA, Darmstadt, Germany)



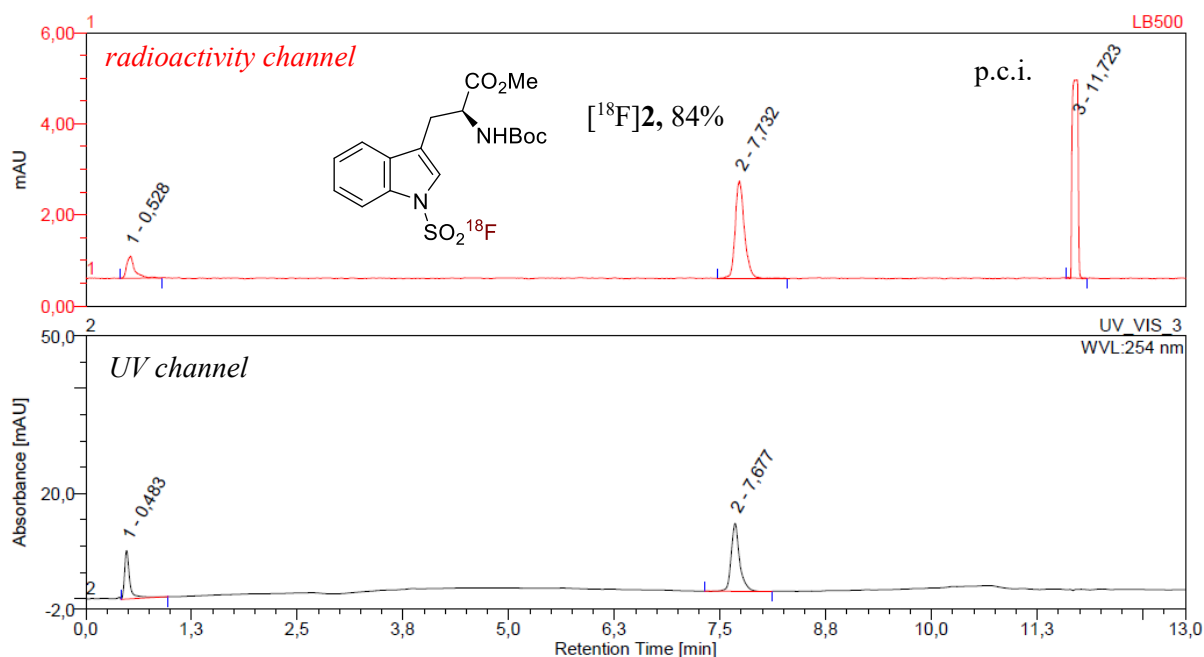
Eluent: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN, 10–12.5 min: 90% MeCN, 12.5–13 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min. P.c.i. – post-column injection.^[1]

9*H*-Carbazole-9-sulfonyl [¹⁸F]fluoride ([¹⁸F]5)

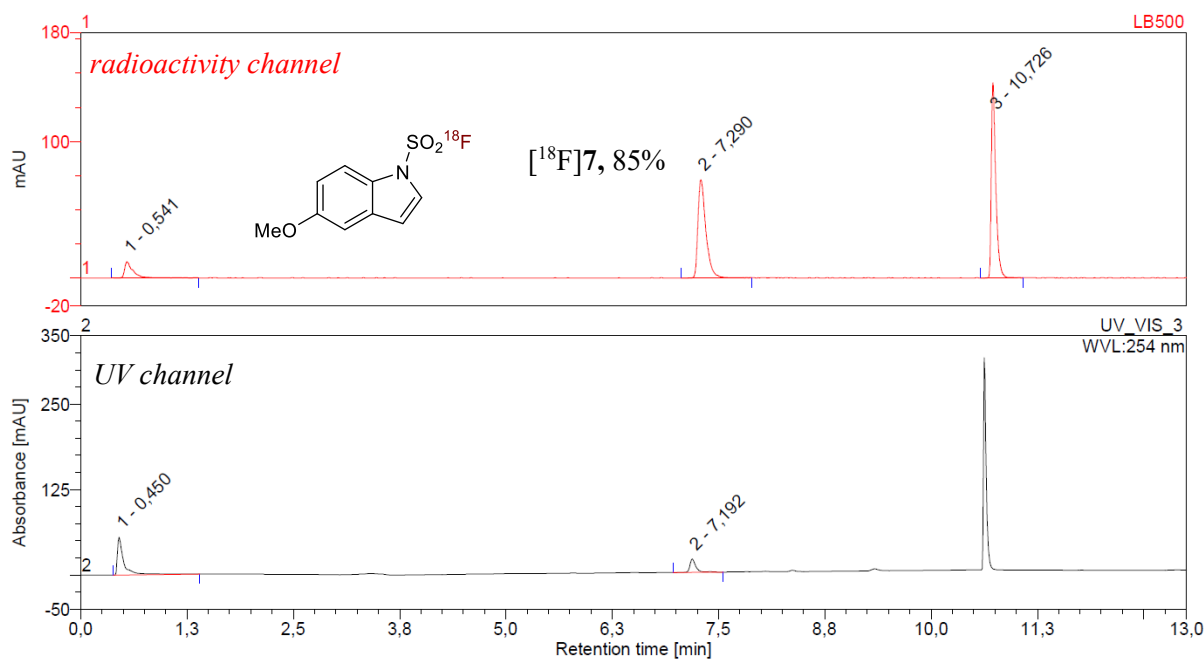
Column: Chromolith® SpeedROD RP-18e 50 × 4.6mm (Merck KGaA, Darmstadt, Germany)



Eluent: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN, 10–12.5 min: 90% MeCN, 12.5–13 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min. P.c.i. – post-column injection.

N α -(*tert*-Butoxycarbonyl)-1-([18 F]fluorosulfonyl)-L-tryptophan methyl ester ([18 F]**2**)Column: Chromolith® SpeedROD RP-18e 50 $\times$ 4.6mm (Merck KGaA, Darmstadt, Germany)

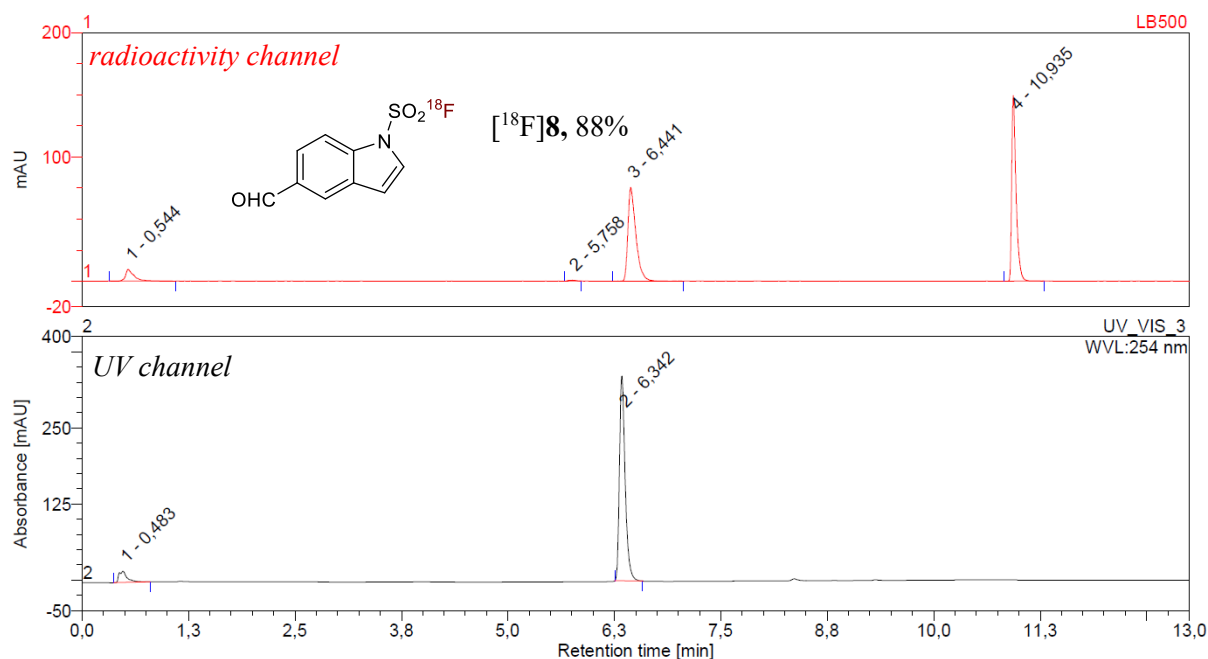
Eluent: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN $\rightarrow$ 90% MeCN, 10–12.5 min: 90% MeCN, 12.5–13 min: 10% MeCN $\rightarrow$ 90% MeCN; flow-rate: 2 mL/ min. P.c.i. – post-column injection.

5-Methoxy-1*H*-indole-1-sulfonyl fluoride ([18 F]**7**)Column: Chromolith® SpeedROD RP-18e 50 $\times$ 4.6mm (Merck KGaA, Darmstadt, Germany)

Eluent: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN $\rightarrow$ 90% MeCN, 10–12.5 min: 90% MeCN, 12.5–13 min: 10% MeCN $\rightarrow$ 90% MeCN; flow-rate: 2 mL/ min. P.c.i. – post-column injection.

5-Formyl-1*H*-indole-1-sulfonyl fluoride ($[^{18}\text{F}]\mathbf{8}$)

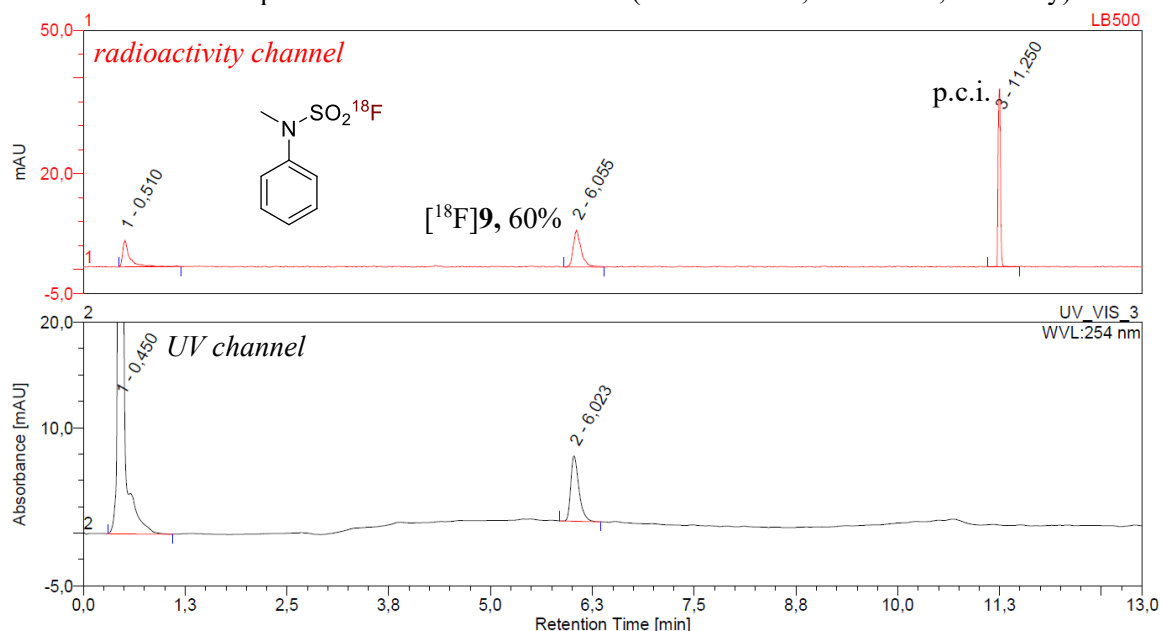
Column: Chromolith® SpeedROD RP-18e 50 × 4.6mm (Merck KGaA, Darmstadt, Germany)



Eluent: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN, 10–12.5 min: 90% MeCN, 12.5–13 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min. P.c.i. – post-column injection.

Methyl(phenyl)sulfamoyl $[^{18}\text{F}]\text{fluoride}$ ($[^{18}\text{F}]\mathbf{9}$)

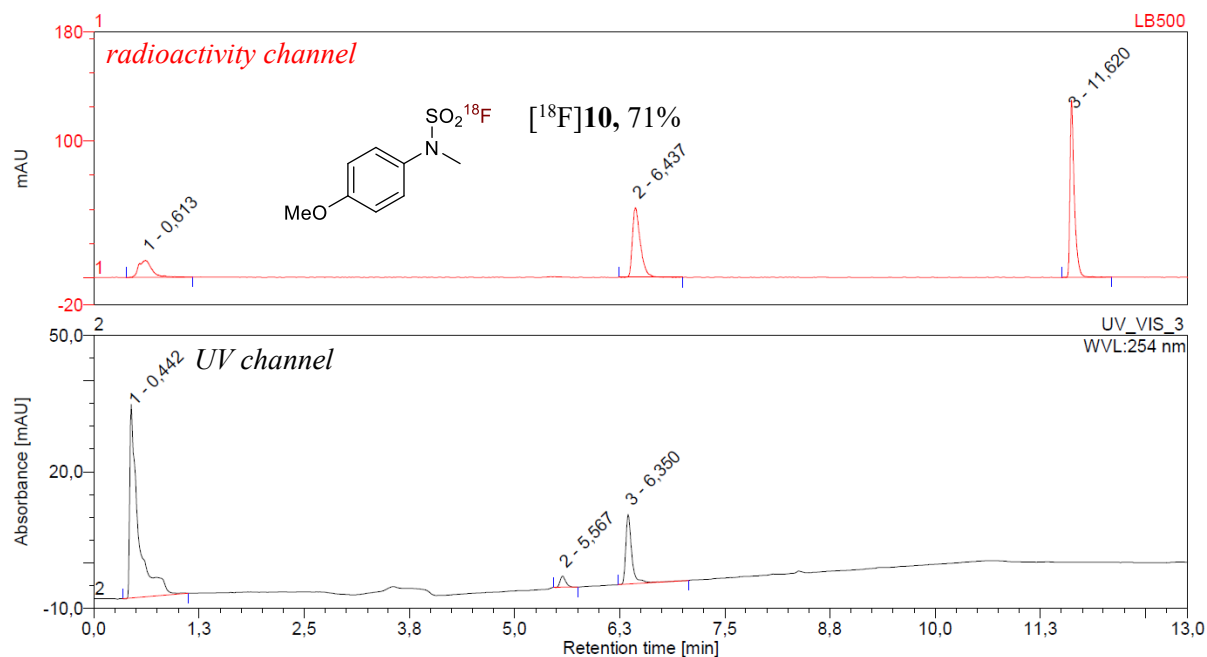
Column: Chromolith® SpeedROD RP-18e 50 × 4.6mm (Merck KGaA, Darmstadt, Germany)



Eluent: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN, 10–12.5 min: 90% MeCN, 12.5–13 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min. P.c.i. – post-column injection.

(4-Methoxyphenyl)(methyl)sulfamoyl fluoride ($[^{18}\text{F}]\mathbf{10}$)

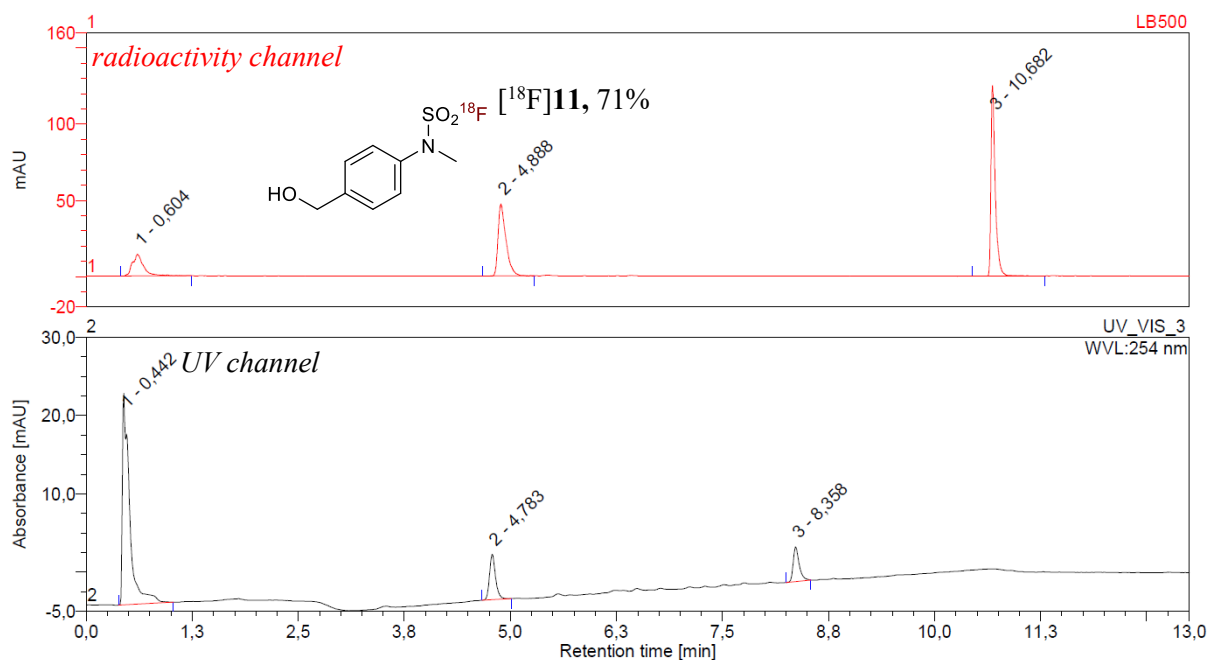
Column: Chromolith® SpeedROD RP-18e 50 × 4.6mm (Merck KGaA, Darmstadt, Germany)



Eluent: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN, 10–12.5 min: 90% MeCN, 12.5–13 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min. P.c.i. – post-column injection.

(4-(Hydroxymethyl)phenyl)(methyl)sulfamoyl fluoride ($[^{18}\text{F}]\mathbf{11}$)

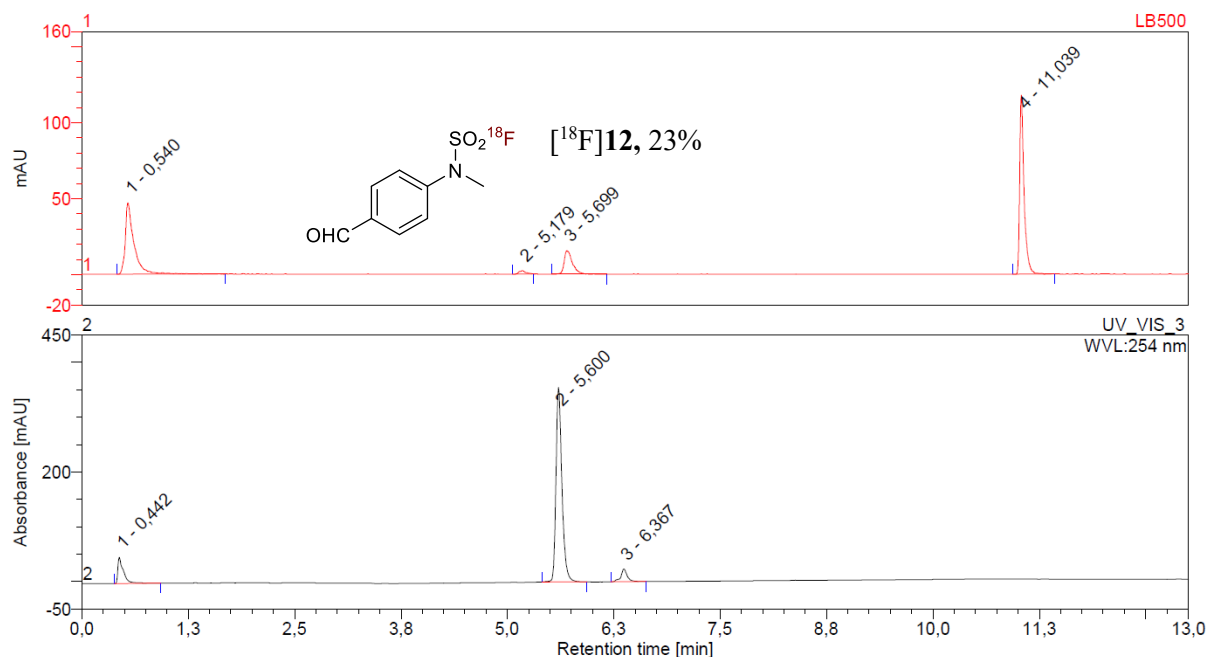
Column: Chromolith® SpeedROD RP-18e 50 × 4.6mm (Merck KGaA, Darmstadt, Germany)



Eluent: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN, 10–12.5 min: 90% MeCN, 12.5–13 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min. P.c.i. – post-column injection.

(4-Formylphenyl)(methyl)sulfamoyl fluoride ($[^{18}\text{F}]\mathbf{12}$)

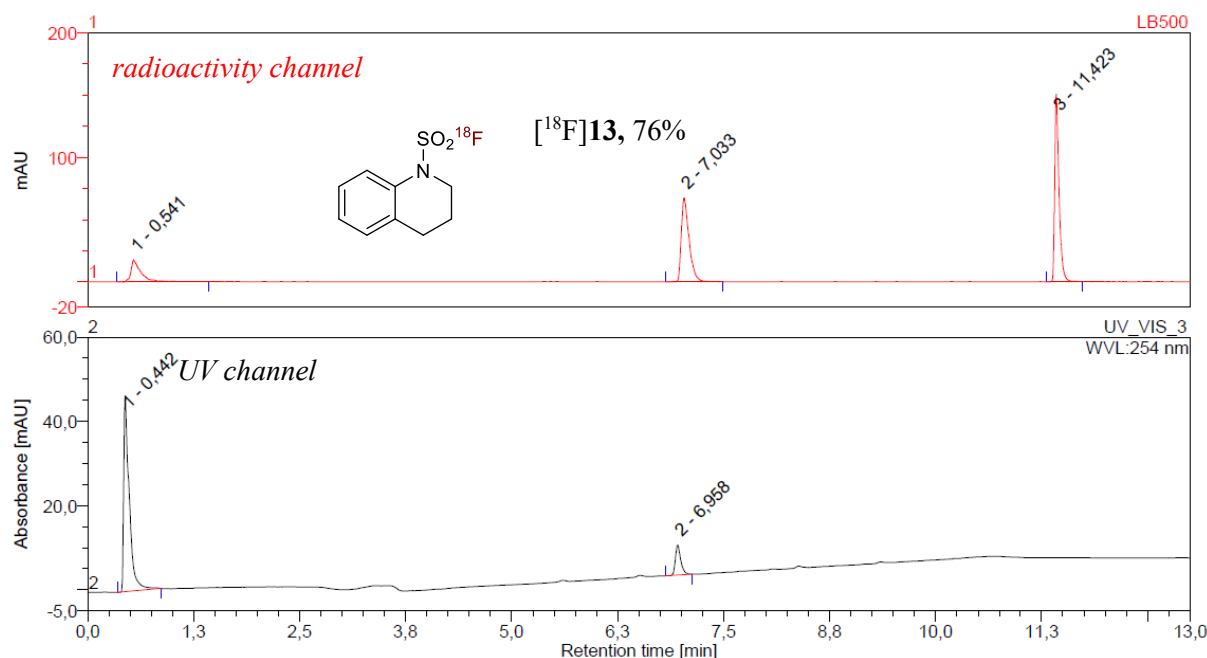
Column: Chromolith® SpeedROD RP-18e 50 × 4.6mm (Merck KGaA, Darmstadt, Germany)



Eluent: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN, 10–12.5 min: 90% MeCN, 12.5–13 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min. P.c.i. – post-column injection.

3,4-Dihydroquinoline-1(2H)-sulfonyl fluoride ($[^{18}\text{F}]\mathbf{13}$)

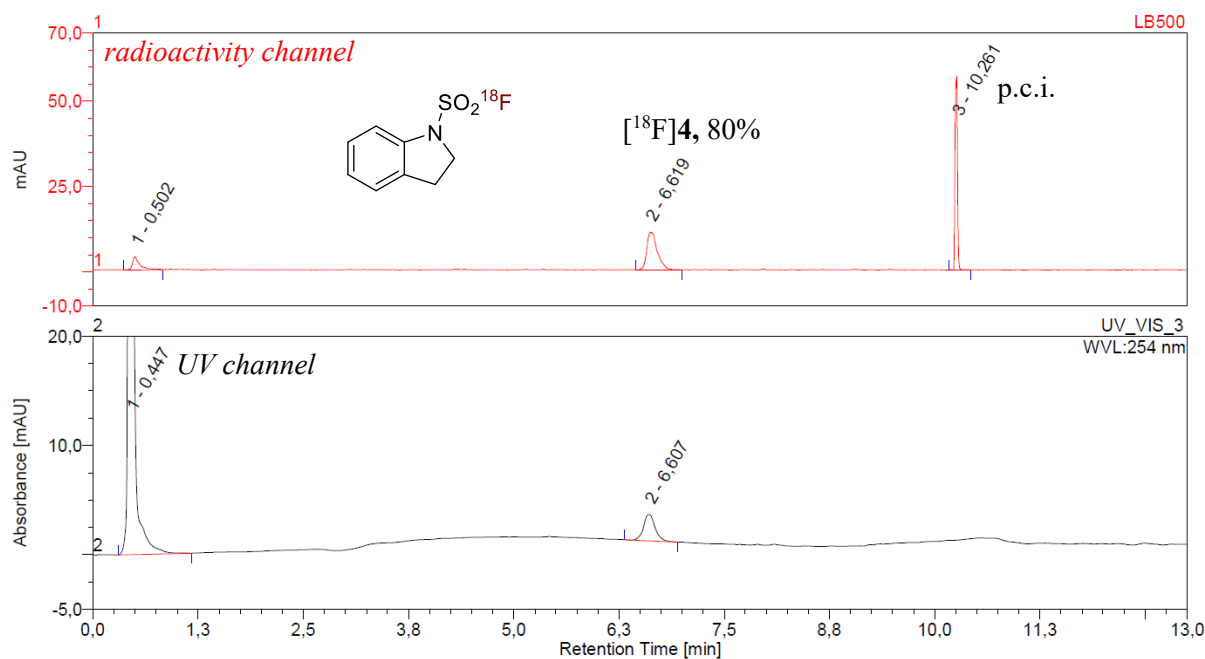
Column: Chromolith® SpeedROD RP-18e 50 × 4.6mm (Merck KGaA, Darmstadt, Germany)



Eluent: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN, 10–12.5 min: 90% MeCN, 12.5–13 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min. P.c.i. – post-column injection.

Indoline-1-sulfonyl $[^{18}\text{F}]$ fluoride ($[^{18}\text{F}]\mathbf{4}$)

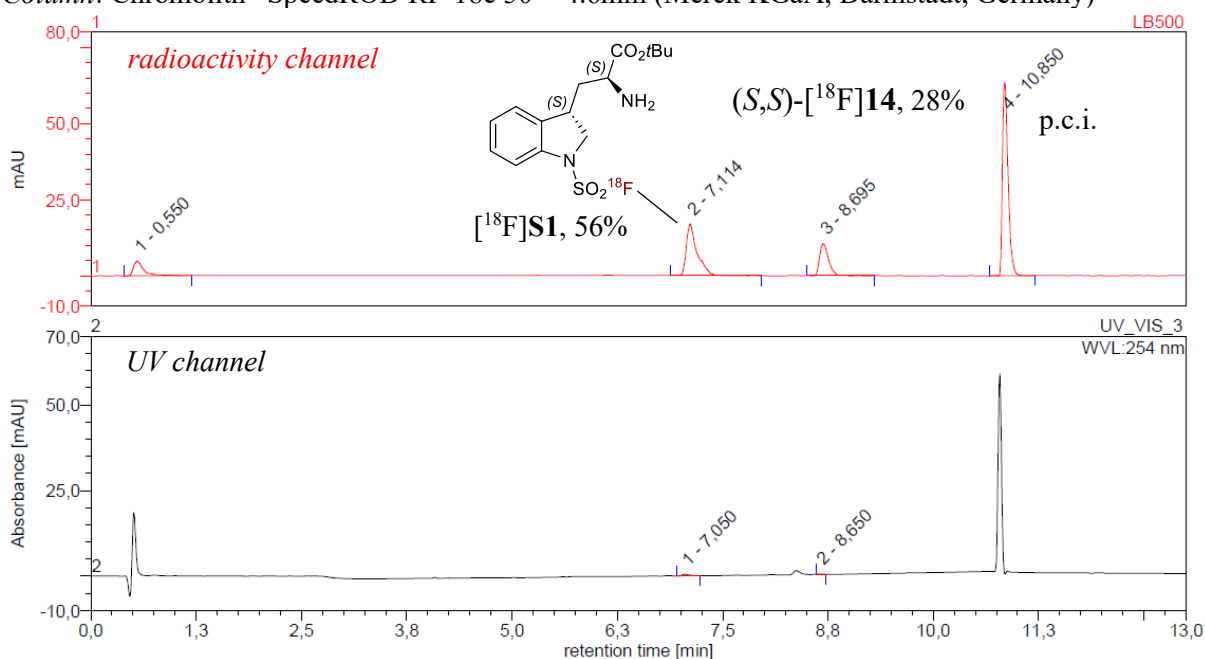
Column: Chromolith® SpeedROD RP-18e 50 × 4.6mm (Merck KGaA, Darmstadt, Germany)



Eluent: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN, 10–12.5 min: 90% MeCN, 12.5–13 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min. P.c.i. – post-column injection.

tert-Butyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-[(*S*)-1-([¹⁸F]fluorosulfonyl)indolin-3-yl]propanoate {(*S,S*)-[¹⁸F]14}

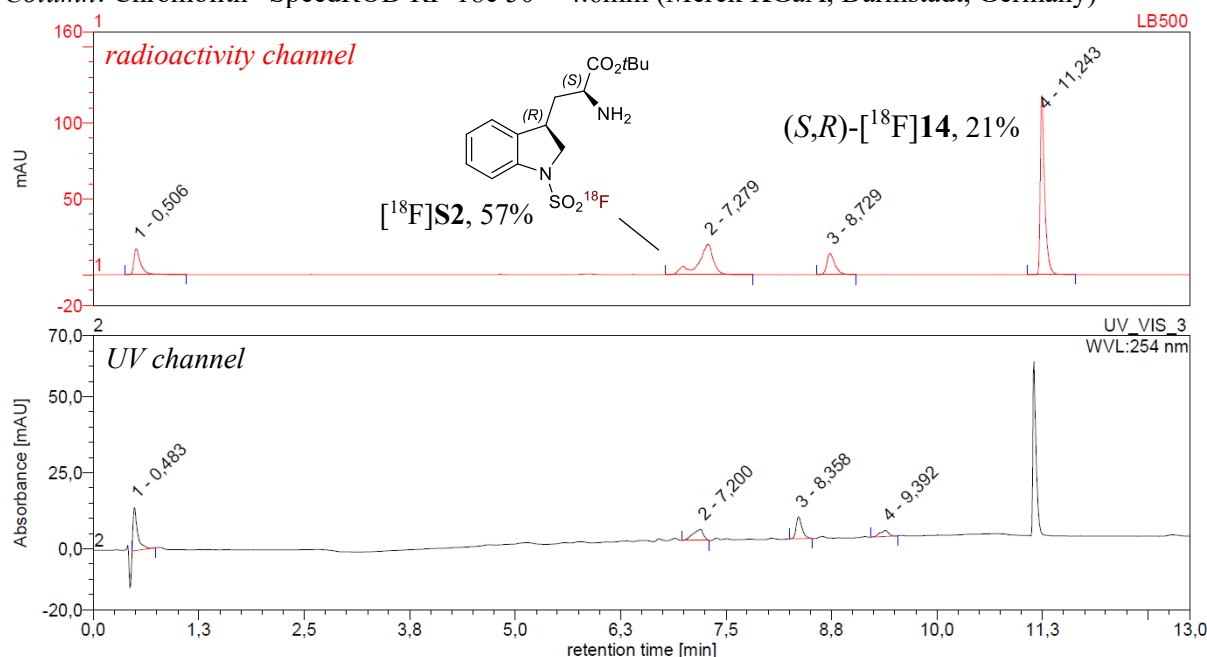
Column: Chromolith® SpeedROD RP-18e 50 × 4.6mm (Merck KGaA, Darmstadt, Germany)



Eluent: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN, 10–12.5 min: 90% MeCN, 12.5–13 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min. P.c.i. – post-column injection.

tert-Butyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-[(*R*)-1-([¹⁸F]fluorosulfonyl)indolin-3-yl]propanoate {(*S,R*)-[¹⁸F]**14**}

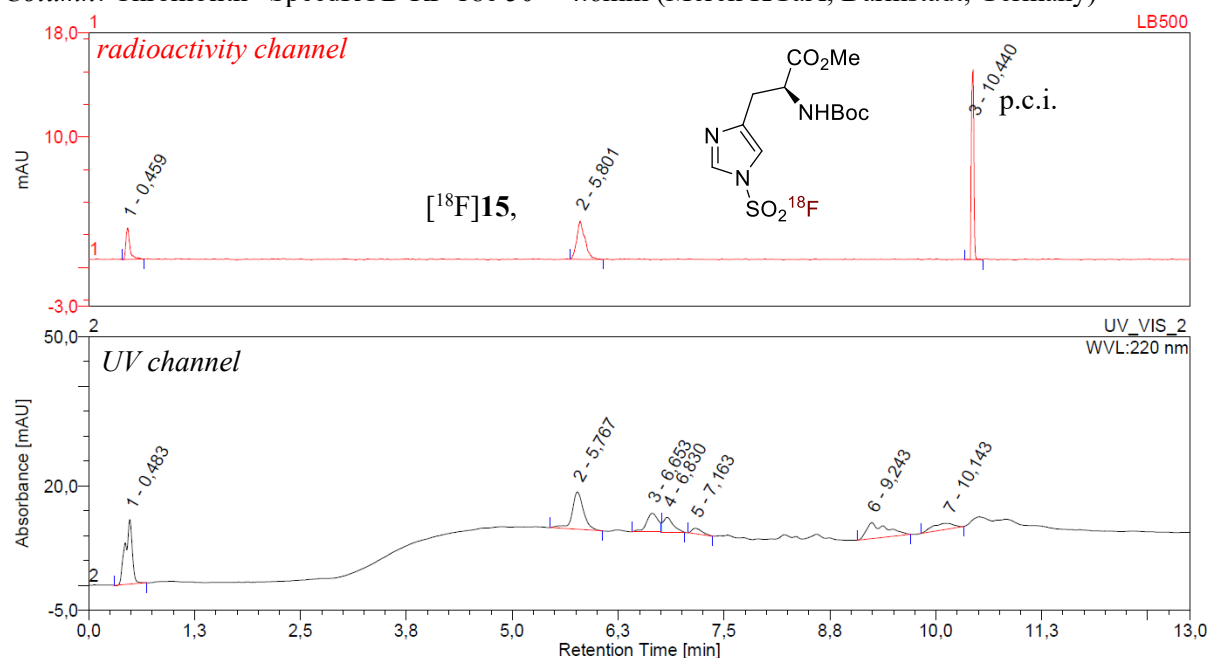
Column: Chromolith® SpeedROD RP-18e 50 × 4.6mm (Merck KGaA, Darmstadt, Germany)



Eluent: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN, 10–12.5 min: 90% MeCN, 12.5–13 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min. P.c.i. – post-column injection.

Methyl *N*_α-(*tert*-butoxycarbonyl)-*N*_{im}-([¹⁸F]fluorosulfonyl)-L-histidinate ([¹⁸F]**15**)

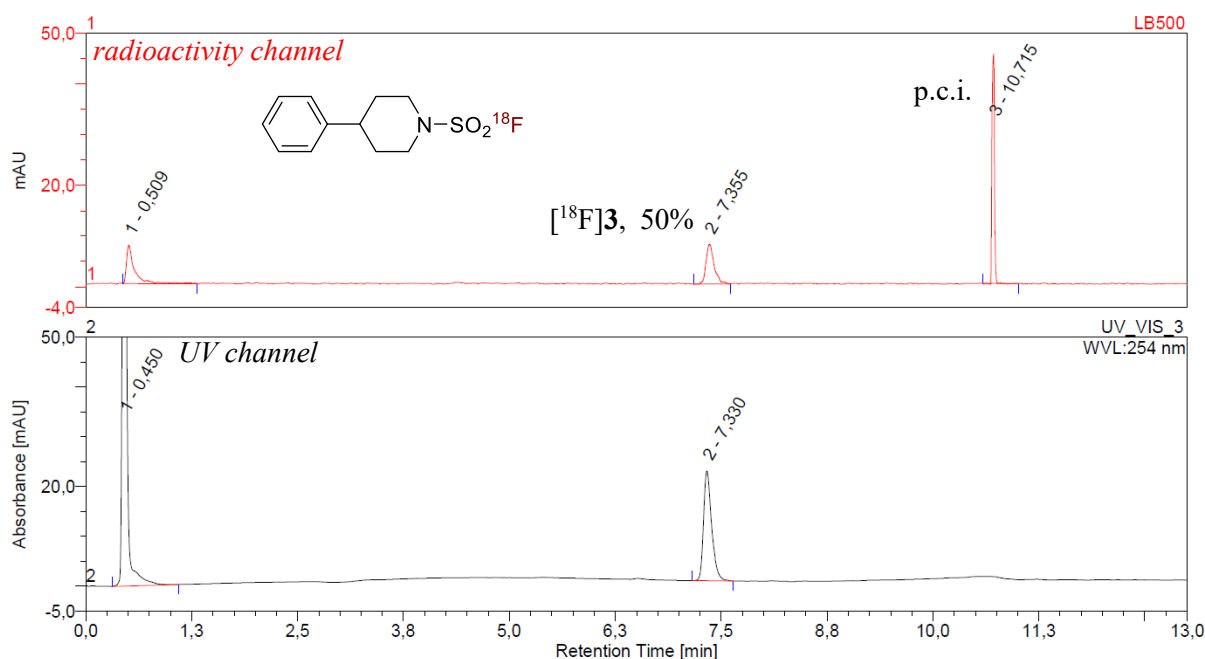
Column: Chromolith® SpeedROD RP-18e 50 × 4.6mm (Merck KGaA, Darmstadt, Germany)



Eluent: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN, 10–12.5 min: 90% MeCN, 12.5–13 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min. P.c.i. – post-column injection.

4-Phenylpiperidine-1-sulfonyl [¹⁸F]fluoride ([¹⁸F]**3**)

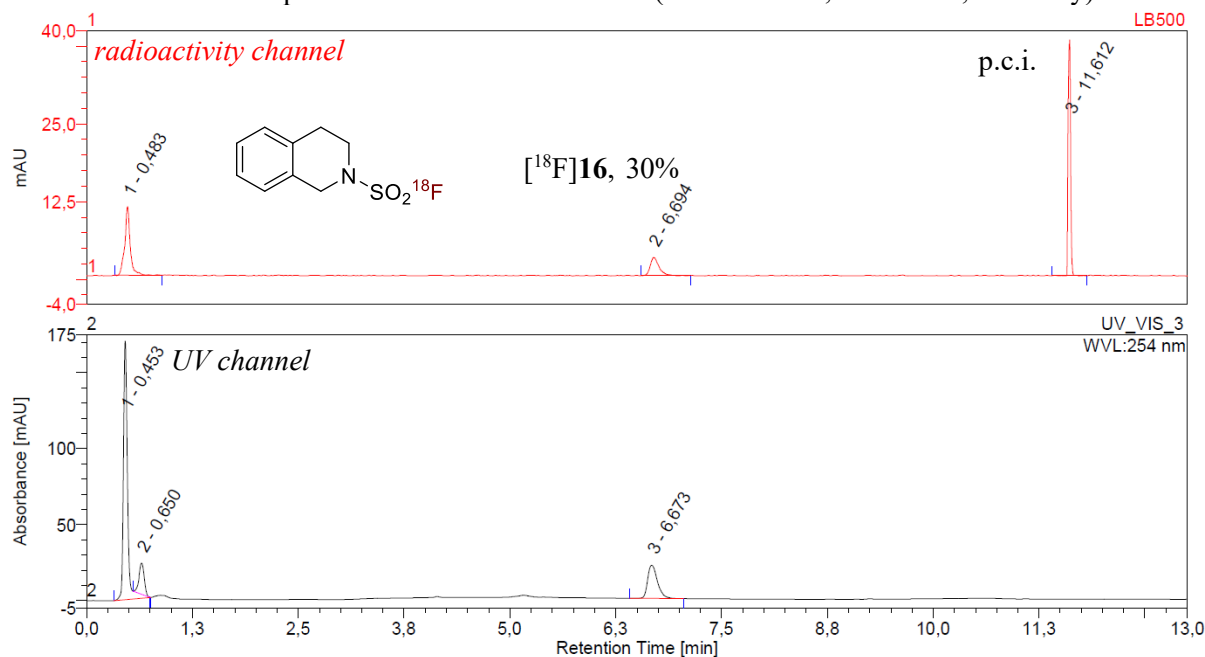
Column: Chromolith® SpeedROD RP-18e 50 × 4.6mm (Merck KGaA, Darmstadt, Germany)



Eluent: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN, 10–12.5 min: 90% MeCN, 12.5–13 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min. P.c.i. – post-column injection.

1,2,3,4-Tetrahydroisoquinoline-2-sulfonyl [¹⁸F]fluoride ([¹⁸F]16)

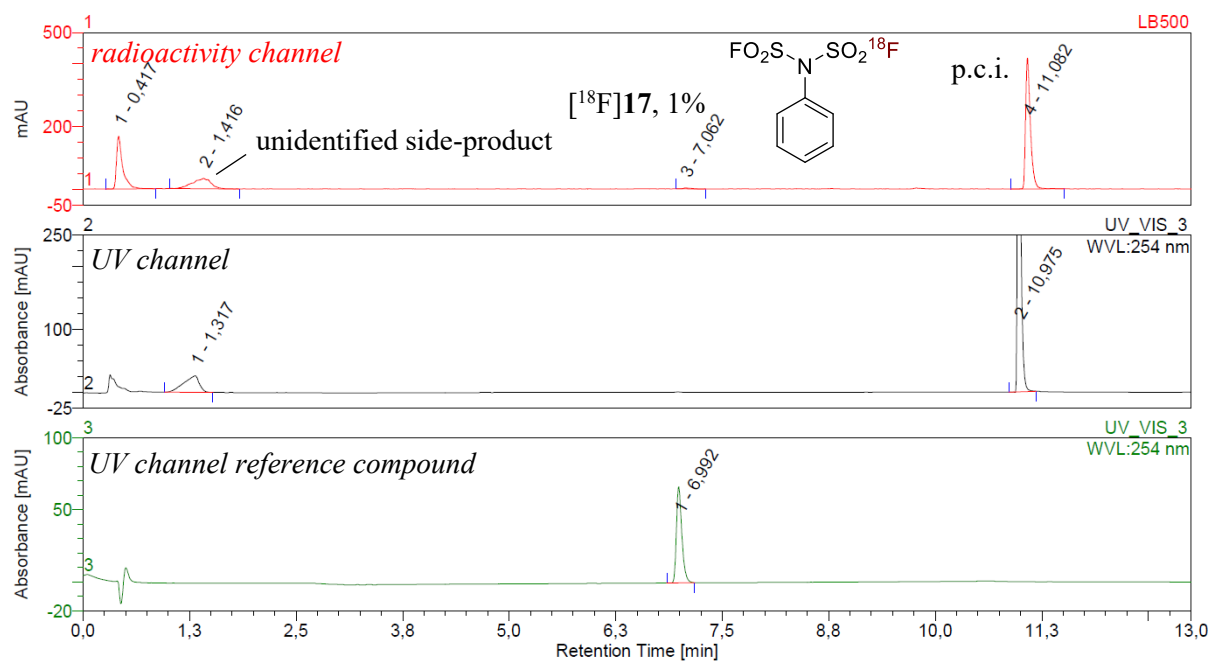
Column: Chromolith® SpeedROD RP-18e 50 × 4.6mm (Merck KGaA, Darmstadt, Germany)



Eluent: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN, 10–12.5 min: 90% MeCN, 12.5–13 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min. P.c.i. – post-column injection.

Phenyliminodisulfonyl [¹⁸F]difluoride ([¹⁸F]17)

Column: Chromolith® SpeedROD RP-18e 50 × 4.6mm (Merck KGaA, Darmstadt, Germany)

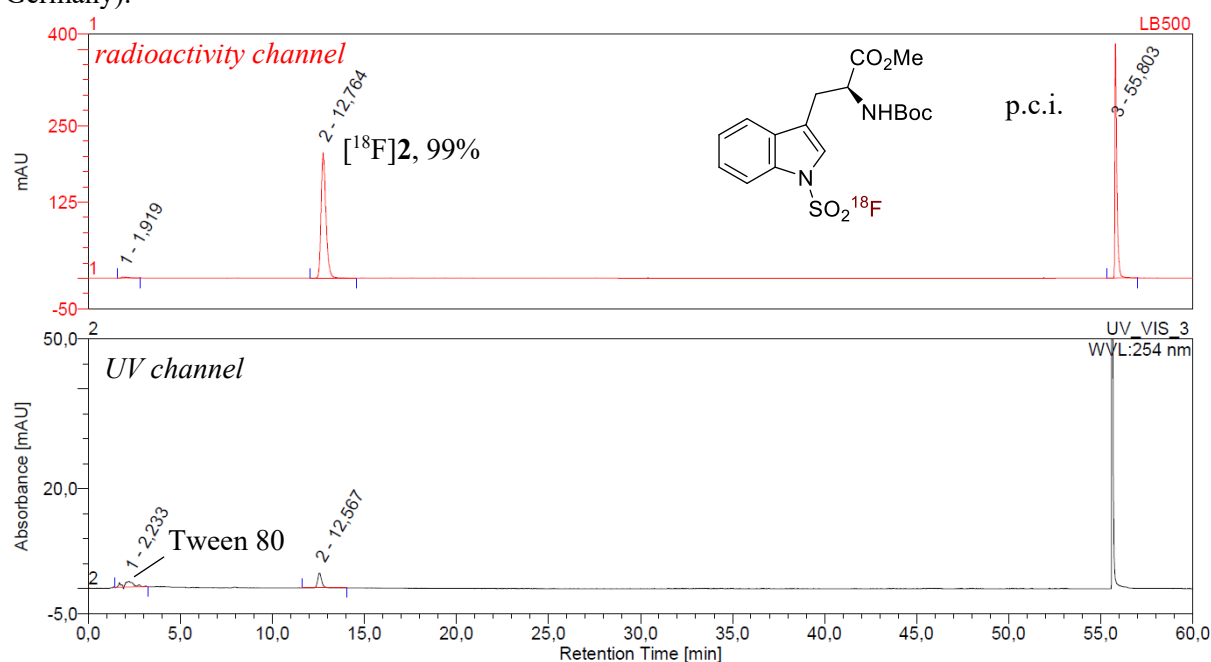


Eluent: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN, 10–12.5 min: 90% MeCN, 12.5–13 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min. P.c.i. – post-column injection.

Chromatograms of purified compounds

*N*_α-(*tert*-Butoxycarbonyl)-1-([¹⁸F]fluorosulfonyl)-L-tryptophan methyl ester ([¹⁸F]**2**)

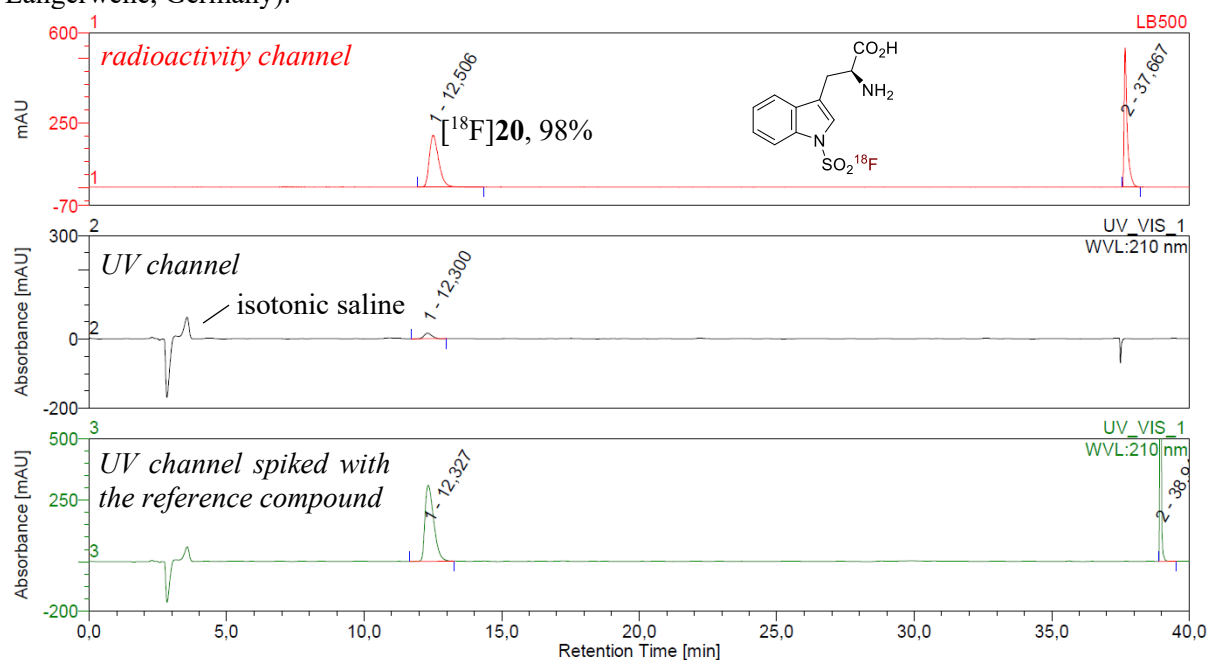
Column: MultoKrom® 100–5 C18 (250×2 mm) (CS-Chromatographie Service GmbH, Langerwehe, Germany).



Eluent: 0–60 min: 70% MeCN; flow-rate: 1 mL/ min.

1-([¹⁸F]Fluorosulfonyl)-L-tryptophan ([¹⁸F]**20**)

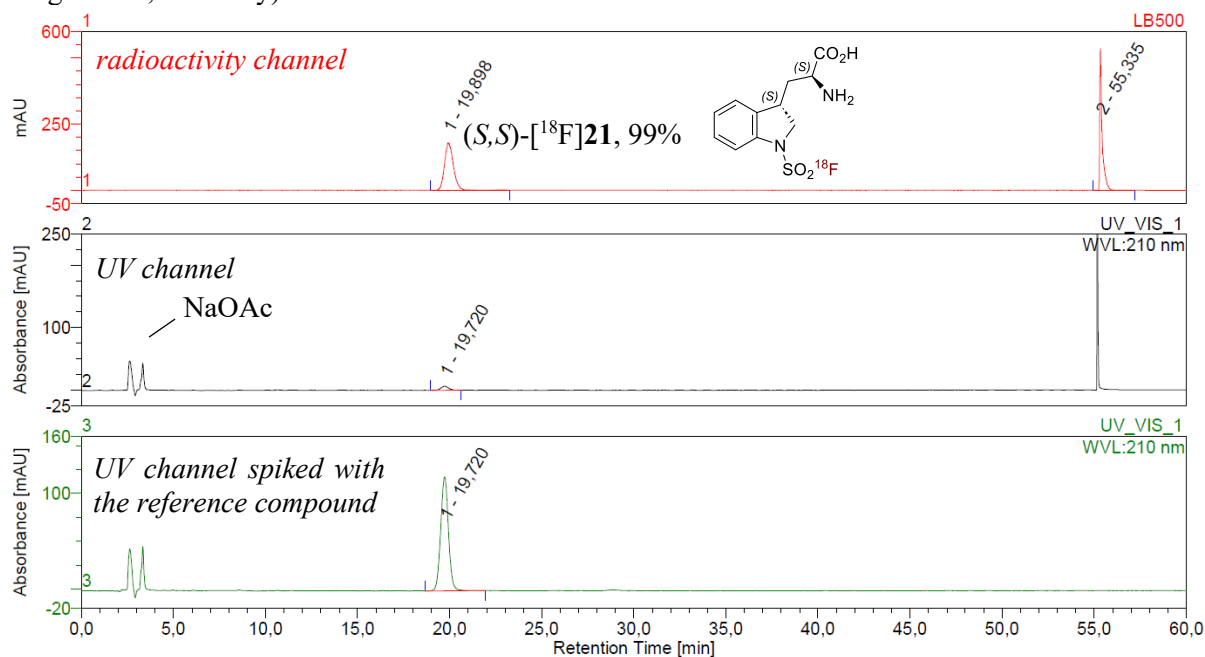
Column: MultoKrom® 100–5 C18 AQ (250×2 mm) (CS-Chromatographie Service GmbH, Langerwehe, Germany).



Eluent: 0–40 min: 30% MeCN (0.1% TFA); flow-rate: 1 mL/ min.

(S)-2-Amino-3--{(S)-1-([¹⁸F]fluorosulfonyl)indolin-3-yl}propanoic acid {(S,S)-[¹⁸F]21}

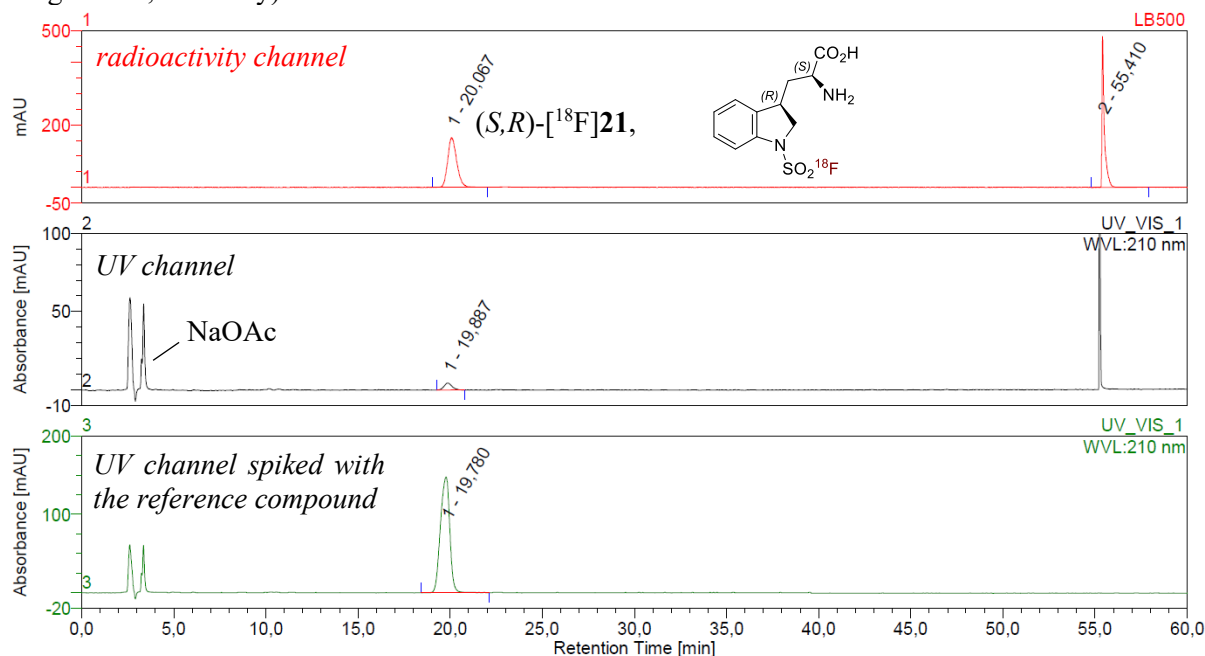
Column: MultoKrom® 100–5 C18 AQ (250×2 mm) (CS-Chromatographie Service GmbH, Langerwehe, Germany).



Eluent: 0 – 60 min: 30% EtOH in 0.01 M NaOAc-buffer (pH 5.3); flow-rate: 1 mL/ min.

(S)-2-Amino-3--{(R)-1-([¹⁸F]fluorosulfonyl)indolin-3-yl}propanoic acid {(S,R)-[¹⁸F]16}

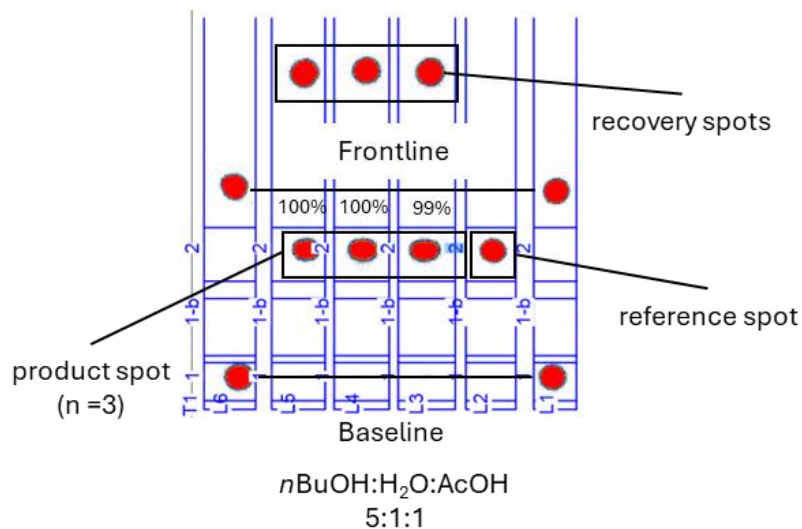
Column: MultoKrom® 100–5 C18 AQ (250×2 mm) (CS-Chromatographie Service GmbH, Langerwehe, Germany).



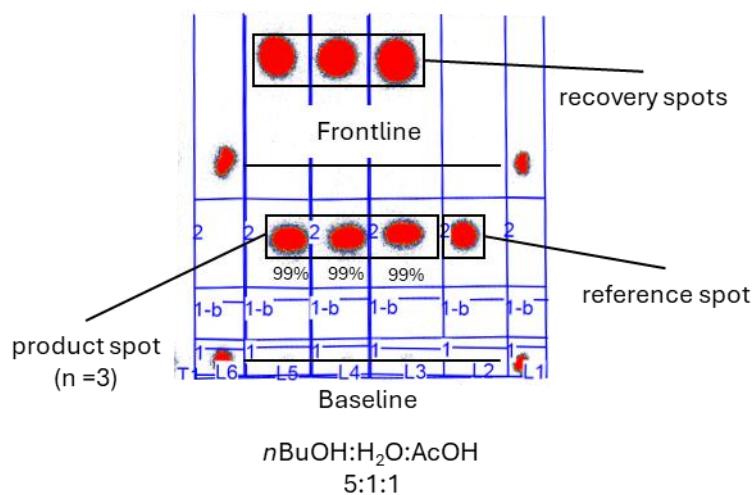
Eluent: 0 – 60 min: 30% EtOH in 0.01 M NaOAc-buffer (pH 5.3); flow-rate: 1 mL/ min.

Radio-TLCs: Blood serum stability tests (after 120 min)

1-([¹⁸F]Fluorosulfonyl)-L-tryptophan ([¹⁸F]**20**)



(*S*)-2-Amino-3--{(*S*)-1-([¹⁸F]fluorosulfonyl)indolin-3-yl}propanoic acid {(*S,S*)-[¹⁸F]**21**}



References

- [1] S. Humpert, C. Hoffmann, F. Neumaier, B. D. Zlatopolskiy, B. Neumaier, *Journal of Chromatography B* **2023**, 1228, 123847.

Supporting Information for

Aliphatic Sulfamoyl [^{18}F]Fluorides: Preparation via “Minimalist Green” Radiofluorination and Initial Biological Assessment

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^c University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Nuclear Medicine, Kerpener Straße 62, 50937, Cologne, Germany

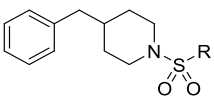
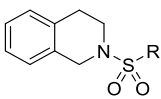
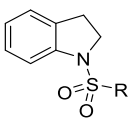
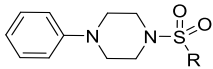
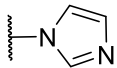
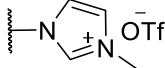
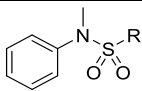
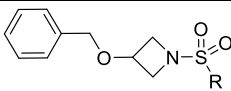
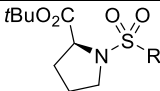
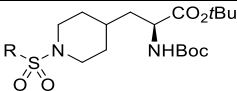
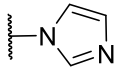
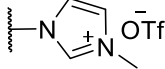
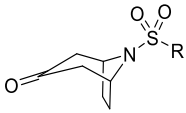
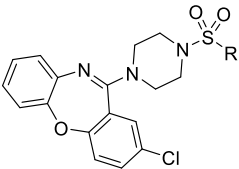
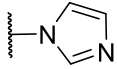
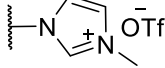
* correspondence: b.neumaier@fz-juelich.de

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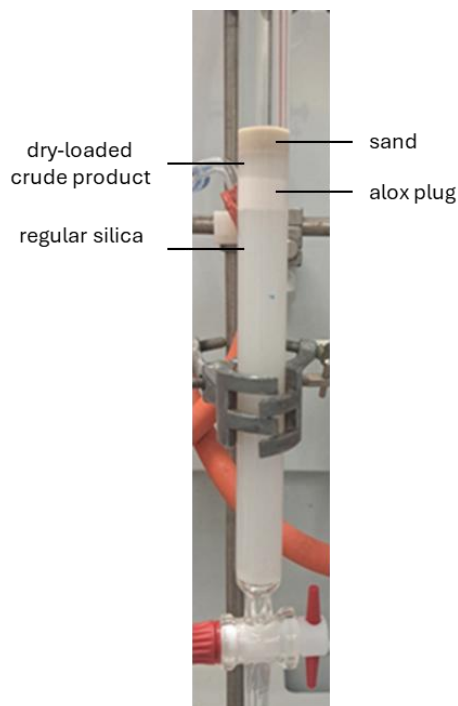
Overview on yields for each imidazolium precursor

Table S1 Overview on yields for each imidazolium precursor.

Nr.	Yield [%]								
R:									
		2a	97	2b	83	2c	85	2d	94
		3a	95	3b	91	3c	86	3d	95
		4a	82	4b	91	4c	90	4d	88
Σ		76		69		66		79	
									
		2e	70	2f	87	2g	81	2h	49
		3e	61	3f	67	3g	67	3h	84
		4e	85	4f	90	4g	90	4h	68
Σ		36		52		49		28	
									
		2i	90			2j	93		
		3i	11			3j	96		
		4i	92			4j	53		
Σ		9				47			

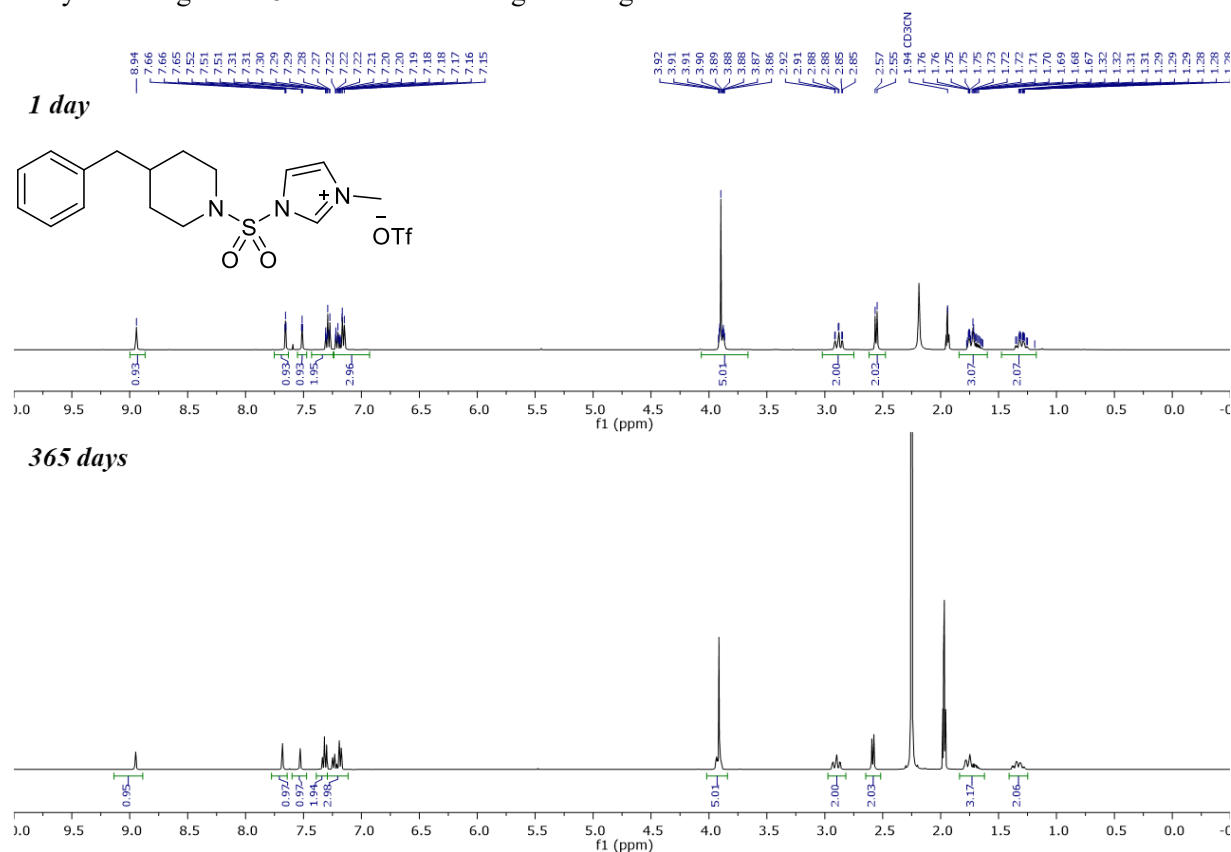
Column setup for sulfonyl imidazole purification

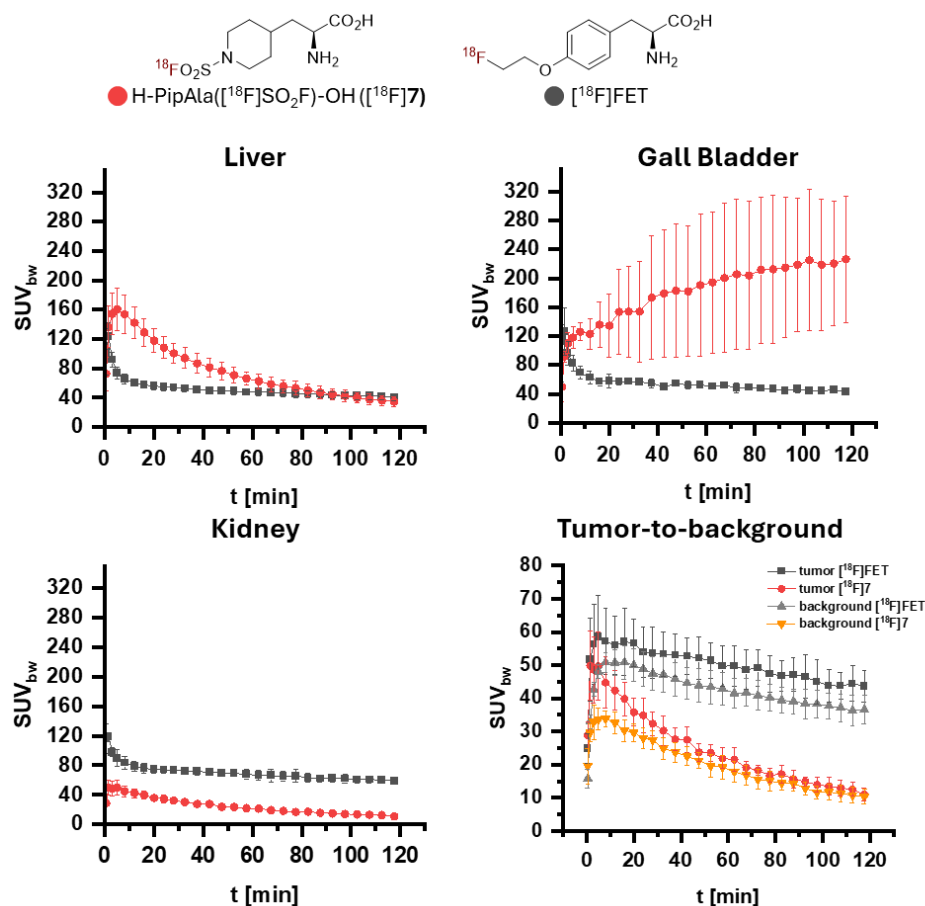
Fig. S1 Column setup for purification of sulfonyl imidazoles to prevent breakthrough of bistriflimide.



Stability of imidazolium salt **4a** during storage

Fig. S2 ^1H -NMR-spectrum (CD_3CN) of imidazolium precursor **4a** directly after preparation and after one year storage at -18°C under Ar. No signs of degradation were observed.

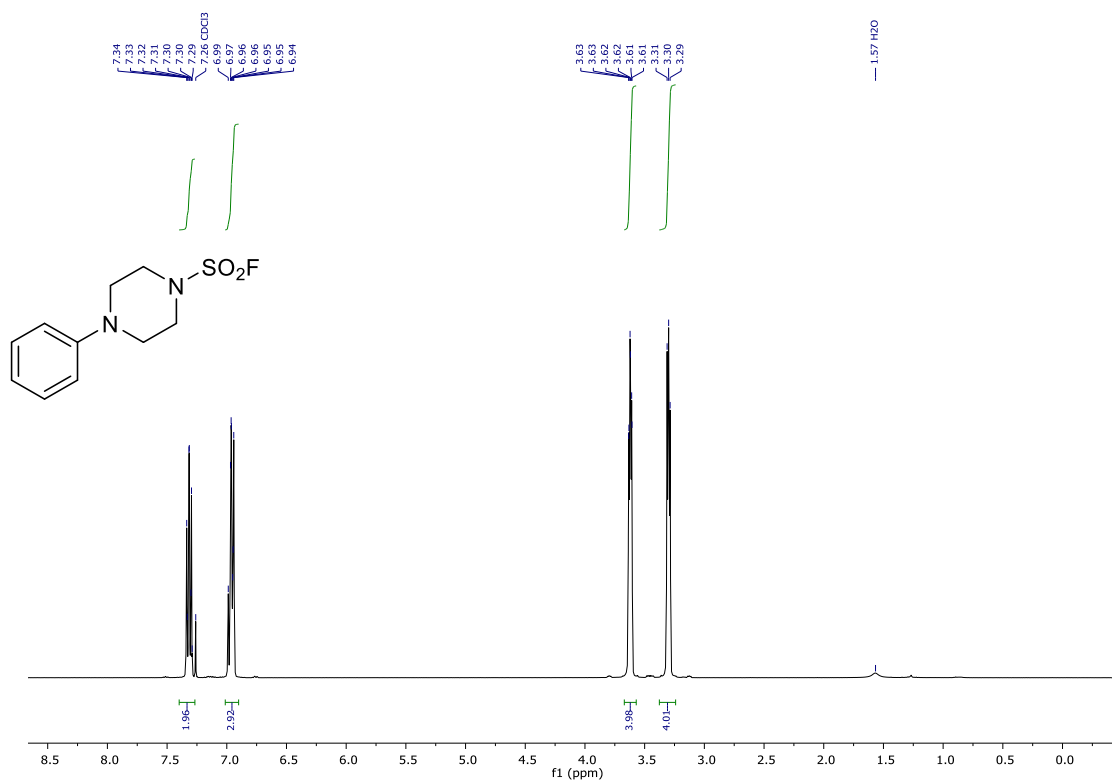
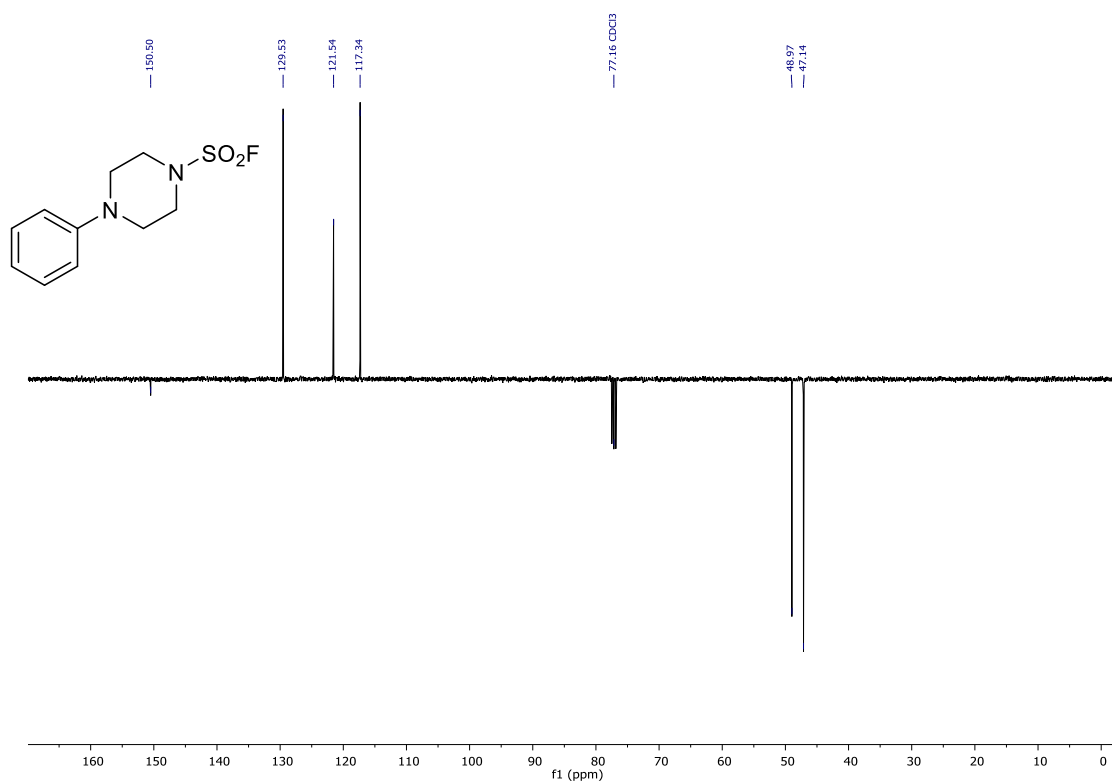


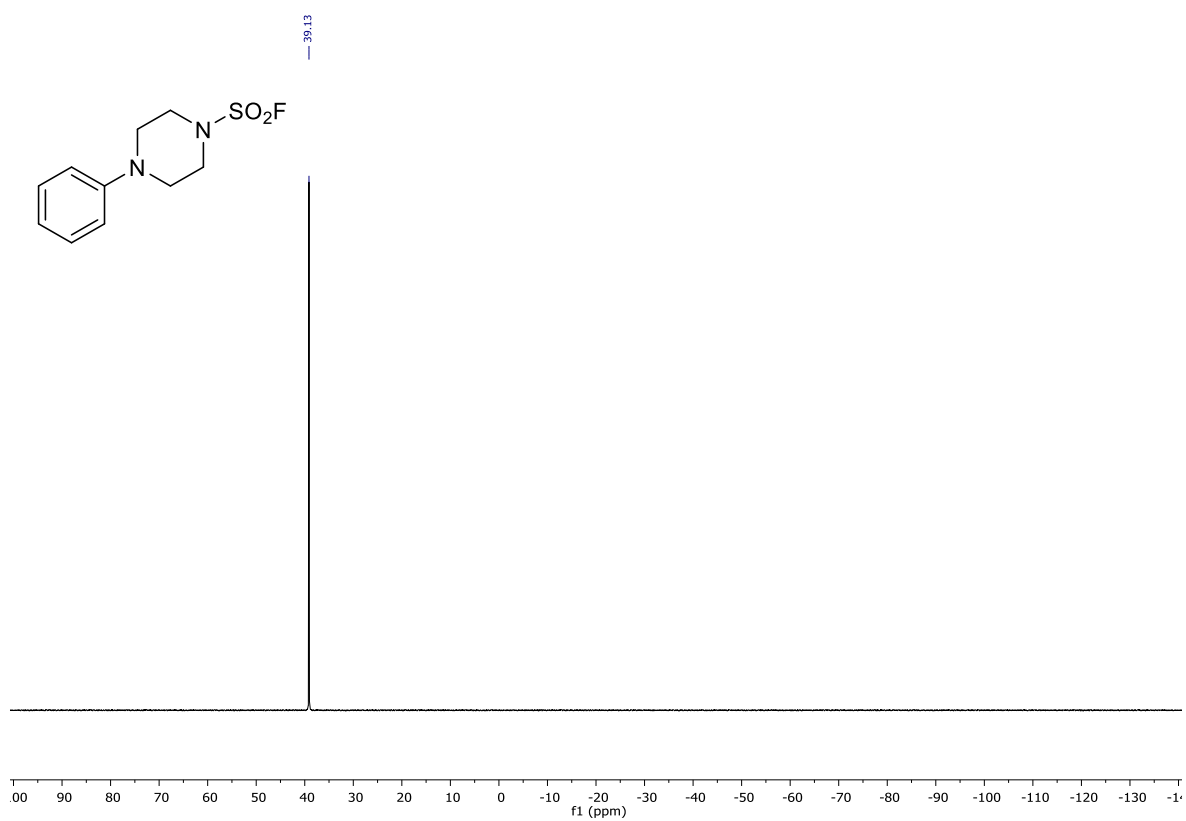
Time activity curves of [^{18}F]7 in subcutaneous mouse modelFig. S3 TACs of H-PipAla([^{18}F]SO $_2$ F)-OHPreparation of Ca(NTf $_2$) $_2$ Calcium(II) bis(trifluoromethanesulfonimide)^[1]

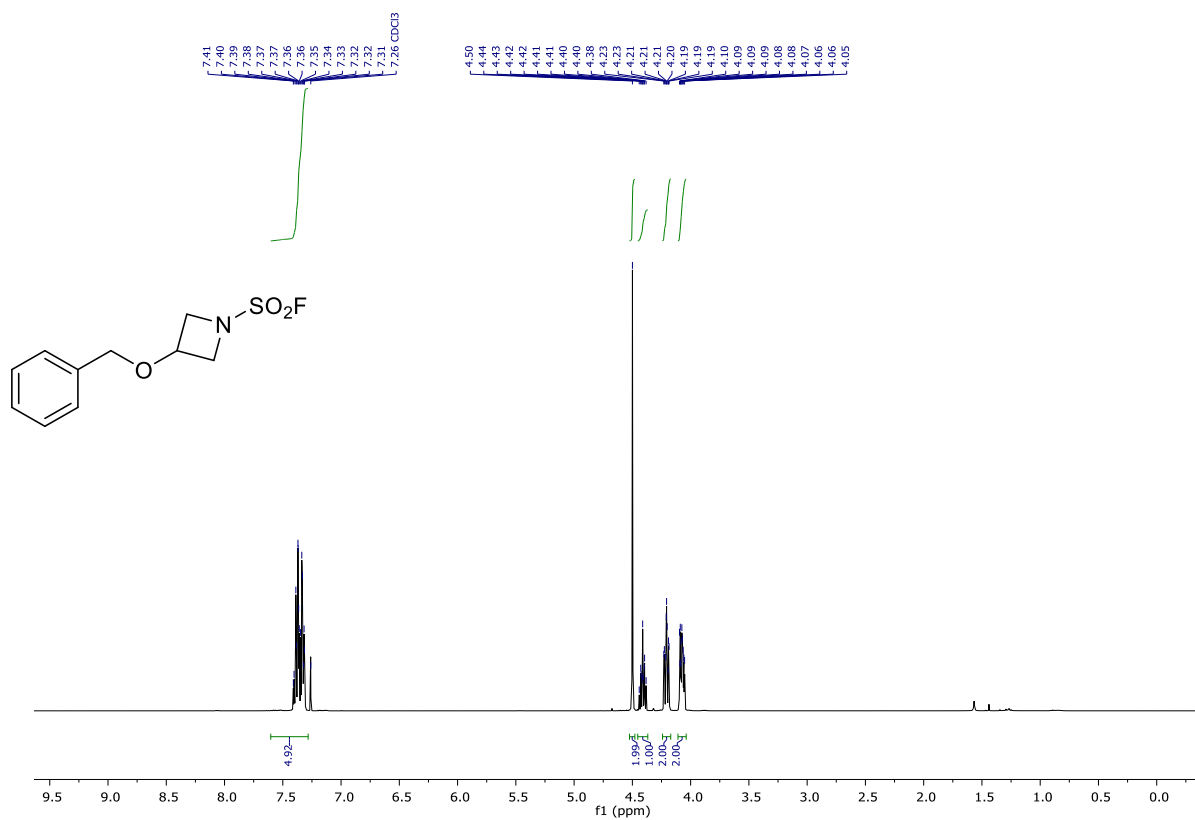
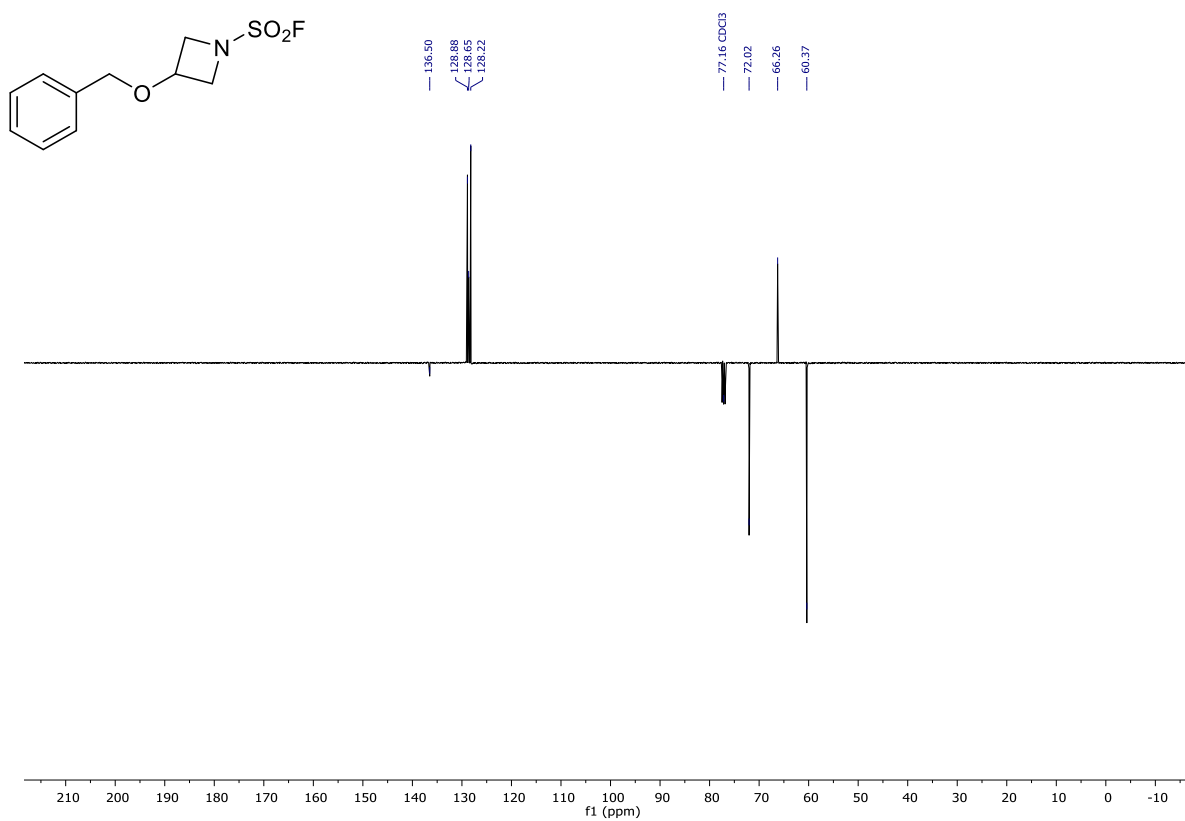
$\text{Ca}^{2+} \left[\begin{array}{c} \text{F}_3\text{C}-\text{S}(=\text{O})_2-\text{N}^--\text{S}(=\text{O})_2-\text{CF}_3 \\ \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \end{array} \right]_2$

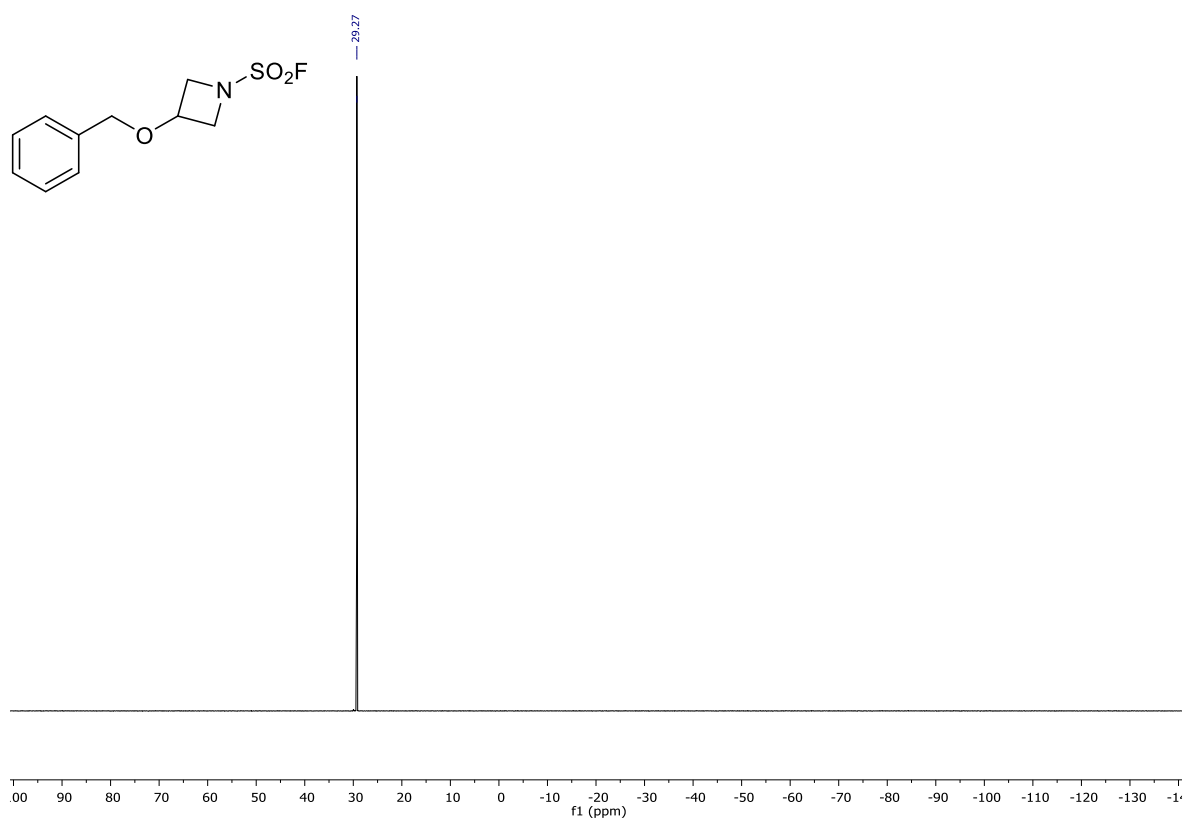
A solution of bistriflimidic acid (14.2 g, 50.5 mmol, 2.0 eq.) and CaCO $_3$ (2.52 g, 25.25 mmol, 1.0 eq.) in H $_2$ O (120 mL) was stirred for 24 h and concentrated under reduced pressure to afford the title compound (15.16 g, 25.25 mmol, quant.) as a colorless solid. ^{19}F NMR (376 MHz, D $_2$ O): δ -79.08.

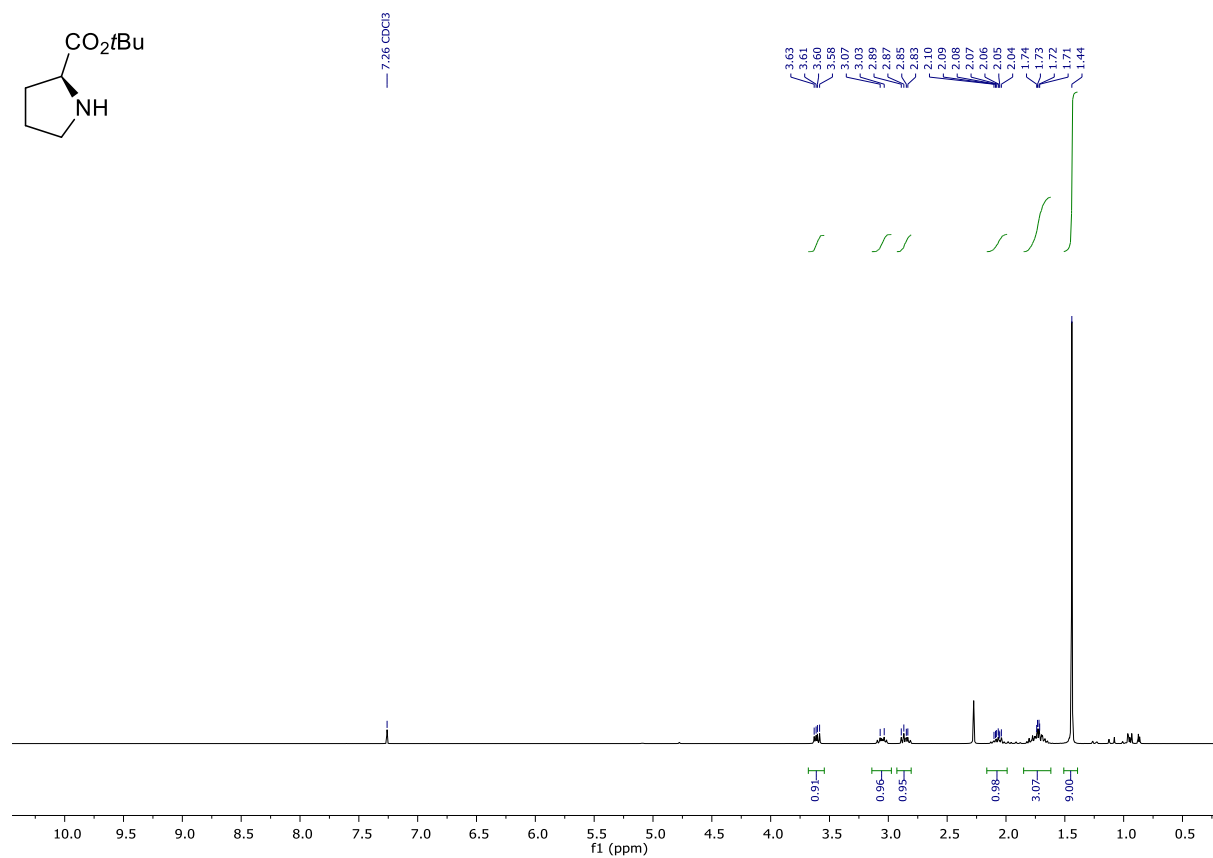
NMR spectra

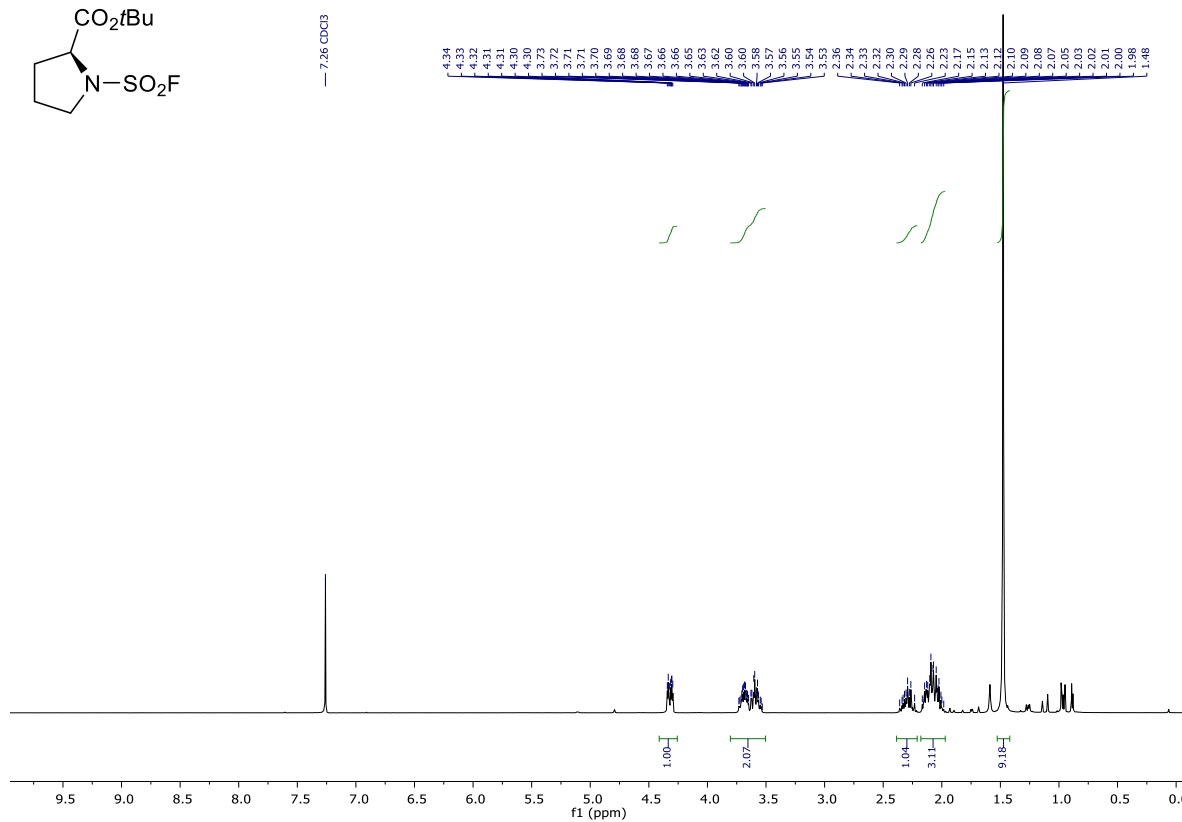
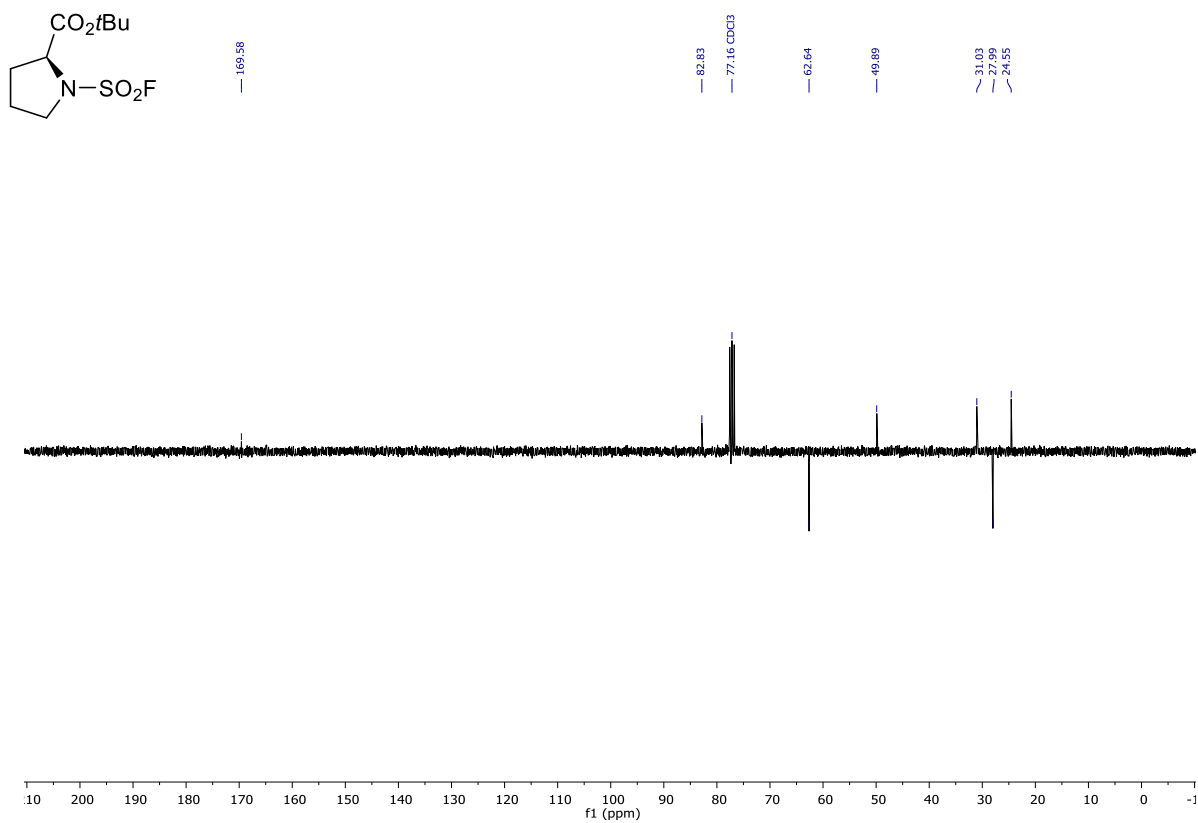
4-Phenylpiperazine-1-sulfonyl fluoride (**2d**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

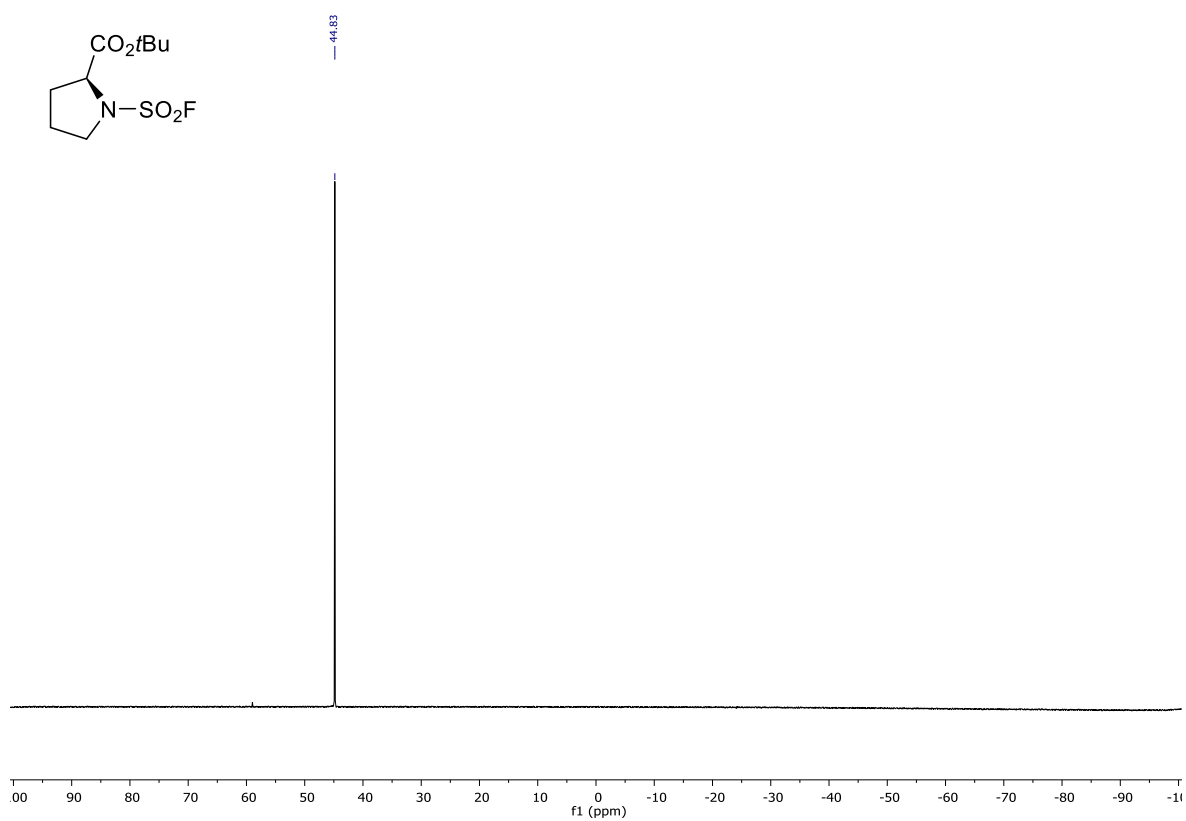
^{19}F NMR

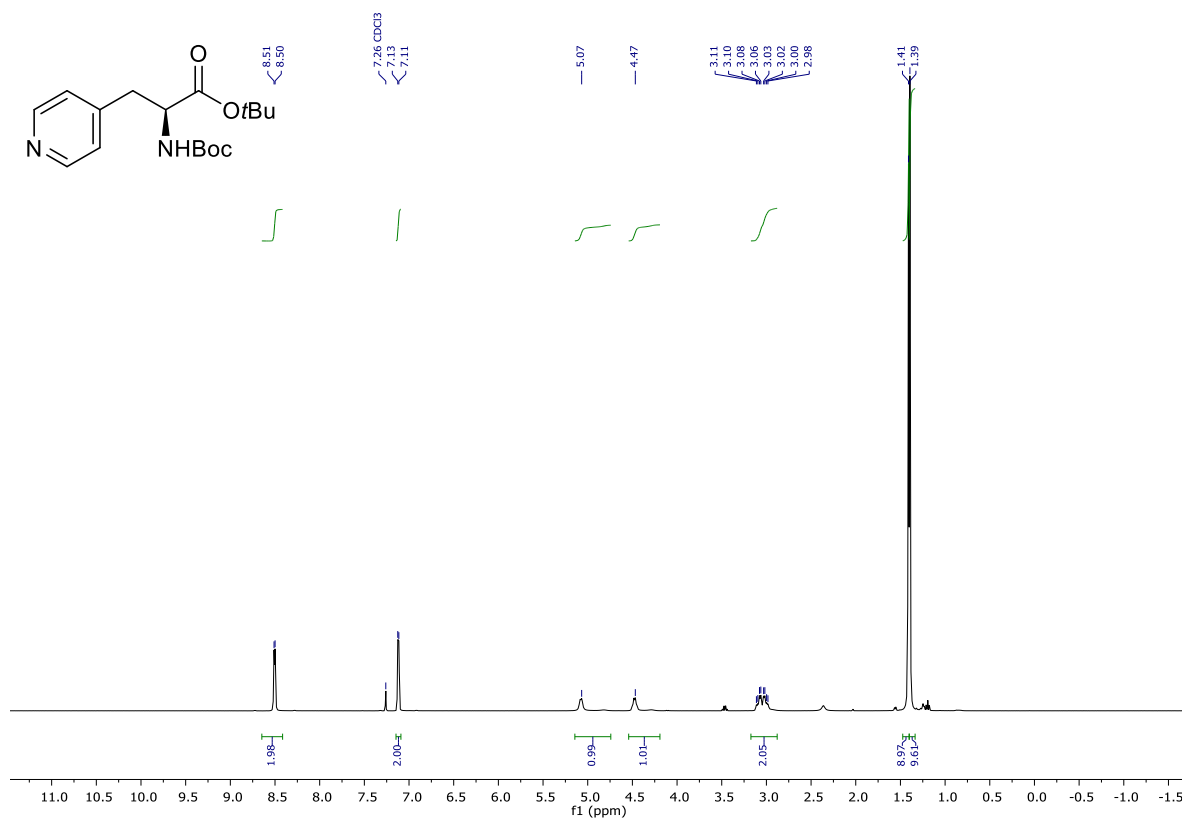
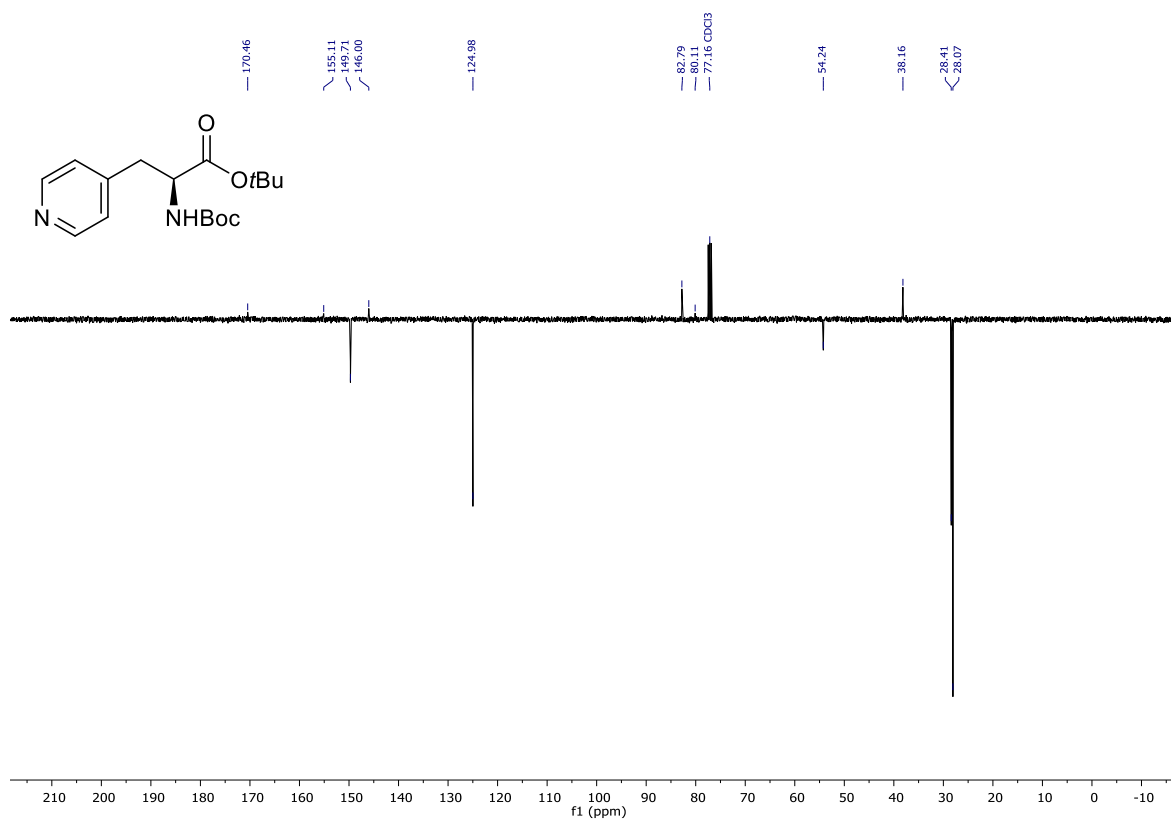
3-(Benzyloxy)azetidine-1-sulfonyl fluoride (**2f**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

^{19}F NMR

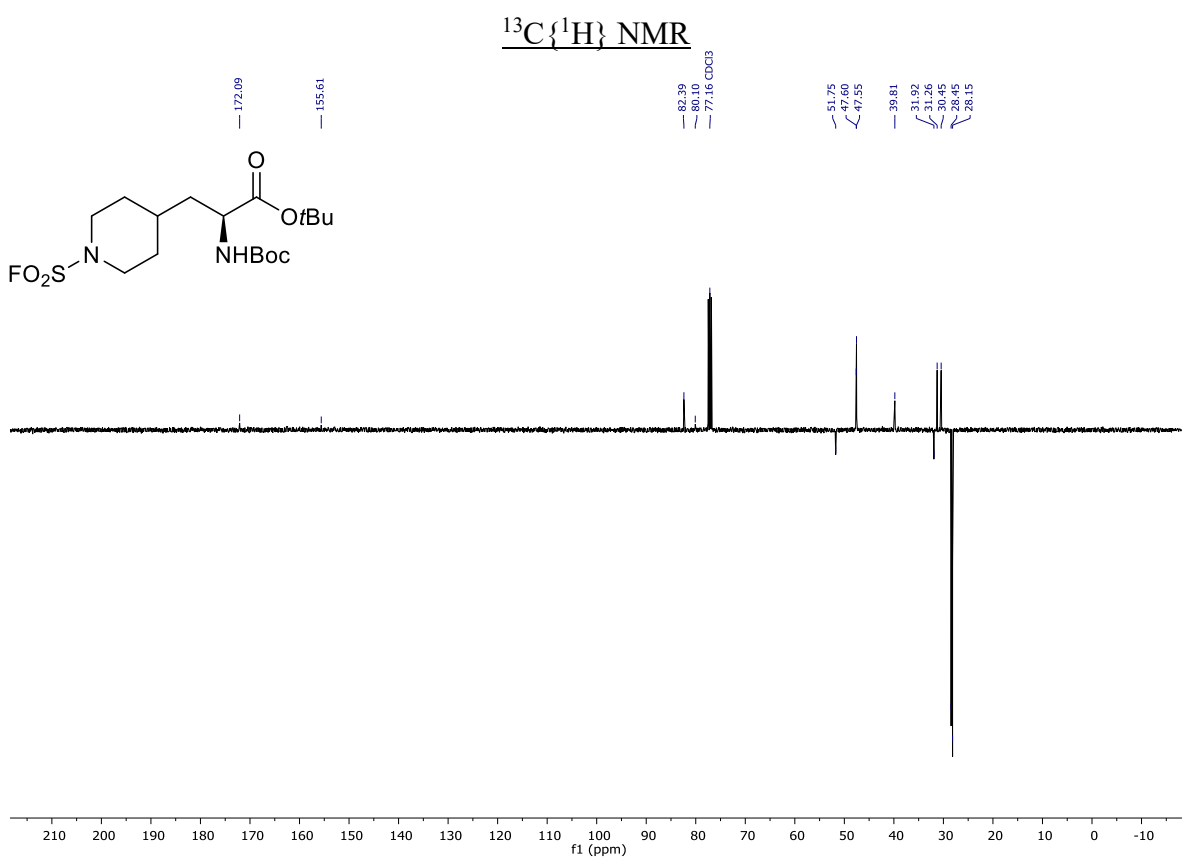
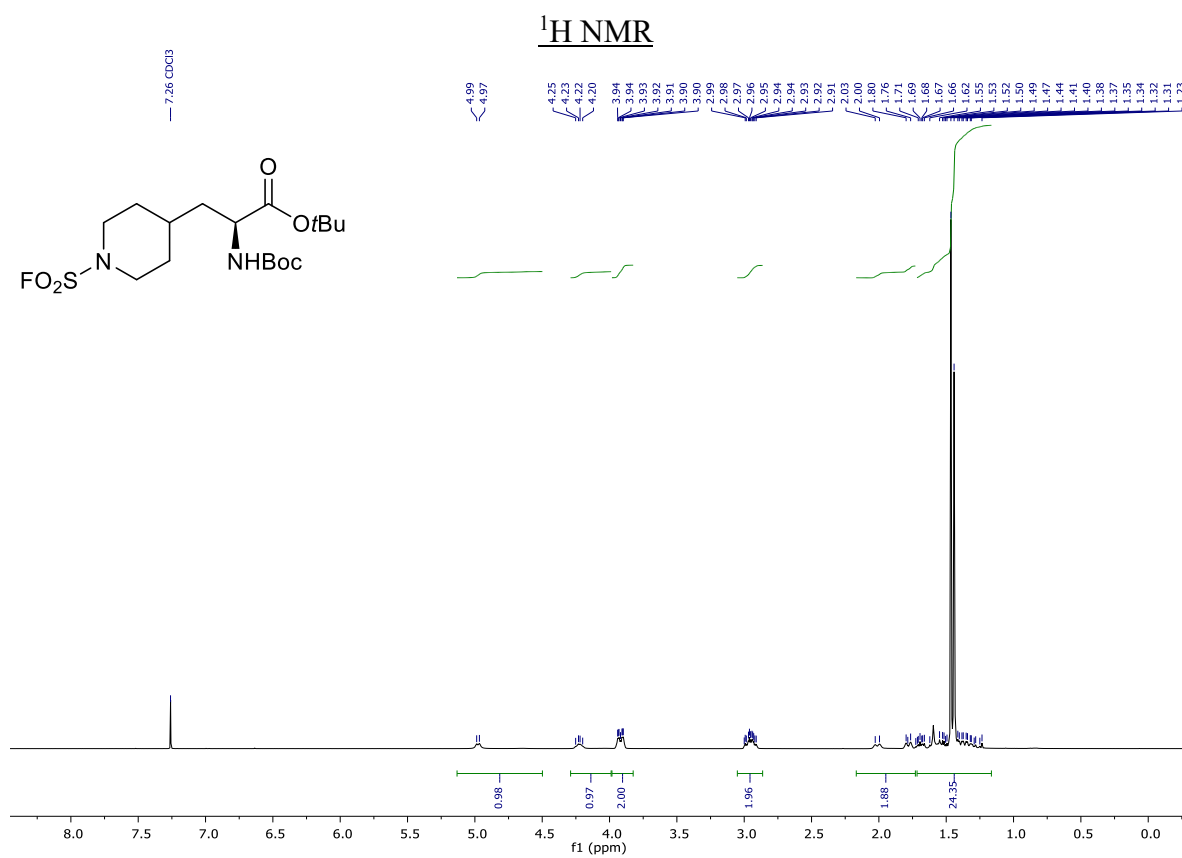
tert-Butyl L-prolinate (**10**)¹H NMR

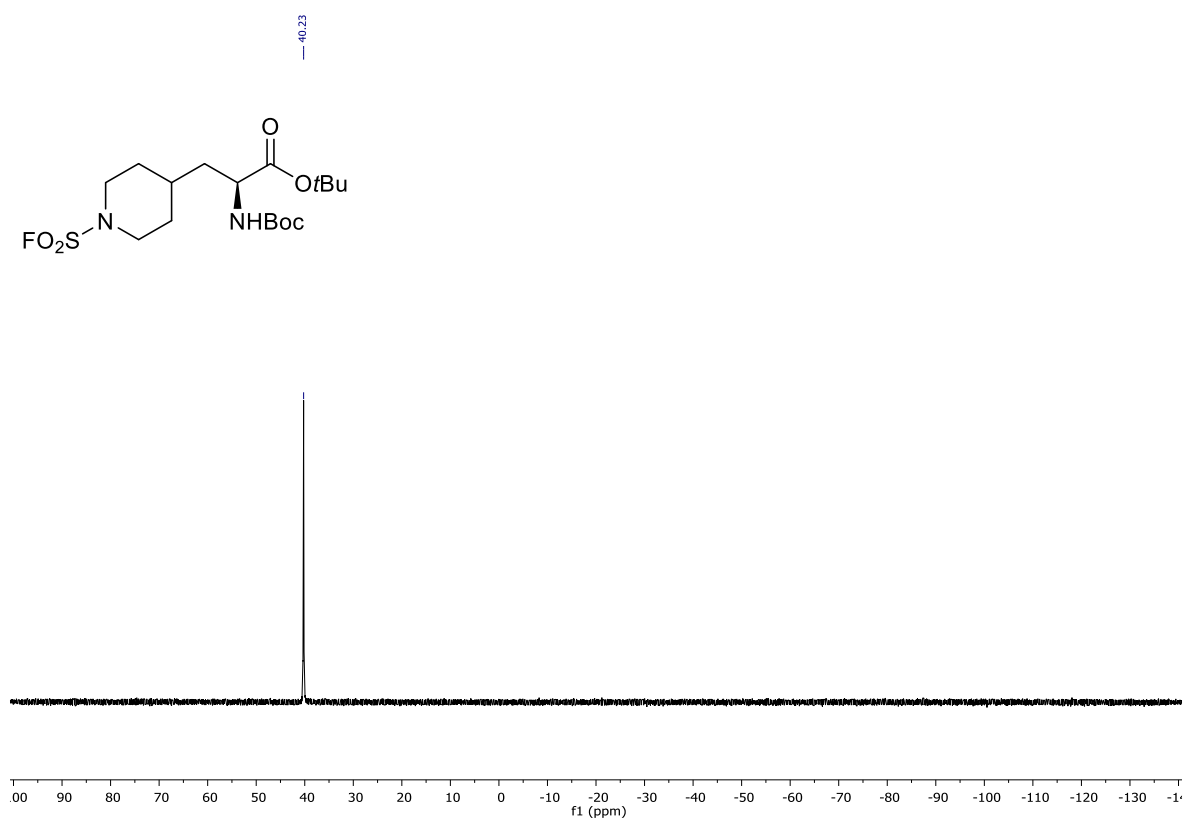
tert-Butyl (fluorosulfonyl)-L-prolinate (**2g**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

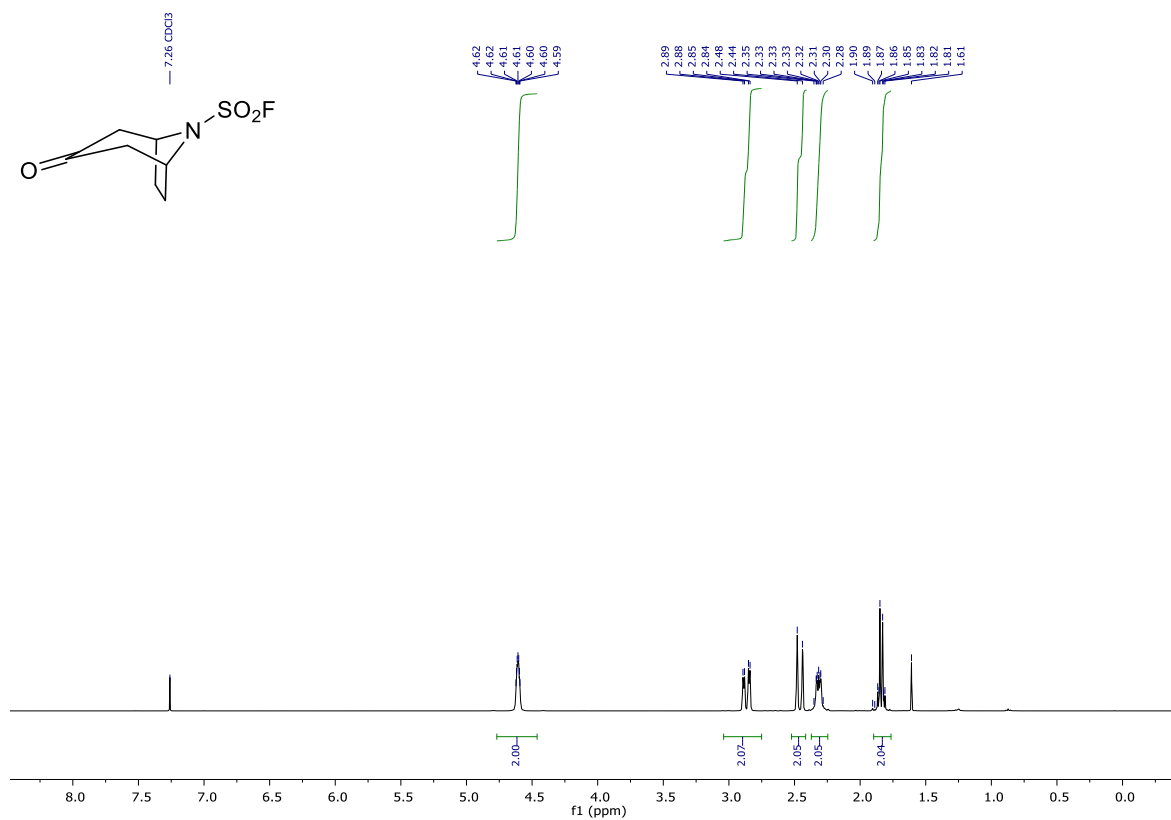
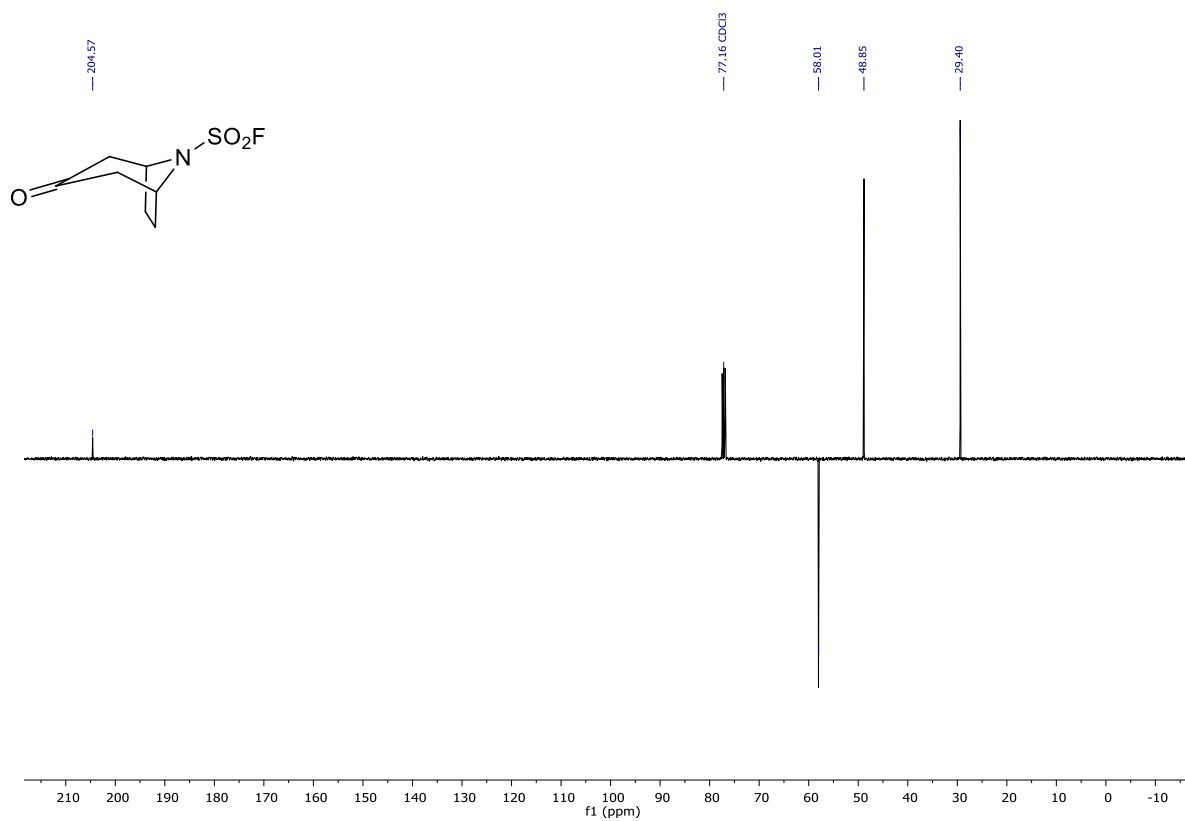
^{19}F NMR

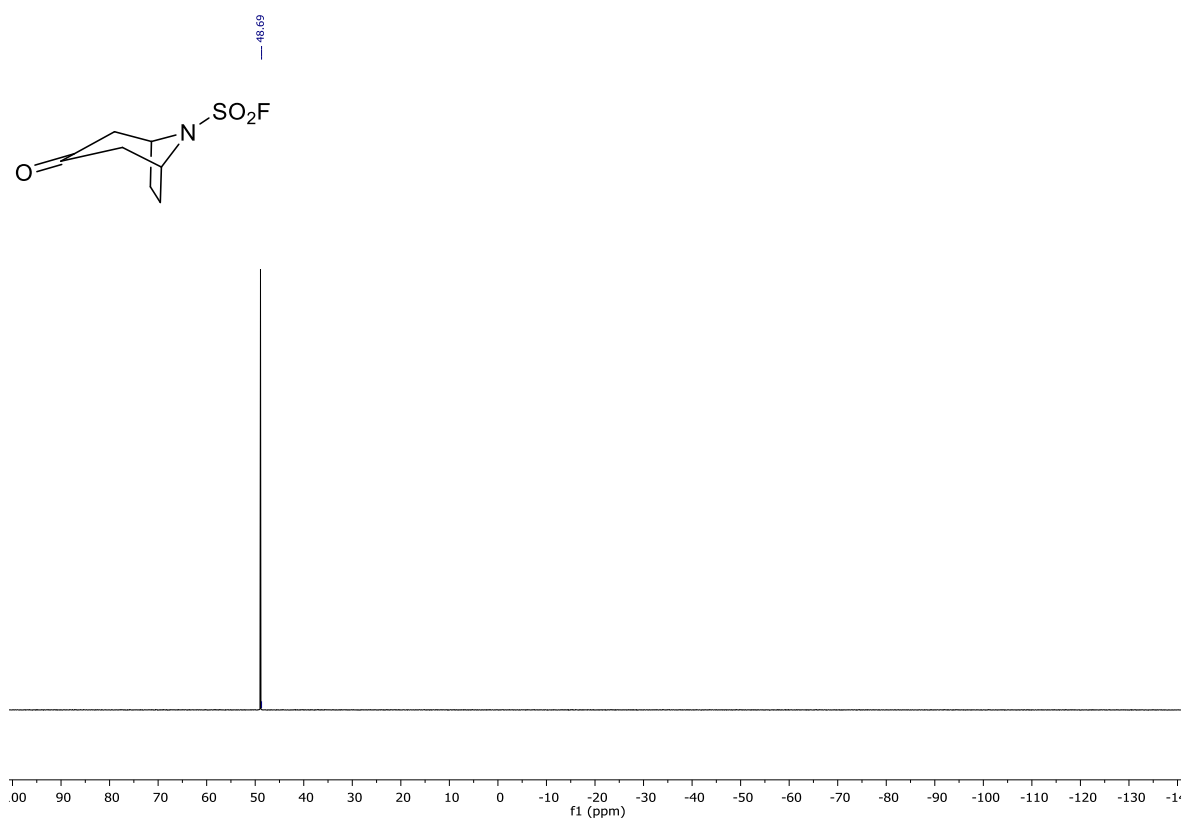
tert-Butyl (*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-(pyridin-4-yl)propanoate (**9**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

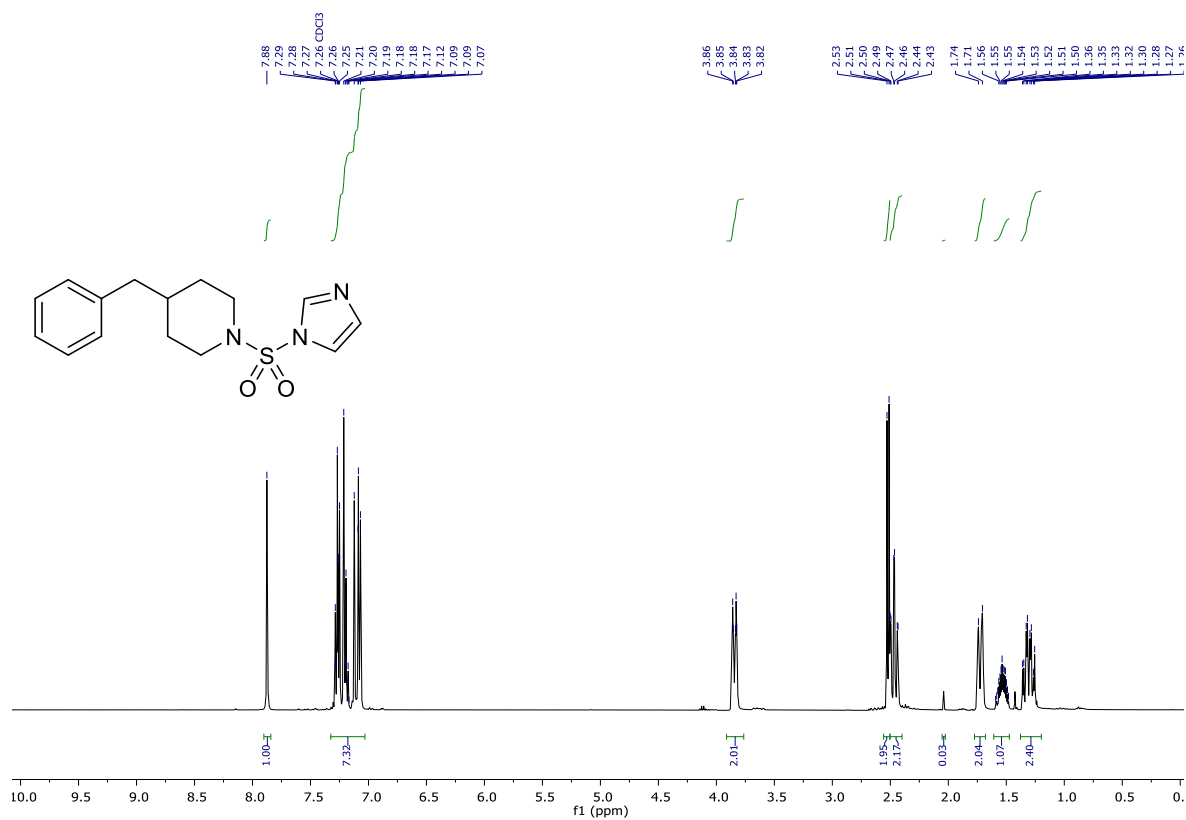
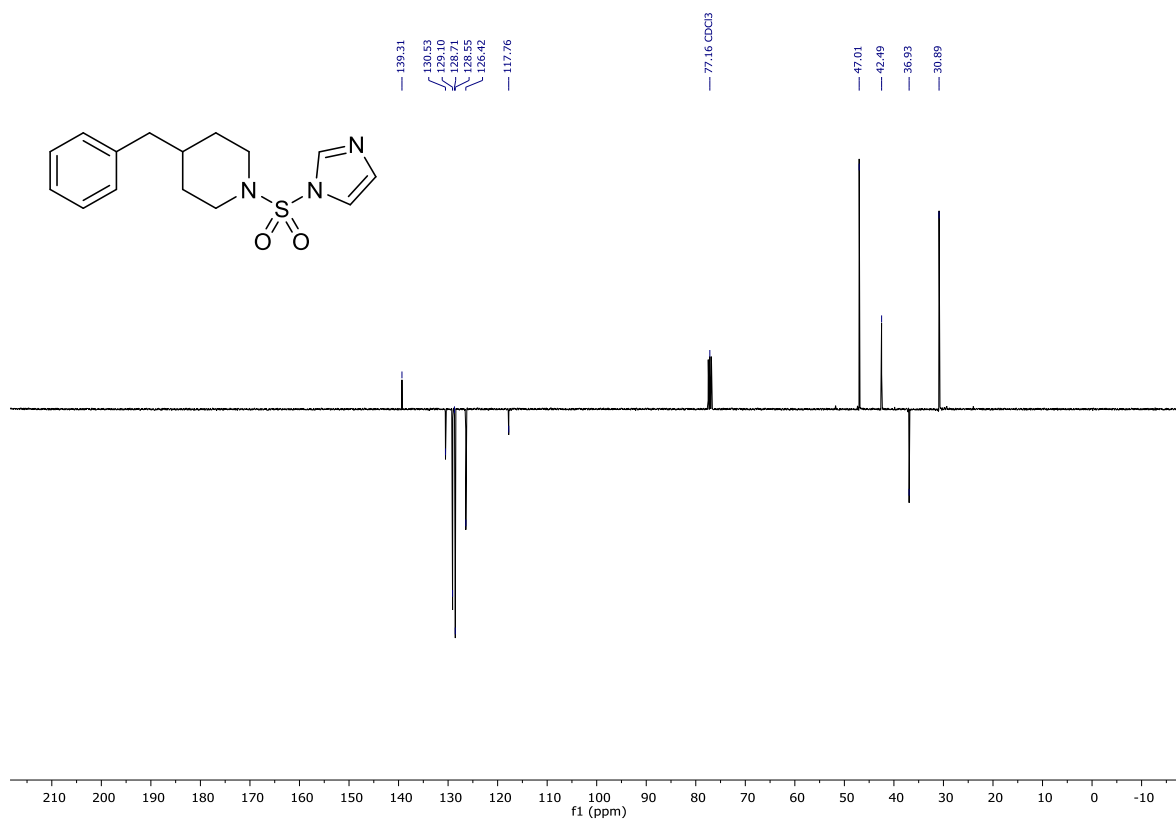
tert-Butyl (S)-2-[(*tert*-butoxycarbonyl)amino]-3-[1-(fluorosulfonyl)piperidin-4-yl]propanoate
(2h)

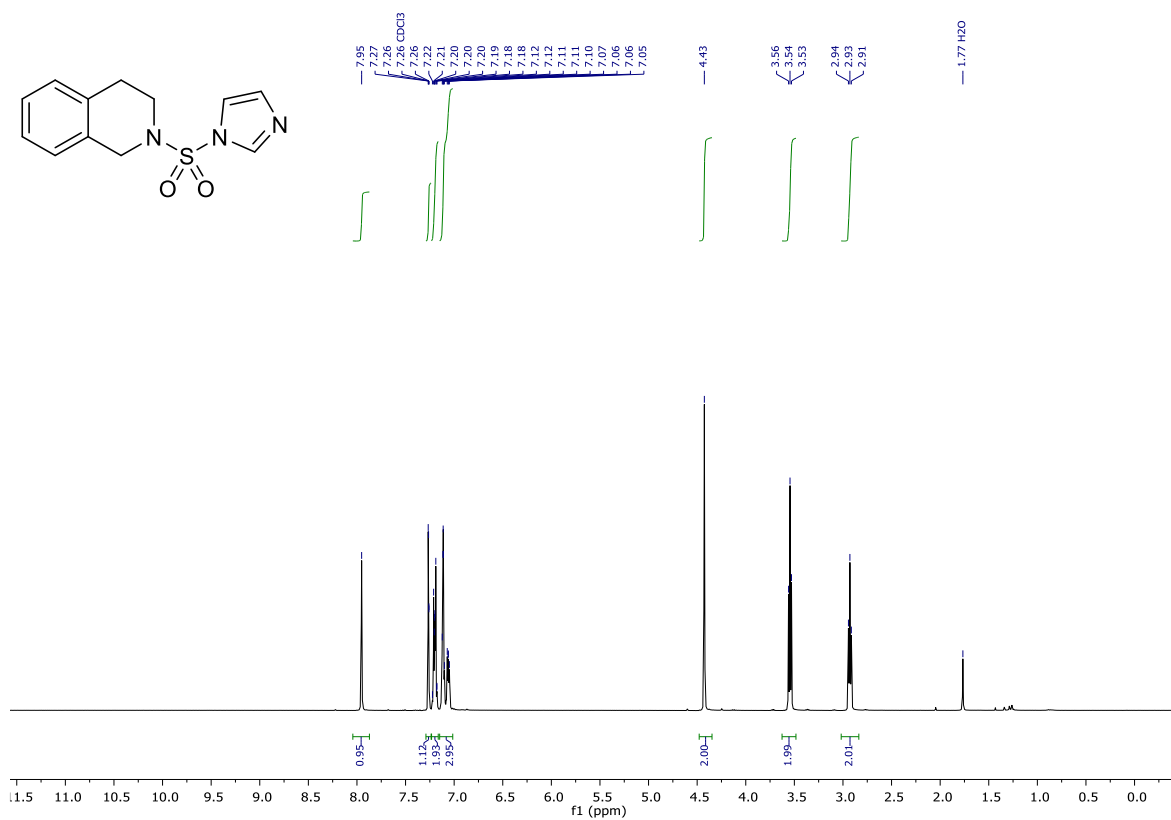
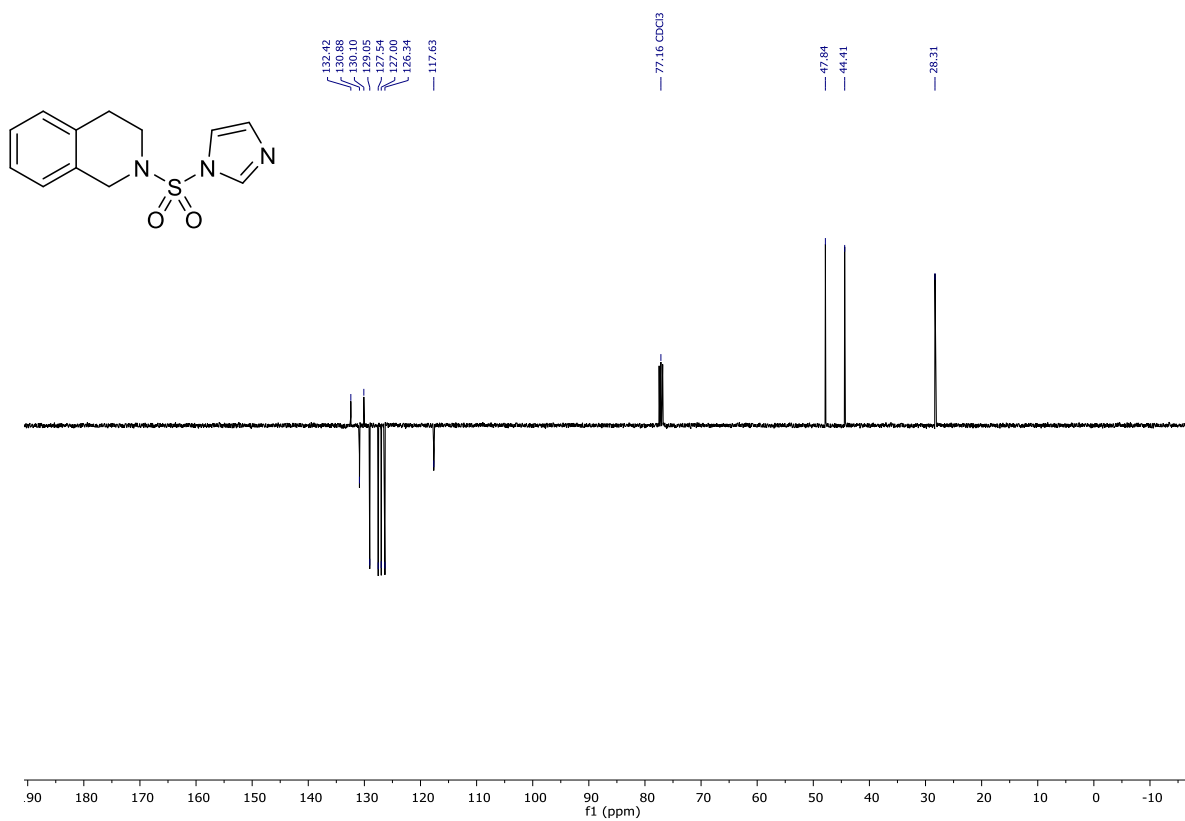


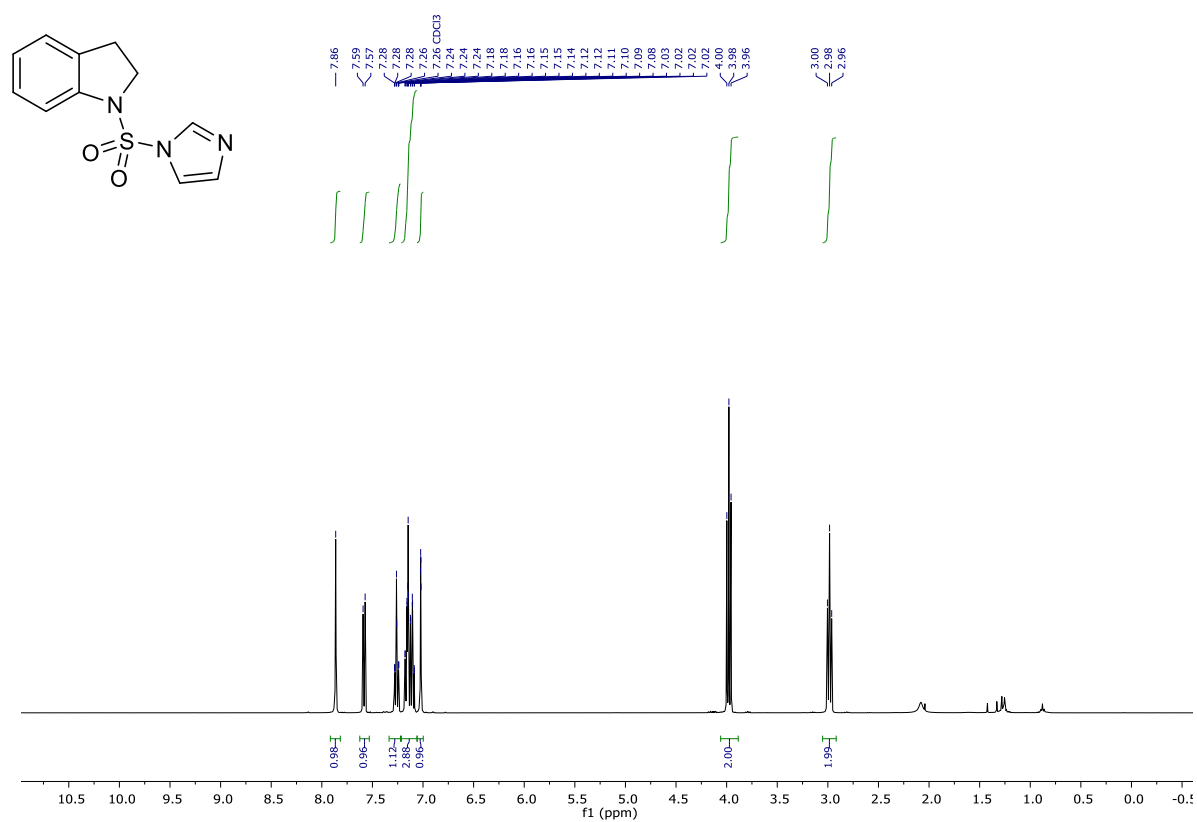
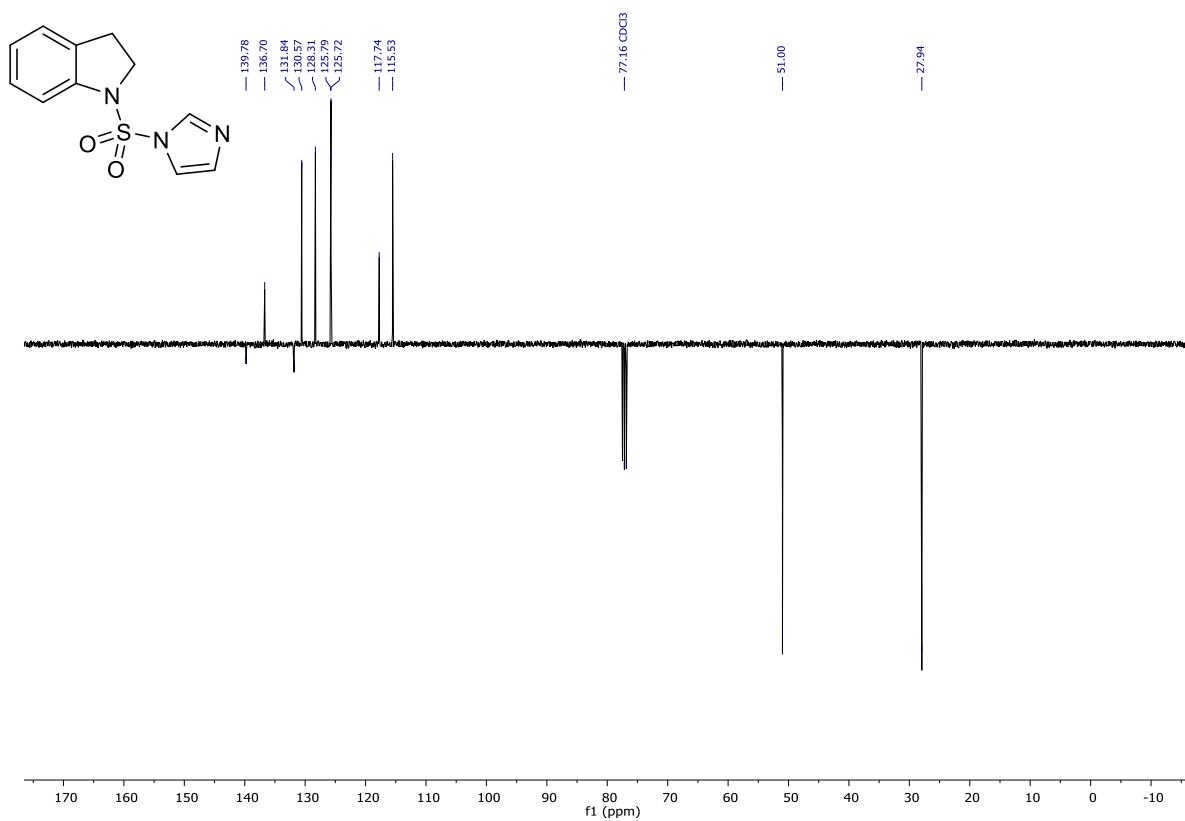
^{19}F NMR

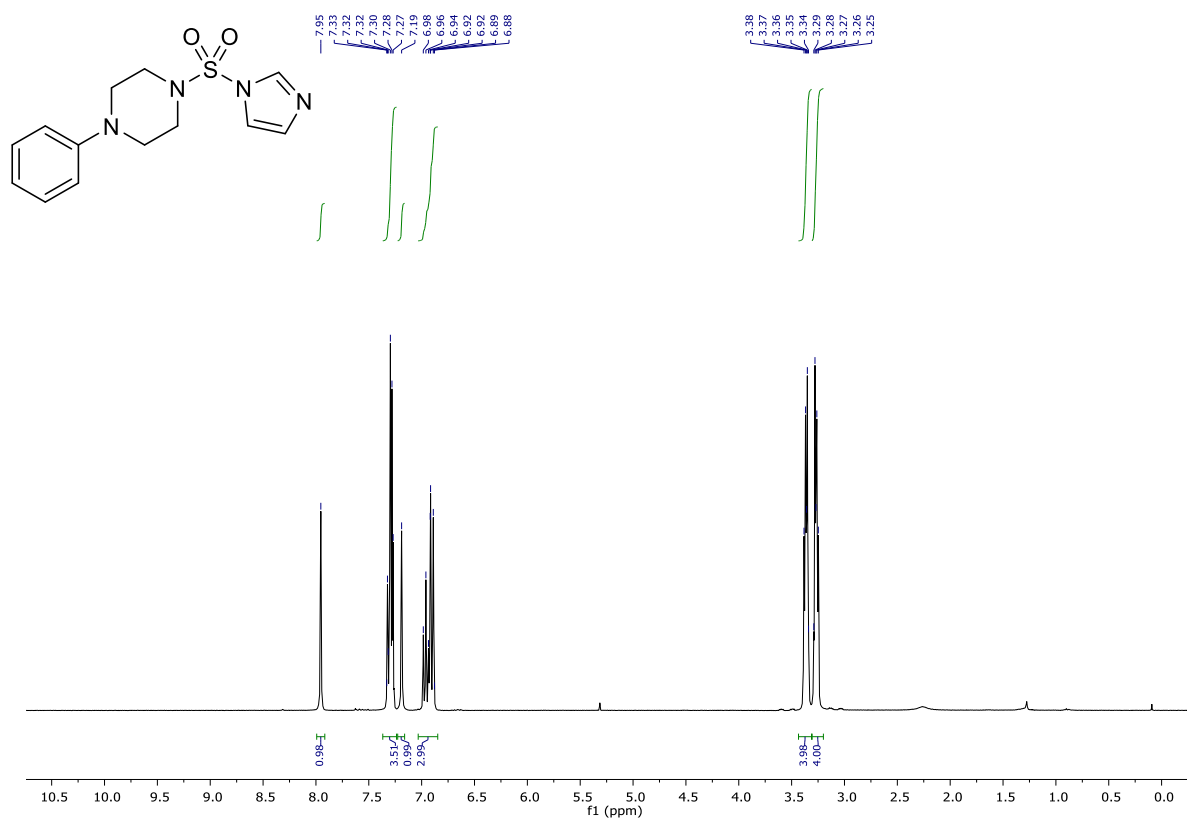
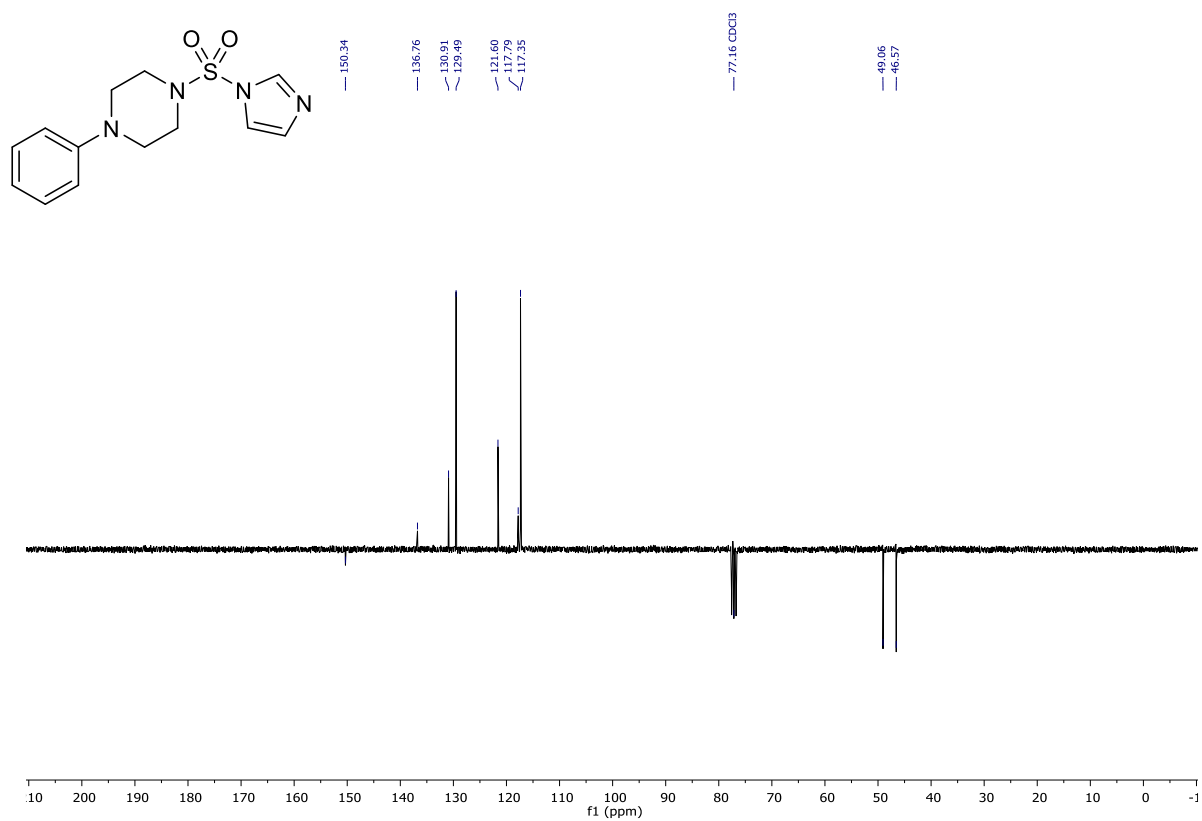
3-Oxo-8-azabicyclo[3.2.1]octane-8-sulfonyl fluoride (**2i**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

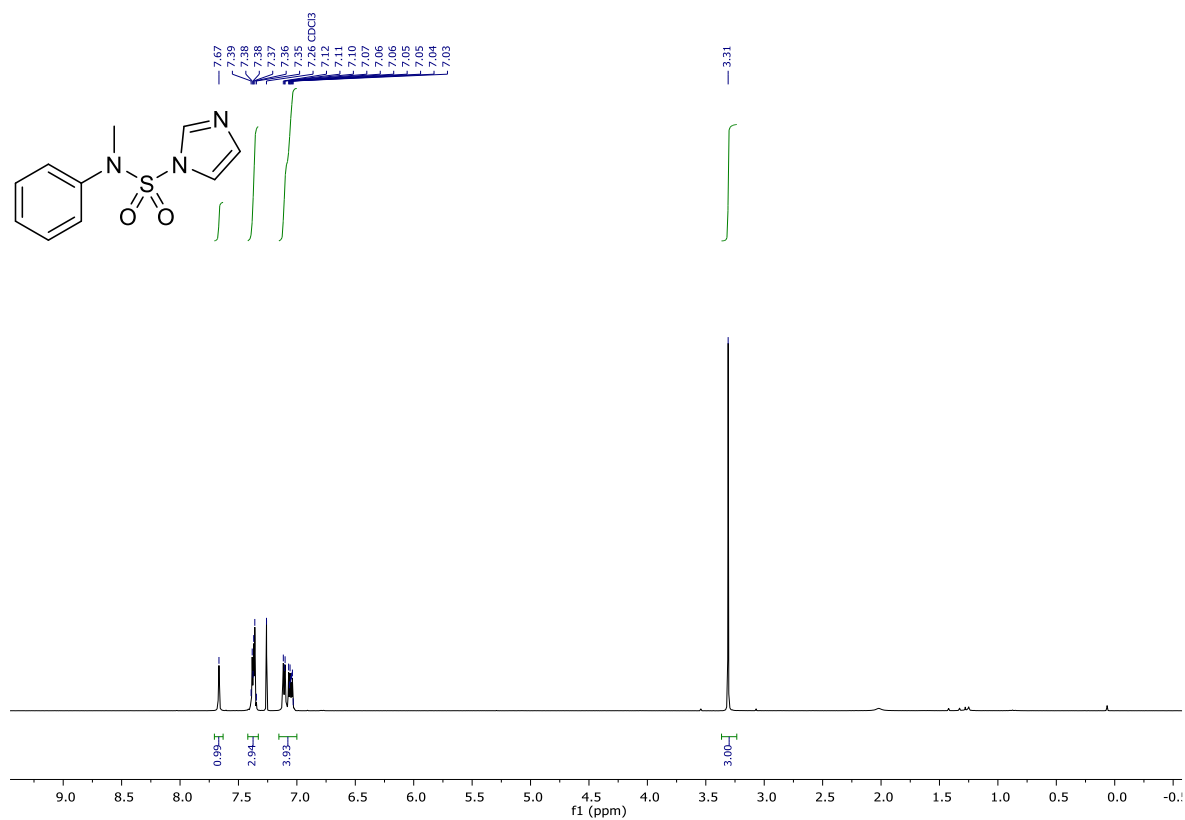
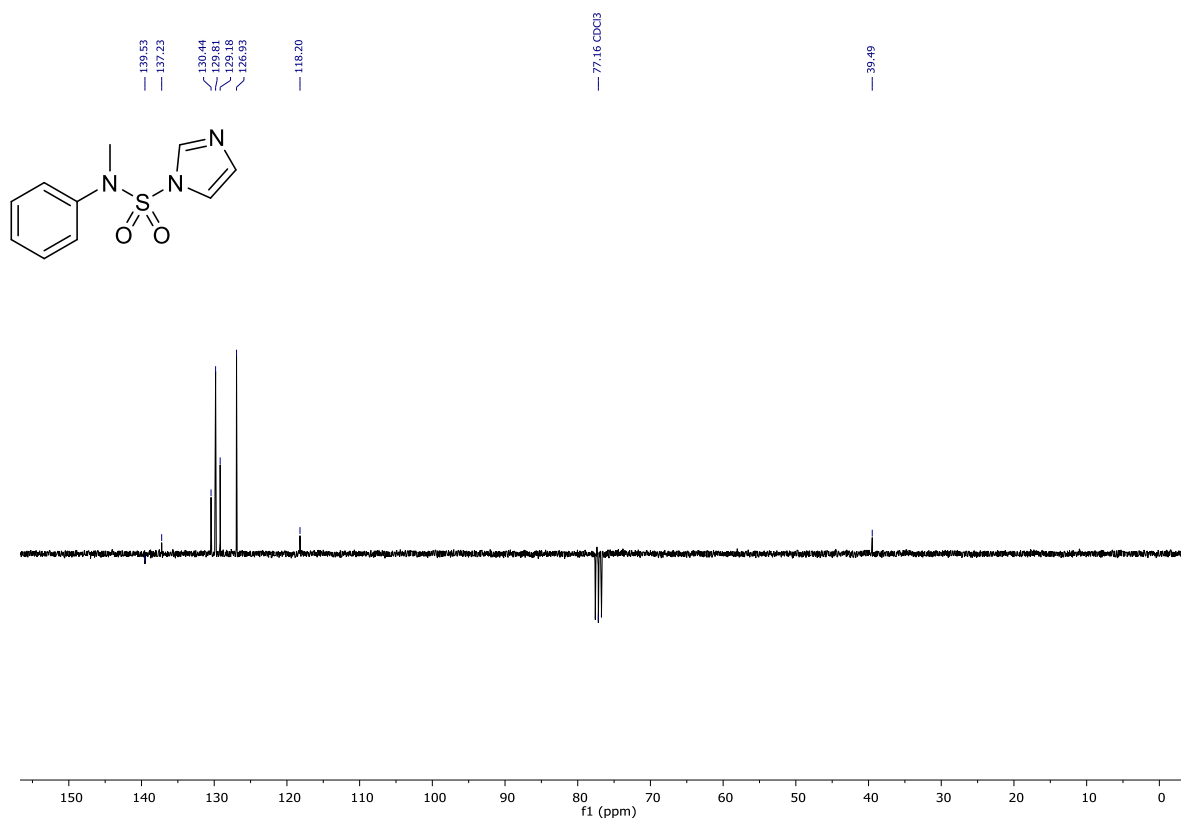
^{19}F NMR

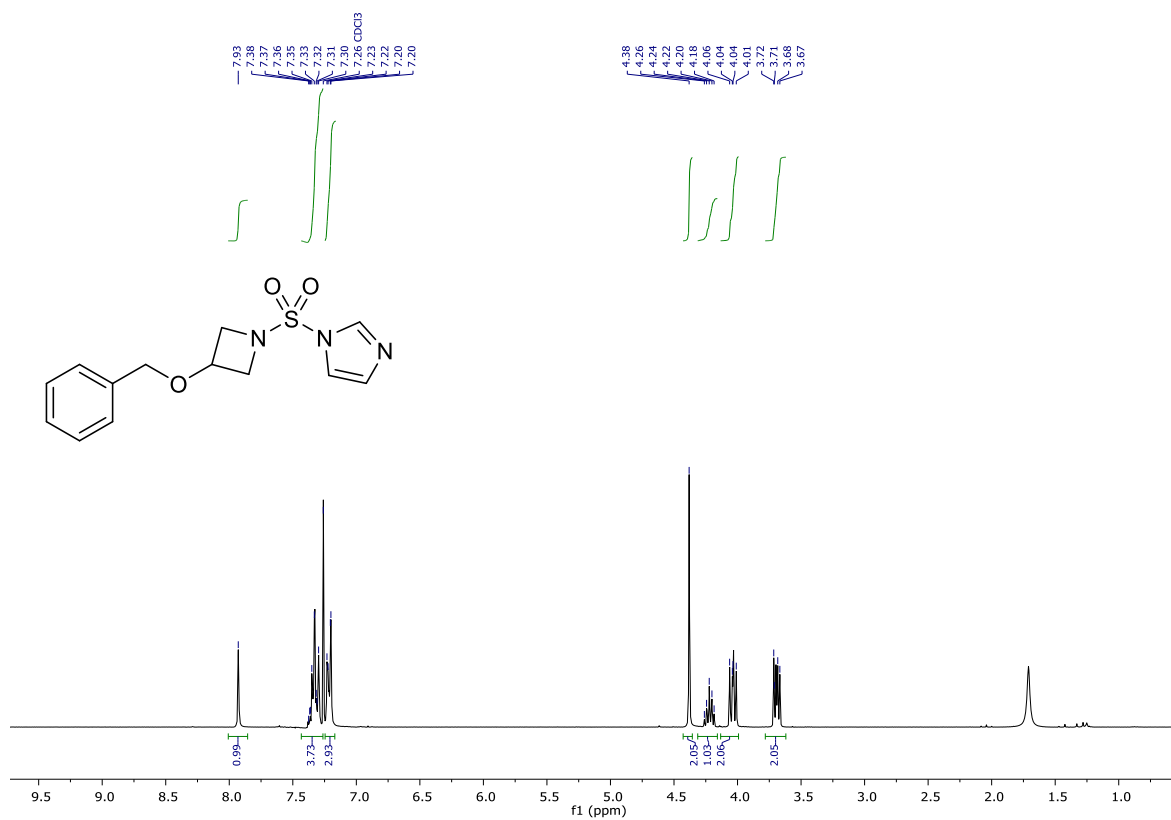
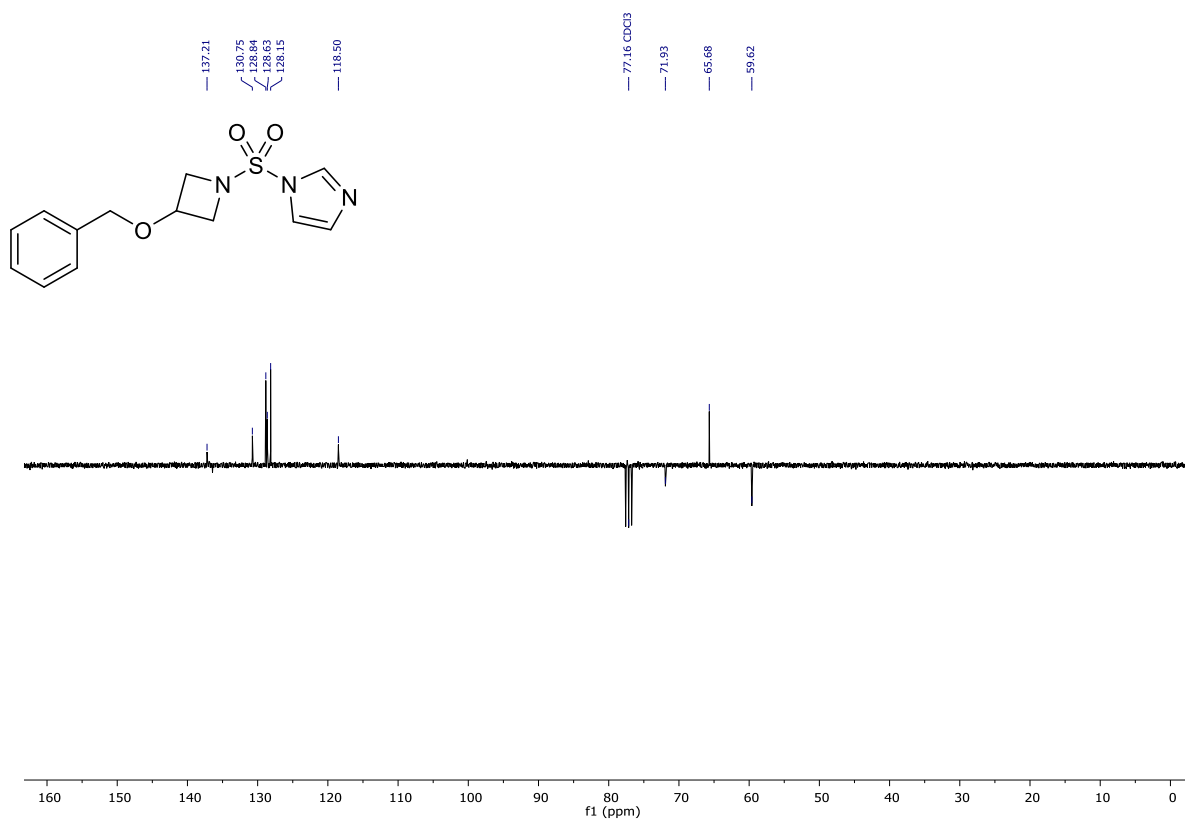
1-[(1*H*-Imidazol-1-yl)sulfonyl]-4-benzylpiperidine (**3a**)¹H NMR¹³C{¹H} NMR

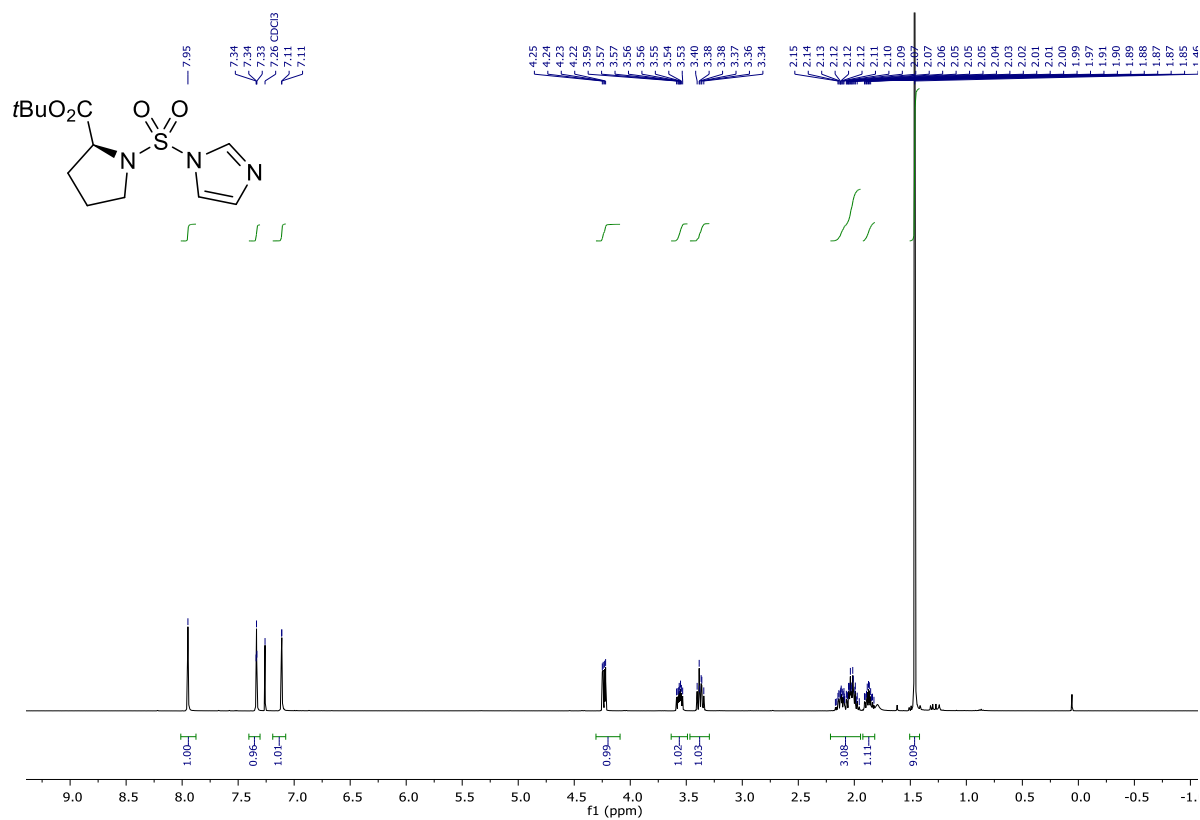
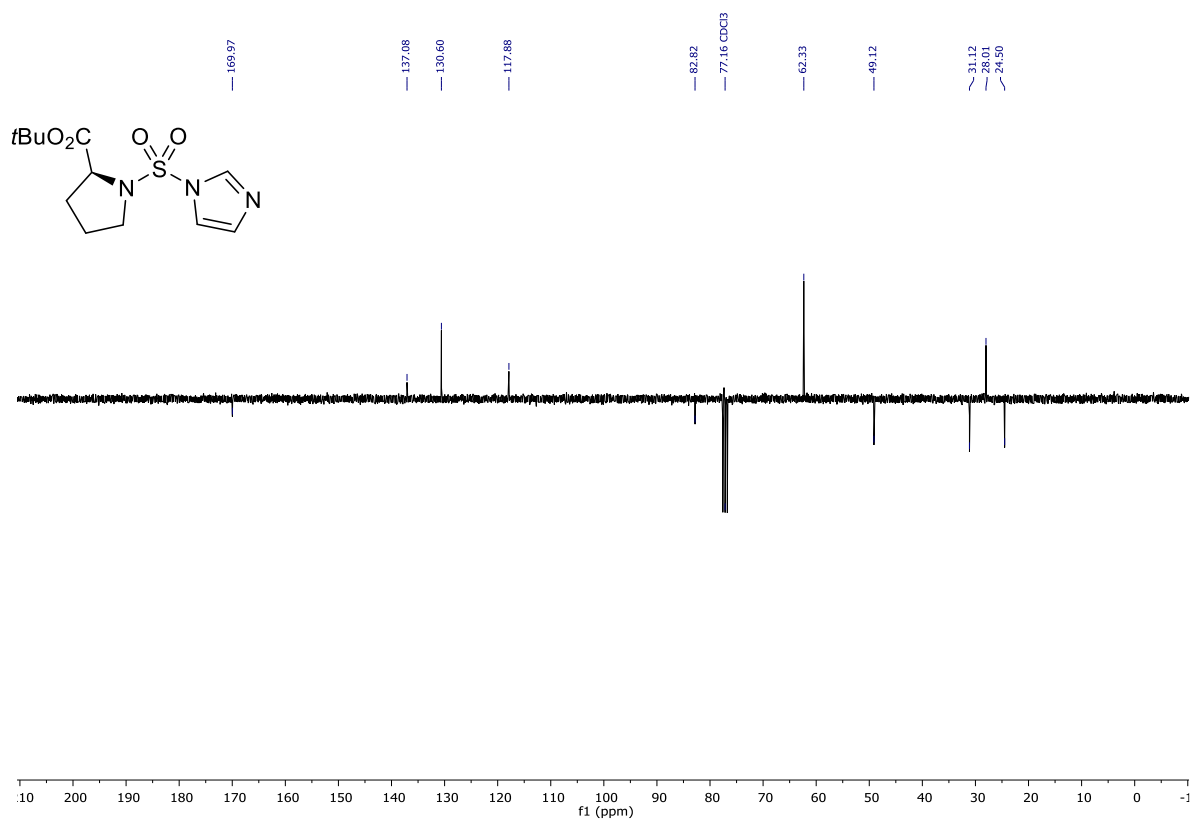
2-[(1*H*-Imidazol-1-yl)sulfonyl]-1,2,3,4-tetrahydroisoquinoline (**3b**)¹H NMR¹³C{¹H} NMR

1-[(1*H*-Imidazol-1-yl)sulfonyl]indoline (**3c**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

1-[(1*H*-Imidazol-1-yl)sulfonyl]-4-phenylpiperazine (**3d**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

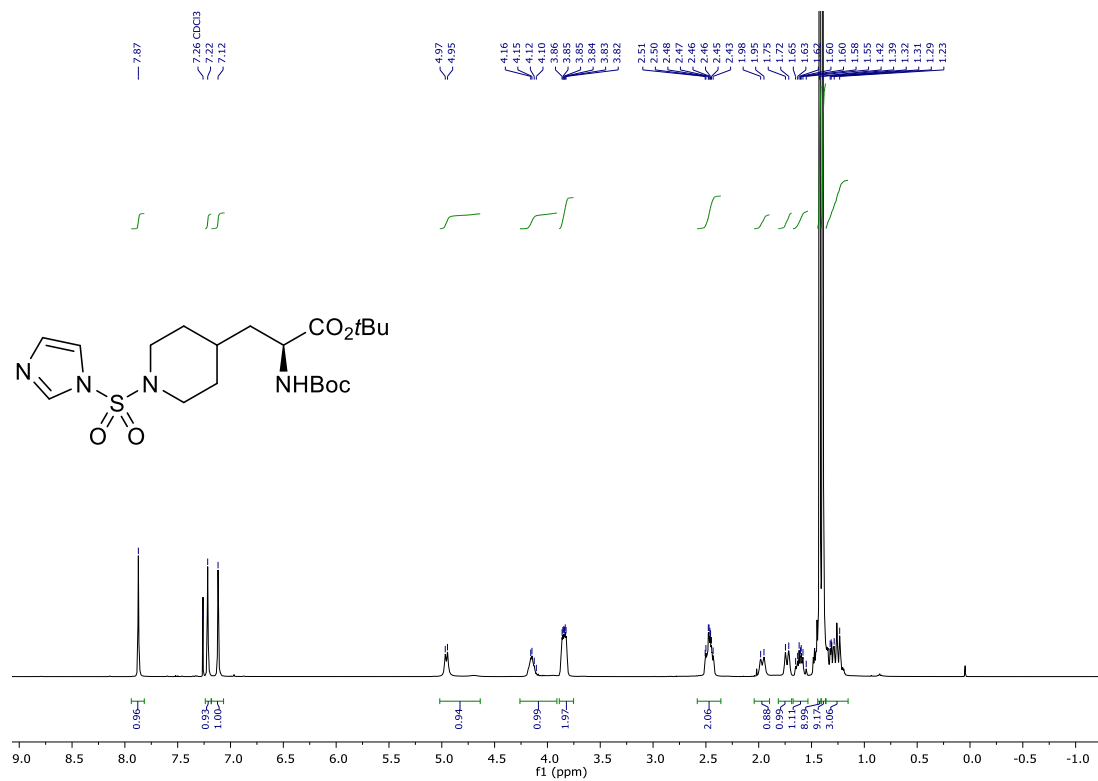
N-Methyl-*N*-phenyl-1*H*-imidazole-1-sulfonamide (**3e**)¹H NMR¹³C{¹H} NMR

1-[(1*H*-Imidazol-1-yl)sulfonyl]-3-(benzyloxy)azetidine (**3f**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

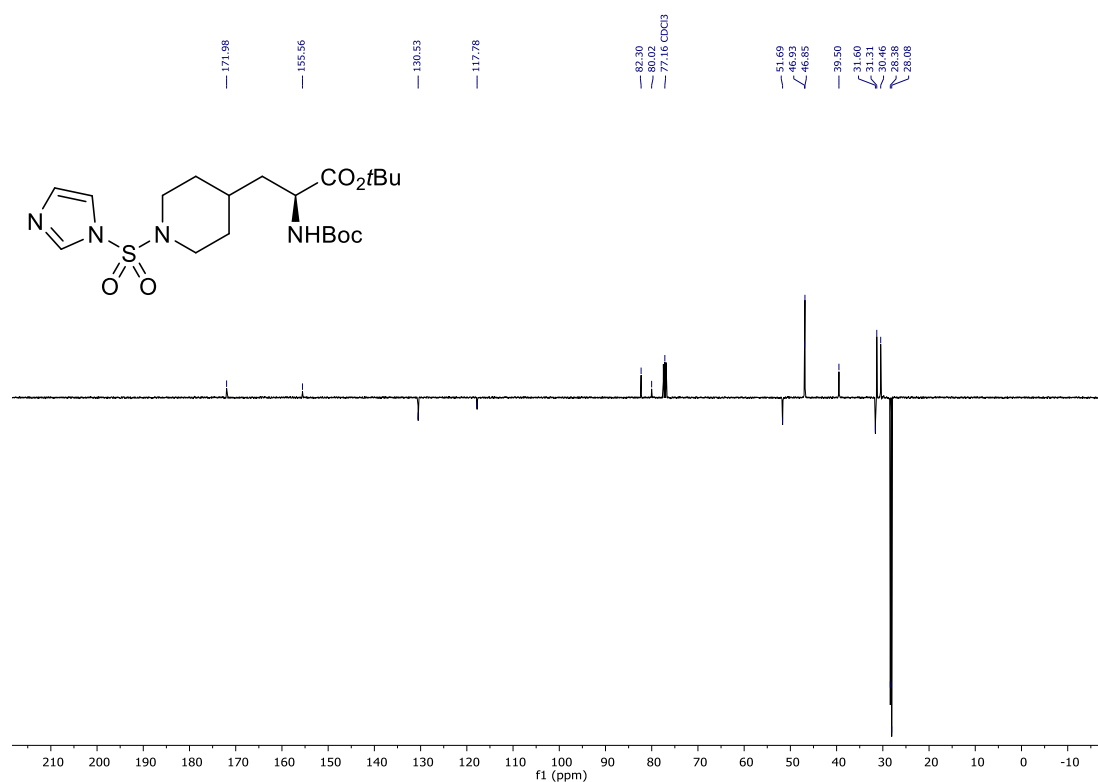
tert-Butyl [(1*H*-imidazol-1-yl)sulfonyl]-L-prolinate (**3g**)¹H NMR¹³C{¹H} NMR

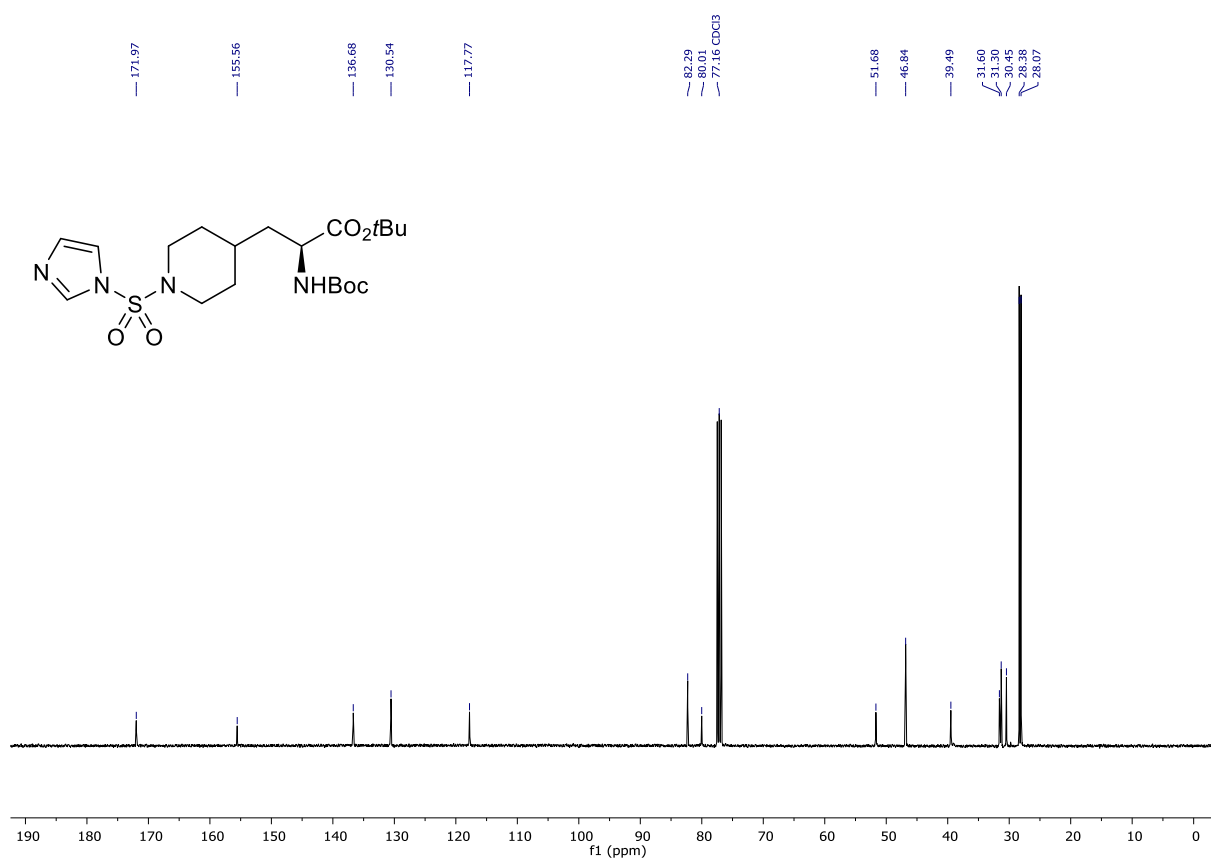
tert-Butyl (S)-3-{1-[(1*H*-imidazol-1-yl)sulfonyl]piperidin-4-yl}-2-[(*tert*-butoxycarbonyl)-amino]propanoate (**3h**)

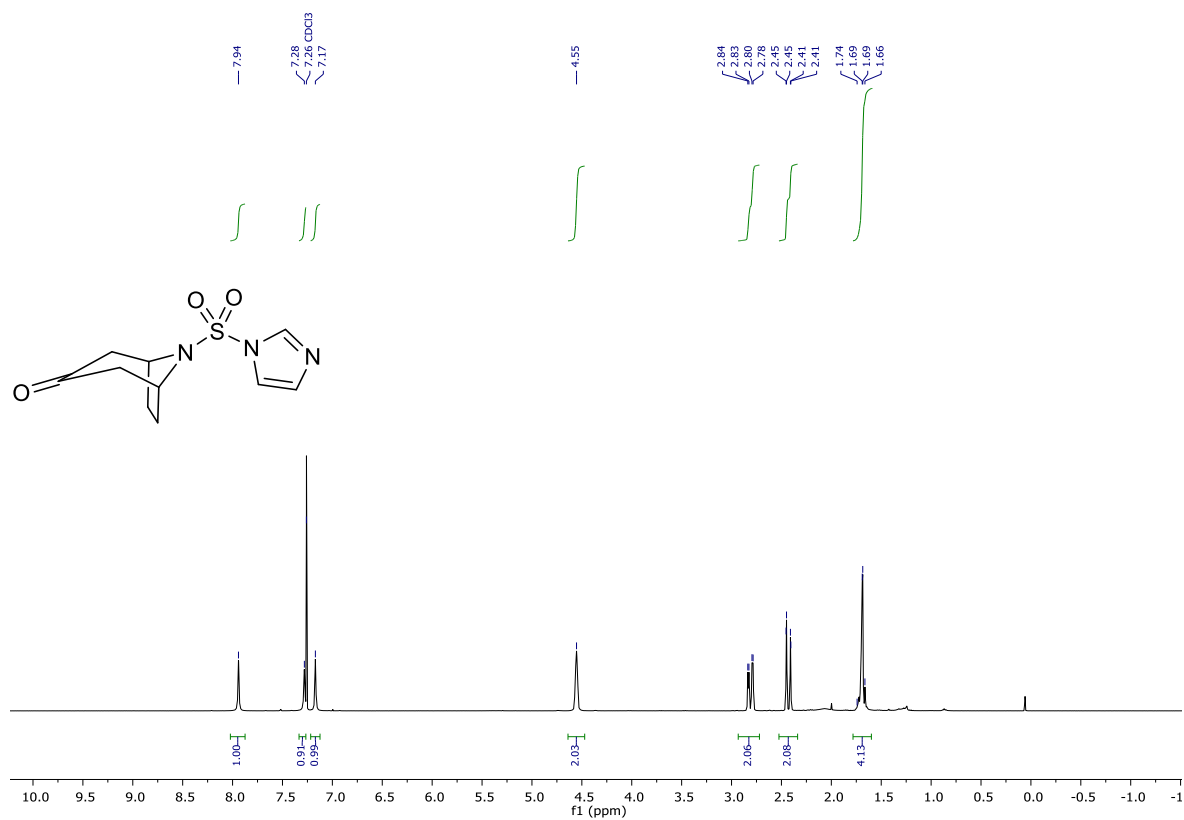
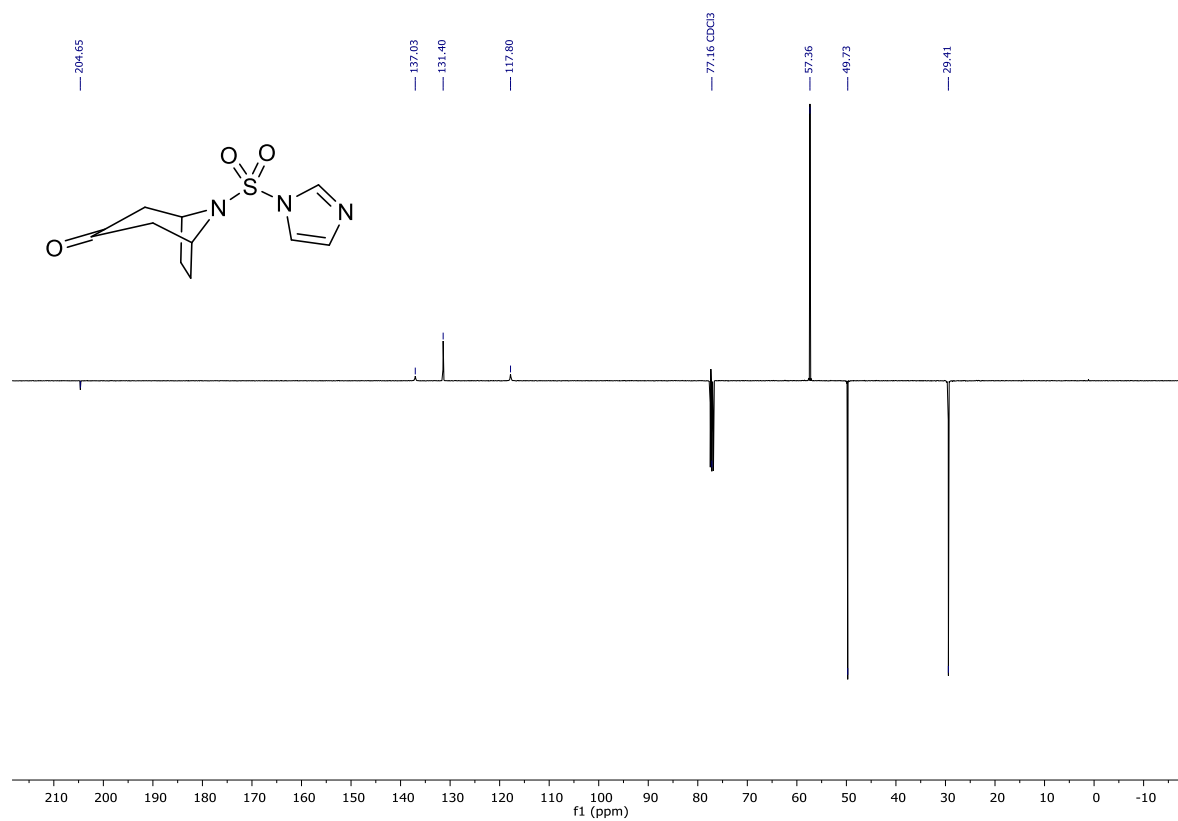
^1H NMR

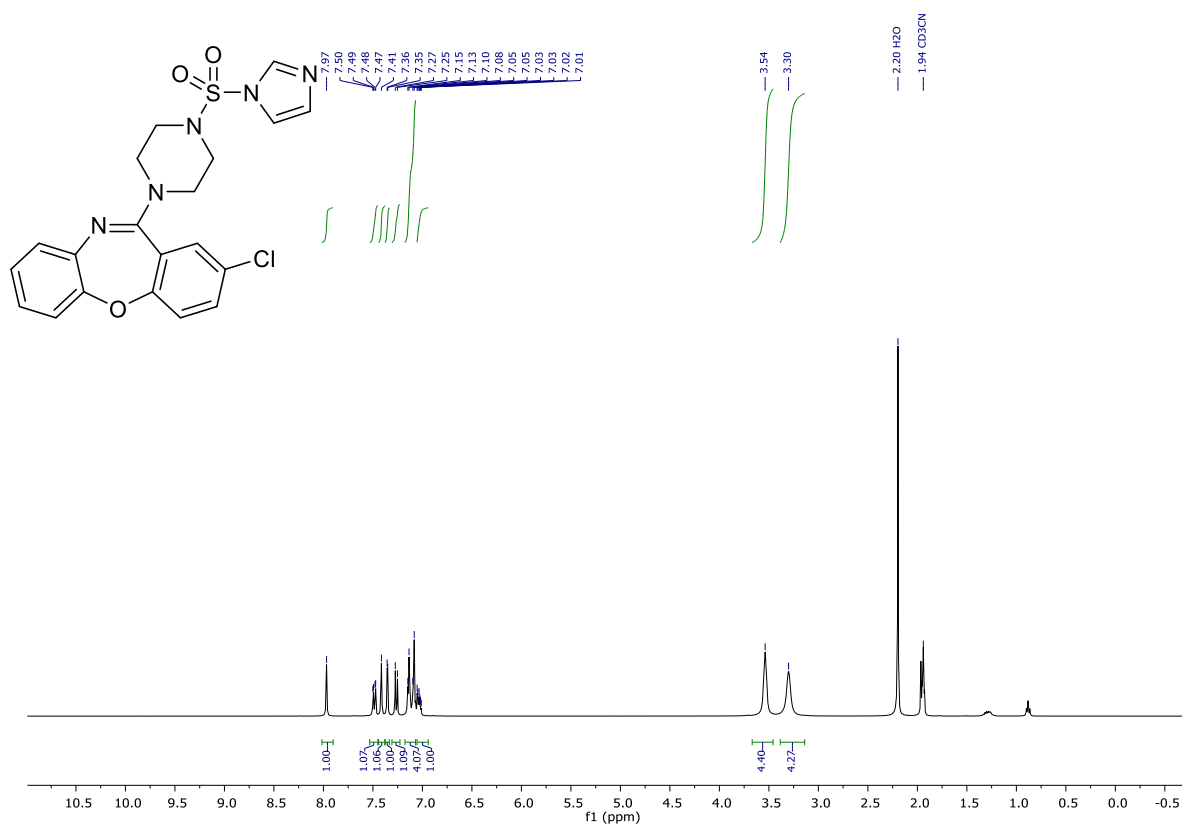
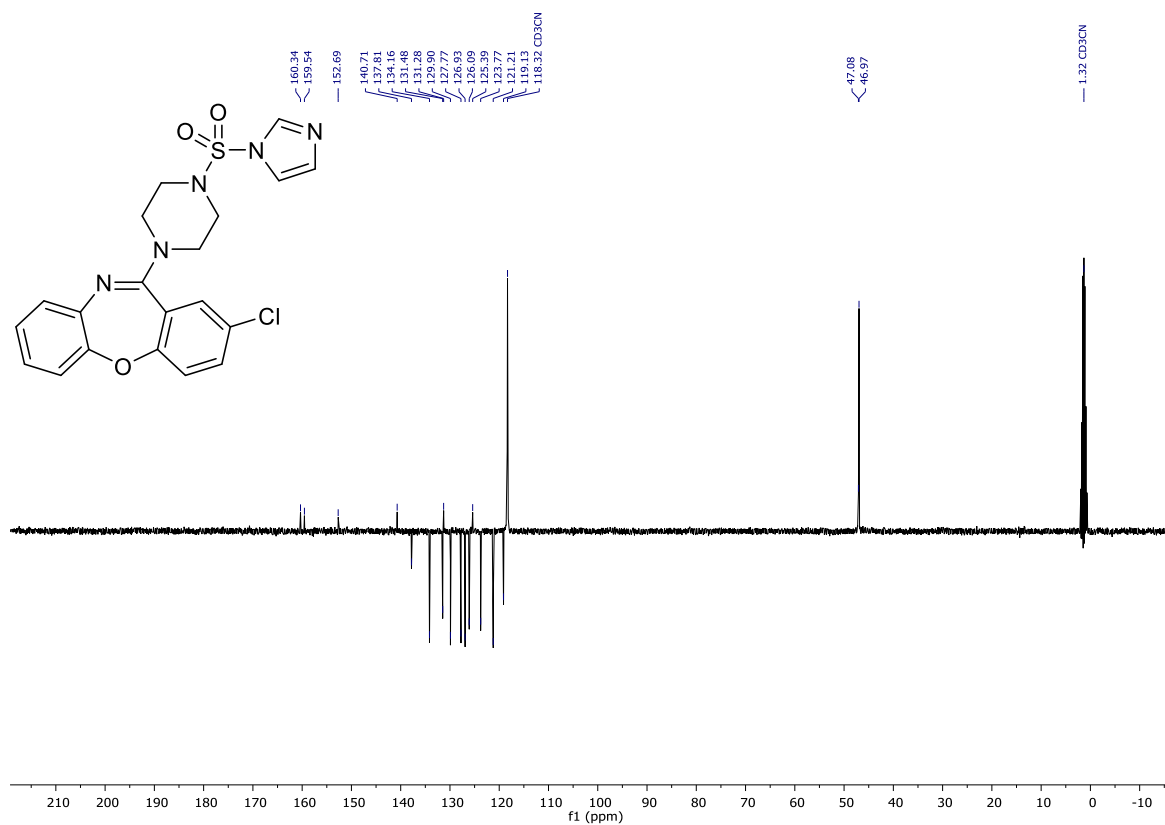


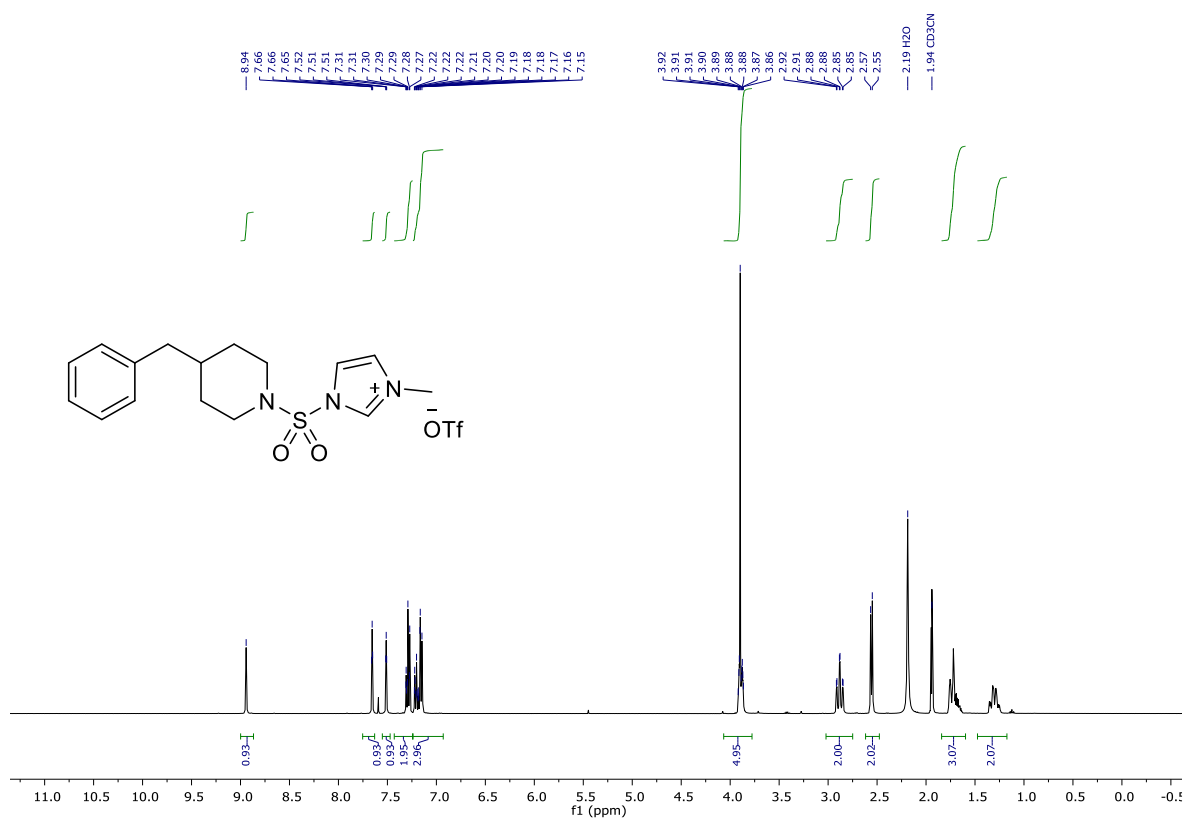
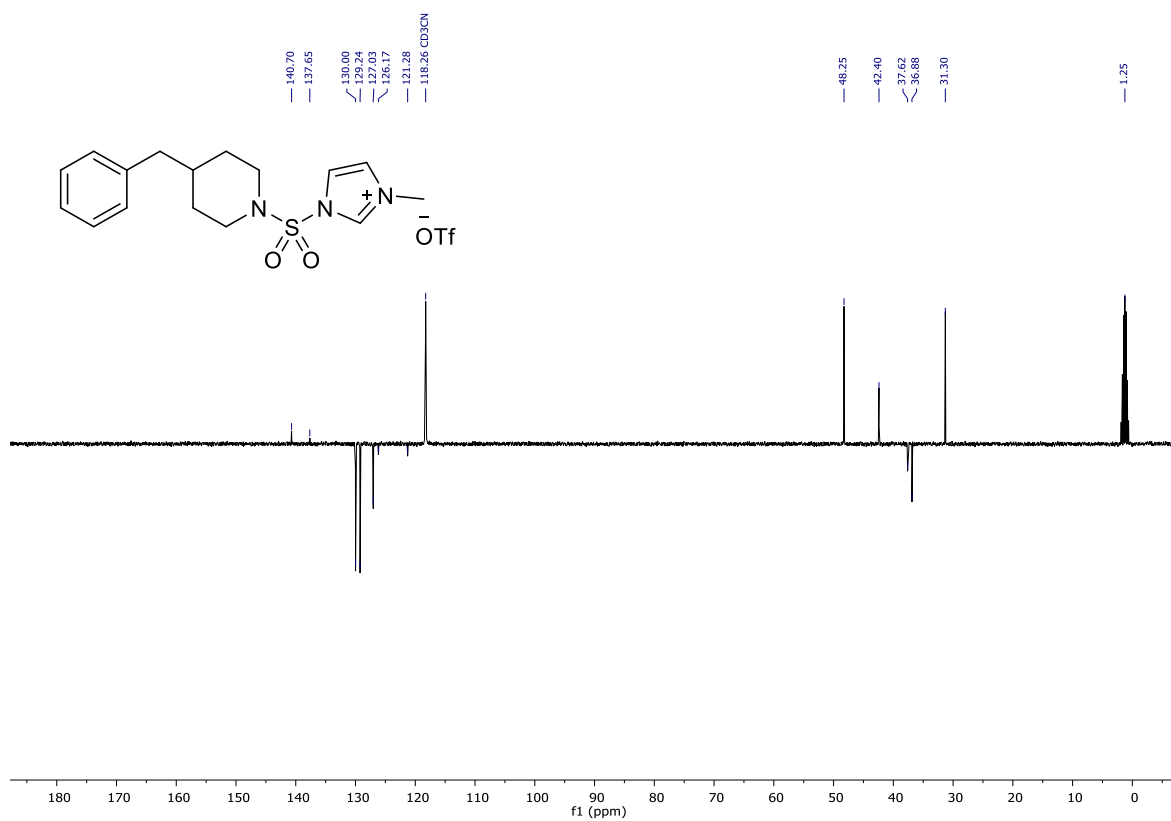
$^{13}\text{C}\{^1\text{H}\}$ NMR-APT

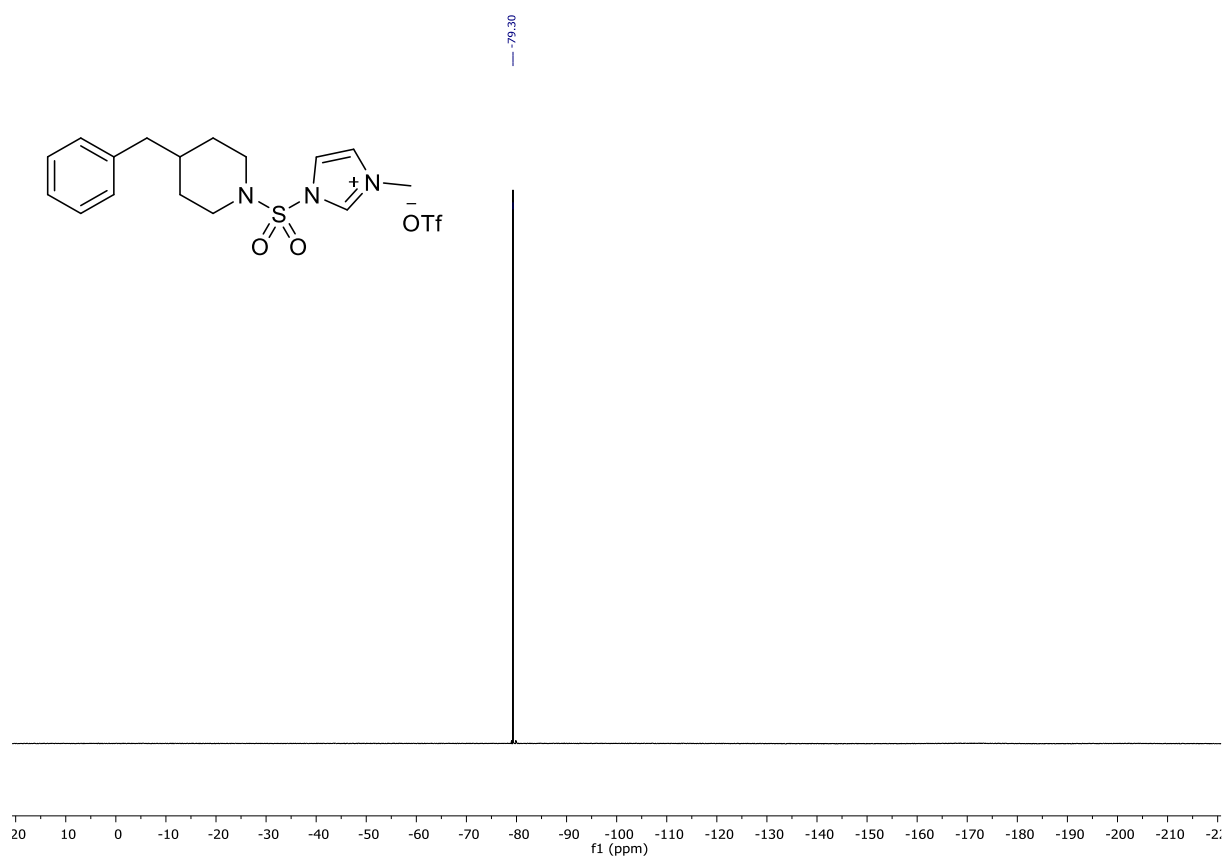


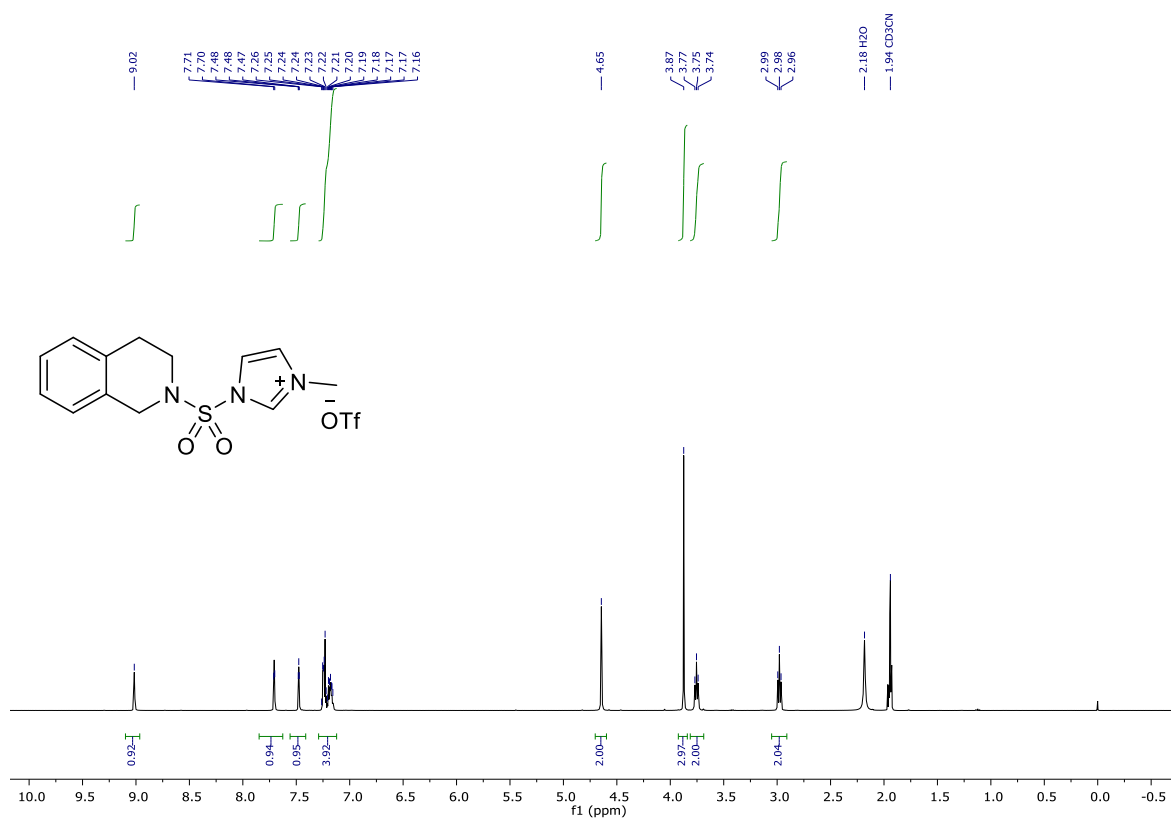
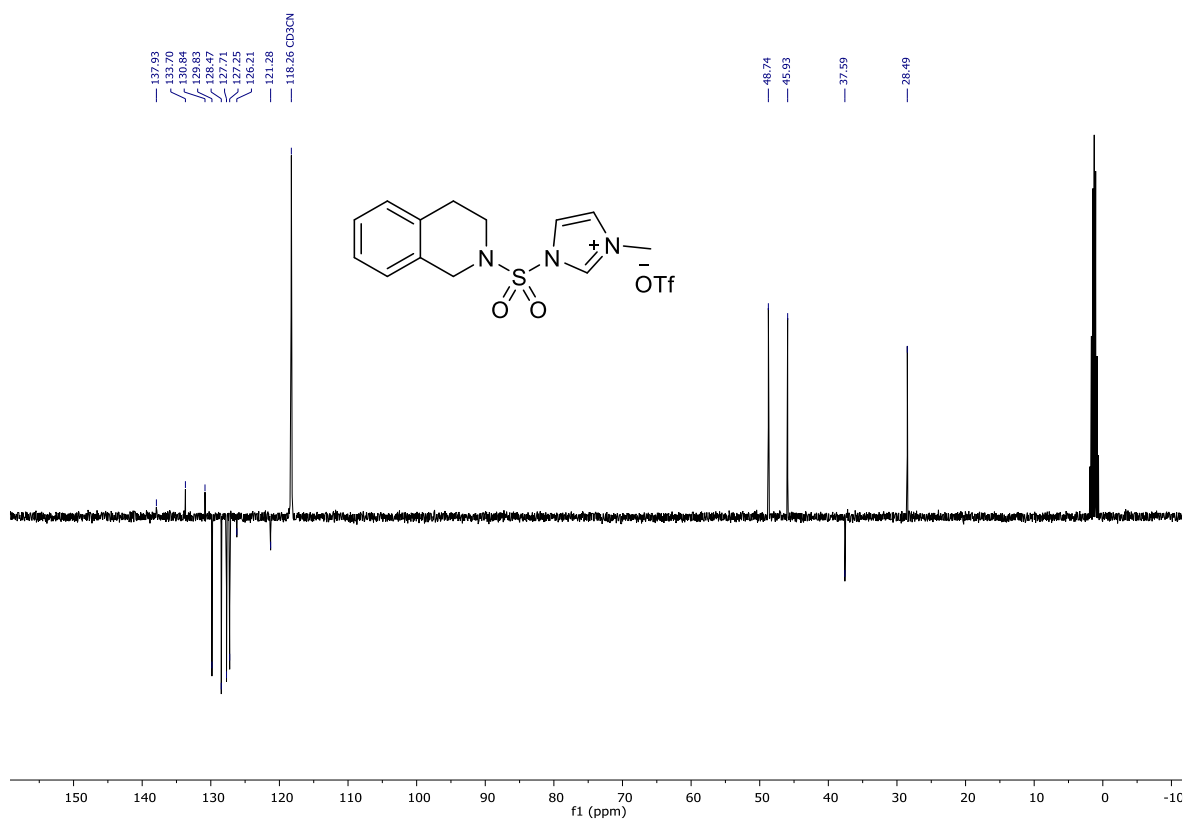
$^{13}\text{C}\{^1\text{H}\}$ NMR (standard)

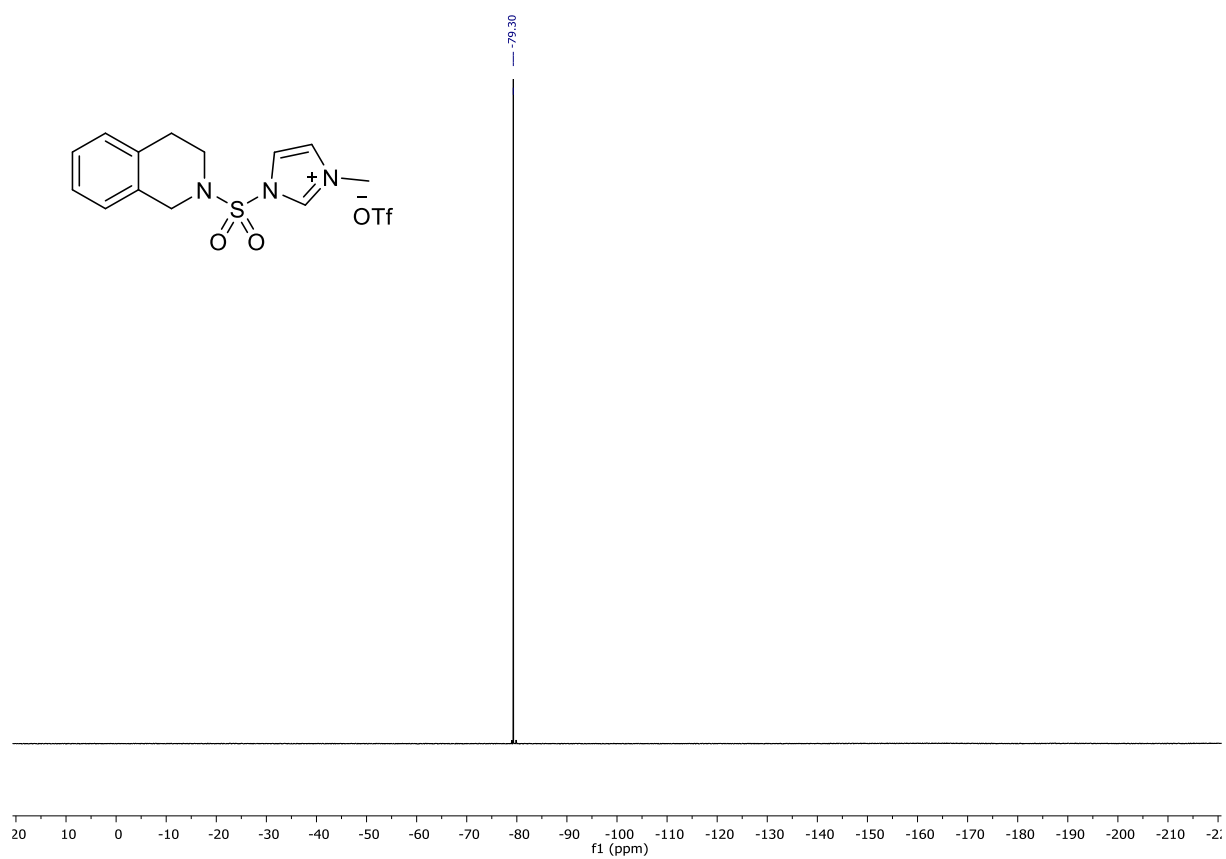
8-[(1*H*-Imidazol-1-yl)sulfonyl]-8-azabicyclo[3.2.1]octan-3-one (**3i**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

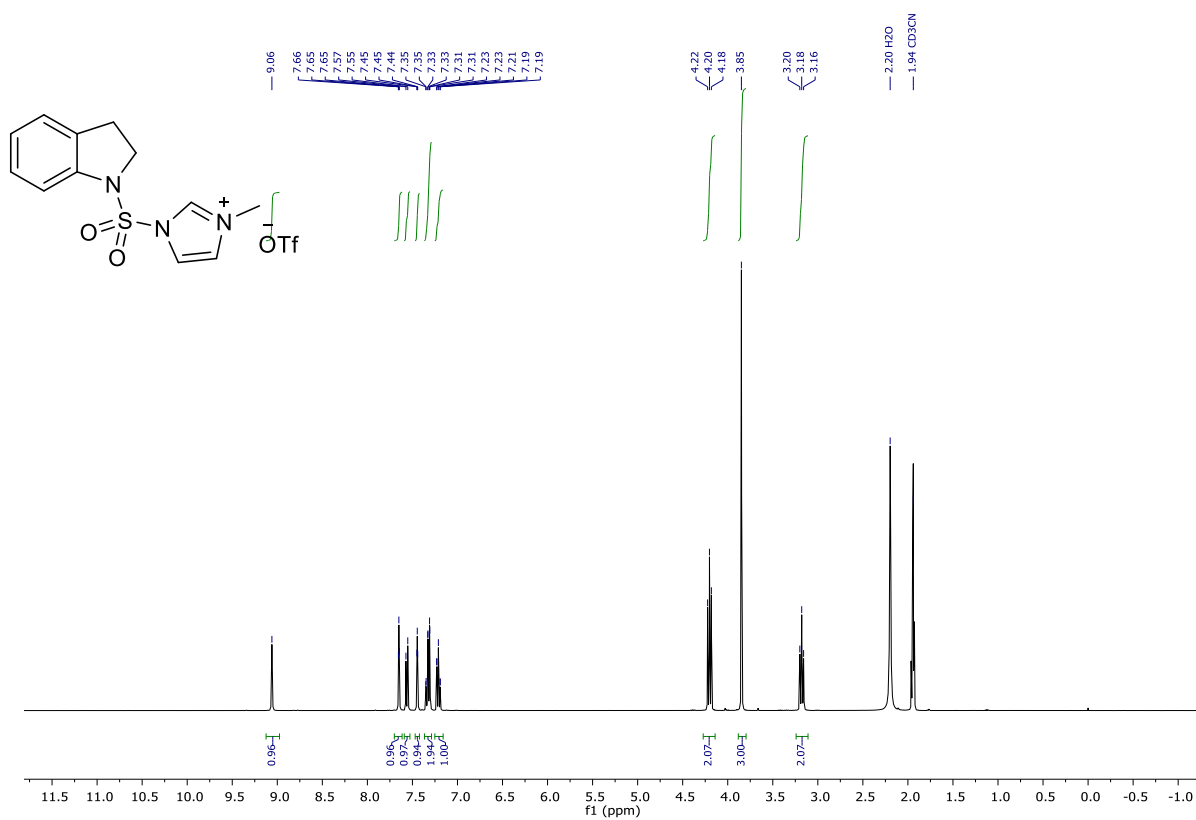
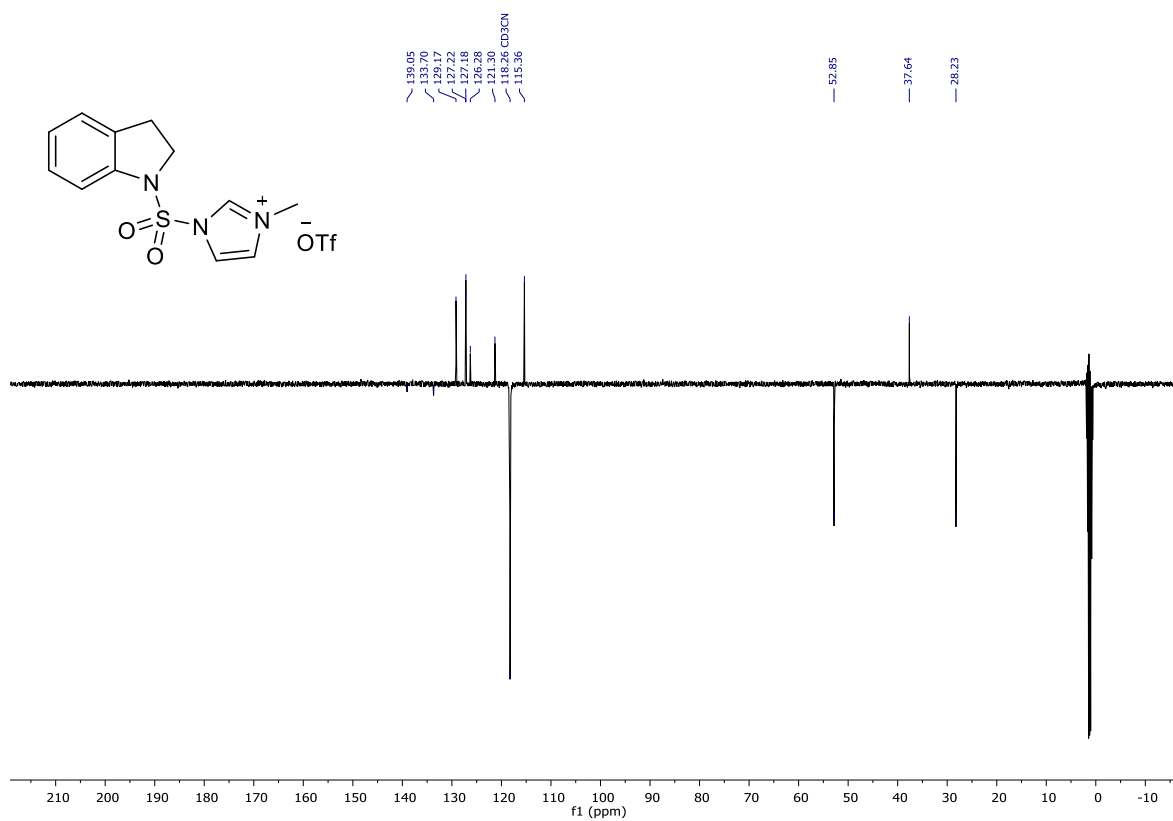
11-{4-[(1*H*-Imidazol-1-yl)sulfonyl]piperazin-1-yl}-2-chlorodibenzo[b,f][1,4]oxazepine (**3j**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

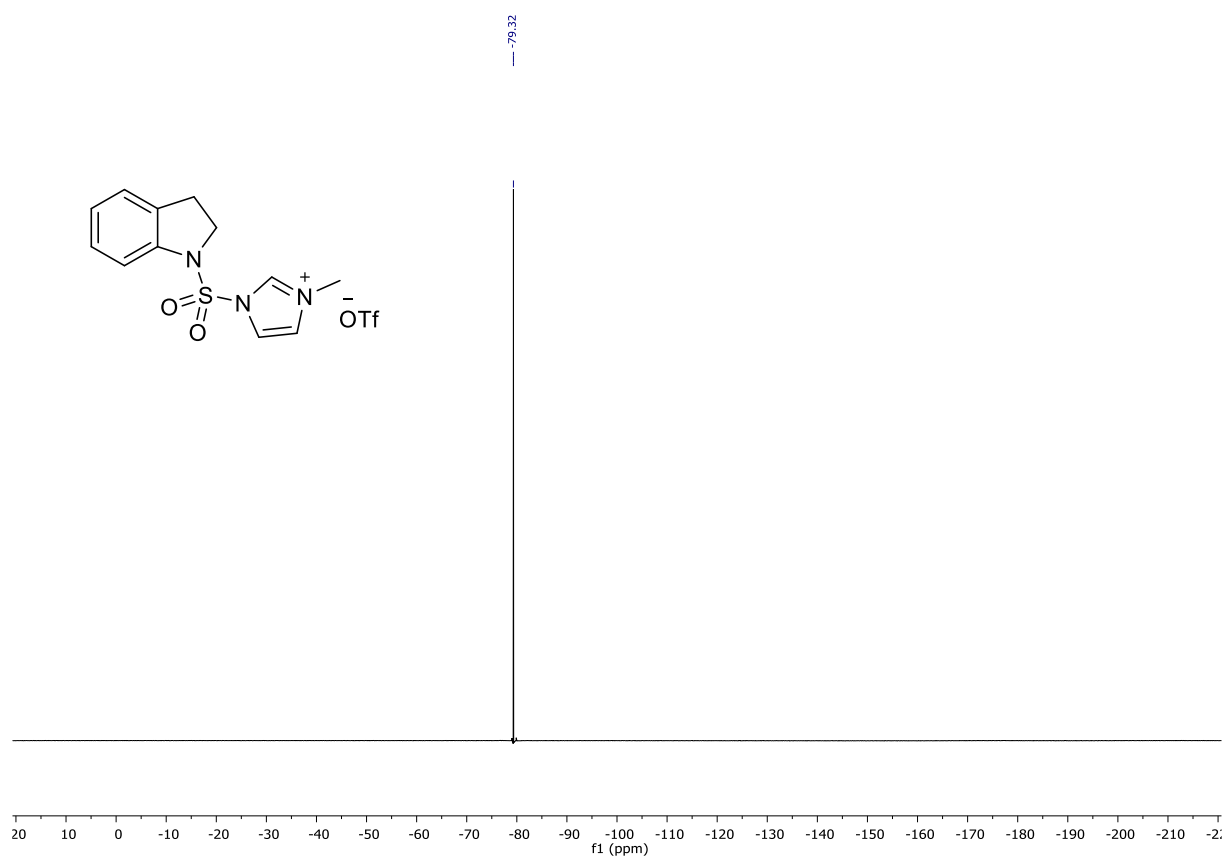
1-[(4-Benzylpiperidin-1-yl)sulfonyl]-3-methyl-1*H*-imidazol-3-ium triflate (**4a**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

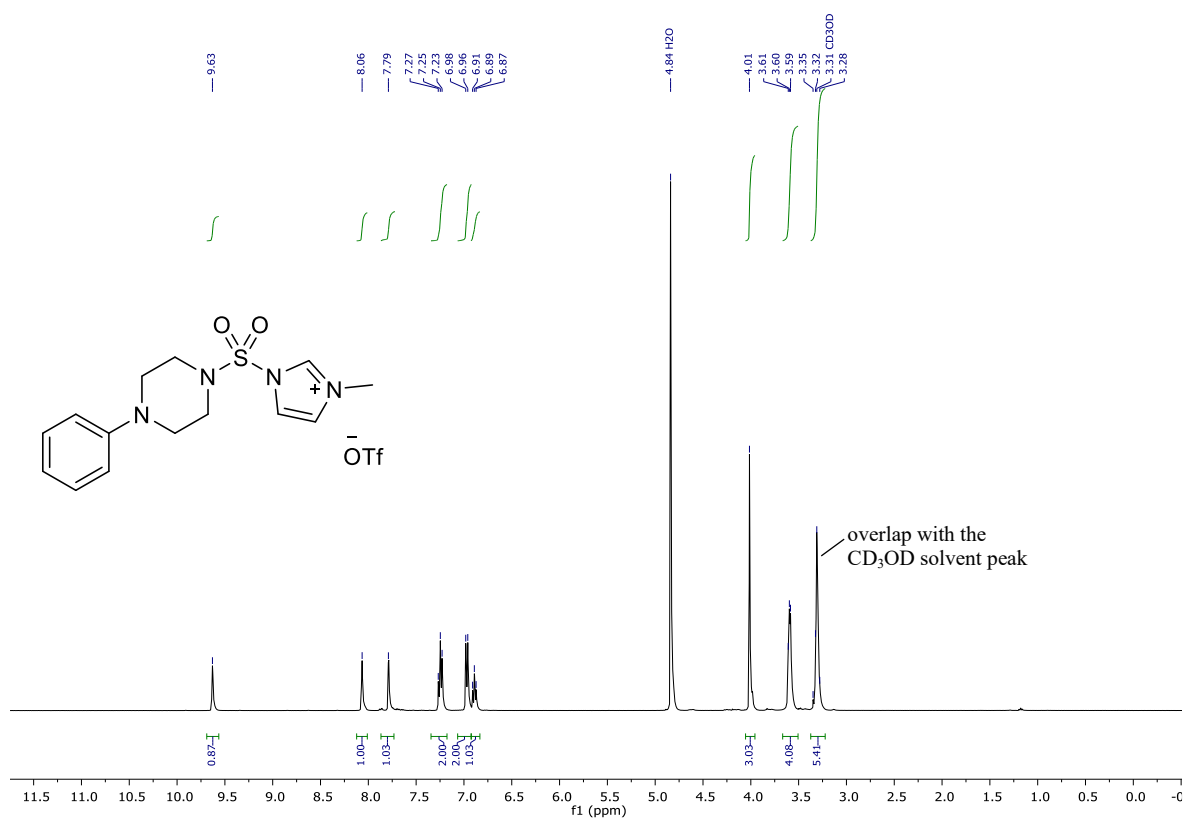
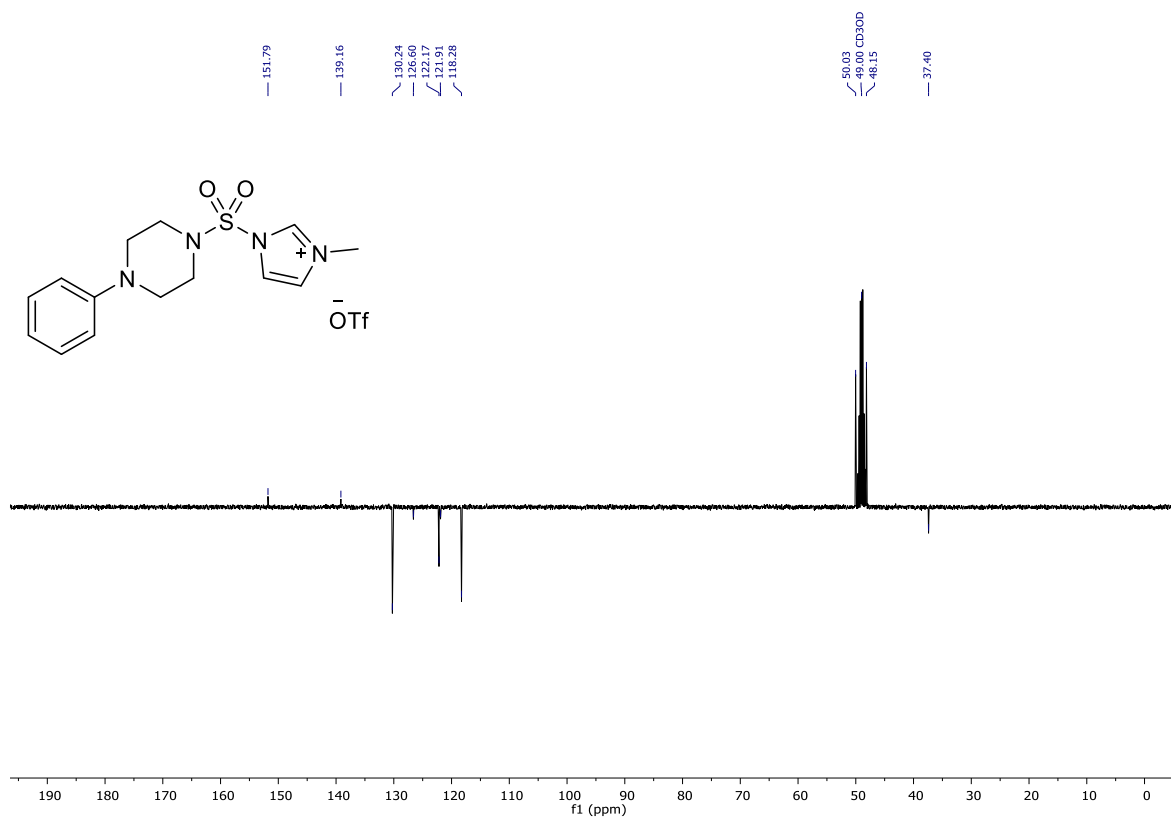
^{19}F NMR

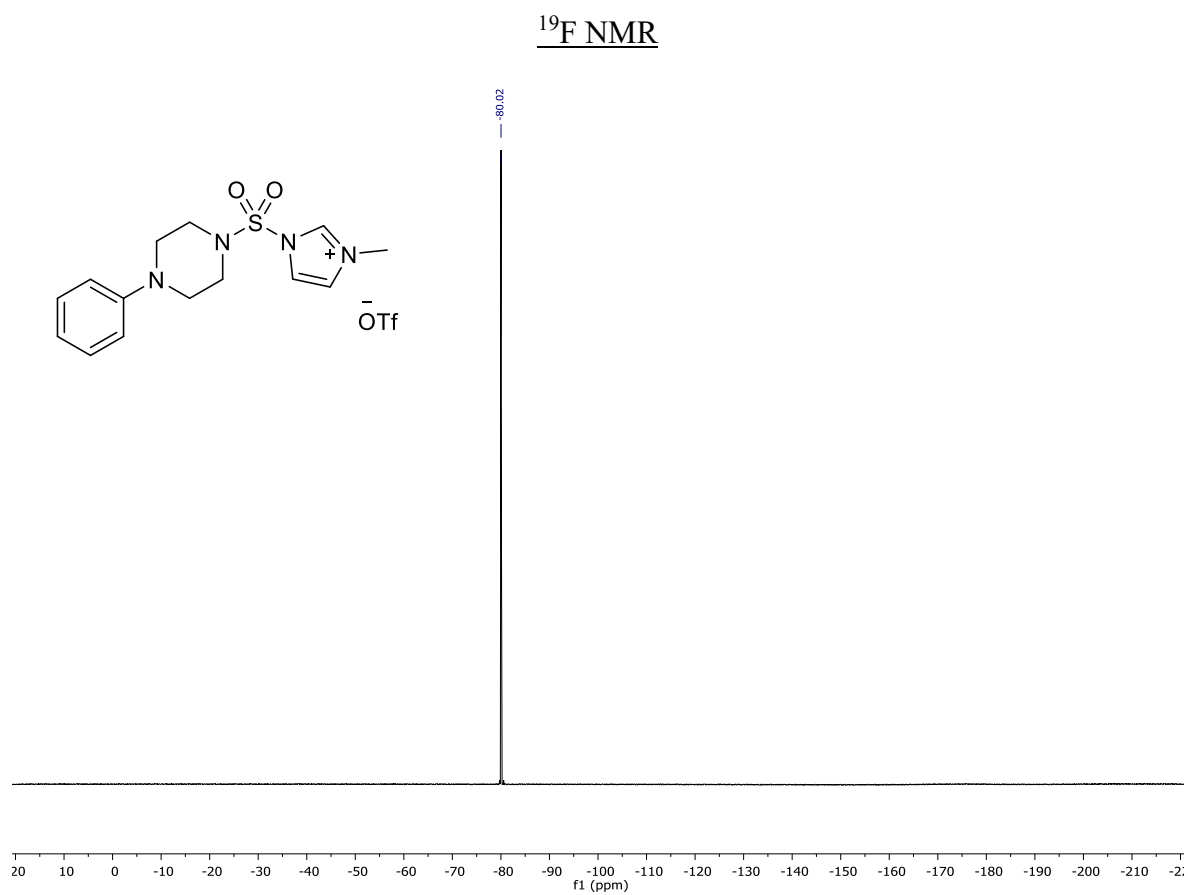
1-{[3,4-Dihydroisoquinolin-2(1*H*)-yl]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (**4b**)¹H NMR¹³C{¹H} NMR

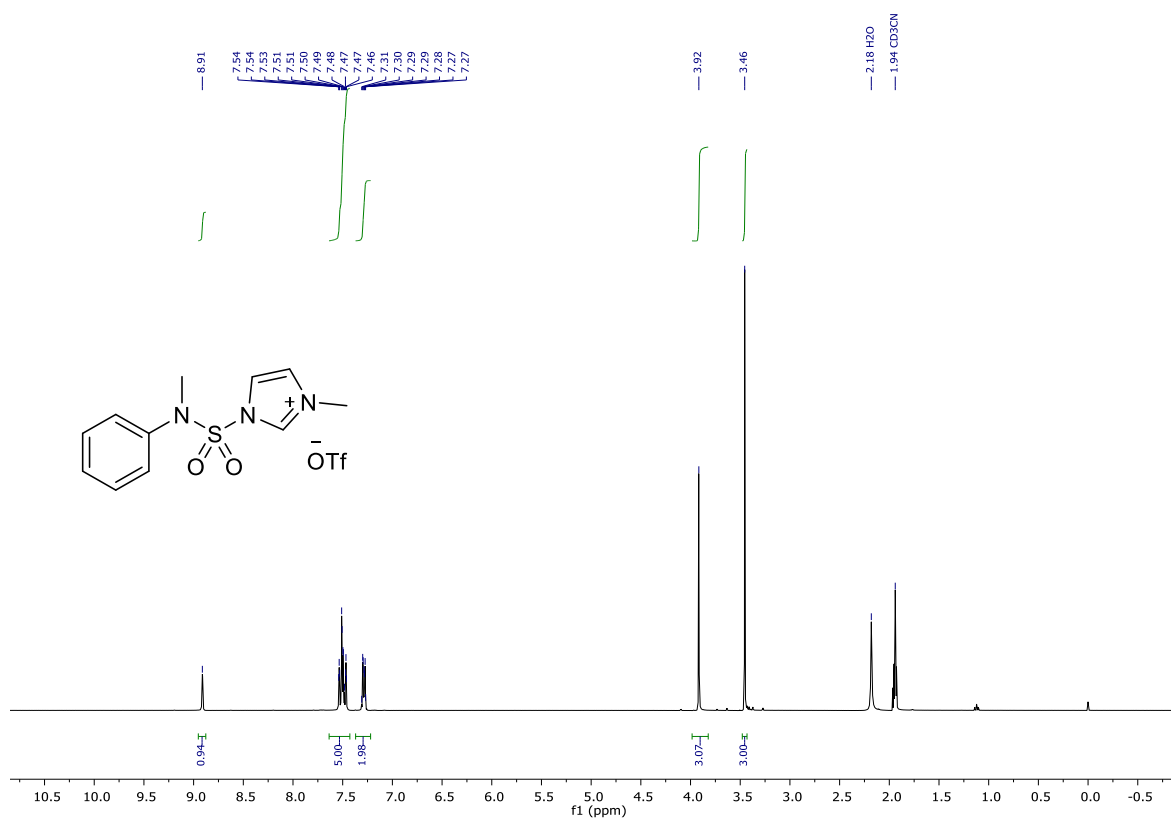
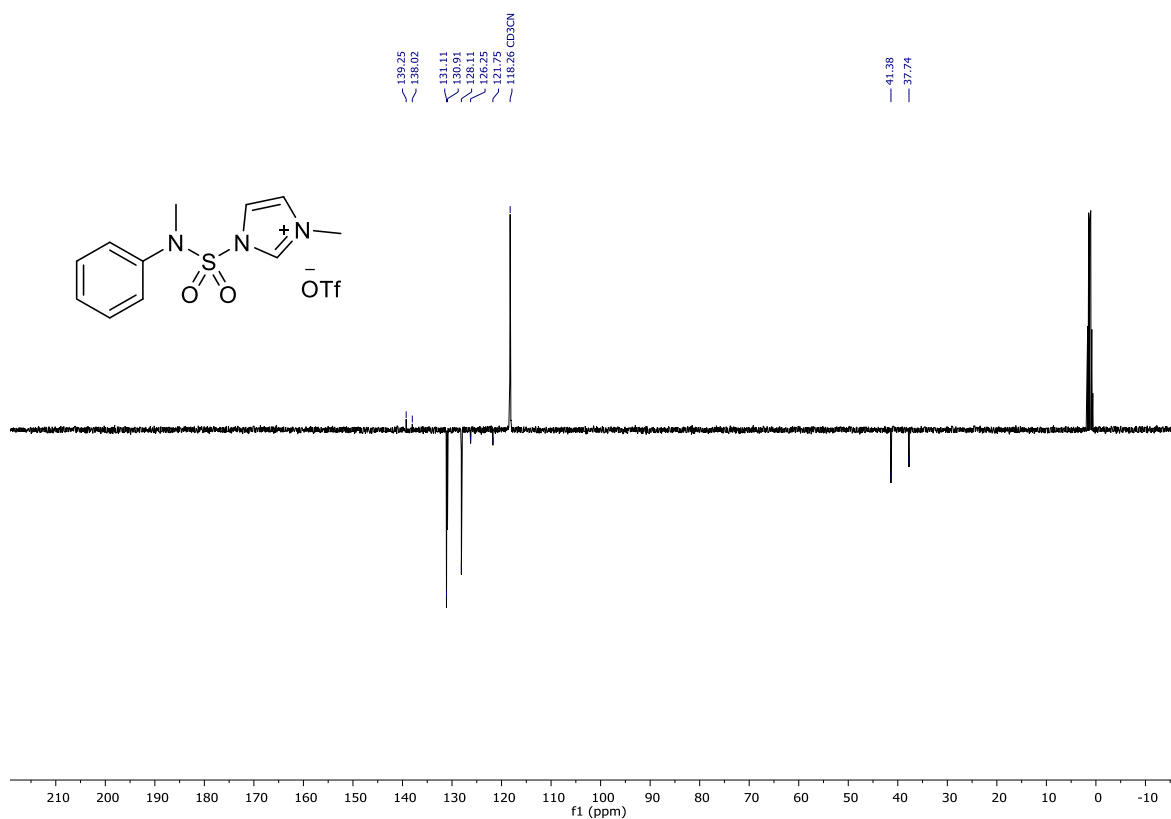
^{19}F NMR

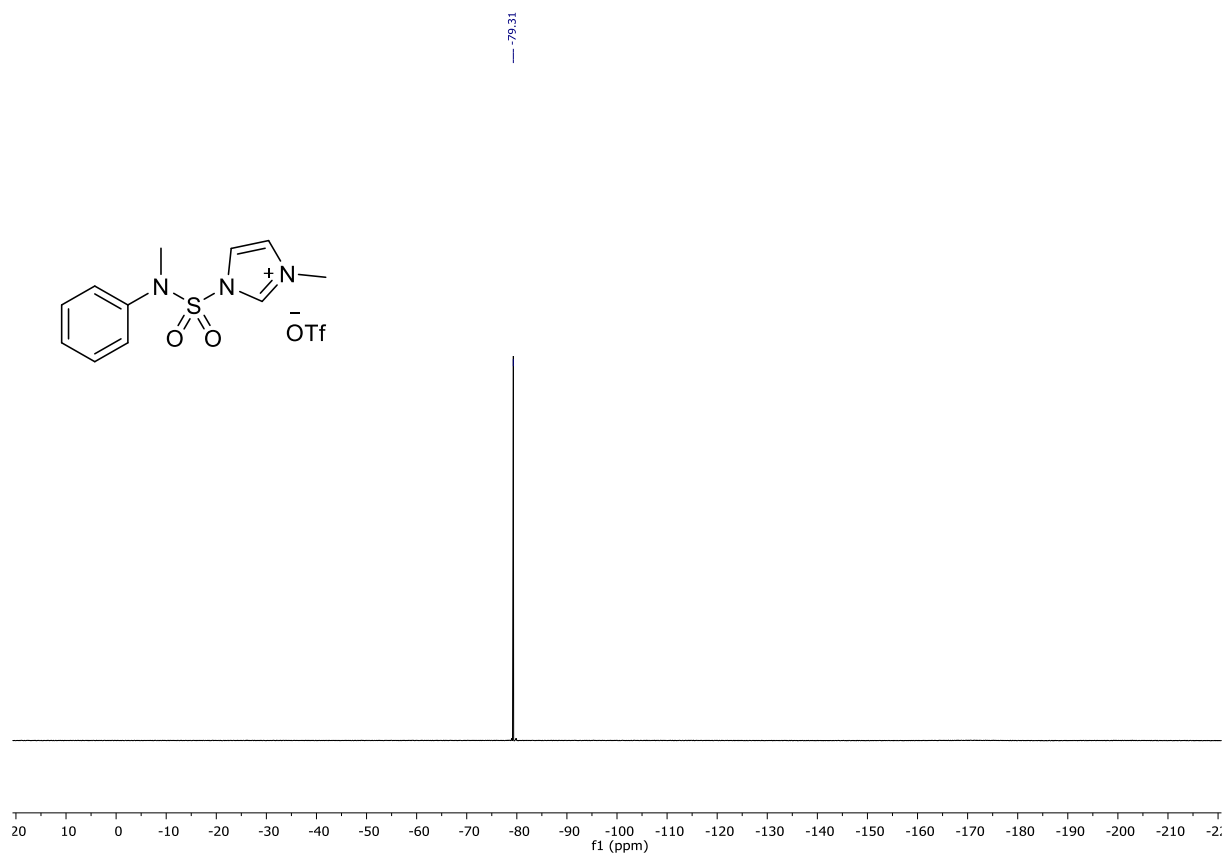
1-[(Indolin-1-yl)sulfonyl]-3-methyl-1*H*-imidazol-3-ium triflate (**4c**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

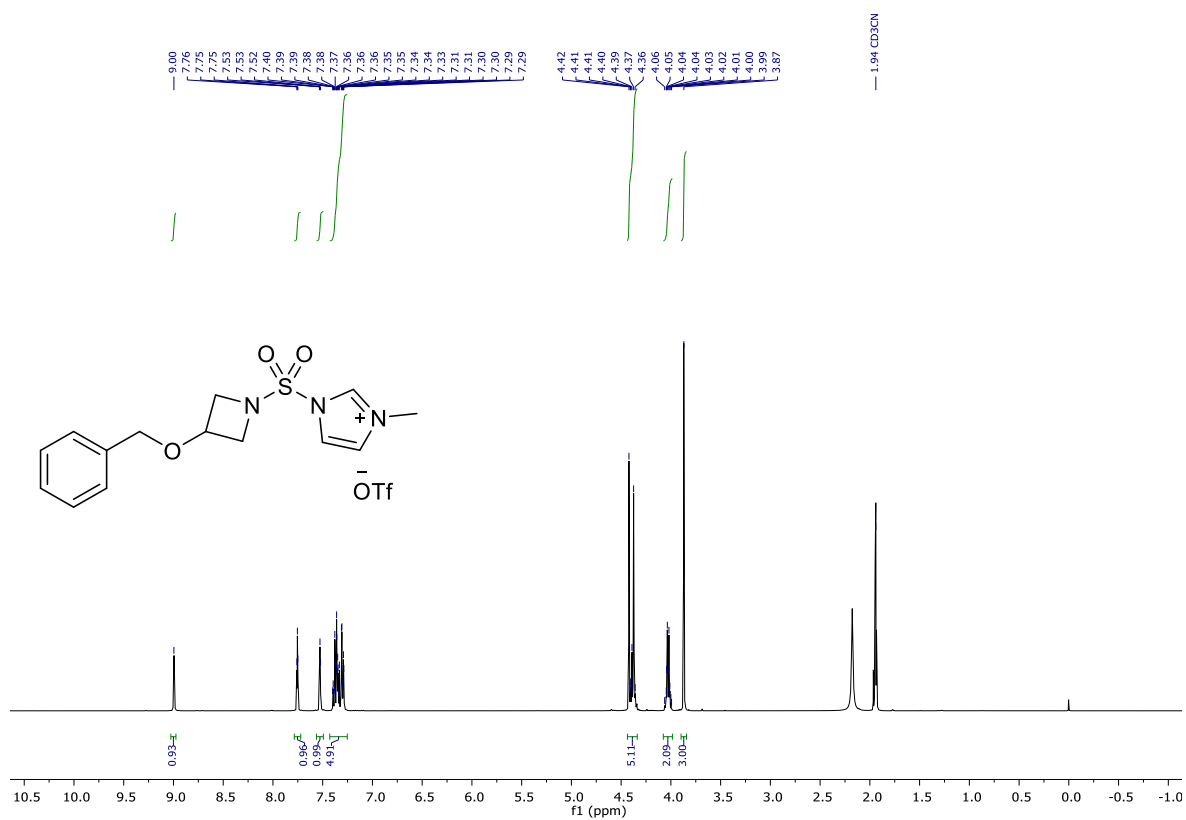
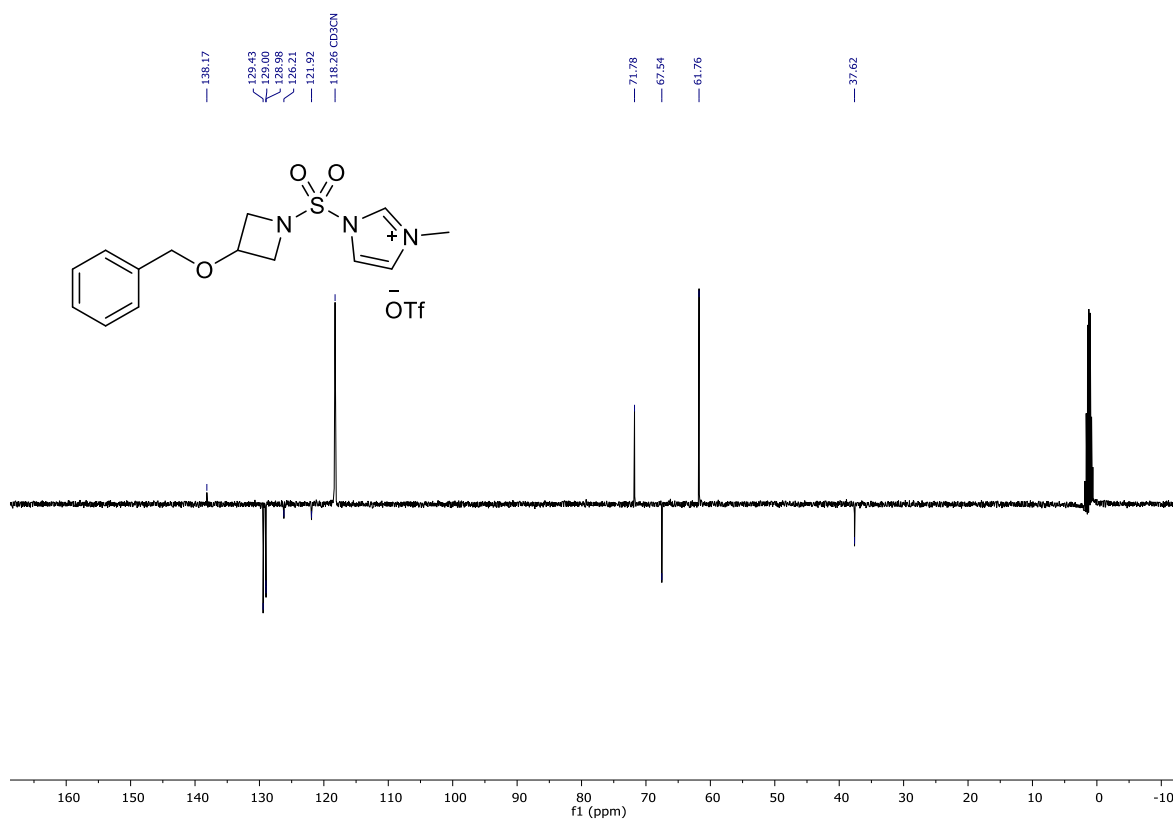
^{19}F NMR

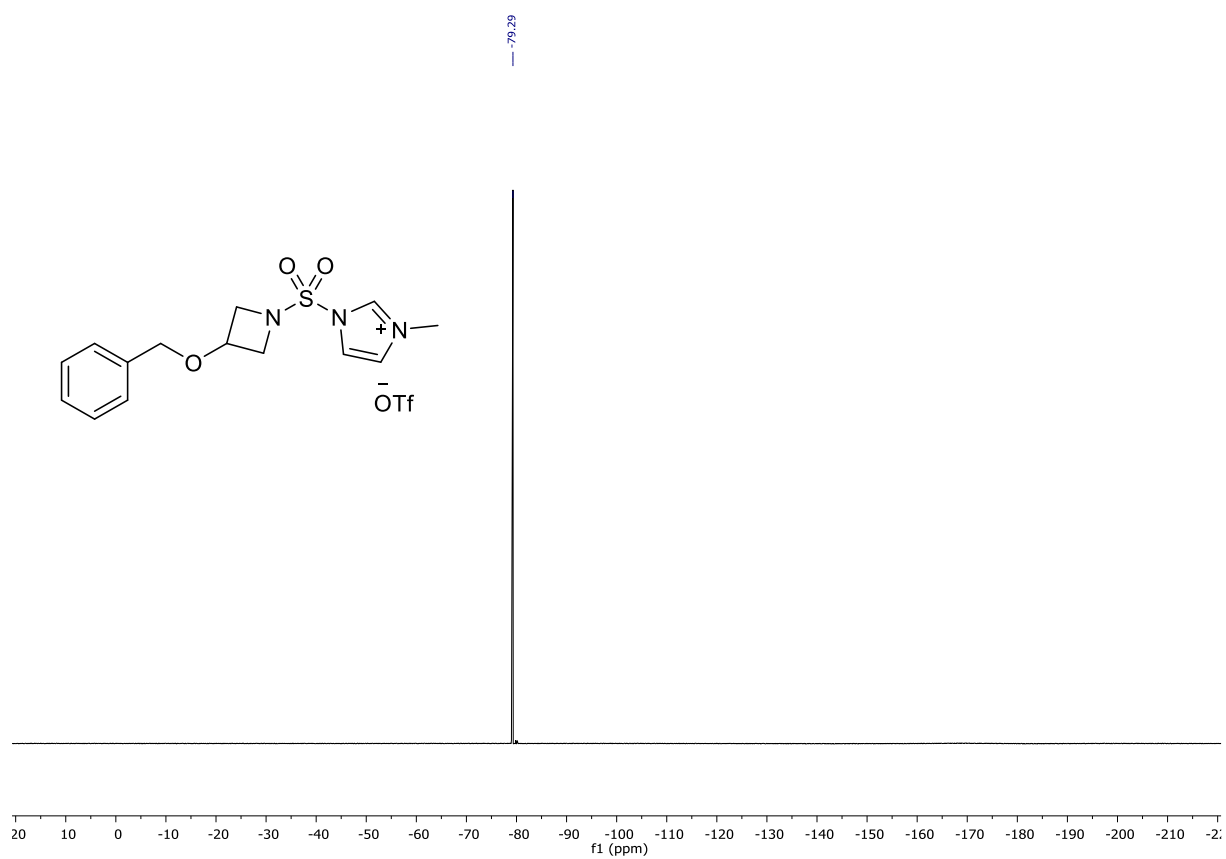
1-[(4-Phenylpiperazin-1-yl)sulfonyl]-3-methyl-1*H*-imidazol-3-ium triflate (**4d**)¹H NMR¹³C{¹H} NMR



1-(*N*-Methyl-*N*-phenylsulfamoyl)-3-methyl-1*H*-imidazol-3-ium triflate (**4e**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

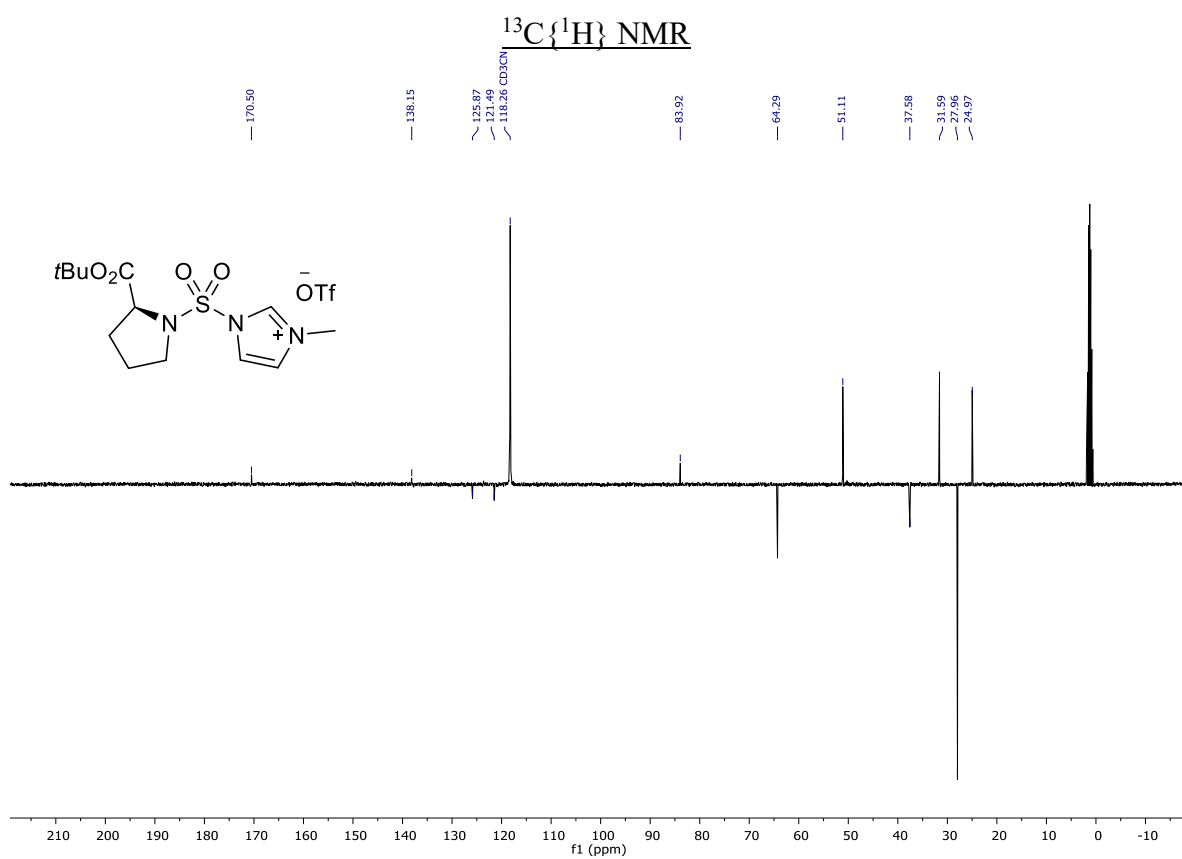
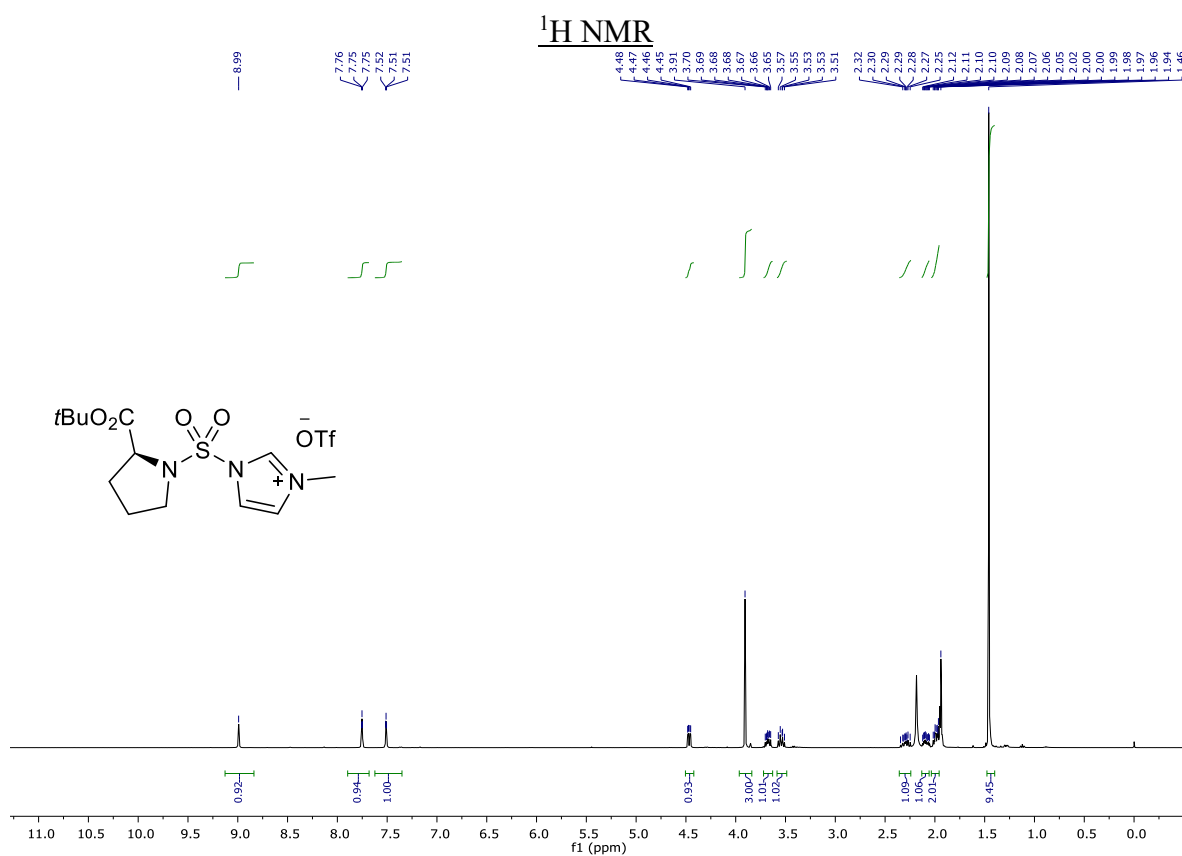
^{19}F NMR

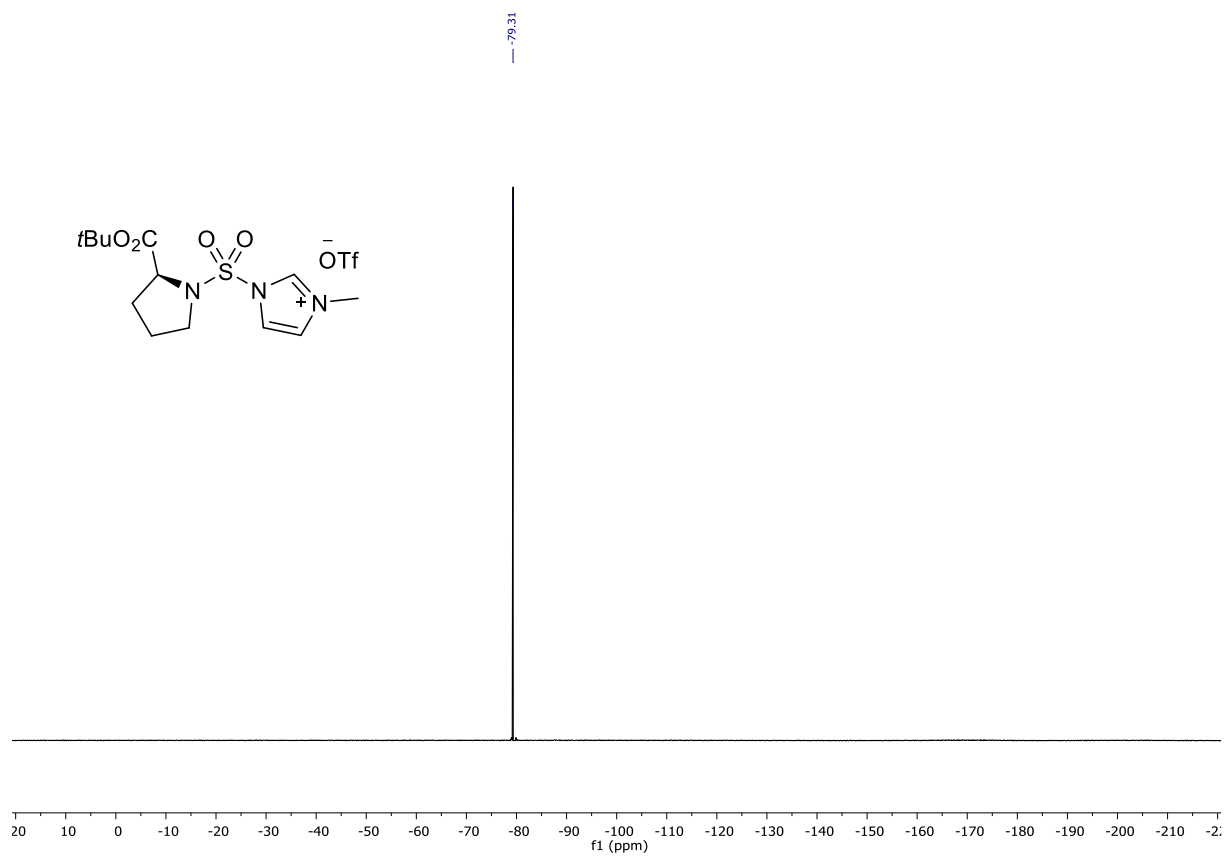
1-{[3-(Benzyloxy)azetidin-1-yl]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (**4f**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

^{19}F NMR

(*S*)-1-([2-(*tert*-Butoxycarbonyl)pyrrolidin-1-yl]sulfonyl)-3-methyl-1*H*-imidazol-3-ium triflate

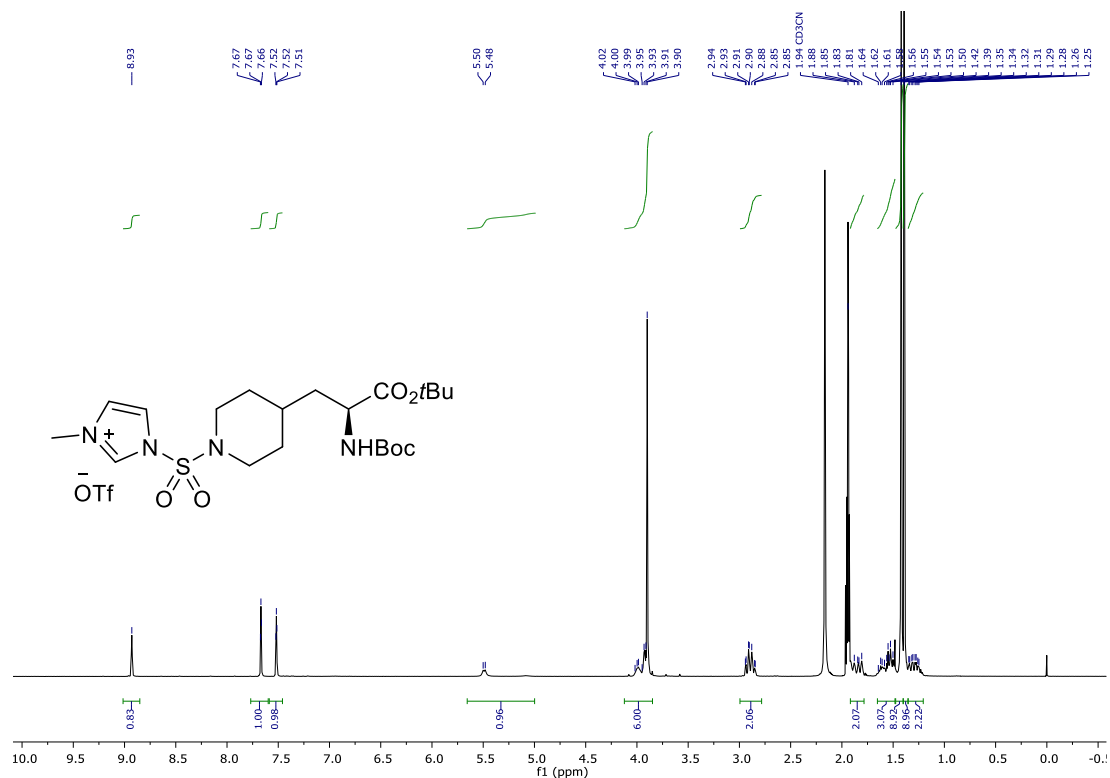
(4g)



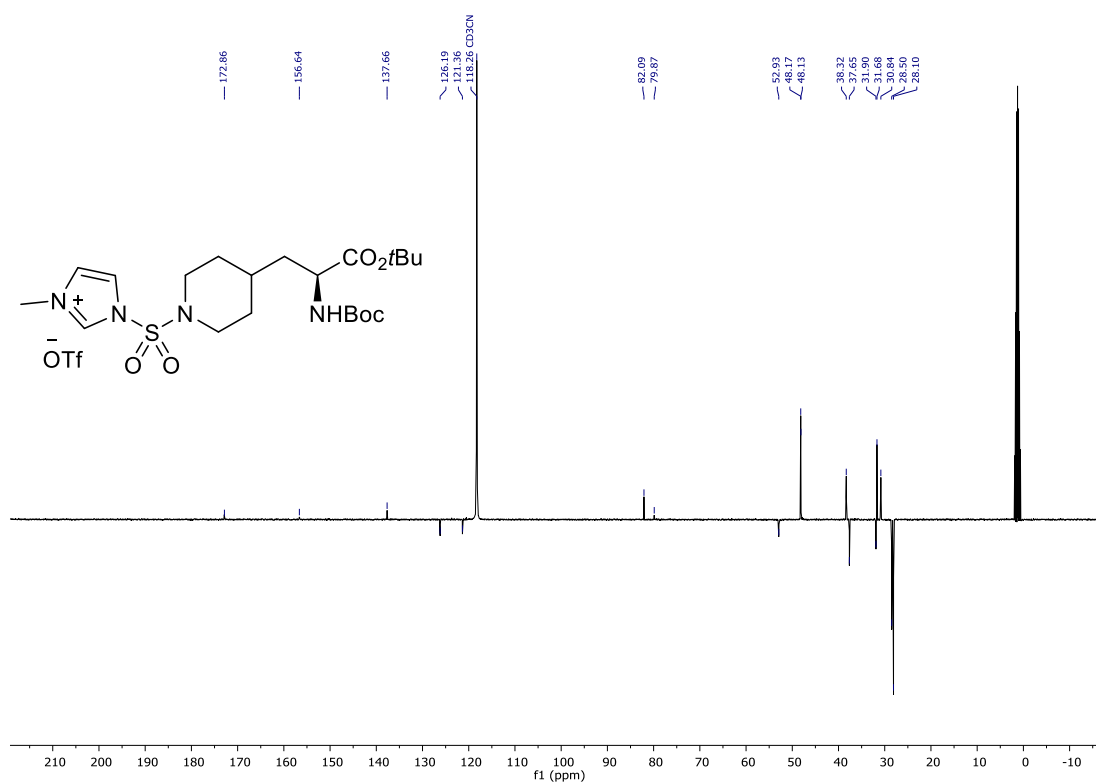
^{19}F NMR

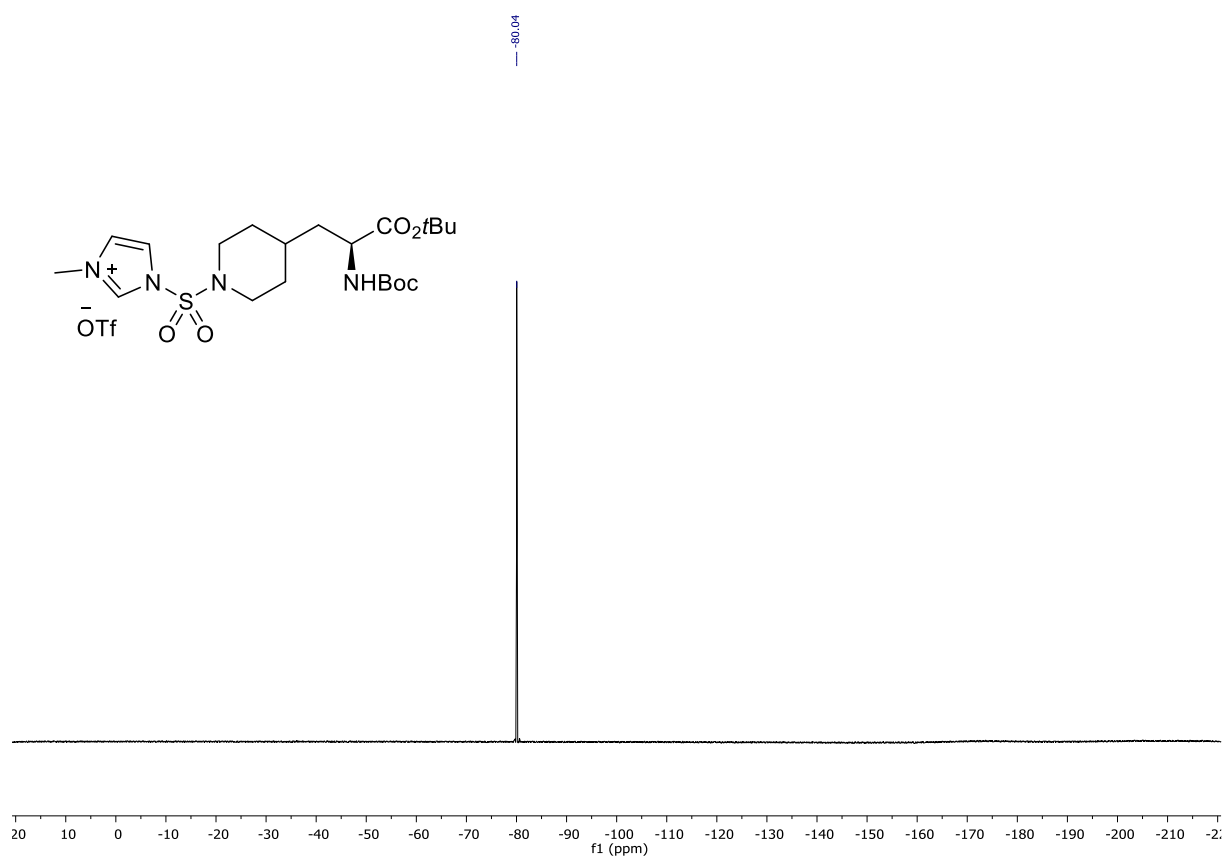
(*S*)-1-(4-[3-(*tert*-Butoxy)-2-[(*tert*-butoxycarbonyl)amino]-3-oxopropyl]piperidin-1-yl)sulfonyl)-3-methyl-1*H*-imidazol-3-ium triflate (**4h**)

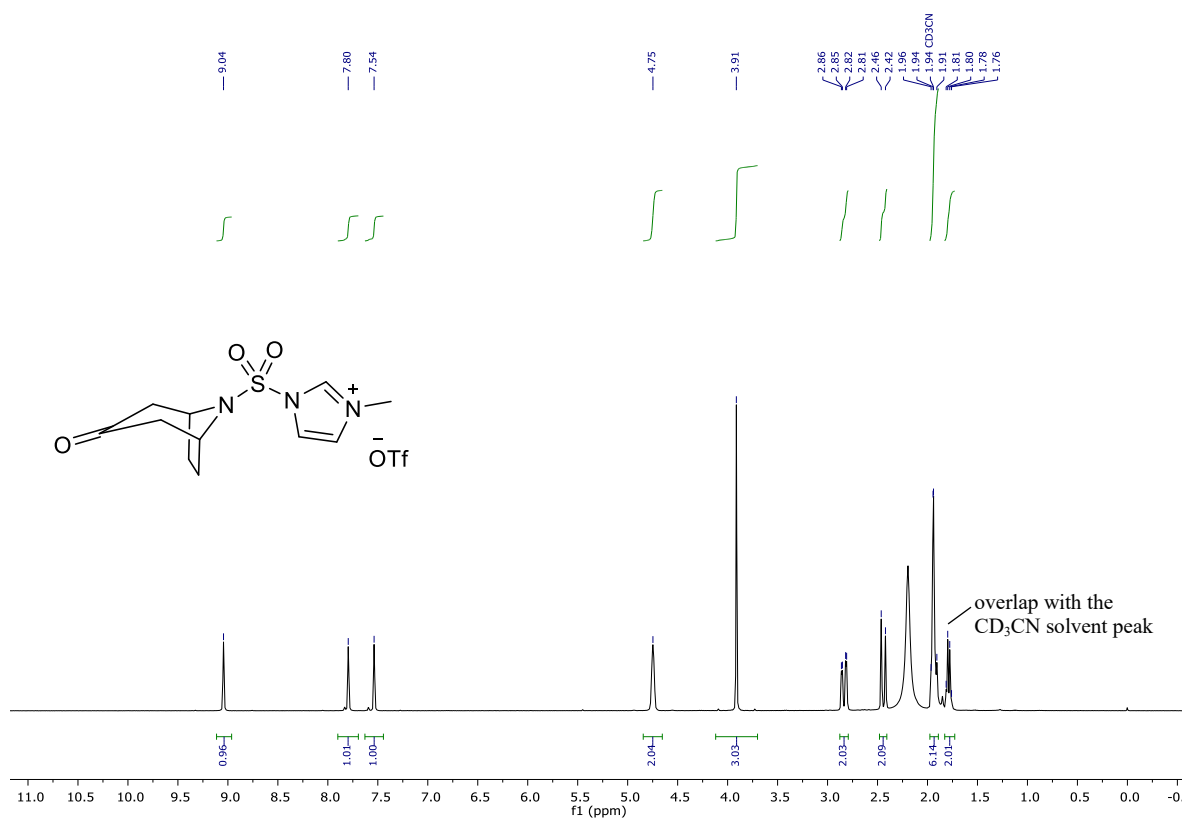
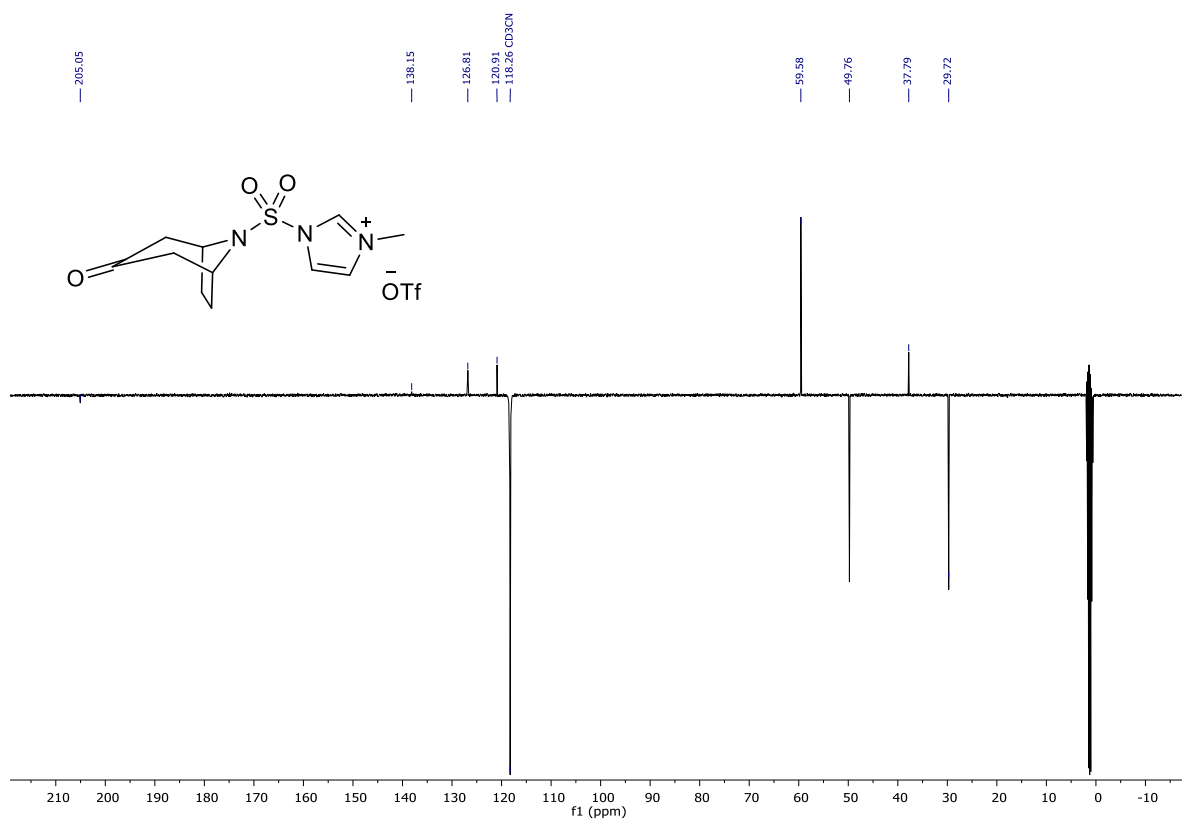
¹H NMR

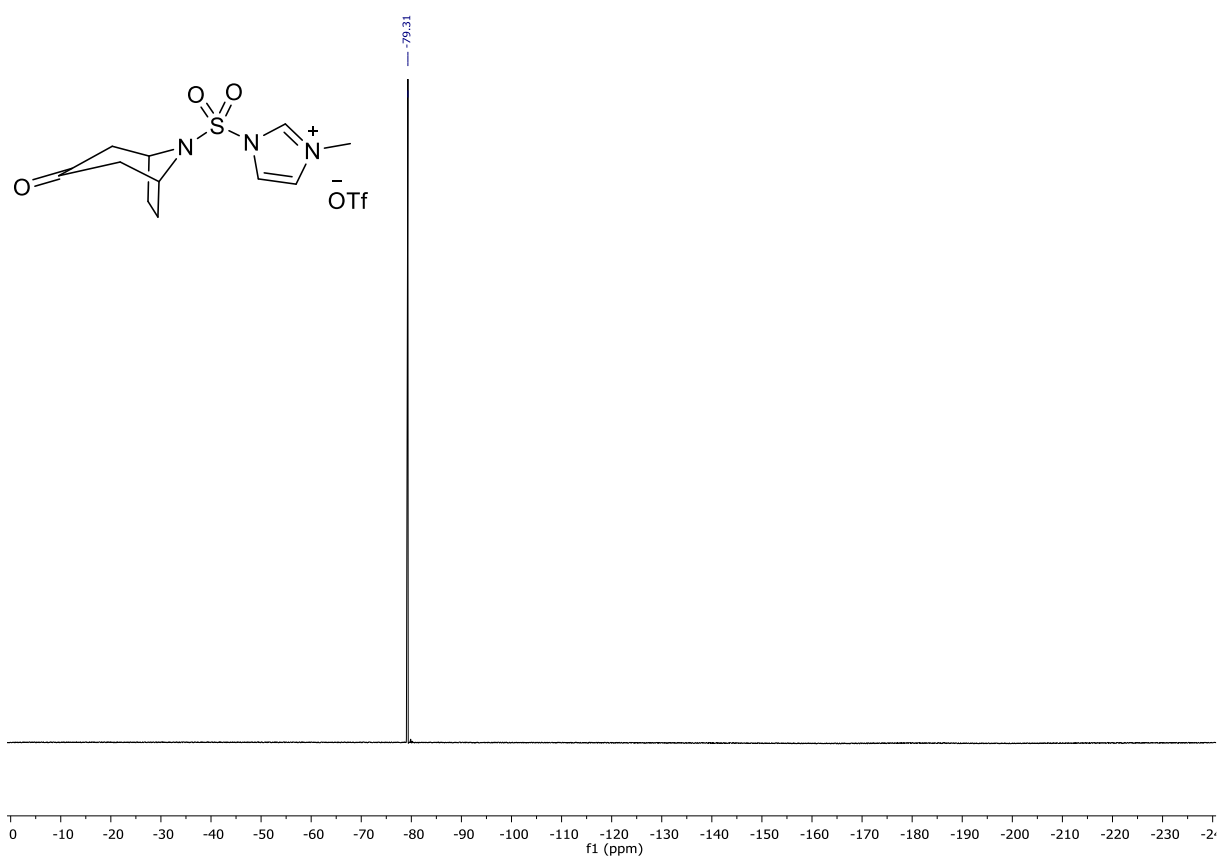


¹³C{¹H} NMR



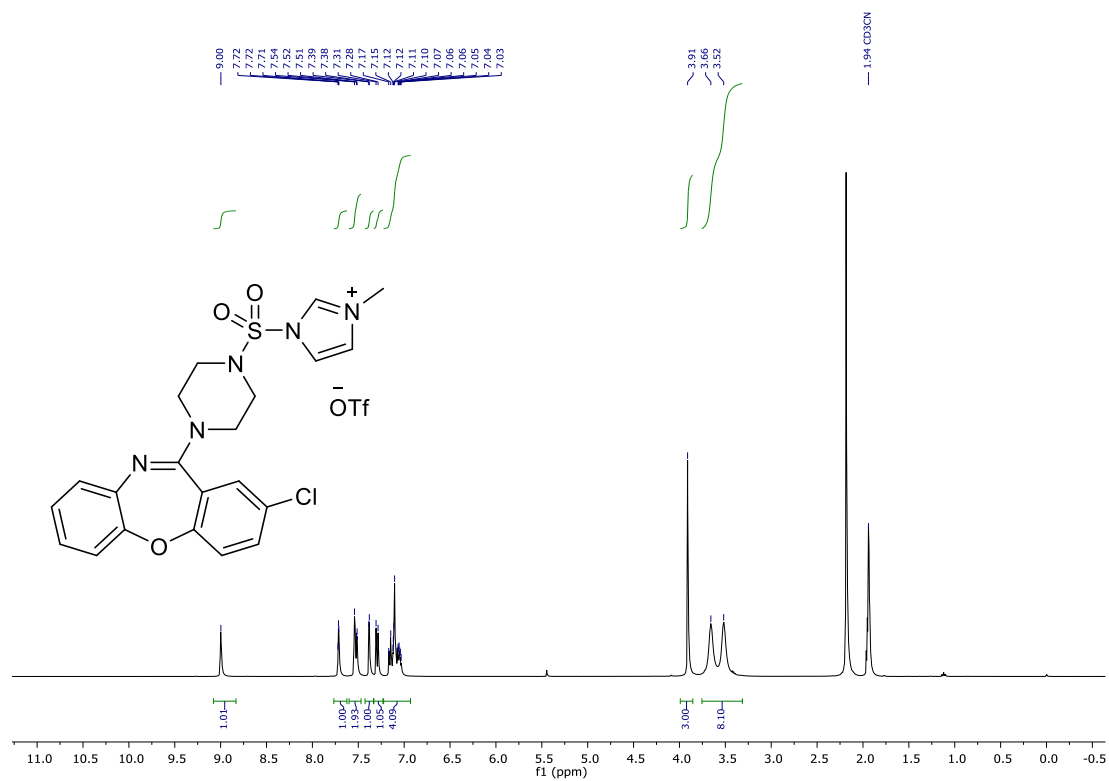
^{19}F NMR

1-[(3-Oxo-8-azabicyclo[3.2.1]octan-8-yl)sulfonyl]-3-methyl-1*H*-imidazol-3-ium triflate (**4i**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

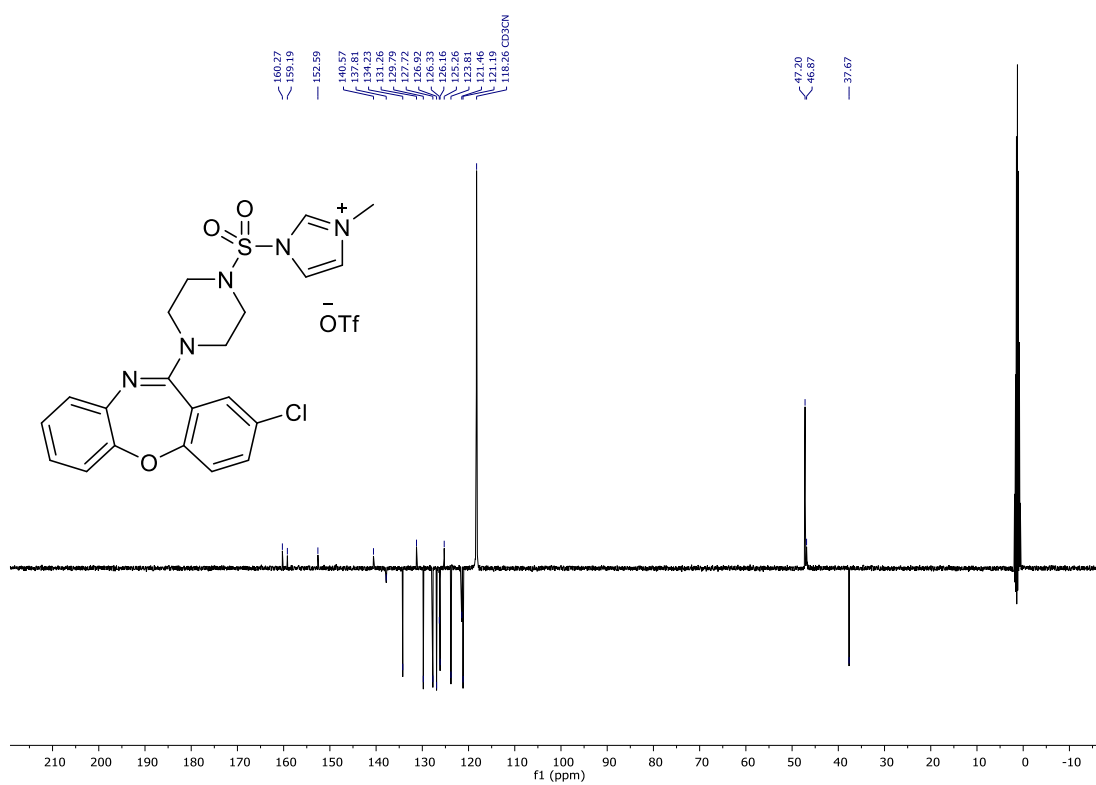
^{19}F NMR

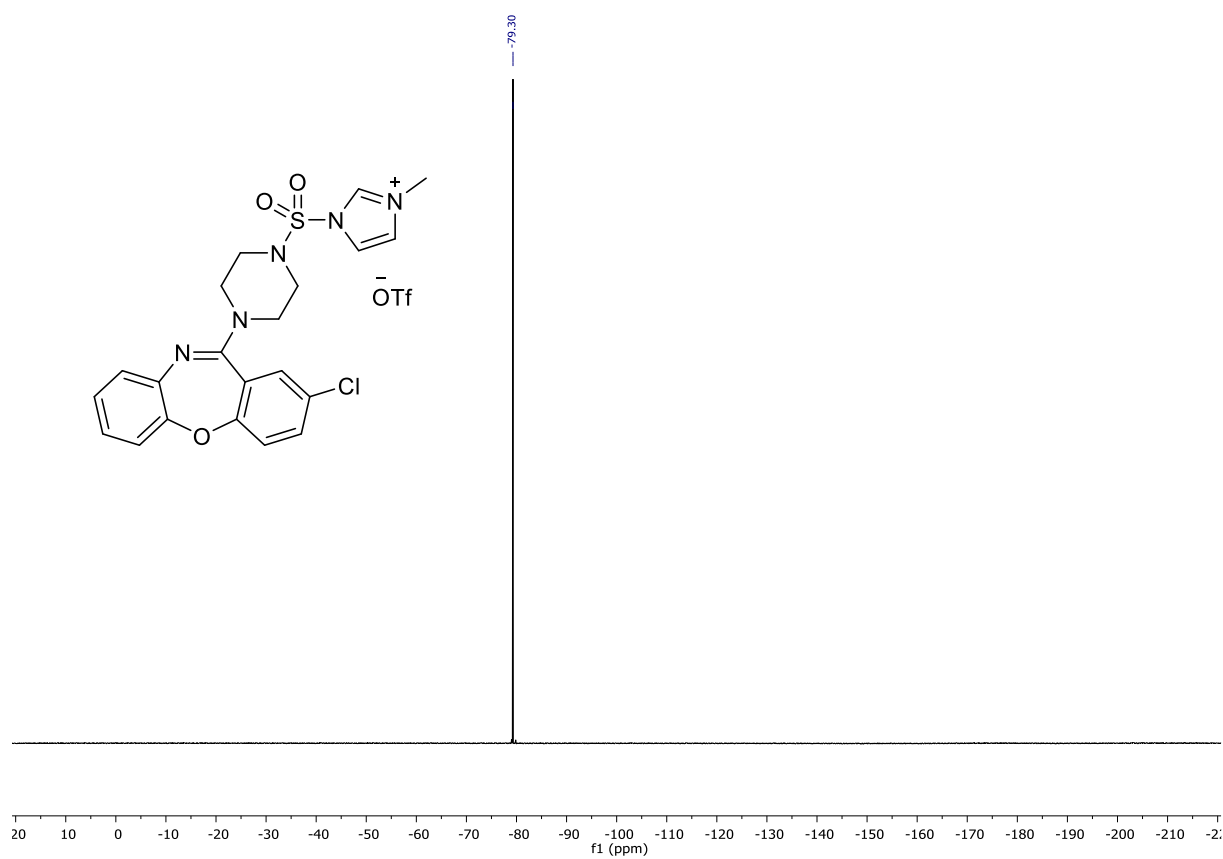
1-[4-(2-Chlorodibenzo[b,f][1,4]oxazepin-11-yl)piperazin-1-yl]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (**4j**)

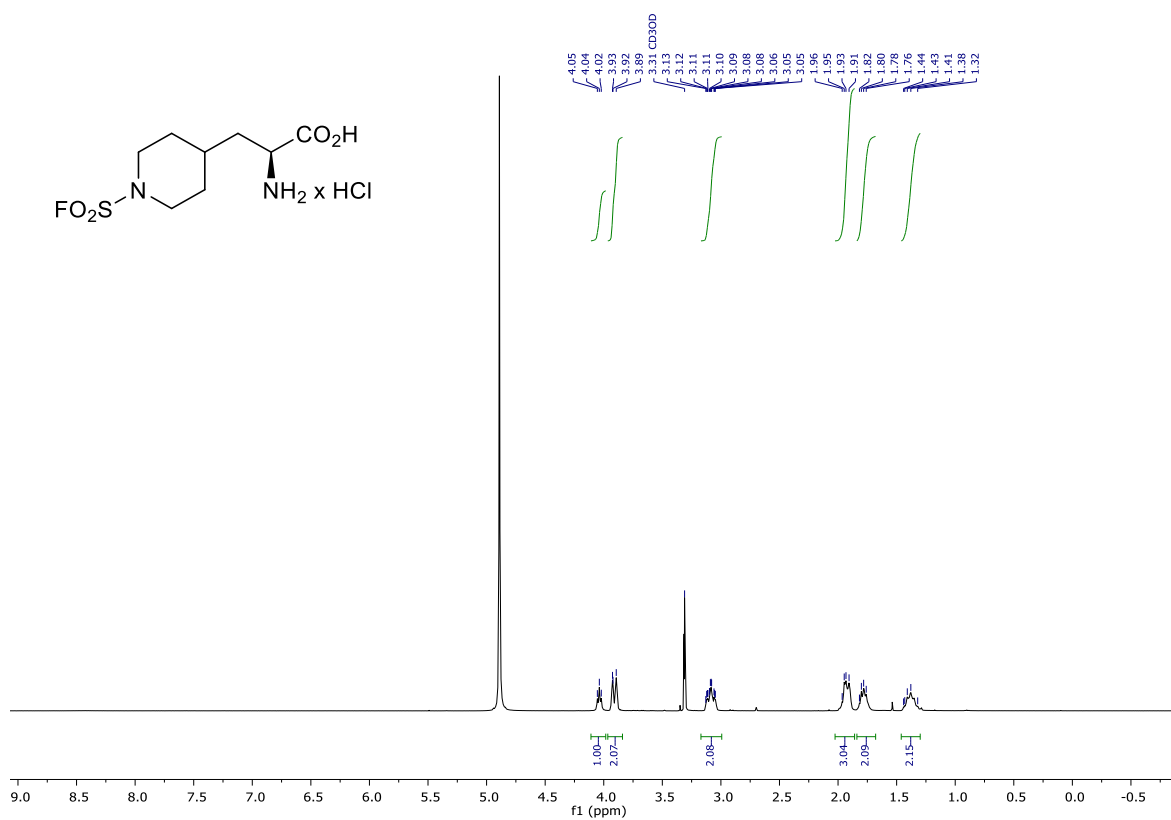
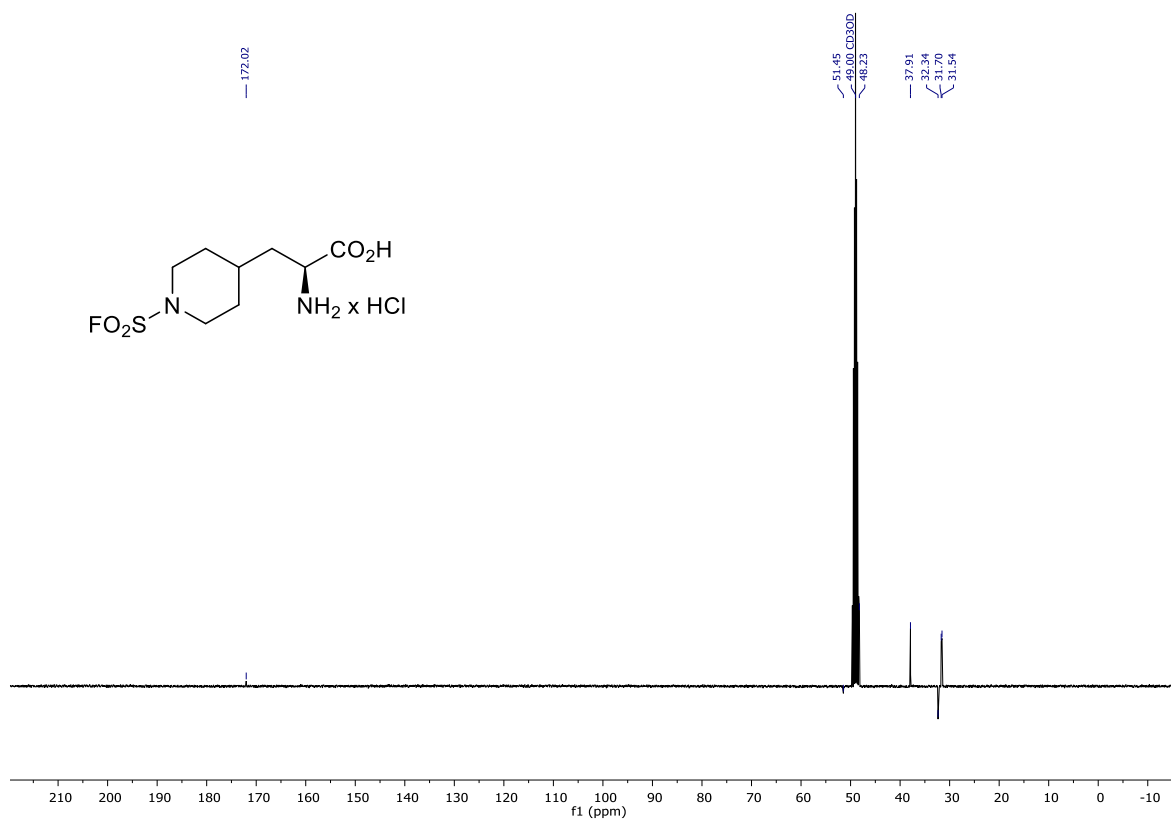
¹H NMR

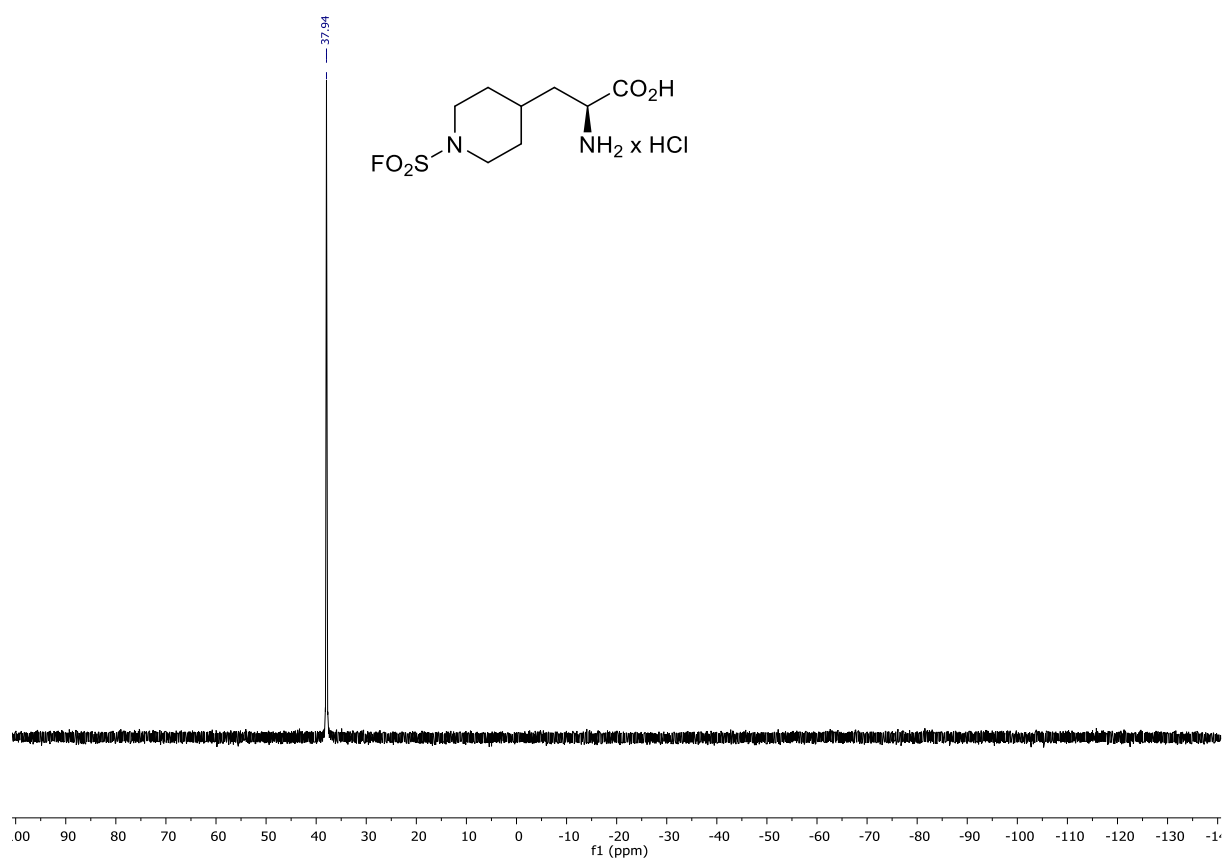


¹³C{¹H} NMR



^{19}F NMR

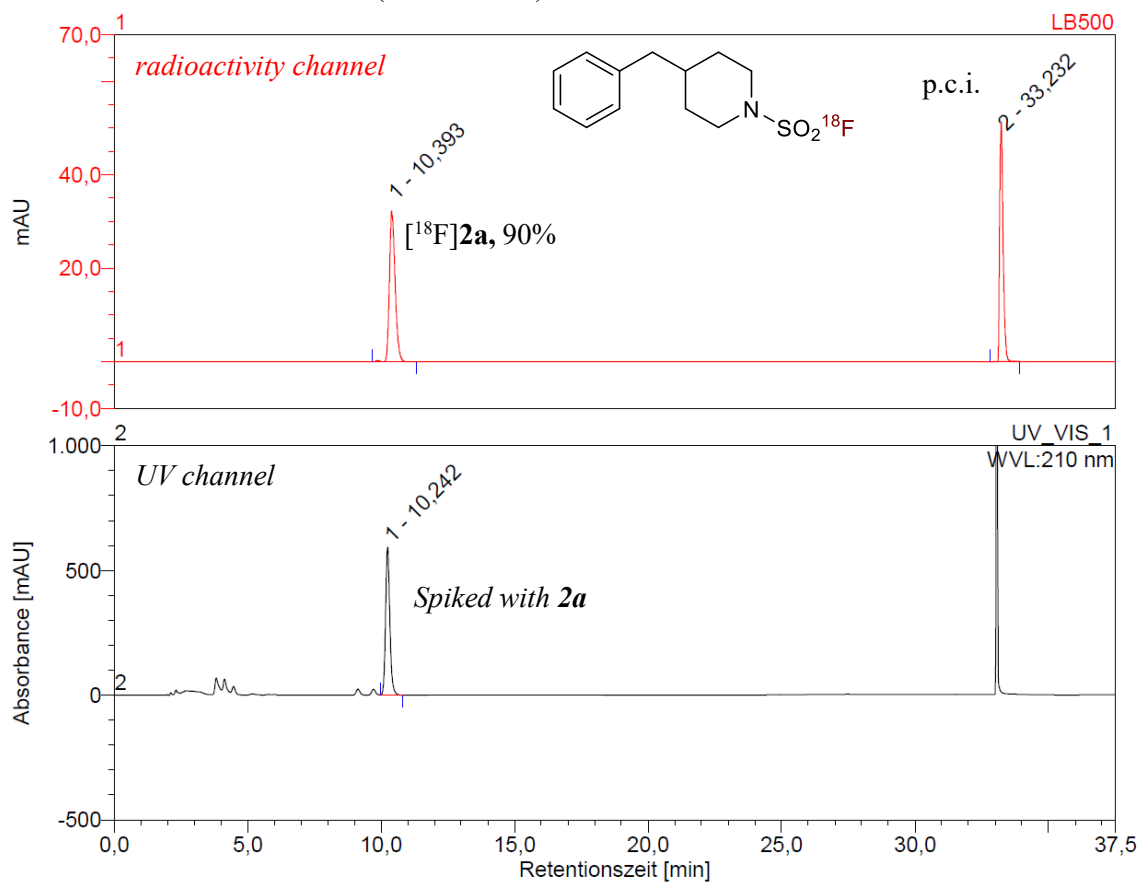
(S)-2-Amino-3-[1-(fluorosulfonyl)piperidin-4-yl]propanoic acid hydrochloride (7) **^1H NMR** **$^{13}\text{C}\{^1\text{H}\}$ NMR**

^{19}F NMR

Chromatograms

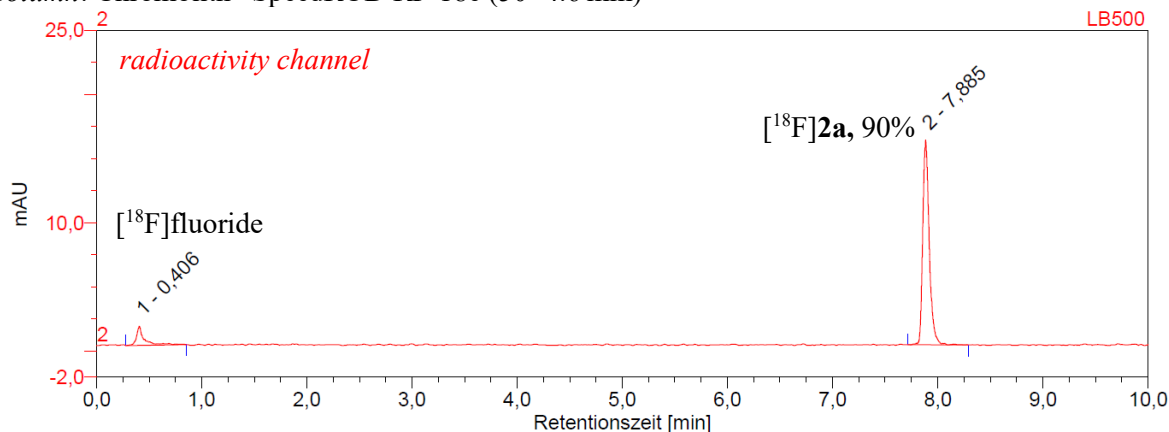
4-Benzylpiperidine-1-sulfonyl [^{18}F]fluoride ([^{18}F]2a)

Column: MultoKrom[®] 100–5 C18 (250×4.6 mm)



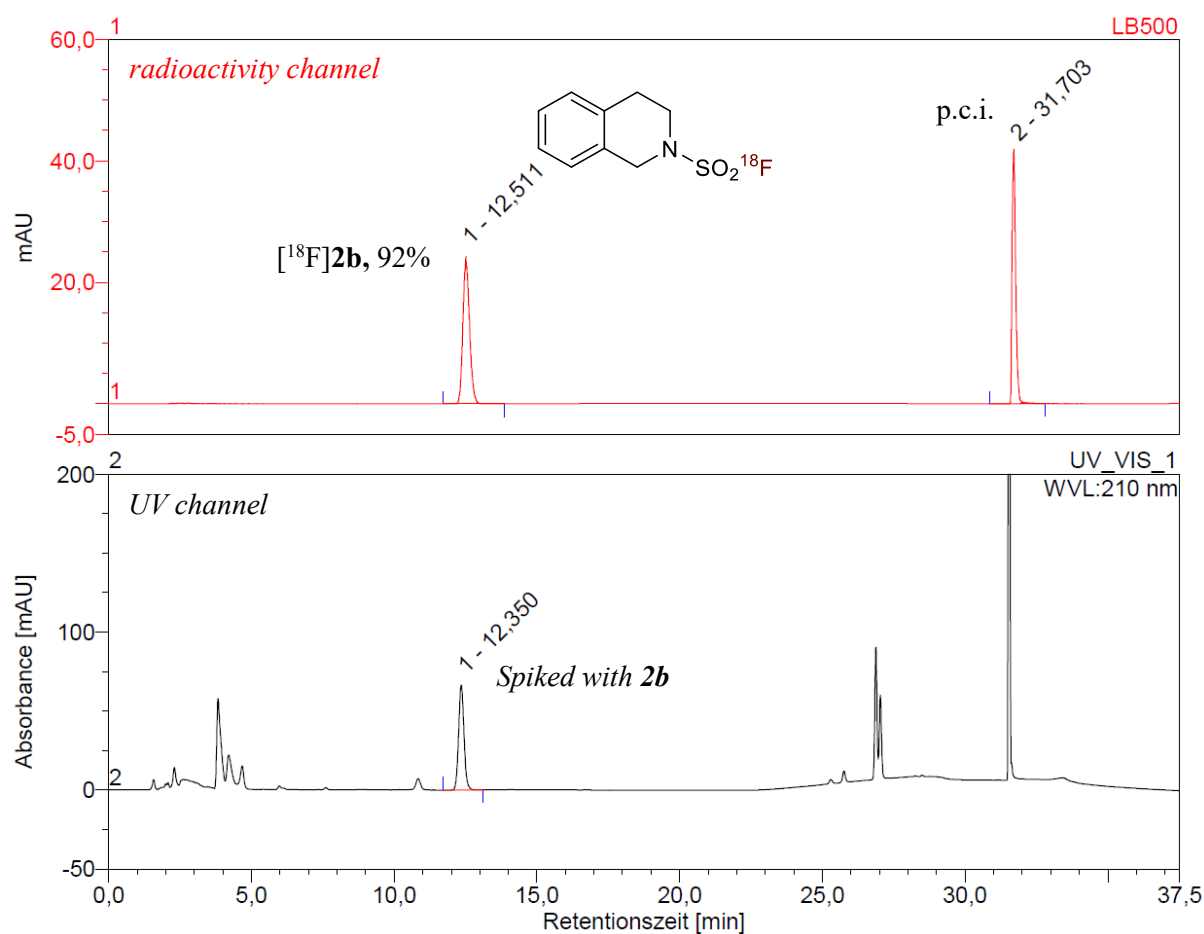
Gradient: 0–20 min: 75% MeCN, 20 min–25 min: 75 → 95% MeCN, 25 min–30 min: 95% MeCN, 30 min–35 min: 95 → 75% MeCN, 30 min–35 min: 75% MeCN; flow-rate: 1 mL/ min detection: radioactivity, UV: $\lambda=210$ nm. Abbreviations: p.c.i., post-column injection.^[2]

Column: Chromolith[®] SpeedROD RP-18e (50×4.6 mm)*



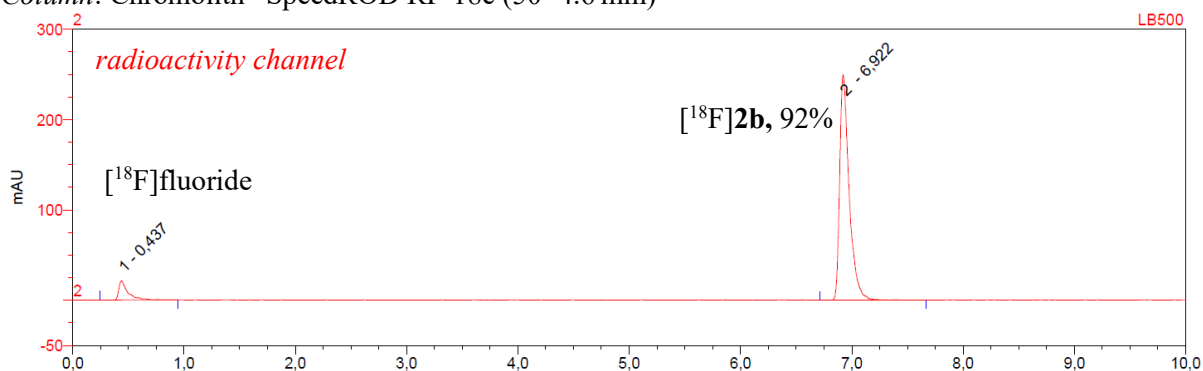
Gradient: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min.

*Second chromatogram using Chromolith SpeedROD shown to illustrate complete adsorption of [^{18}F]fluoride on MultoKrom[®] 100–5 C18 column. In contrast, recovery of [^{18}F]fluoride from the Chromolith SpeedROD column under neutral conditions (without addition of TFA) exceeded 98%.

1,2,3,4-Tetrahydroisoquinoline-2-sulfonyl [^{18}F]fluoride ($[^{18}\text{F}]\mathbf{2b}$)Column: MultoKrom[®] 100–5 C18 (250×4.6 mm)

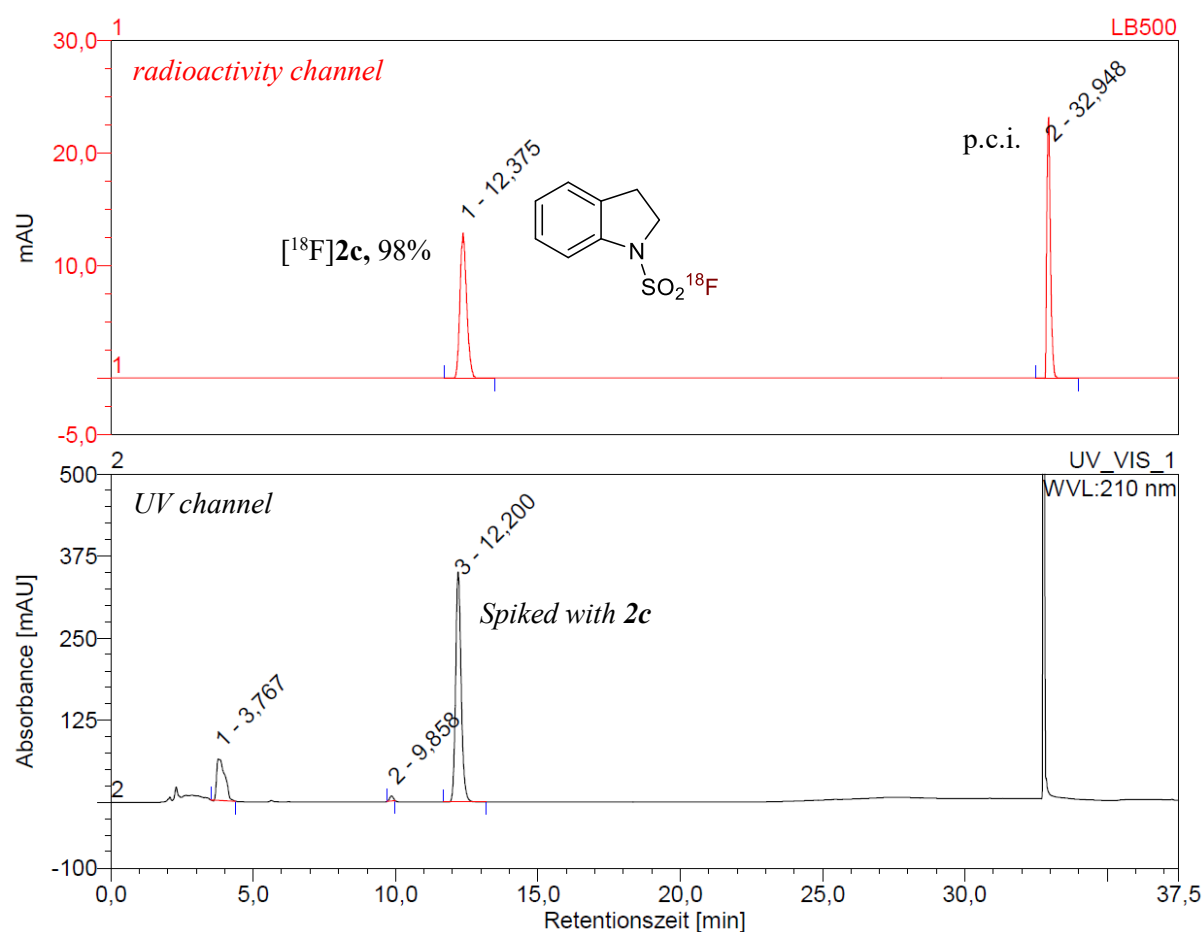
Gradient: 0–20 min: 60% MeCN, 20 min–25 min: 60 → 95% MeCN, 25 min–30 min: 95% MeCN, 30 min–35 min: 95 → 60% MeCN, 30 min–35 min: 60% MeCN; flow-rate: 1 mL/ min detection: radioactivity, UV: $\lambda=210$ nm. Abbreviations: p.c.i., post-column injection.

Column: Chromolith[®] SpeedROD RP-18e (50×4.6 mm)*

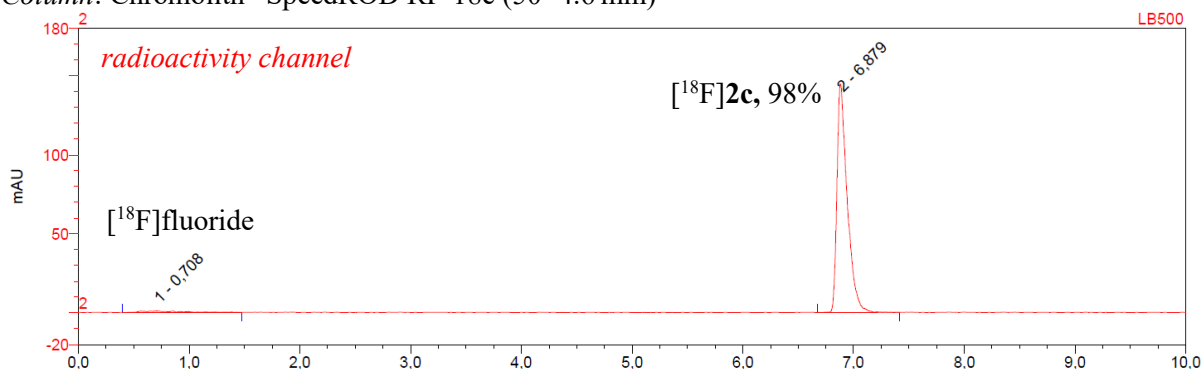


Gradient: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min.

*Second chromatogram using Chromolith SpeedROD shown to illustrate complete adsorption of [^{18}F]fluoride on MultoKrom[®] 100–5 C18 column. In contrast, recovery of [^{18}F]fluoride from the Chromolith SpeedROD column under neutral conditions (without addition of TFA) exceeded 98%.

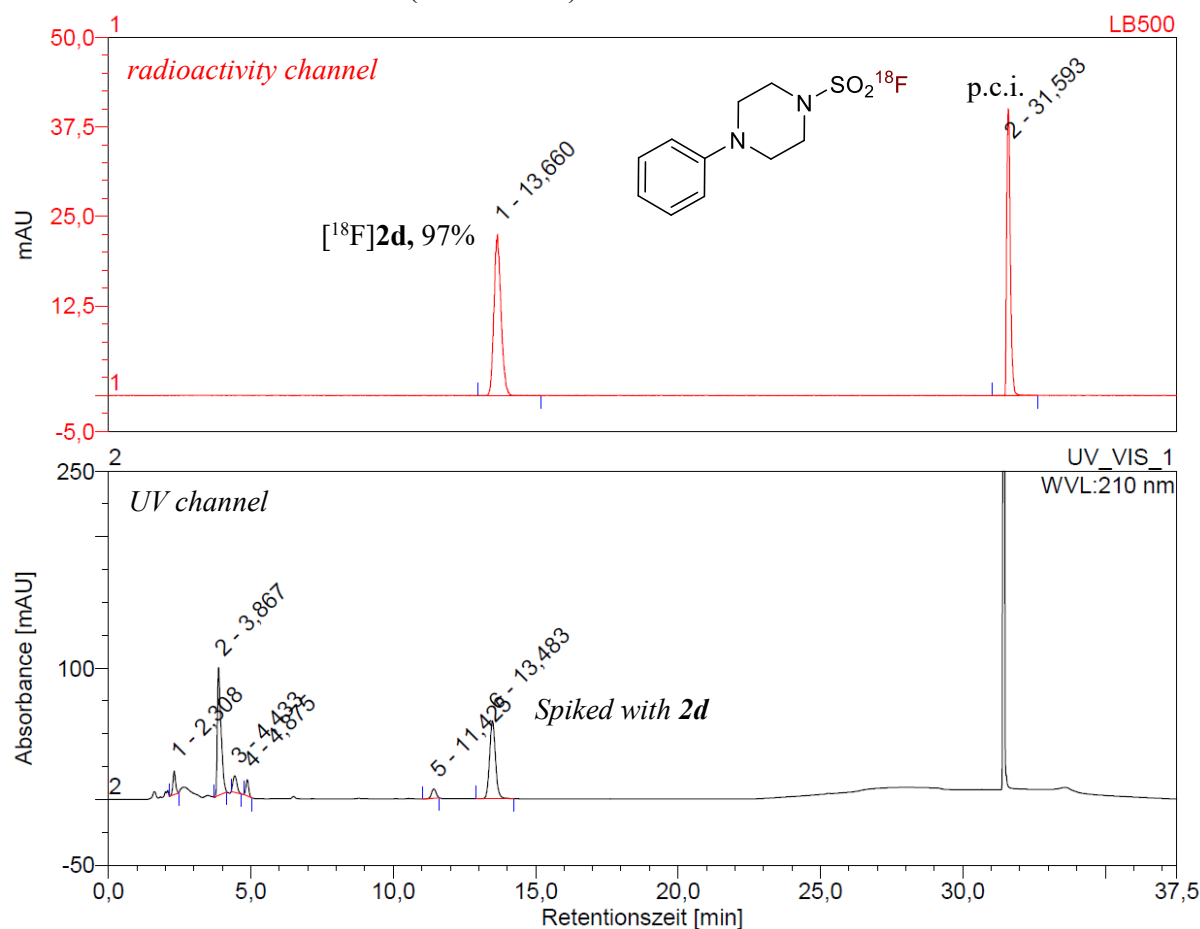
Indoline-1-sulfonyl [^{18}F]fluoride ($[^{18}\text{F}]\mathbf{2c}$)Column: MultoKrom[®] 100–5 C18 (250×4.6 mm)

Gradient: 0–20 min: 60% MeCN, 20 min–25 min: 60 → 95% MeCN, 25 min–30 min: 95% MeCN, 30 min–35 min: 95 → 60% MeCN, 30 min–35 min: 60% MeCN; flow-rate: 1 mL/ min detection: radioactivity, UV: $\lambda=210$ nm. Abbreviations: p.c.i., post-column injection.

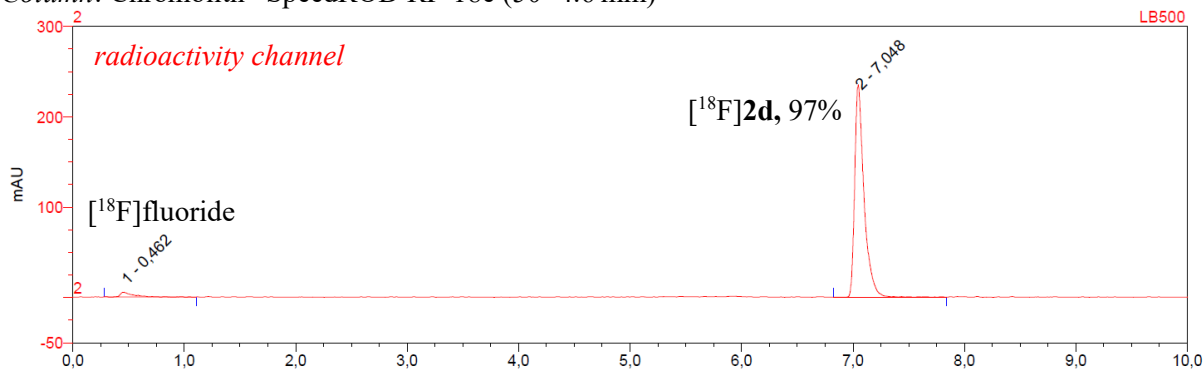
Column: Chromolith[®] SpeedROD RP-18e (50×4.6 mm)*

Gradient: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min.

*Second chromatogram using Chromolith SpeedROD shown to illustrate complete adsorption of $[^{18}\text{F}]\text{fluoride}$ on MultoKrom[®] 100–5 C18 column. In contrast, recovery of $[^{18}\text{F}]\text{fluoride}$ from the Chromolith SpeedROD column under neutral conditions (without addition of TFA) exceeded 98%.

4-Phenylpiperazine-1-sulfonyl [^{18}F]fluoride ($[^{18}\text{F}]\mathbf{2d}$)Column: MultoKrom[®] 100–5 C18 (250×4.6 mm)

Gradient: 0–20 min: 60% MeCN, 20 min–25 min: 60 → 95% MeCN, 25 min–30 min: 95% MeCN, 30 min–35 min: 95 → 60% MeCN, 30 min–35 min: 60% MeCN; flow-rate: 1 mL/ min detection: radioactivity, UV: $\lambda=210$ nm. Abbreviations: p.c.i, post-column injection.

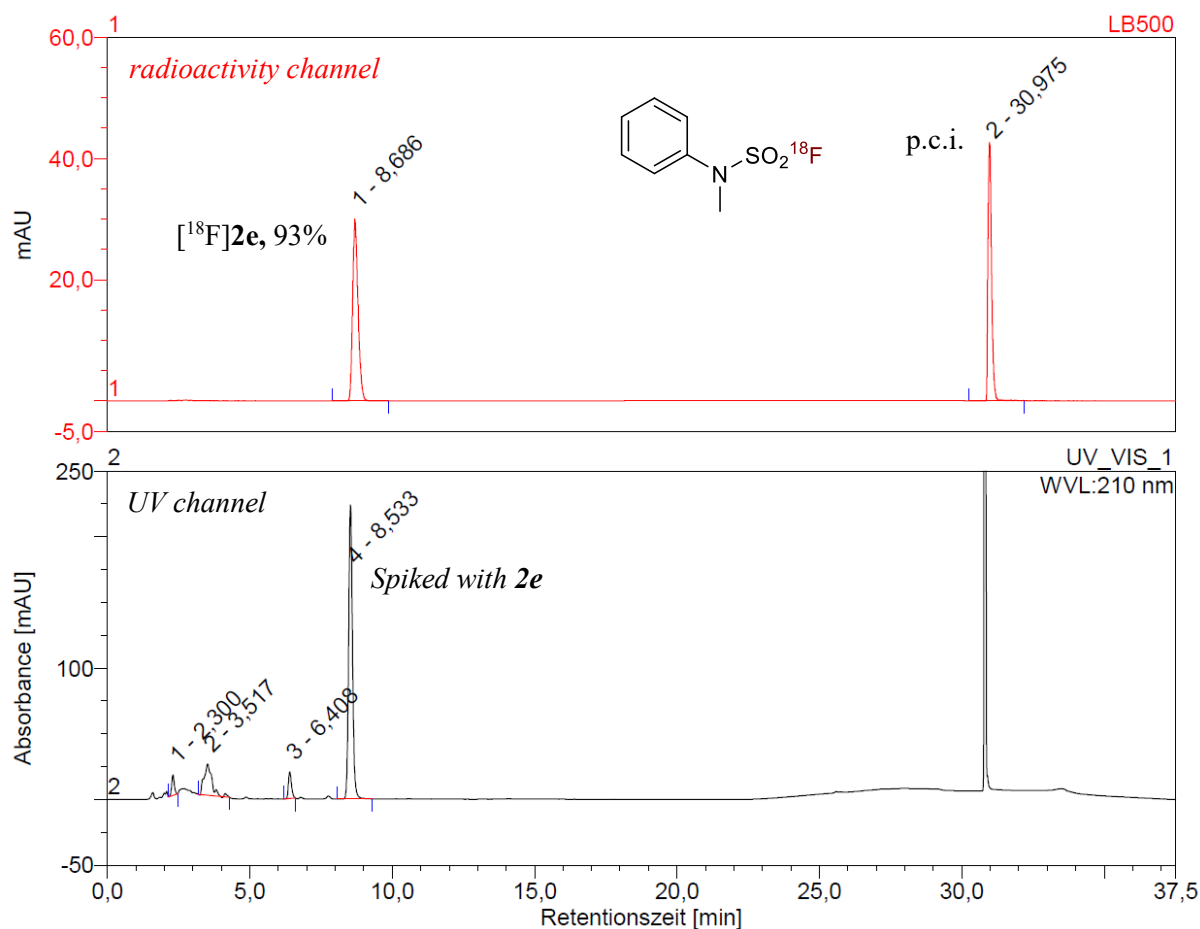
Column: Chromolith[®] SpeedROD RP-18e (50×4.6 mm)*

Gradient: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min.

*Second chromatogram using Chromolith SpeedROD shown to illustrate complete adsorption of $[^{18}\text{F}]\text{fluoride}$ on MultoKrom[®] 100–5 C18 column. In contrast, recovery of $[^{18}\text{F}]\text{fluoride}$ from the Chromolith SpeedROD column under neutral conditions (without addition of TFA) exceeded 98%.

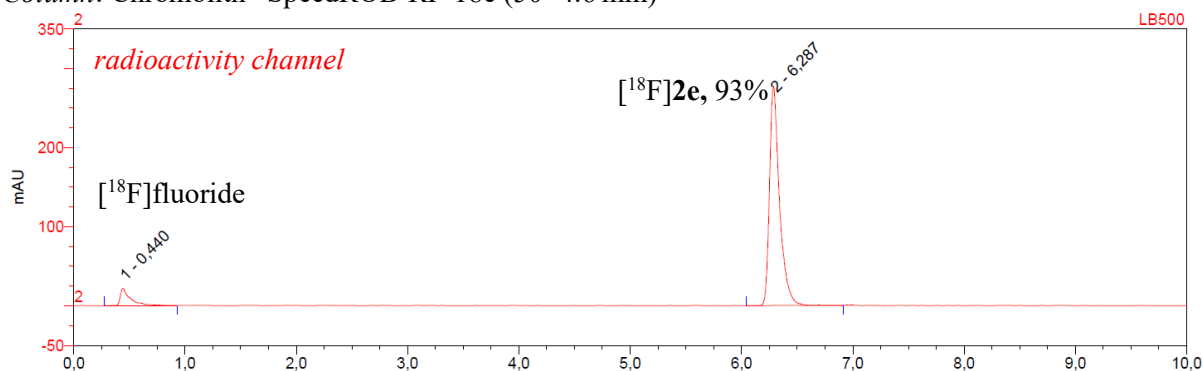
Methyl(phenyl)sulfamoyl [^{18}F]fluoride ($[^{18}\text{F}]\mathbf{2e}$)

Column: MultoKrom® 100–5 C18 (250×4.6 mm)



Gradient: 0–20 min: 60% MeCN, 20 min–25 min: 60 → 95% MeCN, 25 min–30 min: 95% MeCN, 30 min–35 min: 95 → 60% MeCN, 30 min–35 min: 60% MeCN; flow-rate: 1 mL/ min detection: radioactivity, UV: $\lambda=210$ nm. Abbreviations: p.c.i., post-column injection.

Column: Chromolith® SpeedROD RP-18e (50×4.6 mm)*

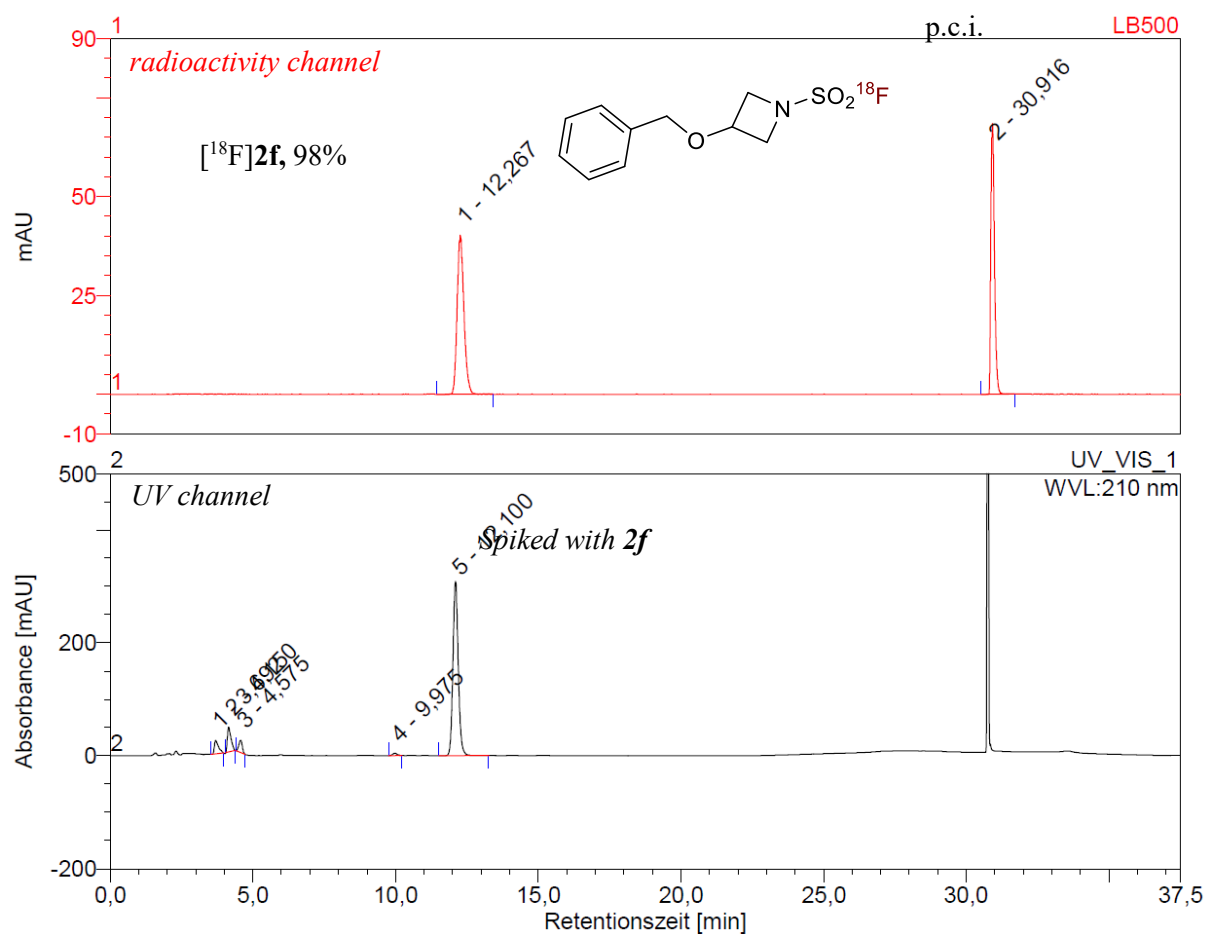


Gradient: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min.

*Second chromatogram using Chromolith SpeedROD shown to illustrate complete adsorption of $[^{18}\text{F}]\text{fluoride}$ on MultoKrom® 100–5 C18 column. In contrast, recovery of $[^{18}\text{F}]\text{fluoride}$ from the Chromolith SpeedROD column under neutral conditions (without addition of TFA) exceeded 98%.

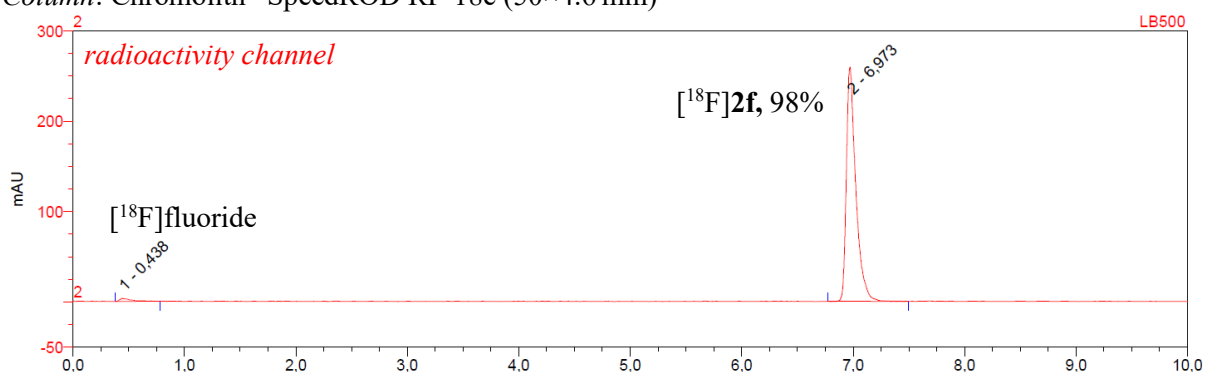
3-(Benzyloxy)azetidine-1-sulfonyl [^{18}F]fluoride ($[^{18}\text{F}]\mathbf{2f}$)

Column: MultoKrom® 100–5 C18 (250×4.6 mm)



Gradient: 0–20 min: 60% MeCN, 20 min–25 min: 60 → 95% MeCN, 25 min–30 min: 95% MeCN, 30 min–35 min: 95 → 60% MeCN, 30 min–35 min: 60% MeCN; flow-rate: 1 mL/ min detection: radioactivity, UV: $\lambda=210$ nm. Abbreviations: p.c.i, post-column injection.

Column: Chromolith® SpeedROD RP-18e (50×4.6 mm)*

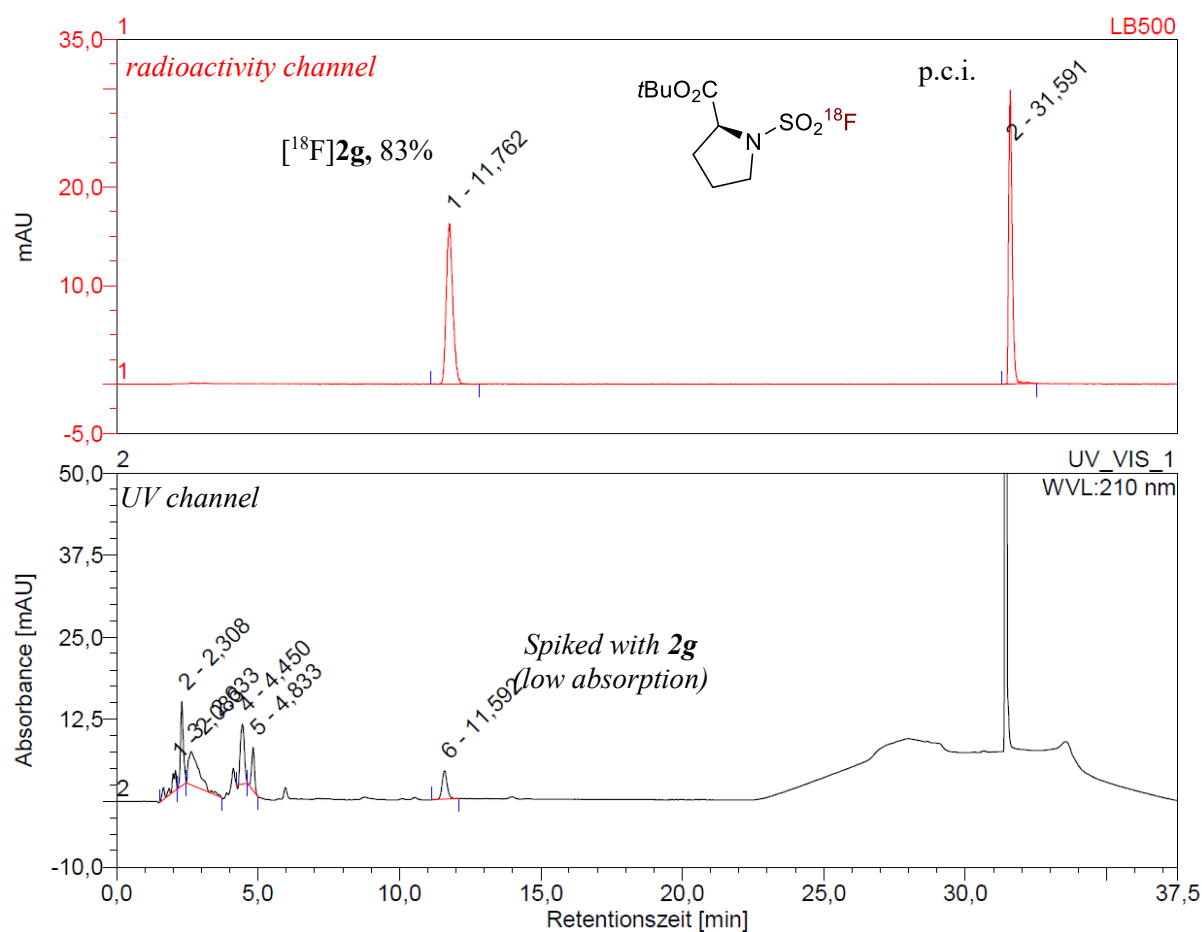


Gradient: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min.

*Second chromatogram using Chromolith SpeedROD shown to illustrate complete adsorption of $[^{18}\text{F}]\text{fluoride}$ on MultoKrom® 100–5 C18 column. In contrast, recovery of $[^{18}\text{F}]\text{fluoride}$ from the Chromolith SpeedROD column under neutral conditions (without addition of TFA) exceeded 98%.

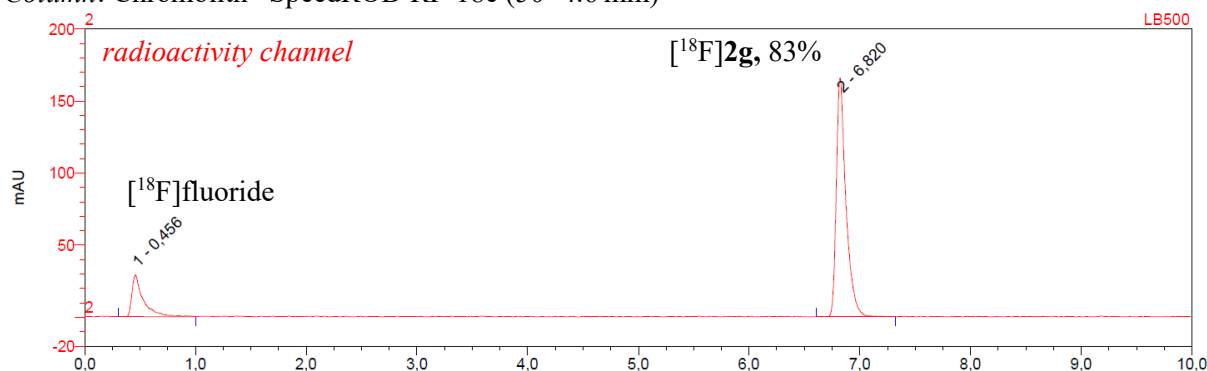
tert-Butyl ([^{18}F]fluorosulfonyl)-L-prolinate ([^{18}F]2g)

Column: MultoKrom® 100–5 C18 (250×4.6 mm)



Gradient: 0–20 min: 60% MeCN, 20 min–25 min: 60 → 95% MeCN, 25 min–30 min: 95% MeCN, 30 min–35 min: 95 → 60% MeCN, 30 min–35 min: 60% MeCN; flow-rate: 1 mL/ min detection: radioactivity, UV: $\lambda=210$ nm. Abbreviations: p.c.i, post-column injection.

Column: Chromolith® SpeedROD RP-18e (50×4.6 mm)*

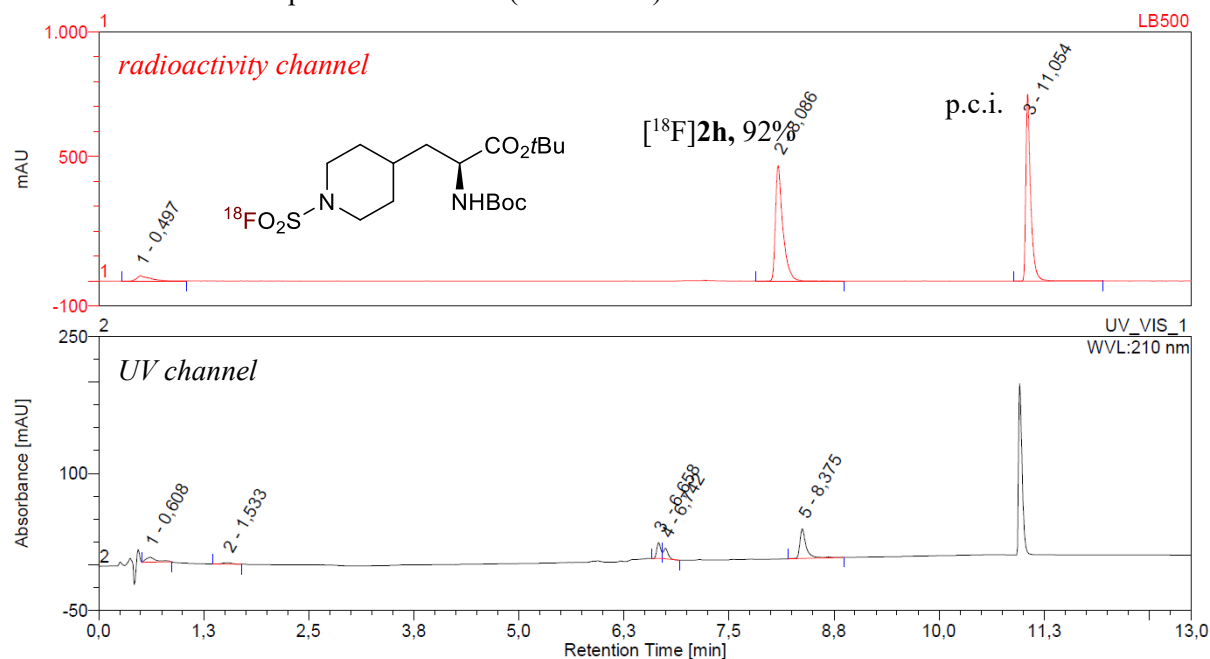


Gradient: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min.

*Second chromatogram using Chromolith SpeedROD shown to illustrate complete adsorption of [^{18}F]fluoride on MultoKrom® 100–5 C18 column. In contrast, recovery of [^{18}F]fluoride from the Chromolith SpeedROD column under neutral conditions (without addition of TFA) exceeded 98%.

tert-Butyl (S)-2-[(*tert*-butoxycarbonyl)amino]-3-[1-([¹⁸F]fluorosulfonyl)piperidin-4-yl]propanoate ([¹⁸F]**2h**)

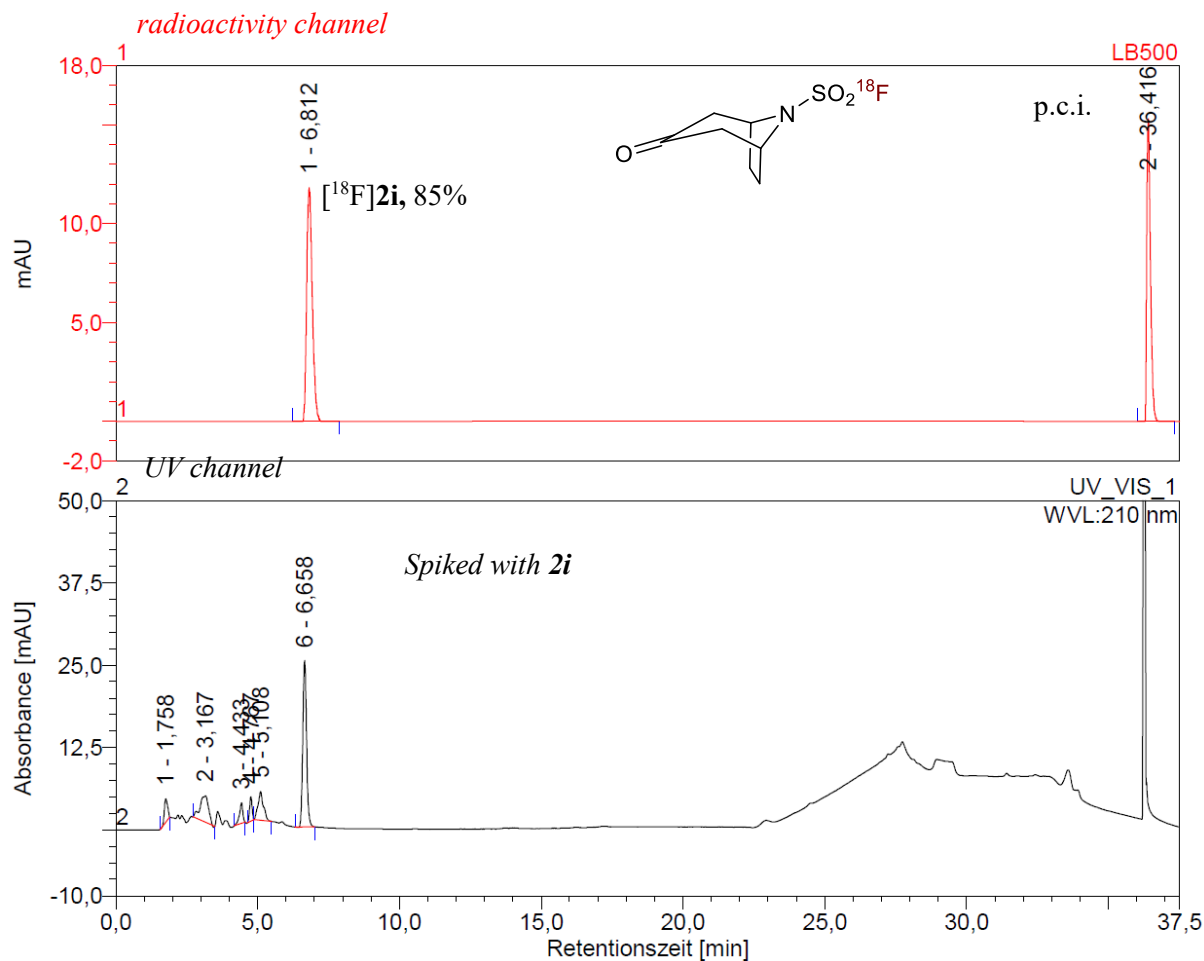
Column: Chromolith® SpeedROD RP-18e (50×4.6 mm)*



Gradient: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN, 10–12.5 min: 90% MeCN, 12.5–13 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min. P.c.i. – post-column injection.

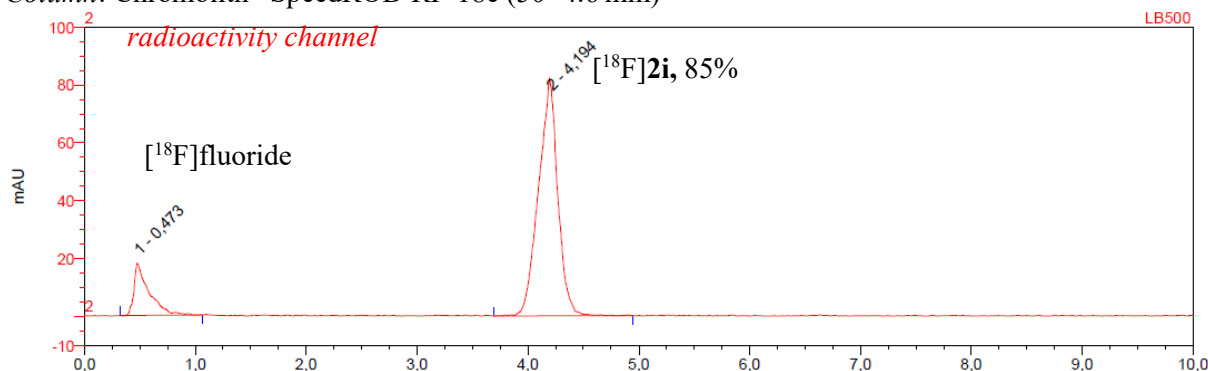
3-Oxo-8-azabicyclo[3.2.1]octane-8-sulfonyl [^{18}F]fluoride ([^{18}F]2i)

Column: MultoKrom® 100–5 C18 (250×4.6 mm)



Gradient: 0–20 min: 50% MeCN, 20 min–25 min: 50 → 95% MeCN, 25 min–30 min: 95% MeCN, 30 min–35 min: 95 → 50% MeCN, 30 min–35 min: 50% MeCN; flow-rate: 1 mL/ min detection: radioactivity, UV: $\lambda=210$ nm. Abbreviations: p.c.i., post-column injection.

Column: Chromolith® SpeedROD RP-18e (50×4.6 mm)*

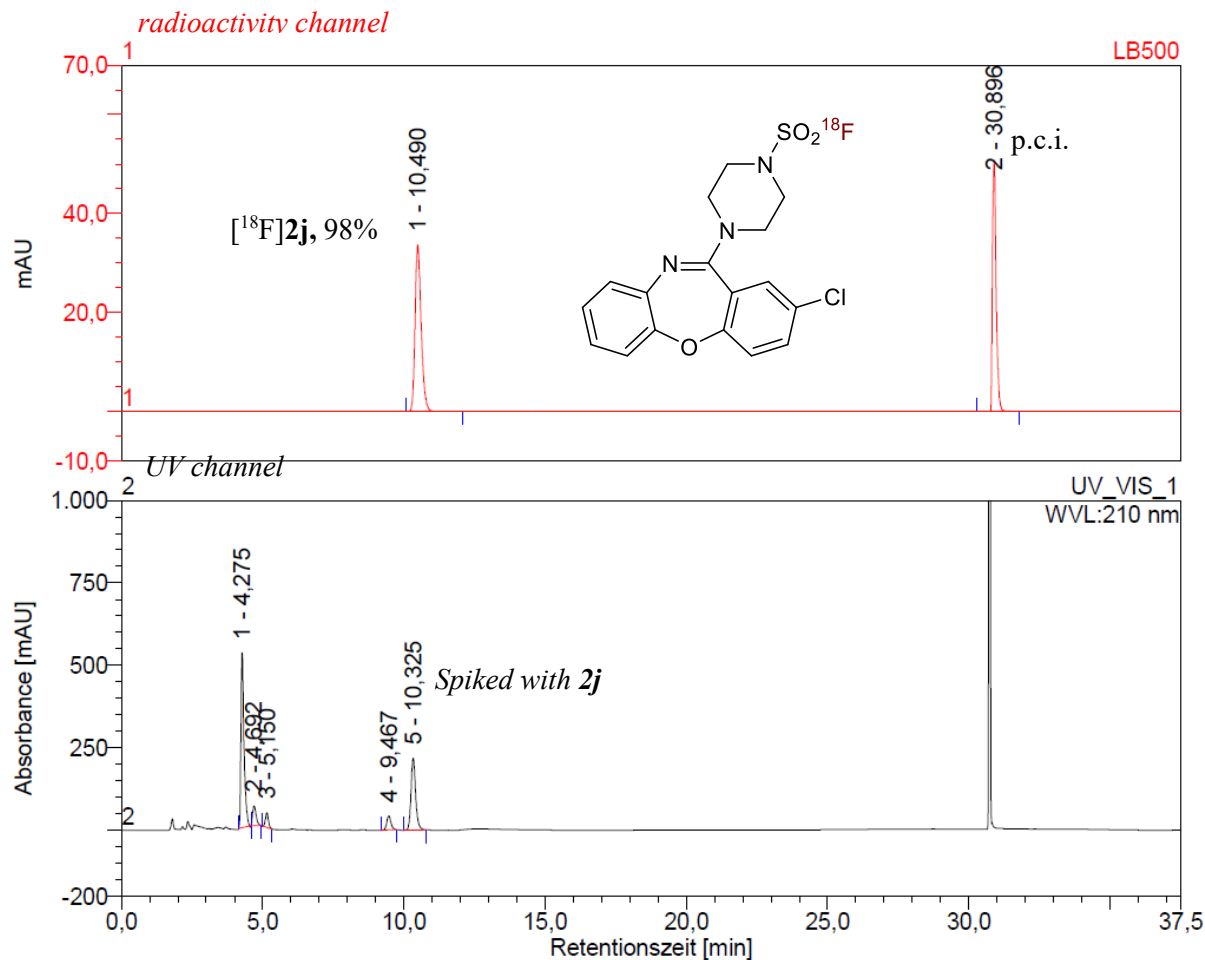


Gradient: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min.

*Second chromatogram using Chromolith SpeedROD shown to illustrate complete adsorption of [^{18}F]fluoride on MultoKrom® 100–5 C18 column. In contrast, recovery of [^{18}F]fluoride from the Chromolith SpeedROD column under neutral conditions (without addition of TFA) exceeded 98%.

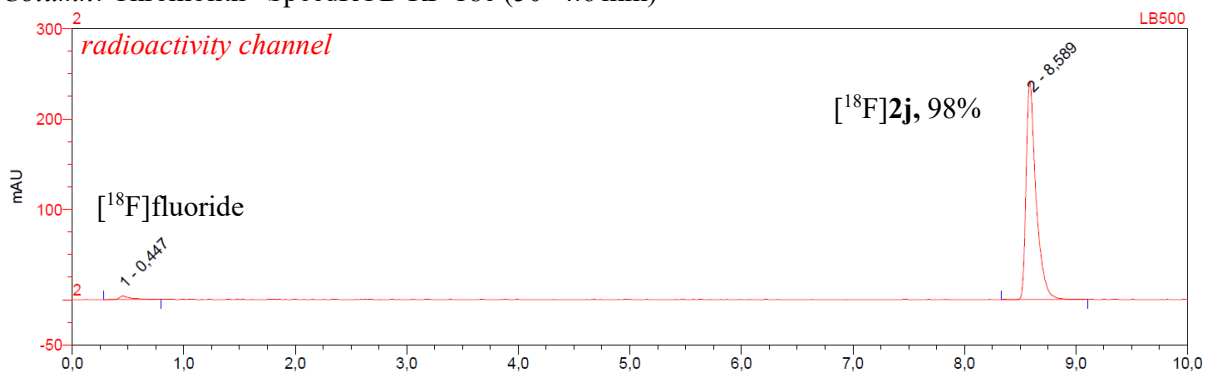
4-(2-Chlorodibenzo[b,f][1,4]oxazepin-11-yl)piperazine-1-sulfonyl [^{18}F]fluoride ([^{18}F]2j)

Column: MultoKrom® 100–5 C18 (250×4.6 mm)



Gradient: 0–20 min: 80% MeCN, 20 min–25 min: 80 → 95% MeCN, 25 min–30 min: 95% MeCN, 30 min–35 min: 95 → 80% MeCN, 30 min–35 min: 80% MeCN; flow-rate: 1 mL/ min detection: radioactivity, UV: λ=210 nm. Abbreviations: p.c.i, post-column injection.

Column: Chromolith® SpeedROD RP-18e (50×4.6 mm)*



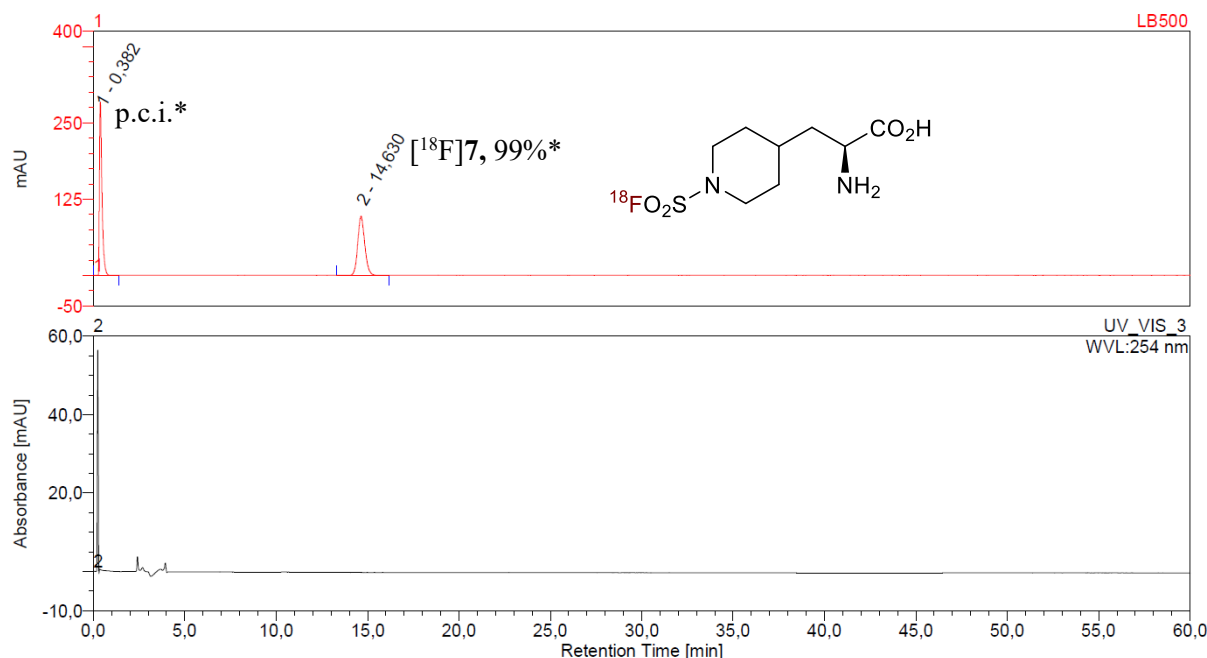
Gradient: 0–2 min: 10% MeCN, 2–10 min: 10% MeCN → 90% MeCN; flow-rate: 2 mL/ min.

*Second chromatogram using Chromolith SpeedROD shown to illustrate complete adsorption of [¹⁸F]fluoride on MultoKrom® 100–5 C18 column. In contrast, recovery of [¹⁸F]fluoride from the Chromolith SpeedROD column under neutral conditions (without addition of TFA) exceeded 98%.

Chromatogram of isolated [^{18}F]7

HPLC

Column: MultoKrom® 100 – 5 C18 AQ (250 x 4.6 mm)

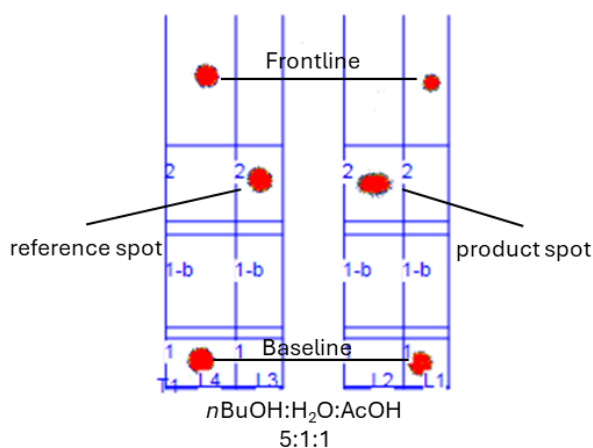


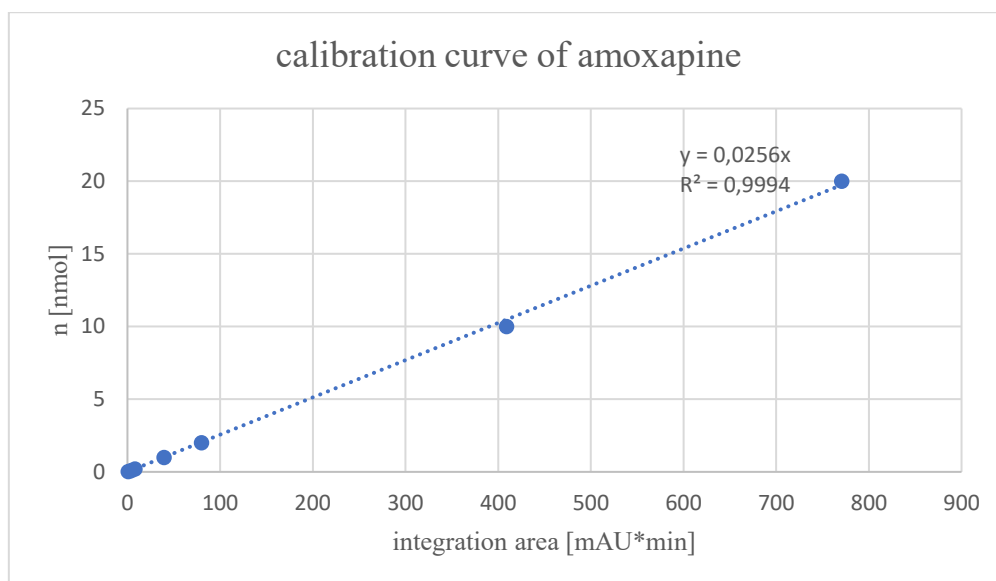
Eluent: **A** H₂O (0.1 v% TFA): **B** MeCN (**B** 20%, 0 – 60 min), flow-rate: 1 mL/ min. Abbreviations: p.c.i., post-column injection.

*p.c.i. was conducted in dead time between point of injection and injection peak in UV-channel.

TLC

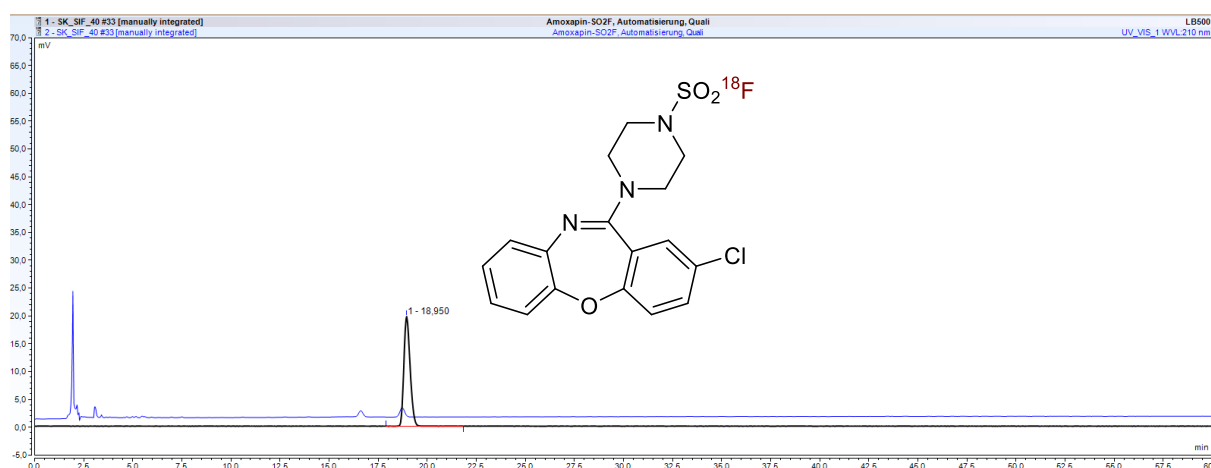
The reference compound **7** showed no detectable UV-absorption. Therefore, identity of the product [^{18}F]7 was confirmed by radio-TLC. The reference spot was visualized using commercially available ninhydrin solution from VWR. Then aliquots of the radioactive product solution were spotted on the TLC plate to mark the frontline, baseline and reference spot.



Determination of molar activity**Fig. S6:** Calibration curve for determination of molar activity of [^{18}F]**2j****Tab. S2:** Data for determination of molar activity of [^{18}F]**2j**

n	Starting activity [GBq]	AY [%]	Injected activity [kBq]	Integral area [mAU*min]	A _m [GBq/μmol]
1	1.45	/*	837	0.5288	61.83
2	2.96	26%	894	0.5058	69.04
3	2.97	29%	496	0.4870	39.78
4	3.98	27%	140	0.0780	69.91

*Not determined because of leakage during synthesis.

Chromatogram of isolated [^{18}F]2j****

References

- [1] F. C. Sousa e Silva, K. Doktor, Q. Michaudel, *Organic Letters* **2021**, 23, 5271-5276.
- [2] S. Humpert, C. Hoffmann, F. Neumaier, B. D. Zlatopolskiy, B. Neumaier, *Journal of Chromatography B* **2023**, 1228, 123847.

Supporting Information of Further Results

Experimental Section

Unless noted otherwise, all chemicals and solvents were purchased from VWR International GmbH (Darmstadt, Germany), Sigma-Aldrich Chemie GmbH (Steinheim, Germany), ABCR GmbH (Karlsruhe, Germany), Apollo Scientific Ltd. (Bredbury, United Kingdom), Alfa Aesar GmbH (Karlsruhe, Germany), or BLD Pharmatech GmbH (Kaiserslautern, Germany) and used without further purification.

All reactions were carried out with magnetic stirring (unless noted otherwise) and organic extracts were dried over anhydrous MgSO_4 . Air- or moisture-sensitive reagents were handled under argon (>99.999%, Air Liquide GmbH, Düsseldorf, Germany). Solutions were concentrated under reduced pressure (1–900 mbar) at 40–50 °C using a rotary evaporator (Heidolph GmbH & Co. KG, Schwabach, Germany).

Nuclear magnetic resonance (NMR) spectroscopy

NMR spectra were measured at ambient temperature in deuteriochloroform (CDCl_3) or tetradeuteromethanol (CD_3OD) as indicated, using a Bruker Ascend™ 400 (^1H : 400 MHz; $^{13}\text{C}\{^1\text{H}\}$: 101 MHz; ^{19}F : 376 MHz; Bruker Biospin GmbH, Rheinstetten, Germany). The measured chemical shifts are reported in δ [ppm] relative to residual peaks of non-deuterated solvents. Higher order NMR spectra were approximately interpreted as first-order spectra if possible. The observed signal multiplicities are characterized as follows: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, and td = triplet of doublets. Coupling constants J are reported in hertz (Hz).

Mass spectrometry (MS)

Low resolution electrospray ionization mass spectrometry (LR-ESI-MS) was performed with an MSQ Plus™ mass spectrometer (Thermo Electron Corporation, San Jose, USA). High resolution electrospray ionization mass spectrometry (HR-ESI-MS) was performed with an LTQ XL™ Orbitrap™ (Thermo Fisher Scientific Inc., Bremen, Germany). High resolution electron ionization mass spectrometry (HR-EI-MS) and high resolution positive chemical ionization mass spectrometry (HR-PCI-MS) were performed with an Exactive™ GC Orbitrap™ (Thermo Fisher Scientific Inc., Bremen, Germany).

Column chromatography

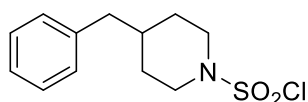
Manual column chromatography was performed with silica gel, 60 Å, 230–400 mesh particle size from VWR International GmbH (Darmstadt, Germany) or silica gel (w/0.1% Ca), 60 Å, 230–400 mesh particle size from Sigma-Aldrich GmbH (Steinheim, Germany). Automated column chromatography was performed on a Büchi Pure C-815 flash system (Büchi Labortechnik GmbH, Essen, Germany) using Reveleris™ C₁₈ reversed phase cartridges (Büchi Labortechnik GmbH, Essen, Germany).

Thin layer chromatography (TLC)

TLC was performed using aluminum sheets coated with silica gel 0.25 mm SIL G/UV 254 (Merck KGaA, Darmstadt, Germany). Chromatograms were inspected under UV light ($\lambda = 254$ nm) and/or stained with phosphomolybdic acid (4% in EtOH), ninhydrin (0.5% in 1-butanol) or potassium permanganate solution (0.75% KMnO₄, 5% K₂CO₃ and 0.07% NaOH in H₂O).

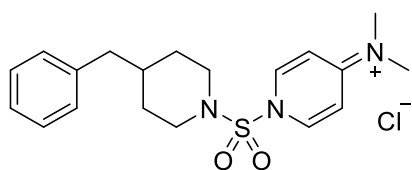
Procedures

4-benzylpiperidine-1-sulfonyl chloride (**FR2**)



Sulfonyl chloride (923 μ L, 1.54 g, 11.42 mmol, 2.0 eq.) in CH₂Cl₂ (15 mL) was added slowly to a cooled solution (–78°C) of 4-benzylpiperidine (1 g, 5.71 mmol, 1.0 eq.) and DIPEA (2.91 mL, 2.21 g, 17.13 mmol) in CH₂Cl₂ (20 mL). The mixture was stirred for 30 min at –78°C and for another 2 h at 23°C. The solution was cooled again to –30°C and another equivalent of sulfonyl chloride (461 μ L, 0.77 g, 5.71 mmol, 1.0 eq.) and DIPEA (971 μ L, 738 mg, 5.71 mmol, 1.0 eq.) was added. The mixture was stirred for 30 min and another 90 min at 23°C. Then 1 M HCl (50 mL) was added and the aqueous phase was extracted with CH₂Cl₂ (2×40 mL). The organic phase was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residual oil was filtered over a silica plug with CH₂Cl₂/*n*-hexane (1:1) and the filtrate was concentrated under reduced pressure. After addition of *n*-hexane the concentrated solution was stored in the fridge for 16 h for crystallization. After filtration the title compound was obtained as colorless needles (1.21 g, 4.40 mmol, 78%). Molecular formula (molecular mass): C₁₂H₁₆ClNO₂S (273.78 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 7.38 – 7.27 (m, 2H), 7.26 – 7.20 (m, 1H), 7.18 – 7.10 (m, 2H), 3.95 – 3.77 (m, 2H), 2.76 (td, *J* = 12.2, 2.6 Hz, 2H), 2.60 (d, *J* = 7.2 Hz, 2H), 1.92 – 1.79 (m, 2H), 1.78 – 1.63 (m, 1H), 1.54 – 1.40 (m, 2H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 139.40, 129.15, 128.53, 126.47, 77.16, 48.41, 42.43, 36.87, 30.52. HR-EI-MS *m/z*: [M]⁺ calcd for C₁₂H₁₆ClNO₂S 273.0585; found, 273.0583.

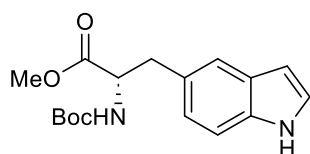
N-{1-[(4-benzylpiperidin-1-yl)sulfonyl]pyridin-4(1*H*)-ylidene}-*N*-methylmethanaminium
(FR3)



4-benzylpiperidine-1-sulfonyl chloride (150 mg, 549 μ mol, 1.2 eq.) was added to a solution of DMAP (56 mg, 457 μ mol, 1.0 eq.) in EtOAc (10 mL). The mixture was stirred for 16 h at room temperature- The precipitate was filtered off and

washed with EtOAc. This step was repeated after concentration of the filtrate to obtain the title compound as a colorless solid (131 mg, 330 μ mol, 60%). $C_{19}H_{26}ClN_3O_2S$ (395.95 g/mol). 1H NMR (400 MHz, CD_3OD): δ 8.60 – 8.39 (m, 2H), 7.25 (t, J = 7.3 Hz, 2H), 7.20 – 7.03 (m, 5H), 4.07 – 3.88 (m, 2H), 3.38 (s, 6H), 2.90 (td, J = 12.5, 2.2 Hz, 2H), 2.56 (d, J = 6.6 Hz, 2H), 1.88 – 1.64 (m, 3H), 1.37 – 1.12 (m, 2H). ^{13}C $\{^1H\}$ NMR (101 MHz, CD_3COD): δ 159.01, 140.65, 138.69, 130.23, 129.30, 127.19, 108.94, 48.68, 43.08, 41.15, 37.63, 31.94. HR-ESI-MS m/z : HR-ESI-MS m/z : $[M]^+$ calcd for $C_{19}H_{26}N_3O_3S$ 360.17402; found, 360.17326.

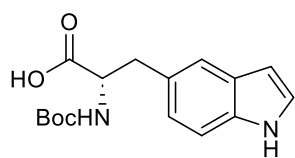
Preparation of methyl (*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-(1*H*-indol-5-yl)propanoate
(FR4)^[120]



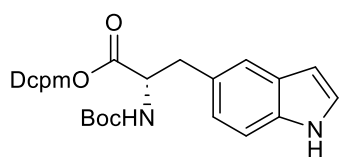
5-Bromoindole (1.63 g, 8.29 mmol, 1.0 eq.), *N*-(*tert*-butoxycarbonyl)-3-iodo-L-alanine methyl ester (3.00 g, 9.11 mmol, 1.1 eq.), $Pd(amphos)_2Cl_2$ (293 mg, 415 μ mol, 0.05 eq.) and zinc

powder (813 mg, 12.43 mmol, 1.5 eq.) were added to a flame-dried flask and suspended in dry DMF (10 mL). The mixture was stirred for 48 h at 23 °C. The mixture was filtered over a plug of silica and the plug was washed with EtOAc. The solvent was removed under reduced pressure. The crude product was first purified by column chromatography (*n*-hexane:EtOAc/3.5:1, TLC: R_f = 0.20) and then recrystallized from Et_2O at $-18^\circ C$ to afford the title compound as a colorless solid (1.19 g, 3.74 mmol, 45%). $C_{17}H_{22}N_2O_4$ (318.37 g/mol). 1H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.41 (s, 1H), 7.33 (d, J = 8.3 Hz, 1H), 7.24 – 7.19 (m, 1H), 6.97 (dd, J = 8.3, 1.6 Hz, 1H), 6.58 – 6.47 (m, 1H), 5.00 (d, J = 7.7 Hz, 1H), 4.62 (q, J = 6.0 Hz, 1H), 3.74 (s, 3H), 3.20 (t, J = 7.7 Hz, 2H), 1.44 (s, 9H).* HR-ESI-MS m/z : $[M+H]^+$ Calcd for $C_{17}H_{22}N_2O_4Na$ 341.14718; Found: 341.14778.

* 1H NMR is in accordance with the literature.^[120]

Preparation of (*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-(1*H*-indol-5-yl)propanoic acid (**FR5**)

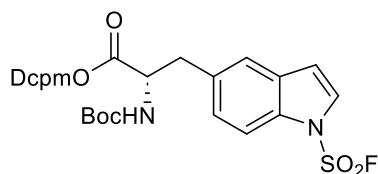
NaOH (139 mg, 3.49 mmol, 1.5 eq.) was added to a solution of **FR4** (740 mg, 2.32 mmol, 1.0 eq.) in MeOH/H₂O (9 mL, 7:1) and the reaction mixture was stirred for 16 h. The solution was concentrated under reduced pressure, acidified to pH 3 with 0.1 M HCl and extracted with EtOAc (6×30 mL). The organic phase was dried and concentrated to afford the title compound as a yellow foam (698 mg, 2.29 mmol, 98%). C₁₆H₂₀N₂O₄S (304.35 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 8.29 (s, 1H), 7.43 (s, 1H), 7.37 – 7.24 (m, 1H), 7.17 (s, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.49 (s, 1H), 5.00 (d, *J* = 6.8 Hz, 1H), 4.74 – 4.26 (m, 1H), 3.47 – 2.78 (m, 2H), 1.41 (s, 9H). ¹³C {¹H} NMR (101 MHz, CDCl₃): δ 176.86, 155.82, 135.20, 128.27, 126.97, 124.79, 123.45, 121.44, 111.45, 102.51, 80.38, 54.97, 37.89, 28.43. HR-ESI-MS *m/z*: [M+Na]⁺ Calcd for C₁₆H₂₀N₂O₄SNa 327.13153; Found: 327.13183.

Preparation of dicyclopropylmethyl (*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-(1*H*-indol-5-yl)propanoate (**FR6**)

Dicyclopropylmethanol (DcpmOH; 174 μL, 1.48 mmol, 1.0 eq.) was added dropwise to a solution of **FR5** (450 mg, 1.48 mmol, 1.0 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC×HCl; 368 mg, 1.92 mmol, 1.3 eq.) and 4-dimethylaminopyridine (DMAP; 36 mg, 296 μmol, 0.2 eq.) in CH₂Cl₂ (5 mL). The reaction mixture was stirred for 16 h at 23 °C and then concentrated under reduced pressure. The concentrated solution was filtered over a plug of deactivated silica* that was washed with *n*-hexane/EtOAc (1:1) thereafter. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography with deactivated silica* (*n*-hexane:EtOAc/3:1, TLC: *R_f* = 0.28) to afford the title compound as a colorless foam (397 mg, 995 μmol, 67 %). C₂₃H₃₀N₂O₄ (398.50 g/mol). ¹H NMR (400 MHz, CDCl₃): δ 8.21 (s, 1H), 7.45 (s, 1H), 7.29 (d, *J* = 8.3 Hz, 1H), 7.21 – 7.16 (m, 1H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.51 – 6.41 (m, 1H), 4.98 (d, *J* = 8.0 Hz, 1H), 4.60 (q, *J* = 5.6 Hz, 1H), 3.92 (t, *J* = 8.3 Hz, 1H), 3.23 (d, *J* = 5.6 Hz, 2H), 1.42 (s, 9H), 1.13 – 1.02 (m, 2H), 0.60 – 0.29 (m, 9H). ¹³C {¹H} NMR (101 MHz, CDCl₃): δ 172.04, 155.38, 135.13, 128.21, 127.30, 124.60, 123.81, 121.63, 111.12, 102.50, 83.49, 79.72, 55.14, 38.22, 28.47, 14.82, 14.81, 3.27, 3.07, 3.03, 2.81. HR-ESI-MS *m/z*: [M+Na]⁺ Calcd for C₂₃H₃₀N₂O₄Na 421.20977; Found: 421.21005.

*Silica was deactivated by flushing one column volume of the solvent system with additional 5% Et₃N and three column volumes of the solvent system.

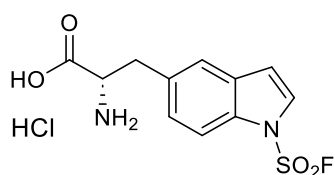
Preparation of dicyclopropylmethyl (*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-[1-(fluorosulfonyl)-1*H*-indol-5-yl]propanoate (**FR7**)



DBU (303 μ L, 2.04 mmol, 2.2 eq.) was added to a solution of **FR6** (367 mg, 921 μ mol, 1.0 eq.) and AISF (347 mg, 1.11 mmol, 1.2 eq.) in CH_2Cl_2 (10 mL) and the mixture was stirred for 30 min at 23 $^\circ\text{C}$. Then AISF was added every 30 min (5 $\times$ 145 mg, 461 μ mol, 0.5 eq.) and another portion of DBU (137 μ L, 921 μ mol, 1.0 eq.) after 90 min until no further conversion was observed via HPLC. The reaction mixture was washed with 0.1 M phosphate buffer (pH 7.6, 5 $\times$ 10 mL), the organic phase was dried and filtered over aluminium oxide 90 active neutral. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography with deactivated silica* (*n*-hexane:EtOAc/5:1, TLC: R_f = 0.31) to afford the title compound as colorless solid (146 mg, 304 μ mol, 33%). $\text{C}_{23}\text{H}_{29}\text{FN}_2\text{O}_6\text{S}$ (480.55 g/mol). ^1H NMR (400 MHz, CDCl_3): δ 7.80 (d, J = 8.5 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.40 (d, J = 3.8 Hz, 1H), 7.28 (dd, J = 8.5, 1.5 Hz, 1H), 6.73 (d, J = 3.8 Hz, 1H), 5.02 (d, J = 7.9 Hz, 1H), 4.62 (q, J = 6.0 Hz, 1H), 3.88 (t, J = 8.5 Hz, 1H), 3.25 (qd, J = 13.8, 5.7 Hz, 2H), 1.42 (s, 9H), 1.15 – 1.02 (m, 2H), 0.64 – 0.52 (m, 2H), 0.52 – 0.40 (m, 2H), 0.39 – 0.26 (m, 4H). ^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 171.52, 155.18, 134.06, 133.21, 130.68, 127.66, 126.51, 122.90, 113.49, 110.99, 84.15, 80.03, 54.85, 38.17, 28.45, 14.83, 14.79, 3.33, 3.15, 3.13, 2.87. ^{19}F NMR (376 MHz, CDCl_3): δ 54.33. HR-ESI-MS m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{23}\text{H}_{29}\text{FN}_2\text{O}_6\text{SNa}$ 503.16226; Found: 503.16235.

[†] (Synthesis described in supporting information)

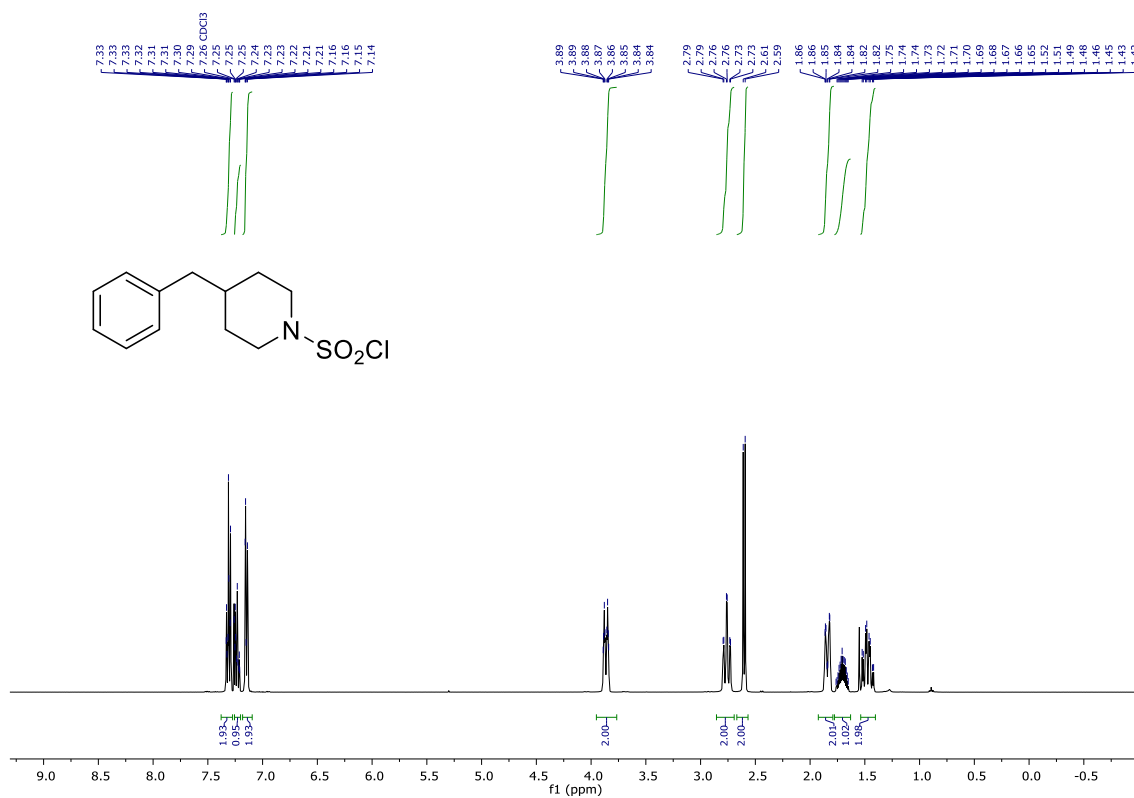
(*S*)-2-amino-3-(1-(fluorosulfonyl)-1*H*-indol-5-yl)propanoic acid hydrochloride (**FR8** $\times$ HCl)



For deprotection of **FR7** a solvent-free method described by Verschueren et al. was used.^[121] To this end NaCl (61 mg, 1.04 mmol, 10.0 eq.) was placed in chamber one of a two-chamber reactor and **22** (50 mg, 104 μ mol, 1.0 eq.) in chamber two. Concentrated H_2SO_4 (0.5 mL) was added to chamber one via a syringe to generate HCl and the setup was left for reaction for 16 h. The title compound was collected from chamber one as a colorless solid (31 mg, 96 μ mol, 92 %). $\text{C}_{11}\text{H}_{12}\text{ClFN}_2\text{O}_4\text{S}$ (322.74 g/mol). ^1H NMR (400 MHz, CD_3OD): δ 7.89 (d, J = 8.6 Hz, 1H), 7.67 (d, J = 1.3 Hz, 1H), 7.64 (d, J = 3.8 Hz, 1H), 7.42 (dd, J = 8.6, 1.7 Hz, 1H), 6.96 (dd, J = 3.8, 0.7 Hz, 1H), 4.33 (dd, J = 7.7, 5.6 Hz, 1H), 3.46 (dd, J = 14.6, 5.6 Hz, 1H), 3.35 – 3.27 (m, 3H). ^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CD_3OD): δ 171.12, 135.76, 132.70, 128.34, 128.24, 124.20, 114.89, 112.42, 55.26, 49.00, 37.10. ^{19}F NMR (376

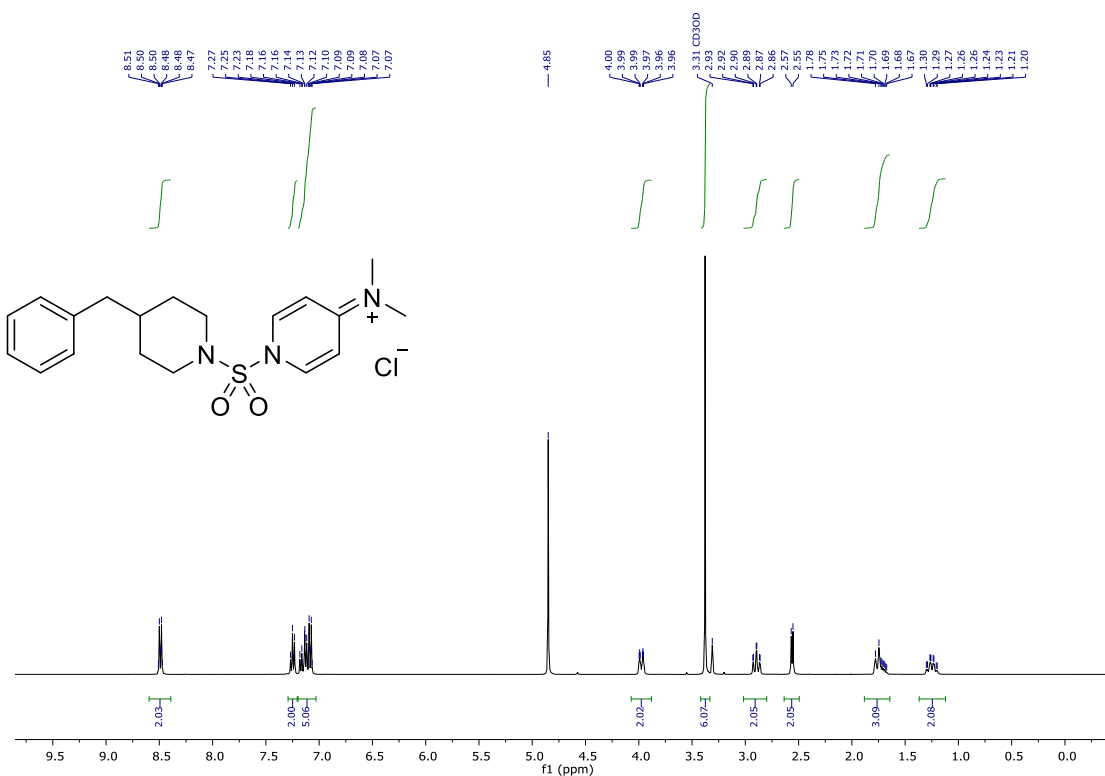
MHz, CD₃OD): δ 51.40. HR-ESI-MS m/z : [M+H]⁺ Calcd for C₁₁H₁₃FN₂O₄S 287.04963; Found: 287.04984.

NMR spectra

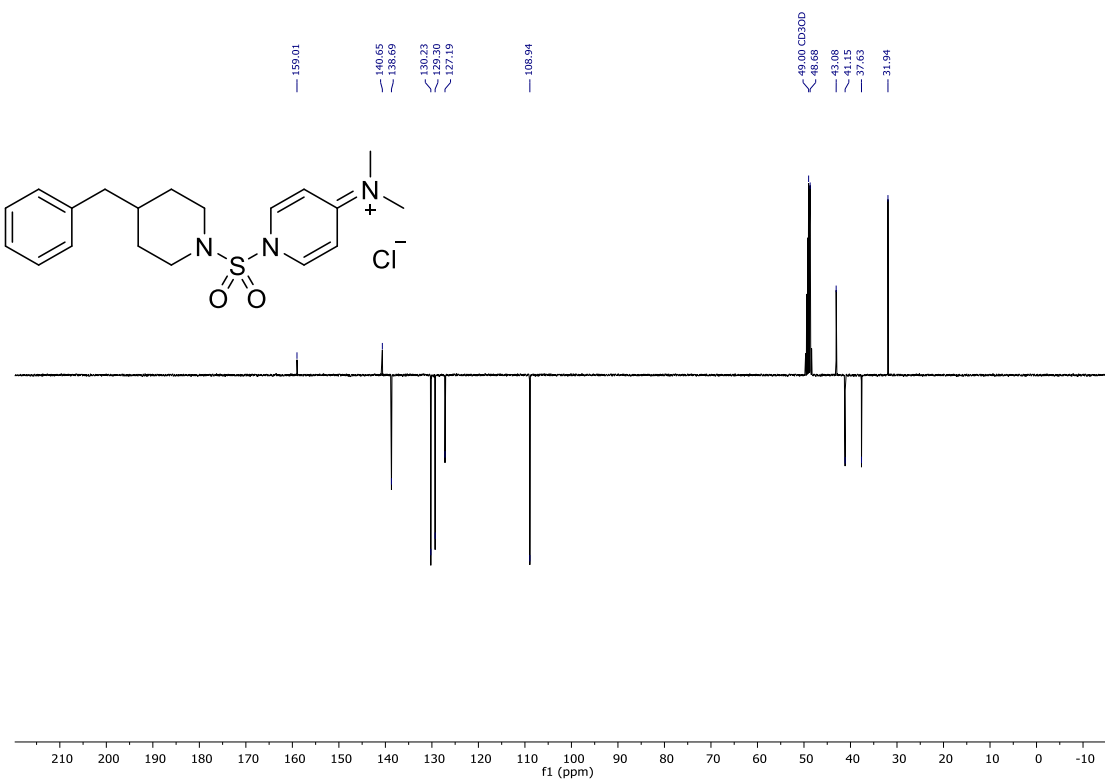
4-benzylpiperidine-1-sulfonyl chloride (**FR2**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

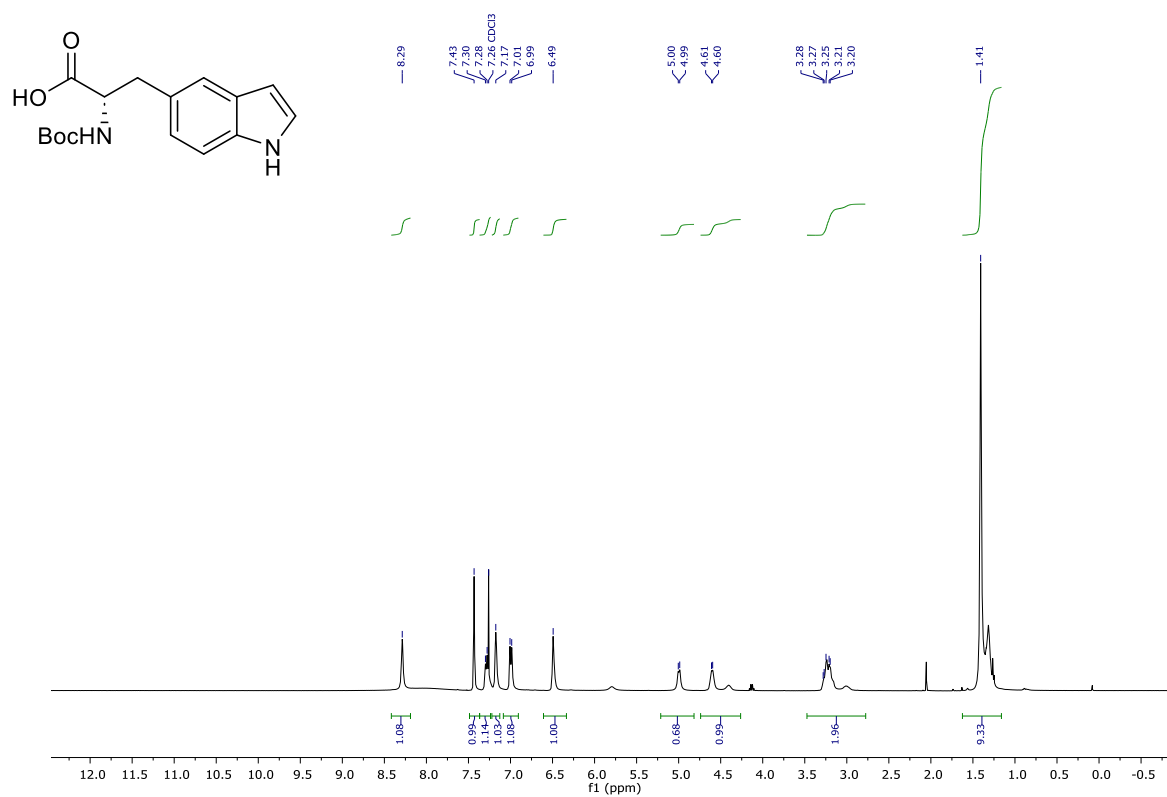
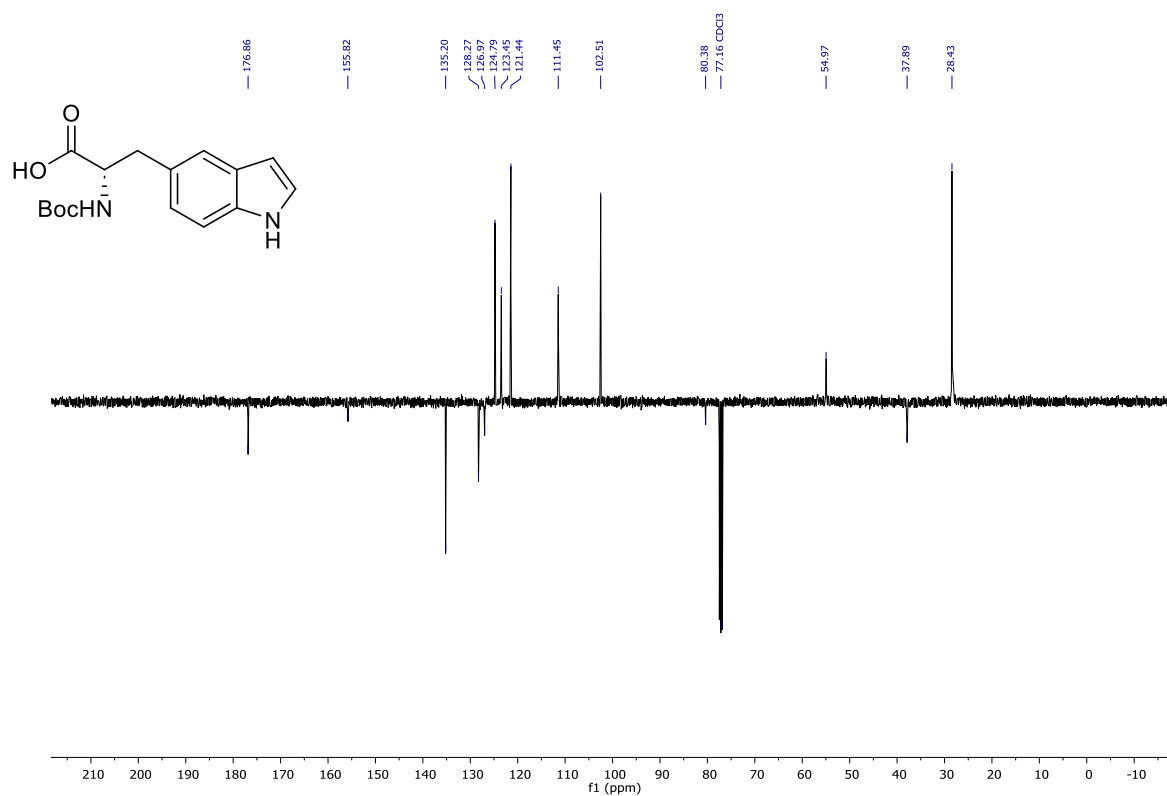
N-{1-[(4-benzylpiperidin-1-yl)sulfonyl]pyridin-4(1*H*)-ylidene}-*N*-methylmethanaminium (FR3)

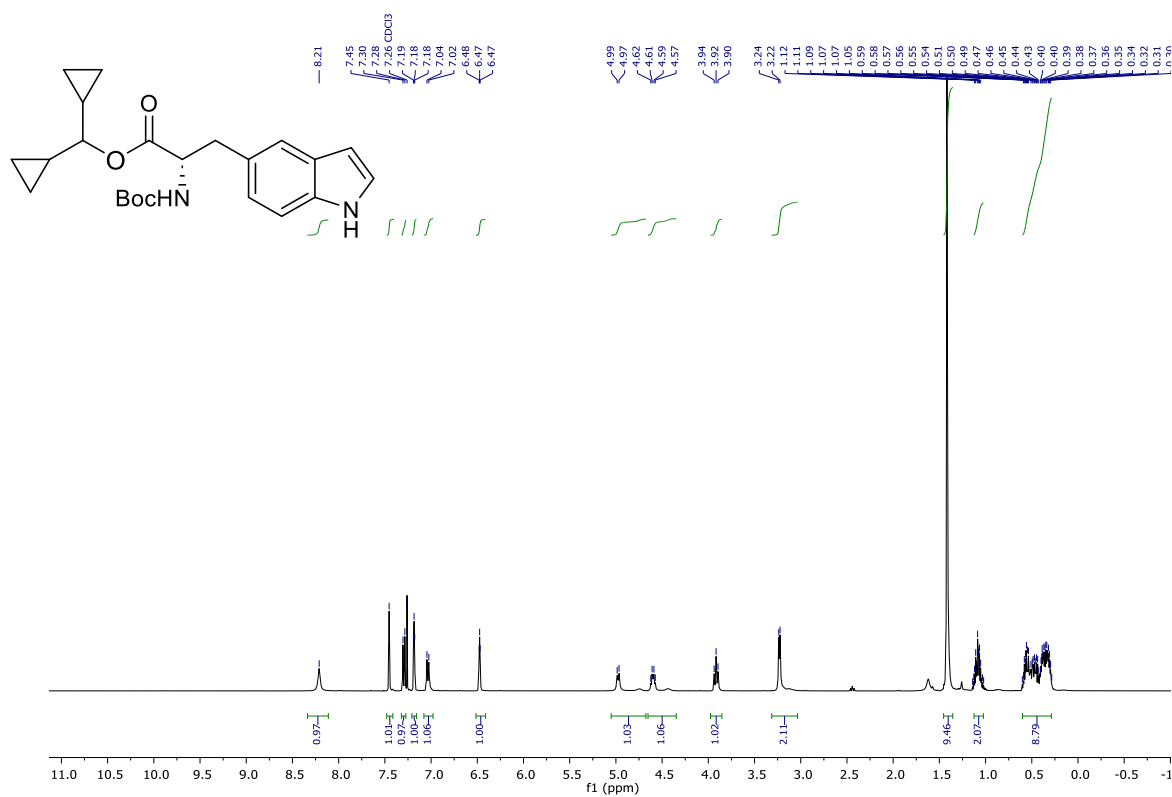
¹H NMR



¹³C{¹H} NMR

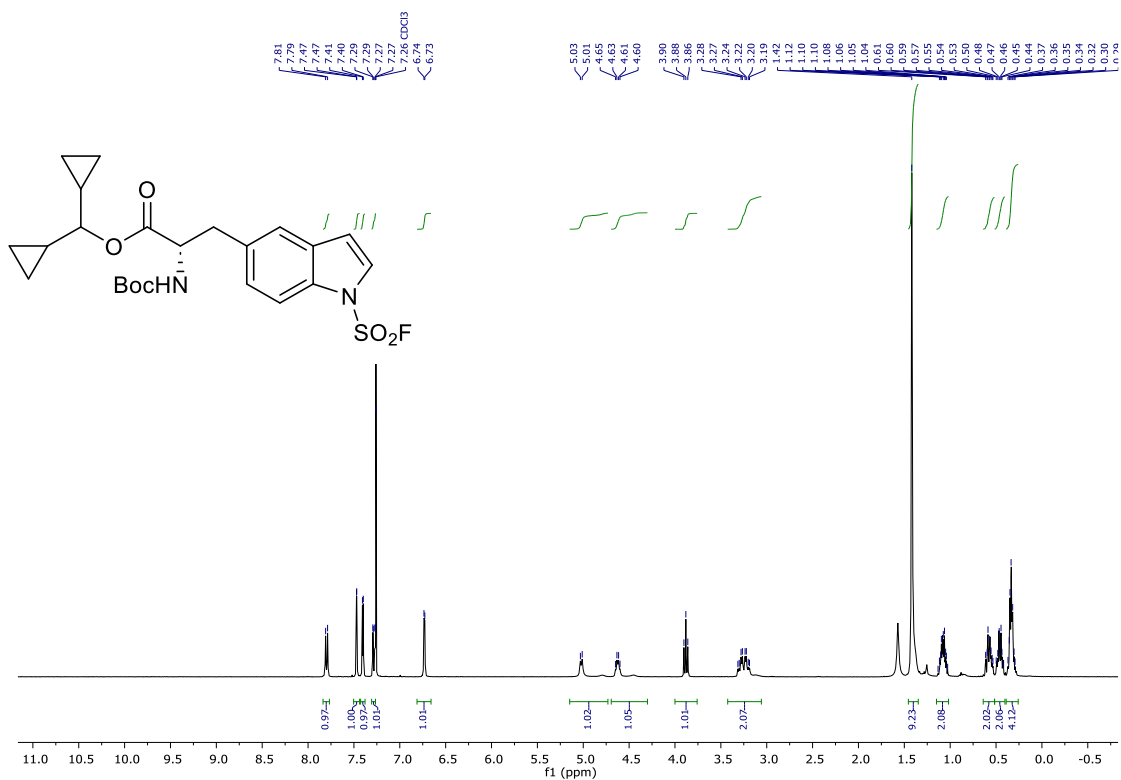


(S)-2-[(*tert*-butoxycarbonyl)amino]-3-(1*H*-indol-5-yl)propanoic acid (FR5)**¹H NMR****¹³C{¹H} NMR**

dicyclopropylmethyl (*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-(1*H*-indol-5-yl)propanoate (**FR6**) ^1H NMR $^{13}\text{C}\{^1\text{H}\}$ NMR

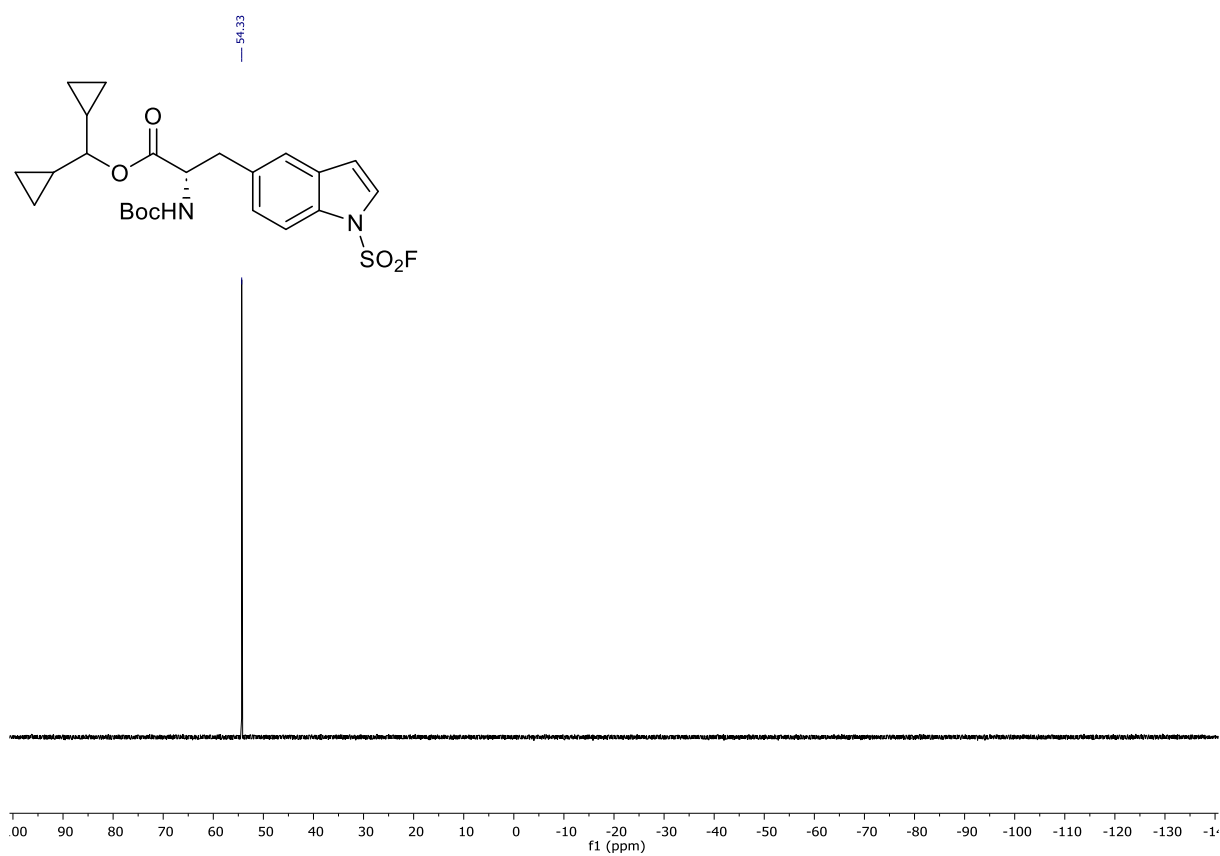
dicyclopropylmethyl (*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-[1-(fluorosulfonyl)-1*H*-indol-5-yl]propanoate (**FR7**)

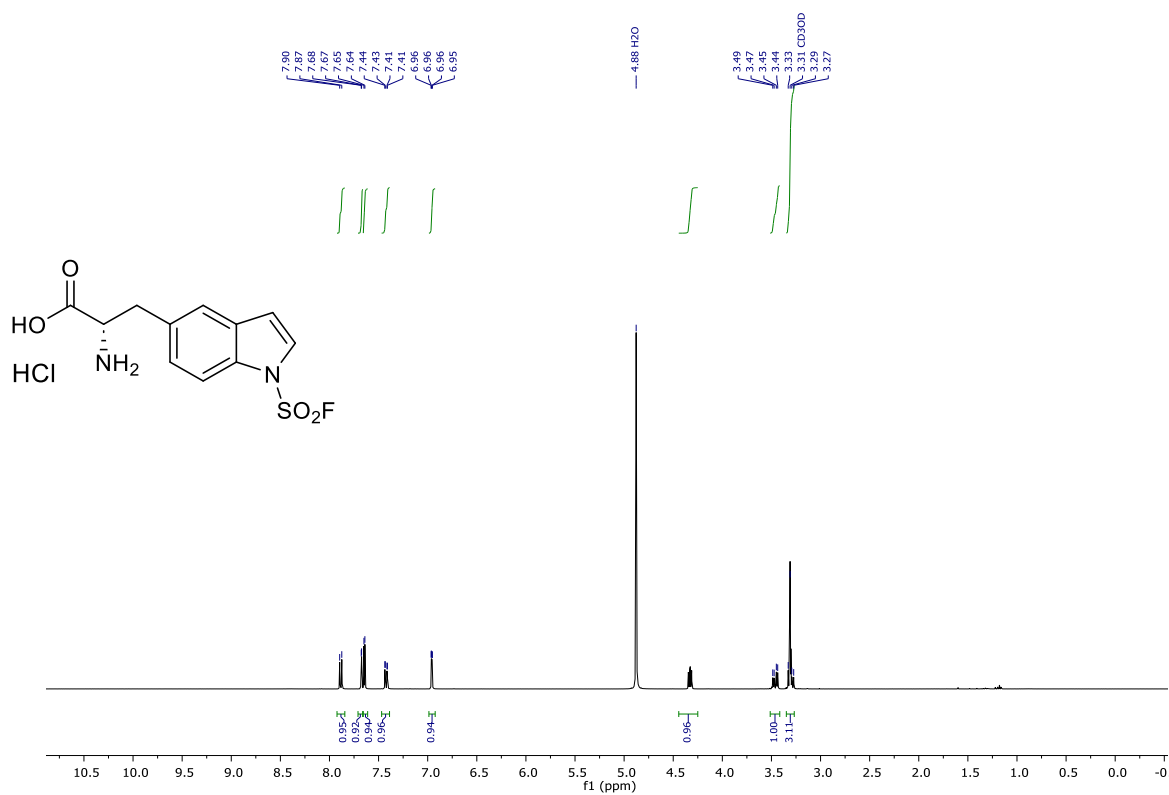
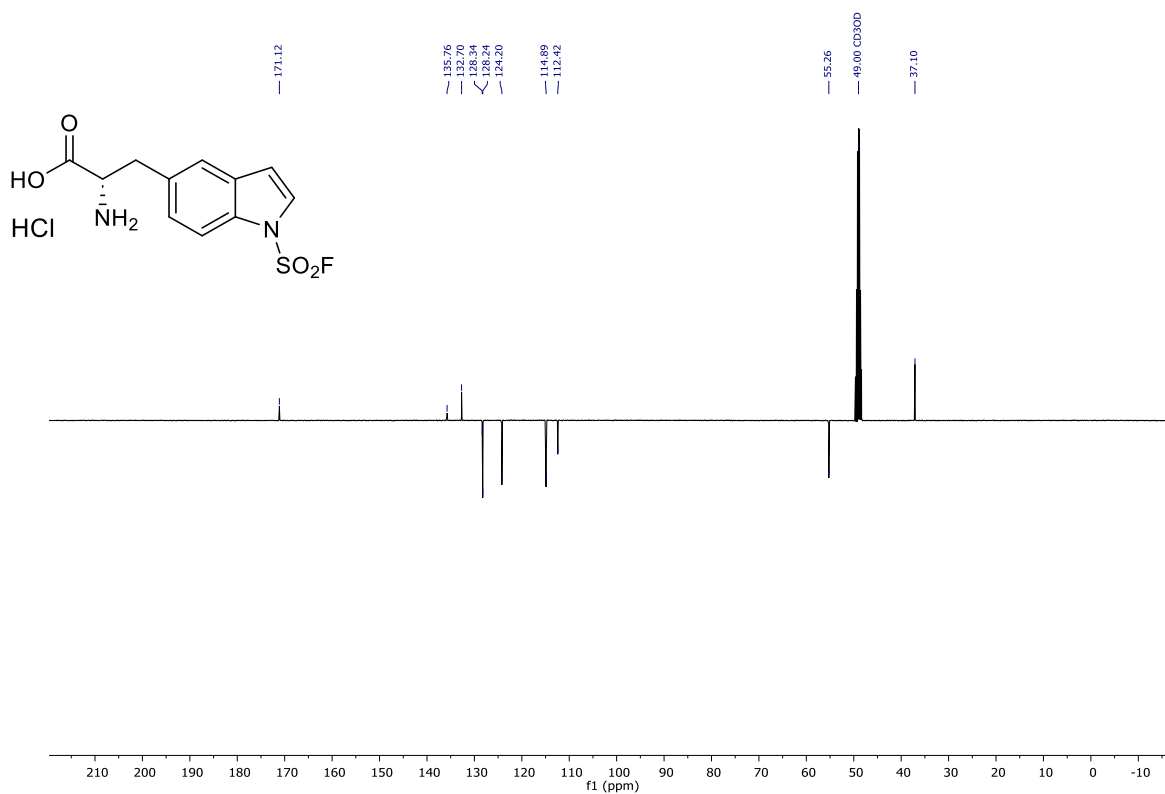
^1H NMR



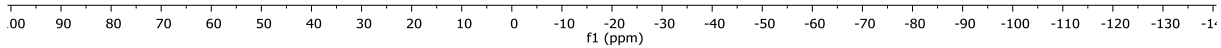
$^{13}\text{C}\{^1\text{H}\}$ NMR



^{19}F NMR

(S)-2-amino-3-(1-(fluorosulfonyl)-1*H*-indol-5-yl)propanoic acid hydrochloride (FR8) **^1H NMR** **$^{13}\text{C}\{^1\text{H}\}$ NMR**

¹⁹F NMR

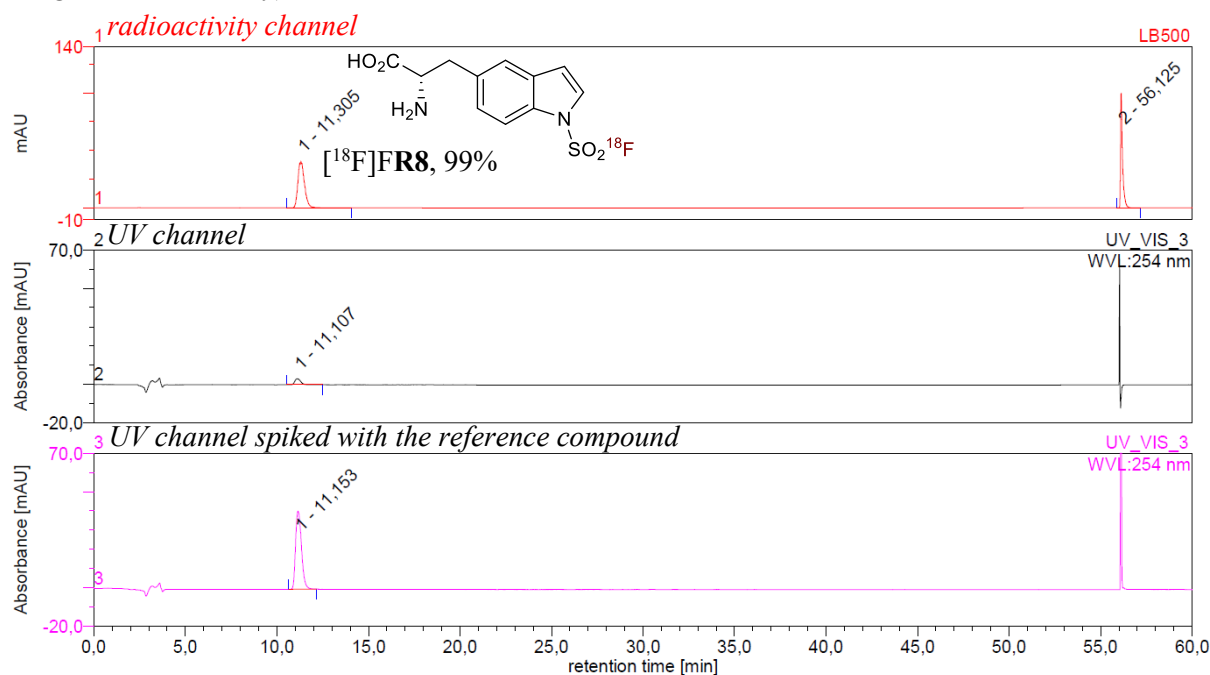


Radiochemistry

General radiochemical specifications are described in the experimental sections of Manuscript 1 and 2. For the preparation of H-5-*iso*-Trp([¹⁸F]SO₂F)-OH, the procedure described in Manuscript 1 for H-Trp([¹⁸F]SO₂F)-OH (*MI* [¹⁸F]**20**) was followed except 70 °C was used during the deprotection step. H-PipAla([¹⁸F]SO₂F)-OH was prepared as described in Manuscript 2.

Chromatogram of isolated H-5-*iso*-Trp([¹⁸F]SO₂F)-OH

Column: MultoKrom® 100–5 C18 AQ (250×2 mm) (CS-Chromatographie Service GmbH, Langerwehe, Germany).



Eluent: 0–60 min: 30% MeCN (0.1% TFA); flow-rate: 1 mL/ min.

Biological Evaluation

Experimental Animals

All animal studies were conducted in accordance with the EU directive 2010/63/EU for animal experiments and the German Animal Welfare Act (TierSchG, 2006) and were approved by the regional authorities (LANUV, NRW; 81-02.04.2023.A034). In total, 3 immunodeficient male Rowett nude rats (CrI:NIH-Foxn1^{rnu}, Charles River) were used for the orthotopic glioblastoma model. Three healthy C57BL/6 mice (1 male, 2 females; Janvier Labs) were used for biodistribution experiments. The animals were housed in groups of up to 5 animals in individually ventilated cages (NexGen Ecoflo; Allentown Inc., Allentown, NJ, USA) under controlled ambient conditions (22 ± 1 °C and $55 \pm 5\%$ relative humidity) and on a 12 h light/dark schedule. Food and water were provided ad libitum. The health status of the animals was monitored daily and showed no changes throughout the experiments.

Orthotopic U87 MG Glioblastoma Xenograft Rat Model

For induction of the orthotopic glioblastoma model, rats were anesthetized with isoflurane (5% for induction and 3–4% for maintenance) in O₂/air (3:7), and 105 U87 MG cells in 3 μ L Matrigel were stereotactically implanted into the brain. To this end, the skin was incised, the periosteum was removed, and a small trepanation (one mm in diameter) was drilled 0.5 mm anterior and 2.5 mm lateral from Bregma. The tumor cells were then injected at a depth of 4.5 mm with a 10 μ L Hamilton syringe equipped with a 28G needle, which was left in situ for at least 10 min before and 10 min after application to prevent the liquid from escaping along the puncture channel. Following slow (1 mm/min) retraction of the syringe, the drill hole was closed with bone wax, the wound was treated with povidone-iodine (Betasisodona), and the skin was closed by sutures. Before wound closure, intraoperative infiltration analgesia was performed by infiltrating the skin and periosteum with a mixture (50:50) of 0.5% lidocaine and 0.25% bupivacaine in isotonic saline. In addition, the rats were given subcutaneous injections of carprofen (5 mg/kg in 0.1 mL/kg isotonic saline) 30 min prior to the start of the implantation (for preemptive analgesia) and on the following 3 days (for postoperative analgesia). To monitor tumor growth and determine the size and exact location of the intracranial tumors, MRI scans were performed 1, 2, and 3 weeks after tumor cell implantation. The measurements were performed under inhalation anesthesia with isoflurane as described above using a 3T Achieva MRI scanner (Philips Healthcare, Best, The Netherlands) in combination with an 8-channel volumetric rat array (Rapid Biomedical GmbH, Rimpf, Germany). Three-dimensional T2-

weighted MR images were acquired using a turbo-spin echo sequence with repetition time = 14 s, echo time = 30 ms, field of view = $60 \times 60 \times 60 \text{ mm}^3$, and voxel size = $0.5 \times 0.5 \times 0.5 \text{ mm}^3$.

PET Measurements

Prior to the PET measurements, rats were anesthetized with isoflurane (5% for induction and 1.5–2.5% for maintenance) in O_2/air (3:7), placed in an animal holder (Minerve, Esternay, France), and fixed with a tooth bar in a respiratory mask. The respiratory rate was monitored with a pressure sensor placed under the animals and maintained at around 40–60 breaths per minute by adjusting the isoflurane concentration. Core body temperature was maintained at about 37°C by warm air flow through the animal bed. Dynamic PET scans in list mode were performed with a Focus 220 micro-PET scanner (CTI-Siemens, Knoxville, TN, USA) with a resolution at the center of the field of view of 1.4 mm. Data acquisition started with tracer injection (49–65 MBq in 0.5 mL i.v.), proceeded for 120 min, and was followed by a 10 min transmission scan with a ^{57}Co point source. After full 3D rebinning, data were reconstructed using an iterative OSEM3D/MAP procedure with attenuation and decay correction in two different ways: (1) 28 frames ($2 \times 1 \text{ min}$, $2 \times 2 \text{ min}$, $6 \times 4 \text{ min}$, $18 \times 5 \text{ min}$) for the compilation of regional time activity curves (TACs), and (2) 4 frames ($4 \times 30 \text{ min}$) for visual display. The resulting voxel sizes were $0.38 \text{ mm} \times 0.38 \text{ mm} \times 0.80 \text{ mm}$. Data analysis was performed using the software VINCI.43 Standardized uptake values normalized by body weight (SUV_{bw}) were determined by dividing each image by the injected dose and multiplying the result by body weight times 100. To obtain TACs, an elliptical volume of interest (VOI) was placed over the tumor, and the mean SUV_{bw} values were extracted from each of the 28 frames and then plotted over time.

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