Accepted Manuscript

Submission Date: 2021-03-28
Accepted Date: 2021-04-30
Publication Date: 2021-04-30

Synlett

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DOI: 10.1055/a-1495-7966

Please cite this article as: Wang L, Chen H, Zhao W et al. Copper-Catalyzed Oxydifluoroalkylation of β,γ-Unsaturated Oximes for the Construction of Isoxazolines with a Difluoroalkyl Sidechain. Synlett 2021. doi: 10.1055/a-1495-7966

Conflict of Interest: The authors declare that they have no conflict of interest.

Abstract:
A copper-catalyzed oxydifluoroalkylation of β,γ-unsaturated oximes has been developed. This reaction proceeded through a cascade of difluoroalkylation of alkene followed by nucleophilic attack of the hydroxyl group of oximes. This protocol features mild reaction conditions, low-cost catalyst, and broad substrate scope, which provides a facile method to synthesize isoxazolines with a fluorinated sidechain.

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Copper-Catalyzed Oxydifluoroalkylation of β,γ-Unsaturated Oximes for the Construction of Isoxazolines with a Difluoroalkyl Sidechain

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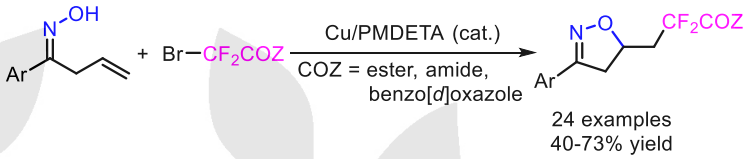


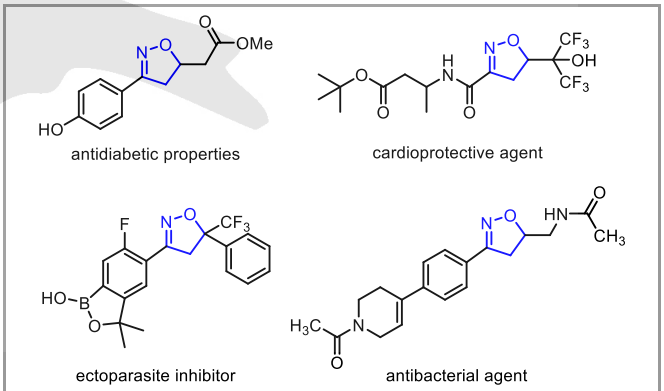
Received:
Accepted:
Published online:
DOI:

Abstract A copper-catalyzed oxydifluoroalkylation of β,γ-unsaturated oximes has been developed. This reaction proceeded through a cascade of difluoroalkylation of alkene followed by nucleophilic attack of the hydroxyl group of oximes. This protocol features mild reaction conditions, low-cost catalyst, and broad substrate scope, which provides a facile method to synthesize isoxazolines with a fluorinated sidechain.

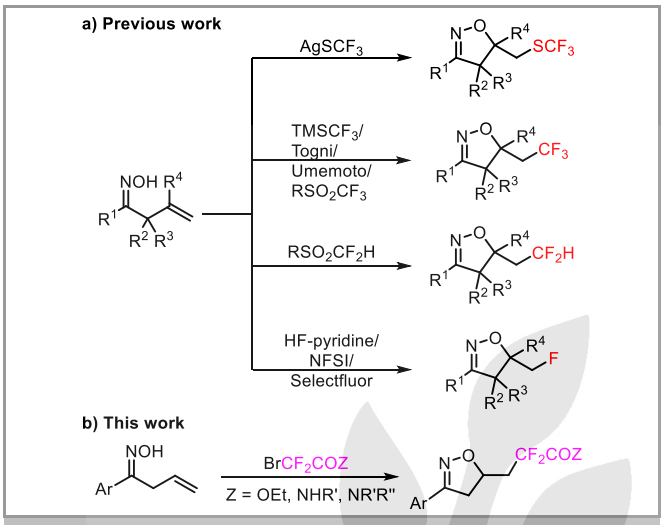
Key words copper-catalyzed, oxydifluoroalkylation, isoxazoline, oximes, radical cyclization

Isoxazoline is an important structural motif, which is widely present in numerous natural products, biologically active molecules (Scheme 1),[1] intermediates in organic synthesis,[2] as well as chiral ligands in asymmetric catalysis.[3] Therefore, the synthesis of isoxazoline has drawn great attention from organic synthetic chemists. In the past years, several strategies have been developed for the synthesis of isoxazolines.[4]

Besides traditional 1,3-dipolar cycloaddition of nitrile oxides with alkenes, transition metal (such as palladium[5], iron[6], copper[7], cobalt,[8] and gold[9]) catalyzed intramolecular radical cyclization of β,γ-unsaturated oximes has been developed recently for the synthesis of isoxazolines. From other perspective, this strategy features difunctionalization of olefins, through which other functional groups could be introduced together with the incorporation of oxygen. Due to the unique bioactivity and biocompatibility of fluorine containing compounds,[10] several strategies have been reported for the synthesis of isoxazolines with fluorine-containing motifs. In 2014, Xu and his co-workers reported a Cu(II) catalyzed intramolecular oxytrifluoro-methylthiolation of unactivated olefins using $AgSCF_3$ to obtain isoxazoline containing SCF_3.[11] Then, Hu's, Liang's, and Chen's groups reported the trifluoromethylation of allylic oximes for the synthesis of trifluoromethylated isoxazolines using $TMSCF_3$, Togni's reagent, or Umemoto's reagent as a trifluoromethylation reagent.[12] In 2019, Fun's group realized a iridium catalysed visible light induced radical di- and trifluoromethylation of β,γ-unsaturated oximes with fluorinated sulfones as difluoromethylation and trifluoromethylation reagents for the synthesis of di- and trifluoromethylated isoxazolines.[13] Oxyfluorination of allyl oximes has also been developed for the synthesis of monofluoromethyl substituted isoxazoline with HF-pyridine, NFSI, or Selectfluor as a source of fluorine (Scheme 2).[14] Despite above progresses, there are still much room for the synthesis of fluorinated isoxazolines through intramolecular radical cyclization of allyl oximes. Ethyl bromodifluoroacetate is a common and low-cost difluoroalkylation reagent which can be derived into diverse difluoromethylene-containing sidechains. So, it is necessary to develop a simple and general intramolecular radical cyclization of allyl oximes with bromodifluoroacetate as the fluorinating reagent and radical initiating reagent.



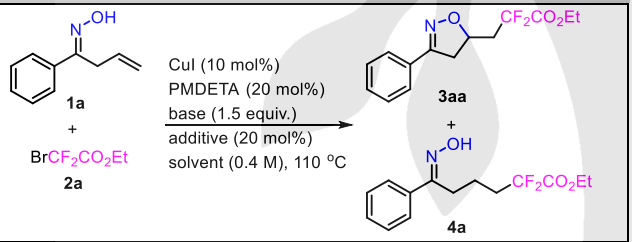
Scheme 1 Biologically Active Molecules with an Isoxazoline Unit



Scheme 2 Synthetic Routes of Fluorine-Containing Isoxazolines

Our group is dedicated to the study of Cu/triamine catalytic system, which has been proved to be useful for difluoroalkylation and perfluoroalkylation reaction of olefins, alkynes, aromatics, heteroaromatics, and enol ether compounds.[15] In addition, similar strategy has been successfully applied to oxydifluoroalkylation of unsaturated carboxylic acids and alcohols, accomplishing effective synthesis of various *γ*-butyrolactone and tetrahydrofuran compounds containing difluoroalkyl sidechains.[16] Based on the above results, we want to exploit the application of Cu/triamine catalytic system into difluoroalkylation of allyl oximes so that a convenient synthesis of difluoroalkylated isoxazolines could be established.

Table 1 Optimization of Reaction Conditions[a]



Entry	Base	Additive	Solvent	Yield (%)[b]	
				3aa	**4aa**
1[c]	PMDETA	—	DMSO	45	30
2[c,d]	PMDETA	—	DMSO	85	14
3[c]	PMDETA	$Na_2S_2O_5$	DMSO	77	17
4[c]	PMDETA	Cu	DMSO	68	24
5[c]	PMDETA	quinol	DMSO	53	41
6	NEt_3	$Na_2S_2O_5$	DMSO	32	24
7	pyridine	$Na_2S_2O_5$	DMSO	48	<1
8	NaOH	$Na_2S_2O_5$	DMSO	33	<1
9	Na_2CO_3	$Na_2S_2O_5$	DMSO	49	34
10	$NaHCO_3$	$Na_2S_2O_5$	DMSO	82(70)	12
11	$NaHCO_3$	$Na_2S_2O_5$	DMF	12	24
12[e]	$NaHCO_3$	$Na_2S_2O_5$	THF	7	41
13[e]	$NaHCO_3$	$Na_2S_2O_5$	CH_3CN	6	14

[a]Reaction conditions: **1a** (1.0 mmol, 1.0 equiv.), **2a** (1.5 mmol, 1.5 equiv.), CuI (0.1 mmol, 10 mol%), PMDETA (0.2 mmol, 20 mol%), base (1.5 mmol, 1.5 equiv.), additive (0.2 mmol, 20 mol%), solvent (0.4 M), Ar, 110 °C, 12 h.
[b]yields determined by GC. The value in parentheses is the isolated yield.
[c]PMDETA (1.5 mmol, 1.5 equiv.).
[d]CuI (1.5 mmol, 1.5 equiv.)
[e]The reaction was performed in a seal reaction tube.

Initially, (*E*)-1-phenylbut-3-en-1-one oxime (**1a**) was chosen as the model substrate. Substrate **1a** reacted with ethyl bromodifluoroacetate (**2a**) in the presence of CuI (10 mol%) and PMDETA (pentamethyldiethylenetriamine) (1.5 equiv.) in DMSO under an Ar atmosphere at 110 °C. The target product **3aa** was obtained with a yield of 45% (Table 1, entry 1) together with the formation of addition product **4a** in 30% yield. Then, we screened the reaction conditions to increase the yield of the target addition-cyclization product while suppressing the addition products.

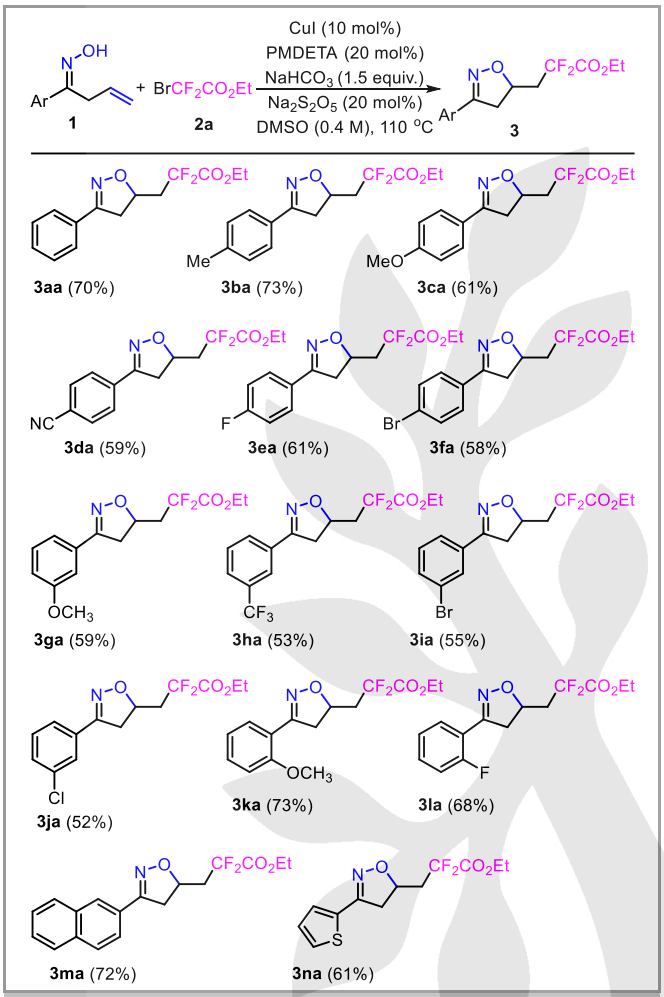
First, when the dose of CuI was increased to 1.5 equivalents, the target product **3aa** (entry 2) can be obtained in 85% yield, and the yield of by-product **4a** was effectively reduced to 14%. The catalytic amount of CuI is not enough to complete the catalytic cycle, which may be due to the relatively slow reduction of Cu(II) to Cu(I) in this reaction system. We suspect that the addition of reducing agent might accelerate the conversion of Cu(II) to Cu(I), thus reducing the amount of copper to catalytic amount. Therefore, we screened several reducing agents, such as $Na_2S_2O_5$, Cu, and hydroquinone, and obtained good yields (entries 3-5), among which $Na_2S_2O_5$ served as the most effective reductant. PMDETA served as both a ligand and a base. Therefore, we try to add organic bases (NEt_3, pyridine (entries 6-7)) or inorganic bases (NaOH, Na_2CO_3, $NaHCO_3$ (entries 8-10)) in order to reduce the amount of PMDETA to a catalytic amount. To our delight, the yield of the target product **3aa** was significantly increased to 82%, when $NaHCO_3$ was used as an additional base (entry 10). Finally, various solvents were examined such as DMF, THF, CH_3CN, but no better yield was obtained. Based on the above various screening results, the reaction conditions in entry 10 was chosen as the optimized conditions.

With the optimized conditions in hand, the substrate scope of (*E*)-1-arylbut-3-en-1-one oxime was investigated (Scheme 3). First, various substrates with electron-withdrawing or electron donating groups at the *ortho*-, *meta*- or *para*-position of aromatic ring proceeded smoothly, affording the corresponding products with moderate to good yields (**3ba-3la**). This indicates that the steric and electronic properties of substituents on the aromatic ring have a weak influence on the cyclization reaction. Next, when phenyl group is replaced by naphthalene or thiophene, the corresponding products **3ma** and **3na** can also be obtained with 72% and 61% yields, respectively.

Then the scope of bromodifluoroalkyl compounds was also studied (Scheme 4). Various *N*-substituted bromodifluoroacetamides can participate this process, leading to the corresponding compounds (**3ab-3aj**) with moderate yields (40-62%). The reason for the low yields is due to the formation of the linear by-products. Besides, **3ak** was obtained with 67% yield when 2-(bromodifluoromethyl)benzo[d]oxazole served as the difluoroalkylation reagent.

To probe the reaction mechanism, several control experiments were conducted. When TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, 2.0 equiv.) was added to the reaction mixture under standard reaction conditions (Scheme 5), the reaction was completely inhibited with the formation of TEMPO-trapped 4,5-dihydroisoxazole (**5**) in 85% yield. This result indicated that the cyclization process might be initiated by oxime radicals. Meanwhile, when free radical inhibitor BHT (2,6-di-*tert*-butyl-4-

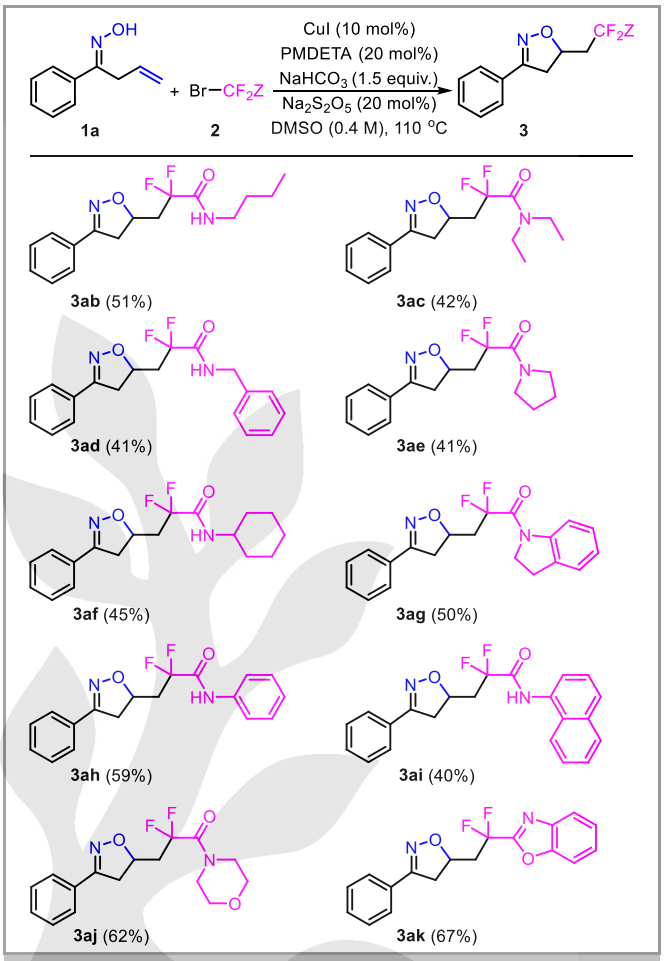
methylphenol) was added to the optimal conditions, GC results showed that the yield of **3aa** is only 13%, which is indicates that the reaction could be inhibited by BHT. Therefore, the reaction involves a radical pathway.



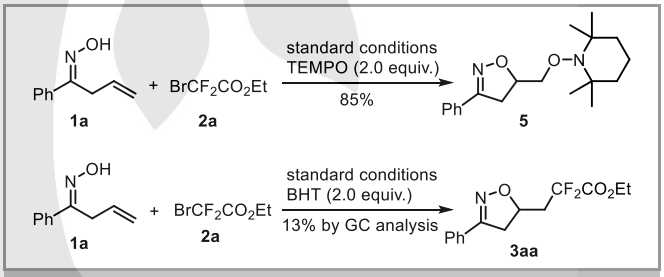
Scheme 3 Scope of Unsaturated Oximes. *Reagents and conditions*: **1** (1.0 mmol, 1.0 equiv.), **2a** (1.5 mmol, 1.5 equiv.), CuI (0.1 mmol, 10 mol%), PMDETA (0.2 mmol, 20 mol%), $NaHCO_3$ (1.5 mmol, 1.5 equiv.), $Na_2S_2O_5$ (0.2 mmol, 20 mol%), DMSO (0.4 M), Ar, 110 °C, 12 h. Isolated yields.

Based on the above experimental results and previous studies,[11,12,17] we proposed a possible radical pathway as shown in Scheme 6. The oxidative addition of Cu(I) and ethyl bromodifluoroacetate (**2a**) gave a Cu(III) intermediate **A**. In the presence of base, **A** reacts with oxime **1a** via a SET pathway affording a Cu(II) intermediate **B** and an oxime radical **C**, which undergoes a further radical cyclization to form a new radical **D**. The reaction between the intermediate **B** and the radical **D** gives a Cu(III) intermediate **E**, which undergoes a further reductive elimination to give the final product **3aa** and regenerate the Cu(I) catalyst.

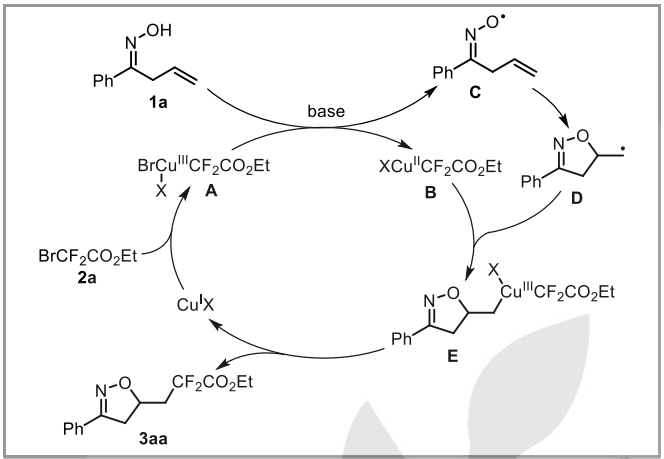
In conclusion, a copper-catalyzed difluoroalkylation of β,γ-unsaturated oximes followed by intramolecular nucleophilic attack of the hydroxyl group of oximes has been realized.[18] Featuring mild reaction conditions, low-cost catalyst, and wide functional group compatibility, this method provides a facile pathway for the construction of diverse difluoroalkylated isoxazolines.



Scheme 4 Scope of Bromodifluoroalkyl Compounds. *Reagents and conditions*: **1a** (1.0 mmol, 1.0 equiv.), **2** (1.5 mmol, 1.5 equiv.), CuI (0.1 mmol, 10 mol%), PMDETA (0.2 mmol, 20 mol%), $NaHCO_3$ (1.5 mmol, 1.5 equiv.), $Na_2S_2O_5$ (0.2 mmol, 20 mol%), DMSO (0.4 M), Ar, 110 °C, 12 h. Isolated yields.



Scheme 5 TEMPO and BHT Trap Experiment



Scheme 6 Proposed Mechanism

Funding Information

The authors are grateful to the financial support of Major National Science and Technology Projects (2017ZX07402003). We also thank the Natural Science Foundation of Tianjin (No. 19JCYBJC20200) and Tianjin University for support of this research.

Acknowledgment

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Supporting Information

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Primary Data

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(18) **Copper-Catalyzed Oxydifluoroalkylation of β,γ-Unsaturated Oximes: Typical Procedure**

To a 25 mL of Schlenk tube was added CuI (19.0 mg, 0.1 mmol), $Na_2S_2O_5$ (38.0 mg, 0.2 mmol), $NaHCO_3$ (126.0 mg, 1.5 mmol), 1-phenylbut-3-en-1-one oxime (161.2 mg, 1.0 mmol) under Ar atmosphere. DMSO (2.0 mL), PMDETA (42 μL, 0.2 mmol), and ethyl bromodifluoroacetate (192 μL, 1.5 mmol) were added subsequently. The reaction mixture was stirred at 110 °C (oil bath) for 12 h. After completion by TLC detection, the reaction mixture was cooled to room temperature and quenched with water and ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified with silica gel chromatography (petroleum ether/ethyl acetate = 10:1) to give **3aa** (198 mg, 70% yield) as a light yellow solid.

Ethyl 2,2-difluoro-3-(3-phenyl-4,5-dihydroisoxazol-5-yl)propanoate (3aa). m.p. 87.4-91.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.62 (m, 2H), 7.43-7.35 (m, 3H), 5.02-4.91(m, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.52 (dd, *J* = 16.7 Hz, 10.3 Hz, 1H), 3.12 (dd, *J* = 16.7 Hz, 7.7 Hz, 1H), 2.46-2.31 (m, 1H), 2.77-2.60 (m, 1H), 1.37 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6 (t, $^2J_{C\text{-}F}$ = 32.0 Hz), 156.7, 130.4, 129.2, 128.9, 126.8, 114.7 (t, $^1J_{C\text{-}F}$ = 252.0.48 Hz), 75.0 (dd, $^3J_{C\text{-}F}$ = 6.2 Hz, 3.2 Hz), 63.3, 40.7, 40.0 (t, $^2J_{C\text{-}F}$ = 22.9 Hz), 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.58 (ddd, *J* = 264.1 Hz, 16.0 Hz, 11.5 Hz, 1F), -106.96 (ddd, *J* = 264.0 Hz, 19.2 Hz, 17.6 Hz, 1F). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{16}NO_3F_2^+$ 284.1093; Found 284.1102.

***N*-butyl-2,2-difluoro-3-(5-phenyl-3,4-dihydro-2*H*-pyrrol-3-yl)propanamide (3ab).** This compound was prepared according to *Typical Procedure* and purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as a light yellow solid (158.3 mg, 51% yield). m.p. 104.7-105.6 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66-7.63 (m, 2H), 7.42-7.38 (m, 3H), 6.50 (s, 1H), 5.01-4.95 (m, 1H), 3.53 (dd, *J* = 16.6 Hz, 10.3 Hz, 1H), 3.34 (q, *J* = 6.9 Hz, 2H), 3.13 (dd, *J* = 16.6 Hz, 8.1 Hz, 1H), 2.69-2.58 (m, 1H), 2.56-2.45 (m, 1H), 1.59-1.53 (m, 2H), 1.41-1.34 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.7 (t, $^2J_{C\text{-}F}$ = 27.9 Hz), 156.8, 130.4, 129.3, 128.9, 126.8, 116.7 (t, $^1J_{C\text{-}F}$ = 253.4 Hz), 75.4 (t, $^3J_{C\text{-}F}$ = 4.0 Hz), 40.9, 39.6, 39.4 (t, $^2J_{C\text{-}F}$ = 22.8 Hz), 31.3, 20.0, 13.8. ^{19}F NMR (565 MHz, $CDCl_3$) δ -103.64 (dt, *J* = 258.8 Hz, 17.3 Hz, 1F), -104.64 (dt, *J* = 258.7 Hz, 16.4 Hz, 1F). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{21}N_2O_2F_2^+$ 311.1566; Found 311.1572.

Supporting Information

Copper-Catalyzed Oxydifluoroalkylation of β,γ-Unsaturated Oximes for the Construction of Isoxazolines with a Difluoroalkyl Sidechain

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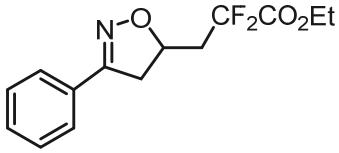
Table of Contents

1. General Information

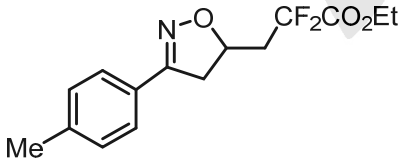
All experiments were conducted under argon atmosphere. CH_3CN, DMF, DMSO, and THF were dried and distilled by the standard methods. Other commercially available reagents were purchased and used without further purification, unless otherwise stated. Flash chromatographic separations were carried out on 200-300 mesh silica gel. Reactions were monitored by TLC and GC analysis of reaction aliquots. GC analysis was performed on an Agilent 7890 Gas Chromatography using a HP-5 capillary column (30 m × 0.32 mm, 0.5 μm film). ^1H, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$ on a Bruker AVANCE III spectrometer. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High resolution mass spectrometry spectra (HRMS) were recorded on a QTOF mass analyzer with electrospray ionization (ESI) through Waters G2-XS QTOF. Melting points were measured in a X-6 micro melting point apparatus purchased from Beijing TECH Instrumental Company.

Ethyl bromodifluoroacetate (**2a**) are commercially available and used without further purification. Compounds **1a-1n** were prepared according to literature.[1] The bromodifluoroamides **2b-2k** were prepared according to literature.[2,3] The polarities of the target products and their **4a**-like by-products are similar, and silica chromatography separations for two times are needed in most cases for obtaining a pure product.

2. Representative procedure and characterization of 3aa-3na, 3ab-3ak, and 5

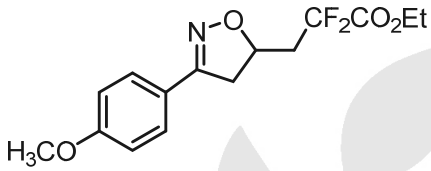


Ethyl 2,2-difluoro-3-(3-phenyl-4,5-dihydroisoxazol-5-yl)propanoate (3aa). *Representative Procedure I.* To a 25 mL of Schlenk tube was added CuI (19.0 mg, 0.1 mmol), $Na_2S_2O_5$ (38 mg, 0.2 mmol), $NaHCO_3$ (126 mg, 1.5 mmol), 1-phenylbut-3-en-1-one oxime (161.2 mg, 1.0 mmol) under Ar atmosphere. DMSO (2.0 mL), PMDETA (42 μL, 0.2 mmol), and ethyl bromodifluoroacetate (192 μL, 1.5 mmol) was added subsequently. The reaction mixture was stirred at 110 °C (oil bath) for 12 h. After completion by TLC detection, the reaction was cooled to room temperature and quenched with water and ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified with silica gel chromatography (petroleum ether/ethyl acetate = 10:1) as light yellow solid (198 mg, 70% yield). m.p. 87.4-91.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.62 (m, 2H), 7.43-7.35 (m, 3H), 5.02-4.91(m, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.52 (dd, *J* = 16.7 Hz, 10.3 Hz, 1H), 3.12 (dd, *J* = 16.7 Hz, 7.7 Hz, 1H), 2.46-2.31 (m, 1H), 2.77-2.60 (m, 1H), 1.37 (t, *J* = 7.2 Hz, 3H).^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.6 (t, $^2J_{C\text{-}F}$ = 32.0 Hz), 156.7, 130.4, 129.2, 128.9, 126.8, 114.7 (t, $^1J_{C\text{-}F}$ = 252.0.48 Hz), 75.0 (dd, $^3J_{C\text{-}F}$ = 6.2 Hz, 3.2 Hz), 63.3, 40.7, 40.0 (t, $^2J_{C\text{-}F}$ = 22.9 Hz), 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.58 (ddd, *J* = 264.1 Hz, 16.0 Hz, 11.5 Hz, 1F), -106.96 (ddd, *J* = 264.0 Hz, 19.2 Hz, 17.6 Hz, 1F). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{16}NO_3F_2^+$ 284.1093; Found 284.1102.

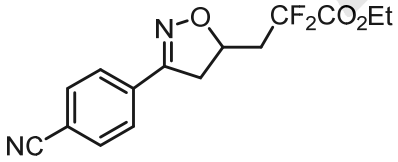


Ethyl 2,2-difluoro-3-(3-(p-tolyl)-4,5-dihydroisoxazol-5-yl)propanoate (3ba). The title compound was prepared according to *Representative Procedure I* and purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as a light yellow solid (217 mg, 73% yield). m.p. 68.7-69.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 4.99-4.89 (m, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.50 (dd, *J* = 16.7, 10.3 Hz, 1H), 3.09 (dd, *J* = 16.7, 7.6 Hz, 1H), 2.76-2.59 (m, 1H), 2.46-2.28 (m, 1H), 2.37 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 163.6 (t, $^2J_{C\text{-}F}$ = 32.0 Hz), 156.7, 140.7, 129. 6, 126.8, 126.4, 114.7 (t, $^1J_{C\text{-}F}$

= 250.66 Hz), 74.8 (dd, $^{3}J_{C\text{-}F}$ = 6.1 Hz, 3.1 Hz), 63.3, 40. 9, 40.0 (t, $^{2}J_{C\text{-}F}$ = 22.8 Hz), 21.5, 14.0. ^{19}F NMR (565 MHz, $CDCl_3$) δ -102.48 (ddd, *J* = 264.0 Hz, 15.4 Hz, 11.5 Hz, 1F), -106.88 (dt, *J* = 263.0 Hz, 17.9 Hz, 1F). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{18}NO_3F_2^+$ 298.1249; Found 298.1256.

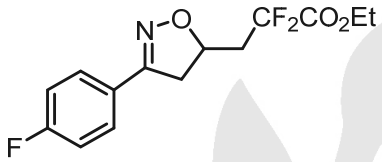


Ethyl 2,2-difluoro-3-(3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl)propanoate (3ca). The title compound was prepared according to *Representative Procedure I* and purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as a light brown oil (191.1 mg, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 5.02-4.84 (m, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 3.49 (dd, *J* = 16.6, 10.2 Hz, 1H), 3.08 (dd, *J* = 16.6, 7.6 Hz, 1H), 2.78-2.56 (m, 1H), 2.46-2.27 (m, 1H), 1.36 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 163.6 (t, $^{2}J_{C\text{-}F}$ = 32.1 Hz), 161.4, 156.3, 128.4, 121.8, 114.8 (t, $^{1}J_{C\text{-}F}$ = 250.66 Hz), 114.3, 74.7 (dd, $^{3}J_{C\text{-}F}$ = 6.0 Hz, 3.0 Hz), 63.4, 55.5, 41.0, 40.0 (t, $^{2}J_{C\text{-}F}$ = 22.8 Hz), 14.0. ^{19}F NMR (565 MHz, $CDCl_3$) δ -102.49 (ddd, *J* = 263.9 Hz, 16.4 Hz, 11.7 Hz, 1F), -106.89 (dt, *J* = 264.3 Hz, 18.2 Hz, 1F). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{18}NO_4F_2^+$ 314.1198; Found 314.1204.

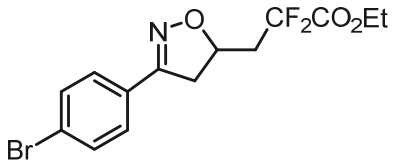


Ethyl 3-(3-(4-cyanophenyl)-4,5-dihydroisoxazol-5-yl)-2,2-difluoropropanoate (3da). The title compound was prepared according to *Representative Procedure I* and purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as a light yellow solid (181.9 mg, 59% yield). m.p. 73.1-74.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 5.07-4.97 (m, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.53 (dd, *J* = 16.8, 10.5 Hz, 1H), 3.12 (dd, *J* = 16.8, 7.9 Hz, 1H), 2.76-2.59 (m, 1H), 2.50-2.30 (m, 1H), 1.34 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz,

$CDCl_3$) δ 163.5 (t, $^2J_{C\text{-}F}$ = 32.0 Hz), 155.6, 133.5, 132.7, 127.9, 118.3, 114.5 (t, $^1J_{C\text{-}F}$ = 250.66 Hz), 113.8, 76.0 (dd, $^3J_{C\text{-}F}$ = 5.1 Hz, 3.1 Hz), 63.5, 40.1, 39.8 (t, $^2J_{C\text{-}F}$ = 23.0 Hz), 14.0. ^{19}F NMR (565 MHz, $CDCl_3$) δ -102.64 (ddd, *J* = 265.0 Hz, 16.8 Hz, 11.2 Hz, 1F), -106.61 (dt, *J* = 265.0 Hz, 17.9 Hz, 1F). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{15}N_2O_3F_2^+$ 309.1045; Found 309.1056.

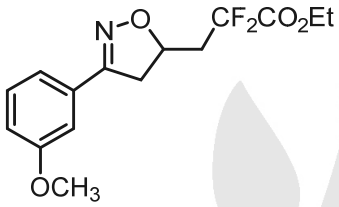


Ethyl 2,2-difluoro-3-(3-(4-fluorophenyl)-4,5-dihydroisoxazol-5-yl)propanoate (3ea). The title compound was prepared according to *Representative Procedure I* and purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as light yellow oil (183.8 mg, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, $^2J_{H\text{-}F}$ = 8.8, 5.3 Hz, 2H), 7.15-7.06 (m, 2H), 5.10-4.87 (m, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.53 (dd, *J* = 16.6, 10.3 Hz, 1H), 3.12 (dd, *J* = 16.6, 7.8 Hz, 1H), 2.81-2.58 (m, 1H), 2.49-2.28 (m, 1H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 164.9, 163.6 (t, $^2J_{C\text{-}F}$ = 32.1 Hz), 155.9, 128.9 (d, $^3J_{C\text{-}F}$ = 8.4 Hz), 116.2, 116.0, 114.7 (t, $^1J_{C\text{-}F}$ = 250.66 Hz), 75.2 (dd, *J* = 5.6 Hz, 3.1 Hz), 63.4, 40.9, 40.0 (t, $^2J_{C\text{-}F}$ = 22.9 Hz), 14.1. ^{19}F NMR (565 MHz, $CDCl_3$) δ -102.56 (ddd, *J* = 264.5, 17.1, 11.0 Hz, 1F), -106.50-107.08 (m, 1F), -109.35 (s, 1F). HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{14}H_{15}NO_3F_3^+$ 302.0999; Found 302.1005.

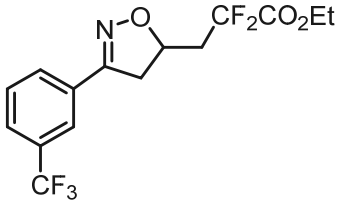


Ethyl 3-(3-(4-bromophenyl)-4,5-dihydroisoxazol-5-yl)-2,2-difluoropropanoate (3fa). The title compound was prepared according to *Representative Procedure I* and purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as light yellow oil (210.1 mg, 58% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H),5.03-4.95 (m, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.50 (dd, *J* = 16.6 Hz, 10.4 Hz, 1H), 3.10 (dd, *J* = 16.7 Hz, 7.8 Hz, 1H), 2.75-2.63 (m, 1H), 2.45-2.34 (m, 1H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} (151 MHz, $CDCl_3$) δ 163.5 (t,

$^{2}J_{C\text{-}F}$ = 31.9 Hz), 156.0, 132.1, 128.3, 128.2, 124.8, 114.6 (t, $^{1}J_{C\text{-}F}$ = 250.66 Hz), 75.4 (dd, $^{3}J_{C\text{-}F}$ = 5.8 Hz, 3.2 Hz), 63.4, 40.6, 39.9 (t, $^{2}J_{C\text{-}F}$ = 22.8 Hz), 14.0. ^{19}F NMR (565 MHz, $CDCl_3$) δ -102.55 (ddd, *J* = 264.4 Hz, 17.1 Hz, 11.0 Hz, 1F), -106.75 (dt, *J* = 264.7 Hz, 18.4 Hz, 1F). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{15}NO_3F_2Br^+$ 362.0198; Found 362.0208.

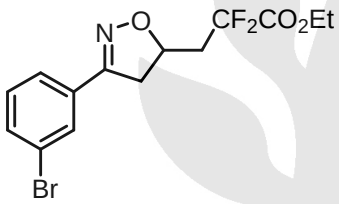


Ethyl 2,2-difluoro-3-(3-(3-methoxyphenyl)-4,5-dihydroisoxazol-5-yl)propanoate (3ga). The title compound was prepared according to *Representative Procedure I* and purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as light brown oil. (187.5 mg, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, *J* = 8.0 Hz, 1H), 7.25-7.22 (m, 1H), 7.18-7.12 (m, 1H), 6.98-6.91 (m, 1H), 5.05-4.89 (m, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 3.51 (dd, *J* = 16.7, 10.3 Hz, 1H), 3.10 (dd, *J* = 16.7, 7.7 Hz, 1H), 2.78-2.59 (m, 1H), 2.47-2.29 (m, 1H), 1.36 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 163.6 (t, $^{2}J_{C\text{-}F}$ = 31.9 Hz), 159.9, 156.8, 130.5, 129.9, 119.5, 116.8, 114.7 (t, $^{1}J_{C\text{-}F}$ = 250.66 Hz), 111.5, 75.1 (dd, $^{3}J_{C\text{-}F}$ = 6.0 Hz, 3.1 Hz), 63.4, 55.5, 40.9, 40.0 (t, $^{2}J_{C\text{-}F}$ = 22.9 Hz), 14.0. ^{19}F NMR (565 MHz, $CDCl_3$) δ -102.51 (ddd, *J* = 264.5 Hz, 16.3 Hz, 11.8 Hz, 1F), -106.83 (dt, *J* = 264.3 Hz, 18.5 Hz, 1F). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{18}NO_4F_2^+$ 314.1198; Found 314.1203.

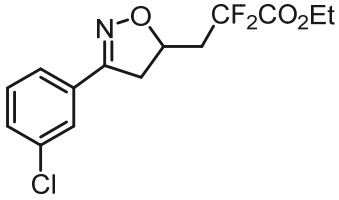


Ethyl 2,2-difluoro-3-(3-(3-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-5-yl) propanoate (3ha). The title compound was prepared according to *Representative Procedure I* and purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as light yellow oil (186.2 mg, 53% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 5.08-5.01 (m, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 3.57 (dd, *J* = 16.7 Hz, 10.4 Hz, 1H),

3.16 (dd, J = 16.7 Hz, 7.9 Hz, 1H), 2.77-2.66 (m, 1H), 2.47-2.37 (m, 1H), 1.38 (t, J = 7.2 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 163.6 (t, $^{2}J_{C\text{-}F}$ = 31.9 Hz), 155.8, 131.5 (q, $^{2}J_{C\text{-}F}$ = 32.8 Hz), 130.2, 129.9, 129.5, 127.0 (q, $^{3}J_{C\text{-}F}$ = 3.4 Hz), 124.7 (q, $^{1}J_{C\text{-}F}$ = 270.7 Hz), 123.6 (q, $^{3}J_{C\text{-}F}$ = 3.6 Hz), 114.6 (t, $^{1}J_{C\text{-}F}$ = 250.66 Hz), 75.6 (dd, $^{3}J_{C\text{-}F}$ = 5.5 Hz, 3.1 Hz), 63.5, 40.5, 40.0 (t, $^{2}J_{C\text{-}F}$ = 22.9 Hz), 14.1. ^{19}F NMR (565 MHz, $CDCl_3$) δ -62.80 (s, 3F), -102.56 (ddd, J = 264.5 Hz, 17.1 Hz, 11.1 Hz, 1F), -106.73 (dt, J = 265.0 Hz, 18.4 Hz, 1F). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{15}NO_3F_5^+$ 352.0967; Found 352.0970.

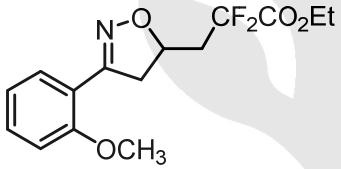


Ethyl 3-(3-(3-bromophenyl)-4,5-dihydroisoxazol-5-yl)-2,2-difluoropropanoate (3ia). The title compound was prepared according to *Representative Procedure I* and purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as light yellow oil (199.2 mg, 55% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ7.78 (s, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H), 5.02-4.96 (m, 1H), 4.36 (q, J = 7.2 Hz, 2H), 3.50 (dd, J = 16.7 Hz, 10.4 Hz, 1H), 3.09 (dd, J = 16.7 Hz, 7.8 Hz, 1H), 2.73-2.63 (m, 1H), 2.43-2.34 (m, 1H), 1.36 (t, J = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 163.5 (t, $^{2}J_{C\text{-}F}$ = 32.0 Hz), 155.7, 133.4, 131.2, 130.4, 129.8, 125.4, 123.0, 114.6 (t, $^{1}J_{C\text{-}F}$ = 250.66 Hz), 75.4 (dd, $^{3}J_{C\text{-}F}$ = 5.5 Hz, 3.0 Hz), 63.4, 40.5, 39.9 (t, $^{2}J_{C\text{-}F}$ = 22.8 Hz), 14.0. ^{19}F NMR (565 MHz, $CDCl_3$) δ -102.53 (ddd, J = 264.7 Hz, 16.3 Hz, 11.4 Hz, 1F), -106.76 (dt, J = 264.7 Hz, 18.2 Hz, 1F). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{15}NO_3F_2Br^+$ 362.0198; Found 362.0204.

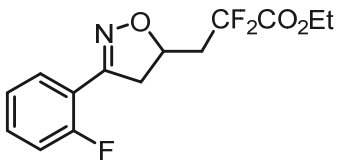


Ethyl 3-(3-(3-chlorophenyl)-4,5-dihydroisoxazol-5-yl)-2,2-difluoropropanoate (3ja). The title compound was prepared according to *Representative Procedure I* and purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as light

brown oil (165.2 mg, 52% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ7.64 (s, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 5.04-4.96 (m, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 3.51 (dd, *J* = 16.7 Hz, 10.4 Hz, 1H), 3.11 (dd, *J* = 16.7 Hz, 7.8 Hz, 1H), 2.76-2.63 (m, 1H), 2.46-2.34 (m, 1H), 1.38 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 163.6 (t, $^{2}J_{C\text{-}F}$ = 32.0 Hz), 155.8, 135.0, 131.0, 130.4, 130.2, 126.9, 124.9, 114.6 (t, $^{1}J_{C\text{-}F}$ = 250.66 Hz), 75.4 (dd, $^{3}J_{C\text{-}F}$ = 5.6 Hz, 2.9 Hz), 63.4, 40.5, 39.9 (t, $^{2}J_{C\text{-}F}$ = 22.9 Hz), 14.0. ^{19}F NMR (565 MHz, $CDCl_3$) δ -102.54 (ddd, *J* = 264.6 Hz, 16.4 Hz, 11.3 Hz, 1F), -106.77 (dt, *J* = 264.6 Hz, 18.2 Hz, 1F). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{15}NO_3F_2Cl^+$ 318.0703; Found 318.0709.

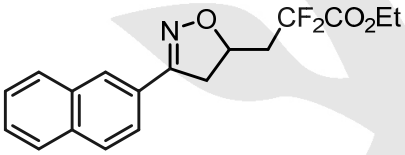


Ethyl 2,2-difluoro-3-(3-(2-methoxyphenyl)-4,5-dihydroisoxazol-5-yl)propanoate (3ka). The title compound was prepared according to *Representative Procedure I* and purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as light yellow oil (228.7 mg, 73% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 3.5 Hz, 1H), 7.38 (d, *J* = 4.8 Hz, 1H), 7.00-6.90 (m, 2H), 4.95-4.86 (m, 1H), 4.42-4.29 (m, 2H), 3.84 (s, 3H), 3.62 (dd, *J* = 16.7 Hz, 10.6 Hz, 1H), 3.24 (dd, *J* = 17.3 Hz, 5.8 Hz, 1H), 2.73-2.60 (m, 1H), 2.40-2.30 (m, 1H), 1.37 (t, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 163.7 (t, $^{2}J_{C\text{-}F}$ = 32.1 Hz), 157.7, 156.5, 131.7, 129.5, 121.0, 118.5, 114.8 (t, $^{1}J_{C\text{-}F}$ = 250.66 Hz), 111.5, 74.9 (dd, $^{3}J_{C\text{-}F}$ = 5.8 Hz, 2.9 Hz), 63.3, 55.6, 43.5, 40.0 (t, $^{2}J_{C\text{-}F}$ = 22.8 Hz), 14.0. ^{19}F NMR (565 MHz, $CDCl_3$) δ -102.42 (ddd, *J* = 263.3 Hz, 19.3 Hz, 7.6 Hz), -107.01 (dt, *J* = 263.3 Hz, 18.4 Hz). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{18}NO_4F_2^+$ 314.1198; Found 314.1202.

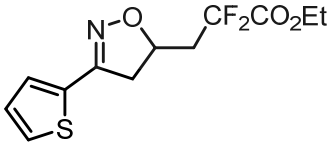


Ethyl 2,2-difluoro-3-(3-(2-fluorophenyl)-4,5-dihydroisoxazol-5-yl)propanoate (3la). The title compound was prepared according to *Representative Procedure I* and

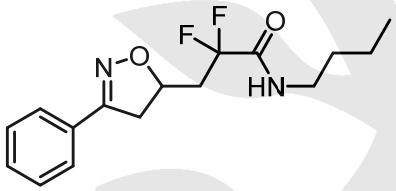
purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as light yellow oil (204.9 mg, 68% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (t, *J* = 7.6 Hz, 1H), 7.43-7.37 (m, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.14-7.09 (m, 1H), 5.02-4.94 (m, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.62 (dd, *J* = 17.3 Hz, 10.3 Hz, 1H), 3.21 (dd, *J* = 17.3 Hz, 7.7 Hz, 1H), 2.75-2.63 (m, 1H), 2.44-2.34 (m, 1H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 163.6 (t, $^{2}J_{C\text{-}F}$ = 31.9 Hz), 160.5 (d, $^{1}J_{C\text{-}F}$ = 252.4 Hz), 153.6 (d, $J_{C\text{-}F}$ = 3.0 Hz), 132.1 (d, $J_{C\text{-}F}$ = 8.6 Hz), 129.1 (d, $J_{C\text{-}F}$ = 3.0 Hz), 124.7 (d, $J_{C\text{-}F}$ = 3.4 Hz), 117.4 (d, $^{2}J_{C\text{-}F}$ = 11.7 Hz), 116.6 (d, $^{2}J_{C\text{-}F}$ = 22.1 Hz), 114.7 (t, $^{1}J_{C\text{-}F}$ = 250.66 Hz), 75.4-75.2 (m), 63.4, 42.6 (d, $J_{C\text{-}F}$ = 7.0 Hz), 40.0 (t, $^{2}J_{C\text{-}F}$ = 22.9 Hz), 14.0. ^{19}F NMR (565 MHz, $CDCl_3$) δ -102.57 (ddd, *J* = 264.4 Hz, 15.6 Hz, 11.8 Hz, 1F), -106.77 (dt, *J* = 264.4 Hz, 18.2 Hz, 1F), -112.51 (s, 1F). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{15}NO_3F_3^+$ 302.0999; Found 302.1005.



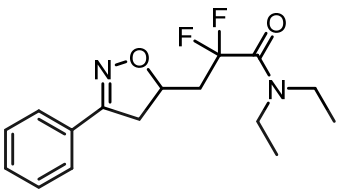
Ethyl 2,2-difluoro-3-(3-(naphthalen-2-yl)-4,5-dihydroisoxazol-5-yl)propanoate (3ma). The title compound was prepared according to *Representative Procedure I* and purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as light yellow solid (96.3 mg, 72% yield). m.p. 49.1-52.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.93 (m, 1H), 7.92-7.88 (m, 1H), 7.88-7.83 (m, 3H), 7.58-7.47 (m, 2H), 5.11-4.97 (m, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.67 (dd, *J* = 16.6, 10.3 Hz, 1H), 3.26 (dd, *J* = 16.6, 7.7 Hz, 1H), 2.85-2.65 (m, 1H), 2.52-2.35 (m, 1H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.66 (t, $^{2}J_{C\text{-}F}$ = 32.3 Hz), 156.9, 134.2, 133.0, 128.8, 128.5, 128.0, 127.4, 127.2, 126.9, 126.8, 123.6, 117.6-111.9 (m), 75.2 (dd, $^{3}J_{C\text{-}F}$ = 6.0, 3.1 Hz), 63.4, 40.8, 40.0 (t, $^{2}J_{C\text{-}F}$ = 22.9 Hz), 14.1. ^{19}F NMR (565 MHz, $CDCl_3$) δ -102.47 (ddd, *J* = 264.3 Hz, 16.4 Hz, 11.1 Hz, 1F), -106.77 (dt, *J* = 264.1 Hz, 18.4 Hz, 1F). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{18}NO_3F_2^+$ 334.1249; Found 334.1252.



Ethyl 2,2-difluoro-3-(3-(thiophen-2-yl)-4,5-dihydroisoxazol-5-yl)propanoate (3na). The title compound was prepared according to *Representative Procedure I* and purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as dark green oil (176.5 mg, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 5.0 Hz, 1H), 7.21 (d, *J* = 3.4 Hz, 1H), 7.12-7.04 (m, 1H), 5.05-4.91 (m, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.55 (dd, *J* = 16.5, 10.2 Hz, 1H), 3.15 (dd, *J* = 16.5, 7.7 Hz, 1H), 2.81-2.60 (m, 1H), 2.48-2.30 (m, 1H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 163.9-163.3 (m), 152.6, 131.7, 128.83, 128.78, 127.5, 114.7 (t, $^{1}J_{C\text{-}F}$ = 250.66 Hz), 75.3 (dd, $^{3}J_{C\text{-}F}$ = 5.4 Hz, 2.7 Hz), 63.4, 41.6, 39.9 (t, $^{2}J_{C\text{-}F}$ = 22.8 Hz), 14.1. ^{19}F NMR (565 MHz, $CDCl_3$) δ -102.50 (dt, *J* = 264.4 Hz, 13.3 Hz, 1F), -106.86 (dt, *J* = 264.1 Hz, 18.3 Hz, 1F). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{12}H_{14}NO_3F_2S^+$ 290.0657; Found 290.0666.

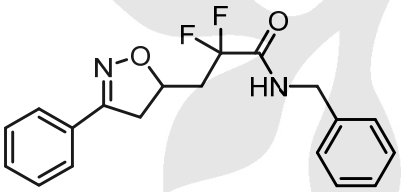


N-butyl-2,2-difluoro-3-(5-phenyl-3,4-dihydro-2H-pyrrol-3-yl)propanamide (3ab). The title compound was prepared according to *Representative Procedure I* and purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as light yellow solid (158.3 mg, 51% yield). m.p. 104.7-105.6 ºC. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66-7.63 (m, 2H), 7.42-7.38 (m, 3H), 6.50 (s, 1H), 5.01-4.95 (m, 1H), 3.53 (dd, *J* = 16.6 Hz, 10.3 Hz, 1H), 3.34 (q, *J* = 6.9 Hz, 2H), 3.13 (dd, *J* = 16.6 Hz, 8.1 Hz, 1H),, 2.69-2.58 (m, 1H), 2.56-2.45 (m, 1H), 1.59-1.53 (m, 2H), 1.41-1.34 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 163.7 (t, $^{2}J_{C\text{-}F}$ = 27.9 Hz), 156.8, 130.4, 129.3, 128.9, 126.8, 116.7 (t, $^{1}J_{C\text{-}F}$ = 253.4 Hz), 75.4 (t, $^{3}J_{C\text{-}F}$ = 4.0 Hz), 40.9, 39.6, 39.4 (t, $^{2}J_{C\text{-}F}$ = 22.8 Hz), 31.3, 20.0, 13.8. ^{19}F NMR (565 MHz, $CDCl_3$) δ -103.64 (dt, *J* = 258.8 Hz, 17.3 Hz, 1F), -104.64 (dt, *J* = 258.7 Hz, 16.4 Hz, 1F). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{21}N_2O_2F_2^+$ 311.1566; Found 311.1572.



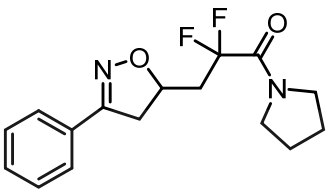
N,N-diethyl-2,2-difluoro-3-(3-phenyl-4,5-dihydroisoxazol-5-yl)propanamide *(3ac).*

The title compound was prepared according to *Representative Procedure I* and purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as light yellow oil (130.3 mg, 42% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.62 (m, 2H), 7.41-7.35 (m, 3H), 5.09-4.97 (m, 1H), 3.58-3.49 (m, 3H), 3.39 (q, *J* = 7.1 Hz, 2H), 3.15 (dd, *J* = 16.7 Hz, 8.5 Hz, 1H), 2.82-2.50 (m, 2H), 1.22 (t, *J* = 7.0 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.3 (t, $^{2}J_{C\text{-}F}$ = 28.5 Hz), 156.9, 130.2, 129.5, 128.8, 126.8, 118.5 (t, $^{1}J_{C\text{-}F}$ =257.55 Hz), 76.0 (t, $^{3}J_{C\text{-}F}$ = 4.2 Hz), 42.0 (t, *J* = 6.3 Hz), 41.7, 41.2, 40.5 (t, $^{2}J_{C\text{-}F}$ = 22.5 Hz), 14.4, 12.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -97.67 (ddd, *J* = 282.7 Hz, 21.0 Hz, 13.8 Hz, 1F), -99.10 (ddd, *J* = 282.7 Hz, 21.5 Hz, 15.4 Hz, 1F). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{21}N_2O_2F_2^+$ 311.1566; Found 311.1569.

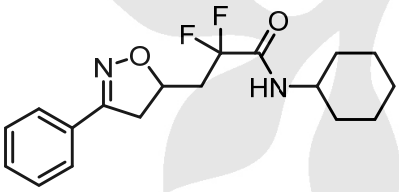


N-benzyl-2,2-difluoro-3-(3-phenyl-4,5-dihydroisoxazol-5-yl)propanamide (3ad).

The title compound was prepared according to *Representative Procedure I* and purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as white solid (141.2mg, 41% yield). m.p. 120.3-121.8 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.62 (m, 2H), 7.44-7.27 (m, 8H), 6.82 (s, 1H), 5.04-4.93 (m, 1H), 4.52 (d, *J* = 5.8 Hz, 2H), 3.50 (dd, *J* = 16.7 Hz, 10.3 Hz, 1H), 3.12 (dd, *J* = 16.7 Hz, 8.0 Hz, 1H), 2.78-2.44 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.7 (t, $^{2}J_{C\text{-}F}$ = 28.3 Hz), 156.8, 136.8, 130.4, 129.3, 129.1, 128.9, 128.1, 128.0, 126.9, 116.7 (t, $^{1}J_{C\text{-}F}$ = 253.4 Hz), 75.3 (t, $^{3}J_{C\text{-}F}$ = 4.4 Hz), 43.8, 40.9, 39.4 (t, $^{2}J_{C\text{-}F}$ = 22.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.45 (dt, *J* = 259.9 Hz, 17.0 Hz), -104.93 (dt, *J* = 259.7 Hz, 16.4 Hz). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{19}N_2O_2F_2^+$ 345.1409; Found 345.1412.

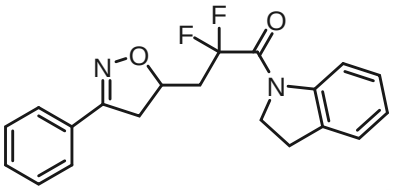


2,2-difluoro-3-(3-phenyl-4,5-dihydroisoxazol-5-yl)-1-(pyrrolidin-1-yl)propan-1-one (3ae). The title compound was prepared according to *Representative Procedure I* and purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as white solid (126.4 mg, 41% yield). m.p. 89.2-89.6 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.62 (m, 2H), 7.42-7.35 (m, 3H), 5.10-4.98 (m, 1H), 3.71 (t, *J* = 6.7 Hz, 2H), 3.58-3.47 (m, 3H), 3.16 (dd, *J* = 16.7 Hz, 8,4 Hz, 1H), 2.81-2.47 (m, 2H), 1.97 (p, *J* = 6.7 Hz, 2H), 1.86 (p, *J* = 6.6 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.7 (t, $^{2}J_{C\text{-}F}$ = 29.5 Hz), 156.9, 130.3, 129.5, 128.8, 126.8, 117.9 (t, $^{1}J_{C\text{-}F}$ = 254.4 Hz), 75.8 (t, $^{3}J_{C\text{-}F}$ = 4.2 Hz), 47.6, 46.7 (t, *J* = 6.4 Hz), 41.1, 39.9 (t, $^{2}J_{C\text{-}F}$ = 22.6 Hz), 26.6, 23.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -100.81 (ddd, *J* = 281.1 Hz, 19.3 Hz, 14.8 Hz, 1F), -101.81 (dt, *J* = 281.0 Hz, 17.7 Hz). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{19}N_2O_2F_2^+$ 309.1409; Found 309.1411.

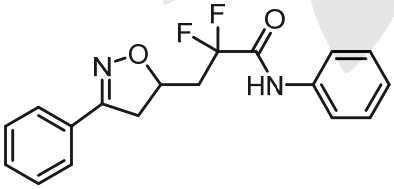


N-cyclohexyl-2,2-difluoro-3-(3-phenyl-4,5-dihydroisoxazol-5-yl)propanamide (3af). The title compound was prepared according to *Representative Procedure I* and purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as white solid (151.4 mg, 45% yield). m.p. 141.7-143.1 **ºC.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.62 (m, 2H), 7.43-7.36 (m, 3H), 6.30 (d, *J* = 7.9 Hz, 1H), 5.03-4.92 (m, 1H), 3.86-3.74 (m, 1H), 3.52 (dd, *J* = 16.7 Hz, 10.3 Hz, 1H), 3.13 (dd, *J* = 16.7 Hz, 8.0 Hz, 1H), 2.72-2.41 (m, 2H), 2.02-1.90 (m, 2H), 1.80-1.71 (m, 2H), 1.69-1.60 (m, 1H), 1.44-1.32 (m, 2H), 1.28-1.17 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.1-162.4 (m), 156.8, 130.4, 129.3, 128.9, 126.9, 116.7 (t, $^{1}J_{C\text{-}F}$ = 253.7 Hz), 75.4 (t, $^{3}J_{C\text{-}F}$ = 4.4 Hz), 48.9, 41.0, 39.5 (t, $^{2}J_{C\text{-}F}$ = 22.9 Hz), 32.7 (d, *J* = 6.7 Hz), 25.5, 24.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.74 (dt, *J* = 258.1 Hz, 17.2 Hz, 1F), -104.91 (dt, *J*

= 258.0 Hz, 16.3 Hz, 1F). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{23}N_2O_2F_2^+$ 337.1722; Found 337.1727.

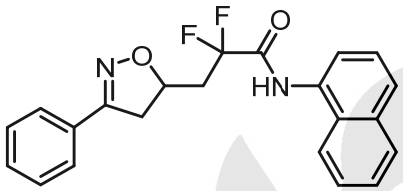


2,2-difluoro-1-(indolin-1-yl)-3-(3-phenyl-4,5-dihydroisoxazol-5-yl)propan-1-one (3ag). The title compound was prepared according to *Representative Procedure I* and purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as light yellow solid (178.2 mg, 50% yield). m.p. 116.2-117.1 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.24 (d, J = 8.0 Hz, 1H), 7.73-7.69 (m, 2H), 7.46-7.43 (m, 3H), 7.28 (d, J =7.8 Hz, 2H), 7.15 (t, J =7.4 Hz, 1H), 5.18-5.12 (m, 1H), 4.40 (t, J = 8.2 Hz, 2H), 3.60 (dd, J = 16.6 Hz, 10.3 Hz, 1H), 3.27-3.22 (m, 3H), 2.93-2.81 (m, 1H), 2.77-2.65 (m, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 160.8 (t, $^2J_{C\text{-}F}$ = 29.6 Hz), 156.9, 142.6, 131.9, 130.3, 129.4, 128.8, 127.7, 126.8, 125.4, 124.9, 118.2 (t, $^1J_{C\text{-}F}$ = 255.8 Hz), 118.0, 75.8 (t, $^3J_{C\text{-}F}$ = 4.0 Hz), 47.9 (t, J = 7.5 Hz), 41.2, 39.9 (t, $^2J_{C\text{-}F}$ = 22.3 Hz), 28.7. ^{19}F NMR (565 MHz, $CDCl_3$) δ -100.62 (ddd, J = 286.0 Hz, 20.7 Hz, 13.9 Hz, 1F), -101.77 (ddd, J = 286.1 Hz, 21.4 Hz, 15.2 Hz, 1F). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{19}N_2O_2F_2^+$ 357.1409; Found 357.1422.

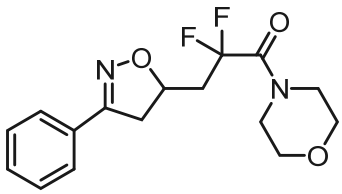


2,2-difluoro-N-phenyl-3-(3-phenyl-4,5-dihydroisoxazol-5-yl)propanamide (3ah). The title compound was prepared according to *Representative Procedure I* and purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as white solid (194.9 mg, 59% yield). m.p. 145.5-146.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.70-7.61 (m, 2H), 7.59 (d, J = 7.7 Hz, 2H), 7.47-7.35 (m, 5H), 7.21 (t, J = 7.4 Hz, 1H), 5.14-4.98 (m, 1H), 3.58 (dd, J = 16.7, 10.3 Hz, 1H), 3.17 (dd, J = 16.7, 7.9 Hz, 1H), 2.83-2.54 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 161.5 (t, $^2J_{C\text{-}F}$ = 28.0 Hz), 156.9, 136.0, 130.5, 129.4, 129.2, 128.9, 126.9, 125.9, 120.6, 116.8 (t, $^1J_{C\text{-}F}$

= 253.68 Hz), 75.3 (t, $^{3}J_{C\text{-}F}$ = 4.0 Hz), 41.1, 39.4 (t, $^{2}J_{C\text{-}F}$ = 22.9 Hz).^{19}F NMR (565 MHz, $CDCl_3$) δ -102.76 (dt, *J* = 259.7 Hz, 17.3 Hz), -104.03 (dt, *J* = 259.9 Hz, 16.4 Hz). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{17}N_2O_2F_2^+$ 331.1253; Found 331.1260.

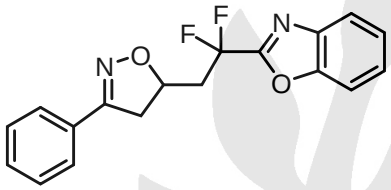


2,2-difluoro-N-(naphthalen-1-yl)-3-(3-phenyl-4,5-dihydroisoxazol-5-yl)propanamide (3ai). The title compound was prepared according to *Representative Procedure I* and purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as white solid (152.3 mg, 40% yield). m.p. 118.3-120.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.98 (d, *J* = 7.5 Hz, 1H), 7.90 (t, *J* = 7.1 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 2H), 7.62-7.49 (m, 3H), 7.45-7.37 (m, 3H), 5.18-5.08 (m, 1H), 3.60 (dd, *J* = 16.7 Hz, 10.3 Hz, 1H), 3.20 (dd, *J* = 16.7 Hz, 7.8 Hz, 1H), 2.94-2.59 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.3 (t, $^{2}J_{C\text{-}F}$ = 10.61 Hz), 156.8, 154.2, 134.3, 130.5, 130.3, 129.3, 129.0, 128.9, 127.3, 127.1, 126.9, 126.5, 125.8, 121.5, 120.4, 114.3 (t, $^{1}J_{C\text{-}F}$ = 272.70 Hz), 75.4 (t, $^{3}J_{C\text{-}F}$ = 4.5 Hz), 41.1, 39.6 (t, $^{2}J_{C\text{-}F}$ = 22.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.24 (dt, *J* = 259.9 Hz, 17.0 Hz, 1F), -103.82 (dt, *J* = 259.8 Hz, 16.2 Hz, 1F). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{19}N_2O_2F_2^+$ 381.1409; Found 381.1415.

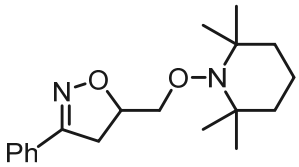


2,2-difluoro-1-morpholino-3-(3-phenyl-4,5-dihydroisoxazol-5-yl)propan-1-one (3aj). The title compound was prepared according to *Representative Procedure I* and purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as white solid (201.1 mg, 62% yield). m.p. 103.9-105.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.69-7.64 (m, 2H), 7.43-7.37 (m, 3H), 5.11-5.01 (m, 1H), 3.80-3.70 (m, 6H), 3.69-3.64 (m, 2H), 3.55 (dd, *J* = 16.7 Hz, 10.3 Hz, 1H), 3.16 (dd, *J* = 16.7 Hz, 8.4 Hz,

1H), 2.84-2.49 (m, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 161.6 (t, $^{2}J_{C\text{-}F}$ = 29.4 Hz), 156.9, 130.4, 129.5, 128.9, 126.8, 118.4 (t, $^{3}J_{C\text{-}F}$ = 256.54 Hz), 75.8 (t, $^{3}J_{C\text{-}F}$ = 4.1 Hz), 66.9, 66.8, 46.6 (t, *J* = 5.9 Hz), 43.6, 41.2, 40.4 (t, $^{2}J_{C\text{-}F}$ = 22.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -96.99 (ddd, *J* = 286.1 Hz, 20.9 Hz, 14.2 Hz, 1F), -98.38 (ddd, *J* = 286.3 Hz, 21.5 Hz, 15.5 Hz, 1F). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{19}N_2O_3F_2^+$ 325.1358; Found 325.1365.



2-(1,1-difluoro-2-(3-phenyl-4,5-dihydroisoxazol-5-yl)ethyl)benzo[d]oxazole (3ak). The title compound was prepared according to *Representative Procedure I* and purified with silica gel chromatography (petroleum ether/ethyl acetate = 5:1) as white solid (219.9 mg, 67% yield). m.p. 113.2-114.1 ºC. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 1.7 Hz, 1H), 7.65 (d, *J* = 2.1 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.44-7.38 (m, 4H), 5.18-5.11 (m, 1H), 3.57 (dd, *J* = 16.7 Hz, 10.3 Hz, 1H), 3.23 (dd, *J* = 16.7 Hz, 8.2 Hz, 1H), 3.16-3.04 (m, 1H), 2.88-2.77 (m, 1H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 157.3 (t, $^{2}J_{C\text{-}F}$ = 33.0 Hz), 156.8, 150.7, 139.9, 130.4, 129.2, 128.8, 127.2, 126.8, 125.5, 121.4, 115.4 (t, $^{1}J_{C\text{-}F}$ = 242.4 Hz), 111.6, 75.3 (t, $^{3}J_{C\text{-}F}$ = 3.6 Hz), 41.2 (t, $^{2}J_{C\text{-}F}$ = 22.8 Hz), 40.9. ^{19}F NMR (565 MHz, $CDCl_3$) δ -94.78 (ddd, *J* = 280.4 Hz, 19.3 Hz, 11.6 Hz, 1F), -98.45 (dt, *J* = 279.8 Hz, 17.8 Hz, 1F). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{15}N_2O_2F_2^+$ 329.1096; Found 329.1105.



3-Phenyl-5-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)-4,5-dihydroisoxazole (5).[4] The title compound was obtained according to *Representative Procedure I* except TEMPO (312.5 mg, 2.0 mmol) was added. Purification with silica gel chromatography (petroleum ether/ethyl acetate = 10:1) gave the title compound (268.9 mg, 85% yield)

as light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73-7.63 (m, 2H), 7.45-7.34 (m, 3H), 4.92-4.81 (m, 1H), 4.02-3.93 (m, 2H), 3.37 (dd, *J* = 16.4 Hz, 10.9 Hz, 1H), 3.24 (dd, *J* = 16.4 Hz, 7.5 Hz, 1H), 1.55-1.36 (m, 5H), 1.31 (s, 1H), 1.19 (s, 6H), 1.07 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2, 130.0, 129.8, 128.7, 126.7, 79.3, 77.7, 60.2 (d, *J* = 5.3 Hz), 39.7, 37.1, 33.1 (d, *J* = 10.0 Hz), 20.2, 17.1.

3. References

(1) He, Y.-T.; Li, L.-H.; Yang, Y.-F.; Wang, Y.-Q.; Luo, J.-Y.; Liu, X.-Y.; Liang, Y.-M. Copper-catalyzed synthesis of trifluoromethyl-substituted isoxazolines. *Chem. Commun.* **2013**, *49*, 5687-5689.

(2) (a) Wang, X.; Zhao, S.; Liu, J.; Zhu, D.; Guo, M.; Tang, X.; Wang, G. Copper-Catalyzed C-H Difluoroalkylations and Perfluoroalkylations of Alkenes and (Hetero)arenes. *Org. Lett.* **2017**, *19*, 4187-4190. (b) Chen, H.; Wang, X.; Guo, M.; Zhao, W.; Tang, X.; Wang, G. Highly efficient and versatile synthesis of *α,α*-difluoro-*γ*-lactams via aminodifluoroalkylation of alkenes. *Org. Chem. Front.* **2017**, *4*, 2403-2407. (c) Li, Y.; Liu, J.; Zhao, S.; Du, X.; Guo, M.; Zhao, W.; Tang, X.; Wang, G. Copper-Catalyzed Fluoroolefination of Silyl Enol Ethers and Ketones toward the Synthesis of *β*-Fluoroenones. *Org. Lett.* **2018**, *20*, 917-920. (d) Feng, X.; Wang, X.; Chen, H.; Tang, X.; Guo, M.; Zhao, W.; Wang, G. Copper-mediated regioselective hydrodifluoroalkylation of alkynes. *Org. Biomol. Chem.* **2018**, *16*, 2841-2845. (e) Wang, X.; Li, M.; Yang, Y.; Guo, M.; Tang, X.; Wang, G. One-pot Construction of Difluorinated Pyrrolizidine and Indolizidine Scaffolds via Copper-Catalyzed Radical Cascade Annulation. *Adv. Synth. Catal.* **2018**, *360*, 2151-2156. (f) Wang, X.; Liu, J.; Yu, Z.; Guo, M.; Tang, X.; Wang, G. Desulfonylation-Initiated Distal Alkenyl Migration in Copper-Catalyzed Alkenylation of Unactivated Alkenes. *Org. Lett.* **2018**, *20*, 6516-6519.

(3) (a) Yuan, F.; Zhou, S.; Yang, Y.; Guo, M.; Tang, X.; Wang, G. Copper catalyzed one-pot difluoroalkylation and lactonization of unsaturated carboxylic acids. *Org. Chem. Front.* **2018**, *5*, 3306-3309. (b) Yang, Y.; Yuan, F.; Ren, X.; Wang, G.; Zhao, W.;

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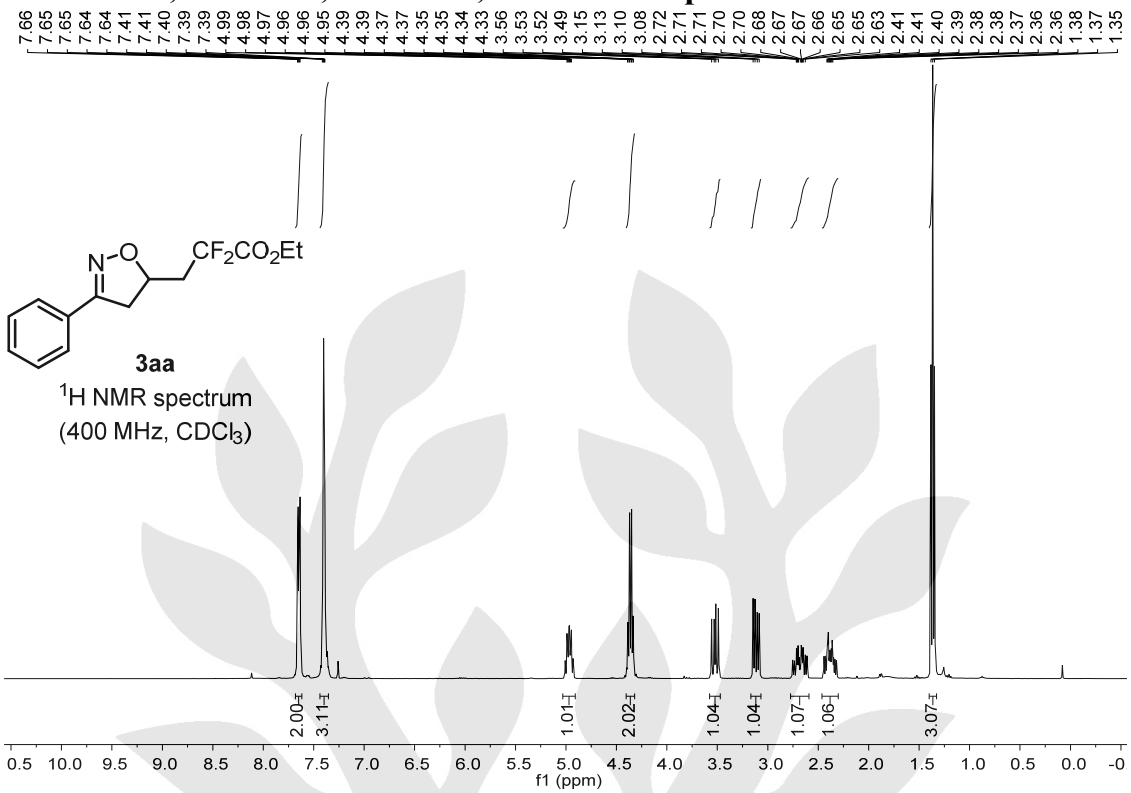
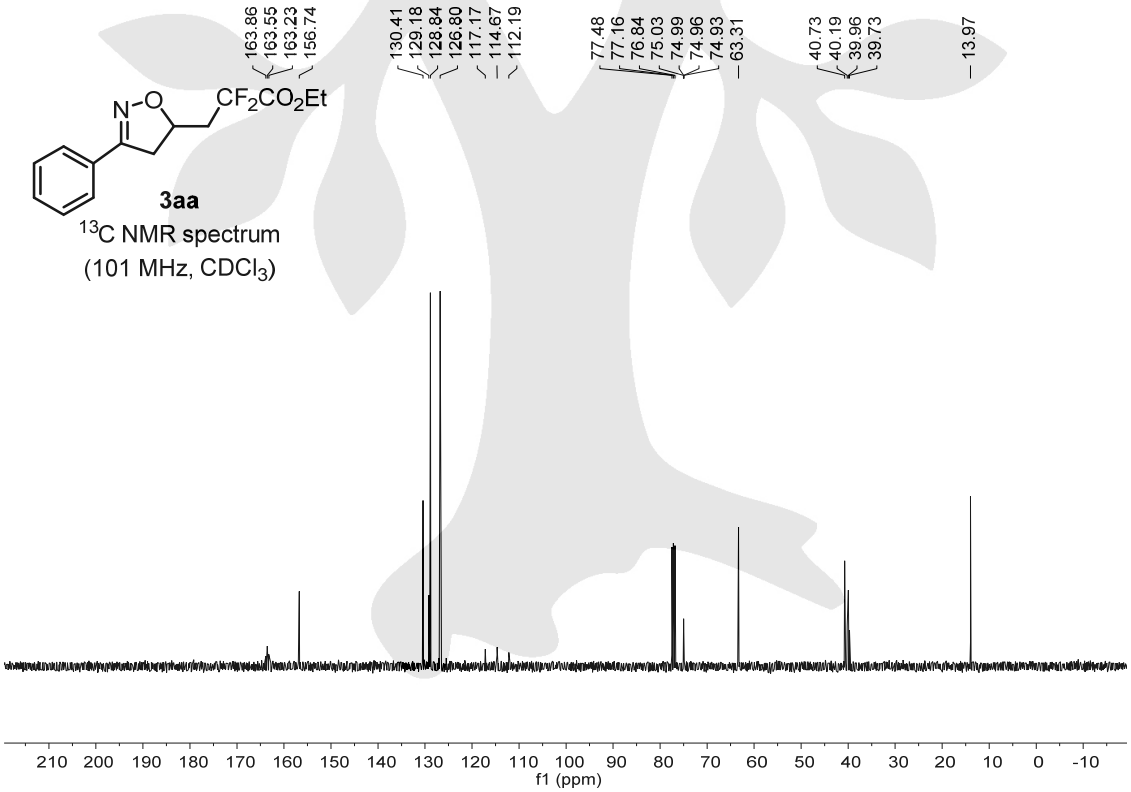
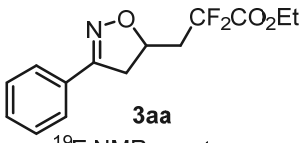
4. ^{1}H NMR, ^{19}F NMR, ^{13}C NMR, and HRMS spectra



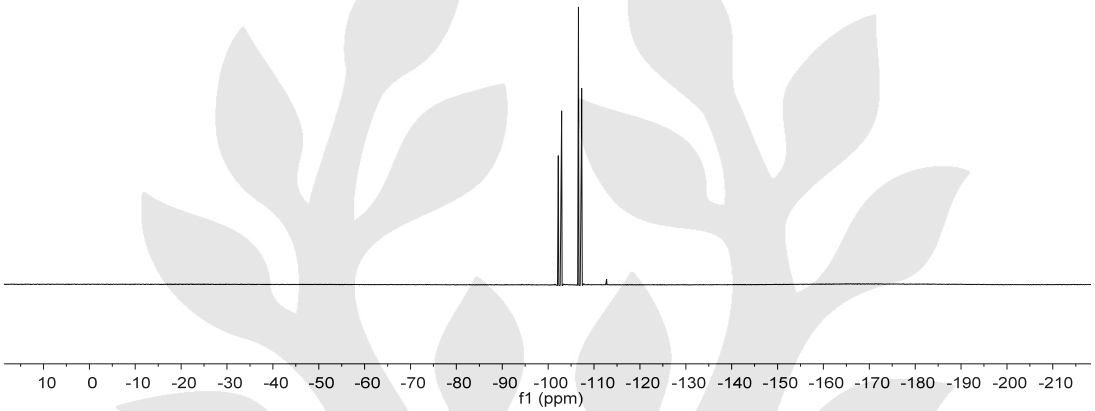


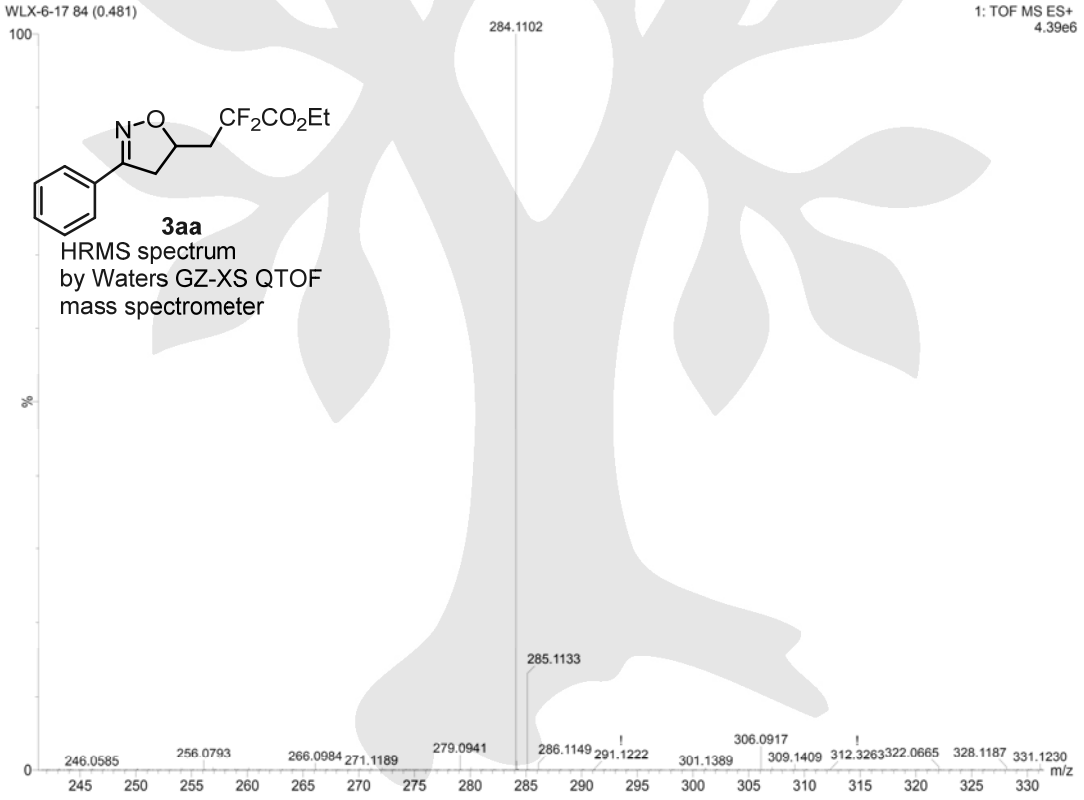


3aa

^{19}F NMR spectrum

(376 MHz, $CDCl_3$)



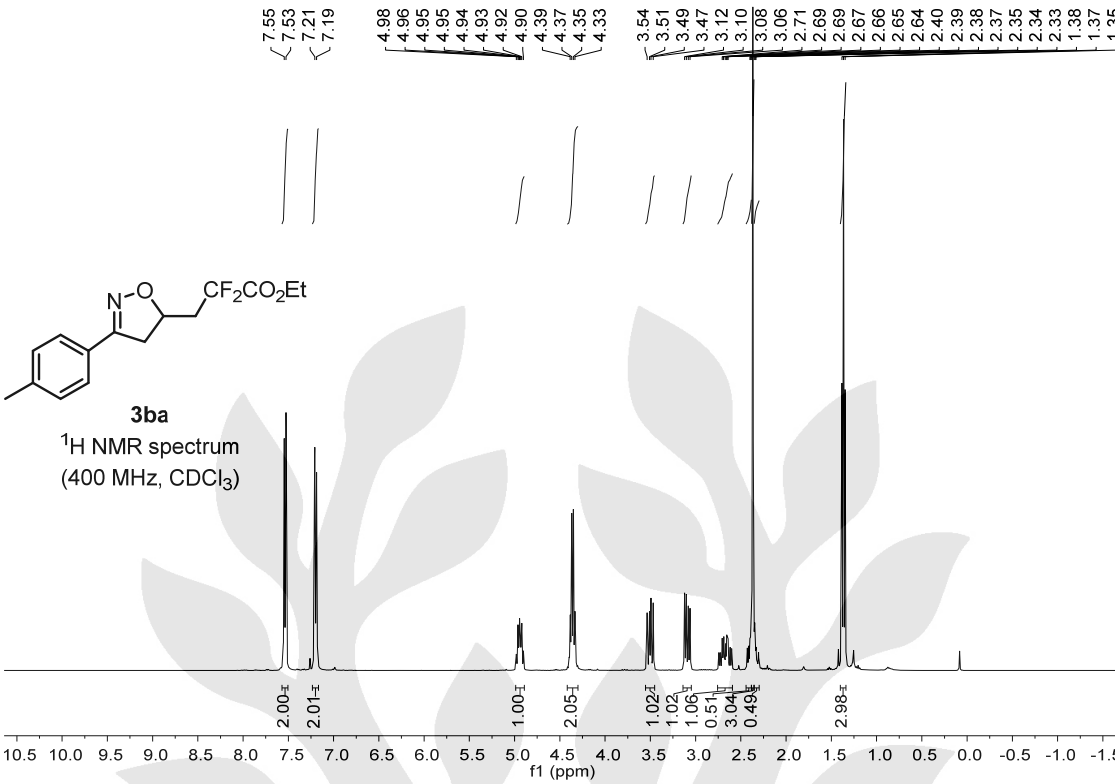


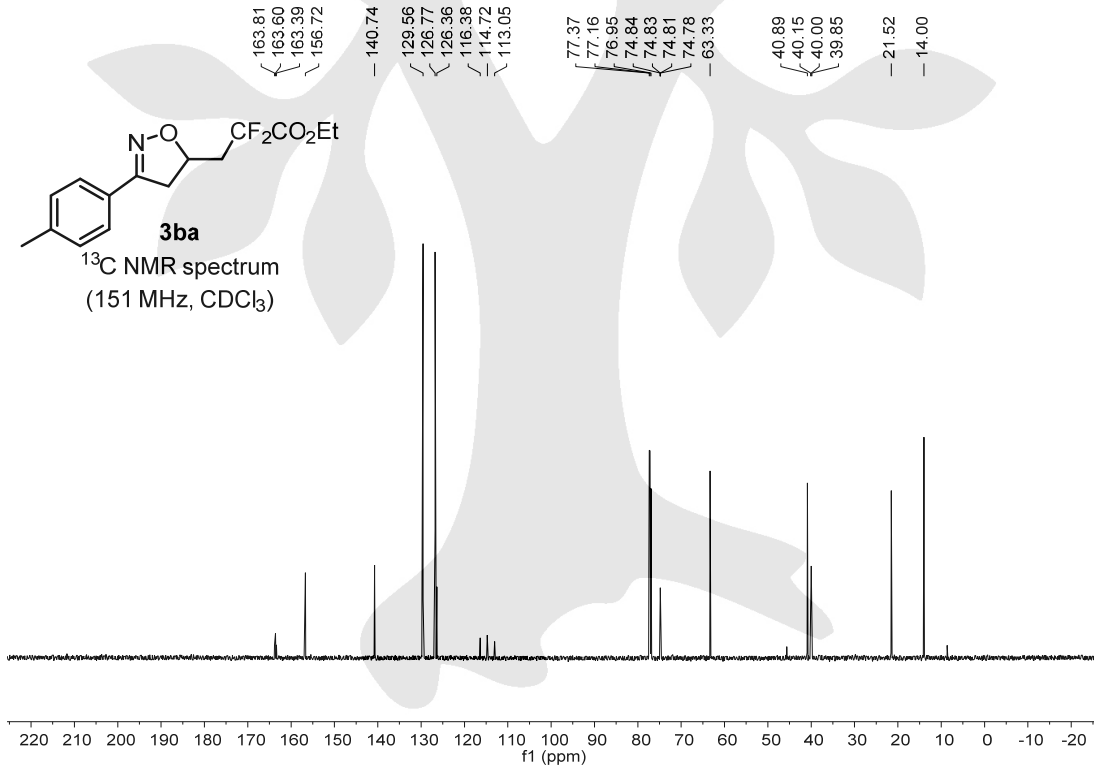
3aa

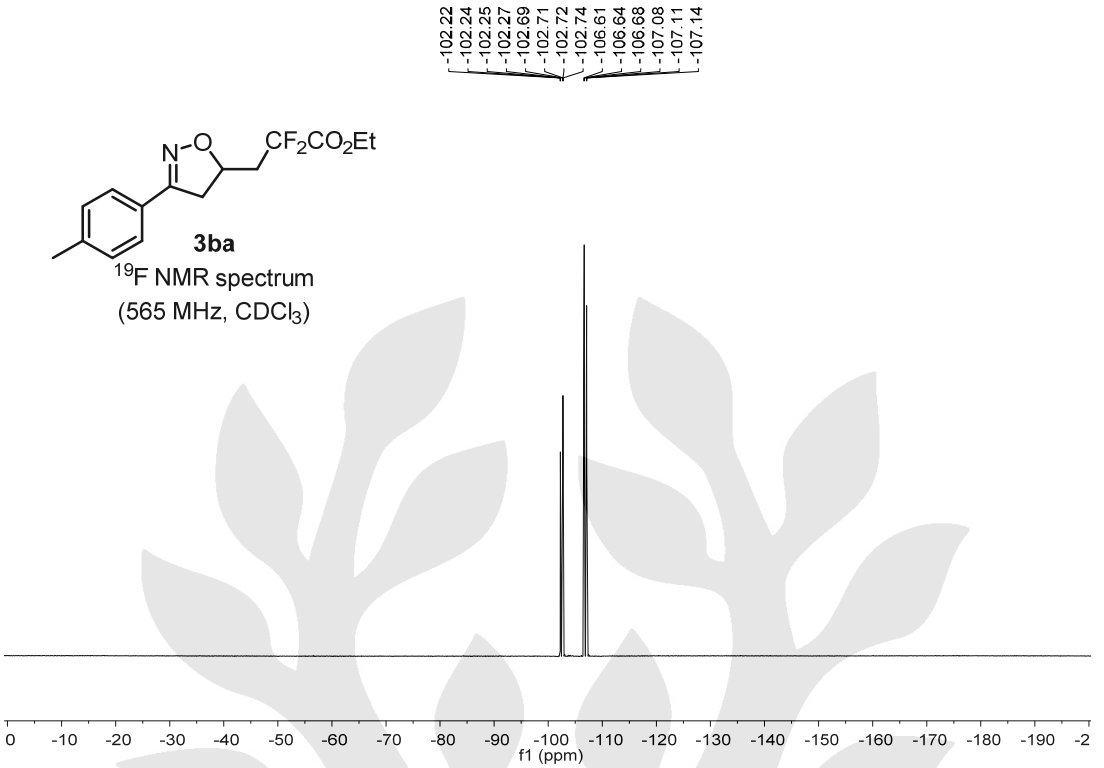
HRMS spectrum

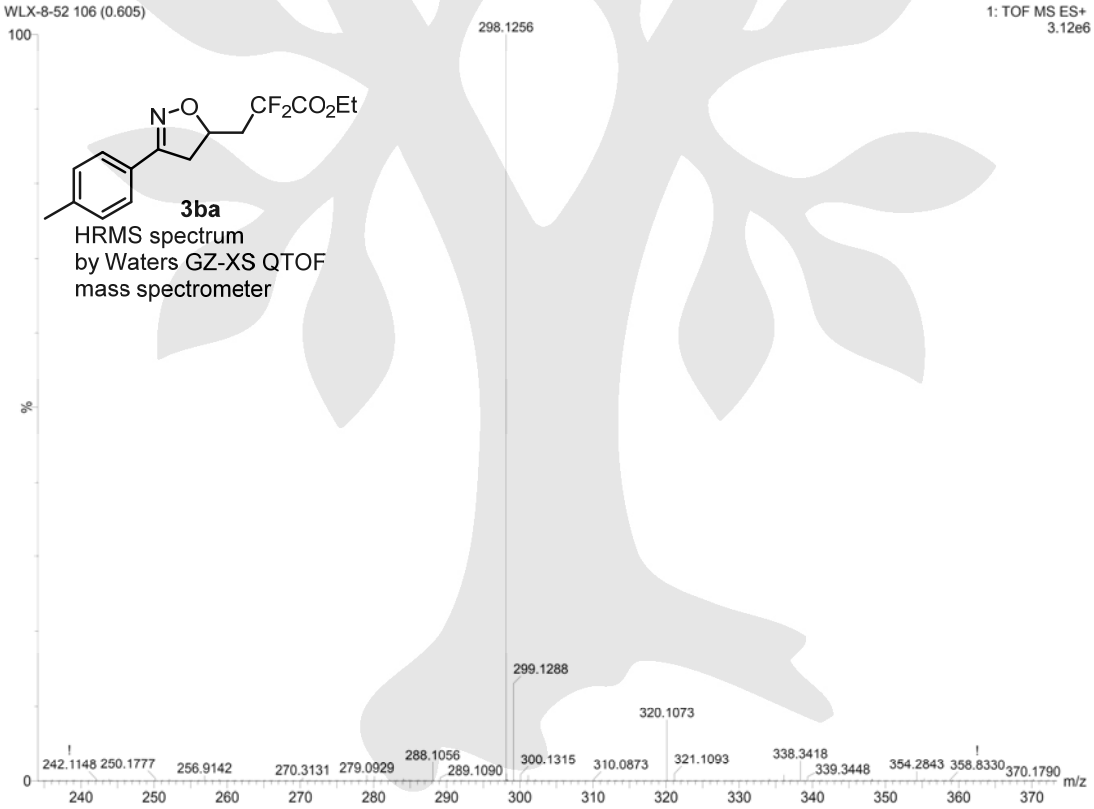
by Waters GZ-XS QTOF

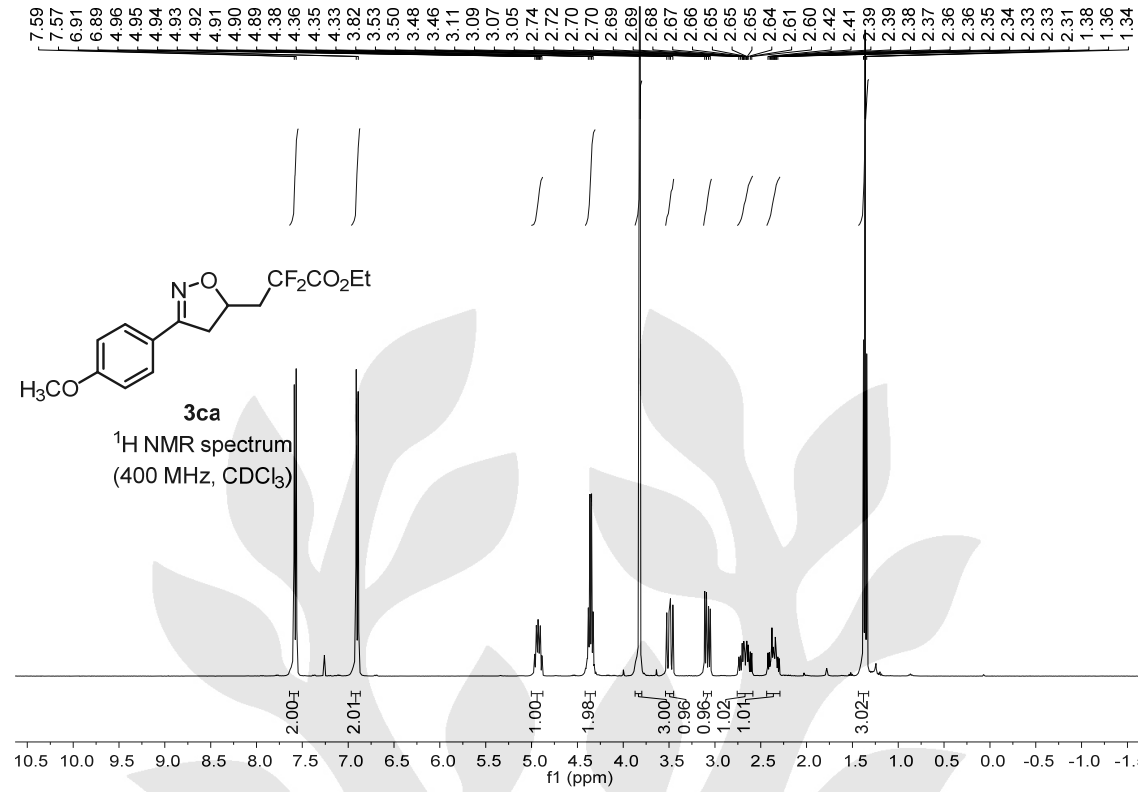
mass spectrometer

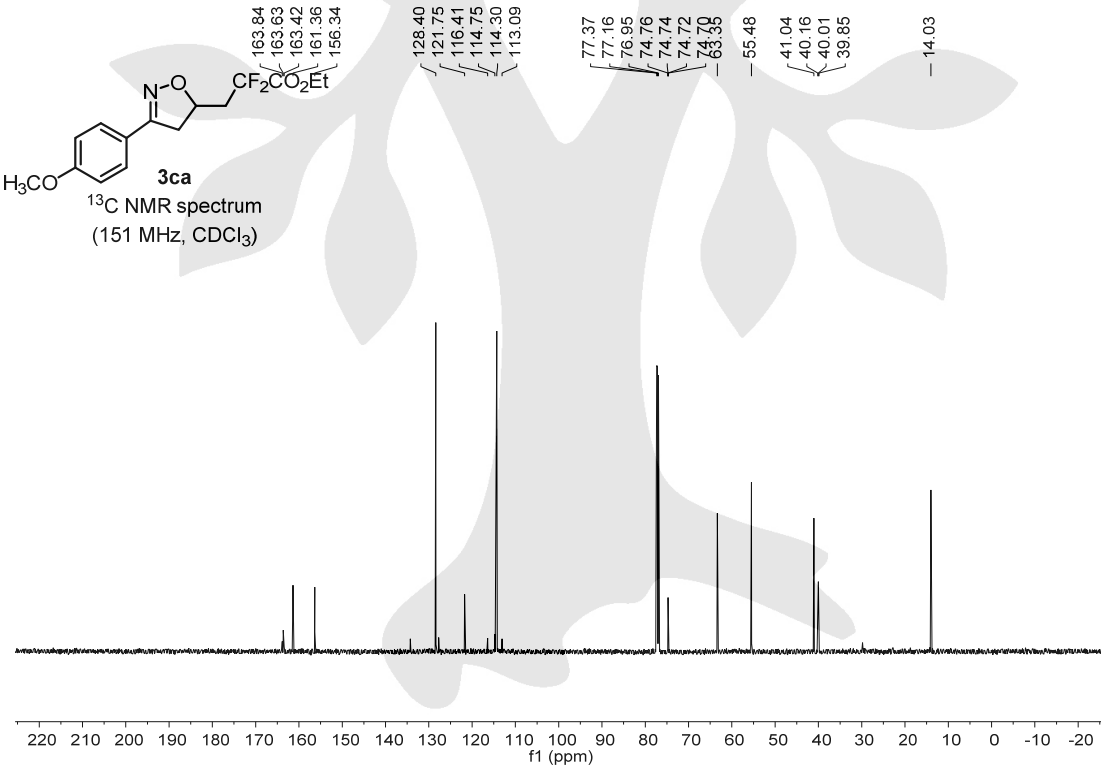












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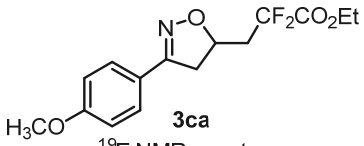
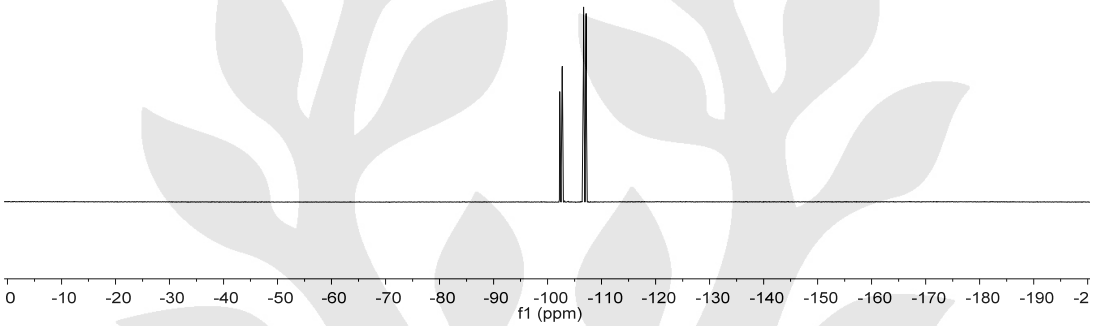
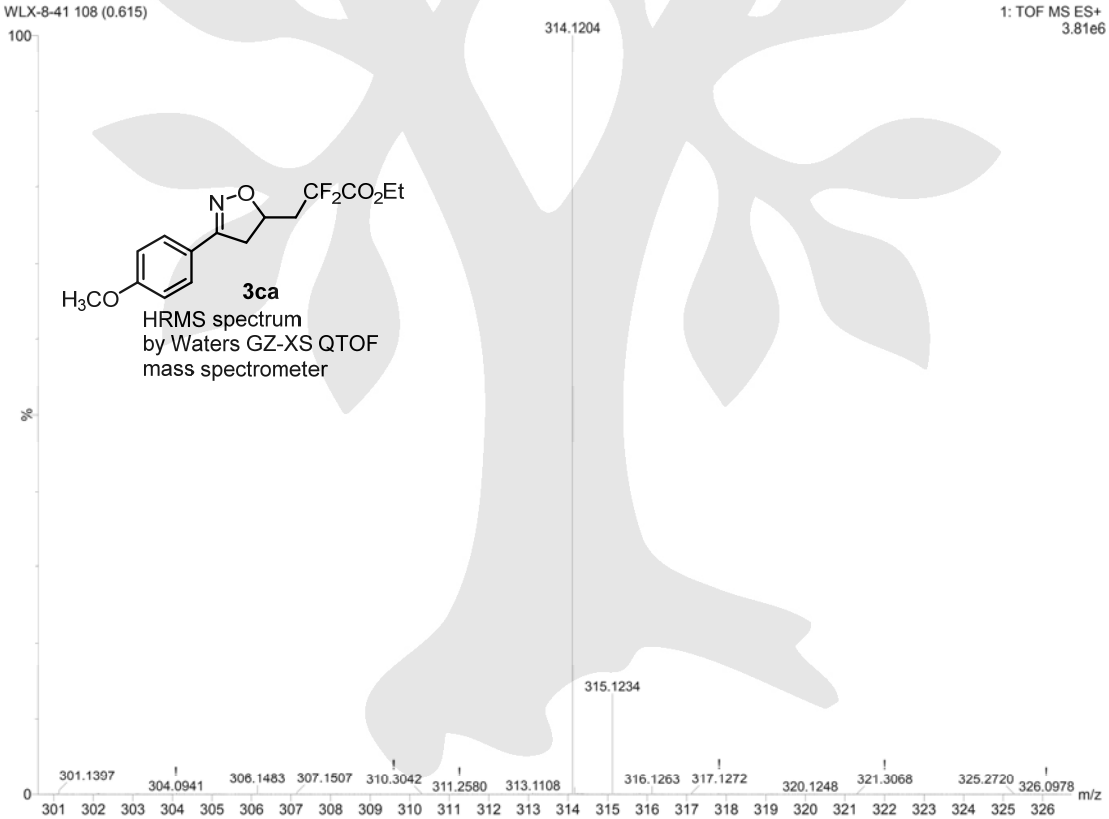


3ca

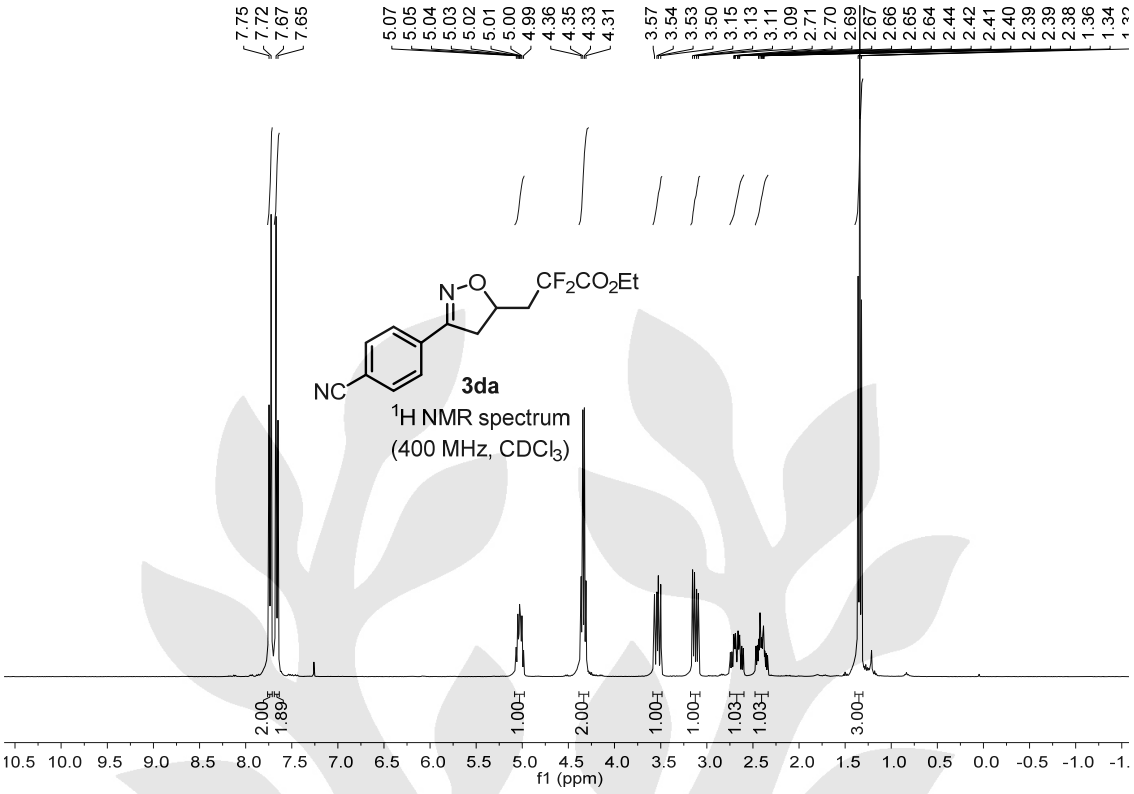
^{19}F NMR spectrum
(565 MHz, $CDCl_3$)

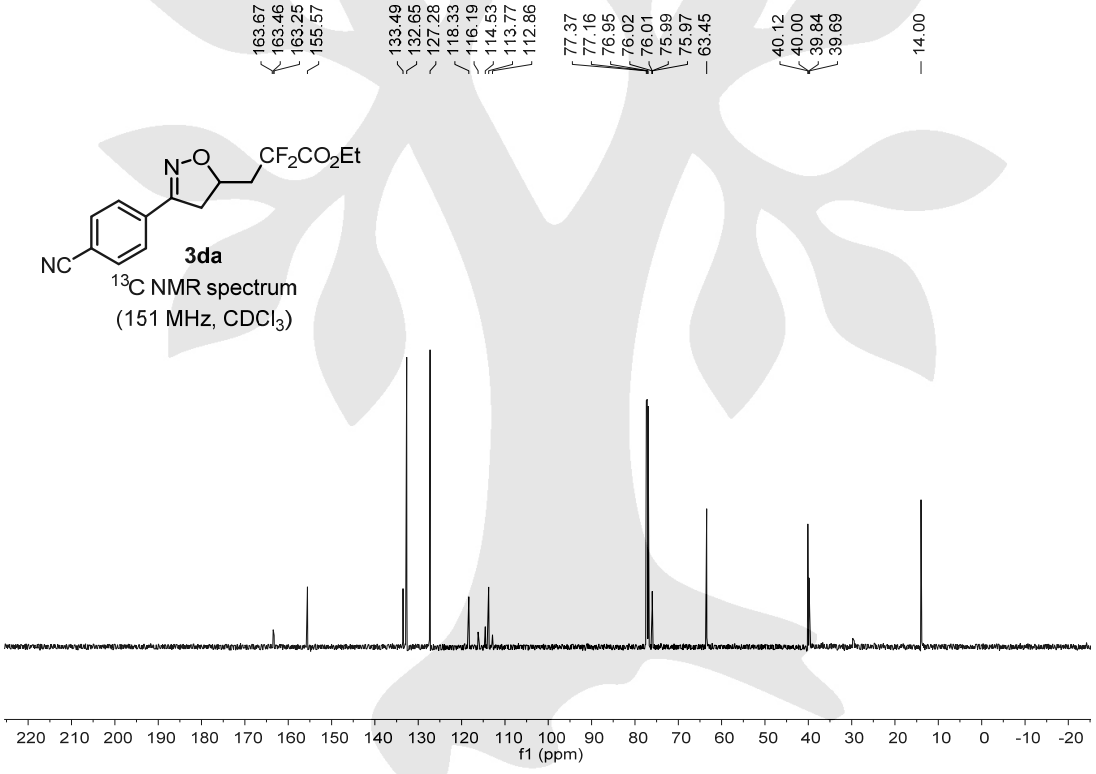


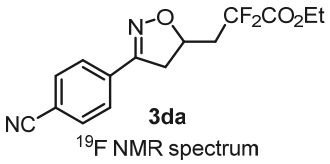


3ca

HRMS spectrum
by Waters GZ-XS QTOF
mass spectrometer



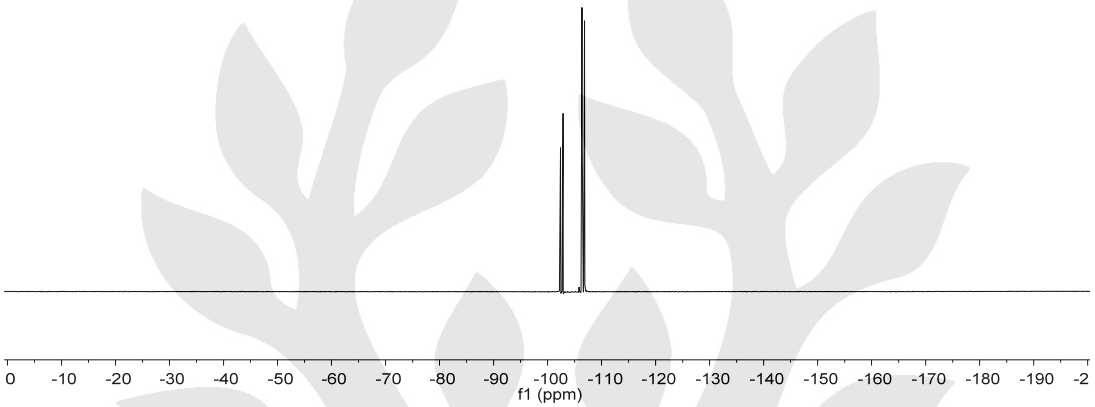


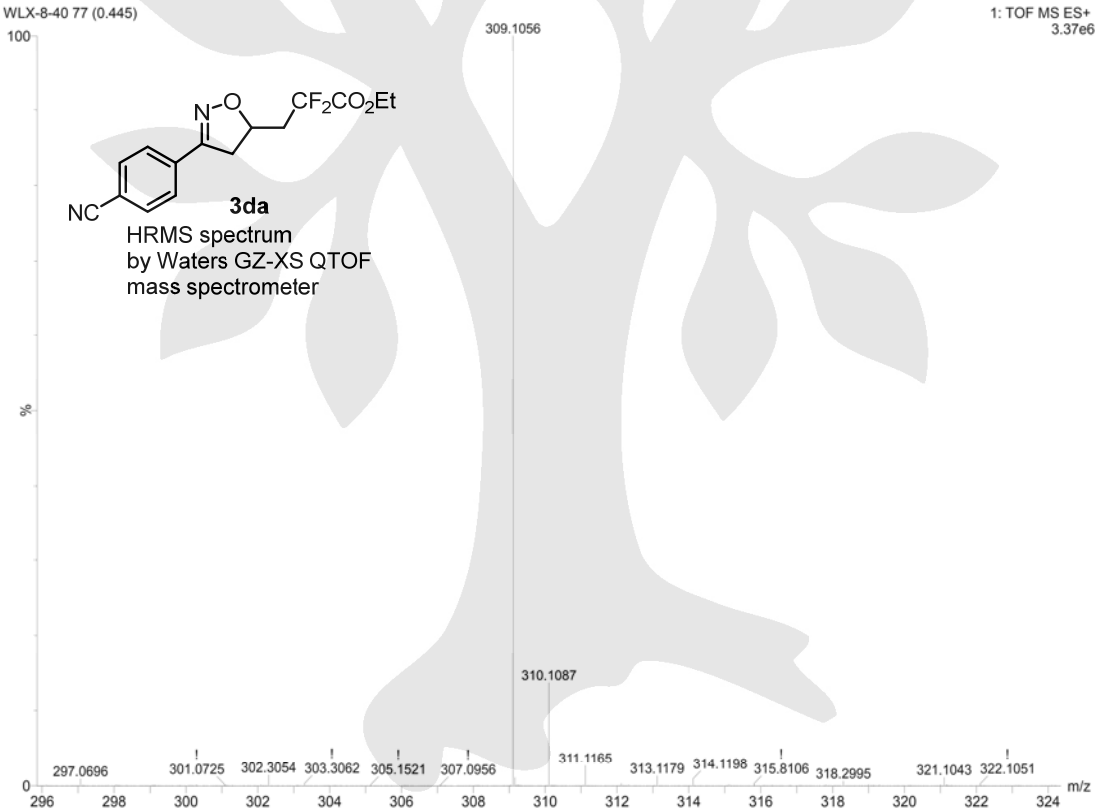


3da

^{19}F NMR spectrum

(565 MHz, $CDCl_3$)



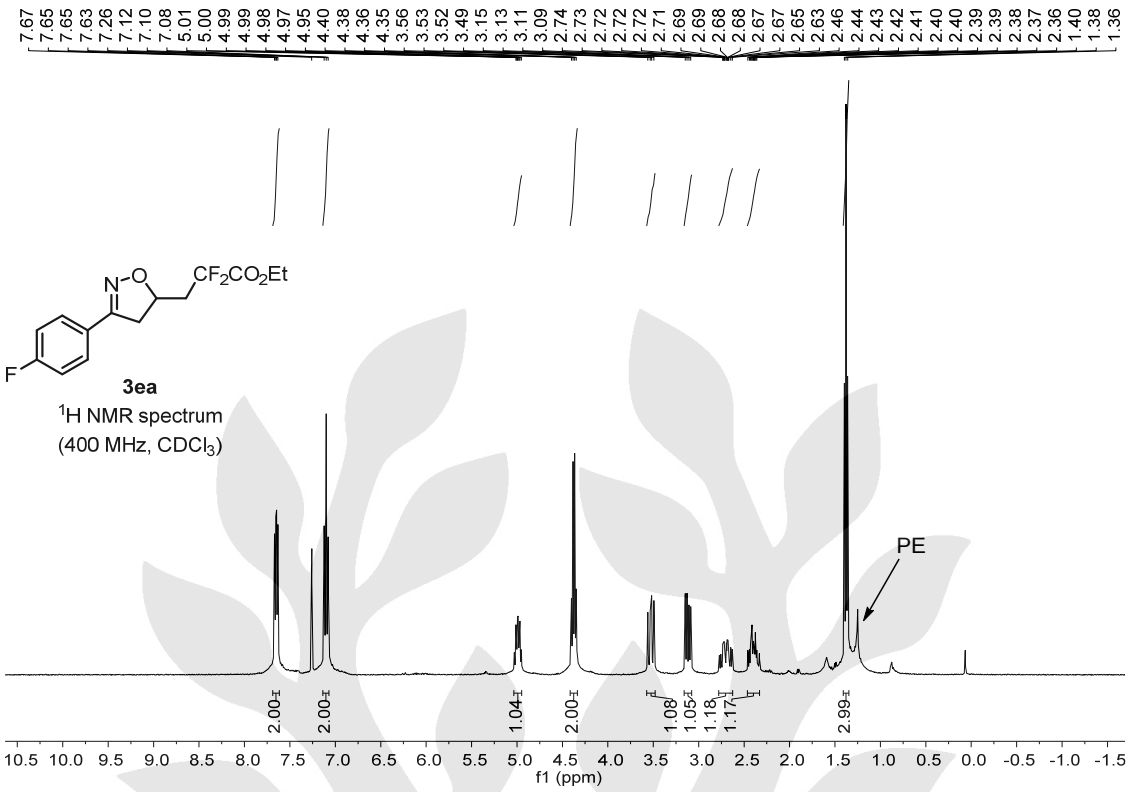


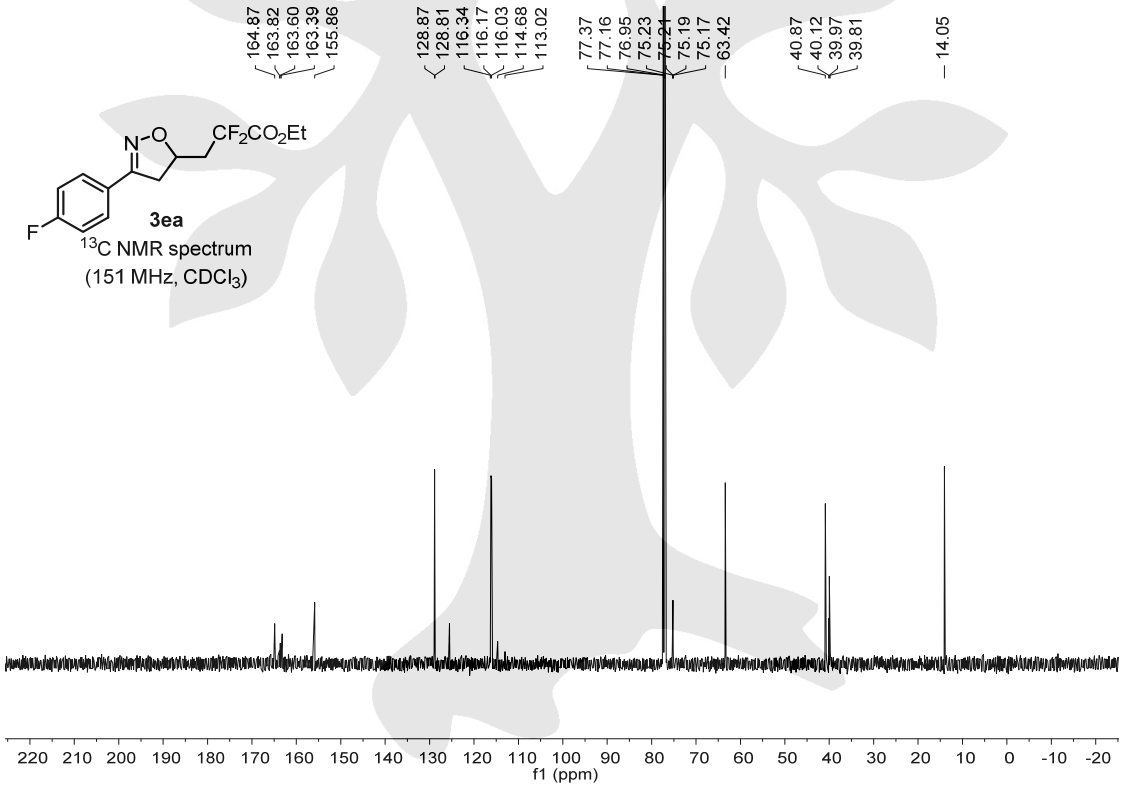
3da

HRMS spectrum

by Waters GZ-XS QTOF

mass spectrometer





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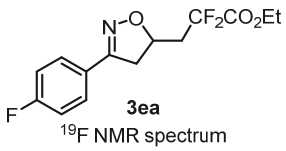
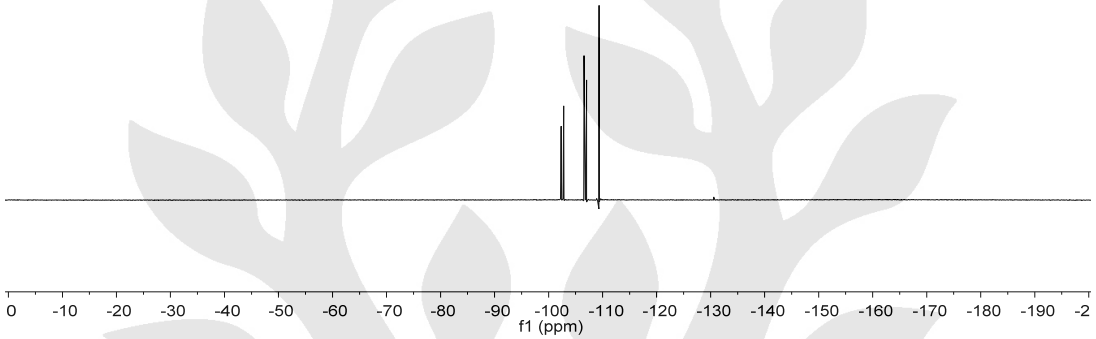
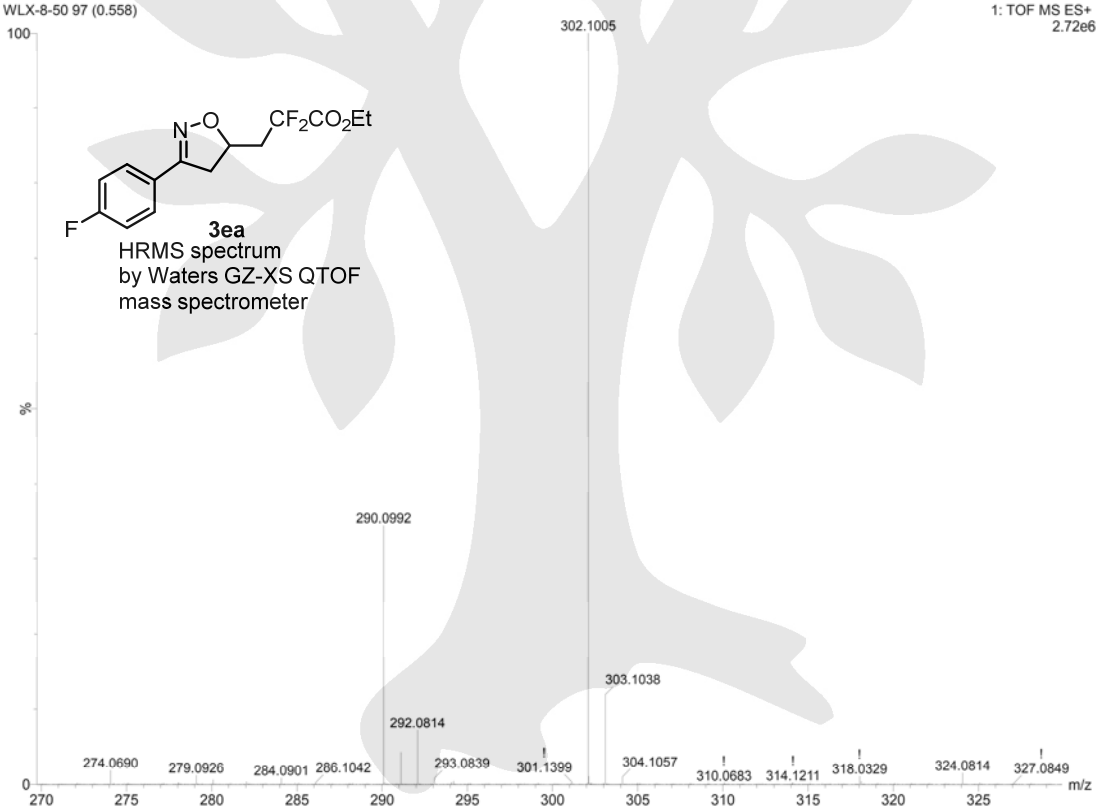


3ea

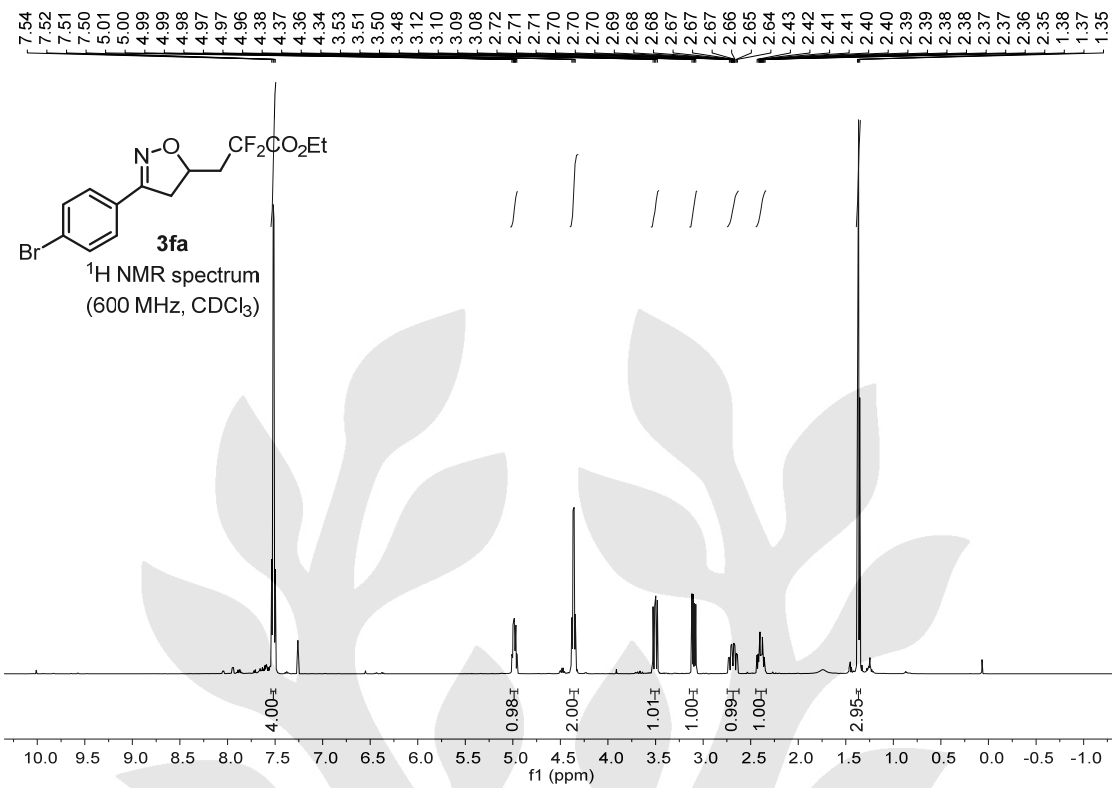
^{19}F NMR spectrum
(565 MHz, $CDCl_3$)

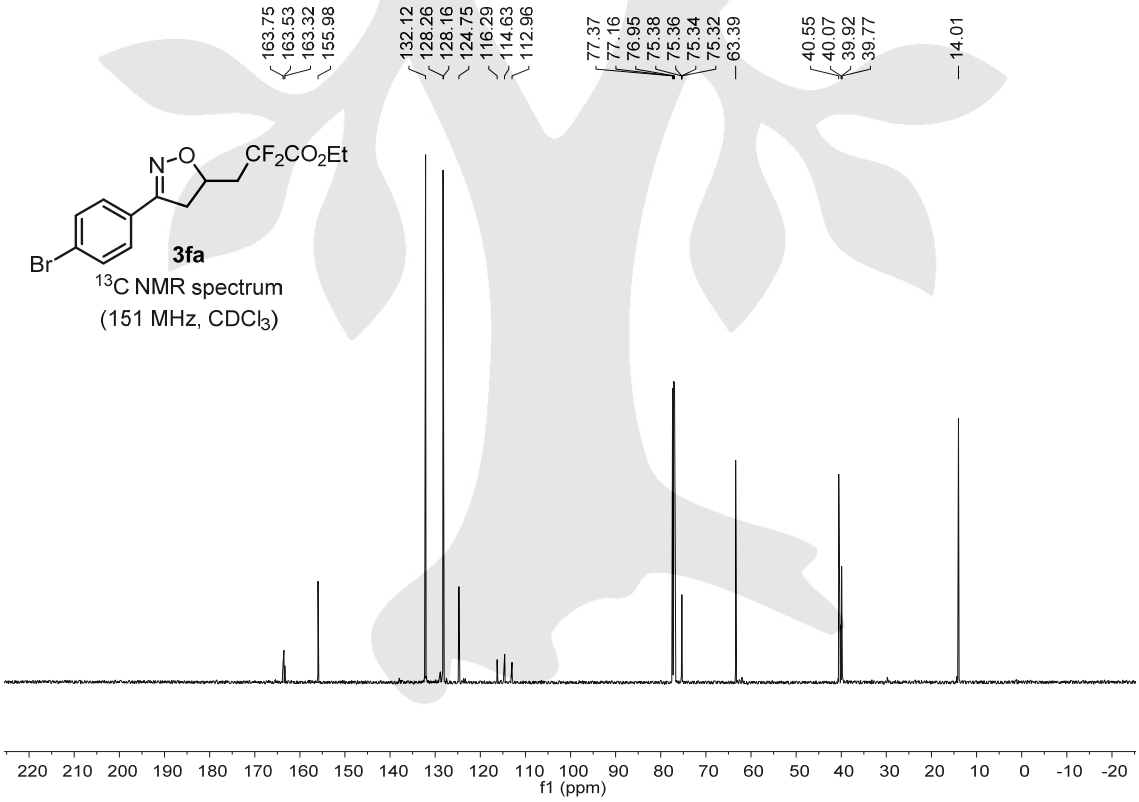


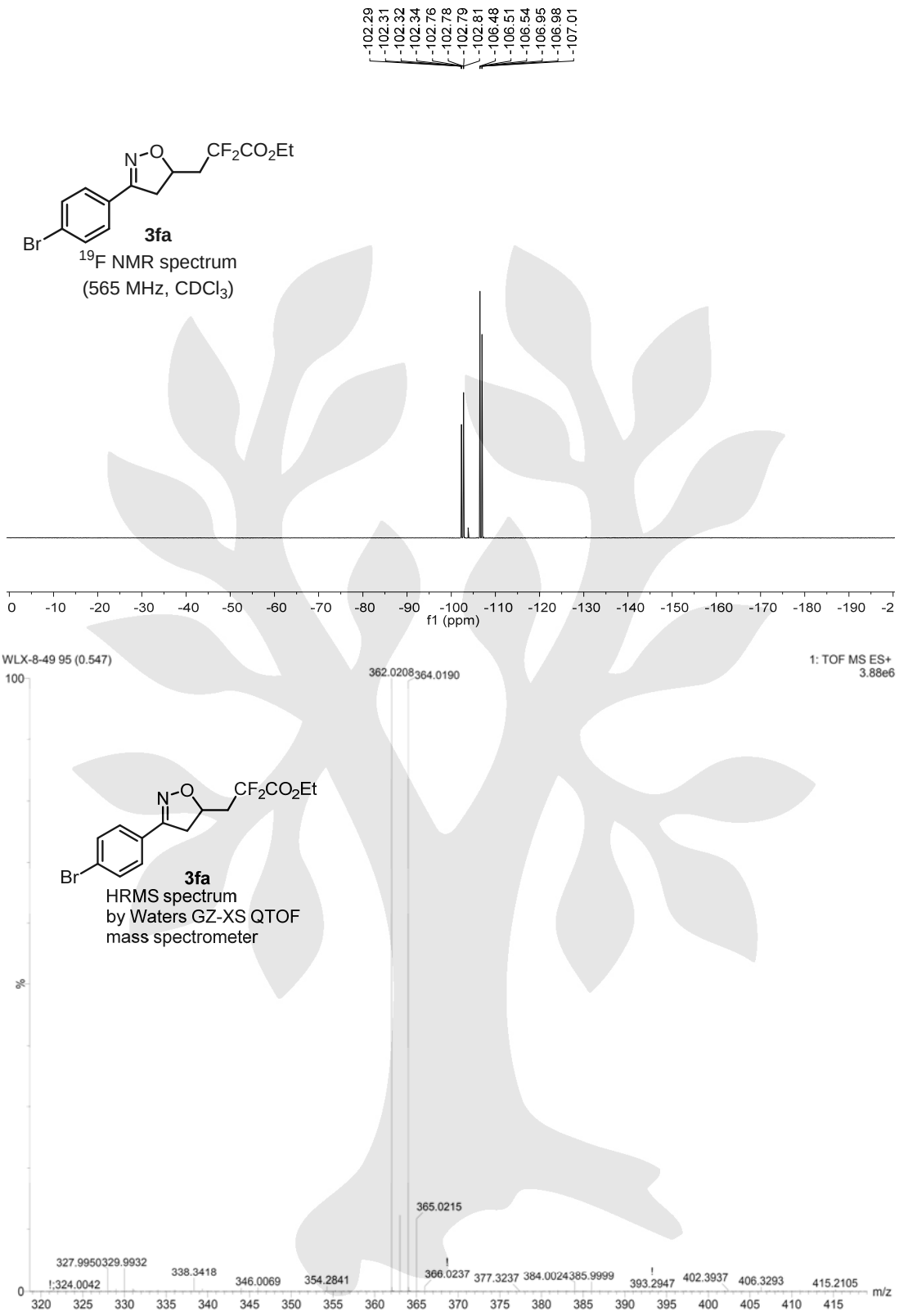


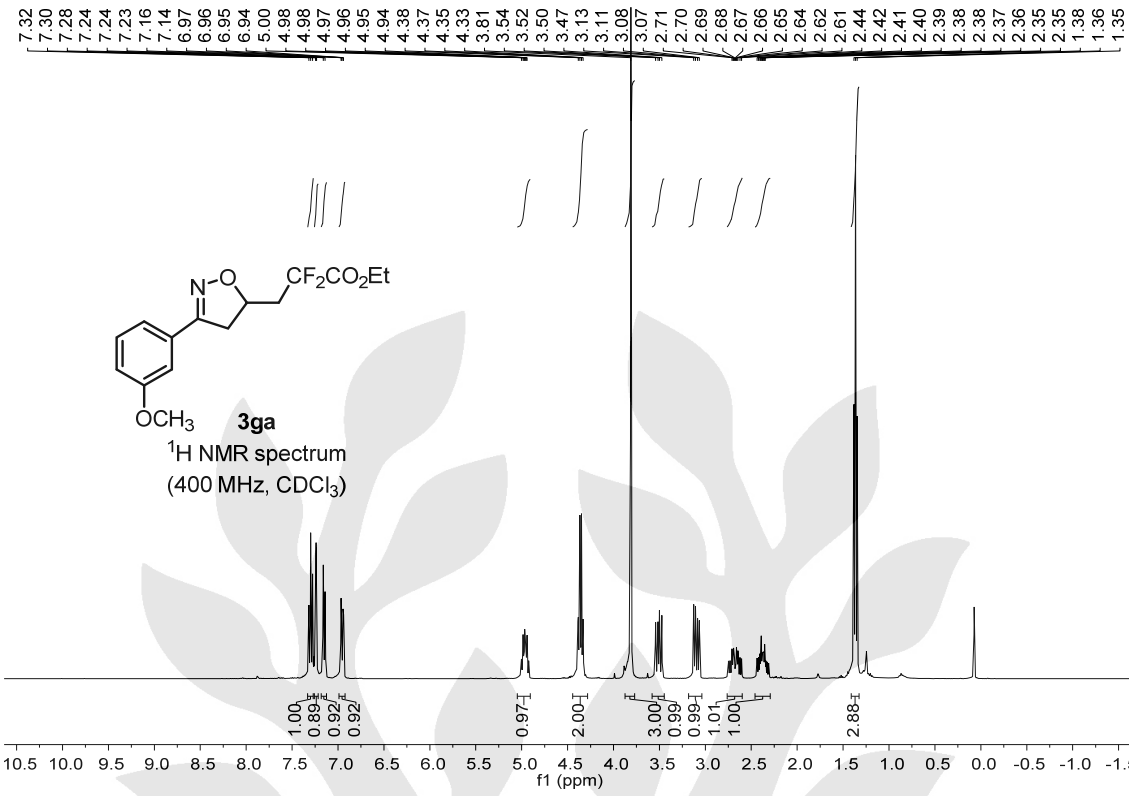
3ea

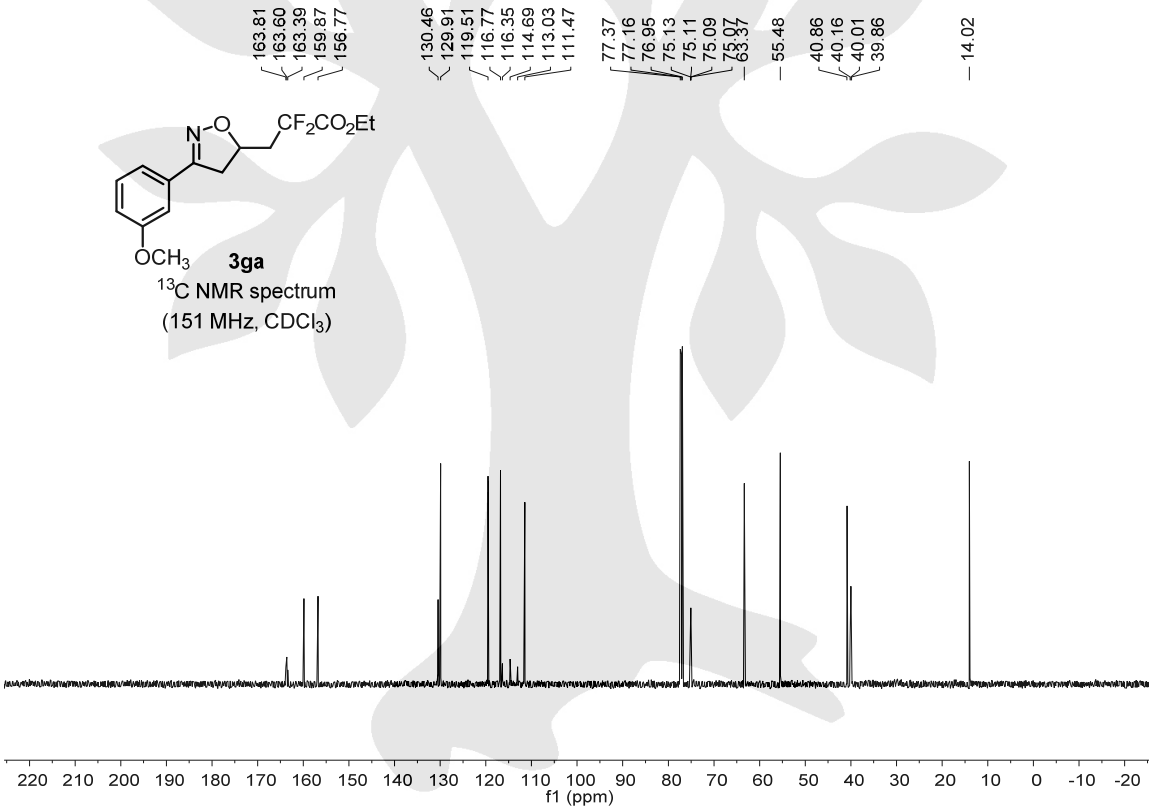
HRMS spectrum
by Waters GZ-XS QTOF
mass spectrometer

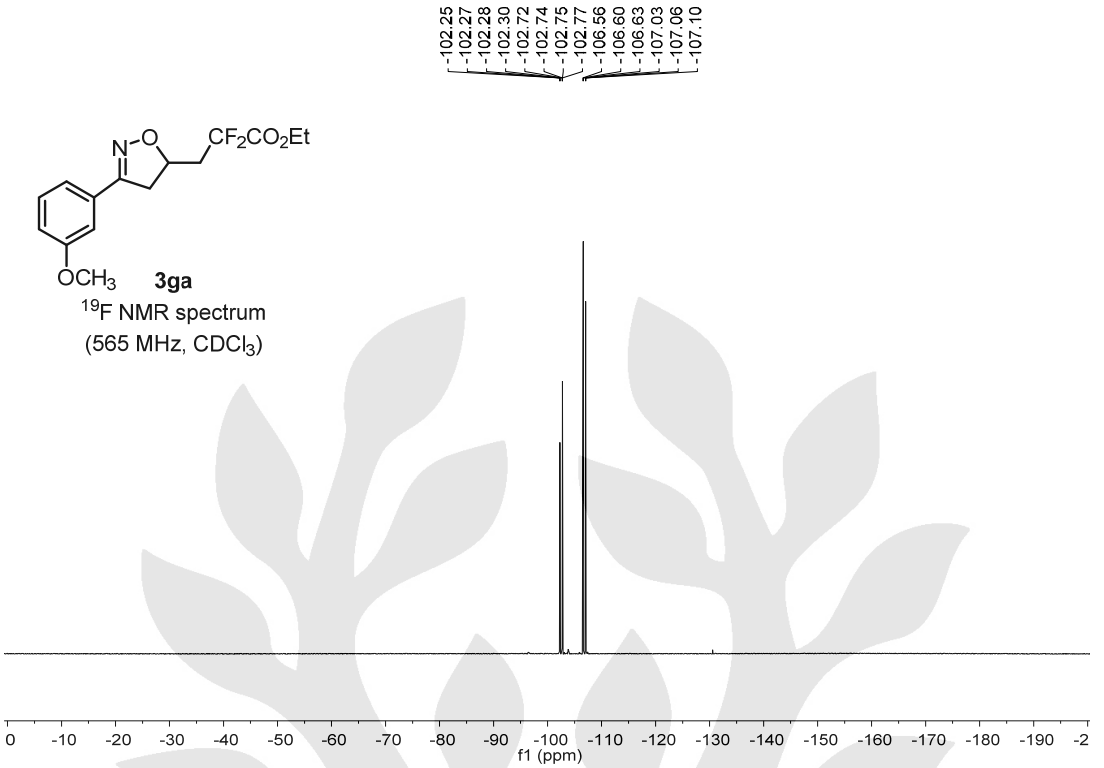


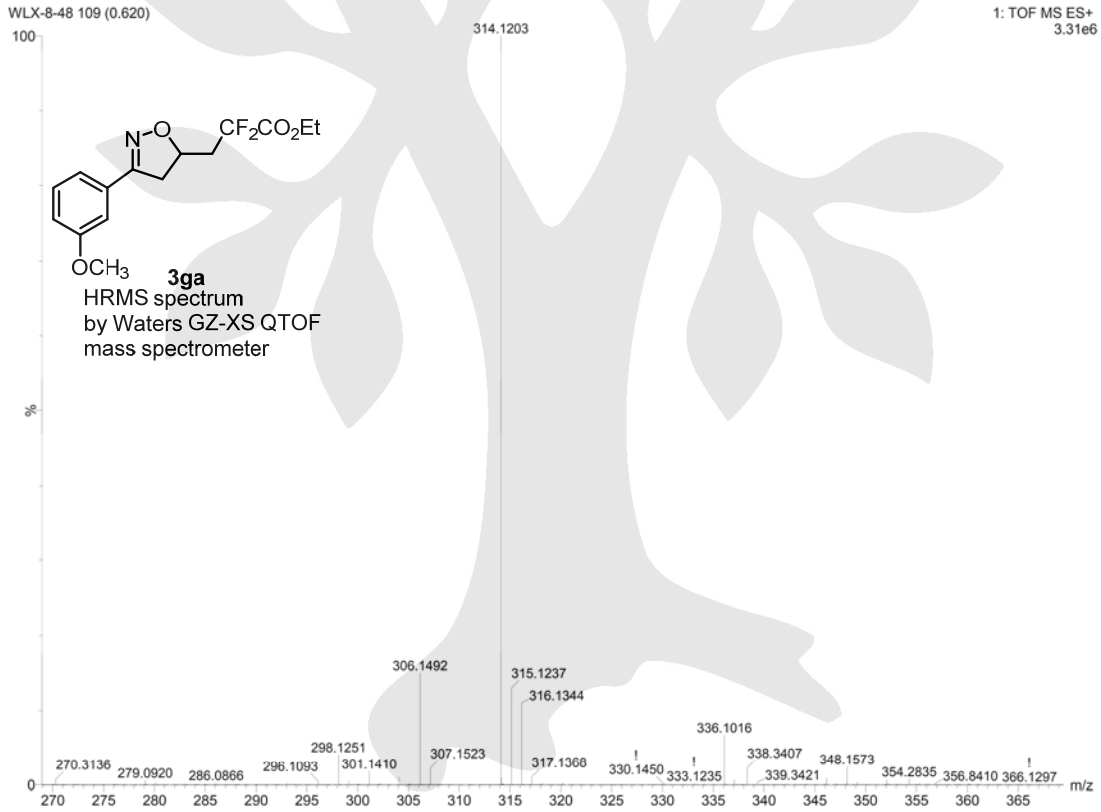


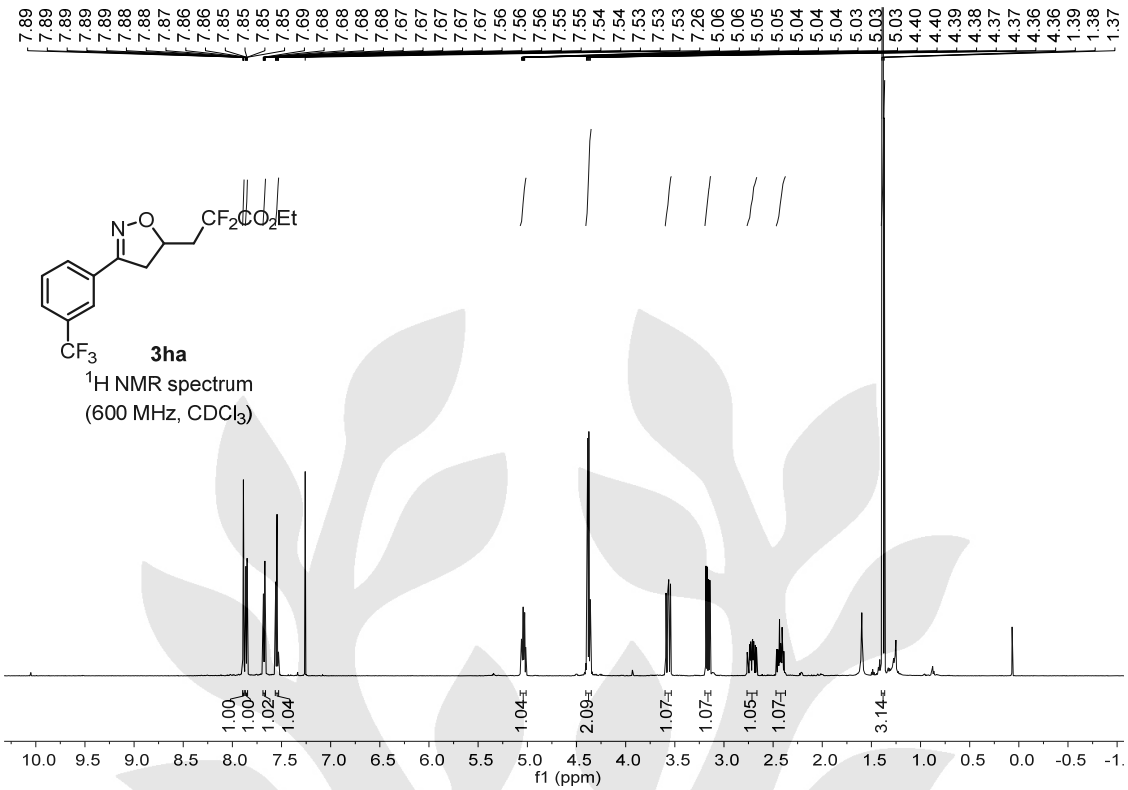


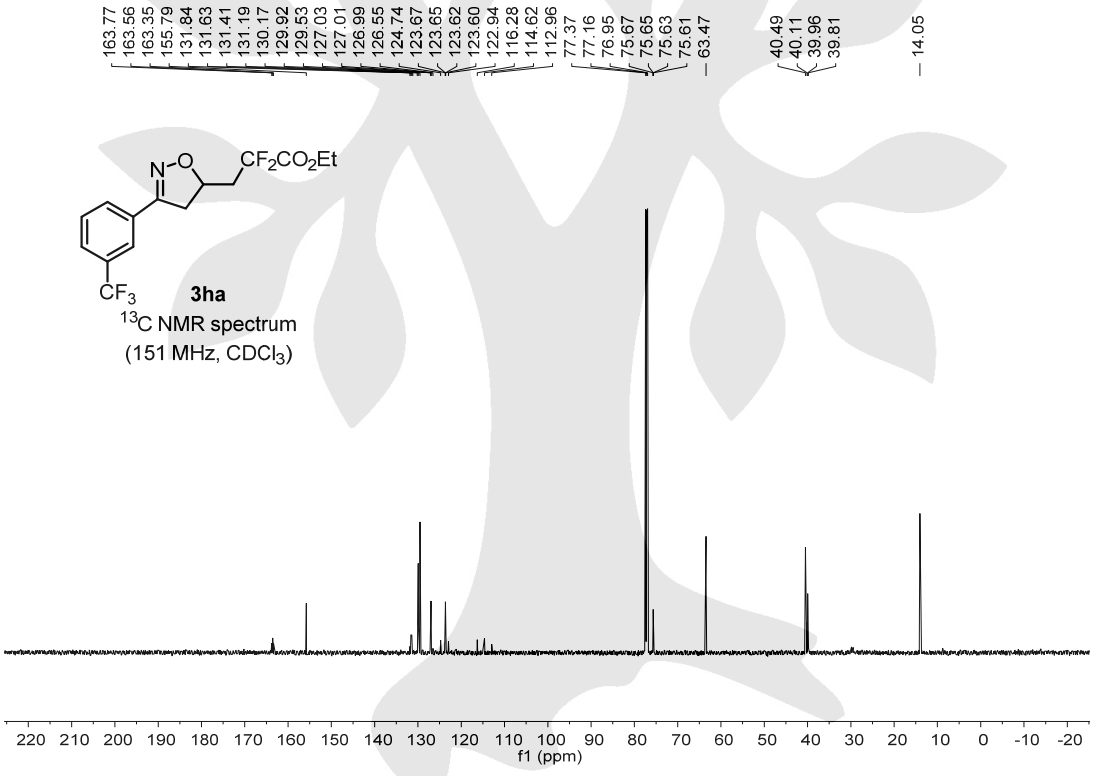


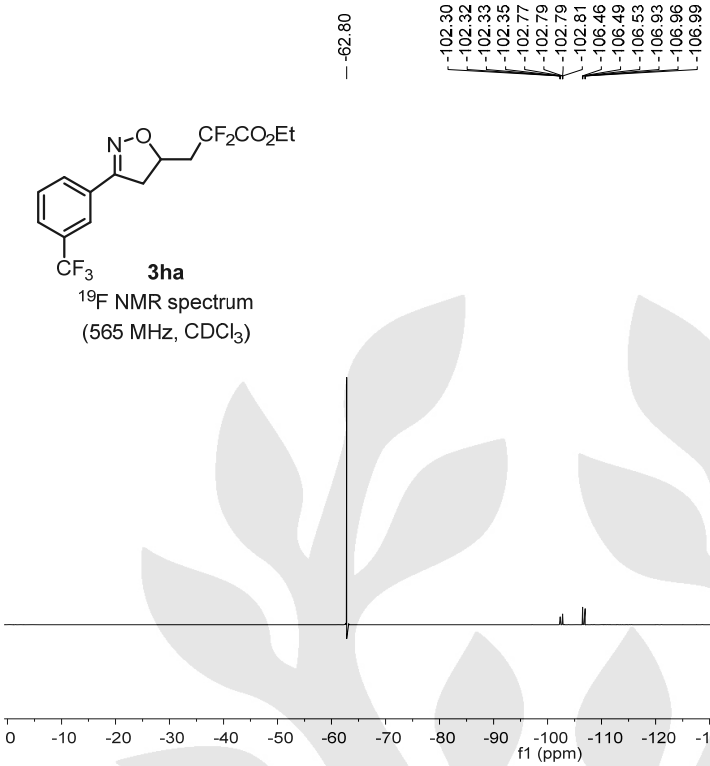


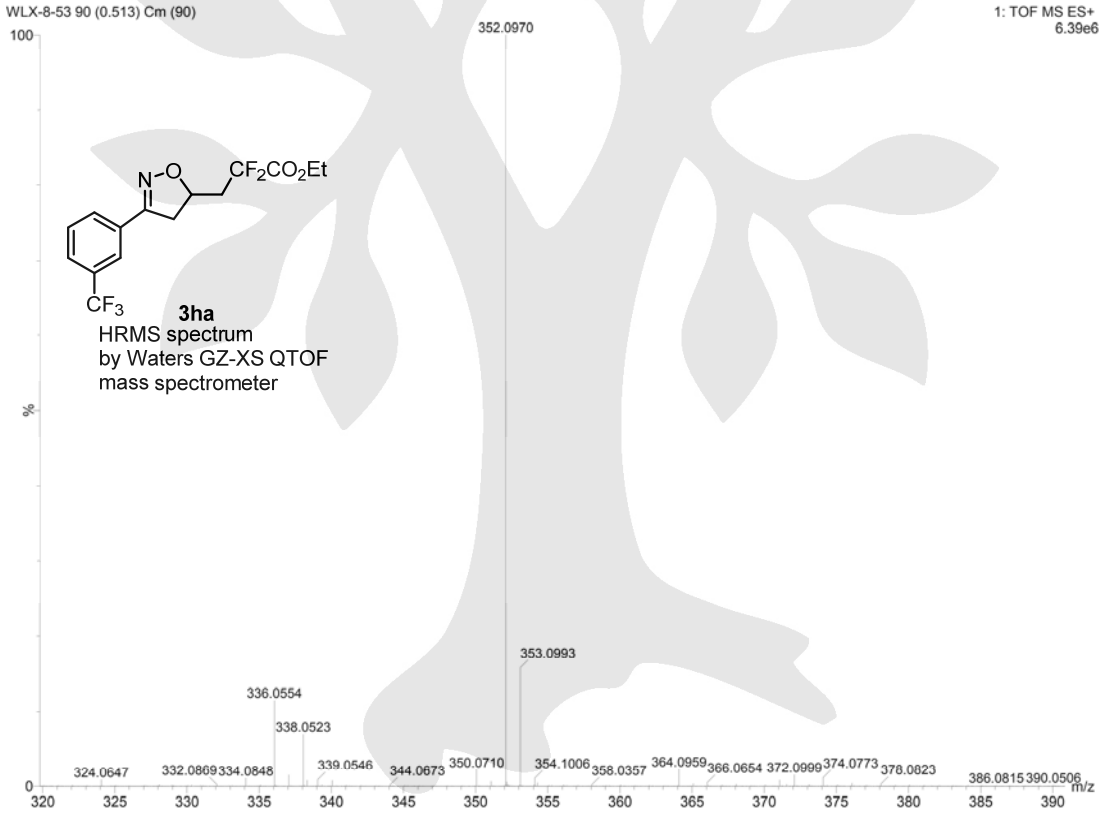


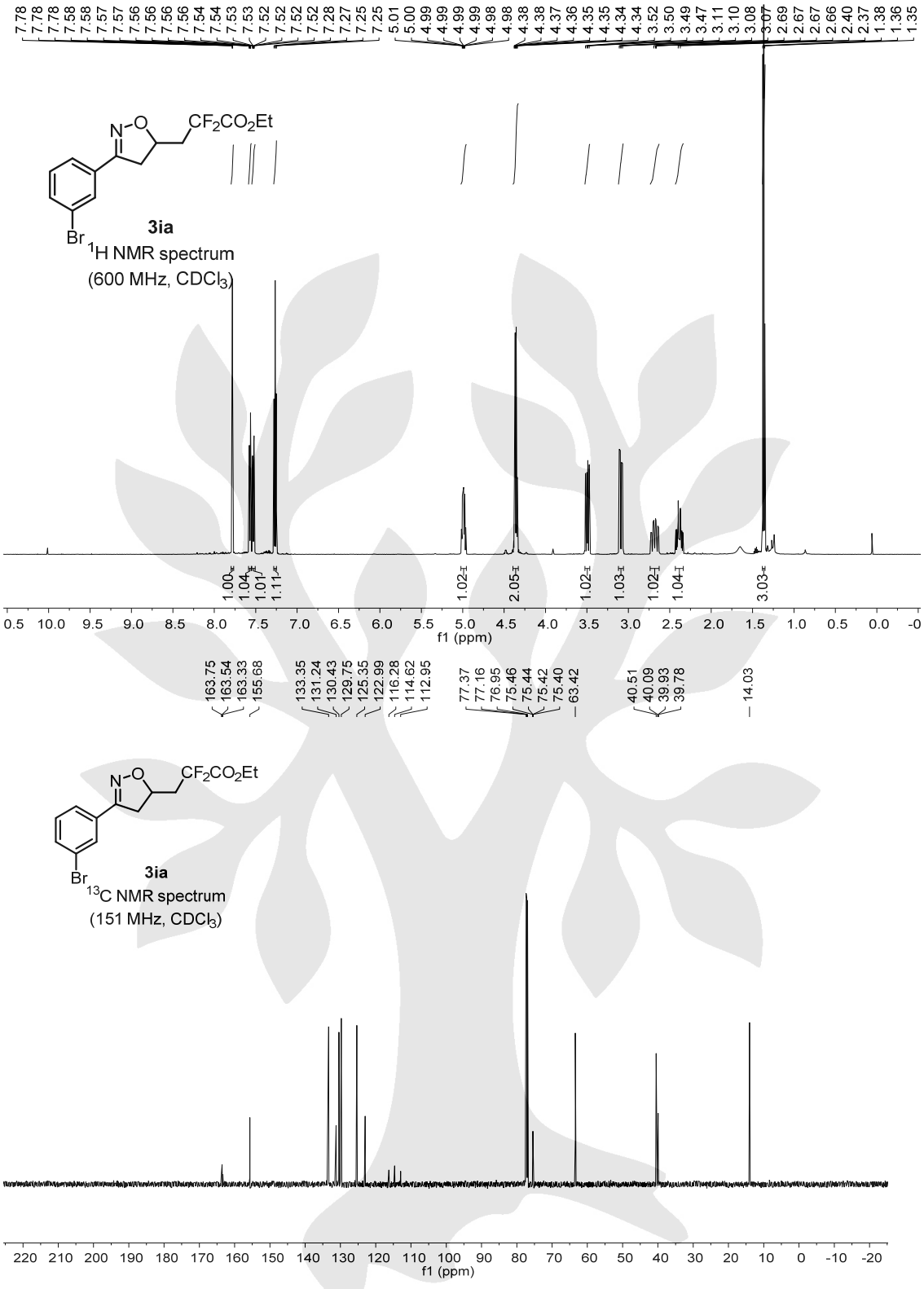


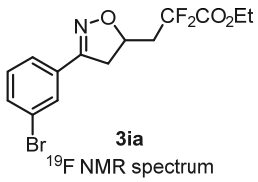






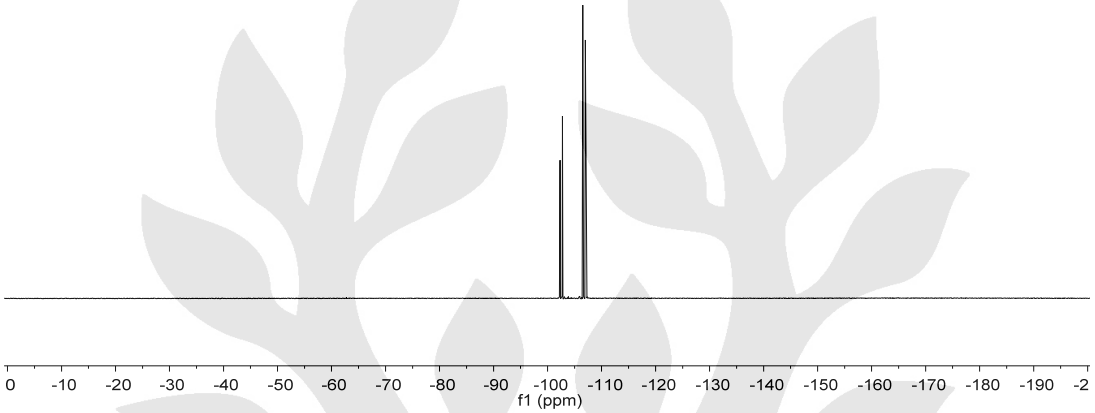


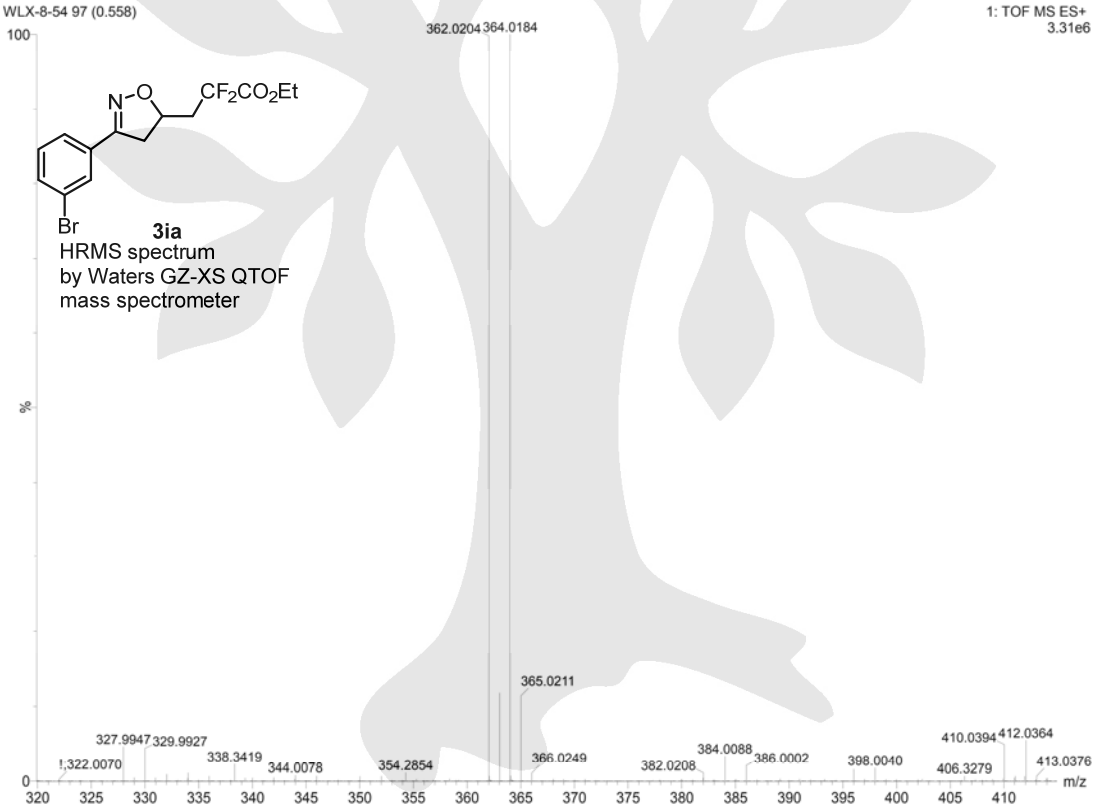




3ia

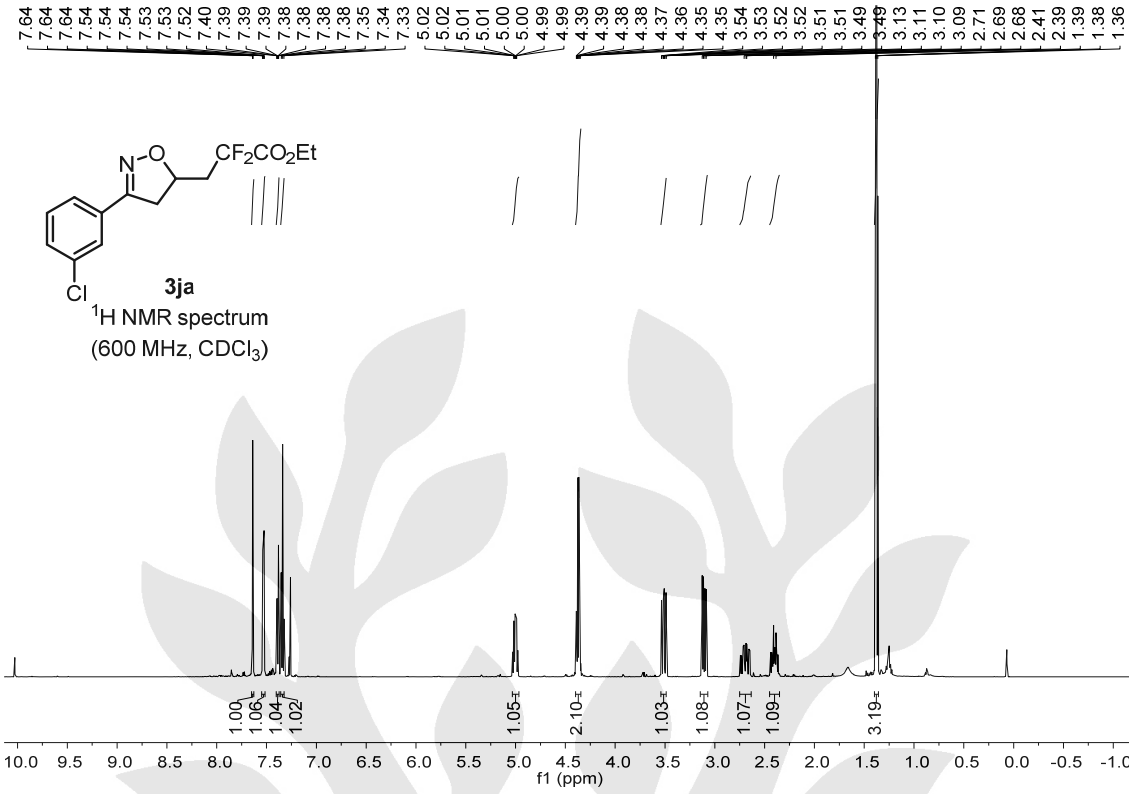
^{19}F NMR spectrum
(565 MHz, $CDCl_3$)

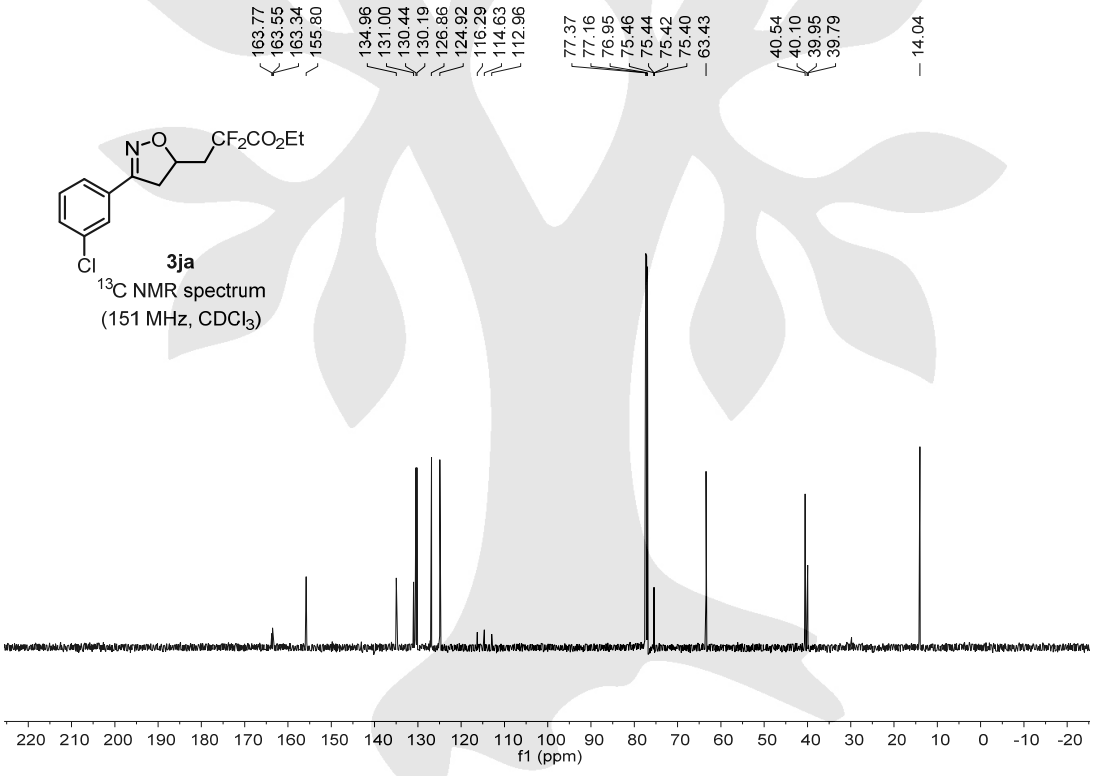


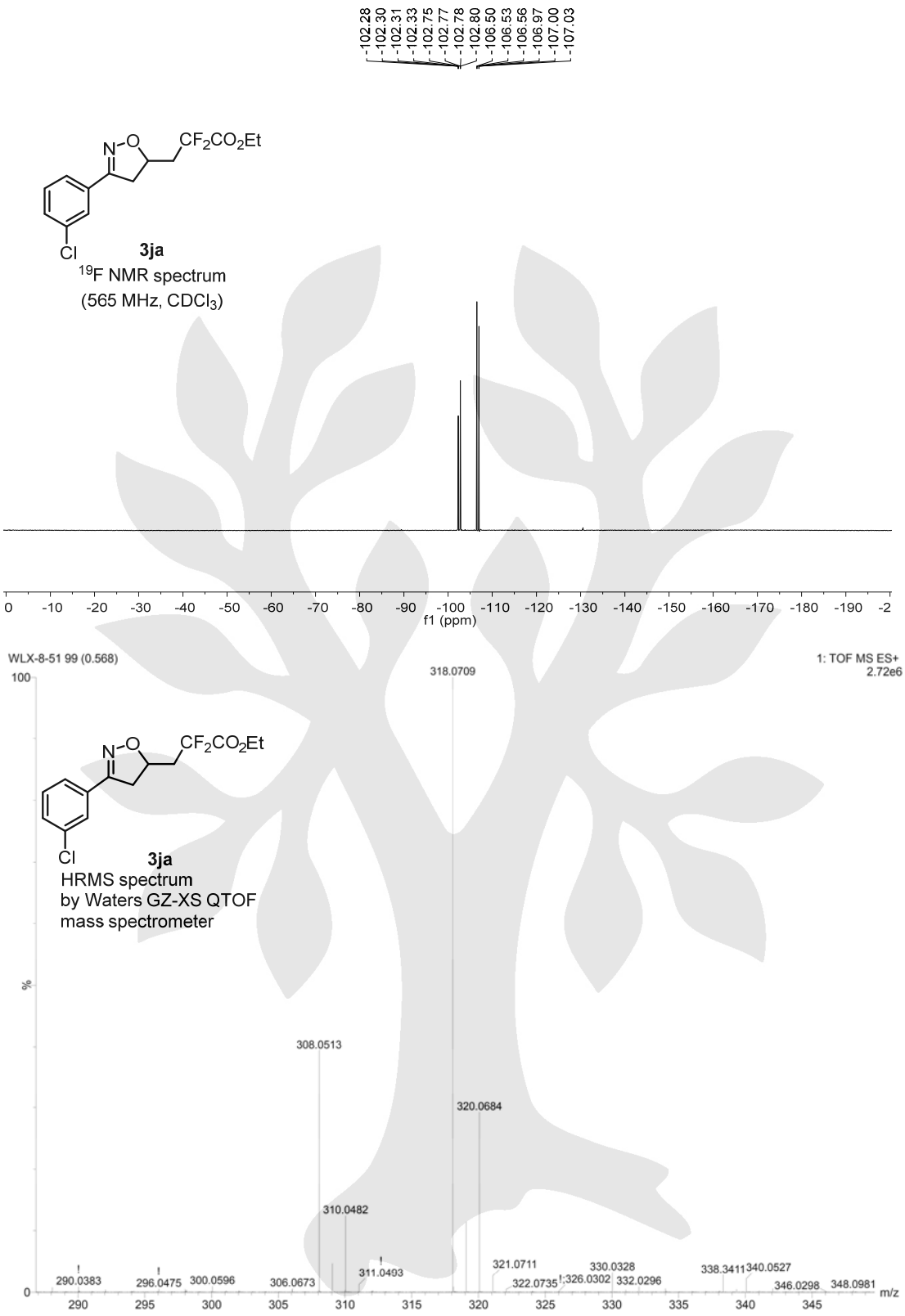


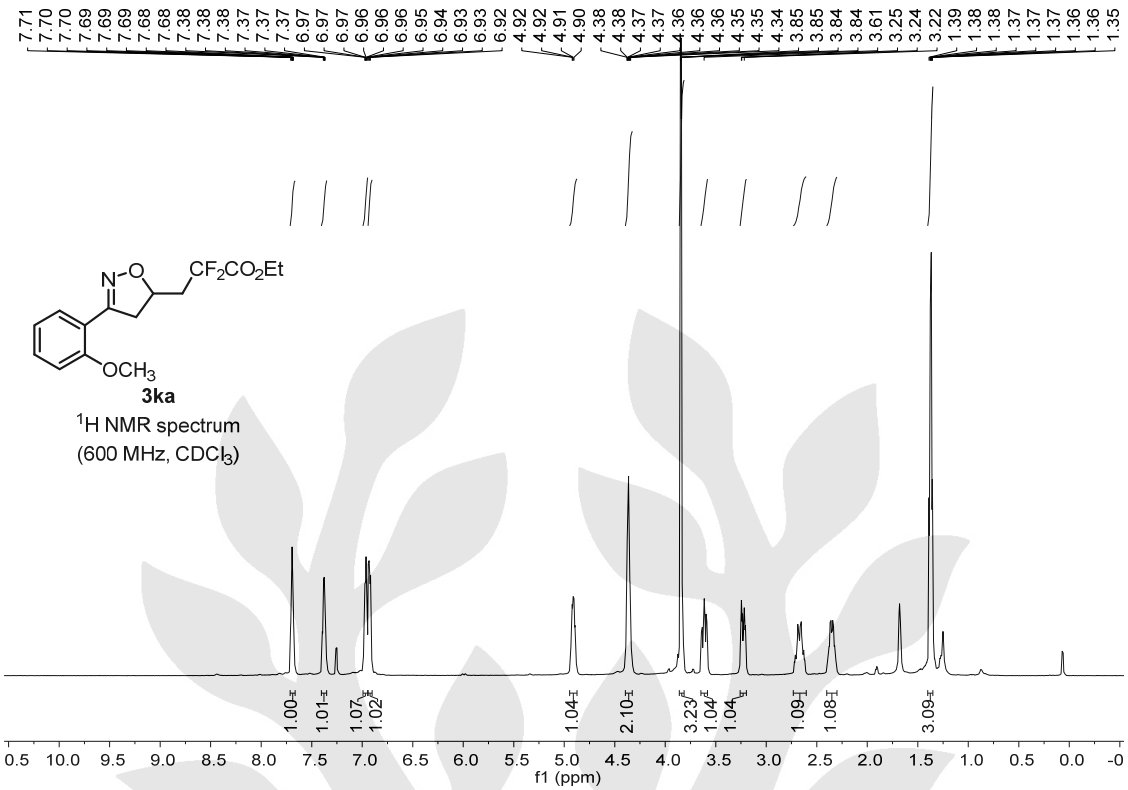
3ia

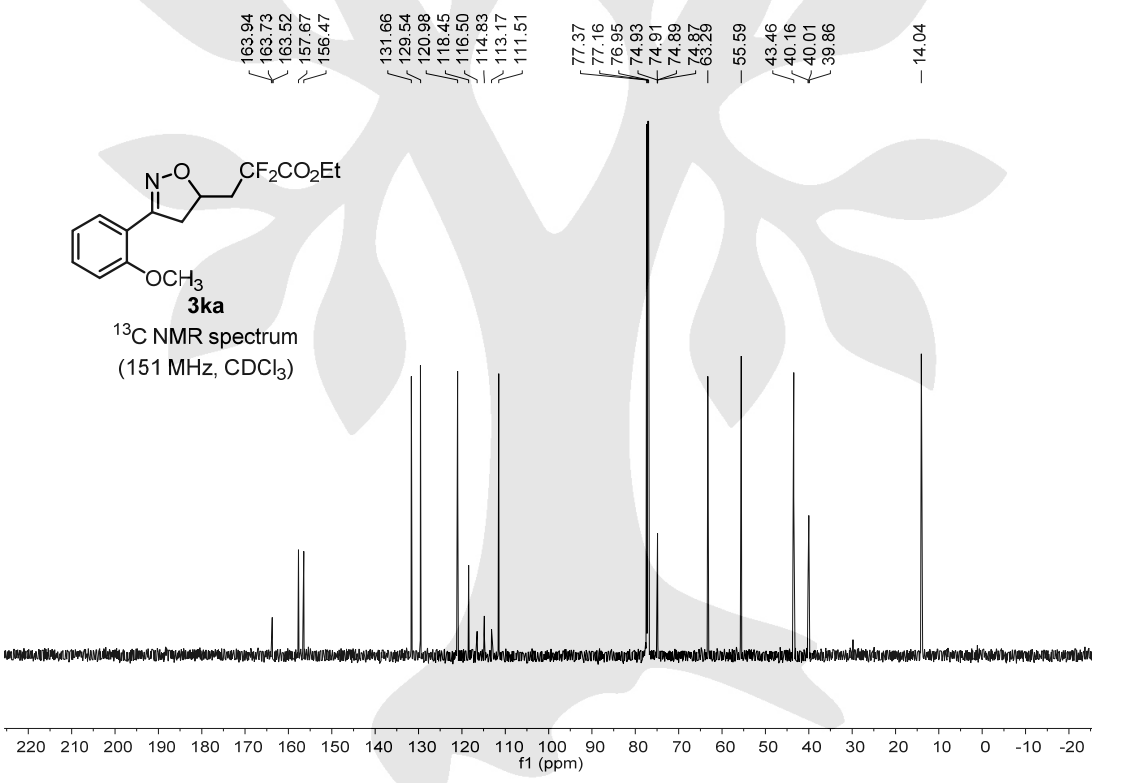
HRMS spectrum
by Waters GZ-XS QTOF
mass spectrometer











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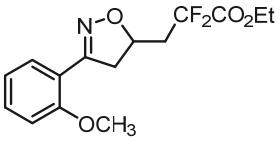
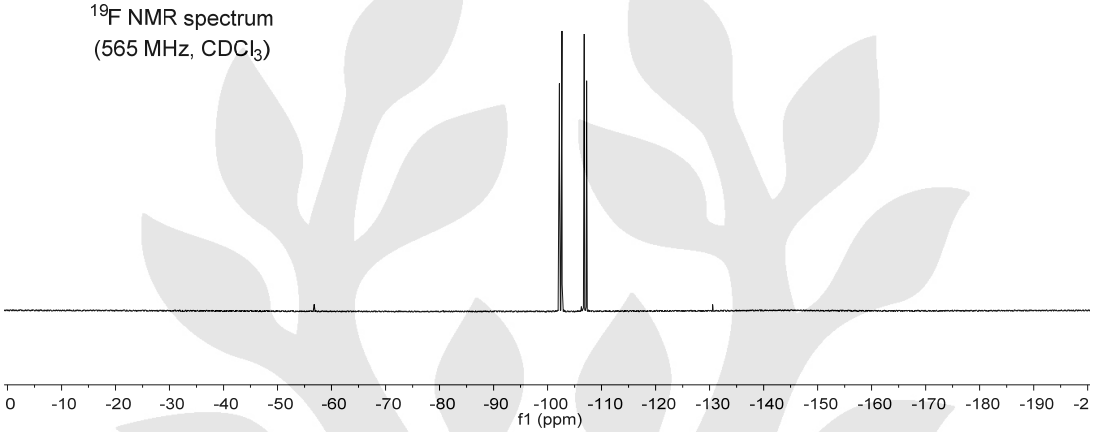
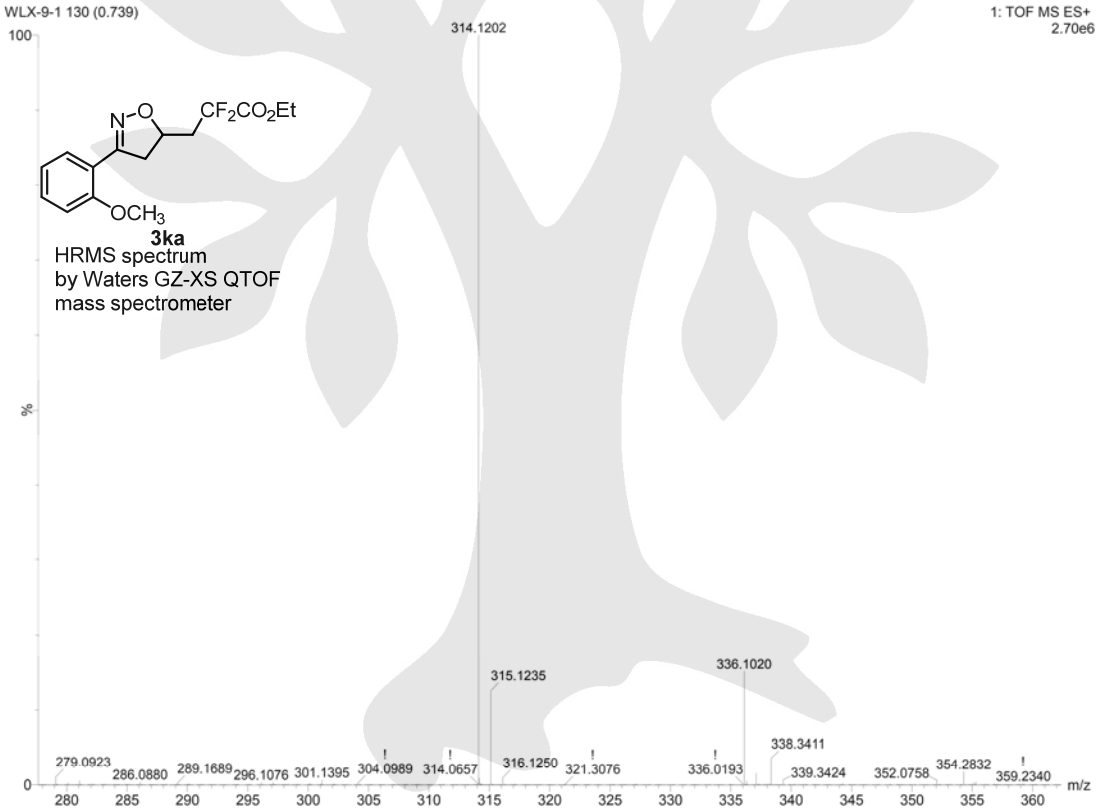


3ka

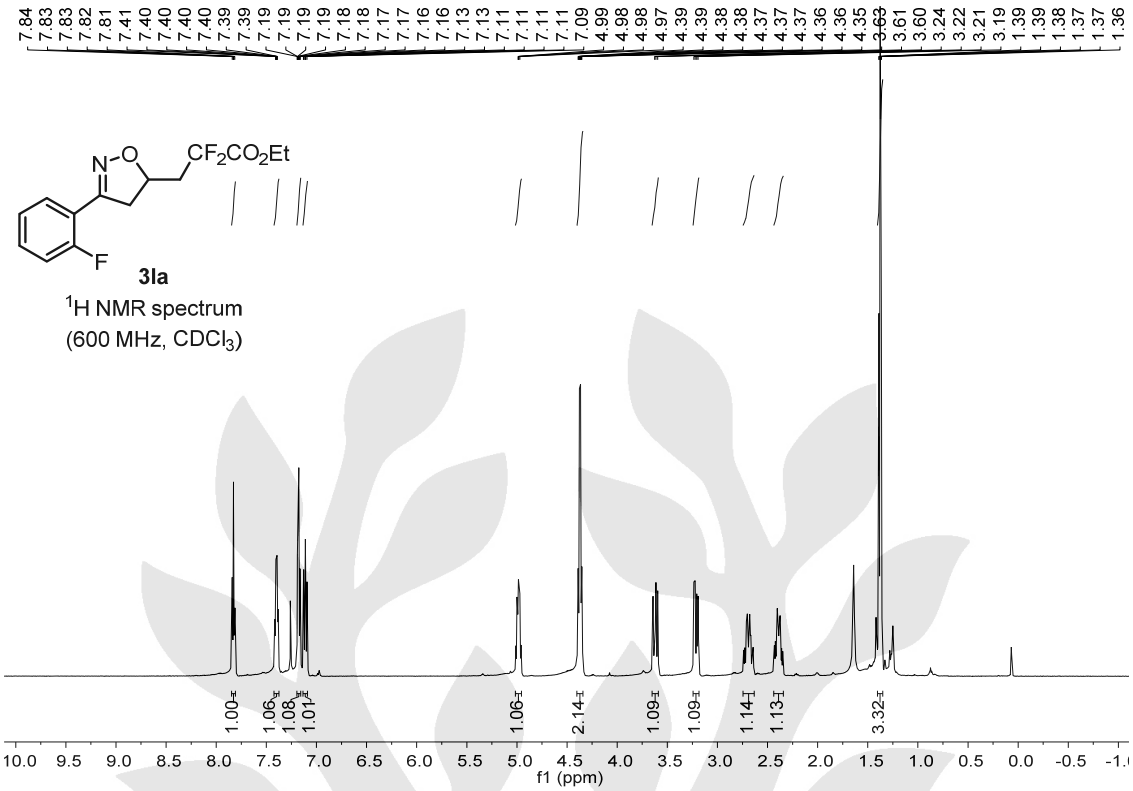
^{19}F NMR spectrum
(565 MHz, $CDCl_3$)

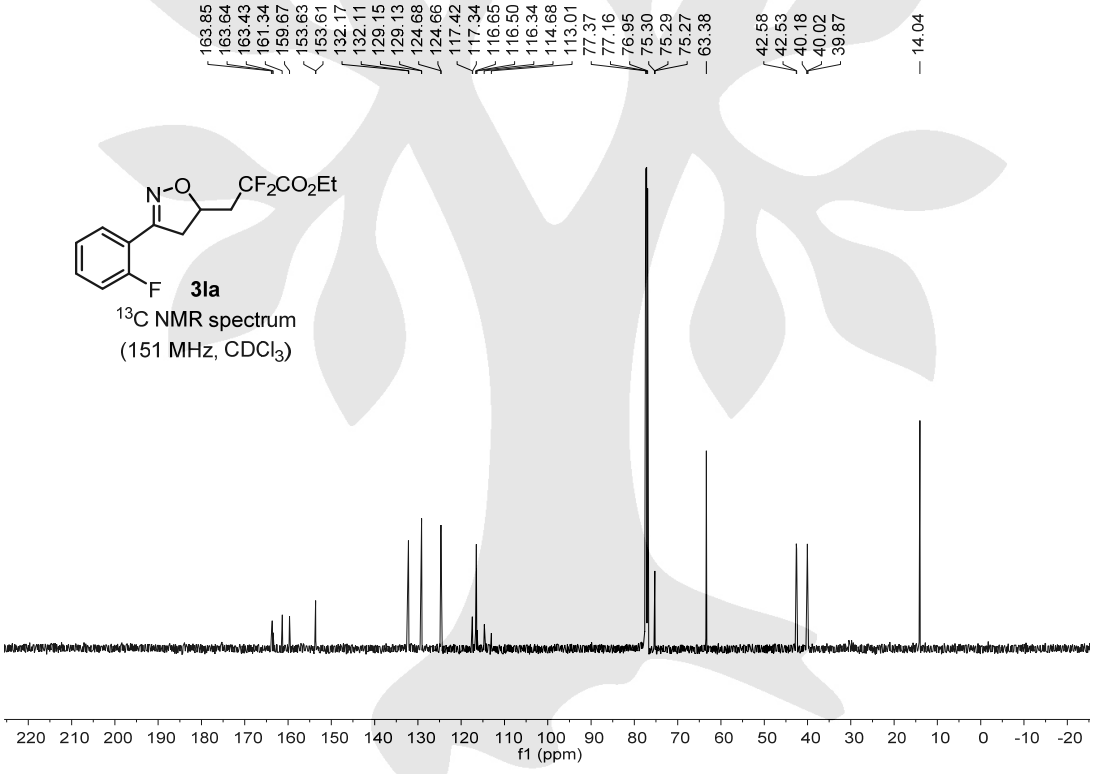


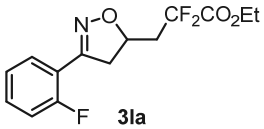


3ka

HRMS spectrum
by Waters GZ-XS QTOF
mass spectrometer

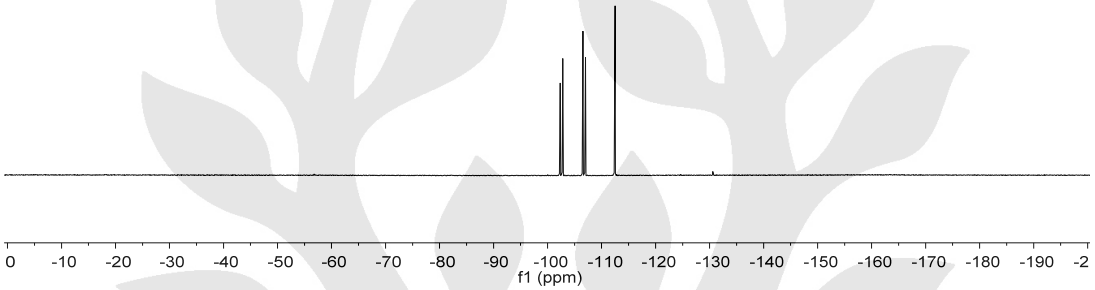


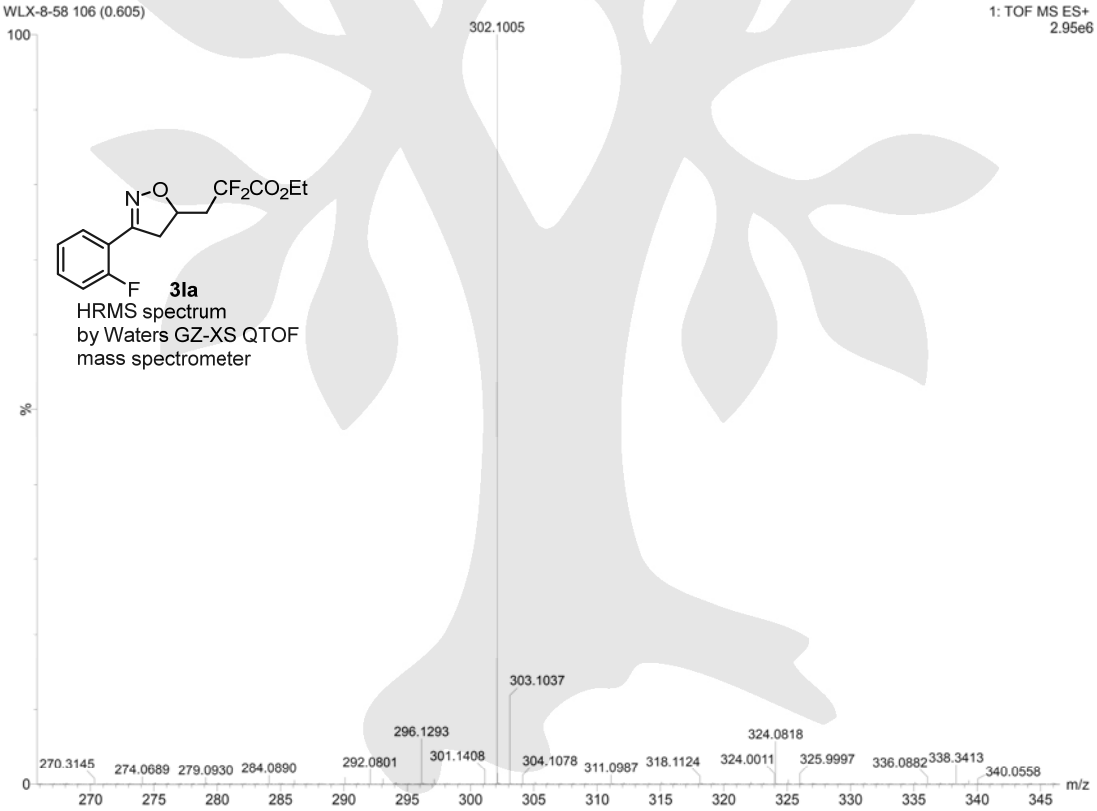




3la

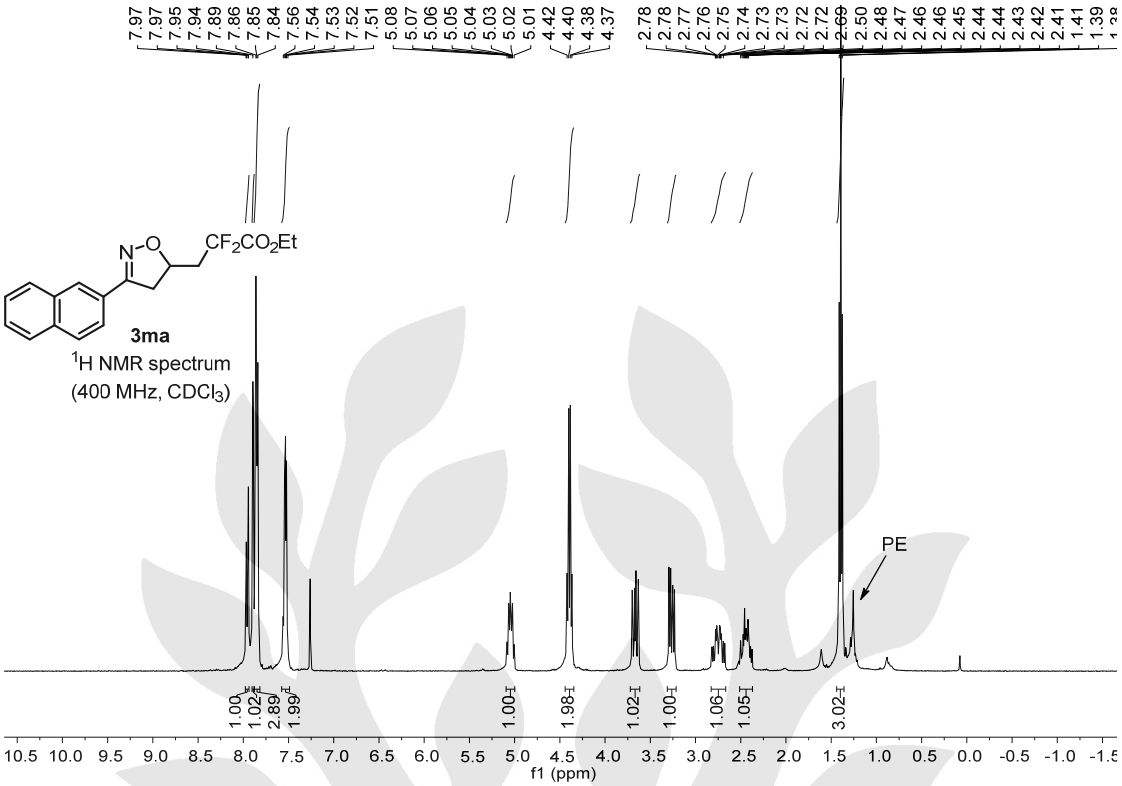
^{19}F NMR spectrum
(565 MHz, $CDCl_3$)

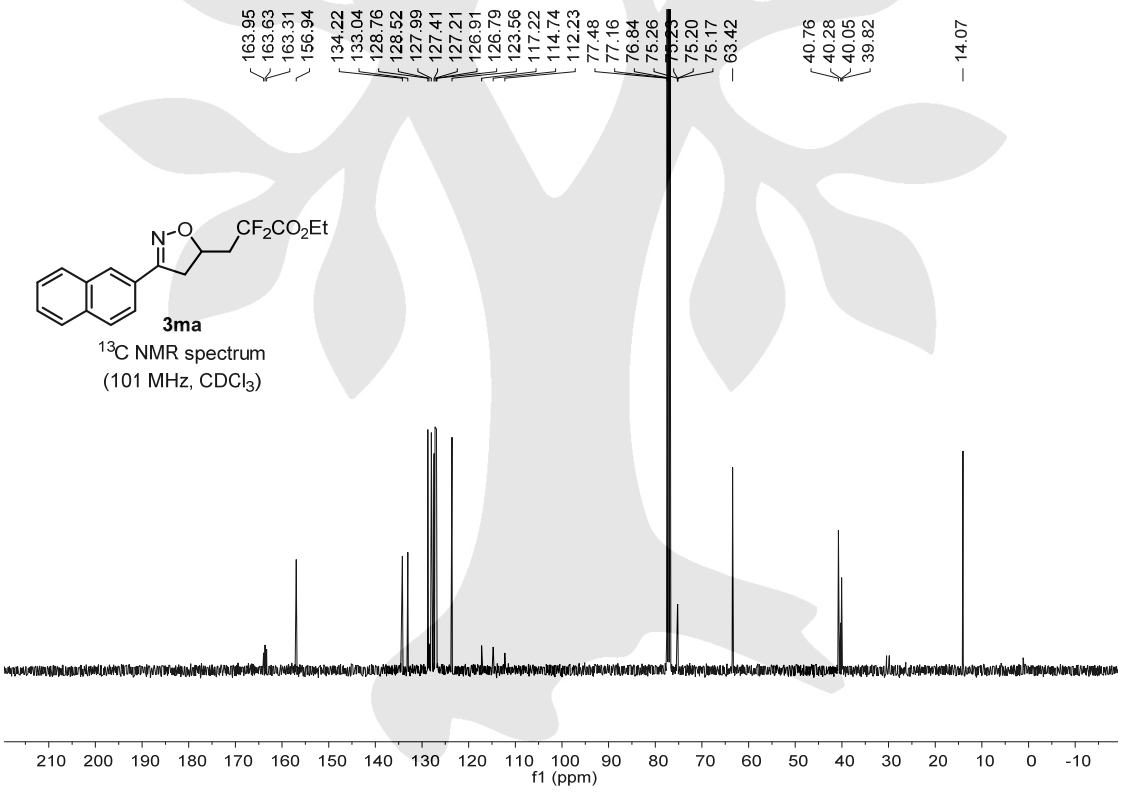


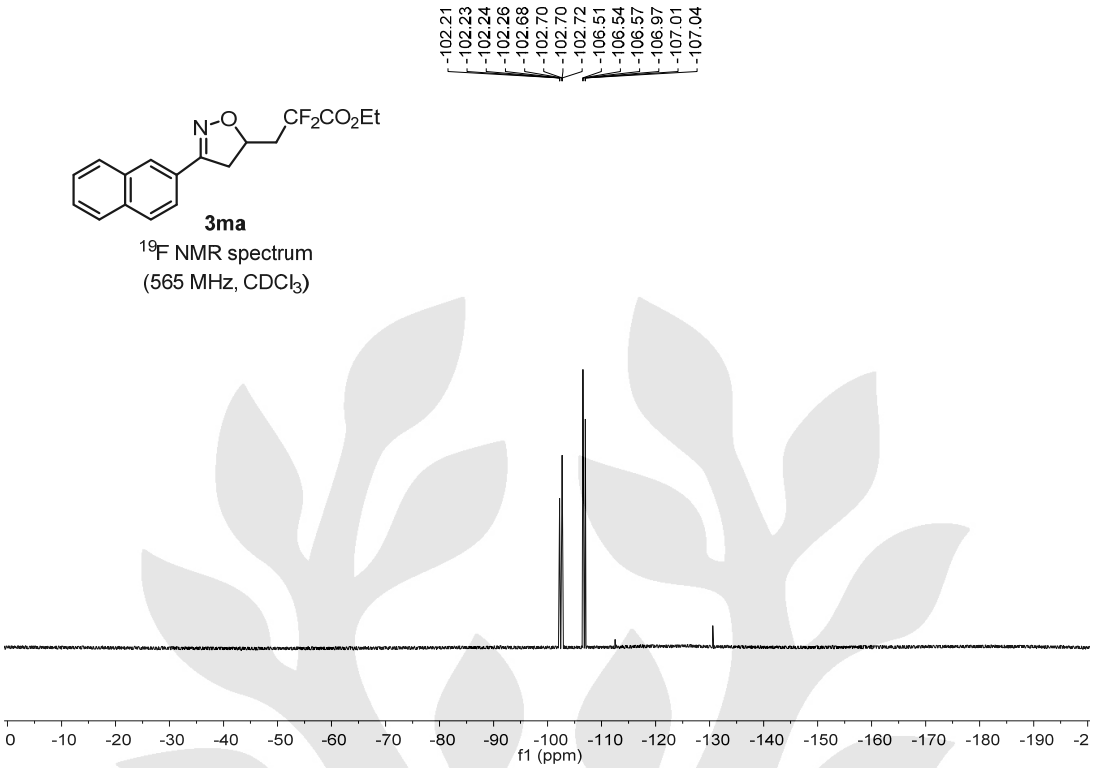


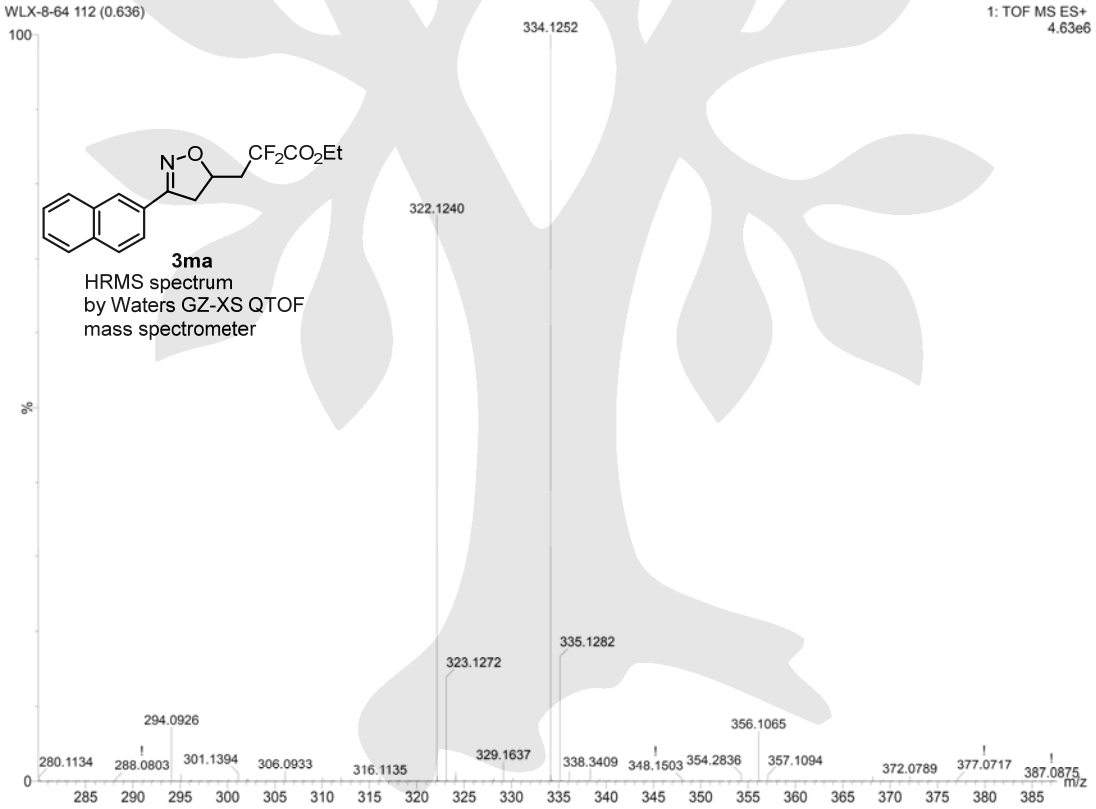
3la

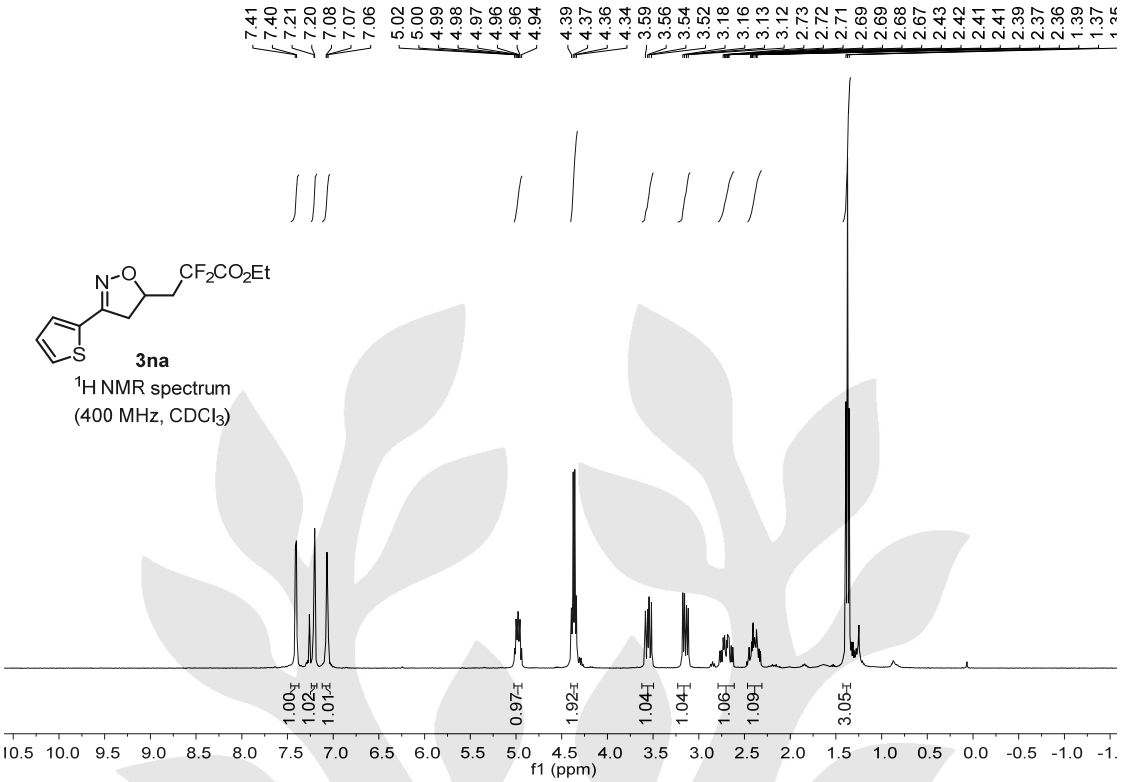
HRMS spectrum
by Waters GZ-XS QTOF
mass spectrometer

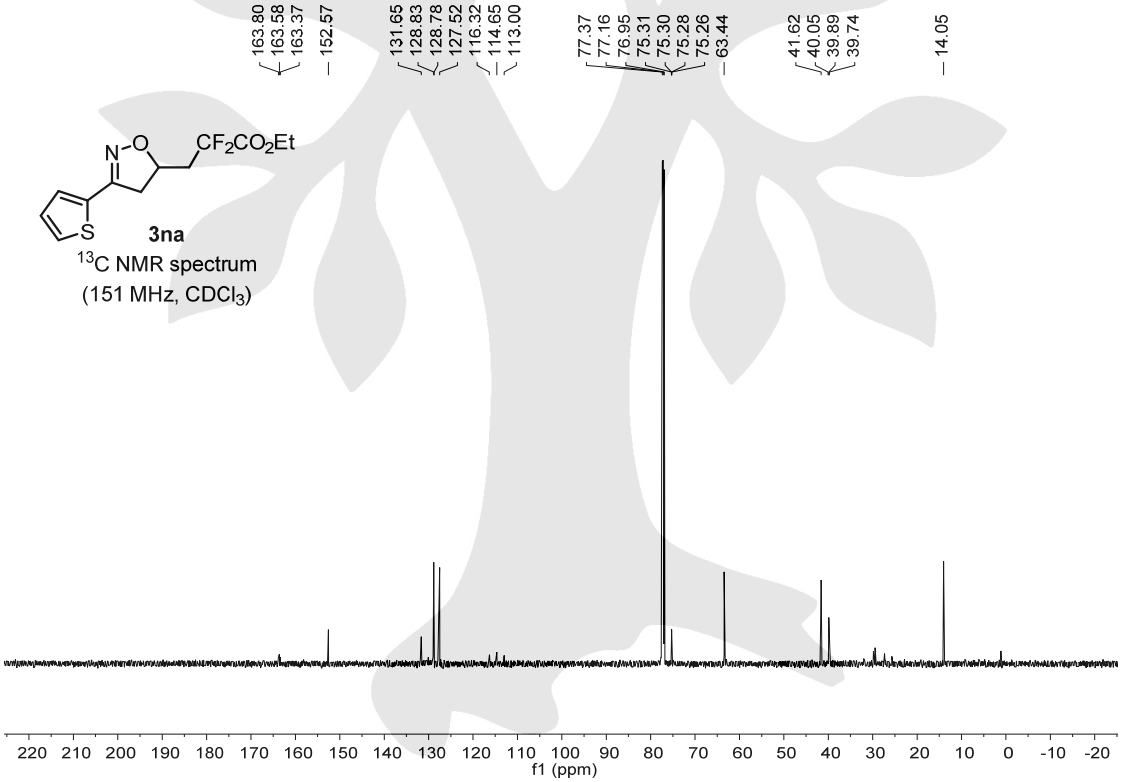


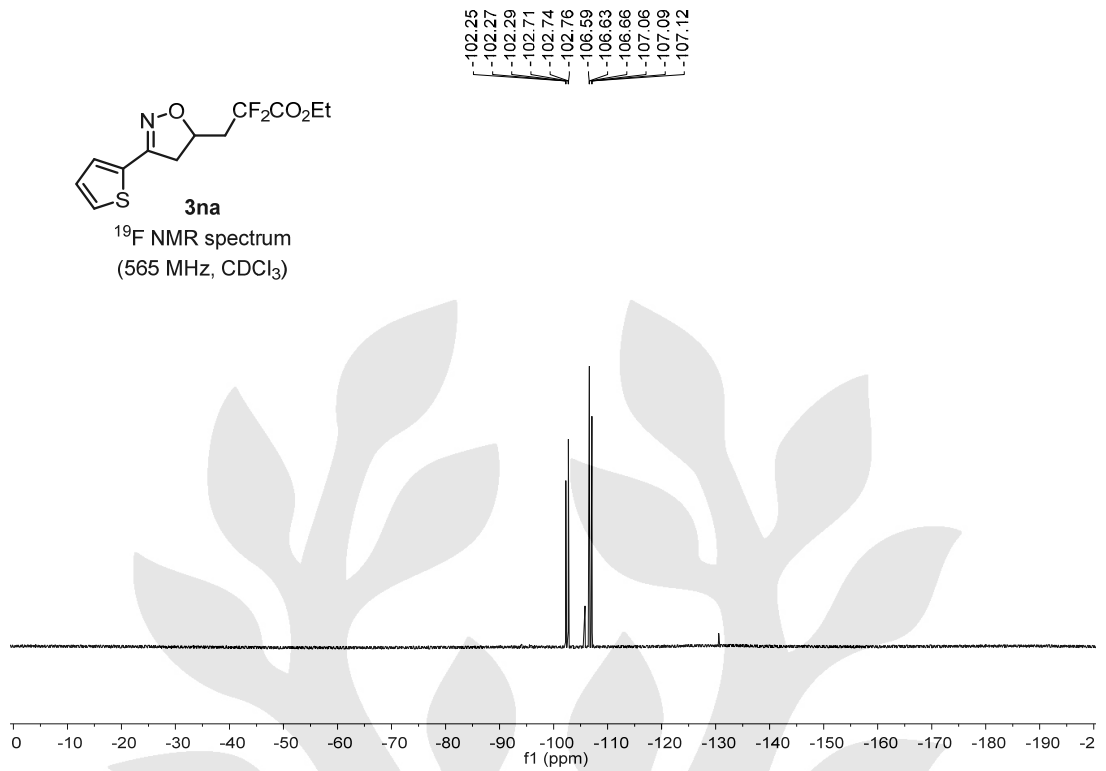


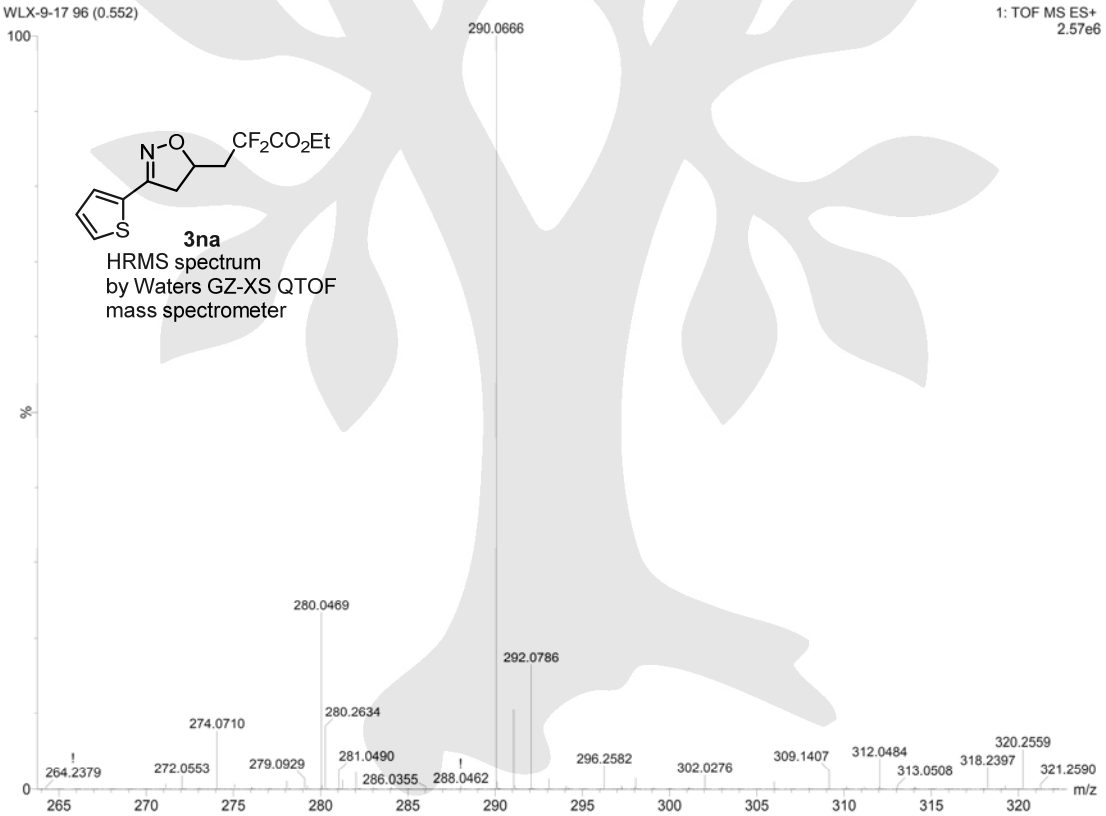


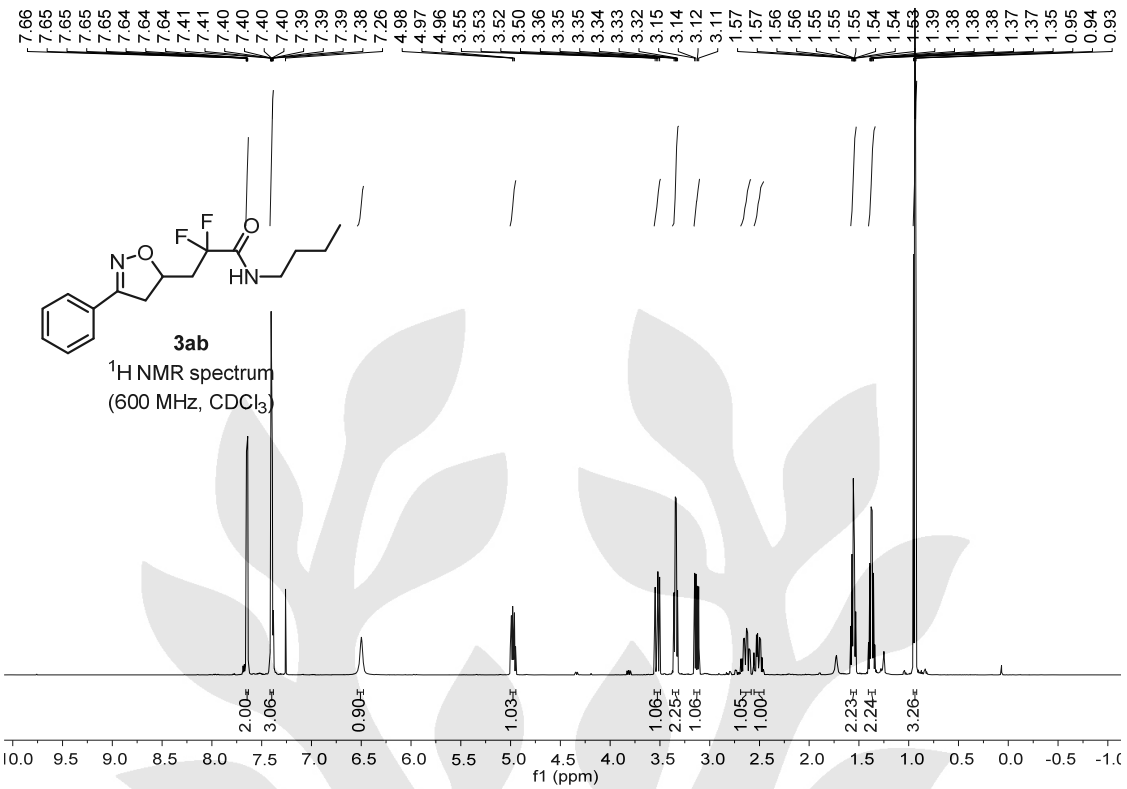


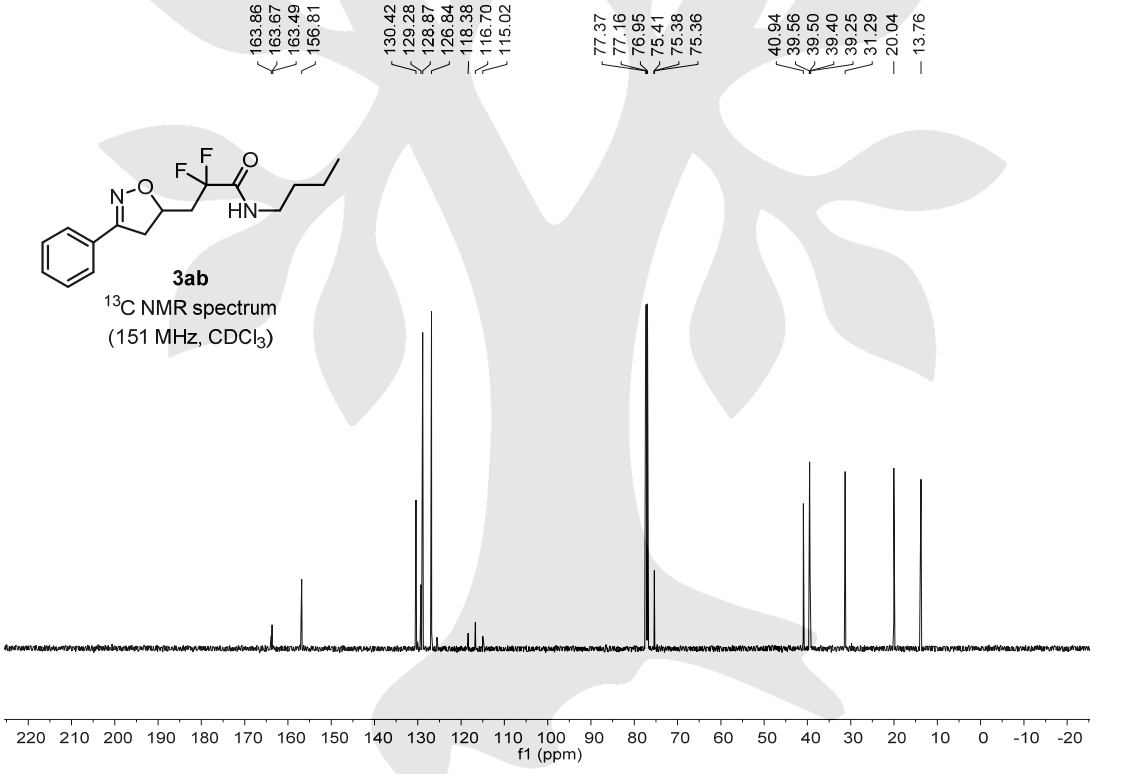


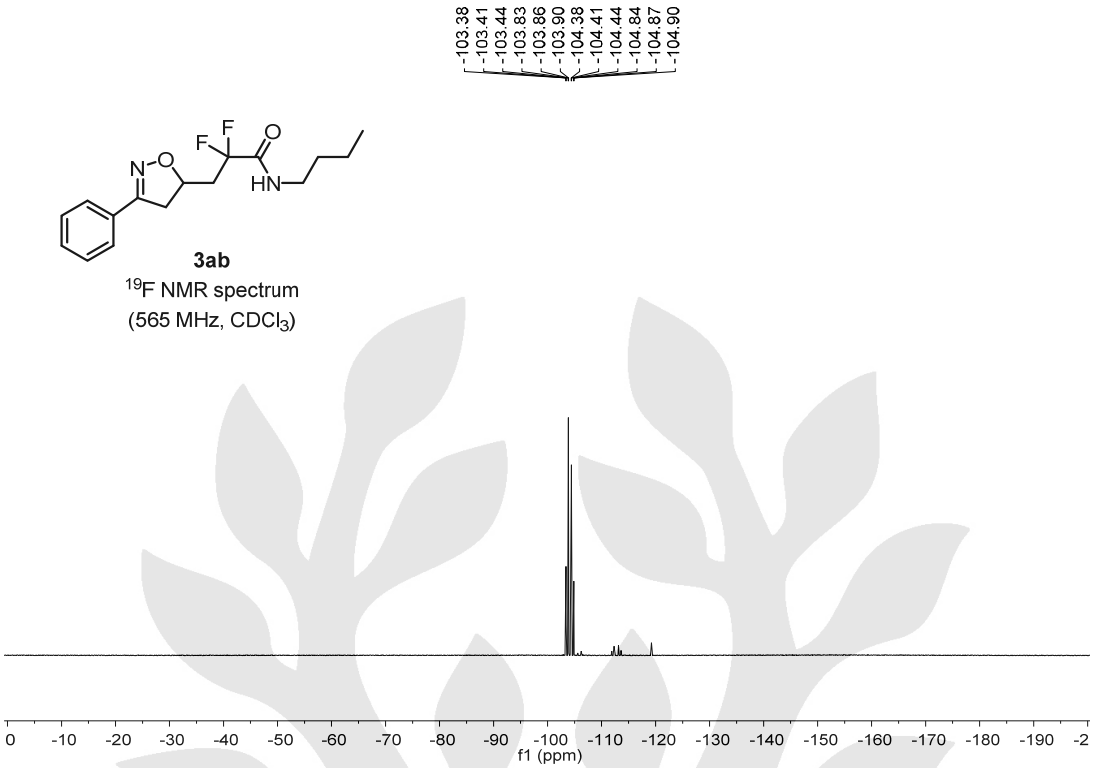








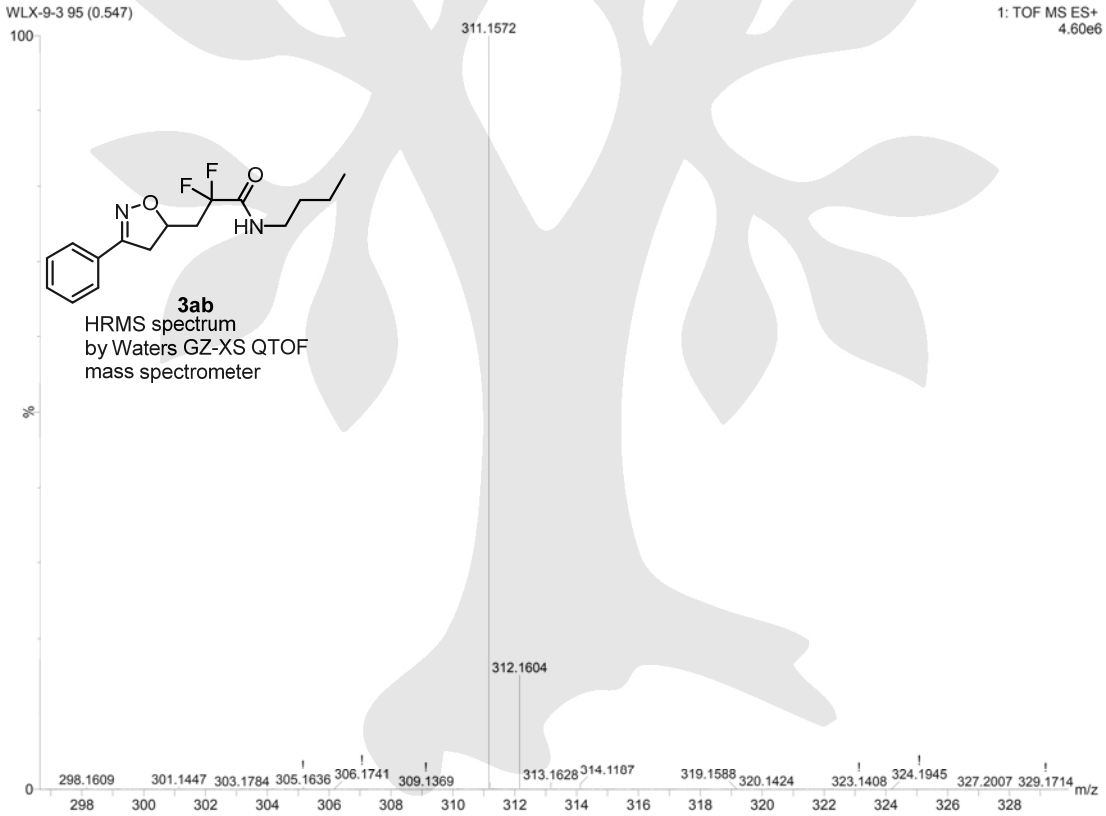




3ab

^{19}F NMR spectrum

(565 MHz, $CDCl_3$)

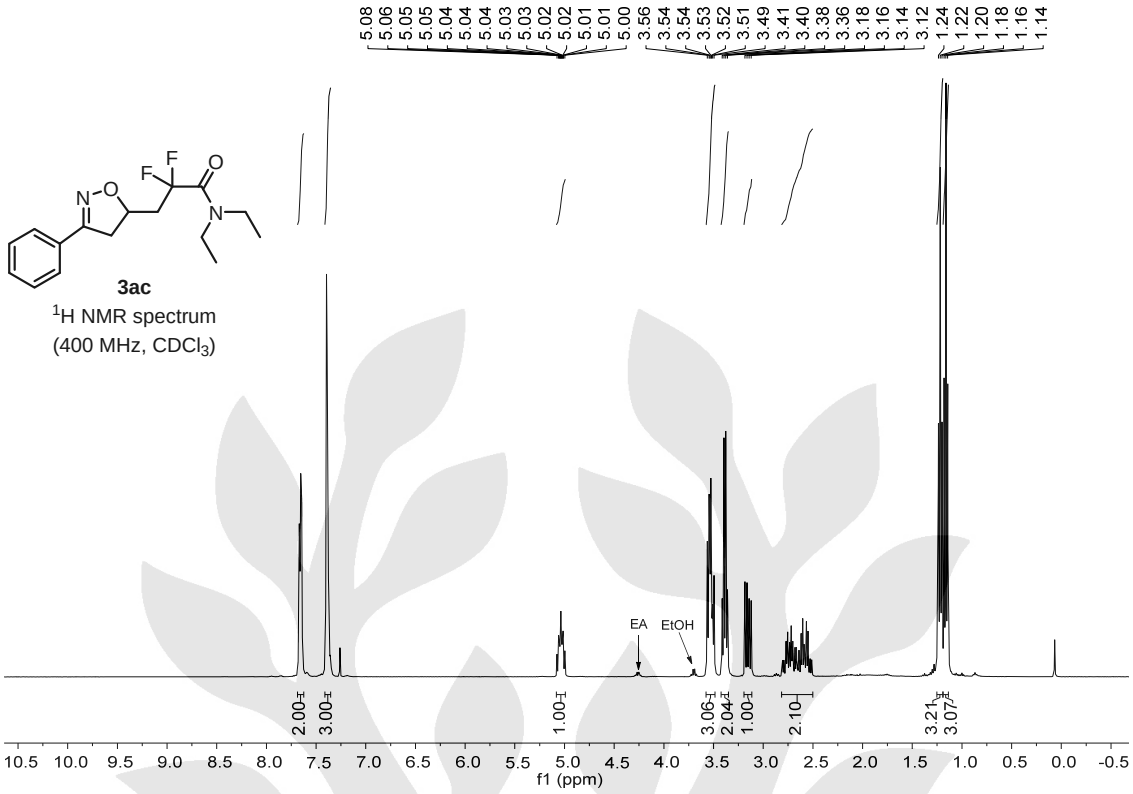


3ab

HRMS spectrum

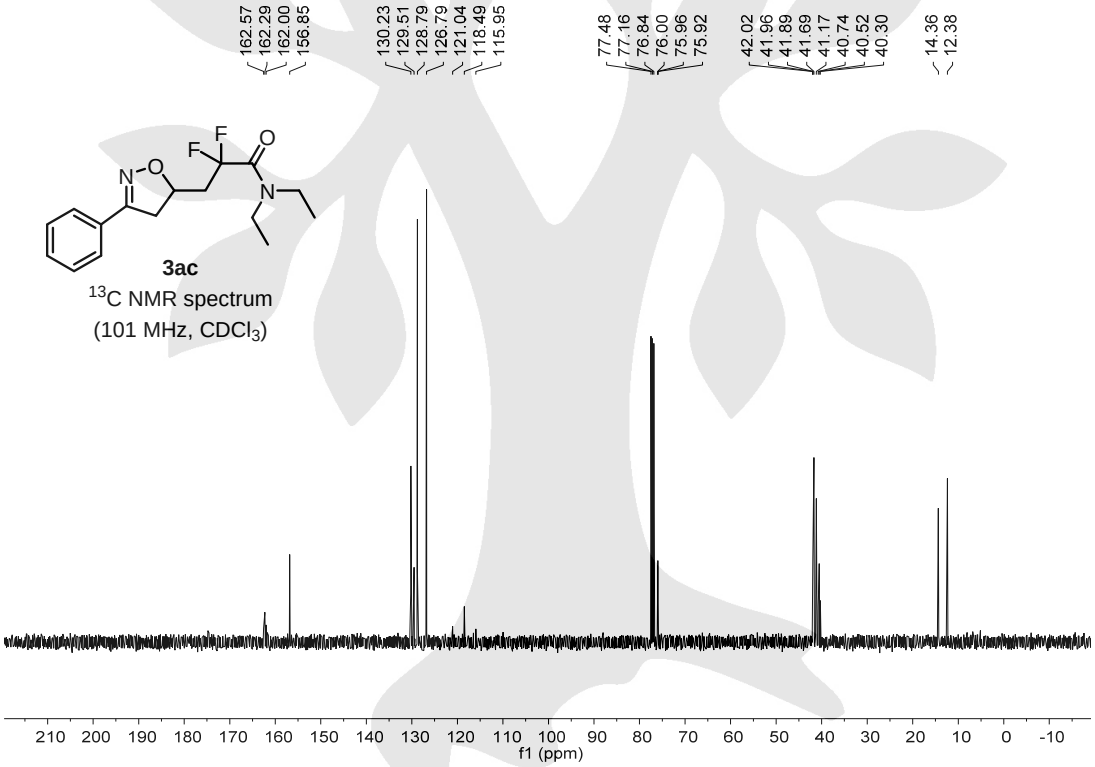
by Waters GZ-XS QTOF

mass spectrometer



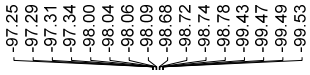
3ac

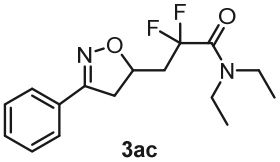
^{1}H NMR spectrum
(400 MHz, $CDCl_3$)



3ac

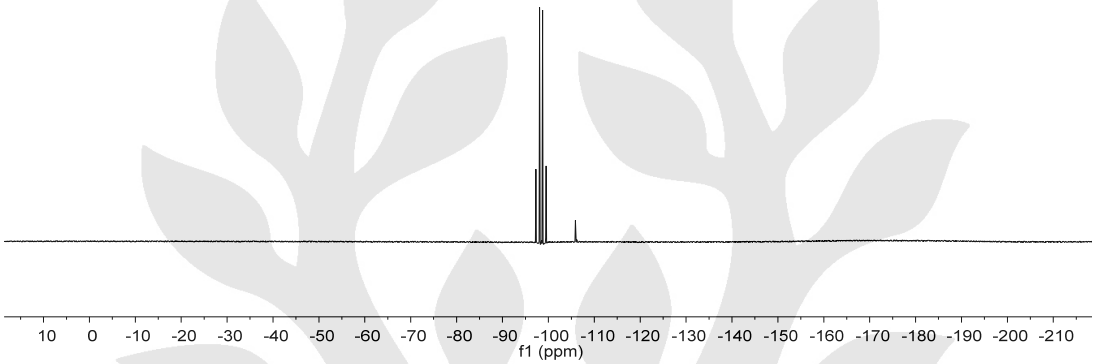
^{13}C NMR spectrum
(101 MHz, $CDCl_3$)

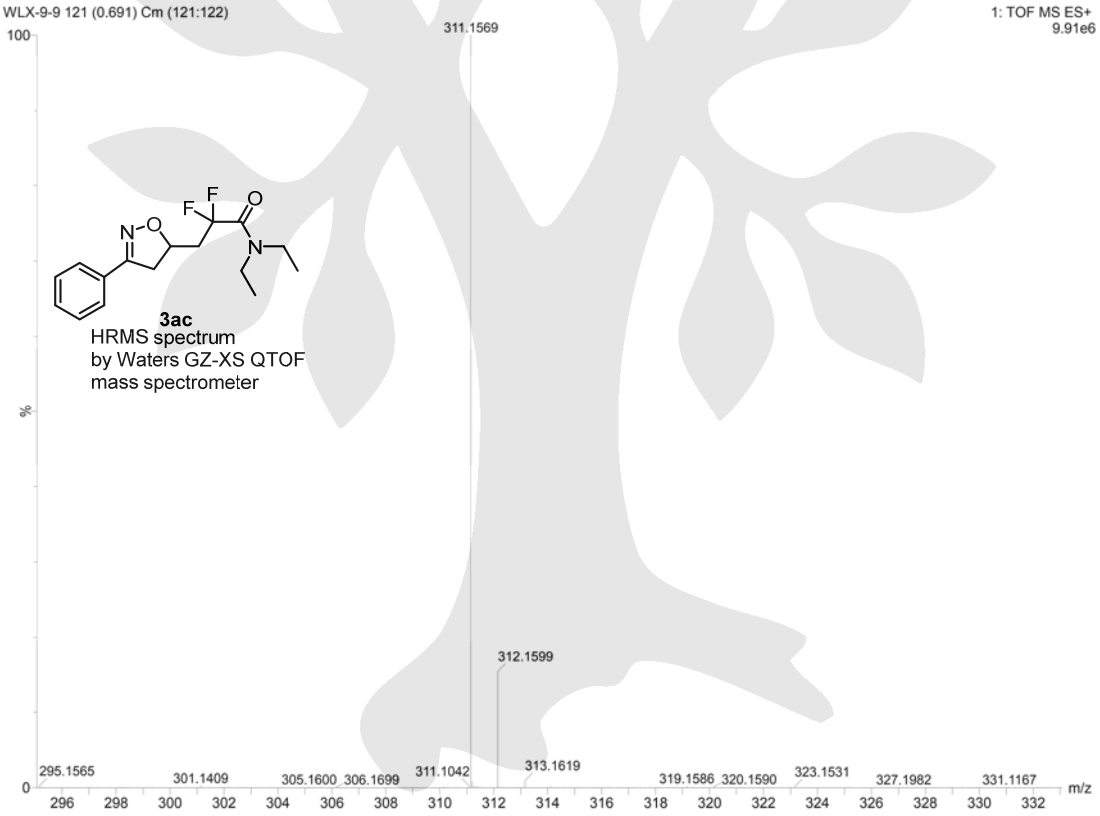




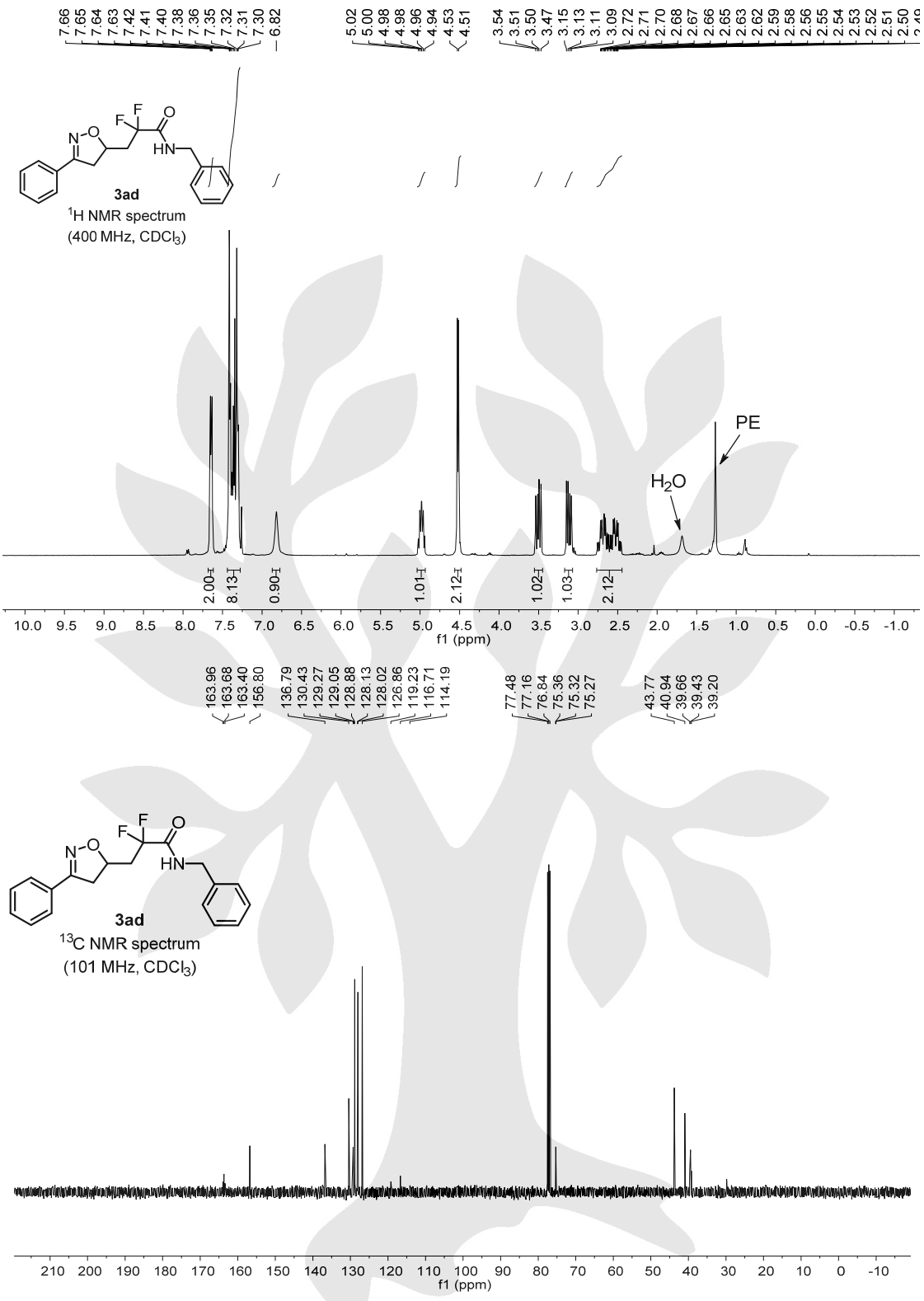
3ac

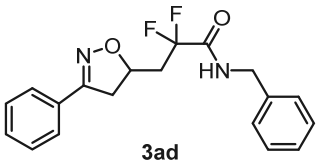
^{19}F NMR spectrum
(376 MHz, $CDCl_3$)





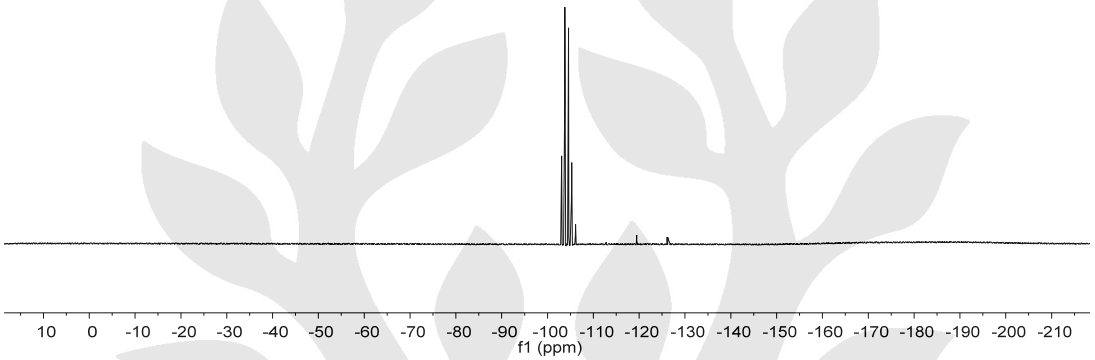
3ac
HRMS spectrum
by Waters GZ-XS QTOF
mass spectrometer

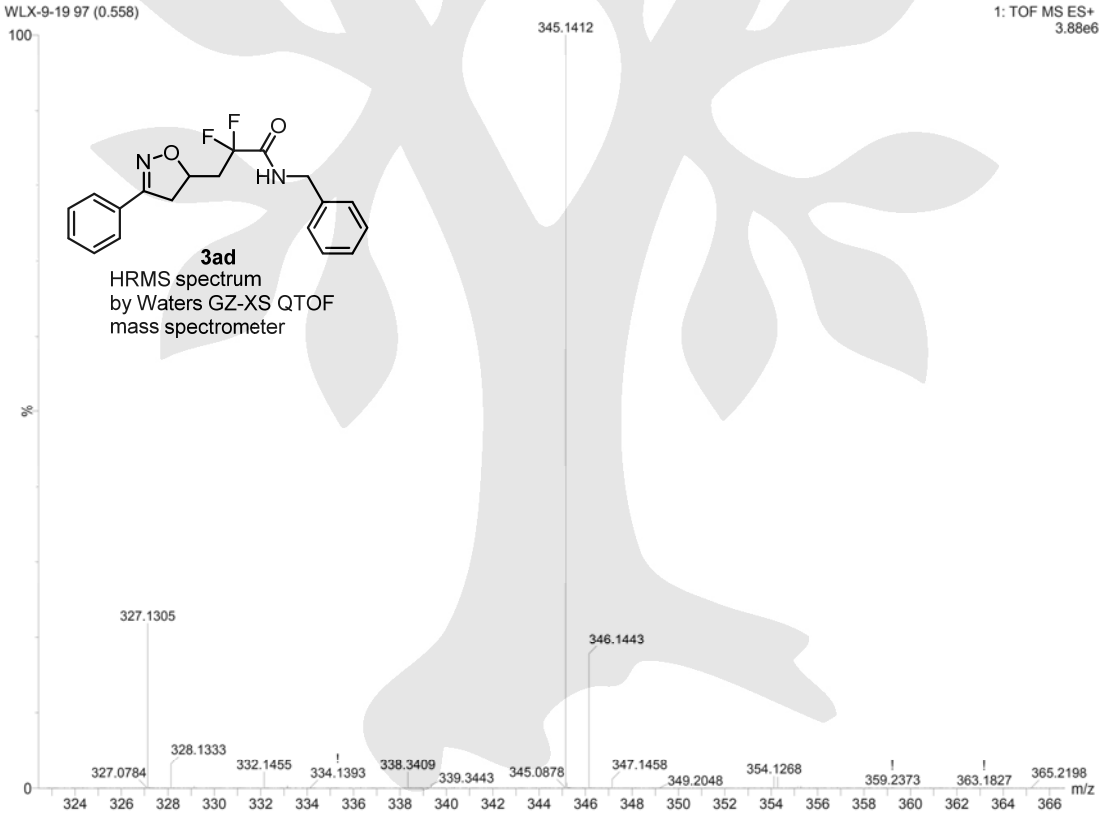




3ad

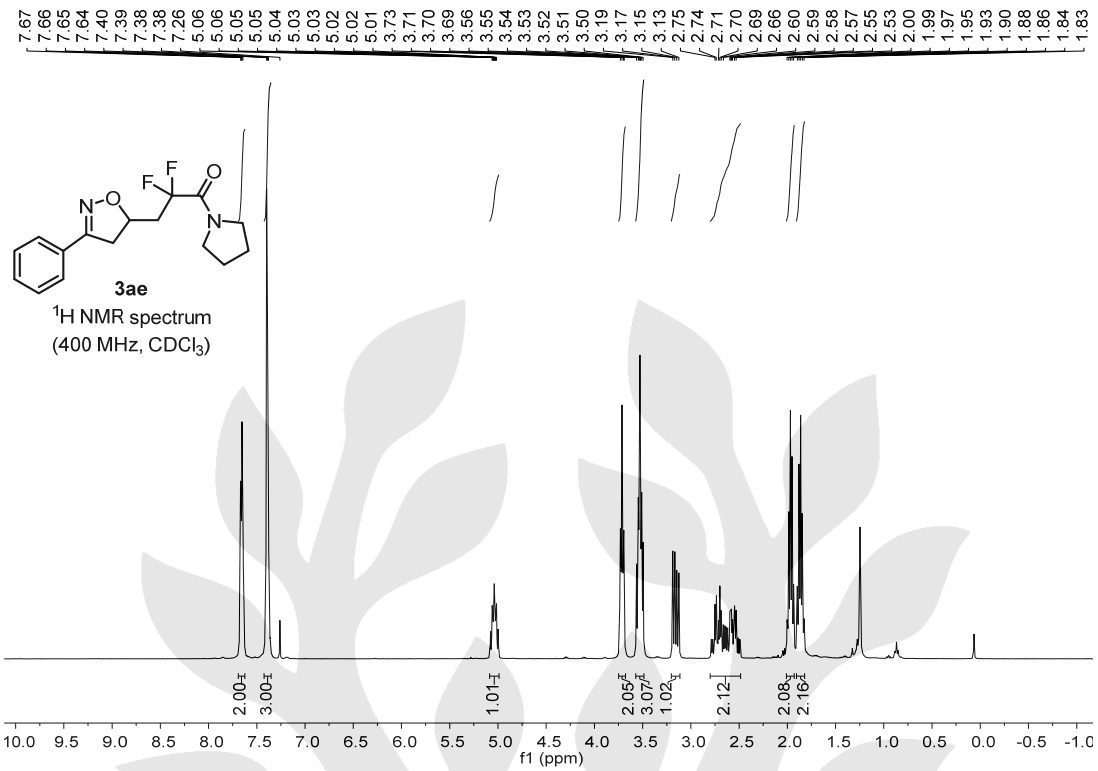
^{19}F NMR spectrum
(376 MHz, $CDCl_3$)



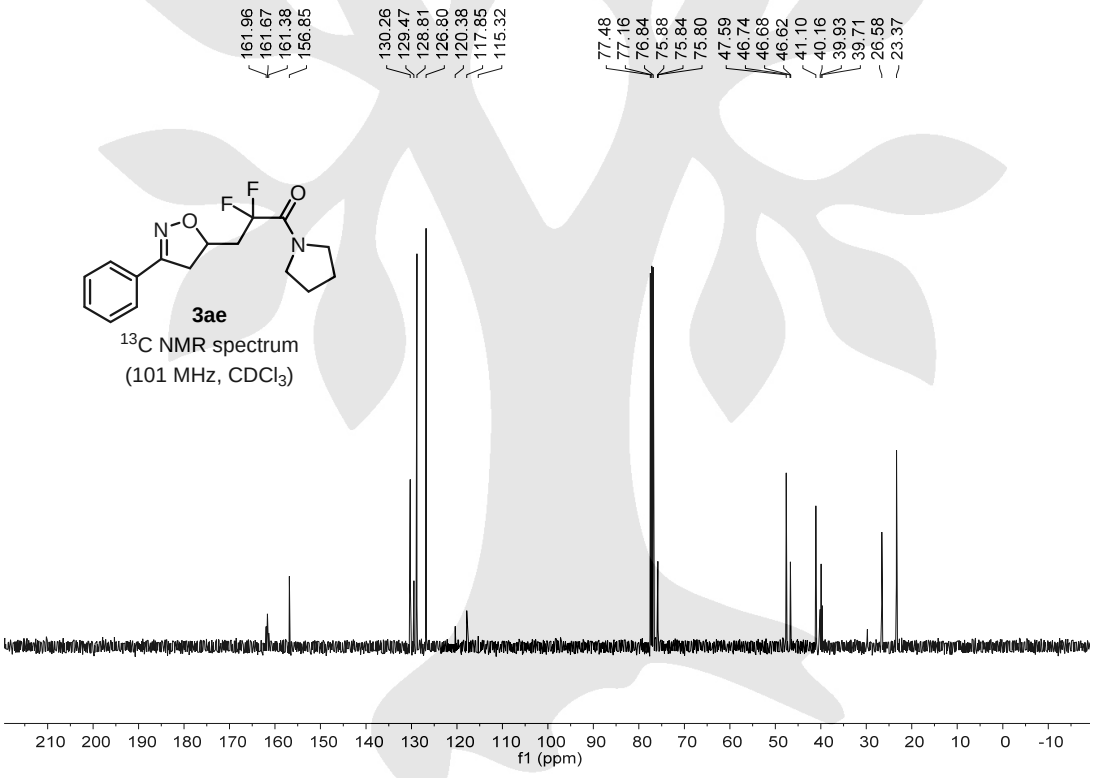


3ad

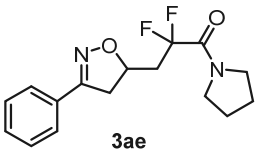
HRMS spectrum
by Waters GZ-XS QTOF
mass spectrometer



^{1}H NMR spectrum
(400 MHz, $CDCl_3$)

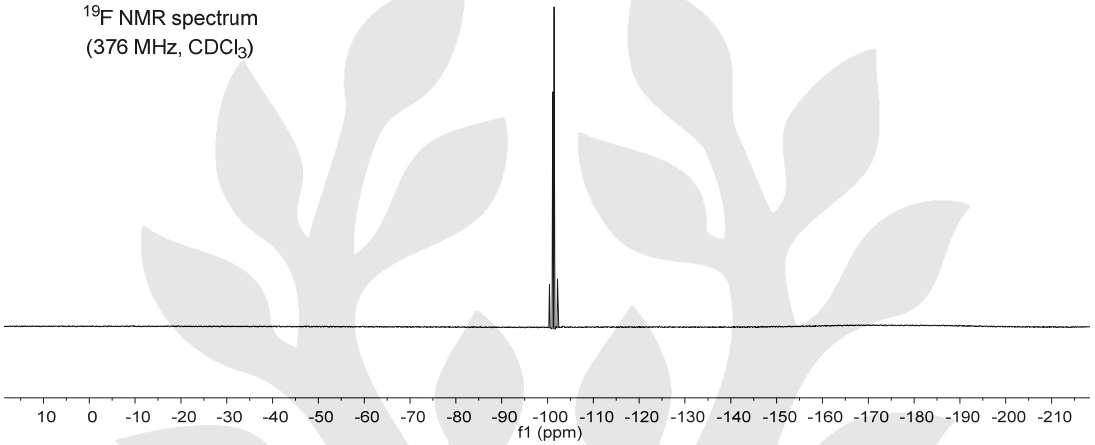


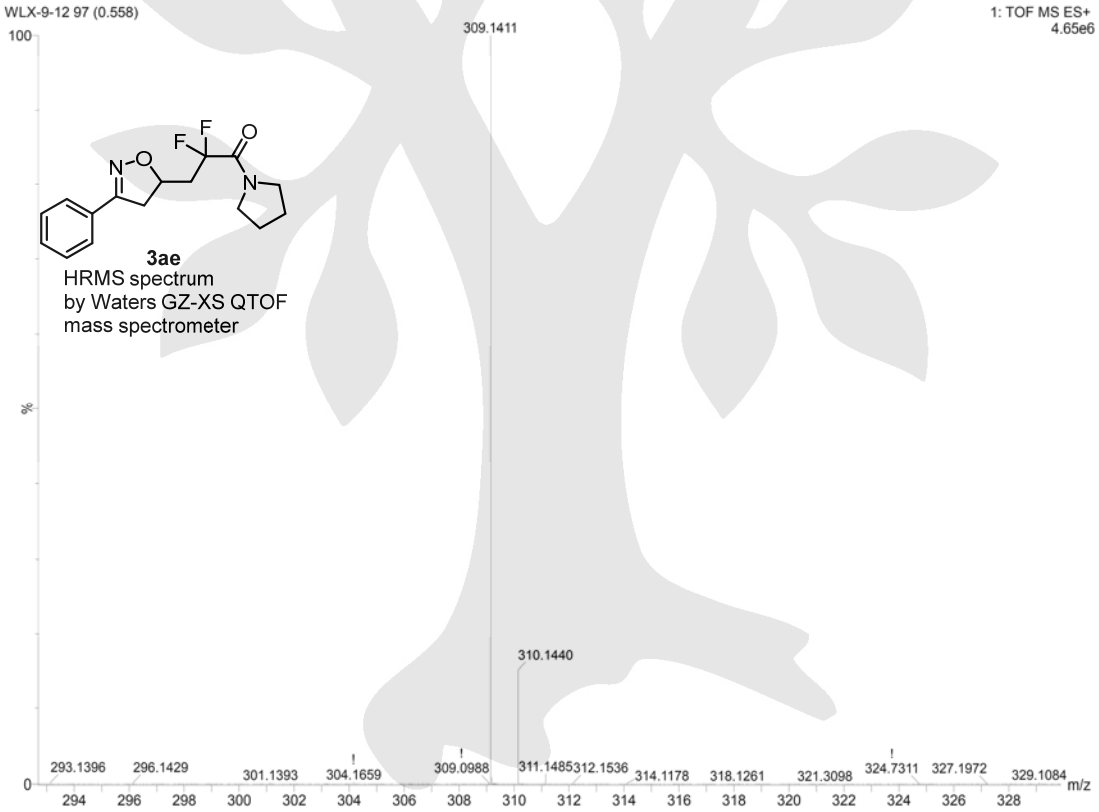
^{13}C NMR spectrum
(101 MHz, $CDCl_3$)



3ae

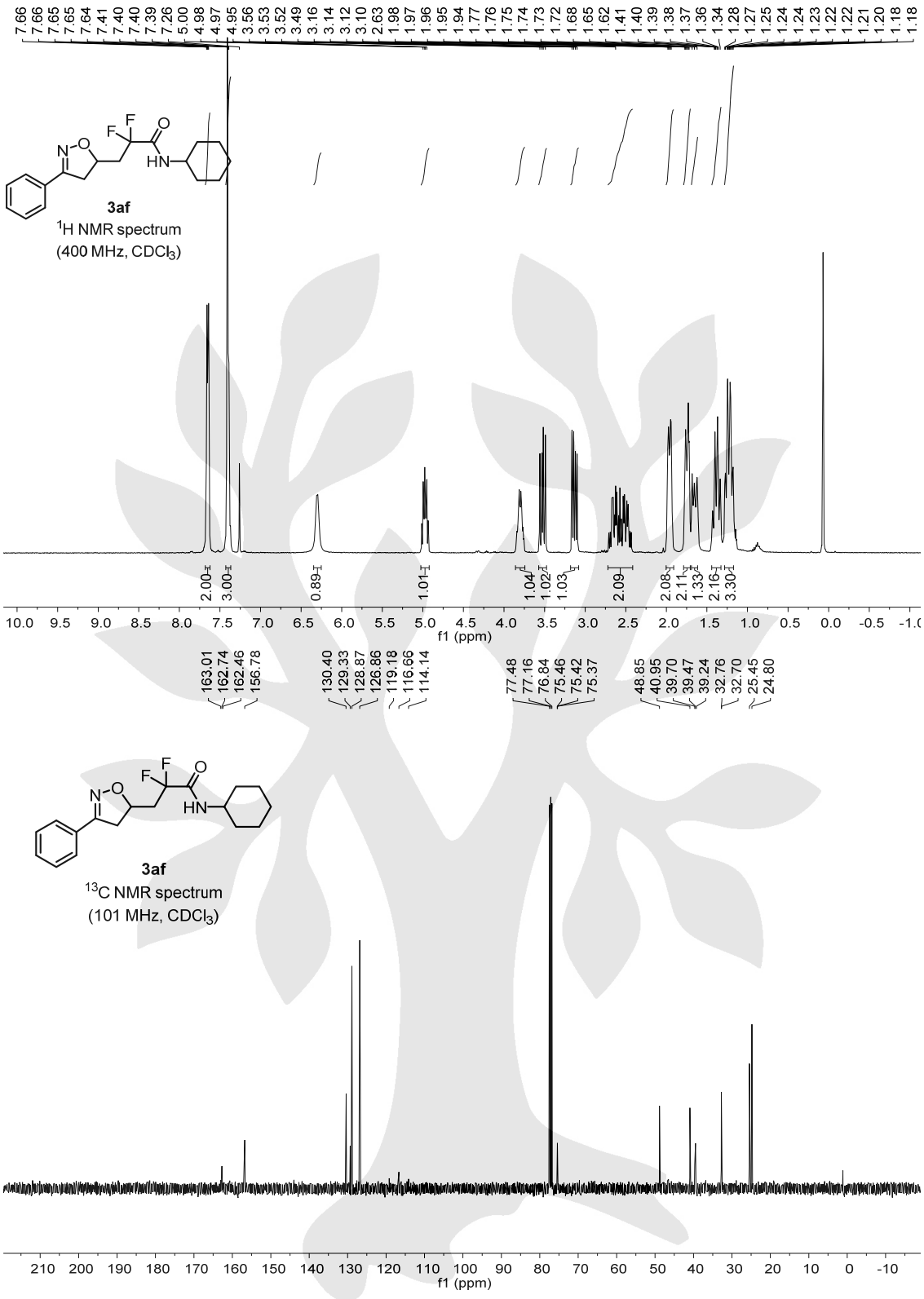
^{19}F NMR spectrum
(376 MHz, $CDCl_3$)

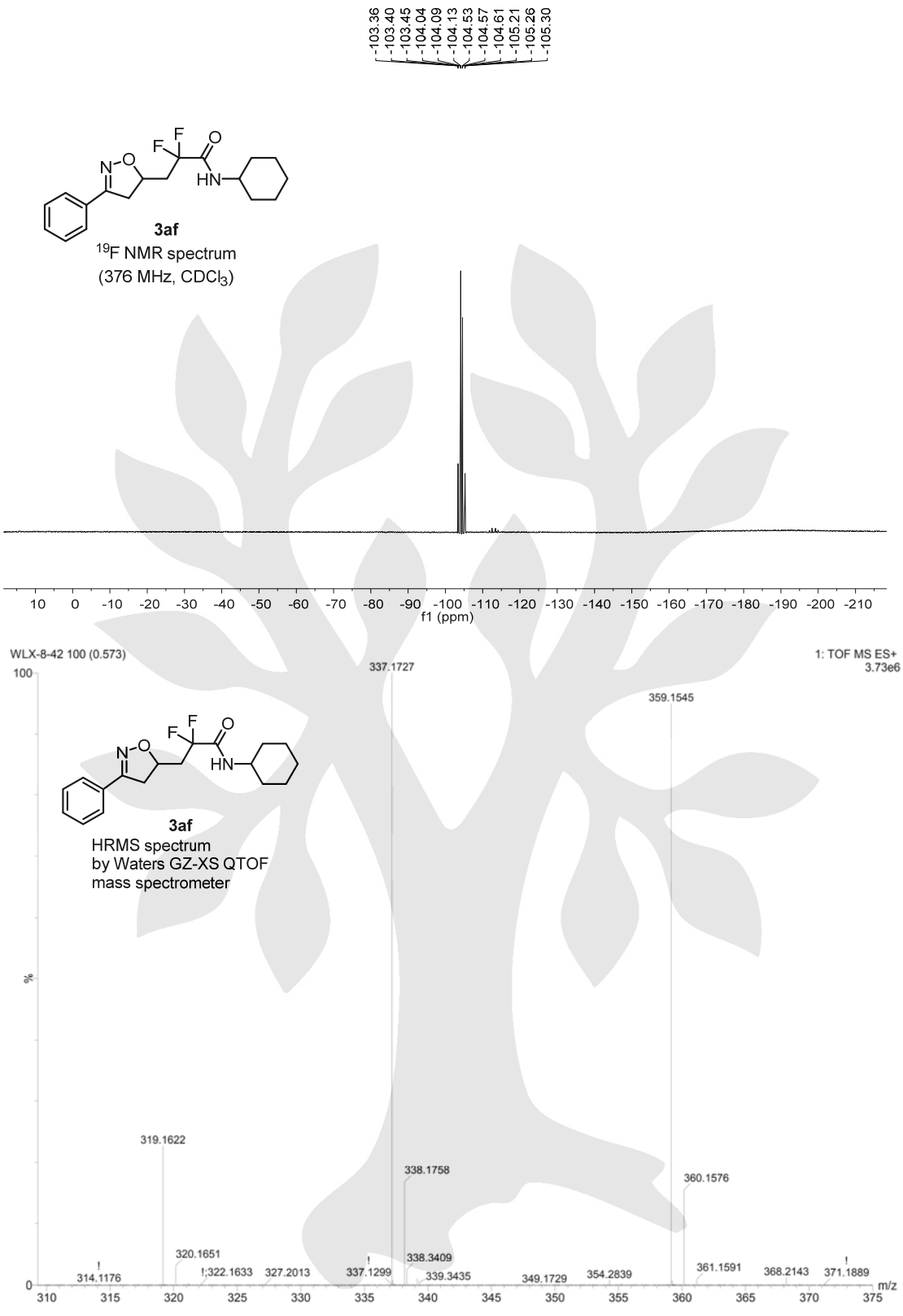


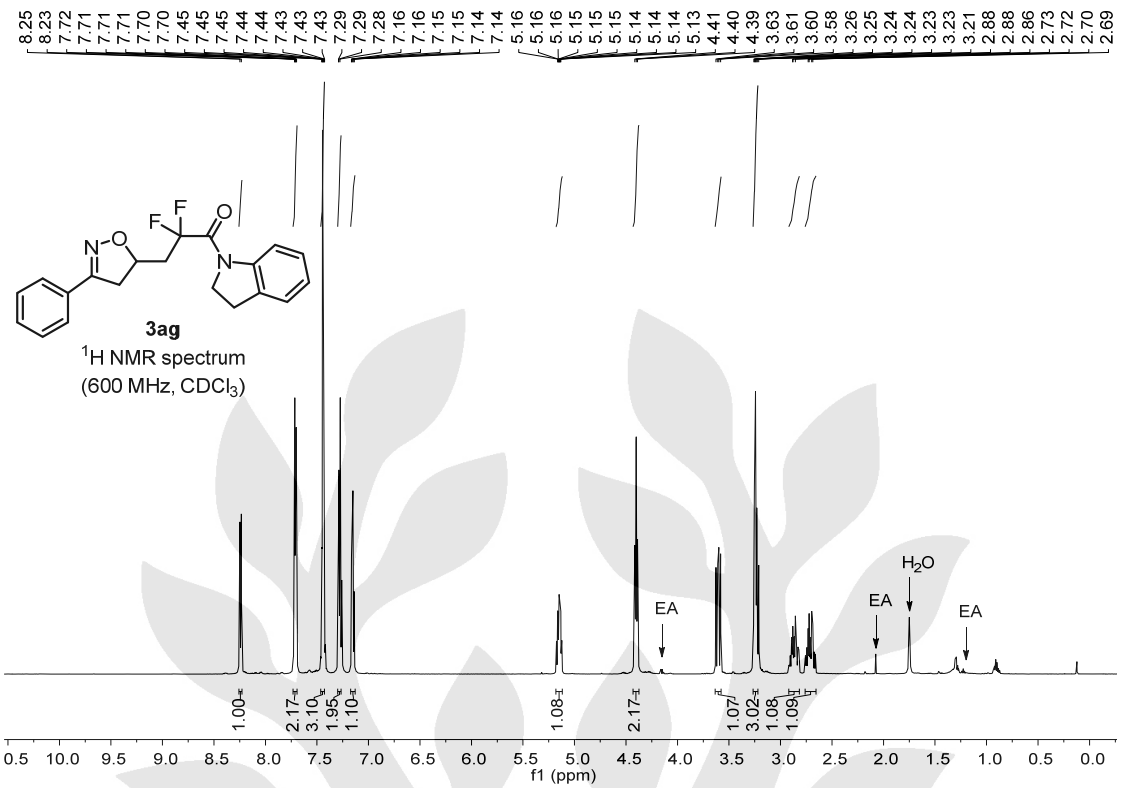


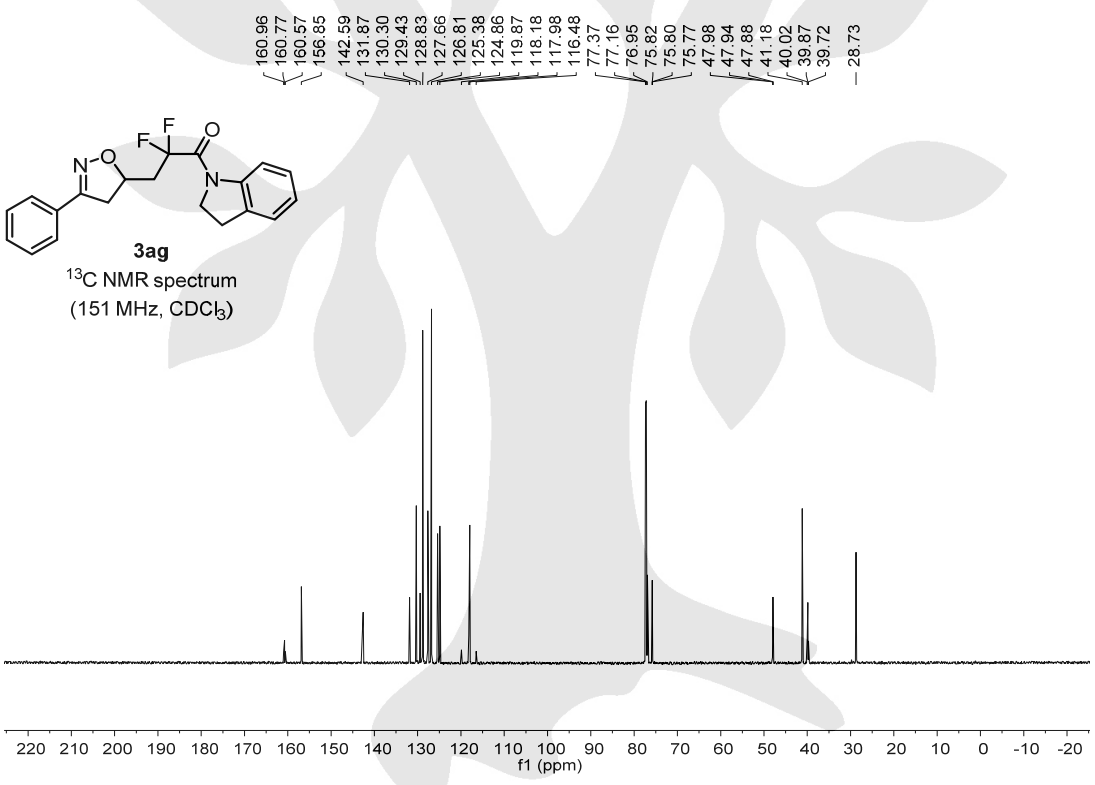
3ae

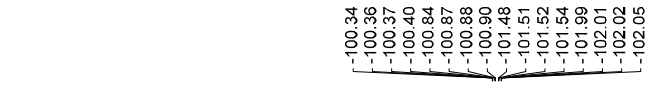
HRMS spectrum
by Waters GZ-XS QTOF
mass spectrometer

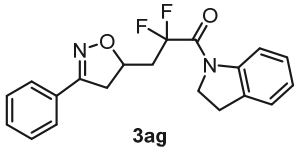






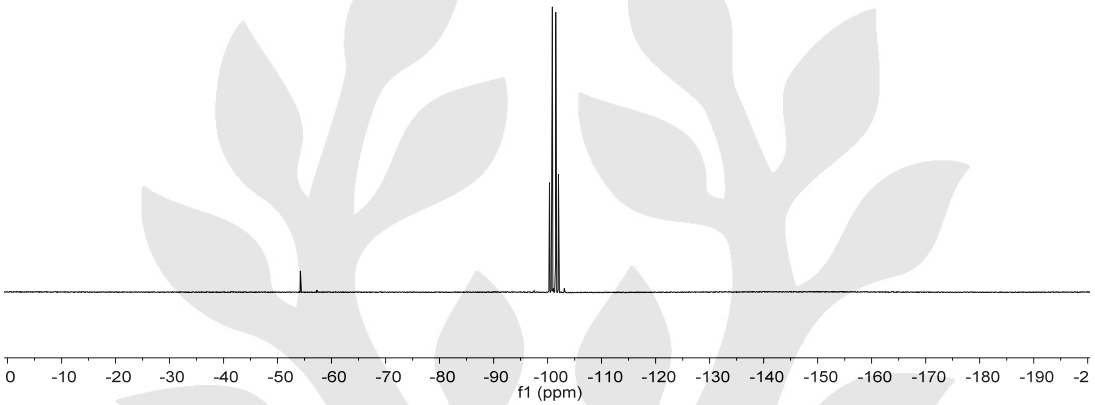


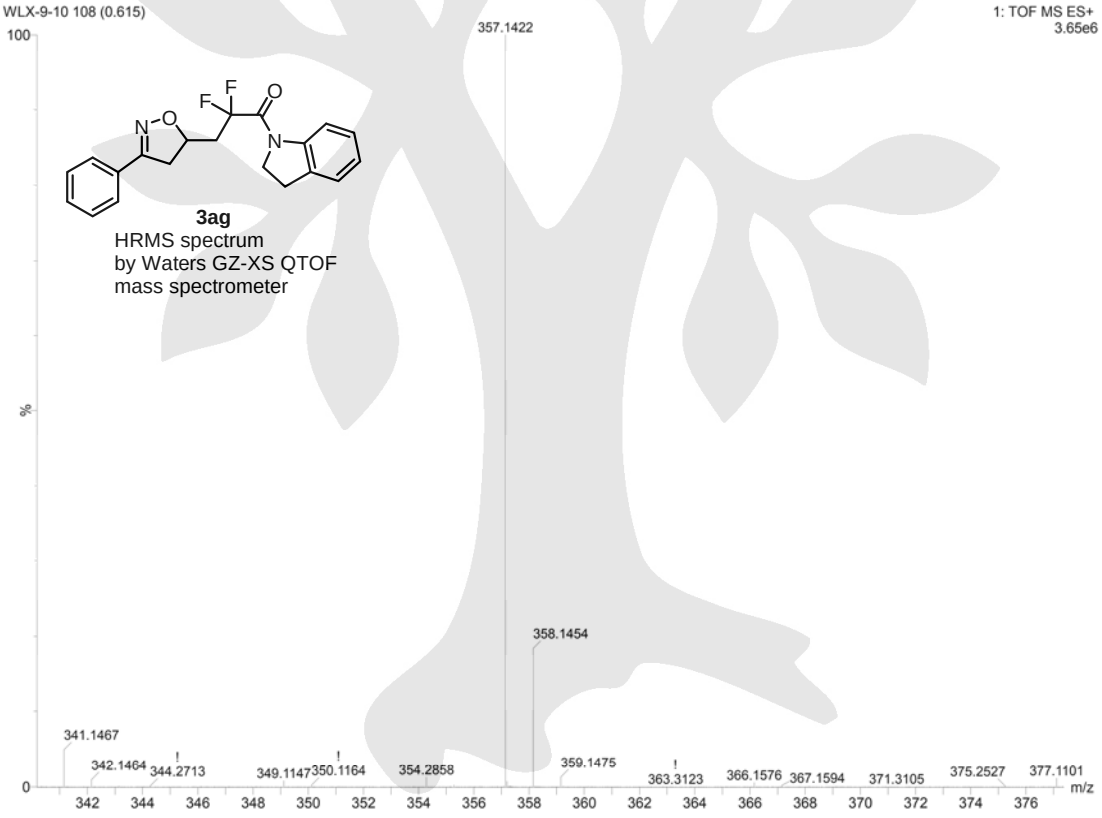




3ag

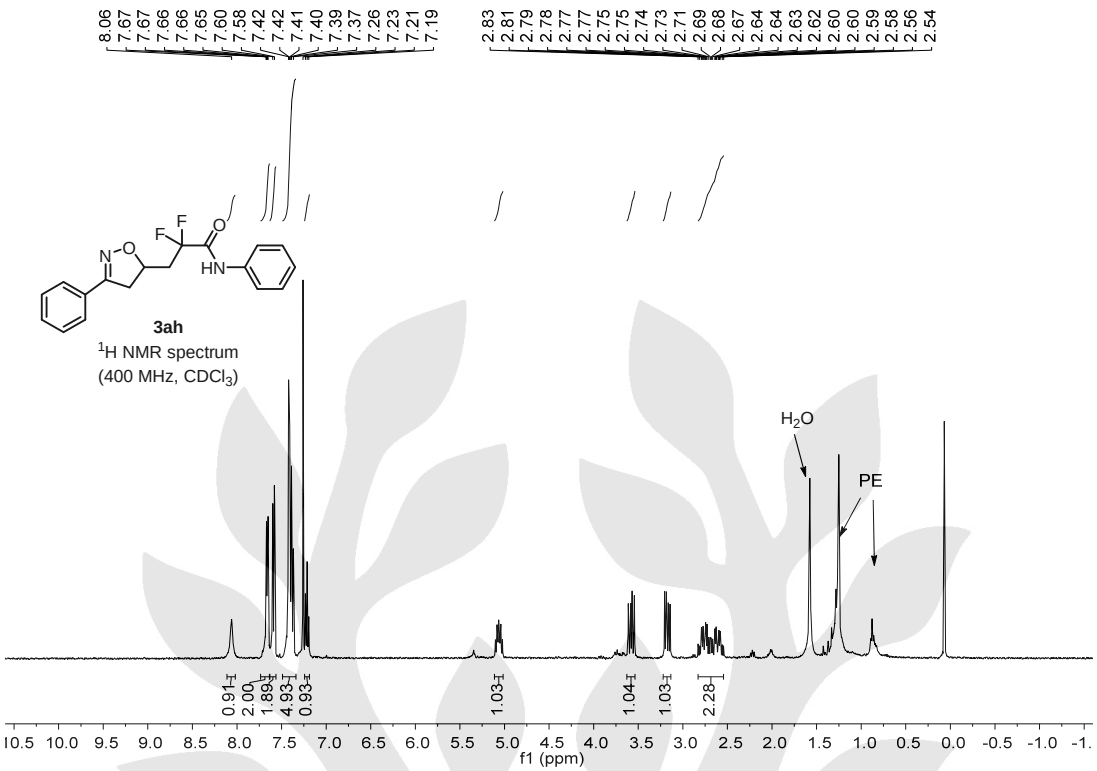
^{19}F NMR spectrum
(565 MHz, $CDCl_3$)

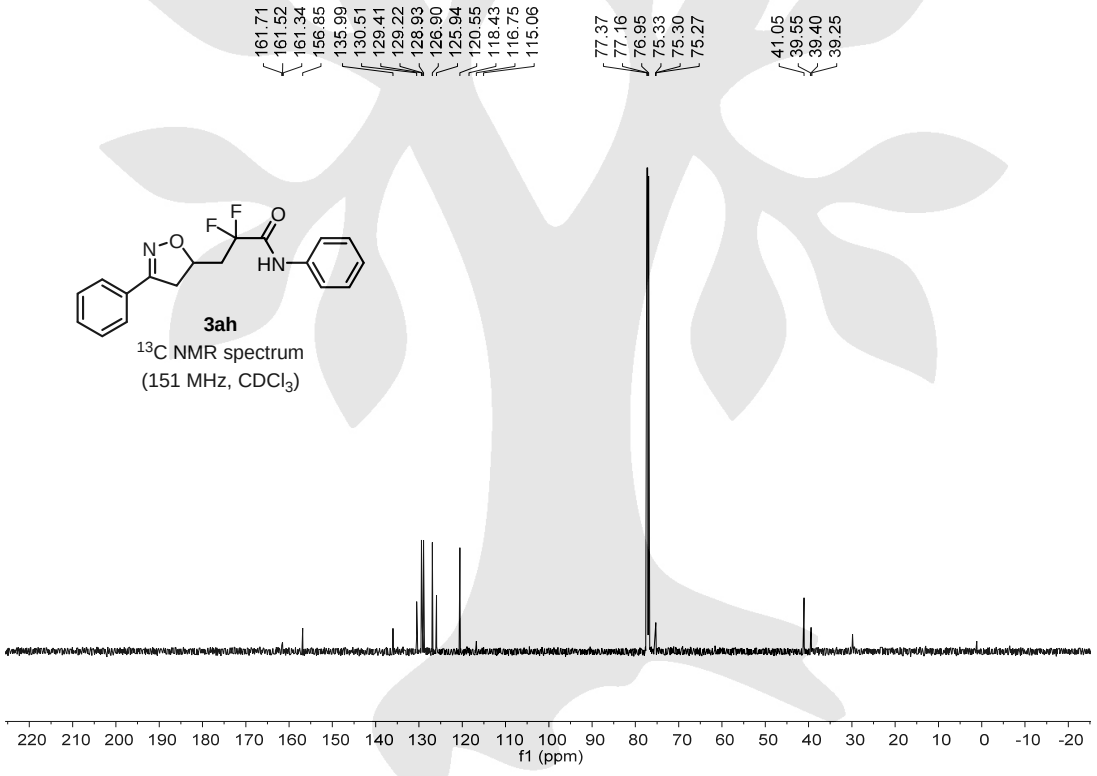


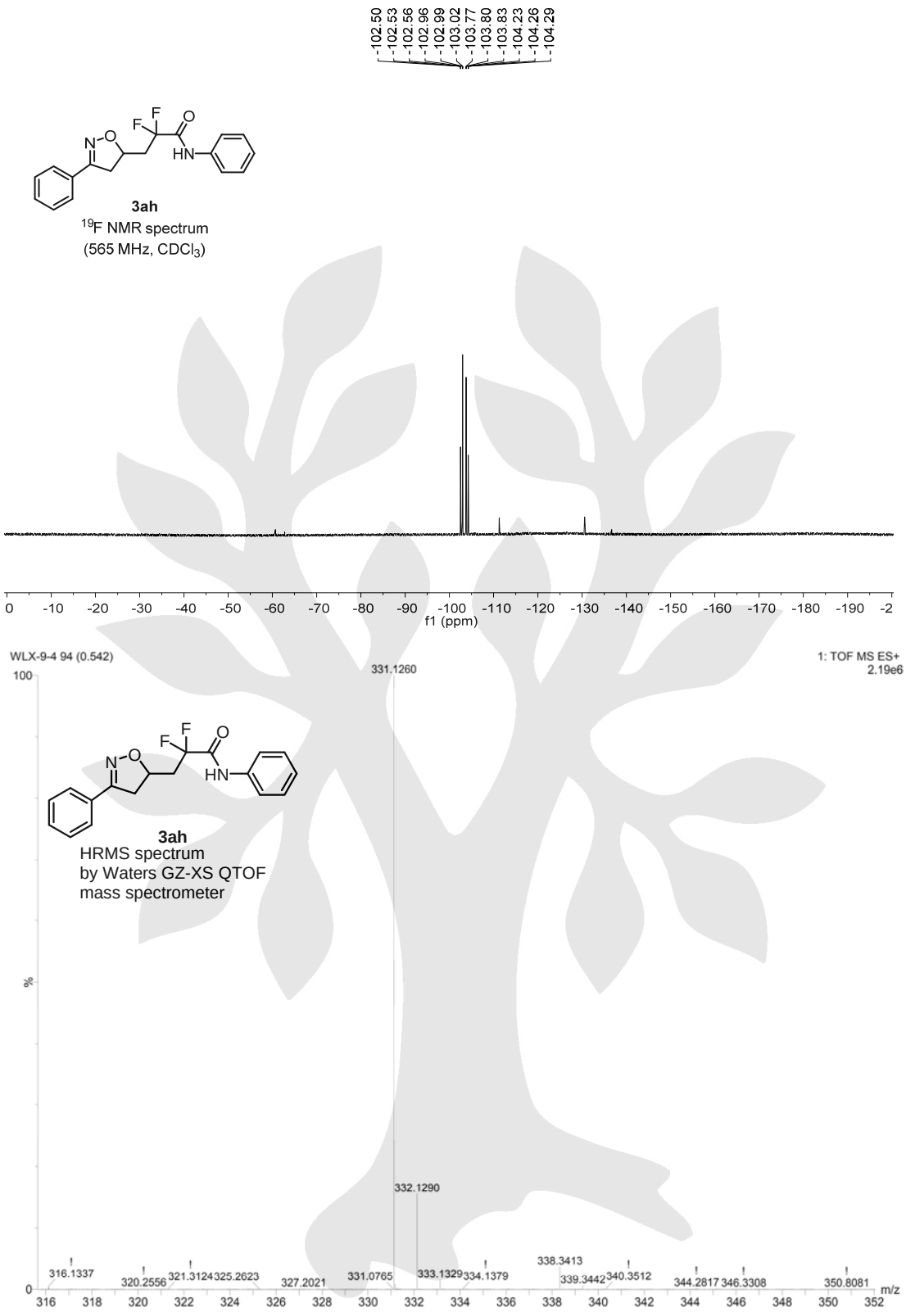


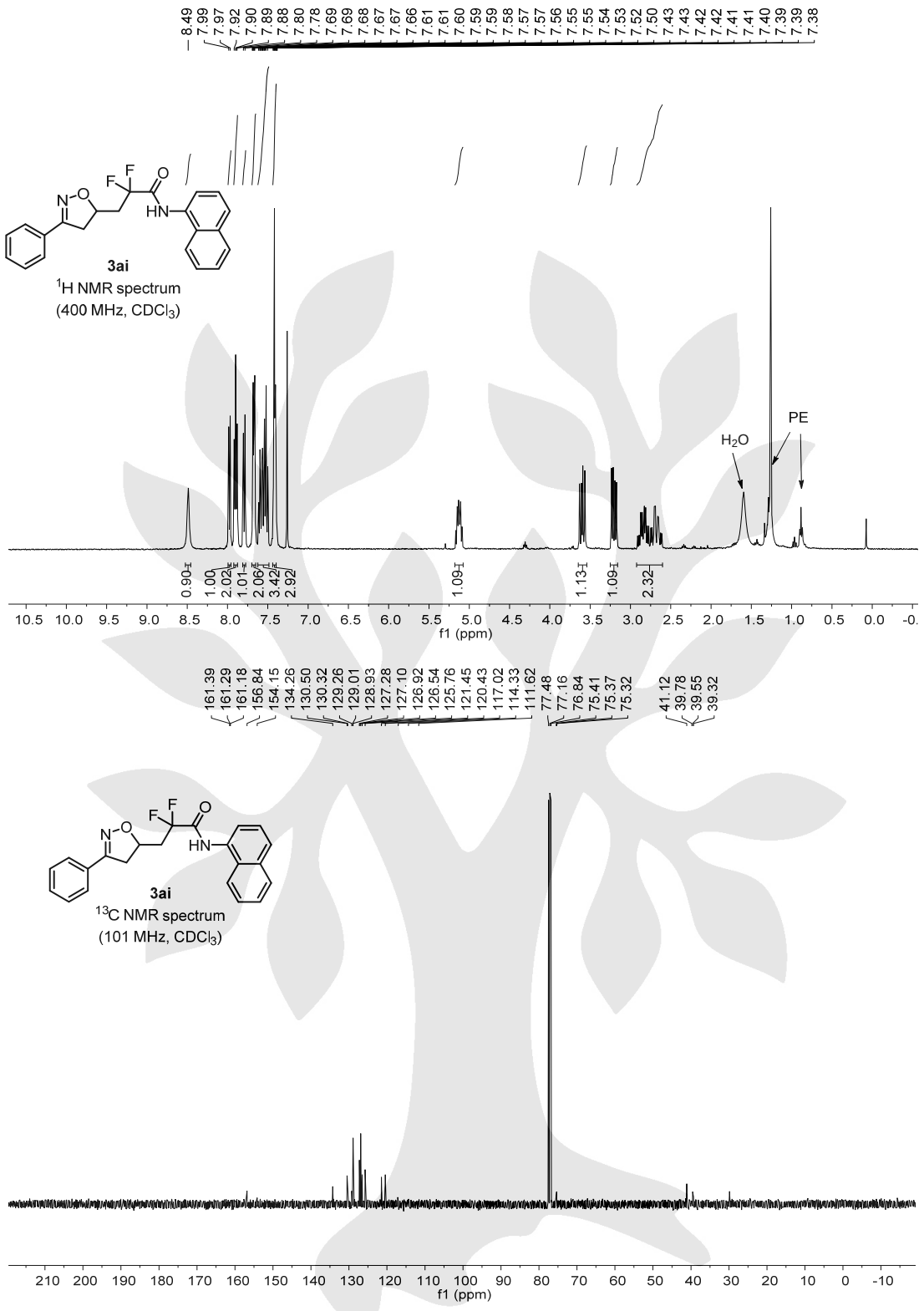
3ag

HRMS spectrum
by Waters GZ-XS QTOF
mass spectrometer









-101.85
-101.90
-101.94
-102.54
-102.59
-102.64
-103.43
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-104.17
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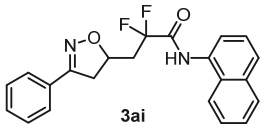
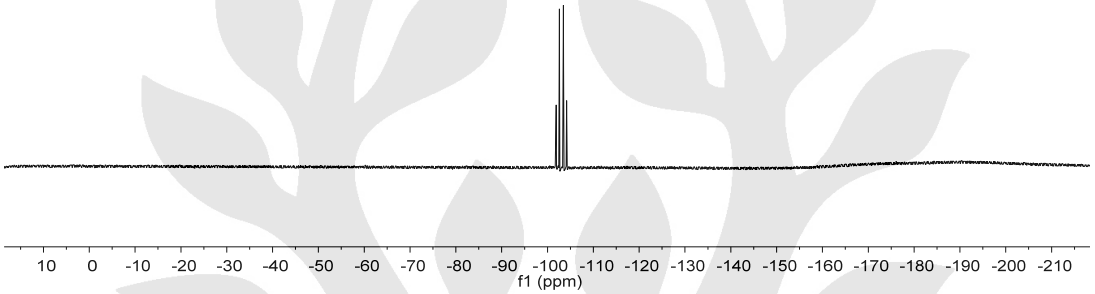
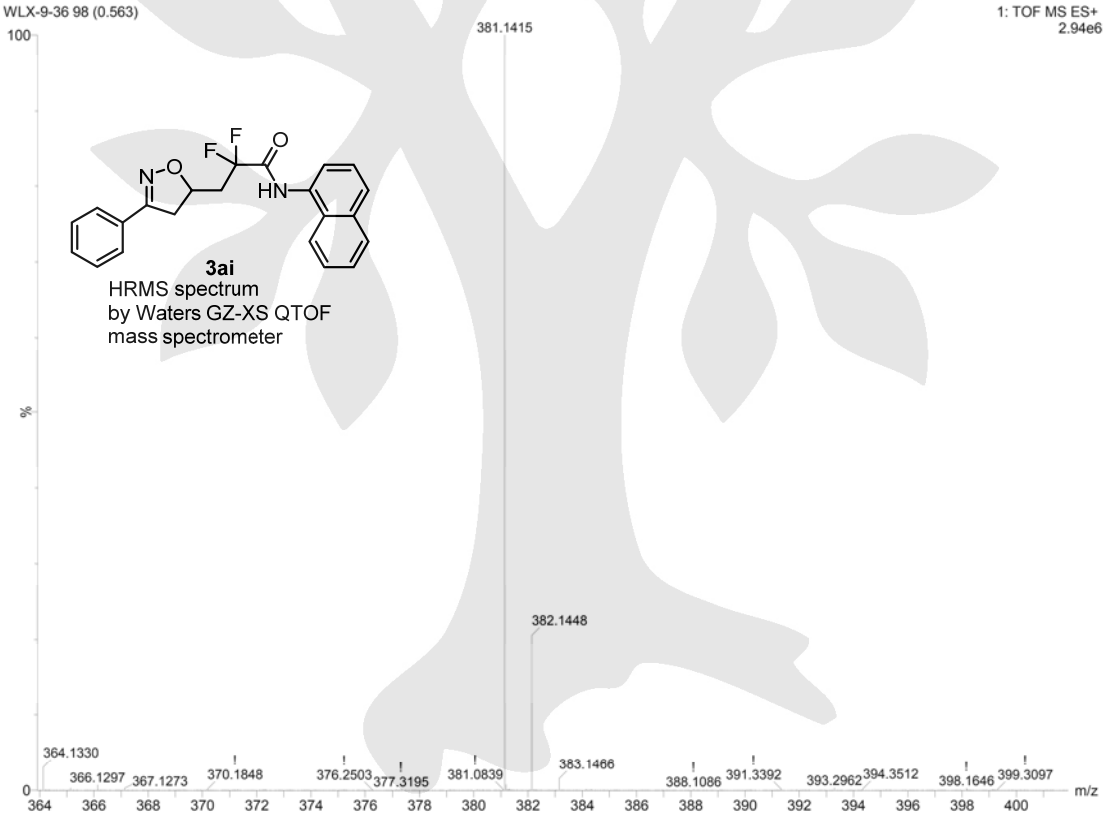


3ai

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





3ai

HRMS spectrum
by Waters GZ-XS QTOF
mass spectrometer