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Synthesis and biological evaluation of fluoro-substituted spiro-isoxazolines as potential anti-viral and anti-cancer agents†

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Electrophilic fluorine-mediated dearomative spirocyclization has been developed to synthesize a range of fluoro-substituted spiro-isoxazoline ethers and lactones. The *in vitro* biological assays of synthesized compounds were probed for anti-viral activity against human cytomegalovirus (HCMV) and cytotoxicity against glioblastomas (GBM6) and triple negative breast cancer (MDA MB 231). Interestingly, compounds **4d** and **4n** showed significant activity against HCMV ($IC_{50} \sim 10$ μM), while **4l** and **5f** revealed the highest cytotoxicity with $IC_{50} = 36$ to 80 μM. The synthetic efficacy and biological relevance offer an opportunity to further drug-discovery development of fluoro-spiro-isoxazolines as novel anti-viral and anti-cancer agents.

Introduction

Spiro-heterocycles are prevalent in plant and animal domains and have become the cornerstone of pharmaceutical and medicinal chemistry.[1] While their conformations, chirality, and structural implications are suitable for biological systems, a diverse group of spiro-heterocycles has widely been used in the drug-discovery process.[1] Among heterocycles, the significance of isoxazole[2] has been driven by a broader biological spectrum, including analgesic,[3] anti-bacterial,[4] anti-depressant,[5] anti-cancer,[6] and anti-herpetic[7] of activities; it is worth mentioning that the synthesis of isoxazoles and isoxazolines is therefore receiving attention from organic chemists.[2c] In this context, the spiro-architecture represents a potential avenue for a diverse range of siblings[8] for further synthetic and biological exploration. Moreover, the unique spiro-isoxazoline core, found in bromotyrosine derived marine natural products, delivering a wide range of biological activities,[9,10] has attracted much synthetic attention. Due to their outstanding biological profile in combination with an intriguing molecular structure, we have focussed our research interest toward the synthesis of spiro-isoxazoline natural products and its congeners as potential leads for anti-cancer, anti-HCMV, and anti-GBM6 agents.[11]

It is worth mentioning that the introduction of fluorine in a biologically active molecules can dramatically modify several parameters, such as acidity, basicity, and dipole moments, delivering its drug-like properties, such as lipophilicity, metabolic stability, and bioavailability of molecules.[12] As a result, these unique properties of the fluorine atom make it relevant in pharmaceutical,[12,13] agrochemical,[12,14] and material sciences.[15] Hence, inspired by the medicinal relevance of spiro-isoxazolines and fluorine, we herein report an electrophilic fluorine-mediated dearomative spirocyclization to various fluoro-spiro-isoxazolines and probe their biological activity (Scheme 1). The novelty of the current method includes the identity of effective fluorocyclization, the exploration of the chemistry for several fluoro-spiro-isoxazolines, and their anti-viral and anti-cancer activities (Scheme 1).

Electrophilic fluorination has led to a powerful tool to access various fluorinated hetero- and carbocycles.[16] Moreover, electrophilic dearomative-fluorination[17] of aromatic compounds has received much attention since they produce 3D-molecular skeletons with two consecutive stereogenic centers. Though the mechanism of electrophilic fluorination remains controversial to date, isoxazole can act like a glycal system,[16c,18] in which an oxonium ion mediated electrophilic fluorocyclization leads to the desired spirocyclization. If successful, this strategy would serve as a practical route to readily access a range of fluoro-spiro-isoxazolines in order to probe biological activity.

In the line with our continued interest in the synthesis of spiro-isoxazoline (Scheme 1),[11] we herein report a two-step

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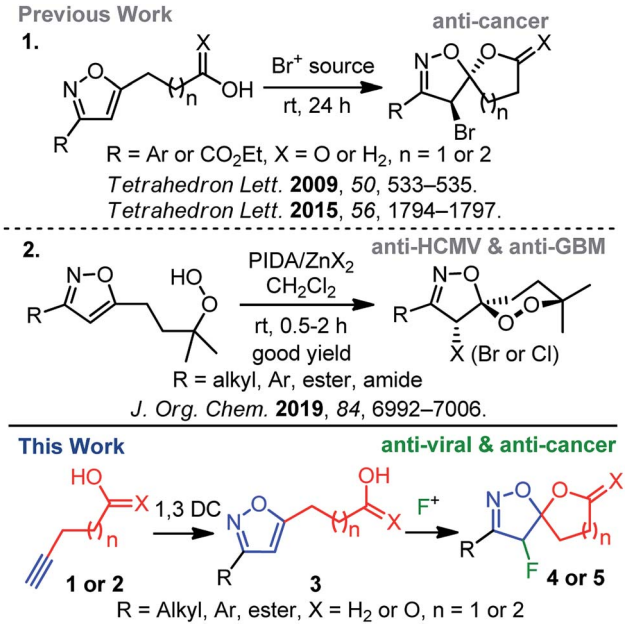
† Electronic supplementary information (ESI) available: Copies of ^{1}H, ^{13}C, and ^{19}F NMR for synthesized compounds have been included. See DOI: 10.1039/d0ra06148d



Scheme 1 Synthesis of 4-halo-spiro-isoxazoline derivatives.

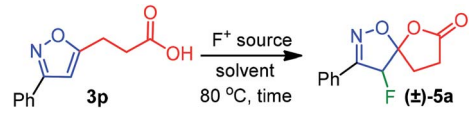
method that includes 1,3-dipolar cycloaddition and electrophilic fluoro-cyclization to access fluorinated variants of this important motifs. The effectiveness of this strategy is also examined using various substituted nitrile oxides and alkynes to obtain a diverse group.

Results and discussion

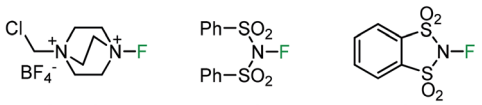
Chemistry

The fluorolactonization of isoxazoline **3p** was selected as a model reaction to optimize the reaction conditions, including electrophilic fluorine sources, solvents, and temperatures (Table 1). As Selectfluor is inexpensive, commercially available, and widely used for electrophilic fluorocyclization, we chose to screen Selectfluor on **3p** while using various protic, aprotic, and halogenated solvents at room temperature. However, since the role of the solvents was crucial for the desired transformation, none of the solvents were found suitable for the fluorolactonization at room temperature. To our surprise, as depicted in Table 1, when the temperature of the reaction was elevated to 80 °C, we observed remarkable changes in reactivity. However, the chlorinated solvents CH_2Cl_2, $CHCl_3$, and $ClCH_2CH_2Cl$ (DCE) were abortive to bring about the fluorolactonization, even at refluxed temperature. This prompted us to examine the reaction in aprotic polar and nonpolar solvents, such as THF, Et_2O, acetone, and ethyl acetate (entry 5–7, Table 1). To our disappointment, the desired fluorolactonization was unsuccessful, and we recovered the substrate **3p**, quantitatively. In mark contrast, when we performed the reaction in polar solvents, such as CH_3CN and MeOH at 80 °C (entry 8 and 9, Table 1), a significant enhancement in reactivity was observed, and we were able to isolate **5a** in 90% and 85% yields. Notably, when trifluoroethanol (TFE) was used as a fluorinated polar solvent,

Table 1 Optimization of reaction conditions for (±)-**5a**[a]



Entry	F+-source	Solvent	Time[b] (h)	Yield[c] (%)
1	Selectfluor	CH_2CI_2	24 h	—
2	Selectfluor	$CHCI_3$	24 h	—
3	Selectfluor	DCE	24	10
4	Selectfluor	THF	12 h	—
5	Selectfluor	Ether	24	—
6	Selectfluor	Ethyl acetate	24 h	—
7	Selectfluor	Acetone	24 h	—
8	Selectfluor	CH_3CN	24 h	90
9	Selectfluor	MeOH	24 h	85
10	Selectfluor	CF_3CH_2OH	24 h	10
11	NFSI	CH_3CN	24 h	—
12	NFOBS	CH_3CN	24 h	—

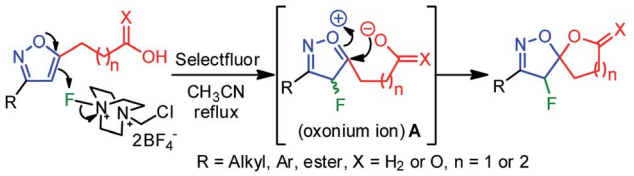


[a] General conditions: isoxazoline acid **3p** (0.2 mmol, 1.0 equiv.) and F-source (1.5 equiv.) in 2 mL solvent was refluxed at 80 °C. [b] Time required for the reaction. [c] Based on isolated product after purification by chromatography.

the desired reaction was completely absent (entry 10, Table 1). We speculated that due to the electronegativity of the trifluoromethyl group in TFE, the corresponding alcohol exhibits a stronger acidic character compared to methanol; thereby, plausible complexation with isoxazole, protonation of alkoxide or carboxylate anion was detrimental to reactivity. At this point, based on the reaction time, we chose CH_3CN as our optimized solvent for the desired reaction. To further our investigation, we used two other fluorine sources that are also known for fluorination.[19] In doing so, we performed a similar reaction but using 1.5 equiv. of *N*-fluorobenzenesulfonimide (NFSI) or *N*-fluoro-*o*-benzenedisulfonimide (NFOBS); unpredictably, no desired fluorolactonizations were observed (entries 11 and 12, Table 1). Therefore, we decided to use Selectfluor (1.5 equiv.) in CH_3CN at 80 °C as an optimized reaction condition to achieve the desired transformation (Table 1).

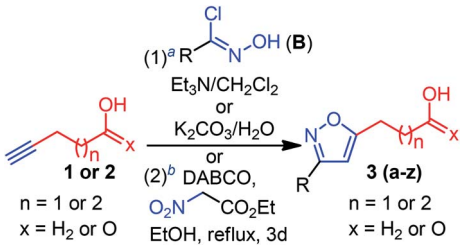
A plausible mechanistic pathway has been proposed in Scheme 2. Under the refluxed condition, Selectfluor could dearomatize the isoxazole ring *via* an oxonium-ion mediated electrophilic fluorination on C4–C5 double bond, regioselectivity, leading to a reactive intermediate **A**. Subsequently, the neighboring group participation of the carboxylate anion to the intermediate **A** produced the fluoro-spiro-isoxazoline (Scheme 2).

Having optimized conditions at hand, we proceeded to explore the synthetic compatibility, first by introducing various substituents on the isoxazole ring, and then, by evaluating the feasibility of five and six-membered ether and



Scheme 2 Plausible mechanism for 4-fluoro-spiro-isoxazolines.

Table 2 Synthesis of isoxazole precursors 3(a–z)[a,b,c]



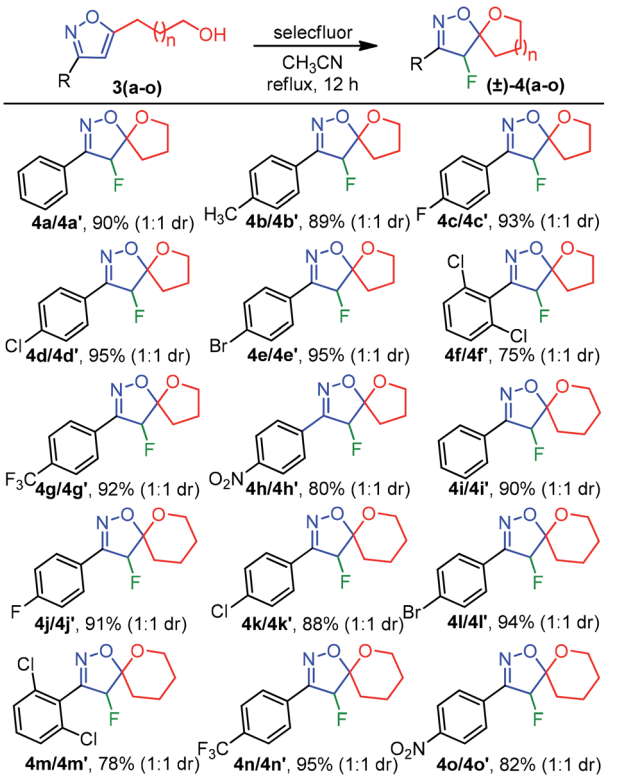
Entry	Alkyne	R	3(a–z)	Yield[c] (%)
1	**1a**, $n = 1$, $x = H_2$	Ph	**3a**	96
2	**1a**, $n = 1$, $x = H_2$	4-Me-Ph	**3b**	83
3	**1a**, $n = 1$, $x = H_2$	4-F-Ph	**3c**	95
4	**1a**, $n = 1$, $x = H_2$	4-Cl-Ph	**3d**	95
5	**1a**, $n = 1$, $x = H_2$	4-Br-Ph	**3e**	95
6	**1a**, $n = 1$, $x = H_2$	2,6-Di-Cl-Ph	**3f**	96
7	**1a**, $n = 1$, $x = H_2$	4-CF_3-Ph	**3g**	94
8	**1a**, $n = 1$, $x = H_2$	4-NO_2-Ph	**3h**	80
9	**1b**, $n = 2$, $x = H_2$	Ph	**3i**	92
10	**1b**, $n = 2$, $x = H_2$	4-F-Ph	**3j**	94
11	**1b**, $n = 2$, $x = H_2$	4-Cl-Ph	**3k**	92
12	**1b**, $n = 2$, $x = H_2$	4-Br-Ph	**3l**	93
13	**1b**, $n = 2$, $x = H_2$	2,6-Di-Cl-Ph	**3m**	94
14	**1b**, $n = 2$, $x = H_2$	4-CF_3-Ph	**3n**	95
15	**1b**, $n = 2$, $x = H_2$	4-NO_2-Ph	**3o**	78
16	**2a**, $n = 1$, $x = O$	Ph	**3p**	96
17	**2a**, $n = 1$, $x = O$	4-Me-Ph	**3q**	89
18	**2a**, $n = 1$, $x = O$	4-F-Ph	**3r**	80
19	**2a**, $n = 1$, $x = O$	4-Cl-Ph	**3s**	82
20	**2a**, $n = 1$, $x = O$	4-Br-Ph	**3t**	85
21	**2a**, $n = 1$, $x = O$	2,6-Di-Cl-Ph	**3u**	80
22	**2a**, $n = 1$, $x = O$	4-CF_3-Ph	**3v**	92
23	**2a**, $n = 1$, $x = O$	Me	**3w**	76
24	**2a**, $n = 2$, $x = O$	*n*-Pr	**3x**	78
25	**2a**, $n = 2$, $x = O$	2,6-Di-Cl-Ph	**3y**	80
26[b]	**2a**, $n = 2$, $x = O$	CO_2Et	**3z**	82

[a] General conditions 1: alkynol **1** (1.0 equiv.), hydroximoyl chloride (1.2 equiv.), triethylamine (1.5 equiv.) in CH_2Cl_2 (10 mL) at rt for 24 h or alkynoic acid **2** (1 equiv.), hydroximoyl chloride (2 equiv.), and K_2CO_3 (2.5 equiv.) in deionized water (1 M) at rt for 24 h. [b] General conditions 2: alkynoic acid **2b** (1.0 equiv.), ethylnitroacetate (2.5 equiv.), DABCO (0.2 equiv.), ethanol (10 mL) at 80 °C in sealed vessel for 3 days. [c] Based on isolated product after purification by chromatography.

lactone ring formation. The desired precursors **3(a–z)**, possessing an isoxazole and pendant alcohol or acid, were initially synthesized by using a 1,3-dipolar cycloaddition reaction between alkynol **1** or alkynoic acid **2** and 1,3-dipole precursors **B** (Table 2).[11a]

Although the substrate scope for the desired fluorocyclization was examined at the final stage, various functionalities were introduced by using several 1,3-dipole precursors **B** (Table 2). Therefore, as illustrated in Table 2, electron-donating, electron-withdrawing, and halo-functionality were introduced on an aromatic system; a couple of alkyl functionalities were also incorporated to introduce hydrophobic nature to the molecule for biological investigation. The 1,3-dipolar reaction was performed between **1** or **2** and *in situ* generated nitrile oxide from the corresponding chloro-oxime **B** upon treatment with Et_3N/CH_2Cl_2.[11a] As summarized in Table 2, a range of substituted isoxazoles **3(a–z)**, comprising pendant alcohol **1** and acid **2** of different chain lengths, were successfully synthesized in high yields (Table 2). To determine the ester functionality that could facilitate obtaining an acid and amide functional group, we conducted a base-catalyzed 1,3-dipolar cycloaddition reaction, using ethyl-nitroacetate and alkynoic acid **2**, under sealed tube refluxed condition, which provided the desired product **3z** in 82% yield (Table 2).[11a] It is worth mentioning that the 1,3-dipolar cycloaddtion produced the 3,5-disubstituted isoxazole as a major isomers; however, 3,4-disubstituted isoxazole was insignificant to be isolated.

Table 3 Synthesis of 4-fluoro-spiro-isoxazoline-ethers (±)-4(a–o)[a]



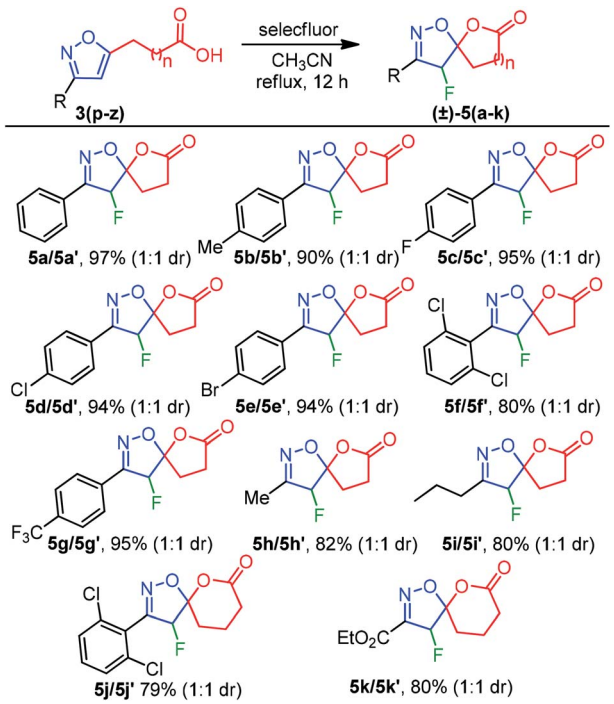
[a] Reaction conditions: isoxazole alcohol **3(a–o)** (0.2 mmol), Selectfluor (0.3 mmol, 1.5 equiv.), CH_3CN (2 mL) at 80 °C for 12 h, product isolated after purification by chromatography.

To evaluate the feasibility of five and six-membered ether ring formations, the list of alcohols **3(a–o)** from Table 2 was executed for the fluorocyclization (Table 3), following our optimized reaction condition. As summarized in Table 3, the electron-donating effect of 4-Me was tolerated under our standard reaction conditions to afford **4b** in 89% yield. Next, for the halo substitutions, 4-F-Ph, 4-Cl-Ph, 4-Br-Ph, and 4-CF_3-Ph afforded **4(c–e)** and **4g** in 93%, 95%, 95%, and 92% isolated yields, respectively (Table 3). A similar pattern of reactivity was also observed for a six-membered etherification **4(i–l)** and **4n** with high yields. On the other hand, the spirocyclization of 2,6-dichloro substituted isoxazoles **3f** and **3m** were also successful to produce **4f** and **4m**, albeit with decreased efficiencies (75% and 78%) due to the steric environment generated between 2,6-di-Cl and F-atoms. The electrophilic fluoro-cyclization was also found to be effective in the presence of an electron-withdrawing group such as NO_2, producing the desired cyclized products **4h** and **4o** in 80% and 82% yields, respectively. Therefore, the reaction conditions were found to be well tolerated for a wide range of functionalities leading to (±)-4-fluoro-spiro-isoxazoline-ether **4(a–o)** (Table 3). Importantly, the diastereomers were isolated with a 1 : 1 diastereomeric ratio with an identical chemical shifts (δ) in NMR for most cases. However, a well-defined chemical shift for the CHF proton was observed for few diastereomers.

Inspired by this success, we next explored the scope of isoxazole acids **3** to afford about five and six-membered fluoro-spiro-isoxazoline-lactones. As depicted in Table 4, regardless of various substitution on the phenyl ring and electronic properties, the reaction proceeded smoothly and provided the desired products **5(a–k)** in excellent yields (Table 4). The direct alkyl substituents (Me and Pr) on the isoxazoline also endured the reaction conditions and resulted **5h** and **5i** in 82% and 80% yield, respectively (Table 4).

Furthermore, an ester functionality that is directly connected to an isoxazoline system also exhibited good compatibility to provide **5k** in 80% yield. To our surprise, spiro-lactones **5(a–k)** were separated well, which delivered a dr 1 : 1 (Table 4).

Table 4 Synthesis of 4-fluoro-spiro-isoxazoline-lactones (±)-**5(a–k)**[a]



[a] Reaction conditions: isoxazole acid **3(p–z)** (0.2 mmol), Selectfluor (0.3 mmol, 1.5 equiv.), CH_3CN (2 mL) at reflux for 12 h, product isolated after purification by chromatography.

Biology

Having synthesized diverse fluoro-containing spiro-ethers and -lactones in Tables 3 and 4, we were interested in evaluating their anti-viral and anti-cancer activity.

Antiviral activity against HCMV. Initial screening for the test compounds **4(a–o)** and **5(a–k)** having a potential HCMV inhibitory effect was performed using quantitative fluorescence microscopy. HFF-1 cells were pre-treated with the test compounds (10 μM) or DMSO (control) for 1 hour followed by infection with HCMV (Towne-BAC-GFP strain) at a multiplicity of infection (MOI) of 3.0. This engineered HCMV strain contains a green fluorescent protein (GFP) and thus the infection is associated with the expression of GFP.[20] If a compound inhibits HCMV replication, the expression of GFP, quantified as mean fluorescence intensity (MFI), is reduced. Based on preliminary screening of test compounds, only five compounds (**4h**, **4o**, **4i**, **4n**, and **4d**) showed a reduction in GFP levels. On further analysis, significant reduction in MFI was evident upon the

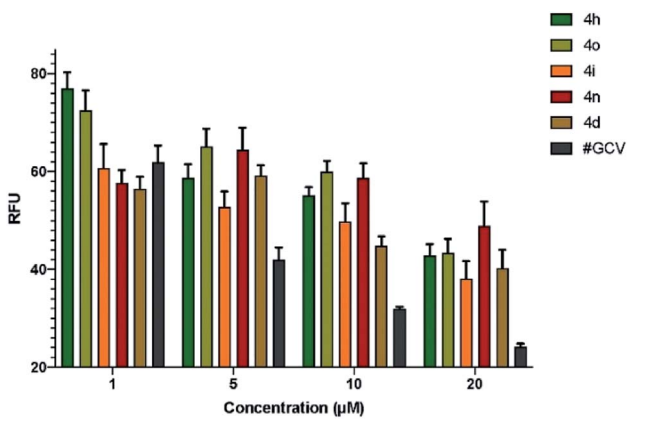


Fig. 1 Determination of IC_{50} of the test compounds. Confluent HFF cells were pre-treated with serial dilutions (0–20 μM) of test compounds **4h**, **4o**, **4i**, **4n**, and **4d**. As a control, cells were pre-treated with ganciclovir (GCV) followed by infection with HCMV (Towne-BAC-GFP) strain at a MOI of 3.0. At 5 days post infection, cells were fixed in 3.7% formaldehyde, and relative fluorescence units (RFU) were quantified using a microwell image cytometer (Celigo, Nexcelom Bioscience LLC, Lawrence, MA). Estimation of IC_{50} for the compounds **4o**, **4i**, **4n**, and **4d** as 2.54 mM, 11.2 mM, 10.47 μM, and 9.47 μM, respectively, is based on non-linear curve fitting on transformed data in Prism GraphPad software. Error bars represent standard error of mean (SEM) from three independent experiments. IC_{50} for GCV was 4.96 μM, which is close to the reported value of 5.2 μM.[21]

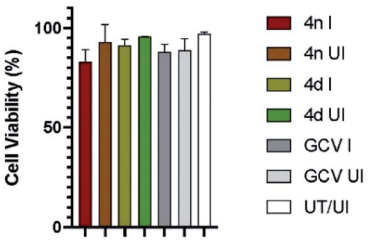


Fig. 2 Effect of the test compounds on cell viability. HFF-1 cells were treated with the test compounds at 2× the IC_{50} concentrations or untreated (UT). Cells were either infected (I) with HCMV at MOI of 3.0 or left uninfected (UI). Cell viability was quantified by trypan blue exclusion assay at day 5 post infection. Error bars represent standard error of mean (SEM) from three independent experiments.

treatment with these compounds **4h**, **4o**, **4i**, **4n**, and **4d**, indicating that these five compounds may have potential anti-HCMV properties.

Next, we determined the half maximal inhibitory concentration (IC_{50}) for the five compounds that showed promise in the preliminary screening against HCMV. Based on the number of GFP+ cells present in infected cells pre-treated with serial dilutions of test compounds, the IC_{50} for the compounds **4o**, **4i**, **4n**, and **4d** was calculated as 2.54 mM, 11.2 mM, 10.47 μM, and 9.47 μM, respectively (Fig. 1). IC_{50} for ganciclovir (GCV), a clinically approved drug for HCMV treatment, was calculated as 4.96 μM, which is very close to the reported IC_{50} of 5.2 μM,[21] proving the validity of this assay. Since IC_{50} values are inversely proportional to the potency of a compound, this data showed that compounds **4d** and **4n** are the most effective inhibitors of HCMV in cell culture among the compounds tested (Fig. 1).

The compounds **4o** and **4i** showed virus inhibition in this assay; however, much more concentration is required, which may be impractical to attain physiologically.

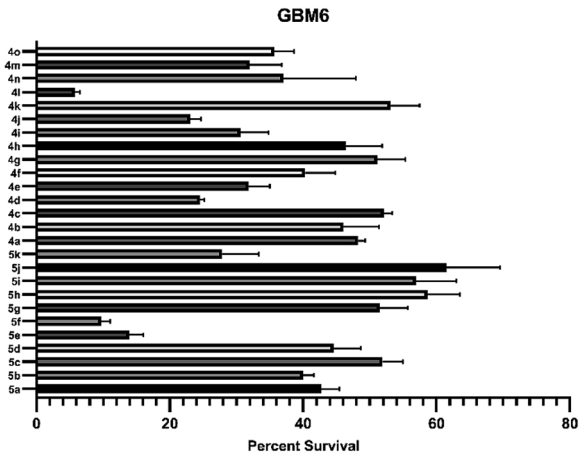


Fig. 3 GBM6 were plated at 1000 cells per well on 96-well format. After 24 hours, the cells were treated at 100 μM concentration of each given compound. The MTT assay was performed 72 hours after treatment and the absorbance (570 nm) data from each experimental group ($n = 3$) was normalized to control average, bars are S.E.M.

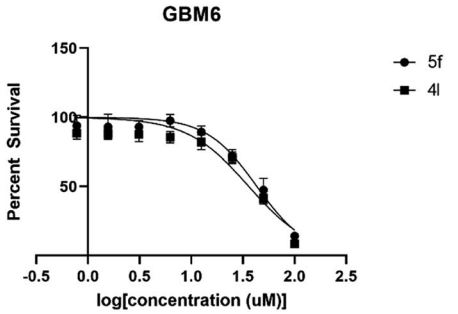


Fig. 4 GBM6 were plated at 1000 cells per well on 96-well format. After 24 hours, the cells were treated with a range of concentrations (0.8–100 μM). MTT assay was performed 72 hours after treatment. $n = 3$, bars are S.E.M.

Finally, we determined the possible cytotoxicity of the test compounds on HFF cells (Fig. 2). Cells were treated with the test compounds (**4d** and **4n**) at 2× the IC_{50} concentrations or left untreated (UT). Cells were then either infected (I) with HCMV at MOI of 3.0 or left uninfected (UI), and cell viability at the end point was quantified by trypan blue exclusion assay.[22] As presented in Fig. 2, cell viability for all tested compounds remained near 100%. Most importantly, the compounds **4n** and **4d** did not show significant cytotoxicity even when maintained on cells for a period of 5 days.

Based on the biological assay, it is depicted that spirolactones **5(a–k)** were more inactive against HCMV than the corresponding ether derivatives. Likewise, the phenyl and electron-donating groups on fluoro-spiro derivatives did not show an acceptable range of inhibition against HCMV replication. It is also imperative to highlight that compounds (**4h**, **4o**, **4i**, **4n**, and **4d**) containing electron-withdrawing groups such as NO_2, –Cl, and $–CF_3$ were primarily found to have potential anti-HCMV properties. The Ph and 4-NO_2-Ph substituted fluoro-isoxazoline **4o** and **4i** proved to be moderately active against HCMV with IC_{50} 2.54 mM and 11.2 mM. Interestingly, replacement of functionality to halo substituents such as the 4-Cl-Ph and 4-CF_3-Ph in **4d** and **4n** lead to substantial increase in potency (IC_{50} values 9.47 μM and 10.47 μM). Although, their potency is comparatively lower than that of the control

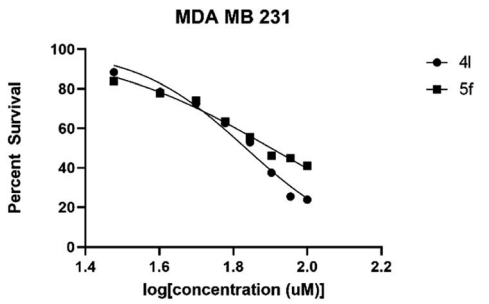


Fig. 5 MDA MB 231 were plated at 2000 cells per well on 96-well format. After 24 hours, the cells were treated with a range of concentrations. MTT assay was performed 72 hours after treatment. $n = 6$, bars are S.E.M.

Table 5 IC_{50} Values from Fig. 4 and 5

	4l	5f
IC_{50} in GBM6	**36.08**	**43.21**
95% C.I. in GBM6	23.21 to 55.06	35.69 to 52.38
IC_{50} in MDA MB 231	**68.18**	**79.80**
95% C.I. in MDA MB 231	64.27 to 72.25	75.58 to 84.95

compound ganciclovir (GCV), considering widespread resistance against GCV in clinical strains of HCMV, and the well-known side effects such as neutropenia, the compounds **4d**, and **4n** may be developed into potential future drugs for HCMV.[23–25]

Cytotoxicity against glioblastomas (GBM6). The synthesized compounds were next evaluated against human glioblastoma cell line GBM6 to determine antiproliferative activity using MTT assay. Treatment concentration for all compounds was 100 μM, and these experiments indicated robust anti-proliferative activity of **4l** and **5f** (Fig. 3).

The IC_{50} value was evaluated using an increased concentration (0.8–100 μM) for **4l** and **5f**. Survival percentages were plotted in Fig. 4 and IC_{50} values predicted based on non-linear regression curve fit, using Graphpad 8. These values are shown in Table 5.

Cytotoxicity against triple negative breast cancer (MDA MB 231). Similarly, MDA MB 231 cells were treated initially with 100 μM concentration of each compound (data not shown). Compounds **4l** and **5f** showed the highest anti-proliferative effect at this concentration, so these two compounds were chosen for dose–response experiments (Fig. 5). MDA MB 231 cells were treated for 72 hours with concentrations ranging from 0.8 μM to 100 μM. Survival percentages were plotted in Fig. 5 and IC_{50} values predicted based on non-linear regression curve fit, using Graphpad Prism 8. These values are shown in Table 5.

As depicted in Table 5, compound **4l** shows better activity than **5f** against both GBM6 and MDA MB 231 cells suggesting that spiro-ether is more effective to show cytotoxicity than the corresponding spiro-lactone. The Br substitution on **4l**, situated at the periphery of the molecular geometry, shows anti-GBM activity; however, the dichloro substitutions at 2,6-position are away from the periphery shows anti-MDA MB 231 activity.

Conclusion

In conclusion, we have developed an efficient and practical route to access various 4-fluoro-substituted spiro-isoxazolines. The efficacy of this strategy mainly relies on 1,3-dipolar cycloaddition and electrophilic fluoro-etherification or -lactonization mediated by commercially available Selectfluor. The protocol has been shown to be useful for accessing spirocyclic compound comprising alkyl, aromatic, and ester substituted isooxazoline and five and six membered cyclic-ethers and lactones. Additionally, few synthetic compounds showed selective and moderate anti-HCMV, anti-GBM6, and anti-MDA MB 231 activity. The structural implication along with biological activity validates that the fluoro-spiro-isoxazolines have the potential to serve as inhibitors of HCMV infection as well as anti-cancer agents.

Experimental section

Materials and methods

General consideration. NMR, IR, and HRMS techniques have been used for the characterization of all new compounds. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 500 MHz and 125 MHz, respectively. ^{19}F measurements were performed at 376 MHz on Bruker 400 MHz. All NMR spectra were measured at 25 °C in the indicated deuterated solvents. Proton, carbon, and fluorine chemical shifts (δ) were reported in parts per million (ppm) and coupling constants (J) were reported in Hertz (Hz). The resonance multiplicities in the ^{1}H NMR spectra are described as s(singlet), d(doublet), t(triplet), and m(multiplet), and broad resonances indicated by br. The residual protic solvent, $CDCl_3$ (^{1}H, δ 7.26 ppm; ^{13}C, δ 77.0 ppm, the central resonance of the triplet), was utilized as the internal reference for ^{1}H and ^{13}C NMR, while $CFCl_3$ (δ = 0.00) was utilized as reference for ^{19}F NMR. Melting points remain uncorrected. IR spectra of the synthesized compounds were recorded using Perkin-Elmer-Spectrum where all types of samples (*e.g.* solids and liquids) are placed directly on the ATR crystal with absorptions measurements taken within spectrometer range of 4000–4500 cm^{-1}. High-resolution mass spectrometry (HRMS) analyses were performed based on positive electrospray ionization on a Bruker 12 Tesla APEX – Qe FTICR-MS with an Apollo II ion source. Either protonated molecular ions $[M + nH]^{n+}$ or sodium adducts $[M + Na]^+$ were used for empirical formula confirmation.

The reactions mentioned below are performed in non-inert atmosphere using HPLC grade CH_2Cl_2, commercial grade EtOH, anhydrous DMF, and deionized water as solvent. All reagents were used as supplied without prior purification unless otherwise stated. The progress of the reaction is monitored by analytical thin-layer chromatography comprised of 60 Å silica gel medium with layer-thickness 250 μm and visualized on 254 nm light, or $KMnO_4$/Na_2CO_3/NaOH mixture and subsequent development with either no or gentle heating. Purifications by flash column chromatography were performed using flash silica gel (60 Å, 0.060–0.200 mm) with the indicated eluent.

Biological assay for antiviral activity against human cytomegalovirus (HCMV)

Cell culture. Human foreskin fibroblasts (HFF-1) (Catalog #SCRC1041, American Type Culture Collection, Manassas, VA) cells were maintained in Dulbecco's modified Eagle's medium (DMEM) (Cellgro, Manassas, VA) supplemented with 4.5 g mL^{-1} glucose, 10% fetal bovine serum (FBS) (Atlanta Biologicals, Flowery Branch, GA), 1 mM sodium pyruvate, 2 mM L-glutamine, and 100 U mL^{-1} penicillin-streptomycin (Cellgro) at 37 °C with 5% CO_2.

Cytotoxic assessment. HFF-1 cells were grown in 12 well tissue-culture plates. At confluency, cells were treated with the test compounds at 2× the IC_{50} concentrations (control) or left

untreated and incubated further. At five days post treatment, cell viability was determined by trypan blue exclusion assay as described earlier (PMID: 26529666) using a TC20 automated cell counter (Bio-Rad Laboratories, Hercules, CA). In brief, medium was removed, and cells were harvested using 0.025% Trypsin-EDTA (ThermoFisher Scientific, Waltham, MA) diluted in phosphate-buffered saline (PBS) and neutralized with FBS-supplemented DMEM. Ten μL of cell suspension and 10 μL of 0.4% trypan blue dye (Hyclone Laboratories, Logan, UT) were mixed, and 10 μL of this sample was loaded immediately onto the outer chamber of the counting slide. The slide was inserted into TC20, which automatically determined the percentage of viable cells.

Virus titers and IC_{50} determination. HFF-1 cells were grown to confluency in 96-well tissue culture plates and pre-treated with serial dilutions (0–20 μM) of the test compounds for 1 hour. As a control, cells were pre-treated with ganciclovir (GCV). The cells were infected with HCMV (Towne-BAC-GFP) strain at a MOI of 3.0. At 5 days post infection, cells were fixed in 3.7% formaldehyde and relative fluorescence units (RFU) were quantified using a microwell image cytometer (Celigo, Nexcelom Bioscience LLC, Lawerence, MA). Ganciclovir (GCV), a known inhibitor of HCMV (PMID: 8393055) was used as a positive control in this assay.

Biological assay for cytotoxicity against glioblastomas (GBM6)

Cell culture. GBM6 cells were propagated in Dulbecco's Modified Eagles Medium (Corning, Manassas, VA) supplemented by 10% fetal bovine serum (Atlanta Biologicals, Flowery Branch, GA) and 100 U mL^{-1} penicillin-streptomycin (Cellgro, Manassas, VA). Cells were incubated at 37 °C and 5% CO_2. To maintain log-phase, cells were trypsinized and split every 2–3 days.

Proliferation assay. GBM6 proliferation was assessed after 72 hours of treatment. Briefly, 1000 cells per well were plated on 96-well plates. After overnight incubation, medium was removed and replaced with treatment. After 72 hours 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, 5 mg mL^{-1}) was added, and plates were incubated for 4 hours at 37 °C.[26] Then all media was removed and replaced with 100 μL DMSO per well to dissolve formazan. Absorbance was measured at 570 nm with a reference wavelength of 630 nm with a Synergy 4 plate reader (Biotek, Winooski, VT).

IC_{50} determination. Survival percentages from proliferation experiments (treatment concentrations ranging from 0.78 μM to 100 μM) were plotted using Graphpad Prism 8. Non-linear regression curve fit analysis was used to predict the concentration at which cell survival would have been 50%.

Biological assay for MDA MB 231 breast carcinoma cells

Cell culture. MDA MB 231 cells were propagated in Dulbecco's Modified Eagles Medium (Corning, Manassas, VA) supplemented by 10% fetal bovine serum (Atlanta Biologicals, Flowery Branch, GA) and 100 U mL^{-1} penicillin-streptomycin (Cellgro, Manassas, VA). Cells were incubated at 37 °C and 5% CO_2. To maintain log-phase, cells were trypsinized and split every 3–4 days.

Proliferation assay. MDA-MB-231 proliferation was assessed after 72 hours of treatment. Briefly, 2000 cells per well were plated on 96-well plates. After overnight incubation, medium was removed and replaced with treatment. After 72 hours 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide (MTT, 5 mg mL^{-1}) was added, and plates were incubated for 4 hours at 37 °C. Then all media was removed and replaced with 100 μL DMSO per well to dissolve formazan. Absorbance was measured at 570 nm with a reference wavelength of 630 nm with a Synergy 4 plate reader (Biotek, Winooski, VT).

IC_{50} determination. Survival percentages from proliferation experiments (treatment concentrations ranging from 0.78 μM to 100 μM) were plotted using Graphpad Prism 8. Non-linear regression curve fit analysis was used to predict the concentration at which cell survival would have been 50%.

General procedure for 1,3-dipolar cycloaddition of the alkynol (condition 1)

A solution of the alkynol (1 equiv.) and the hydroximoyl chloride (1.2 equiv.) in 10 mL of dichloromethane was treated with triethylamine (1.5 equiv.). The reaction mixture was stirred at rt for 24 h until complete consumption of starting material as monitored by TLC analysis. After the reaction was complete, a minimum amount of silica gel was added, and the solvent was evaporated under reduced pressure. The crude products were purified by column chromatography over silica gel using hexanes/ethyl acetate as eluent to provide the desired products.

3-(3-(*p*-Tolyl)isoxazol-5-yl)propan-1-ol (3b). Following the general procedure for 1,3-dipolar cycloaddition (condition 1), alkynol **1a** (0.14 g, 1.66 mmol), (*Z*)-*N*-hydroxy-4-methylbenzimidoyl chloride (0.34 g, 1.99 mmol), and Et_3N (0.35 mL, 2.49 mmol) provided **3b** (0.30 g, 83%) as a white solid after column chromatography (hexanes/EtOAc, 4/1); R_f 0.4 (1 : 1 ethyl acetate : hexanes); mp: 48–50 °C; IR ν_{max} 3261, 3018, 2922, 2871, 2853, 1606, 1430, 1062, 1040, 798 cm^{-1}; ^1H NMR (500 MHz, CDCl3): δ 7.65 (d, $J = 8.1$ Hz, 2H), 7.23 (d, $J = 8.0$ Hz, 2H), 6.28 (s, 1H), 3.71 (t, $J = 6.2$ Hz, 2H), 2.88 (t, $J = 7.6$ Hz, 2H), 2.37 (s, 3H), 2.00–1.95 (m, 2H); $^{13}C\{1H\}$NMR (125 MHz, CDCl3): δ 173.4, 162.4, 140.0, 129.6 (2C), 126.6 (2C), 126.3, 99.1, 61.4, 30.3, 23.2, 21.4; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{13}H_{15}NO_2Na$: 240.0995; found 240.0995.

3-(3-(4-Fluorophenyl)isoxazol-5-yl)propan-1-ol (3c). Following the general procedure for 1,3-dipolar cycloaddition (condition 1), alkynol **1a** (0.20 g, 2.37 mmol), (*Z*)-4-fluoro-*N*-hydroxybenzimidoyl chloride (0.49 g, 2.85 mmol), and Et_3N (0.5 mL, 3.55 mmol) provided **3c** (0.50 g, 95%) as a white solid after column chromatography (hexanes/EtOAc, 4/1); R_f 0.4 (1 : 1 ethyl acetate : hexanes); mp: 70–72 °C; IR ν_{max} 3241, 3122, 2931, 2870, 1612, 1524, 1432, 1236, 1035, 842, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.76–7.72 (m, 2H), 7.11 (t, $J = 8.7$ Hz, 2H), 6.27 (s, 1H), 3.72 (t, $J = 6.2$ Hz, 2H), 2.90 (t, $J = 7.6$ Hz, 2H), 2.26 (br s, 1H, OH), 1.98 (tt, $J = 7.3$, 6.2 Hz, 2H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ 173.7, 163.7 (d, $J = 249.6$ Hz), 161.5, 128.6 (d, $J = 8.4$ Hz, 2C), 125.4 (d, $J = 3.4$ Hz), 115.9 (d, $J = 21.8$ Hz, 2C), 99.0, 61.4, 30.3, 23.2; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{12}H_{12}Cl_2FNO_2Na$: 244.0744; found 244.0743.

3-(3-(4-Bromophenyl)isoxazol-5-yl)propan-1-ol (3e). Following the general procedure for 1,3-dipolar cycloaddition (condition 1),

alkynol **1a** (0.20 g, 2.37 mmol), (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (0.67 g, 2.84 mmol), and Et_3N (0.5 mL, 3.55 mmol) provided **3e** (0.62 g, 93%) as a white solid after column chromatography (hexanes/EtOAc, 4/1); R_f 0.55 (1 : 1 hexanes/ethyl acetate); mp 80–82 °C; IR ν_{max} 3240, 3150, 2931, 2873, 1605, 1426, 1061, 1041, 833, 801 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, $J = 8.6$ Hz, 2H), 7.56 (d, $J = 8.6$ Hz, 2H), 6.29 (s, 1H), 3.73 (t, $J = 6.2$ Hz, 2H), 2.91 (t, $J = 7.6$ Hz, 2H), 2.07 (br s, 1H, OH), 1.98 (dd, $J = 14.3$, 6.9 Hz, 2H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ 173.8, 161.5, 132.1 (2C), 128.2 (2C), 128.1, 124.1, 99.0, 61.4, 30.2, 23.2; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{12}H_{12}BrNO_2Na$: 303.9943; found 303.9942.

3-(3-(4-(Trifluoromethyl)phenyl)isoxazol-5-yl)propan-1-ol (3g). Following the general procedure for 1,3-dipolar cycloaddition (condition 1), alkynol **1a** (0.30 g, 3.57 mmol), (*Z*)-*N*-hydroxy-4-(trifluoromethyl)benzimidoyl chloride (0.96 g, 4.28 mmol), and Et_3N (0.75 mL, 5.35 mmol) provided **3g** (0.91 g, 94%) as a white solid after column chromatography (hexanes/EtOAc, 4/1); R_f 0.5 (1 : 1 ethyl acetate : hexanes); mp: 50–52 °C; IR ν_{max} 331, 2955, 2936, 2874, 1603, 1438, 1462, 1324, 1164, 1111, 1063, 848 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, $J = 8.1$ Hz, 2H), 7.70 (d, $J = 9.1$ Hz, 2H), 6.37 (s, 1H), 3.75 (t, $J = 6.1$ Hz, 2H), 2.95 (t, $J = 7.6$ Hz, 2H), 2.04–1.99 (m, 2H), 1.80 (br s, 1H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ 174.2, 161.3, 132.6, 131.7 (q, $J = 32.7$ Hz), 127.1 (d, $J = 8.2$ Hz, 2C), 125.8 (q, $J = 3.8$ Hz, 2C), 123.8 (q, $J = 272.3$ Hz), 99.2, 61.4, 30.2, 23.2; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{13}H_{12}F_3NO_2Na$: 294.0712; found 294.0711.

3-(3-(4-Nitrophenyl)isoxazol-5-yl)propan-1-ol (3h). Following the general procedure for 1,3-dipolar cycloaddition (condition 1), alkynol **1a** (0.10 g, 1.19 mmol), (*Z*)-*N*-hydroxy-4-nitrobenzimidoyl chloride (0.29 g, 1.43 mmol), and Et_3N (0.25 mL, 1.78 mmol) provided **3h** (0.24 g, 80%) as a brown oil after column chromatography (hexanes/EtOAc, 5/2); R_f 0.4 (1 : 1 ethyl acetate : hexanes); IR ν_{max} 3350, 3130, 2960, 2928, 2850, 1590, 1514, 1460, 1340, 1175, 1105, 1003, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.30 (d, $J = 8.7$ Hz, 2H), 7.96 (d, $J = 8.7$ Hz, 2H), 6.41 (s, 1H), 3.76 (t, $J = 5.9$ Hz, 2H), 2.97 (t, $J = 7.6$ Hz, 2H), 2.05–2.00 (m, 2H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ 174.6, 160.6, 148.5, 135.4, 126.6 (2C), 124.2 (2C), 99.3, 61.4, 30.2, 23.2; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{12}H_{12}N_2O_4Na$: 271.0689; found 271.0688.

4-(3-(4-Fluorophenyl)isoxazol-5-yl)butan-1-ol (3j). Following the general procedure for 1,3-dipolar cycloaddition (condition 1), alkynol **1b** (0.31 g, 3.16 mmol), (*Z*)-4-fluoro-*N*-hydroxybenzimidoyl chloride (0.66 g, 3.79 mmol), and Et_3N (0.66 mL, 4.74 mol) provided **3j** (0.70 g, 94%) as a white solid after column chromatography (hexanes/EtOAc, 3/1); R_f 0.4 (1 : 1 ethyl acetate : hexanes); mp: 58–60 °C; IR ν_{max} 3443, 3405, 3132, 2940, 2929, 2861, 1606, 1591, 1524, 1433, 1346, 1231, 910, 842 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.74–7.72 (m, 2H), 7.10 (t, $J = 8.9$ Hz, 2H), 6.24 (s, 1H), 3.66 (t, $J = 6.4$ Hz, 2H), 2.79 (t, $J = 7.8$ Hz, 2H), 2.61 (br s, 1H OH), 1.83–1.77 (m, 2H), 1.66–1.623 (m, 2H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ 174.1, 163.6 (d, $J = 249.7$ Hz), 161.4, 128.6 (d, $J = 8.4$ Hz, 2C), 125.4 (d, $J = 3.3$ Hz), 115.9 (d, $J = 21.8$ Hz, 2C), 98.9, 62.0, 31.8, 26.5, 23.8; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{13}H_{14}FNO_2Na$: 258.0900; found 258.0900.

4-(3-(4-Bromophenyl)isoxazol-5-yl)butan-1-ol (3l). Following the general procedure for 1,3-dipolar cycloaddition (condition 1), alkynol **1b** (0.30 g, 3.06 mmol), (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (0.86 g, 3.67 mmol), and Et_3N (0.64 mL, 4.59 mmol) provided **3l** (0.84 g, 93%) as a pale yellow solid after column chromatography (hexanes/EtOAc, 3/1); R_f 0.5 (2 : 3 ethyl acetate : hexanes); mp: 60–62 °C; IR ν_{max} 3468, 3132, 2945, 2923, 2853, 1601, 1417, 1343, 1054, 902, 818, 721, 518 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, $J = 8.5$ Hz, 2H), 7.54 (d, $J = 8.5$ Hz, 2H), 6.26 (s, 1H), 3.66 (t, $J = 6.4$ Hz, 2H), 2.8 (t, $J = 7.6$ Hz, 2H), 2.12 (br s, 1H, OH), 1.81 (dt, $J = 15.4$, 7.6 Hz, 2H), 1.67–1.61 (m, 2H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ 174.2, 161.4, 132.1 (2C), 128.2 (2C), 128.1, 124.1, 98.8, 62.1, 31.8, 26.5, 23.8; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{13}H_{14}BrNO_2Na$: 318.0100; found 318.0099.

4-(3-(4-(Trifluoromethyl)phenyl)isoxazol-5-yl)butan-1-ol (3n). Following the general procedure for 1,3-dipolar cycloaddition (condition 1), alkynol **1b** (0.32 g, 3.26 mmol), (*Z*)-*N*-hydroxy-4-(trifluoromethyl)benzimidoyl chloride (0.87 g, 3.91 mmol), and Et_3N (0.68 mL, 4.89 mmol) provided **3n** (0.88 g, 95%) as a white solid after column chromatography (hexanes/EtOAc, 3/1); R_f 0.5 (2 : 3 ethyl acetate : hexanes); mp: 58–60 °C; IR ν_{max} 3400, 3137, 2947, 2922, 2871, 1601, 1461, 1321, 1175, 1123, 1111, 1060, 1015, 912, 851 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, 8.3 Hz, 2H), 7.68 (d. $J = 8.3$ Hz, 2H), 6.34 (s, 1H), 3.69 (t, $J = 6.4$ Hz, 2H), 2.84 (t, $J = 7.6$ Hz, 2H), 1.97 (br s, 1H, OH), 1.97–1.81 (m, 2H), 1.66 (dt, $J = 13.3$, 6.4 Hz, 2H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ 174.5, 161.2, 132.7, 131.6 (q, $J = 32.6$ Hz), 127.0 (2C), 125.8 (q, $J = 3.8$ Hz, 2C), 123.8 (q, $J = 272.2$ Hz), 99.0, 62.1, 31.8, 26.5, 23.8; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{14}H_{14}F_3NO_2Na$: 308.0868; found 308.0867.

4-(3-(4-Nitrophenyl)isoxazol-5-yl)butan-1-ol (3o). Following the general procedure for 1,3-dipolar cycloaddition (condition 1), alkynol **1b** (0.21 g, 2.14 mmol), (*Z*)-*N*-hydroxy-4-nitrobenzimidoyl chloride (0.52 g, 2.57 mmol), and Et_3N (0.45 mL, 3.21 mmol) provided **3o** (0.44 g, 78%) as a white solid after column chromatography (hexanes/EtOAc, 3/1); R_f 0.4 (1 : 1 ethyl acetate : hexanes); mp: 62–64 °C; IR ν_{max} 3349, 3132, 2955, 2923, 2854, 1593, 1514, 1460, 1342, 1175, 1105, 1003, 862, 809 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.31 (d, $J = 8.9$ Hz, 2H), 7.97 (d, $J = 8.9$ Hz, 2H), 6.4 (s, 1H), 3.72 (t, $J = 6.3$ Hz, 2H), 2.89 (t, $J = 7.6$ Hz, 2H), 1.88 (dt, $J = 15.4$, 7.6 Hz, 2H), 1.69 (dt, $J = 13.5$, 6.4 Hz, 2H), 1.34 (br s, 1H, OH); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ 175.0, 160.5, 148.5, 135.4, 127.6 (2C), 124.1 (2C), 99.2, 62.2, 31.8, 26.5, 23.8; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{13}H_{14}N_2O_4Na$: 285.0845; found 285.0844.

General procedure for 1,3-dipolar cycloaddition of the alkynoic acid (condition 1).

Deionized water (10 mL) was added into a round-bottomed flask containing the hydroximoyl chloride (2 equiv.) with stirring. The alkynoic acid **2a** (1 equiv.) was added into this mixture. Potassium carbonate (2.5 equiv.) was then added in small portions. The reaction mixture was stirred at rt until the reaction was complete as evidenced by TLC/NMR analysis. The reaction mixture was acidified with 4 N HCl and treated with diethyl ether and water (1 : 1, 20 mL). Sodium hydroxide was added to this mixture until the mixture was basic (litmus paper). The mixture was extracted with diethyl ether (3 × 10 mL), and 4 M HCl was then added to the aqueous layer until it was acidic

(litmus paper). The acidified aqueous layer was extracted with ethyl acetate (3 × 15 mL), and the resulting organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product, which was purified *via* column chromatography over silica gel using an appropriate hexanes–ethyl acetate ratio as an eluent system.

3-(3-(*p*-Tolyl)isoxazol-5-yl)propanoic acid (3q). Following the general procedure for 1,3-dipolar cycloaddition (condition 1), alkynoic acid **2a** (0.25 g, 2.54 mmol), (*Z*)-*N*-hydroxy-4-methylbenzimidoyl chloride (0.86 g, 5.08 mmol), and K_2CO_3 (0.88 g, 6.35 mmol) provided **3q** (0.52 g, 89%) as a white solid after column chromatography (hexanes/EtOAc, 1 : 1); R_f 0.4 (1 : 1 ethyl acetate : hexanes); mp: 162–164 °C; IR ν_{max} 3122, 2912, 2856, 1693, 1601, 1421, 1243, 1206, 951, 809 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): δ 7.74 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 7.9 Hz, 2H), 6.64 (s, 1H), 3.11 (t, J = 7.4 Hz, 2H), 2.80 (d, J = 7.4 Hz, 2H), 2.37 (s, 3H); $^{13}C\{^1H\}$NMR (125 MHz, CD_3COCD_3): δ 172.7, 172.3, 162.0, 139.8, 129.5 (2C), 126.7, 126.4 (2C), 98.9, 30.9, 21.9, 20.4; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_{13}NO_3Na$: 254.0787; found 254.0787.

3-(3-(4-Fluorophenyl)isoxazol-5-yl)propanoic acid (3r). Following the general procedure for 1,3-dipolar cycloaddition (condition 2), alkynoic acid **2a** (0.22 g, 2.24 mmol), (*Z*)-4-fluoro-*N*-hydroxybenzimidoyl chloride (0.78 g, 4.48 mmol), and K_2CO_3 (0.77 g, 5.60 mmol) provided **3r** (0.42 g, 80%) as a white solid after column chromatography (hexanes/EtOAc, 1 : 1); R_f 0.4 (1 : 1 ethyl acetate : hexanes); mp: 160–162 °C; IR ν_{max} 3117, 2927, 2848, 1691, 1605, 1589, 1524, 1428, 1233, 1204, 1233, 1204, 1156, 903, 815 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): δ 7.92 (dd, J = 8.4, 5.6 Hz, 2H), 7.27 (t, J = 8.7 Hz, 2H), 6.69 (s, 1H), 3.12 (t, J = 7.3 Hz, 2H), 2.81 (t, J = 7.3 Hz, 2H); $^{13}C\{^1H\}$NMR (125 MHz, CD_3COCD_3): δ 173.1, 172.2, 163.6 (d, J = 247.4 Hz), 161.2, 128.7 (d, J = 8.6 Hz, 2C), 125.9 (d, J = 2.8 Hz), 115.8 (d, J = 22.0 Hz, 2C), 99.0, 30.8, 21.9; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{12}H_{10}FNO_3Na$: 258.0537; found 258.0536.

3-(3-(4-Bromophenyl)isoxazol-5-yl)propanoic acid (3t). Following the general procedure for 1,3-dipolar cycloaddition (condition 2), alkynoic acid **2a** (0.31 g, 3.16 mmol), (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (1.48 g, 6.32 mmol), and K_2CO_3 (1.09 g, 7.90 mmol) provided **3t** (0.79 g, 85%) as a white solid after column chromatography (hexanes/EtOAc, 1 : 1); R_f 0.4 (1 : 1 ethyl acetate : hexanes); mp: 180–182 °C; IR ν_{max} 3120, 2928, 2849, 1690, 1600, 1590, 1525, 1425, 1230, 1200, 1155, 900 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): δ 7.82 (d, J = 8.6 Hz, 2H), 7.68 (d, J = 8.6 Hz, 2H), 6.72 (s, 1H), 3.13 (t, J = 7.3 Hz, 2H), 2.81 (t, J = 7.3 Hz, 2H); $^{13}C\{^1H\}$NMR (125 MHz, CD_3COCD_3): δ 173.3, 172.2, 161.2, 132.1 (2C), 128.7, 128.4 (2C), 123.5, 99.0, 30.8, 21.9; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{12}H_{10}BrNO_3Na$: 317.9736; found 317.9736.

3-(3-(4-(Trifluoromethyl)phenyl)isoxazol-5-yl)propanoic acid (3v). Following the general procedure for 1,3-dipolar cycloaddition (condition 2), alkynoic acid **2a** (0.25 g, 2.55 mmol), (*Z*)-*N*-hydroxy-4-(trifluoromethyl)benzimidoyl chloride (1.13 g, 5.10 mmol), and K_2CO_3 (0.88 g, 6.38 mmol) provided **3v** (0.67 g, 92%) as a white solid after column chromatography (hexanes/EtOAc, 1 : 1); R_f 0.4 (1 : 1 ethyl acetate : hexanes); mp: 173–175 °C; IR ν_{max} 3129, 2929, 2851, 1702, 1599, 1441, 1320, 1166, 1133, 1062, 929, 846, 815 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): δ 8.1 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 6.82 (s, 1H), 3.15 (t, J = 6.3 Hz, 2H), 2.83 (t, J = 6.4 Hz, 2H); $^{13}C\{^1H\}$NMR (125 MHz, CD_3COCD_3): δ 173.7, 172.3, 161.0, 133.3, 130.9 (q, J = 32.3 Hz), 127.2 (2C), 125.9 (d, J = 3.5 Hz, 2C), 124.2 (q, J = 271.4 Hz), 99.3, 30.8, 21.9; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_{10}F_3NO_3Na$: 308.0505; found 308.0504.

3-(3-Methylisoxazol-5-yl)propanoic acid (3w). Following the general procedure for 1,3-dipolar cycloaddition (condition 2), alkynoic acid **2a** (0.26 g, 2.65 mmol), (*Z*)-*N*-hydroxyacetimidoyl chloride 3-(3-methylisoxazol-5-yl)propanoate (0.46 g, 5.30 mmol), and K_2CO_3 (0.92 g, 6.63 mmol) provided **3v** (0.31 g, 76%) as a white solid after column chromatography (hexanes/EtOAc, 1 : 1); R_f 0.4 (1 : 1 ethyl acetate : hexanes); mp: 80–82 °C; IR ν_{max} 3129, 3033, 2993, 2927, 2866, 1690, 1600, 1436, 1412, 1309, 1196, 1001, 924, 881, 827, 671 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): δ 6.01 (s, 1H), 3.00 (t, J = 7.4 Hz, 2H), 2.71 (t, J = 7.4 Hz, 2H), 2.2 (s, 3H); $^{13}C\{^1H\}$NMR (125 MHz, CD_3COCD_3): δ 172.3, 171.6, 159.4, 101.5, 30.8, 21.7, 10.3; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_7H_9NO_3Na$: 178.0474; found 178.0474.

3-(3-Propylisoxazol-5-yl)propanoic acid (3x). Following the general procedure for 1,3-dipolar cycloaddition (condition 2), alkynoic acid **2a** (0.22 g, 2.24 mmol), (*Z*)-*N*-hydroxybutyrimidoyl chloride 3-(3-propylisoxazol-5-yl)propanoate (0.54 g, 4.48 mmol), and K_2CO_3 (0.77 g, 5.60 mmol) provided **3x** (0.32 g, 78%) as a white solid after column chromatography (hexanes/EtOAc, 1 : 1); R_f 0.4 (1 : 1 ethyl acetate : hexanes); mp: 98–100 °C; IR ν_{max} 3124, 2958, 2931, 2871, 1690, 1598, 1431, 1414, 1309, 1227, 1215, 1000, 924, 828, 878 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): δ 6.07 (s, 1H), 3.01 (t, J = 7.4 Hz, 2H), 2.72 (t, J = 7.4 Hz, 2H), 2.56 (t, J = 7.5 Hz, 2H), 1.69–1.61 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$NMR (125 MHz, CD_3COCD_3): δ 172.3, 171.5, 163.4, 100.4, 30.9, 27.6, 21.8, 21.3, 13.1; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_9H_{13}NO_3Na$: 206.0787; found 206.0789.

General procedure for fluoro-etherification 4(a–o)

A solution of isoxazole alcohol **3(a–o)** (0.2 mmol) and Selectfluor (0.11 g, 0.3 mmol) in CH_3CN (2 mL) was refluxed under N_2 for 24 h. Then the reaction mixture was cooled, and water was added and extracted with ethyl acetate. The organic phase was washed several times with water and finally with brine. The combined organic layer was dried over anhydrous $MgSO_4$ and filtered. The filtrate was evaporated under reduced pressure to give the crude product which was purified over silica gel column chromatography using hexane/ethyl acetate (9 : 1) as eluent.

4-Fluoro-3-phenyl-1,6-dioxa-2-azaspiro[4.4]non-2-ene ((±)-4a/4a′). Oil; 39.8 mg (90%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); IR ν_{max} 3063, 2990, 2957, 2926, 1447, 1375, 1275, 1260, 1060, 1039, 907, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta_{4a/4a'}$ 7.8–7.76 (m, 2H), 7.44 (d, J = 3.5 Hz, 3H), 5.76 (d, J = 53.2 Hz, 1H), 4.17 (dd, J = 14.8, 7.4 Hz, 1H), 4.09 (dd, J = 14.8, 7.4 Hz, 1H), 2.52–2.45 (m, 1H), 2.34–2.22 (m, 2H), 2.13–2.05 (m, 1H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$) $\delta_{4a/4a'}$ 162.2 (d, J = 16.0 Hz), 130.6, 128.9 (2C), 127.8, 126.7 (2C), 116.2 (d, J = 28.3 Hz), 96.7 (d, J = 187.6 Hz), 69.7, 28.8 (d, J = 5.6 Hz), 23.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ_{4a} −185.4 (d, J = 53.1 Hz); ^{19}F NMR (376 MHz,

$CDCl_3$): $\delta_{4a'}$ −201.6 (d, J = 52.5 Hz); HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{12}H_{12}FNO_2Na$: 244.0744; found 244.0745.

4-Fluoro-3-(*p*-tolyl)-1,6-dioxa-2-azaspiro[4.4]non-2-ene ((±)-4b/4b′). Oil; 41.8 mg (89%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); IR ν_{max} 3036, 2987, 2957, 2922, 2894, 1611, 1456, 1372, 1275, 1260, 1059, 036, 906, 782 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta_{4b/4b'}$ 7.66 (d, J = 7.5 Hz, 2H), 7.24 (d, J = 7.9 Hz, 2H), 5.74 (d, J = 53.2 Hz, 1H), 4.16 (dd, J = 14.9, 7.3 Hz, 1H), 4.08 (dd, J = 14.3 Hz, 7.4 Hz, 1H), 2.50–2.44 (m, 1H), 2.39 (s, 3H), 2.32–2.19 (m, 2H), 2.13–2.04 (m, 1H); ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$) $\delta_{4b/4b'}$ 155.6 (d, J = 15 Hz), 141.0, 129.6 (2C), 126.6 (2C), 125.0, 116.0 (d, J = 27.8 Hz), 96.8 (d, J = 187.6 Hz), 69.6, 28.8 (d, J = 5.4 Hz), 23.9, 21.5; ^{19}F NMR (376 MHz, $CDCl_3$): δ_{4b} −185.52 (d, J = 53.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta_{4b'}$ −201.7 (d, J = 52.5 Hz); HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{13}H_{14}FNO_2Na$: 258.0900; found 258.0901.

4-Fluoro-3-(4-fluorophenyl)-1,6-dioxa-2-azaspiro[4.4]non-2-ene ((±)-4c/4c′). Oil; 44.5 mg (93%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); IR ν_{max} 2990, 2962, 2896, 1602, 1512, 1415, 1371, 1229, 1059, 1033, 907, 887 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_{4c} 7.76 (dd, J = 8.0, 5.8 Hz, 2H), 7.13 (t, J = 8.5 Hz, 2H), 5.73 (d, J = 53.3 Hz, 1H), 4.17 (dd, J = 14.6, 7.4 Hz, 1H), 4.1 (dd, J = 14.2, 7.5 Hz, 1H), 2.50–2.44 (m, 1H), 2.33–2.20 (m, 2H), 2.14–2.05 (m, 1H); ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$) δ_{4c} 164.0 (d, J = 251.6 Hz), 154.7 (d, J = 15.1 Hz), 128.7 (d, J = 8.6 Hz, 2C), 124.1 (d, J = 3.4 Hz), 116.3 (d, J = 27.7 Hz), 116.1 (d, J = 22.1 Hz, 2C), 96.7 (d, J = 187.9 Hz), 69.7, 28.8 (d, J = 5.5 Hz), 23.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ_{4c} −108 (m), −185.8 (d, J = 53.2 Hz); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta_{4c'}$ 7.79 (ddd, J = 8.8, 5.3, 1.1 Hz, 2H), 7.13 (t, J = 8.7 Hz, 2H), 5.86 (d, J = 52.6 Hz, 1H), 4.28–4.22 (m, 1H), 4.13–4.09 (m, 1H), 2.47–2.41 (m, 1H), 2.35–2.22 (m, 2H), 2.17–2.09 (m, 1H); ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$) $\delta_{4c'}$ 164.2 (d, J = 251.9 Hz), 155.3 (d, J = 16.2 Hz), 128.9 (d, J = 8.6 Hz, 2C), 123.9 (d, J = 2.2 Hz), 116.1 (d, J = 22.1 Hz, 2C), 112.7 (d, J = 13.1 Hz), 93.6 (d, J = 201.7 Hz), 70.1, 34.1, 24.2; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta_{4c'}$ −108 (tt, J = 8.4, 5.3 Hz), −202.5 (d, J = 52.6 Hz); HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{12}H_{11}F_2NO_2Na$: 262.0650; found 262.0651.

3-(4-Chlorophenyl)-4-fluoro-1,6-dioxa-2-azaspiro[4.4]non-2-ene ((±)-4d/4d′). Oil; 48.6 mg (95%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); IR ν_{max} 2987, 2957, 2851, 2922, 2896, 2597, 1494, 1405, 1355, 1275, 1091, 1062, 1014, 833 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_{4d} 7.72 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 5.72 (d, J = 53.3 Hz, 1H), 4.20–4.15 (m, 1H), 4.10 (dd, J = 14.9, 7.5 Hz, 1H), 2.55–2.41 (m, 2H), 2.31–2.20 (m, 1H), 2.13–2.05 (m, 1H); ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$) δ_{4d} 156.9, 136.7, 129.2 (2C), 128.2 (2C), 125.8, 110.0, 96.5 (d, J = 187.9 Hz), 70.2, 31.2, 23.9; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta_{4d'}$ −185.9 (d, J = 52.6 Hz); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta_{4d'}$ 7.71 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.7 Hz, 2H), 5.86 (d, J = 52.6 Hz, 1H), 4.33–4.26 (m, 1H), 4.14–4.09 (m, 1H), 2.47–2.42 (m, 1H), 2.35–2.27 (m, 2H), 2.18–2.12 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta_{4d'}$ −202.3 (d, J = 52.5 Hz); HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{12}H_{11}ClFNO_2Na$: 278.0354; found 278.0356.

3-(4-Bromophenyl)-4-fluoro-1,6-dioxa-2-azaspiro[4.4]non-2-ene ((±)-4e/4e′). Oil; 57.0 mg (95%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); IR ν_{max} 3005, 2987, 2960, 2927, 2899, 2858, 1594, 1491, 1457, 1275, 1260, 1067, 912, 754 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_{4e} 7.66–7.62 (m, 2H), 7.58–7.56 (m, 2H), 5.72 (d, J = 53.3 Hz, 1H), 4.23–4.14 (m, 1H), 4.13–4.07 (m, 1H), 2.56–2.51 (m, 1H), 2.33–2.20 (m, 2H), 2.13–2.06 (m, 1H); ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$) δ_{4e} 157.1 (d, J = 16.5 Hz), 132.2 (2C), 132.1, 128.1 (2C), 125.1, 101.6 (d, J = 23.1 Hz), 96.4 (d, J = 188.1 Hz), 69.8, 28.9 (d, J = 5.6 Hz), 23.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ_{4e} −186.1 (d, J = 53.8 Hz); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta_{4e'}$ 7.66 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 6.8 Hz, 2H), 5.86 (d, J = 52.7 Hz, 1H), 4.25–4.22 (m, 1H), 4.18–4.10 (m, 1H), 2.47–2.43 (m, 1H), 2.36–2.22 (m, 2H), 2.17–2.08 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta_{4e'}$ −190.4 (d, J = 52.2 Hz); HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{12}H_{11}BrFNO_2Na$: 321.9849; found 321.9851.

3-(2,6-Dichlorophenyl)-4-fluoro-1,6-dioxa-2-azaspiro[4.4]non-2-ene ((±)-4f/4f′). Oil; 43.5 mg (75%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); IR ν_{max} 2988, 2956, 2850, 2920, 2890, 2595, 1494, 1400, 1350, 1272, 1090, 1060, 1010, 833 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta_{4f/4f'}$ 7.40 (dd, J = 7.7, 3.3 Hz, 2H), 7.31 (ddd, J = 8.9, 7.4, 2.7 Hz, 1H), 6.13 (d, J = 10.1 Hz, 1H), 4.23 (t, J = 6.3 Hz, 1H), 3.21 (t, J = 7.5 Hz, 1H), 2.95 (t, J = 7.5 Hz, 1H), 2.84 (t, J = 7.5 Hz, 1H), 2.36–2.31 (m, 1H), 2.17–2.11 (m, 1H); ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$) $\delta_{4f/4f'}$ 158.8, 135.5 (2C), 130.9, 128.3, 128.2 (2C), 102.8 (d, J = 12.42 Hz), 97.3 (d, J = 154.9 Hz), 63.6, 31.7, 23.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ_{4f} −187.2 (d, J = 52.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta_{4f'}$ −202.4 (d, J = 53.4 Hz); HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{12}H_{10}Cl_2FNO_2Na$: 311.9965; found 311.9967.

4-Fluoro-3-(4-(trifluoromethyl)phenyl)-1,6-dioxa-2-azaspiro[4.4]non-2-ene ((±)-4g/4g′). Oil; 53.2 mg (92%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); IR ν_{max} 3005, 2954, 2928, 2850, 1460, 1325, 1270, 1265, 1170, 1130, 1070, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_{4g} 7.89 (d, J = 8.1 Hz, 2H), 7.70 (d, J = 8.2 Hz, 2H), 5.77 (d, J = 53.3 Hz, 1H), 4.19 (dd, J = 14.6, 7.3 Hz, 1H), 4.12 (dd, J = 14.5, 7.4 Hz, 1H), 2.53–2.46 (m, 1H), 2.35–2.30 (m, 1H), 2.29–2.22 (m, 1H), 2.15–2.08 (m, 1H); ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$) δ_{4g} 154.6 (d, J = 15.2 Hz), 131.2, 128.2, 126.9 (2C), 125.9 (dd, J = 7.5, 3.9 Hz, 2C), 123.7 (q, J = 276.6 Hz), 116.8 (d, J = 27.8 Hz), 96.2 (d, J = 188.1 Hz), 69.9, 28.9 (d, J = 5.6 Hz), 23.9; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta_{4g'}$ 7.90 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 8.3 Hz, 2H), 5.94 (d, J = 52.2 Hz, 1H), 3.00–2.85 (m, 3H), 2.79–2.73 (m, 1H), 2.62–2.57 (m, 1H), 2.36–2.31 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): δ_{4g} −62.9 (s), −191.6 (d, J = 52.4 Hz); HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{26}H_{20}F_8N_2O_4Na$: 599.1187; found 599.1200.

4-Fluoro-3-(4-nitrophenyl)-1,6-dioxa-2-azaspiro[4.4]non-2-ene ((±)-4h/4h′). Oil; 42.6 mg (80%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); IR ν_{max} 3008, 2987, 2950, 2921, 2852, 1607, 1518, 1458, 1345, 1275, 1260, 1055, 914, 853 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta_{4h/4h'}$ 8.30 (d, J = 8.9 Hz, 2H), 7.94 (d, J = 8.0 Hz, 2H), 5.79 (d, J = 53.3 Hz, 1H), 4.20 (dd, J = 14.5, 7.4 Hz, 1H), 4.13 (dd, J = 14.7, 7.5 Hz, 1H), 2.53–2.48 (m, 1H), 2.37–2.25 (m, 2H), 2.17–2.12 (m, 1H); ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$) $\delta_{4h/4h'}$ 167.6, 148.7, 133.8, 127.4 (2C), 124.2 (2C), 117.2 (d, J = 28.0 Hz), 95.9 (d, J = 188.3 Hz), 70.1, 28.9 (d, J = 5.5 Hz), 23.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ_{4h} −186.1 (d, J = 53.9 Hz); HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{12}H_{11}FN_2O_4Na$: 289.0595; found 289.0594.

4-Fluoro-3-phenyl-1,6-dioxa-2-azaspiro[4.5]dec-2-ene ((±)-4i/4i′). Oil; 42.3 mg (90%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl

acetate : hexanes); IR ν_{max} 3061, 3003, 2954, 2886, 2853, 1446, 1377, 1275, 1260, 1203, 905, 889, 764, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta_{4i/4i'}$ 7.78–7.76 (m, 2H), 7.43 (dd, J = 5.2, 1,8 Hz, 3H), 5.5 (d, J = 53.1 Hz, 1H). 4.08 (td, J = 12.3, 2.7 Hz, 1H), 3.76 (dd, J = 11.4, 4.4 Hz, 1H), 2.03–1.89 (m, 4H), 1.81–1.74 (m, 1H), 1.69–1.66 (m, 1H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$) $\delta_{4i/4i'}$ 155.9 (d, J = 15.2 Hz), 130.6, 130.9 (2C), 127.8, 126.7 (2C), 107.4 (d, J = 26.4 Hz), 98.01 (d, J = 188.8 Hz), 63.6, 26.2 (d, J = 7.3 Hz), 24.8, 18.6 (d, J = 2.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ_{4i} −185.5 (d, J = 53.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta_{4i'}$ −201.8 (d, J = 52.5 Hz); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_{14}FNO_2Na$: 258.0900; found 258.0901.

4-Fluoro-3-(4-fluorophenyl)-1,6-dioxa-2-azaspiro[4.5]dec-2-ene ((±)-4j/4j′). Oil; 46.1 mg (91%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); IR ν_{max} 3003, 2950, 2927, 2889, 2851, 1603, 1513, 1375, 1233, 1160, 1078, 0146, 905, 838, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta_{4j/4j'}$ 7.76 (d, J = 7.8, 5.5 Hz, 2H), 7.12 (t, J = 8.6 Hz, 2H), 5.51 (d, J = 53.2 Hz, 1H), 4.08 (td, J = 12.1, 2.7 Hz, 1H), 3.77 (dd, J = 11.4, 4.3 Hz, 1H), 2.03–1.89 (m, 4H), 1.82–1.73 (m, 1H), 1.69–1.67 (br m, 1H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$) $\delta_{4j/4j'}$ 164.0 (d, J = 251.6 Hz), 155.0 (d, J = 14.1 Hz), 128.7 (d, J = 8.6 Hz, 2C), 124.1 (d, J = 3.4 Hz), 116.1 (d, J = 22.1 Hz, 2C), 107.5 (d, J = 26.3 Hz), 98.0 (d, J = 188.8 Hz), 63.6, 26.1 (d, J = 7.2 Hz), 24.8, 18.6 (d, J = 2.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ_{4j} −109.1 (m), −186.0 (d, J = 53.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta_{4j'}$ −112.3 (m), −206.2 (d, J = 52.5 Hz); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_{13}F_2NO_2Na$: 276.0806; found 276.0807.

3-(4-Chlorophenyl)-4-fluoro-1,6-dioxa-2-azaspiro[4.5]dec-2-ene ((±)-4k/4k′). Oil; 47.5 mg (88%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); IR ν_{max} 2985, 2958, 2850, 2925, 2898, 2595, 1490, 1400, 1352, 1276, 1093, 1060, 1010, 833 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta_{4k/4k'}$ 7.70 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 5.51 (d, J = 53.2 Hz, 1H), 4.07 (td, J = 12.3, 2.7 Hz, 1H), 3.77 (dd, J = 11.4, 4.4 Hz, 1H), 2.02–1.89 (m, 4H), 1.82–1.73 (m, 1H), 1.69–1.67 (m, 1H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$) $\delta_{4k/4k'}$ 155.1 (d, J = 15.1 Hz), 136.6, 129.2 (2C), 128.0 (2C), 126.4, 107.7 (d, J = 26.3 Hz), 97.8 (d, J = 188.9 Hz), 63.7, 26.1 (d, J = 7.3 Hz), 24.8, 18.6 (d, J = 2.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ_{4k} −185.6 (d, J = 53.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta_{4k'}$ −192.7 (d, J = 53.2 Hz); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_{10}Cl_2FNO_3 \cdot H_2ONa$: 358.0019; found 358.0021.

3-(4-Bromophenyl)-4-fluoro-1,6-dioxa-2-azaspiro[4.5]dec-2-ene ((±)-4l/4l′). Oil; 59.1 mg (94%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); IR ν_{max} 3010, 2950, 2927, 2886, 2851, 1588, 1492, 1401, 1267, 1079, 1046, 1010, 908, 878, 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta_{4l/4l'}$ 7.63 (d, J = 7.7 Hz, 2H), 7.56 (d, J = 8.6 Hz, 2H), 5.5 (d, J = 53.2 Hz, 1H), 4.10–4.04 (m, 1H), 3.78–3.75 (m, 1H), 2.02–1.91 (m, 4H), 1.81–1.72 (m, 1H), 1.69–1.67 (m, 1H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$) $\delta_{4l/4l'}$ 155.37 (d, J = 15.1 Hz), 132.3 (2C), 128.8, 128.3 (2C), 125.1, 107.8 (d, J = 26.2 Hz), 97.9 (d, J = 188.9 Hz), 63.8, 26.3 (d, J = 7.3 Hz), 24.9, 18.7 (d, J = 2.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ_{4l} −190.5 (d, J = 52.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta_{4l'}$ −206.0 (d, J = 52.5 Hz); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_{13}BrFNO_2Na$: 336.0005; found 336.0006.

3-(2,6-Dichlorophenyl)-4-fluoro-1,6-dioxa-2-azaspiro[4.5]dec-2-ene ((±)-4m/4m′). Oil; 47.4 mg (78%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); IR ν_{max} 3000, 2955, 2925, 2853, 1578, 1560, 1430, 1333, 1275, 1196, 876, 780 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta_{4m/4m'}$ 7.41–7.39 (m, 2H), 7.33 (dd, J = 8.9, 7.1 Hz, 1H), 5.54 (d, J = 53.2 Hz, 1H), 4.14 (td, J = 12.2, 2.7 Hz, 1H), 3.84 (dd, J = 11.6, 4.5 Hz, 1H), 2.06–1.89 (m, 4H), 1.82–1.76 (m, 1H), 1.72–1.68 (m, 1H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$) $\delta_{4m/4m'}$ 153.1 (d, J = 16.2 Hz), 135.9, 131.5 (2C), 128.4, 128.3 (2C), 108.0 (d, J = 25.8 Hz), 99.1 (d, J = 191.1 Hz), 63.9, 26.2 (d, J = 7.6 Hz), 24.8, 18.6 (d, J = 2.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ_{4m} −188.1 (d, J = 53.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta_{4m'}$ −193.3 (d, J = 53.7 Hz); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_{12}Cl_2FNO_2Na$: 326.0121; found 326.0120.

4-Fluoro-3-(4-(trifluoromethyl)phenyl)-1,6-dioxa-2-azaspiro [4.5]dec-2-ene ((±)-4n/4n′). Oil; 57.6 mg (95%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); IR ν_{max} 3003, 2952, 2924, 2853, 1459, 1324, 1275, 1260, 1169, 1130, 1070, 879, 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta_{4n/4n'}$ 7.88 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.2 Hz, 2H), 5.55 (d, J = 53.2 Hz, 1H), 4.11–4.05 (m, 1H), 3.78 (dd, J = 11.5, 4.2 Hz, 1H), 2.04–1.91 (m, 4H), 1.80–1.74 (m, 1H), 1.71–1.67 (m, 1H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$) $\delta_{4n/4n'}$ 156.2 (d, J = 15.1 Hz), 130.9 (q, J = 31.6 Hz), 128.8 (d, J = 3.0 Hz), 126.9 (2C), 125.87 (dd, J = 6.7, 3.4 Hz, 2C), 123.7 (q, J = 265.0 Hz), 108.1 (d, J = 25.9 Hz), 97.6 (d, J = 189.9 Hz), 63.7, 29.7, 26.1 (d, J = 7.2 Hz), 18.5 (d, J = 2.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta_{4n'}$ −62.8 (s), −191.4 (d, J = 52.3 Hz); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_{10}Cl_2FNO_3 \cdot H_2ONa$: 358.0019; found 358.0021.

4-Fluoro-3-(4-nitrophenyl)-1,6-dioxa-2-azaspiro[4.5]dec-2-ene ((±)-4o/4o′). Oil; 46.0 mg (82%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); ^1H NMR (500 MHz, $CDCl_3$): $\delta_{4o/4o'}$ 8.30 (d, J = 8.8 Hz, 2H), 7.97 (d, J = 8.2 Hz, 2H), 5.56 (d, J = 53.3 Hz, 1H) 4.11–4.06 (td, J = 12.2, 2.7 Hz, 1H), 3.80 (dd, J = 11.3, 4.2 Hz, 1H), 2.05–1.92 (m, 4H), 1.84–1.79 (m, 1H), 1.72–1.69 (m, 1H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$) $\delta_{4o/4o'}$ 154.5 (d, J = 15.2 Hz), 148.7, 133.4, 127.5 (2C), 124.2 (2C), 108.6 (d, J = 26.2 Hz), 97.2 (d, J = 189.4 Hz), 63.9, 26.0 (d, J = 7.3 Hz), 24.7, 18.5 (d, J = 1.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ_{4o} −185.7 (d, J = 54.0 Hz); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_{13}Cl_2FN_2O_4Na$: 303.0751; found 303.0752.

General procedure for fluoro-lactonization 5(a–k)

A solution of isoxazole acid **3(p–z)** (0.2 mmol) and Selectfluor (0.11 g, 0.3 mmol) in CH_3CN (2 mL) was refluxed under N_2 for 24 h. Then, the reaction mixture was cooled, and water was added and extracted with ethyl acetate. The organic phase was washed several times with water and finally with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The filtrate was evaporated under reduced pressure to give the crude product which was purified over silica gel column chromatography using hexane/ethyl acetate (4 : 1) as eluent.

4-Fluoro-3-phenyl-1,6-dioxa-2-azaspiro[4.4]non-2-en-7-one ((±)-5a/5a′). Oil; 45.6 mg (97%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); IR ν_{max} 2987, 2950, 2924, 2848, 1798, 1448, 1370, 1185, 1108, 1012, 880, 768 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_{5a} 7.77 (d, J = 7.8 Hz, 2H), 7.51–7.47 (m, 3H), 5.93 (d, J = 52.2 Hz, 1H), 2.98–2.83 (m, 2H), 2.76–2.70 (m, 1H), 2.59–2.54 (m, 1H);

$^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ_{5a} 173.5, 156.1 (d, $J = 14.8$ Hz), 131.5, 129.2 (2C), 127.0 (2C), 126.4, 112.7 (d, $J = 30.1$ Hz), 96.8 (d, $J = 191.8$ Hz), 27.1 (d, $J = 1.7$ Hz), 24.8 (d, $J = 7.1$ Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ_{5a} −190.2 (d, $J = 51.6$ Hz); ^1H NMR (500 MHz, $CDCl_3$): $\delta_{5a'}$ 7.79 (d, $J = 7.4$ Hz, 2H), 7.49 (dt, $J = 14.6$, 6.8 Hz, 3H), 6.08 (d, $J = 51.4$ Hz, 1H), 2.95–2.85 (m, 1H), 2.77–2.71 (m, 3H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): $\delta_{5a'}$ 173.0, 157.1 (d, $J = 16.4$ Hz), 137.7, 129.0 (2C), 127.1 (d, $J = 2.1$ HZ, 2C), 126.1 (d, $J = 2.0$ Hz), 108.9 (d, $J = 14.0$ Hz), 95.7 (d, $J = 207.5$ Hz), 28.7, 27.7; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta_{5a'}$ −205.9 (d, $J = 51.4$ Hz); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{12}H_{10}FNO_3Na$: 258.0537; found 258.0536.

4-Fluoro-3-(*p*-tolyl)-1,6-dioxa-2-azaspiro[4.4]non-2-en-7-one ((±)-5b/5b′). White solid; 44.8 mg (90%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); mp: 112–114 °C; IR ν_{max} 3028, 2990, 2955, 2922, 2848, 1795, 1608, 1452, 1371, 1278, 1247, 1176, 1128, 1005, 873, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_{5b} 7.65 (d, $J = 8.0$ Hz, 2H), 7.27 (d, $J = 8.0$ Hz, 2H), 5.91 (d, $J = 52.2$ Hz, 1H), 2.98–2.82 (m, 2H), 2.75–2.70 (m, 1H), 2.59–2.53 (m, 1H), 2.41 (s, 3H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ_{5b} 173.6, 156.0 (d, $J = 14.7$ Hz), 142.1, 129.9 (2C), 125.9 (2C), 123.5, 112.6 (d, $J = 30.1$ Hz), 96.9 (d, $J = 191.8$ Hz), 27.1 (d, $J = 1.8$ Hz), 24.8 (d, $J = 7.0$ Hz), 21.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ_{5b} −190.1 (d, $J = 51.9$ Hz); ^1H NMR (500 MHz, $CDCl_3$): $\delta_{5b'}$ 7.67 (d, $J = 7.1$ Hz, 2H), 7.26 (d, $J = 7.6$ Hz, 2H), 6.1 (d, $J = 51.5$ Hz, 1H), 2.93–2.86 (m, 1H), 2.79–2.70 (m, 3H), 2.40 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta_{5b'}$ −205.8 (d, $J = 51.5$ Hz); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_{12}FNO_3Na$: 272.0693; found 272.0692.

4-Fluoro-3-(4-fluorophenyl)-1,6-dioxa-2 azaspiro[4.4]-non-2-en-7-one ((±)-5c/5c′). Oil; 48.1 mg (95%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); IR ν_{max} 3076, 3013, 2952, 2924, 2852, 1796, 1602, 1513, 1416, 1376, 1232, 1022, 882 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_{5c} 7.77 (dd, $J = 8.0$, 5.5 Hz, 2H), 7.16 (t, $J = 8.5$ Hz, 2H), 5.90 (d, $J = 52.5$ Hz, 1H), 2.90 (ddt, $J = 22.6$, 19.4, 9.5 Hz, 2H), 2.73 (ddd, $J = 16.4$, 9.2, 2.9 Hz, 1H), 2.59–2.54 (m, 1H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ_{5c} 173.4, 164.5 (d, $J = 253.3$ Hz), 155.2 (d, $J = 14.0$ Hz), 129.2 (d, $J = 8.7$ Hz, 2C), 122.6 (d, $J = 3.4$ Hz), 116.5 (d, $J = 22.2$ Hz, 2C), 112.7 (d, $J = 30.1$ Hz), 96.7 (d, $J = 192.0$ Hz), 27.1 (d, $J = 1.8$ Hz), 24.8 (d, $J = 7.0$ Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ_{5c} −107.1 (m), −190.4 (d, $J = 52.2$ Hz); ^1H NMR (500 MHz, $CDCl_3$): $\delta_{5c'}$ 7.80 (dd, $J = 7.7$, 5.4 Hz, 2H), 7.16 (t, $J = 8.6$ Hz, 2H), 6.1 (d, $J = 51.5$ Hz, 1H), 2.95–2.85 (m, 1H), 2.79–2.71 (m, 3H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): $\delta_{5c'}$ 172.9, 164.7 (d, $J = 253.5$ Hz), 156.1 (d, $J = 16.4$ Hz), 129.3 (d, $J = 8.4$ Hz, 2C), 122.4 (d, $J = 1.8$ Hz), 116.4 (d, $J = 22.1$ Hz, 2C), 108.9 (d, $J = 14.2$ HZ), 95.6 (d, $J = 207.5$ Hz), 28.6, 27.7; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta_{5c'}$ −106.7 (m), −206.2 (d, $J = 51.5$ Hz); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{12}H_9F_2NO_3Na$: 276.0443; found 276.0445.

3-(4-Chlorophenyl)-4-fluoro-1,6-dioxa-2-azaspiro[4.4]non-2-en-7-one ((±)-5d/5d′). Oil; 50.7 mg (94%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); IR ν_{max} 3099, 2957, 2922, 2848, 1798, 1608, 1446, 1275, 1123, 1024, 880, 747 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_{5d} 7.70 (d, $J = 8.4$ Hz, 2H), 7.45 (d, $J = 8.3$ Hz, 2H), 5.95 (d, $J = 52.1$ Hz, 1H), 2.98–2.83 (m, 1H), 2.77–2.69 (m, 1H), 2.59–2.54 (m, 1H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ_{5d} 173.4, 155.23 (d, $J = 14.9$ Hz), 137.7, 129.5 (2C), 128.2 (2C), 124.8, 112.8 (d, $J = 30.2$ Hz), 96.56 (d, $J = 192.1$ Hz), 27.02 (d, $J = 1.87$ Hz), 24.81 (d, $J = 7.1$ Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ_{5d} −190.4 (d, $J = 52.6$ Hz); ^1H NMR (500 MHz, $CDCl_3$): $\delta_{5d'}$ 7.73 (d, $J = 8.5$ Hz, 2H), 7.45 (d, $J = 8.5$ Hz, 2H), 6.1 (d, $J = 51.5$ Hz, 1H), 2.95–2.86 (m, 1H), 2.78–2.71 (m, 3H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): $\delta_{5d'}$ 172.8, 156.2 (d, $J = 16.5$ Hz), 137.9, 129.4 (2C), 128.3 (d, $J = 2.2$ Hz, 2C), 124.6 (d, $J = 2.2$ Hz), 109.0 (d, $J = 14.1$ Hz), 95.5 (d, $J = 207.7$ Hz), 28.7, 27.7; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta_{5d'}$ −206.4 (d, $J = 51.4$ Hz); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{12}H_9ClFNO_3Na$: 292.0147; found 292.0146.

3-(4-Bromophenyl)-4-fluoro-1,6-dioxa-2-azaspiro[4.4]non-2-en-7-one ((±)-5e/5e′). Oil; 59.0 mg (94%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); IR ν_{max} 3025, 2957, 2927, 2848, 1793, 1591, 1487, 1412, 1269, 1134, 1009, 886 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_{5e} 7.66–7.60 (m, 4H), 5.89 (d, $J = 52.3$ Hz, 1H), 3.00–2.83 (m, 2H), 2.77–2.69 (m, 1H), 2.60–2.54 (m, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ_{5e} 173.5, 155.3 (d, $J = 15.9$ Hz), 132.5, 132.3 (2C), 128.4 (2C), 126.1, 112.8 (d, $J = 30.1$ Hz), 96.5 (d, $J = 192.1$ Hz), 27.0 (d, $J = 1.8$ Hz), 24.8 (d, $J = 7.1$ Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ_{5e} −190.4 (d, $J = 52.4$ Hz); ^1H NMR (500 MHz, $CDCl_3$): $\delta_{5e'}$ 7.66 (d, $J = 8.3$ Hz, 2H), 7.61 (d, $J = 8.4$ Hz, 2H), 6.1 (d, $J = 51.5$ Hz, 1H), 2.95–2.89 (m, 1H), 2.76–2.74 (m, 3H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): $\delta_{5e'}$ 172.8, 156.3 (d, $J = 16.7$ Hz), 132.4 (2C), 131.7 (d, $J = 29.1$ Hz), 128.4 (d, $J = 2.3$ Hz, 2C), 126.4, 109.0 (d, $J = 14.2$ Hz), 95.5 (d, $J = 207.6$ Hz) 28.7, 27.6; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta_{5e'}$ −206.4 (d, $J = 51.5$ Hz); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{12}H_9BrFNO_3Na$: 335.9642; found 335.9645.

3-(2,6-Dichlorophenyl)-4-fluoro-1,6-dioxa-2-azaspiro[4.4] non-2-en-7-one ((±)-5f/5f′). Oil; 48.6 mg (80%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); IR ν_{max} 3010, 2955, 2924, 2854, 1710, 1560, 1432, 1275, 1260, 1194 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_{5f} 7.48–7.37 (m, 3H), 5.89 (d, $J = 52.1$ Hz, 1H), 3.00–2.91 (m, 1H), 2.90–2.81 (m, 1H), 2.78–2.71 (m, 1H), 2.64–2.59 (m, 1H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ_{5f} 173.5, 153.5 (d, $J = 16.2$ Hz), 135.8, 132.2 (2C), 128.4 (2C), 125.2, 112.8 (d, $J = 29.8$ Hz), 97.6 (d, $J = 94.4$ Hz), 27.0 (d, $J = 1.8$ Hz), 24.8 (d, $J = 7.1$ Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ_{5f} −187.6 (d, $J = 50.5$ Hz); ^1H NMR (500 MHz, $CDCl_3$): $\delta_{5f'}$ 7.48–7.37 (m, 3H), 6.1 (d, $J = 51.2$ Hz, 1H), 2.98–2.88 (m, 1H), 2.83–2.71 (m, 3H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): $\delta_{5f'}$ 176.1, 153.6, 135.7, 132.3 (2C), 128.3 (2C), 116.2, 109.1 (d, $J = 13.2$ Hz), 95.7 (d, $J = 209.4$ Hz), 28.8, 27.6; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta_{5f'}$ −191.5 (d, $J = 51.9$ Hz); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{12}H_8Cl_2FNO_3Na$: 325.9757; found 325.9757.

4-Fluoro-3-(4-(trifluoromethyl)phenyl)-1,6-dioxa-2-azaspiro [4.4]non-2-en-7-one ((±)-5g/5g′). White solid; 57.6 mg (95%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); mp: 130–132 °C; IR ν_{max} 3005, 2955, 2921, 2851, 1798, 1416, 1325, 1269, 1163, 1115, 1025, 883 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_{5g} 7.90 (d, $J = 8.2$ Hz, 2H), 7.74 (d, $J = 8.2$ Hz, 2H), 5.94 (d, $J = 52.2$ Hz, 1H), 3.00–2.85 (m, 2H), 2.75 (d, $J = 16.3$, 9.1, 2.8 Hz, 1H), 2.62–2.57 (m, 1H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ_{5g} 173.2, 155.1 (d, $J = 13.6$ Hz), 133.1 (q, $J = 32.1$ Hz), 129.8, 127.3 (2C), 126.2 (d, $J = 3.3$ Hz, 2C), 125.5 (q, $J = 272.6$ Hz), 112.9 (d, $J = 30.4$ Hz), 96.3 (d, $J = 192.4$ Hz), 26.9, 24.8 (d, $J = 7.2$ Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ_{5g} −63.1 (s), −190.5 (d, $J = 52.2$ Hz); ^1H NMR (500 MHz,

$CDCl_3$): $\delta_{5g'}$ 7.92 (d, J = 8.3 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 6.1 (d, J = 51.4 Hz, 1H), 2.97–2.88 (m, 1H), 2.79–2.73 (m, 3H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): $\delta_{5g'}$ 172.7, 156.0 (d, J = 16.9 Hz), 133.3 (dd, J = 63.7, 30.71 Hz), 129.5 (dd, J = 3.7, 2.3 Hz), 127.4 (d, J = 2.2 Hz, 2C), 126.0 (dd, J = 7.7, 3.9 Hz, 2C), 125.5 (q, J = 272.5 Hz), 109.1 (d, J = 13.9 Hz), 95.3 (d, J = 207 Hz) 28.7, 27.6; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta_{5g'}$ −63.2 (s), −206.6 (d, J = 51.5 Hz); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_9ClF_4NO_3Na$: 326.0411; found 326.0413.

4-Fluoro-3-methyl-1,6-dioxa-2-azaspiro[4.4]non-2-en-7-one ((±)-5h/5h′). Oil; 28.4 mg (82%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); IR ν_{max} 3008, 2957, 2929, 2853, 1797, 1436,1 1391, 1260, 1182, 1123, 1033, 905, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_{5h} 5.37 (d, J = 52.0 Hz, 1H), 2.88 (dt, J = 17.2, 9.5 Hz, 1H), 2.79–2.72 (m, 1H), 2.67 (ddd, J = 17.2, 9.8, 2.8 Hz, 1H), 2.45 (ddd, J = 13.4, 9.6, 2.8 Hz, 1H), 2.19 (d, J = 2.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ_{5h} 173.7, 154.8 (d, J = 15.1 Hz), 111.9 (d, J = 29.6 Hz), 98.6 (d, J = 191.2 Hz), 27.1, 24.7 (d, J = 6.8 Hz), 11.1; ^{19}F NMR (376 MHz, $CDCl_3$): δ_{5h} −189.9 (d, J = 55.9 Hz); ^1H NMR (500 MHz, $CDCl_3$): $\delta_{5h'}$ 5.57 (d, J = 51.2 Hz, 1H), 2.87–2.79 (m, 1H), 2.71–2.63 (m, 3H), 2.14 (s, 3H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): $\delta_{5h'}$ 173.1, 157.6 (d, J = 17.7 Hz), 108.5 (d, J = 13.5 Hz), 97.1 (d, J = 206.1 Hz), 28.1, 27.7, 10.7; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta_{5h'}$ −197.9 (d, J = 52.7 Hz); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_7H_8FNO_3Na$: 196.0380; found 196.0380.

4-Fluoro-3-propyl-1,6-dioxa-2-azaspiro[4.4]non-2-en-7-one ((±)-5i/5i′). Oil; 32.2 mg (80%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); IR ν_{max} 3008, 2965, 2937, 2876, 1796, 1713, 1447, 1275, 1177, 1042, 915, 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_{5i} 5.61 (d, J = 51.2 Hz, 1H), 2.87–2.79 (m, 2H), 2.66–2.63 (m, 2H), 2.53–2.41 (m, 2H), 1.77–1.64 (m, 2H), 1.02 (t, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$) δ_{5i} 173.2, 160.6 (d, J = 18.4 Hz), 108.4 (d, J = 13.7 Hz), 96.7 (d, J = 206.5 Hz), 28.1, 27.8, 27.5, 18.8, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ_{5i} −188.8 (d, J = 52.2 Hz); ^1H NMR (500 MHz, $CDCl_3$): $\delta_{5i'}$ 5.4 (d, J = 51.9 Hz, 1H), 2.92–2.85 (m, 2H), 2.72–2.64 (m, 2H), 2.54–2.48 (m, 2H), 1.77–1.65 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta_{5i'}$ −192.7 (d, J = 50.7 Hz); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_9H_{12}FNO_3Na$: 224.0693; found 224.0695.

3-(2,6-Dichlorophenyl)-4-fluoro-1,6-dioxa-2-azaspiro[4.5]dec-2-en-7-one ((±)-5j/5j′). Oil; 50.3 mg (79%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); IR ν_{max} 3008, 2957, 2926, 2851, 1707, 1560, 1430, 1275, 1260, 1194, 1052, 782, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta_{5j/5j'}$ 7.46–7.36 (m, 3H), 5.84 (d, J = 52.5 Hz, 1H), 2.91–2.85 (m, 1H), 2.75–2.62 (m, 2H), 2.35–2.24 (m, 2H), 2.09–2.03 (m, 1H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$) $\delta_{5j/5j'}$ 168.0, 162.5 (d, J = 16.1 Hz), 135.9, 132.1 (2C), 128.4 (2C), 125.3, 110.6 (d, J = 26.9 Hz), 98.8 (d, J = 195.4 Hz), 29.3, 23.6 (d, J = 7.8 Hz), 15.4 (d, J = 1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ_{5j} −187.7 (d, J = 52.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta_{5j'}$ −191.5 (d, J = 52.0 Hz); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_{10}Cl_2FNO_3 \cdot H_2ONa$: 358.0019; found 358.0021.

Ethyl 4-fluoro-7-oxo-1,6-dioxa-2-azaspiro[4.5]dec-2-ene-3-carboxylate ((±)-5k/5k′). Oil; 39.2 mg (80%, dr 1 : 1); R_f 0.4 (1 : 3 ethyl acetate : hexanes); IR ν_{max} 3005, 2950, 2923, 2853, 1719, 1462, 1275, 1259, 1016, 925, 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta_{5k/5k'}$ 5.67 (d, J = 51.8 Hz, 1H), 4.43 (q, J = 7.2 Hz, 2H), 2.87–2.81 (m, 1H), 2.69–2.63 (m, 1H), 2.35–2.23 (m, 3H), 2.08–2.04 (m, 1H), 1.40 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$) $\delta_{5k/5k'}$ 167.1, 164.7, 160.5 (d, J = 16.0 Hz), 111.9 (d, J = 13.8), 95.1 (d, J = 193.7 Hz), 62.9, 29.3, 23.1 (d, J = 7.2 Hz), 15.5, 14.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ_{5k} −191.3 (d, J = 55.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta_{5k'}$ −198.1 (d, J = 52.7 Hz); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{10}H_{12}FNO_3 \cdot H_2ONa$: 286.0697; found 286.0699.

Conflicts of interest

There are no conflicts to declare.

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