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Synthesis of Difluoroalkyl Unsaturated *β*-Amino Acid Derivatives Exclusively through Alkynes Difunctionalization

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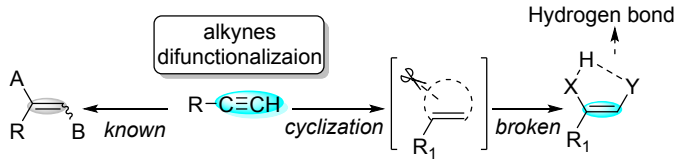


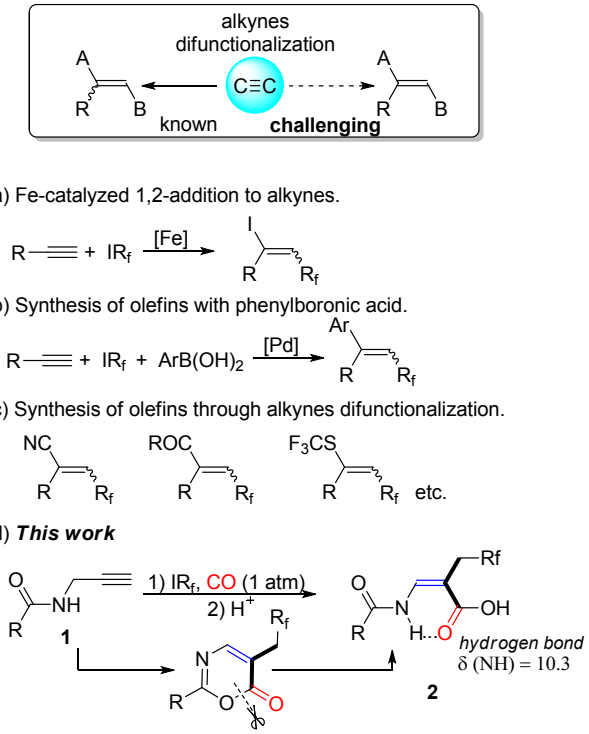
ABSTRACT: Alkynes difunctionalization is a powerful strategy in organic synthesis, which provides a convenient synthetic entry for internal alkenes. The main challenges in this filed was considered as the geometry control of newly formed double bond (thermodynamically controlled or kinetically controlled). Herein, we report a novel procedure (through the cyclic compounds broken) to completely control the regioselectivity of olefins. The products, difluoroalkyl unsaturated *β*-amino acid derivatives, have potential applications in some important pharmaceuticals on account of special nature of fluorine atoms.

KEYWORDS: *β*-amino acids, difluoroalkyl, regioselectivity, 1,3-oxazin-6-one

INTRODUCTION

As a powerful method, alkynes difunctionalization is widely used to construct multi-substituted olefins.[1] Since both (Z)- and (*E*)-isomers of olefins are obtained simultaneously in most synthetic protocols,[2] poor regioselectivity has seriously hampered the further exploitation of their synthetic potential. Precisely controlling the configuration of double bonds is extremely challenging. The issue of trisubstituted olefins (prochiral molecules) is that the configuration of olefins has a direct relationship with the construction of the substrate chirality. Zhang and co-workers disclose that the (Z)-isomer gives better enantioselectivity than the (*E*)-isomer for under their Rh catalysed hydrogenation condition.[3] A more direct method to synthesize *β*-difluoroalkyl olefins from Heck-type reaction has been developed by Zhang.[4] An approach that has not yet been satisfied the design requirements is the selective difunctionalization of alkynes. Hu and co-workers make a marvellous progress in the alkynes difunctionalization to afford *β*-fluoroalkyl vinyl iodides, which holds a wide substrate scope and high functional-group tolerance. The *E*/*Z* ratio of products are generally located at 6: 1,[2d] as well as similar ratios of work to build mutisubstituted olefins,[5, 2b] *β*-difluoroalkyl unsaturated esters/amides/ketones,[6] acrylonitriles,[7] etc.[8] Considering the restriction of spatial structure of cyclic olefinic bond, single-configuration olefins can be obtained while opening the ring to farm a hydrogen bond to limit the variation of the double bond configuration. At this point, finding an easy-to-build, and easy-to-open cyclic compound is the key to complete this approach.

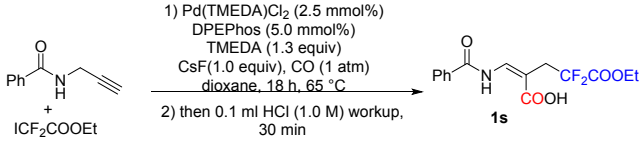
In fact, such a strategy has great potential applications within the synthesis of organic molecules, especially for the



Scheme 1. Muti-substituted olefin synthesis through alkynes difunctionalization

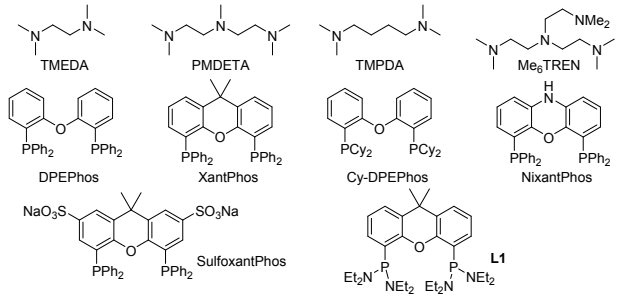
construction of *β*-amino acids,[9] as the important building blocks for foldamers, oligomers, which are applied in the peptide chemistry and pharmaceutical industry. An extensive research

Table 1. Screening conditions.



Entry	Change in reaction conditions	Yield[b] [%]
1	standard conditions[a]	63
2	NaOAc	trace
3	K_3PO_4	trace
4	Et_3N	50
5	PMDETA	32
6	TMPDA	37
7	Me_6TREN	30
8	XantPhos	45
9	Cy-DPEPhos	28
10	Nixantphos	trace
11	Sulfoxantphos	33
13	**L1**	trace
14	No TMEDA	trace
15	No DPEPhos	N.R.
16	No CsF	60

[a]Standard conditions: N-propargylbenzamide (0.2 mmol), ICF_2COOEt (0.34 mmol), $Pd(TMEDA)Cl_2$ (0.0025 mmol), DPEPhos (0.005 mmol), TMEDA (0.26 mmol) and CsF (0.2mmol) in dioxane were stirred at 65℃ for 18 h under CO. [b]Isolated yield.



has been proved that the incorporation of *β*-amino acids is one of the most effective ways in peptidomimetics.[9e] Asymmetric hydrogenation of *Z*/*E* mixture of unsaturated *β*-amino acids derivatives are reported by Zhang and Gridnev with excellent yields and enantioselectivities utilizing expensive and complex chiral ligands.[10] However, these problems can be completely avoided by controlling the double bond configuration. Also, due to the unusual properties of fluorine atoms, introducing fluorine into organic compounds could significantly improve solubility, cell permeability, and metabolic stability.[11] Fluorochemicals have made great progress in the last few decades. As one member of the fluorochemistry family, difluoroalkyl species,[12] served as lipophilic hydrogen- bond donors and a bioisostere of alcohols in biologically active molecules,[13] have been widely explored. Herein, we disclose a Pd-catalyzed system for the construction of difluoroalkyl unsaturated *β*-amino acids with excellent exclusive regioselectivity through a ring-operated strategy.

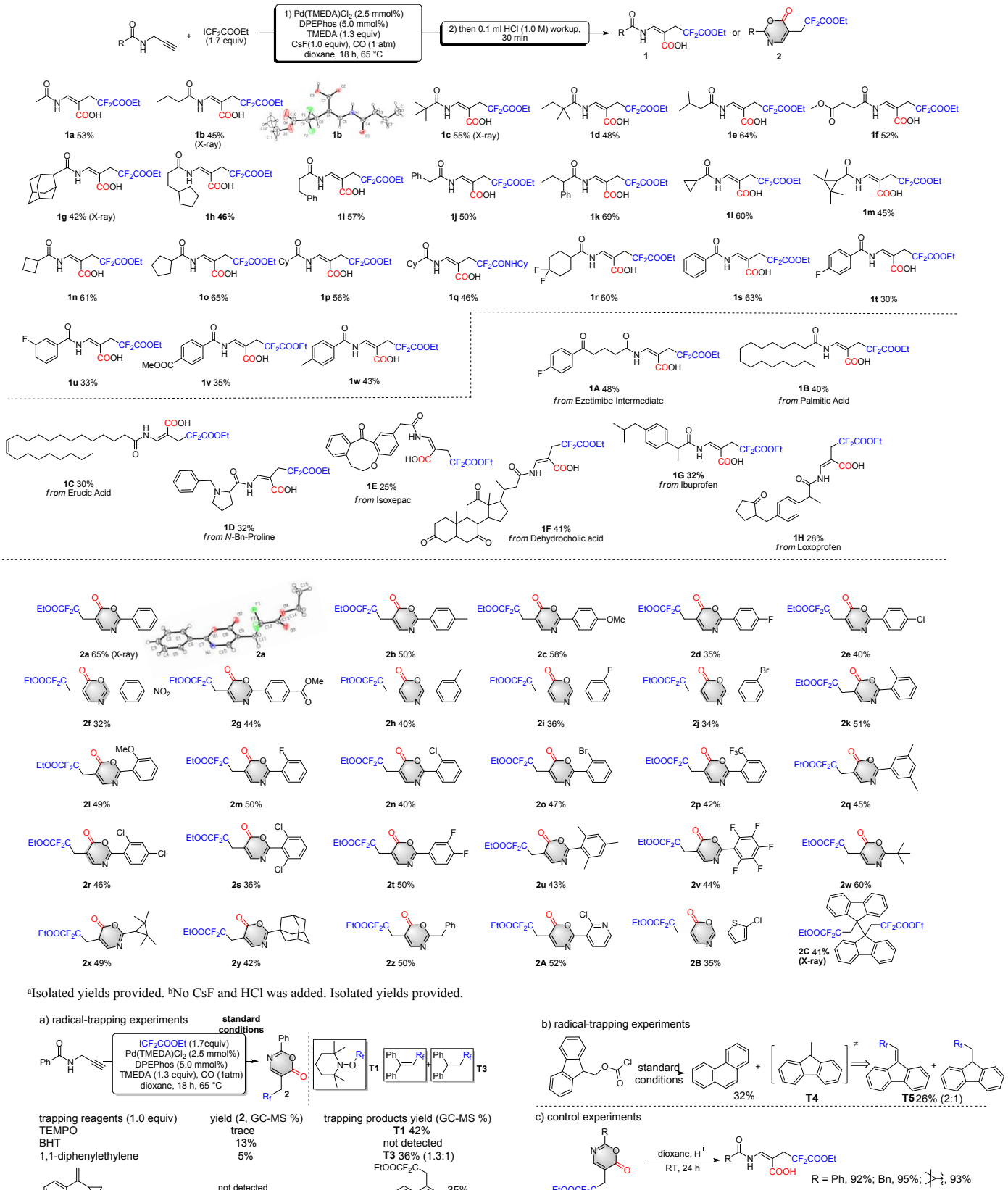
RESULTS AND DISCUSSION

At the outset, a model reaction between N-propargylbenzamide and ICF_2COOEt was carried out in neat 1,4-dioxane (Table 1). After a lot of screening tests, the formation of difluoroalkyl unsaturated *β*-amino acids (**1s**) was isolated in 63% yield with $Pd(TMEDA)Cl_2$/DPEPhos as the catalyst, TMEDA as base and CsF as additive under a CO atmosphere at 65℃ in a one-pot fashion (entry 1). It was found that organic bases were superior to inorganic bases for this reaction, probably due to their ability of stabilizing the palladium complexes by chelation (entries 2-7). The ligands screening showed that bidentate diphosphines based on xanthene-like backbones which had good electron chelation and delocalization more beneficial to this transformation (entries 8-13).[14] The reaction gave no desired product when the base or ligand was absence (entries 14-15). Notably, CsF could significantly decrease the amount of pigment byproduct of the reaction, which made the subsequent separation difficult to carry out (entry 16).

With the optimized reaction conditions in hand (Table1, entry 1), the scope of the reactions was extensively investigated with numerous of *N*-propargylamides (Table 2). The strategy to synthesize regioselective difluoroalkyl unsaturated *β*-amino acids derivatives was then systematically studied. Generally, the reaction possesses high functional group tolerance. Especially, aliphatic substituted N-propargylamide (**1a-1r**) exhibited high yields in the reaction conditions in the yields. The result may be due to that the strong electron-donating effect is more beneficial to open the ring. Moreover, various ring-substituted *N*-propargylamides were well tolerated and gave the products in good yields (**1l-1r**). In contrast, much lower yields were obtained while *N*-propargylamide with electron-withdrawing substituents on aromatic rings were used(**1t-1v**). Importantly, difluoride source existed as amides (**1q**) gave the desired products with satisfactory yields. To further demonstrate the synthetic utility of this ring-operated strategy to control the configuration of double bonds, we probed our optimized catalytic system for the difunctionalization of alkynes with some natural products and pharmaceutical intermediates (**1A-1H**), which indicated that our reaction system could be potentially applied in much more complex molecular settings.

It's worth noting that the difluoroalkyl 1,3-oxazin-6-one moieties (**2**) were easily prepared while no dilute hydrochloric acid was added into the reaction system. The structure of **2a** was determined by X-ray crystallographic analysis. Considering that the 1,3-oxazin-6-one moiety is an attractive structural motif in pharmaceuticals and biologically active molecules,[15] Then, the reactions of a broad range of amides were evaluated in detail. In order to prove the breadth of the substrate, we used a large number of substrates different from the previous amides to react. We carried out the reactions with the utilization of ICF_2COOEt (1.7 equiv), $Pd(TMEDA)Cl_2$ (2.5 mmol%)/DPEPhos (5.0 mmol%), TMEDA (1.3 equiv) and 1 atm of CO in dioxane at 65℃. As a series of *N*-propargylamides were screened, this novel carbonylation reaction was proved to be a fairly mild reaction with high functional-group tolerance. Regardless

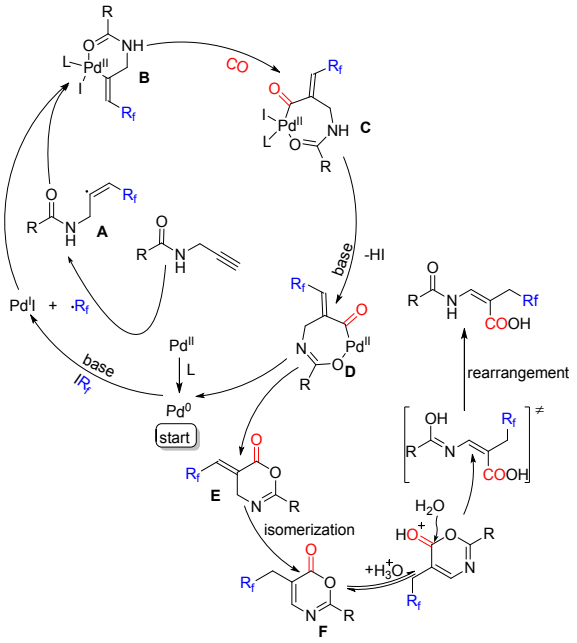
Table 2. Pd-catalyzed alkynes difunctionalization to synthesis difluoroalkyl unsaturated *β*-amino acids[a] and 1,3-oxazin-6-ones[b].



[a]Isolated yields provided. [b]No CsF and HCl was added. Isolated yields provided.

Scheme 2. Radical-trapping experiments and control experiments for mechanistic insight.

of the steric effect and electronic effect of the substituents on the aryl ring at *α* position of *N*-propargylamides, desired products were isolated in moderate yields. For example, electron-donating groups (R = Me, OMe) or electron-withdrawing groups (R = F, Cl, Br, NO_2, CF_3, COOMe) at any position on the aryl ring of propargylamides generated the corresponding products **2b-2p** in 32−58% yields, as well as multi-substitutes on the aryl ring (**2q-2u**). Polyfluoroarenes play important roles in complex biologically active natural products, pharmaceuticals and active materials.[16] And we succeed in obtaining the substituted pentafluorobenzene (**2v**) with 44% yield. We then focused on the aliphatic amides to further expand the scope of this reaction. Employing tert-butyl, cyclopropyl, adamantly or benzyl substrates, the reactions proceeded smoothly and furnished the desired products **2w-2z** in 42−60% yields. The heterocyclic substrates **2A** and **2B** also afforded the products with 52% and 35% yields, respectively. Interesting, the product **2C** was isolated with 41% yield while the substituent is Fmoc.



Scheme 3. Proposed mechanism.

To elucidate the mechanism, some radical-trapping experiments were performed by employing 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), butylated hydroxytoluene (BHT), 1,1-diphenylethylene and (1-cyclopropylvinyl)benzene under the standard conditions, respectively. The reaction was remarkably inhibited by these reagents and the trapping products were observed by GC-MS (Scheme 2a). Fmoc-Cl removed carbon dioxide to form intermediate **T4** (acted as radical-trapping reagent) under the standard conditions, which further converted to the trapping products **T5** (Scheme 2b). Combining previous mechanism studies on radical difunctionalization of alkynes,[2b, 2d] a process involving a free difluroalkyl radical, isomerization of the exocyclic olefin, and the ring-broken rearrangement is proposed in Scheme 3. Initially, the difluroalkyl species, in situ generated in the presence of palladium catalyst and base, attacks the alkynes to afford the vinyl radical intermediate **A**, which then reacts with Pd(I)I and generates the key Pd(II) intermediate **B**. The insertion of CO into intermediate **B** furnishes the intermediate **C**, then the intermediate **C** is-transformed into **D** with the assistant of base, which undergoes reductive elimination to produce the intermediate **E** while regenerating Pd(0). Olefin isomerization of the intermediate **E** occurs because of the product **F** has lower delocalizationenergy.[17] After a cleavage of C-O bond through acidic hydrolysis and followed by an intramolecular rearrangement, the final product is obtained.

CONCLUSION

In summary, we have successfully developed a ring-operated strategy to synthesize difluoroalkyl unsaturated *β*-amino acids derivatives through alkynes difunctionalization with exclusive regioselectivity. The present strategy provides a new entry to the synthesis of single configuration of olefins and completely avoiding subsequent reactions, which requires complex metal catalysts and chiral ligands for amino acids preparation. Meanwhile, the process serves as a novel and efficient approach to build difluoroalkyl unsaturated *β*-amino acids derivatives with satisfactory yields, holding a broad substrate scope. Furthermore, the products, unsaturated *β*-amino acids and 1,3-oxazin-6-ones, have potential applications in medicine due to the special natures of fluorine atoms and easily undergo further chemical transformation.

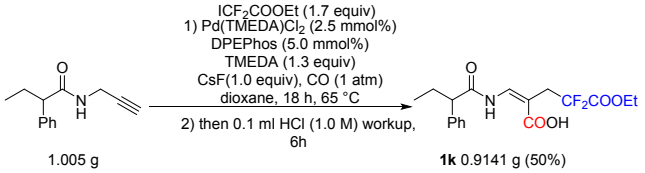
EXPERIMENTAL SECTION

General Information: All commercially available organic compounds were purchased from adamas-beta, Alfa Asar, and accelachem in China. Unless otherwise noted, reactions were carried out under a carbon monoxide atmosphere.

For Column chromatography, 200-300 mesh silica gel was employed. Analytical TLC was performed with silica gel GF254 plates. ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz) and ^{19}F NMR (376 MHz) were recorded in $CDCl_3$ using TMS as internal standard. All new products were further characterized by high resolution mass spectra (HRMS); copies of their ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra are provided. All solvents were dried under standard method.

General Procedure for the Synthesis of Difluoroalkyl Unsaturated *β*-Amino Acid Derivatives: An oven-dried tube was charged with N-propargylamide (0.20 mmol), DPEPhos (5.0 mmol%), Pd(TMEDA)Cl_2 (2.5 mmol%) and CsF (1.0 equiv). The tube was evacuated and backfilled with CO (repeated three times). Then, 1,4-dioxane (1.0 mL) was injected after ethyl difluoroiodoacetate (1.7 equiv) and TMEDA (1.3 equiv) were added into the tube. The reaction mixture was stirring at 65 °C (oil both) for 18 h. Then 0.1 mL HCl (1.0 M) was added into tube and continue to stir for a further 30 minutes at 65 °C. the reaction mixture was cooled to room temperature. Concentrated in vacuum and purified by flash column chromatography (silica gel) to afford the product.

Gram-Scale Synthesis of 1k:



An oven-dried round-bottomed flask was charged with N-propargylamide (5.00 mmol, 1.005 g), DPEPhos (5.0 mmol%, 134.6 mg), Pd(TMEDA)Cl_2 (2.5 mmol%, 36.7 mg) and CsF (1.0 equiv, 759.5

mg). The round-bottomed flask was evacuated and backfilled with CO. Then, ethyl difluoroiodoacetate (1.7 equiv, 2.125g) and TMEDA (1.3 equiv, 755.0 mg) was injected after 1,4-dioxane (20.0 mL) were added into the tube. The reaction mixture was stirring at 65 °C (oil both) for 18 h. Then 3.0 mL HCl (1.0 M) was added into tube and continue to stir for a further 6 h at 65 °C. the reaction mixture was cooled to room temperature. Concentrated in vacuum and purified by flash column chromatography (silica gel) to afford the product**.**

(Z)-2-(acetamidomethylene)-5-ethoxy-4,4-difluoro-5-oxopentanoic acid (1a): white solid, 53% yield, (0.2 mmol, 28 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/15/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.30 (d, *J* = 11.6 Hz, 1H), 7.68 (d, *J* = 11.6 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.07 (t, *J* = 16.0 Hz, 2H), 2.22 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 173.1, 168.3, 163.8, 141.7, 114.4 (t, *J* = 252.9 Hz), 97.4, 63.1, 34.9 (t, *J* = 25.3 Hz), 23.8, 13.9; ^{19}F NMR (376 MHz, Chloroform-d) δ -105.9; Melting Point: 78~80 °C; HRMS (ESI) *m/z* Calcd for $C_{10}H_{13}F_2NO_5Na^+$ 288.0654; found 288.0648.

(Z)-2-(butyramidomethylene)-5-ethoxy-4,4-difluoro-5-oxopentanoic acid (1b): white solid, 45% yield, (0.2 mmol, 26 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/15/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.29 (d, *J* = 11.6 Hz, 1H), 7.70 (d, *J* = 11.6 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.07 (t, *J* = 16.0 Hz, 2H), 2.39 (t, *J* = 7.2 Hz, 2H), 1.74 (h, *J* = 7.6 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.00 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 173.3, 171.2, 163.8 (t, *J* = 32.5 Hz), 141.9, 114.5 (t, *J* = 252.8 Hz), 97.1, 63.1, 38.7, 34.9 (t, *J* = 25.3 Hz), 18.3, 13.9, 13.6 ; ^{19}F NMR (376 MHz, Chloroform-d) δ -105.9; Melting Point: 84~86 °C; HRMS (ESI) *m/z* Calcd for $C_{12}H_{17}F_2NO_5Na^+$ 316.0967; found 316.0959.

(Z)-5-ethoxy-4,4-difluoro-5-oxo-2-(pivalamidomethylene)pentanoic acid (1c): white solid, 55% yield, (0.2 mmol, 34 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/15/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.71 (d, *J* = 11.6 Hz, 1H), 7.70 (d, *J* = 11.6 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.08 (t, *J* = 16.0 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.27 (s, 9H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 176.7, 173.5, 163.8 (t, *J* = 32.6 Hz), 142.8, 114.5 (t, *J* = 252.6 Hz), 97.3, 63.0, 39.3, 34.9 (t, *J* = 25.1 Hz), 27.0, 13.9; ^{19}F NMR (376 MHz, Chloroform-d) δ -105.8; Melting Point: 118~120 °C; HRMS (ESI) *m/z* Calcd for $C_{13}H_{19}F_2NO_5Na^+$ 330.1124; found 330.1119.

(Z)-2-((2,2-dimethylbutanamido)methylene)-5-ethoxy-4,4-difluoro-5-oxopentanoic acid (1d): yellow solid, 48% yield, (0.2 mmol, 31 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/15/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.72 (d, *J* = 11.6 Hz, 1H), 7.72 (d, *J* = 11.6 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.09 (t, *J* = 16.0 Hz, 2H), 1.62 (q, *J* = 7.6 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.23 (s, 6H), 0.87 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 176.2, 173.5, 163.8 (t, *J* = 32.6 Hz), 142.5, 114.5 (t, *J* = 252.7 Hz), 97.3, 63.0, 43.1, 34.9 (t, *J* = 25.4 Hz), 33.5, 24.4, 13.8, 9.0; ^{19}F NMR (376 MHz, Chloroform-d) δ -105.7; Melting Point: 108~110 °C; HRMS (ESI) *m/z* Calcd for $C_{14}H_{21}F_2NO_5Na^+$ 344.1280; found 344.1273.

(Z)-5-ethoxy-4,4-difluoro-2-((3-methylbutanamido)methylene)-5-oxopentanoic acid (1e): white solid, 64% yield, (0.2 mmol, 39 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/15/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.29 (d, *J* = 11.6 Hz, 1H), 7.70 (d, *J* = 11.6 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.07 (t, *J* = 16.0 Hz, 2H), 2.28 (d, *J* = 7.2 Hz, 2H), 2.23 – 2.13 (m, 1H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.01 (s, 3H), 1.00 (s, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 173.3, 170.7, 163.8 (t, *J* = 32.7 Hz), 141.8, 114.5 (t, *J* = 252.8 Hz), 97.2, 63.0, 46.0, 34.9 (t, *J* = 24.9 Hz), 25.8, 22.4, 13.8; ^{19}F NMR (376 MHz, Chloroform-d) δ -105.8; Melting Point: 112~114 °C; HRMS (ESI) *m/z* Calcd for $C_{13}H_{19}F_2NO_5Na^+$ 330.1124; found 330.1116.

(Z)-5-ethoxy-4,4-difluoro-2-((4-methoxy-4-oxobutanamido)methylene)-5-oxopentanoic acid (1f): white solid, 52% yield, (0.2 mmol, 35 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/15/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.40 (d, *J* = 11.6 Hz, 1H), 7.66 (d, *J* = 11.2 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.71 (s, 3H), 3.06 (t, *J* = 16.0 Hz, 2H), 2.73 (s, 4H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 172.9, 172.8, 169.8, 163.8 (t, *J* = 32.7 Hz), 141.1, 114.5 (t, *J* = 252.8 Hz), 97.9, 63.0, 52.0, 35.0 (t, *J* = 25.3 Hz), 31.3, 28.5, 13.8. ^{19}F NMR (376 MHz, Chloroform-d) δ -105.7; Melting Point: 88~90 °C; HRMS (ESI) *m/z* Calcd for $C_{13}H_{17}F_2NO_7Na^+$ 360.0865; found 360.0859.

(Z)-2-(((1r,3r,5r,7r)-adamantane-2-carboxamido)methylene)-5-ethoxy-4,4-difluoro-5-oxopentanoic acid (1g): white solid, 42% yield, (0.2 mmol, 32 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/15/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.58 (d, *J* = 11.6 Hz, 1H), 7.72 (d, *J* = 11.6 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.08 (t, *J* = 16.0 Hz, 2H), 2.10 (s, 3H), 1.91 (d, *J* = 2.8 Hz, 6H), 1.76 (q, *J* = 12.6 Hz, 6H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 176.15, 173.26, 163.85 (t, *J* = 32.7 Hz), 142.51, 114.52 (t, *J* = 252.7 Hz), 97.34, 63.00, 41.23, 38.72, 36.25, 35.03 (t, *J* = 25.5 Hz), 27.83, 13.88. ^{19}F NMR (376 MHz, Chloroform-d) δ -105.7; Melting Point: 146~148 °C; HRMS (ESI) *m/z* Calcd for $C_{19}H_{25}F_2NO_5Na^+$ 408.1593; found 408.1582.

(Z)-2-((3-cyclopentylpropanamido)methylene)-5-ethoxy-4,4-difluoro-5-oxopentanoic acid (1h): white solid, 46% yield, (0.2 mmol, 32 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/15/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.30 (d, *J* = 11.6 Hz, 1H), 7.69 (d, *J* = 11.6 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.07 (t, *J* = 16.0 Hz, 2H), 2.43 – 2.40 (m, 2H), 1.80 – 1.79 (m, 3H), 1.74 – 1.70 (m, 2H), 1.64 – 1.61 (m, 2H), 1.55 – 1.52 (m, 2H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.12 – 1.10 (m, 2H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 173.2, 171.5, 163.8 (t, *J* = 32.7 Hz), 141.9, 114.5 (t, *J* = 252.9 Hz), 97.2, 63.0, 39.5, 36.2, 34.9 (t, *J* = 25.3 Hz), 32.4, 31.0, 25.1, 13.9. ^{19}F NMR (376 MHz, Chloroform-d) δ -105.8; Melting Point: 96~99 °C; HRMS (ESI) *m/z* Calcd for $C_{16}H_{23}F_2NO_5Na^+$ 370.1437; found 370.1426.

(Z)-5-ethoxy-4,4-difluoro-5-oxo-2-((3-phenylpropanamido)methylene)pentanoic acid (1i): yellow solid, 57% yield, (0.2 mmol, 40 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/15/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 11.33 (s, 1H), 10.25 (d, *J* = 11.2 Hz, 1H), 7.67 (d, *J* = 11.2 Hz, 1H), 7.30 – 7.25 (m, 2H), 7.22 – 7.19 (m, 3H), 4.29 (q, *J* = 7.2 Hz, 2H), 3.09 – 2.99 (m, 4H), 2.71 (t, *J* = 7.6 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 173.0, 170.4, 163.7 (t, *J* = 32.7 Hz), 141.4, 139.8, 128.6, 128.2, 126.4, 114.4 (t, *J* = 252.9 Hz), 97.6, 63.0, 38.3, 34.8 (t, *J* = 25.3 Hz), 30.6, 13.8. ^{19}F NMR (376 MHz, Chloroform-d) δ -105.8; Melting Point: 118~120 °C; HRMS (ESI) *m/z* Calcd for $C_{17}H_{19}F_2NO_5Na^+$ 378.1124; found 378.1114.

(Z)-5-ethoxy-4,4-difluoro-5-oxo-2-((2-phenylacetamido)methylene)pentanoic acid (1j): white solid, 50% yield, (0.2 mmol, 34 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/15/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.32 (d, *J* = 11.6 Hz, 1H), 7.61 (d, *J* = 11.5 Hz, 1H), 7.41 – 7.35 (m, 3H), 7.28 – 7.26 (m, 2H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.74 (s, 2H), 3.03 (t, *J* = 16.0 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 173.3, 169.4, 163.8 (t, *J* = 33.0 Hz), 141.6, 132.5, 129.5, 129.3, 128.1, 114.4 (t, *J* = 254.5 Hz), 98.0, 63.1, 43.8, 34.7 (t, *J* = 24.9 Hz), 13.8. ^{19}F NMR (376 MHz, Chloroform-d) δ -106.1; Melting Point: 94~96 °C; HRMS (ESI) *m/z* Calcd for $C_{16}H_{17}F_2NO_5Na^+$ 364.0967; found 364.0962.

(Z)-5-ethoxy-4,4-difluoro-5-oxo-2-((2-phenylbutanamido)methylene)pentanoic acid (1k): yellow solid, 69% yield, (0.2 mmol, 51 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/15/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.30 (d, *J* = 11.6 Hz, 1H), 7.61 (d, *J* = 11.6 Hz, 1H), 7.39 – 7.35 (m, 2H), 7.32 – 7.27 (m, 3H), 4.29 (q, *J* = 7.2 Hz, 2H), 3.42 (t, *J* = 7.6 Hz, 1H), 3.03 (t, *J* = 16.0 Hz, 2H), 2.28 – 2.21 (m, 1H), 1.93 – 1.86 (m, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 173.3, 171.9, 163.8 (t, *J* = 32.6 Hz), 141.9, 137.6, 129.2, 128.1, 128.0, 114.5 (t, *J* = 252.7 Hz), 97.6, 63.0, 55.4, 34.8 (t, *J* = 25.3 Hz), 25.5, 13.8, 12.1. ^{19}F NMR (376 MHz, Chloroform-d) δ -105.8; Melting Point: 104~107 °C; HRMS (ESI) *m/z* Calcd for $C_{18}H_{21}F_2NO_5Na^+$ 392.1280; found 392.1271.

(**Z**)-2-(cyclopropanecarboxamidomethylene)-5-ethoxy-4,4-difluoro-5-oxopentanoic acid (**1l**): yellow solid, 60% yield, (0.2 mmol, 35 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/15/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.53 (d, *J* = 12.0 Hz, 1H), 7.69 (d, *J* = 11.6 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.07 (t, *J* = 16.0 Hz, 2H), 1.62 – 1.56 (m, 1H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.17 – 1.13 (m, 2H), 1.00 – 0.96 (m, 2H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 173.3, 172.3, 163.9 (t, *J* = 32.8 Hz), 142.0, 114.5 (t, *J* = 252.6 Hz), 96.5, 63.1, 34.9 (t, *J* = 24.0 Hz), 15.6, 13.9, 9.6. ^{19}F NMR (376 MHz, Chloroform-d) δ -105.7; Melting Point: 132~134 °C; HRMS (ESI) *m/z* Calcd for $C_{12}H_{15}F_2NO_5Na^+$ 314.0811; found 314.0806.

(Z)-5-ethoxy-4,4-difluoro-5-oxo-2-((2,2,3,3-tetramethylcyclopropane-1-carboxamido)methylene)pentanoic acid (1m): yellow solid, 45% yield, (0.2 mmol, 31 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/15/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.40 (d, *J* = 12.0 Hz, 1H), 7.66 (d, *J* = 11.6 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.04 (t, *J* = 16.0 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.29 (s, 6H), 1.24 (s, 6H), 1.03 (s, 1H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 173.4, 169.7, 164.0 (t, *J* = 33.0 Hz), 142.2, 114.7 (t, *J* = 252.7 Hz), 95.0, 63.0, 38.5, 35.1 (t, *J* = 24.4 Hz), 32.6, 23.7, 16.5, 13.9. ^{19}F NMR (376 MHz, Chloroform-d) δ -105.7; Melting Point: 142~146 °C; HRMS (ESI) *m/z* Calcd for $C_{16}H_{23}F_2NO_5Na^+$ 370.1437; found 370.1430.

(Z)-2-(cyclobutanecarboxamidomethylene)-5-ethoxy-4,4-difluoro-5-oxopentanoic acid (1n): yellow solid, 61% yield, (0.2 mmol, 37 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/15/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.25 (d, *J* = 11.6 Hz, 1H), 7.69 (d, *J* = 11.6 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.19 (p, *J* = 8.4 Hz, 1H), 3.07 (t, *J* = 16.0 Hz, 2H), 2.38 – 2.25 (m, 4H), 2.08 – 2.01 (m, 1H), 1.97 – 1.90 (m, 1H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 173.3, 171.2, 163.8 (t, *J* = 32.8 Hz), 141.9, 114.5 (t, *J* = 252.7 Hz), 97.1, 63.1, 38.7, 34.9 (t, *J* = 25.3 Hz), 18.3, 13.9, 13.6. ^{19}F NMR (376 MHz, Chloroform-d) δ -105.8; Melting Point: 104~107 °C; HRMS (ESI) *m/z* Calcd for $C_{13}H_{17}F_2NO_5Na^+$ 328.0967; found 328.0958.

(Z)-2-(cyclopentanecarboxamidomethylene)-5-ethoxy-4,4-difluoro-5-oxopentanoic acid (1o): yellow solid, 65% yield, (0.2 mmol, 41 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/15/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.36 (d, *J* = 11.6 Hz, 1H), 7.70 (d, *J* = 11.6 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.07 (t, *J* = 16.0 Hz, 2H), 2.74 (p, *J* = 8.0 Hz, 1H), 2.00 – 1.96 (m, 2H), 1.87 – 1.76 (m, 4H), 1.67 – 1.64 (m, 2H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 174.6, 173.4, 163.8 (t, *J* = 32.4 Hz), 142.2, 114.5 (t, *J* = 252.6 Hz), 97.0, 63.0, 46.1, 34.9 (t, *J* = 24.9 Hz), 30.1, 25.8, 13.8. ^{19}F NMR (376 MHz, Chloroform-d) δ -105.8; Melting Point: 104~106 °C; HRMS (ESI) *m/z* Calcd for $C_{14}H_{19}F_2NO_5Na^+$ 342.1124; found 342.1116.

(Z)-2-(cyclohexanecarboxamidomethylene)-5-ethoxy-4,4-difluoro-5-oxopentanoic acid (1p): yellow solid, 56% yield, (0.2 mmol, 37 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/15/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.40 (d, *J* = 11.6 Hz, 1H), 7.70 (d, *J* = 11.6 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.08 (t, *J* = 16.0 Hz, 2H), 2.30 (tt, *J* = 11.6, 3.6 Hz, 1H), 1.95 – 1.92 (m, 2H), 1.85 – 1.82 (m, 2H), 1.74 – 1.69 (m, 1H), 1.53 – 1.44 (m, 2H), 1.37 – 1.26 (m, 6H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 174.3, 173.2, 163.8 (t, *J* = 32.8 Hz), 142.1, 114.5 (t, *J* = 252.7 Hz), 97.3, 63.0, 45.3, 34.9 (t, *J* = 25.4 Hz), 29.0, 25.5, 25.3, 13.8. ^{19}F NMR (376 MHz, Chloroform-d) δ -105.8; Melting Point: 114~116 °C; HRMS (ESI) *m/z* Calcd for $C_{15}H_{21}F_2NO_5Na^+$ 356.1280; found 356.1269.

(Z)-2-(cyclohexanecarboxamidomethylene)-5-((cyclohexylamino)oxy)-4,4-difluoro-5-oxopentanoic acid (1q): yellow solid, 46% yield, (0.2 mmol, 35 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/25/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.54 (d, *J* = 11.2 Hz, 1H), 7.64 (d, *J* = 11.6 Hz, 1H), 6.23 (d, *J* = 8.4 Hz, 1H), 3.78 – 3.76 (m, 1H), 3.09 (t, *J* = 16.8 Hz, 2H), 2.30 – 2.24 (m, 1H), 1.93 – 1.87 (m, 4H), 1.83 – 1.60 (m, 6H), 1.52 – 1.42 (m, 2H), 1.36 – 1.25 (m, 6H), 1.22 – 1.15 (m, 2H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 174.2, 172.8, 163.0 (t, *J* = 28.1 Hz), 141.6, 116.5 (t, *J* = 254.9 Hz), 97.8, 48.6, 45.4, 34.2 (t, *J* = 25.8 Hz), 32.5, 29.1, 25.5, 25.4, 25.3, 24.6. ^{19}F NMR (376 MHz, Chloroform-d) δ -106.5; Melting Point: 179~181 °C; HRMS (ESI) *m/z* Calcd for $C_{19}H_{28}F_2N_2O_4Na^+$ 409.1909; found 409.1899.

(Z)-2-((4,4-difluorocyclohexane-1-carboxamido)methylene)-5-ethoxy-4,4-difluoro-5-oxopentanoic acid (1r): yellow solid, 60% yield, (0.2 mmol, 44 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/15/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.46 (d, *J* = 11.6 Hz, 1H), 7.69 (d, *J* = 11.6 Hz, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 3.08 (t, *J* = 16.0 Hz, 2H), 2.43 – 2.37 (s, 1H), 2.22 – 2.19 (m, 2H), 2.04 – 2.01 (s, 2H), 1.91 – 1.82 (m, 4H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 173.1, 172.3, 163.8 (t, *J* = 32.5 Hz), 141.9, 122.2 (t, *J* = 242.4 Hz), 114.4 (t, *J* = 252.8 Hz), 97.9, 63.1, 34.9 (t, *J* = 25.0 Hz), 32.5 (t, *J* = 24.9 Hz), 25.4, 25.3, 13.9. ^{19}F NMR (376 MHz, Chloroform-d) δ -105.9; Melting Point: 166~168 °C; HRMS (ESI) *m/z* Calcd for $C_{15}H_{19}F_4NO_5Na^+$ 392.1092; found 392.1088.

(Z)-2-(benzamidomethylene)-5-ethoxy-4,4-difluoro-5-oxopentanoic acid (1s): yellow solid, 63% yield, (0.2 mmol, 41 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/15/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 11.32 (d, *J* = 11.6 Hz, 1H), 7.95 – 7.91 (m, 3H), 7.65 – 7.62 (m, 1H), 7.56 – 7.52 (m, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 3.16 (t, *J* = 16.0 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 173.5, 164.5, 163.8 (t, *J* = 32.8 Hz), 142.6, 133.3, 131.8, 129.1, 127.7, 114.5 (t, *J* = 253.1 Hz), 98.2, 63.1, 35.0 (t, *J* = 25.0 Hz), 13.9. ^{19}F NMR (376 MHz, Chloroform-d) δ -105.7; Melting Point: 98~100 °C; HRMS (ESI) *m/z* Calcd for $C_{15}H_{15}F_2NO_5Na^+$ 350.0811; found 350.0809.

(Z)-5-ethoxy-4,4-difluoro-2-((4-fluorobenzamido)methylene)-5-oxopentanoic acid (1t): yellow solid, 30% yield, (0.2 mmol, 21 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/15/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 11.27 (d, *J* = 11.6 Hz, 1H), 7.96 – 7.90 (m, 3H), 7.22 (t, *J* = 8.4 Hz, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 3.16 (t, *J* = 16.0 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 166.1 (d, *J* = 257.4 Hz), 163.2 (t, *J* = 32.4 Hz), 163.1, 159.1, 154.4, 131.1 (d, *J* = 9.4 Hz), 125.5 (d, *J* = 3.0 Hz), 116.3 (d, *J* = 22.3 Hz), 113.9 (t, *J* = 253.7 Hz), 113.1 (t, *J* = 3.8 Hz), 63.4, 32.4 (t, *J* = 25.8 Hz), 13.9. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.5, -105.8; Melting Point: 112~114 °C; HRMS (ESI) *m/z* Calcd for $C_{15}H_{14}F_3NO_5Na^+$ 368.0716; found 368.0708.

(Z)-5-ethoxy-4,4-difluoro-2-((3-fluorobenzamido)methylene)-5-oxopentanoic acid (1u): yellow solid, 33% yield, (0.2 mmol, 23 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/15/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 11.27 (d, *J* = 11.2 Hz, 1H), 7.91 (d, *J* = 11.2 Hz, 1H), 7.67 – 7.63 (m, 2H), 7.55 – 7.50 (m, 1H), 7.35 – 7.31 (m, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.16 (t, *J* = 15.8 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 173.3, 163.6 (t, *J* = 33.0 Hz), 163.3 (d, *J* = 2.2 Hz), 162.9 (d, *J* = 249.9 Hz), 142.2, 134.1 (d, *J* = 7.2 Hz), 130.8 (d, *J* = 7.8 Hz), 123.0 (d, *J* = 1.9 Hz), 120.4 (d, *J* = 21.3 Hz), 115.2 (d, *J* = 23.3 Hz), 114.4 (t, *J* = 253.2 Hz), 99.0, 63.1, 35.0 (t, *J* = 24.9 Hz), 13.9. ^{19}F NMR (376 MHz, Chloroform-d) δ -105.6, -110.6; Melting Point: 102~104 °C; HRMS (ESI) *m/z* Calcd for $C_{15}H_{14}F_3NO_5Na^+$ 368.0716; found 368.0711.

(Z)-5-ethoxy-4,4-difluoro-2-((4-(methoxycarbonyl)benzamido)methylene)-5-oxopentanoic acid (1v): yellow solid, 35% yield, (0.2 mmol, 27 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/15/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 11.39 (d, *J* = 11.2 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 2H), 7.98 (d, *J* = 8.4 Hz, 2H), 7.92 (d, *J* = 11.6 Hz, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 3.97 (s, 3H), 3.18 (t, *J* = 16.0 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 173.3, 166.0, 163.8 (t, *J* = 32.3 Hz), 163.7, 142.2, 135.6, 134.2, 130.2, 127.7, 114.4 (t, *J* = 252.8 Hz), 99.0, 63.1, 52.6, 34.9 (t, *J* = 24.9 Hz), 13.9. ^{19}F NMR (376 MHz, Chloroform-d) δ -105.7; Melting Point: 158~161 °C; HRMS (ESI) *m/z* Calcd for $C_{17}H_{17}F_2NO_7Na^+$ 408.0865; found 408.0861.

(Z)-5-ethoxy-4,4-difluoro-2-((4-methylbenzamido)methylene)-5-oxopentanoic acid (1w): yellow solid, 43% yield, (0.2 mmol, 29 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/15/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 11.28 (d, *J* = 11.6 Hz, 1H), 7.94 (d, *J* = 11.2 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.33 (q, *J* = 7.2 Hz,

2H), 3.16 (t, *J* = 16.0 Hz, 2H), 2.45 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 173.7, 164.4, 163.8 (t, *J* = 32.5 Hz), 144.2, 142.8, 129.7, 128.9, 127.8, 114.5 (t, *J* = 253.0 Hz), 97.8, 63.1, 35.0 (t, *J* = 25.0 Hz), 21.6, 13.9. ^{19}F NMR (376 MHz, Chloroform-d) δ -105.7; Melting Point: 144~146 °C; HRMS (ESI) *m/z* Calcd for $C_{16}H_{17}F_2NO_5Na^+$ 364.0967; found 364.0962.

(Z)-5-ethoxy-4,4-difluoro-2-((5-(4-fluorophenyl)-5-oxopentanamido)methylene)-5-oxopentanoic acid (1A): yellow solid, 48% yield, (0.2 mmol, 40 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/20/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.34 (d, *J* = 11.6 Hz, 1H), 8.01 – 7.98 (m, 2H), 7.68 (d, *J* = 11.6 Hz, 1H), 7.15 – 7.11 (m, 2H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.11 – 3.03 (m, 4H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.18 – 2.11 (m, 2H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 197.8, 172.8, 170.7, 165.8 (d, *J* = 249.8 Hz), 163.8 (t, *J* = 32.8 Hz), 141.4, 133.1 (d, *J* = 3.1 Hz), 130.7 (d, *J* = 9.3 Hz), 115.7 (d, *J* = 21.9 Hz), 114.5 (t, *J* = 252.4 Hz), 97.5, 63.1, 37.0, 35.5, 34.9 (t, *J* = 24.5 Hz), 19.0, 13.9. ^{19}F NMR (376 MHz, Chloroform-d) δ -105.0, -105.8; Melting Point: 124~126 °C; HRMS (ESI) m/z Calcd for $C_{19}H_{20}F_3NO_6Na^+$ 438.1135; found 438.1127.

(Z)-5-ethoxy-4,4-difluoro-5-oxo-2-(palmitamidomethylene)pentanoic acid (1B): yellow solid, 40% yield, (0.2 mmol, 37 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/20/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.30 (d, *J* = 11.6 Hz, 1H), 7.69 (d, *J* = 11.6 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.07 (t, *J* = 16.0 Hz, 2H), 2.39 (t, *J* = 7.6 Hz, 2H), 1.71 – 1.67 (m, 2H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.25 (s, 24H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 173.2, 171.4, 163.8 (t, *J* = 32.7 Hz), 141.9, 114.5 (t, *J* = 253.0 Hz), 97.2, 63.0, 36.9, 34.9 (t, *J* = 24.9 Hz), 31.9, 29.7, 29.6, 29.6, 29.6, 29.4, 29.3, 29.2, 29.1, 24.8, 22.7, 14.1, 13.8. ^{19}F NMR (376 MHz, Chloroform-d) δ -105.9; Melting Point: 74~76 °C; HRMS (ESI) *m/z* Calcd for $C_{24}H_{41}F_2NO_5Na^+$ 484.2845; found 484.2834.

(Z)-2-(((Z)-docos-13-enamido)methylene)-5-ethoxy-4,4-difluoro-5-oxopentanoic acid (1C): yellow solid, 43% yield, (0.2 mmol, 47 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/20/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.28 (d, *J* = 11.6, 1H), 7.69 (d, *J* = 11.6, 1H), 5.39 – 5.31 (m, 2H), 4.32 (q, *J* = 7.2, 2H), 3.07 (t, *J* = 16.0, 2H), 2.39 (t, *J* = 7.5, 2H), 2.03 – 1.99 (m, 2H), 1.69 (p, *J* = 7.6, 2H), 1.37 – 1.27 (m, 31H), 0.88 (t, *J* = 7.2, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 172.8, 171.3, 163.8 (t, *J* = 32.8 Hz), 142.0, 129.9, 114.5 (t, *J* = 250.6 Hz), 96.9, 63.0, 36.9, 35.0 (t, *J* = 25.0 Hz), 31.9, 29.8, 29.7, 29.6, 29.6, 29.6, 29.5, 29.4, 29.3, 29.3, 29.1, 27.2, 24.8, 22.7, 14.1, 13.9. ^{19}F NMR (376 MHz, Chloroform-d) δ -105.8; Melting Point: 66~68 °C; HRMS (ESI) *m/z* Calcd for $C_{30}H_{51}F_2NO_5Na^+$ 566.3628; found 566.3622.

(S,Z)-2-((1-benzylpyrrolidine-2-carboxamido)methylene)-5-ethoxy-4,4-difluoro-5-oxopentanoic acid (1D): yellow solid, 32% yield, (0.2 mmol, 26 mg), column chromatography using petroleum ether/EtOAc/acetic acid (50/100/1); ^{1}H NMR (400 MHz, DMSO-d6) δ 11.48 (d, *J* = 11.6 Hz, 1H), 7.41 – 7.39 (m, 2H), 7.30 – 7.23 (m, 3H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.82 (d, *J* = 12.8 Hz, 1H), 3.52 (d, *J* = 12.8 Hz, 1H), 3.29 – 3.25 (m, 1H), 3.08 (t, *J* = 16.0 Hz, 2H), 2.94 – 2.90 (m, 2H), 2.36 – 2.30 (m, 1H), 2.24 – 2.16 (m, 1H), 1.77 – 1.74 (m, 2H), 1.67 – 1.62 (m, 1H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, DMSO-d6) δ 173.1, 168.8, 163.4 (t, *J* = 32.9 Hz), 138.3, 137.6, 128.8, 128.2, 127.1, 115.2 (t, *J* = 250.5 Hz), 100.1 (t, *J* = 5.2 Hz), 66.9, 62.9, 59.4, 53.5, 35.1 (t, *J* = 25.0 Hz), 30.3, 23.7, 13.6. ^{19}F NMR (376 MHz, DMSO-d6) δ -104.1. HRMS (ESI) *m/z* Calcd for $C_{20}H_{24}F_2N_2O_5Na^+$ 433.1545; found 433.1534.

(Z)-5-ethoxy-4,4-difluoro-5-oxo-2-((2-(12-oxo-7,12-dihydro-6H-dibenzo[b,e]oxocin-2-yl)acetamido)methylene)pentanoic acid (1E): yellow solid, 25% yield, (0.4 mmol, 48 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/100/1); ^{1}H NMR (400 MHz, DMSO-d6) δ 10.68 (d, *J* = 11.2 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8. Hz, 2H), 7.49 (d, *J* = 11.2 Hz, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 1H), 6.73 (dd, *J* = 8.8, 2.0 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.76 (s, 2H), 3.33 (s, 2H), 3.04 (t, *J* = 16.0 Hz, 2H), 2.25 (s, 2H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, DMSO-d6) δ 169.3, 168.5, 168.0, 163.3 (t, *J* = 32.7 Hz), 155.8, 138.8, 137.8, 136.1, 134.1, 131.2, 130.5, 130.3, 129.2, 115.2 (t, *J* = 251.6 Hz), 114.8, 112.2, 112.0, 101.4, 99.5, 62.86, 55.5, 34.8 (t, *J* = 24.6 Hz), 31.5, 13.6, 13.2. ^{19}F NMR (376 MHz, DMSO-d6) δ -99.5. HRMS (ESI) *m/z* Calcd for $C_{25}H_{23}F_2NO_7Na^+$ 510.1335; found 510.1329.

(Z)-2-(((R)-3-((5S,8R,9S,10S,13R,14S,17R)-10,13-dimethyl-3,7,12-trioxohexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)butanamido)methylene)-5-ethoxy-4,4-difluoro-5-oxopentanoic acid (1F): yellow solid, 43% yield, (0.2 mmol, 51 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/100/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.42 (d, *J* = 11.6 Hz, 1H), 7.64 (d, *J* = 11.6 Hz, 1H), 4.31 – 4.29 (m, 2H), 3.06 (t, *J* = 16.0 Hz, 1H), 2.94 – 2.85 (m, 3H), 2.34 – 2.33 (m, 4H), 2.25 – 2.21 (m, 3H), 2.15 – 2.12 (m, 2H), 2.05 – 2.02 (m, 4H), 1.87 – 1.85 (m, 3H), 1.67 – 1.62 (m, 1H), 1.41 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 6H), 1.07 (s, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 212.2, 209.4, 208.8, 177.1, 172.6, 171.5, 164.1 (t, *J* = 32.9 Hz), 140.1, 114.8 (t, *J* = 253.0 Hz), 102.2, 63.0, 56.9, 51.8, 48.9, 46.8, 45.5, 44.9, 42.7, 38.6, 36.4, 36.0, 35.4, 33.7, 30.2, 27.6, 25.1, 21.8, 21.1, 18.6, 13.9, 11.8. ^{19}F NMR (376 MHz, Chloroform-d) δ -105.3. HRMS (ESI) *m/z* Calcd for $C_{31}H_{41}F_2NO_8Na^+$ 616.2692; found 616.2688.

(R,Z)-5-ethoxy-4,4-difluoro-2-((2-(4-isobutylphenyl)propanamido)methylene)-5-oxopentanoic acid (1G): yellow oil, 32% yield, (0.4 mmol, 52 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/50/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.25 (d, *J* = 11.6 Hz, 1H), 7.60 (d, *J* = 11.6 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 3.68 (q, *J* = 7.2 Hz, 1H), 3.03 (td, *J* = 15.6, 4.8 Hz, 2H), 2.45 (d, *J* = 7.2 Hz, 2H), 1.84 (dp, *J* = 13.6, 6.8 Hz, 1H), 1.57 (d, *J* = 7.2 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 0.88 (s, 3H), 0.86 (s, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 173.1, 172.7, 163.7 (t, *J* = 32.6 Hz), 141.9, 141.5, 136.3, 129.9, 127.4, 114.6 (t, *J* = 252.7 Hz), 97.4, 63.0, 47.1, 45.0, 34.8 (t, *J* = 25.3 Hz), 30.1, 22.3, 17.6, 13.8. ^{19}F NMR (376 MHz, Chloroform-d) δ -105.6. HRMS (ESI) *m/z* Calcd for $C_{21}H_{27}F_2NO_5Na^+$ 434.1750; found 434.1742.

(Z)-5-ethoxy-4,4-difluoro-5-oxo-2-((2-(4-((2-oxocyclopentyl)methyl)phenyl)propanamido)methylene)pentanoic acid (1H): yellow oil, 28% yield, (0.4 mmol, 46 mg), column chromatography using petroleum ether/EtOAc/acetic acid (100/30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.35 (d, *J* = 11.6 Hz, 1H), 7.54 (d, *J* = 11.2 Hz, 1H), 7.22 – 7.15 (m, 4H), 4.26 (q, *J* = 7.2 Hz, 2H), 3.66 (q, *J* = 7.2 Hz, 1H), 3.10 – 2.96 (m, 3H), 2.59 – 2.53 (m, 1H), 2.35 – 2.29 (m, 2H), 2.13 – 2.06 (m, 3H), 1.99 – 1.92 (m, 1H), 1.80 – 1.68 (m, 1H), 1.55 (d, *J* = 7.2 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 220.8, 172.5, 172.5, 164.1 (t, *J* = 32.6 Hz), 140.2, 139.5, 137.2, 129.6, 127.8, 114.7 (t, *J* = 251.6 Hz), 99.2, 63.0, 50.7, 47.0, 38.1, 35.2, 30.9, 29.3, 20.5, 17.6, 13.8. ^{19}F NMR (376 MHz, Chloroform-d) δ -105.7. HRMS (ESI) *m/z* Calcd for $C_{23}H_{27}F_2NO_6Na^+$ 474.1699; found 474.1690.

Ethyl 2,2-difluoro-3-(6-oxo-2-phenyl-6H-1,3-oxazin-5-yl)propanoate (2a): yellow solid, 65% yield, (0.2 mmol, 40 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 8.23 – 8.18 (m, 2H), 7.84 (s, 1H), 7.65 – 7.56 (m, 1H), 7.54 – 7.46 (m, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 3.31 (t, *J* = 16.0 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 164.0, 163.2 (t, *J* = 32.3 Hz), 159.3, 154.4, 133.6, 129.3, 128.9, 128.5, 114.0 (t, *J* = 253.8 Hz), 113.3 (t, *J* = 4.0 Hz), 63.4, 32.4 (t, *J* = 25.8 Hz), 13.8. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.6; Melting Point: 80~82 °C; HRMS (ESI) Calcd for $C_{15}H_{13}F_2NO_4H^+$ 310.0885; found 310.0892.

Ethyl 2,2-difluoro-3-(6-oxo-2-(p-tolyl)-6H-1,3-oxazin-5-yl)propanoate (2b): yellow solid, 50% yield, (0.2 mmol, 32 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 8.10 (d, *J* = 8.0 Hz, 2H), 7.82 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 3.30 (t, *J* = 16.0 Hz, 2H), 2.44 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 164.3, 163.2 (t, *J* = 32.1 Hz), 159.5, 154.7, 144.7, 129.7, 128.6, 126.4, 115.2 (t, *J* = 253.7 Hz), 112.7 (t, *J* = 4.1 Hz), 63.4, 32.4 (t, *J* = 25.8 Hz), 21.8, 13.8. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.6; Melting Point: 88~90 °C; HRMS (ESI) *m/z* Calcd for $C_{16}H_{15}F_2NO_4H^+$ 324.1042; found 324.1046.

Ethyl 2,2-difluoro-3-(2-(4-methoxyphenyl)-6-oxo-6H-1,3-oxazin-5-yl)propanoate (2c): yellow solid, 58% yield, (0.2 mmol, 39 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 8.17 (d, *J* = 8.4 Hz, 2H), 7.79 (s, 1H), 6.98 (d, *J* = 8.4 Hz, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 3.89 (s, 3H), 3.29 (t, *J* = 16.0 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 164.1, 164.1, 163.3 (t, *J* = 32.3 Hz), 159.6, 154.9, 130.7, 121.6, 114.3, 114.1 (t, *J* = 253.8 Hz), 111.9 (t, *J* = 4.2 Hz), 63.3, 55.6, 32.4 (t, *J* = 25.8 Hz), 13.9. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.7; Melting Point: 95~98 °C; HRMS (ESI) *m/z* Calcd for $C_{16}H_{15}F_2NO_5H^+$ 340.0991; found 340.0996.

Ethyl 2,2-difluoro-3-(2-(4-fluorophenyl)-6-oxo-6H-1,3-oxazin-5-yl)propanoate (2d): white solid, 35% yield, (0.2 mmol, 23 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 8.25 – 8.22 (m, 2H), 7.82 (s, 1H), 7.19 (t, *J* = 8.8 Hz, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 3.30 (t, *J* = 16.0 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 166.1 (d, *J* = 257.4 Hz), 163.2 (t, *J* = 32.4 Hz), 163.1, 159.1, 154.4, 131.1 (d, *J* = 9.4 Hz), 125.5 (d, *J* = 3.0 Hz), 116.3 (d, *J* = 22.3 Hz), 113.9 (t, *J* = 253.7 Hz), 113.1 (t, *J* = 3.8 Hz), 63.4, 32.4 (t, *J* = 25.6 Hz), 13.9; ^{19}F NMR (376 MHz, Chloroform-d) δ -103.8, -104.6; Melting Point: 84~86 °C; HRMS (ESI) Calcd for $C_{15}H_{12}F_3NO_4H^+$ 328.0791; found 328.0796.

Ethyl 3-(2-(4-chlorophenyl)-6-oxo-6H-1,3-oxazin-5-yl)-2,2-difluoropropanoate (2e): yellow solid, 40% yield, (0.2 mmol, 27 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 8.17 (s, 1H), 8.14 (s, 1H), 7.84 (s, 1H), 7.50 (s, 1H), 7.48 (s, 1H);4.35 (q, *J* = 7.2 Hz, 2H), 3.31 (t, *J* = 16.0 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 163.2 (t, *J* = 32.3 Hz), 163.1, 159.0, 154.3, 140.2, 129.8, 129.3, 127.7, 113.9 (t, *J* = 253.8 Hz), 113.5 (t, *J* = 4.0 Hz), 63.4, 32.4 (t, *J* = 25.9 Hz), 13.9. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.7; Melting Point: 80~82 °C; HRMS (ESI) Calcd for $C_{15}H_{12}ClF_2NO_4H^+$ 344.0496; found 344.0502.

Ethyl 2,2-difluoro-3-(2-(4-nitrophenyl)-6-oxo-6H-1,3-oxazin-5-yl)propanoate (2f): yellow solid, 32% yield, (0.2 mmol, 23 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 8.42 – 8.35 (m, 4H), 7.90 (s, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 3.35 (t, *J* = 16.0 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 163.1 (t, *J* = 32.1 Hz), 161.6, 158.5, 153.8, 150.6, 134.7, 129.5, 124.0, 115.1 (t, *J* = 4.0 Hz), 113.8 (t, *J* = 254.0 Hz), 63.5, 32.4 (t, *J* = 25.7 Hz), 13.9. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.6; Melting Point: 92~94 °C; HRMS (ESI) Calcd for $C_{15}H_{12}F_2N_2O_6H^+$ 355.0736; found 355.0739.

Methyl 4-(5-(3-ethoxy-2,2-difluoro-3-oxopropyl)-6-oxo-6H-1,3-oxazin-2-yl)benzoate (2g): yellow solid, 44% yield, (0.2 mmol, 33 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 8.29 (d, *J* = 8.4 Hz, 2H), 8.16 (d, *J* = 8.4 Hz, 2H), 7.88 (s, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.97 (s, 3H), 3.33 (t, *J* = 16.0 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 166.0, 163.2 (t, *J* = 32.2 Hz), 162.9, 158.9, 154.1, 134.3, 133.0, 130.0, 128.5, 114.2 (t, *J* = 4.2 Hz), 112.6 (t, *J* = 254.2 Hz), 63.4, 52.5, 32.4 (t, *J* = 25.8 Hz), 13.9. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.6; Melting Point: 80~82 °C; HRMS (ESI) *m/z* Calcd for $C_{17}H_{15}F_2NO_6H^+$ 368.0940; found 368.0944.

Ethyl 2,2-difluoro-3-(6-oxo-2-(m-tolyl)-6H-1,3-oxazin-5-yl)propanoate (2h): white solid, 40% yield, (0.2 mmol, 26 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 8.03 – 8.00 (m, 2H), 7.84 (s, 1H), 7.44 – 7.37 (m, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 3.31 (t, *J* = 16.0 Hz, 2H), 2.43 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 164.3, 163.2 (t, *J* = 32.3 Hz), 159.4, 154.5, 138.8, 134.5, 129.1, 129.0, 128.8, 125.8, 114.0 (t, *J* = 253.9 Hz), 113.1 (t, *J* = 4.0 Hz), 63.4, 32.4 (t, *J* = 25.8 Hz), 21.3, 13.9. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.6; Melting Point: 82~84 °C; HRMS (ESI) *m/z* Calcd for $C_{16}H_{15}F_2NO_4H^+$ 324.1042; found 324.1046.

Ethyl 2,2-difluoro-3-(2-(3-fluorophenyl)-6-oxo-6H-1,3-oxazin-5-yl)propanoate (2i): yellow solid, 36% yield, (0.2 mmol, 24 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 8.02 – 8.00 (m, 1H), 7.93 – 7.89 (m, 1H), 7.85 (s, 1H), 7.52 – 7.47 (m, 1H), 7.34 – 7.29 (m, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.32 (t, *J* = 16.0 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 163.2 (t, *J* = 32.3 Hz), 162.8 (d, *J* = 249.0 Hz), 162.7 (d, *J* = 3.6 Hz), 158.9, 154.2, 131.4 (d, *J* = 8.3 Hz), 130.6 (d, *J* = 8.1 Hz), 124.3 (d, *J* = 2.8 Hz), 120.7 (d, *J* = 21.4 Hz), 115.4 (d, *J* = 24.1 Hz), 114.0 (t, *J* = 3.8 Hz), 112.6 (d, *J* = 254.0 Hz), 63.4, 32.4 (t, *J* = 25.9 Hz), 13.9. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.7, -111.2; Melting Point: 72~74 °C; HRMS (ESI) *m/z* Calcd for $C_{15}H_{12}F_3NO_4H^+$ 328.0791; found 328.0796.

Ethyl 3-(2-(3-bromophenyl)-6-oxo-6H-1,3-oxazin-5-yl)-2,2-difluoropropanoate (2j): yellow solid, 34% yield, (0.2 mmol, 26 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 8.36 (s, 1H), 8.14 (d, *J* = 7.6 Hz, 1H), 7.85 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.32 (t, *J* = 16.0 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 163.2 (t, *J* = 32.1 Hz), 162.5, 158.9, 154.1, 136.4, 131.4, 131.2, 130.4, 127.0, 123.0, 114.0 (t, *J* = 3.9 Hz), 113.9 (t, *J* = 254.1 Hz), 63.4, 32.4 (t, *J* = 25.8 Hz), 13.9. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.6; Melting Point: 75~77 °C; HRMS (ESI) *m/z* Calcd for $C_{15}H_{12}BrF_2NO_4H^+$ 387.9991; found 387.9995.

Ethyl 2,2-difluoro-3-(6-oxo-2-(o-tolyl)-6H-1,3-oxazin-5-yl)propanoate (2k): yellow solid, 51% yield, (0.2 mmol, 33 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 8.04 (d, *J* = 8.0 Hz, 1H), 7.87 (s, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.34 – 7.30 (m, 2H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.32 (t, *J* = 16.0 Hz, 2H), 2.68 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 165.1, 163.2 (t, *J* = 31.9 Hz), 159.5, 154.2, 140.0, 132.6, 132.2, 130.5, 128.5, 126.2, 114.0 (t, *J* = 254.0 Hz), 113.0 (t, *J* = 4.1 Hz), 63.4, 32.4 (t, *J* = 25.8 Hz), 22.5, 13.9. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.6; Melting Point: 78~80 °C; HRMS (ESI) *m/z* Calcd for $C_{16}H_{15}F_2NO_4H^+$ 324.1042; found 324.1045.

Ethyl 2,2-difluoro-3-(2-(2-methoxyphenyl)-6-oxo-6H-1,3-oxazin-5-yl)propanoate (2l): yellow solid, 49% yield, (0.2 mmol, 33 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.91 – 7.89 (m, 1H), 7.87 (s, 1H), 7.56 – 7.52 (m, 1H), 7.08 – 7.03 (m, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 3.94 (s, 3H), 3.31 (t, *J* = 16.0 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 164.2, 163.2 (t, *J* = 32.3 Hz), 159.6, 159.1, 154.4, 134.4, 131.7, 120.6, 118.9, 114.0 (t, *J* = 253.9 Hz), 113.0 (t, *J* = 4.0 Hz), 112.2, 63.4, 56.1, 32.4 (t, *J* = 25.8 Hz), 13.8. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.6; Melting Point: 79~81 °C; HRMS (ESI) *m/z* Calcd for $C_{16}H_{15}F_2NO_5H^+$ 340.0991; found 340.0996.

Ethyl 2,2-difluoro-3-(2-(2-fluorophenyl)-6-oxo-6H-1,3-oxazin-5-yl)propanoate (2m): yellow solid, 50% yield, (0.2 mmol, 33 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 8.08 (td, *J* = 8.0, 2.0 Hz, 1H), 7.88 (s, 1H), 7.62 – 7.57 (m, 1H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.25 – 7.21 (m, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.33 (t, *J* = 16.0 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 163.3 (t, *J* = 32.0 Hz), 161.6 (d, *J* = 5.4 Hz), 161.5 (d, *J* = 263.4 Hz), 158.9, 154.1, 135.1 (d, *J* = 9.3 Hz), 131.2, 124.5 (d, *J* = 3.8 Hz), 117.9 (d, *J* = 8.5 Hz), 117.4 (d, *J* = 22.0 Hz), 113.9, 113.9 (t, *J* = 254.2 Hz), 63.4, 32.4 (t, *J* = 25.9 Hz), 13.8. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.6, -108.0; Melting Point: 64~66 °C; HRMS (ESI) *m/z* Calcd for $C_{15}H_{12}F_3NO_4H^+$ 328.0791; found 328.0795.

Ethyl 3-(2-(2-chlorophenyl)-6-oxo-6H-1,3-oxazin-5-yl)-2,2-difluoropropanoate (2n): yellow solid, 40% yield, (0.2 mmol, 27 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.93 – 7.89 (m, 2H), 7.54 – 7.47 (m, 2H), 7.42 – 7.38 (m, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.33 (t, *J* = 16.0 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 163.1, 161.1 (t, *J* = 32.2 Hz), 159.0, 153.8, 133.7, 133.2, 131.8, 131.5, 128.8, 127.0, 114.2 (t, *J* = 4.1 Hz), 113.9 (t, *J* = 253.8 Hz), 63.5, 32.4 (t, *J* = 25.8 Hz), 13.9. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.5; Melting Point: 58~60 °C; HRMS (ESI) Calcd for $C_{15}H_{12}ClF_2NO_4H^+$ 344.0496; found 344.0501.

Ethyl 3-(2-(2-bromophenyl)-6-oxo-6H-1,3-oxazin-5-yl)-2,2-difluoropropanoate (2o): yellow solid, 47% yield, (0.2 mmol, 36 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.89 (s, 1H), 7.88 – 7.85 (m, 1H), 7.74 – 7.72 (m, 1H), 7.47 – 7.43 (m, 1H), 7.42 – 7.37 (m, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.33 (t, *J* = 16.0 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR

{^{1}H} (101 MHz, Chloroform-d) δ 163.7, 163.1 (t, *J* = 32.2 Hz), 159.0, 153.7, 134.7, 133.1, 131.8, 130.8, 127.5, 121.8, 114.3 (t, *J* = 4.1 Hz), 113.8 (t, *J* = 253.8 Hz), 63.5, 32.4 (t, *J* = 25.8 Hz), 13.9. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.5; Melting Point: 62~64 °C; HRMS (ESI) *m/z* Calcd for $C_{15}H_{12}BrF_2NO_4H^+$ 387.9991; found 387.9996.

Ethyl 2,2-difluoro-3-(6-oxo-2-(2-(trifluoromethyl)phenyl)-6H-1,3-oxazin-5-yl)propanoate (2p): yellow solid, 42% yield, (0.2 mmol, 32 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.92 – 7.90 (m, 1H), 7.87 (s, 1H), 7.85 – 7.83 (m, 1H), 7.72 – 7.70 (m, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 3.33 (t, *J* = 16.0 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 163.7, 163.1 (t, *J* = 32.2 Hz), 158.6, 153.5, 132.0, 132.0, 131.2, 129.1 (q, *J* = 1.8 Hz), 129.1 (q, *J* = 31.5 Hz), 127.3 (q, *J* = 5.3 Hz), 123.2 (q, *J* = 274.7 Hz), 114.6 (t, *J* = 4.1 Hz), 113.8 (t, *J* = 253.8 Hz), 63.5, 32.4 (t, *J* = 26.0 Hz), 13.8. ^{19}F NMR (376 MHz, Chloroform-d) δ -58.5, -104.4; Melting Point: 64~66 °C; HRMS (ESI) *m/z* Calcd for $C_{16}H_{12}F_5NO_4H^+$ 378.0759; found 378.0754.

Ethyl 3-(2-(3,5-dimethylphenyl)-6-oxo-6H-1,3-oxazin-5-yl)-2,2-difluoropropanoate (2q): yellow solid, 45% yield, (0.2 mmol, 30 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.83 (s, 3H), 7.23 (s, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 3.31 (t, *J* = 16.0 Hz, 2H), 2.38 (s, 6H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 164.4, 163.2 (t, *J* = 32.2 Hz), 159.5, 154.6, 138.6, 135.5, 129.0, 126.2, 113.9 (t, *J* = 253.7 Hz), 112.9 (t, *J* = 4.0 Hz), 63.4, 32.4 (t, *J* = 25.8 Hz), 21.1, 13.9. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.6; Melting Point: 94~96 °C; HRMS (ESI) *m/z* Calcd for $C_{17}H_{17}F_2NO_4H^+$ 338.1198; found 338.1210.

Ethyl 3-(2-(2,4-dichlorophenyl)-6-oxo-6H-1,3-oxazin-5-yl)-2,2-difluoropropanoate (2r): yellow solid, 48% yield, (0.2 mmol, 36 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.92 – 7.88 (m, 2H), 7.55 (d, *J* = 2.1 Hz, 1H), 7.39 (dd, *J* = 8.5, 2.0 Hz, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.33 (t, *J* = 16.0Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 163.1 (t, *J* = 32.2 Hz), 162.2, 158.7, 153.7, 139.1, 134.7, 132.7, 131.5, 127.5, 127.1, 114.4 (t, *J* = 3.9 Hz), 113.8 (t, *J* = 253.8 Hz), 63.5, 32.4 (t, *J* = 25.8 Hz), 13.9. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.5; Melting Point: 80~82 °C; HRMS (ESI) Calcd for $C_{15}H_{11}Cl_2F_2NO_4H^+$ 378.0106; found 378.0108.

Ethyl 3-(2-(2,6-dichlorophenyl)-6-oxo-6H-1,3-oxazin-5-yl)-2,2-difluoropropanoate (2s): yellow solid, 36% yield, (0.2 mmol, 27 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.90 (s, 1H), 7.43 – 7.41 (m, 3H), 4.35 (q, *J* = 7.2 Hz, 2H), 3.35 (t, *J* = 16.0Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 163.0 (t, *J* = 32.3 Hz), 161.1, 158.9, 153.0, 134.1, 132.3, 130.4, 128.2, 115.6 (t, *J* = 4.0 Hz), 112.5 (t, *J* = 254.6 Hz), 63.5, 32.5 (t, *J* = 25.8 Hz), 13.8. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.3; Melting Point: 60~62 °C; HRMS (ESI) *m/z* Calcd for $C_{15}H_{11}Cl_2F_2NO_4H^+$ 378.0106; found 378.0110.

Ethyl 3-(2-(3,4-difluorophenyl)-6-oxo-6H-1,3-oxazin-5-yl)-2,2-difluoropropanoate (2t): yellow solid, 50% yield, (0.2 mmol, 35 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 8.07 – 8.00 (m, 2H), 7.83 (s, 1H), 7.34 – 7.30 (m, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.31 (t, *J* = 16.0 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 163.1 (t, *J* = 32.2 Hz), 161.9 (t, *J* = 2.5 Hz), 158.7, 154.1, 153.9 (dd, *J* = 259.2, 12.8 Hz), 150.5 (dd, *J* = 251.5, 12.9 Hz), 126.3 (dd, *J* = 6.5, 3.7 Hz), 125.5 (dd, *J* = 7.6, 3.7 Hz), 117.9 (t, *J* = 18.3 Hz), 117.8, 113.9 (t, *J* = 254.0 Hz), 113.8 (t, *J* = 4.1 Hz), 63.4, 32.4 (t, *J* = 25.8 Hz), 13.8. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.7, -128.3 (d, *J* = 21.0 Hz), -135.2 (d, *J* = 21.0 Hz); Melting Point: 82~84 °C; HRMS (ESI) *m/z* Calcd for $C_{15}H_{11}F_4NO_4H^+$ 346.0697; found 346.0699.

Ethyl 2,2-difluoro-3-(2-mesityl-6-oxo-6H-1,3-oxazin-5-yl)propanoate (2u): yellow solid, 43% yield, (0.2 mmol, 30 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.86 (s, 1H), 6.92 (s, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 3.32 (t, *J* = 16.0 Hz, 2H), 2.31 (s, 3H), 2.29 (s, 6H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 166.6, 163.2 (t, *J* = 32.0 Hz), 159.9, 153.5, 140.7, 136.7, 128.8, 128.1, 115.2 (t, *J* = 253.7 Hz), 113.7 (t, *J* = 4.1 Hz), 63.4, 32.4 (t, *J* = 25.9 Hz), 21.2, 19.9, 13.8. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.5; Melting Point: 95~98 °C; HRMS (ESI) *m/z* Calcd for $C_{18}H_{19}F_2NO_4H^+$ 352.1355; found 352.1357.

Ethyl 2,2-difluoro-3-(6-oxo-2-(perfluorophenyl)-6H-1,3-oxazin-5-yl)propanoate (2v): Brown oil, 44% yield, (0.2 mmol, 35 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.88 (s, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.34 (t, *J* = 16.0 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 162.9 (t, *J* = 32.2 Hz), 157.8, 155.2, 153.0, 113.7, 111.2, 106.9 (td, *J* = 13.8, 3.7 Hz), 63.6, 32.4 (t, *J* = 25.9 Hz), 13.8. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.4, -137.4 – -137.5 (m), -146.1 – -146.2 (m), -159.4 – -159.5 (m). HRMS (ESI) *m/z* Calcd for $C_{15}H_8F_7NO_4H^+$ 400.0414; found 400.0418.

Ethyl 3-(2-(tert-butyl)-6-oxo-6H-1,3-oxazin-5-yl)-2,2-difluoropropanoate (2w): white solid, 60% yield, (0.2 mmol, 35 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.67 (s, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 3.24 (t, *J* = 16.0 Hz, 2H), 1.38 – 1.34 (m, 12H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 176.1, 163.2 (t, *J* = 32.4 Hz), 159.8, 153.7, 113.9 (t, *J* = 253.4 Hz), 113.1 (t, *J* = 4.0 Hz), 63.3, 38.3, 32.2 (t, *J* = 25.7 Hz), 27.5, 13.8. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.8; Melting Point: 110~113 °C; HRMS (ESI) Calcd for $C_{13}H_{17}F_2NO_4H^+$ 290.1198; found 290.1200.

Ethyl 2,2-difluoro-3-(6-oxo-2-(2,2,3,3-tetramethylcyclopropyl)-6H-1,3-oxazin-5-yl)propanoate (2x): yellow solid, 49% yield, (0.2 mmol, 32 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.60 (s, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 3.20 (t, *J* = 16.0 Hz, 2H), 1.43 (s, 1H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.31 (s, 6H), 1.27 (s, 6H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 170.4, 163.3 (t, *J* = 32.5 Hz), 160.3, 153.9, 114.1 (t, *J* = 254.0 Hz), 111.4 (t, *J* = 4.0 Hz), 63.3, 37.5, 33.3, 32.2 (t, *J* = 25.9 Hz), 23.8, 16.8, 13.8. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.7; Melting Point: 127~130 °C; HRMS (ESI) *m/z* Calcd for $C_{16}H_{21}F_2NO_4H^+$ 330.1511; found 330.1516.

Ethyl 3-(2-((3r,5r,7r)-adamantan-1-yl)-6-oxo-6H-1,3-oxazin-5-yl)-2,2-difluoropropanoate (2y): white solid, 42% yield, (0.2 mmol, 32 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.67 (s, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 3.23 (t, *J* = 16.0 Hz, 2H), 2.10 – 2.09 (m, 3H), 1.99 (d, *J* = 2.8 Hz, 6H), 1.79 – 1.70 (m, 6H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 175.4, 163.2 (t, *J* = 32.4 Hz), 160.0, 154.0, 115.2 (t, *J* = 253.6 Hz), 113.1 (t, *J* = 4.0 Hz), 63.3, 40.0, 39.0, 36.2, 32.3 (t, *J* = 25.8 Hz), 27.7, 13.8. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.7; Melting Point: 142~144 °C; HRMS (ESI) *m/z* Calcd for $C_{19}H_{23}F_2NO_4H^+$ 368.1668; found 368.1670.

Ethyl 3-(2-benzyl-6-oxo-6H-1,3-oxazin-5-yl)-2,2-difluoropropanoate (2z): yellow oil, 50% yield, (0.2 mmol, 32 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Acetone-d6) δ 8.32 (d, *J* = 8.4 Hz, 2H), 8.19 (d, *J* = 8.4 Hz, 2H), 8.04 (s, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 3.94 (s, 3H), 3.42 (t, *J* = 16.0 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 166.3, 163.8 (t, *J* = 32.4 Hz), 159.4, 155.0, 135.0, 134.5, 130.6, 129.2, 115.5 (t, *J* = 4.2 Hz), 115.3 (t, *J* = 252.5 Hz), 64.0, 52.8, 33.0 (t, *J* = 25.8 Hz), 14.1. ^{19}F NMR (376 MHz, Acetone-d6) δ -105.1. HRMS (ESI) *m/z* Calcd for $C_{16}H_{15}F_2NO_4H^+$ 324.1042; found 324.1044.

Ethyl 3-(2-(2-chloropyridin-3-yl)-6-oxo-6H-1,3-oxazin-5-yl)-2,2-difluoropropanoate (2A): yellow oil, 52% yield, (0.2 mmol, 36 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 8.60 – 8.59 (m, 1H), 8.30 – 8.28 (m, 1H), 7.91 (s, 1H), 7.46 – 7.43 (m, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 3.35 (t, *J* = 16.0 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 163.0 (t, *J* = 32.2 Hz), 161.6, 158.4, 153.4, 152.2, 149.7, 140.4, 125.9, 122.3, 114.9 (t, *J* = 3.8 Hz), 112.5 (d, *J* = 254.2 Hz), 63.5, 32.3 (t, *J* = 25.8 Hz), 13.8. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.5. HRMS (ESI) *m/z* Calcd for $C_{14}H_{11}ClF_2N_2O_4H^+$ 345.0448; found 345.0452.

Ethyl 3-(2-(5-chlorothiophen-2-yl)-6-oxo-6H-1,3-oxazin-5-yl)-2,2-difluoropropanoate (2B): yellow oil, 35% yield, (0.2 mmol, 24 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.74 – 7.72 (m, 2H), 7.01 (d, *J* = 4.0 Hz, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 3.27 (t, *J* = 16.0 Hz, 2H), 1.37 (t, *J*

= 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 163.2 (t, *J* = 32.3 Hz), 159.2, 158.4, 154.5, 139.4, 132.5, 131.4, 128.2, 112.6 (t, *J* = 254.0 Hz), 112.6 (t, *J* = 4.0 Hz), 63.4, 32.5 (t, *J* = 25.8 Hz), 13.9. ^{19}F NMR (376 MHz, Chloroform-d) δ -104.8. HRMS (ESI) *m/z* Calcd for $C_{13}H_{10}ClF_2NO_4SH^+$ 350.0060; found 350.0063.

Diethyl 3,3'-(9H,9'H-[9,9'-bifluorene]-9,9'-diyl)bis(2,2-difluoropropanoate) (2C): white solid, 41% yield, (0.2 mmol, 49 mg), column chromatography using petroleum ether/EtOAc (30/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.36 – 7.34 (m, 4H), 7.21 (s, 4H), 7.01 (s, 4H), 6.63 (s, 4H), 3.62 (t, *J* = 14.1 Hz, 4H), 3.49 (q, *J* = 7.2 Hz, 4H), 0.95 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR {^{1}H} (101 MHz, Chloroform-d) δ 163.4 (t, *J* = 32.0 Hz), 142.9, 141.8, 128.1, 125.6, 125.2, 119.2, 115.1 (t, *J* = 252.9 Hz), 62.5, 57.1, 37.5 (t, *J* = 23.5 Hz), 13.3. ^{19}F NMR (376 MHz, Chloroform-d) δ -96.8. HRMS (ESI) *m/z* Calcd for $C_{36}H_{30}F_4O_4Na^+$ 625.1972; found 625.1975.

ASSOCIATED CONTENT *

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:.

Data for the optimization of reaction conditions, NMR spectra of products and ORTEP figures of compounds **1b**, **1c**, **1g**, **2a** and **2C** (PDF).

Crystal data **1b** (CIF)

Crystal data **1c** (CIF)

Crystal data **1g** (CIF)

Crystal data **2a** (CIF)

Crystal data **2C** (CIF)

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Notes

The authors declare no competing financial interest.

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