

A mild and efficient synthesis of monofluorinated α -lactam pseudopeptides via a novel dehydrofluorination of Ugi products

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Abstract Six novel monofluorinated α -lactam pseudopeptide derivatives were synthesized via Ugi reaction using *gem*-difluoromethylene-containing isocyanide as a key component, followed by dehydrofluorination of Ugi products in one pot without additional base.

Keywords Monofluorinated α -lactam pseudopeptide · Ugi reaction · Dehydrofluorination

Introduction

Many natural peptides cannot be directly used as drugs because of problems associated with low absorption, poor biostability, bioselectivity, and oral bioavailability [1,2]. Pseudopeptides obtained by modifying the amino acid sequence of bioactive peptides can enhance biologically relevant properties of proteins to solve the above problems [3,4]. In recent years, incorporation of tailored fluorinated groups has also been widely used to replace or mimic critical peptide bonds [5–7].

Lactams are important moieties in conformationally restricted pseudopeptides with various biologic activities [8–10]. Up to now, a large number of examples contain-

ing four- to higher-membered lactams in conformationally restricted pseudopeptide drugs have been reported [11–13]. In particular, β -lactams have been widely incorporated into peptide chains resulting in β -lactam antibiotics which can be regarded as prototypical examples that play a key role in the fight against pathogenic bacteria [14–16].

From the first report of *N*-*t*-butyl-3-phenylaziridinone by Baumgarten in 1961, α -lactams (aziridinones) have received a lot of attention as useful reactive intermediates due to their ring-opening capability when exposed to a broad variety of nucleophiles [17–19]. α -Lactams also exhibit antimicrobial and antiviral activities [20,21]. Aminoglycoside/ α -lactam combination has afforded effective antibiotics with a wide spectrum of bactericidal activity and an opportunity to be used as monotherapies for the treatment of febrile neutropenic in children [22]. However, not only there are a few limited methods to synthesize α -lactams [23–25], but also these methods are associated with some shortcomings such as unwanted side reactions resulting from the use of a strong base. Thus, the search for an efficient method for the synthesis of α -lactam derivatives under mild conditions is not only highly desirable but also necessary. In this short communication, we would like to report a new and simple method to prepare novel monofluorinated α -lactam pseudopeptide derivatives via Ugi reaction using *gem*-difluoromethylene-containing isocyanide as a key component, followed by dehydrofluorination of Ugi products in one pot under similar conditions without additional base.

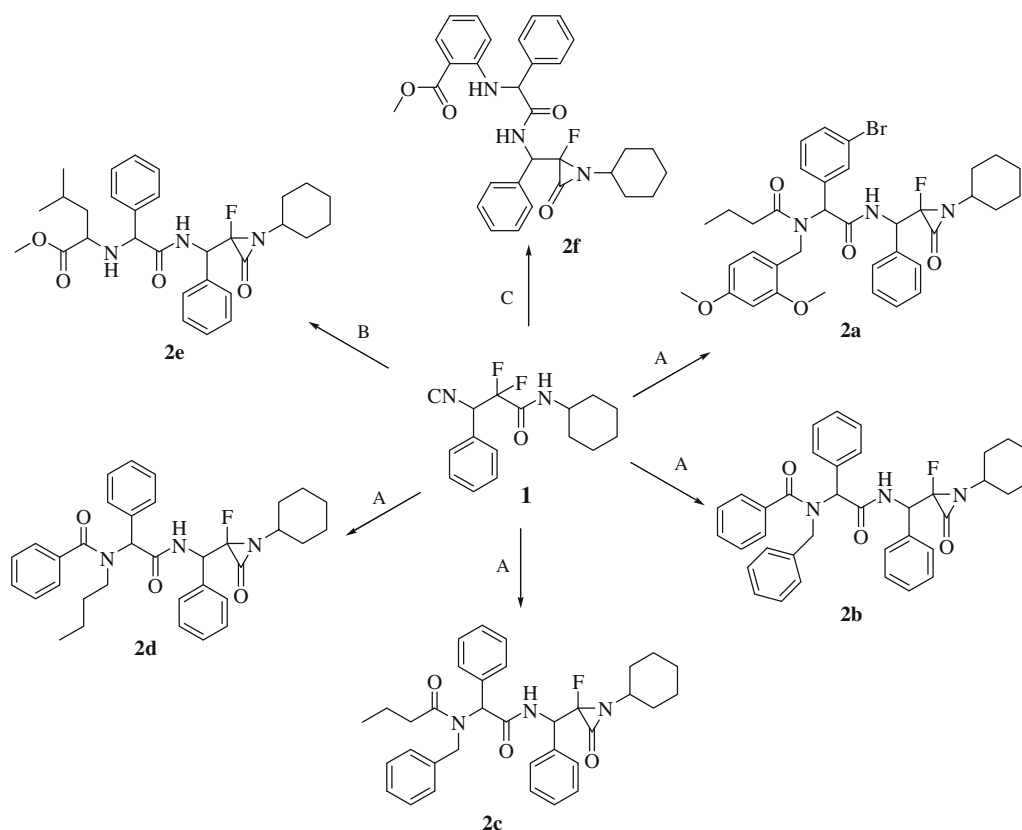
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Results and discussion

In our previous article, we reported a novel approach to synthesize a new fluoro-containing building block, α , α -difluoro- β -amino amide bearing the isocyanide functionality



Scheme 1 A No solvent, 60 °C; B CH₃OH, rt; C CH₃OH, reflux

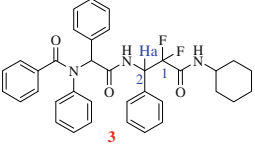
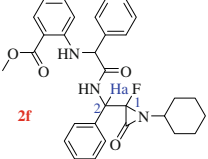
1, and then used it to prepare several difluorinated pseudo-peptides via Ugi reaction under solvent-free conditions [26]. In order to determine the limitations of this Ugi reaction for functional group tolerance and continue our isocyanide research, we tested **1** on several additional substrates (a variety of different carboxylic acids, aldehydes, and amines). Some substrates could be transformed to the desired Ugi products easily, whereas, to our surprise, other substrates were unexpectedly converted into mono fluorinated pseudo-peptides containing an α -lactam moiety (**2a–f**, Scheme 1). This reaction is very unusual. From literatures, α -lactams (aziridinones) were prepared via the cyclization of α -haloamide precursors in the presence of strong base, such as potassium *t*-butoxide or sodium hydride [23–25]. In general, dehydrofluorination can be promoted by different bases, for example, DBU [27], sodium hydroxide [28], lithium bis (trimethylsilyl)amide (LHMDS) in THF [29], or triethylamine [30]. To the best of our knowledge, there is no report on the synthesis of α -lactams via the cyclization of α -fluoroamide under such mild reaction conditions.

The structures of compound **2a–f** were identified on the basis of the ¹H NMR, ¹³C NMR, ¹⁹F NMR, and HRMS or elemental analysis. Thus, **3** (Ugi product, which has been reported earlier [26]) and **2f** (dehydrofluorination of Ugi product) were chosen as representative examples to illustrate

the structural differences between them. The main NMR data of characteristic signals of **3** and **2f** are outlined in Table 1. It is obvious that there are some distinct differences between **3** and **2f** in NMR. In the ¹H NMR spectrum of **3**, the proton of two NH appeared at $\delta = 9.28$ and 8.37 ppm as a triplet and doublet of doublets, respectively, due to coupling with proton and fluoro atom. The Ha appeared at $\delta = 5.95$ –5.77 ppm, as a multiplet due to ortho coupling with the two fluoro atoms and the proton of NH. While in spectrum of **2f**, the proton of two NH appeared at $\delta = 8.59$ and 8.03 ppm. However, it is different NH when compared with that of **3**. If the structure of **2f** is similar to that of **3**, the number of the proton of NH should be 3. The proton of Ha resonated at $\delta = 5.81$ ppm, as a doublet with a coupling constant of 7.6 Hz owing to coupling with only one fluoro atom.

In the ¹³C NMR spectrum of **3**, C-1 ($\delta = 114.7$ ppm) and C-2 ($\delta = 56.4$ ppm) were split into two doublet of doublets because of coupling with the two fluoro atoms. While in spectrum of **2f**, C-1 ($\delta = 142.6$ ppm) and C-2 ($\delta = 48.2$ ppm) were split into doublet because of coupling with the a fluoro atom. The ¹⁹F NMR of **3** is very complicated. There are a lot of signals in the spectrum, whereas **2f** has a relatively simple ¹⁹F NMR spectrum; the fluorine nucleus resonated as a sharp single at $\delta = 127.5$ ppm. The HRMS spectra or elemental analysis of **2f** also indicated that the dehydrofluorinated

Table 1 NMR data of characteristic signals of **3** and **2f**

Compound	¹ H NMR, δ, ppm		¹³ C NMR, δ, ppm		¹⁹ F NMR, δ, ppm
	NH	Ha	C-1	C-2	
	9.28 (t, <i>J</i> = 8.8 Hz), 8.37 (dd, <i>J</i> = 8.0, 36.5 Hz)	5.95–5.77 (m)	114.7 (dd, ¹ <i>J</i> _{CF} = 255.5, 257.4 Hz)	56.4 (dd, ² <i>J</i> _{CF} = 23.9, 28.2 Hz)	–110.9, –111.5, –111.9, –112.5, –113.0 (dd, <i>J</i> = 9.5, 57.0 Hz), –113.6 (dd, <i>J</i> = 9.5, 61.8 Hz)
	8.59 (d, <i>J</i> = 3.2 Hz), 8.03 (s)	5.81 (d, <i>J</i> _{HF} = 7.6 Hz)	142.6 (d, ¹ <i>J</i> _{CF} = 260.8 Hz)	48.2 (d, ² <i>J</i> _{CF} = 24.3 Hz)	–127.5 (s)

product was formed. Unfortunately, attempts to cultivate their (**2a–f**) single crystal were failed.

In addition, due to the different substrates of Ugi reaction, first reaction step was carried out under different conditions. Of them, **2a–d** were prepared under solvent-free conditions, **2e** was synthesized in methanol at room temperature, whereas **2f** was obtained in refluxing methanol, and then followed by an intramolecular cyclization with the loss of HF to afford monofluorinated α -lactams.

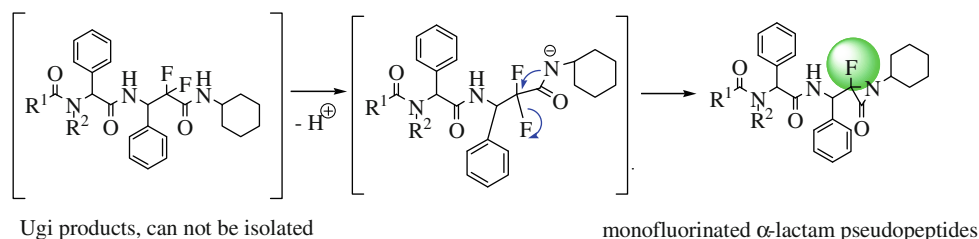
Although the dehydrofluorination process to form aziridinone under such mild reaction conditions is interesting, the mechanism of the dehydrofluorination step is not clear. A possible mechanism could be analogous to those proposed in the literature which suggested the abstraction of the N–H proton in the presence of base and followed by intramolecular displacement [21–23]. The Ugi intermediates of **2a–f** are unstable and rapidly convert into α -lactams (Scheme 2). At the present stage, we are not sure what kind of Ugi products can further undergo the dehydrofluorination. It is possible that the conformation of the N–H bond (attached with cyclohexyl) in the structures of the Ugi intermediates of **2a–f** is more favorable for the elimination of HF.

In conclusion, we have reported an efficient alternative for the preparation of mono fluorinated α -lactam pseudopep-

tides via Ugi/dehydrofluorination under mild reaction conditions without additional base. The new monofluorinated aziridinone pseudopeptides may have potent application in medicinal field, especially in peptide chemistry. Further investigation is ongoing to survey the generality and limitations of this mono fluorinated α -lactams synthesis, as well as the exact mechanism with the aid of computer.

Experimental section

¹H and ¹³C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer (400 and 100 MHz, respectively). The ¹⁹F NMR spectra were recorded using a Bruker Avance-500 spectrometer (470 MHz) and the ¹⁹F NMR spectra were recorded using CF₃CO₂H as internal standard. High-resolution mass spectra (HRMS, ESI) were recorded on a MicroMass LCTTM spectrometer. Melting points were measured on a Büchi B-540 and were uncorrected. All the reagents were of analytic grade and obtained from commercial suppliers and used without further purification with the following exception. Methanol was heated to reflux over magnesium methoxide for 12 h and then distilled. Column

Scheme 2 Possible mechanism of formation of α -lactams

chromatography was carried out with Merck 60 (230–400 mesh) silica gel.

General procedure for the synthesis of compounds (**2a–d**) under solvent-free conditions

Aldehyde (0.34 mmol) was added in portions for about 5 min to amine (0.34 mmol) under stirring. The mixture was stirred for another 25 min at room temperature. The reaction mixture was then heated to 60 °C. Isocyanide **1** (0.34 mmol) and carboxylic acid (0.34 mmol) were added in portions for 10 min. Stirring was continued at 60 °C until completion of the reaction (TLC). The crude residue was purified by chromatography (AcOEt/heptane = 1 : 5) to give the desired products.

N-(2,4-Dimethoxy-benzyl)-*N*-((3-bromo-phenyl)-[(1-cyclohexyl-2-fluoro-3-oxo-aziridin-2-yl)-phenyl-methyl]-carbamoyl)-methyl)-butyramide (**2a**)

Yield: 59%; white solid, m.p.: 233–235 °C. ^1H NMR (400 MHz, CDCl_3): δ 7.72 (s, 1H), 7.38 (s, 7H), 7.12 (t, $J = 8.0$ Hz, 1H), 6.99 (d, $J = 8.4$ Hz, 1H), 6.42 (dd, $J = 2.4$, 8.4 Hz, 1H), 6.34 (s, 1H), 6.26–6.18 (m, 1H), 5.77 (d, $J_{\text{HF}} = 7.2$ Hz, 1H), 5.24 (s, 1H), 4.57 (d, $J = 16$ Hz, 1H), 4.46 (d, $J = 16$ Hz, 1H), 3.81 (s, 3H), 3.75 (s, 1H), 3.65 (s, 3H), 2.57–2.40 (m, 2H), 1.81–1.70 (m, 4H), 1.33–0.87 (m, 11H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 174.9 (d, $^2J_{\text{CF}} = 21.9$ Hz), 168.6, 168.5, 160.8, 157.9, 142.0 (d, $^1J_{\text{CF}} = 254.7$ Hz), 140.5, 133.6, 133.5, 131.9, 131.8, 129.3, 129.2, 128.6, 128.5, 128.3, 128.2, 118.6, 116.2, 111.5, 104.0, 98.5, 64.5, 64.0, 55.8 (d, $^2J_{\text{CF}} = 25.3$ Hz), 55.4, 55.2, 48.4, 47.7, 35.7, 32.2, 32.1, 25.2, 24.5, 18.5, 13.9 ppm; ^{19}F NMR (470 MHz, CDCl_3): $\delta = -109.9$ to -114.9 (m, 1F) ppm; HRMS (ESI): m/z : 716.2089 $[\text{M} + \text{Na}]^+$; calcd for $\text{C}_{36}\text{H}_{41}\text{BrFN}_3\text{O}_5 + \text{Na}$: 716.2111.

N-Benzyl-*N*-([[(1-cyclohexyl-2-fluoro-3-oxo-aziridin-2-yl)-phenyl-methyl]-carbamoyl]-phenyl-methyl)-benzamide (**2b**)

Yield: 62%; white solid, m.p.: 225–227 °C. ^1H NMR (400 MHz, CDCl_3): δ 7.52–7.33 (m, 15H), 7.17 (s, 3H), 7.03 (d, $J = 2.8$ Hz, 2H), 7.01 (s, 1H), 5.78 (d, $J_{\text{HF}} = 7.6$ Hz, 1H), 5.53 (s, 1H), 4.78 (d, $J = 16.0$ Hz, 1H), 4.43 (d, $J = 16.8$ Hz, 1H), 3.77–3.69 (m, 1H), 1.81–0.95 (m, 10H); ^{13}C NMR (100 MHz, CDCl_3): δ 173.4, 166.8, 158.5 (d, $^2J_{\text{CF}} = 28.1$ Hz), 141.98 (d, $^1J_{\text{CF}} = 260.1$ Hz), 136.9, 136.8, 135.7, 135.6, 133.8, 131.6, 130.1, 129.7, 129.5, 129.0, 128.5, 128.4, 128.1, 127.2, 126.9, 126.8, 65.4, 52.8 (d, $^2J_{\text{CF}} = 32.2$ Hz), 48.0, 32.7, 25.4, 25.3, 24.8, 24.7; ^{19}F NMR (470 MHz, CDCl_3): $\delta = -128.1$ ppm; HRMS (ESI): m/z : 612.2610 $[\text{M} + \text{Na}]^+$; calcd for $\text{C}_{37}\text{H}_{36}\text{FN}_3\text{O}_3 + \text{Na}$:

612.2638; Anal. Calcd for $\text{C}_{37}\text{H}_{36}\text{FN}_3\text{O}_3$: C 74.20 (75.36), H 6.16 (6.15), N 6.49 (7.13).

N-Benzyl-*N*-([[(1-cyclohexyl-2-fluoro-3-oxo-aziridin-2-yl)-phenyl-methyl]-carbamoyl]-phenyl-methyl)-butyramide (**2c**)

Yield: 67%; white solid, m.p.: 193–195 °C. ^1H NMR (400 MHz, CDCl_3): δ 7.41–7.34 (m, 10H), 7.17 (d, $J = 7.2$ Hz, 3H), 6.96 (d, $J = 6.0$ Hz, 2H), 5.93 (s, 1H), 5.78 (d, $J_{\text{HF}} = 7.6$ Hz, 1H), 4.71 (d, $J = 17.6$ Hz, 1H), 4.49 (d, $J = 17.2$ Hz, 1H), 3.76–3.68 (m, 1H), 2.43–2.22 (m, 2H), 1.82–0.89 (m, 15H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 175.2, 167.4, 158.5 (d, $^2J_{\text{CF}} = 28.0$ Hz), 141.9 (d, $^1J_{\text{CF}} = 257.4$ Hz), 137.3, 133.8, 131.5, 129.9, 129.5, 128.9, 128.8, 128.4, 128.1, 127.0, 126.1, 63.9, 50.2 (d, $^2J_{\text{CF}} = 20.2$ Hz), 48.0, 35.8, 32.7, 25.4, 24.7, 18.6, 13.8 ppm; ^{19}F NMR (470 MHz, CDCl_3): $\delta = -128.2$ ppm; HRMS (ESI): m/z : 578.2792 $[\text{M} + \text{Na}]^+$; calcd for $\text{C}_{34}\text{H}_{38}\text{FN}_3\text{O}_3 + \text{Na}$: 578.2897.

N-Butyl-*N*-([[(1-cyclohexyl-2-fluoro-3-oxo-aziridin-2-yl)-phenyl-methyl]-carbamoyl]-phenyl-methyl)-benzamide (**2d**)

Yield: 45%; white solid, m.p.: 187–189 °C. ^1H NMR (400 MHz, CDCl_3): δ 7.55–7.39 (m, 15H), 6.07 (d, $J_{\text{HF}} = 8.0$ Hz, 1H), 5.91 (s, 1H), 5.40–5.32 (m, 1H), 3.86–3.84 (m, 1H), 3.37–3.12 (m, 2H), 2.33 (dd, $J = 5.2$, 7.2 Hz, 1H), 2.08–1.59 (m, 13H), 0.64–0.53 (m, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 173.6, 168.8, 161.6 (d, $^2J_{\text{CF}} = 40.6$ Hz), 142.0 (d, $^1J_{\text{CF}} = 254.4$ Hz), 136.7, 134.5, 130.8, 130.0, 129.4, 129.0, 128.8, 128.7, 128.3, 128.0, 127.7, 126.8, 66.6, 48.2 (d, $^2J_{\text{CF}} = 22.5$ Hz), 32.9, 31.9, 29.7, 25.4, 24.8, 22.7, 19.8, 14.1 ppm; ^{19}F NMR (470 MHz, CDCl_3): $\delta = -158.1$ ppm; HRMS (ESI): m/z : 578.2822 $[\text{M} + \text{Na}]^+$; calcd for $\text{C}_{34}\text{H}_{38}\text{FN}_3\text{O}_3 + \text{Na}$: 578.2795.

4-Methyl-2-([[(1-cyclohexyl-2-fluoro-3-oxo-aziridin-2-yl)-phenyl-methyl]-carbamoyl]-phenyl-methyl)-amino]-pentanoic acid methyl ester (**2e**)

To a solution of benzaldehyde (36 mg, 0.34 mmol) in 2 mL of absolute methanol, *L*-Leucine (22 mg, 0.34 mmol) and **1** (100 mg, 0.34 mmol) were added. The solution was stirred for 3 days (monitored by TLC) at room temperature. After evaporation of methanol by rotary evaporation, a crude product was obtained, and it was purified by chromatography (AcOEt/heptane = 1:5). Yield: 53%; white solid, m.p.: 179–181 °C. ^1H NMR (400 MHz, CDCl_3): δ 8.45 (s, 1H), 7.38–7.34 (m, 10H), 5.72 (d, $J_{\text{HF}} = 7.2$ Hz, 1H), 4.38 (s, 1H), 3.75–3.64 (m, 4H), 3.24 (s, 1H), 1.80–0.94 (m,

14H), 0.90 (d, $J = 6.8$ Hz, 3H), 0.79 (d, $J = 6.8$ Hz, 3H) ppm; ^{13}C NMR(100 MHz, CDCl_3): δ 174.7, 168.9, 158.4 (d, $^2J_{\text{CF}} = 27.9$ Hz), 141.7 (d, $^1J_{\text{CF}} = 256.9$ Hz), 137.3, 131.4, 129.4, 129.3, 129.1, 128.8, 128.1, 127.9, 65.9, 57.2, 51.9, 48.1 (d, $^2J_{\text{CF}} = 20.4$ Hz), 42.2, 32.7, 25.4, 24.8, 24.6, 22.7, 21.9 ppm; ^{19}F NMR(470 MHz, CDCl_3): $\delta = -130.8$ ppm; HRMS (ESI): m/z : 546.2723 $[\text{M} + \text{Na}]^+$; calcd for $\text{C}_{30}\text{H}_{38}\text{FN}_3\text{O}_4 + \text{Na}$: 546.2744; Anal. Calcd for $\text{C}_{30}\text{H}_{38}\text{FN}_3\text{O}_4$: C 68.53 (68.81), H 7.19 (7.31), N 7.61 (8.02).

2-([(1-(1-Cyclohexyl-2-fluoro-3-oxo-aziridin-2-yl)-phenyl-methyl]-carbamoyl)-phenyl-methyl)-amino]-benzoic acid methyl ester (2f)

To a solution of 2-aminobenzoic acid (46 mg, 0.34 mmol) in 2 mL of absolute methanol, benzaldehyde (36 mg, 0.34 mmol) was added and the mixture was stirred for 2 h at room temperature. Then isocyanide **1** (100 mg, 0.34 mmol) was added and the reaction mixture was stirred for 48 h (monitored by TLC) under reflux. After evaporation of methanol by rotary evaporation, a crude product was obtained, and it was purified by chromatography (AcOEt /heptane = 1 : 5). Yield: 63%; white solid, m.p.: 192–194 °C. ^1H NMR(400 MHz, CDCl_3): δ 8.59 (d, $J = 3.2$ Hz, 1H), 8.03 (s, 1H), 8.00 (dd, $J = 1.6$, 8.0 Hz, 1H), 7.56–7.24 (m, 11H), 6.83 (t, $J = 7.6$ Hz, 1H), 6.73 (d, $J = 8.0$ Hz, 1H), 5.81 (d, $J_{\text{HF}} = 7.6$ Hz, 1H), 4.95 (d, $J = 3.2$ Hz, 1H), 3.88 (s, 3H), 3.75–3.66 (m, 1H), 1.64–0.91 (m, 10H) ppm; ^{13}C NMR(100 MHz, CDCl_3): δ 168.9, 168.8, 158.3 (d, $^2J_{\text{CF}} = 27.7$ Hz), 149.1, 142.6 (d, $^1J_{\text{CF}} = 260.8$ Hz), 137.1, 134.9, 131.9, 131.5, 129.5, 129.4, 128.8, 128.0, 126.9, 125.7, 125.6, 117.5, 112.6, 112.2, 64.2, 51.9, 48.2 (d, $^2J_{\text{CF}} = 24.3$ Hz), 32.7, 31.6, 25.3, 24.6, 22.6 ppm; ^{19}F NMR(470 MHz, CDCl_3): $\delta = -127.5$ ppm; HRMS (ESI): m/z : 552.2263 $[\text{M} + \text{Na}]^+$; calcd for $\text{C}_{31}\text{H}_{32}\text{FN}_3\text{O}_4 + \text{Na}$: 552.2275; Anal. Calcd for $\text{C}_{31}\text{H}_{32}\text{FN}_3\text{O}_4$: C 69.65 (70.31), H 6.26 (6.09), N 7.44 (7.93).

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