Electrochemical Radical Tandem Difluoroethylation/Cyclization of Unsaturated Amides to Access MeCF2-Featured Indolo/Benzoimidazo[2,1-A]isoquinolin-6(5H)-Ones

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Posted Date: 15 January 2024

doi: 10.20944/preprints202401.1047.v1

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Article

Electrochemical Radical Tandem Difluoroethylation/Cyclization of Unsaturated Amides to Access $MeCF_2$-Featured Indolo/Benzoimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones

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Abstract: A metal-free electrochemical oxidative difluoroethylation of 2-arylbenzimidazoles was accomplished, which provided an efficient strategy for the synthesis of $MeCF_2$-containing benzo[4,5]imidazo[2,1-*a*]-isoquinolin-6(5*H*)-ones. In addition, the method also enabled the efficient construction of various difluoroethylated indolo[2,1-*a*]isoquinolin-6(5*H*) ones. Notably, this electrochemical synthesis protocol proceeded well under mild conditions without metal catalysts or exogenous additives/oxidants added.

Keywords: electrochemical synthesis; difluoroethylation; radical; polycyclic compounds; tandem cyclization

1. Introduction

Organofluorine compounds are very useful and attractive organic molecules, which play pivotal roles in pharmaceuticals, agrochemicals, and performance materials [1-6]. Among various fluorine-containing groups, the difluoroethyl group (CF_2Me) is receiving more and more attention due to its special chemical and biological properties [7-9]. In particular, the introduction of a difluoroethyl group can improve the metabolic stability and potency of a target molecule [10,11]. Therefore, it is highly demanded to develop new and efficient protocols for the rapid introduction of difluoroethyl group to target compounds. In this context, the radical strategy has emerged as a powerful approach for the synthesis of CF_2Me–containing compounds. However, recent developments in this direction have always involved peroxides or photoredox catalysts [12-16]. On the other hand, electrochemical synthesis has also attracted much attention due to the advantages of avoiding the usage of chemical oxidants and reductants [17-23]. Very recently, much progress in electrochemical difluoroethylation has been made by Hu [24] and our group [25,26]. Although these methods have provided innovative transformations, the preparation of CF_2Me-substituted polycyclic compounds has not been achieved.

Benzo[4,5]imidazo[2,1-*a*]isoquinolines and indolo [2,1-*a*]isoquinolines, which are significant classes of fused polycyclic nitrogen-containing scaffolds and widely exist in natural products and pharmaceuticals (Scheme 1-1) [27-31]. Although substantial efforts have been contributed to the construction of these polycyclic compounds [32-37], the CF_2Me–containing target polycycles remain a great challenge to date (Scheme 1-2). As part of our continuing interest in difluoroethylation functionalizations, we anticipated that the radical cyclization process would provide a feasible platform for the synthesis of CF_2Me–revised target polycycles. Herein, we report an electrochemical-induced radical cascade cyclization strategy, whereby a series of CF_2Me-substituted indolo [2,1-

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a]isoquinolines and benzo[4,5]imidazo[2,1-*a*]isoquinolines could be efficiently prepared under mild and chemical oxidants-free conditions (Scheme 1-3).

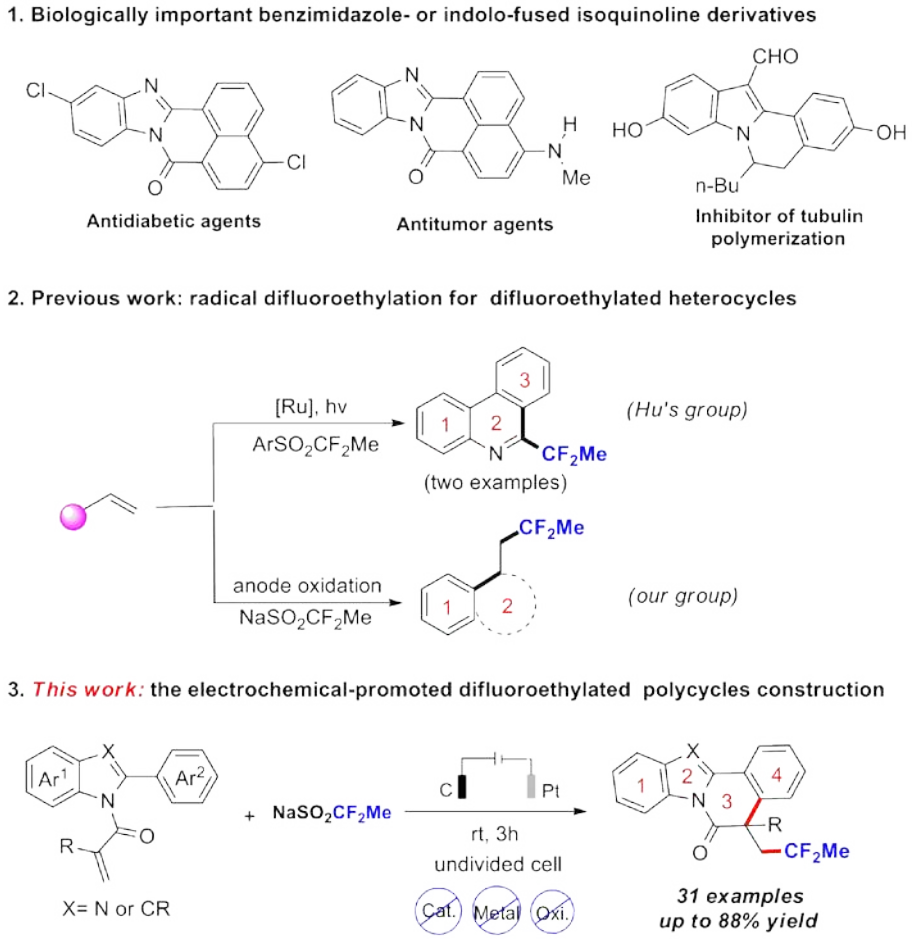
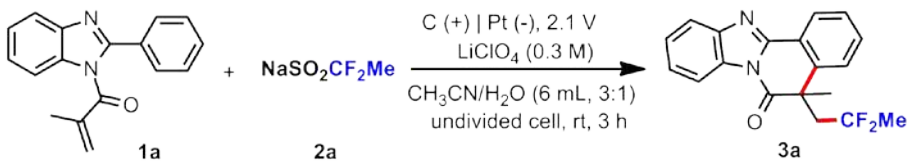


Figure 1. Strategies for radical difluoroethylated heterocycles.

2. Results and Discussion

We began our investigation by examining the electrochemical difluoroethylation reaction of *N*-methacryloyl-2-phenylbenzoimidazole (**1a**) with $NaSO_2CF_2Me$ (**2a**) (Table 1). To our delight, the electrolysis furnished the 86% yield of the desired cyclization product **3a** with a constant voltage of 2.1 V in an undivided cell equipped with a carbon plate anode and a Pt plate cathode (Table 1, entry 1). Then the various conditions, such as voltage, electrode material, electrolyte, and solvent were measured. Neither lower voltage nor higher voltage led to higher efficiency (entry 2-3). C(+) | Pt(−) was proved to be the optimal electrode material combination compared to others (entry 4-6). A switch of electrolytes $LiClO_4$ to other electrolytes such as Et_4NClO_4, $^nBu_4NClO_4$, or $^nBu_4NPF_6$ significantly restrained the reaction (entry 7-9). The change of solvent proportion failed to improve the yield of **3a** (entries 10−11). The cyclization product **3a** could not be observed without electricity (entry 12).

Table 1. Optimization of the typical conditions[a].



Entry	variations from standard conditions	Yield (%)[b]
1	none	86

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2	1.8 V	52
3	2.5 V	65
4	C (+)|Ni (−)	62
5	C (+)|C (−)	56
6	Pt (+)|Pt (−)	39
7	$^{n}Bu_4NClO_4$ as the electrolyte	37
8	Et_4NClO_4 as the electrolyte	61
9	$^{n}Bu_4NPF_6$ as the electrolyte	26
10	CH_3CN/H_2O (9:1)	47
11	CH_3CN/H_2O (1:1)	66
12	No electricity	n.d

[a]Reaction conditions: Carbon plate (10 mm * 10 mm * 3 mm) as the anode, platinum plate (10 mm * 10 mm * 0.20 mm) as the cathode, undivided cell, 2.1 V, **1a** (0.2 mmol), **2a** (0.6 mmol), $LiClO_4$ (0.3 M), CH_3CN (4.5 mL), H_2O (1.5 mL), rt, 3 h. [b]Isolated yields.

With the above-optimized conditions in hand, we investigated the substrate scopes (Scheme 1). It can be seen that a wide range of 2-arylbenzoimidazoles with either electron-donating or electron-withdrawing substituents worked well and afforded the corresponding products in good to high yields (**3a-3h**). The ortho-substituted 2-arylbenzoimidazoles were also tolerated with the reaction, and the desired products were obtained in 70-88% yields (**3i-3m**). When utilizing meta-substituted 2-arylbenzoimidazoles as the starting materials, the reactions demonstrated good site-selectivity with no regioisomers detected (**3n**). It also occurred smoothly on disubstituted substrates to produce the cyclization products in good yields (**3o** and **3p)**. The 3, 5-di substituent was successfully converted to the target product **3q** in 72% yield without the interference of steric hindrance. For Ar1 substituents, the dimethyl-substituted *N*-methacryloyl-2-phenylbenzoimidazoles gave the desired products **3r** in good yields. The substrates with phenyl or benzyl substitution of the terminal olefin were also able to produce the relevant products (**3s** and **3t)**. The substrates containing naphthalene or thiophene were all compatible with this reaction mode, delivering the corresponding products **3u** and **3v** in 74% and 67% yields, respectively.

Subsequently, we turned our attention to the synthesis of indolo[2,1-*a*]isoquinoline derivatives, which are key structural skeletons of various pharmaceuticals. As shown in Scheme 2, the desired CF_2Me-substituted indolo[2,1-*a*]isoquinoline derivatives were obtained in moderate to excellent yields. The halosubstituted (F-, Cl-, Br-) substrates also smoothly underwent a cyclization process to give the corresponding products with good efficiency (**5b-5e**). Moreover, the substrates with ethyl group at the C3 position of the indole ring were demonstrated to be suitable substrates to provide the final products in 65-75% yield (**5f-5h**). Notably, this method was also enable to access cyclopropyldifluoromethylated indolo[2,1-*a*]isoquinoline (**5i**).

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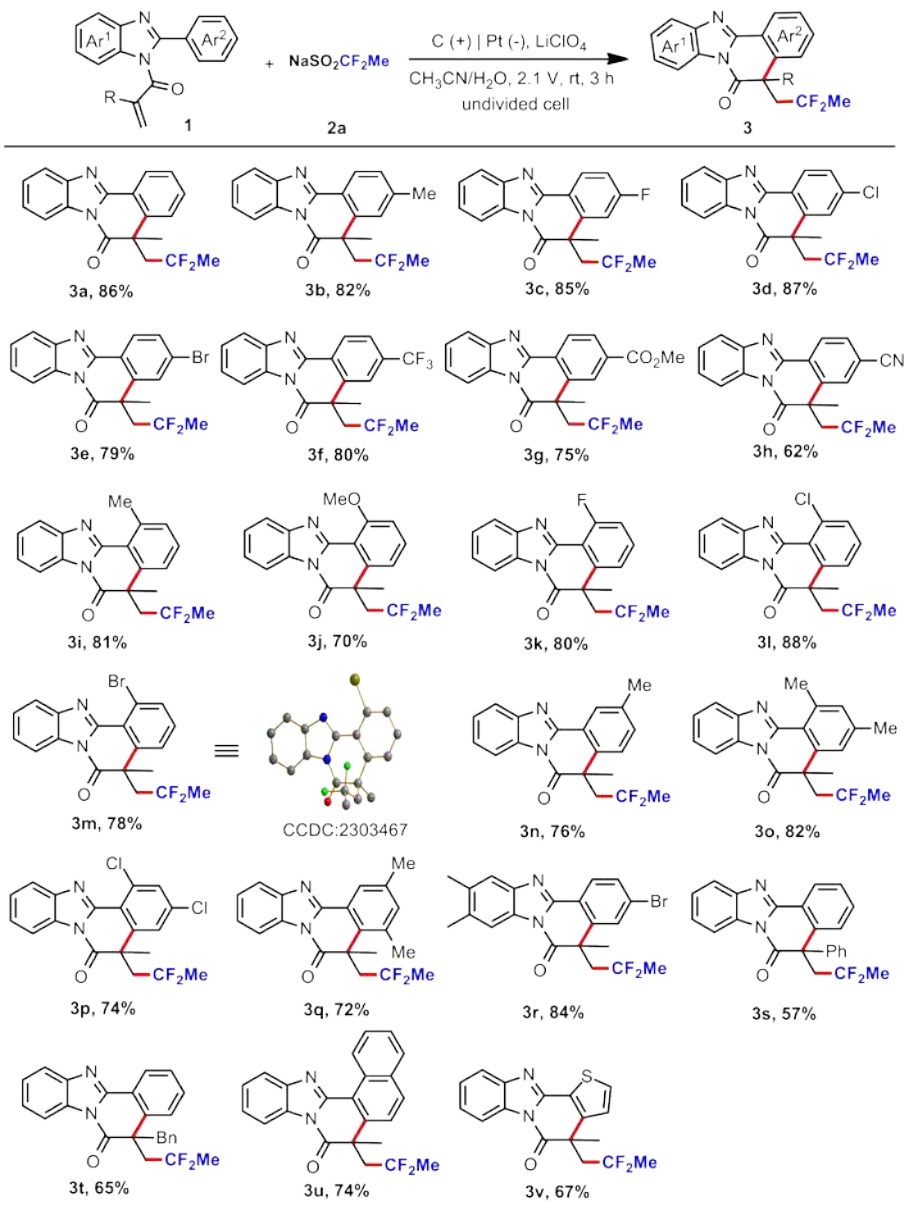

Scheme 1. Scope of the substrates 2-arylbenzimidazoles. Reaction conditions: Carbon plate (10 mm * 10 mm * 3 mm) as the anode, platinum plate (10 mm * 10 mm * 0.20 mm) as the cathode, undivided cell, 2.1 V, **1** (0.2 mmol), **2a** (0.6 mmol), $LiClO_4$ (0.3 M), CH_3CN (4.5 mL), H_2O (1.5 mL), rt, 3 h, isolated yields.

Then some control experiments were carried out to investigate the mechanism of this reaction (Scheme 3). When radical scavenger 2,6-di-tert-butyl-4-methylphenol (BHT) was added to the standard reaction system, the reaction was significantly suppressed, and the desired product was not detected by TLC. When adding the 1,1-diphenylethylene into the system, only the 16% yield of the target product was obtained and the radical adduct was found by HRMS. The two experiments suggested that the reaction may involve a radical pathway. To further understand the details of this reaction mechanism, cyclic voltammetry (CV) experiments were performed. As shown in Figure 2, the oxidation peaks of **1a** and **2a** were at 1.47 V and 0.67 V, respectively. These results indicated that **2a** was more easily oxidized than **1a**.

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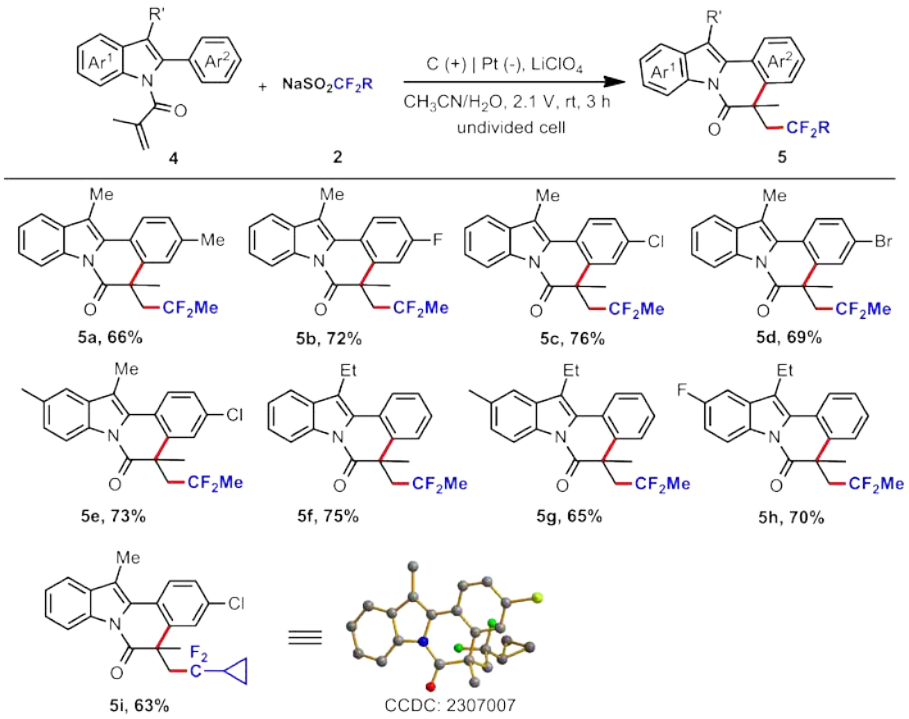
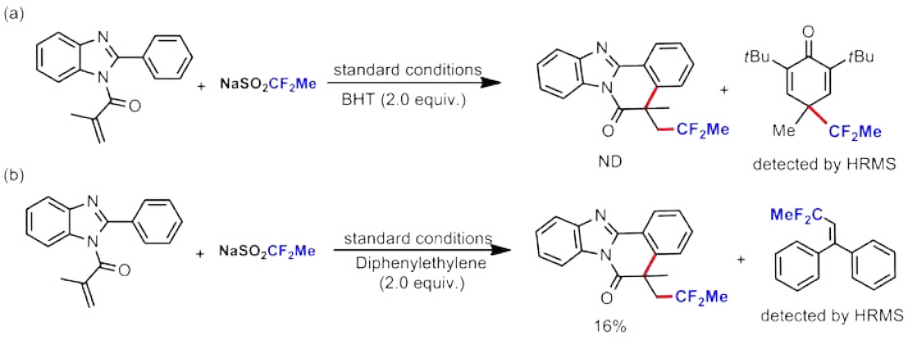


Scheme 2. Scope of the substrates 2-arylindoles. Reaction conditions: Carbon plate (10 mm * 10 mm * 3 mm) as the anode, platinum plate (10 mm * 10 mm * 0.20 mm) as the cathode, undivided cell, 2.1 V, **4** (0.2 mmol), **2** (0.6 mmol), $LiClO_4$ (0.3 M), CH_3CN (4.5 mL), H_2O (1.5 mL), rt, 3 h, isolated yields.



Scheme 3. Reactions for mechanistic determination.

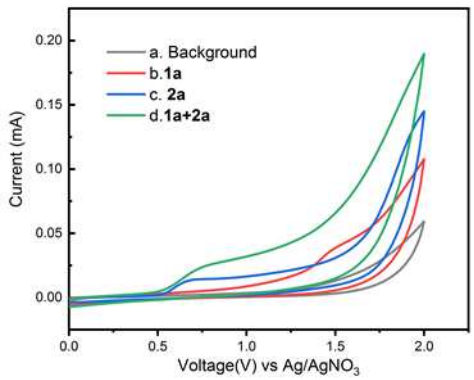


Figure 2. Cyclic voltammograms of substrates in 0.1 M $LiClO_4$/(CH_3CN/H_2O), using glassy carbon working electrode, platinum wire counter electrode, and $Ag/AgNO_3$ reference electrode at 50 mVs^{-1} scan rates: (a) Background, (b) **1a** (5 mM), (c) **2a** (5 mM), (d) **1a** (5 mM) and **2a** (5 mM).

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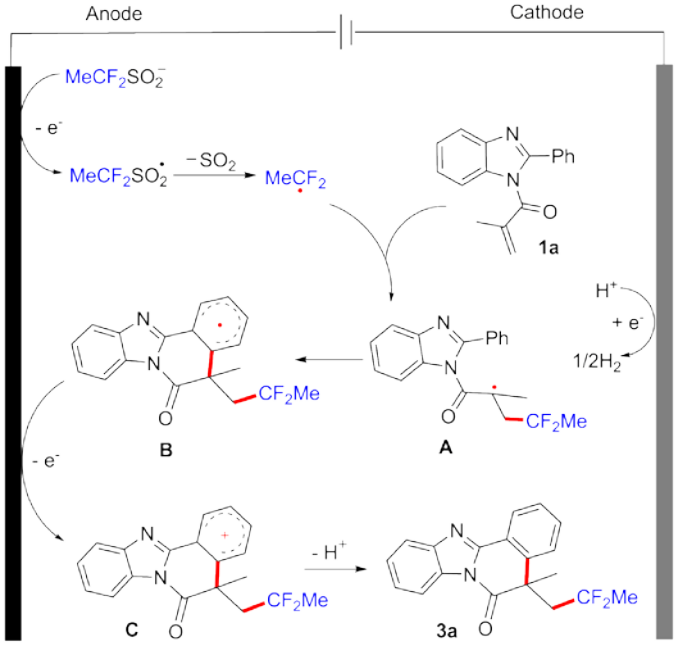
Based on the above results, a plausible mechanism of this reaction was proposed (Scheme 4). First, anodic oxidation of $MeCF_2SO_2Na$ generated the $MeCF_2SO_2$ radical, which then liberated SO_2 to afford $MeCF_2$ radical. Subsequently, the addition of $MeCF_2$ radical to the double bond of **1a** yielded a carbon-centred radical **A**. The intermediate **A** underwent further intramolecular radical cyclization to afford the aryl radical **B**. The intermediate **B** was oxidized at the anode to give aryl cation **C**, which resulted in the expected product **3a** via a deprotonation process.



Scheme 4. Proposed reaction mechanism.

3. Materials and Methods

3.1. General Methods

^1H and ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker advance III 400 or 500 spectrometer in $CDCl_3$ with TMS as the internal standard. High-resolution mass spectral analysis (HRMS (TOF)) data were measured on a Bruker Apex II. All products were identified by ^1H, ^{19}F, ^{13}C NMR and HRMS. The starting materials were purchased from Energy, J&K Chemicals, or Aldrich and used without further purification. The conversion was monitored by thin-layer chromatography (TLC). Flash column chromatography was performed over silica gel (200-300 mesh). Cyclic voltammetry experiments were carried out in an electrochemical workstation (CHI660E, Shanghai, China). 2-arylbenzimidazoles/2-arylindoles were prepared according to reported procedures.[35]

3.2. General Procedure for the Reaction

To a 20 mL test tube with a stir bar was charged with, 2-arylbenzimidazoles/2-arylindoles (1 equiv., 0.2 mmol), $MeCF_2SO_2Na$, or sodium cyclopropyldifluoromethylsulfinate (3 equiv., 0.6 mmol), $LiClO_4$ (0.3 M), MeCN (4.5 mL), H_2O (1.5 mL). The tube was equipped with a carbon plate (10 mm * 10 mm * 3 mm) as the anode and a platinum plate (10 mm × 10 mm × 0.2 mm) as the cathode. The reaction mixture was electrolyzed in an undivided cell at room temperature under a constant voltage of 2.1 V for 3 h. Upon completion, the mixture was extracted with EtOAc (10 mL × 3). The combined organic phases were dried over Na_2SO_4 and condensed under vacuum. The residue was purified by silica gel column chromatography to afford the final products. (^1H NMR, ^{19}F NMR and ^{13}C NMR of compounds (**3a–v and 5a-i**) are shown in Supplementary Materials).

5-(2,2-difluoropropyl)-5-methylbenzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (***3a***). A white solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1), 56.1 mg, 86 % yield. ^1H NMR (400 MHz, $CDCl_3$): δ 8.52 – 8.49 (m, 1H), 8.37 – 8.35 (m, 1H), 7.84 – 7.82 (m, 1H), 7.59

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– 7.55 (m, 1H), 7.50 (t, *J* = 7.2 Hz, 2H), 7.47 – 7.40 (m, 2H), 3.30 – 3.18 (m, 1H), 2.79 – 2.67 (m, 1H), 1.72 (s, 3H), 1.34 (t, *J* = 18.8 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 172.2, 149.6, 144.0, 140.0, 131.5, 131.3, 127.9, 126.8, 126.0, 125.9, 125.6, 122.6 (t, *J* = 240.5 Hz), 122.3, 119.8, 115.7, 48.2 (t, *J* = 23.9 Hz), 45.5, 31.1, 24.7 (t, *J* = 27.3 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ -86.07 – -86.30 (m, 2F). HRMS (ESI-TOF) m/z: Calcd for $C_{19}H_{16}F_2N_2O$ $(M+H)^+$ 327.1303; Found 327.1306.

5-(2,2-difluoropropyl)-3,5-dimethylbenzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (***3b***). A white solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1), 55.7 mg, 82 % yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37 (d, *J* = 8.0 Hz, 1H), 8.35 – 8.33 (m, 1H), 7.80 – 7.79 (m, 1H), 7.44 – 7.38 (m, 2H), 7.30 (d, *J* = 8.5 Hz, 1H), 7.26 (s, 1H), 3.21 (q, *J* = 15.0 Hz, 1H), 2.70 (q, *J* = 15.5 Hz, 1H), 2.45 (s, 3H), 1.70 (s, 3H), 1.32 (t, *J* = 19.0 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 172.3, 149.8, 144.1, 141.8, 140.1, 131.4, 129.0, 127.1, 126.0, 125.8, 125.3, 122.5 (t, *J* = 240.6 Hz), 119.7, 119.6, 115.6, 48.2 (t, *J* = 24.1 Hz), 45.5, 31.0, 24.7(t, *J* = 27.4 Hz), 21.8. ^{19}F NMR (471 MHz, $CDCl_3$): δ -86.01 – -86.20 (m, 2F). HRMS (ESI-TOF) m/z: Calcd for $C_{20}H_{18}F_2N_2O$ $(M+H)^+$ 341.1460; Found 341.1461.

5-(2,2-difluoropropyl)-3-fluoro-5-methylbenzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (***3c***). A white solid after purification by flash column chromatography (petroleum ether/ethyl acetate =10/1), 58.5 mg, 85 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (dd, *J* = 8.4, 6.0 Hz, 1H), 8.34 (d, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.46 – 7.39 (m, 2H), 7.22 – 7.15 (m, 2H), 3.29 – 3.17 (m, 1H), 2.71 – 2.59 (m, 1H), 1.70 (s, 3H), 1.40 (t, *J* = 18.8 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 171.6, 164.6 (d, *J* = 252.5 Hz), 148.8, 144.0, 142.9 (d, *J* = 7.9 Hz), 131.4, 128.5 (d, *J* = 9.1 Hz), 125.7 (d, *J* = 37.5 Hz), 122.4 (t, *J* = 240.6 Hz), 119.7, 118.9, 115.9 (d, *J* = 22.4 Hz), 115.6, 113.7 (d, *J* = 23.2 Hz), 48.3 (t, *J* = 23.7 Hz), 45.7, 30.9, 24.7 (t, *J* = 27.3 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ -85.51 – -86.22 (m, 1F), -87.32 – -88.02 (m, 1F), -106.94 – -106.99 (m, 1F). HRMS (ESI-TOF) m/z: Calcd for $C_{19}H_{15}F_3N_2O$ $(M+H)^+$ 345.1209; Found 345.1211.

3-chloro-5-(2,2-difluoropropyl)-5-methylbenzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (***3d***). A white solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1), 62.6 mg, 87 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (d, *J* = 8.4 Hz, 1H), 8.34 (d, *J* = 6.8 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.47 – 7.42 (m, 4H), 3.28 – 3.16 (m, 1H), 2.73 – 2.61 (m, 1H), 1.71 (s, 3H), 1.40 (t, *J* = 18.8 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 171.5, 148.7, 143.9, 141.8, 137.5, 131.4, 128.5, 127.4, 127.0, 126.0, 125.8, 122.5 (t, *J* = 239.0 Hz), 120.9, 119.8, 115.6, 48.2, 45.5 (d, *J* = 3.3 Hz), 30.9, 24.8 (t, *J* = 27.2 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ -85.56 – -86.27 (m, 1F), -87.33 – -88.03 (m, 1F). HRMS (ESI-TOF) m/z: Calcd for $C_{19}H_{15}ClF_2N_2O$ $(M+H)^+$ 361.0914; Found 361.0915.

3-bromo-5-(2,2-difluoropropyl)-5-methylbenzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (***3e***). A white solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1), 64.0 mg, 79 % yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37 – 8.33 (m, 2H), 7.82 – 7.80 (m, 1H), 7.63 – 7.61 (m, 2H), 7.46 – 7.41 (m, 2H), 3.27 – 3.17 (m, 1H), 2.72 – 2.63 (m, 1H), 1.71 (s, 3H), 1.41 (t, *J* = 18.5 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 171.4, 148.7, 143.9, 141.9, 131.4 (d, *J* = 7.8 Hz), 129.9, 127.5, 126.0, 125.8, 122.5 (t, *J* = 238.5 Hz), 121.4, 119.9, 115.6, 48.2 (t, *J* = 23.7 Hz), 45.5 (d, *J* = 3.3 Hz), 30.8, 24.8 (t, *J* = 27.2 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ -85.57 – -86.28 (m, 1F), -87.26 – -87.96 (m, 1F). HRMS (ESI-TOF) m/z: Calcd for $C_{19}H_{15}BrF_2N_2O$ $(M+H)^+$ 405.0408; Found 405.0409.

5-(2,2-difluoropropyl)-5-methyl-3-(trifluoromethyl)benzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (***3f***). A light yellow solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1), 63.0 mg, 80 % yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (d, *J* = 8.0 Hz, 1H), 8.38 – 8.36 (m, 1H), 7.86 – 7.85 (m, 1H), 7.75 – 7.72 (m, 2H), 7.49 – 7.45 (m, 2H), 3.33 – 3.24 (m, 1H), 2.80 – 2.71 (m, 1H), 1.75 (s, 3H), 1.43 (t, *J* = 18.5 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 171.4, 148.1, 143.9, 140.7, 132.8 (q, *J* = 32.8 Hz), 131.5, 126.7, 126.24, 126.20, 125.6, 124.7 (q, *J* = 3.6 Hz), 124.0 – 123.9 (m), 122.5 (q, *J* = 271.1 Hz), 122.5 (t, *J* = 240.1 Hz), 120.2, 115.8, 48.1 (t, *J* = 23.5 Hz), 45.7 (d, *J* = 3.3 Hz), 30.8, 24.8 (t, *J* = 27.2 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ -62.91 (s, 3F), -85.44 – -86.13 (m, 1F), -87.85 – -88.51 (m, 1F). HRMS (ESI-TOF) m/z: Calcd for $C_{20}H_{15}F_5N_2O$ $(M+H)^+$ 395.1177; Found 395.1179.

methyl 5-(2,2-difluoropropyl)-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline-3-carboxylate (***3g***). A light yellow liquid after purification by flash column chromatography (petroleum ether/ethyl acetate = 7/1), 57.6 mg, 75 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (d, *J* = 8.0 Hz, 1H), 8.38 – 8.36 (m, 1H), 8.18 (s, 1H), 8.13 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.86 – 7.84 (m, 1H), 7.49 – 7.44 (m, 2H), 3.98 (s, 3H), 3.31 – 3.19 (m, 1H), 2.87 – 2.75 (m, 1H), 1.76 (s, 3H), 1.40 (t, *J* = 18.8 Hz, 3H). $^{13}C\{^{1}H\}$ NMR

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(125 MHz, $CDCl_3$): δ 171.7, 166.1, 148.6, 144.1, 140.3, 132.4, 131.5, 128.7, 128.3, 126.18, 126.16, 126.14, 126.12, 122.6 (t, J = 238.6 Hz), 120.1, 115.8, 52.5, 48.3 (t, J = 23.5 Hz), 45.7 (d, J = 3.4 Hz), 30.8, 24.8 (t, J = 27.2 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ -85.83 – -86.54 (m, 1F), -87.26 – -87.96 (m, 1F). HRMS (ESI-TOF) m/z: Calcd for $C_{21}H_{18}F_2N_2O_3$ $(M+H)^+$ 385.1358; Found 385.1360.

5-(2,2-difluoropropyl)-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline-3-carbonitrile (***3h***). A white solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 7/1), 43.5 mg, 62% yield. ^1H NMR (500 MHz, $CDCl_3$): δ 8.59 (d, *J* = 8.0 Hz, 1H), 8.36 – 8.34 (m, 1H), 7.86 – 7.84 (m, 1H), 7.78 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.48 – 7.46 (m, 2H), 3.31 – 3.21 (m, 1H), 2.76 – 2.66 (m, 1H), 1.73 (s, 3H), 1.46 (t, *J* = 19.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 170.9, 147.6, 143.9, 141.0, 131.4, 131.0, 130.9, 126.7, 126.5, 126.3, 122.5 (t, *J* = 238.6 Hz), 120.3, 118.0, 115.8, 114.5, 48.1 (t, *J* = 23.3 Hz), 45.5 (d, *J* = 3.1 Hz), 30.6, 29.6, 24.8 (t, *J* = 27.1 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ -85.22 – -85.93 (m, 1F), -88.52 – -89.22 (m, 1F) HRMS (ESI-TOF) m/z: Calcd for $C_{20}H_{15}F_2N_3O$ $(M+H)^+$ 352.1256; Found 352.1260.

5-(2,2-difluoropropyl)-1,5-dimethylbenzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (***3i***). A white solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1), 55.1 mg, 81% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, *J* = 8.0 Hz, 1H), 8.36 – 7.34 (m, 1H), 7.81 – 7.79 (m, 1H), 7.45 – 7.38 (m, 2H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.27 (s, 1H), 3.22 (q, *J* = 15.2 Hz, 1H), 2.72 (q, *J* = 15.2 Hz, 1H), 2.47 (s, 3H), 1.71 (s, 3H), 1.34 (t, *J* = 18.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.3, 149.8, 144.0, 141.8, 140.0, 131.4, 129.1, 127.2, 125.9, 125.8, 125.3, 122.6 (t, *J* = 240.6 Hz), 119.7, 119.6, 115.6, 48.2 (t, *J* = 23.9 Hz), 45.5, 31.1, 24.7 (t, *J* = 27.3 Hz), 21.9. ^{19}F NMR (471 MHz, $CDCl_3$): δ -85.99 – -86.18 (m, 2F). HRMS (ESI-TOF) m/z: Calcd for $C_{20}H_{18}F_2N_2O$ $(M+H)^+$ 341.1460; Found 341.1462.

5-(2,2-difluoropropyl)-1-methoxy-5-methylbenzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (***3j***). A brown solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1), 49.8 mg, 70% yield. ^1H NMR (500 MHz, $CDCl_3$): δ 8.39 – 8.37 (m, 1H), 7.91 – 7.89 (m, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.43 – 7.39 (m, 2H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 4.14 (s, 3H), 3.23 (q, *J* = 15.0 Hz, 1H), 2.71 (q, *J* = 15.5 Hz, 1H), 1.72 (s, 3H), 1.32 (t, *J* = 18.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.1, 158.7, 147.7, 144.3, 142.6, 131.7, 130.3, 125.6, 124.8 (t, *J* = 463.0 Hz), 122.5, 120.5, 119.1, 115.5, 111.8, 110.4, 56.6, 48.6 (t, *J* = 23.9 Hz), 45.4, 31.5, 24.7 (t, *J* = 27.4 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ -85.88 – -86.06 (m, 2F). HRMS (ESI-TOF) m/z: Calcd for $C_{20}H_{18}F_2N_2O_2$ $(M+H)^+$ 357.1409; Found 357.1410.

5-(2,2-difluoropropyl)-1-fluoro-5-methylbenzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (***3k***). A yellow solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1), 55.0 mg, 80% yield. ^1H NMR (500 MHz, $CDCl_3$): δ 8.38 – 8.37 (m, 1H), 7.94 – 7.92 (m, 1H), 7.51 (td, J = 8.0, 5.0 Hz, 1H), 7.47 – 7.43 (m, 2H), 7.31 (d, J = 8.0 Hz, 1H), 7.24 – 7.21 (m, 1H), 3.29 – 3.19 (m, 1H), 2.76 – 2.67 (m, 1H), 1.72 (s, 3H), 1.39 (t, J = 19.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.6, 160.4 (d, *J* = 262.1 Hz), 145.8 (d, *J* = 8.4 Hz), 144.2, 142.5, 131.8 (d, *J* = 9.6 Hz), 130.4, 126.0 (d, *J* = 14.0 Hz), 122.8, 122.5 (t, *J* = 240.6 Hz), 120.5, 115.8, 115.6, 115.5, 111.8 (d, *J* = 9.9 Hz), 48.5 (t, *J* = 23.7 Hz), 45.4, 31.3, 24.8 (t, *J* = 27.3 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ -85.44 – -86.11 (m, 1F), -87.00 – -87.69 (m, 1F), -107.12 – -107.16 (m, 1F). HRMS (ESI-TOF) m/z: Calcd for $C_{19}H_{15}F_3N_2O$ $(M+H)^+$ 345.1209; Found 345.1211.

1-chloro-5-(2,2-difluoropropyl)-5-methylbenzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (***3l***). A white solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1), 63.4 mg, 88% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 8.39 (dd, *J* = 6.0, 3.2 Hz, 1H), 7.93 (dd, *J* = 6.0, 3.2 Hz, 1H), 7.58 – 7.56 (m, 1H), 7.47 – 7.42 (m, 4H), 3.30 – 3.19 (m, 1H), 2.77 – 2.65 (m, 1H), 1.72 (s, 3H), 1.38 (t, *J* = 18.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.4, 147.0, 143.9, 142.9, 133.5, 131.5, 130.6, 130.4, 126.3, 125.9, 125.7, 122.5 (t, *J* = 238.8 Hz), 120.7, 120.5, 115.7, 48.49 (t, *J* = 23.7 Hz), 45.76 (d, *J* = 3.5 Hz), 31.43 (s), 24.80 (t, *J* = 27.3 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ -85.21 – -85.92 (m, 1F), -86.99 – -87.70 (m, 1F). HRMS (ESI-TOF) m/z: Calcd for $C_{19}H_{15}ClF_2N_2O$ $(M+H)^+$ 361.0914; Found 361.0916.

1-bromo-5-(2,2-difluoropropyl)-5-methylbenzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (***3m***). A white solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1), 63.2 mg, 78% yield. ^1H NMR (500 MHz, $CDCl_3$): δ 8.38 (dd, *J* = 6.0, 3.0 Hz, 1H), 7.93 (dd, *J* = 6.0, 3.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.49 – 7.44 (m, 3H), 7.33 (t, *J* = 8.0 Hz, 1H), 3.29 – 3.20 (m, 1H), 2.76 – 2.67 (m, 1H), 1.72 (s, 3H), 1.38 (t, *J* = 19.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.3, 147.1, 143.5,

 doi:10.20944/preprints202401.1047.v1

143.1, 135.3, 130.8, 130.6, 126.4, 126.3, 125.9, 122.5 (t, J = 240.7 Hz), 121.8, 121.3, 120.8, 115.7, 48.4 (t, J = 23.5 Hz), 45.9 (d, J = 3.2 Hz), 31.5, 24.8 (t, J = 27.3 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ -85.15 – -85.86 (m, 1F), -86.99 – -87.69 (m, 1F). HRMS (ESI-TOF) m/z: Calcd for $C_{19}H_{15}BrF_2N_2O$ $(M+H)^+$ 405.0408; Found 405.0412.

5-(2,2-difluoropropyl)-2,5-dimethylbenzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (***3n***). A white solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1), 51.7 mg, 76% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37 – 8.35 (m, 1H), 8.32 (s, 1H), 7.83 – 7.81 (m, 1H), 7.45 – 7.40 (m, 2H), 7.37 (s, 2H), 3.22 (q, J = 15.5 Hz, 1H), 2.70 (q, J = 15.5 Hz, 1H), 2.46 (s, 3H), 1.69 (s, 3H), 1.33 (t, J = 18.8 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.4, 149.8, 143.9, 137.9, 137.2, 132.4, 131.5, 126.7, 126.1, 125.8, 125.5, 122.6 (t, J = 240.5 Hz), 122.0, 119.7, 115.6, 48.2 (t, J = 24.0 Hz), 45.3 (d, J = 2.2 Hz), 31.1, 24.7 (t, J = 27.3 Hz), 20.9. ^{19}F NMR (471 MHz, $CDCl_3$): δ -86.02– -86.20 (m, 2F). HRMS (ESI-TOF) m/z: Calcd for $C_{20}H_{18}F_2N_2O$ $(M+H)^+$ 341.1460; Found 341.1462.

5-(2,2-difluoropropyl)-1,3,5-trimethylbenzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (***3o***). A white solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1), 58.0 mg, 82% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39 – 8.38 (m, 1H), 7.83 – 7.81 (m, 1H), 7.44 – 7.39 (m, 2H), 7.15 (s, 2H), 3.27 – 3.18 (m, 1H), 3.02 (s, 3H), 2.76 – 2.67 (m, 1H), 2.42 (s, 3H), 1.71 (s, 3H), 1.32 (t, J = 19.0 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.5, 150.0, 144.2, 141.1, 140.2, 139.7, 132.3, 130.6, 125.5, 125.4, 125.3, 122.7 (t, J = 240.6 Hz), 119.9, 118.4, 115.6, 48.5 (t, J = 24.1 Hz), 45.4, 31.7, 24.7 (t, J = 27.3 Hz), 24.6, 21.6. ^{19}F NMR (471 MHz, $CDCl_3$): δ -85.66 – -85.96 (m, 2F). HRMS (ESI-TOF) m/z: Calcd for $C_{21}H_{20}F_2N_2O$ $(M+H)^+$ 355.1616; Found 355.1619.

1,3-dichloro-5-(2,2-difluoropropyl)-5-methylbenzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (***3p***). A white solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1), 58.5 mg, 74% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 – 8.36 (m, 1H), 7.92 – 7.91 (m, 1H), 7.58 (d, J = 2.0 Hz, 1H), 7.48 – 7.44 (m, 2H), 7.40 (d, J = 1.5 Hz, 1H), 3.29 – 3.20 (m, 1H), 2.72 – 2.63 (m, 1H), 1.73 (s, 3H), 1.45 (t, J = 19.0 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.7, 146.3, 144.1, 143.8, 136.2, 134.4, 131.3, 130.5, 126.5, 126.1, 122.4 (t, J = 240.8 Hz), 120.8, 119.2, 115.6, 48.4 (t, J = 23.4 Hz), 45.8 (d, J = 3.0 Hz), 31.3, 24.9 (t, J = 27.1 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ -85.15 – -85.86 (m, 1F), -87.94 – -88.64 (m, 1F). HRMS (ESI-TOF) m/z: Calcd for $C_{19}H_{14}Cl_2F_2N_2O$ $(M+H)^+$ 395.0524; Found 395.0527.

5-(2,2-difluoropropyl)-2,4,5-trimethylbenzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (***3q***). A white solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1), 51.0 mg, 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 – 8.33 (m, 2H), 7.81 (dd, J = 7.0, 1.6 Hz, 1H), 7.42 (pd, J = 7.2, 1.6 Hz, 2H), 7.18 (s, 1H), 3.34 – 3.11 (m, 2H), 2.62 (s, 3H), 2.41 (s, 3H), 1.80 (s, 3H), 1.38 (t, J = 18.8 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.5, 150.4, 144.1, 137.7, 137.5, 136.4, 134.6, 131.5, 125.9, 125.2, 122.9 (t, J = 240.3 Hz), 122.9, 119.6, 115.7, 46.6, 44.9 (t, J = 23.5 Hz), 27.2, 24.5 (t, J = 27.5 Hz), 22.8, 20.6. ^{19}F NMR (471 MHz, $CDCl_3$): δ -88.43 – -88.61 (m, 1F), -88.66 – -88.85 (m, 1F). HRMS (ESI-TOF) m/z: Calcd for $C_{21}H_{20}F_2N_2O$ $(M+H)^+$ 355.1616; Found 355.1619.

3-bromo-5-(2,2-difluoropropyl)-5,9,10-trimethylbenzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (***3r***). A yellow solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1), 72.7 mg, 84% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31 (d, J = 9.0 Hz, 1H), 8.12 (s, 1H), 7.60 – 7.58 (m, 2H), 7.56 (s, 1H), 3.26 – 3.16 (m, 1H), 2.70 – 2.61 (m, 1H), 2.41 (s, 3H), 2.39 (s, 3H), 1.70 (s, 3H), 1.39 (t, J = 18.5 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 171.3, 148.0, 142.4, 141.7, 135.2, 135.0, 131.2, 129.9, 129.7, 127.2, 125.3, 122.4 (t, J = 240.7 Hz), 121.7, 120.0, 115.9, 48.2 (t, J = 23.8 Hz), 45.4 (d, J = 3.3 Hz), 30.8, 24.7 (t, J = 27.2 Hz), 20.5, 20.4. ^{19}F NMR (471 MHz, $CDCl_3$): δ -85.57 – -86.28 (m, 1F), -87.17 – -87.87 (m, 1F). HRMS (ESI-TOF) m/z: Calcd for $C_{21}H_{19}BrF_2N_2O$ $(M+H)^+$ 433.0721; Found 433.0723.

5-(2,2-difluoropropyl)-5-phenylbenzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (***3s***). A yellow liquid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1), 44.2 mg, 57% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (dd, J = 8.0, 1.2 Hz, 1H), 8.26 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.56 – 7.37 (m, 4H), 7.32 – 7.24 (m, 4H), 7.22 – 7.17 (m, 3H), 3.98 – 3.07 (m, 1H), 3.18 – 3.07 (m, 1H), 1.47 (t, J = 18.8 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 170.3, 149.7, 144.1, 142.3, 139.8, 131.6, 131.2, 129.3, 129.1, 128.2, 128.1, 126.8, 125.93, 125.87, 125.7, 123.6, 122.8 (t, J = 239.8 Hz), 119.9, 115.7, 53.4, 46.0 (t, J = 23.5 Hz), 25.3 (t, J = 27.5 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ -84.84 – -85.02 (m,

 doi:10.20944/preprints202401.1047.v1

1F), -85.04 – -85.22 (m, 1F). HRMS (ESI-TOF) m/z: Calcd for $C_{24}H_{18}F_2N_2O$ $(M+H)^+$ 389.1460; Found 389.1463.

*5-benzyl-5-(2,2-difluoropropyl)benzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**3t**).* A white solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1), 52.3 mg, 65% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.36 – 8.34 (m, 1H), 8.29 (d, J = 8.0 Hz, 1H), 7.68 – 7.66 (m, 1H), 7.63 – 7.62 (m, 2H), 7.49 – 7.46 (m, 1H), 7.41 – 7.36 (m, 2H), 6.87 (t, J = 7.5 Hz, 1H), 6.77 (t, J = 7.5 Hz, 2H), 6.49 (d, J = 7.5 Hz, 2H), 3.53 (d, J = 12.5 Hz, 1H), 3.49 – 3.41 (m, 1H), 3.17 (d, J = 12.5 Hz, 1H), 2.99 – 2.90 (m, 1H), 1.43 (t, J = 19.0 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.2, 149.2, 143.6, 137.4, 133.2, 130.9, 130.8, 129.1, 128.0, 127.8, 127.3, 125.72, 125.69, 125.4, 124.1, 122.6 (t, J = 240.8 Hz), 119.6, 115.4, 51.9, 50.7, 46.5 (t, J = 23.8 Hz), 25.1 (t, J = 27.3 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ -83.32 – -84.00 (m, 1F), -84.83 – -85.51 (m, 1F). HRMS (ESI-TOF) m/z: $C_{25}H_{20}F_2N_2O$ $(M+H)^+$ 403.1616; Found 403.1617.

*7-(2,2-difluoropropyl)-7-methylbenzo[h]benzo[4,5]imidazo[2,1-a]isoquinolin-8(7H)-one (**3u**).* A yellow solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1), 55.6 mg, 74% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.56 (d, J = 8.5 Hz, 1H), 8.47 – 8.45 (m, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.96 – 7.94 (m, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.84– 7.81 (m, 1H), 7.64 (t, J = 7.5 Hz, 1H), 7.56 (d, J = 8.5 Hz, 1H), 7.50 – 7.46 (m, 2H), 3.37 – 3.27 (m, 1H), 2.90 – 2.81 (m, 1H), 1.78 (s, 3H), 1.33 (t, J = 19.0 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.3, 149.7, 144.0, 140.6, 132.7, 132.0, 130.4, 130.3, 128.7, 128.4, 128.2, 126.9, 125.9, 125.8, 122.5 (d, J = 240.5 Hz), 123.7, 120.1, 117.6, 115.7, 47.9 (t, J = 24.1 Hz), 45.9, 31.0, 24.6 (t, J = 27.3 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ -86.07 – -86.30 (m, 1F), -86.32 – -86.46 (m, 1F). HRMS (ESI-TOF) m/z: Calcd for $C_{23}H_{18}F_2N_2O$ $(M+H)^+$ 377.1460; Found 377.1462.

*4-(2,2-difluoropropyl)-4-methylbenzo[4,5]imidazo[1,2-a]thieno[2,3-c]pyridin-5(4H)-one (**3v**).* A yellow solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1), 44.5 mg, 67% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 – 8.30 (m, 1H), 7.78 – 7.75 (m, 1H), 7.59 (d, J = 4.8 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.11 (d, J = 5.2 Hz, 1H), 3.24 – 3.12 (m, 1H), 2.66 – 2.54 (m, 1H), 1.67 (s, 3H), 1.38 (t, J = 18.8 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 172.6, 146.4, 145.9, 143.9, 130.9, 130.4, 125.9, 125.8, 125.5, 123.6, 122.4 (t, J = 240.5 Hz), 119.7, 115.2, 48.2 (t, J = 24.3 Hz), 45.6 – 45.5 (m), 29.9, 24.5 (t, J = 27.3 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ -86.86 – -87.18 (m, 2F). HRMS (ESI-TOF) m/z: Calcd for $C_{17}H_{14}F_2N_2OS$ $(M+H)^+$333.0868; Found 333.0870.

*5-(2,2-difluoropropyl)-3,5,12-trimethylindolo[2,1-a]isoquinolin-6(5H)-one (**5a**).* A white gummy after purification by flash column chromatography (petroleum ether/ethyl acetate = 20/1), 46.6 mg, 66% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, J = 7.2 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.60 – 7.58 (m, 1H), 7.41 – 7.34 (m, 3H), 7.23 (d, J = 8.4 Hz, 1H), 3.28 – 3.16 (m, 1H), 2.71 – 2.60 (m, 1H), 2.65 (s, 3H), 2.44 (s, 3H), 1.69 (s, 3H), 1.31 (t, J = 18.8 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.0, 137.3, 137.0, 134.0 (d, J = 30.9 Hz), 132.6, 129.7, 129.4, 128.3, 127.4, 125.2 (d, J = 48.0 Hz), 124.2, 123.2, 122.9 (t, J = 240.2 Hz), 118.2, 116.7, 113.6, 48.1 (t, J = 24.2 Hz), 45.0 – 44.8 (m), 31.4, 24.5 (t, J = 27.4 Hz), 21.5, 11.5. ^{19}F NMR (471 MHz, $CDCl_3$): δ -84.11 – -84.82 (m, 1F), -85.19 – -85.89(m, 1F). HRMS (ESI-TOF) m/z: Calcd for $C_{22}H_{21}F_2NO$ $(M+H)^+$ 354.1664; Found 354.1666.

*5-(2,2-difluoropropyl)-3-fluoro-5,12-dimethylindolo[2,1-a]isoquinolin-6(5H)-one (**5b**).* A yellow liquid after purification by flash column chromatography (petroleum ether/ethyl acetate = 20/1), 51.4 mg, 72 % yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.61 (d, J = 8.0 Hz, 1H), 8.03 (dd, J = 8.8, 6.0 Hz, 1H), 7.59 (d, J = 7.0 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.17 – 7.11 (m, 2H), 3.28 – 3.18 (m, 1H), 2.63 (s, 3H), 2.62 – 2.55 (m, 1H), 1.69 (s, 3H), 1.38 (t, J = 19.0 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 171.2, 161.8 (d, J = 248.4 Hz), 139.8 (d, J = 6.9 Hz), 134.2, 132.4, 128.9, 126.9 (d, J = 8.3 Hz), 125.7, 124.3, 122.7 (t, J = 240.6 Hz), 122.4 (d, J = 2.5 Hz), 118.3, 116.7, 114.9 (d, J = 21.8 Hz), 114.1, 113.9, 48.1 (t, J = 24.1 Hz), 45.1, 31.2, 24.6 (t, J = 27.4 Hz), 11.4. ^{19}F NMR (471 MHz, $CDCl_3$): δ -84.17 – -84.88 (m, 1F), -86.70 – -87.41 (m, 1F), -112.80 – -112.85 (m, 1F). HRMS (ESI-TOF) m/z: Calcd for $C_{21}H_{18}F_3NO$ $(M+H)^+$ 358.1413; Found 358.1415.

*3-chloro-5-(2,2-difluoropropyl)-5,10,12-trimethylindolo[2,1-a]isoquinolin-6(5H)-one (**5c**).* A yellow liquid after purification by flash column chromatography (petroleum ether/ethyl acetate = 20/1), 56.8 mg, 76 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62– 8.59 (m, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.61 – 7.58 (m, 1H), 7.43 (d, J = 1.6 Hz, 1H), 7.41 – 7.35 (m, 3H), 3.28 – 3.16 (m, 1H), 2.63 (s, 3H), 2.67 – 2.55 (m, 1H), 1.69 (s, 3H), 1.38 (t, J = 18.8 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.2, 138.9, 134.2, 133.1,

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132.3, 128.6, 127.6, 127.4, 126.2, 125.9, 124.5, 124.4, 122.8 (t, *J* = 240.4 Hz), 118.4, 116.7, 114.9, 48.0 (t, *J* = 23.9 Hz), 44.9, 31.2, 24.7 (t, *J* = 27.3 Hz), 11.5. ^{19}F NMR (471 MHz, $CDCl_3$): δ -84.35 – -85.06 (m, 1F), -86.79 – -87.49 (m, 1F). HRMS (ESI-TOF) m/z: Calcd for $C_{21}H_{18}ClF_2NO$ $(M+H)^+$ 374.1118; Found 374.1120.

3-bromo-5-(2,2-difluoropropyl)-5,12-dimethylindolo[2,1-a]isoquinolin-6(5H)-one (***5d***). A yellowish liquid after purification by flash column chromatography (petroleum ether/ethyl acetate = 20/1), 57.7 mg, 69% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.60 (d, *J* = 7.5 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.60 – 7.58 (m, 2H), 7.52 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.43 – 7.35 (m, 2H), 3.27 – 3.17 (m, 1H), 2.63 (s, 3H), 2.65 – 2.56 (m, 1H), 1.68 (s, 3H), 1.38 (t, *J* = 19.0 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 171.1, 139.2, 134.3, 132.3, 130.5, 130.3, 128.7, 126.4, 126.0, 124.9, 124.4, 122.7 (t, *J* = 240.5 Hz), 121.2, 118.5, 116.8, 115.1, 48.1 (t, *J* = 23.9 Hz), 44.9, 31.2, 24.7 (t, *J* = 27.3 Hz), 11.5. ^{19}F NMR (471 MHz, $CDCl_3$): δ -84.40 – -85.07 (m, 1F), -86.79 – -87.47 (m, 1F). HRMS (ESI-TOF) m/z: Calcd for $C_{21}H_{18}BrF_2NO$ $(M+H)^+$ 420.0594; Found 420.0598.

3-chloro-5-(2,2-difluoropropyl)-5,10,12-trimethylindolo[2,1-a]isoquinolin-6(5H)-one (***5e***). A yellow liquid after purification by flash column chromatography (petroleum ether/ethyl acetate = 20/1), 56.6 mg, 73% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (d, *J* = 8.5 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.30 (s, 1H), 7.25 (d, *J* = 9.0 Hz, 1H), 7.15 (s, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 3.14 – 3.04 (m, 1H), 2.50 (s, 3H), 2.52 – 2.43 (m, 1H), 2.38 (s, 3H), 1.56 (s, 3H), 1.25 (t, *J* = 19.0 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 170.9, 139.0, 134.1, 133.0, 132.5, 132.5, 128.8, 127.6, 127.4, 127.2, 126.1, 124.6, 122.7 (t, *J* = 240.4 Hz), 118.5, 116.4, 114.7, 48.1 (t, *J* = 24.0 Hz), 44.9, 31.2, 24.6 (t, *J* = 27.4 Hz), 21.6, 11.5. ^{19}F NMR (471 MHz, $CDCl_3$): δ -84.19 – -84.90 (m, 1F), -86.72 – -87.42 (m, 1F). HRMS (ESI-TOF) m/z: Calcd for $C_{22}H_{20}ClF_2NO$ $(M+H)^+$ 388.1274; Found 388.1275.

5-(2,2-difluoropropyl)-12-ethyl-5-methylindolo[2,1-a]isoquinolin-6(5H)-one (***5f***). A yellow liquid after purification by flash column chromatography (petroleum ether/ethyl acetate = 20/1), 52.9 mg, 75% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.64 (d, *J* = 7.5 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 7.0 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.44 – 7.35 (m, 4H), 3.26 – 3.13 (m, 3H), 2.70 – 2.61 (m, 1H), 1.70 (s, 3H), 1.42 (t, *J* = 7.5 Hz, 3H), 1.31 (t, *J* = 19.0 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 172.0, 137.1, 134.5, 131.8, 128.8, 127.5, 127.4, 127.3, 125.7, 124.7, 124.3, 122.9 (t, *J* = 240.2 Hz), 121.1, 118.2, 116.9, 48.1 (t, *J* = 24.3 Hz), 44.9, 31.3, 24.5 (t, *J* = 27.4 Hz), 18.6, 13.3. ^{19}F NMR (471 MHz, $CDCl_3$): δ -84.21 – -84.92 (m, 1F), -85.41 – -86.12 (m, 1F). HRMS (ESI-TOF) m/z: Calcd for $C_{22}H_{21}F_2NO$ $(M+H)^+$ 354.1664; Found 354.1667.

5-(2,2-difluoropropyl)-12-ethyl-5,10-dimethylindolo[2,1-a]isoquinolin-6(5H)-one (***5g***). A yellow solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 20/1), 47.7 mg, 65% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.50 (d, *J* = 8.5 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.45 – 7.35 (m, 3H), 7.22 (d, *J* = 8.0 Hz, 1H), 3.25 – 3.16 (m, 1H), 3.13 (q, *J* =7.5 Hz, 2H), 2.69 – 2.60 (m, 1H), 2.51 (s, 3H), 1.69 (s, 3H), 1.41 (t, *J* = 7.5 Hz, 3H), 1.30 (t, *J* = 19.0 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 171.7, 137.0, 133.9, 132.6, 131.9, 128.9, 127.4, 127.3, 127.0, 125.8, 124.6, 122.9 (t, *J* = 240.2 Hz), 121.0, 118.2, 116.6, 48.1 (t, *J* = 24.4 Hz), 44.8, 31.2, 24.4 (t, *J* = 27.4 Hz), 21.6, 18.6, 13.3. ^{19}F NMR (471 MHz, $CDCl_3$): δ -84.10 – -84.77 (m, 1F), -85.39 – -86.06 (m, 1F). HRMS (ESI-TOF) m/z: Calcd for $C_{23}H_{23}F_2NO$ $(M+H)^+$ 368.1820; Found 368.1824.

5-(2,2-difluoropropyl)-12-ethyl-10-fluoro-5-methylindolo[2,1-a]isoquinolin-6(5H)-one (***5h***). A yellow liquid after purification by flash column chromatography (petroleum ether/ethyl acetate = 20/1), 51.9 mg, 70% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.57 (dd, *J* = 9.0, 5.0 Hz, 1H), 7.98 (d, *J* = 7.5 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.23 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.09 (td, *J* = 9.0, 2.5 Hz, 1H), 3.24 – 3.15 (m, 1H), 3.12 – 3.07 (m, 2H), 2.69 – 2.60 (m, 1H), 1.69 (s, 3H), 1.40 (t, *J* = 7.5 Hz, 3H), 1.31 (t, *J* = 19.0 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 171.8, 160.4 (d, *J* = 241.1 Hz), 137.3, 133.2 (d, *J* = 9.4 Hz), 130.7, 130.4, 127.65 (d, *J* = 41.6 Hz), 127.3, 125.4, 124.8, 122.8 (d, *J* = 240.4 Hz), 120.6 (d, *J* = 4.1 Hz), 118.0 (d, *J* = 9.0 Hz), 113.1 (d, *J* = 24.6 Hz), 104.0 (d, *J* = 24.0 Hz), 48.3 (t, *J* = 24.2 Hz), 44.8, 31.2, 24.6 (t, *J* = 27.4 Hz), 18.7, 13.2. ^{19}F NMR (471 MHz, $CDCl_3$): δ -84.78 – -85.42 (m, 1F), -85.86 – -86.52 (m, 1F), -118.11 – -118.16 (m, 1F). HRMS (ESI-TOF) m/z: Calcd for $C_{22}H_{20}F_3NO$ $(M+H)^+$ 372.1570; Found 372.1575.

3-chloro-5-(2-cyclopropyl-2,2-difluoroethyl)-5,12-dimethylindolo[2,1-a]isoquinolin-6(5H)-one (***5i***). A yellow solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 20/1), 50.4 mg, 63% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.61 (d, *J* = 7.5 Hz, 1H), 7.97 (d, *J* = 8.5 Hz,

 doi:10.20944/preprints202401.1047.v1

1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.44 (s, 1H), 7.42 – 7.36 (m, 3H), 3.40 – 3.30 (m, 1H), 2.76 – 2.67 (m, 1H), 2.63 (s, 3H), 1.69 (s, 3H), 1.02 – 0.95 (m, 1H), 0.44 – 0.23 (m, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 171.2, 139.2, 134.3, 133.1, 132.3, 128.8, 127.5, 126.1, 125.9, 124.4, 124.3, 122.4 (t, *J* = 242.3 Hz), 118.4, 116.8, 114.7, 47.7 (t, *J* = 25.9 Hz), 45.0, 31.7, 16.6 (t, *J* = 28.9 Hz), 11.5, 1.25 (dt, *J* = 6.3, 3.1 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ -94.49 – -95.10 (m, 1F), -99.95 – -100.56 (m, 1F). HRMS (ESI-TOF) m/z: Calcd for $C_{23}H_{20}ClF_2NO$ $(M+H)^+$ 400.1274; Found 400.1279.

4. Conclusions

In summary, a novel electrochemical tandem cyclization/difluoroethylation reaction of 2-arylbenzimidazoles/2-arylindoles was reported by our group. Various CF_2Me-substituted benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones and indolo[2,1-*a*]isoquinolin-6(5*H*) ones could be readily synthesized with good to high yield. Additionally, it also offered a convenient protocol for the preparation of cyclopropyldifluoromethylated indolo[2,1-*a*]isoquinolin-6(5*H*) ones. Further investigation to construct other useful substituted heterocycles by electrochemical oxidative difluoroethylation is currently underway in our laboratory as well.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: HRMS analysis of adduct products; Figure S2: Cyclic voltammograms of substrates; Figure S3: Structure of product **3m**; Figure S4: Structure of product **5i**; Tables S1 and S2: crystal and structure refinement data for **3m** and **5i**; ^1H NMR, ^{19}F NMR and ^{13}C NMR of compounds **3a–v** and **5a-i**.

Author Contributions: Conceptualization, Y.T.; methodology, D.G. and Y.T.; investigation, Y.T., L.Z., D.G., S.Y. and N.Z.; writing—original draft preparation, Y.T.; writing—review and editing, Y.T. and Z.L.; supervision, W.F.; funding acquisition, Y.T. and Z.L. All authors have read and agreed to the published version of the manuscript.

Funding: This project is supported by the National Natural Science Foundation of China (22302088 and 21702044), the Natural Science Foundation of Hebei Province (B2022201059), the Key Scientific Research Project of Higher Education of Henan Province (24B150022) and the Key Laboratory of Photochemical Conversion and Optoelectronic Materials, TIPC, CAS (PCOM202304).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data underlying this study are available in the published article and its Supporting Information. Deposition Numbers 2303467 (for **3m**) and 2307007 (for **5i**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe "http://www.ccdc.cam.ac.uk/structures".

Conflicts of Interest: The authors declare no conflicts of interest.

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