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Copper-Mediated, Palladium-Catalyzed Cross-Coupling of 3-Iodochromones, Thiochromones, and Quinolones with Ethyl Bromodifluoroacetate

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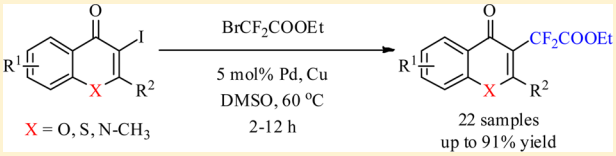
Supporting Information

ABSTRACT: The palladium-catalyzed cross-coupling reaction of 3-iodochromones, thiochromones, and quinolones with ethyl bromodifluoroacetate in the presence of a copper mediator is reported. Under optimized conditions, all reactions worked well and provided difluoro-containing products in moderate to excellent yields.



INTRODUCTION

Chromones[1] and quinolones[2] are important scaffolds of natural products. These scaffolds are useful building blocks and display various biological activities, such as anti-inflammatory, antitumor, and antibacterial effects.[3] Substituted chromones and quinolones also play the valuable role of progenitor in medicinal chemistry.[4] Thiochromones, unlike the previously mentioned abundant chromones and quinolones, have not been found in natural products, but they display interesting activities.[5]

Molecules containing fluorine atom(s) regularly exhibit beneficial effects in the life science field.[6] Recently, compounds containing a CF_2 unit have attracted a considerable amount of attention, particularly in medicinal chemistry,[7] and several efficient methods for introducing the *gem*-difluoro unit into organic compounds have been reported.[8] In fact, several drugs containing *gem*-difluoro moieties have been approved for sale in the market, such as pantoprazole,[9] gemcitabine,[10] lubiprostone,[11] tafluprost,[12] maraviroc,[13] and roflumilast[14] (Figure 1). As part of our program to develop novel anticancer agents, we require a facile route to 3-difluoroacetate-substituted chromones/quinolones. To the best of our knowledge, there are several reported pathways to prepare alkoxycarbonyldifluoromethylated aromatic compounds (Figure 2).

As illustrated in Figure 2, ethoxycarbonyldifluoromethylation can be achieved by fluorination the carbonyl of oxoarylacetate esters with a nucleophilic reagent such as SF_4 or DAST (path A). This type of reaction is limited because of the toxic nature of SF_4/DAST and the lack of general available substrates. Hazardous selenium-containing agents have been adopted as the starting material in path B.[15] Although direct ethoxycarbonyldifluoromethylation via an $RCF_2\bullet$ radical process has been reported recently (path C),[16] this transformation is not suitable for our substrates, and attempts to introduce a $-CF_2CO_2Et$ group at the C-3 position of chromone were fruitless in our study. The copper-mediated cross-coupling of commercially available $BrCF_2CO_2Et$/$ClCF_2CO_2Et$ reagent with aryl halide has been well-documented. In 1999, Kumadaki et al. reported the synthesis of aryldifluoroacetate by $BrCF_2CO_2Et$ and aryl iodide in the presence of copper (path D).[17] Later, in 2002, Ashwood et al. developed a facile process to achieve 2′-pyridyldifluoroacetate from 2-halopyridine (path D).[18] Recently, Amii et al. described an efficient and simple copper-catalyzed route (path E).[19] Unfortunately, the application of paths D and E in our study failed, which led us to develop a novel and convenient method to construct 3-ethoxycarbonyldifluoromethyl chromones, -thiochromones, and -quinolones. In this study, we report an efficient palladium-catalyzed cross-coupling reaction of 3-iodochromones, thiochromones, and quinolones with ethyl bromodifluoroacetate in the presence of copper with moderate to excellent yields.

RESULTS AND DISCUSSION

Initially, 3-iodo-4*H*-chromen-4-one (**1a**) was selected as the template substrate to determine the optimal conditions, and the outcomes are summarized in Table 1. Surprisingly, reactions in the presence of copper alone had not occurred, even after 12 additional hours at 125 °C (Table 1, entries 1−3). Considering the application of palladium in Ullmann cross-coupling for the synthesis of heteroaromatic compounds,[20] we introduced a palladium catalyst to facilitate this reaction. As expected, **1a** could be converted to **2a** with the use of $Pd_2(dba)_3$ in 32% yield (Table 1, entry 4). Motivated by this result, a range of palladium catalysts were tested. However, only moderate yields were obtained (entries 4−7). Among all of the tested palladium

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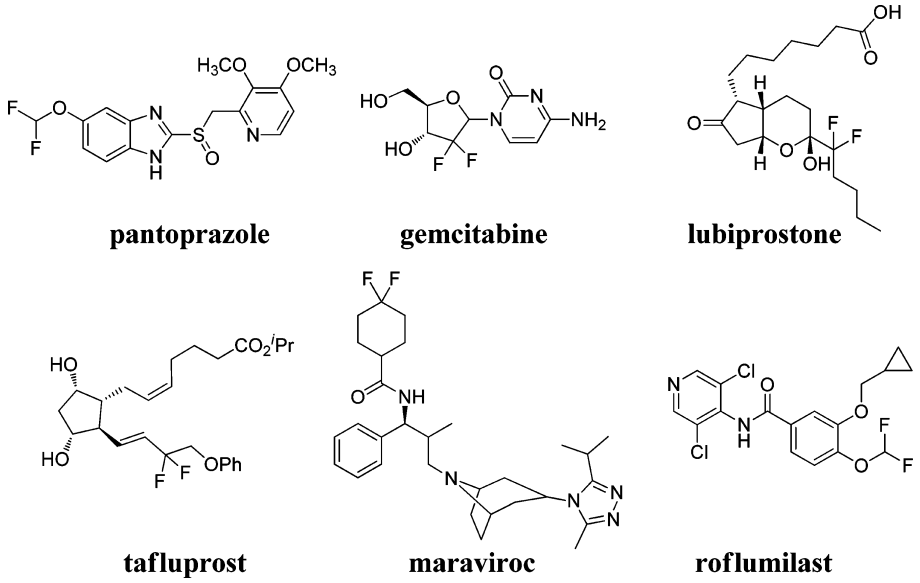

Figure 1. Several *gem*-difluoro-containing drugs.

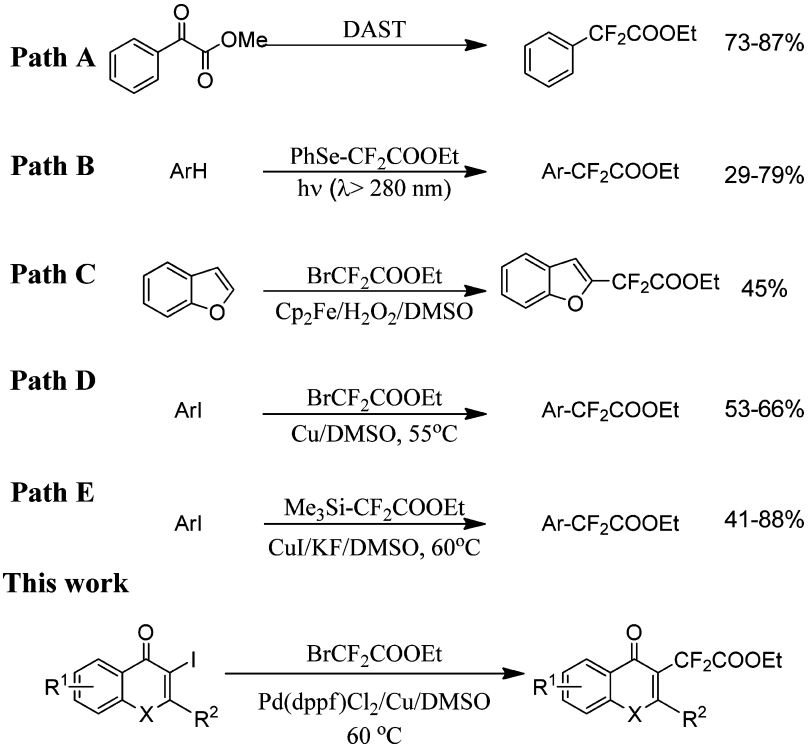

Figure 2. Examples of procedures reported to synthesize aryl difluoroacetates.

catalysts, $Pd(dppf)Cl_2$ provided **2a** in less time and higher yields (entry 7). The solvent was shown to have a marked impact on the yields, with DMSO providing the best result (Table 1, entries 7−9). We found that 2 equiv of $BrCF_2COOEt$ was necessary to ensure the completion of the reaction (Table 1, entries 7, 10, and 12). Finally, the effect of the amount of copper powder was investigated. The results showed that 2 equiv of copper could not lead to the full conversion of the starting material (SM) **1a**, whereas 3 equiv of copper amount could (Table 1, entries 7 and 13). When the copper content was increased to 4 or 5 equiv, **2a** was obtained in good yield (entries 14 and 15).

Utilizing these optimized reaction conditions (5 mol % of $Pd(dppf)Cl_2$, 2 equiv of $BrCF_2COOEt$, 4 equiv of copper powder, DMSO as solvent at 60 °C), the reactions of various 3-iodo-substituted chromones, thiochromones, and quinolones with $BrCF_2CO_2Et$ were investigated. As depicted in Table 2, this reaction was compatible with a variety of functional groups, including electron-donating methyl, methoxy, and aryl groups as well as electron-withdrawing fluoro and chloro groups. The effect of the substituent position on the benzene ring was subtle (Table 2, compound **2b** vs **2c**; **2e** vs **2f**; **2i** vs **2j**; **2k** vs **2l**). The yields for different electron-donating groups seem contradictory. Methoxy-substituted substrates provided a good yield

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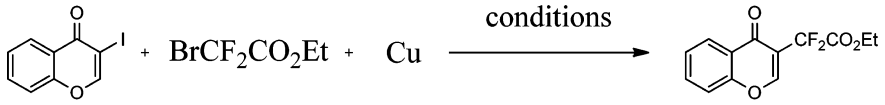
Table 1. Optimization of the Reaction Conditions[a]



1a **2a**

entry	catalyst[b]	solvent	1a/$BrCF_2CO_2Et$/Cu molar ratio	time (h)	yield (%)[c]
1		DMSO	1:1.1:5	2	nd
2		DMSO	1:1.1:5	2[d]	nd
3		DMSO	1:1.1:5	12[d]	nd
4	$Pd_2(dba)_3$	DMSO	1:2:3	4	32[e]
5	$Pd(PPh_3)_4$	DMSO	1:2:3	4	37[e]
6	$Pd(OAc)_2$	DMSO	1:2:3	2	53
7	Pd(dppf)Cl_2	DMSO	1:2:3	2	58
8	Pd(dppf)Cl_2	DMF	1:2:3	3	40
9	Pd(dppf)Cl_2	NMP	1:2:3	3.5	9[e]
10	Pd(dppf)Cl_2	DMSO	1:1:3	2	22[e]
11	Pd(dppf)Cl_2	DMSO	1:1:4	5	51[e]
12	Pd(dppf)Cl_2	DMSO	1:1.5:3	2	54[e]
13	Pd(dppf)Cl_2	DMSO	1:2:2	4	19[e]
14	Pd(dppf)Cl_2	DMSO	1:2:4	2	78
15	Pd(dppf)Cl_2	DMSO	1:2:5	2	76

[a]**1a** (0.5 mmol) and solvent (5 mL) were used, 60 °C, under argon atmosphere. [b]Catalyst (0.025 mmol, 0.05 equiv) was employed. [c]Isolated yields. [d]Reaction was performed at 125 °C. [e]SM was incompletely converted.

(Table 2, compounds **2b**, **2c**, **2d**, and **2p**), whereas methyl anywhere on the chromones provided lower yields (Table 2, compound **2e** vs 2**b**; **2f** vs **2c**; **2g** vs **2a**; **2o** vs **2l**). We suspect that these results may be caused by the less stable palladium oxidative intermediates of the methyl substrates compared to the methoxy group. The results for **2g** and **2m** can also be explained by the stability of the palladium intermediate. On the basis of these results, we extended the reaction scope to thiochromone and aza analogues. Thiochromones and quinolones also worked well, with good to excellent yields, except for **2u**. Surprisingly, using this method, thiochromones[21] showed more favorable reactivity (Table 2, **2q** and **2s**) than their oxo, aza analogues, even with methyl substituents (Table 2, **2r** and **2q**). Finally, this method was exploited in the modification of a natural product. Graveolinine is a natural quinolone alkaloid[22] isolated from *Ruta graveolens L* with interesting antibacterial, spasmolysis, and antitumor activities (Scheme 1). 3-Iodograveolinine (**1v**) was prepared following reported methods[23] and then subjected to the previously determined optimal conditions. The target compound **2v** was obtained in good yield (78%).

A plausible mechanism for the cross-coupling of 3-iodochromones, thiochromones, quinolones, and $BrCF_2CO_2Et$ is depicted in Scheme 2.[20a,24] First, if a Pd(II) catalyst is employed, it may be reduced by copper into an active Pd(0) species, which then reacts via an oxidative addition into the C−I bond of compound **1** to form intermediate I. Meanwhile, the unstable copper ethyl difluoroacetate complex II is formed, and then intermediate III is generated rapidly via a reaction between intermediates I and II. Finally, reduction elimination affords the corresponding products **2**, regenerating the Pd(0) catalyst.

In conclusion, we have demonstrated an efficient synthesis of C-3 ethoxycarbonyldifluoromethylated chromones, thiochromones, and quinolones with functional group compatibility by a Pd-catalyzed reaction in the presence of copper. This method is useful for the synthesis of various chromone analogues, especially for the modification of natural bioactive compounds.

EXPERIMENTAL SECTION

General Experimental Information. ^1H and ^{13}C NMR spectra were recorded on a standard spectrometer operating at 300, 400, and 500 MHz (^1H 300/400 MHz, ^{13}C 125 MHz). Chemical shifts (δ) are given in parts per million. The abbreviations of splitting patterns are described as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets. $SiMe_4$ (TMS) was used as internal references in $CDCl_3$ (δ 7.26) for ^1H NMR, and ^{13}C NMR spectra were calibrated with $CDCl_3$ (δ 77.00) or DMSO-d_6 (δ 39.97). High-resolution mass spectra were recorded using the EI method with a double focusing magnetic mass analyzer. Melting points were measured uncorrected. Reactions were monitored by thin-layer chromatography or LC-MS analysis. Column chromatography (petroleum ether/ethyl acetate) was performed on silica gel (200−300 mesh). Ethyl bromodifluoroacetate was purchased from commercial source. Unless otherwise noted, all reactions were run under argon atmosphere and all solvents are commercially available without further purification.

Starting Materials. Compound **1f** was prepared by the iodination of 2-methyl-4*H*-chromen-4-one using the I_2/CF_3COOAg system according to a previously reported protocol.[25] **1g**, **1m**, **1q**, **1r**, and **1s** were prepared according to a known iodination procedure using the $I_2/Ce(NH_4)_2(NO_3)_6/CH_3CN$ system.[21b] **1n** was prepared by C-3 lithiation using LDA followed by the addition of iodine according to a reported method.[26] Other chromones were prepared by the addition of the corresponding substituted *o*-hydroxyacetophenone with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA), followed by cyclization and an iodination process by iodine according to a reported protocol.[27] **1q** was generated by the iodination of 1-methylquinolin-4(1*H*)-one using the I_2/Na_2CO_3 system based on a previously reported protocol.[23b] **1r** and **1s** were prepared from 2-aminoacetophenone and the corresponding benzoyl chloride according to a previously mentioned protocol.[23]

General Procedure for Preparing Target Compound 2 (Typical Example: 2a). In a two-neck flask, **1a** (0.5 mmol) and Pd(dppf)Cl_2 (19 mg, 0.025 mmol, 0.05 equiv) were added. The flask was capped and then purged under vacuum and filled with argon three

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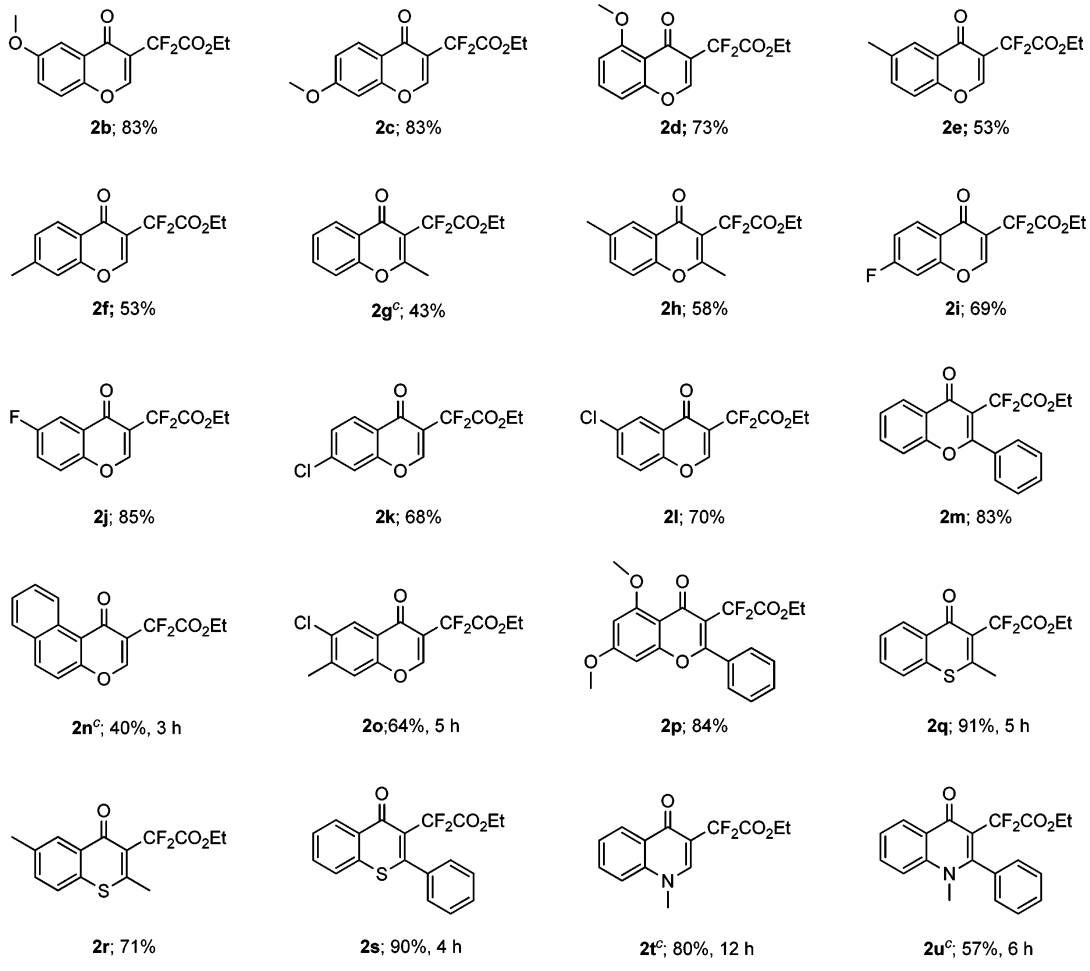
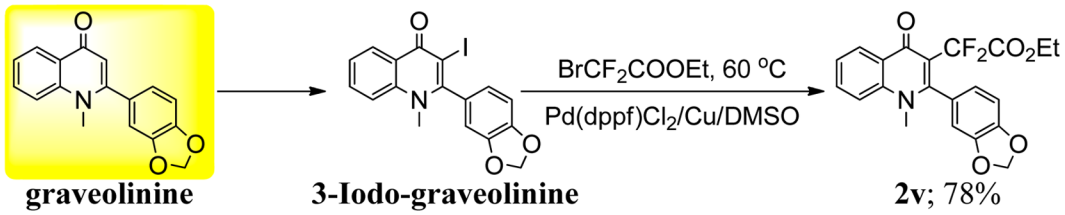
Table 2. Synthesis of 2b−2v *via* Cross-Coupling Reactions between 1b−1v and $BrCF_2CO_2Et$[a,b]



[a]Reaction conditions: **1** (0.5 mmol), copper powder (2 mmol), Pd(dppf)CI_2 (0.025 mmol, 0.05 equiv) in DMSO at 60 °C, 2 h. [b]Isolated yield. [c]Substrate converted incompletely.

Scheme 1. Preparation of the Graveolinine Ethyldifluoroacetate Derivative



times. $BrCF_2CO_2Et$ (0.13 mL, 1 mmol) and DMSO (2 mL) were then added, and the whole mixture was heated to 60 °C. Meanwhile, copper powder (128 mg, 2 mmol) was added to another two-neck flask under argon, followed by the addition of DMSO (3 mL). Then, the suspension was stirred at 60 °C. After 1 h, the substrate solution was transferred into copper powder suspension rapidly under argon using a syringe maintaining the temperature around 60 °C. Once the reaction was complete, at room temperature, ethyl acetate (15 mL) was added. Aqueous solution of KH_2PO_4 (1.27 M, 6 mL) was added, then the mixture was stirred for 10 min. The mixture was filtered through Celite, the copper salt residue was washed with EtOAc, and the filtrate was washed with brine and dried over anhydrous Na_2SO_4. The organic layer was concentrated and purified on silica gel eluted with PE/EtOAc to afford product **2a**.

Ethyl 2,2-Difluoro-2-(4-oxo-4*H*-chromen-3-yl)acetate (2a): White powder (105 mg, 78%); mp 104−105 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (t, J = 1.2 Hz, 1H), 8.20 (dd, J = 8.0, 1.6 Hz, 1H), 7.74 (td, J = 7.8, 1.7 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6 (t, $^3J_{CF}$ = 3.1 Hz), 162.7 (t, $^2J_{CF}$ = 32.6 Hz), 156.3, 155.1 (t, $^3J_{CF}$ = 9.7 Hz), 134.8, 126.2, 125.9, 123.9,

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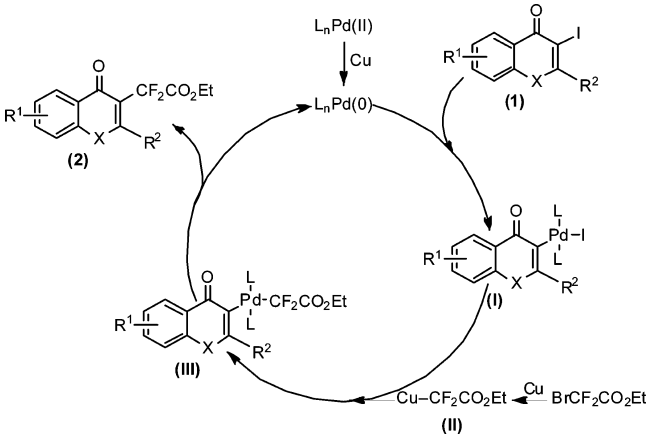
Scheme 2. Mechanism for Copper-Mediated Palladium-Catalyzed Cross-Coupling Reaction



118.9 (t, $^2J_{CF}$ = 22.5 Hz), 118.4, 111.3 (t, $^1J_{CF}$ = 250.6 Hz), 63.4, 13.9; HRMS (EI+) *m*/*z* 268.0544 [$C_{13}H_{10}F_2O_4$ (M^+) requires 268.0547].

Ethyl 2,2-Difluoro-2-(6-methoxy-4-oxo-4*H*-chromen-3-yl)-acetate (2b): Yellow powder (123 mg, 83%); mp 101−102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (t, *J* = 1.3 Hz, 1H), 7.54 (d, *J* = 3.1 Hz, 1H), 7.47 (d, *J* = 9.2 Hz, 1H), 7.32 (dd, *J* = 9.2, 3.1 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5 (t, $^3J_{CF}$ = 3.0 Hz), 162.7 (t, $^2J_{CF}$ = 32.5 Hz), 157.6, 154.8 (t, $^3J_{CF}$ = 9.6 Hz), 151.2, 124.8, 124.5, 119.8, 118.1 (t, $^2J_{CF}$ = 22.5 Hz), 111.5 (t, $^1J_{CF}$ = 250.3 Hz), 104.8, 63.4, 56.0, 13.9; HRMS (EI+) *m*/*z* 298.0643 [$C_{14}H_{12}F_2O_5$ (M^+) requires 298.0653].

Ethyl 2,2-Difluoro-2-(7-methoxy-4-oxo-4*H*-chromen-3-yl)-acetate (2c): Light yellow solid (126 mg, 85%); mp 70−71 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (t, *J* = 1.3 Hz, 1H), 8.09 (d, *J* = 8.9 Hz, 1H), 7.01 (dd, *J* = 8.9, 2.3 Hz, 1H), 6.90 (d, *J* = 2.3 Hz, 1H), 4.38 (q, *J* = 7.0 Hz, 2H), 3.92 (s, 3H), 1.35 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8 (t, $^3J_{CF}$ = 2.8 Hz), 164.8, 162.8 (t, $^2J_{CF}$ = 32.5 Hz), 158.2, 154.7 (t, $^3J_{CF}$ = 9.7 Hz), 127.2, 118.8 (t, $^2J_{CF}$ = 22.3 Hz), 117.6, 115.4, 111.4 (t, $^1J_{CF}$ = 250.3 Hz), 100.6, 63.4, 56.0, 13.9; HRMS (EI+) *m*/*z* 298.0649 [$C_{14}H_{12}F_2O_5$ (M^+) requires 298.0653].

Ethyl 2,2-Difluoro-2-(5-methoxy-4-oxo-4*H*-chromen-3-yl)-acetate (2d): Yellow solid (109 mg, 73%); mp 98−99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (t, *J* = 1.2 Hz, 1H), 7.61 (t, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.96 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3 (t, $^3J_{CF}$ = 3.1 Hz), 162.7 (t, $^2J_{CF}$ = 32.4 Hz), 160.1, 158.3, 153.3 (t, $^3J_{CF}$ = 10.0 Hz), 134.9, 120.1 (t, $^2J_{CF}$ = 22.6 Hz), 114.4, 111.5 (t, $^1J_{CF}$ = 250.3 Hz), 110.1, 107.3, 63.3, 56.6, 13.9; HRMS (EI+) *m*/*z* 298.0644 [$C_{14}H_{12}F_2O_5$ (M^+) requires 298.0653].

Ethyl 2,2-Difluoro-2-(6-methyl-4-oxo-4*H*-chromen-3-yl)-acetate (2e): White solid (75 mg, 53%); mp 64−65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (t, *J* = 1.2 Hz, 1H), 7.97 (d, *J* = 1.5 Hz, 1H), 7.54 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.42(d, *J* = 8.6 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 2.46 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7 (t, $^3J_{CF}$ = 3.1 Hz), 162.7 (t, $^2J_{CF}$ = 32.5 Hz), 155.0 (t, $^3J_{CF}$ = 9.6 Hz), 154.7, 136.4, 135.9, 125.1, 123.5, 118.7 (t, $^2J_{CF}$ = 22.4 Hz), 118.1, 111.4 (t, $^1J_{CF}$ = 250.2 Hz), 63.4, 21.0, 13.9; HRMS (EI+) *m*/*z* 282.0698 [$C_{14}H_{12}F_2O_4$ (M^+) requires 282.0704].

Ethyl 2,2-Difluoro-2-(7-methyl-4-oxo-4*H*-chromen-3-yl)-acetate (2f): White solid (75 mg, 53%); mp 127−128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.08 (d, *J* = 8.1 Hz, 1H), 7.31 (d, *J* = 9.3 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.51 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4 (t, $^3J_{CF}$ = 3.0 Hz), 162.7 (t, $^2J_{CF}$ = 32.4 Hz), 156.5, 154.9 (t, $^3J_{CF}$ = 9.7 Hz), 146.4, 127.7, 125.6, 121.6, 118.8 (t, $^2J_{CF}$ = 22.4 Hz), 118.1, 111.4 (t, $^1J_{CF}$ = 250.4 Hz), 63.4, 21.9, 13.9; HRMS (EI+) *m*/*z* 282.0704 [$C_{14}H_{12}F_2O_4$ (M^+) requires 282.0704].

Ethyl 2,2-Difluoro-2-(2-methyl-4-oxo-4*H*-chromen-3-yl)-acetate (2g): Light yellow powder (61 mg, 43%); mp 88−89 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.69 (t, *J* = 7.9 Hz, 1H), 7.43 (q, *J* = 7.9 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 2.68 (t, *J* = 3.4 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4 (t, $^3J_{CF}$ = 3.5 Hz), 168.3, 163.3 (t, $^2J_{CF}$ = 32.1 Hz), 155.7, 134.4, 125.8, 125.8, 122.5, 117.8, 116.2 (t, $^2J_{CF}$ = 22.8 Hz), 112.7 (t, $^1J_{CF}$ = 249.8 Hz), 63.1, 19.8 (t, $^4J_{CF}$ = 5.1 Hz), 13.9; HRMS (EI+) *m*/*z* 282.0702 [$C_{14}H_{12}F_2O_4$ (M^+) requires 282.0704].

Ethyl 2-(2,6-Dimethyl-4-oxo-4*H*-chromen-3-yl)-2,2-difluoro-acetate (2h): White solid (86 mg, 58%); mp 105−106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 4.41 (q, *J* = 7.0 Hz, 2H), 2.66 (s, 3H), 2.44 (s, 3H), 1.36 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4 (t, $^3J_{CF}$ = 3.4 Hz), 168.2, 163.4 (t, $^2J_{CF}$ = 32.0 Hz), 154.0, 135.9, 135.6, 125.1, 122.2, 117.5, 116.0 (t, $^2J_{CF}$ = 22.6 Hz), 112.8 (t, $^1J_{CF}$ = 249.8 Hz), 63.0, 21.0, 19.8 (t, $^4J_{CF}$ = 5.1 Hz), 13.9; HRMS (EI+) *m*/*z* 296.0868 [$C_{15}H_{14}F_2O_4$ (M^+) requires 296.0860].

Ethyl 2,2-Difluoro-2-(7-fluoro-4-oxo-4*H*-chromen-3-yl)-acetate (2i): White solid (98 mg, 69%); mp 79−80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (t, *J* = 1.3 Hz, 1H), 8.25−8.18 (m, 1H), 7.24−7.16 (m, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6 (t, $^3J_{CF}$ = 2.6 Hz), 166.1 (d, $^1J_{CF}$ = 257.4 Hz), 162.5 (t, $^2J_{CF}$ = 32.3 Hz), 157.4 (d, $^3J_{CF}$ = 13.4 Hz), 155.3 (t, $^3J_{CF}$ = 9.7 Hz), 128.5 (d, $^3J_{CF}$ = 10.7 Hz), 120.7, 119.1 (t, $^2J_{CF}$ = 22.5 Hz), 115.1 (d, $^2J_{CF}$ = 22.9 Hz), 111.2 (t, $^1J_{CF}$ = 250.9 Hz), 105.3 (d, $^2J_{CF}$ = 25.6 Hz), 63.5, 13.9; HRMS (EI+) *m*/*z* 286.0456 [$C_{13}H_9F_3O_4$ (M^+) requires 286.0453].

Ethyl 2,2-Difluoro-2-(6-fluoro-4-oxo-4*H*-chromen-3-yl)-acetate (2j): Light yellow solid (122 mg, 85%); mp 102−103 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (t, *J* = 1.3 Hz, 1H), 7.83 (dd, *J* = 7.9, 3.0 Hz, 1H), 7.56 (dd, *J* = 9.2, 4.1 Hz, 1H), 7.50−7.45 (m, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.39−1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9 (t, $^3J_{CF}$ = 2.8 Hz), 162.5 (t, $^2J_{CF}$ = 32.4 Hz), 160.0 (d, $^1J_{CF}$ = 249.1 Hz), 157.9, 155.3 (t, $^3J_{CF}$ = 9.6 Hz), 152.6, 123.0 (d, $^2J_{CF}$ = 25.5 Hz), 120.7 (d, $^3J_{CF}$ = 8.2 Hz), 118.3 (t, $^2J_{CF}$ = 22.8 Hz), 111.2 (t, $^1J_{CF}$ = 250.9 Hz), 110.9 (d, $^2J_{CF}$ = 24.0 Hz), 63.5, 13.9; HRMS (EI+) *m*/*z* 286.0448 [$C_{13}H_9F_3O_4$ (M^+) requires 286.0453].

Ethyl 2-(7-Chloro-4-oxo-4*H*-chromen-3-yl)-2,2-difluoro-acetate (2k): White solid (103 mg, 68%); mp 66−67 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (t, *J* = 1.4 Hz, 1H), 8.13 (d, *J* = 8.6 Hz, 1H), 7.56 (d, *J* = 1.9 Hz, 1H), 7.44 (dd, *J* = 8.6, 1.9 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.39−1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7 (t, $^3J_{CF}$ = 3.2 Hz), 162.5 (t, $^2J_{CF}$ = 32.4 Hz), 156.4, 155.2 (t, $^3J_{CF}$ = 9.7 Hz), 141.0, 127.2, 127.1, 122.4, 119.3 (t, $^2J_{CF}$ = 22.6 Hz), 118.5, 111.1 (t, $^1J_{CF}$ = 250.9 Hz), 63.5, 13.9; HRMS (EI+) *m*/*z* 302.0160 [$C_{13}H_9ClF_2O_4$ (M^+) requires 302.0157].

Ethyl 2-(6-Chloro-4-oxo-4*H*-chromen-3-yl)-2,2-difluoro-acetate (2l): Yellow solid (105 mg, 70%); mp 90−91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (t, *J* = 1.2 Hz, 1H), 8.16 (d, *J* = 2.6 Hz, 1H), 7.69 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.50 (d, *J* = 8.9 Hz, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5 (t, $^3J_{CF}$ = 3.0 Hz), 162.5 (t, $^2J_{CF}$ = 32.4 Hz), 155.3 (t, $^3J_{CF}$ = 9.7 Hz), 154.7, 135.0, 132.4, 125.3, 124.8, 120.2, 119.0 (t, $^2J_{CF}$ = 22.7 Hz), 111.2 (t, $^1J_{CF}$ = 250.9 Hz), 63.5, 13.9; HRMS (EI+) *m*/*z* 302.0184 [$C_{13}H_9ClF_2O_4$ (M^+) requires 302.0157].

Ethyl 2,2-Difluoro-2-(4-oxo-2-phenyl-4*H*-chromen-3-yl)-acetate (2m): White powder (143 mg, 83%); mp 129−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.78−7.68 (m, 3H), 7.59−7.44 (m, 5H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4 (t, $^3J_{CF}$ = 2.8 Hz), 166.7, 163.3 (t, $^2J_{CF}$ = 32.4 Hz), 156.0, 134.8, 132.4, 131.3, 129.0, 128.2 (3 ×), 126.0, 125.8, 122.6, 118.2, 115.9 (t, $^2J_{CF}$ = 22.0 Hz), 111.8 (t, $^1J_{CF}$ = 251.5 Hz), 63.0, 13.9; HRMS (EI+) *m*/*z* 344.0851 [$C_{19}H_{14}F_2O_4$ (M^+) requires 344.0860].

Ethyl 2,2-Difluoro-2-(1-oxo-1*H*-benzo[*f*]chromen-2-yl)-acetate (2n): White solid (64 mg, 40%); mp 119−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (d, *J* = 8.2 Hz, 1H), 8.36 (s, 1H), 8.16 (d, *J* = 9.1 Hz, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.76 (t, *J* = 7.4 Hz, 1H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.56 (d, *J* = 9.1 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 176.2 (t, $^3J_{CF}$ = 2.9 Hz), 162.5 (t, $^2J_{CF}$ = 32.6 Hz), 158.2, 155.4 (t, $^3J_{CF}$

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= 9.1 Hz), 137.7, 131.1, 130.3, 129.7, 129.4, 127.8, 126.3, 120.6 (t, $^2J_{CF}$ = 22.1 Hz), 118.4, 116.5, 112.1 (t, $^1J_{CF}$ = 247.7 Hz), 63.6, 14.2; HRMS (EI+) *m/z* 318.0713 [$C_{17}H_{12}F_2O_4$ (M^+) requires 318.0704].

Ethyl 2-(6-Chloro-7-methyl-4-oxo-4*H*-chromen-3-yl)-2,2-difluoroacetate (2o): White powder (101 mg, 64%); mp 120−121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.14 (s, 1H), 7.42 (s, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 2.52 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3 (t, $^3J_{CF}$ = 3.1 Hz), 162.5 (t, $^2J_{CF}$ = 32.4 Hz), 155.0 (t, $^3J_{CF}$ = 9.7 Hz), 154.5, 144.3, 133.0, 125.4, 122.8, 120.1, 118.8 (t, $^2J_{CF}$ = 22.5 Hz), 111.2 (t, $^1J_{CF}$ = 250.9 Hz), 63.4, 20.9, 13.8; HRMS (EI+) *m/z* 316.0313 [$C_{14}H_{11}ClF_2O_4$ (M^+) requires 316.0314].

Ethyl 2-(5,7-Dimethoxy-4-oxo-2-phenyl-4*H*-chromen-3-yl)-2,2-difluoroacetate (2p): Light yellow solid (258 mg, 84% yield from 0.76 mmol of **1p**); mp 219−220 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.7 Hz, 2H), 7.55−7.44 (m, 3H), 6.47 (d, *J* = 2.2 Hz, 1H), 6.38 (d, *J* = 2.1 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.93 (s, 3H), 3.87 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0 (t, $^3J_{CF}$ = 2.9 Hz), 164.9, 164.0, 163.4 (t, $^2J_{CF}$ = 32.1 Hz), 161.1, 159.6, 132.3, 131.0, 129.0, 128.1 (3×), 116.8 (t, $^2J_{CF}$ = 21.8 Hz), 112.1 (t, $^1J_{CF}$ = 251.0 Hz), 107.8, 96.8, 92.6, 62.8, 56.5, 55.9, 13.9; HRMS (EI+) *m/z* 404.1073 [$C_{21}H_{18}F_2O_6$ (M^+) requires 404.1071].

Ethyl 2,2-Difluoro-2-(2-methyl-4-oxo-4*H*-thiochromen-3-yl)-acetate (2q): Yellow solid (135 mg, 91%); mp 140−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45−8.39 (d, *J* = 8.2 Hz, 1H), 7.64 (td, *J* = 8.1, 1.5 Hz, 1H), 7.58−7.51 (m, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.71 (t, *J* = 4.5 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4 (t, $^3J_{CF}$ = 3.6 Hz), 163.4 (t, $^2J_{CF}$ = 32.1 Hz), 155.8, 136.5, 132.2, 130.2, 128.9, 128.2, 126.5 (t, $^2J_{CF}$ = 21.7 Hz), 125.2, 113.7 (t, $^1J_{CF}$ = 251.6 Hz), 62.7, 22.1 (t, $^4J_{CF}$ = 6.4 Hz), 13.9; HRMS (EI+) *m/z* 298.0479 [$C_{14}H_{12}F_2O_3S$ (M^+) requires 298.0475].

Ethyl 2-(2,6-Dimethyl-4-oxo-4*H*-thiochromen-3-yl)-2,2-difluoroacetate (2r): White solid with pale yellow (111 mg, 71%); mp 122−123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.44 (s, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 2.69 (t, *J* = 4.5 Hz, 3H), 2.45 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5 (t, $^3J_{CF}$ = 3.5 Hz), 163.5 (t, $^2J_{CF}$ = 32.1 Hz), 155.7, 138.8, 133.6, 133.5, 130.0, 128.6, 126.3 (t, $^2J_{CF}$ = 21.7 Hz), 125.1, 113.8 (t, $^1J_{CF}$ = 251.5 Hz), 62.7, 22.2 (t, $^4J_{CF}$ = 6.3 Hz), 21.4, 14.0; HRMS (EI+) *m/z* 312.0635 [$C_{15}H_{14}F_2O_3S$ (M^+) requires 312.0632].

Ethyl 2,2-Difluoro-2-(4-oxo-2-phenyl-4*H*-thiochromen-3-yl)-acetate (2s): White powder (160 mg, 90%); mp 99−100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, *J* = 8.4 Hz, 1H), 7.72−7.64 (m, 1H), 7.62−7.54 (m, 2H), 7.55−7.41 (m, 5H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1 (t, $^3J_{CF}$ = 2.4 Hz), 163.4 (t, $^2J_{CF}$ = 32.0 Hz), 157.6, 137.2, 135.0, 132.5, 130.3, 130.0, 128.9, 128.4, 128.2 (3×), 128.1, 125.9 (t, $^2J_{CF}$ = 20.4 Hz), 125.4, 112.6 (t, $^1J_{CF}$ = 253.4 Hz), 62.7, 13.9; HRMS (EI+) *m/z* 360.0633 [$C_{19}H_{14}F_2O_3S$ (M^+) requires 360.0632].

Ethyl 2,2-Difluoro-2-(1-methyl-4-oxo-1,4-dihydroquinolin-3-yl)acetate (2t): White solid (112 mg, 80%); mp 143−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.98 (s, 1H), 7.74 (td, *J* = 8.8, 1.6 Hz, 1H), 7.45 (dd, *J* = 8.2, 7.0 Hz, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9 (t, $^3J_{CF}$ = 3.4 Hz), 163.7 (t, $^2J_{CF}$ = 33.2 Hz), 142.4 (t, $^3J_{CF}$ = 8.4 Hz), 140.4, 133.1, 126.8, 126.8, 124.9, 115.7, 114.3 (t, $^2J_{CF}$ = 22.7 Hz), 112.4 (t, $^1J_{CF}$ = 249.0 Hz), 63.1, 41.4, 14.0; HRMS (EI+) *m/z* 281.0860 [$C_{14}H_{13}F_2NO_3$ (M^+) requires 281.0863].

Ethyl 2,2-Difluoro-2-(1-methyl-4-oxo-2-phenyl-1,4-dihydroquinolin-3-yl)acetate (2u): Pale yellow powder (102 mg, 57%); mp 181−182 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.0 Hz, 1H), 7.79−7.73 (m, 1H), 7.60−7.35 (m, 7H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.46 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3 (t, $^3J_{CF}$ = 3.1 Hz), 164.2 (t, $^2J_{CF}$ = 32.4 Hz), 154.3, 141.3, 133.4, 133.3, 129.7, 128.6 (3×), 128.3, 126.8, 126.2, 124.7, 116.3, 114.7 (t, $^2J_{CF}$ = 21.1 Hz), 113.0 (t, $^1J_{CF}$ = 250.2 Hz), 62.4, 36.9, 13.9; HRMS (EI+) *m/z* 357.1182 [$C_{20}H_{17}F_2NO_3$ (M^+) requires 357.1176].

Ethyl 2-(2-(Benzo[*d*][1,3]dioxol-5-yl)-1-methyl-4-oxo-1,4-dihydroquinolin-3-yl)-2,2-difluoroacetate (2v): Gray white solid (156 mg, 78%); mp 116−117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, *J* = 8.0 Hz, 1H), 7.76 (t, *J* = 7.9 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.89−6.83 (m, 2H), 6.09 (d, *J* = 1.4 Hz, 1H), 6.07 (d, *J* = 1.4 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.52 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4 (t, $^3J_{CF}$ = 2.6 Hz), 164.2 (t, $^2J_{CF}$ = 32.6 Hz), 153.9, 148.8, 147.9, 141.3, 133.3, 126.8, 126.7, 126.2, 124.8, 122.6, 116.3, 114.9 (t, $^2J_{CF}$ = 20.6 Hz), 113.1 (t, $^1J_{CF}$ = 249.9 Hz), 109.0, 108.6, 101.7, 62.5, 36.9, 14.0; HRMS (EI+) *m/z* 401.1076 [$C_{21}H_{17}F_2NO_5$ (M^+) requires 401.1075].

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR for all synthesized compounds; ^{13}C NMR spectra for **1g**, **1h**, **1k**, **1n**, **1v**, and all compounds of **2a**−**2v**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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