Development of direct C-3 difluoromethylation reaction for application in synthesis of quinoline-related drugs

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Abstract:

Fluorine holds a prominent position within the realm of drug discovery and development, substantiated by its presence in approximately 25% of drugs approved by the US Food and Drug Administration (FDA). Consequently, the advancement of new fluorination reactions stands as a pivotal area in medicinal chemistry. In particular, the monofluoro-, difluoromethyl-, and trifluoromethyl- are three groups that appear most frequently in drug structure. Quinoline, owing to its privileged structural status, plays a crucial role in drug design and synthesis. Various approaches have been documented for the direct difluoromethylation of the C-2 and C-4 positions of the quinoline ring. However, achieving direct C-3 difluoromethylation has remained an elusive objective. In this study, we introduce a novel method for effecting the direct difluoromethylation at the C-3 position of the quinoline ring. Comprehensive characterizations, including ^{1}H-NMR, ^{13}C-NMR, and ^{19}F-NMR for all compounds are performed. We believe that this novel method will open a new way to access the hitherto untapped C-3-difluoromethylation active compounds.

Keywords: **C-H activation, difluoromethylation, drug synthesis, quinoline.**

Classification numbers: **2.2, 3.3**

1. Introduction

The fluorine atom assumes a pivotal role in medicinal chemistry, particularly in drug design and development [1, 2]. Approximately 25% of FDA-approved drugs presently incorporate fluorine (F) or related functional groups such as monofluoromethyl ($-CFH_2$), difluoromethyl ($-CF_2H$), trifluoromethyl ($-CF_3$), among others [1-4]. Notable examples of such fluorinated drugs encompass voriconazole for fungal infection treatment, Sitagliptin for type II diabetes management, and Fulvestrant for cancer therapy (Fig. 1A). Among these fluorinated moieties, it is well-established that the difluoromethyl CF_2H group serves as a bioisostere substitute for numerous functional groups, including OH, SH, and NH [5]. This bioisosteric replacement significantly enhances the biological activity of compounds [5, 6]. Consequently, a substantial body of research is dedicated to developing

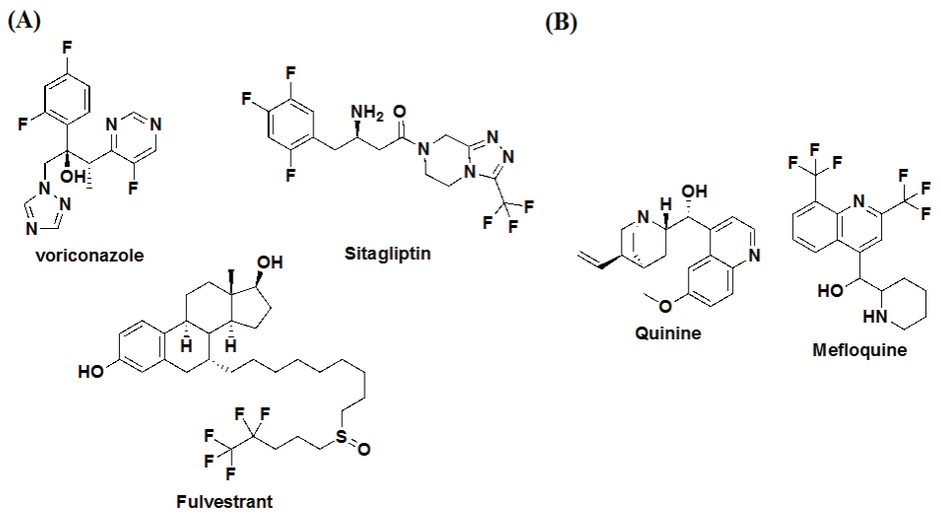

Fig. 1. Most notable drugs containing (A) fluorine atoms and (B) quinoline.

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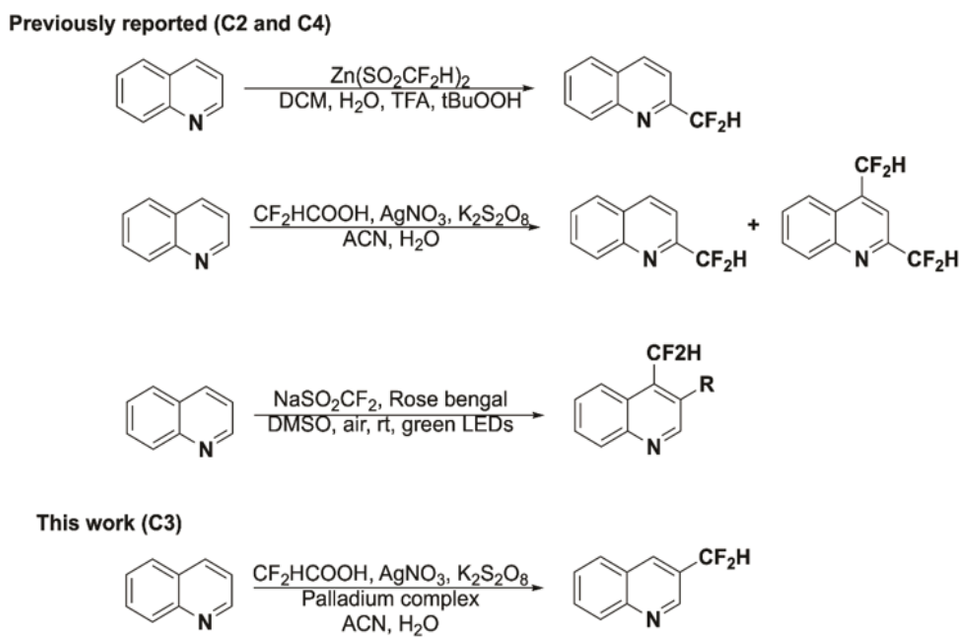
novel difluoromethylation reactions to introduce the CF_2H group into bioactive compounds [7].

Quinoline represents a privileged structural motif in drug design, with numerous bioactive compounds and drugs featuring this moiety (Fig. 1B) [8]. Therefore, our research group is keenly interested in discovering new methodologies for constructing currently inaccessible quinoline derivatives. To date, only a limited number of methods have been reported for the direct difluoromethylation of quinoline (Scheme 1) [9-11]. However, all of these reported methods exclusively yield the C-2-CF_2H and C-4-CF_2H derivatives. In this report, we present the inaugural controlled-direct C-3 difluoromethylation of quinoline.

2. Materials and methods

2.1. Chemicals

Reagents and solvents were procured from commercially available suppliers, including Deajung (South Korea), Sigma Aldrich, and Alfa Aesar. All reagents and solvents exhibited a minimum purity of 98% and were utilized without further purification. Reaction progress was monitored via thin-layer chromatography (Merck Kieselgel 60F254) and visualized under UV light at wavelengths of 254 or 365 nm. NMR analyses were conducted using a Bruker Avance 400 MHz instrument with TMS serving as the internal standard.



Scheme 1. Current methods of direct difluoromethylation.

2.2. Methods

General procedure: Quinoline (1 equiv.), palladium complex (0.5 mol%), $AgNO_3$ (0.5 equiv.), and $K_2S_2O_8$ (5 equiv.) were combined in a 10 ml round-bottom flask. Acetonitrile (1 ml) was subsequently added, followed by H_2O (0.5 ml). The difluoromethylating reagent CF_2HCOOH (2 equiv.) was introduced. The mixture was stirred at 50°C for 6 hours. Reaction progress was monitored by thin-layer chromatography until completion. The reaction mixture was then diluted with H_2O (20 ml), followed by the addition of saturated $NaHCO_3$ (20 ml). Extraction was performed using ethyl acetate. The product was purified via silica-gel flash column chromatography.

3. Results and discussion

3.1. Investigation of direct C-3 difluoromethylation

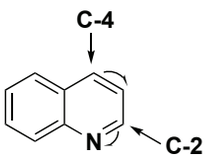


Fig. 2. Electron flow of quinoline.

Previously, difluoroacetic acid and its derivatives have been reported as a new means for direct difluoromethylation of quinoline [9-11]. However, the authors exclusively yielded the C-2-CF_2H/C-4-CF_2H and bis-difluoromethylated products (C-2 + C-4) (Scheme 1). The common mechanism underlying this reaction involves the nucleophilic CF2H radical species generated through the redox process of $AgNO_3/K_2S_2O_8$, which preferentially attaches to the electron-deficient carbons within the quinoline system (C-2 and C-4) (Fig. 2) [9-11]. Building upon these findings, we hypothesized that the inclusion of a metal catalyst could stabilise the electrophilic CF_2H radical species, thereby enabling attachment to C-3 of quinoline. Among metal catalysts, palladium

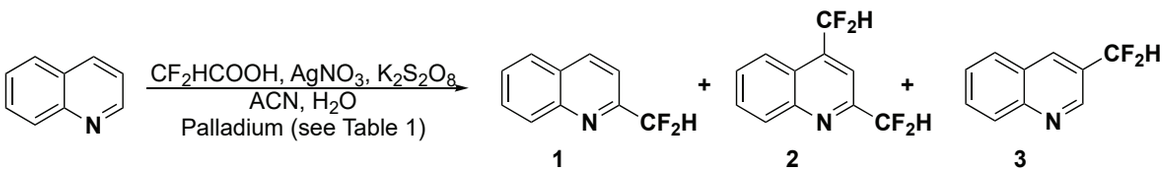
is renowned for its involvement in various mechanisms of both nucleophilic and electrophilic radical reactions [12]. Consequently, we conducted a screening of several palladium catalysts using the previously optimised reaction conditions (Table 1, Scheme 2).

Table 1. Representative results of the screening of palladium complexes.

Entry	Pd Catalyst	Catalyst (mol%)	Yields (%)*		
			1	*2*	*3*
1	None	-	50	<1	-
2	$Pd(OAc)_2$	0.5	44	<1	0
3	$Pd(PPh_3)_4$	0.5	31	<5	0
4	$Pd(PPh_3)_4Cl_2$	0.5	<5	<1	72
5	$Pd(PPh_3)_4Cl_2$	1	<5	<1	70

Reactions were carried out at 50°C. *NMR yields. Other palladium complexes did not exhibit any significant effects on the reaction (data not shown).

As illustrated in Table 1, the standard reaction conditions without palladium yielded a 50% yield of C-2 product 1 and less than 1% of product 2, consistent with the literature [10] (Entry 1, Table 1). No C-3 product was obtained when employing $Pd(OAc)_2$ and $Pd(PPh_3)_4$, though the overall reaction yield was diminished (Entries 2 and 3, Table 1). Among the tested palladium complexes, $Pd(PPh_3)_4Cl_2$ emerged as a regioselective catalyst for the formation of the C-3 product, with a minor amount of C-2 (1) and bis C-2/C-4 (2) (Entry 4, Table 1). The TLC pattern also indicated that the more polar spot corresponds to C-3 (3) (Fig. 3). This observation can be elucidated by the presence of the electron-withdrawing group $-CF_2H$ at C-2 in 1 and 2, rendering these compounds less polar in comparison to 3. Employing 0.5 mol% of $Pd(PPh_3)_4Cl_2$ was deemed optimal, as increasing the amount did not enhance the reaction yield (Entry 5, Table 1).



Scheme 2. Synthetic scheme corresponding to the experiments detailed in Table 1.

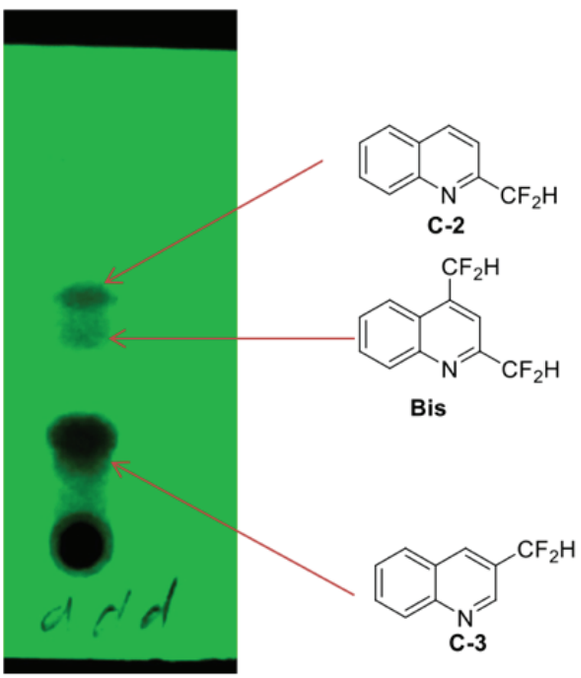


Fig. 3. TLC of reaction mixture when adding $Pd(PPh_3)_4Cl_2$.

3.2. Confirmation of compound's structures

Comparison of the ^{19}F-NMR spectra of 1, 2, and 3 (Fig. 4) revealed distinct features: a single peak at -114.2 ppm for compound 1, corresponding to C-2-CF_2H; a single peak at -115.1 ppm for compound 2, indicative of C-3-CF_2H; and two peaks at -114.5 and -115.2 corresponding to C-2-CF_2H & C-3-CF_2H in compound 3. Overall, the ^{19}F-NMR analysis unequivocally differentiated the CF_2H group in compounds 1-3.

In terms of ^{1}H-NMR, the presence of triplet peaks within the range of 6.60-7.30 ppm (JH-F~55 Hz) for the hydrogen atoms of the CF_2H group confirmed the existence of C-2-CF_2H and C-3-CF_2H in the synthesised compounds 1-3 (Fig. 5). Furthermore, the proton peak at 8.96 ppm for compound 3 affirmed that the hydrogen at C-2 of quinoline remained unaltered, a feature not

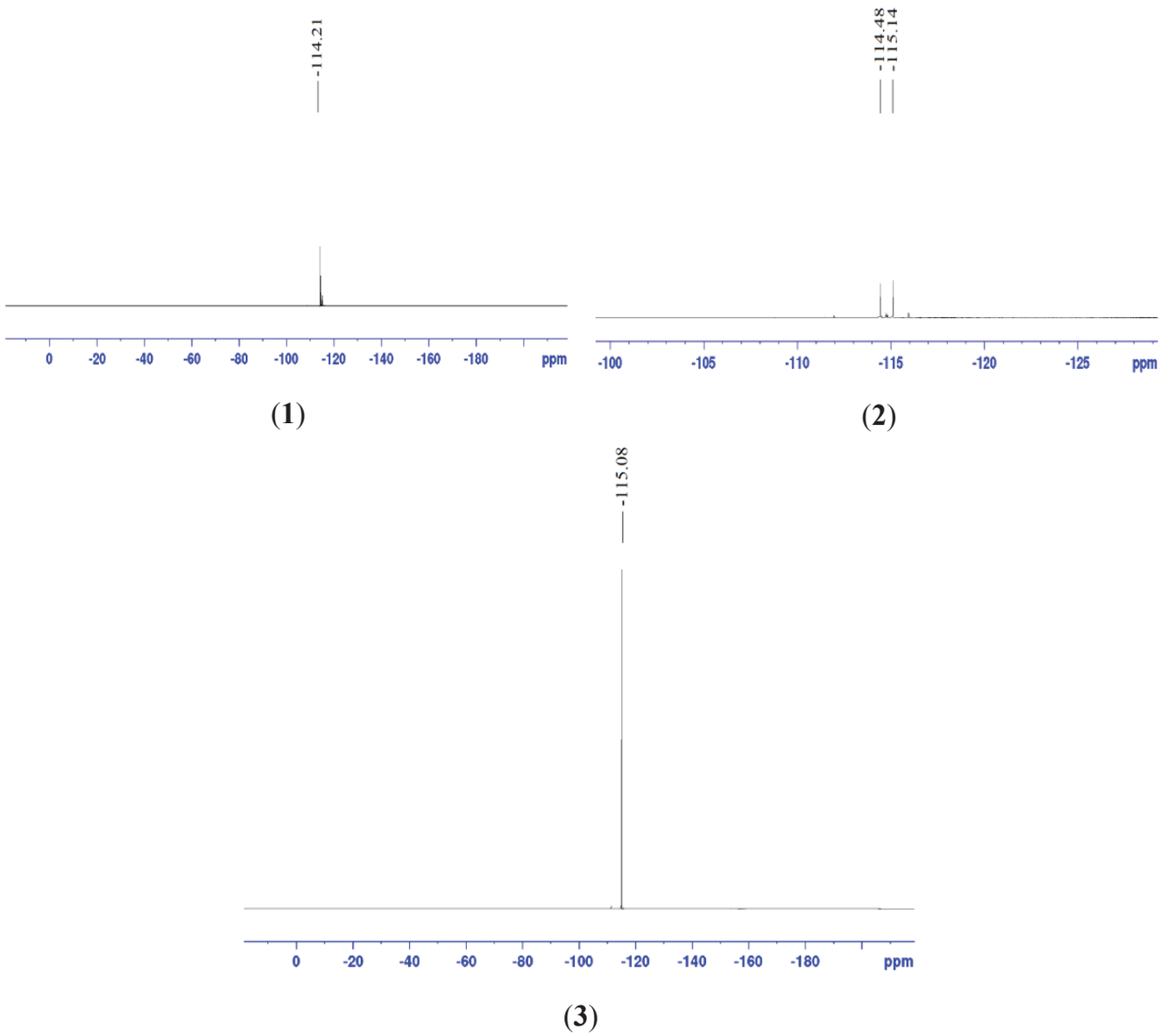


Fig. 4. ^{19}F-NMR spectra of compounds 1, 2, and 3.

observed in compounds 1 and 2. Collectively, the NMR data have substantiated the structures of the compounds.

In summary, we have developed novel reaction conditions to achieve direct C-3 difluoromethylation. Comprehensive characterisations, including ^{1}H-NMR and ^{19}F-NMR for known compounds 1,2, along with full characterisation for compound 3, are shown below:

Compound 1: ^{1}H NMR (400 MHz, Chloroform-d) δ=8.26 (d, J=8.5, 1H), 8.07 (d, J=8.5, 1H), 7.86-7.78 (m, 1H), 7.71 (ddd, J=8.5, 6.8, 1.4, 1H), 7.66 (d, J=8.4, 1H), 7.56 (t, J=7.5, 1H), 6.71 (t, J=55.3, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.22.

Compound 2: ^{1}H NMR (400 MHz, Chloroform-d) δ 8.23 (d, J=8.6 Hz, 1H), 8.14 (dd, J=8.4 Hz, 1H), 7.92 (s, 1H), 7.82-7.89 (m, 1H), 7.74 (ddd, J=8.2, 6.7, 1.2 Hz, 1H), 7.18 (t, J=54.3 Hz, 1H), 6.81 (t, J=55.1 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.5, -115.2.

Compound 3: yellow oil. ^{1}H NMR (400 MHz, Chloroform-d) δ=9.03 (s, 2H), 8.22 (d, J=8.4, 2H), 8.10 (d, J=8.4, 2H), 7.80 (t, J=7.6, 2H), 7.66 (t, J=7.6, 2H),

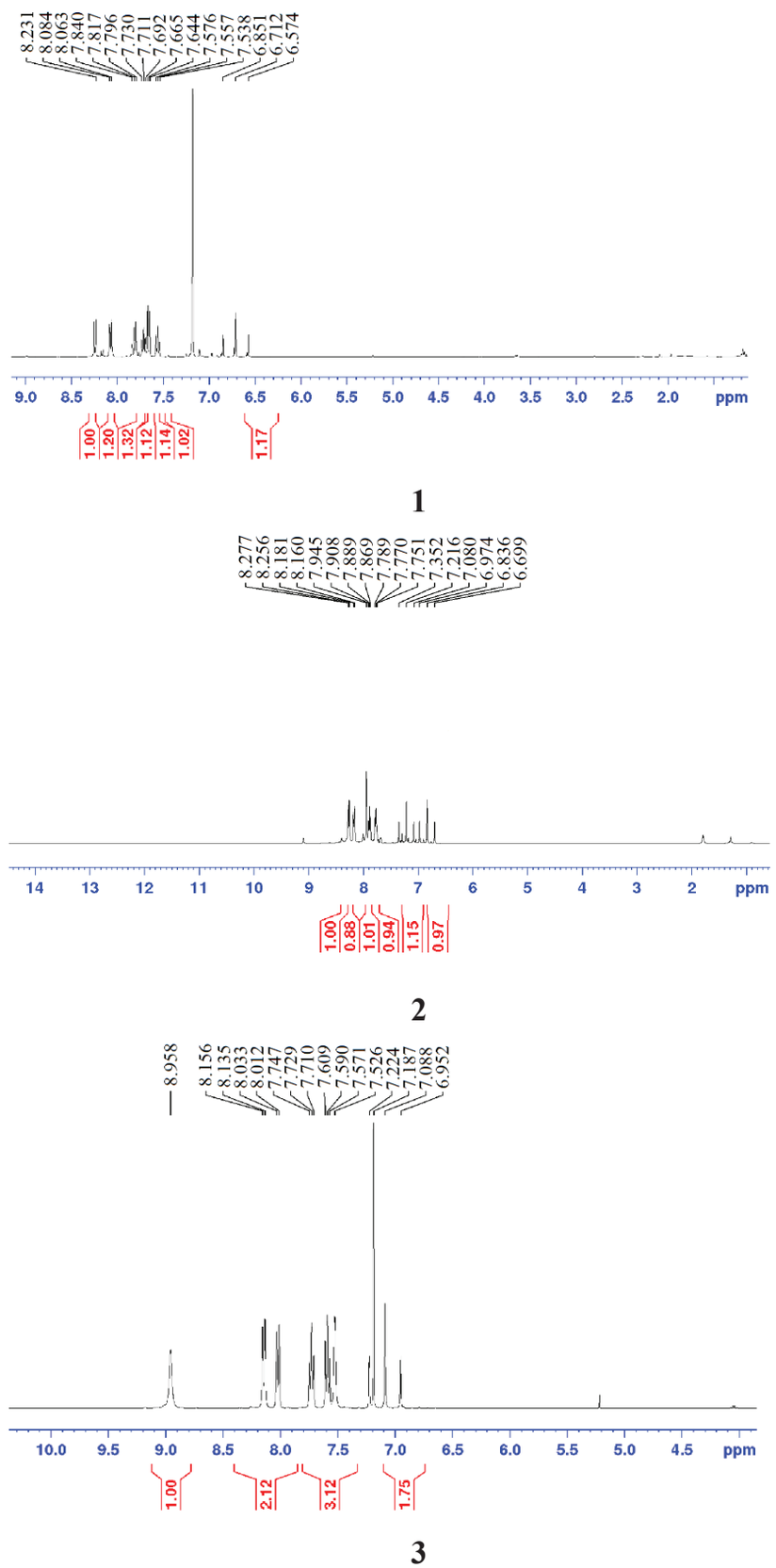


Fig. 5. ^{1}H-NMR spectra of compounds 1, 2, and 3.

7.62-7.57 (m, 2H), 7.16 (t, t, J=55.3, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.05, 148.55, 137.91(t), 130.41, 130.00, 127.87, 124.19, 123.31, 118.00(t), 113.31(t). ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.09.

4. Conclusions

We have successfully conducted the direct C-3 difluoromethylation of quinoline, employing difluoroacetic acid as the difluoromethylating reagent under the redox conditions of $AgNO_3/K_2S_2O_8$ and employing $Pd(PPh_3)_2Cl_2$ as the catalyst. The structure of the C-3 compound was meticulously confirmed through state-of-the-art NMR techniques, encompassing ^{1}H-NMR, ^{13}C-NMR, and ^{19}F-NMR. As of now, this represents the sole direct method documented in the literature for synthesizing the C-3-CF_2H derivative of quinoline. We anticipate that this work will serve as an accessible route for the direct synthesis of drugs containing the C-3-CF_2H moiety.

CRediT author statement

Thanh Tung Truong: Study conception, Design, Data collection, Analysis and Interpretation, Original draft preparation; John Nielsen: Analysis and Interpretation, Original draft preparation.

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COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

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