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Volume 28 (2025), p. 561-571

Online since: 20 June 2025

<https://doi.org/10.5802/crchim.403>



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Research article

Synthesis of C5-arylated pyrazoles from a pyrazole-4-carboxylate by a palladium-catalyzed C5–H bond activation/C4-decarboxylation sequence

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Abstract. In the context of palladium-catalyzed C–H bond arylation, it has been well-established that pyrazoles, with both C4 and C5 available positions, typically result in the formation of mixtures of C4-, C5-arylated, and also C4, C5-diarylated products. In this study, the reactivity of ethyl 1-methylpyrazole-4-carboxylate in palladium-catalyzed C–H arylation was investigated. The objective was to determine the effectiveness of the presence of an ester substituent at the C4 position of the pyrazole as a blocking group in controlling the regioselectivity of such C–H bond arylations. It was observed that the presence of such an ester substituent acted as a convenient blocking group, thereby enabling the control of regioselectivity in the arylation process at the C5 position of the pyrazole. The reaction exhibits a high degree of tolerance to a wide variety of aryl bromides, including a diverse array of functional groups at the *para*, *meta*, and *ortho* positions of the aryl bromides. Heteroarylation is also possible. In the course of these couplings, no decarboxylation of the pyrazole unit was observed, and the reaction requires only 2 mol% of an air-stable phosphine-free palladium catalyst and KOAc as an inexpensive base. Furthermore, the removal of the pyrazole ester substituent was found to be easy, which demonstrates the potential of such an ester substituent as a removable blocking group.

Keywords. C–H bond functionalization, Direct arylation, Homogeneous catalysis, Palladium, Pyrazoles.

Funding. Scientific Ministry of Higher Education and Research of Tunisia.

Manuscript received 5 March 2025, revised 14 April 2025, accepted 7 May 2025.

1. Introduction

Several pharmaceutical compounds possess a 5-(hetero)arylpyrazole unit [1]. Examples include celecoxib, a nonsteroidal anti-inflammatory drug, and nidufexor, an experimental treatment for non-alcoholic steatohepatitis (Figure 1). Other examples include rimonabant, a 5-(4-chlorophenyl)pyrazole, which has been shown to have anti-obesity properties, and voxelotor, a 2-(pyrazol-5-yl)pyridine, which

has been found to be beneficial in the treatment of sickle cell disease (Figure 1). While numerous approaches have been reported for the synthesis of substituted pyrazoles [2,3], there remains a need for the development of simple and straightforward methods for the synthesis of 5-arylpyrazoles.

Direct C–H bond functionalization of (hetero)arenes by palladium catalysis is an important research topic in organic chemistry [4–18], and a number of methods for controlling the regioselectivity of such a C–H bond functionalization have been reported over the past few decades.

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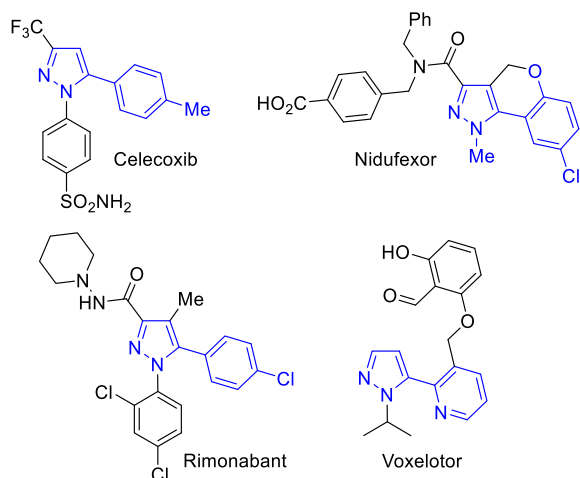


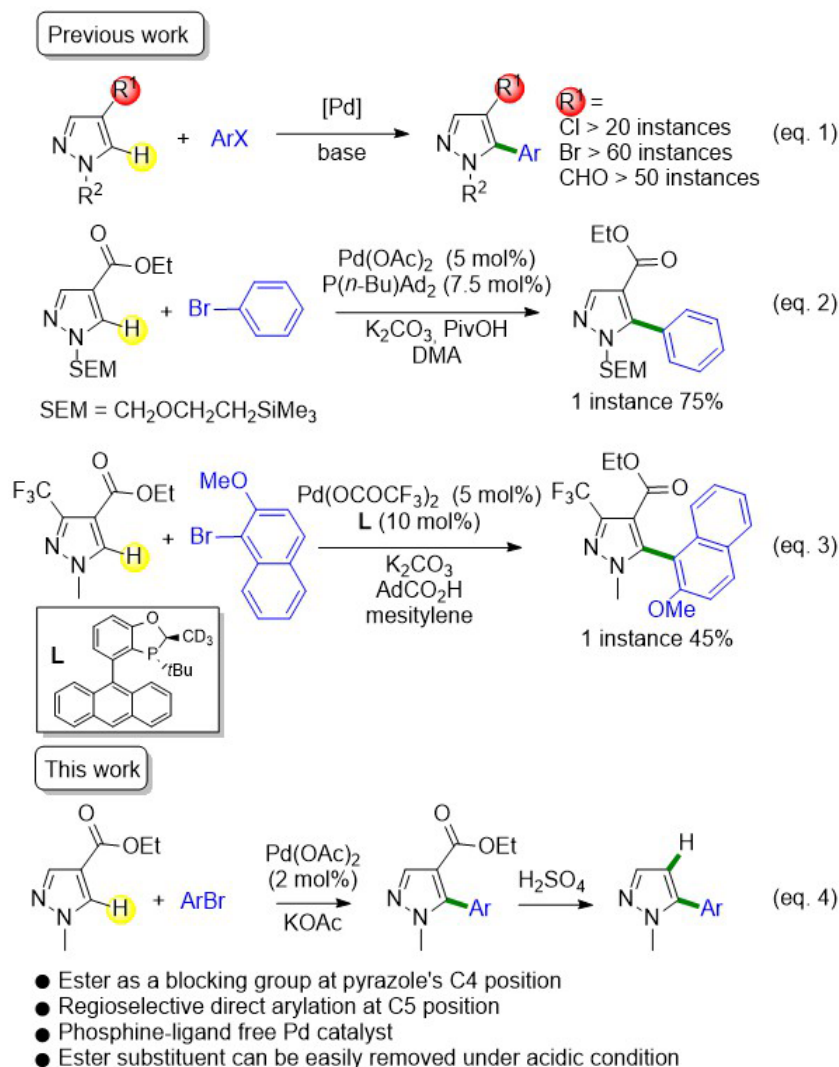
Figure 1. Selected drugs containing an arylpyrazole unit.

Palladium-catalyzed C–H bond arylation of five-membered ring heteroarenes has emerged as an increasingly reliable method for one-step access to (poly)arylated heteroarenes. This method constitutes a promising alternative to existing methods, particularly the Stille, the Suzuki, or the Negishi coupling reactions [19]. The palladium-catalyzed C–H bond arylation approach exhibits a notable advantage as it circumvents the need for preliminary synthesis of organometallic derivatives. In the case of five-membered ring heteroarenes, the positions that exhibit the greatest reactivity in Pd-catalyzed C–H bond activation are generally C2 and C5, as evidenced by studies involving furan, thiophene, and pyrrole rings [20]. However, this approach is not without limitations when it comes to certain substrates, as the regioselectivity of the coupling process can be sometimes challenging to control [20]. The pyrazole scaffold has been identified as one of the most challenging substrates, as demonstrated in the seminal study by Sames and colleagues [21]. They reported that the reaction of 1-SEM-pyrazole (SEM = 2-(trimethylsilyl)ethoxymethyl) with bromobenzene resulted in the formation of 5-phenylpyrazole, 4-phenylpyrazole, and 4,5-diphenylpyrazole in a 4:1:3 ratio. As a result, due to the presence of the C4 and C5 free positions in a significant number of pyrazoles, several groups obtained mixtures of arylated products [22–26]. At present, the most reliable method for controlling the regioselectivity of Pd-catalyzed pyra-

zoles arylation at the C5 position is the introduction of a formyl [27,28], chloro [29,30], or bromo [31,32] blocking group at the C4 position of the pyrazole (Scheme 1, Equation (1)). The introduction of an ester substituent as a blocking group has the potential to be a highly practical approach, primarily due to the ease with which it can be removed following arylation and also due to its considerable potential in organic synthesis. However, the use of such ester substituents on pyrazoles as a blocking groups remains limited. Sames and coworkers described a single example of the C5-arylation of ethyl 1-SEM-pyrazole-4-carboxylate with bromobenzene as coupling partner using $\text{Pd}(\text{OAc})_2$ (5 mol%) associated to expensive and air-sensitive ligand $\text{P}(n\text{Bu})\text{Ad}_2$ (7.5 mol%) as the catalytic system (Scheme 1, Equation (2)) (for a study on the regioselectivity of the Pd-catalyzed CH arylation of pyrazoles [21]). Very recently, an enantioselective palladium-catalyzed C–H arylation of ethyl 1-methyl-3-(trifluoromethyl)pyrazole-4-carboxylate was reported, using $\text{Pd}(\text{OCOCF}_3)_2$ associated to a sophisticated phosphine ligand as the catalyst (Scheme 1, Equation (3)) [27]. The objective of the present study was to provide more robust evidence for the potential of an ester substituent as a blocking group at the C4 position of pyrazoles in Pd-catalyzed direct arylation. To achieve this objective, our study focused on the reactivity of ethyl 1-methylpyrazole-4-carboxylate (Scheme 1, Equation (4)). Herein we describe: (1) the conditions for the Pd-catalyzed regioselective C–H C5-arylation of ethyl 1-methylpyrazole-4-carboxylate without decarboxylation; (2) the spectrum of aryl bromides in this process; and (3) the conditions for the decarboxylation of a prepared 5-arylpyrazole derivative.

2. Results and discussion

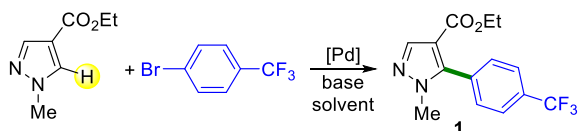
The reactivity of ethyl 1-methylpyrazole-4-carboxylate (1.5 equiv.) using 1-bromo-4-(trifluoromethyl)benzene (1 equiv.) as reaction partners in the presence of 5 mol% $\text{PdCl}(\text{C}_3\text{H}_5)(\text{dppb})$ catalyst [33] and a set of bases in DMA as the solvent, at 150 °C, was established (Table 1). This catalyst and solvent system had previously demonstrated its potential for Pd-catalyzed C–H bond arylation of five-membered ring heteroarenes [28]. Under these conditions, by using KOAc as the base, the desired C5-arylated pyrazole **1** was obtained in 88% yield



Scheme 1. Pd-catalyzed direct C5-arylation of 4-substituted pyrazoles.

(Table 1, entry 1). It should be mentioned that no trace of products coming from the decarboxylation of the pyrazole ring was detected during the course of this reaction. A very similar yield of 87% in product **1** was obtained using KO₂Piv as the base (Table 1, entry 2). The CsOAc base was also very effective, as **1** was isolated in 71% yield (Table 1, entry 3). Conversely, NaOAc resulted in the production of **1** in only 23% yield (Table 1, entry 4). The carbonate bases, namely K₂CO₃ and Cs₂CO₃, were less effective compared to KOAc or KO₂Piv, affording **1** in only 35% and 9% yields, respectively (Table 1, entries 5 and 6). These results are consistent with the Coordi-

nated Metalation Deprotonation (CMD) mechanism, where the base coordinates to the palladium complex to activate the C–H bond. The most effective bases in this CMD process have been shown to be acetates and pivalates [34–36]. Lowering the reaction temperature to 130 °C instead of 150 °C slightly decreased the yield in product **1** due to an incomplete conversion of 1-bromo-4-(trifluoromethyl)benzene (Table 1, entry 7). The effect of different solvents on the reaction yield was then evaluated. Both DMF and NMP resulted in slightly lower yields in **1** compared to the reaction carried out in DMA, while xylene and 3-methylbutan-1-ol were found to be much less

Table 1. Influence of the reaction conditions on the Pd-catalyzed arylation of ethyl 1-methylpyrazole-4-carboxylate with 1-bromo-4-(trifluoromethyl)benzene

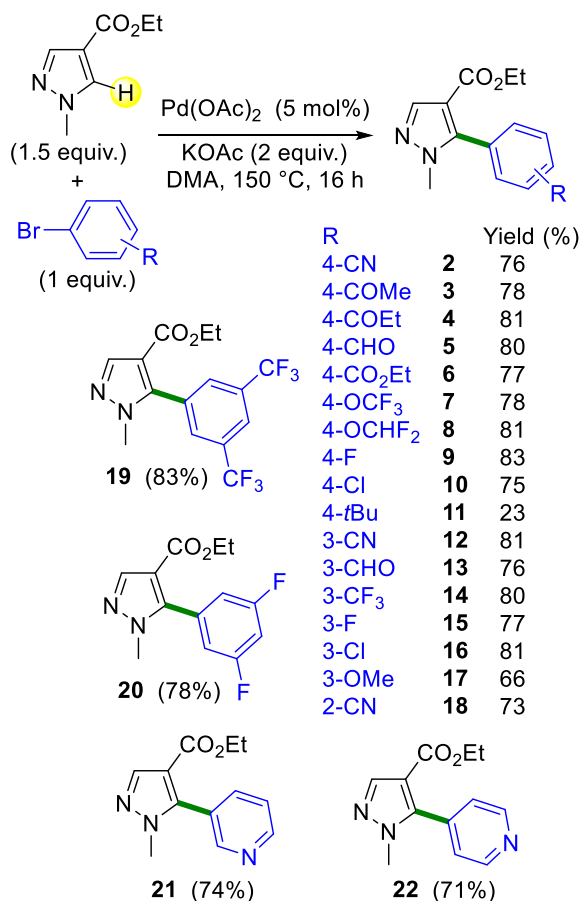
Entry	Catalyst	Solvent	Base	Temp. (°C)	Conv. (%)	Yield in 1 (%)
1	PdCl(C ₃ H ₅)(dppb)	DMA	KOAc	150	100	88
2	PdCl(C ₃ H ₅)(dppb)	DMA	KOPiv	150	100	87
3	PdCl(C ₃ H ₅)(dppb)	DMA	CsOAc	150	100	71
4	PdCl(C ₃ H ₅)(dppb)	DMA	NaOAc	150	100	23
5	PdCl(C ₃ H ₅)(dppb)	DMA	K ₂ CO ₃	150	100	35
6	PdCl(C ₃ H ₅)(dppb)	DMA	Cs ₂ CO ₃	150	100	9
7	PdCl(C ₃ H ₅)(dppb)	DMA	KOAc	130	95	84
8	PdCl(C ₃ H ₅)(dppb)	DMF	KOAc	150	100	80
9	PdCl(C ₃ H ₅)(dppb)	NMP	KOAc	150	100	67
10	PdCl(C ₃ H ₅)(dppb)	Xylene	KOAc	150	100	38
11	PdCl(C ₃ H ₅)(dppb)	3-methyl-butan-1-ol	KOAc	150	100	12
12	Pd(OAc) ₂	DMA	KOAc	150	100	85

Conditions: [Pd] (0.05 mmol), 1-bromo-4-(trifluoromethyl)benzene (1 mmol), ethyl 1-methylpyrazole-4-carboxylate (1.5 mmol), base (2 mmol), 16 h, conversion of 1-bromo-4-(trifluoromethyl)benzene, isolated yields.

effective than DMA (Table 1, entries 8–11). Finally, the desired product **1** was obtained in a very good yield (85%) using a phosphine-free catalyst, namely Pd(OAc)₂ (Table 1, entry 12).

Ethyl 1-methylpyrazole-4-carboxylate was then subjected to a series of Pd-catalyzed direct arylation reactions with a variety of *ortho*-, *meta*-, and *para*-substituted aryl bromides (Scheme 2). The reactions were carried out using the phosphine-free Pd(OAc)₂ catalyst (2 mol%), in the presence of KOAc as an inexpensive base, in DMA at 150 °C. Electron-deficient aryl bromides substituted at the *para* position with nitrile, acetyl, propionyl, formyl, ester, or trifluoromethoxy groups were selected as the reactant for the synthesis of C5-arylated pyrazoles. All these electron-deficient aryl bromides afforded the target compounds **2–8** in yields ranging from 76 to 81%. The presence of a fluorine substituent at the *para* position of the aryl bromide, which does not exert a significant electronic influence, resulted in a yield of product **9** comparable to that observed in the previous experiments. By using 4-bromo-1-chlorobenzene, the desired prod-

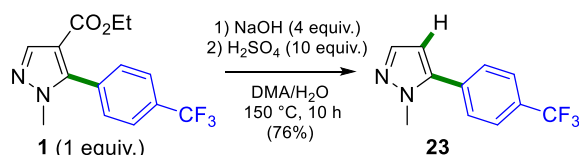
uct **10** was obtained in 75% yield. It is noteworthy that the C–Cl bond remained intact during the course of this reaction, thereby enabling subsequent transformations. It is also worth noting that the electron-rich 4-*tert*-butylbromobenzene afforded **11** in a low yield of 23%, which is due to the low conversion of the aryl bromide. From the electron-deficient nitrile, formyl and trifluoromethyl *meta*-substituted aryl bromides, the C5-arylated pyrazoles **12–14** were obtained in good yields. In a similar manner, 3-fluorobromobenzene and 3-bromo-1-chlorobenzene were converted into the target products **15** and **16** in 77% and 81% yield, respectively. In addition, when less activated 3-bromoanisole was used as the starting material, the target product **17** was produced in 66% yield. The reactivity of the *ortho*-substituted 2-bromobenzonitrile was also investigated. Again, the reaction was successful, and compound **18** was obtained in 73% yield. The disubstituted 1,3-bis(trifluoromethyl)-5-bromobenzene and 1-bromo-3,5-difluorobenzene also afforded the expected products **19** and **20** in good yields. In addition, the N-containing heteroaromatics



Scheme 2. Scope of the Pd-catalyzed direct C5-arylation of ethyl 1-methylpyrazole-4-carboxylate.

3- and 4-bromopyridines were found to be effective reagents in the synthesis of the desired heteroarylated pyrazoles **21** and **22**, with isolated yields of 74 and 71%, respectively. Therefore, a comparison of our method with previous ones employing an ester blocking group [21,27] (Scheme 1, b and c), reveals several advantages: our procedure is phosphine-free, a cost-effective base is employed, and several functional groups at the *para*, *meta*, and *ortho* positions of the aryl bromide are tolerated.

The decarboxylation of pyrazole-4-carboxylates has previously been described by several research groups [37–39]. In order to further demonstrate the effectiveness of using an ester substituent as a removable blocking group on pyrazoles, the decarboxylation of ethyl 1-methyl-5-



Scheme 3. Decarboxylation of ethyl 1-methyl-5-(4-(trifluoromethyl)phenyl)pyrazole-4-carboxylate.

(4-(trifluoromethyl)phenyl)pyrazole-4-carboxylate **1** was achieved (Scheme 3). Under basic conditions followed by acidification, in DMA at 150 °C, a complete decarboxylation was observed, resulting in the formation of the desired 1-methyl-5-(4-(trifluoromethyl)phenyl)pyrazole **23** in 76% yield.

In summary, the results of this study show that an ester function is an effective and easily removable blocking group at the C4 position of a pyrazole, which enables a regioselective arylation at the C5 position. The reaction exhibits high tolerance to a wide array of functional groups, at the *para*, *meta*, and even *ortho* positions of the aryl bromides. It should be noted that the ester function remained unaltered by the reaction conditions. The utility of ester substituents in a variety of organic reactions, as well as their easy elimination has been well-documented. Therefore, using such blocking groups on pyrazoles is an attractive approach. Furthermore, the use of only 2 mol% of an air-stable phosphine-free palladium catalyst in conjunction with KOAc as an inexpensive base renders this one-step process highly appealing for the synthesis of 5-arylpyrazole derivatives.

2.1. Experimental section

2.1.1. General

Pd(OAc)₂ (98%) was purchased from Aldrich. DMA (99+%) extra pure and KOAc (99%) were purchased from Acros. Ethyl 1-methylpyrazole-4-carboxylate (95%) was purchased from Doug Discovery. These compounds were not purified before use. All reagents were weighed and handled in air. All reactions were carried out under an inert atmosphere with standard Schlenk techniques. ¹H, ¹⁹F and ¹³C NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer. Melting points were determined with a Kofler hot bench

system. High-resolution mass spectra were measured on a Thermo Fisher Q-Exactive spectrometer. Flash column chromatography was performed using Macherey-Nagel silica 60 M (0.04–0.063 mm).

2.1.2. General procedure for palladium-catalyzed direct C5-arylations of ethyl 1-methylpyrazole-4-carboxylate

To a 25 mL oven-dried Schlenk tube, aryl bromide (1 mmol, 1 equiv.), ethyl 1-methylpyrazole-4-carboxylate (0.231 g, 1.5 mmol, 1.5 equiv.), KOAc (0.196 g, 2 mmol, 2 equiv.) and Pd(OAc)₂ (11.2 mg, 0.05 mmol, 0.05 equiv.) and DMA (4 mL) were successively added. The reaction mixture was evacuated by vacuum-argon cycles (5 times) and stirred at 150 °C (oil bath temperature) for 16 h. After cooling the reaction at room temperature and concentration, the crude mixture was purified by flash column chromatography on silica gel to afford the C5-arylated ethyl 1-methylpyrazole-4-carboxylate derivatives.

2.1.3. Ethyl 1-methyl-5-(4-(trifluoromethyl)phenyl)pyrazole-4-carboxylate (**1**)

From 1-bromo-4-(trifluoromethyl)benzene (0.225 g, 1 mmol) and ethyl 1-methylpyrazole-4-carboxylate (0.231 g, 1.5 mmol), product **1** was obtained in 85% yield (0.253 g) as a yellow solid: mp 96–98 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.02 (s, 1H), 7.78 (d, *J* = 8.1 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ –63.0. ¹³C NMR (101 MHz, CDCl₃) δ 162.7, 144.4, 141.2, 132.8, 131.5 (q, *J* = 32.8 Hz), 130.5, 125.2 (q, *J* = 3.8 Hz), 123.8 (q, *J* = 272.4 Hz), 113.2, 60.0, 37.4, 14.1. HRMS calcd for [M+H]⁺ C₁₄H₁₄N₂O₂F₃ 299.1002, found 299.1002.

2.1.4. Ethyl 5-(4-cyanophenyl)-1-methylpyrazole-4-carboxylate (**2**)

From 4-bromobenzonitrile (0.182 g, 1 mmol) and ethyl 1-methylpyrazole-4-carboxylate (0.231 g, 1.5 mmol), product **2** was obtained in 76% yield (0.194 g) as a colorless solid: mp 117–119 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.02 (s, 1H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 162.6, 143.8, 141.3, 133.8, 132.0, 130.9, 118.2, 113.4, 60.1, 37.5, 14.1. HRMS calcd for [M+H]⁺ C₁₄H₁₄N₃O₂ 256.1080, found 256.1080.

2.1.5. Ethyl 5-(4-acetylphenyl)-1-methylpyrazole-4-carboxylate (**3**)

From 4-bromoacetophenone (0.199 g, 1 mmol) and ethyl 1-methylpyrazole-4-carboxylate (0.231 g, 1.5 mmol), product **3** was obtained in 78% yield (0.212 g) as a colorless solid: mp 79–81 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.09 (d, *J* = 8.4 Hz, 2H), 8.02 (s, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 2.68 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 197.4, 162.8, 144.8, 141.2, 137.6, 133.7, 130.4, 128.2, 113.2, 60.0, 37.4, 26.7, 14.1. HRMS calcd for [M+H]⁺ C₁₅H₁₇N₂O₃ 273.1234, found 273.1233.

2.1.6. Ethyl 1-methyl-5-(4-propionylphenyl)pyrazole-4-carboxylate (**4**)

From 4-bromopropiophenone (0.213 g, 1 mmol) and ethyl 1-methylpyrazole-4-carboxylate (0.231 g, 1.5 mmol), product **4** was obtained in 81% yield (0.232 g) as a colorless solid: mp 77–78 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, *J* = 8.5 Hz, 2H), 8.02 (s, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 3.08 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.20 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 200.1, 162.8, 144.8, 141.2, 137.4, 133.5, 130.3, 127.8, 113.1, 60.0, 37.4, 31.9, 14.1, 8.2. HRMS calcd for [M+H]⁺ C₁₆H₁₉N₂O₃ 287.1390, found 287.1390.

2.1.7. Ethyl 5-(4-formylphenyl)-1-methylpyrazole-4-carboxylate (**5**)

From 4-bromobenzaldehyde (0.185 g, 1 mmol) and ethyl 1-methylpyrazole-4-carboxylate (0.231 g, 1.5 mmol), product **5** was obtained in 80% yield (0.206 g) as a yellow solid: mp 107–109 °C. ¹H NMR (400 MHz, CDCl₃) δ 10.13 (s, 1H), 8.04–8.02 (m, 3H), 7.60 (d, *J* = 8.2 Hz, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 191.5, 162.7, 144.5, 141.3, 136.7, 135.1, 130.8, 129.4, 113.3, 60.1, 37.5, 14.1. HRMS calcd for [M+H]⁺ C₁₄H₁₅N₂O₃ 259.1077, found 259.1077.

2.1.8. Ethyl 5-(4-(ethoxycarbonyl)phenyl)-1-methylpyrazole-4-carboxylate (**6**)

From ethyl 4-bromobenzoate (0.229 g, 1 mmol) and ethyl 1-methylpyrazole-4-carboxylate (0.231 g, 1.5 mmol), product **6** was obtained in 77% yield (0.232 g) as a yellow solid: mp 69–71 °C. ¹H NMR

(400 MHz, CDCl_3) δ 8.18 (d, J = 8.3 Hz, 2H), 8.02 (s, 1H), 7.48 (d, J = 8.3 Hz, 2H), 4.44 (q, J = 7.1 Hz, 2H), 4.17 (q, J = 7.1 Hz, 2H), 3.75 (s, 3H), 1.44 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.0, 162.8, 144.8, 141.2, 133.5, 131.3, 130.1, 129.4, 113.1, 61.3, 60.0, 37.4, 14.3, 14.1. HRMS calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_4$ 303.1339, found 303.1339.

2.1.9. Ethyl 1-methyl-5-(4-(trifluoromethoxy)phenyl)pyrazole-4-carboxylate (**7**)

From 1-bromo-4-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and ethyl 1-methylpyrazole-4-carboxylate (0.231 g, 1.5 mmol), product **7** was obtained in 78% yield (0.245 g) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 8.00 (s, 1H), 7.44 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 7.8 Hz, 2H), 4.17 (q, J = 7.1 Hz, 2H), 3.75 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -57.8. ^{13}C NMR (101 MHz, CDCl_3) δ 162.8, 149.9 (q, J = 1.9 Hz), 144.5, 141.2, 131.7, 127.7, 120.6, 120.2 (q, J = 258.1 Hz), 113.07, 60.0, 37.4, 14.0. HRMS calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_3\text{F}_3$ 315.0951, found 315.0950.

2.1.10. Ethyl 5-(4-(difluoromethoxy)phenyl)-1-methylpyrazole-4-carboxylate (**8**)

From 1-bromo-4-(difluoromethoxy)benzene (0.223 g, 1 mmol) and ethyl 1-methylpyrazole-4-carboxylate (0.231 g, 1.5 mmol), product **8** was obtained in 81% yield (0.240 g) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.01 (s, 1H), 7.42 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 8.7 Hz, 2H), 6.61 (t, J = 73.4 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.76 (s, 3H), 1.22 (t, J = 7.1 Hz, 4H). ^{19}F NMR (376 MHz, CDCl_3) δ -81.6. ^{13}C NMR (101 MHz, CDCl_3) δ 162.9, 151.9 (t, J = 3.0 Hz), 144.8, 141.2, 131.7, 126.1, 119.2, 115.6 (t, J = 260.7 Hz), 112.9, 59.9, 37.3, 14.1. HRMS calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{14}\text{H}_{15}\text{F}_2\text{N}_2\text{O}_3$ 297.1045, found 297.1045.

2.1.11. Ethyl 5-(4-fluorophenyl)-1-methylpyrazole-4-carboxylate (**9**)

From 1-bromo-4-fluorobenzene (0.175 g, 1 mmol) and ethyl 1-methylpyrazole-4-carboxylate (0.231 g, 1.5 mmol), product **9** was obtained in 83% yield (0.206 g) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 8.00 (s, 1H), 7.41–7.37 (m, 2H), 7.20 (t, J = 8.6 Hz, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.75 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -111.3. ^{13}C NMR (101 MHz, CDCl_3) δ 163.3 (J = 249.6 Hz), 162.9, 144.9, 141.2, 139 (d, J = 8.5 Hz), 125.0, 115.5

(d, J = 22.0 Hz), 112.9, 59.9, 37.3, 14.1. HRMS calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_2\text{F}$ 249.1034, found 249.1033.

2.1.12. Ethyl 5-(4-chlorophenyl)-1-methylpyrazole-4-carboxylate (**10**) [40]

From 1-bromo-4-chlorobenzene (0.192 g, 1 mmol) and ethyl 1-methylpyrazole-4-carboxylate (0.231 g, 1.5 mmol), product **10** was obtained in 75% yield (0.199 g) as a colorless solid: mp 123–125 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.01 (s, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 4.17 (q, J = 7.2 Hz, 2H), 3.76 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 162.6, 143.8, 141.3, 133.8, 132.0, 130.9, 118.2, 113.4, 60.2, 37.5, 14.1. HRMS calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{13}\text{H}_{14}\text{ClN}_2\text{O}_2$ 265.0738, found 265.0738.

2.1.13. Ethyl 5-(4-(tert-butyl)phenyl)-1-methylpyrazole-4-carboxylate (**11**)

From 1-bromo-4-(tert-butyl)benzene (0.213 g, 1 mmol) and ethyl 1-methylpyrazole-4-carboxylate (0.231 g, 1.5 mmol), product **11** was obtained in 23% yield (0.066 g) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.00 (s, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.77 (s, 3H), 1.39 (s, 9H), 1.20 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 163.1, 152.4, 146.2, 141.1, 129.6, 125.9, 125.2, 112.5, 59.8, 37.4, 34.8, 31.3, 14.1. HRMS calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{17}\text{H}_{23}\text{N}_2\text{O}_2$ 287.1754, found 287.1753.

2.1.14. Ethyl 5-(3-cyanophenyl)-1-methylpyrazole-4-carboxylate (**12**)

From 3-bromobenzonitrile (0.182 g, 1 mmol) and ethyl 1-methylpyrazole-4-carboxylate (0.231 g, 1.5 mmol), product **12** was obtained in 81% yield (0.207 g) as a yellow solid: mp 137–139 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.02 (s, 1H), 7.80 (ddd, J = 6.5, 2.5, 1.6 Hz, 1H), 7.72 (s, 1H), 7.68–7.61 (m, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.77 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 162.6, 143.3, 141.3, 134.4, 133.6, 132.9, 130.6, 129.3, 118.0, 113.4, 112.9, 60.1, 37.5, 14.1. HRMS calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{14}\text{H}_{14}\text{N}_3\text{O}_2$ 256.1080, found 256.1080.

2.1.15. Ethyl 5-(3-formylphenyl)-1-methylpyrazole-4-carboxylate (**13**)

From 3-bromobenzaldehyde (0.185 g, 1 mmol) and ethyl 1-methylpyrazole-4-carboxylate (0.231 g,

1.5 mmol), product **13** was obtained in 76% yield (0.196 g) as a yellow solid: mp 94–96 °C. ^1H NMR (400 MHz, CDCl_3) δ 10.10 (s, 1H), 8.04–7.99 (m, 2H), 7.93 (s, 1H), 7.71–7.65 (m, 2H), 4.17 (q, $J = 7.1$ Hz, 2H), 3.78 (s, 3H), 1.19 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 191.4, 162.7, 144.4, 141.2, 136.4, 135.9, 131.1, 130.5, 130.2, 129.1, 113.2, 60.0, 37.4, 14.1. HRMS calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}_3$ 259.1077, found 259.1078.

2.1.16. *Ethyl 1-methyl-5-(3-(trifluoromethyl)phenyl)pyrazole-4-carboxylate (14)*

From 1-bromo-3-(trifluoromethyl)benzene (0.225 g, 1 mmol) and ethyl 1-methylpyrazole-4-carboxylate (0.231 g, 1.5 mmol), product **14** was obtained in 80% yield (0.238 g) as a yellow solid: mp 85–87 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.03 (s, 1H), 7.78 (d, $J = 8.2$ Hz, 1H), 7.68 (s, 1H), 7.65–7.60 (m, 2H), 4.17 (q, $J = 7.1$ Hz, 2H), 3.77 (s, 3H), 1.16 (t, $J = 7.1$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ –62.7. ^{13}C NMR (101 MHz, CDCl_3) δ 162.7, 144.1, 141.3, 133.4, 130.8 (q, $J = 32.8$ Hz), 130.0, 128.9, 127.0 (q, $J = 3.8$ Hz), 126.1 (q, $J = 3.7$ Hz), 123.8 (q, $J = 272.5$ Hz), 113.3, 60.1, 37.4, 14.0. HRMS calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_2\text{F}_3$ 299.1002, found 299.1001.

2.1.17. *Ethyl 5-(3-fluorophenyl)-1-methylpyrazole-4-carboxylate (15)*

From 1-bromo-3-fluorobenzene (0.175 g, 1 mmol) and ethyl 1-methylpyrazole-4-carboxylate (0.231 g, 1.5 mmol), product **15** was obtained in 77% yield (0.191 g) as a colorless solid: mp 79–81 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.01 (s, 1H), 7.51–7.45 (m, 1H), 7.23–7.12 (m, 3H), 4.19 (q, $J = 7.1$ Hz, 2H), 3.76 (s, 3H), 1.20 (t, $J = 7.1$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ –112.5. ^{13}C NMR (101 MHz, CDCl_3) δ 162.8, 162.2 (d, $J = 247.3$ Hz), 144.5, 141.2, 131.1 (d, $J = 8.3$ Hz), 129.9 (d, $J = 8.3$ Hz), 125.7 (d, $J = 3.2$ Hz), 117.2 (d, $J = 22.6$ Hz), 116.4 (d, $J = 20.9$ Hz), 113.1, 59.9, 37.4, 14.1. HRMS calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_2\text{F}$ 249.1034, found 249.1033.

2.1.18. *Ethyl 5-(3-chlorophenyl)-1-methylpyrazole-4-carboxylate (16)*

From 1-bromo-3-chlorobenzene (0.192 g, 1 mmol) and ethyl 1-methylpyrazole-4-carboxylate (0.231 g, 1.5 mmol), product **16** was obtained in 81% yield (0.214 g) as a colorless oil. ^1H NMR (400 MHz,

CDCl_3) δ 8.01 (s, 1H), 7.52–7.39 (m, 4H), 4.17 (q, $J = 7.1$ Hz, 2H), 3.76 (s, 3H), 1.21 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 162.8, 144.3, 141.2, 134.2, 130.8, 130.1, 129.6, 129.5, 128.2, 113.1, 60.00, 37.4, 14.1. HRMS calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{13}\text{H}_{14}\text{ClN}_2\text{O}_2$ 265.0738, found 265.0738.

2.1.19. *Ethyl 5-(3-methoxyphenyl)-1-methylpyrazole-4-carboxylate (17)*

From 1-bromo-3-methoxybenzene (0.187 g, 1 mmol) and ethyl 1-methylpyrazole-4-carboxylate (0.231 g, 1.5 mmol), product **17** was obtained in 66% yield (0.172 g) as a yellow solid: mp 87–89 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.99 (s, 1H), 7.40 (dd, $J = 8.4$, 7.5 Hz, 1H), 7.02 (ddd, $J = 8.4$, 2.6, 1.0 Hz, 1H), 6.95 (dt, $J = 7.5$, 1.2 Hz, 1H), 6.92 (dd, $J = 2.6$, 1.5 Hz, 1H), 4.17 (q, $J = 7.1$ Hz, 2H), 3.85 (s, 3H), 3.75 (s, 3H), 1.19 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 162.9, 159.3, 145.7, 141.1, 130.3, 129.4, 122.2, 115.7, 114.8, 112.8, 59.8, 55.3, 37.4, 14.1. HRMS calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{14}\text{H}_{17}\text{N}_2\text{O}_3$ 261.1234, found 261.1232.

2.1.20. *Ethyl 5-(2-cyanophenyl)-1-methylpyrazole-4-carboxylate (18)*

From 2-bromobenzonitrile (0.182 g, 1 mmol) and ethyl 1-methylpyrazole-4-carboxylate (0.231 g, 1.5 mmol), product **18** was obtained in 73% yield (0.186 g) as a yellow solid: mp 86–88 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.05 (s, 1H), 7.85 (dd, $J = 7.8$, 1.4 Hz, 1H), 7.75 (td, $J = 7.7$, 1.4 Hz, 1H), 7.63 (td, $J = 7.7$, 1.4 Hz, 1H), 7.48 (dd, $J = 7.8$, 1.3 Hz, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 3.77 (s, 3H), 1.19 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 162.4, 141.7, 141.2, 133.1, 133.0, 132.6, 131.2, 129.9, 116.9, 114.4, 114.1, 60.1, 37.3, 14.0. HRMS calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{14}\text{H}_{14}\text{N}_3\text{O}_2$ 256.1080, found 256.1083.

2.1.21. *Ethyl 5-(3,5-bis(trifluoromethyl)phenyl)-1-methylpyrazole-4-carboxylate (19)*

From 1-bromo-3,5-bis(trifluoromethyl)benzene (0.293 g, 1 mmol) and ethyl 1-methylpyrazole-4-carboxylate (0.231 g, 1.5 mmol), product **19** was obtained in 83% yield (0.304 g) as a colorless solid: mp 119–121 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.06 (s, 1H), 8.03 (s, 1H), 7.89 (s, 2H), 4.18 (q, $J = 7.2$ Hz, 2H), 3.80 (s, 3H), 1.16 (t, $J = 7.2$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ –62.9. ^{13}C NMR (101 MHz, CDCl_3) δ 162.3, 142.3, 141.5, 131.9 (q,

$J = 34.0$ Hz), 131.4, 130.5 (q, $J = 3.7$ Hz), 123.2 (m), 122.9 (q, $J = 273.1$ Hz), 113.9, 60.3, 37.5, 13.9. HRMS calcd for $[M+H]^+$ $C_{15}H_{13}F_6N_2O_2$ 367.0876, found 367.0876.

2.1.22. Ethyl 5-(3,5-difluorophenyl)-1-methylpyrazole-4-carboxylate (**20**)

From 1-bromo-3,5-difluorobenzene (0.193 g, 1 mmol) and ethyl 1-methylpyrazole-4-carboxylate (0.231 g, 1.5 mmol), product **20** was obtained in 78% yield (0.208 g) as a colorless solid: mp 110–112 °C. 1H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 6.98–6.92 (m, 3H), 4.19 (q, $J = 7.1$ Hz, 2H), 3.77 (s, 3H), 1.22 (t, $J = 7.1$ Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ –108.9. ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7 (dd, $J = 249.9$, 12.8 Hz), 162.6, 143.3, 141.2, 132.0 (t, $J = 8.0$ Hz), 113.3 (m), 105.0 (t, $J = 24.9$ Hz), 60.1, 37.5, 14.1. HRMS calcd for $[M+H]^+$ $C_{13}H_{13}F_2N_2O_2$ 267.0940, found 267.0940.

2.1.23. Ethyl 1-methyl-5-(pyridin-3-yl)pyrazole-4-carboxylate (**21**)

From 3-bromopyridine (0.157 g, 1 mmol) and ethyl 1-methylpyrazole-4-carboxylate (0.231 g, 1.5 mmol), product **21** was obtained in 74% yield (0.171 g) as a yellow solid: mp 109–111 °C. 1H NMR (400 MHz, $CDCl_3$) δ 8.74 (dd, $J = 4.9$, 1.7 Hz, 1H), 8.67–8.62 (m, 1H), 8.05 (s, 1H), 7.80–7.74 (m, 1H), 7.46 (ddd, $J = 7.9$, 4.9, 0.9 Hz, 1H), 4.18 (q, $J = 7.2$ Hz, 2H), 3.80 (s, 3H), 1.20 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 150.4, 150.3, 142.5, 141.4, 137.7, 125.4, 123.0, 113.7, 60.1, 37.5, 14.1. HRMS calcd for $[M+H]^+$ $C_{12}H_{14}N_3O_2$ 232.1080, found 232.1079.

2.1.24. Ethyl 1-methyl-5-(pyridin-4-yl)pyrazole-4-carboxylate (**22**)

From 4-bromopyridine (0.157 g, 1 mmol) and ethyl 1-methylpyrazole-4-carboxylate (0.231 g, 1.5 mmol), product **22** was obtained in 71% yield (0.164 g) as a colorless solid: mp 97–99 °C. 1H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, $J = 6.0$ Hz, 2H), 8.03 (s, 1H), 7.35 (d, $J = 6.0$ Hz, 2H), 4.19 (q, $J = 7.1$ Hz, 2H), 3.78 (s, 3H), 1.21 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 149.9, 143.0, 141.3, 137.3, 124.6, 113.4, 60.2, 37.5, 14.1. HRMS calcd for $[M+H]^+$ $C_{12}H_{14}N_3O_2$ 232.1080, found 232.1080.

2.1.25. 1-Methyl-5-(4-(trifluoromethyl)phenyl)pyrazole (**23**) [23]

A mixture of **1** (0.149 g, 0.5 mmol) and 2 N aqueous NaOH (1 mL, 2 mmol) in DMA (1 mL) was stirred at 100 °C for 1 h. After cooling, the mixture was acidified by H_2SO_4 (0.25 mL, 5 mmol) and stirred at 150 °C for 10 h. The mixture was basicified by 2 N aqueous NaOH and extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to yield **23** (0.86 g, 76%) as a colorless oil. 1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, $J = 7.8$ Hz, 2H), 7.57 (d, $J = 7.8$ Hz, 2H), 7.56 (dd, $J = 2.0$ Hz, 1H), 6.39 (d, $J = 2.0$ Hz, 1H), 3.94 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.7. ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1, 138.8, 134.3, 130.5 (q, $J = 32.7$ Hz), 129.0, 125.7 (q, $J = 3.8$ Hz), 124.0 (q, $J = 272.3$ Hz), 106.7, 37.6.

Declaration of interests

The authors do not work for, advise, own shares in, or receive funds from any organization that could benefit from this article, and have declared no affiliations other than their research organizations.

Acknowledgment

We are grateful to the Scientific Ministry of Higher Education and Research of Tunisia for providing financial support to AR.

Supplementary data

Supporting information for this article is available on the journal's website under <https://doi.org/10.5802/crchim.403> or from the author.

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