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N-heterocyclic carbene-Pd(II)-1-methylimidazole complex-catalyzed Suzuki-Miyaura coupling of 2-chloro-4-aminoquinazolines with arylboronic acids

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ABSTRACT

The Suzuki-Miyaura coupling between 2-chloro-4-aminoquinazolines and arylboronic acids catalyzed by the well-defined N-heterocyclic carbene-PdCl₂-1-methylimidazole complex was performed at room temperature, giving the desired products in good to high yields. Through this methodology, a variety of 2-aryl-4-aminoquinazoline derivatives with potential pharmaceutical activities can be achieved under mild reaction conditions.

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1. Introduction

2-Aryl-4-aminoquinazolines are interesting compounds in biological and pharmaceutical chemistry [1]. For example, 4-((2-phenylquinazolin-4-yl)amino)benzonitrile **I** was found to show high inhibitory activities toward the ATP-binding cassette transport proteins [1c,1e]. N-(3-Nitrophenyl)-2-phenylquinazolin-4-amine **II** was reported to be potential inhibitor for breast cancer resistance protein [1d]. N-4-Tolyl-2-(3,4,5-trimethoxyphenyl)quinazolin-4-amine **III** was found to be a good inhibitor for the proliferation of T cells from human peripheral blood mononuclear cells and Jurkat cells (Fig. 1) [1g].

Consequently, some different methods have been developed for the synthesis of 2-aryl-4-aminoquinazolines. For example, such compounds can be obtained by the cyclization of N,N'-disubstituted thioureas under ultraviolet light irradiation (Scheme 1, route a) [2]. N-Arylamino-1,3-diazabuta-1,3-dienes are also reported as the starting materials for the synthesis of 2-aryl-4-aminoquinazolines via electrocycloaddition (Scheme 1, route b) [3]. The reactions of 2-aryl-4-chloroquinazolines, usually prepared from the 4-oxo

derivatives, with amines under normal heating or microwave irradiation are the most popular pathway for the synthesis of 2-aryl-4-aminoquinazolines (Scheme 1, route c) [1a-g,4]. The palladium-phosphine system-catalyzed Suzuki-Miyaura coupling reactions of 2-chloro-4-aminoquinazolines with arylboronic acids was also used for the synthesis of 2-aryl-4-aminoquinazolines (Scheme 1, route d) [1h,5]. It seems that the palladium-catalyzed Suzuki-Miyaura coupling between 2-chloro-4-aminoquinazolines and arylboronic acids is an interesting alternative due to its broad substrate tolerance. However, the reported methods still suffer from the drawbacks of harsh reaction conditions such as high temperature and complicated procedure. Therefore, much room still remains for such method especially under mild conditions and easy operation. In the present work, a well-defined and easily available N-heterocyclic carbene-Pd(II)-1-methylimidazole [NHC-Pd(II)-Im] complex **1** catalyzed Suzuki-Miyaura coupling [6] of 2-chloro-4-aminoquinazolines **2** [7] with arylboronic acids **3** was reported, which can be performed at room temperature, with good to high yields for a variety of starting materials.

2. Results and discussion

First, initial studies were carried out using 2-chloro-4-

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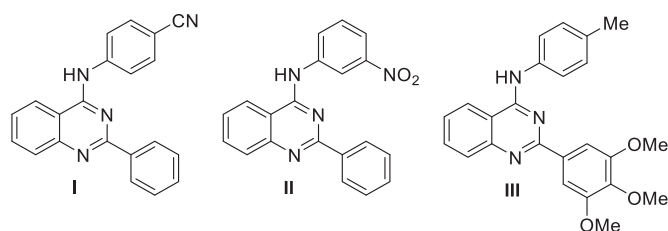
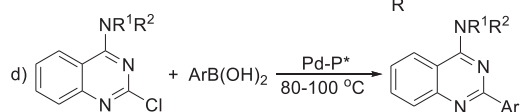
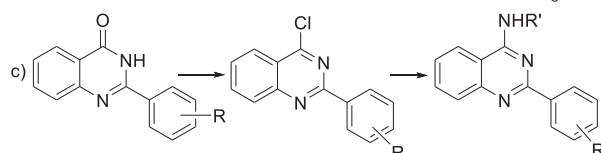
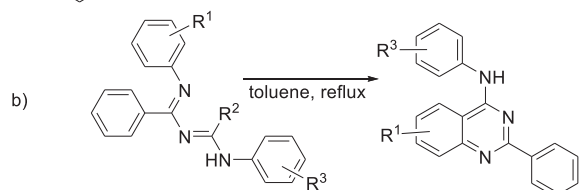
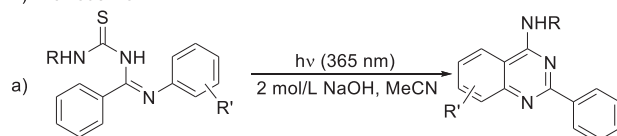
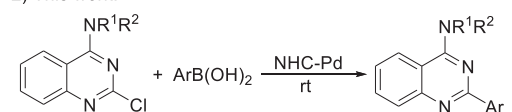


Fig. 1. Representative structure of 2-aryl-4-amino-quinazolines having pharmaceutical activities.

1) Previous work:



2) This work:



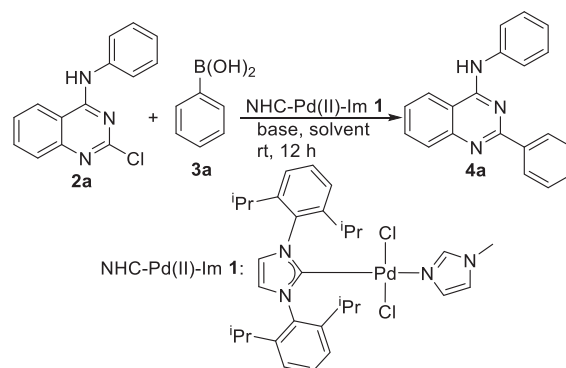
Scheme 1. Synthesis of 2-aryl-4-aminoquinazolines.

anilinoquinazoline **2a** (0.4 mmol) and phenylboronic acid **3a** (0.5 mmol) as the substrates, NHC-Pd(II)-Im complex **1** (1.0 mol%) as the catalyst, EtOH (2.0 mL) as the solvent at room temperature for 12 h to test some conventional inorganic bases (2.0 equiv). High yields were observed when NaOH, K₂CO₃ and KOH were used (Table 1, entries 1–3). Moderate to good yields can also be obtained if KO^tBu, Cs₂CO₃, K₃PO₄·3H₂O and LiOH were tested (Table 1, entries 4–7). When weak bases such as Na₂CO₃, KOAc, NaHCO₃ and KHCO₃ were used, very low yields (<10%) were found. Using KOH as the base, some common solvents were then investigated. In these cases, ⁿPrOH gave the best result, giving product **4a** in 98% yield (Table 1, entry 9). In ⁱPrOH and MeOH, 31 and 48% yields were observed, respectively (Table 1, entries 8 and 10). In all other solvents such as dioxane, DMSO, ^tBuOH and H₂O, almost no reaction occurred or very low yields (<5%) were given. Considering the cost and easy availability, the optimal conditions were then established using KOH (2.0 equiv) as the base and EtOH (2.0 mL) as the solvent (Table 1, entry 3).

Since 2-(3,4,5-trimethoxyphenyl)quinazolin-4-amine derivatives had some activity in the inhibition of the proliferation of T cells [1g], the reactions between a variety of 2-chloro-4-

Table 1

Optimization for the NHC-Pd(II)-Im complex **1**-catalyzed reaction of 2-chloro-4-anilinoquinazoline **2a** with phenylboronic acid **3a**.



Entry ^a	Base	Solvent	Yield (%) ^b
1	NaOH	EtOH	91
2	K ₂ CO ₃	EtOH	96
3	KOH	EtOH	95
4	KO ^t Bu	EtOH	83
5	Cs ₂ CO ₃	EtOH	73
6	K ₃ PO ₄ ·3H ₂ O	EtOH	77
7	LiOH	EtOH	58
8	KOH	ⁱ PrOH	31
9	KOH	ⁿ PrOH	98
10	KOH	MeOH	48

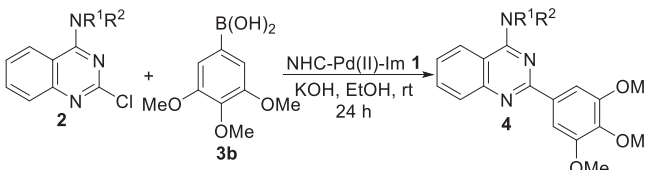
^a All reactions were carried out using **2a** (0.4 mmol), **3a** (0.5 mmol), NHC-Pd(II)-Im **1** (1.0 mol%), base (2.0 equiv) in solvent (2.0 mL) at rt for 12 h.

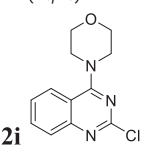
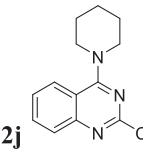
^b Isolated yields.

aminoquinazolines **2** and 3,4,5-trimethoxyphenylboronic acid **3b** were first investigated under the optimal conditions. The results are shown in Table 2. All reactions performed well to give the desired products in good to high yields. Substituents on the amino group have some effect on the reactions. For instance, for the anilino-substituted substrates **2**, the best yield was achieved when the electron-poor fluorine atom was attached on the *para*-position (Table 2, entry 5), and better yields were obtained when the electron-rich methyl and methoxy groups were used (Table 2, entries 2–4). Finally, the worst yield was found when the electron-neutral aniline substituted **2a** was used as the substrate (Table 2, entry 1). To our pleasure, once the free NH was replaced by methyl group, high yield can be still achieved (Table 1, entries 6 vs 1). Alkyl amino-substituted substrates **2g–j** are also suitable for such coupling reaction, giving the desired products **4h–k** in 73–96% yields (Table 2, entries 7–10). It may be noted here that compared to the previous method performed in refluxing mixture solvent of ethylene glycol dimethyl ether/water [1h], the current one can take place at room temperature with higher yields.

Based on the above results, the reactions of kinds of 2-chloro-4-aminoquinazolines **2** and arylboronic acids **3** were further carried out to test the limitation and scope of such methodology. As can be seen from Table 3, all reactions performed smoothly under the optimal conditions to give products **4** in good to high yields. In these cases, it seems that substituents on both substrates do not affect the reactions significantly. For instance, for all substituents shown in Table 3, such as electron-rich, -neutral, -poor and sterically-hindered ones on the anilino-groups of substrates **2** and on the phenyl rings of arylboronic acids **3**, are all tolerated under the reaction conditions, giving products **4** in 80–99% yields (Table 3, entries 1–10). In addition, alkyl amino-substituted substrates **2** are also good partners with various arylboronic acids **3**, giving the corresponding products **4v–4ac** in 81–99% yields

Table 2
NHC-Pd(II)-Im complex **1**-catalyzed reactions of 2-chloro-4-aminoquinazolines **2** with 3,4,5-trimethoxyphenylboronic acid **3b**.



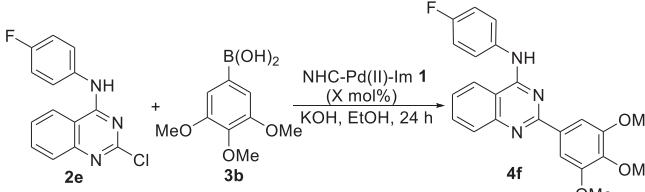
Entry ^a	2 (R ¹ /R ²)	Yield (%) ^b
1	2a (H/C ₆ H ₅)	4b , 76
2	2b (H/2-MeC ₆ H ₄)	4c , 93
3	2c (H/4-MeC ₆ H ₄)	4d , 89
4	2d (H/4-MeOC ₆ H ₄)	4e , 80
5	2e (H/4-FC ₆ H ₄)	4f , 97
6	2f (Me/C ₆ H ₅)	4g , 95
7	2g (Me/benzyl)	4h , 82
8	2h (Et/Et)	4i , 96
9		4j , 73
10		4k , 88
		

^a All reactions were carried out using **2** (0.4 mmol), **3b** (0.5 mmol), NHC-Pd(II)-Im **1** (1.0 mol%), KOH (2.0 equiv) in EtOH (2.0 mL) at rt for 24 h.

^b Isolated yields.

(Table 3, entries 11–18). It should be noted here that for the reactions involving arylboronic acids bearing strongly electron-poor groups such as ester group, nitro group and acetyl group, no desired product was given.

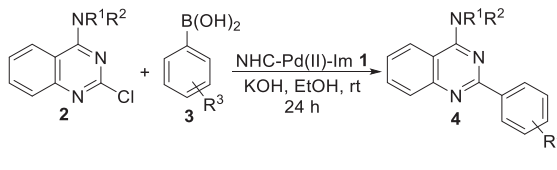
To further investigate the applicability of this methodology, the model reaction of 2-chloro-*N*-(4-fluorophenyl)quinazolin-4-amine **2e** with 3,4,5-trimethoxyphenylboronic acid **3b** was performed under identical conditions at lower catalyst loadings. As can be seen from Scheme 2, the same yield was obtained under the same reaction conditions when the catalyst loading decreased from 1.0 to 0.1 mol%. Comparable high yield can still be achieved at elevated

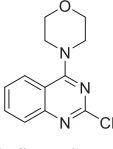


[X]	Temp	Yield (%)
1.0	rt	97
0.1	rt	97
0.01	50 °C	93
0.001	70 °C	74

Scheme 2. Reaction of **2e** with **3b** at varied catalyst loading.

Table 3
NHC-Pd(II)-Im complex **1**-catalyzed reactions of 2-chloro-4-aminoquinazolines **2** with arylboronic acids.



Entry ^a	2 (R ¹ /R ²)	3 (R ³)	Yield (%) ^b
1	2a (H/C ₆ H ₅)	3c (3-F)	4l , 98
2	2c (H/4-MeC ₆ H ₄)	3a (H)	4m , 90
3	2c	3d (4-Me)	4n , 87
4	2d (H/4-MeOC ₆ H ₄)	3d	4o , 99
5	2e (H/4-FC ₆ H ₄)	3d	4p , 97
6	2e	3f (2-Me)	4q , 97
7	2e	3g (3-MeO)	4r , 83
8	2e	3h (4-MeO)	4s , 80
9	2f (Me/C ₆ H ₅)	3d	4t , 91
10	2k (H/2-FC ₆ H ₄)	3e (3,5-Me ₂)	4u , 93
11	2g (Me/benzyl)	3a	4v , 82
12	2h (Et/Et)	3c	4w , 96
13	2h	3d	4x , 95
14	2h	3f	4y , 99
15	2h	3i (4-F)	4z , 98
16	2h	3j (3-NH ₂)	4aa , 81
17		3a	4ab , 95
18			
	2j (H/benzyl)	3f	4ac , 86

^a All reactions were carried out using **2** (0.4 mmol), **3** (0.5 mmol), NHC-Pd(II)-Im **1** (1.0 mol%), KOH (2.0 equiv) in EtOH (2.0 mL) at rt for 24 h.

^b Isolated yields.

temperature (50 °C) when 0.01 mol% NHC-Pd(II)-Im **1** was used. To our pleasure, once the reaction was performed at 70 °C, moderate yield can still be observed when only 0.001 mol% catalyst was added, implying its potential application toward synthetic medicinal chemistry.

3. Conclusion

In conclusion, an easily available NHC-Pd(II)-Im complex **1** has been used as an efficient catalyst in the Suzuki-Miyaura coupling of 2-chloro-4-aminoquinazolines with arylboronic acids. All reactions took place well enough at room temperature, giving the desired coupling products in good to high yields. By this methodology, a variety of 2-aryl-4-aminoquinazolines having previously reported or potential pharmaceutical activities can be achieved under mild reaction conditions.

4. Experimental section

4.1. General remarks

NMR spectra were recorded at 400 or 500 MHz (for ¹H NMR) or 125 MHz (for ¹³C NMR), respectively. ¹H and ¹³C NMR spectra recorded in CDCl₃ solutions were referenced to TMS (0.00 ppm) and the residual solvent peak (77.0 ppm), respectively. *J*-values are given in Hz. All solvents were dried by standard methods. The mass analyzer type for the high resolution mass spectra (HRMS) is Q-TOF. Flash column chromatography was performed on silica gel (300–400 mesh).

4.2. Experimental procedure

4.2.1. General procedure for the NHC-Pd(II)-Im complex 1-catalyzed Suzuki-Miyaura coupling of 2-chloro-4-aminoquinazolines 2 with arylboronic acids 3

Under a N₂ atmosphere, KOH (0.8 mmol), 2-chloro-4-aminoquinazolines **2** (0.40 mmol), arylboronic acids **3** (0.50 mmol), NHC-Pd(II)-Im complex **1** (1.0 mol%) and EtOH (2.0 mL) were successively added into a Schlenk reaction tube. The mixture was stirred vigorously at room temperature for 24 h. Then the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (SiO₂) to give the corresponding products.

4.2.1.1. Compound 4a [1f]: white solid. ¹H NMR (500 MHz, CDCl₃, TMS) δ 8.55 (d, *J* = 6.5 Hz, 2H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.91–7.87 (m, 3H), 7.80 (t, *J* = 7.5 Hz, 1H), 7.54–7.46 (m, 7H), 7.20 (t, *J* = 7.5 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 160.4, 157.3, 151.1, 138.7, 132.9, 130.3, 129.4, 129.0, 128.5, 128.4, 126.1, 124.1, 121.3, 120.2, 113.8.

4.2.1.2. Compound 4b [1h]: white solid. ¹H NMR (500 MHz, CDCl₃, TMS) δ 8.00 (d, *J* = 8.0 Hz, 1H), 7.91–7.88 (m, 5H), 7.80 (t, *J* = 7.5 Hz, 1H), 7.54–7.51 (m, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 4.00 (s, 6H), 3.93 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 159.7, 157.2, 153.1, 151.2, 140.1, 138.7, 134.0, 132.9, 129.3, 128.7, 126.0, 124.2, 121.7, 120.2, 113.7, 105.6, 60.9, 56.0.

4.2.1.3. Compound 4c: white solid. *m.p.* 160.2–161.4 °C. ¹H NMR (500 MHz, CDCl₃, TMS) δ 8.06 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.79–7.76 (m, 3H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.38 (s, 1H), 7.29–7.25 (m, 2H), 7.15 (t, *J* = 7.5 Hz, 1H), 3.92 (s, 6H), 3.90 (s, 3H), 2.38 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 159.5, 157.6, 152.9, 151.1, 140.0, 136.8, 133.9, 132.8, 131.1, 130.5, 129.1, 126.2, 125.8, 125.2, 124.5, 120.4, 113.7, 105.4, 60.8, 55.9, 18.0. IR (neat) ν 2978, 2900, 1550, 1517, 1453, 1410, 1371, 1220, 1127, 1063, 1009, 898, 798, 773, 751 cm⁻¹. HRMS (ESI) Calcd for C₂₄H₂₄N₃O₃ [M + H⁺] 402.1812, found 402.1808.

4.2.1.4. Compound 4d [1h]: white solid. ¹H NMR (500 MHz, CDCl₃, TMS) δ 7.98 (d, *J* = 8.0 Hz, 1H), 7.89–7.86 (m, 3H), 7.81–7.78 (m, 3H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.45 (s, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 4.01 (s, 6H), 3.93 (s, 3H), 2.39 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 159.7, 157.2, 153.1, 150.9, 136.1, 134.1, 133.9, 132.8, 129.3, 125.9, 121.7, 120.2, 113.7, 105.6, 60.9, 56.0, 20.9.

4.2.1.5. Compound 4e [1h]: white solid. ¹H NMR (400 MHz, CDCl₃, TMS) δ 7.97 (d, *J* = 8.4 Hz, 1H), 7.88–7.86 (m, 3H), 7.80–7.75 (m, 3H), 7.51–7.47 (m, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 3.98 (s, 6H), 3.92 (s, 3H), 3.84 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 159.7, 157.4, 156.6, 153.0, 151.0, 140.1, 134.0, 132.8, 131.7, 129.0, 125.8, 123.7, 120.4, 113.9, 113.6, 105.6, 60.9, 56.0, 55.5.

4.2.1.6. Compound 4f: white solid. *m.p.* 163.9–165.0 °C. ¹H NMR (500 MHz, CDCl₃, TMS) δ 7.95 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.83–7.71 (m, 6H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 8.5 Hz, 2H), 3.94 (s, 6H), 3.92 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 160.3, 159.5, 158.4, 157.3, 153.0, 151.0, 140.1, 134.7, 134.6, 133.9, 132.9, 129.0, 125.9, 123.75, 123.68, 120.4, 115.3, 115.1, 113.5, 105.5, 60.9, 55.9. IR (neat) ν 2928, 2846, 1614, 1557, 1510, 1432, 1364, 1439, 1292, 1213, 1152, 1120, 952, 826, 791, 762 cm⁻¹. HRMS (ESI) Calcd for C₂₃H₂₁FN₃O₃ [M + H⁺] 406.1561, found 406.1564.

4.2.1.7. Compound 4g: white solid. *m.p.* 180.5–181.6 °C. ¹H NMR (500 MHz, CDCl₃, TMS) δ 7.95 (s, 2H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 7.0 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 7.5 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 4.03 (s, 6H), 3.94 (s, 3H), 3.77 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 161.9, 159.2, 153.2, 152.6, 148.7, 134.3, 131.9, 130.0, 128.7, 126.2, 125.9, 124.4, 115.4, 105.7, 60.9, 56.2, 42.3. IR (neat) ν 2934, 1683, 1615, 1547, 1509, 1410, 1365, 1217, 1126, 1099, 1027, 1001, 921, 804, 773, 751 cm⁻¹. HRMS (ESI) Calcd for C₂₄H₂₄N₃O₃ [M + H⁺] 402.1812, found 402.1808.

4.2.1.8. Compound 4h: white solid. *m.p.* 190.0 °C (decomposed). ¹H NMR (400 MHz, CDCl₃, TMS) δ 7.95 (dd, *J* = 8.4, 2.8 Hz, 2H), 7.83 (s, 2H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.42–7.36 (m, 4H), 7.33–7.27 (m, 2H), 5.03 (s, 2H), 3.92 (s, 6H), 3.91 (s, 3H), 3.39 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 164.4, 152.7, 149.7, 138.9, 135.7, 130.9, 128.8, 127.8, 126.2, 125.0, 116.9, 51.9, 34.6, 31.3. IR (neat) ν 2942, 1566, 1520, 1456, 1403, 1350, 1259, 1213, 1122, 1069, 1012, 902, 857, 770, 743, 705 cm⁻¹. HRMS (ESI) Calcd for C₂₅H₂₆N₃O₃ [M + H⁺] 416.1969, found 416.1977.

4.2.1.9. Compound 4i: white solid. *m.p.* 94.8–96.2 °C. ¹H NMR (400 MHz, CDCl₃, TMS) δ 7.92 (t, *J* = 6.8 Hz, 2H), 7.88 (s, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 4.01 (s, 6H), 3.92 (s, 3H), 3.82 (q, *J* = 7.2 Hz, 4H), 1.48 (t, *J* = 7.2 Hz, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 165.1, 159.0, 153.1, 152.8, 140.1, 134.4, 132.2, 128.8, 125.1, 124.5, 115.5, 105.7, 60.9, 56.2, 51.0, 26.0, 24.9. IR (neat) ν 2972, 1562, 1513, 1460, 1406, 1342, 1293, 1217, 1118, 1061, 1005, 898, 861, 758, 747, 686 cm⁻¹. HRMS (ESI) Calcd for C₂₁H₂₆N₃O₃ [M + H⁺] 368.1969, found 368.1967.

4.2.1.10. Compound 4j: white solid. *m.p.* 135.1–136.2 °C. ¹H NMR (500 MHz, CDCl₃, TMS) δ 8.00 (t, *J* = 8.0 Hz, 1H), 7.92–7.87 (m, 3H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 4.03–3.93 (m, 13H), 3.86 (t, *J* = 4.5 Hz, 4H). ¹³C NMR (125 MHz, CDCl₃) δ 165.0, 159.0, 153.2, 152.8, 140.4, 134.0, 132.5, 129.1, 125.0, 124.6, 115.3, 105.8, 66.7, 60.9, 56.2, 50.4. IR (neat) ν 2978, 2900, 1578, 1471, 1403, 1263, 1231, 1056, 862, 816 cm⁻¹. HRMS (ESI) Calcd for C₂₁H₂₃N₃NaO₄ [M + Na⁺] 404.1581, found 404.1594.

4.2.1.11. Compound 4k [8]: white solid. ¹H NMR (400 MHz, CDCl₃, TMS) δ 7.94 (d, *J* = 8.4 Hz, 1H), 7.89–7.87 (m, 3H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 4.02 (s, 6H), 3.92 (s, 3H), 3.80–3.79 (m, 4H), 1.85–1.82 (m, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 165.1, 159.0, 153.1, 152.8, 140.1, 134.4, 132.2, 128.8, 125.1, 124.5, 115.5, 105.7, 60.9, 56.2, 51.0, 26.0, 24.9.

4.2.1.12. Compound 4l [1f]: white solid. ¹H NMR (500 MHz, CDCl₃, TMS) δ 8.32 (d, *J* = 7.5 Hz, 1H), 8.23 (d, *J* = 10.5 Hz, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 3H), 7.79 (t, *J* = 7.5 Hz, 1H), 7.53–7.42 (m, 5H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 163.1 (d, *J*_{C-F} = 242.75 Hz), 159.2, 157.4, 151.0, 141.2 (d, *J*_{C-F} = 7.625 Hz), 138.5, 133.0, 129.7 (d, *J*_{C-F} = 7.875 Hz), 129.4, 129.0, 126.4, 124.3, 124.1 (d, *J*_{C-F} = 2.625 Hz), 121.4, 120.2, 117.0 (d, *J*_{C-F} = 21.25 Hz), 115.3 (d, *J*_{C-F} = 22.875 Hz), 113.9.

4.2.1.13. Compound 4m [1c]: pale yellow solid. ¹H NMR (500 MHz, CDCl₃, TMS) δ 8.53 (d, *J* = 7.0 Hz, 2H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.77–7.71 (m, 4H), 7.49–7.39 (m, 5H), 7.22 (d, *J* = 8.0 Hz, 2H), 2.37 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 160.4, 157.3, 151.0, 138.7, 136.0,

133.7, 132.7, 130.2, 129.4, 129.2, 128.5, 128.3, 125.9, 121.4, 120.2, 113.8, 20.9.

4.2.1.14. Compound 4n [9]: pale yellow solid. ^1H NMR (500 MHz, CDCl_3 , TMS) δ 8.44 (d, J = 8.5 Hz, 2H), 7.97 (d, J = 9.5 Hz, 1H), 7.85 (d, J = 10.0 Hz, 1H), 7.78–7.76 (m, 3H), 7.49 (t, J = 9.5 Hz, 1H), 7.41 (br, 1H), 7.31–7.26 (m, 4H), 2.43 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 160.5, 157.3, 151.1, 140.3, 136.1, 136.0, 133.6, 132.7, 129.4, 129.2, 129.1, 128.5, 125.7, 121.3, 120.2, 113.8, 21.5, 20.9.

4.2.1.15. Compound 4o [8]: yellow solid. ^1H NMR (400 MHz, CDCl_3 , TMS) δ 8.41 (d, J = 8.0 Hz, 2H), 7.96 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 9.2 Hz, 1H), 7.79–7.75 (m, 3H), 7.48 (td, J = 8.0, 0.8 Hz, 1H), 7.37 (br, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 9.2 Hz, 2H), 3.87 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 160.5, 157.5, 156.4, 151.0, 140.3, 136.0, 132.7, 131.7, 129.1, 128.5, 125.7, 123.3, 120.2, 114.2, 113.7, 55.6, 21.5.

4.2.1.16. Compound 4p: white solid. m.p. 177.0–179.0 °C. ^1H NMR (500 MHz, CDCl_3 , TMS) δ 8.38 (d, J = 8.0 Hz, 2H), 7.93 (d, J = 8.0 Hz, 1H), 7.79–7.71 (m, 4H), 7.44–7.41 (m, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.10 (t, J = 8.5 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 160.3, 159.3 (d, $J_{\text{C-F}}$ = 242.0 Hz), 157.3, 151.0, 140.4, 135.8, 134.6, 132.8, 129.1, 128.4, 125.8, 123.2 (d, $J_{\text{C-F}}$ = 7.75 Hz), 120.1, 115.5 (d, $J_{\text{C-F}}$ = 22.375 Hz), 113.6, 21.4. IR (neat) ν 2978, 2903, 1679, 1607, 1575, 1503, 1442, 1399, 1360, 1317, 1213, 1063, 837, 755 cm^{-1} . HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{17}\text{FN}_3$ [$\text{M} + \text{H}^+$] 330.1401, found 330.1396.

4.2.1.17. Compound 4q: white solid. m.p. 165.7–166.5 °C. ^1H NMR (500 MHz, CDCl_3 , TMS) δ 7.97 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 7.0 Hz, 1H), 7.79 (t, J = 8.0 Hz, 1H), 7.71 (dd, J = 7.0, 5.0 Hz, 2H), 7.55–7.50 (m, 2H), 7.32–7.25 (m, 3H), 7.05 (t, J = 8.5 Hz, 2H), 2.55 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 163.4, 159.4 (d, $J_{\text{C-F}}$ = 242.25 Hz), 157.2, 150.7, 139.3, 137.2, 134.5, 132.9, 131.1, 130.4, 129.2, 128.9, 126.2, 125.7, 123.5 (d, $J_{\text{C-F}}$ = 7.875 Hz), 120.2, 115.5 (d, $J_{\text{C-F}}$ = 22.375 Hz), 113.0, 21.2. IR (neat) ν 2982, 2896, 1625, 1568, 1510, 1424, 1403, 1353, 1224, 1152, 1052, 952, 837, 805, 758, 733 cm^{-1} . HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{17}\text{FN}_3$ [$\text{M} + \text{H}^+$] 330.1401, found 330.1409.

4.2.1.18. Compound 4r: yellow solid. m.p. 165.3–167.2 °C. ^1H NMR (400 MHz, CDCl_3 , TMS) δ 8.12–8.10 (m, 2H), 8.00 (d, J = 8.4 Hz, 1H), 7.88–7.79 (m, 4H), 7.53 (t, J = 7.2 Hz, 1H), 7.42 (br, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.16 (t, J = 8.8 Hz, 2H), 7.03 (dd, J = 7.6, 1.6 Hz, 1H), 3.92 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 160.1, 159.8, 159.4 (d, $J_{\text{C-F}}$ = 242.75 Hz), 157.4, 151.1, 140.1, 134.6, 132.9, 129.4 (d, $J_{\text{C-F}}$ = 8.625 Hz), 126.1, 123.5 (d, $J_{\text{C-F}}$ = 7.75 Hz), 121.0, 120.1, 117.0, 115.6 (d, $J_{\text{C-F}}$ = 22.375 Hz), 113.7, 113.0, 55.3. IR (neat) ν 2978, 2903, 1564, 1521, 1424, 1353, 1224, 1063, 1041, 902, 869, 816, 758, 737 cm^{-1} . HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{17}\text{FN}_3\text{O}$ [$\text{M} + \text{H}^+$] 346.1350, found 346.1365.

4.2.1.19. Compound 4s: yellow solid. m.p. 173.6–175.3 °C. ^1H NMR (400 MHz, CDCl_3 , TMS) δ 8.45 (d, J = 8.8 Hz, 2H), 7.94 (d, J = 8.4 Hz, 1H), 7.83–7.74 (m, 4H), 7.45 (t, J = 8.0 Hz, 1H), 7.41 (br, 1H), 7.14 (t, J = 8.8 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 161.6, 160.1, 159.4 (d, $J_{\text{C-F}}$ = 242.0 Hz), 157.3, 151.2, 134.6, 132.9, 131.2, 130.0, 129.1, 125.6, 123.3 (d, $J_{\text{C-F}}$ = 7.75 Hz), 120.1, 115.6 (d, $J_{\text{C-F}}$ = 22.375 Hz), 113.7, 113.4, 55.3. IR (neat) ν 2989, 2900, 1611, 1568, 1532, 1507, 1449, 1414, 1356, 1220, 1170, 1056, 1027, 948, 862, 826, 758 cm^{-1} . HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{17}\text{FN}_3\text{O}$ [$\text{M} + \text{H}^+$] 346.1350, found 346.1355.

4.2.1.20. Compound 4t: yellow solid. m.p. 159.2–160.1 °C. ^1H NMR (400 MHz, CDCl_3 , TMS) δ 8.52 (d, J = 8.0 Hz, 2H), 7.90 (d, J = 8.4 Hz, 1H), 7.58–7.53 (m, 1H), 7.38 (t, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz,

2H), 7.28–7.20 (m, 3H), 7.06–7.04 (m, 1H), 7.00–6.95 (m, 1H), 3.76 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 161.9, 159.7, 152.7, 148.8, 140.2, 136.1, 131.7, 129.8, 129.0, 128.7, 128.4, 126.2, 126.1, 125.8, 124.2, 115.5, 42.3, 21.4. IR (neat) ν 2989, 2903, 1611, 1564, 1539, 1482, 1442, 1389, 1356, 1288, 1170, 1074, 927, 837, 766, 698 cm^{-1} . HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{20}\text{N}_3$ [$\text{M} + \text{H}^+$] 326.1652, found 326.1664.

4.2.1.21. Compound 4u: white solid. m.p. 132.7–133.4 °C. ^1H NMR (400 MHz, CDCl_3 , TMS) δ 8.91 (d, J = 8.4, 6.8 Hz, 1H), 8.16 (s, 2H), 8.01 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.81 (td, J = 8.4, 1.2 Hz, 1H), 7.72 (br, 1H), 7.54 (td, J = 8.0, 0.8 Hz, 1H), 7.29–7.10 (m, 4H), 2.44 (s, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 160.6, 156.9, 153.3 (d, $J_{\text{C-F}}$ = 241.25 Hz), 151.1, 138.4, 137.8, 132.9, 132.1, 129.3, 127.4, 126.4, 126.2, 124.3 (d, $J_{\text{C-F}}$ = 3.5 Hz), 123.6 (d, $J_{\text{C-F}}$ = 7.625 Hz), 122.7, 120.1, 114.8 (d, $J_{\text{C-F}}$ = 19.25 Hz), 114.0, 21.5. IR (neat) ν 2993, 2900, 1628, 1568, 1535, 1503, 1482, 1449, 1417, 1353, 1260, 1177, 1113, 1066, 894, 859, 787, 751, 669 cm^{-1} . HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{19}\text{FN}_3$ [$\text{M} + \text{H}^+$] 344.1558, found 344.1571.

4.2.1.22. Compound 4v [10]: white solid. ^1H NMR (500 MHz, CDCl_3 , TMS) δ 8.56 (dd, J = 7.2, 1.6 Hz, 2H), 7.97 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.50–7.40 (m, 7H), 7.36–7.28 (m, 2H), 5.07 (s, 2H), 3.38 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 163.9, 159.3, 153.1, 132.1, 130.0, 128.83, 128.81, 128.4, 127.4, 127.3, 124.9, 124.4, 114.8, 56.9, 39.4.

4.2.1.23. Compound 4w: yellow solid. m.p. 87.5–88.7 °C. ^1H NMR (400 MHz, CDCl_3 , TMS) δ 8.34 (d, J = 7.6 Hz, 1H), 8.24 (dd, J = 9.2, 1.2 Hz, 1H), 7.92 (d, J = 8.4 Hz, 2H), 7.71–7.67 (m, 1H), 7.46–7.41 (m, 1H), 7.38–7.35 (m, 1H), 7.14 (td, J = 8.4, 2.8 Hz, 1H), 3.82 (q, J = 7.2 Hz, 4H), 1.45 (t, J = 7.2 Hz, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 163.1 (d, $J_{\text{C-F}}$ = 242.375 Hz), 162.6, 158.0 (d, $J_{\text{C-F}}$ = 3.125 Hz), 153.0, 141.7 (d, $J_{\text{C-F}}$ = 7.625 Hz), 131.9, 129.6 (d, $J_{\text{C-F}}$ = 7.875 Hz), 129.0, 124.7, 124.4, 123.9 (d, $J_{\text{C-F}}$ = 2.625 Hz), 116.6 (d, $J_{\text{C-F}}$ = 21.375 Hz), 115.2 (d, $J_{\text{C-F}}$ = 4.125 Hz), 115.0, 45.1, 13.1. IR (neat) ν 2971, 2896, 1600, 1560, 1514, 1471, 1410, 1378, 1346, 1288, 1213, 1145, 1063, 1013, 859, 755, 726 cm^{-1} . HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{19}\text{FN}_3$ [$\text{M} + \text{H}^+$] 296.1558, found 296.1568.

4.2.1.24. Compound 4x [11]: white solid. ^1H NMR (400 MHz, CDCl_3 , TMS) δ 8.44 (d, J = 8.4 Hz, 2H), 7.90 (t, J = 8.4 Hz, 2H), 7.68–7.64 (m, 1H), 7.35–7.31 (m, 1H), 7.28 (d, J = 8.0 Hz, 2H), 3.80 (q, J = 7.2 Hz, 4H), 2.42 (s, 3H), 1.44 (t, J = 7.2 Hz, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 162.6, 159.3, 153.1, 139.8, 136.4, 131.7, 128.9, 128.8, 128.3, 124.6, 123.9, 115.1, 45.0, 21.4, 13.1.

4.2.1.25. Compound 4y: white solid. m.p. 91.1–91.6 °C. ^1H NMR (500 MHz, CDCl_3 , TMS) δ 7.94 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.87–7.85 (m, 1H), 7.69 (t, J = 7.5 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.30–7.28 (m, 3H), 3.79 (q, J = 7.0 Hz, 4H), 2.59 (s, 3H), 1.41 (t, J = 7.0 Hz, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 162.6, 162.5, 152.7, 139.8, 137.1, 131.8, 130.9, 130.3, 128.9, 128.5, 125.6, 124.7, 124.3, 114.6, 45.0, 21.2, 13.4. IR (neat) ν 2989, 2907, 1603, 1553, 1517, 1381, 1242, 1177, 1070, 869, 823, 794, 762, 733 cm^{-1} . HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{22}\text{N}_3$ [$\text{M} + \text{H}^+$] 292.1808, found 292.1817.

4.2.1.26. Compound 4z: white solid. m.p. 87.1–89.0 °C. ^1H NMR (500 MHz, CDCl_3 , TMS) δ 8.54 (dd, J = 8.5, 5.5 Hz, 2H), 7.90 (d, J = 8.5 Hz, 2H), 7.68 (t, J = 7.0 Hz, 1H), 7.35 (t, J = 7.0 Hz, 1H), 7.15 (t, J = 8.5 Hz, 2H), 3.82 (q, J = 6.5 Hz, 4H), 1.45 (t, J = 6.5 Hz, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 164.3 (d, $J_{\text{C-F}}$ = 247.5 Hz), 162.6, 158.3, 153.0, 135.2, 131.9, 130.3 (d, $J_{\text{C-F}}$ = 8.5 Hz), 128.8, 124.7, 124.1, 115.02 (d, $J_{\text{C-F}}$ = 21.375 Hz), 115.00, 45.1, 13.1. IR (neat) ν 2980, 2919, 1596, 1558, 1505, 1463, 1376, 1353, 1206, 1065, 845, 796, 751, 682 cm^{-1} .

HRMS (ESI) Calcd for $C_{18}H_{19}FN_3$ [$M + H^+$] 296.1558, found 296.1565.

4.2.1.27. **Compound 4aa**: red liquid. 1H NMR (500 MHz, $CDCl_3$, TMS) δ 7.96–7.89 (m, 4H), 7.69–7.65 (m, 1H), 7.36–7.33 (m, 1H), 7.27 (d, $J = 6.5$ Hz, 1H), 6.79 (ddd, $J = 8.0, 2.5, 1.0$ Hz, 1H), 3.81 (q, $J = 7.0$ Hz, 4H), 1.44 (t, $J = 7.0$ Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 159.2, 152.9, 146.3, 140.1, 131.8, 129.1, 128.8, 124.7, 124.0, 119.1, 116.9, 115.1, 115.0, 45.0, 13.2. IR (neat) ν 3344, 3224, 2976, 2930, 1618, 1560, 1518, 1432, 1344, 1294, 1194, 1076, 998, 904, 836, 764, 732 cm^{-1} . HRMS (ESI) Calcd for $C_{18}H_{20}N_4Na$ [$M + Na^+$] 315.1580, found 315.1577.

4.2.1.28. **Compound 4ab**: white solid. m.p. 123.3–124.4 °C. 1H NMR (500 MHz, $CDCl_3$, TMS) δ 8.55 (dd, $J = 8.0, 2.0$ Hz, 2H), 7.99 (d, $J = 8.0$ Hz, 1H), 7.88 (d, $J = 8.5$ Hz, 1H), 7.75–7.71 (m, 1H), 7.51–7.45 (m, 3H), 7.43–7.40 (m, 1H), 3.94 (t, $J = 5.0$ Hz, 4H), 3.85 (t, $J = 5.0$ Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 159.4, 152.8, 138.4, 132.5, 130.2, 129.1, 128.4, 128.3, 125.0, 124.6, 115.3, 66.7, 50.3. IR (neat) ν 2978, 2846, 1614, 1564, 1535, 1507, 1449, 1435, 1349, 1267, 1156, 1109, 1070, 1023, 1020, 948, 855, 769, 712 cm^{-1} . HRMS (ESI) Calcd for $C_{18}H_{18}N_3O$ [$M + H^+$] 292.1444, found 292.1447.

4.2.1.29. **Compound 4ac**: yellow solid. 1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.93 (d, $J = 8.0$ Hz, 1H), 7.86–7.84 (m, 1H), 7.77–7.70 (m, 2H), 7.46–7.25 (m, 9H), 5.99 (br, 1H), 4.92 (d, $J = 5.6$ Hz, 2H), 2.56 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9, 159.1, 150.3, 139.7, 138.5, 137.1, 132.5, 131.0, 130.2, 128.9, 128.75, 128.71, 127.9, 127.6, 125.7, 125.6, 120.4, 112.9, 45.3, 21.2.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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