Microwave-assisted synthesis of new substituted anilides of quinaldic acid

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Abstract:

In this study a method for preparation of substituted anilides of 2-quinaldic acid in one step, based on the direct reaction of an acid or ester with substituted anilines using microwave irradiation have been developed. The optimized method was used for the synthesis of a series of eighteen substituted quinoline-2-carboxanilides.

Keywords: microwave-assisted synthesis; amide formation; quinoline-2-carboxanilides;

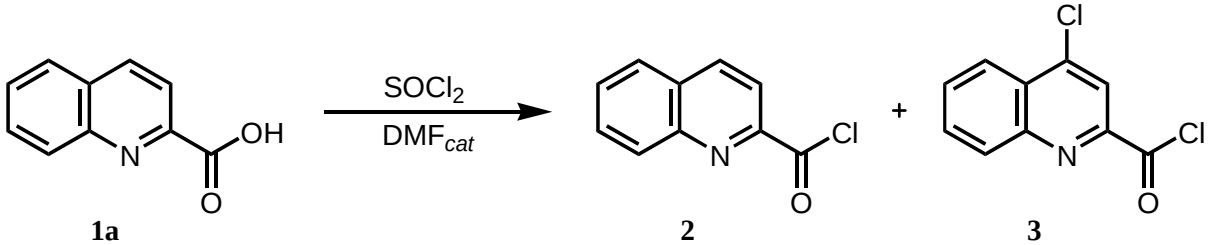
INTRODUCTION

Derivatives of quinoline and its isosters are remarkable compounds with many different kinds of biological effects. A number of quinoline related compounds expressed antifungal [1-3], antibacterial [4-6], antiviral [7-9], antineoplastic [10-12], and other activities [13-15].
The stable and polar amide group is an important functionality among the organic substances present in common natural materials like proteins. Moreover, this unit is found in many synthetic compounds as active pharmaceutical ingredients (APIs) or prodrugs [16]. Due to its interest in drug discovery, formation of amides from amines and carboxylic acids and their derivatives is one of the most described transformations. The formation of the amide bond requires activation of a carboxylic acid functional group. The most common methods involve either its activation through acyl chlorides, anhydrides, active esters and other reactive carboxylic acid derivatives, or in situ activation by using large family of various coupling reagents. Although both approaches usually afford satisfactory results, they often need expensive coupling reagents, or lead to the formation of by-products requiring further separations [17-18].
Microwave-assisted organic synthesis has been successfully applied in organic and medicinal chemistry over the last decades. The use of microwave irradiation as non-conventional energy source to simplify and improve classic organic reactions has become a very popular method, because it often leads to higher yields, improved conversions, clean product formation and shorter reaction times [19-25].

RESULTS AND DISCUSSION

Substituted quinoline-2-carboxanilides were initially synthesised from 2-quinaldic acid and corresponding substituted anilines. The activation of carboxylic function was carried out by using an excess of thionyl chloride and catalytic amount of dimethylformamide in standard manner. When this type of activation was performed, besides desired acyl chloride **2** also formation of undesired chloro- compound **3**, where chlorine is attached in position 4 of quinoline ring, was observed (Scheme 1).

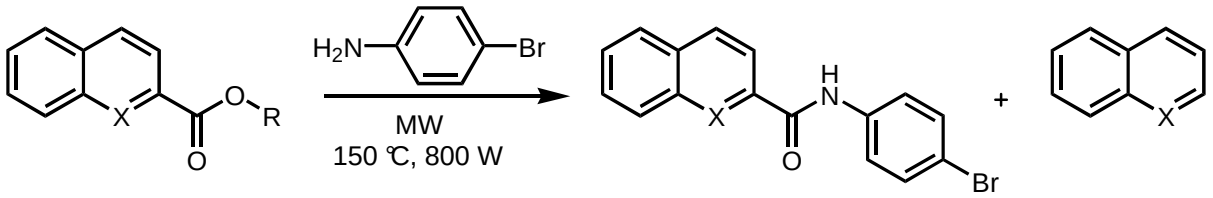
Scheme 1. Standard synthesis of quinoline-2-carbonyl chloride **2** together with 4-chloro-quinoline-2-carbonyl chloride **3**.



1a **2** **3**

It is well-known that chlorination occurred on a pyridine ring which is similar to quinoline, when pyridine carboxylic acid is treated with thionyl chloride with presence of small amount of anhydrous dimethylformamide. Formed so called Vilsmeier reagent is well described and used for formation of 4-chloropyridines as intermediates in the synthesis of multiple kinase inhibitor – sorafenib [26]. The method for direct chlorination of quinoline in position 4 was not described in the literature so far. On the other hand, formation of 4-chloroquinoline derivative hampered our efforts to prepare pure quinoline-2-carboxanilides. When anilides were prepared from the mixture of acyl chloride **2** and **3** (20-30%), there was no other possibility to separate them, than chromatography. Attempts to optimize reaction conditions (temperature, ratio of reagents, reaction time, etc.) in view to reduce amount of undesired intermediate **3** failed.

Scheme 2. Optimization process of the synthesis of *N*-(4-bromophenyl)quinoline-2-carboxamide **5c** and *N*-(4-bromophenyl)naphthalene-2-carboxamide **6** under microwave irradiation.



X = N R = H **1a**, CH_3 **1b**, Ph **1c** X = N **5c** X = N **7**

X = CH R = H **4a**, CH_2CH_3 **4b** X = CH **6** X = CH **8**

The other possibility for the synthesis of the desired quinoline-2-carboxanilides is to perform direct amidation process starting from an acid or ester precursor and substituted anilines under microwave irradiation [25, 27]. In order to screen this method under microwave-assisted conditions, we performed the reaction in a StartSynth microwave reactor. The method was tested on compounds: 2-quinaldic acid **1a** and its methylester **1b** and phenylester **1c**, 2-naphthoic acid **4a** and its ethylester **4b**. All those compounds reacted with 4-bromaniline as a model amine (Scheme 2). The synthesis was carried out at various conditions: solvent-free, in dimethylformamide (DMF) and in chlorobenzene. All of the reactions were performed without or with catalysts: *p*-toluenesulfonic acid (PTSA), potassium *tert*-butoxide (^{t}BuOK), Silica gel, KF/Al_2O_3. Microwave output power of the reactor in all experiments was set to

800W. The reaction temperature was 150 °C in order to shift the equilibrium by water removal. The ratio of an acid derivative and amine was 1:1.5. The reactions were irradiated up to maximum 2 hours and were monitored by HPLC analysis. The results are summarized in Table 1.

Already from the first tests was evident, that the direct amidation of 2-quinaldic acid **1a** is hampered by formation of decarboxylated product – quinoline **7**. It was determined, that when the reaction was carried out in DMF and catalysed either with PTSA or ^{t}BuOK only decarboxylated product **7** was produced. On the other hand, in case of naphthalene-2-carboxylic acid **4a** there were no traces of decarboxylated product **8** observed.

Table 1. Reaction of 4-bromoaniline with 2-quinaldic and naphthalene-2-carboxylic acids and their derivatives under microwave irradiation.

Comp.	Solvent	Catalyst	Conversion after 0.5 h		Conversion after 1 h		Conversion after 2 h	
			Amide **5c** or **6**	Product **7** or **8**	Amide **5c** or **6**	Product **7** or **8**	Amide **5c** or **6**	Product **7** or **8**
1a	-	-	57%	37%	-[a]	-[a]	-[a]	-[a]
4a	-	-	-	-	-	-	9%	-
1b	-	-	6%	-	21%	-	51%	-
4b	-	-	-	-	-	-	-	-
1a	DMF	-	-	-	-	-	-	-
4a	DMF	-	-	-	-	-	-	-
1b	DMF	-	-	-	-	-	-	-
4b	DMF	-	-	-	-	-	-	-
1a	PhCl	-	-	-	-	-	-	-
4a	PhCl	-	-	-	-	-	7%	-
1b	PhCl	-	-	-	-	-	-	-
4b	PhCl	-	-	-	-	-	-	-
1a	-	PTSA	53%	46%	55%	44%	33%[b]	67%[b]
4a	-	PTSA	20%	-	46%	-	100%[a]	-[a]
1b	-	PTSA	35%	-	-[a]	-[a]	-[a]	-[a]
4b	-	PTSA	-	-	-	-	-	-
1a	DMF	PTSA	-[c]	100%	-[c]	100%	-[c]	100%
1b	DMF	PTSA	-	-	-	-	-[c]	-
4b	DMF	PTSA	-	-	-	-	-	-
1a	PhCl	PTSA	19%	24%	28%	25%	32%	30%
4a	PhCl	PTSA	-	-	-	-	-	-
1b	PhCl	PTSA	20%	-	25%	-	34%	-
4b	PhCl	PTSA	-	-	-	-	-	-
1a	-	^{t}BuOK	59%	41%	61%	39%	62%	38%
4a	-	^{t}BuOK	11%	-	20%	-	44%	-
1b	-	^{t}BuOK	26%	74%	43%[a]	56%[a]	-[a]	-[a]
4b	-	^{t}BuOK	-	-	-	-	-	-
1a	DMF	^{t}BuOK	-	100%	-	100%	-	100%
4a	DMF	^{t}BuOK	-	-	-	-	-	-
1b	DMF	^{t}BuOK	-[c]	-	-[c]	-	-[c]	-
4b	DMF	^{t}BuOK	-	-	-	-	-	-
1a	PhCl	^{t}BuOK	13%	27%	30%	34%	35%	41%
4a	PhCl	^{t}BuOK	-	-	-	-	-	-
1b	PhCl	^{t}BuOK	17%	-	18%	-	16%[b]	-
4b	PhCl	^{t}BuOK	-	-	-	-	-	-
1a	-	Silica gel	63%	37%	17%	83%	53%	47%
4a	-	Silica gel	-	-	22%	-	100%[d]	-
1b	-	Silica gel	11%	-	30%	-	19%	19%
4b	-	Silica gel	-	-	-	-	-	-

[a] decomposition, [b] partial decomposition, [c] traces of product, [d] many impurities, [e] not performed

Table 1. Reaction of 4-bromoaniline with 2-quinaldic and naphthalene-2-carboxylic acids and their derivatives under microwave irradiation (cont.).

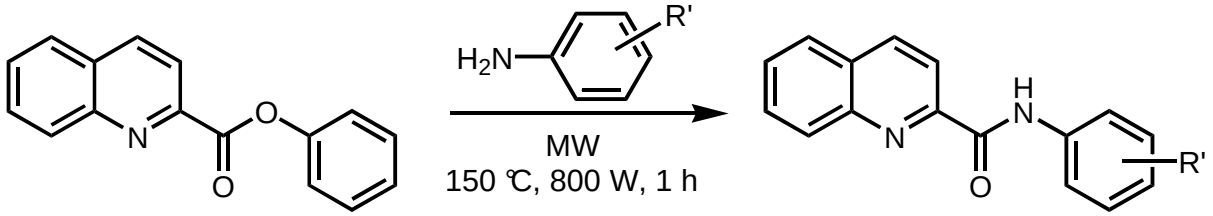
Comp.	Solvent	Catalyst	Conversion after 0.5 h		Conversion after 1 h		Conversion after 2 h	
			Amide **5c** or **6**	Product **7** or **8**	Amide **5c** or **6**	Product **7** or **8**	Amide **5c** or **6**	Product **7** or **8**
1a	DMF	Silica gel	-[c]	-	-[c]	-	-[c]	-
4a	DMF	Silica gel	-	-	-	-	-	-
1b	DMF	Silica gel	-	-	-	-	-[c]	-
4b	DMF	Silica gel	-	-	-	-	-	-
1a	PhCl	Silica gel	-[c]	26%	9%	23%	68%	8%
4a	PhCl	Silica gel	-	-	-	-	-	-
1b	PhCl	Silica gel	-	-	6%	-	9%	-
4b	PhCl	Silica gel	-	-	-	-	-	-
1a	-	KF/Al_2O_3	-	-	-	-	90%	8%
4a	-	KF/Al_2O_3	-	-	-[c]	-	-[c]	-
1b	-	KF/Al_2O_3	10%	-	18%	-	35%	-
4b	-	KF/Al_2O_3	-	-	-	-	-	-
1a	DMF	KF/Al_2O_3	-	73%	-	89%	-	98%
4a	DMF	KF/Al_2O_3	-	-	-	-	-	-
1b	DMF	KF/Al_2O_3	-	-	-	-	-	-
4b	DMF	KF/Al_2O_3	-	-	-	-	-	-
1a	PhCl	KF/Al_2O_3	-	-	7%	24%	20%	20%
4a	PhCl	KF/Al_2O_3	-	-	-	-	-	-
1b	PhCl	KF/Al_2O_3	-	-	-	-	-[c]	-
4b	PhCl	KF/Al_2O_3	-	-	-	-	-	-
1c	-	-	96%	-	100%	-	-[e]	-[e]

[a] decomposition, [b] partial decomposition, [c] traces of product, [d] many impurities, [e] not performed

When the reaction was performed in solvents like DMF or chlorobenzene, it generally did not lead to any improvement. Although the use of methyl ester of 2-quinaldic acid **1b** suppressed decarboxylation, it did not enhance reactivity towards the amides significantly. The same applies to ethyl naphthalene-2-carboxylate **4a**. The results showed that, in almost all cases, the reactions proceeded not cleanly, and the formation of side products and impurities was noticed. Finally, utilization of phenyl quinoline-2-carboxylate **1c** in reaction with 4-bromoaniline under microwave irradiation in solvent-free conditions showed spectacular acceleration, high conversion, in relatively short reaction time and high product purity.

Having optimized the substrate structure and the conditions in hand, we next evaluated the scope of the procedure by varying the aniline. Eighteen commercially available ring-substituted anilines were explored as reaction partners to phenyl quinoline-2-carboxylate **1c** and very good yields (61-89%) and satisfactory purities of the products **5-5c**, **9-13c** were obtained. All of the studied compounds were prepared according to Scheme 3.

Scheme 3. Optimized microwave-assisted synthesis of substituted quinoline-2-carboxanilides **5-5c**, **9-13c**.



1c **5-5c, 9-13c**

R' = Br, Cl, F, OCH_3, CH_3, CF_3

In conclusion, we have successfully developed a novel microwave-assisted one-pot coupling of phenyl ester of 2-quinaldic acid and ring-substituted anilines, providing an efficient approach for the synthesis of substituted quinoline-2-carboxanilides in solvent-free conditions. Interestingly, the reactions were applicable to eighteen substituted anilines. Desired carboxanilides were isolated in very good yields and purities.

EXPERIMENTAL

General

All chemicals were reagent grade and were purchased from Sigma-Aldrich and Acros. TLC analysis was performed on precoated 60 F_{254} plates (Merck, Darmstadt, Germany). Compounds were visualized by UV light (254 nm) and evaluated in iodine vapour. Small scale microwave-assisted synthesis was carried out in a StartSynth multimode microwave instrument producing controlled irradiation at 2.45 GHz (Milestone S.r.l., Sorisole, Italy). The instrument is equipped with an industrial magnetron and a microwave diffuser located above the microwave chamber, with continuous microwave output power from 0 to 1400 W. Reaction times refer to hold times at the temperatures indicated, not to total irradiation times. The temperature was measured with an IR sensor on the outside of the reaction vessel. The melting points were determined on Boetius PHMK 05 (VEB Kombinat Nagema, Radebeul, Germany) and are uncorrected. Infrared (IR) spectra were recorded on a Smart MIRacle™ ATR ZnSe for Nicolet™ Impact 410 FT-IR Spectrometer (Thermo Scientific, USA). The spectra were obtained by accumulation of 256 scans with 2 cm^{-1} resolution in the region of 4000-600 cm^{-1}. All ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 solutions at ambient temperature on a Bruker Avance III 400 MHz spectrometer (Karlsruhe, Bruker, Germany, 400 MHz for ^{1}H, 100 MHz for ^{13}C). Chemical shifts are reported in ppm (δ). Proton chemical shifts in DMSO-d_6 are related to the middle of the solvent multiplet (δ = 2.50). ^{13}C-NMR spectra were measured using APT pulse sequences. Carbon chemical shifts are referenced to the middle of the solvent multiplet (δ = 39.5 in DMSO-d_6). Mass spectra were measured using a LTQ Orbitrap Hybrid Mass Spectrometer (Thermo Electron Corporation, USA) with direct injection into an APCI source (400 °C) in the positive mode. HPLC analysis was carried out on the system Agilent 1200 Series with DAD detector. The separations were carried out using a C18 reversed phase analytical column, Gemini-NX 100 (Phenomenex, 100×2 mm, particle size 3 µm) at 35 °C and a mobile phase from 50:50 water/MeCN (all solvents were HPLC grade, Sigma-Aldrich).

Procedure for the optimization of microwave-assisted synthesis

2-Quinaldic acid or naphthalene-2-carboxylic acid or their esters (1.7 mmol) and 4-bromoaniline (0.45g, 2.6 mmol) were mixed in 10 mL round bottom flask and placed to microwave reactor. Outlet of the reaction flask was connected with a tube attached to a condenser outside of the microwave reactor. Microwave output power was selected to maximum 800W. The stirred reaction mixture was preheated to 150 °C by microwave irradiation and let to react at the same temperature for 2 h. The reaction was monitored by HPLC in time periods: 0.5 h, 1 h and 2 h. The results are presented in Table 1.

General procedure for the microwave-assisted synthesis of ring-substituted quinoline-2-carboxanilides

Phenyl quinoline-2-carboxylate (250 mg, 1 mmol) and substituted aniline (1.5 mmol) were mixed in 10 mL round bottom flask and placed to microwave reactor. Outlet of the reaction flask was connected with a tube attached to a condenser outside of the microwave reactor. Microwave output power was selected to maximum 800W. The stirred reaction mixture was preheated to 150 °C by microwave irradiation and let to react at the same temperature for 1 h. After cooling, the reaction mixture was diluted with chloroform (20 mL), washed with

saturated sodium bicarbonate solution (2×10 mL) and brine (10 mL). The organic phase was then dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude product was recrystallized from isopropanol to yield pure substituted quinoline-2-carboxanilides **5-5c**, **9-13c**.

N-(2-bromophenyl)quinoline-2-carboxamide (**5a**). Yield 61%; Mp. 134-135 °C; IR (Zn/Se ATR, cm^{-1}): 3277*w*, 1689*s*, 1588*m*, 1579*m*, 1543*m*, 1530*s*, 1496*m*, 1440*m*, 1427*m*, 1302*w*, 1132*w*, 1204*m*, 908*w*, 842*m*, 768*s*, 736*m*, 698*m*; ^{1}H-NMR (DMSO-d_6), δ: 10.82 (bs, 1H), 8.60 (d, *J*=8.5 Hz, 1H), 8.44 (d, *J*=8.3 Hz, 1H), 8.23 (d, *J*=8.5 Hz, 1H), 8.13 (d, *J*=8.5 Hz, 1H), 8.07 (d, *J*=8.3 Hz, 1H), 7.87 (t, *J*=7.5 Hz, 1H), 7.64-7.77 (m, 2H), 7.44 (t, *J*=7.8 Hz, 1H), 7.10 (t, *J*=7.7 Hz, 1H); ^{13}C-NMR (DMSO-d_6), δ: 161.61, 148.71, 145.50, 138.60, 135.46, 132.58, 130.83, 129.26, 129.13, 128.55, 128.53, 128.08, 125.74, 121.39, 118.19, 114.08; HR-MS: for $C_{16}H_{12}BrN_2O$ $[M+H]^+$ calculated 327.0133 m/z, found 327.0138 m/z.

N-(3-bromophenyl)quinoline-2-carboxamide (**5b**). Yield 75%; Mp. 139-140 °C; IR (Zn/Se ATR, cm^{-1}): 3318*w*, 1687*m*, 1581*m*, 1519*m*, 1478*w*, 1408*m*, 1296*w*, 1124*m*, 1067*w*, 912*w*, 847*m*, 764*s*, 685*m*; ^{1}H-NMR (DMSO-d_6), δ: 10.89 (bs, 1H), 8.60 (d, *J*=8.3 Hz, 1H), 8.19-8.32 (m, 3H), 8.09 (d, *J*=8.0 Hz, 1H), 7.96 (d, *J*=7.5 Hz, 1H), 7.87-7.93 (m, 1H), 7.68-7.78 (m, 1H), 7.27-7.40 (m, 2H); ^{13}C-NMR (DMSO-d_6), δ: 163.02, 149.67, 145.86, 139.98, 138.21, 130.69, 130.67, 129.32, 128.97, 128.44, 128.14, 126.59, 122.66, 121.55, 119.14, 118.77; HR-MS: for $C_{16}H_{12}BrN_2O$ $[M+H]^+$ calculated 327.0133m/z, found 327.0143 m/z.

N-(4-bromophenyl)quinoline-2-carboxamide (**5c**). Yield 88%; Mp. 157-158 °C; IR (Zn/Se ATR, cm^{-1}): 3355*w*, 1693*s*, 1581*m*, 1522*s*, 1496*s*, 1423*w*, 1389*m*, 1305*w*, 1120*m*, 1095*w*, 1068*m*, 998*w*, 907*w*, 839*s*, 807*s*, 769*s*, 693*w*; ^{1}H-NMR (DMSO-d_6), δ: 10.84 (bs, 1H), 8.58 (d, *J*=8.5 Hz, 1H), 8.18-8.30 (m, 2H), 8.07 (d, *J*=8.3 Hz, 1H), 7.95 (d, *J*=8.8 Hz, 2H), 7.86-7.92 (m, 1H), 7.67-7.78 (m, 1H), 7.56 (d, *J*=8.8 Hz, 2H); ^{13}C-NMR (DMSO-d_6), δ: 162.86, 149.82, 145.87, 138.16, 137.74, 131.53, 130.64, 129.33, 128.94, 128.37, 128.12, 122.28, 118.77, 115.80; HR-MS: for $C_{16}H_{12}BrN_2O$ $[M+H]^+$ calculated 327.0133m/z, found 327.0129 m/z.

N-(2-chlorophenyl)quinoline-2-carboxamide (**9a**) [28]. Yield 70%; Mp. 130-131 °C; ^{1}H-NMR (DMSO-d_6), δ: 10.77 (bs, 1H), 8.58 (d, *J*=8.5 Hz, 1H), 8.43 (d, *J*=8.0 Hz, 1H), 8.21 (d, *J*=8.5 Hz, 1H), 8.10 (d, *J*=8.5 Hz, 1H), 8.05 (d, *J*=8.3 Hz, 1H), 7.85 (t, *J*=7.5 Hz, 1H), 7.64-7.75 (m, 1H), 7.54 (d, *J*=7.8 Hz, 1H), 7.39 (t, *J*=7.7 Hz, 1H), 7.10-7.24 (m, 1H); ^{13}C-NMR (DMSO-d_6), δ: 161.54, 148.70, 145.47, 138.50, 134.21, 130.75, 129.29, 129.20, 129.07, 128.46, 128.00, 127.88, 125.23, 123.38, 121.27, 118.15; HR-MS: for $C_{16}H_{12}ClN_2O$ $[M+H]^+$ calculated 283.0638 m/z, found 283.0652 m/z.

N-(3-chlorophenyl)quinoline-2-carboxamide (**9b**) [28]. Yield 81%; Mp. 127-128 °C; ^{1}H-NMR (DMSO-d_6), δ: 10.90 (bs, 1H), 8.58 (d, *J*=8.5 Hz, 1H), 8.18-8.31 (m, 2H), 8.15 (s, 1H), 8.07 (d, *J*=8.0 Hz, 1H), 7.82-7.97 (m, 2H), 7.66-7.78 (m, 1H), 7.40 (t, *J*=8.0 Hz, 1H), 7.11-7.23 (m, 1H); ^{13}C-NMR (DMSO-d_6), δ: 163.02, 149.67, 145.87, 139.85, 138.20, 133.12, 130.68, 130.36, 129.34, 128.98, 128.43, 128.14, 123.70, 119.82, 118.77; HR-MS: for $C_{16}H_{12}ClN_2O$ $[M+H]^+$ calculated 283.0638 m/z, found 283.0648 m/z.

N-(4-chlorophenyl)quinoline-2-carboxamide (**9c**). Yield 80%; Mp. 134-135 °C (Mp. 135-135.5 °C [29]); ^{1}H-NMR (DMSO-d_6), δ: 10.88 (bs, 1H), 8.58 (d, *J*=8.5 Hz, 1H), 8.17-8.30 (m, 2H), 8.08 (d, *J*=8.0 Hz, 1H), 8.01 (d, *J*=8.8 Hz, 2H), 7.84-7.93 (m, 1H), 7.68-7.77 (m, 1H), 7.43 (d, *J*=8.8 Hz, 2H); ^{13}C-NMR (DMSO-d_6), δ: 162.87, 149.85, 145.88, 138.16, 137.34, 130.65, 129.34, 128.95, 128.62, 128.37, 128.14, 127.69, 121.92, 118.78; HR-MS: for $C_{16}H_{12}ClN_2O$ $[M+H]^+$ calculated 283.0638 m/z, found 283.0631 m/z.

N-(2-fluorophenyl)quinoline-2-carboxamide (**10a**). Yield 63%; Mp. 116-117 °C; IR (Zn/Se ATR, cm^{-1}): 3328*w*, 1691*m*, 1615*m*, 1591*w*, 1530*s*, 1504*m*, 1477*w*, 1454*m*, 1428*m*, 1317*w*, 1247*w*, 1185*w*, 1126*m*, 1088*w*, 910*w*, 837*m*, 772*s*, 746*s*, 683*m*; ^{1}H-NMR (DMSO-d_6), δ: 10.48 (bs, 1H), 8.57 (d, *J*=8.5 Hz, 1H), 8.17-8.25 (m, 2H), 8.13 (d, *J*=8.5 Hz, 1H), 8.05 (d, *J*=8.0 Hz, 1H), 7.85 (t, *J*=7.3 Hz, 1H), 7.65-7.76 (m, 1H), 7.28-7.40 (m, 1H), 7.13-7.27 (m, 2H); ^{13}C-NMR (DMSO-d_6), δ: 162.00, 153.58 (d, $^{1}J_{FC}$=244 Hz), 148.95, 145.67, 138.39, 130.76, 129.24, 129.15 (d, $^{2}J_{FC}$=19.1 Hz), 128.45, 128.08, 125.70 (d, $^{3}J_{FC}$=11.0 Hz), 125.53 (d, $^{3}J_{FC}$=7.3 Hz), 124.63 (d, $^{4}J_{FC}$=3.7 Hz), 122.91, 118.37, 115.43 (d, $^{2}J_{FC}$=19.1 Hz); HR-MS: for $C_{16}H_{12}FN_2O$ $[M+H]^+$ calculated 267.0934 m/z, found 267.0950 m/z.

N-(3-fluorophenyl)quinoline-2-carboxamide (**10b**). Yield 80%; Mp. 126-127 °C; IR (Zn/Se ATR, cm^{-1}): 3343*w*, 1690*s*, 1588*m*, 1531*s*, 1504*m*, 1481*s*, 1409*s*, 1170*m*, 1137*m*, 899*m*, 841*s*, 791*m*, 768*s*, 738*m*, 682*s*; ^{1}H-NMR (DMSO-d_6), δ: 10.91 (bs, 1H), 8.58 (d, *J*=8.5 Hz, 1H), 8.16-8.31 (m, 2H), 8.08 (d, *J*=8.3 Hz, 1H), 7.95 (d, *J*=11.8 Hz, 1H), 7.86-7.92 (m, 1H), 7.79 (d, *J*=8.3 Hz, 1H), 7.68-7.75 (m, 1H), 7.35-7.49 (m, 1H), 6.96 (td, *J*=8.4 Hz, *J*=2.0 Hz, 1H); ^{13}C-NMR (DMSO-d_6), δ: 163.01, 162.15 (d, $^{1}J_{FC}$=241 Hz), 149.73, 145.86, 140.11 (d, $^{3}J_{FC}$=11.0 Hz), 138.18, 130.65, 130.31 (d, $^{3}J_{FC}$=9.5 Hz), 129.33, 128.97, 128.39, 128.12, 118.77, 116.15 (d, $^{4}J_{FC}$=2.9 Hz), 110.47 (d, $^{2}J_{FC}$=21.3 Hz), 107.09 (d, $^{2}J_{FC}$=26.4 Hz); HR-MS: for $C_{16}H_{12}FN_2O$ $[M+H]^+$ calculated 267.0934 m/z, found 267.0953 m/z.

N-(4-fluorophenyl)quinoline-2-carboxamide (**10c**) [30,28]. Yield 81%; Mp. 115-116 °C; ^{1}H-NMR (DMSO-d_6), δ: 10.83 (bs, 1H), 8.57 (d, *J*=8.3 Hz, 1H), 8.17-8.29 (m, 2H), 8.06 (d, *J*=8.0 Hz, 1H), 7.94-8.02 (m, 2H), 7.87 (td, *J*=7.7 Hz, *J*=1.3 Hz, 1H), 7.66-7.76 (m, 1H), 7.17-7.28 (m, 2H); ^{13}C-NMR (DMSO-d_6), δ: 162.76, 158.58 (d, $^{1}J_{FC}$=237 Hz), 150.03, 145.95, 138.18, 134.81 (d, $^{4}J_{FC}$=2.2 Hz), 130.67, 129.39, 128.98, 128.37, 128.17, 122.31 (d, $^{3}J_{FC}$=7.3 Hz), 118.83, 115.26 (d, $^{2}J_{FC}$=22.7 Hz); HR-MS: for $C_{16}H_{12}FN_2O$ $[M+H]^+$ calculated 267.0934 m/z, found 267.0954 m/z.

N-(2-methoxyphenyl)quinoline-2-carboxamide (**11a**) [31]. Yield 79%; Mp. 111-112 °C; IR (Zn/Se ATR, cm^{-1}): 3382*w*, 1676*s*, 1596*m*, 1532*s*, 1485*w*, 1454*m*, 1426*m*, 1334*w*, 1288*w*, 1253*m*, 1138*m*, 1129*m*, 1093*w*, 1020*s*, 951*w*, 908*m*, 873*w*, 840*m*, 820*w*, 770*s*, 732*s*; ^{1}H-NMR (DMSO-d_6), δ: 10.68 (bs, 1H), 8.59 (d, *J*=8.5 Hz, 1H), 8.49 (d, *J*=7.8 Hz, 1H), 8.25 (d, *J*=8.5 Hz, 1H), 8.15 (d, *J*=8.5 Hz, 1H), 8.07 (d, *J*=8.3 Hz, 1H), 7.87 (t, *J*=7.3 Hz, 1H), 7.67-7.75 (m, 1H), 7.11 (d, *J*=4.0 Hz, 2H), 7.01 (dt, *J*=8.2 Hz, *J*=4.2 Hz, 1H), 3.98 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 161.25, 149.34, 148.51, 145.62, 138.55, 130.82, 129.30, 129.06, 128.44, 128.14, 126.87, 124.25, 120.68, 118.84, 118.27, 110.91, 56.05; HR-MS: for $C_{17}H_{15}N_2O_2$ $[M+H]^+$ calculated 279.1134 m/z, found 279.1148 m/z.

N-(3-methoxyphenyl)quinoline-2-carboxamide (11**b**). Yield 77%; Mp. 117-118 °C; IR (Zn/Se ATR, cm^{-1}): 3352*w*, 1687*m*, 1589*m*, 1524*m*, 1503*m*, 1456*m*, 1425 *m*, 1334*w*, 1284*m*, 1203 *m*, 1157*m*, 1128*m*, 1049*s*, 906*w*, 876*m*, 854 *m*, 823 *w*, 798*w*, 762*s*, 740*s*, 685*m*; ^{1}H-NMR (DMSO-d_6), δ: 10.73 (bs, 1H), 8.58 (d, *J*=8.5 Hz, 1H), 8.19-8.32 (m, 2H), 8.07 (d, *J*=8.0 Hz, 1H), 7.82-7.96 (m, 1H), 7.65-7.79 (m, 2H), 7.59 (dd, *J*=8.0 Hz, *J*=1.0 Hz, 1H), 7.29 (t, *J*=8.2 Hz, 1H), 6.72 (dd, *J*=8.3 Hz, *J*=2.01 Hz, 1H), 3.78 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 162.70, 159.61, 149.99, 145.88, 139.53, 138.23, 130.67, 129.61, 129.37, 128.97, 128.37, 128.16, 118.75, 112.47, 109.68, 105.91, 55.09; HR-MS: for $C_{17}H_{15}N_2O_2$ $[M+H]^+$ calculated 279.1134 m/z, found 279.1129 m/z.

N-(4-methoxyphenyl)quinoline-2-carboxamide (**11c**) [28]. Yield 84%; Mp. 130-131 °C; ^{1}H-NMR (DMSO-d_6), δ: 10.65 (bs, 1H), 8.57 (d, *J*=8.5 Hz, 1H), 8.24 (d, *J*=8.5 Hz, 2H), 8.07 (d, *J*=7.8 Hz, 1H), 7.82-7.95 (m, 3H), 7.63-7.78 (m, 1H), 6.97 (d, *J*=9.0 Hz, 2H), 3.75 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 162.28, 155.80, 150.25, 145.90, 138.09, 131.47, 130.59, 129.32,

128.87, 128.22, 128.11, 121.85, 118.73, 113.87, 55.17; HR-MS: for $C_{17}H_{15}N_2O_2$ $[M+H]^+$ calculated 279.1134 m/z, found 279.1145 m/z.

N-(2-methylphenyl)quinoline-2-carboxamide (**12a**). Yield 71%; Mp. 100-101 °C; IR (Zn/Se ATR, cm^{-1}): 3334*w*, 1686*s*, 1587*s*, 1528*s*, 1498*M*, 1454*s*, 1427*s*, 1422 *m*, 1373*w*, 1305*m*, 1249*w*, 1201*w*, 1132*m*, 1091*w*, 1040*w*, 1013*w*, 981*w*, 954*m*, 932*w*, 907*m*, 872*m*, 842*s*, 793*w*, 765*s*, 750*s*, 731*s*, 681*s*; ^{1}H-NMR (DMSO-d_6), δ: 10.45 (bs, 1H), 8.60 (d, *J*=8.5 Hz, 1H), 8.24 (d, *J*=8.5 Hz, 1H), 8.17 (d, *J*=8.3 Hz, 1H), 8.08 (d, *J*=8.0 Hz, 1H), 7.95 (d, *J*=7.8 Hz, 1H), 7.83-7.91 (m, 1H), 7.69-7.77 (m, 1H), 7.22-7.31 (m, 2H), 7.08-7.16 (m, 1H), 2.37 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 161.92, 149.67, 145.74, 138.35, 135.97, 130.72, 130.42, 130.01, 129.38, 129.01, 128.38, 128.11, 126.40, 124.96, 122.65, 118.49, 17.49; HR-MS: for $C_{17}H_{15}N_2O$ $[M+H]^+$ calculated 263.1184 m/z, found 263.1182 m/z.

N-(3-methylphenyl)quinoline-2-carboxamide (**12b**). Yield 65%; Mp. 82-83 °C; IR (Zn/Se ATR, cm^{-1}): 3355*w*, 1685*m*, 1592 *m*, 1527*s*, 1503*s* 1457*w*, 1424 *m*, 1300*w*, 1171*w*, 1125*m*, 908*w*, 852*m*, 773*s*, 740*w*, 690*s*; ^{1}H-NMR (DMSO-d_6), δ: 10.66 (bs, 1H), 8.61 (d, *J*=8.5 Hz, 1H), 8.25 (dd, *J*=7.9 Hz, *J*=5.40 Hz, 2H), 8.10 (d, *J*=8.0 Hz, 1H), 7.90 (t, *J*=7.5 Hz, 1H), 7.67-7.84 (m, 3H), 7.27 (t, *J*=7.7 Hz, 1H), 6.96 (d, *J*=7.3 Hz, 1H), 2.32 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 162.54, 150.03, 145.88, 138.22, 138.20, 138.03, 130.68, 129.35, 128.94, 128.65, 128.35, 128.15, 124.75, 120.72, 118.70, 117.35, 21.23; HR-MS: for $C_{17}H_{15}N_2O$ $[M+H]^+$ calculated 263.1184 m/z, found 263.1191 m/z.

N-(4-methylphenyl)quinoline-2-carboxamide (**12c**). Yield 89%; Mp. 107-108 °C (Mp. 109.5-110 °C [29]); ^{1}H-NMR (DMSO-d_6), δ: 10.67 (bs, 1H), 8.59 (d, *J*=8.5 Hz, 1H), 8.18-8.30 (m, 2H), 8.08 (d, *J*=8.0 Hz, 1H), 7.79-7.94 (m, 3H), 7.72 (t, *J*=7.4 Hz, 1H), 7.18 (d, *J*=8.3 Hz, 2H), 2.27 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 162.51, 150.17, 145.93, 138.21, 135.86, 133.09, 130.69, 129.39, 129.24, 128.94, 128.35, 128.18, 120.27, 118.77, 20.59; HR-MS: for $C_{17}H_{15}N_2O$ $[M+H]^+$ calculated 263.1184 m/z, found 263.1193 m/z.

N-(2-trifluoromethylphenyl)quinoline-2-carboxamide (**13a**). Yield 74%; Mp. 120-121 °C; IR (Zn/Se ATR, cm^{-1}): 3316*w*, 1698*s*, 1590*s*, 1537*s*, 1498*w*, 1452*m*, 1423*m*, 1320*m*, 1288*m*, 1244*w*, 1202*w*, 1165*m*, 1124*m*, 1094*m*, 1054*m*, 1026*m*, 953*w*, 906*w*, 871*w*, 836*m*, 792*w*, 763*s*, 676*m*; ^{1}H-NMR (DMSO-d_6), δ: 10.78 (bs, 1H), 8.61 (d, *J*=8.3 Hz, 1H), 8.36 (d, *J*=8.3 Hz, 1H), 8.23 (d, *J*=8.3 Hz, 1H), 8.07 (t, *J*=8.3 Hz, 2H), 7.87 (t, *J*=7.5 Hz, 1H), 7.64-7.81 (m, 3H), 7.38 (t, *J*=7.7 Hz, 1H); ^{13}C-NMR (DMSO-d_6), δ: 162.05, 148.48, 145.53, 138.74, 135.14, 133.57, 131.01, 129.48 (q, $^2J_{FC}$=37 Hz), 129.21, 129.17, 128.68, 128.16, 126.41 (q, $^3J_{FC}$=5.1 Hz), 125.05, 124.10 (q, $^1J_{FC}$=274 Hz), 123.89 (q, $^3J_{FC}$=5.9 Hz), 118.31; HR-MS: for $C_{17}H_{12}F_3N_2O$ $[M+H]^+$ calculated 317.0902 m/z, found 317.0891 m/z.

N-(3-trifluoromethylphenyl)quinoline-2-carboxamide (**13b**). Yield 71%; Mp. 121-122 °C; IR (Zn/Se ATR, cm^{-1}): 3339*w*, 1692*s*, 1614*w*, 1536*m*, 1490*m*, 1424*w*, 1330*s*, 1223*w*, 1166*m*, 1109*s*, 1091*s*, 1065*m*, 952*w*, 933*w*, 874*s*, 844*m*, 08*s*, 771*s*, 744*w*, 698*s*; ^{1}H-NMR (DMSO-d_6), δ: 11.08 (bs, 1H), 8.59 (d, *J*=8.5 Hz, 1H), 8.46 (s, 1H), 8.17-8.31 (m, 3H), 8.08 (d, *J*=8.0 Hz, 1H), 7.89 (t, *J*=7.4 Hz, 1 H), 7.68-7.78 (m, 1 H), 7.61 (t, *J*=8.0 Hz, 1 H), 7.46 (d, *J*=7.5 Hz, 1H); ^{13}C-NMR (DMSO-d_6), δ: 163.26, 149.64, 145.90, 139.23, 138.21, 130.69, 129.86, 129.35 (q, $^2J_{FC}$=32 Hz), 129.34, 129.03, 128.45, 128.16, 124.20 (q, $^1J_{FC}$=273 Hz), 123.91, 120.24 (q, $^3J_{FC}$=3.7 Hz), 118.78, 116.61 (q, $^3J_{FC}$=3.7 Hz); HR-MS: for $C_{17}H_{12}F_3N_2O$ $[M+H]^+$ calculated 317.0902 m/z, found 317.0892 m/z.

N-(4-trifluoromethylphenyl)quinoline-2-carboxamide (**13c**) [30,32]. Yield 87%; Mp. 147-148 °C; ^{1}H-NMR (DMSO-d_6), δ: 11.02 (bs, 1H), 8.59 (d, *J*=8.3 Hz, 1H), 8.26 (d, *J*=8.5 Hz, 1H), 8.23 (d, *J*=8.3 Hz, 1H), 8.19 (d, *J*=8.5 Hz, 2H), 8.08 (d, *J*=8.0 Hz, 1H), 7.86-7.93 (m, 1H), 7.69-7.77 (m, 3H); ^{13}C-NMR (DMSO-d_6), δ: 163.27, 149.63, 145.88, 141.95, 138.23, 130.69, 129.38, 129.03, 128.48, 128.14, 125.96 (q, $^3J_{FC}$=3.7 Hz), 124.39 (q,

$^1J_{FC}$=271 Hz), 124.00 (q, $^2J_{FC}$=32 Hz), 120.29, 118.81; HR-MS: for $C_{17}H_{12}F_3N_2O$ $[M+H]^+$ calculated 317.0902 m/z, found 317.0890 m/z.

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