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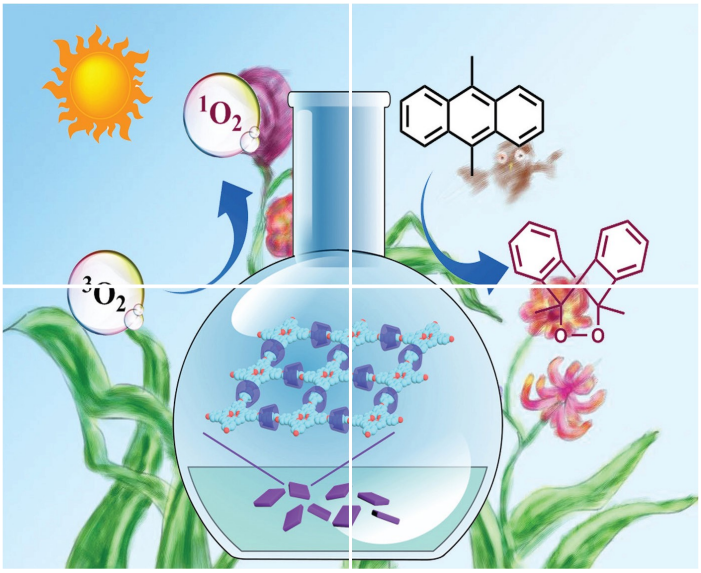

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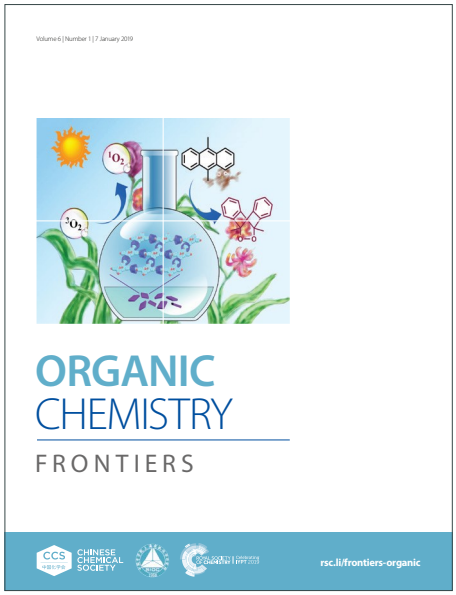

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Palladium Direct Arylation and Annulation for the Catalyzed Regiocontrolled Synthesis of Quinolone Derivatives

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A palladium-catalyzed strategy for the one pot synthesis of quinolone derivatives from (hetero)arylamides and functionalized 1,2-dihalobenzenes is described. The transformation likely proceeds through a Pd 1,4-migration from the amide nitrogen atom to the (hetero)aryl ring or via a direct *ortho*-metalation process, enabling first the *ortho*-arylation of the (hetero)arylamide. The key C–C bond is formed via the direct functionalization of two distinct C–H bonds, avoiding the need for prefunctionalized amide coupling partner. Subsequent intramolecular C–N bond formation via Pd-catalyzed coupling efficiently furnishes the quinolone scaffold. The protocol exhibits broad functional group tolerance, accommodating diverse substituents on the 1,2-dihalobenzene as well as a range of (hetero)aryl amides. This methodology allows the installation of functional groups at defined positions on the (hetero)aromatic rings. Additionally, the use of an air-stable, readily accessible palladium catalyst in combination with an inexpensive base enhances the synthetic utility of the process.

Introduction

2-Quinolone motifs are prevalent structural units in medicinal chemistry and are found in numerous clinically important drugs (Figure 1).[1] For example, indacaterol is used to relax bronchial smooth muscle and improve airflow obstruction in respiratory diseases. Rebamipide is employed for the treatment of gastric ulcers due to its mucosal protective properties. Brexpiprazole is an atypical antipsychotic approved for the treatment of major depressive disorder, while olutasidenib is an anticancer agent used to treat relapsed or refractory acute myeloid leukemia. Zavegepant is a recently developed medication for the acute treatment of migraine. In addition, PJ-34, which contains a phenanthridin-6(5H)-one core, is widely used in laboratory studies of cancer and inflammation.[2a] YCJ-02 is used in cancer research, particularly for studying therapies targeting tumors with high Topoisomerase I activity.[2b] Currently, such compounds are generally prepared using several synthetic steps.[3] Therefore, the discovery of simpler methods for the preparation of derivatives of such compounds is currently an important research topic.

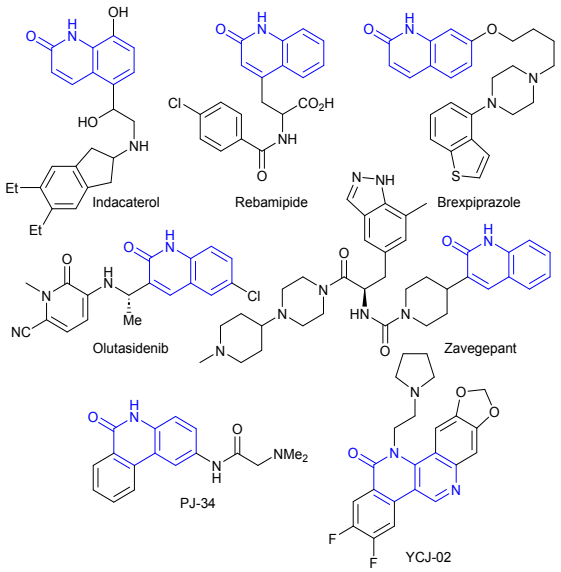

Figure 1. Representative examples of clinically relevant drugs containing a 2-quinolone core.

Catalytic C–H bond functionalization offers a straightforward and efficient approach to organic synthesis.[4] In particular, Pd-catalyzed C–H activation of heteroarenes, first reported by Ohta et al. in 1990, has become a robust and economical method for the synthesis of heteroarylated arenes.[5,6]

In the field of 2-quinolone derivative synthesis, intramolecular Pd-catalyzed direct arylation of 2-halobenzene-substituted amides, such as *N*-(2-bromophenyl)thiophene-2-carboxamide (Scheme 1a), represents an efficient route to these heterocycles.[7] Nevertheless, the requirement for a pre-functionalized 2-halophenyl substrate represents a significant

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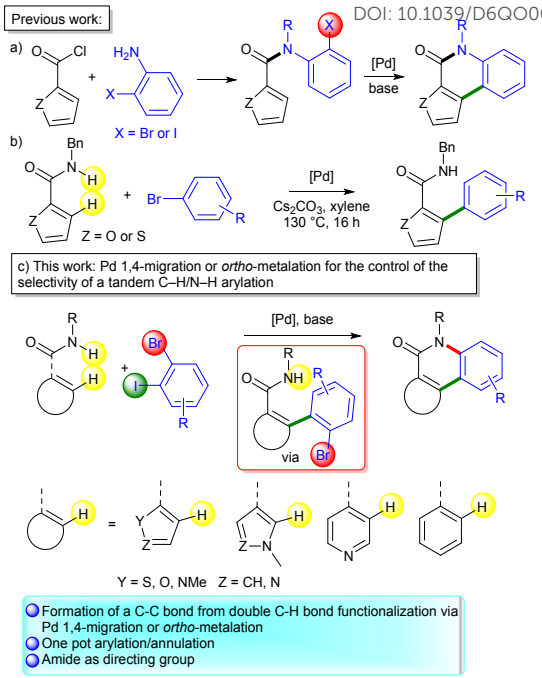
drawback. The preparation of such substrates requires an additional synthetic step. Consequently, although this approach provides efficient access to 2-quinolone frameworks, its dependence on pre-functionalized substrates highlights the need for more direct and convergent synthetic strategies. In 2017, Banerji and co-workers reported a one-pot synthesis of 2-quinolone derivatives through the tandem N–H/C–H arylation of amides with 1-bromo-2-iodobenzene.[8] According to the proposed mechanism, the reaction is initiated by Pd-catalyzed *N*-arylation of the amide, generating an *N*-(2-bromophenyl)benzamide intermediate. Subsequent intramolecular direct arylation then forms the C–C bond, furnishing the corresponding 2-quinolone derivative. The scope of this methodology was limited to benzamides and a single thiophene-2-carboxamide derivative, and exclusively employed 1-bromo-2-iodobenzene as the arylating partner. Despite their synthetic utility, these methods suffer from a limited substrate scope. In particular, reactions with amides containing benzothiophene-, benzofuran-, or pyrazole-based acyl fragments have not been reported. Moreover, the diversity of substituents tolerated on the aryl group attached to the amide nitrogen atom remains very limited.

In 2012, we reported that the Pd-catalyzed direct arylation of thiophene-2-carboxamides with aryl bromides predominantly afforded the C3-arylated thiophene derivatives in the presence of the relatively strong base Cs_2CO_3 (Scheme 1, b); whereas the use of KOAc as the base selectively promoted activation at the C5 position of the thiophene ring.[9] This reaction which likely proceeds via a Pd 1,4-migration from the amide nitrogen atom to the thienyl ring[10-12] or a via direct *ortho*-metalation process at β-C3-position of thiophene derivatives provides an effective method to functionalize such difficult to activate thienyl C-H bonds. As demonstrated by this 2012 study,[9] Pd-catalyzed direct arylation with aryl bromides preferentially led to C-C bond formation rather than C-N bond formation. On this basis, we sought to further investigate the reaction outcome using substituted 1-bromo-2-iodobenzenes. Such substrates should enable to elucidate which bond is formed first during the synthesis of quinolone derivatives. To the best of our knowledge, quinolone synthesis through C–H bond activation of (hetero)arylamides in a sequence involving initial C–C bond formation followed by annulation has not been reported. As such method would allow the preparation of several functionalized 2-quinolone derivatives such as phenanthridin-6-ones or benzonaphthyridinones in only one step from (hetero)arylamides its potential needed to be studied.

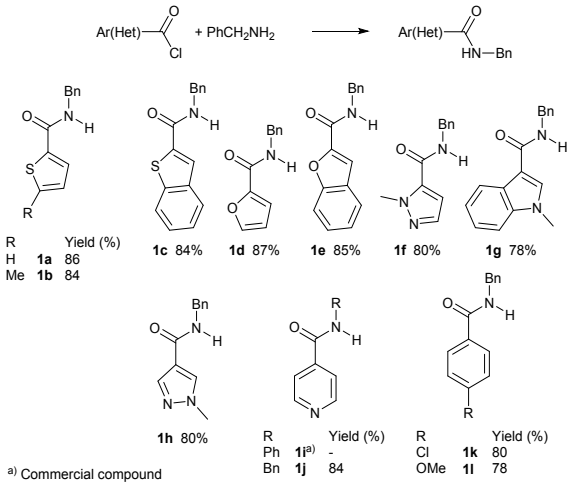
Herein, we report 1) on the mechanism of the coupling reactions of the Pd-catalyzed annulation of thiophene-2-carboxamide, 2) on the scope the reaction using substituted 1,2-dihalobenzenes and various (hetero)arylamides (Scheme 1, bottom).



Scheme 1. Pd-catalyzed direct arylations of (hetero)aryl-substituted carboxamides.

Results and discussion

Initially, the (hetero)benzamides required for this study were synthesized via the reaction of benzylamine with the corresponding (hetero)aryl carbonyl chlorides, following a previously reported procedure (Scheme 2).[9] The desired products **1a–1l** were obtained in excellent yields.



Scheme 2. Preparation of the carboxamides **1a**-**1l**.

First, the reaction outcome of the palladium-catalyzed coupling between *N*-benzylthiophene-2-carboxamide **1a** and 2-bromo-1-iodo-4-(trifluoromethyl)benzene was investigated (Table 1). Depending on the reaction mechanism, products **2c** or **2d** could be obtained via the formation of intermediates **2a** or **2b**. Using 5 mol% of $PdCl(C_3H_5)$(dppb) catalyst and Cs_2CO_3 as the base in

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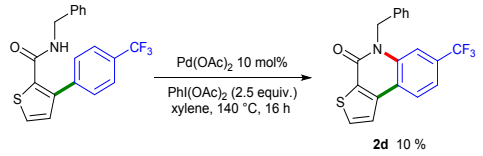
xylene at 140 °C,[9] only one isomer arising from the C–H/N–H arylation was observed by GC/MS analysis of the crude mixture (Table 1, entry 1). It should be mentioned that no trace of the intermediates **2a** and **2b** were detected, even when the reaction was performed at lower temperatures (100 °C and 120 °C), the intramolecular Pd-catalyzed reaction appearing to be fast compared to the intermolecular one. In order to determine which isomer (**2c** or **2d**) was formed in the course of the reaction, we prepared *N*-benzyl-3-(4-(trifluoromethyl)phenyl)thiophene-2-carboxamide by a reported procedure.[9] This reagent was then reacted with $Pd(OAc)_2$ (10 mol%) in the presence of $PhI(OAc)_2$, as such conditions have been described to give the corresponding thieno[2,3-*c*]quinolin-4-one (Scheme 3).[13] The product **2d** was obtained in only 10% yield. However, it confirms that the formation of thieno[2,3-*c*]quinolin-4-one proceeds via the initial formation of a C-C bond at thienyl C3-position to give **2b**, then an intramolecular reaction forms the C-N bond affording **2d**.



2d 10 %

Scheme 3. Determination of the structure of the annulation product **2d**.

Subsequently, we investigated the impact of several solvents on the outcome of the reaction using 5 mol% of $PdCl(C_3H_5)(dppb)$ catalyst and Cs_2CO_3 base. As shown in the table 1, entries 2 and 3, both DMF and NMP also produced the desired product **2b** with complete selectivity. However, a low conversion of **1a** was again observed. In contrast, the use of less polar solvent xylene, resulted in enhanced efficiency, yielding **2d** in 64% yield, with a conversion of **1a** of 91% (Table 1, entry 4). Diethyl carbonate and cyclopentyl methyl ether (CPME) also provided selective formation of **2d**; however, the conversion of **1a** remained moderate (Table 1, entries 5 and 6). The other carbonate bases, Na_2CO_3 and K_2CO_3, using xylenes as the solvent, led to unsatisfactory results due to poor conversion of **1a** (Table 1, entries 7 and 8). The use of acetate bases, KOAc, and CsOAc resulted in a reversed selectivity of the reaction, favoring the formation of the C5-arylated thiophene **2e** (Table 1, entries 9 and 10). A similar selectivity in favor of the formation of product **2e** was observed when the PivOK base was used, but again a low conversion of **1a** was observed (Table 1, entry 11). These reversed selectivities, which depend on the nature of the base, are consistent with a concerted metalation-deprotonation (CMD) mechanism for reactions involving acetate or pivalate bases, and a coordination-assisted mechanism for reactions involving Cs_2CO_3 base. Then a few different catalysts were employed. Phosphine-free $Pd(OAc)_2$ catalyst led to a poor conversion of **1a** (Table 1, entry 13). The use of $Pd(OAc)_2$ associated to the phosphine ligands dppe, dppb or PPh_3, resulted in improved conversions of **1a** with complete selectivities in **2d** (Table 1, entries 14-16). The $PdCl_2(dppb)$ catalyst led to a good conversion of **1a**, but the formation of some side-products was also observed, and desired product **2d** was only isolated in 47% yield (Table 1, entry 17). Reducing the catalyst loading of $Pd(OAc)_2$ / 2 PPh_3 from 5 mol% to 2 mol% resulted in a lower yield of product **2d**, due to increased formation of side products (Table 1, entry 18). Using a 1:1 $Pd(OAc)_2$ / PPh_3 ratio proved effective, affording the desired product **2d** in a yield comparable to that obtained with a 1:2 ratio (Table 1, entry 19). In contrast, increasing the ligand loading to a 1:4 $Pd(OAc)_2$ / PPh_3 ratio led to a significant decrease in the yield of **2d**, again due to the formation of side products (Table 1, entry 20). Decreasing the reaction temperature from 150 °C to 120 °C had little effect on the reaction outcome, providing very high conversion of **1a** and a good yield of **2d** (Table 1, entry 21). In contrast, performing the reaction at 100 °C resulted in only 5% yield of **2d**, due to the low conversion of **1a** (Table 1, entry 22).

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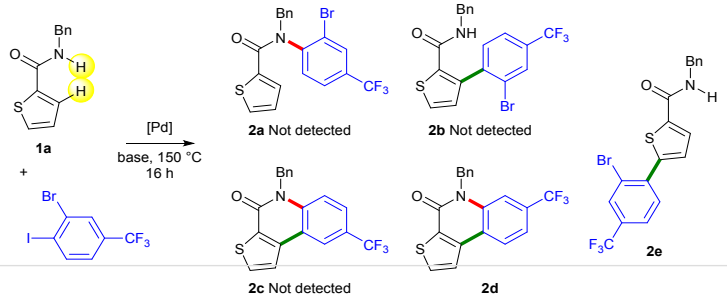
Table 1. Influence of the reaction conditions on the Pd-catalyzed coupling of *N*-benzylthiophene-2-carboxamide **1a** with 2-bromo-1-iodo-4-(trifluoromethyl)benzene.[a)]



Entry	Catalyst	Solvent	Base	Conv. (%)	Ratio **2d:2e**	Yield in **2d** (%)
1	$PdCl(C_3H_5)(dppb)$	DMA	Cs_2CO_3	35	100:0	24
2	$PdCl(C_3H_5)(dppb)$	NMP	Cs_2CO_3	<10	100:0	<5
3	$PdCl(C_3H_5)(dppb)$	DMF	Cs_2CO_3	42	100:0	27
4	$PdCl(C_3H_5)(dppb)$	Xylene	Cs_2CO_3	91	100:0	68
5	$PdCl(C_3H_5)(dppb)$	DEC	Cs_2CO_3	52	100:0	33
6	$PdCl(C_3H_5)(dppb)$	CPME	Cs_2CO_3	50	100:0	31
7	$PdCl(C_3H_5)(dppb)$	Xylene	Na_2CO_3	<5	-	-
8	$PdCl(C_3H_5)(dppb)$	Xylene	K_2CO_3	15	33:67	-
9	$PdCl(C_3H_5)(dppb)$	Xylene	KOAc	6	0:100	-
10	$PdCl(C_3H_5)(dppb)$	Xylene	CsOAc	66	0:100	52 of **2e**
11	$PdCl(C_3H_5)(dppb)$	Xylene	KOPiv	40	0:100	-
12	$PdCl(C_3H_5)(dppb)$	DMA	CsOAc	100	0:100	35 of **2e**
13	$Pd(OAc)_2$	Xylene	Cs_2CO_3	20	100:0	<2
14	$Pd(OAc)_2$ / dppb	Xylene	Cs_2CO_3	65	100:0	41
15	$Pd(OAc)_2$ / dppe	Xylene	Cs_2CO_3	86	100:0	64
16	$Pd(OAc)_2$ / 2 PPh_3	Xylene	Cs_2CO_3	95	100:0	70
17	$PdCl_2(dppb)$	Xylene	Cs_2CO_3	87	100:0	47
18	$Pd(OAc)_2$ / 2 PPh_3	Xylene	Cs_2CO_3	85	100:0	53[b)]
19	$Pd(OAc)_2$ / PPh_3	Xylene	Cs_2CO_3	93	100:0	69
20	$Pd(OAc)_2$ / 4 PPh_3	Xylene	Cs_2CO_3	84	100:0	34
21	$Pd(OAc)_2$ / 2 PPh_3	Xylene	Cs_2CO_3	94	100:0	69[c)]
22	$Pd(OAc)_2$ / 2 PPh_3	Xylene	Cs_2CO_3	15	100:0	5[d)]

[a)] [Pd] (0.05 equiv.), *N*-benzylthiophene-2-carboxamide **1a** (1 equiv.), 2-bromo-1-iodo-4-(trifluoromethyl)benzene (1.2 equiv.), base (3 equiv.), 140 °C, 16 h, isolated yields. b) $Pd(OAc)_2$ / 2 PPh_3 (0.02 equiv.). c) 120 °C. d) 100 °C.

Next, the scope of the C–H/N–H arylation of *N*-benzylthiophene-2-carboxamide **1a** with a series of substituted 2-bromo-1-iodobenzenes for the synthesis of thieno[2,3-*c*]quinolin-4(5H)-ones was investigated (Scheme 4). We first evaluated substrates bearing substituents in the *para*-position relative to the C–I bond under the standard conditions (5 mol% $Pd(OAc)_2$, 10 mol% PPh_3, Cs_2CO_3, xylene, 150 °C). Methoxy and methyl substituents were not tolerated, as no formation of the desired products was detected by GC/MS analysis of the crude reaction mixtures. This lack of reactivity may be attributed to the electron-donating nature of these substituents, which could hinder one of the two oxidative addition steps required for the reaction to proceed. In contrast, moderate yields of products **3** and **4** were obtained from 2-bromo-1-iodobenzenes bearing fluoro and chloro substituents, respectively. These results suggest that electron-withdrawing groups are beneficial for the transformation. This trend was further corroborated by the strongly electron-withdrawing nitrile substituent, which was well tolerated and afforded product **5** in 80% yield. The best yield, was obtained with methyl 3-bromo-4-iodobenzoate which gave product **6** in 76% yield. When 2-bromo-1-iodobenzenes bearing chloro- and trifluoromethyl-substituents in the *meta*-position relative to the C–I bond were employed, the corresponding products **7** and **8** were obtained in quite

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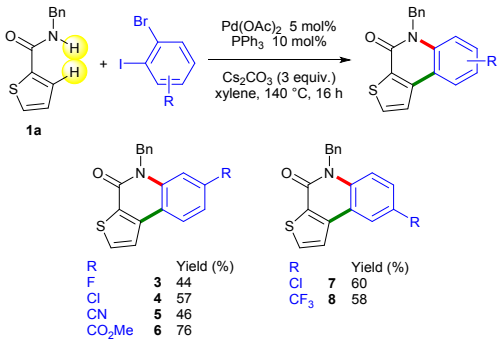
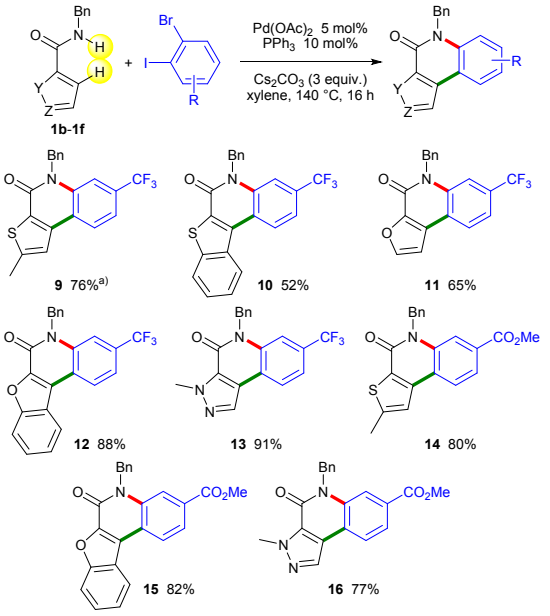
good yields (60% and 58%, respectively). Conversely, 1-bromo-3-fluoro-2-iodobenzene, bearing a fluorine atom *ortho* to the iodo substituent, was unreactive.



Scheme 4. Pd-catalyzed direct arylation of *N*-benzylthiophene-2-carboxamide **1a** followed by annulation.

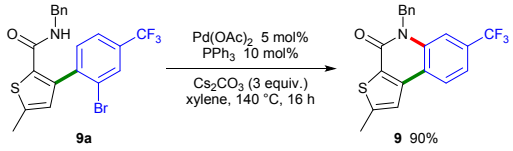
Then, the scope of amides substituted at their C2-position by various heteroarenes was investigated using 2-bromo-1-iodo-4-(trifluoromethyl)benzene as the coupling partner (Scheme 5). Incorporation of a 5-methylthiophene moiety **1b** afforded the desired product **9** in slightly higher yield compared to *N*-benzylthiophene-2-carboxamide **1a**. The benzothiophene derivative **1c** was also quite well tolerated, delivering product **10** in 52% yield. Similarly, *N*-benzylfuran-2-carboxamide **1d** and *N*-benzylbenzofuran-2-carboxamide **1e** exhibited reactivity comparable to that of **1a**, providing products **11** and **12** in good yields. This method enables selective functionalization of the C3 position of the furan ring in **1d**, despite the C5 position generally being more reactive under Pd-catalyzed direct arylation conditions. Furthermore, the nitrogen-containing heteroarene *N*-benzyl-1-methyl-1H-pyrazole-5-carboxamide **1f** underwent smooth conversion to furnish product **13** in 91% yield. The reaction with these heteroarenes also proceeds nicely with a CO_2Me-substituted 1-bromo-2-iodobenzene, affording products **14**-**16** in 77-82% yield.



a) 8% of intermediate **9a** (see scheme 6) were also isolated.

Scheme 5. Pd-catalyzed direct arylation followed by annulation of heteroaryl-2-carboxamides.

In the course of the reaction between *N*-benzyl-5-methylthiophene-2-carboxamide **1b** and 2-bromo-1-iodo-4-(trifluoromethyl)benzene, intermediate **9a** was isolated in low yield along with product **9** (see scheme 5). To further confirm that C–C bond formation occurs prior to C–N bond formation, intermediate **9a** was subjected to the same reaction conditions as those described in Scheme 5. As anticipated, product **9** was formed from **9a**, supporting the proposed mechanistic pathway.



Scheme 6. Determination of the structure of the annulation product **9**.

Heteroarenes bearing an amide substituent at C3-position were also tolerated (Scheme 7). For example, from indole-3-carboxamide derivative **1h** and 2-bromo-1-iodo-4-(trifluoromethyl)benzene, the desired product **17** was obtained in 79% yield. *N*-benzyl-1-methyl-1H-pyrazole-4-carboxamide **1g** also furnished the desired 1,5-pyrazolo[4,3-*c*]quinolin-4-ones **18**-**20** in good yields upon reaction with CF_3, Cl, and CO_2Me substituted 1-bromo-2-iodobenzenes.

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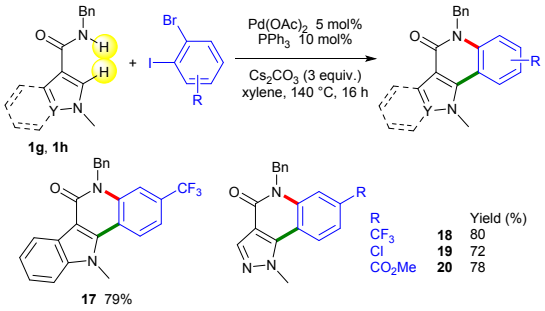
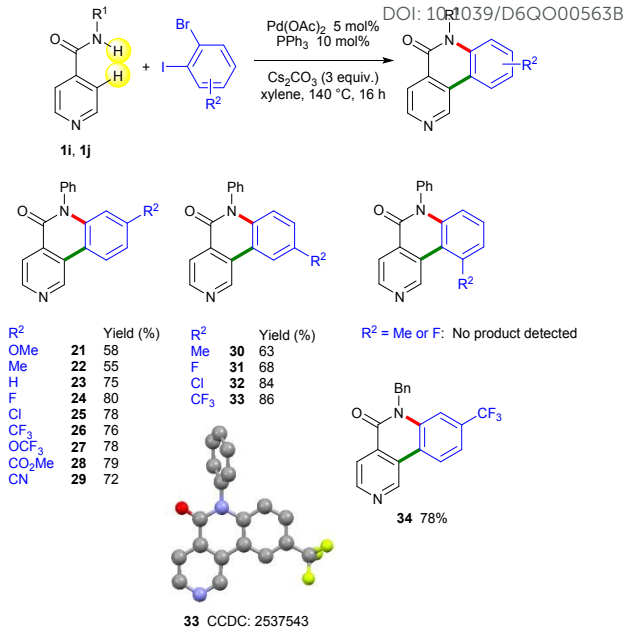


Scheme 7. Pd-catalyzed direct arylation followed by annulation of heteroaryl-3-carboxamides **1g** and **1h**.

The reactivity of *N*-phenylisonicotinamide **1i** was next examined (Scheme 8). This amide derivative exhibit broad compatibility with a diverse range of 1,2-dihalobenzenes. We first evaluated the effect of substituents positioned *para* to the C–I bond. Electron-donating methoxy and methyl groups on 2-bromo-1-iodobenzene furnished the corresponding products **21** and **22** in 58% and 55% yield, respectively. In the absence of substitution, 1-bromo-2-iodobenzene delivered product **23** in 75% yield. Substrates bearing poor electron-withdrawing fluoro and chloro substituents afforded products **24** and **25** in slightly improved yields of 80% and 78%, respectively. More strongly electron-withdrawing groups, including CF_3, OCF_3, and CO_2Me, were also well tolerated, providing products **26**-**28** in 76–79% yield. Notably, the strongly electron-withdrawing cyano group also proved compatible, delivering product **29** in 72% yield. When methyl, fluoro, chloro, and trifluoromethyl substituents were located *meta* to the C–I bond, comparable efficiencies were observed, and products **30–33** were obtained in 63–86% yield. The structure of product **33** was unambiguously confirmed by X-ray crystallographic analysis. This result demonstrates that C–C bond formation also occurs prior to C–N bond formation with this substrate. In contrast, *ortho* substitution proved detrimental: methyl- or fluoro-substituted substrates at the position *ortho* to the C–I bond were unreactive, and starting material **1i** was recovered unchanged. A benzyl substituent on the nitrogen atom of the isonicotinamide, in place of the phenyl group, was well tolerated and afforded product **34** in 78% yield. Overall, these results demonstrate that both electron-donating and electron-withdrawing substituents at the *para*- and *meta*-positions relative to the C–I bond on the 1-bromo-2-iodobenzenes are well tolerated under the optimized conditions, consistently delivering the desired products in good to high yields. This broad functional group tolerance enables the selective incorporation of diverse substituents at the 8- and 9-positions of the synthesized benzonaphthyridin-5-ones.



Scheme 8. Pd-catalyzed direct arylation followed by annulation of *N*-phenylisonicotinamide **1i** and *N*-benzylisonicotinamide **1j**.

By contrast, under identical reaction conditions, benzamides displayed significantly lower reactivity (Scheme 9). For example, the reaction of *N*-benzyl-4-chlorobenzamide **1k** with 2-bromo-1-iodo-4-methylbenzene or 2-bromo-1-iodo-4-methoxybenzene failed to afford the desired phenanthridinones, and the starting material **1k** was recovered. When the more electron-deficient 2-bromo-4-chloro-1-iodobenzene was employed, the desired phenanthridin-6(5H)-one **35** was obtained in only 15% yield, due to a low conversion of **1k**. In contrast, use of the more electron-deficient 2-bromo-1-iodo-4-(trifluoromethyl)benzene led to an improved yield of 51% in product **36**. The reaction of *N*-benzyl-4-chlorobenzamide **1k** with methyl 3-bromo-4-iodobenzoate was also successful affording target product **37** in 57% yield. Further enhancement was observed with 1-bromo-2-iodo-4-(trifluoromethyl)benzene, which afforded the desired product **38** in 64% yield. Conversely, benzamide **1l** bearing a *para*-methoxy substituent in the presence of 2-bromo-1-iodo-4-(trifluoromethyl)benzene was completely unreactive and was recovered, indicating that increased electron density within the arene ring of the 1,2-dihalobenzene alone is insufficient to confer the reactivity required. Overall, these results suggest that the present method is not reliable for the synthesis of phenanthridinone derivatives, as the outcome is highly sensitive to electronic variations in both the benzamide substrate and the 1,2-dihalobenzene coupling partner. This explains the widespread use of directing groups on amides, such as quinoline, to promote C–H bond activation of benzamides.[14]

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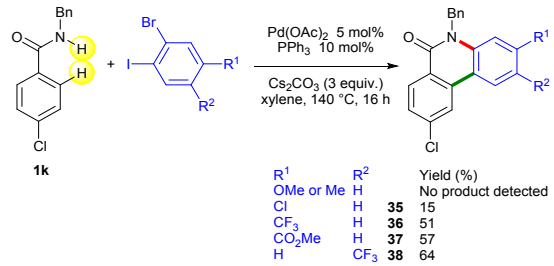
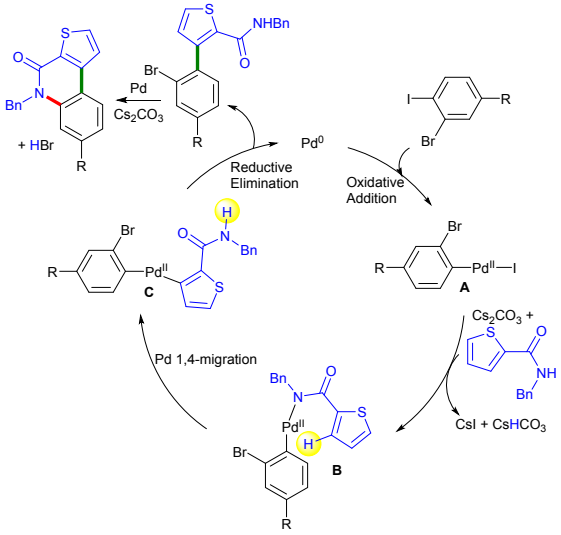


Scheme 9. Pd-catalyzed direct arylation followed by annulation using *N*-benzyl-4-chlorobenzamide **1k**.

Mechanism for accessing quinolone derivatives from *N*-benzylthiophene-2-carboxamide **1a** likely proceed *via* a Pd-1,4-migration — although a direct *ortho*-metalation process cannot be excluded — , followed by C–C and C–N bond-forming steps as described in the scheme 10. The first step of the catalytic cycle certainly involves the oxidative addition of the 1-bromo-2-iodobenzene derivative to palladium to give the intermediate **A**. Then, the deprotonation of *N*-benzylthiophene-2-carboxamide by Cs_2CO_3 followed by ligand exchange on palladium occurs to give the intermediate **B**. From **B**, a Pd-1,4-migration[10] to the C3-position of the thienyl ring of the thiophene-2-carboxamide ligand generates intermediate **C**. Then, reductive elimination regenerates a Pd(0) species and affords the C3-arylated thiophene derivative. Finally, the thieno[2,3-*c*]quinolin-4-ones are obtained via classical oxidative addition of the 3-(2-bromophenyl)thiophene-2-carboxamide to palladium followed by reductive elimination.



Scheme 10. Proposed catalytic cycle for the access to quinolone derivatives.

Conclusions

In conclusion, the Pd-catalyzed annulation method described herein provides an efficient strategy for the synthesis of quinolone derivatives from easily available (hetero)arylamides and 1,2-dihalobenzenes. The process is initiated by a regioselective *ortho*-arylation of the (hetero)arylamide moiety. In this key step, the amide substituent functions as a traceless directing group, ensuring regioselective (hetero)arene C–H bond functionalization without the need for additional directing auxiliaries. The C–C bond between the two (hetero)arenes is formed via the functionalization of two C–H bonds. Subsequent intramolecular C-N bond formation furnishes the quinolone scaffold. This methodology enables the installation of functional groups at defined positions on the (hetero)aromatic rings and demonstrates broad substrate scope, tolerating diverse (hetero)arenes on the amide as well as a variety of substituents on 1-bromo-2-iodobenzenes. Furthermore, the use of an air-stable palladium catalyst in combination with an inexpensive phosphine ligand and base enhances the practicability of the protocol. Overall, this strategy constitutes a powerful and operationally simple approach to quinolone derivatives and represents a valuable addition to the toolbox of metal-catalyzed C–H bond activation methodologies.

Experimental

General

$PdCl(C_3H_5)]_2$ (98%) was purchased from Aldrich. $Pd(OAc)_2$ (99.9%), dppb (1,4-bis(diphenylphosphino)butane) (98%), Cs_2CO_3 (99%), 1,2-dihalobenzenes, *N*-phenylisonicotinamide **1i** (98%) was purchased from Fluorochem. 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, ^{19}F and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer. High-resolution mass spectra were measured on a Thermo Fisher Scientific Q-Exactive spectrometer. Melting points were determined with a Kofler hot bench system.

General procedure for the preparation of products 1a-1h and 1j-1l:[9]

As a typical experiment, the phenylmethanamine (0.321 g, 3 mmol) was dissolved in CH_2Cl_2 (10 mL) and NEt_3 (2 mL) and the solution was cooled to 0 °C. The acyl chloride derivative (3.3 mmol, 1.1 equiv.) was added dropwise with stirring. The reaction mixture was then allowed to warm to room temperature and stirred for 16 h. The reaction was quenched by the addition of water (10 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel to afford the corresponding amide derivatives **1a–1l**. The NMR data of products **1a**-**1h**, **1j** and **1l** are in agreement with previously reported literature values.

N-Benzylthiophene-2-carboxamide (1a)[9]

From phenylmethanamine (0.321 g, 3 mmol) and thiophene-2-carbonyl chloride (0.484 g, 3.3 mmol), **1a** was isolated in 86% (0.560 g) yield as a white solid: mp 115-117 °C.

^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 3.7, 1.2 Hz, 1H), 7.48 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.42 – 7.25 (m, 5H), 7.06 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.70 (bs, 1H), 4.60 (d, *J* = 5.8 Hz, 2H).

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^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0, 138.9, 138.2, 130.1, 128.7, 128.2, 127.9, 127.7, 127.6, 44.0.

***N*-Benzyl-5-methylthiophene-2-carboxamide (1b)**[15]

From phenylmethanamine (0.321 g, 3 mmol) and 5-methylthiophene-2-carbonyl chloride (0.528 g, 3.3 mmol), **1b** was isolated in 84% (0.582 g) yield as a white solid: mp 144-146 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 3.7 Hz, 1H), 7.36 – 7.24 (m, 5H), 6.71 (dq, *J* = 3.7, 1.2 Hz, 1H), 6.65 (t, *J* = 5.7 Hz, 1H), 4.56 (d, *J* = 5.8 Hz, 2H), 2.51 (d, *J* = 1.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 145.3, 138.4, 136.2, 128.7, 128.6, 127.8, 127.5, 126.1, 43.8, 15.6.

***N*-Benzylbenzo[*b*]thiophene-2-carboxamide (1c)**[15]

From phenylmethanamine (0.321 g, 3 mmol) and benzo(*b*)thiophene-2-carbonyl chloride (0.648 g, 3.3 mmol), **1c** was isolated in 84% (0.673 g) yield as a white solid: mp 145-147 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.1 Hz, 1H), 7.82 (s, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.47 – 7.29 (m, 7H), 6.72 (t, *J* = 5.9 Hz, 1H), 4.66 (d, *J* = 5.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 140.9, 139.1, 138.3, 137.9, 128.8, 128.0, 127.7, 126.4, 125.4, 125.1, 124.9, 122.7, 44.2.

***N*-Benzylfuran-2-carboxamide (1d)**[9]

From phenylmethanamine (0.321 g, 3 mmol) and furan-2-carbonyl chloride (0.431 g, 3.3 mmol), **1d** was isolated in 87% (0.525 g) yield as a white solid: mp 110-112 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.38 (s, 1H), 7.36 – 7.25 (m, 5H), 7.12 (d, *J* = 3.5 Hz, 1H), 7.00 (bs, 1H), 6.46 (dd, *J* = 3.5, 1.8 Hz, 1H), 4.59 (d, *J* = 6.0 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 148.0, 144.0, 138.2, 128.7, 127.8, 127.5, 114.3, 112.1, 43.1.

***N*-Benzylbenzofuran-2-carboxamide (1e)**[16]

From phenylmethanamine (0.321 g, 3 mmol) and benzofuran-2-carbonyl chloride (0.596 g, 3.3 mmol), **1e** was isolated in 85% (0.640 g) yield as a white solid: mp 100-102 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.6 Hz, 1H), 7.51 (s, 1H), 7.49 – 7.18 (m, 9H), 4.69 (d, *J* = 6.0 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 154.8, 148.8, 138.1, 128.8, 128.0, 127.6, 126.9, 123.7, 122.7, 111.8, 110.6, 43.4.

***N*-Benzyl-1-methyl-1H-pyrazole-5-carboxamide (1f)**[17]

From phenylmethanamine (0.321 g, 3 mmol) and 1-methyl-1H-pyrazole-5-carbonyl chloride (0.477 g, 3.3 mmol), **1f** was isolated in 80% (0.516 g) yield as a white solid: mp 81-83 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, *J* = 6.0 Hz, 1H), 7.30 (d, *J* = 2.1 Hz, 1H), 7.28 – 7.13 (m, 5H), 6.59 (d, *J* = 2.1 Hz, 1H), 4.45 (d, *J* = 6.0 Hz, 2H), 4.03 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 138.0, 137.5, 135.3, 128.7, 127.6, 127.5, 106.8, 43.3, 39.1.

***N*-Benzyl-1-methyl-1H-indole-3-carboxamide (1g)**[16]

From phenylmethanamine (0.321 g, 3 mmol) and 1-methyl-1H-indole-3-carbonyl chloride (0.639 g, 3.3 mmol), **1g** was isolated in 78% (0.618 g) yield as a white solid: mp 179-181 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.7 Hz, 1H), 7.69 (s, 1H), 7.48 – 7.22 (m, 8H), 6.27 (bs, 1H), 4.73 (d, *J* = 5.7 Hz, 2H), 3.82 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 139.0, 137.3, 132.4, 128.7, 127.8, 127.4, 125.4, 122.6, 121.5, 120.2, 110.7, 110.1, 43.5, 33.3.

***N*-Benzyl-1-methyl-1H-pyrazole-4-carboxamide (1h)**[18]

From phenylmethanamine (0.321 g, 3 mmol) and 1-methyl-1H-pyrazole-4-carbonyl chloride (0.477 g, 3.3 mmol), **1h** was isolated in 80% (0.516 g) yield as a white solid: mp 158-160 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.75 (s, 1H), 7.40 – 7.23 (m, 5H), 6.54 (bs, 1H), 4.55 (d, *J* = 5.8 Hz, 2H), 3.86 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 138.5, 138.0, 131.8, 128.7, 127.8, 127.5, 118.7, 43.4, 39.2.

***N*-Benzylisonicotinamide (1j)**[19]

From phenylmethanamine (0.321 g, 3 mmol) and isonicotinoyl chloride (0.467 g, 3.3 mmol), **1j** was isolated in 84% (0.534 g) yield as a white solid: mp 87-89 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (t, *J* = 5.8 Hz, 1H), 8.39 (d, *J* = 5.7 Hz, 2H), 7.54 (d, *J* = 5.7 Hz, 2H), 7.23 – 6.90 (m, 5H), 4.44 (d, *J* = 5.9 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 150.0, 141.7, 137.9, 128.6, 127.5, 127.5, 121.4, 43.9.

***N*-Benzyl-4-chlorobenzamide (1k)**[20]

From phenylmethanamine (0.321 g, 3 mmol) and 4-chlorobenzoyl chloride (0.578 g, 3.3 mmol), **1k** was isolated in 80% (0.590 g) yield as a white solid: mp 163-165 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.40 – 7.30 (m, 5H), 6.46 (bs, 1H), 4.65 (d, *J* = 5.6 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 138.0, 137.8, 132.8, 128.9, 128.4, 128.0, 127.8, 44.3.

***N*-Benzyl-4-methoxybenzamide (1l)**[20]

From phenylmethanamine (0.321 g, 3 mmol) and 4-methoxybenzoyl chloride (0.563 g, 3.3 mmol), **1l** was isolated in 78% (0.564 g) yield as a white solid: mp 129-131 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.9 Hz, 2H), 7.37 – 7.27 (m, 5H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.71 (t, *J* = 6.0 Hz, 1H), 4.61 (d, *J* = 5.7 Hz, 2H), 3.84 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 162.2, 138.6, 128.9, 128.7, 127.8, 127.5, 126.7, 113.7, 55.4, 44.0.

General procedure for the preparation of products 2d, 3-38: As a typical experiment, the reaction of the (hetero)arylamide derivative **1a**-**1k** (1 mmol), 1,2-dihalobenzene (1.2 mmol) and Cs_2CO_3 (0.978 g, 3 mmol) at 140 °C during 16 h in xylene (4 mL) in the presence of $Pd(OAc)_2$ (0.011 g, 0.05 mmol), PPh_3 (0.026 g, 0.1 mmol) under argon affords the coupling product after evaporation of the solvent and purification by chromatography on silica gel.

5-Benzyl-7-(trifluoromethyl)thieno[2,3-*c*]quinolin-4-one (2d)

From *N*-benzylthiophene-2-carboxamide **1a** (0.217 g, 1 mmol) and 2-bromo-1-iodo-4-(trifluoromethyl)benzene (0.421 g, 1.2 mmol), **2d** was isolated in 66% (0.237 g) yield as a yellow solid: mp 181-183 °C.

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^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 5.2 Hz, 1H), 7.81 (d, *J* = 5.2 Hz, 1H), 7.70 (s, 1H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.42 – 7.22 (m, 5H), 5.71 (s, 2H).
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.5.
^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 141.2, 137.8, 135.9, 134.3, 132.2, 130.7 (q, *J* = 32.7 Hz), 129.0, 127.7, 126.9, 125.2, 122.5, 123.6 (q, *J* = 266.3 Hz), 121.2, 119.0 (q, *J* = 3.5 Hz), 113.3 (q, *J* = 4.3 Hz), 46.2.
HRMS calcd for $[M+H]^+$ $C_{19}H_{13}F_3NOS$ 360.0664, found: 360.0662.

_N_-benzyl-5-(2-bromo-4-(trifluoromethyl)phenyl)thiophene-2-carboxamide (2e)

The reaction of *N*-benzylthiophene-2-carboxamide **1a** (0.217 g, 1 mmol) and 2-bromo-1-iodo-4-(trifluoromethyl)benzene (0.421 g, 1.2 mmol), and CsOAc (0.576 g, 3 mmol) at 140 °C during 16 h in xylene (4 mL) in the presence of $PdCl(C_3H_5)$(dppb) (30.5 mg, 0.05 mmol) under argon affords the coupling product **2e** after evaporation of the solvent and purification by chromatography on silica gel in 52% (0.229 g) yield as a yellow solid: mp 149-151 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.66 – 7.60 (m, 2H), 7.52 (d, *J* = 3.9 Hz, 1H), 7.41 – 7.34 (m, 5H), 7.33 (d, *J* = 3.8 Hz, 1H), 6.29 (bs, 1H), 4.68 (d, *J* = 5.7 Hz, 2H).
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9.
^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4, 144.5, 139.9, 138.0, 137.9, 132.0, 131.7 (q, *J* = 33.5 Hz), 130.9 (q, *J* = 4.0 Hz), 129.0, 128.9, 128.0, 127.9, 127.8, 124.5 (q, *J* = 3.6 Hz), 123.0 (q, *J* = 272.5 Hz), 122.9, 44.2.
HRMS calcd for $[M+H]^+$ $C_{19}H_{14}BrF_3NOS$ 439.9848, found: 439.9852.

5-Benzyl-7-fluorothieno[2,3-*c*]quinolin-4-one (3)

From *N*-benzylthiophene-2-carboxamide **1a** (0.217 g, 1 mmol) and 2-bromo-4-fluoro-1-iodobenzene (0.361 g, 1.2 mmol), **3** was isolated in 44% (0.136 g) yield as a yellow white solid: mp 101-103 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.7, 6.1 Hz, 1H), 7.86 (d, *J* = 5.2 Hz, 1H), 7.72 (d, *J* = 5.3 Hz, 1H), 7.37 – 7.24 (m, 5H), 7.09 (dd, *J* = 11.3, 2.4 Hz, 1H), 7.02 (td, *J* = 8.0, 2.4 Hz, 1H), 5.64 (s, 2H).
^{19}F NMR (376 MHz, $CDCl_3$) δ -109.2.
^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8 (d, *J* = 247.5 Hz), 158.6, 141.9, 139.5 (d, *J* = 10.8 Hz), 136.0, 134.1, 129.5 (d, *J* = 1.9 Hz), 129.0, 127.5, 126.7, 126.2 (d, *J* = 10.0 Hz), 122.1, 115.4 (d, *J* = 2.5 Hz), 110.4 (d, *J* = 23.1 Hz), 103.3 (d, *J* = 27.2 Hz), 46.3.
HRMS calcd for $[M+H]^+$ $C_{18}H_{13}FNOS$ 310.0696, found: 310.0695.

5-Benzyl-7-chlorothieno[2,3-*c*]quinolin-4-one (4)

From *N*-benzylthiophene-2-carboxamide **1a** (0.217 g, 1 mmol) and 2-bromo-4-chloro-1-iodobenzene (0.380 g, 1.2 mmol), **4** was isolated in 57% (0.186 g) yield as a yellow white solid: mp 176-178 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 5.2 Hz, 1H), 7.71 (d, *J* = 5.3 Hz, 1H), 7.39 (d, *J* = 1.9 Hz, 1H), 7.37 – 7.23 (m, 6H), 5.64 (s, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 141.7, 138.9, 136.0, 134.9, 134.1, 130.4, 129.0, 127.5, 126.7, 125.6, 122.9, 122.2, 117.3, 116.1, 46.2.
HRMS calcd for $[M+H]^+$ $C_{18}H_{13}ClNOS$ 326.0401, found: 326.0399.

5-Benzyl-4-oxo-4,5-dihydrothieno[2,3-*c*]quinoline-7-carbonitrile (5)

From *N*-benzylthiophene-2-carboxamide **1a** (0.217 g, 1 mmol) and 3-bromo-4-iodobenzonitrile (0.370 g, 1.2 mmol), **5** was isolated in 46% (0.145 g) yield as a white solid: mp 235-237 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.2 Hz, 1H), 7.93 (d, *J* = 5.2 Hz, 1H), 7.80 (d, *J* = 5.3 Hz, 1H), 7.65 (d, *J* = 1.4 Hz, 1H), 7.54 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.40 – 7.24 (m, 5H), 5.68 (s, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 140.9, 137.9, 135.4, 134.6, 132.8, 129.2, 127.8, 126.5, 125.4, 122.5, 121.9, 119.9, 118.5, 112.2, 46.2.
HRMS calcd for $[M+H]^+$ $C_{19}H_{13}N_2OS$ 317.0743, found: 317.0742.

Methyl 5-benzyl-4-oxo-4,5-dihydrothieno[2,3-*c*]quinoline-7-carboxylate (6)

From *N*-benzylthiophene-2-carboxamide **1a** (0.217 g, 1 mmol) and methyl 3-bromo-4-iodobenzoate (0.341 g, 1.2 mmol), **6** was isolated in 76% (0.265 g) yield as a white solid: mp 204-206 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 1.5 Hz, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.90 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.86 (d, *J* = 5.2 Hz, 1H), 7.77 (d, *J* = 5.3 Hz, 1H), 7.39 – 7.30 (m, 4H), 7.30 – 7.22 (m, 1H), 5.72 (s, 2H), 3.94 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 158.3, 141.4, 137.7, 136.4, 134.0, 132.3, 130.2, 128.9, 127.5, 127.1, 124.6, 123.2, 122.6, 122.0, 117.6, 52.5, 46.1.
HRMS calcd for $[M+H]^+$ $C_{20}H_{16}NO_3S$ 350.0845, found: 350.0844.

5-Benzyl-8-chlorothieno[2,3-*c*]quinolin-4-one (7)

From *N*-benzylthiophene-2-carboxamide **1a** (0.217 g, 1 mmol) and 1-bromo-4-chloro-2-iodobenzene (0.380 g, 1.2 mmol), **7** was isolated in 60% (0.196 g) yield as a white solid: mp 142-144 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 2.3 Hz, 1H), 7.86 (d, *J* = 5.2 Hz, 1H), 7.71 (d, *J* = 5.3 Hz, 1H), 7.43 – 7.20 (m, 7H), 5.66 (s, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1, 141.1, 136.5, 136.2, 134.1, 131.3, 129.0, 128.9, 128.1, 127.5, 126.6, 124.0, 122.2, 119.9, 117.6, 46.2.
HRMS calcd for $[M+H]^+$ $C_{18}H_{13}ClNOS$ 326.0401, found: 326.0400.

5-Benzyl-8-(trifluoromethyl)thieno[2,3-*c*]quinolin-4-one (8)

From *N*-benzylthiophene-2-carboxamide **1a** (0.217 g, 1 mmol) and 1-bromo-2-iodo-4-(trifluoromethyl)benzene (0.421 g, 1.2 mmol), **8** was isolated in 58% (0.208 g) yield as a white solid: mp 121-123 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.92 (d, *J* = 5.2 Hz, 1H), 7.82 (d, *J* = 5.2 Hz, 1H), 7.64 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.48 (d, *J* = 8.9 Hz, 1H), 7.38 – 7.22 (m, 5H), 5.71 (s, 2H).
^{19}F NMR (376 MHz, $CDCl_3$) δ -61.8.
^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 141.6, 140.0, 135.9, 134.5, 131.4, 129.0, 127.6, 126.6, 125.5 (q, *J* = 3.5 Hz), 124.7 (q, *J* = 33.2 Hz), 123.9 (q, *J* = 271.6 Hz), 122.3, 121.9 (q, *J* = 3.9 Hz), 118.6, 116.6, 46.3.
HRMS calcd for $[M+H]^+$ $C_{19}H_{13}F_3NOS$ 360.0664, found: 360.0663.

5-Benzyl-2-methyl-7-(trifluoromethyl)thieno[2,3-*c*]quinolin-4(5H)-one (9)

From *N*-benzyl-5-methylthiophene-2-carboxamide **1b** (0.231 g, 1 mmol) and 2-bromo-1-iodo-4-(trifluoromethyl)benzene (0.421 g, 1.2 mmol), **9** was isolated in 76% (0.283 g) yield as a white solid: mp 179-181 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.2 Hz, 1H), 7.66 (s, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.46 (s, 1H), 7.38 – 7.23 (m, 5H), 5.68 (s, 2H), 2.73 (d, *J* = 1.1 Hz, 3H).
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.5.
^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 150.0, 141.7, 137.8, 136.1, 130.5, 130.3 (q, *J* = 32.5 Hz), 129.0, 127.6, 126.9, 125.1, 123.8 (q, *J* = 272.0 Hz), 121.0, 120.7, 118.8 (q, *J* = 3.6 Hz), 113.2 (q, *J* = 4.3 Hz), 46.1, 16.4.

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HRMS calcd for $[M+H]^+$ $C_{20}H_{15}F_3NOS$ 374.0821, found: 374.0820.

Intermediate *N*-benzyl-3-(2-bromo-4-(trifluoromethyl)phenyl)-5-methylthiophene-2-carboxamide **9a** was also isolated in low yield as a yellow oil:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.32 – 7.22 (m, 3H), 7.08 – 7.01 (m, 2H), 6.65 (s, 1H), 5.43 (bs, 1H), 4.40 (d, *J* = 5.4 Hz, 2H), 2.55 (d, *J* = 1.0 Hz, 3H).

5-Benzyl-3-(trifluoromethyl)benzo[4,5]thieno[2,3-*c*]quinolin-6(5H)-one (10)

From *N*-benzylbenzo[*b*]thiophene-2-carboxamide **1c** (0.267 g, 1 mmol) and 2-bromo-1-iodo-4-(trifluoromethyl)benzene (0.421 g, 1.2 mmol), **10** was isolated in 52% (0.213 g) yield as a white solid: mp 213-215 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 8.5 Hz, 1H), 8.67 (d, *J* = 9.5 Hz, 1H), 8.09 (d, *J* = 9.3 Hz, 1H), 7.79 (s, 1H), 7.71 – 7.58 (m, 3H), 7.41 – 7.24 (m, 5H), 5.76 (s, 2H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6.

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 142.8, 137.8, 135.7, 135.5, 134.6 (q, *J* = 1.9 Hz), 130.1 (d, *J* = 33.1 Hz), 129.0, 127.8, 127.5, 126.9, 125.8, 125.3, 124.7, 124.1, 123.6 (q, *J* = 272.6 Hz), 122.1, 119.0 (q, *J* = 3.6 Hz), 113.4 (q, *J* = 4.1 Hz), 46.6.

HRMS calcd for $[M+H]^+$ $C_{23}H_{15}F_3NOS$ 410.0821, found: 410.0819.

5-Benzyl-7-(trifluoromethyl)furo[2,3-*c*]quinolin-4(5H)-one (11)

From *N*-benzylfuran-2-carboxamide **1d** (0.201 g, 1 mmol) and 2-bromo-1-iodo-4-(trifluoromethyl)benzene (0.421 g, 1.2 mmol), **11** was isolated in 65% (0.223 g) yield as a white solid: mp 171-173 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 2.0 Hz, 1H), 7.70 (s, 1H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.39 – 7.23 (m, 5H), 7.15 (d, *J* = 2.0 Hz, 1H), 5.71 (s, 2H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.5.

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9, 148.9, 143.0, 137.2, 135.8, 130.5 (q, *J* = 32.7 Hz), 129.1, 129.0, 127.7, 126.85, 125.3, 123.8 (q, *J* = 272.5 Hz), 119.5, 119.1 (q, *J* = 3.5 Hz), 113.3 (q, *J* = 4.3 Hz), 106.1, 46.0.

HRMS calcd for $[M+H]^+$ $C_{19}H_{13}F_3NO_2$ 344.0893, found: 344.0893.

5-Benzyl-3-(trifluoromethyl)benzofuro[2,3-*c*]quinolin-6(5H)-one (12)

From *N*-benzylbenzofuran-2-carboxamide **1e** (0.251 g, 1 mmol) and 2-bromo-1-iodo-4-(trifluoromethyl)benzene (0.421 g, 1.2 mmol), **12** was isolated in 88% (0.346 g) yield as a white solid: mp 224-226 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 8.2 Hz, 1H), 8.30 (d, *J* = 7.9 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.78 (s, 1H), 7.68 (dd, *J* = 8.5, 7.2 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.41 – 7.23 (m, 5H), 5.79 (s, 2H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.5.

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.9, 154.7, 144.3, 136.9, 135.7, 130.3 (q, *J* = 32.8 Hz), 129.0, 129.0, 127.8, 126.9, 125.3, 124.7, 123.7 (q, *J* = 272.3 Hz), 123.4, 123.0, 122.7, 120.3, 119.4 (q, *J* = 3.6 Hz), 113.5, 113.4 (q, *J* = 4.2 Hz), 46.3.

HRMS calcd for $[M+H]^+$ $C_{23}H_{15}F_3NO_2$ 394.1049, found: 394.1049.

5-Benzyl-3-methyl-7-(trifluoromethyl)-3,5-dihydropyrazolo[3,4-*c*]quinolin-4-one (13)

From *N*-benzyl-1-methyl-1H-pyrazole-5-carboxamide **1f** (0.215 g, 1 mmol) and 2-bromo-1-iodo-4-(trifluoromethyl)benzene (0.421 g, 1.2 mmol), **13** was isolated in 91% (0.325 g) yield as a white solid: mp 161-163 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.61 (s, 1H), 7.51 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.31 – 7.25 (m, 3H), 5.64 (s, 2H), 4.51 (s, 3H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.3.

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2, 136.2, 135.8, 132.0, 129.4 (q, *J* = 32.7 Hz), 129.3, 129.0, 127.7, 126.6, 124.2, 123.7 (q, *J* = 272.4 Hz), 122.1, 119.6, 119.5 (q, *J* = 3.6 Hz), 113.3 (q, *J* = 4.3 Hz), 45.9, 39.0.

HRMS calcd for $[M+H]^+$ $C_{19}H_{15}F_3N_3O$ 358.1162, found: 358.1161.

Methyl 5-benzyl-2-methyl-4-oxo-4,5-dihydrothieno[2,3-*c*]quinoline-7-carboxylate (14)

From *N*-benzyl-5-methylthiophene-2-carboxamide **1b** (0.231 g, 1 mmol) and methyl 3-bromo-4-iodobenzoate (0.341 g, 1.2 mmol), **14** was isolated in 80% (0.290 g) yield as a yellow solid: mp 199-201 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 1.4 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.88 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.44 (q, *J* = 1.2 Hz, 1H), 7.39 – 7.30 (m, 4H), 7.26 – 7.23 (m, 1H), 5.70 (s, 2H), 3.93 (s, 3H), 2.71 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 158.0, 149.7, 141.9, 137.7, 136.5, 130.7, 130.0, 128.8, 127.5, 127.1, 124.5, 123.0, 121.9, 120.8, 117.6, 52.4, 46.0, 16.4.

HRMS calcd for $[M+H]^+$ $C_{21}H_{18}NO_3S$ 364.1002, found: 364.1001.

Methyl 5-benzyl-6-oxo-5,6-dihydrobenzofuro[2,3-*c*]quinoline-3-carboxylate (15)

From *N*-benzylbenzofuran-2-carboxamide **1e** (0.251 g, 1 mmol) and methyl 3-bromo-4-iodobenzoate (0.341 g, 1.2 mmol), **15** was isolated in 82% (0.314 g) yield as a white solid: mp 262-264 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.3 Hz, 1H), 8.31 (d, *J* = 7.9 Hz, 1H), 8.28 (s, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.41 – 7.31 (m, 4H), 7.26 (t, *J* = 7.1 Hz, 1H), 5.81 (s, 2H), 3.96 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 156.9, 154.8, 144.4, 136.8, 136.1, 129.8, 128.9, 128.8, 127.7, 127.1, 124.7, 124.6, 123.5, 123.4, 123.1, 122.8, 121.2, 117.8, 113.4, 52.5, 46.2.

HRMS calcd for $[M+H]^+$ $C_{24}H_{18}NO_4$ 384.1230, found: 384.1229.

Methyl 5-benzyl-3-methyl-4-oxo-4,5-dihydropyrazolo[3,4-*c*]quinoline-7-carboxylate (16)

From *N*-benzyl-1-methyl-1H-pyrazole-5-carboxamide **1f** (0.215 g, 1 mmol) and methyl 3-bromo-4-iodobenzoate (0.341 g, 1.2 mmol), **16** was isolated in 77% (0.267 g) yield as a white solid: mp 199-201 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.12 (s, 1H), 8.01 – 7.87 (m, 2H), 7.41 – 7.22 (m, 5H), 5.66 (s, 2H), 4.50 (s, 3H), 3.92 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 155.2, 136.2, 136.1, 132.2, 129.4, 129.0, 128.9, 127.6, 126.8, 123.8, 123.6, 122.3, 120.6, 117.6, 52.4, 45.8, 39.0.

HRMS calcd for $[M+H]^+$ $C_{20}H_{18}N_3O_3$ 348.1343, found: 348.1341.

5-Benzyl-11-methyl-3-(trifluoromethyl)-5,11-dihydro-6H-indolo[3,2-*c*]quinolin-6-one (17)

From *N*-benzyl-1-methyl-1H-indole-3-carboxamide **1g** (0.264 g, 1 mmol) and 2-bromo-1-iodo-4-(trifluoromethyl)benzene (0.421 g, 1.2 mmol), **17** was isolated in 79% (0.321 g) yield as a yellow solid: mp 241-243 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 8.7 Hz, 1H), 8.34 (d, *J* = 8.5 Hz, 1H), 7.68 (s, 1H), 7.51 – 7.43 (m, 2H), 7.43 – 7.36 (m, 2H), 7.35 – 7.22 (m, 5H), 5.66 (s, 2H), 4.15 (s, 3H).
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6.
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 139.9, 138.4, 138.0, 136.5, 130.0 (q, *J* = 32.9 Hz), 128.9, 127.5, 126.8, 125.3, 124.1, 123.6 (q, *J* = 272.4 Hz), 123.5, 122.5, 122.4, 117.8 (q, *J* = 3.4 Hz), 117.1, 113.4 (q, *J* = 4.3 Hz), 109.2, 108.7, 45.5, 33.5.
HRMS calcd for $[M+H]^+$ $C_{24}H_{18}F_3N_2O$ 407.1366, found: 407.1364.

5-Benzyl-1-methyl-7-(trifluoromethyl)-1,5-dihydropyrazolo[4,3-*c*]quinolin-4-one (18)
From *N*-benzyl-1-methyl-1H-pyrazole-4-carboxamide **1h** (0.215 g, 1 mmol) and 2-bromo-1-iodo-4-(trifluoromethyl)benzene (0.421 g, 1.2 mmol), **18** was isolated in 80% (0.286 g) yield as a white solid: mp 231-233 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 7.70 (s, 1H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.39 – 7.20 (m, 5H), 5.64 (s, 2H), 4.46 (s, 3H).
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9.
^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 138.6, 138.3, 137.3, 136.0, 131.2 (q, *J* = 32.8 Hz), 129.0, 127.6, 126.7, 123.4, 123.5 (q, *J* = 272.6 Hz), 118.6 (q, *J* = 3.5 Hz), 115.4, 114.5, 113.9 (q, *J* = 4.2 Hz), 45.8, 40.6.
HRMS calcd for $[M+H]^+$ $C_{19}H_{15}F_3N_3O$ 358.1162, found: 358.1161.

5-Benzyl-7-chloro-1-methyl-1,5-dihydropyrazolo[4,3-*c*]quinolin-4-one (19)
From *N*-benzyl-1-methyl-1H-pyrazole-4-carboxamide **1h** (0.215 g, 1 mmol) and 2-bromo-4-chloro-1-iodobenzene (0.380 g, 1.2 mmol), **19** was isolated in 72% (0.233 g) yield as a yellow solid: mp 287-289 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.05 (d, *J* = 8.6 Hz, 1H), 7.42 (d, *J* = 2.0 Hz, 1H), 7.38 – 7.22 (m, 6H), 5.59 (s, 2H), 4.42 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 158.7, 139.7, 138.8, 137.2, 136.1, 135.9, 129.0, 127.5, 126.5, 123.7, 122.5, 117.0, 113.5, 111.5, 45.8, 40.5.
HRMS calcd for $[M+H]^+$ $C_{18}H_{15}ClN_3O$ 324.0898, found: 324.0898.

Methyl 5-benzyl-1-methyl-4-oxo-4,5-dihydro-1H-pyrazolo[4,3-*c*]quinoline-7-carboxylate (20)
From *N*-benzyl-1-methyl-1H-pyrazole-4-carboxamide **1h** (0.215 g, 1 mmol) and methyl 3-bromo-4-iodobenzoate (0.341 g, 1.2 mmol), **20** was isolated in 78% (0.271 g) yield as a white solid: mp 240-242 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.18 (d, *J* = 1.5 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.90 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.36 – 7.22 (m, 5H), 5.66 (s, 2H), 4.42 (s, 3H), 3.93 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 158.7, 138.5, 138.4, 137.2, 136.5, 130.7, 128.9, 127.5, 126.9, 122.7, 118.2, 116.1, 114.6, 52.6, 45.7, 40.6.
HRMS calcd for $[M+H]^+$ $C_{20}H_{18}N_3O_3$ 348.1343, found: 348.1342.

8-Methoxy-6-phenylbenzo[*c*][2,6]naphthyridin-5-one (21)
From *N*-phenylisonicotinamide **1i** (0.198 g, 1 mmol) and 2-bromo-1-iodo-4-methoxybenzene (0.376 g, 1.2 mmol), **21** was isolated in 58% (0.175 g) yield as a white solid: mp 229-231 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (bs, 1H), 8.79 (bs, 1H), 8.33 (d, *J* = 8.9 Hz, 1H), 8.26 (d, *J* = 5.0 Hz, 1H), 7.69 – 7.62 (m, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 6.94 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.21 (d, *J* = 2.5 Hz, 1H), 3.72 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0, 160.8, 147.1, 145.3, 141.1, 137.7, 130.4, 129.7, 129.2, 128.8, 124.0, 120.9, 110.6, 110.1, 102.3, 55.4.
HRMS calcd for $[M+H]^+$ $C_{19}H_{15}N_2O_2$ 303.1128, found: 303.1127.

8-Methyl-6-phenylbenzo[*c*][2,6]naphthyridin-5(6H)-one (22)
From *N*-phenylisonicotinamide **1i** (0.198 g, 1 mmol) and 2-bromo-1-iodo-4-methylbenzene (0.356 g, 1.2 mmol), **22** was isolated in 55% (0.157 g) yield as a yellow solid: mp 199-201 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (bs, 1H), 8.83 (bs, 1H), 8.34 – 8.25 (m, 2H), 7.70 – 7.62 (m, 2H), 7.59 (t, *J* = 8.3 Hz, 1H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.2 Hz, 1H), 6.53 (s, 1H), 2.33 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6, 147.7, 145.6, 140.7, 139.6, 137.7, 130.6, 130.4, 129.1, 128.9, 128.4, 124.6, 122.4, 120.9, 117.5, 114.6, 21.8.
HRMS calcd for $[M+H]^+$ $C_{19}H_{15}N_2O$ 287.1179, found: 287.1179.

6-Phenylbenzo[*c*][2,6]naphthyridin-5-one (23)
From *N*-phenylisonicotinamide **1i** (0.198 g, 1 mmol) and 1-bromo-2-iodobenzene (0.340 g, 1.2 mmol), **23** was isolated in 75% (0.204 g) yield as a white solid: mp 240-242 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (bs, 1H), 8.85 (d, *J* = 5.2 Hz, 1H), 8.43 (d, *J* = 9.5 Hz, 1H), 8.31 (d, *J* = 5.1 Hz, 1H), 7.69 – 7.61 (m, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.44 – 7.33 (m, 4H), 6.75 (d, *J* = 9.0 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4, 148.3, 145.8, 139.5, 137.6, 131.1, 130.4, 130.1, 129.2, 128.9, 128.2, 123.4, 122.6, 120.9, 117.3, 117.0.
HRMS calcd for $[M+H]^+$ $C_{18}H_{13}N_2O$ 273.1022, found: 273.1020.

8-Fluoro-6-phenylbenzo[*c*][2,6]naphthyridin-5(6H)-one (24)
From *N*-phenylisonicotinamide **1i** (0.198 g, 1 mmol) and 2-bromo-4-fluoro-1-iodobenzene (0.361 g, 1.2 mmol), **24** was isolated in 80% (0.232 g) yield as a white solid: mp 186-188 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.84 (d, *J* = 5.2 Hz, 1H), 8.40 (dd, *J* = 8.9, 5.9 Hz, 1H), 8.28 (d, *J* = 5.1 Hz, 1H), 7.71 – 7.63 (m, 2H), 7.63 – 7.50 (m, 1H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.08 (ddd, *J* = 8.9, 7.7, 2.6 Hz, 1H), 6.45 (dd, *J* = 10.8, 2.5 Hz, 1H).
^{19}F NMR (376 MHz, $CDCl_3$) δ -107.7.
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4 (d, *J* = 249.8 Hz), 160.5, 148.1, 145.5, 141.2 (d, *J* = 10.5 Hz), 137.2, 130.6, 130.4 (d, *J* = 1.3 Hz), 129.5, 128.6, 127.8, 124.6 (d, *J* = 9.9 Hz), 120.9, 113.5 (d, *J* = 2.8 Hz), 111.1 (d, *J* = 22.8 Hz), 104.4 (d, *J* = 27.5 Hz).
HRMS calcd for $[M+H]^+$ $C_{18}H_{12}FN_2O$ 291.0928, found: 291.0927.

8-Chloro-6-phenylbenzo[*c*][2,6]naphthyridin-5(6H)-one (25)
From *N*-phenylisonicotinamide **1i** (0.198 g, 1 mmol) and 2-bromo-4-chloro-1-iodobenzene (0.380 g, 1.2 mmol), **25** was isolated in 78% (0.239 g) yield as a white solid: mp 209-211 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 8.86 (d, *J* = 5.2 Hz, 1H), 8.33 (d, *J* = 8.6 Hz, 1H), 8.28 (d, *J* = 5.3 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 2H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.33 (m, 3H), 6.73 (d, *J* = 2.1 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 148.6, 145.6, 140.4, 137.1, 136.1, 130.8, 130.6, 129.5, 128.7, 127.6, 123.8, 123.7, 120.9, 117.1, 115.5.
HRMS calcd for $[M+H]^+$ $C_{18}H_{12}ClN_2O$ 307.0633, found: 307.0632.

6-Phenyl-8-(trifluoromethyl)benzo[*c*][2,6]naphthyridin-5-one (26)
From *N*-phenylisonicotinamide **1i** (0.198 g, 1 mmol) and 2-bromo-1-iodo-4-(trifluoromethyl)benzene (0.421 g, 1.2 mmol), **26** was isolated in 76% (0.258 g) yield as a white solid: mp 172-174 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 8.93 (d, *J* = 5.2 Hz, 1H), 8.55 (d, *J* = 8.3 Hz, 1H), 8.33 (d, *J* = 5.1 Hz, 1H), 7.74 – 7.65 (m, 2H), 7.65 – 7.57 (m, 2H), 7.35 (d, *J* = 7.0 Hz, 2H), 6.99 (s, 1H).
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9.
^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 149.5, 146.0, 139.6, 136.8, 131.8 (q, *J* = 33.1 Hz), 131.7, 130.7, 129.7, 128.6, 127.1, 123.5, 123.4 (q, *J* = 272.4 Hz), 121.0, 119.8, 119.7 (q, *J* = 3.7 Hz), 114.2 (q, *J* = 4.2 Hz).
HRMS calcd for $[M+H]^+$ $C_{19}H_{12}F_3N_2O$ 341.0896, found: 341.0895.

6-Phenyl-8-(trifluoromethoxy)benzo[*c*][2,6]naphthyridin-5(6H)-one (27)

From *N*-phenylisonicotinamide **1i** (0.198 g, 1 mmol) and 2-bromo-1-iodo-4-(trifluoromethoxy)benzene (0.440 g, 1.2 mmol), **27** was isolated in 78% (0.278 g) yield as a white solid: mp 174-176 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 8.86 (s, 1H), 8.43 (d, *J* = 8.9 Hz, 1H), 8.29 (d, *J* = 5.1 Hz, 1H), 7.67 (dd, *J* = 8.4, 6.6 Hz, 2H), 7.60 (t, *J* = 8.2 Hz, 1H), 7.34 (d, *J* = 7.0 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 1H), 6.58 (d, *J* = 2.3 Hz, 1H).
^{19}F NMR (376 MHz, $CDCl_3$) δ -57.8.
^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 150.1 (q, *J* = 2.0 Hz), 148.7, 145.7, 140.8, 137.0, 130.9, 130.6, 129.6, 128.6, 127.4, 124.3, 120.9, 120.2 (q, *J* = 258.7 Hz), 115.5, 115.3, 109.6.
HRMS calcd for $[M+H]^+$ $C_{19}H_{12}F_3N_2O_2$ 357.0845, found: 357.0844.

Methyl 5-oxo-6-phenyl-5,6-dihydrobenzo[*c*][2,6]naphthyridine-8-carboxylate (28)

From *N*-phenylisonicotinamide **1i** (0.198 g, 1 mmol) and methyl 3-bromo-4-iodobenzoate (0.341 g, 1.2 mmol), **28** was isolated in 79% (0.261 g) yield as a white solid: mp 240-242 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 8.92 (d, *J* = 5.2 Hz, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 8.33 (d, *J* = 5.1 Hz, 1H), 7.99 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.68 (dd, *J* = 8.3, 6.5 Hz, 2H), 7.61 (t, *J* = 7.3 Hz, 1H), 7.43 (d, *J* = 1.6 Hz, 1H), 7.35 (d, *J* = 7.0 Hz, 2H), 3.87 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 160.2, 149.3, 146.2, 139.4, 137.1, 131.8, 131.4, 130.6, 129.5, 128.7, 127.4, 123.9, 122.8, 121.0, 120.6, 118.4, 52.5.
HRMS calcd for $[M+H]^+$ $C_{20}H_{15}N_2O_3$ 331.1077, found: 331.1077.

5-Oxo-6-phenyl-5,6-dihydrobenzo[*c*][2,6]naphthyridine-8-carbonitrile (29)

From *N*-phenylisonicotinamide **1i** (0.198 g, 1 mmol) and 2-bromo- 3-bromo-4-iodobenzonitrile (0.370 g, 1.2 mmol), **29** was isolated in 72% (0.214 g) yield as a white solid: mp 234-236 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.99 (s, 1H), 8.54 (d, *J* = 8.3 Hz, 1H), 8.36 (d, *J* = 5.1 Hz, 1H), 7.75 – 7.60 (m, 4H), 7.33 (d, *J* = 7.0 Hz, 2H), 7.04 (d, *J* = 1.5 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 150.0, 146.1, 139.7, 136.5, 131.9, 130.9, 129.9, 128.6, 126.0, 123.6, 121.1, 120.9, 120.7, 118.0, 113.4.
HRMS calcd for $[M+H]^+$ $C_{19}H_{12}N_3O$ 298.0975, found: 298.0974.

9-Methyl-6-phenylbenzo[*c*][2,6]naphthyridin-5(6H)-one (30)

From *N*-phenylisonicotinamide **1i** (0.198 g, 1 mmol) and 1-bromo-2-iodo-4-methylbenzene (0.356 g, 1.2 mmol), **30** was isolated in 63% (0.180 g) yield as a white solid: mp 243-245 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 8.85 (d, *J* = 5.2 Hz, 1H), 8.31 (d, *J* = 5.2 Hz, 1H), 8.22 (s, 1H), 7.65 (dd, *J* = 8.3, 6.6 Hz, 2H), 7.58 (d, *J* = 7.3 Hz, 1H), 7.34 (d, *J* = 7.0 Hz, 2H), 7.20 (dd, *J* = 8.6, 1.9 Hz, 1H), 6.64 (d, *J* = 8.6 Hz, 1H), 2.51 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2, 148.1, 145.7, 137.8, 137.5, 133.0, 131.2, 131.1, 130.3, 129.1, 128.8, 128.2, 122.5, 121.0, 117.2, 116.9, 21.0.
HRMS calcd for $[M+H]^+$ $C_{19}H_{15}N_2O$ 287.1179, found: 287.1178.

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9-Fluoro-6-phenylbenzo[*c*][2,6]naphthyridin-5(6H)-one (31)

From *N*-phenylisonicotinamide **1i** (0.198 g, 1 mmol) and 1-bromo-4-fluoro-2-iodobenzene (0.361 g, 1.2 mmol), **31** was isolated in 68% (0.197 g) yield as a white solid: mp 265-267 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 8.93 (s, 1H), 8.34 (s, 1H), 8.09 (dd, *J* = 9.3, 2.8 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 2H), 7.62 – 7.56 (m, 1H), 7.34 (d, *J* = 7.1 Hz, 2H), 7.11 (ddd, *J* = 9.3, 7.6, 2.8 Hz, 1H), 6.73 (dd, *J* = 9.3, 4.8 Hz, 1H).
^{19}F NMR (376 MHz, $CDCl_3$) δ -118.8.
^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 158.7 (d, *J* = 243.8 Hz), 148.9, 145.8, 137.5, 136.0 (d, *J* = 2.2 Hz), 131.4, 130.5, 129.3, 128.8, 121.1, 119.0 (d, *J* = 8.1 Hz), 118.3 (d, *J* = 8.1 Hz), 117.5 (d, *J* = 23.4 Hz), 108.6 (d, *J* = 24.2 Hz).
HRMS calcd for $[M+H]^+$ $C_{18}H_{12}FN_2O$ 291.0928, found: 291.0928.

9-Chloro-6-phenylbenzo[*c*][2,6]naphthyridin-5(6H)-one (32)

From *N*-phenylisonicotinamide **1i** (0.198 g, 1 mmol) and 1-bromo-4-chloro-2-iodobenzene (0.380 g, 1.2 mmol), **32** was isolated in 84% (0.258 g) yield as a white solid: mp 275-277 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 8.90 (s, 1H), 8.37 (d, *J* = 2.3 Hz, 1H), 8.31 (d, *J* = 5.0 Hz, 1H), 7.66 (dd, *J* = 8.3, 6.6 Hz, 2H), 7.62 – 7.55 (m, 1H), 7.35 – 7.30 (m, 3H), 6.69 (d, *J* = 9.0 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 149.0, 145.7, 138.0, 137.3, 131.3, 130.5, 130.0, 129.4, 129.2, 128.7, 127.2, 122.3, 121.0, 118.7, 118.3.
HRMS calcd for $[M+H]^+$ $C_{18}H_{12}ClN_2O$ 307.0633, found: 307.0633.

6-Phenyl-9-(trifluoromethyl)benzo[*c*][2,6]naphthyridin-5(6H)-one (33)

From *N*-phenylisonicotinamide **1i** (0.198 g, 1 mmol) and 1-bromo-2-iodo-4-(trifluoromethyl)benzene (0.421 g, 1.2 mmol), **33** was isolated in 86% (0.292 g) yield as a white solid: mp 233-235 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 8.92 (d, *J* = 5.2 Hz, 1H), 8.67 (s, 1H), 8.32 (d, *J* = 5.2 Hz, 1H), 7.68 (dd, *J* = 8.3, 6.6 Hz, 2H), 7.64 – 7.58 (m, 2H), 7.34 (d, *J* = 7.0 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 1H).
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.0.
^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 149.2, 145.7, 141.6, 137.1, 131.3, 130.6, 129.6, 128.7, 127.3, 126.5 (q, *J* = 3.5 Hz), 125.6 (q, *J* = 33.4 Hz), 123.9 (q, *J* = 272.1 Hz), 120.9, 120.1 (q, *J* = 4.0 Hz), 117.8, 117.1.
HRMS calcd for $[M+H]^+$ $C_{19}H_{12}F_3N_2O$ 341.0896, found: 341.0896.

6-Benzyl-8-(trifluoromethyl)benzo[*c*][2,6]naphthyridin-5(6H)-one (34)

From *N*-benzylisonicotinamide **1j** (0.212 g, 1 mmol) and 2-bromo-1-iodo-4-(trifluoromethyl)benzene (0.421 g, 1.2 mmol), **34** was isolated in 78% (0.276 g) yield as a yellow solid: mp 189-191 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 8.95 (s, 1H), 8.51 (d, *J* = 8.3 Hz, 1H), 8.41 (s, 1H), 7.67 (s, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.40 – 7.20 (m, 5H), 5.68 (s, 2H).
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9.

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5, 149.3, 145.9, 137.7, 135.3, 132.1 (q, *J* = 33.0 Hz), 131.2, 129.1, 127.9, 126.8, 123.7, 123.4 (q, *J* = 272.0 Hz), 121.2, 120.4, 119.7 (q, *J* = 3.5 Hz), 113.4 (q, *J* = 4.2 Hz), 46.9.
HRMS calcd for $[M+H]^+$ $C_{20}H_{14}F_3N_2O$ 355.1053, found: 355.1051.

5-Benzyl-3,9-dichlorophenanthridin-6(5H)-one (35)
From *N*-benzyl-4-chlorobenzamide **1k** (0.246 g, 1 mmol) and 2-bromo-4-chloro-1-iodobenzene (0.380 g, 1.2 mmol), **35** was isolated in 15% (0.053 g) yield as a yellow solid: mp 176-178 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 8.6 Hz, 1H), 8.21 (d, *J* = 1.9 Hz, 1H), 8.16 (d, *J* = 2.3 Hz, 1H), 7.62 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.38 (dd, *J* = 9.0, 2.3 Hz, 1H), 7.36 – 7.21 (m, 6H), 5.64 (s, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0, 139.8, 136.3, 135.9, 134.2, 131.2, 130.2, 129.2, 129.0, 128.6, 127.5, 126.4, 124.0, 123.2, 121.8, 119.8, 117.6, 46.6.
HRMS calcd for $[M+H]^+$ $C_{20}H_{14}Cl_2NO$ 354.0447, found: 354.0445.

5-Benzyl-9-chloro-3-(trifluoromethyl)phenanthridin-6(5H)-one (36)
From *N*-benzyl-4-chlorobenzamide **1k** (0.246 g, 1 mmol) and 2-bromo-1-iodo-4-(trifluoromethyl)benzene (0.421 g, 1.2 mmol), **36** was isolated in 51% (0.197 g) yield as a white solid: mp 164-166 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 8.6 Hz, 1H), 8.31 (d, *J* = 8.3 Hz, 1H), 8.29 (d, *J* = 2.0 Hz, 1H), 7.66 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.63 (s, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.38 – 7.25 (m, 5H), 5.67 (s, 2H).
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9.
^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1, 140.0, 137.8, 135.7, 134.1, 131.9 (q, *J* = 33.0 Hz), 131.2, 129.7, 129.0, 127.7, 126.8, 124.4, 124.2, 123.4 (q, *J* = 272.4 Hz), 122.2, 121.2, 119.1 (q, *J* = 3.7 Hz), 113.2 (q, *J* = 4.3 Hz), 46.7.
HRMS calcd for $[M+H]^+$ $C_{21}H_{14}ClF_3NO$ 388.0710, found: 388.0709.

Methyl 5-benzyl-9-chloro-6-oxo-5,6-dihydrophenanthridine-3-carboxylate (37)
From *N*-benzyl-4-chlorobenzamide **1k** (0.246 g, 1 mmol) and methyl 3-bromo-4-iodobenzoate (0.341 g, 1.2 mmol), **37** was isolated in 57% (0.215 g) yield as a white solid: mp 203-205 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 8.6 Hz, 1H), 8.25 (d, *J* = 1.9 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 8.10 (s, 1H), 7.88 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.62 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.40 – 7.25 (m, 5H), 5.68 (s, 2H), 3.93 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 161.1, 139.8, 137.6, 136.1, 134.3, 131.4, 131.1, 129.5, 128.9, 127.6, 127.0, 124.5, 123.6, 123.2, 122.3, 122.0, 117.5, 52.5, 46.6.
HRMS calcd for $[M+H]^+$ $C_{22}H_{17}ClNO_3$ 378.0892, found: 378.0890.

5-Benzyl-9-chloro-2-(trifluoromethyl)phenanthridin-6(5H)-one (38)
From *N*-benzyl-4-chlorobenzamide **1k** (0.246 g, 1 mmol) and 1-bromo-2-iodo-4-(trifluoromethyl)benzene (0.421 g, g, 1.2 mmol), **38** was isolated in 64% (0.248 g) yield as a white solid: mp 186-188 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 8.6 Hz, 1H), 8.43 (s, 1H), 8.27 (d, *J* = 2.0 Hz, 1H), 7.70 – 7.60 (m, 2H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.37 – 7.23 (m, 5H), 5.67 (s, 2H).
^{19}F NMR (376 MHz, $CDCl_3$) δ -61.9.
^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2, 140.1, 140.0, 135.7, 134.3, 131.2, 129.4, 129.0, 127.6, 126.7 (q, *J* = 3.5 Hz), 126.5, 125.0 (q, *J* = 33.2 Hz), 124.1 (q, *J* = 271.7 Hz), 124.0, 121.8, 120.8 (q, *J* = 3.9 Hz), 118.4, 116.6, 46.7.
HRMS calcd for $[M+H]^+$ $C_{21}H_{14}ClF_3NO$ 388.0711, found: 388.0710

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Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data underlying this study are available in the published article and its ESI.

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Data availability

The data underlying this study are available in the published article and its ESI. CCDC 2537543 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.