Metal-free construction of aminated isoquinoline frameworks from 2-(2-oxo-2-arylethyl) benzonitrile in an aqueous medium

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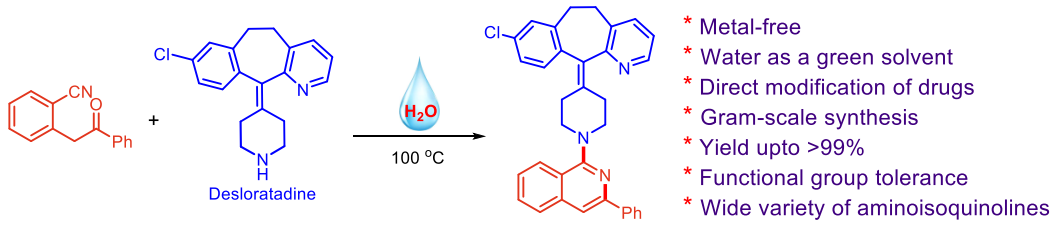


ABSTRACT: Herein, we report a metal-free protocol for the activation of nitrile towards the nucleophilic addition and subsequent annulation under an aqueous medium for the first time. The protocol divulges an efficient route for the construction of diversified aminated isoquinolines. Differently substituted primary as well as secondary amines underwent the reaction in a highly regioselective manner. The reaction is operationally simple, shows high functional group tolerance, easier modification of well-known drugs, and successfully extended to gram-scale synthesis.

INTRODUCTION

Isoquinolines represent important structural motifs in medicinal chemistry. Apart from forming the foundation of various medicines, isoquinoline and its derivatives play an important role in material science, functional material, chiral ligands, natural products, dyes, paints, etc.[1] Among the many known isoquinoline derivatives, aminated isoquinolines are of utmost importance owing to their ubiquity in pharmaceuticals, therefore, considerable attention has long been paid to their development (Figure 1).[2]

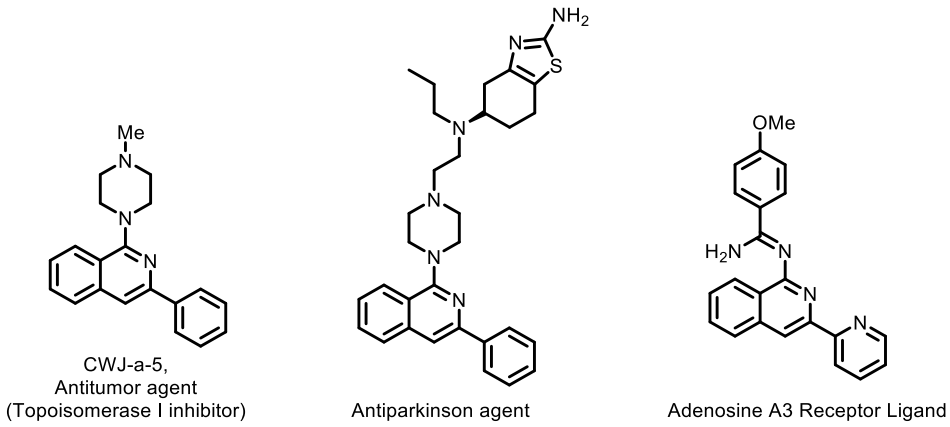
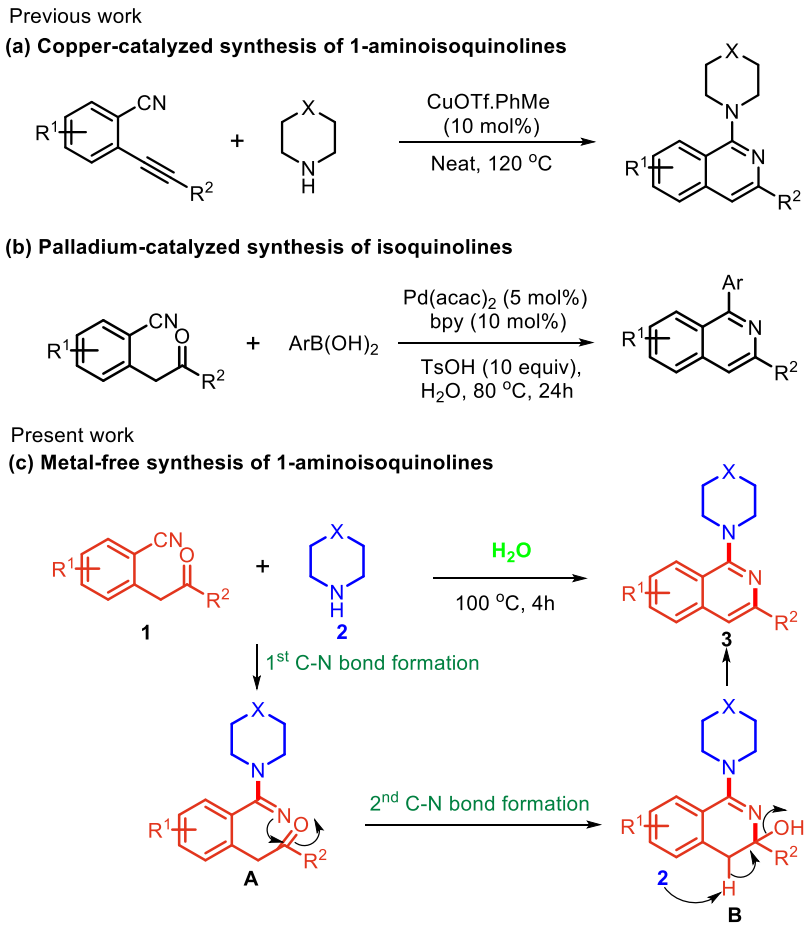


Figure 1. 1-aminoisoquinoline core containing bioactive molecules.

The reported procedures largely rely on the transition-metal-catalyzed C-N cross-coupling reactions[3] and S_NAr reactions of 1-haloisoquinolines with amines.[4] In the recent past, several groups have accomplished major advances in this field using C-H functionalization reactions.[5] Despite showing great potential, these procedures often require multiple steps for the pre-functionalization of substrates, use of toxic reagents, precious metal catalysts and show region-selectivity issues. Therefore, the development of a cost-economical approach addressing the drawbacks of previous protocols is highly desirable. In the last few years, many reports have focused on the reactivity of carbonitriles. The carbonitriles lack electrophilic properties and are generally activated by the transition-metal/acid/base catalysts towards nucleophilic additions and ensuing annulation.[6] Many groups have utilized differently substituted nitrile-containing functionalities for the synthesis of aryl/alkyl ketones, diketones, benzofurans, etc.[7] In all such reactions the nitrogen atom was not found to be incorporated into the product due to the

tendency of ketimines intermediates to undergo hydrolysis. It is imperative to develop protocols that could also make use of nitrogen of nitriles to produce *N*-heterocycles. Recently, a palladium-catalyzed nucleophilic addition of organoboron reagents to 2-(2-oxo-2-aryl/alkylethyl)benzonitriles was reported, which incorporates the nitrogen atom and results in the formation of isoquinolines (Scheme 1b).[8] In addition, based on domino electrophilic cyclization,[9] a Cu-catalysed domino reaction of 2-alkynylbenzonitriles (Scheme 1a) with secondary amines was also developed.[9a] To the best of our knowledge, no metal/additive-free reaction of carbonitriles in an aqueous medium has yet been delineated. Herein, we report an efficacious and direct protocol for the synthesis of aminated isoquinoline. The method utilizes readily accessible amines and 2-(2-oxo-2-aryl/alkylethyl)benzonitrile under acid/base/metal-free conditions in an aqueous medium (Scheme 1c).



Scheme 1. Different approaches for the activation of nitrile towards the synthesis of isoquinoline.

RESULTS AND DISCUSSION

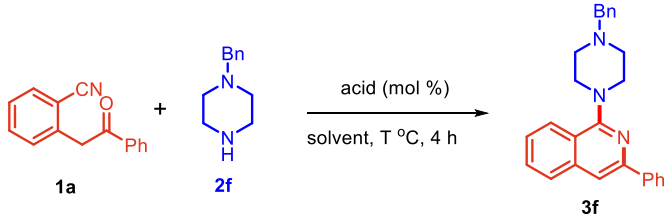
At the outset, 2-(2-oxo-2-phenylethyl)benzonitrile **1a** and 1-benzylpiperazine **2f** were chosen as a model substrate and allowed to react in toluene with 10 mol% of PTSA at 110 °C. To our delight, the reaction was completed in 4 h to yield 78% of the desired product **3f** (Table 1, entry 1). Increment in the loading of PTSA from 10 to 20 mol % enhanced the yield of product **3f** to 86% (entry 2). There was no significant improvement with increased loading of PTSA (entry 3). We next screened different solvents *i.e.*, THF, DCE, and MeOH, and found them to be unfavorable (entry 4-6). With DMF, the starting material was not completely consumed, giving only 56% yield of **3f** (entry 7). However, we obtained a comparable yield in DMSO (entry 8). Interestingly, when we performed this reaction in absence of PTSA, **3f** was obtained in 86% yield (entry 9). To top that, the use of water as a solvent furnished the product **3f** in 92% yield (entry 10). Decreasing the temperature slightly showed a marked impact on the yield, giving 99% yield of **3f** (entry 11). Further, decreasing the temperature led to a drop in the yield (entry 12).

We also evaluated the effect of the loading of amine on the reaction. Decreasing its loading from 0.6 mmol to 0.5 mmol provided a comparatively lower yield of the product (entry 13). This indicated that the amine might be self-catalyzing the reaction. While conducting the reaction in toluene, the absence of PTSA gave inferior results (entry 14).

With the established reaction conditions (Table 1, entry 11), we first explored the substrate scope of various cyclic secondary amines **2a-q** employing 2-(2-oxo-2-phenylethyl)benzonitrile **1a** as reacting partner (Scheme 2a). Initially, the reaction of **1a** with 6-membered amines **2a-d** afforded the corresponding amine substituted isoquinolines **3a-d** in excellent yields *i.e.,* 89-97%. 7-membered amine (Azepane) **2e** also reacted well to provide product **3e** with 96% yield. Electron-rich benzyl piperazine **2f-i** offered the desired isoquinolines **3f-i** in high yields (94-99%). Besides, 1-(bis(4-fluorophenyl)methyl)piperazine **2j** was efficiently converted to the desired product **3j** in 86% yield. It is noteworthy that various substitutions of *N*-atom of

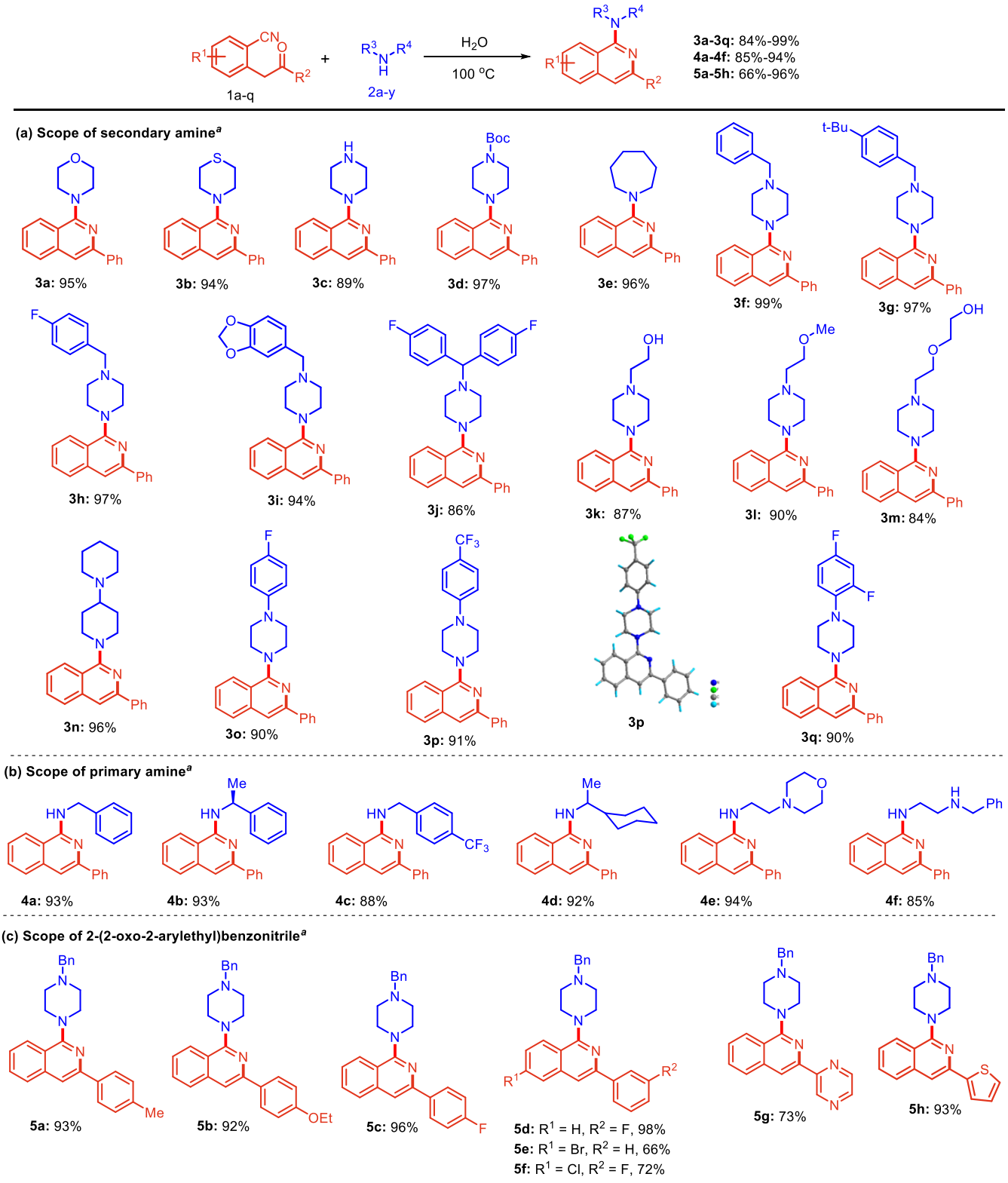
piperazine **2k-m** were also well tolerated and gave the expected products **3k-m** in 84-90% yields. Such scaffolds containing free -OH group are otherwise difficult to access with other methods.

Table 1. Optimization of reaction conditions[a]



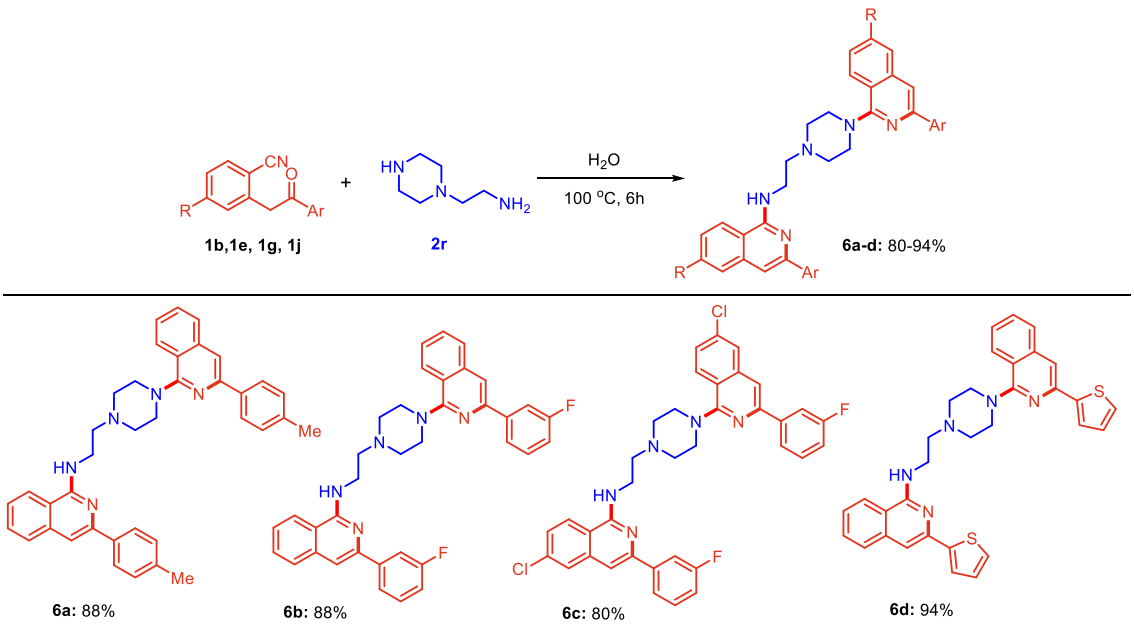
entry	solvent	acid (mol %)	temp (T °C)	yield (%)[b] **3f**
1	toluene	PTSA (10)	110	78
2	toluene	PTSA (20)	110	86
3	toluene	PTSA (30)	110	85
4	THF	PTSA (20)	110	n.r.
5	DCE	PTSA (20)	110	n.r.
6	MeOH	PTSA (20)	110	n.r.
7 [c]	DMF	PTSA (20)	110	56
8	DMSO	PTSA (20)	110	84
9	DMSO	-	110	86
10	H_2O	-	110	92
11	H_2O	-	100	99
12 [c]	H_2O	-	90	62
13[d]	H_2O	-	100	82
14 [c]	toluene	-	110	44

[a]Reactions were performed using 0.5 mmol of **1a**, and 0.6 mmol of **2f** in 2.0 mL of solvent. [b]Isolated yield. [c]Incomplete consumption of starting material. [d]0.5 mmol of **2f**.



Scheme 2. Scope for the synthesis of amino isoquinolines. [a]Reactions were performed using 0.5 mmol of **1**, and 0.6 mmol of **2** in 2.0 mL of H_2O at 100 °C for 4h. [b]Isolated yield. (**3p;** CCDC No. 2204378).

Additionally, the reaction of 1,4'-bipiperidine **2n** and various phenyl substituted piperazines **2o-q** containing -fluoro and trifluoromethyl group proceeded smoothly, affording the corresponding isoquinolines **3n-q** in 90-96% yields. Compound **3p** was further characterized by single crystal X-ray crystallography. Next, we focused on extending the versatility of the protocol by using primary amines **2t-y** with **1a**. We were pleased to obtain the free *NH*-containing isoquinolines as the desired product (Scheme 2b). The reaction of benzylamine **2t**, (*S*)-1-phenylethan-1-amine **2u,** and 1-(4-(trifluoromethoxy) phenyl)ethan-1-amine **2v** furnished the desired product **4a-c** in 88-93% yields. Likewise, 1-cyclohexylethan-1-amine **2w** and 2-morpholinoethan-1-amine **2x** also worked well to give **4d** and **4e** in 92% and 94% yield, respectively. Notably, N^1-benzylethane-1,2-diamine **2y** possessing secondary as well as primary amine was also amenable to the reaction conditions giving the product **4f** in 85% yield.



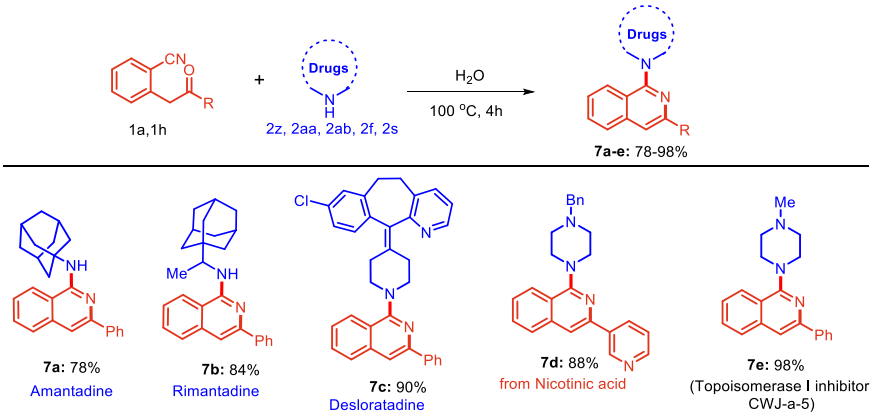
Scheme 3. Scope for the synthesis of bis-amino isoquinolines. [a]Reactions were performed using 0.5 mmol of **1**, and 0.3 mmol of **2r** in 2.0 mL of H_2O at 100 °C for 4h. [b]Isolated yield.

Thereafter, a broad range of 2-(2-oxo-2-arylethyl)benzonitrile **1b-g** was investigated (Scheme 2c) with 1-benzylpiperazine **2f** under the standard reaction conditions (Table 1, entry 11). It is evident from scheme 2c that there was no profound electronic effect of electron-releasing and

withdrawing substituents. Methyl, ethoxy, and fluoro **1b-c** at the *para* position of phenyl rings were tolerated well to provide excellent yield. *Meta* fluoro substituted substrate **1e** also reacted to give the product **5d** in 98% yield.

Further, various substitutions (fluoro, chloro, and bromo) at the *meta* and *para*-position of 2-(2-oxo-2-arylethyl)benzonitriles **1f** and **1g** were also found to be compatible provided the desired products **5e** and **5f** in 66% and 72% yields, respectively. Heteroaromatic substituents *i.e.,* pyrazine and thiophene **1i-j** also underwent the reaction smoothly to provide the corresponding product 5**g** and **5h** in 73% and 93% yields respectively. To further extend the scope of protocol, 2-(piperazin-1-yl)ethan-1-amine **2r,** bearing a primary as well as secondary amine was considered. Interestingly, the reaction of **2r** with substituted 2-(2-oxo-2-arylethyl)benzonitriles gave the bis-isoquinoline-containing products **6a-d** in 86-94% yields. In this case, both the amines acted as nucleophiles.

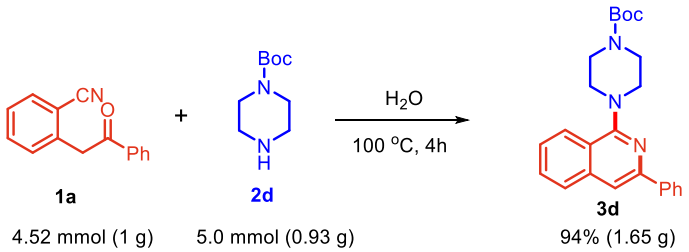
A large number of pharmaceuticals are derivatives of isoquinolines, therefore, we attempted to derivatize some amine-based drugs utilizing the developed protocol. Gratifyingly, the reaction of substrate **1a** with amantadine **2z**, rimantadine **2aa**, and desloratadine **2ab** delivered the corresponding products **7a-c** in very good yields.



Scheme 4. Scope of drugs containing isoquinolines. [a]Reactions were performed using 0.5 mmol of **1**, and 0.6 mmol of **2** in 2.0 mL of H_2O at 100 °C for 4h. [b]Isolated yield.

Furthermore, nicotinic acid-derived substrates **1h** with **2f** furnished the target products **7d** in

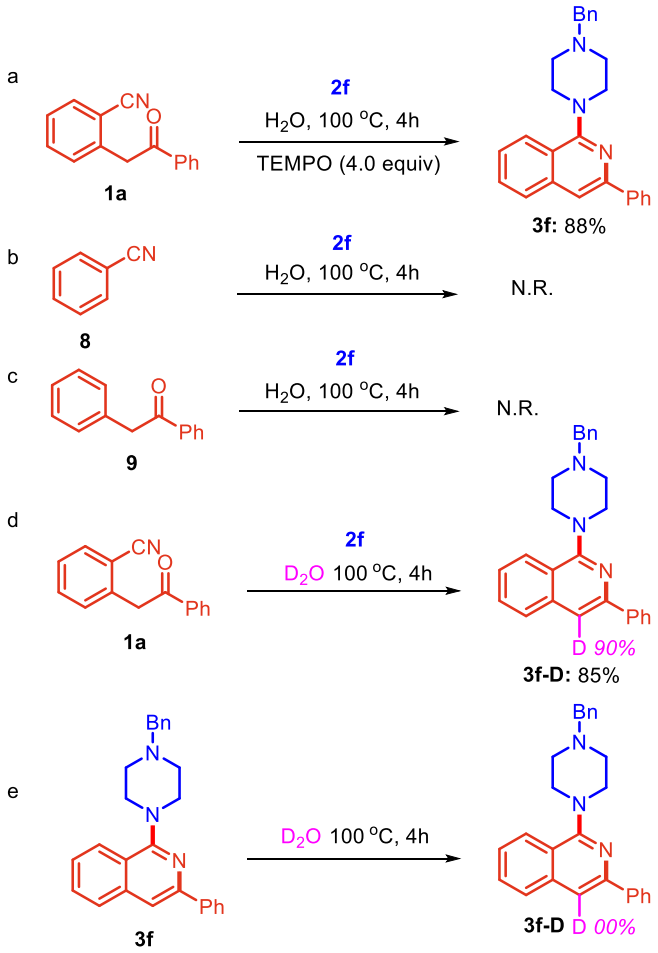
good yield. Similarly, substrate **1a** reacts with *N*-methyl piperazine **2s** to form compound **7e** in excellent yield. It is noteworthy that compound **7e** is a well-known antitumor agent (CWJ-a-5) acting as a topoisomerase I inhibitor. Additionally, to demonstrate the synthetic potential of the strategy, a reaction of substrate **1a** was conducted with *tert*-butyl piperazine-1-carboxylate **2d** at the gram scale, which yielded the targeted product **3d**, demonstrating its applicability for large-scale synthesis (Scheme 5).



Scheme 5. Gram-scale synthesis.

Next, a series of experiments were performed to gain some mechanistic insights. Initially, the reaction of substrate **1a** was conducted with **2f** in the presence of TEMPO (4.0 equiv) under identical reaction conditions (Table 1, entry 11), which did not show any profound impact on the yield of the product **3f** (Scheme 6a).

The result indicated that the reaction does not proceed through a radical mechanism. Further, to ascertain the electrophilic center for the amine, the reaction of benzonitrile **8** and 1,2-diphenylethan-1-one **9** was also performed with **2f** separately. However, no reaction was observed in both cases. This suggests that the reaction is sensitive to the relative arrangement of nitrile and 1,2-diphenylethan-1-one (Scheme 6b-c). It shows that the presence of both the groups adjacent is necessary for this reaction. Further, the reaction was performed in D_2O as a solvent under standard reaction (Table 1, entry 11) and product **3f-D** was obtained in 85% yield with 90% deuterium incorporation at cyclised position (Scheme 6d).

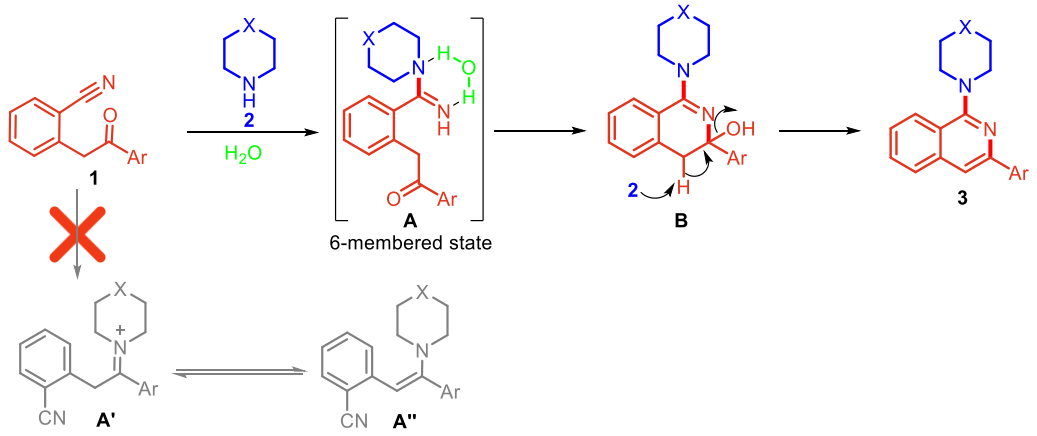


Scheme 6. Control experiments.

Further, to confirm whether the incorporation of deuterium in product **3f-D** is before the formation of **3f-D** or after the formation of **3f-D.** We perform a reaction using **3f** as a starting substrate in D_2O and found that there is no deuterium incorporation at cyclized position (Scheme 6e). It shows that active CH_2 protons present in substrate **1a** were exchangeable in D_2O due to keto-enol tautomerization and deuterium was incorporated before the formation of **3f-D**.

Based on the results of control experiments (Scheme 6), and precedents,[9] we have proposed a reasonable mechanistic pathway for the reaction (Scheme 7). The reaction proceeds through a nucleophilic attack of amine on the nitrile of 2-(2-oxo-2-phenylethyl)benzonitrile **1**. The nitrile is activated by an intricate network of hydrogen bonds forming a 6-membered transition state **A**.[10] Next, the intermediate **A** reacts with the carbonyl carbon leading to the cyclization to form intermediate **B**. Excess amine present in the reaction abstract the benzylic proton from intermediate **B** followed-by aromatization lead to the

formation of compound **3**.



Scheme 7. Plausible reaction mechanism.

CONCLUSION

In summary, the utilization of metal-free activation of nitrile in an aqueous medium towards sequential nucleophilic addition and annulation provides an economical and clean methodology for the generation of an array of diversified aminated isoquinolines in excellent yields. This modular synthesis shows wide functional group tolerance and was compatible with electron-rich, electron- deficient as well as hetero-aromatic moieties. The approach presented herein allows the effortless synthesis of aminated isoquinolines and thus could be of high pharmaceutical interest. The proposed reaction pathway is well supported by a series of control experiments.

EXPERIMENTAL SECTION

General Information and Method

^{1}H NMR (400 MHz) and ^{13}C{H}NMR (100 MHz) spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$. Chemical shifts for protons and carbons are reported in ppm from tetramethylsilane and are referenced to the carbon resonance of the solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet), coupling constants in Hertz and integration. High-resolution mass spectra were recorded on q-TOF electrospray mass

spectrometer. Crystal structure analysis was accomplished on single needles X-ray diffractometer. TLC analysis was performed on commercially prepared 60 F_{254} silica gel plates and visualized by either UV irradiation or by staining with I_2. All purchased chemicals were used as received. All melting points are uncorrected.

Reagents

All reagents were used directly as obtained commercially unless otherwise noted. HPLC grade ACN, THF, DMF, DMSO, MeOH, dioxane, hexane, ethyl acetate, and DCM were purchased from Merck Chemical Co. Sodium hydride, Aryl ester, 2-Methyl benzonitrile derivatives, Primary/Secondary amines, and Drugs were purchased from Sigma-Aldrich Chemical Co., Inc.

General procedure for the preparation of 2-(2-oxo-2-arylethyl)benzonitrile (1a-j)

To probe the viability of the designed tandem strategy, 2-(2-oxo-2-arylethyl)benzonitrile **1a-j** were readily prepared by standard reported general procedure[11]. Initially, sodium hydride (4.0 equiv) was added to dimethoxyethane (DME) under a nitrogen atmosphere and stirred at room temperature for 20 min then aryl ester 1.0 equiv, (10.0 mol) and 2-methylbenzonitrile 1.0 equiv, were added drop-wise via syringe and reaction mixture stirred at 90 ºC for 4 hours. After the complete consumption of starting material, the reaction was monitored by TLC and cooled to room temperature, quenched in the brine solution. The mixture was extracted with ethyl acetate (2×40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under a rotary evaporator. The residue was purified by column chromatography using (100-200) silica gel, furnishing the corresponding products as white solids. The structure and purity of the starting materials **1a-1j** were confirmed by spectral data ^{1}H NMR, ^{13}C NMR and HRMS.

2-(2-(4-Ethoxyphenyl)-2-oxoethyl)benzonitrile **(1c).** The product was obtained as pale-yellow solid (1.51 g, 57%): mp 105–106 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.9 Hz, 2H), 7.67 (d, J = 8.9 Hz, 1H), 7.54 (t, J = 7.7 Hz, 1H), 7.37 (d, J = 7.6 Hz, 2H), 6.94 (d, J = 8.9 Hz, 2H), 4.48 (s, 2H), 4.10 (q, J = 7.0 Hz, 2H), 1.44 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 163.4, 139.4, 132.9,

131.1, 130.9, 129.12, 127.6, 118.3, 114.5, 113.5, 63.6, 43.3, 14.6; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{17}H_{16}NO_2$ 266.1176, found 266.1178.

2-(2-(3-Fluorophenyl)-2-oxoethyl)benzonitrile **(1e).** The product was obtained as off pale-yellow solid (1.31 g, 55%): mp 107-108 °C: ^{1}H NMR (400 MHz $CDCl_3$) δ 7.84 (d, *J* = 7.7 Hz, 1H), 7.70 (t, *J* = 7.0 Hz, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.49 (dd, *J* = 13.5, 8.0 Hz, 1H), 7.43 – 7.35 (m, 2H), 7.30 (t, *J* = 8.2 Hz, 1H), 4.52 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 164.2, 161.7, 138.3, 138.1, 133.0, 132.9, 131.1, 130.7, 130.6, 127.9, 124.2, 121.0, 120.7, 117.9, 115.3, 115.1, 113.7, 43.7; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{15}H_{11}FNO$ 240.0819, found 240.0837.

4-Bromo-2-(2-oxo-2-phenylethyl)benzonitrile **(1f).** The product was obtained as light-brown solid (1.08 g, 36%): mp119-120 °C: ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.03 (d, *J* = 8.6 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.58 – 7.48 (m, 5H), 4.51 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 194.7, 140.4, 136.0, 134.5, 134.0, 133.8, 131.2, 129.0, 128.5, 128.0, 117.4, 112.7, 43.4; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{15}H_{11}Br^{81}NO$ 301.9998, found 301.9988.

4-Chloro-2-(2-(3-fluorophenyl)-2-oxoethyl)benzonitrile **(1g).** The product was obtained as light-brown solid (1.15 g, 42%): mp 123-124 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.8 Hz, 1H), 7.74 – 7.67 (m, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.51 (td, *J* = 8.0, 5.5 Hz, 1H), 7.40 (dd, *J* = 10.0, 1.8 Hz, 2H), 7.33 (td, *J* = 8.2, 2.6 Hz, 1H), 4.49 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 139.9, 139.6, 133.9, 131.6, 128.4, 124.2, 121.2, 121.0, 117.2, 115.3, 115.1, 112.2, 43.6; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{15}H_{10}ClFNO$ 274.0429, found 274.0437.

2-(2-oxo-2-(pyrazin-2-yl)ethyl)benzonitrile **(1i).** The product was obtained as light-brown solid (0.69 g, 31%): mp 165-166 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.79 (d, *J* = 2.4 Hz, 1H), 8.72 – 8.66 (m, 1H), 7.69 (d, *J* = 7.1 Hz, 1H), 7.56 (t, *J* = 8.3 Hz, 1H), 7.43 – 7.33 (m, 2H), 4.77 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 148.4, 146.9, 144.0, 143.7, 138.2, 133.0, 132.9, 131.2, 127.8, 117.9, 114.0, 43.20; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{13}H_{10}N_3O$ 224.0818, found 224.0823.

2-(2-Oxo-2-(thiophen-2-yl)ethyl)benzonitrile **(1j).** The product was obtained as brown solid (1.3 g,

56%): mp123-124 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.71 – 7.64 (m, 2H), 7.57 (td, *J* = 7.7, 1.4 Hz, 1H), 7.45 (d, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 8.2 Hz, 1H), 7.17 (dd, *J* = 4.9, 3.8 Hz, 1H), 4.46 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 188.5, 143.4, 138.0, 134.9, 133.0, 132.9, 131.0, 128.5, 127.8, 118.0, 113.5, 44.0; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{13}H_{10}NOS$ 228.0478, found 228.0480.

General procedure for the synthesis of functionalized 1-amino-3-arylisoquinoline (3, 4, and 5)

In an oven-dried 10 mL sealed tube, a mixture of 2-(arylethyl)benzonitrile **1** (0.5 mmol) and corresponding amine **2** (0.6 mmol) in 2 mL of H_2O was heated at 100 °C for 4h. The progression of the reaction was monitored by TLC analysis; after the complete consumption of starting material, the reaction was cooled to room temperature. The reaction mixture was diluted with ethyl acetate (10 mL). The layers were separated, and the organic layer was dried over Na_2SO_4. The organic layer was concentrated under reduced pressure. The crude material so obtained was purified by column chromatography on silica gel (100−200) (hexane: ethyl acetate). The structure and purity of products were confirmed by comparison of their physical and spectral data (^{1}H NMR, ^{13}C NMR, and HRMS).

4-(3-Phenylisoquinolin-1-yl)morpholine **(3a).** The crude product was purified by column chromatography (hexane/EtOAc = 90/10) to afford **3a** as white-solid (137.7 mg, 95%): mp 200–201 °C: ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.20 (d, *J* = 9.5 Hz, 2H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.74 (s, 1H), 7.62-7.58 (m, 1H), 7.52-7.47 (m, 3H), 7.43-7.39 (m, 1H), 4.02 (t, *J* = 4.7 Hz, 4H), 3.55 (t, *J* = 4.7 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 160.7, 148.4, 139.7, 139.2, 129.9, 128.7, 128.5, 127.9, 126.8, 126.1, 125.4, 120.7, 111.7, 67.2, 51.9; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{19}H_{19}N_2O$ 291.1492, found 291.1508.

4-(3-Phenylisoquinolin-1-yl)thiomorpholine **(3b).** The crude product was purified by column chromatography (hexane/EtOAc = 90/10) to afford **3b** as light green-solid (143.8 mg, 94%): mp 177–178 °C: ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.18 (d, *J* = 8.4 Hz, 2H), 8.03 (d, J = 8.5 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.73 (s, 1H), 7.60 (t, *J* = 8.1 Hz, 1H), 7.52-7.46 (m, 3H), 7.42-7.39 (m, 1H), 3.82 (t, *J* = 5.1 Hz,

4H), 2.96 (t, J = 5.1 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 148.2, 138.5, 138.0, 128.7, 127.5, 127.3, 126.6, 125.6, 124.9, 124.2, 119.7, 110.5, 52.6, 26.7; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{19}H_{19}N_2S$ 307.1263, found 307.1262.

3-Phenyl-1-(piperazin-1-yl)isoquinoline **(3c).** The crude product was purified by column chromatography ($CHCl_3$/MeOH = 90/10) to afford **3c** as white-solid (128.6 mg, 89%): mp 156–157 °C: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, J = 7.4 Hz, 2H), 8.10 (d, J = 8.4 Hz, 1H), 8.03 (s, 1H), 7.94 (d, J = 8.2 Hz, 1H), 7.71-7.67 (m, 1H), 7.58-7.54 (m, 1H), 7.47 (t, J = 7.5 Hz, 2H), 7.39-7.36 (m, 1H), 3.56 (s, 4H), 3.33 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.1, 147.5, 139.3, 130.9, 129.2, 129.1, 128.4, 127.2, 126.8, 125.7, 120.3, 112.3, 49.1, 43.9; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{19}H_{20}N_3$ 290.1652, found 290.1648.

tert-Butyl 4-(3-phenylisoquinolin-1-yl)piperazine-1-carboxylate **(3d).** The crude product was purified by column chromatography (hexane/EtOAc = 90/10) to afford **3d** as white-solid (188.6 mg, 97%): mp 154–155 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.5 Hz, 2H), 8.07 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.73 (s, 1H), 7.62-7.58 (m, 1H), 7.50-7.45 (m, 3H), 7.39-7.35 (m, 1H), 3.73 (t, J = 5.0 Hz, 4H), 3.49 (t, J = 5.1 Hz, 4H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 155.1, 148.4, 139.6, 139.2, 129.9, 128.7, 127.8, 126.7, 126.1, 125.3, 120.8, 111.7, 79.9, 51.6, 51.6, 51.5, 51.4, 51.3, 51.2, 51.0, 50.8, 44.5, 44.4, 44.2, 44.0, 43.8, 43.7, 43.6, 43.4, 28.6; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{24}H_{28}N_3O_2$ 390.2176, found 390.2187.

1-(Azepan-1-yl)-3-phenylisoquinoline **(3e).** The crude product was purified by column chromatography (hexane/EtOAc = 95/5) to afford **3e** as white-solid (144.9 mg, 96%): mp 98–99 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.5 Hz, 2H), 8.10 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.54 (t, J = 7.3 Hz, 2H), 7.46 (t, J = 7.6 Hz, 2H), 7.41-7.34 (m, 2H), 3.83 (t, J = 5.8 Hz, 4H), 1.98 (s, 4H), 1.78-1.75 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 148.0, 140.2, 139.9, 129.3, 128.6, 128.1, 127.5, 126.8, 126.1, 124.8, 120.2, 109.1, 53.2, 29.3, 27.7; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{21}H_{23}N_2$303.1856,

found 303.1851.

1-(4-Benzylpiperazin-1-yl)-3-phenylisoquinoline **(3f).** The crude product was purified by column chromatography (hexane/EtOAc = 90/10) to afford **3f** as white-solid (191.4 mg, 99%): mp 144–145 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 7.4 Hz, 2H), 8.08 (d, J = 8.2 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.70 (s, 1H), 7.58 (t, J = 7.4 Hz, 1H), 7.49-7.44 (m, 3H), 7.41-7.33 (m, 5H), 7.28 (t, J = 7.1 Hz, 1H), 3.66 (s, 2H), 3.57 (s, 4H), 2.77 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 148.2, 139.3, 139.2, 131.2, 130.3, 130.2, 129.5, 128.8, 128.7, 128.3, 128.1, 126.7, 124.7, 120.2, 112.5, 60.9, 50.7, 47.8; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{26}H_{26}N_3$ 380.2121, found 380.2111.

1-(4-(4-(tert-Butyl)benzyl)piperazin-1-yl)-3-phenylisoquinoline **(3g).** The crude product was purified by column chromatography (hexane/EtOAc = 90/10) to afford **3g** as white-solid (211.0 mg, 97%): mp 136–137 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 7.6 Hz, 2H), 8.10 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.72 (s, 1H), 7.59 (t, J = 7.1 Hz, 1H), 7.51-7.45 (m, 3H), 7.41-7.39 (m, 3H), 7.436-7.34 (m, 2H), 3.65 (s, 2H), 3.60 (s, 4H), 2.79 (t, J = 4.3 Hz, 4H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 150.0, 148.3, 139.9, 139.2, 135.0, 129.6, 129.0, 128.6, 128.3, 127.7, 126.7, 125.7, 125.6, 125.2, 120.8, 111.1, 62.9, 53.3, 51.3, 34.6, 31.5; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{30}H_{34}N_3$ 436.2747, found 436.2738.

1-(4-(4-Fluorobenzyl)piperazin-1-yl)-3-phenylisoquinoline **(3h).** The crude product was purified by column chromatography (hexane/EtOAc = 90/10) to afford **3h** as white-solid (204.6 mg, 97%): mp 157–158 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 7.6 Hz, 2H), 8.11 (d, J = 8.2 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.73 (s, 1H), 7.59 (t, J = 7.4 Hz, 1H), 7.52-7.46 (m, 3H), 7.42-7.36 (m, 3H), 7.06 (t, J = 8.4 Hz, 2H), 3.60 (d, J = 9.5 Hz, 6H), 2.76 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 160.9, 160.9, 148.4, 139.8, 139.2, 134.0, 130.8, 130.7, 129.8, 128.7, 128.4, 127.8, 126.8, 125.9, 125.6, 120.8, 115.3, 115.1, 111.3, 62.5, 53.3, 51.3; HRMS (ESI-TOF) $[M+H]^+$ Calcd. for $C_{26}H_{25}FN_3$ 398.2027, found 398.2017.

1-(4-(Benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)-3-phenylisoquinoline **(3i).** The crude product was

purified by column chromatography (hexane/EtOAc = 80/20) to afford **3i** as white-solid (198.8 mg, 94%): mp 145–146 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 7.1 Hz, 2H), 8.08 (d, J = 8.2 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.70 (s, 1H), 7.58 (t, J = 8.1 Hz, 1H), 7.46 (dd, J = 15.0, 7.1 Hz, 3H), 7.39-7.35 (m, 1H), 6.94 (s, 1H), 6.83-6.77 (m, 2H), 5.96 (s, 2H), 3.56 (s, 6H), 2.74 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 148.3, 147.8, 146.7, 139.8, 139.2, 132.1, 129.7, 128.7, 128.2, 127.7, 126.7, 125.8, 125.6, 122.4, 120.8, 111.3, 109.7, 108.0, 101.0, 63.0, 53.2, 51.3; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{27}H_{26}N_3O_2$ 424.2020, found 424.2024.

1-(4-(Bis(4-fluorophenyl)methyl)piperazin-1-yl)-3-phenylisoquinoline **(3j).** The crude product was purified by column chromatography (hexane/EtOAc = 90/10) to afford **3j** as white-solid (175.5 mg, 86%): mp 174–175 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 7.6 Hz, 2H), 8.03 (d, J = 8.2 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.70 (s, 1H), 7.58-7.54 (m, 1H), 7.48-7.37 (m, 8H), 7.00 (t, J = 8.7 Hz, 4H), 4.36 (s, 1H), 3.54 (s, 4H), 2.67 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 160.8, 160.7, 148.3, 139.8, 139.1, 138.4, 129.7, 129.4, 129.4, 128.7, 128.4, 127.7, 126.7, 125.8, 125.5, 120.8, 115.7, 115.4, 111.3, 74.8, 52.1, 51.5; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{32}H_{28}F_2N_3$ 492.2246, found 492.2243.

2-(4-(3-Phenylisoquinolin-1-yl)piperazin-1-yl)ethan-1-ol **(3k).** The crude product was purified by column chromatography ($CHCl_3$/MeOH = 95/5) to afford **3k** as white semi-solid (144.8 mg, 87%): mp 132–133 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.5 Hz, 2H), 8.06 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.70 (s, 1H), 7.59-7.55 (m, 1H), 7.50-7.44 (m, 3H), 7.40-7.36 (m, 1H), 3.71 (t, J = 5.4 Hz, 2H), 3.57 (s, 4H), 3.28 (s, 1H), 2.81 (t, J = 4.5 Hz, 4H), 2.67 (t, J = 5.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 148.4, 139.8, 139.2, 129.8, 128.7, 128.4, 127.8, 126.8, 125.9, 125.5, 120.8, 111.4, 59.8, 58.0, 53.2, 51.3; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{21}H_{24}N_3O$ 334.1914, found 334.1907.

1-(4-(2-Methoxyethyl)piperazin-1-yl)-3-phenylisoquinoline **(3l).** The crude product was purified by column chromatography ($CHCl_3$/MeOH = 95/5) to afford **3l** as white semi-solid (147.2 mg, 90%): mp 128–129 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 9.5 Hz, 2H), 8.06 (d, J = 8.2 Hz, 1H), 7.77 (d, J

= 8.1 Hz, 1H), 7.69 (s, 1H), 7.58-7.55 (m, 1H), 7.49-7.43 (m, 3H), 7.39-7.35 (m, 1H), 3.60 (t, *J* = 5.6 Hz, 6H), 3.39 (s, 3H), 2.85 (d, *J* = 4.5 Hz, 4H), 2.74 (t, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*159.5, 147.2, 138.6, 138.0, 128.6, 127.5, 127.2, 126.6, 125.6, 124.7, 124.4, 119.5, 110.1, 69.0, 57.9, 56.9, 52.5, 49.8; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{22}H_{26}N_3O$ 348.2070, found 348.2067.

2-(2-(4-(3-Phenylisoquinolin-1-yl)piperazin-1-yl)ethoxy)ethan-1-ol **(3m).** The crude product was purified by column chromatography ($CHCl_3$/MeOH = 95/5) to afford **3m** as white semi-solid (158.4 mg, 84%): mp141–142 °C: ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.15 (d, *J* = 8.4 Hz, 2H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.70 (s, 1H), 7.58 (t, *J* = 7.1 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 3H), 7.36 (t, *J* = 7.3 Hz, 1H), 3.81 (s, 1H), 3.73 (dd, *J* = 9.8, 5.3 Hz, 4H), 3.66 – 3.57 (m, 6H), 2.89 (s, 4H), 2.76 (t, *J* = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 160.4, 148.3, 139.6, 139.2, 129.8, 128.7, 128.4, 127.8, 126.7, 126.0, 125.5, 120.6, 111.4, 72.6, 67.3, 62.0, 58.0, 53.4, 50.6; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{23}H_{28}N_3O_2$ 378.2176,found 378.2181.

1-([1,4'-Bipiperidin]-1'-yl)-3-phenylisoquinoline **(3n).** The crude product was purified by column chromatography (hexane/EtOAc = 90/10) to afford **3n** as white solid (178.0 mg, 96%): mp 128–129 °C: ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.17 (d, *J* = 7.3 Hz, 2H), 8.04 (d, *J* = 8.2 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.67 (s, 1H), 7.54 (t, *J* = 7.1 Hz, 1H), 7.49-7.42 (m, 3H), 7.37 (t, *J* = 7.3 Hz, 1H), 4.02 (d, *J* = 12.8 Hz, 2H), 3.02 (t, *J* = 11.8 Hz, 2H), 2.62-2.52 (m, 5H), 2.02-1.86 (m, 4H), 1.67 (t, *J* = 5.1 Hz, 4H), 1.49-1.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 161.2, 148.3, 139.9, 139.1, 129.7, 128.7, 128.3, 127.7, 126.8, 125.8, 125.7, 120.9, 111.1, 63.3, 51.4, 50.4, 28.4, 26.3, 24.8; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{25}H_{30}N_3$ 372.2434, found 372.2430.

1-(4-(4-Fluorophenyl)piperazin-1-yl)-3-phenylisoquinoline **(3o).** The crude product was purified by column chromatography (hexane/EtOAc = 90/10) to afford **3o** as white-solid (172.4 mg, 90%): mp 166–167 °C: ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.18 (d, *J* = 9.2 Hz, 2H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.74 (s, 1H), 7.63-7.59 (m, 1H), 7.51-7.46 (m, 3H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.03-6.96 (m, 4H), 3.70 (t, *J* = 4.9 Hz, 4H), 3.42-3.39 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 160.6, 158.5, 156.1,

148.4, 148.2, 139.7, 139.2, 129.9, 128.7, 128.4, 127.8, 126.8, 126.0, 125.4, 120.8, 118.0, 117.9, 115.8, 115.6, 111.6, 51.3, 50.4; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{25}H_{23}FN_3$ 384.1871, found 384.1867.

3-Phenyl-1-(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)isoquinoline **(3p).** The crude product was purified by column chromatography (hexane/EtOAc = 90/10) to afford **3p** as yellow-solid (197.0 mg, 91%): mp 178–178 °C: HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{26}H_{23}F_3N_3$ 434.1839, found 434.1842.

1-(4-(2,4-Difluorophenyl)piperazin-1-yl)-3-phenylisoquinoline **(3q).** The crude product was purified by column chromatography (hexane/EtOAc = 90/10) to afford **3q** as white-solid (180.5 mg, 90%): mp 152–153 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.5 Hz, 2H), 8.14 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.75 (s, 1H), 7.63-7.59 (m, 1H), 7.53-7.48 (m, 3H), 7.43-7.39 (m, 1H), 7.03-6.97 (m, 1H), 6.90-6.83 (m, 2H), 3.73 (t, J = 4.8 Hz, 4H), 3.33 (t, J = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 159.2 (d, J = 11.5 Hz), 156.9 (dd, J = 26.0, 11.6 Hz), 154.6 (d, J = 11.6 Hz), 148.4, 139.7, 139.2, 136.9 (dd, J = 8.9, 3.4 Hz), 129.8, 128.7, 128.4, 127.8, 126.7, 125.9, 125.4, 120.7, 119.7 (dd, J = 9.3, 4.2 Hz), 111.5, 110.7 (dd, J = 21.4, 3.7 Hz), 105.1, 104.8, 104.6, 51.6, 51.1; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{25}H_{22}F_2N_3$ 402.1776, found 402.1770.

N-Benzyl-3-phenylisoquinolin-1-amine **(4a).** The crude product was purified by column chromatography (hexane/EtOAc = 95/5) to afford **4a** as pale-yellow-solid (144.2 mg, 93%): mp 147–148 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 7.3 Hz, 2H), 7.78 (d, J = 8.1 Hz, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.62-7.58 (m, 1H), 7.55-7.50 (m, 5H), 7.44-7.41 (m, 4H), 7.36 (t, J = 7.3 Hz, 1H), 5.55 (s, 1H), 5.02 (d, J = 5.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 149.1, 140.3, 138.2, 129.9, 128.8, 128.7, 128.3, 127.9, 127.4, 126.9, 125.8, 121.6, 117.5, 107.3, 46.1; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{22}H_{19}N_2$ 311.1543, found 311.1537.

(S)-3-Phenyl-N-(1-phenylethyl)isoquinolin-1-amine **(4b).** The crude product was purified by column chromatography (hexane/EtOAc = 95/5) to afford **4b** as pale-yellow-solid (151.1 mg, 93%): mp 127–128 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.2 Hz, 1H), 7.73 (d, J =

8.1 Hz, 1H), 7.59-7.53 (m, 3H), 7.45-7.41 (m, 4H), 7.38-7.33 (m, 3H), 7.27 (d, *J* = 8.4 Hz, 1H), 5.70-5.63 (m, 1H), 5.51 (d, *J* = 5.8 Hz, 1H), 1.74 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 149.0, 145.4, 140.2, 138.1, 129.7, 128.5, 128.4, 128.0, 127.7, 126.9, 126.7, 126.4, 125.6, 121.3, 117.3, 106.9, 50.8, 22.7; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{23}H_{21}N_2$ 325.1699, found 325.1697.

3-Phenyl-N-(4-(trifluoromethoxy)benzyl)isoquinolin-1-amine **(4c).** The crude product was purified by column chromatography (hexane/EtOAc = 95/5) to afford **4c** as white-solid (173.4 mg, 88%): mp 156–157 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.5 Hz, 2H), 7.74 (dd, *J* = 17.1, 8.2 Hz, 2H), 7.62-7.58 (m, 1H), 7.51-7.47 (m, 5H), 7.44-7.38 (m, 2H), 7.22 (d, *J* = 7.8 Hz, 2H), 5.58 (s, 1H), 4.96 (d, *J* = 5.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 149.0, 148.4, 140.1, 139.1, 138.2, 130.0, 129.4, 128.6, 128.3, 127.9, 126.8, 125.9, 121.4, 121.2, 117.4, 107.5, 45.2; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{23}H_{18}F_3N_2O$ 395.1366, found 395.1363.

N-(1-Cyclohexylethyl)-3-phenylisoquinolin-1-amine **(4d).** The crude product was purified by column chromatography (hexane/EtOAc = 95/5) to afford **4d** as white-solid (151.8 mg, 92%): mp 116–117 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 9.5 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.61-7.51 (m, 3H), 7.44 (dd, *J* = 16.0, 8.5 Hz, 3H), 5.18 (d, *J* = 7.4 Hz, 1H), 4.63 (dd, *J* = 12.0, 5.7 Hz, 1H), 2.00 (d, *J* = 12.5 Hz, 1H), 1.88 (t, *J* = 16.1 Hz, 3H), 1.74 (d, *J* = 11.5 Hz, 2H), 1.37-1.19 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 149.2, 140.6, 138.3, 129.7, 128.6, 128.2, 127.9, 126.8, 125.5, 121.3, 117.5, 106.2, 50.7, 43.5, 29.8, 29.2, 26.8, 26.7, 26.6, 17.9; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{23}H_{27}N_2$ 331.2169, found 331.2163.

N-(2-Morpholinoethyl)-3-phenylisoquinolin-1-amine **(4e).** The crude product was purified by column chromatography ($CHCl_3$/MeOH = 98/2) to afford **4e** as white semi-solid (156.5 mg, 94%): mp 112–113 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.1 Hz, 2H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.58-7.54 (m, 1H), 7.49-7.36 (m, 5H), 3.85-3.80 (m, 5H), 2.61-2.54 (m, 6H), 1.97-1.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 149.2, 140.5, 138.1, 129.7, 128.5, 128.2, 127.7, 126.8, 125.4, 122.0, 117.7, 106.3, 67.1, 58.9, 54.0, 42.2, 24.6; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{21}H_{24}N_3O$

334.1914, found 334.1907.

N^1-Benzyl-N^2-(3-phenylisoquinolin-1-yl)ethane-1,2-diamine **(4f).** The crude product was purified by column chromatography ($CHCl_3$/MeOH = 98/2) to afford **4f** as white semi-solid (144.0 mg, 85%): mp 126–127 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.4 Hz, 2H), 7.92 (d, J = 8.3 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.44 – 7.36 (m, 3H), 7.27 (dd, J = 16.0, 7.7 Hz, 5H), 6.43 (s, 1H), 4.91 (s, 1H), 3.90 (s, 2H), 3.84 (s, 2H), 3.10 (t, J = 5.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 148.8, 140.2, 138.0, 136.5, 130.0, 128.9, 128.7, 128.6, 128.2, 128.0, 127.51, 126.8, 125.9, 122.4, 117.7, 107.1, 52.7, 47.8, 40.3; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{24}H_{24}N_3$ 354.165, found 354.1971.

1-(4-Benzylpiperazin-1-yl)-3-(p-tolyl)isoquinoline **(5a)**. The crude product was purified by column chromatography (hexane/EtOAc = 90/10) to afford **5a** as white-solid (182.7 mg, 93%): mp 138–139 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.1 Hz, 3H), 7.77 (d, J = 8.1 Hz, 1H), 7.66 (s, 1H), 7.58-7.54 (m, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.40 (d, J = 8.7 Hz, 2H), 7.36-7.33 (m, 2H), 7.29-7.25 (m, 3H), 3.65 (s, 2H), 3.56 (s, 4H), 2.75 (t, J = 4.6 Hz, 4H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 148.4, 139.2, 138.3, 138.2, 137.1, 129.6, 129.4, 129.3, 128.4, 127.6, 127.2, 126.6, 125.6, 120.7, 110.6, 63.3, 53.6, 51.5, 21.3; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{27}H_{28}N_3$ 394.2278, found 394.2267.

1-(4-Benzylpiperazin-1-yl)-3-(4-ethoxyphenyl)isoquinoline **(5b).** The crude product was purified by column chromatography (hexane/EtOAc = 85/15) to afford **5b** as white-solid (195.0 mg, 92%): mp 129–130 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.8 Hz, 2H), 8.07 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.62 (s, 1H), 7.56 (t, J = 7.1 Hz, 1H), 7.45-7.36 (m, 5H), 7.32-7.29 (m, 1H), 7.01 (d, J = 12.0 Hz, 2H), 4.10 (q, J = 7.0 Hz, 2H), 3.68 (s, 2H), 3.59 (s, 4H), 2.79 (s, 4H), 1.46 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 159.5, 148.2, 139.4, 138.1, 132.4, 129.7, 129.4, 128.4, 128.0, 127.6, 127.3, 125.6, 125.4, 120.4, 114.6, 110.1, 63.6, 63.3, 53.3, 51.3, 15.0; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{28}H_{30}N_3O$ 424.2383, found 424.2375.

1-(4-Benzylpiperazin-1-yl)-3-(4-fluorophenyl)isoquinoline **(5c).** The crude product was purified by column chromatography (hexane/EtOAc = 90/10) to afford **5c** as white-solid (190.6 mg, 96%): mp 118–119 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, J = 8.8, 5.5 Hz, 2H), 8.01 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.65 (s, 1H), 7.59 (t, J = 7.5 Hz, 1H), 7.48-7.44 (m, 1H), 7.42-7.33 (m, 5H), 7.14 (t, J = 8.7 Hz, 2H), 3.88 (s, 2H), 3.68 (s, 4H), 2.99 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 162.0, 160.2, 147.4, 139.2, 135.8, 130.0, 129.9, 128.7, 128.5, 128.4, 128.2, 127.8, 126.1, 125.4, 120.5, 115.6, 115.4, 111.3, 62.5, 52.5, 50.2; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{26}H_{25}FN_3$ 398.2027, found 398.2017.

1-(4-Benzylpiperazin-1-yl)-3-(3-fluorophenyl)isoquinoline **(5d).** The crude product was purified by column chromatography (hexane/EtOAc = 90/10) to afford **5d** as white-solid (194.5 mg, 98%): mp 123–124 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.4 Hz, 1H), 7.93-7.90 (m, 2H), 7.79 (d, J = 8.1 Hz, 1H), 7.68 (s, 1H), 7.61-7.57 (m, 1H), 7.49-7.33 (m, 6H), 7.28 (t, J = 8.5 Hz, 1H), 7.08-7.04 (m, 1H), 3.66 (s, 2H), 3.58-3.55 (m, 4H), 2.76 (t, J = 4.7 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 162.3, 160.9, 147.0, 142.4, 142.3, 139.1, 138.3, 130.0, 129.9, 129.9, 129.3, 128.4, 127.8, 127.2, 126.1, 125.7, 122.1, 121.1, 115.1, 114.9, 113.8, 113.5, 111.5, 63.3, 53.4, 51.3; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{26}H_{25}FN_3$ 398.2027,398.2017.

1-(4-Benzylpiperazin-1-yl)-6-bromo-3-phenylisoquinoline **(5e).**The crude product was purified by column chromatography (hexane/EtOAc = 90/10) to afford **5e** as white-solid (150.8 mg, 66%): mp 147–148 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 160.27, 153.37, 148.02, 142.54, 139.34, 129.90, 128.56, 128.31, 127.68, 126.50, 126.27, 126.12, 125.14, 114.46, 111.54, 50.71, 47.77, 29.69; ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.17 (d, J = 8.5 Hz, 2H), 8.12 (d, J = 8.3 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.76 (s, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.55 – 7.45 (m, 5H), 7.38 (t, J = 8.4 Hz, 1H), 7.03 (d, J = 8.7 Hz, 1H), 3.74 – 3.66 (m, 4H), 3.61 – 3.53 (m, 4H); HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{26}H_{25}Br^{81}N_3$ 460.1206, found 460.1212.

1-(4-Benzylpiperazin-1-yl)-6-chloro-3-(3-fluorophenyl)isoquinoline **(5f).** The crude product was purified by column chromatography (hexane/EtOAc = 90/10) to afford **5f** as white-solid (155.2 mg,

72%): mp 143–144 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.9 Hz, 1H), 7.87 (d, J = 11.8 Hz, 2H), 7.75 (d, J = 2.1 Hz, 1H), 7.56 (s, 1H), 7.44-7.33 (m, 6H), 7.28 (t, J = 7.1 Hz, 1H), 7.09-7.05 (m, 1H), 3.65 (s, 2H), 3.54-3.52 (m, 4H), 2.74 (t, J = 4.5 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 162.2, 160.9, 148.2, 141.8, 141.8, 140.1, 138.1, 136.0, 130.1, 130.1, 129.3, 128.4, 127.5, 127.3, 126.8, 126.5, 122.2, 119.2, 115.5, 115.3, 113.9, 113.6, 110.5, 63.2, 53.2, 51.3; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{26}H_{24}ClFN_3$ 432.1637, found 432.1632.

1-(4-Benzylpiperazin-1-yl)-3-(pyrazin-2-yl)isoquinoline **(5g).** The crude product was purified by column chromatography (hexane/EtOAc = 60/40) to afford **5g** as white-solid (139.0 mg, 73%): mp 155–156 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 8.64 – 8.58 (m, 1H), 8.54 (d, J = 2.5 Hz, 1H), 8.34 (s, 1H), 8.09 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 8.1 Hz, 1H), 7.41 – 7.32 (m, 4H), 7.28 (t, J = 7.1 Hz, 1H), 3.66 (s, 2H), 3.58 (s, 4H), 2.79 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 152.0, 145.2, 143.8, 143.6, 138.8, 137.8, 130.1, 129.4, 128.52, 128.4, 127.3, 127.0, 125.7, 122.0, 113.5, 63.2, 53.2, 51.2; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{24}H_{24}N_5$ 382.2026, found 382.2031.

1-(4-Benzylpiperazin-1-yl)-3-(thiophen-2-yl)isoquinoline **(5h).** The crude product was purified by column chromatography (hexane/EtOAc = 90/10) to afford **5h** as white-solid (179.0 mg, 93%): mp 141–142 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.1 Hz, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 3.6 Hz, 1H), 7.55 (t, J = 8.1 Hz, 2H), 7.43-7.33 (m, 6H), 7.30-7.26 (m, 1H), 7.12-7.10 (m, 1H), 3.64 (s, 2H), 3.55 (s, 4H), 2.74 (t, J = 4.6 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 146.3, 144.1, 139.1, 138.3, 129.9, 129.3, 128.4, 128.0, 127.5, 127.2, 126.5, 125.8, 125.5, 123.4, 120.7, 109.1, 63.3, 53.3, 51.2; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{24}H_{24}N_3S$ 386.1685, found 386.1677.

General procedure for the synthesis of functionalized 3-aryl-N-(2-(4-(3-phenylisoquinolin-1-yl)piperazin-1-yl)ethyl)isoquinolin-1-amine (6a-d)

In an oven-dried 10 mL sealed tube, a mixture of 2-(arylethyl)benzonitrile **1** (0.5 mmol) and 2-

(piperazin-1-yl)ethan-1-amine **2r** (0.3 mmol) in 2 mL of H_2O was heated at 100 °C for 4h. Progression of the reaction was monitored by TLC analysis; after complete consumption of starting material, the reaction was cooled to room temperature. The reaction mixture was diluted with ethyl acetate (10 mL). The layers were separated, and the organic layer was dried over Na_2SO_4. Organic layer was concentrated under reduced pressure. The crude material so obtained was purified by column chromatography on silica gel (100−200) (hexane: ethyl acetate). The structure and purity of products were confirmed by comparison of their physical and spectral data (^{1}H NMR, ^{13}C NMR, and HRMS).

3-*(p-Tolyl)-N-(2-(4-(3-(p-tolyl)isoquinolin-1-yl)piperazin-1-yl)ethyl)isoquinolin-1-amine* **(6a).** The crude product was purified by column chromatography (hexane/EtOAc = 70/30) to afford **6a** as white-solid (247.7 mg, 88%): mp 162–163 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12-8.08 (m, 5H), 7.85-7.81 (m, 2H), 7.73-7.71 (M, 2H), 7.65-7.55 (m, 2H), 7.49-7.41 (m, 3H), 7.39-7.29 (m, 4H), 6.44 (s, 1H), 3.96 (s, 2H), 3.66 (s, 4H), 3.00 (d, J = 19.1 Hz, 6H), 2.41 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 154.9, 149.1, 148.5, 139.3, 138.3, 138.1, 137.9, 137.6, 136.9, 129.8, 129.5, 129.3, 127.7, 127.5, 126.6, 125.8, 125.6, 125.5, 122.0, 120.6, 117.6, 111.1, 106.2, 56.8, 53.0, 50.9, 37.8, 21.4; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{38}H_{38}N_5$ 564.3122, found 564.3108.

3-(3-Fluorophenyl)-N-(2-(4-(3-(3-fluorophenyl)isoquinolin-1-yl)piperazin-1-yl)ethyl)isoquinolin-1-amine **(6b).** The crude product was purified by column chromatography (hexane/EtOAc = 70/30) to afford **6b** as white-solid (257.0 mg, 90%): mp 157–158 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, J = 10.2, 6.5 Hz, 1H), 8.04 (d, J = 8.2 Hz, 1H), 7.91 (dd, J = 19.6, 7.9 Hz, 3H), 7.86 – 7.77 (m, 2H), 7.69 (dd, J = 13.2, 6.9 Hz, 2H), 7.58 (dd, J = 16.8, 9.9 Hz, 2H), 7.45 (dt, J = 13.7, 7.4 Hz, 5H), 7.14 (dd, J = 10.2, 5.1 Hz, 1H), 7.05 (d, J = 10.6 Hz, 1H), 6.77 (s, 1H), 4.03 (s, 2H), 3.74 (s, 4H), 3.26 – 3.04 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 162.2, 160.1, 154.8, 147.4, 146.9, 142.8, 142.0, 139.0, 137.8, 130.2, 130.1, 129.9, 129.8, 128.4, 128.0, 127.6, 127.4, 126.6, 126.4, 125.3, 122.2, 122.1, 122.0, 120.8, 120.4, 118.0, 115.5, 115.3, 115.3, 115.1, 114.9, 114.7, 113.7, 113.5, 112.2, 107.3, 56.8, 52.8, 50.0, 37.5; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{36}H_{32}F_2N_5$ 572.2620, found 572.2611.

6-Chloro-N-(2-(4-(6-chloro-3-(3-fluorophenyl)isoquinolin-1-yl)piperazin-1-yl)ethyl)-3-(3-fluorophenyl)isoquinolin-1-amine **(6c).** The crude product was purified by column chromatography (hexane/EtOAc = 70/30) to afford **6c** as white-solid (257.0 mg, 90%): mp 171–172 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.84 (m, 5H), 7.70 (t, J = 5.7 Hz, 2H), 7.62 (d, J = 1.9 Hz, 1H), 7.52 (s, 1H), 7.45 – 7.32 (m, 4H), 7.23 (s, 1H), 7.07 (td, J = 8.2, 3.9 Hz, 2H), 6.23 (t, J = 3.8 Hz, 1H), 3.89 – 3.81 (m, 2H), 3.56 (s, 4H), 2.88 (dd, J = 13.6, 7.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 162.2, 160.8, 154.7, 148.9, 148.1, 142.4, 142.3, 141.7, 141.6, 140.0, 139.0, 136.1, 136.0, 130.2, 130.1, 130.0, 129.9, 127.3, 127.0, 126.6, 126.5, 126.5, 123.5, 122.1, 119.1, 116.0, 115.6, 115.4, 115.3, 115.1, 113.8, 113.6, 110.8, 106.0, 56.6, 53.0, 51.4, 38.0; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{36}H_{30}Cl_2F_2N_5$ 640.1841, found 640.1838.

3-(Thiophen-2-yl)-N-(2-(4-(3-(thiophen-2-yl)isoquinolin-1-yl)piperazin-1-yl)ethyl)isoquinolin-1-amine **(6d).**The crude product was purified by column chromatography (hexane/EtOAc = 70/30) to afford **6d** as white-solid (257.1 mg, 94%): mp 147–148 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 7.4 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.66-7.52 (m, 6H), 7.42 (q, J = 7.7 Hz, 2H), 7.33-7.29 (m, 3H), 7.12-7.08 (m, 2H), 6.66 (s, 1H), 3.99 (s, 2H), 3.76 (s, 4H), 3.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 154.7, 146.8, 146.0, 144.5, 144.0, 139.0, 137.8, 130.1, 130.0, 128.1, 128.0, 127.6, 127.3, 126.6, 126.0, 125.8, 125.7, 125.6, 123.6, 123.0, 122.2, 120.5, 117.8, 109.6, 104.8, 56.8, 52.8, 50.5, 37.7, 30.2; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{32}H_{30}N_5S_2$ 548.1937, found 548.1927.

General procedure for the synthesis of drugs containing isoquinoline (7a-e)

In an oven-dried 10 mL sealed tube, a mixture of 2-(arylethyl)benzonitrile **1** (0.5 mmol) and corresponding drugs (0.6 mmol) in 2 mL of H_2O was heated at 100 °C for 4h. The progression of the reaction was monitored by TLC analysis; after the complete consumption of starting material, the reaction was cooled to room temperature. The reaction mixture was diluted with ethyl acetate (10 mL). The layers were separated, and the organic layer was dried over Na_2SO_4. The organic layer was concentrated under reduced pressure. The crude material so obtained was purified by column

chromatography on silica gel (100−200) (hexane: ethyl acetate). The structure and purity of products were confirmed by comparison of their physical and spectral data (^{1}H NMR, ^{13}C NMR, and HRMS).

N-((3S,5S)-Adamantan-1-yl)-3-phenylisoquinolin-1-amine **(7a).** The crude product was purified by column chromatography (hexane/EtOAc = 95/5) to afford **7a** as white-solid (138.0 mg, 78%): mp 109–110 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 7.3 Hz, 2H), 7.68 (q, J = 4.1 Hz, 2H), 7.53 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.41-7.34 (m, 3H), 5.08 (s, 1H), 2.38 (s, 6H), 2.19 (s, 3H), 1.80 (dd, J = 19.8, 12.4 Hz, 6H), 1.25 (s, 3H), 0.89-0.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 148.7, 140.5, 138.2, 129.4, 128.5, 128.0, 127.9, 126.7, 125.5, 121.4, 117.8, 105.9, 52.5, 42.1, 37.0, 29.9; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{25}H_{27}N_2$ 355.2169, found 355.2170.

N-(1-((3R,5R,7R)-Adamantan-1-yl)ethyl)-3-phenylisoquinolin-1-amine **(7b).** The crude product was purified by column chromatography (hexane/EtOAc = 95/5) to afford **7b** as white-solid (160.5 mg, 84%): mp 116–117 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 7.3 Hz, 2H), 7.73 (t, J = 7.6 Hz, 2H), 7.58-7.55 (m, 1H), 7.50-7.41 (m, 3H), 7.39-7.35 (m, 2H), 5.19 (d, J = 8.9 Hz, 1H), 4.55-4.48 (m, 1H), 2.03 (s, 3H), 1.78-1.68 (m, 7H), 1.25 (d, J = 6.7 Hz, 3H), 0.91-0.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 149.2, 140.6, 138.3, 129.7, 128.5, 128.1, 127.8, 126.8, 125.5, 121.2, 117.4, 106.0, 54.0, 39.0, 37.4, 36.6, 28.6, 14.8; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{27}H_{31}N_2$ 383.2482, found 383.2475.

8-Chloro-11-(1-(3-phenylisoquinolin-1-yl)piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine **(7c).** The crude product was purified by column chromatography (hexane/EtOAc = 80/20) to afford **7c** as white-solid (230.8 mg, 90%): mp 184–185 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 5.9 Hz, 1H), 8.13-8.09 (m, 3H), 7.78 (d, J = 8.1 Hz, 1H), 7.68 (s, 1H), 7.60-7.56 (m, 1H), 7.47-7.42 (m, 4H), 7.34 (t, J = 7.3 Hz, 1H), 7.22 (d, J = 8.2 Hz, 1H), 7.16 (d, J = 7.7 Hz, 2H), 7.12-7.09 (m, 1H), 3.87 (dd, J = 12.2, 3.8 Hz, 2H), 3.48-3.36 (m, 2H), 3.20-3.12 (m, 2H), 2.89-2.59 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 157.6, 148.3, 146.7, 139.8, 139.7, 139.2, 139.1, 138.0, 137.6, 133.6, 133.3, 132.9, 131.0, 129.8, 129.1, 128.6, 128.3, 127.7, 126.7, 126.2, 125.9, 125.6, 122.3, 120.9, 111.3, 52.8, 52.7, 31.9, 31.6, 31.4, 31.3; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{34}H_{29}ClN_3$

514.2045, found 514.2038.

1-(4-Benzylpiperazin-1-yl)-3-(pyridin-3-yl)isoquinoline **(7d).** The crude product was purified by column chromatography (hexane/EtOAc = 60/40) to afford **7d** as white-solid (167.2 mg, 88%): mp 145–146 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.59 (d, J = 4.8 Hz, 1H), 8.41 (d, J = 9.9 Hz, 1H), 8.06 (d, J = 8.3 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.67 (s, 1H), 7.58 (t, J = 7.1 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.42 – 7.31 (m, 5H), 7.31 – 7.22 (m, 1H), 3.64 (s, 2H), 3.55 (s, 4H), 2.74 (s, 4H);^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 149.1, 148.3, 145.6, 138.9, 138.0, 135.3, 134.0, 130.0, 129.4, 128.4, 127.8, 127.3, 126.4, 125.7, 123.5, 121.0, 111.6, 63.3, 53.3, 51.2; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{25}H_{25}N_4$ 381.2074, found 381.2070.

1-(4-Methylpiperazin-1-yl)-3-phenylisoquinoline **(7e).** The crude product was purified by column chromatography ($CHCl_3$/MeOH = 95/5) to afford **7e** as white semi-solid (148.5 mg, 98%): mp 77–78 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 7.2 Hz, 2H), 8.06 (d, J = 8.3 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.69 (s, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.53 – 7.43 (m, 3H), 7.38 (t, J = 7.3 Hz, 1H), 3.61 (s, 4H), 2.75 (s, 4H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 148.3, 139.8, 139.2, 129.8, 128.7, 128.4, 127.8, 126.8, 125.9, 125.5, 120.7, 111.4, 55.2, 51.0, 46.2; HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{20}H_{22}N_3$ 304.1808, found 304.1802.

Gram-scale synthesis of 3d

In an oven-dried 50 mL sealed tube, a mixture of 2-(phenylethyl)benzonitrile **1a** (4.52 mmol) and *tert*-butyl piperazine-1-carboxylate **2d** (5.0 mmol) in 20 mL of H_2O was heated at 100 °C for 4h. The progression of the reaction was monitored by TLC analysis; after the complete consumption of starting material, the reaction was cooled to room temperature. The reaction mixture was diluted with ethyl acetate (50 mL). The layers were separated, and the organic layer was dried over Na_2SO_4. The organic layer was concentrated under reduced pressure. The crude material so obtained was purified by column chromatography on silica gel (100−200) (hexane: ethyl acetate; 90/10). The product was obtained **3d** as

a white solid (1.65g, 94%).

ASSOCIATED CONTENT

Supporting Information

Electronic Supplementary Information (ESI) available: Data and spectral Copies of ^{1}H, $^{13}C\{^{1}H\}$NMR and HRMS data for target compounds. See DOI:

X-ray crystallographic data of compound **3p** (CCDC deposit number 2204378)

^{1}H, $^{13}C\{^{1}H\}$NMR and HRMS spectra of synthesized compounds and X-ray data (ESI).

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REFERENCES

1) (a) Sweetman, B.-A.; Müller, B.-H.; Guiry, P.-J. Synthesis, resolution and racemization studies of newtridentate ligands for asymmetric catalysis. *Tetrahedron Lett.* **2005**, *46,* 4643-4646. (b) Durola, F.; Sauvage, J.-P.; Wenger, O.-S. Sterically non-hindering endocyclic ligands of the bi-isoquinoline family. *Chem. Commun.* **2006,** 171-173. (c) Fang, K.-H.; Wu, L.-L.; Huang, Y.-T.; Yang, C.-H.; Sun, I.-W. Color tuning of iridium complexes - Part I: Substituted phenylisoquinoline-based iridium complexes as the triplet emitter. *Inorg. Chim. Acta.* **2006,** *359,* 441-450. (d) Tsuboyama, A.; Iwawaki, H.; Furugori, M.; Mukaide, T.; Kamatani, J.; Igawa, Moriyama, S.-T.; Miura, S.; Takiguchi, T.; Okada, S.; Hoshino, M.; Ueno, K. Homoleptic Cyclometalated Iridium Complexes with Highly Efficient Red Phosphorescence and Application to Organic Light-Emitting Diode. *J. Am. Chem. Soc.* **2003**, *125,* 12971-12979. (e) Giri, P.; Kumar, G.-S. Isoquinoline Alkaloids and their Binding with Polyadenylic Acid: Potential Basis of Therapeutic Action. *Mini-Rev. Med. Chem.* **2o1o**, *10,* 568-577. (f) Khan, A.-Y.; Kumar, G.-S. Natural isoquinoline alkaloids: binding aspects to functional proteins, serum albumins, hemoglobin, and lysozyme. *Biophys. Rev.***2015,** *7,* 407–420.

2. (a) Smith, A.-L.; DeMorin, F.; Paras, N.; Huang, Q.; Petkus, K.; Doherty, E.; Nixey, T.; Kim, J.; Whittington, D.; Epstein, L.; Lee, M.; Rose, M.; Babij, C.; Fernando, M.; Hess, K.; Le, Q.; Beltran, P.; Carnahan, J. Selective Inhibitors of the Mutant B-Raf Pathway: Discovery of a Potent and Orally Bioavailable Aminoisoquinoline. *J. Med. Chem.* **2009,** *52,* 6189. (b) Yang, S.; Van, H.; Le, T.; Khadka, D.; Cho, S.; Lee, K.; Chung, H.; Lee, S.; Ahn, C.; Lee, Y.; Cho, W. Synthesis, in vitro and in vivo evaluation of 3-arylisoquinolinaminesas potent antitumor agents. *Bioorg. Med. Chem. Lett.* **2010,** *20,* 5277.

3. Zhu, C.; M.; Yi, M.; Wei, D.; Chen, X.; Wu, Y.; Cui, X. Copper-Catalyzed Direct Amination of Quinoline *N*-Oxides via C–H Bond Activation under Mild Conditions. *Org. Lett.* **2014,** 16, 7, 1840–1843.

4. (a) Shen, Q.; Ogata, T.; Hartwig, J.-F. Highly Reactive, General and Long-Lived Catalysts for Palladium-Catalyzed Amination of Heteroaryl and Aryl Chlorides, Bromides, and Iodides: Scope and

Structure-Activity Relationships. *J. Am. Chem. Soc.* **2008,** *130,* 6586–6596. (b) Shen, Q.; Shekhar, S.; Stambuli,J.-P.; Hartwig, J.-F. Highly Reactive, General, and Long-Lived Catalysts for Coupling Heteroaryl and Aryl Chlorides with Primary Nitrogen Nucleophiles. *Angew. Chem. Int. Ed.* **2005,** *44,* 1371 –1375.

5. (a) Wei, X.; Zhao, M.; Du, Z.; Li, X. Synthesis of 1-Aminoisoquinolines via Rh(III)-Catalyzed Oxidative Coupling. *Org. Lett.* **2011,** *13,* 4636. (b) Li, J.; John, M.; Ackermann, L. Amidines for Versatile Ruthenium(II)-Catalyzed Oxidative C-H Activations with Internal Alkynes and Acrylates. *Chem. Eur. J.* **2014,** *20,* 5403. (c) Li, J.; Tang, M.; Zang, L.; Zhang, X.; Zhang, Z.; Ackermann, L. Amidines for Versatile Cobalt(III)-Catalyzed Synthesis of Isoquinolines through C–H Functionalization with Diazo Compounds. *Org. Lett.* **2016,** *18,* 11, 2742–2745. (d)Yang, F.; Yu, J.-J.; Liu, Y.; Zhu, J. Cobalt(III)-Catalyzed Oxadiazole-Directed C–H Activation for the Synthesis of 1-Aminoisoquinolines. *Org. Lett.* **2017,** *19,* 2885−2888.

6. (a) Kukushkin, V.-Y.; Pombeiro, A.-J. Additions to metal-activated organonitriles. *Chem. Rev.* **2002,** *102,* 1771−1802. (b) Fleming, F.-F.; Wang, Q. Unsaturated nitriles: conjugate additions of carbon nucleophiles to a recalcitrant class of acceptors. *Chem. Rev.* **2003,** *103,* 2035−2077. (c) Yang, X.; Yu, H.; Xu, Y.; Shao, L. Regioselective Access to 3-Aryl-1-aminoisoquinolines via Nickel(I)-Catalyzed C–C and C–N Cascade Coupling Reactions from the Substituted 2-(Cyanomethyl)benzonitriles. *J. Org. Chem.* **2018,** *83,* 9682−9695. (d) Chandrashekhar, V.- G.; Baumann, W.; Beller, M.; Jagadeesh, R.- V. Nickel-catalyzed hydrogenative coupling of nitriles and amines for general amine synthesis. *Science*, **2022,** *376*, 1433–1441. (e) Zhou, C.; Lei, T.; Wei, X.-Z.; Ye, C.; Liu, Z.; Chen, B.; Tung, C.-H.; Wu, L-Z. Metal-Free, Redox-Neutral, Site-Selective Access to Heteroarylamine via Direct Radical-Radical Cross-Coupling Powered by Visible Light Photocatalysis. *J. Am. Chem. Soc.* **2020**, *142,* 39, 16805–16813. (f) Hosseinijei, R.; Tejeneki, Z.-H.; Nikbakht, A.; Rominger, F.; Balalaie, S. Synthesis of functionalized 1-aminoisoquinolines through cascade three-component reaction of ortho-alkynylbenzaldoximes, 2H-azirines, and electrophiles. *Org. Biomol. Chem.,* **2022,** *20,* 3076. (d) Adusumalli, K. M.-S.; Konidena1, L. N.-S.; Gandham, H.-B. Kumari, K.; Valluru, K.-

R.; Nidasanametla, S. K.-R.; Battula, V. R.; Namballa, H.-K. Me3Al-mediated domino nucleophilic addition/intramolecular cyclization of 2-(2-oxo-2-phenylethyl)benzonitriles with amines; a convenient approach for the synthesis of substituted 1-aminoisoquinolines. *Beilstein J. Org. Chem.* **2021,** *17,* 2765–2772.

7. (a) Yousuf, M.; Das, T.; Adhikari, S. Palladium-catalyzed decarboxylative acylation of aryl boronic acid with ethyl cyanoacetate as a new acylating agent: synthesis of alkyl aryl ketones. *New J. Chem.* **2015,** *39,* 8763. (b) Wong, Y.- C.; Parthasarathy, K.; Cheng, C.-H. Direct Synthesis of Arylketones by Nickel-Catalyzed Addition of Arylboronic Acids to Nitriles. *Org. Lett.* **2010,** *12,* 1736. (c) Tsui, G.-C.; Glenadel, Q.; Lau, C.; Lautens, M. Rhodium (I)-Catalyzed Addition of Arylboronic Acids to (Benzyl-/Arylsulfonyl)acetonitriles: Efficient Synthesis of (Z)-β-Sulfonylvinylamines and β-Keto Sulfones. *Org. Lett.* **2011,** *13,* 208. (d) Wang, X.; Liu, M.; Xu, L.; Wang, Q.; Chen, J.; Ding, J.; Wu, H. Palladium-Catalyzed Addition of Potassium Aryltrifluoroborates to Aliphatic Nitriles: Synthesis of Alkyl Aryl Ketones, Diketone Compounds, and 2-Arylbenzo[b]furans. *J. Org. Chem.* **2013,** *78,* 5273. (e) Chen, J.; Ye, L.; Su, W. Palladium-catalyzed direct addition of arylboronic acids to 2-aminobenzonitrile derivatives: synthesis, biological evaluation and in silico analysis of 2-aminobenzophenones, 7-benzoyl-2-oxoindolines, and 7-benzoylindoles. *Org. Biomol. Chem.* **2014,** *12,* 8204. (f) Zhao, B.; Lu, X. Cationic Palladium(II)-Catalyzed Addition of Arylboronic Acids to Nitriles. One-Step Synthesis of Benzofurans from Phenoxyacetonitriles. *Org. Lett.* **2006,** *8,* 5987.

8. Qi, L.; Hu, K.; Yu, S.; Zhu, J.; Cheng, T.; Wang, X.; Chen, J; Wu, H. Tandem Addition/Cyclization for Access to Isoquinolines and Isoquinolones via Catalytic Carbopalladation of Nitriles. *Org. Lett.* **2017,** *19,* 1, 218–221.

9. (a) Reddy, V.; Jadhav, A.- S.; Anand, R.-V. Catalyst-Controlled Regioselective Approach to 1-Aminoisoquinolines and/or 1-Aminoisoindolines through Aminative Domino Cyclization of 2-Alkynylbenzonitriles. *Eur. J. Org. Chem.* **2016,** 453–458. (b) Long, Y.; She, Z.; Liu, X.; Chen, Y.Synthesis of 1-Aminoisoquinolines by Gold(III)-Mediated Domino Reactions from 2-Alkynylbenzamides and Ammonium Acetate. *J. Org. Chem.* **2013,** *78,* 2579−2588.

10. Kuznetsov, M.-L.; Bokach, N.-A.; Kharlampidi, D.-D.; Medvedev, Y.-N.; Kukushkin, V.-Y. Dementiev, A.-I. Theoretical Study of Nucleophilic Addition of Amines to Organic Nitriles. *Russ. J. Gen. Chem.* **2010,** *80,* 458-467.

11. Tang, L.; Jiang, S.; Huang, X.; Song, Z.; Wang, J-b.; Ma, M.; Chen, B.; Ma, Y. Cascade of C(sp^2)–H Addition to Carbonyl and C(sp^2)–CN/C(sp^2)–H Coupling Enabled by Brønsted Acid: Construction of Benzo[*a*]carbazole Frameworks. *Org. Lett.* **2022,** *24,* 17, 3232–3237.