JOC The Journal of Organic Chemistry

Article

Catalyst-Free Synthesis of 2-Anilinoquinolines and 3-Hydroxyquinolines via Three-Component Reaction of Quinoline N-oxides, Aryldiazonium salts and Acetonitrile

Ankit Kumar Dhiman, Devesh Chandra, Rakesh Kumar, and Upendra Sharma

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b00739 • Publication Date (Web): 09 May 2019

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Catalyst-Free Synthesis of 2-Anilinoquinolines and 3-Hydroxyquinolines *via* Three-Component Reaction of Quinoline *N*-oxides, Aryldiazonium salts and Acetonitrile

Ankit Kumar Dhiman, Devesh Chandra, Rakesh Kumar and Upendra Sharma*

Natural Product Chemistry & Process Development Division and AcSIR, CSIR-IHBT, Palampur-176061, India

Supporting Information

ABSTRACT: A rapid microwave-assisted catalyst-free, three-component synthesis of various 2-anilinoquinolines from quinoline *N*-oxides and aryldiazonium salts in acetonitrile under microwave irradiation is reported. This reaction utilizes acetonitrile as a single nitrogen source and involves the formation of two new C-N bonds *via* formal [3+2] cycloaddition reaction. In the case of 2-substituted quinolines, 3-hydroxyquinoline was observed as the main product *via* 1,3 shift of oxygen atom from *N*-oxide to the C3 position of quinolines.

KEYWORDS: *catalyst-free, microwave, 2-anilinoquinolines, quinoline N-oxides, aryl diazonium salts, acetonitrile.*

INTRODUCTION

Quinoline is one amongst the key structural components in a range of natural and synthetic molecules, which possess a variety of biological activities including antimalarial, antimicrobial, anti-tumor, and antiviral etc.[1] Owing to the importance[2] of quinolines various methods have been established for its functionalization at different positions.[3] Among them, the C2 selective functionalization of quinolines is studied most as various methods have been developed for C-C,[4] C-O,[5] and C-S[6] bond formation. Recently, C2 selective functionalization of quinoline through direct C-N[7], bond formation became a significant area of attention as 2-aminoquinoline constitute the core structures of many bioactive and therapeutic molecules (Figure 1)[7i, 8]

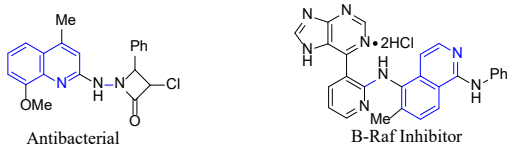
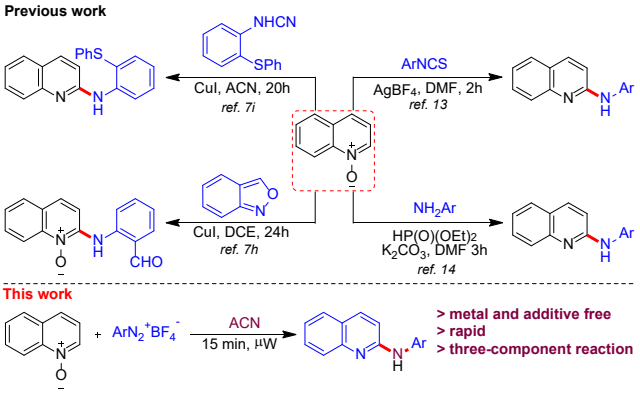


Figure 1. Representative Examples of bioactive amino-quinolines.

Efforts have already been made for the direct C2-amination of quinolines by reacting quinoline *N*-oxides with Ts_2O-t-$BuNH_2$,[9] primary amides,[10] lactams/cyclamines,[7a] nitriles,[11] and *O*-benzoylhydroxylamines.[12] Among the various C2-aminated quinolines, the 2-anilinoquinolines are important heterocyclic compounds due to their numerous pharmacological and therapeutic effects,[7i] but the direct synthesis of these compounds remains a challenge. Recently, copper-catalyzed direct arylamination of quinoline was reported using N-(2-(Arylthio)aryl)cyanamides[7j] and anthranil[7h] as a secondary amine source. Isothiocyanates have also been utilized for the direct synthesis of 2-anilinoquinolines by using silver tetrafluoroborates as a catalyst.[13] Use of metal-catalyst and need for particular aminating reagent limited the broad applicability of these methods (Scheme 1). Metal-free approach for the direct synthesis of 2-anilinoquinolines includes diethyl *H*-phosphonate promoted amination of quinoline *N*-oxides with arylamines.[14] Although this method represents a significant advancement in terms of avoiding any metal catalyst, the requirement of a stoichiometric amount of reducing agent and base warrant further improvement in this area (scheme 1).



Scheme 1. Direct Synthesis of 2-Anilinoquinolines from Quinoline *N*-Oxides.

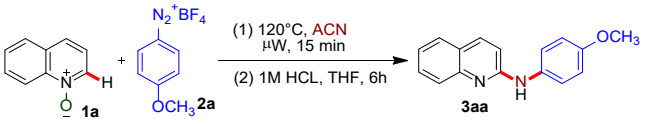
RESULTS AND DISCUSSION

In continuation of our work on quinolines functionalization,[4c, 4d, 15] herein we report the microwave assisted metal-free direct synthesis of 2-anilinoquinolines by reacting quinoline *N*-oxides and aryl diazonium tetrafluoroborate salts in acetonitrile (ACN). In this three-component reaction, acetonitrile forms two C-N bonds, one with quinoline and other with aryl moiety (Scheme 1).

Quinoline *N*-oxide (**1a**) and *p*-methoxybenzenediazonium tetrafluoroborate (**2a**) were selected as a standard substrate for the optimization study. Treatment of **1a** with 1.0 equiv. of **2a** in acetonitrile (ACN, 0.1M) under microwave irradiation at 50˚C leads to the formation of C2-aminated product (**3aa**) in traces (entry 2, Table 1). Increase in temperature from 50˚C to 120˚C enhances **3aa** yield up to 42% (entry 3, Table 1). Further increase in temperature did not prove helpful (entry 6, Table 1). A decrease in reaction concentration from 0.1M to 0.05M proved fruitful, providing the desired product **3aa** in 55% yield (entry 4, Table 1) and further decrease in concentration from 0.1M to 0.04M leads to 65% of the desired product **3aa** (entry 1, Table 1). Use of acid and base as an additive has a negative effect on the yield of **3aa** (entry 6 and 7, Table 1). Further, screening of solvents revealed

that reaction only proceeds in ACN, indicating the critical role of ACN in the reaction (Table S1). At conventional heating desired product was obtained in 30% yield (entry 12, Table 1). The highest yield of **3aa** was observed with **1a** (0.1 mmol) and **2a** (1.0 equiv.) in ACN (2.5 ml) under microwave irradiation at 120°C for 15 min followed by the acidic hydrolysis (Table S1).

Table 1. Optimization Study[a]

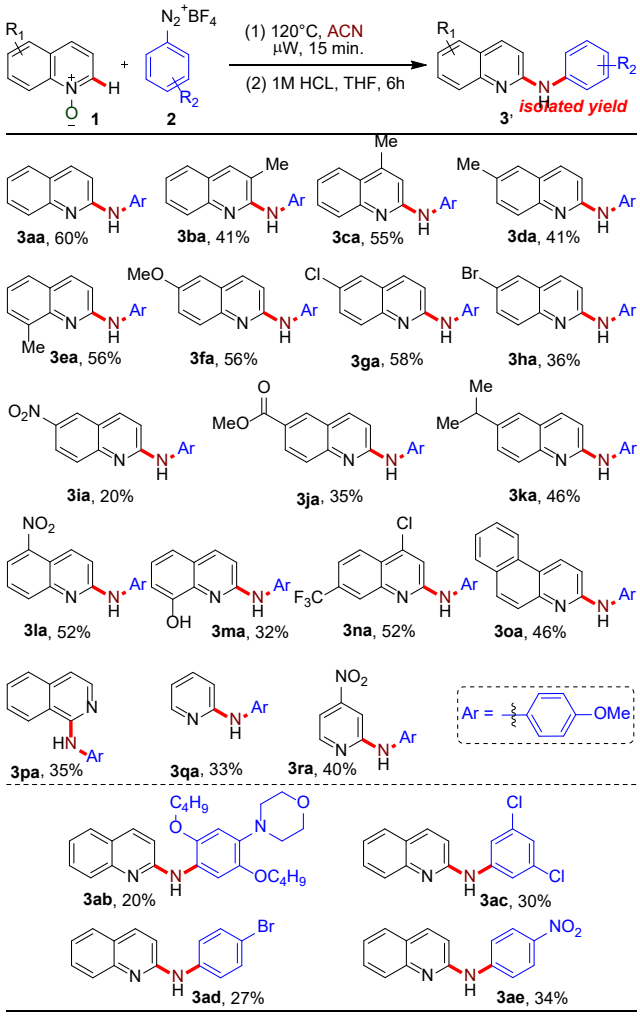


Entry	Deviation from standard conditions	**3aa** Yield (%)[b]
1	no deviation	65 (60)[c]
2	at 50 °C instead of 120 °C	<5
3	at 120 °C in 0.05M	42
4	0.05M instead of 0.04M	55
5	at 100 °C instead of 120 °C	25
6	at 150 °C instead of 120 °C	40
7	AcOH (1 equiv.) as an additive	54
8	NaOAc (1 equiv.) as an additive	<5
9	TFE instead of ACN	n.d.
10	DCE instead of ACN	n.d.
11	THF instead of ACN	n.d.
12	heating (24h) instead of µW	30

[a]Reaction condition: **1a** (0.1 mmol), **2a** (0.1 mmol), ACN (0.04M), µW irradiation, 120 °C, 15 min. followed by treatment with 1M HCl in THF at 50 °C for 6 h. [b]NMR yields calculated by using 1,1,2,2-tetrachloroethane as an internal standard. [c]Isolated yield in parenthesis. n.d. stands for not detected.

Next, various substituted quinoline *N*-oxides were reacted with aryl diazonium salts under optimized reaction condition (Table 2). Quinoline *N*-oxides with methyl-substituent at a different position (**1b-e**) provided the products in 41-56% yields (**3ba-ea**). Other electron donating groups such as –methoxy and -isopropyl at C6-position of quinoline *N*-oxide were also well tolerated (**3fa** and **3ka**). Halogen substituted quinoline *N*-oxide (**1g-h**) reacted successfully affording the desired product in 36-58% yields (**3ga-ha**). Electron withdrawing groups such as –nitro and -ester at C6-position of quinoline *N*-oxide (**1i-1j**) gave lower yields of the desired products (**3ia-ja**). 5-Nitro quinoline *N*-oxide and 8-hydroxyquinoline *N*-oxide afforded the corresponding products (entries **3la** and **3ma**) in 52% and 32% yield, respectively. The reaction of **2a** with 4-chloro-7-trifluoromethyl-quinoline *N*-oxide proceed smoothly to afford the C2-aminated product (**3na**) in good yield. The reaction is also applicable to a polyaromatic compound such as benzo[*f*]quinoline *N*-oxide (**1o**). Importantly, isoquinoline *N*-oxide (**1p**) and pyridine *N*-oxide (**1q-1r**) were also compatible under current reaction condition and provided the C2-aminated products (**3pa-ra**) in 33-40% yields. Next, quinoline *N*-oxide (**1a**) was reacted with different aryldiazonium salts under standard reaction condition. Tri- and di-substituted aryl diazonium salts (**2b-c**) reacted successfully providing the corresponding desired products albeit in lower yields (**3ab-c,** 20-30%). 4-Bromo and 4-nitrophenyl diazonium tetrafluoroborate (**2d-e**) also afforded C2-aminated quinoline in lower yields (**3ad-e**).

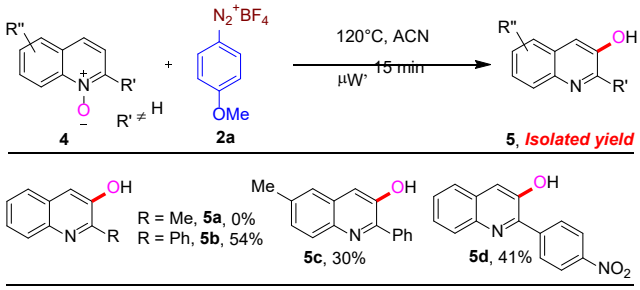
Table 2. Substrate Scope with Quinoline *N*-Oxides and Diazonium Salts[a]



[a]Reaction condition: **1a** (0.1 mmol), **2a** (0.1 mmol), ACN (0.04 M) µW irradiation, 120 °C, 15 min. followed by treatment with 1M HCl in THF at 50 °C for 6 h.

After successful demonstration of the regioselective direct C2-amination, the reaction of C2-substituted quinoline *N*-oxides with aryl diazonium salt was studied (Table 3).

Table 3. Substrate Scope with C2 Substituted Quinoline *N*-oxides[a]

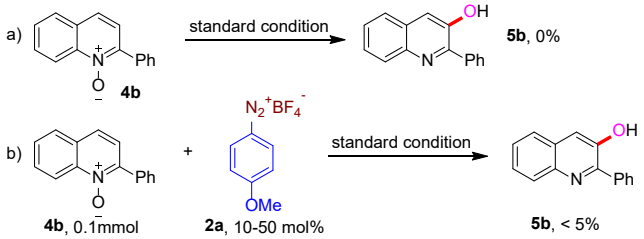


[a]Reaction condition: **4a** (0.1 mmol), **2a** (0.1 mmol), ACN (0.04 M) µW irradiation, 120 °C, 15 min.

Surprisingly, 2-phenylquinoline *N*-oxide forms 3-hydroxy-2-phenylquinolin-ol (**5b**) in 54% yield under the standard reaction condition, which is unprecedented in the literature (Table, 3). The compound **5b** was characterized on the basis of NMR and LC-MS

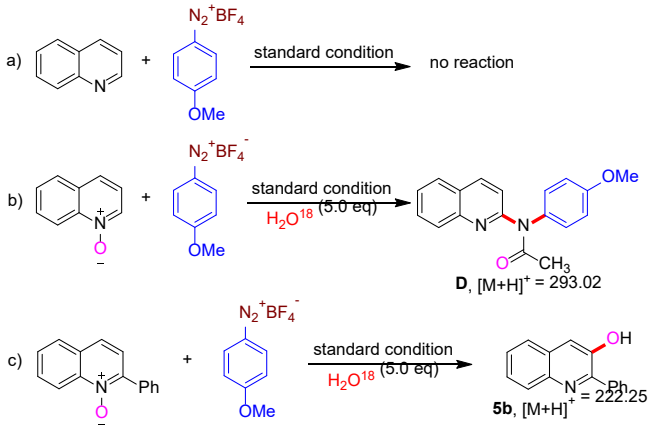
analysis and finally confirmed with previous literature.[16] 2-Methylquinoline *N*-oxide (**4a**) and 4-methyl-2-phenylquinoline *N*-oxide was unable to provide corresponding product. The reaction proceeded well with 6-methyl-2-phenylquinoline *N*-oxide and furnished the desired product **5c** in 30% yield**.** Quinoline *N*-oxide substituted with a 4-nitroaryl (**4d**) at C2 position, afford the desired product **5d** in 41 % yield.

Without diazonium salt **2a** no product was observed **(**Scheme 2a**)**. Also, variation in the quantity of **2a** from catalytic to a sub-stoichiometric amount with respect to 2-phenylquinoline *N*-oxide (**4b**) leads to the traces of the desired product **5b** (Scheme 2b). These results concluded that the diazonium salt is necessary in a stoichiometric amount to carry out the reaction.



Scheme 2. Variation in the quantity of *p*-methoxybenzenediazonium tetrafluoroborate.

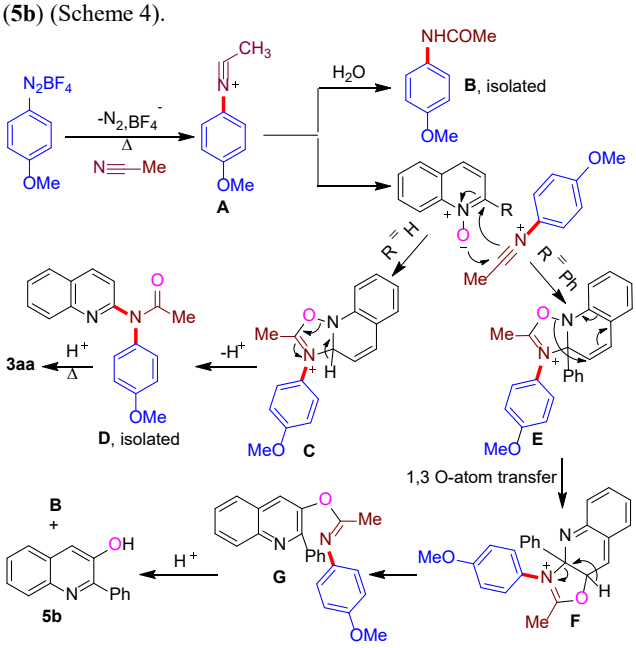
Further for mechanistic understanding, quinoline was treated with 2**a** under standard reaction condition. No desired product was observed confirming the essentiality of *N*-oxide for C2-amination reaction (Scheme 3a).



Scheme 3. Mechanistic Study.

When the standard reaction carried out in the presence of H_2O^{18}, no O^{18} incorporation product was formed, suggesting intramolecular oxygen atom transfer during the reaction (Scheme 3b, Fig S1). Similarly, in the presence of H_2O^{18} product, **5b** was formed without O^{18} incorporation indicating possible 1,3-oxygen atom transfer (Scheme 3c, Fig S2).

On the basis of these preliminary experiments and literature reports,[17] the plausible reaction mechanism is proposed (Scheme 4). The reaction initiated through the formation of intermediate **A** from aryldiazonium tetrafluoroborate and acetonitrile under microwave heating. Intermediate **A** can form acetanilide (**B**)[17a] in the presence of water undergo [3+2] cycloaddition with quinoline *N*-oxide to provide intermediate **C.** Proton abstraction from intermediate **C** and rearomatization can afford **D** which on hydrolysis lead to the desired product, **3aa**. In the case of 2-substituted quinoline, the reaction may proceed through intermediate **E,** which on 1,3-oxygen transfer followed by rearomatization gave **G.** The hydrolysis of **G** lead to the 3-hydroxy-2-phenylquinoline (**5b**) (Scheme 4).



Scheme 4. Plausible Mechanism for Double C-N Bond Formation

CONCLUSIONS

In summary, we have developed a rapid microwave-assisted metal-free method for the direct synthesis of 2-anilinoquinolines and 3-hydroxyquinolines. The protocol is highly regioselective and applicable to a wide range of substrates. This development provides a new strategy for the synthesis of 2-anilinoquinolines and 3-hydroxyquinolines from readily accessible starting materials through a simple experimental procedure.

EXPERIMENTAL SECTION

General Information. All chemicals were purchased from the Sigma-Aldrich and TCI. TLC plates (Aluminium sheet silica gel 60 F254) were purchased from Merck. Flash chromatography was performed over silica gel (230−400 mesh) using n-hexane and ethyl acetate as eluents. All experiments were performed in CEM Discover using SynergyTM software. All pure compounds were characterized on the basis of ^{1}H NMR, ^{13}C NMR, LC-MS, HRMS, and IR analysis. Mass spectra were recorded on Water Q-ToF Micro and maXis Impact mass spectrometer. IR was analyzed by Shimadzu IR Prestige-21 with ZnSe Single reflection ATR accessory. Nuclear magnetic resonance spectra were recorded on a Bruker-Avance 600 or 300 MHz instrument. All ^{1}H NMR experiments are reported in units, parts per million (ppm), and were measured relative to the signals for residual chloroform (7.26) and acetone (2.05, 2.84), dimethyl sulfoxide (2.50, 3.33), water (1.5) in the deuterated solvents. All ^{13}C NMR spectra were reported in ppm relative to deuterated chloroform (77.23) and acetone (29.84, 206.26), dimethyl sulfoxide (39.52) and all were obtained with ^{1}H decoupling. Optimization studies were done by NMR by using TCE as an internal standard. The melting points were recorded on a Bronsted Electro thermal 9100.

General procedure for the preparation of Quinoline *N*-Oxides[4d, 7h, 18]

All solid reactants, *m*-CPBA (4 mmol) and quinoline (2 mmol) were added in schlenk tube and put under vacuum for 2 h, then CH_2Cl_2 (4 mL) was added at 0 °C. The reaction allowed stirring at room temperature for 12 h. On completion, the reaction mixture was extracted with ethyl acetate and organic extract was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (230-400 mesh size) with n-hexane: EtOAc to afford desired *N*-Oxide. All synthesized *N*-oxides were known compounds. [(**1b-d**, **1g**, **1h**, **1i**, **1j**, **1k**)[18a], **1e**[18b] **1f**,[18c] **1l**,[18d] **1n**,[4d] **1o**,[7h] **1p**,[18e] (**4b-d**)[4d]]. The quinoline *N*-oxides (**1a**, **1m**, **1q**, **1r**, **4a**) were used from commercial available sources.

Synthesis of 2-aminated quinolines. To a solution of quinoline-*N*-Oxide (0.3 mmol) in ACN (0.04M), 4-methoxybenzenediazonium tetrafluoroborate (0.3 mmol) was added in a closed reaction vessel and irradiated with microwave in CEM Discover using Synergy™ software for 15 min. at 120 °C, 125 Psi and 80 W. The crude reaction mixture was concentrated at reduced pressure, 1M HCl (7.5 mL) and THF (7.5 mL) were added, and the mixture was stirred at 50°C for 6 h. Saturated aqueous potassium bicarbonate (10 mL) was added to neutralize the solution to approximately pH 7, and then the volatile organics were removed under reduced pressure. Ethyl acetate (15 mL) was added, and the organics were washed with water (2 × 10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Isolation and purification were done by flash chromatography using *n*-hexane and ethyl acetate mixture as eluent.

Characterization Data. *N-(4-methoxyphenyl) quinolin-2-amine[19] (Table 2, entry **3aa**).* White solid, yield = 45.0 mg (60%). mp 94-95 °C. Isolated from flash chromatography (10% EtOAc/*n*-hexane). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 7.87 (d, J = 9.0 Hz, 1H), 7.72 (d, J = 8.4, 1H), 7.62 (dd, J = 7.8, 1.2 Hz, 1H), 7.55-7.58 (m, 1H), 7.41-7.43 (m, 2H), 7.25-7.28 (m, 1H), 6.92-6.94 (m, 2H), 6.87 (d, J = 9.0 Hz, 1H), 3.83 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, δ): 156.6, 155.6, 147.8, 137.9, 133.1, 129.9, 127.6, 126.4, 124.2, 124.1, 122.9, 114.7, 111.0, 55.7. IR (ZnSe) ν_{max} (cm^{-1}): 3169, 3032, 2924, 2320, 1921, 1614, 1573, 1423, 1346, 1284, 1120, 1031, 925, 779. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{16}H_{15}N_2O$, 251.1179; found, 251.1189.

*(4-Methoxy-phenyl)-(3-methyl-quinolin-2-yl)-amine (Table 2, entry **3ba**).* Light brown solid, 32.5 mg (41%). mp 139- 140 °C. Isolated from flash chromatography (15% EtOAc/*n*-hexane). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 7.79 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 9.0 Hz, 2H), 7.71 (s, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.50-7.53 (m, 1H), 7.25-7.27 (m, 1H), 6.94 (d, J = 9.0 Hz, 2H), 6.38 (br, s, 1H, NH), 3.83 (s, 3H), 2.38 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, δ): 155.4, 153.2, 146.6, 136.4, 133.9, 128.6, 126.8, 126.6, 124.5, 122.9, 121.8, 119.9, 114.3, 55.7, 17.8. IR (ZnSe) ν_{max} (cm^{-1}): 3421, 1629, 1571, 1473, 1354, 1236, 1153, 1010, 956, 829, 750. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{17}H_{17}N_2O$, 265.1335; found, 265.1350.

*(4-Methoxy-phenyl)-(4-methyl-quinolin-2-yl)-amine[19] (Table 2, entry **3ca**).* Brown solid, yield = 43.6 mg (55%). mp 125-129 °C. Isolated from flash chromatography (15% EtOAc/*n*-hexane). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 7.80 (dd, J = 7.2 Hz, 1.2 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.55-7.58 (m, 1H), 7.38-7.40 (m, 2H), 7.28-7.30 (m, 1H), 6.93-6.94 (m, 2H), 6.73 (s, 1H), 3.84 (s, 3H), 2.56 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, δ): 156.6, 155.4, 147.7, 146.0, 133.2, 129.7, 126.8, 124.4, 124.3, 123.8, 122.7, 114.8, 110.9, 55.7, 19.1. IR (ZnSe) ν_{max} (cm^{-1}): 2956, 2852, 1606, 1512, 1402, 1246, 1028, 943, 827, 754. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{17}H_{17}N_2O$, 265.1335; found, 265.1348.

*(4-Methoxy-phenyl)-(6-methyl-quinolin-2-yl)-amine (Table 2, entry **3da**).* Brown solid, yield = 32.5 mg (41%). (m.p. 159-160 °C. Isolated from flash chromatography (15% EtOAc/*n*-hexane)). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 7.78 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.39-7.42 (m, 4H), 6.92 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 9.0 Hz, 1H), 3.82 (s, 3H), 2.46 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, δ): 156.4, 155.2, 146.3, 137.3, 133.5, 132.4, 131.9, 126.7, 126.4, 124.1, 123.9, 114.7, 111.1, 55.7, 21.3. IR (ZnSe) ν_{max} (cm^{-1}): 3705, 3697, 2958, 1612, 1492, 1228, 1126, 1033, 887, 696. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{17}H_{17}N_2O$ $[M+H]^+$ 265.1335; found, 265.1357.

*(4-Methoxy-phenyl)-(8-methyl-quinolin-2-yl)-amine (Table 2, entry **3ea**).* Brown solid, yield = 44.4 mg (56%). m.p. 84 - 86 °C. Isolated from flash chromatography (10% EtOAc/n-hexane). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 7.86 (d, J = 9.0 Hz, 1H), 7.60 (d, J = 9.0 Hz, 2H), 7.49 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 6.6 Hz, 1H), 7.18-7.20 (m, 1H), 6.93- 6.96 (m, 2H), 6.82 (dd, J = 9.0, J = 1.8 Hz, 1H), 3.84 (s, 3H), 2.72 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, δ): 155.7, 153.9, 146.7, 137.9, 134.5, 133.8, 130.0, 125.5, 123.8, 122.6, 122.4, 114.5, 111.3, 55.7, 18.3. IR (ZnSe) ν_{max} (cm^{-1}): 3680, 3381, 2951, 2845, 1610, 1543, 1463, 1296, 1145, 1033, 819, 771. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{17}H_{17}N_2O$, 265.1335; found, 265.1340.

*(4-Methoxy-phenyl)-(6-methoxy-quinolin-2-yl)-amine (Table 2, entry **3fa**).* Brown solid, yield = 47.0 mg (56%). mp 140-142 °C. Isolated from flash chromatography (20% EtOAc/*n*-hexane). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 7.80 (d, J = 9.0 Hz, 1H), 7.66 (d, J = 9.0 Hz, 1H), 7.38-7.41 (m, 2H), 7.25 (dd, J = 9.0, J = 3.0 Hz, 1H), 6.97 (d, J = 3.0 Hz, 1H), 6.90-6.93 (m, 2H), 6.87 (d, J = 9.0 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, δ): 156.3, 155.5, 154.2, 143.2, 136.9, 133.5, 127.8, 124.5, 123.7, 121.5, 114.7, 111.3, 106.5, 55.7, 55.6. IR (ZnSe) ν_{max} (cm^{-1}): 2922, 2852, 1616, 1502, 1462, 1361, 1247, 1161, 1031, 964, 842, 763; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{17}H_{17}N_2O_2$, 281.1285; found, 281.1262.

*(6-Chloro-quinolin-2-yl)-(4-methoxy-phenyl)-amine (Table 2, entry **3ga**).* Light brown solid, yield= 49.4 mg (58%). mp 114-116 °C. Isolated from flash chromatography (10% EtOAc/*n*-hexane). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 7.78 (d, J = 9.0 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.59 (d, J = 2.4 Hz, 1H), 7.49 (dd, J = 9.0, J = 2.4 Hz, 1H), 7.40 – 7.42 (m, 2H), 6.92 – 6.94 (m, 2H), 6.87 (d, J = 9.0 Hz, 1H), 3.83 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, δ): 156.8, 155.7, 146.3, 136.9, 132.8, 130.5, 128.1, 127.9, 126.3, 124.7, 124.2, 114.8, 112.0, 55.7. IR (ZnSe) ν_{max} (cm^{-1}): 3421, 2924, 2831, 1629, 1571, 1478, 1354, 1234, 1182, 1029, 954, 860, 771. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{16}H_{14}ClN_2O$, 285.0789; found, 285.0773.

*(6-Bromo-quinolin-2-yl)-(4-methoxy-phenyl)-amine (Table 2, entry **3ha**).* Brown solid, yield = 35.4 mg (36%). mp 219-220°C. Isolated from flash chromatography (20% EtOAc/*n*-hexane). ^{1}H NMR (600 MHz, CD_3COCD_3, δ): 9.20 (br, s, 1H, NH), 8.20 (d, J = 9.0 Hz, 2H), 8.14 (d, J = 8.4 Hz, 2H), 8.00 (d, J = 9.0 Hz, 1H), 7.74 (d, J = 9.0 Hz, 1H), 7.26 (dd, J = 9.0, J = 2.4 Hz, 1H), 7.16 (d, J = 3.0 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 3.83 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, CD_3COCD_3, δ): 157.3, 152.7, 149.0, 143.3, 141.4, 137.7, 129.5, 126.2, 125.8, 122.3, 117.9, 115.1, 107.2, 55.9. IR (ZnSe) ν_{max} (cm^{-1}): 3350, 2349, 1581, 1498, 1390, 1288, 1182, 1064, 954, 756. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{16}H_{14}BrN_2O$, 329.0284; found, 329.0294.

*(6-Nitro-quinolin-2-yl)-phenyl-amine (Table 2, entry **3ia**).* Orange solid, yield = 28.3 mg (32%). mp 157-158 °C. Isolated from flash chromatography (20% EtOAc/*n*-hexane). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 8.57 (d, J = 8.4 Hz, 1H), 8.34 (dd, J = 9.0, 2.4 Hz, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.72 (d, J = 9.6 Hz, 1H), 7.45

(d, J = 9.0 Hz, 2H), 7.03 (br, s, 1H, NH), 6.96-6.97 (m, 2H), 6.94 (d, J = 9.0 Hz, 1H), 3.85 (s, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, δ): 157.7, 157.4, 151.6, 142.6, 139.0, 131.6, 127.4, 124.8, 124.5, 123.9, 122.5, 114.9, 112.9, 55.7. IR (ZnSe) ν_{max} (cm^{-1}): 2922, 2845, 1735, 1624, 1575, 1462, 1325, 1278, 1226, 948, 837, 792. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{16}H_{14}N_3O_3$, 296.1030; found, 296.1045.

*2-(4-Methoxy-phenylamino)-quinoline-6-carboxylic acid methyl ester (Table 2, entry **3ja**).* Brown solid, yield = 40.1 mg (35%). mp 125-126 °C. Isolated from flash chromatography (20% EtOAc/*n*-hexane). ^1H NMR (600 MHz, $CDCl_3$, δ): 8.37 (s, 1H), 8.15 (dd, J = 8.4, 1.2 Hz, 1H), 7.92 (d, J = 9.0 Hz, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.43 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 1H), 3.95 (s, 3H), 3.83 (s, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, δ): 167.2, 157.1, 150.8, 138.8, 132.4, 130.7, 129.9, 126.6, 124.6, 124.3, 123.2, 116.5, 114.9, 111.8, 55.7, 52.2. IR (ZnSe) ν_{max} (cm^{-1}): 3363, 2837, 1710, 1620, 1537, 1508, 1242, 1128, 1033, 962, 756. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{18}H_{17}N_2O_3$, 309.1234; found, 309.1231.

*6-Isopropyl-N-(4-methoxyphenyl) quinolin-2-amine (Table 2, entry **3ka**).* Yellow viscous compound, yield = 40.3 mg (46%). Isolated from flash chromatography (10% EtOAc/*n*-hexane). ^1H NMR (600 MHz, $CDCl_3$, δ): 7.83 (d, J = 9.0 Hz, 1H), 7.68 (d, J = 9.0 Hz, 1H), 7.48 (dd, J = 8.4, 1.8 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.39-7.41 (m, 2H), 6.91 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 9.0 Hz, 1H), 3.82 (s, 3H), 3.00-3.06 (m, 1H), 1.32 (d, J = 7.2 Hz, 6H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, δ): 156.4, 155.1, 146.4, 143.4, 137.7, 133.3, 129.6, 126.3, 123.98, 123.94, 114.7, 110.9, 55.7, 33.9, 24.2. IR (ZnSe): ν_{max} (cm^{-1}) 3392, 2958, 1604, 1494, 1398, 1230, 1178, 1033, 885, 829, 734. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{19}H_{21}N_2O$, 293.1648; found, 293.1640.

*(4-Methoxy-phenyl)-(5-nitro-quinolin-2-yl)-amine (Table 2, entry **3la**).* Yellow solid, yield = 46.0 mg (52%). mp 135-136 °C. Isolated from flash chromatography (15% EtOAc/*n*-hexane). ^1H NMR (600 MHz, $CDCl_3$, δ): 8.62 (d, J = 9.6 Hz, 1H), 7.98 (d, J = 7.8 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.54 (t, J = 7.8 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.23 (br, s, 1H, NH), 7.01 (d, J = 9.6 Hz, 1H), 6.93 (d, J = 8.4 Hz, 2H), 3.82 (s, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, δ): 156.9, 155.8, 148.6, 145.9, 133.2, 133.1, 132.1, 127.9, 124.2, 120.3, 116.6, 114.7, 114.3, 55.7. IR (ZnSe) ν_{max} (cm^{-1}): 2972, 2326, 1710, 1508, 1217, 1186, 1033, 954, 871, 790; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{16}H_{14}N_3O_3$, 296.1030; found, 296.1048.

2-(4-Methoxy-phenylamino)-quinolin-8-ol (Table 2, entry **3ma**). Brown solid, yield = 25.5 mg (32%). mp 141-142 °C. Isolated from flash chromatography (20% EtOAc/n-hexane). ^1H NMR (600 MHz, $CDCl_3$, δ): 7.88 (d, J = 9.0 Hz, 1H), 7.38 (dd, J = 6.6, J = 2.4 Hz, 2H), 7.15 – 7.19 (m, 2H), 7.08- 7.09 (m, 1H), 6.93 – 6.96 (m, 2H), 6.84 (d, J = 9.0 Hz, 1H), 6.58 (br, s, 1H, NH), 3.84 (s, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, δ): 156.7, 154.0, 150.3, 138.0, 137.1, 132.6, 124.1, 123.9, 123.5, 117.9, 114.7, 112.0, 110.7, 55.7. IR (ZnSe): ν_{max} (cm^{-1}) 3697, 3354, 2949, 2864, 1602, 1521, 1438, 1344, 1232, 1033, 956, 756. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{16}H_{15}N_2O_2$, 267.1128; found, 267.1137.

*(4-Chloro-7-trifluoromethyl-quinolin-2-yl)-4-methoxyphenylamine (Table 2, entry **3na**).* Pale yellow solid, yield = 55.0 mg (52%). mp 191-192°C. Isolated from flash chromatography (15% EtOAc/*n*-hexane). ^1H NMR (600 MHz, $CDCl_3$, δ): 8.16 (d, J = 8.4 Hz, 1H), 8.11 (s, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.28 (d, J = 7.2 Hz, 2H), 7.11 (s, 1H), 6.97 (d, J = 6.0 Hz, 2H), 3.84 (s, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, δ): δ 159.4, 154.1, 148.4, 138.8, 135.3 (q, J = 34.5 Hz, 1C), 127.5, 126.7, 126.6, 125.7, 122.3, 121.69, 121.67, 123.02 (q, J = 271.5 Hz, 1C), 118.1, 115.5, 112.5, 55.8. ^{19}F (565 MHz, $CDCl_3$, δ): -63.1. IR (ZnSe) ν_{max} (cm^{-1}): 3354, 2320, 1604, 1570, 1544, 1330, 1234, 1114, 1031, 966, 891, 763. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{17}H_{13}ClF_3N_2O$, 353.0663; found, 353.0688.

*N-(4-methoxyphenyl) benzo[f]quinolin-3-amine (Table 2, entry **3oa**).* Off white solid, yield = 41.4 mg (46%). mp 174-175 °C. Isolated from flash chromatography (10% EtOAc/*n*-hexane). ^1H NMR (600 MHz, DMSO-d_6, δ): 9.30 (s, br, NH, 1H), 8.89 (d, J = 9.0 Hz, 1H), 8.60 (d, J = 8.4 Hz, 1H), 7.94-7.98 (m, 2H), 7.86 (d, J = 9.0 Hz, 2H), 7.68 (d, J = 9.0 Hz, 1H), 7.64-7.66 (m, 1H), 7.52-7.55 (m, 1H), 7.12 (d, J = 9.0 Hz, 1H), 6.94 (d, J = 9.0 Hz, 2H), 3.75 (s, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6, δ): 154.9, 153.9, 146.7, 134.7, 132.3, 130.3, 129.9, 129.6, 128.4, 126.9, 126.8, 125.2, 121.9, 120.1, 118.2, 113.9, 112.4, 55.2. IR (ZnSe): ν_{max} (cm^{-1}) 3410, 2536, 1597, 1506, 1473, 1394, 1246, 1174, 1029, 819, 761. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{20}H_{17}N_2O$, 301.1335; found, 301.1355.

*Isoquinolin-1-yl-(4-methoxy-phenyl)-amine (Table 2, entry **3pa**).* Red-brown solid, yield = 26.3 mg (35%). mp 123-124 °C. Isolated from flash chromatography (10% EtOAc/*n*-hexane). ^1H NMR (300 MHz, $CDCl_3$, δ): 8.05 (d, J = 5.7 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.60-7.65 (m, 1H), 7.49 – 7.54 (m, 3H), 7.07 (d, J = 5.7 Hz, 1H), 6.91-6.95 (m, 2H), 3.81 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, δ): 155.9, 153.2, 141.2, 137.6, 133.7, 129.9, 127.5, 126.4, 123.2, 121.6, 118.7, 114.5, 112.9, 55.7. IR (ZnSe): ν_{max} (cm^{-1}) 3695, 3664, 3421, 2964, 1562, 1477, 1388, 1247, 1055, 960, 864, 796. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{16}H_{15}N_2O$, 251.1179; found, 251.1175.

*(4-Methoxy-phenyl)-pyridin-2-yl-amine (Table 2, entry **3qa**).*[20] Red-brown solid, yield = 24.8 mg (33%). mp 80-81 °C. Isolated from flash chromatography (25% EtOAc/n-hexane). ^1H NMR (600 MHz, $CDCl_3$, δ): 8.14 (d, J = 6.0 Hz, 1H), 7.41-7.44 (m, 1H), 7.23 (dd, J = 6.6, J = 1.8 Hz, 2H), 6.88-6.91 (m, 2H), 6.65-6.69 (m, 2H), 3.81 (s, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, δ): 157.5, 156.4, 148.4, 137.8, 133.4, 124.3, 114.8, 114.4, 107.3, 55.7. IR (ZnSe): ν_{max} (cm^{-1}) 3705, 2937, 2845, 1597, 1454, 1330, 1244, 1168, 1033, 989, 812, 754. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{12}H_{13}N_2O$, 201.1022; found, 201.1043.

*(4-Methoxy-phenyl)-(4-nitro-pyridin-2-yl)-amine (Table 2, entry **3ra**).* Red-brown solid, yield: 29.4 mg (40%). mp 128-129 °C. Isolated from flash chromatography (20% EtOAc/*n*-hexane). ^1H NMR (600 MHz, $CDCl_3$, δ): 8.42 (d, J = 5.4 Hz, 1H), 7.40 (d, J = 4.8 Hz, 1H), 7.37 (s, 1H), 7.34 (d, J = 9.0 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 3.93 (s, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, δ): 159.5, 157.6, 155.8, 150.9, 131.5, 125.3, 115.2, 106.4, 99.8, 55.7. IR (ZnSe): ν_{max} (cm^{-1}) 3705, 2951, 1627, 1543, 1438, 1354, 1240, 1182, 1033, 995, 866, 731. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{12}H_{12}N_3O_3$, 246.0873; found, 246.0870.

*[4-(2,5-Dibutoxy-morpholin-4-yl)-phenyl]-quinolin-2-yl-amine (Table 2, entry **3ab**).* White solid, yield: 27.0 mg (20%). m.p. 65-69 °C. Isolated from flash chromatography (10% EtOAc/n-hexane). ^1H NMR (600 MHz, $CDCl_3$, δ): 8.52 (s, 1H), 7.88 (d, J = 9.0 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 7.2 Hz, 1H), 7.56-7.59 (m, 1H), 7.26-7.29 (m, 1H), 7.13 (br, s, NH, 1H), 6.84 (d, J = 9.0 Hz, 1H), 6.58(s, 1H), 4.13 (t, J = 6.6 Hz, 2H), 4.02 (t, J = 6.6 Hz, 2H), 3.89 – 3.91 (m, 4H), 3.08-3.09 (m, 4H), 1.86-1.90 (m, 2H), 1.78-1.83 (m, 2H), 1.54-1.59 (m, 2H), 1.48-1.53 (m, 2H), 1.01-1.04 (m, 3H), 0.98-1.00 (m, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, δ): 154.1, 145.9, 137.3, 135.5, 129.7, 127.5, 126.9, 124.04, 123.03, 113.4, 110.3, 106.4, 104.1, 69.8, 68.6, 67.5, 51.7, 31.78, 31.76, 19.7, 19.5, 14.09, 14.06. IR (ZnSe): ν_{max} (cm^{-1}) 3427, 2924, 2852, 1606, 1514, 1413, 1373, 1195, 1043, 947, 869, 758. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{27}H_{36}N_3O_3$, 450.2751; found, 450.2771.

*(3,5-Dichloro-phenyl)-quinolin-2-yl-amine (Table 2, entry **3ac**)*. Orange-brown solid, yield = 26.0 mg (30%). mp 143-145 °C. Isolated from flash chromatography (20% EtOAc/*n*-hexane). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 7.98 (d, J = 9.0 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.69 (d, J = 1.8 Hz, 2H), 7.67-7.69 (m, 1H), 7.62-7.65 (m, 1H), 7.35-7.37 (m, 1H), 7.02 (t, J = 1.8 Hz, 1H), 6.88 (d, J = 9.0 Hz, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, δ): 152.9, 147.3, 142.5, 138.3, 135.4, 130.2, 127.6, 127.4, 124.5, 124.2, 122.2, 117.4, 112.6. IR (ZnSe) ν_{max} (cm^{-1}): 3406, 3068, 2922, 2852, 1683, 1585, 1529, 1481, 1448, 1394, 1224, 885, 798. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{15}H_{11}Cl_2N_2$, 289.0294; found, 289.0299.

*N-(4-bromophenyl) quinolin-2-amine[19] (Table 2, entry **3ad**)*. Brown solid, yield = 24.1 mg (27%). mp 144-145 °C. Isolated from flash chromatography (10% EtOAc/*n*-hexane). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 7.93 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.59 – 7.62 (m, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.31 – 7.34 (m, 1H), 6.90 (d, J = 8.4 Hz, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, δ): 153.8, 147.6, 139.5, 138.0, 132.2, 130.1, 127.6, 127.0, 124.3, 123.6, 121.6, 115.1, 112.2. IR (ZnSe) ν_{max} (cm^{-1}): 3402,2920, 2850, 1620, 1506, 1519, 1483, 1390, 1238, 1068, 954, 750. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{15}H_{12}BrN_2$, 299.0178; found, 299.0160.

*N-(4-nitrophenyl) quinolin-2-amine[21] (Table 2, entry **3ae**)*. Brown solid, yield = 27.0 mg (34%). mp 144-145 °C. Isolated from flash chromatography (20% EtOAc/*n*-hexane). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 8.80 (d, J = 2.4 Hz, 1H), 8.27 (dd, J = 7.2, 2.4 Hz, 2H), 8.16 (d, J = 8.4 Hz, 1H), 7.80 (s, 1H), 7.79 (d, J = 6.0 Hz, 1H), 7.72-7.75(m, 1H), 7.59-7.62 (m, 1H), 7.13 (dd, J = 7.2, 1.8 Hz, 2H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, δ): 162.6, 148.6, 145.9, 145.4, 143.6, 129.7, 129.3, 128.5, 127.9, 127.5, 126.3, 123.9, 117.8. IR (ZnSe) ν_{max} (cm^{-1}): 3402, 2920, 2850, 1620, 1506, 1519, 1483, 1390, 1238, 1068, 954, 750. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{15}H_{12}N_3O_2$, 266.0924; found, 266.0947.

*N-phenylacetamide[22] (Intermediate **B**, Scheme 4)*. Off white solid; ^{1}H NMR (600 MHz, $CDCl_3$, δ): 7.38 (d, J = 9.0 Hz, 2H), 6.82 (d, J = 9.0 Hz, 2H), 3.77 (s, 3H), 2.14 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, δ): 168.8, 156.6, 131.0, 122.2, 114.2, 55.6, 24.2.

*N-(4-methoxyphenyl)-N-(quinolin-2-yl) acetamide (Intermediate **D**, Scheme 4)*. Brown viscous liquid. ^{1}H NMR (600 MHz, $CDCl_3$, δ): 8.10 (d, J = 9.0 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.66-7.69 (m, 1H), 7.49-7.52 (m, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 9.0 Hz, 1H), 3.82 (s, 3H), 2.24 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, δ): 171.8, 158.9, 154.7, 147.1, 138.0, 134.6, 129.9, 129.8, 129.0, 127.5, 126.6, 126.6, 119.5, 114.8, 55.6, 24.6. IR (ZnSe) ν_{max} (cm^{-1}): 3061, 2931, 1674, 1595, 1568, 1502, 1463, 1367, 1284, 1168, 1031, 918, 825, 758, 638. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{18}H_{17}N_2O_2$, 293.1285; found, 293.1295.

General procedure for synthesis of 3-hydroxy 2-phenylquinoline. To a solution of 2-phenylquinoline-*N*-oxide (0.1 mmol) in ACN (0.04M), 4-methoxybenzenediazonium tetrafluoroborate (0.1 mmol) was added in a closed reaction vessel and irradiated with microwave in CEM Discover using Synergy™ software for 15 minutes at 120 °C, 125 Psi and 80 W. The crude reaction mixture was concentrated at reduced pressure. Isolation and purification done by flash chromatography using *n*-hexane and ethyl acetate as eluent.

*2-phenylquinolin-3-ol[16] (**5b**, Table 3)*. Yellow solid, yield = 12.0 mg (54%). mp 220-222 °C. Isolated from flash chromatography (10% EtOAc/*n*-hexane). ^{1}H NMR (600 MHz, CD_3COCD_3, δ): 9.25 (s, 1H), 8.09-8.10 (m, 2H), 7.90 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.59 (s, 1H), 7.43-7.46 (m, 1H), 7.38-7.40 (m, 3H), 7.33-7.36 (m, 1H). ^{13}C{^{1}H} NMR (150 MHz, CD_3COCD_3, δ): 151.1, 150.3, 144.1, 139.2, 130.6, 130.0, 129.9, 129.3, 128.6, 127.4, 127.2, 126.7, 117.9. IR (ZnSe) ν_{max} (cm^{-1}): 3057, 2918, 1591, 1492, 1382, 1265, 1180, 1012, 921, 889, 759, 632. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{15}H_{12}NO$, 222.0913; found, 222.0935.

6-methyl-2-phenylquinolin-3-ol (***5c**, Table 3*) Brown solid, yield = 7.1 mg (30%). mp 225-227 °C. Isolated from flash chromatography (15% EtOAc/*n*-hexane). ^{1}H NMR (600 MHz, CD_3OD, δ): 7.85 (d, J = 7.2 Hz, 2H), 7.81 (d, J = 8.4 Hz, 1H), 7.47 (s, 1H), 7.46 (s, 1H), 7.43-7.45 (m, 2H), 7.39 – 7.41 (m, 1H), 7.33-7.35 (m, 1H), 2.46 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, Methanol-d_4, δ): 151.9, 150.9, 148.1, 146.2, 142.4 138.1, 130.75, 129.9, 129.7, 128.9, 128.7, 125.9, 118.2, 21.6. IR (ZnSe) ν_{max} (cm^{-1}): 3059, 2918, 1596, 1494, 1352, 1269, 1199, 1018, 900, 813, 759, 692. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{16}H_{14}NO$, 236.1070; found, 236.1089.

2-(4-nitrophenyl)quinolin-3-ol (***5d**, Table 3*) Brown solid, yield = 10.9 mg (41%). mp 262-264 °C. Isolated from flash chromatography (20% EtOAc/*n*-hexane). ^{1}H NMR (600 MHz, CD_3COCD_3, δ): 8.45 (d, J = 9.0 Hz, 2H), 8.32 (d, J = 9.0 Hz, 2H), 7.98 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.73 (s, 1H), 7.53 – 7.56 (m, 1H), 7.48 – 7.51 (m, 1H). ^{13}C{^{1}H}NMR (150 MHz, DMSO-d_6, δ): 149.8, 147.6, 147.4, 144.2, 142.4, 130.8, 129.4, 129.1, 127.6, 126.9, 126.2, 123.2, 117.7. IR (ZnSe) ν_{max} (cm^{-1}): 3057, 2924, 1597, 1494, 1352, 1269, 1180, 1018, 900, 813, 759, 692, 572. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{15}H_{11}N_2O_3$, 267.0764; found, 267.0789.

Reaction of Quinoline with 4-Methoxybenzenediazonium tetrafluoroborate (2b). To a solution of quinoline (0.1mmol) in ACN (0.04M), 4-Methoxybenzenediazonium tetrafluoroborate (0.1 mmol) was added in a glass tube and irradiated with microwave for 15 minutes at 120 °C. No transformation was observed between quinoline and 4-Methoxybenzenediazonium tetrafluoroborate (scheme 3a).

Isotope labelling experiment (Scheme 3b). To a solution of quinoline N-oxide (0.1mmol), 4-Methoxybenzenediazonium tetrafluoroborate (0.1 mmol) in ACN (0.04M), in the presence of 5 equiv. H_2O^{18} was added in a glass tube and irradiated with microwave for 15 minutes at 120 °C. No O^{18} –D was detected by LC-MS (Fig S1).

Isotope labelling experiment (Scheme 3c). To a solution of 2-phenylquinoline *N*-oxide (0.1mmol), 4-Methoxybenzenediazonium tetrafluoroborate (0.1 mmol) in ACN (0.04M) in the presence of 5 equiv. H_2O^{18} was added in a glass tube and irradiated with microwave for 15 minutes at 120 °C. No O^{18} – **5b** was detected by LC-MS (Fig S2).

ASSOCIATED CONTENT

Supporting Information

Details of optimization studies, characterization data for all synthesized compounds including ^{1}H and ^{13}C NMR spectra. This material is available at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author:

*upendra@ihbt.res.in; upendraihbt@gmail.com

Web address: http://www.ihbt.res.in/en/staff/scientific-staff?chronoform=sctdetail&task=detail&id=41

ORCID

Ankit Kumar Dhiman: 0000-0002-1703-3947

Devesh Chandra: 0000-0003-1640-5865

Rakesh Kumar: 0000-0002-8588-5615

Upendra Sharma: 0000-0002-7693-8690

Notes

The authors declare no competing financial interest.

ACKNOWLEDGEMENTS

Authors thanks Director, CSIR-IHBT for continuous encouragement and providing necessary facilities. AKD, D.C. and R.K. acknowledge CSIR, DST and UGC, New Delhi, respectively for the research fellowship. Financial support from CSIR (MLP0148) is also acknowledged. CSIR-IHBT communication no. for this manuscript is 4403.

REFERENCES

1. (a) Garuti, L.; Roberti, M.; Pizzirani, D., Nitrogen-containing Heterocyclic Quinones: a Class of Potential Selective Antitumor Agents. *Mini-Rev. Med. Chem.* **2007,** *7*, 481-489; (b) Priya, N.; Gupta, A.; Chand, K.; Singh, P.; Kathuria, A.; Raj, H. G.; Parmar, V. S.; Sharma, S. K., Characterization of 4-Methyl-2-oxo-1, 2-Hihydroquinolin-6-yl acetate as an Effective Antiplatelet Agent. *Bioorganic Med. Chem.* **2010,** *18*, 4085-4094; (c) R Solomon, V.; Lee, H., Quinoline as a Privileged Scaffold in Cancer Drug Discovery. *Curr. Med. Chem.* **2011,** *18*, 1488-1508; (d) Tseng, C.-H.; Chen, Y.-L.; Chung, K.-Y.; Wang, C.-H.; Peng, S.-I.; Cheng, C.-M.; Tzeng, C.-C., Synthesis and Antiproliferative Evaluation of 2, 3-diarylquinoline Derivatives. *Org. Biomol. Chem.* **2011,** *9*, 3205-3216; (e) Gorka, A. P.; de Dios, A.; Roepe, P. D., Quinoline Drug–Heme Interactions and Implications for Antimalarial Cytostatic versus Cytocidal Activities. *J. Med. Chem.* **2013,** *56*, 5231-5246; (f) Vennila, K. N.; Elango, K. P., Understanding the Binding of Quinoline Amines with Human Serum Albumin by Spectroscopic and Induced Fit Docking Methods. *J Biomol Struct Dyn.* **2018**, 1-13; (g) Erguc, A.; Altintop, M. D.; Atli, O.; Sever, B.; Iscan, G.; Gormus, G.; Ozdemir, A., Synthesis and Biological Evaluation of New Quinoline-Based Thiazolyl Hydrazone Derivatives as Potent Antifungal and Anticancer Agents. *Lett Drug Des Discov.* **2018,** *15* (2), 193-202.

2. (a) Peng, H.-K.; Lin, C.-K.; Yang, S.-Y.; Tseng, C.-K.; Tzeng, C.-C.; Lee, J.-C.; Yang, S.-C., Synthesis and Anti-HCV Activity Evaluation of Anilinoquinoline Derivatives. *Bioorganic Med. Chem. Lett.* **2012,** *22*, 1107-1110; (b) Kharb, R.; Kaur, H., Therapeutic Significance of Quinoline Derivatives as Antimicrobial agents. *Int. Res. J. Pharm.* **2013,** *4*, 63-69; (c) Liu, L.; Lee, M. R.; Kim, J. L.; Whittington, D. A.; Bregman, H.; Hua, Z.; Lewis, R. T.; Martin, M. W.; Nishimura, N.; Potashman, M., Purinylpyridinylamino-based DFG-in/αC-helix-out B-Raf Inhibitors: Applying Mutant Versus Wild-Type B-Raf Selectivity Indices for Compound Profiling. *Bioorganic Med. Chem* **2016,** *24*, 2215-2234.

3. (a) Iwai, T.; Sawamura, M., Transition-Metal-Catalyzed Site-Selective C–H Functionalization of Quinolines beyond C2 Selectivity. *ACS Catalysis* **2015,** *5*, 5031-5040; (b) Murakami, K.; Yamada, S.; Kaneda, T.; Itami, K., C–H Functionalization of Azines. *Chem. Rev.* **2017,** *117*, 9302-9332.

4. (a) Cho, S. H.; Hwang, S. J.; Chang, S., Palladium-Catalyzed C− H Functionalization of Pyridine N-oxides: Highly Selective Alkenylation and Direct Arylation with Unactivated Arenes. *J. Am. Chem. Soc.* **2008,** *130*, 9254-9256; (b) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S., Recent Advances in the Transition Metal-Catalyzed Twofold Oxidative C–H Bond Activation Strategy for C–C and C–N Bond Formation. *Chem. Soc. Rev.* **2011,** *40*, 5068-5083; (c) Kumar, R.; Kumar, I.; Sharma, R.; Sharma, U., Catalyst and Solvent-Free Alkylation of Quinoline N-Oxides with Olefins: A Direct Access to Quinoline-Substituted α-Hydroxy Carboxylic Derivatives. *Org. Biomol. Chem.* **2016,** *14*, 2613-2617; (d) Kumar, R.; Kumar, R.; Dhiman, A. K.; Sharma, U., Regioselective Metal-Free C2− H Arylation of Quinoline N-Oxides with Aryldiazonium Salts/Anilines under Ambient Conditions. *Asian J. Org. Chem.* **2017,** *6*, 1043-1053.

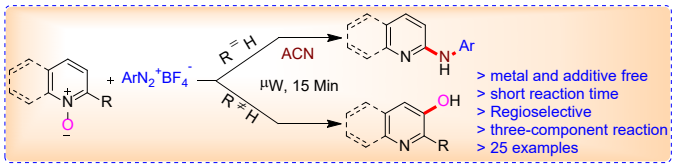
5. Chen, X.; Zhu, C.; Cui, X.; Wu, Y., Direct 2-Acetoxylation of Quinoline N-oxides via Copper Catalyzed C–H Bond Activation. *Chem. Commun.* **2013,** *49*, 6900-6902.

6. (a) Wu, Z.; Song, H.; Cui, X.; Pi, C.; Du, W.; Wu, Y., Sulfonylation of Quinoline N-Oxides with Aryl Sulfonyl Chlorides via Copper-Catalyzed C–H Bonds Activation. *Org. Lett.* **2013,** *15*, 1270-1273; (b) Du, B.; Qian, P.; Wang, Y.; Mei, H.; Han, J.; Pan, Y., Cu-Catalyzed Deoxygenative C2-Sulfonylation Reaction of Quinoline N-Oxides with Sodium Sulfinate. *Org. Lett.* **2016,** *18*, 4144-4147.

7. (a) Li, G.; Jia, C.; Sun, K., Copper-Catalyzed Intermolecular Dehydrogenative Amidation/Amination of Quinoline N-oxides with Lactams/Cyclamines. *Org. Lett.* **2013,** *15*, 5198-5201; (b) Zhu, C.; 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*, 1840-1843; (c) Sun, K.; Wang, X.; Liu, L.; Sun, J.; Liu, X.; Li, Z.; Zhang, Z.; Zhang, G., Copper-Catalyzed Cross-Dehydrogenative C–N Bond Formation of Azines with Azoles: Overcoming the Limitation of Oxidizing N–O Activation Strategy. *ACS Catalysis* **2015,** *5*, 7194-7198; (d) Li, G.; Jia, C.; Sun, K.; Lv, Y.; Zhao, F.; Zhou, K.; Wu, H., Copper (II)-Catalyzed Electrophilic Amination of Quinoline N-oxides with O-benzoyl Hydroxylamines. *Org. Biomol. Chem.* **2015,** *13*, 3207-3210; (e) Yu, H.; Dannenberg, C. A.; Li, Z.; Bolm, C., Copper-Catalyzed Direct Sulfoximination of Heteroaromatic N-Oxides by Dual C− H/N− H Dehydrogenative Cross-Coupling. *Chem. Asian J.* **2016,** *11*, 54-57; (f) Li, Y.; Gao, M.; Wang, L.; Cui, X., Copper-Catalysed Oxidative Amination of Quinoxalin-2 (1 H)-ones with Aliphatic Amines. *Org. Biomol. Chem.* **2016,** *14*, 8428-8432; (g) T Parvatkar, P.; S Parameswaran, P.; Bandyopadhyay, D.; Mukherjee, S.; K Banik, B., Microwave-Assisted Iodine-Catalyzed Rapid Synthesis of 6H-indolo [2, 3-b] Quinolines: Formal Synthesis of Cryptotackieine. *Curr. Microwave Chem.* **2017,** *4*, 238-241; (h) Biswas, A.; Karmakar, U.; Nandi, S.; Samanta, R., Copper-Catalyzed Direct, Regioselective Arylamination of N-Oxides: Studies to Access Conjugated π-Systems. *J. Org. Chem.* **2017,** *82*, 8933-8942; (i) Liang, Y.; Jiang, H.; Tan, Z.; Zhang, M., Direct α-C–H amination using various amino agents by selective oxidative copper catalysis: a divergent access to functional quinolines. *Chem. Commun.* **2018,** *54*, 10096-10099; (j) Behera, A.; Sau, P.; Sahoo, A. K.; Patel, B. K., Cyano-Sacrificial (Arylthio) arylamination of

Quinoline and Isoquinoline N-Oxides Using N-(2-(Arylthio) aryl) Cyanamides. *J. Org. Chem.* **2018,** *83*, 11218-11231.
8. (a) Clark, D. E.; Higgs, C.; Wren, S. P.; Dyke, H. J.; Wong, M.; Norman, D.; Lockey, P. M.; Roach, A. G., A Virtual Screening Approach to Finding Novel and Potent Antagonists at The Melanin-Concentrating Hormone 1 Receptor. *J. Med. Chem* **2004,** *47*, 3962-3971; (b) Li, J.-S.; Chen, F.-X.; Shikiya, R.; Marky, L. A.; Gold, B., Molecular Recognition via Triplex Formation of Mixed Purine/Pyrimidine DNA Sequences using OligoTRIPs. *J. Am. Chem. Soc.* **2005,** *127*, 12657-12665; (c) Wang, N.; Wicht, K. J.; Imai, K.; Wang, M.-q.; Ngoc, T. A.; Kiguchi, R.; Kaiser, M.; Egan, T. J.; Inokuchi, T., Synthesis, β-haematin Inhibition, and in Vitro Antimalarial Testing of Isocryptolepine Analogues: SAR Study of Indolo [3, 2-c] quinolines with Various Substituents at C2, C6, and N11. *Bioorganic Med. Chem* **2014,** *22*, 2629-2642.
9. Yin, J.; Xiang, B.; Huffman, M. A.; Raab, C. E.; Davies, I. W., A General and Efficient 2-Amination of Pyridines and Quinolines. *J. Org. Chem.* **2007,** *72*, 4554-4557.
10. Couturier, M.; Caron, L.; Tumidajski, S.; Jones, K.; White, T. D., Mild and Direct Conversion of Quinoline N-oxides to 2-Amidoquinolines with Primary Amides. *Org. Lett.* **2006,** *8*, 1929-1932.
11. (a) Xie, L. Y.; Peng, S.; Liu, F.; Yi, J. Y.; Wang, M.; Tang, Z.; Xu, X.; He, W. M., Metal-free Deoxygenative 2-Amidation of Quinoline N-oxides with Nitriles via a Radical Activation Pathway. *Adv. Synth. Catal.* **2018,** *360*, 4259-4264; (b) Xie, L.-Y.; Peng, S.; Lu, L.-H.; Hu, J.; Bao, W.-H.; Zeng, F.; Tang, Z.; Xu, X.; He, W.-M., Brønsted Acidic Ionic Liquid-Promoted Amidation of Quinoline N-Oxides with Nitriles. *ACS Sustain. Chem. Eng.* **2018,** *6* (6), 7989-7994; (c) Chen, X.; Peng, M.; Huang, H.; Zheng, Y.; Tao, X.; He, C.; Xiao, Y., TsOH· H2O-mediated N-amidation of quinoline N-oxides: facile and regioselective synthesis of N-(quinolin-2-yl) amides. *Org. Biomol. Chem.* **2018,** *16*, 6202-6205.
12. Li, G.; Jia, C.; Sun, K.; Lv, Y.; Zhao, F.; Zhou, K.; Wu, H., Copper (II)-Catalyzed Electrophilic Amination of Quinoline N-oxides with O-benzoyl Hydroxylamines. *Org. Biomol. Chem.* **2015,** *13*, 3207-3210.
13. Xie, L.-Y.; Peng, S.; Jiang, L.-L.; Peng, X.; Xia, W.; Yu, X.; Wang, X.-X.; Cao, Z.; He, W.-M., AgBF4-Catalyzed Deoxygenative C2-Amination of Quinoline N-Oxides with Isothiocyanates. *Org. Chem. Front.* **2019**, *6*, 167-171
14. Bi, W.-Z.; Sun, K.; Qu, C.; Chen, X.-L.; Qu, L.-B.; Zhu, S.-H.; Li, X.; Wu, H.-T.; Duan, L.-K.; Zhao, Y.-F., A direct metal-free C2–H functionalization of quinoline N-oxides: a highly selective amination and alkylation strategy towards 2-substituted quinolines. *Org. Chem. Front.* **2017,** *4*, 1595-1600.
15. (a) Sharma, R.; Kumar, R.; Kumar, I.; Sharma, U., RhIII-Catalyzed Dehydrogenative Coupling of Quinoline N-Oxides with Alkenes: N-Oxide as Traceless Directing Group for Remote C–H Activation. *Eur. J. Org. Chem.* **2015,** *2015*, 7519-7528; (b) Dhiman, A. K.; Kumar, R.; Kumar, R.; Sharma, U., Metal-Free Synthesis of 2-Substituted 3-(2-Hydroxyaryl) quinolines and 4-(2-Hydroxyaryl) acridines via Benzyne Chemistry. *J. Org. Chem.* **2017,** *82*, 12307-12317; (c) Sharma, R.; Kumar, I.; Kumar, R.; Sharma, U., Rhodium-Catalyzed Remote C-8 Alkylation of Quinolines with Activated and Unactivated Olefins: Mechanistic Study and Total Synthesis of EP4 Agonist. *Adv. Synth. Catal.* **2017,** *359*, 3022-3028; (d) Kumar, R.; Chaudhary, S.; Kumar, R.; Upadhyay, P.; Sahal, D.; Sharma, U., Catalyst and Additive-Free Diastereoselective 1, 3-Dipolar Cycloaddition of Quinolinium Imides with Olefins, Maleimides, and Benzynes: Direct Access to Fused N, N′-Heterocycles with Promising Activity against a Drug-Resistant Malaria Parasite. *J. Org. Chem.* **2018,** *83*, 11552-11570; (e) Sharma, R.; Kumar, R.; Kumar, R.; Upadhyay, P.; Sahal, D.; Sharma, U., Rh (III)-Catalyzed C (8)–H Functionalization of Quinolines via Simultaneous C–C and C–O Bond Formation: Direct Synthesis of Quinoline Derivatives with Antiplasmodial Potential. *J. Org. Chem.* **2018,** *83*, 12702-12710; (f) Kumar, R.; Kumar, R.; Chandra, D.; Sharma, U., Cp*CoIII-Catalyzed Alkylation of Primary and Secondary C (sp3)-H Bonds of 8-Alkylquinolines with Maleimides. *J. Org. Chem.* **2019,** *84*, 1542-1552; (g) Sharma, R.; Kumar, R.; Sharma, U., Rh/O2-Catalyzed C8 Olefination of Quinoline N-oxides with Activated and Unactivated Olefins. *J. Org. Chem.* **2019,** *84,* 2786-2797; (h) Chandra, D.; Dhiman, A. K.; Kumar, R.; Sharma, U., Microwave-Assisted Metal-Free Rapid Synthesis of C4-Arylated Quinolines *via* Povarov Type Multicomponent Reaction. *Eur. J. Org. Chem.* **2019,** *2019,* 2753-2758.
16. Mamedov, V. A.; Mamedova, V. L.; Syakaev, V. V.; Korshin, D. E.; Gul'naz, Z. K.; Mironova, E. V.; Bazanova, O. B.; Latypov, S. K., Simple Synthesis of 3-Hydroxyquinolines via Na2S2O4-Mediated Reductive Cyclization of (2-(2-Nitrophenyl) Oxiran-1-yl)(Aryl) Methanones (o-Nitrobenzalacetophenone Oxides). *Tetrahedron* **2017,** *73*, 5082-5090.
17. (a) Saez, R.; Otero, M. D.; Batanero, B.; Barba, F., Microwave Reaction of Diazonium Salts with Nitriles. *J. Chem. Res.* **2008,** *2008*, 492; (b) Vamos, M.; Cosford, N. D. P., 2-Aminopyridines via Reaction of Pyridine N-Oxides and Activated Isocyanides. *J. Org. Chem.* **2014,** *79*, 2274-2280.
18. (a) Xie, L.-Y.; Duan, Y.; Lu, L.-H.; Li, Y.-J.; Peng, S.; Wu, C.; Liu, K.-J.; Wang, Z.; He, W.-M., Fast, Base-Free and Aqueous Synthesis of Quinolin-2 (1H)-ones under Ambient Conditions. *ACS Sustain. Chem. Eng.* **2017,** *5*, 10407-10412; (b) Wang, B.; Li, C.; Liu, H., Cp* Rh (III)-Catalyzed Directed C− H Methylation and Arylation of Quinoline N-Oxides at the C-8 Position. *Adv. Synth. Catal.* **2017,** *359*, 3029-3034; (c) Ma, X.; Dang, H.; Rose, J. A.; Rablen, P.; Herzon, S. B., Hydroheteroarylation of Unactivated Alkenes Using N-Methoxyheteroarenium Salts. *J. Am. Chem. Soc.* **2017,** *139*, 5998-6007; (d) Gwon, D.; Hwang, H.; Kim, H. K.; Marder, S. R.; Chang, S., Synthesis of 8-Aminoquinolines by Using Carbamate Reagents: Facile Installation and Deprotection of Practical Amidating Groups. *Chem. Eur. J.* **2015,** *21*, 17200-17204; (e) Limnios, D.; Kokotos, C. G., 2, 2, 2-Trifluoroacetophenone as an Organocatalyst for the Oxidation of Tertiary Amines and Azines to N-Oxides. *Chem. Eur. J.* **2014,** *20*, 559-563.
19. Sharma, P.; Liu, R. S., Cu-Catalyzed Aerobic Oxidative Cyclizations of 3-N-Hydroxyamino-1, 2-propadienes with Alcohols, Thiols, and Amines To Form α-O-, S-, and N-Substituted 4-Methylquinoline Derivatives. *Chem. Eur. J.* **2015,** *21*, 4590-4594.
20. Chakraborti, G.; Paladhi, S.; Mandal, T.; Dash, J., "On Water''Promoted Ullmann-Type C–N Bond-Forming Reactions: Application to Carbazole Alkaloids by Selective N-Arylation of Aminophenols. *J. Org. Chem.* **2018**.
21. Peng, H.-K.; Lin, I. L.; Lee, C.-C.; Wang, L.-Y.; Tzeng, C.-C.; Chang, J.-G.; Yang, S.-C., Synthesis and Antitumor Activity Evaluation of Anilinoquinoline Derivatives by the Effect on the Expression of Polo-Like Kinase. *Med Chem Res* **2014,** *23*, 1437-1446.
22. Gao, Y.; Mao, Y.; Zhang, B.; Zhan, Y.; Huo, Y., Regioselective Nitration of Anilines with Fe (NO3) 3· 9H2O as a Promoter and a Nitro Source. *Org. Biomol. Chem.* **2018,** *16*, 3881-3884.

TOC


ACN
µW, 15 Min
> metal and additive free
> short reaction time
> Regioselective
> three-component reaction
> 25 examples