Efficient and Versatile Synthesis of 2,3-Dialkylimidazo[4,5-*b*]quinolin-9-ols by Microwave-Assisted One-Pot Beckmann Rearrangement

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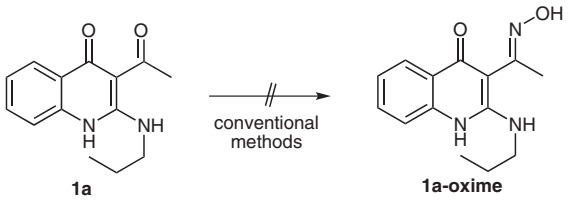
Abstract: A direct microwave-assisted one-pot Beckmann rearrangement of 3-acyl-2-(alkylamino)quinolin-4-(1*H*)-ones in ethanol–pyridine (2:1) provides 2,3-dialkylimidazo[4,5-*b*]quinolin-9-ols as major products along with 2-alkyl-*N*-alkyloxazolo[4,5-*c*]quinolin-4-amines and 3-alkyl-*N*-alkylisooxazolo[4,5-*c*]quinolin-4-amines as minor products. Reactions of 3-acylquinolin-4-(1*H*)-ones containing secondary amine substituent at C-2 give 2-alkyloxazolo[5,4-*b*]quinolin-9-ols as major products via elimination of the secondary amine group. A mechanism proposed for the formation of Beckmann rearrangement products involves initial generation of a nitrilium ion intermediate, which is trapped either by the adjacent nitrogen of the γ-amino group to form imidazoquinolinols or by the oxygen of γ-hydroxy group of the tautomeric form of the ketoxime to form oxazoloquinolinamines.

Key words: microwave, one-pot Beckmann rearrangement, cyclization, imidazoquinolinol, oxazoloquinoline

Substances possessing the imidazoquinoline[1] and oxazoloquinoline[2] skeletons exhibit novel biological activities. Imidazolo[4,5-*b*]quinoline derivatives have been probed as nitric oxide synthase (NOS) inhibitors in the context of potential use in the treatment of acute inflammatory disorders including septic shock, hemorrhagic shock, transplant rejection, and chronic inflammatory disorders such as inflammatory bowel disease, asthma, arthritis, Alzheimer's disease, pain, and ischemia-reperfusion injury.[3] Oxazolo[4,5-*c*]quinolin-4-amine derivatives serve as modulators of cytokine production, which act as the immunomodulator and inducer of the biosynthesis of cytokines, particularly interferon-α (IFN-α) and TNF-α. As a result, these substances are potentially useful in the treatment of cancer and viral diseases.[2] In addition, imidazoquinolines and oxazoloquinolines have been explored as novel immunostimulant drugs.[4] The previous methods developed for the preparation of imidazoquinolines and oxazoloquinolines are tedious and start with substances that are difficult to secure. In connection with a biological screening program, we required a number of modified imidazoloquinoline and oxazoloquinoline derivatives. We have previously described the synthesis of oxazoloquinolines from 2-alkylthio-3-acylquinolinones via Beckmann rearrangement of the corresponding oxime derivatives using indium(III) chloride as a catalyst.[5] In this case, the oximes were prepared by the reaction of 2-alkylthio-3-acylquinolinones with hydroxylamine hydrochloride in ethanol–pyridine (2:1) mixture at room temperature.[6] In contrast to that of 2-alkylthio-3-acylquinolinones, oximation of 2-alkylamino-3-acylquinolinones **1**[7] is a formidable task (Equation 1). Initial attempts to promote reaction of **1a** with hydroxylamine hydrochloride in refluxing ethanol–pyridine (2:1) failed to generate the oxime even after three days and led to complete recovery of **1a**. Modification of the reaction conditions, such as using 50% aqueous hydroxylamine[8] without base or in ethanol in the presence of different kinds of bases (e.g., triethylamine,[9] sodium acetate,[10] potassium carbonate,[11] sodium hydroxide[12]) did not result in any reaction of **1a**. Furthermore, a solid state reaction using $FeCl_3 \cdot 6H_2O$[13] was also unsuccessful. Application of another procedure for oximation[14] using *n*-butylamine as a base to form the oxime salt did not produce the desired product.



1a 1a-oxime

Equation 1 Attempted oximation of 2-alkylamino-3-acylquinolinones **1** using conventional methods failed

Since microwave irradiation is known to effectively initiate oximation,[15] this technique was applied in an effort to overcome the drawbacks associated with the use of conventional methods[16] (Table 1). To our knowledge no report has been published describing attempts to employ microwave irradiation for the one-pot synthesis of imidazo- and oxazoloquinolines in the absence of heterogeneous catalysts.

Although one-pot Beckmann rearrangements using solvent-free microwave irradiation in the presence of catalysts such as alumina,[17] $FeCl_3 \cdot 6H_2O$,[13] HY-Zeolite, $NaHSO_4 \cdot SiO_2$, silica chloride have been described,[18] applications of these reaction conditions to **1a** was not successful. Under microwave condition in the absence of solvent (Method D) and in the presence of $FeCl_3 \cdot 6H_2O$, reaction of **1a** with hydroxylamine hydrochloride proceeded smoothly to completion. The highly polar, water soluble product generated in this process in a yield of 43%

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Table 1 Optimization of Microwave Reaction Condition of 3-Acetyl-2-(propylamino)quinolin-4(1*H*)-one (**1a**)

Catalyst	Solvent	Base	Temp (°C)	Time (h)	Method (NH_2OH, equiv)[a]	Yield (%)
–	EtOH	pyridine	130	0.5	A (1.2)	73
–	EtOH	pyridine	60	2.5	A (1.0)	20[b]
–	EtOH	pyridine	130	2.0	B (1.2)	NR[c]
–	EtOH	–	130	2.0	C (1.2)	NR
Basic Al_2O_3	–	–	100	0.5	A (1.2)	NR
$FeCl_3 \cdot 6H_2O$	–	–	25	0.5	D (1.2)	–[d]
HY-Zeolite	–	–	130	0.5	D (1.3)	NR
$NaHSO_4 \cdot SiO_2$		–	130	0.5	D (1.3)	NR
silica gel chloride	–	–	130	0.5	D (1.3)	NR

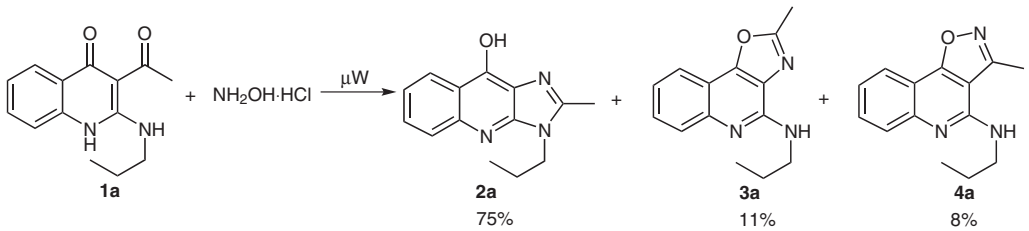
[a] A: $NH_2OH \cdot HCl$, EtOH–pyridine = 2:1; B: 50% aq NH_2OH, EtOH–pyridine = 2:1; C: 50% aq NH_2OH, EtOH; D: $NH_2OH \cdot HCl$, solvent-free.
[b] More than 80% of starting material remained.
[c] NR: no reaction.
[d] Deacetylated product, 2-(propylamino)quinolin-4(1*H*)-one, was obtained in a yield of 43%.

was identified as the deacylated quinolinone, 2-(propylamino)quinolin-4(1*H*)-one. This substance is identical with the product obtained by refluxing the same substrate in aqueous trifluoroacetic acid.

Instead of the expected oxime, microwave irradiation (Method A) of a mixture of **1a** and hydroxylamine hydrochloride in ethanol–pyridine (2:1) leads to the formation of a mixture of imidazoquinolinol **2a**, oxazoloquinoline **3a**, and isooxazoloquinoline **4a** in 75, 11, and 8% yield, respectively (Scheme 1).

This reaction is complete within 0.5 hour and the formed imidazoquinolinol **2a** can be simply separated by filtration. The filtrate contained the other products **3a** and **4a**, which are then separated by preparative TLC. Since **3a** and **4a** are not well resolved, only analytical samples can be obtained by preparative TLC. The one-pot Beckmann rearrangement of **1a** does not take place (even after 2 h) to give **2a** and **3a** when 50% aqueous NH_2OH (Methods B, C) instead of $NH_2OH \cdot HCl$ is used. It is likely that HCl plays an important role in the process. When the reaction temperature is lowered to 60 °C, the reaction proceeds sluggishly, and more than 80% of starting material remained even after 2.5 hours. To our knowledge no previous attempt has been made to employ microwave irradiation conditions for a one-pot synthesis of imidazoles. To probe the scope of this methodology, various 2-alkylamino-3-acylquinolinones **1** were subjected to microwave reaction with hydroxylamine in order to prepare 2,3-dialkylimidazo[4,5-*b*]quinolin-9-ols **2**. It was found that these processes take place in moderate to good yields (Table 2).

The mixtures obtained from these reactions display similar TLC patterns exhibiting fluorescence for isooxazoloquinolinols **4**. Selected reaction mixtures (entries 1, 3, 5, 6, 10, 13) were analyzed, and three isomeric products **2**, **3**, **4** were identified (see Experimental). It was not sufficient to discern the structural identity of the isomeric products by using spectroscopic analysis. In order to identify structures unambiguously, X-ray crystallographic analysis was performed with isomeric products **2m**, **3m**, and **4m** (Figures 1– 3) derived from substrate **1m**. The formation of imidazoquinolinol **2a** and oxazoloquinoline **3a** in the reaction of **1a** with hydroxylamine can be explained by a mechanism involving a nitrilium ion intermediate. Preferential addition of the more nucleophilic nitrogen of the 2-amino group to the nitrilium ion leads to the production of **2a** while addition of oxygen of 4-hydroxyl group affords **3a**. These cyclization processes can occur either by way of the trapping reactions described above or following formation of an amide, the typical Beckmann rearrangement product. Examples of intramolecular cyclization taking place in the course of Beckmann rearrangement have been



Scheme 1 Microwave reaction products of 3-acetyl-2-(propylamino)quinolin-4(1*H*)-one (**1a**) with hydroxylamine hydrochloride

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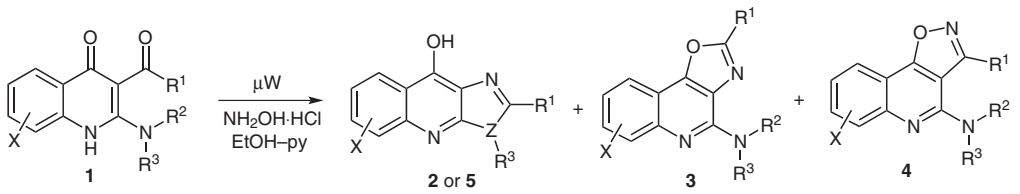
Table 2 One-pot Beckmann Rearrangement Products Using microwave Reaction Condition



Entry	1	Substituents of 1				Product 2 or 5[a]			
		X	R^1	R^2	R^3	Z	Time (min)	Yield (%)[b]	Mp (°C)
1	**1a**	H	Me	H	*n*-Pr	N	40	75	307–310
2	**1b**	8-Me	Me	H	*n*-Pr	N	20	70	232–233
3	**1c**	5,7-Me_2	Me	H	*i*-Pr	N	20	44	395–397
4	**1d**	8-Me	Me	H	allyl	N	30	47	242–245
5	**1e**	5,8-Cl_2	Me	H	allyl	N	20	75	162–163
6	**1f**	6-*t*-Bu	Me	H	*c*-Bu	N	20	88	277–279
7	**1g**	6-*t*-Bu	Me	H	*n*-C_5H_{11}	N	20	88	279–280
8	**1h**	6-MeO	Me	H	Me	N	20	83	311–312
9	**1i**	7,8-Cl_2	Me	H	Me	N	40	74	341–342
10	**1j**	6-*t*-Bu	Me	H	(2,2-Ph_2)-3-Pr	N	20	48	294–295
11	**1k**	H	Me	H	Ph	N	30	58	315–318
12	**1l**	8-Me	Me	H	Ph	N	40	59	280–283
13	**1m**	8-Cl	Et	H	*i*-Pr	N	30	58	253–255
14	**1n**	H	Ph	H	*i*-Bu	N	20	62	282–284
15	**1o**[c]	H	Me	Me	Me	O	20	49	302–304
16	**1p**[d]	8-Me	Me	Me	Me	O	20	48	297–298
17	**1q**[e]	H	Ph	morpholino[f]		O	120	67	211–213
18	**1r**[g]	5,8-Cl_2	Me	morpholino[f]		O	30	47	296–297
19	**1s**[h]	H	Me	morpholino[f]		O	30	68	301–302

[a] See experimental.
[b] Isolated yields.
[c] 3-Acetyl-2-(dimethylamino)quinolin-4(1*H*)-one.
[d] 3-Acetyl-2-(dimethylamino)-5-methylquinolin-4(1*H*)-one.
[e] 3-Benzoyl-2-morpholinoquinolin-4(1*H*)-one.
[f] $N(R^2R^3)$ = morpholino.
[g] 3-Acetyl-5,8-dichloro-2-morpholinoquinolin-4(1*H*)-one.
[h] 3-Acetyl-2-morpholinoquinolin-4(1*H*)-one. These secondary amino group substituted quinolinones were used as substrates.

observed in the reactions of 2′-hydroxyacetophenone oxime,[19] 2′-amino- and 2′-mercaptoacetophenone oxime, which form the corresponding benzoxazole, benzimidazole, and benzothiazole, respectively.[19d] Cyclization of amides is also known to form either fused oxazoles, such as oxazolopyridine,[20] benzoxazole,[21] naphthooxazole[22] from the corresponding 2′-hydroxyanilides, or fused imidazoles, such as imidazopyridine,[23] imidazopyrimidine[24] from the corresponding 2′-aminoanilides. While 3-acetylquinolinones substituted with primary amino groups at C-2 (entries 1–14) underwent Beckmann rearrangement involving the amine nitrogen as a nucleophile, those with secondary C-2 amino groups (entries 15–18) react via elimination of the amine group.

Whereas the reaction of the quinolinone substituted with a dimethylamino group (entries 15, 16) proceeds to completion in 20 minutes, conversion of the morpholino analogue **1q** requires a prolonged reaction time (2 h). In the

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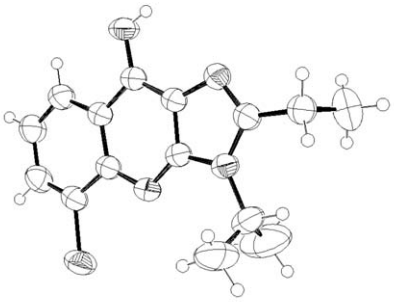


Figure 1 X-ray crystal structure of 5-chloro-2-ethyl-3-isopropyl-3*H*-imidazo[4,5-*b*]quinolin-9-ol (**2m**) at the 50% probability level

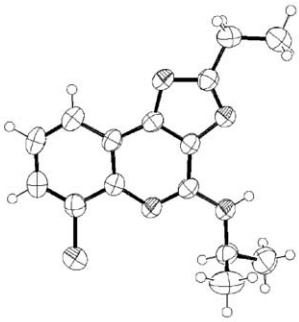


Figure 2 X-ray crystal structure of 6-chloro-2-ethyl-*N*-isopropyl-oxazolo[4,5-*c*]quinolin-4-amine (**3m**) at the 50% probability level

case of **1s**, 2-methyloxazolo[5,4-*b*]quinolin-9-ol (**5s**) as a major product and two isomeric products, 2-methyl-4-morpholinooxazolo[4,5-*c*]quinoline (**3s**), and 3-methyl-4-

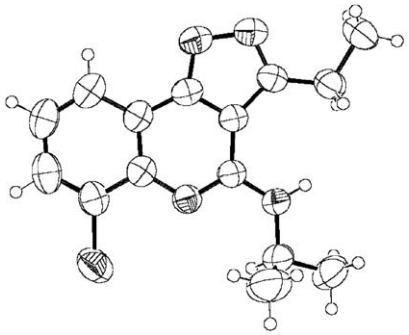
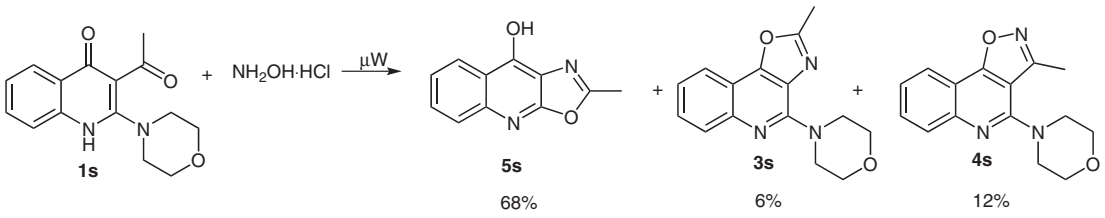


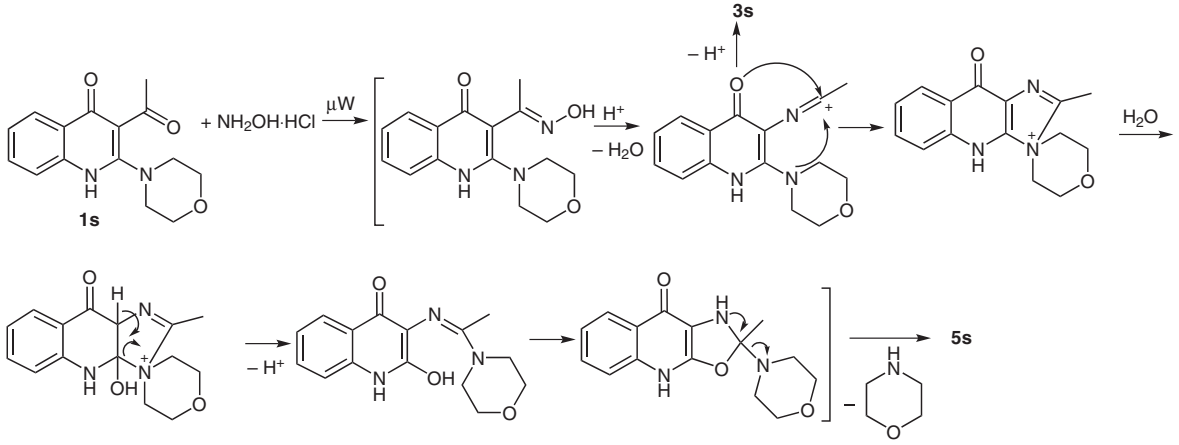
Figure 3 X-ray crystal structure of 6-chloro-3-ethyl-*N*-isopropylisoxazolo[4,5-*c*]quinolin-4-amine (**4m**) at the 50% probability level

morpholinoisoxazolo[4,5-*c*]quinoline (**4s**) are produced in 68, 6, and 12% yield, respectively (Scheme 2). In this process, the morpholine group was eliminated after intramolecular trapping of nitrilium ion intermediate generated during rearrangement as depicted in Scheme 3. Although an amide product was not isolated, it is possible that it is formed by a normal Beckmann rearrangement and then cyclizes (see above).[20–24]Although amide product was not isolated under the reaction condition, another possibility is that cyclization might take place after formation of amide as previously noted.[20–24]

In summary, the results of the study described above demonstrate that by employing microwave irradiation along with normal oximation reaction conditions, a wide variety of imidazoquinoline and oxazoloquinoline products can



Scheme 2 Elimination of morpholine, secondary amino group, in the reaction of **1s**



Scheme 3 Plausible Beckmann rearrangement mechanism for reaction of 3-acetyl-2-morpholinoquinolin-4(1*H*)-one (**1s**)

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be prepared conveniently starting with 2-monoalkylamino-3-acylquinolin-4-ones. In this process, the C-2 amine group is incorporated into the fused heterocycle products. In contrast, microwave promoted reactions of 2-dialkylamino-3-acylquinolin-4-ones take place to yield elimination products.

^{1}H NMR spectra were recorded on a Bruker Avance 300 (300 MHz) spectrometer and ^{13}C NMR spectra were recorded on a Bruker Avance 500 (125 MHz) spectrometer, unless otherwise specified, in $CDCl_3$ solution using TMS as internal standard. Melting points were determined on a MPA100 (SRS) and Thomas-Hoover Unimelt capillary apparatus and are uncorrected. Mass spectra were obtained on a Shimadzu GC/MC-QP 1000 spectrometer. High-resolution mass spectra were obtained on a VGQUATTRO triple quadrupole tandem Micromass Autospec Mass spectrometer with electron beam energy of 70 eV (EI). Column chromatography was performed with Merck Kieselgel 60 (230–400 mesh). Analytical TLC analyses were performed on precoated silica gel plates (0.25 mm 60F-254E, Merck). X-ray crystal structure analyses were performed on a Bruker SMART Apex II X-ray Diffractometer. Reflection data were collected on a Bruker SMART Apex II X-ray Diffractometer with Mo tube and Graphite-Monochromator (50 KV, 30 mA). Cell parameters were determined and refined by Bruker SHELXTL program. All microwave reactions were carried out in 5 mL sealed glass tubes in a focused monomode microwave oven ('Emrys creator' by Personal Chemistry AB company). Microwave oven conditions were set up at a temperature of 130 °C with a maximum power level of 300 W during a reaction time of 20–30 min.

All the reagent grade chemicals, purchased from Aldrich, Fluka, Merck, and TCI chemical company, were used without further purification. All the organic solvents were obtained from Duksan, Samchun, SK chemical company. THF was refluxed over sodium in the presence of benzophenone and distilled prior to use. CH_2Cl_2 was dried by distilling over CaH_2. NMR solvents were purchased from Cambridge Isotope Laboratories, Inc.

X-ray Crystal Structure Determination[25]

Single-crystal X-ray diffraction data were collected at 296K on a Bruker SMART APEX II CCD-based diffractometer with graphite-monochromated MoKα radiation (λ = 0.71073A).[26] The reflection data were collected as Φ and ω scan frames with of 0.5 °/frame and exposure time of 10 s/frame. Cell parameter were determined and refined by SMART program.[26] Among 15241 collected reflections 3589 were unique (R_{int} = 0.0533). Data reductions were performed using SAINT software.[26] Multiscan absorption correction was applied with SADABS program.[26] The structures of the compounds were solved by using direct methods and refined by full matrix least-squares methods using SHELXTL program package[27] with anisotropic thermal parameters for all nonhydrogen atoms; all the hydrogen atoms were put into calculated positions with the isotropic thermal parameters.

One-Pot Microwave Reaction of 1a with Hydroxylamine Hydrochloride; 2-Methyl-3-propyl-3*H*-imidazo[4,5-*b*]quinolin-9-ol (2a); Typical Procedure

A solution of 3-acetyl-2-(propylamino)quinolin-4(1*H*)-one (**1a**; 98 mg, 0.4 mmol) in a mixture of EtOH (3 mL) and pyridine (1.5 mL) containing $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) in a pressure vessel (7 mL) was irradiated in a microwave oven at 130 °C for 30 min. The solvent was removed under vacuum and CH_2Cl_2 (30 mL) was added to the residue. The precipitate **2a** was filtered and washed with CH_2Cl_2 (2 × 15 mL) and dried under vacuum to give 73 mg (75%) of an olive green solid. The filtrate was sequentially washed with aq 5% HCl (30 mL), H_2O (50 mL) and sat. aq $NaHCO_3$ (30 mL). After evaporation of CH_2Cl_2 under vacuum, the residue was subjected to preparative TLC (silica gel) with hexane–EtOAc (2:1) as eluent to afford oxazoloquinoline **3a** (11 mg, 11%) as a waxy solid and isoxazoloquinoline **4a** (7.7 mg, 8%) as a white solid.

2-Methyl-3-propyl-3*H*-imidazo[4, 5-*b*]quinolin-9-ol (2a)
Yield: 75%; olive green solid; mp 307–310 °C; R_f = 0.29 (hexane–EtOAc, 1:1).

^{1}H NMR (CD_3OD): δ = 8.41 (d, *J* = 8.1 Hz, 1 H), 7.85–7.82 (m, 2 H), 7.49 (dt, *J* = 2.3, 8.1 Hz, 1 H), 4.40 (t, *J* = 7.8 Hz, 2 H), 1.97 (sext, *J* = 7.8 Hz, 2 H), 1.12 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 129.723, 126.612, 149.952, 149.112, 118.752, 121.009, 103.617, 48.118, 22.543, 11.425.

MS (EI): *m*/*z* = 241 (M^+), 226, 213, 199, 130, 114, 102, 76.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{15}N_3O$: 241.1215; found: 241.1218.

2,5-Dimethyl-3-propyl-3*H*-imidazo[4,5-*b*]quinolin-9-ol (2b)
Yield: 70%; mp 232–233 °C; R_f = 0.14 (hexane–EtOAc, 1:1).

^{1}H NMR (CD_3OD): δ = 8.41 (d, *J* = 8.1 Hz, 1 H), 7.85–7.82 (m, 2 H), 7.49 (dt, *J* = 2.3, 8.1 Hz, 1 H), 4.40 (t, *J* = 7.8 Hz, 2 H), 1.97 (sext, *J* = 7.8 Hz, 2 H), 1.12 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 148.002, 134.814, 130.272, 127.212, 159.521, 149.426, 119.211, 102.924, 48.117, 22.532, 16.502, 11.411, 7.942.

MS (EI): *m*/*z* = 255 (M^+), 246, 233, 219, 76.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{17}N_3O$: 255.1372; found: 255.1316.

3-Isopropyl-2,6,8-trimethyl-3*H*-imidazo[4,5-*b*]quinolin-9-ol (2c)
Yield: 44%; white solid; mp 395–397 °C; R_f = 0.05 (hexane–EtOAc, 1:1).

^{1}H NMR (CD_3OD): δ = 7.47 (s, 1 H), 6.92 (s, 1 H), 5.19 (d, *J* = 7.8 Hz, 1 H), 4.63–4.56 (m, 1 H), 2.77 (s, 3 H), 2.71 (s, 3 H), 2.44 (s, 3 H), 1.35 (s, 3 H), 1.32 (s, 3 H).

^{13}C NMR (CD_3OD): δ = 161.748, 149.544, 138.381, 131.617, 125.730, 124.644, 124.384, 111.038, 42.340, 23.408, 21.824, 21.202, 14.730.

MS (EI): *m*/*z* = 269 (M^+), 254, 227, 212, 197, 158, 142, 127, 84, 58.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{11}Cl_2N_3O$: 269.1528; found: 269.1520.

3-Allyl-2,5-dimethyl-3*H*-imidazo[4,5-*b*]quinolin-9-ol (2d)
Yield: 47%; brown solid; mp 242–245 °C; R_f = 0.35 (hexane–EtOAc, 1:1).

^{1}H NMR (CD_3OD): δ = 8.29 (d, *J* = 8.6 Hz, 1 H), 7.70 (d, *J* = 7.0 Hz, 1 H), 7.45 (t, *J* = 8.2 Hz, 1 H), 6.20–6.04 (m, 1 H), 5.44–5.35 (m, 1 H), 5.29–5.26 (m, 2 H), 2.87 (s, 3 H), 2.76 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 159.533, 152.432, 149.372, 148.123, 134.842, 132.772, 130.211, 127.242, 119.223, 115.916, 102.927, 49.112, 16.389.

MS (EI): *m*/*z* = 253 (M^+), 238, 212, 171, 144, 116, 89, 63.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{15}N_3O_2$: 253.1210; found: 253.1210.

3-Allyl-5,8-dichloro-2-methyl-3*H*-imidazo[4,5-*b*]quinolin-9-ol (2e)
Yield: 75%; yellow solid; mp 162–163 °C; R_f = 0.17 (hexane–EtOAc, 1:1).

^{1}H NMR (CD_3OD): δ = 7.57 (d, *J* = 8.7 Hz, 1 H), 7.23 (d, *J* = 8.4 Hz, 1 H), 6.06–5.96 (m, 1 H), 5.51 (d, *J* = 17.7 Hz, 1 H), 5.36 (d, *J* = 10.2 Hz, 1 H), 4.12 (d, *J* = 3.8 Hz, 2 H), 2.19 (s, 3 H).

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^{13}C NMR (CD_3OD): δ = 167.730, 153.963, 151.372, 145.827, 134.498, 130.842, 129.986, 127.792, 123.980, 117.535, 113.238, 106.814, 43.966, 12.161.

MS (EI): *m*/*z* = 307 (M^+), 292, 292, 280, 268, 253, 185, 167, 149, 111, 97, 83, 71.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{11}Cl_2N_3O$: 307.0279; found: 307.0254.

7-(*tert*-Butyl)-3-cyclobutyl-2-methyl-3*H*-imidazo[4,5-*b*]quinolin-9-ol (2f)

Yield: 88%; white solid; mp 277–279 °C; R_f = 0.12 (hexane–EtOAc, 1:1).

^{1}H NMR (CD_3OD): δ = 8.41 (s, 1 H), 7.92 (dd, *J* = 11.4, 9.0 Hz, 2 H), 5.22 (quint, *J* = 8.4 Hz, 1 H), 2.87–3.05 (m, 2 H), 2.91 (s, 3 H), 2.76–2.68 (m, 2 H), 2.15–2.01 (m, 2 H), 1.44 (s, 9 H).

^{13}C NMR (DMSO-d_6): δ = 8.41 145.440, 50.006, 34.509, 31.044, 28.415, 14.874, 13.837.

MS (EI): *m*/*z* = 309 (M^+), 294, 281, 266, 240, 133, 119, 55.

HRMS (EI): *m*/*z* calcd for $C_{19}H_{23}N_3O_2$: 309.1841; found: 309.1844.

7-(*tert*-Butyl)-2-methyl-3-pentyl-3*H*-imidazo[4,5-*b*]quinolin-9-ol (2g)

Yield: 88%; white-green solid; mp 279–280 °C; R_f = 0.07 (hexane–EtOAc, 1:1).

^{1}H NMR (CD_3OD): δ = 8.41 8.43 (s, 1 H), 7.77 (d, *J* = 8.7 Hz, 1 H), 7.62 (d, *J* = 8.7 Hz, 1 H), 4.19 (t, *J* = 7.2 Hz, 1 H), 2.54 (s, 3 H), 1.83–1.75 (m, 2 H), 1.41–1.37 (m, 4 H, s, 9 H), 0.90 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 145.429, 142.976, 130.696, 126.787, 119.892, 113.412, 34.463, 31.044, 28.135, 27.688, 21.833, 13.827, 11.592.

MS (EI): *m*/*z* = 325 (M^+), 310, 296, 269, 254, 240, 115, 66.

HRMS (EI): *m*/*z* calcd for $C_{20}H_{27}N_3O$: 325.2154; found: 325.2158.

7-Methoxy-2,3-dimethyl-3*H*-imidazo[4,5-*b*]quinolin-9-ol (2h)

Yield: 83%; white solid; mp 311–312 °C; R_f = 0.06 (CH_2Cl_2–MeOH, 20:1).

^{1}H NMR (CD_3OD): δ = 7.81 (d, *J* = 2.7 Hz, 1 H), 7.61 (d, *J* = 9.0 Hz, 1 H), 7.30 (d, *J* = 9.0 Hz, 1 H), 3.91 (s, 3 H), 3.79 (s, 3 H), 2.55 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 154.253, 140.371, 121.243, 120.992, 119.256, 55.267, 29.892, 13.102.

MS (EI): *m*/*z* = 243 (M^+), 228, 200, 117, 63, 56.

HRMS (EI): *m*/*z* calcd for $C_{13}H_{13}N_3O_2$: 243.1008; found: 243.1006.

5,6-Dichloro-2,3-dimethyl-3*H*-imidazo[4,5-*b*]quinolin-9-ol (2i)

Yield: 74%; dark brown solid; mp 341–342 °C; R_f = 0.13 (hexane–EtOAc, 1:1).

^{1}H NMR (CD_3OD): δ = 8.06 (d, *J* = 8.4 Hz, 1 H), 7.44 (d, *J* = 8.7 Hz, 1 H), 3.23(s, 3 H), 2.70 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 159.212, 151.843, 147.007, 135.627, 131.335, 106.964, 31.057.

MS (EI): *m*/*z* = 281 (M^+), 269, 253, 240, 213, 124, 91, 71, 57.

HRMS (EI): *m*/z calcd for $C_{16}H_9ClN_3O$: 281.0123; found: 281.0123.

7-(*tert*-Butyl)-3-(2, 2-diphenylpropyl)-2-methyl-3*H*-imidazo[4,5-*b*]quinolin-9-ol (2j)

Yield: 48%; white solid; mp 294–295 °C; R_f = 0.11 (hexane–EtOAc, 1:1).

^{1}H NMR (CD_3OD): δ = 8.15 (s, 1 H), 7.65 (d, *J* = 8.4 Hz, 1 H), 7.47 (d, *J* = 8.4 Hz, 1 H), 7.33–7.19 (m, 10 H), 4.12 (s, 2 H), 2.18 (s, 3 H), 2.09 (s, 3 H), 1.38 (s, 9 H).

^{13}C NMR (CD_3OD): δ = 147.757, 130.276, 129.572, 128.556, 127.718, 53.203, 35.651, 31.942, 27.234.

MS (EI): *m*/*z* = 449 (M^+), 286, 268, 252, 240, 181, 103, 57.

HRMS (EI): *m*/*z* calcd for $C_{30}H_{31}N_3O$: 449.2467; found: 449.2468.

2-Methyl-3-phenyl-3*H*-imidazo[4,5-*b*]quinolin-9-ol (2k)

Yield: 58%; white solid; mp 315–318 °C; R_f = 0.24 (hexane–EtOAc, 1:1).

^{1}H NMR (CD_3OD): δ = 8.41 (d, *J* = 8.2 Hz, 1 H), 7.72–7.69 (m, 3 H), 7.62–7.56 (m, 4 H), 7.56–7.31 (m, 1 H), 2.35 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 158.798, 151.641, 150.399, 142.912, 131.855, 128.567, 122.147, 121.476, 120.284, 119.593, 48.808, 21.660, 20.862, 12.945.

MS (EI): *m*/*z* = 275 (M^+), 205, 199, 138, 102, 77.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{13}N_3O$: 275.1059; found: 275.1043.

2,5-Dimethyl-3-phenyl-3*H*-imidazo[4,5-*b*]quinolin-9-ol (2l)

Yield: 59%; white solid; mp 280–283 °C; R_f = 0.35 (hexane–EtOAc, 1:1).

^{1}H NMR (CD_3OD): δ = 8.32 (d, *J* = 8.4 Hz, 1 H), 7.79–7.66 (m, 6 H), 7.45 (d, *J* = 9.3 Hz, 1 H), 2.69 (s, 3 H), 2.58 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 159.542, 149.746, 148.127, 130.224, 129.421, 128.036, 127.248, 121.412, 121.018, 119.218, 118.572, 16.447, 7.637.

MS (EI): *m*/*z* = 289 (M^+), 275, 219, 199, 116, 77.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{15}N_3O_2$: 289.1215; found: 289.1208.

5-Chloro-2-ethyl-3-isopropyl-3*H*-imidazo[4,5-*b*]quinolin-9-ol (2m)

Yield: 58%; white solid; mp 253–255 °C; R_f = 0.37 (hexane–EtOAc, 1:1).

^{1}H NMR (CD_3OD): δ = 8.42 (d, *J* = 8.6 Hz, 1 H), 7.80 (d, *J* = 7.2 Hz, 1 H), 7.30 (t, *J* = 8.4 Hz, 1 H), 4.85–4.80 (m, 1 H), 3.16 (q, *J* = 7.5 Hz, 2 H), 2.05 (s, 3 H), 1.92 (s, 3 H), 1.46 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (CD_3OD): δ = 158.798, 151.641, 150.399, 142.912, 131.855, 128.567, 122.147, 121.476, 120.284, 119.593, 48.808, 21.660, 20.862, 12.945.

MS (EI): *m*/*z* = 289 (M^+), 274, 262, 247, 233, 189, 172, 105, 91, 77, 65.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{16}ClN_3O$: 289.0982; found: 289.0981.

X-ray Crystal Data

$C_{15}H_{16}ClN_3O$, FW = 289.76, monoclinic, $P2_1/n$, *a* = 7.3072(7) Å, *b* = 14.186(1) Å, *c* = 14.066(2) Å, β = 95.725(2)°, *V* = 1450.7(3)Å^3, ρ_{calcd} = 1.327 Mg/m^3, *R*1 = 0.0556, *wR*2 = 0.1498, GOF = 1.019.

3-Isobutyl-2-phenyl-3*H*-imidazo[4,5-*b*]quinolin-9-ol (2n)

Yield: 62%; white solid; mp 282–284 °C; R_f = 0.26 (hexane–EtOAc, 1:1).

^{1}H NMR (CD_3OD): δ = 7.98 (d, *J* = 8.1 Hz, 1 H), 7.59 (m, 2 H), 7.49 (m, 2 H), 7.39 (m, 3 H), 2.75 (t, *J* = 7.2 Hz, 1 H), 3.37 (d, *J* = 6.6 Hz, 2 H), 2.05 (m, 1 H), 1.12 (s, 3 H), 1.10 (s, 3 H).

^{13}C NMR (CD_3OD): δ = 199.947, 179.072, 157.235, 144.541, 139.742, 133.946, 131.229, 130.447, 128.918, 128.741, 126.890, 124.858, 124.613, 117.887, 101.945, 30.831, 29.486, 20.578.

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MS (EI): *m*/*z* = 317 (M^+), 302, 274, 263, 249, 199, 114, 77.

HRMS (EI): *m*/*z* calcd for $C_{20}H_{19}N_3O$: 317.1528; found: 317.1516.

2-Methyl-*N*-propyloxazolo[4,5-*c*]quinolin-4-amine (3a)
Yield: 11%; waxy solid; R_f = 0.11 (CH_2Cl_2–MeOH, 30:1).

^{1}H NMR: δ = 7.89 (d, *J* = 8.4 Hz, 1 H), 7.81 (d, *J* = 8.4 Hz, 1 H), 7.53 (t, *J* = 7.2 Hz, 1 H), 7.29 (t, *J* = 7.2 Hz, 1 H), 5.40 (br s, 1 H), 3.68 (q, *J* = 6.3 Hz, 2 H), 2.71 (s, 3 H), 1.75 (sext, *J* = 7.2 Hz, 2 H), 1.06 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 162.053, 152.082, 150.226, 146.126, 128.608, 126.810, 124.918, 122.213, 119.832, 113.226, 42.674, 23.022, 14.468, 11.598.

MS (EI): *m*/*z* = 242 (M^+), 227, 212, 199, 184, 142, 114, 102, 93.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{15}N_3O$: 241.1215; found: 241.1214.

***N*-Isopropyl-2,7,9-trimethyloxazolo[4,5-*c*]quinolin-4-amine (3c)**
Yield: 8%; white solid; mp 98–99 °C; R_f = 0.31 (hexane–EtOAc, 5:1).

^{1}H NMR: δ = 7.47 (s, 1 H), 6.92 (s, 1 H), 5.19 (d, *J* = 7.8 Hz, 1 H), 4.63–4.56 (m, 1 H), 2.77 (s, 3 H), 2.71 (s, 3 H), 2.44 (s, 3 H), 1.35 (s, 3 H), 1.32 (s, 3 H).

^{13}C NMR: δ = 161.748, 149.544, 138.381, 131.617, 125.730, 124.644, 124.384, 111.038, 42.340, 23.408, 21.824, 21.202, 14.730.

MS (EI): *m*/*z* = 269 (M^+), 254, 227, 212, 197, 158, 142, 127, 84, 58.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{11}Cl_2N_3O$: 269.1528; found: 269.1520.

***N*-Allyl-6,9-dichloro-2-methyloxazolo[4,5-*c*]quinolin-4-amine (3e)**
Yield: 5%; white solid; mp 185–186 °C; R_f = 0.42 (hexane–EtOAc, 3:1).

^{1}H NMR: δ = 7.57 (d, *J* = 8.4 Hz, 1 H), 7.21 (d, *J* = 8.1 Hz, 1 H), 6.15–6.04 (m, 1 H), 5.73 (br s, 1 H), 5.39 (d, *J* = 17.1 Hz, 1 H), 5.22 (d, *J* = 10.2 Hz, 1 H), 4.43 (t, *J* = 5.1 Hz, 2 H), 2.75 (s, 3 H).

^{13}C NMR: δ = 168.623, 150.519, 145.925, 143.362, 135.478, 134.265, 126.684, 122.078, 115.214, 114.897, 54.864, 14.056.

MS (EI): *m*/*z* = 307 (M^+), 292, 279, 267, 252, 198, 182, 148, 111, 97, 85, 57.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{11}Cl_2N_3O$: 307.0279; found: 307.0275.

8-*tert*-Butyl-*N*-cyclobutyl-2-methyloxazolo[4,5-*c*]quinolin-4-amine (3f)
Yield: 8%; white solid; mp 127–128 °C; R_f = 0.58 (hexane–EtOAc, 2:1).

^{1}H NMR: δ = 8.03 (s, 1 H), 7.74 (d, *J* = 7.7 Hz, 1 H), 7.60 (d, *J* = 8.8 Hz, 1 H), 5.53 (d, *J* = 8.1 Hz, 1 H), 4.89 (quint, *J* = 8.1 Hz, 1 H), 2.71 (s, 3 H), 2.57–2.48 (m, 2 H), 2.17–1.86 (m, 2 H), 1.83–1.75 (m, 2 H), 1.41 (s, 9 H).

^{13}C NMR: δ = 166.072, 150.645, 146.739, 144.176, 134.910, 125.321, 122.779, 121.422, 125.352, 111.776, 54.564, 35.192, 31.506, 30.664, 18.102, 14.004.

MS (EI): *m*/*z* = 309 (M^+), 294, 280, 266, 240, 224, 155, 119, 84, 57.

HRMS (EI): *m*/*z* calcd for $C_{19}H_{23}N_3O$: 309.1841; found: 309.1842.

8-*tert*-Butyl-2-methyl-*N*-(2,2-diphenylpropyl)oxazolo[4,5-*c*]quinolin-4-amine (3j)
Yield: 3%; white solid; mp 87–89 °C; R_f = 0.47 (hexane–EtOAc, 3:1).

^{1}H NMR: δ = 7.84 (s, 1 H), 7.78 (d, *J* = 8.7 Hz, 1 H), 7.62 (d, *J* = 8.7 Hz, 1 H), 7.37–7.20 (m, 10 H), 5.16 (t, *J* = 5.7 Hz, 1 H), 4.45 (d, *J* = 5.7 Hz, 2 H), 2.65 (s, 3 H), 1.85 (s, 3 H), 1.41 (s, 9 H).

^{13}C NMR: δ = 147.519, 145.477, 144.325, 128.578, 127.814, 127.264, 126.694, 126.491, 115.484, 50.064, 47.762, 34.903, 31.663, 26.784, 14.656.

MS (EI): *m*/*z* = 449 (M^+), 268, 252, 238, 181, 165, 106, 77.

HRMS (EI): *m*/*z* calcd for $C_{30}H_{31}N_3O$: 449.2467; found: 449.2471.

6-Chloro-2-ethyl-*N*-isopropyloxazolo[4,5-*c*]quinolin-4-amine (3m)
Yield: 12%; white solid; mp 128–129 °C; R_f = 0.58 (hexane–EtOAc, 3:1).

^{1}H NMR: δ = 7.82 (d, *J* = 7.8 Hz, 1 H), 7.65 (d, *J* = 7.8 Hz, 1 H), 7.17 (t, *J* = 7.8 Hz, 1 H), 5.41 (br d, *J* = 7.2 Hz, 1 H), 4.70–4.63 (m, 1 H), 3.03 (q, *J* = 7.8 Hz, 2 H), 1.49 (t, *J* = 7.8 Hz, 3 H), 1.39 (d, *J* = 6.3, 3.0 Hz, 6 H).

^{13}C NMR: δ = 167.093, 151.906, 149.439, 142.176, 130.979, 128.810, 125.221, 121.779, 118.752, 114.422, 42.764, 22.812, 22.233, 11.192.

MS (EI): *m*/*z* = 289 (M^+), 274, 259, 247, 232, 219, 164, 102, 84, 50.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{16}ClN_3O$: 289.0982; found: 289.0979.

X-ray Crystal Data
$C_{15}H_{16}ClN_3O$, FW = 289.76, monoclinic, $P2_1/c$, *a* = 11.4614(4) Å, *b* = 7.9067(3) Å, *c* = 16.7618(5) Å, β = 106.785(2)°, V = 1454.27(9) Å^3, ρ_{calcd} = 1.323 Mg/m^3, *R*1 = 0.0545, *wR*2 = 0.1508, GOF = 1.063.

2-Methyl-4-morpholinooxazolo[4,5-*c*]quinoline (3s)
Yield: 6%; white solid; mp 124–125 °C; R_f = 0.36 (hexane–EtOAc, 3:1).

^{1}H NMR: δ = 8.22 (d, *J* = 8.1 Hz, 1 H), 7.94 (d, *J* = 8.7 Hz, 1 H), 7.71 (t, *J* = 7.2 Hz, 1 H), 7.49 (t, *J* = 7.2 Hz, 1 H), 3.95 (t, *J* = 4.2 Hz, 4 H), 3.50 (t, *J* = 4.5 Hz, 4 H), 2.71 (s, 3 H).

^{13}C NMR: δ = 168.992, 156.249, 154.218, 146.971, 131.266, 128.005, 125.147, 121.638, 113.906, 108.408, 66.880, 51.187, 12.566.

MS (EI): *m*/*z* = 269 (M^+), 238, 224, 212, 198, 184, 142, 120, 114, 102, 84, 76.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{15}N_3O_2$: 269.1164; found: 269.1188.

3-Methyl-*N*-propylisoxazolo[4,5-*c*]quinolin-4-amine (4a)
Yield: 8%; white solid; mp 109–110 °C; R_f = 0.43 (CH_2Cl_2–MeOH, 30:1).

^{1}H NMR: δ = 8.09 (d, *J* = 8.1 Hz, 1 H), 7.79 (d, *J* = 8.1 Hz, 1 H), 7.62 (t, *J* = 8.1 Hz, 1 H), 7.31 (t, *J* = 8.1 Hz, 1 H), 4.87 (br s, 1 H), 3.67 (q, *J* = 7.2 Hz, 2 H), 2.71 (s, 3 H), 1.77 (sext, *J* = 7.2 Hz, 2 H), 1.07 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (CD_3OD): δ = 168.162, 153.305, 151.524, 148.681, 131.086, 126.687, 122.689, 121.490, 112.289, 104.812, 42.863, 22.866, 12.026, 11.574.

MS (EI): *m*/*z* = 242 (M^+), 227, 213, 200, 183, 169, 144, 114, 84, 76, 58.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{15}N_3O$: 241.1215; found: 241.1210.

***N*-Isopropyl-3,7,9-trimethylisoxazolo[4,5-*c*]quinolin-4-amine (4c)**
Yield: 19%; white solid; mp 134–135 °C; R_f = 0.38 (hexane–EtOAc, 5:1).

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^{1}H NMR: δ = 7.44 (s, 1 H), 6.93 (s, 1 H), 4.63–4.58 (s, m, 1 H), 2.85 (s, 3 H), 2.69 (s, 3 H), 2.44 (s, 3 H), 1.36 (s, 3 H), 1.34 (s, 3 H).

^{13}C NMR: δ = 169.544, 152.944, 150.963, 150.135, 141.061, 134.164, 126.327, 124.240, 110.377, 104.625, 42.536, 23.345, 22.031, 21.929, 12.205.

MS (EI): *m*/*z* = 269 (M^+), 254, 239, 227, 212, 197, 158, 142, 127, 115, 58.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{19}N_3O$: 269.1528; found: 269.1525.

_N_-Allyl-6,9-dichloro-3-methylisoxazolo[4,5-*c*]quinolin-4-amine (4e)

Yield: 9%; white solid; mp 179–180 °C; R_f = 0.35 (hexane–EtOAc, 3:1).

^{1}H NMR: δ = 7.64 (d, *J* = 8.1 Hz, 1 H), 7.24 (d, *J* = 8.4 Hz, 1 H), 6.16–6.05 (m, 1 H), 5.38 (d, *J* = 17.4 Hz, 1 H), 5.26 (d, *J* = 10.1 Hz, 1 H), 5.17 (br s, 1 H), 4.42 (t, *J* = 5.1 Hz, 2 H), 2.75 (s, 3 H).

^{13}C NMR: δ = 167.73, 152.963, 151.372, 145.827, 134.498, 130.842, 129.986, 127.792, 123.980, 117.535, 113.238, 106.814, 43.966, 12.161.

MS (EI): *m*/*z* = 307 (M^+), 292, 280, 272, 253, 182, 148, 86, 56.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{11}Cl_2N_3O$: 307.0279; found: 307.0275.

8-*tert*-Butyl-_N_-cyclobutyl-3-methylisoxazolo[4,5-*c*]quinolin-4-amine (4f)

Yield: 4%; white solid; mp 253–254 °C; R_f = 0.62 (hexane–EtOAc, 2:1).

^{1}H NMR: δ = 8.03 (s, 1 H), 7.74–7.67 (m, 2 H), 4.92–4.81 (br s, m, 1 H, 1 H), 2.71 (s, 3 H), 2.59–2.53 (m, 2 H), 1.98–1.82 (m, 2 H, 2 H), 1.41 (s, 9 H).

^{13}C NMR: δ = 166.061, 150.027, 146.723, 144.044, 134.925, 125.361, 122.736, 121.414, 54.505, 35.531, 31.561, 31.532, 30.636, 18.105, 11.629.

MS (EI): *m*/*z* = 309 (M^+), 294, 280, 266, 240, 224, 155, 119, 84, 57.

HRMS (EI): *m*/*z* calcd for $C_{19}H_{23}N_3O$: 309.1841; found: 309.1843.

6,9-Dichloro-_N_,3-dimethylisoxazolo[4,5-*c*]quinolin-4-amine (4i)

Yield: 14%; white solid; mp 145–147 °C; R_f = 0.35 (hexane–EtOAc, 3:1).

^{1}H NMR: δ = 7.64 (d, *J* = 8.1 Hz, 1 H), 7.24 (d, *J* = 8.4 Hz, 1 H), 6.16–6.05 (m, 1 H), 5.38 (d, *J* = 17.4 Hz, 1 H), 5.26 (d, *J* = 10.1 Hz, 1 H), 5.17 (br s, 1 H), 4.42 (t, *J* = 5.1 Hz, 2 H), 2.75 (s, 3 H).

^{13}C NMR: δ = 167.73, 152.963, 151.372, 145.827, 134.498, 130.842, 129.986, 127.792, 123.980, 117.535, 113.238, 106.814, 43.966, 12.161.

MS (EI): *m*/*z* = 307 (M^+), 292, 280, 272, 253, 182, 148, 86, 56.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{11}Cl_2N_3O$: 307.0279; found: 307.0275.

8-*tert*-Butyl-3-methyl-_N_-(2,2-diphenylpropyl)isoxazolo[4,5-*c*]quinolin-4-amine (4j)

Yield: 32%; white solid; mp 193–195 °C; R_f = 0.58 (hexane–EtOAc, 3:1).

^{1}H NMR: δ = 8.03 (s, 1 H), 7.78 (d, *J* = 8.7 Hz, 1 H), 7.71 (d, *J* = 8.7 Hz, 1 H), 4.48 (d, *J* = 5.0 Hz, 1 H), 4.42 (d, *J* = 5.0 Hz, 2 H), 2.13 (s, 3 H), 1.78 (s, 3 H), 1.41 (s, 3 H).

^{13}C NMR: δ = 168.359, 153.578, 151.509, 147.159, 146.989, 146.031, 129.762, 128.787, 127.822, 126.836, 126.523, 117.160, 111.988, 105.009, 50.245, 47.718, 34.939, 31.585, 27.620, 11.537.

MS (EI): *m*/*z* = 449 (M^+), 268, 252, 224, 181, 103, 77.

HRMS (EI): *m*/*z* calcd for $C_{30}H_{31}N_3O$: 449.2467; found: 449.2473.

6-Chloro-3-ethyl-_N_-isopropylisoxazolo[4,5-*c*]quinolin-4-amine (4m)

Yield: 10%; white solid; mp 108–109 °C; R_f = 0.59 (hexane–EtOAc, 3:1).

^{1}H NMR: δ = 8.01 (d, *J* = 8.1 Hz, 1 H), 7.74 (d, *J* = 7.8 Hz, 1 H), 7.21 (t, *J* = 7.8 Hz, 1 H), 4.78 (br d, *J* = 6.3 Hz, 1 H), 4.71–4.64 (m, 1 H), 3.06 (q, *J* = 7.8 Hz, 2 H), 1.51 (t, *J* = 7.5 Hz, 3 H), 1.39 (dd, *J* = 6.5, 3.0 Hz, 6 H).

^{13}C NMR: δ = 168.230, 158.349, 150.480, 144.815, 131.142, 130.983, 122.282, 120.260, 113.336, 104.664, 43.112, 22.744, 20.408, 11.845.

MS (EI): *m*/*z* = 289 (M^+), 274, 259, 247, 232, 219, 164, 102, 84, 50.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{16}ClN_3O$: 289.0982; found: 289.0986.

X-ray Crystal Data

$C_{15}H_{16}ClN_3O$, FW = 289.76, tetragonal, $I4_1/a$, a = 27.6952(2) Å, b = 27.6952(2) Å, c = 15.2512(3) Å, $\alpha = \beta = \gamma = 90°$, V = 11698.0(3) Å^3, ρ_{calcd} = 1.316 Mg/m^3, $R1$ = 0.0561, $wR2$ = 0.1356, GOF = 1.005.

_N_-Isobutyl-3-phenylisoxazolo[4,5-*c*]quinolin-4-amine (4n)

Yield: 22%; white solid; mp 111–112 °C; R_f = 0.70 (hexane–EtOAc, 3:1).

^{1}H NMR: δ = 8.16 (d, *J* = 8.1 Hz, 1 H), 7.79 (d, *J* = 8.4 Hz, 1 H), 7.74 (m, 2 H), 7.63 (m, 4 H), 7.33 (t, *J* = 7.8 Hz, 1 H), 4.90 (br s, 1 H), 3.42 (dd, *J* = 5.4, 5.4 Hz, 2 H), 1.80 (m, 1 H), 0.89 (s, 3 H), 0.86 (s, 3 H).

^{13}C NMR: δ = 168.466, 157.683, 151.304, 148.948, 131.407, 130.798, 129.584, 129.124, 128.670, 126.754, 122.745, 121.673, 112.272, 103.873, 48.421, 28.208, 20.365.

MS (EI): *m*/*z* = 317 (M^+), 302, 274, 261, 190, 114, 77.

HRMS (EI): *m*/*z* calcd for $C_{20}H_{19}N_3O$: 317.1528; found: 317.1519.

3-Methyl-4-morpholinoisoxazolo[4,5-*c*]quinoline (4s)

Yield 12%; white solid; mp 121–122 °C; R_f = 0.45 (hexane–EtOAc, 3:1).

^{1}H NMR: δ = 7.93 (d, *J* = 7.8 Hz, 1 H), 7.79 (d, *J* = 8.4 Hz, 1 H), 7.55 (t, *J* = 8.1 Hz, 1 H), 7.32 (t, *J* = 7.8 Hz, 1 H), 4.21 (t, *J* = 4.5 Hz, 4 H), 3.89 (t, *J* = 4.5 Hz, 4 H), 2.71 (s, 3 H).

^{13}C NMR: δ = 160.702, 153.913, 150.467, 145.328, 128.994, 126.995, 125.670, 122.937, 119.903, 113.254, 67.311, 46.570, 14.528.

MS (EI): *m*/*z* = 269 (M^+), 238, 224, 212, 198, 184, 142, 130, 114, 102, 84, 76.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{15}N_3O_2$: 269.1164; found: 269.1143.

2-Methyloxazolo[5,4-*b*]quinolin-9-ol (5o)

Yield: 49%; yellow solid; mp 302–304 °C; R_f = 0.34 (hexane–EtOAc, 1:1).

^{1}H NMR (CD_3OD): δ = 8.32 (d, *J* = 8.1 Hz, 1 H), 7.75 (t, *J* = 7.7 Hz, 1 H), 7.53 (d, *J* = 8.1 Hz, 1 H), 7.41 (t, *J* = 7.5 Hz, 1 H), 2.62 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 173.661, 165.121, 158.227, 138.773, 133.534, 126.108, 124.562, 123.600, 118.730, 100.494, 11.354.

MS (EI): *m*/*z* = 200 (M^+), 187, 171, 145, 119, 92, 76, 64.

HRMS (EI): *m*/*z* calcd for $C_{11}H_8N_2O_2$: 200.0586; found: 200.0586.

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2,5-Dimethyloxazolo[5,4-*b*]quinolin-9-ol (5p)
Yield: 48%; yellow solid; mp 297–298 °C; R_f = 0.37 (hexane–EtOAc, 1:1).

^{1}H NMR (CD_3OD): δ = 8.19 (d, *J* = 8.2 Hz, 1 H), 7.60 (d, *J* = 7.6 Hz, 1 H), 7.30 (t, *J* = 7.6 Hz, 1 H), 2.62 (s, 3 H), 2.16 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 165.227, 157.617, 134.064, 126.741, 124.378, 123.484, 122.756, 100.024, 17.748, 10.861.

MS (EI): *m*/*z* = 214 (M^+), 185, 172, 159, 133, 105, 89, 77, 63.

HRMS (EI): *m*/*z* calcd for $C_{12}H_{10}N_2O_2$: 214.0742; found: 214.0735.

2-Phenyloxazolo[5,4-*b*]quinolin-9-ol (5q)
Yield: 67%; light green solid; mp 211–213 °C; R_f = 0.17 (hexane–EtOAc, 1:1).

^{1}H NMR (CD_3OD): δ = 8.36 (d, *J* = 8.1 Hz, 1 H), 8.31–8.28 (m, 2 H), 7.77 (t, *J* = 7.6 Hz, 1 H), 7.58–7.51 (m, 4 H), 7.42 (t, *J* = 7.4 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 161.461, 156.920, 137.442, 131.807, 130.392, 129.895, 129.906, 125.998, 122.587, 120.988, 116.191.

MS (EI): *m*/*z* = 262 (M^+), 248, 234, 221, 119, 105, 77, 643.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{10}N_2O_2$: 262.0742; found: 262.0741.

5,8-Dichloro-2-methyloxazolo[5,4-*b*]quinolin-9-ol (5r)
Yield: 47%; light orange solid; mp 296–297 °C; R_f = 0.13 (hexane–EtOAc, 1:1).

^{1}H NMR (CD_3OD): δ = 7.67 (s, 1 H), 7.10 (s, 1 H), 2.64 (s, 3 H).

^{13}C NMR: δ = 160.029, 153.587, 150.241, 142.117, 131.329, 127.215, 120.124, 114.131, 104.275, 11.748.

MS (EI): *m*/*z* = 268 (M^+), 255, 241, 213, 187, 160, 124, 62.

HRMS (EI): *m*/*z* calcd for $C_{11}H_6N_2O_2$: 267.9806; found: 267.9805.

2-Methyloxazolo[5,4-b]quinolin-9-ol (5s)
Yield: 68%; white solid; mp 301–302 °C; R_f = 0.25 (hexane–EtOAc, 1:1).

^{1}H NMR (CD_3OD): δ = 8.32 (d, *J* = 8.4 Hz, 1 H), 7.77 (t, *J* = 8.1 Hz, 1 H), 7.54 (d, *J* = 7.8 Hz, 1 H), 7.41 (t, *J* = 7.8 Hz, 1 H), 3.31 (s, 3 H).

^{13}C NMR (CD_3OD): δ = 173.661, 165.121, 158.227, 138.773, 133.534, 126.108, 124.562, 123.600, 118.730, 100.495, 11.354.

MS (EI): *m*/*z* = 200 (M^+), 171, 145, 130, 119, 103, 92, 76, 52.

HRMS (EI): *m*/*z* calcd for $C_{11}H_8N_2O_2$: 200.0586; found: 200.0584.

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