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PIFA-promoted intramolecular oxidative C(aryl)-H amidation reaction: Synthesis of quinolino[3,4-*b*]quinoxalin-6(5*H*)-ones

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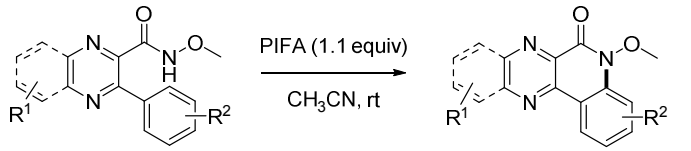

A facile and direct intramolecular oxidative C(aryl)-H amidation reaction was developed for the synthesis of quinolino[3,4-*b*]quinoxalin-6(5*H*)-ones in moderate to excellent yields, starting from readily available materials by tethering the adjacent *N*-methoxyamide and aryl portion in the presence of phenyliodine(III) bis(trifluoroacetate) (PIFA) at room temperature. This metal-free approach is a valuable addition to the traditional methods already available for the preparation of these molecules.

PIFA-Promoted Intramolecular Oxidative C(aryl)-H Amidation Reaction: Synthesis of Quinolino[3,4-*b*]quinoxalin-6(5*H*)-ones

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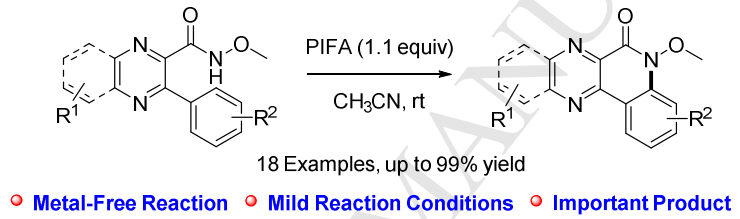


Abstract: A facile and direct intramolecular oxidative C(aryl)-H amidation reaction was developed for the synthesis of quinolino[3,4-*b*]quinoxalin-6(5*H*)-ones in moderate to excellent yields starting from readily available materials by tethering the adjacent *N*-methoxyamide and aryl portions in the presence of phenyliodine(III) bis(trifluoroacetate) at room temperature. This metal-free approach is a valuable addition to the traditional methods already available for the preparation of these molecules.

Keywords: Quinolino[3,4-*b*]quinoxalin-6(5*H*)-ones; Pyrazino[2,3-*c*]quinolin-5(6*H*)-ones; C(aryl)-N Formation; PIFA; Hypervalent organoiodine

1. Introduction

Quinolino[3,4-*b*]quinoxalin-6(5*H*)-ones and their pyrazino[2,3-*c*]quinolin-5(6*H*)-ones analogues are interesting heterocycles of great importance. Quinolino[3,4-*b*]quinoxalin-6(5*H*)-ones and quinolino[3,4-*b*]quinoxalines, such as

5-(3-(dimethylamino)propyl)quinolino[3,4-*b*]quinoxalin-6(5*H*)-one (**I**) and N^1,N^1-dimethyl-N^4-(quinolino[3,4-*b*]quinoxalin-6-yl)butane-1,4-diamine (**II**) have shown interesting topoisomerase IIα (Topo IIα) inhibition activity and G-quadruplex stabilization (Figure 1).[1] Furthermore, the radioiodinated compound 7-(iodo-^{125}I)-5-((1-propylpiperidin-4-yl)methoxy)pyrazino[2,3-*c*]quinoline ([^{125}I]**III**, Figure 1) exhibited excellent binding affinity toward human 5-HT_4R (*Ki* 5-HT_4R = 0.094 nM) and a high selectivity over other serotonin receptor subtypes (5-HTR),[2] which could be used as a radiotracer for brain imaging of the serotonin 4 receptor subtype (5-HT_4R) using single photon emission computed tomography in the future.[3] Interestingly, compounds **I**, **II**, and [^{125}I]**III** can be obtained from the derivatization of quinolino[3,4-*b*]quinoxalin-6(5*H*)-ones or pyrazino[2,3-*c*]quinolin-5(6*H*)-ones through a N^5- or C^6-functionalization, respectively. This conversion indicates that the quinolino[3,4-*b*]quinoxalin-6(5*H*)-ones and their pyrazino[2,3-*c*]quinolin-5(6*H*)-ones analogues are important intermediates in organic synthetic chemistry.

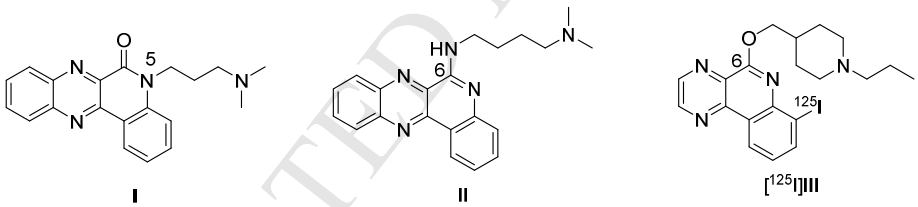
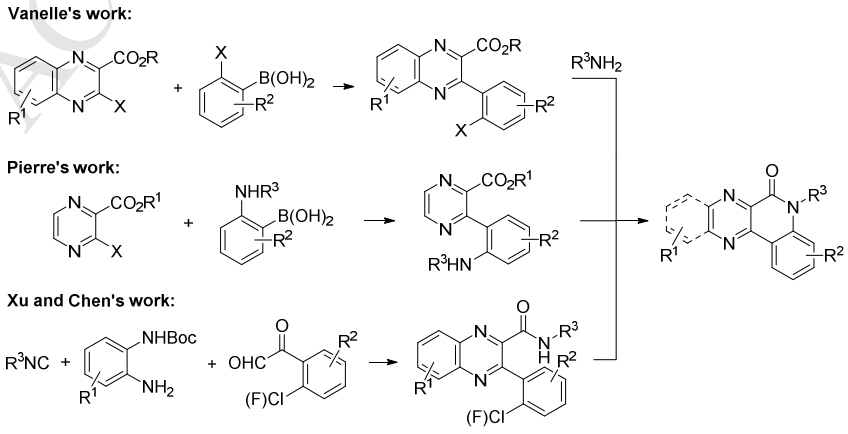
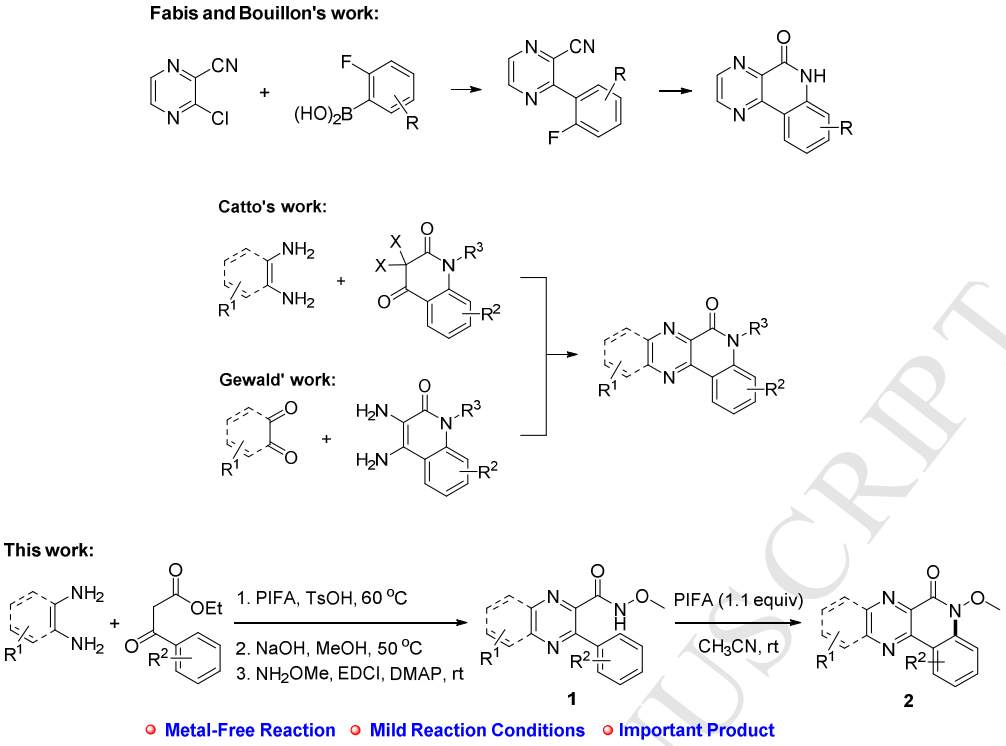


Figure 1. Representative quinolino[3,4-*b*]quinoxalin-6(5*H*)-ones and their derivatives.

Although they have important applications in organic synthesis and pharmaceutical chemistry, a systematic literature review revealed a limited number of existing works addressing the systematic construction of quinolino[3,4-*b*]quinoxalin-6(5*H*)-ones and their pyrazino[2,3-*c*]quinolin-5(6*H*)-ones analogues, and some of them were synthesized as key intermediates in these chemistry. Vanelle's and Pierre's groups reported that the quinolino[3,4-*b*]quinoxalin-6(5*H*)-ones and their pyrazino[2,3-*c*]quinolin-5(6*H*)-ones analogues can be obtained through a stepwise intermolecular cross-coupling reaction of 3-halogenated quinoxaline-2-carboxylate esters with arylboronic acids by a Suzuki–Miyaura reaction, and then an intramolecular coupling–lactamization reaction in the

presence of a palladium catalyst (Scheme 1).[4-6] A microwave-assisted post-Ugi cascade reaction was developed by Xu and Chen et al. to access a series of quinolino[3,4-*b*]quinoxalin-6(5*H*)-ones in good yields (Scheme 1).[7] In addition, the cross-coupling of 3-chloro-2-cyanopyrazine with boronic species resulted in biaryl derivatives, followed by an anionic ring closure route in the presence of 5 equivalents of KOH in a sealed tube containing ^{t}BuOH at 150 ^{o}C to obtain the target pyrazino[2,3-*c*]quinolin-5(6*H*)-ones in a two-step reaction.[8,9] Moreover, Catto's and Gewald's groups reported that these types of angular multi-fused aza-heterocycles can also be prepared in low to moderate yields by a condensation reaction of 1,3-dicarbonyl compounds with *o*-diamines under heat conditions (Scheme 1).[1,10-12] Despite the obvious progress that has been achieved, it is still highly desirable to develop alternative and more flexible methods that lead to structurally diverse libraries of quinolino[3,4-*b*]quinoxalin-6(5*H*)-ones and their pyrazino[2,3-*c*]quinolin-5(6*H*)-ones analogues under mild and environmentally friendly conditions for high-throughput screening in medicinal chemistry. Here, we present our recent efforts for the synthesis of quinolino[3,4-*b*]quinoxalin-6(5*H*)-ones and their pyrazino[2,3-*c*]quinolin-5(6*H*)-ones analogues (**2**) using the phenyliodine(III) bis(trifluoroacetate) (PIFA)-mediated C(aryl)–H bond oxidative C(aryl)-N formation reaction.[13] This highly efficient metal-free intramolecular reaction, which forms a bond between the nitrogen atom of an amide with the carbon atom of a phenyl, can be performed with readily available starting materials and a broad substrate scope and would further enlarged the library of this type of angular fused heterocycle (Scheme 1).

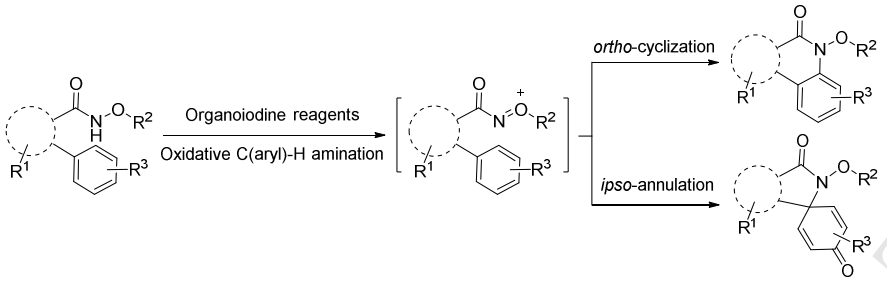




Scheme 1. Representative routes to quinolino[3,4-*b*]quinoxalin-6(5*H*)-ones.

Hypervalent organoiodine reagents have been widely used in organic transformations, especially in C(sp2)-N formation reactions, serving as advanced oxidants that are readily available, nontoxic, ease to handle and environmentally benign.[14-16] It is well documented that the nitrogen atom of *N*-methoxyl secondary amides can couple directly with the sp2 carbon atom of a phenyl by releasing one molecule of H_2 in formal, commonly through an intramolecular oxidative C(aryl)-H amidation reaction in the presence of organoiodine reagents.[17-31] This ring closure procedure proceeds in high yields and allows access to various *N*-containing five-, six-, and seven-membered fused heterocycles through the *ipso*-annulation reaction or *ortho*-cyclization reaction (Scheme 2).[32-34] Combined with our recent work on the synthesis of functional small organic molecules in the presence of hypervalent organoiodine reagents through efficient, green oxidative C(aryl)–N bond formation reactions,[32,35-37] we intended to transfer this *N*-methoxyamide participation C(aryl)-N formation strategy to synthesize other useful fused aza-heterocycles, such as quinolino[3,4-*b*]quinoxalin-6(5*H*)-ones and their pyrazino[2,3-*c*]quinolin-5(6*H*)-ones analogues starting from commercially available β-ketoamides in the presence of hypervalent organoiodine

reagents.

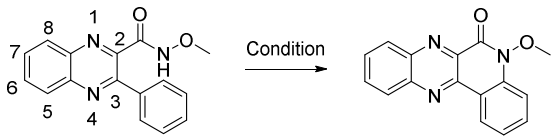


Scheme 2. Direct oxidative C(aryl)-H amidation of adjacent *N*-methoxyamide and phenyl group

2. Results and discussion

We began our evaluation with *N*-methoxy-3-phenylquinoxaline-2-carboxamide (**1a**) as a model substrate, which was readily prepared by the condensation reaction of *o*-diamines with 1,2,3-tricarbonyl compounds (generated in situ from the oxidation reaction of 1,3-dicarbonyl compounds),[38] under [bis-(trifluoroacetoxy)iodo]benzene (PIFA) as a model reaction (Table 1). Acetonitrile (MeCN) was investigated first as a solvent; the desired product 5-methoxyquinolino[3,4-*b*]quinoxalin-6(5*H*)-one (**2a**) was formed in 95% yield in the presence of 1 equivalent of PIFA at room temperature after 1 h (Table 1, entry 1). When the solvent was switched to tetrahydrofuran (THF), dichloromethane (DCM), DMSO and DMF, product **2a** was obtained in lower yields (19-78%) than that in MeCN (Table 1, entry 1 versus 2-5). However, when the reaction was carried out in trifluoroethanol (TFE), a slightly higher yield of 96% was observed; however, because of the significantly higher price of TFE compared with that of MeCN, we did not use TFE as a solvent in subsequent reactions (Table 1, entry 6). Interestingly, when the PIFA loading was reduced from 1 to 0.5 equivalents at room temperature, the yield of **2a** dropped from 95% to 45%, and starting material **1a** was recovered in 47% yield (Table 1, entry 7). Other organoiodine reagents including diacetoxyiodobenzene (PIDA), $PhI(OPiv)_2$ and 2-iodosobenzoic acid were screened and found to not be as efficient as PIFA (Table 1, entries 8-10). After screening, the optimal reaction conditions were PIFA (1.1 equivalent) in MeCN (1.5 mL) at room temperature.

Table 1. Survey of the reaction conditions[a]



1a 2a

Entry	Catalyst (equiv)	Solvent	T (°C)	Time (h)	Yield of **2a**/%
1	PIFA (1.1)	MeCN	rt	1	95
2	PIFA (1.1)	THF	rt	1	31
3	PIFA (1.1)	DCM	rt	1	78
4	PIFA (1.1)	DMSO	rt	1	19
5	PIFA (1.1)	DMF	rt	1	52
6	PIFA (1.1)	TFE	rt	1	96
7	PIFA (0.5)	MeCN	rt	1.5	45[b]
8	PIDA (1.1)	MeCN	rt	1.5	26
9	$PhI(OPiv)_2$ (1.1)	MeCN	rt	1.5	23
10	2-Iodosobenzoic acid (1.1)	MeCN	rt	1.5	0[c]

[a] Unless otherwise indicated, all reactions were carried out with **1a** (0.3 mmol), PIFA (1.1 equiv) and MeCN (1.5 mL) at room temperature.

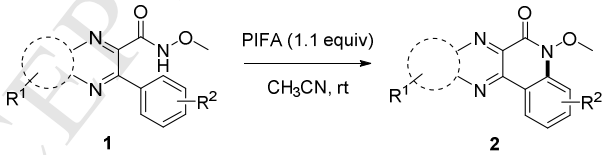
[b] 47% of **1a** was recovered. [c] 91% of **1a** was recovered.

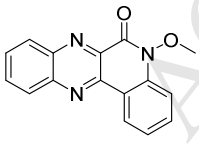
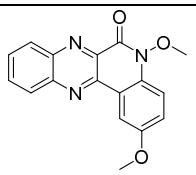
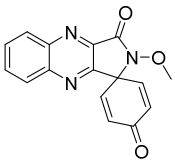
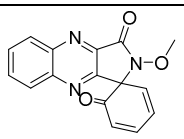
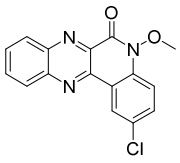
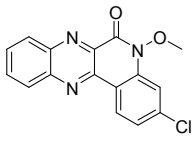
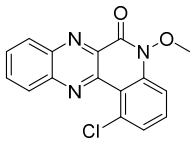
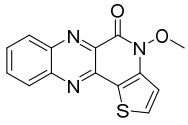
With the optimized conditions in hand (Table 1, entry 1), we investigated the substrate scope (Table 2). Initially, various R^2 substituents were investigated. The starting material **1b** bearing a -OMe at the *meta* position formed the desired *ortho*-cyclized product **2b** in 99% yield. However, the compounds **1c** and **1d** with the -OMe at the *para* and *ortho* positions, respectively, regiospecifically afforded the *ipso*-annulated products **3c** and **3d** in 93% and 87% yield, respectively, without the formation of the *ortho*-cyclized products **2c** and **2d**. All of the reactions in our protocol resulted in a single product **2** or **3** instead of a mixture of *ipso*- and *ortho*-cyclized product, which is different from some previous reports.[17,23] We found the reaction was very unfavorable when a chloro

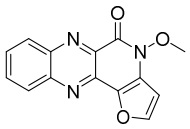
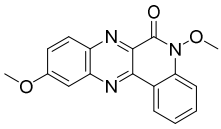
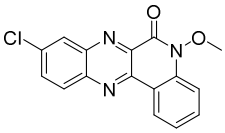
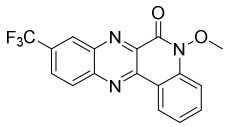
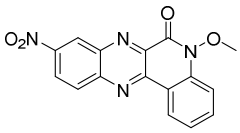
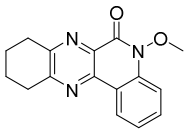
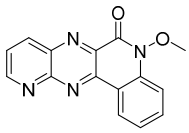
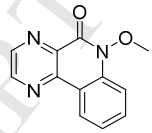
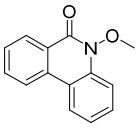
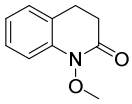
substituent was present in the starting material. Only 16% of compound **2e** was isolated, along with an unidentified complex mixture, starting from **1e** bearing the chloro- group at the -*meta* position. An analogous result was obtained in the case of **1f** and **1g**; the desired products **2f** and **2g** were not observed. Three kinds of heterocyclic substituents 2-pyridinyl, 2-thiophenyl and 2-furanyl were also employed in the reaction. Good yields of **2h** (76%) and **2i** (72%) were achieved for the reactions starting from **1h** and **1i**, respectively.

Next, we screened the reactions using substrates with various R^1 substituents. A number of functional groups bearing -OMe at the 6-position, and -Cl, $-CF_3$, or $-NO_2$ at the 7-position were tolerated well, and the target products **2j**–**m** were obtained in good yields (74−95%). Importantly, starting material **1n** derived from 1,2-cyclohexanediamine also showed high reactivity leading to **2n** in moderate yield (63%). Furthermore, the fused heterocycle starting material **1o** was also reacted under the optimized conditions to give the corresponding product **2o** in 94% yield. These successful examples prompted us to investigate additional modifications at these positions. Compounds **1p** and **1q**, as well as the unmodified starting material **1r** were also viable for the construction of **2p**−**r** in satisfactory yields (47−92%).

Table 2. Reaction extension[a]



			
2a: 1 h, 95%	**2b**: 50 min, 99%	**3c**: 50 min, 93%	**3d**: 40 min, 87%
			

2e: 50 min, 16%	**2f**: 50 min, 0%	**2g**: 50 min, 0%	**2h**: 20 min, 76%
			
2i: 30 min, 72%	**2j**: 20 min, 79%	**2k**: 40 min, 95%	**2l**: 30 min, 74%
			
2m: 40 min, 84%	**2n**: 30 min, 63%	**2o**: 30 min, 94%	**2p**: 35 min, 80%
			
2q: 20 min, 92%	**2r**: 50 min, 47%		

[a] Unless otherwise indicated, all reactions were carried out with **1a** (0.3 mmol), PIFA (1.1 equiv) and MeCN (1.5 mL) at room temperature.

3. Conclusion

We developed a facile, metal-free method for the direct synthesis of quinolino[3,4-*b*]quinoxalin-6(5*H*)-ones and their pyrazino[2,3-*c*]quinolin-5(6*H*)-ones analogues by tethering adjacent *N*-methoxyamide and aryl portions in the presence of phenyliodine(III) bis(trifluoroacetate) (PIFA) at room temperature. The advantages of this intramolecular oxidative C(aryl)-H amidation reaction include the use of readily available starting materials, moderate to good yields and flexible substitution patterns. Moreover, as an alternative and valuable route, it allows enlargement of the library of this type of angular, fused, heterocyclic compounds for biology and pharmacology purposes.

4. Experimental section

4.1. General methods

All reactions were carried out under air atmosphere, unless otherwise indicated. Other all reagents

were purchased from commercial sources and used without further treatment, unless otherwise indicated. Petroleum ether (PE) used refers to the 60-90 °C boiling point fraction of petroleum. Ethyl acetate is abbreviated as EA. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance/600 (^{1}H: 600 MHz, ^{13}C: 150 MHz at 25 °C) or Bruker Avance/400 (^{1}H: 400 MHz, ^{13}C: 100 MHz at 25 °C) and TMS as internal standard. Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz). All high-resolution mass spectra (HRMS) were measured on a mass spectrometer by using electrospray ionization (ESI-oa-TOF), and the purity of all samples used for HRMS (>95%) were confirmed by ^{1}H NMR and ^{13}C NMR spectroscopic analysis. Melting points were measured on a melting point apparatus equipped with a thermometer and were uncorrected. All reactions were monitored by TLC with GF254 silica gel coated plates. Flash chromatography was carried out on SiO_2 (silica gel 200−300 mesh).

4.2. Typical Experimental Procedure For **2** (**2a** as an example):

To a round-bottom flask (25 mL) was added *N*-methoxy-3-phenylquinoxaline-2-carboxamide **1a** (84 mg, 0.3 mmol), PIFA (142 mg, 0.33 mmol), the mixture was well stirred for 1 h in MeCN (1.5 mL) at room temperature (the whole process was closely monitored by TLC). After completion, water (10 mL) was added to the mixture, and the aqueous phase was extracted with ethyl acetate (10 mL×3). The combined organic layer was dried over sodium sulphate. The solvent was evaporated, and the residue was purified by a short flash silica gel column chromatography (eluent: PE/EA = 2/1) to give 5-methoxyquinolino[3,4-*b*]quinoxalin-6(5*H*)-one **2a** as a yellow solid (79 mg, 95%).

*4.2.1. 5-methoxyquinolino[3,4-b]quinoxalin-6(5H)-one (**2a**)*

The product was isolated by flash chromatography (eluent: PE/EA = 2/1) as a yellow solid (79 mg, 95%). mp: 200-201 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.98 (d, J = 7.8 Hz, 1H), 8.47 (d, J = 8.4 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H), 7.96 (t, J = 7.5 Hz, 1H), 7.89 (t, J = 7.2 Hz, 1H), 7.79-7.64 (m, 2H), 7.47 (t, J = 6.9 Hz, 1H), 4.22 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.3, 144.7, 144.3, 142.8,

138.2, 137.3, 133.1, 132.9, 131.1, 131.0, 129.4, 126.1, 124.3, 118.6, 112.7, 63.1. HRMS (ESI), m/z calcd. for $C_{16}H_{12}N_3O_2$ ($[M+H]^+$) 278.0924, found: 278.0926.

*4.2.2. 2,5-dimethoxyquinolino[3,4-b]quinoxalin-6(5H)-one (**2b**)*

The product was isolated by flash chromatography (eluent: PE/EA = 2/1) as a yellow solid (91 mg, 99%). mp: 202-204 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 8.4 Hz, 1H), 8.41 (d, J = 2.8 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H), 7.95 (t, J = 7.4 Hz, 1H), 7.88 (t, J = 7.4 Hz, 1H), 7.61 (d, J = 9.2 Hz, 1H), 7.29 (dd, J = 8.8, 2.8 Hz, 1H), 4.20 (s, 3H), 4.01 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.5, 155.7, 144.2, 144.0, 142.7, 138.4, 133.0, 131.5, 131.0, 130.9, 129.3, 121.1, 119.4, 114.3, 107.9, 63.1, 56.1. HRMS (ESI), *m/z* calcd. for $C_{17}H_{13}NaN_3O_3$ ($[M+Na]^+$) 330.0849, found: 330.0854.

*4.2.3. 2'-methoxyspiro[cyclohexane-1,1'-pyrrolo[3,4-b]quinoxaline]-2,5-diene-3',4(2'H)-dione (**3c**)*

The product was isolated by flash chromatography (eluent: PE/EA = 2/1) as a yellow solid (82 mg, 93%). mp: 216-220 ^oC; ^1H NMR (600 MHz, $CDCl_3$) δ 8.38 (dd, J = 9.0, 5.4 Hz, 1H), 8.17 (dd, J = 9.6, 4.8 Hz, 1H), 7.94 (dd, J = 9.6, 5.4 Hz, 2H), 6.75-6.65 (m, 4H), 4.10 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 184.2, 160.9, 152.0, 144.4, 144.3, 142.5, 142.4, 133.9, 132.9, 132.1, 131.0, 129.8, 66.6, 65.6. HRMS (ESI), m/z calcd. for $C_{16}H_{12}N_3O_3$ ($[M+H]^+$) 294.0873, found: 294.0875.

*4.2.4. 2'-methoxyspiro[cyclohexane-1,1'-pyrrolo[3,4-b]quinoxaline]-2,4-diene-3',6(2'H)-dione (**3d**)*

The product was isolated by flash chromatography (eluent: PE/EA = 2/1) as a yellow solid (76 mg, 87%). mp: 193-195 ^oC; ^1H NMR (600 MHz, $CDCl_3$) δ 8.31 (dd, J = 6.0, 3.6 Hz, 1H), 8.09 (dd, J = 6.3, 3.3 Hz, 1H), 7.85 (dd, J = 6.3, 3.3 Hz, 2H), 7.35-7.30 (m, 1H), 6.79 (dd, J = 9.3, 6.3 Hz, 1H), 6.44 (d, J = 9.0 Hz, 1H), 6.27 (d, J = 10.2 Hz, 1H), 4.05 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.5, 162.6, 152.1, 143.9, 143.6, 143.1, 142.9, 135.5, 132.4, 131.5, 130.9, 129.6, 128.5, 125.9, 72.7, 65.5. HRMS (ESI), *m/z* calcd. for $C_{16}H_{11}NaN_3O_3$ ($[M+Na]^+$) 316.0693, found: 316.0706.

*4.2.5. 2-chloro-5-methoxyquinolino[3,4-b]quinoxalin-6(5H)-one (**2e**)*

The product was isolated by flash chromatography (eluent: PE/EA = 2/1) as a yellow solid (15 mg, 16%). mp: 240-241 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.98-8.92 (m, 1H), 8.48 (d, J = 8.4 Hz, 1H),

8.29 (d, J = 8.8 Hz, 1H), 8.00 (t, J = 7.2 Hz, 1H), 7.93 (t, J = 7.2 Hz, 1H), 7.73-7.63 (m, 2H), 4.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 144.2, 143.6, 143.1, 138.1, 135.9, 133.4, 132.8, 131.6, 131.0, 130.2, 129.5, 125.7, 119.8, 114.4, 63.3. HRMS (ESI), *m/z* calcd. for $C_{16}H_{10}ClNaN_3O_2$ ($[M+Na]^+$) 334.0354, found: 334.0353.

*4.2.6. 4-methoxythieno[2',3':5,6]pyrido[3,4-b]quinoxalin-5(4H)-one (**2h**)*

The product was isolated by flash chromatography (eluent: PE/EA = 2/1) as a yellow solid (65 mg, 76%). mp: 213-214 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.93 (t, *J* = 7.5 Hz, 1H), 7.84 (t, *J* = 7.5 Hz, 1H), 7.77-7.73 (m, 1H), 7.33-7.29 (m, 1H), 4.25 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.7, 144.3, 143.5, 141.9, 140.8, 137.5, 133.4, 131.9, 131.2, 130.4, 128.7, 116.2, 116.1, 63.9. HRMS (ESI), *m/z* calcd. for $C_{14}H_{10}N_3O_2S$ ($[M+H]^+$) 284.0488, found: 284.0496.

*4.2.7. 4-methoxyfuro[2',3':5,6]pyrido[3,4-b]quinoxalin-5(4H)-one (**2i**)*

The product was isolated by flash chromatography (eluent: PE/EA = 2/1) as a yellow solid (58 mg, 72%). mp: 209-210 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, *J* = 7.8 Hz, 1H), 8.21 (t, *J* = 6.9 Hz, 2H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.55 (q, *J* = 14.4 Hz, 7.2 Hz 2H), 7.31 (t, *J* = 7.2 Hz, 1H), 4.12 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.3, 135.8, 132.9, 132.6, 129.9, 128.5, 128.1, 126.3, 123.2, 121.9, 118.6, 112.6, 62.7. HRMS (ESI), *m/z* calcd. for $C_{14}H_9NaN_3O_3$ ($[M+Na]^+$) 290.0536, found: 290.0546.

*4.2.8. 5,10-dimethoxyquinolino[3,4-b]quinoxalin-6(5H)-one (**2j**)*

The product was isolated by flash chromatography (eluent: PE/EA = 2/1) as a yellow solid (73 mg, 79%). mp: 268-270 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.98-8.94 (m, 1H), 8.33 (d, *J* = 9.6 Hz, 1H), 7.74 (m, 2H), 7.54 (dd, *J* = 9.4, 2.6 Hz, 1H), 7.50-7.44 (m, 2H), 4.21 (s, 3H), 4.07 (s, 3H) . ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.5, 156.6, 146.4, 144.8, 139.7, 137.4, 135.8, 132.7, 132.0, 125.9, 124.0, 118.6, 112.7, 105.5, 63.1, 56.3. HRMS (ESI), *m/z* calcd. for $C_{17}H_{14}N_3O_3$ ($[M+H]^+$) 308.1030, found: 308.1037.

*4.2.9. 9-chloro-5-methoxyquinolino[3,4-b]quinoxalin-6(5H)-one (**2k**)*

The product was isolated by flash chromatography (eluent: PE/EA = 2/1) as a yellow solid (89 mg, 95%). mp: 207-209 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.91 (d, J = 7.8 Hz, 1H), 8.42 (s, 1H), 8.19 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 9.0 Hz, 1H), 7.74 (t, J = 7.2 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 7.2 Hz, 1H), 4.22 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.9, 144.7, 142.8, 142.8, 138.7, 137.4, 137.2, 134.3, 133.1, 130.6, 129.4, 126.1, 124.4, 118.2, 112.8, 63.2. HRMS (ESI), *m/z* calcd. for $C_{16}H_{10}ClNaN_3O_2$ ($[M+Na]^+$) 334.0354, found: 334.0357.

*4.2.10. 5-methoxy-9-(trifluoromethyl)quinolino[3,4-b]quinoxalin-6(5H)-one (**2l**)*

The product was isolated by flash chromatography (eluent: PE/EA = 2/1) as a yellow solid (77 mg, 74%). mp: 225-228 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, J = 7.8 Hz, 1H), 8.21 (t, J = 6.9 Hz, 2H), 7.73 (t, J = 7.5 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.55 (q, J = 14.4 Hz, 7.2 Hz 2H), 7.31 (t, J = 7.2 Hz, 1H), 4.12 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.3, 135.8, 132.9, 132.6, 129.9, 128.5, 128.1, 126.3, 123.2, 121.9, 118.6, 112.6, 62.7. HRMS (ESI), *m/z* calcd. for $C_{17}H_{10}F_3NaN_3O_2$ ($[M+Na]^+$) 368.0617, found: 368.0623.

*4.2.11. 5-methoxy-9-nitroquinolino[3,4-b]quinoxalin-6(5H)-one (**2m**)*

The product was isolated by flash chromatography (eluent: PE/EA = 2/1) as a yellow solid (81 mg, 84%). mp: 239-241 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40-9.35 (m, 1H), 9.02-8.97 (m, 1H), 8.73-8.67 (m, 1H), 8.46-8.39 (m, 1H), 7.82 (d, J = 6.0 Hz, 1H), 7.75 (d, J = 7.2 Hz, 1H), 7.53 (d, J = 6.4 Hz, 1H), 4.24 (d, J = 2.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 148.5, 147.1, 146.1, 141.3, 140.1, 138.1, 134.4, 131.1, 127.4, 126.9, 126.1, 124.7, 117.8, 113.1, 63.3. HRMS (ESI), *m/z* calcd. for $C_{16}H_{10}NaN_4O_4$ ($[M+Na]^+$) 345.0594, found: 345.0607.

*4.2.12. 5-methoxy-8,9,10,11-tetrahydroquinolino[3,4-b]quinoxalin-6(5H)-one (**2n**)*

The product was isolated by flash chromatography (eluent: PE/EA = 2/1) as a white solid (53 mg, 63%). mp: 197-200 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 4.0 Hz, 2H), 7.40 (m, 1H), 4.17 (s, 3H), 3.21 (d, J = 20.0 Hz, 4H), 2.03 (s, 4H). ^{13}C NMR (150 MHz, $CDCl_3$)

δ 158.4, 156.7, 155.1, 143.2, 136.8, 134.9, 131.9, 125.2, 123.8, 118.3, 112.4, 63.1, 33.3, 32.7, 22.7, 22.6. HRMS (ESI), *m/z* calcd. for $C_{16}H_{15}NaN_3O_2$ ($[M+Na]^+$) 304.1056, found: 304.1066.

*4.2.13. 5-methoxypyrido[2',3':5,6]pyrazino[2,3-c]quinolin-6(5H)-one (**2o**)*

The product was isolated by flash chromatography (eluent: PE/EA = 2/1) as a yellow solid (78 mg, 94%). mp: 187-189 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 9.14 (d, J = 7.6 Hz, 1H), 8.84 (d, J = 6.4 Hz, 1H), 7.90-7.84 (m, 1H), 7.80 (d, J = 5.6 Hz, 1H), 7.76 (s, 1H), 7.52 (s, 1H), 4.27-4.21 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.2, 155.6, 151.2, 147.6, 139.9, 139.3, 138.5, 137.9, 133.9, 127.2, 126.3, 124.7, 118.1, 112.9, 63.3. HRMS (ESI), *m/z* calcd. for $C_{15}H_{10}NaN_4O_2$ ($[M+Na]^+$) 301.0696, found: 301.0691.

*4.2.14. 6-methoxypyrazino[2,3-c]quinolin-5(6H)-one (**2p**)*

The product was isolated by flash chromatography (eluent: PE/EA = 2/1) as a white solid (54 mg, 80%). mp: 202-204 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.93 (s, 1H), 8.79 (d, J = 8.0 Hz, 1H), 7.74 (m, 2H), 7.45 (t, J = 7.4 Hz, 1H), 4.19 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.3, 148.2, 146.1, 145.3, 137.7, 137.2, 132.9, 125.7, 124.2, 118.0, 112.6, 63.2. HRMS (ESI), *m/z* calcd. for $C_{12}H_{10}N_3O_2$ ($[M+H]^+$) 228.0768, found: 228.0772.

*4.2.15. 5-methoxyphenanthridin-6(5H)-one (**2q**)*

The product was isolated by flash chromatography (eluent: PE/EA = 2/1) as a white solid (62 mg, 92%). mp: 231-234 ^oC; ^1H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, J = 7.8 Hz, 1H), 8.21 (t, J = 6.9 Hz, 2H), 7.73 (t, J = 7.5 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.55 (q, J = 14.4 Hz, 7.2 Hz 2H), 7.31 (t, J = 7.2 Hz, 1H), 4.12 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.3, 135.8, 133.0, 132.6, 130.0 128.5, 128.1, 126.3, 123.2, 122.0, 118.6, 112.6, 62.7. HRMS (ESI), *m/z* calcd. for $C_{14}H_{11}NaNO_2$ ($[M+Na]^+$) 248.0682, found: 248.0686.

*4.2.16. 1-methoxy-3,4-dihydroquinolin-2(1H)-one (**2r**)*

The product was isolated by flash chromatography (eluent: PE/EA = 2/1) as a colorless oily liquid (25 mg, 47%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.22 (m, 1H), 7.20-7.15 (m, 1H), 7.13 (d, J = 7.2

Hz, 1H), 7.00 (td, *J* = 7.4, 1.3 Hz, 1H), 3.87 (s, 3H), 2.89-2.83 (m, 2H), 2.66 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 137.9, 127.9, 127.9, 124.5, 123.7, 112.4, 62.7, 31.7, 25.0. HRMS (ESI), *m/z* calcd. for $C_{10}H_{11}NaNO_2$ ($[M+Na]^+$) 200.0682, found: 200.0692.

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Supplementary data

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