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Syntheses of Fused Tetracyclic Quinolines via Ugi-Variant MCR and Pd-Catalyzed Bis-annulation†

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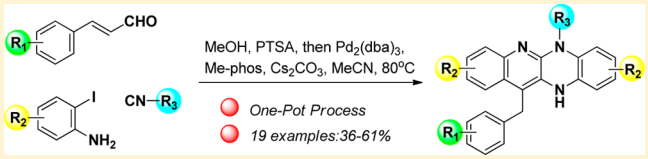
Supporting Information

ABSTRACT: Diversity-oriented synthesis of fused tetracyclic 6,11-dihydroquinoxalino[2,3-*b*]quinolines is described via a sequential Ugi-variant multicomponent reaction and Pd-catalyzed bis-annulation in one-pot process.



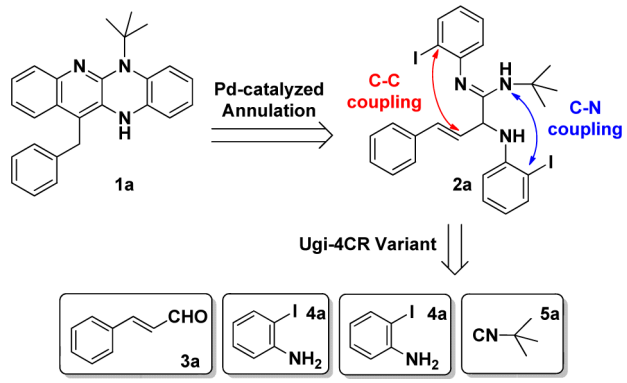
Multicomponent reactions (MCRs) have gained considerable popularity in the field of contemporary organic synthesis.[1] They represent ideal synthetic tools to generate structures of great complexity and diversity from simple starting materials and therefore are extensively applied by medicinal chemists to construct diverse chemical libraries of "drug-likeness".[2]

As a superstar in MCRs, the four-component Ugi reaction (Ugi-4CR) has attracted enduring attention owing to its broad input scope, high diversity of products, unmatched versatility, and simple operation.[3] It is noteworthy that the Ugi-4CR provides a linear dipeptide-like skeleton rather than more valuable heterocyclic ring. In this context, it is of great importance to further expand the structural types of Ugi products. Indeed, structural constraints implicit in the Ugi product nature could be overcome through alternative strategies. The first way utilizes bifunctional inputs to carry out a four-center, three-component reaction (4C-3CR) to form heterocyles.[4] Another way is to develop Ugi post-transformation strategies via its union with other reactions.[5] Over the past decade, plenty of exquisite post-Ugi strategies have been developed and enable quick access to varieties of biologically important heterocyclic skeletons, such as pyrrolinones,[6] imidazo[1,4]diazepin-7-ones,[7] oxindoles,[8] and 1,3,4-oxadiazole.[9] Given the four variants in the Ugi adducts, the heterocycles built in this way possess maximum substitution diversities.

While exploring the potential of post-Ugi strategies, we have previously made structurally diverse heterocyclic scaffolds: chromeno[3,4-*c*]pyrrole-3,4-dione,[10] isoquinolin-3-one,[11] and imidazo[1,2-*a*]pyridine derivatives.[12] As a continuing effort, we were interested in developing new Ugi-involved methods for producing collections of fused 6,11-dihydroquinoxalino[2,3-*b*]quinolines, a family of novel nitrogen heterocycles with potential antitumor activity.[13] It is likely that libraries of low molecular weight polycyclic quinolines will serve as valuable chemical probes for drug discovery. Herein we report our recent effort to develop a novel strategy for two-step and one-pot syntheses of diverse fused tetracyclic quinolines by using an Ugi-variant reaction and Pd-catalyzed bis-annulation.[14]

From a design perspective, we envisioned that the tetracyclic 6,11-dihydroquinoxalino[2,3-*b*]quinoline **1a** could be constructed through intramolecular 6-*exo*-*trig* (C–C coupling) and 6-*endo*-*trig* (C–N coupling) bis-annulations of the precursor α-aminoamidines **2a** (Scheme 1). These processes

Scheme 1. Synthetic Analysis of Fused Tetracyclic Dihydropyridopyrazines



were anticipated to take place simultaneously in the presence of the suitable palladium catalyst. The α-aminoamidines **2a** were in turn produced by the Ugi-4CR variant of cinnamic aldehyde **3a**, two molecules of *o*-iodoaniline **4a**, and isocyanide **5a**.[15]

We first explored the multicomponent reaction of cinnamic aldehyde **3a**, two molecules of *o*-iodoaniline **4a**, and isocyanide **5a**. A preliminary survey revealed that this reaction proceeds

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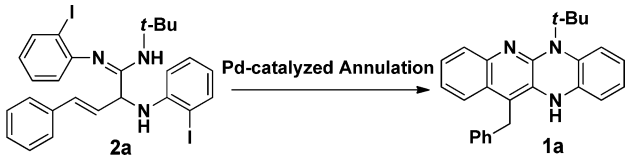
smoothly in the presence of Brønsted acid or Lewis acid in polar and protic solvent. The use of 5% *p*-toluenesulfonic acid (PTSA) in MeOH was found to be most effective to deliver α-aminoamidine **2a** in 73% yield.

α-Aminoamidines obtained from the present Ugi-4CR variant method are versatile, providing access to other interesting scaffolds.[16] Next, we began further investigation toward generating the tetracyclic 6,11-dihydroquinoxalino[2,3-*b*]quinoline framework via a Pd-catalyzed Buchwald−Hartwig[17] and Heck reaction.[18] We selected the α-aminoamidine **2a** as the model reactant to evaluate the effects of bases, ligands, solvents, and palladium sources for this reaction, and the results are summarized in Table 1. When the reaction was carried out in refluxing dioxane/MeCN (85/15) in the presence of $Pd_2(dba)_3$ and Xphos, the base Cs_2CO_3 provided a better yield (40%) than NaO*t*-Bu and K_2CO_3 (Table 1, entries 1−3), and the low yield resulted from some byproduct formation. Next, we turned to screen various ligands and observed that the ligand showed a crucial effect on the reaction and Me-phos was superior to the other ligands (Table 1, entries 3−9), leading to the product **1a** in 64% yield. The yield was further improved to 76% by changing the solvent to MeCN (Table 1, entries 10−14). However, change of the palladium source to $PdCl_2$ or $Pd(OAc)_2$ led to a decrease in the yield (Table 1, entries 14−16).

Table 1. Syntheses of Dihydropyridopyrazines under the Indicated Conditions[a]

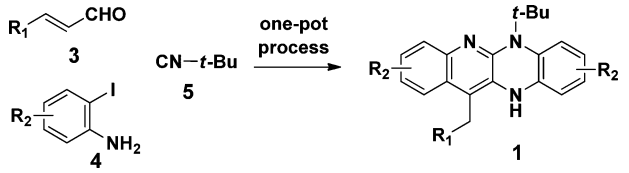


entry	catalyst	ligand	base	solvent[b]	yield[c] (%)
1	$Pd_2(dba)_3$	X-phos	NaO-*t*-Bu	dioxane/MeCN	28
2	$Pd_2(dba)_3$	X-phos	K_2CO_3	dioxane/MeCN	15
3	$Pd_2(dba)_3$	X-phos	Cs_2CO_3	dioxane/MeCN	40
4	$Pd_2(dba)_3$	BINAP	Cs_2CO_3	dioxane/MeCN	26
5	$Pd_2(dba)_3$	TPP	Cs_2CO_3	dioxane/MeCN	38
6	$Pd_2(dba)_3$	*o*-$Toly_3P$	Cs_2CO_3	dioxane/MeCN	36
7	$Pd_2(dba)_3$	Me-phos	Cs_2CO_3	dioxane/MeCN	64
8	$Pd_2(dba)_3$	DPEphos	Cs_2CO_3	dioxane/MeCN	51
9	$Pd_2(dba)_3$	Xantphos	Cs_2CO_3	dioxane/MeCN	21
10	$Pd_2(dba)_3$	Me-phos	Cs_2CO_3	1,4-dioxane	54
11	$Pd_2(dba)_3$	Me-phos	Cs_2CO_3	PhMe	26
12	$Pd_2(dba)_3$	Me-phos	Cs_2CO_3	PhMe/MeCN	59
13	$Pd_2(dba)_3$	Me-phos	Cs_2CO_3	DMF	5
14	**$Pd_2(dba)_3$**	**Me-phos**	**Cs_2CO_3**	**MeCN**	**76**
15	$PdCI_2$	Me-phos	Cs_2CO_3	MeCN	28
16	$Pd(OAc)_2$	Me-phos	Cs_2CO_3	MeCN	51

[a]General conditions for the annulation: substrate **2a** (0.1 mmol), catalyst (10 mol %), ligand (10 mol %), and base (0.3 mmol) in solvent (2 mL) at refluxing temperature for 24 h. [b]Dioxane/MeCN = 85/15, refluxing temp = 98 °C; PhMe/MeCN = 85/15, refluxing temp = 99 °C. [c]Isolated yields.

Following the extensive investigation of annulation reaction conditions, we planned to explore combining MCR and subsequent Pd-catalyzed bis-annulation in a single sequence. This transformation was first carried out in methanol at room temperature in the presence of catalytic PTSA. The reaction was then concentrated after 8 h and treated with optimized condition systems ($Pd_2(dba)_3$, Me-phos, Cs_2CO_3) in refluxing MeCN. We were pleased to find that the one-pot reaction proceeded smoothly to deliver the desired product **1a** in 61% yield (Table 2, entry 1).

Table 2. Substrate Scope for the Syntheses of Dihydropyridopyrazines in One-Pot Process[a]



entry	R_1	R_2	product	yield[b] (%)
1	Ph	H	**1a**	61
2	2-CIPh	H	**1b**	42
3	3-CIPh	H	**1c**	55
4	4-CIPh	H	**1d**	44
5	2-FPh	H	**1e**	45
6	4-FPh	H	**1f**	51
7	4-BrPh	H	**lg**	49
8	2-MeOPh	H	**1h**	59
9	4-MeOPh	H	**1i**	58
10	3-MePh	H	**1j**	52
11	4-MePh	H	**1k**	53
12	naphthalen-1-yl	H	**1l**	47
13	naphthalen-2-yl	H	**1m**	45
14	Ph	4-CI	**1n**	36
15	Ph	4-F	**1o**	39
16	Ph	4-Me	**1p**	42
17	4-MeOPh	4-F	**1q**	46
18	4-MeOPh	4-CI	**1r**	42
19	4-MeOPh	4-Me	**1s**	44

[a]Unless otherwise noted, the reactions were carried out with substrate **3** (0.1 mmol), **4** (0.2 mmol), **5** (0.1 mmol), and PTSA (5%) in MeOH (3 mL) at rt for 8 h and then concentrated. $Pd_2(dba)_3$ (10 mol %), Me-phos (10 mol %), and Cs_2C0_3 (0.3 mmol) in MeCN (2 mL) at 80 °C for 24 h [b]Isolated yields.

Having established the possibility of construction of the 6,11-dihydroquinoxalino[2,3-*b*]quinoline framework in one-pot fashion, we next started to profile the reaction scope. The reaction proceeded well with a variety of cinnamic aldehydes, with aromatic amines leading to formation of a chemical library of fused tetracyclic quinolines (Table 2). The electronic properties of substituents on the aromatic ring of cinnamic aldehyde had no obvious effect on the reactivity (Table 2, entries 2−13), while the anilines with either electron-withdrawing or electron-donating group showed a slightly lower reactivity (Table 2, entries 14−19).

In conclusion, we have developed a rapid access to the fused tetracyclic quinoline scaffold via a sequential Ugi-variant reaction and Pd-catalyzed bis-annulation. The described chemistry represents a facile tool to convert simple starting materials into complex heterocycles of pharmaceutical relevance in a highly efficient and one-pot fashion. We anticipate that this new method will find more applications in library synthesis in drug discovery efforts.

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EXPERIMENTAL SECTION

General Information. Unless noted otherwise, all reactions were performed under a nitrogen atmosphere, and materials obtained from commercial suppliers were used without further purification. Purification of products was conducted by flash column chromatography on silica gel (200−300 mesh). ^{1}H NMR spectra were recorded on a 300 or 500 MHz spectrometer using residual solvent (δ ($CDCl_3$) = 7.26) as internal standard. All of the coupling constants are reported in hertz. ^{13}C NMR spectra were recorded on the same instruments, and chemical shifts were measured relative to solvent resonances (δ ($CDCl_3$) = 77.0). High-resolution mass spectra were obtained on a quadrupole time-of-flight (QqTOF) mass spectrometer utilizing electrospray ionization (ESI) method.

Typical Procedure for Ugi-Variant Multicomponent Reactions. To a solution of cinnamaldehyde (0.2 mmol, 26.4 mg), 2-iodoaniline (0.4 mmol, 87.6 mg), and *tert*-butyl isocyanide (0.2 mmol, 16.6 mg) in 1 mL of methanol was added a catalytic amount of *p*-toluenesulfonic acid (2 mg), and the reaction mixture was stirred at room temperature for 8 h. The precipitate was then filtered, rinsed with methanol, and dried to afford the α-aminoamidine **2a** (93 mg, 73%) as a white solid: mp 121−122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48 (s, 9H), 4.28 (s, 1H), 4.54 (d, J = 5.0 Hz, 1H), 5.60 (s, 1H), 6.22 (dd, J = 7.5, 15.5 Hz, 1H), 6.42 (d, J = 16.0 Hz, 1H), 6.58−6.64 (m, 2H), 6.83−6.85 (m, 2H), 7.13−7.16 (m, 1H), 7.29−7.37 (m, 6H), 7.68 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz,1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.0, 51.4, 57.8, 86.5, 95.3, 113.6, 121.0, 122.4, 123.1, 125.6, 126.9, 128.4, 128.5, 128.8, 129.8, 135.0, 136.2, 139.1, 139.2, 146.1, 151.7, 153.6; HRMS (m/z, ESI) calcd for $C_{26}H_{28}I_2N_3(+)$ 636.0373, found 636.0366.

Typical Procedure for Pd-Catalyzed Bis-annulation. To a solution of α-aminoamidine **2a** (0.1 mmol, 63.5 mg) in 2 mL of acetonitrile were added cesium carbonate (0.3 mmol, 97.5 mg), $Pd_2(dba)_3$ (0.01 mmol, 3.7 mg), and Me-phos (2-dicyclohexylphosphino-2′-methylbiphenyl) (0.01 mmol, 1.5 mg), and the resulting suspension was heated under reflux at inert atmosphere for 24 h. The solvent was then removed under vacuum, and the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 500/1) to afford the desired product **1a**.

Typical Procedure for One-Pot Synthesis of Dihydropyridopyrazines 1. To a solution of cinnamaldehyde (0.1 mmol, 13.2 mg), 2-iodoaniline (0.2 mmol, 43.8 mg), and *tert*-butyl isocyanide (0.1 mmol, 8.3 mg) in 1 mL of methanol was added a catalytic amount of *p*-toluenesulfonic acid (1 mg), and the reaction mixture was stirred at room temperature for 8 h. Then the solution was concentrated under vacuum, and the residue was redissolved in 2 mL of acetonitrile. To the solution were added cesium carbonate (0.3 mmol, 97.5 mg), $Pd_2(dba)_3$ (0.01 mmol, 3.7 mg), and Me-phos (0.01 mmol, 1.5 mg), and the resulting suspension was heated under reflux at inert atmosphere for 24 h. The solvent was then removed under vacuum, and the residue was purified by a flash chromatography (petroleum ether/ethyl acetate, 500/1) to afford the desired product **1**.

*12-Benzyl-6-tert-butyl-6,11-dihydroquinolino[3,2-b]quinoxaline (**1a**):* 23 mg (61%) as a yellow solid; mp 128−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 9H), 4.68 (s, 2H), 5.09 (s, 1H), 6.50 (t, J = 8.0 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 7.14−7.22 (m, 3H), 7.25−7.31 (m, 2H), 7.42 (t, J = 8.0 Hz, 1H), 7.51−7.56 (m, 1H), 7.63−7.67 (m, 2H), 7.87−8.38 (m, 1H), 8.39−8.40 (m, 1H), 8.46 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.1, 30.6, 52.5, 107.6, 114.5, 114.6, 119.8, 122.1, 122.8, 123.1, 123.9, 124.1, 126.9, 128.2, 128.4, 128.9, 130.3, 132.5, 137.1, 139.4, 150.2; HRMS (m/z, ESI) calcd for $C_{26}H_{26}N_3(+)$ 380.2127, found 380.2117.

*6-tert-Butyl-12-(2-chlorobenzyl)-6,11-dihydroquinolino[3,2-b]quinoxaline (**1b**):* 17 mg (42%) as a slight yellow solid; mp 118−119 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (s, 9H), 4.66 (s, 2H), 4.84 (s, 1H), 6.81 (d, J = 7.5 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.28−7.30 (m, 2H), 7.39 (t, J = 7.5 Hz, 1H), 7.47−7.54 (m, 2H), 7.63−7.65 (m, 1H), 7.80 (d, J = 8.0 Hz, 1H), 8.38 (m, 1H), 8.47 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.7, 29.0, 52.4, 106.1, 114.6, 114.8, 119.8, 122.3, 122.9, 123.2, 124.2, 124.3, 127.2, 127.5, 128.2, 128.5, 129.6, 129.9, 130.2, 132.7, 134.2, 137.0, 137.2, 150.0; HRMS (m/z, ESI) calcd for $C_{26}H_{25}ClN_3(+)$ 414.1737, found 414.1723.

*6-tert-Butyl-12-(3-chlorobenzyl)-6,11-dihydroquinolino[3,2-b]quinoxaline (**1c**):* 23 mg (55%) as a slight yellow solid; mp 102−104 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (s, 9H), 4.54 (s, 2H), 4.88 (s, 1H), 6.90 (d, J = 5.5 Hz, 1H), 7.11−7.22 (m, 5H), 7.33 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.55−7.56 (m, 1H), 7.74 (d, J = 8 0.0 Hz, 1H), 8.30 (m, 1H), 8.38 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.2, 30.4, 52.6, 106.6, 114.5, 114.7, 119.6, 122.2, 122.8, 123.3, 124.1, 124.2, 126.5, 127.1, 127.2, 128.1, 128.4, 130.1, 130.2, 132.5, 135.0, 137.0, 141.6, 149.9; HRMS (m/z, ESI) calcd for $C_{26}H_{25}ClN_3(+)$ 414.1737, found 414.1732.

*6-tert-Butyl-12-(4-chlorobenzyl)-6,11-dihydroquinolino[3,2-b]quinoxaline (**1d**):* 18 mg (44%) as a yellow solid; mp 116−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H), 4.61 (s, 2H), 4.98 (s, 1H), 7.12 (d, J = 8.4 Hz, 2H), 7.26−7.30 (m, 4H), 7.40 (t, J = 8.0 Hz, 1H), 7.50−7.54 (m, 1H), 7.63−7.65 (m, 1H), 7.81 (d, J = 8.0 Hz, 1H), 8.37−8.39 (m, 1H), 8.46 (d, J = 8.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.3, 30.2, 52.7, 107.0, 114.6, 114.8, 119.8, 122.3, 122.8, 123.3, 124.2, 124.3, 127.2, 128.2, 129.1, 129.7, 130.1, 130.2, 131.0, 132.6, 132.9, 137.1, 137.9, 150.0; HRMS (m/z, ESI) calcd for $C_{26}H_{25}ClN_3(+)$ 414.1737, found 414.1735.

*6-tert-Butyl-12-(2-fluorobenzyl)-6,11-dihydroquinolino[3,2-b]quinoxaline (**1e**):* 18 mg (45%) as a green solid; mp 103−104 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 9H), 4.63 (s, 2H), 4.98 (s, 1H), 6.84 (t, J = 7.5 Hz, 1H), 6.95 (t, J = 7.0 Hz, 2H), 7.13 (t, J = 9.0 Hz, 1H), 7.21−7.24 (m, 1H), 7.27−7.29 (m, 2H), 7.40 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.62−7.64 (m, 1H), 7.83 (d, J = 8.0 Hz, 1H), 8.37 (m, 1H), 8.47 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.6, 29.1, 52.53, 105.9, 114.6, 114.8, 115.2, 115.4, 119.8, 122.3, 122.9, 123.3, 124.2, 124.3, 124.7, 126.6, 127.2, 128.2, 128.8, 130.1, 130.3, 132.7, 137.2, 150.0; HRMS (m/z, ESI) calcd for $C_{26}H_{25}FN_3(+)$ 398.2033, found 398.2034.

*6-tert-Butyl-12-(4-fluorobenzyl)-6,11-dihydroquinolino[3,2-b]quinoxaline (**1f**):* 20 mg (51%) as a brown gum; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (s, 9H), 4.53 (s, 2H), 4.95 (s, 1H), 6.90 (t, J = 8.5 Hz, 2H), 7.05−7.07 (m, 2H), 7.19−7.21 (m, 2H), 7.32 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.54−7.56 (m, 1H), 7.74 (d, J = 8.0 Hz, 1H), 8.28−8.30 (m, 1H), 8.37 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.2, 29.8, 52.5, 107.3, 114.5, 114.7, 115.6, 115.7, 115.8, 119.7, 122.2, 122.7, 123.2, 124.1, 124.2, 125.9, 127.1, 128.1, 129.7, 129.8, 132.5, 132.8, 135.0, 137.0, 149.9, 160.9, 162.9; HRMS (m/z, ESI) calcd for $C_{26}H_{25}FN_3(+)$ 398.2033, found 398.2026.

*6-tert-Butyl-12-(4-bromobenzyl)-6,11-dihydroquinolino[3,2-b]quinoxaline (**1g**):* 22 mg (49%) as a white solid; mp 126−127 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 9H), 4.59 (s, 2H), 4.97 (s, 1H), 7.05 (d, J = 8.0 Hz, 2H), 7.17−7.19 (m, 2H), 7.40−7.42 (m, 3H), 7.49−7.53 (m, 1H), 7.63−7.64 (m, 1H), 7.79 (d, J = 8.0 Hz, 1H), 8.36−8.38 (m, 1H), 8.46 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.3, 30.3, 52.7, 106.9, 114.6, 114.7, 114.8, 119.7, 120.9, 122.3, 122.8, 123.3, 124.2, 124.3, 127.1, 127.2, 128.2, 128.4, 129.1, 130.1, 130.2, 132.1, 132.6, 137.1, 138.5, 150.0; HRMS (m/z, ESI) calcd for $C_{26}H_{25}BrN_3(+)$ 458.1232, found 458.1229.

*6-tert-Butyl-12-(2-methoxybenzyl)-6,11-dihydroquinolino[3,2-b]quinoxaline (**1h**):* 24 mg (59%) as a brown gum; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (s, 9H), 3.88 (s, 3H), 4.47 (s, 2H), 5.06 (s, 1H), 6.69 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.0 Hz, 1H), 7.14−7.20 (m, 3H), 7.29 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.52−7.57 (m, 1H), 7.76 (d, J = 8.0 Hz, 1H), 8.28−8.30 (m, 1H), 8.37 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.9, 29.8, 52.2, 55.4, 107.5, 109.9, 114.4, 114.6, 120.0, 120.9, 121.9, 122.7, 122.9, 123.8, 124.1, 126.9, 127.6, 128.1, 128.3, 129.3, 130.5, 132.5, 137.3, 150.3, 157.2; HRMS (m/z, ESI) calcd for $C_{27}H_{28}N_3O(+)$ 410.2232, found 410.2225.

*6-tert-Butyl-12-(4-methoxybenzyl)-6,11-dihydroquinolino[3,2-b]quinoxaline (**1i**):* 23 mg (58%) as a slight yellow solid; mp 119−120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (s, 9H), 3.69 (s, 3H), 4.50 (s, 2H), 5.06 (s, 1H), 6.73 (d, J = 8.5 Hz, 2H), 6.99 (d, J = 8.5 Hz, 2H), 7.17−7.19 (m, 2H), 7.31 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.0 Hz, 1H), 7.53−7.55 (m, 1H), 7.76 (d, J = 8.0 Hz, 1H), 8.27−8.29 (m, 1H), 8.37 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.2, 29.7, 52.5,

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55.5, 107.6, 114.4, 114.5, 114.6, 119.9, 122.0, 123.1, 123.9, 124.1, 126.9, 128.2, 129.3, 130.3, 131.3, 132.5, 137.2, 150.2, 158.7; HRMS (*m/z*, ESI) calcd for $C_{27}H_{28}N_3O(+)$ 410.2232, found 410.2231.

*6-tert-Butyl-12-(3-methylbenzyl)-6,11-dihydroquinolino[3,2-b]-quinoxaline (**1j**):* 20 mg (52%) as a white solid; mp 105−106 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 9H), 2.27 (s, 3H), 4.61 (s, 2H), 5.11 (s, 1H), 6.99 (s, 2H), 7.04 (d, J = 7.0 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 7.27−7.29 (m, 2H), 7.40 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.62−7.64 (m, 1H), 7.86 (d, J = 8.0 Hz, 1H), 8.37−8.38 (m, 1H), 8.47 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 29.2, 30.6, 52.6, 107.9, 114.6, 114.7, 119.9, 122.1, 122.9, 123.1, 124.0, 124.2, 125.6, 127.1, 127.8, 128.3, 128.9, 129.1, 130.4, 132.6, 137.2, 138.7, 139.4, 150.3; HRMS (*m/z*, ESI) calcd for $C_{27}H_{28}N_3$ (+) 394.2283, found 394.2280.

*6-tert-Butyl-12-(4-methylbenzyl)-6,11-dihydroquinolino[3,2-b]-quinoxaline (**1k**):* 21 mg (53%) as a white solid; mp 99−100 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 9H), 2.32 (s, 3H), 4.60 (s, 2H), 5.12 (s, 1H), 7.06−7.09 (m, 4H), 7.26−7.28 (m, 2H), 7.39 (t, J = 7.5 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.61−7.63 (m, 1H), 7.84 (d, J = 8.0 Hz, 1H), 8.35−8.37 (m, 1H), 8.45 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 29.3, 30.3, 52.6, 108.0, 114.5, 114.7, 119.9, 122.1, 122.8, 123.1, 124.0, 124.2, 127.1, 128.3, 129.7, 130.4, 132.6, 136.3, 136.7, 137.2, 150.3; HRMS (*m/z*, ESI) calcd for $C_{27}H_{28}N_3$ (+) 394.2283, found 394.2273.

*6-tert-Butyl-12-(naphthalen-1-ylmethyl)-6,11-dihydroquinolino-[3,2-b]quinoxaline (**1l**):* 20 mg (47%) as a yellow solid; mp 154−156 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9H), 4.94 (s, 1H), 5.04 (s, 2H), 6.99 (d, J = 7.0 Hz, 1H), 7.28−7.30 (m, 2H), 7.38 (t, J = 7.0 Hz, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.59−7.64 (m, 3H), 7.68 (t, J = 7.5 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 8.5 Hz, 1H), 8.34 (d, J = 8.0 Hz, 1H), 8.40−8.42 (m, 1H), 8.50 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.8, 28.8, 52.2, 107.1, 114.6, 114.8, 119.9, 122.2, 122.9, 123.2, 123.3, 124.1, 124.3, 125.9, 126.1, 126.3, 126.9, 127.1, 127.9, 128.4, 129.2, 130.4, 132.1, 132.8, 133.9, 134.9, 137.3, 150.3; HRMS (*m/z*, ESI) calcd for $C_{30}H_{28}N_3$ (+) 430.2283, found 430.2275.

*6-tert-Butyl-12-(naphthalen-2-ylmethyl)-6,11-dihydroquinolino-[3,2-b]quinoxaline (**1m**):* 19 mg (45%) as a yellow solid; mp 108−110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H), 4.83 (s, 1H), 5.20 (s, 2H), 7.30−7.45 (m, 2H), 7.47−7.53 (m, 4H), 7.55−7.59 (m, 2H), 7.64−7.67 (m, 2H), 7.81−7.85 (m, 2H), 7.90 (d, J = 9.0 Hz, 1H), 8.41−8.44 (m, 1H), 8.50 (d, J = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.0, 30.7, 52.3, 107.3, 114.3, 114.5, 119.7, 121.9, 122.8, 122.9, 123.8, 123.9, 125.7, 126.3, 126.4, 126.5, 126.8, 127.5, 127.6, 128.0, 128.6, 129.5, 130.1, 132.3, 132.4, 133.5, 136.7, 136.9, 149.9; HRMS (*m/z*, ESI) calcd for $C_{30}H_{28}N_3$ (+) 430.2283, found 430.2278.

*12-Benzyl-6-tert-butyl-2,8-dichloro-6,11-dihydroquinolino[3,2-b]-quinoxaline (**1n**):* 16 mg (36%) as a yellow solid; mp 169−172 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (s, 9H), 4.57 (s, 2H), 5.08 (s, 1H), 7.22 (d, J = 9.5 Hz, 2H), 7.26−7.34 (m, 4H), 7.46 (d, J = 9.0 Hz, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.80 (s, 1H), 8.23 (s, 1H), 8.27 (d, J = 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.1, 30.5, 52.8, 107.7, 114.4, 115.6, 119.4, 123.5, 124.6, 124.7, 127.4, 128.0, 128.1, 128.2, 128.3, 128.5, 129.2, 130.7, 131.7, 135.9, 138.7, 149.9; HRMS (*m/z*, ESI) calcd for $C_{26}H_{24}Cl_2N_3$ (+) 448.1347, found 448.1342.

*12-Benzyl-6-tert-butyl-2,8-difluoro-6,11-dihydroquinolino[3,2-b]-quinoxaline (**1o**):* 16 mg (39%) as a yellow solid; mp 170−172 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (s, 9H), 4.57 (s, 2H), 5.00 (s, 1H), 6.99−7.02 (m, 1H), 7.15 (d, J = 7.5 Hz, 2H), 7.24−7.31 (m, 4H), 7.45 (d, J = 7.5 Hz, 1H), 7.55−7.58 (m, 1H), 7.98 (dd, J = 2.0, 9.5 Hz, 1H), 8.28−8.29 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.2, 30.8, 52.7, 101.4, 101.6, 104.6, 104.7, 107.9, 111.2, 111.4, 112.9, 113.1, 115.5, 115.6, 123.9, 127.3, 127.8, 127.9, 128.3, 129.1, 129.2, 131.5, 131.6, 133.4, 138.9, 149.2, 158.1, 158.3, 160.0, 160.2; HRMS (*m/z*, ESI) calcd for $C_{26}H_{24}F_2N_3$ (+) 416.1938, found 416.1940.

*12-Benzyl-6-tert-butyl-2,8-dimethyl-6,11-dihydroquinolino[3,2-b]quinoxaline (**1p**):* 17 mg (42%) as a yellow solid; mp 191−193 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (s, 9H), 2.54 (s, 6H), 4.62 (s, 2H), 4.96 (s, 1H), 7.06 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 7.0 Hz, 2H), 7.21−7.33 (m, 4H), 7.47−7.51 (m, 1H), 7.61 (s, 1H), 8.15 (s, 1H), 8.33 (d, J = 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 22.1, 29.2, 30.6, 52.5, 106.8, 114.5, 114.8, 114.9, 118.1, 119.3, 123.1, 124.9, 125.7, 126.8, 127.0, 128.1, 128.5, 129.0, 129.3, 129.8, 130.2, 130.3, 130.7, 130.9, 131.6, 131.8, 132.9, 134.9, 139.3, 139.6, 139.7, 149.8, 160.6; HRMS (*m/z*, ESI) calcd for $C_{28}H_{30}N_3$ (+) 408.2440, found 408.2429.

*6-tert-Butyl-2,8-difluoro-12-(4-methoxybenzyl)-6,11-dihydroquinolino[3,2-b]quinoxaline (**1q**):* 20 mg (46%) as a white solid; mp 135−137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 9H), 3.80 (s, 3H), 4.49 (s, 2H), 5.08 (s, 1H), 6.82 (d, J = 8.5 Hz, 2H), 6.98−7.02 (m, 1H), 7.06 (d, J = 8.5 Hz, 2H), 7.23−7.27 (m, 1H), 7.43 (dd, J = 2.0, 9.0 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.99 (dd, J = 2.5, 9.5 Hz, 1H), 8.28 (dd, J = 4.0, 9.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.2, 29.9, 52.6, 55.6, 101.4, 101.6, 104.5, 104.7, 108.4, 111.2, 111.3, 112.9, 113.1, 114.5, 115.4, 115.5, 123.8, 127.8, 127.9, 129.1, 129.3, 130.8, 131.5, 131.6, 133.5, 149.2, 158.1, 158.3, 158.9, 160.0, 160.2; HRMS (*m/z*, ESI) calcd for $C_{27}H_{26}F_2N_3O$ (+) 446.2044, found 446.2038.

*6-tert-Butyl-2,8-dichloro-12-(4-methoxybenzyl)-6,11-dihydroquinolino[3,2-b]quinoxaline (**1r**):* 20 mg (42%) as a yellow solid; mp 218−220 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (s, 9H), 3.78 (s, 3H), 4.49 (s, 2H), 5.15 (s, 1H), 6.82 (d, J = 8.5 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 7.23 (dd, J = 2.0, 8.5 Hz, 1H), 7.44 (dd, J = 2.0, 9.0 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 1.5 Hz, 1H), 8.21 (d, J = 1.5 Hz, 1H), 8.25 (d, J = 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.2, 29.7, 52.8, 55.6, 108.2, 114.4, 114.6, 115.6, 119.4, 123.5, 124.6, 124.7, 127.9, 128.0, 128.2, 128.5, 129.3, 130.5, 130.7, 131.7, 135.9, 149.9, 158.9; HRMS (*m/z*, ESI) calcd For $C_{27}H_{26}Cl_2N_3O$ (+) 478.1453, found 478.1449.

*6-tert-Butyl-12-(4-methoxybenzyl)-2,8-dimethyl-6,11-dihydroquinolino[3,2-b]quinoxaline (**1s**):* 19 mg (44%) as a yellow solid; mp 179−182 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 9H), 2.54 (s, 6H), 3.77 (s, 3H), 4.55 (s, 2H), 5.03 (s, 1H), 6.81−6.85 (m, 2H), 7.03−7.08 (m, 3H), 7.31−7.33 (m, 1H), 7.49−7.50 (m, 1H), 7.59−7.61 (m, 1H), 8.14 (s, 1H), 8.32 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 22.0, 29.3, 29.7, 52.4, 55.5, 107.3, 114.4, 114.5, 114.8, 119.2, 122.9, 124.8, 125.6, 126.7, 128.1, 129.4, 130.6, 130.9, 131.5, 132.8, 134.8, 149.8, 158.7; HRMS (*m/z*, ESI) calcd for $C_{29}H_{32}N_3O$ (+) 438.2545, found 438.2537.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for compounds **1a**−**s**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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DEDICATION

†This paper is dedicated to Professor Zhongning Zhang on the occasion of his 70th birthday.

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