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Intramolecular Functionalization of Benzylic Methylene Adjacent to the Ring Nitrogen Atom in *N*-Aryltetrahydroisoquinoline Derivatives

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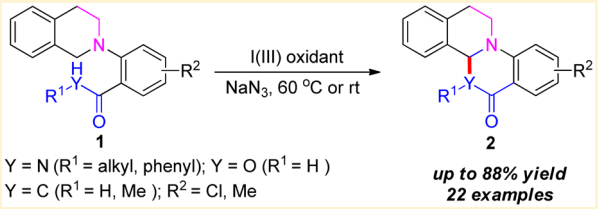
Supporting Information

ABSTRACT: Functionalization at the benzylic methylene group that is adjacent to the ring nitrogen atom in a series of *N*-aryltetrahydroisoquinoline compounds has been realized through intramolecular cross-dehydrogenative coupling reactions. The presented transformation provided straightforward access to the formation of C(sp^3)−Y (Y = C, N or O) bond via I(III) reagent.



Among the many C−H bond activation approaches, cross-dehydrogenative coupling (CDC) reactions enable direct synthesis of complex products from simple starting materials without requiring prior activation.[1] One such example is the oxidation of carbon−hydrogen bonds adjacent to a nitrogen which provides reactive imine or iminium ion intermediates and is regarded as a powerful method for realizing complex organic transformations.[2]

Up until now, many research groups have utilized various metals or transition metals such as Ru,[3] Ir,[4] Cu,[2f,5] Ti,[6] Au,[7] Cd,[8] etc. as catalyst and versatile nucleophiles, including cyanides,[2c,9] nitroalkanes,[10] activated methylene compounds,[11] ketones,[8,12] electron-rich arenes,[13] alkynes,[2f,3b,14] siloxy compounds,[15] and heteroatom nucleophiles,[16] to carry out inter- or intramolecular functionalization of the benzylic methylene group that is adjacent to the ring nitrogen atom in *N*-aryltetrahydroisoquinoline compounds.

1,2,3,4-Tetrahydroisoquinolines show various biological and pharmacological activities. They have been used as inhibitors of phenylethanolamine *N*-methyltransferase[17] and have shown therapeutically valuable in the treating anxiety and ischemic heart conditions.[18] Quinazolinone exhibits many effects on the central nervous system, shows cardiovascular and anti-inflammatory activities, and can act as a psychotropic, hypnotic, cardiotonic, or antihistamine agent.[19] Although the significance of these compounds is obvious, only a few synthetic strategies have been developed for the construction of the skeleton. In 2013, an enantioselective C−N bond-forming reaction catalyzed by chiral phosphate anions, which produced enantiospecific cyclic aminals of the 1,2,3,4-tetrahydroisoquinoline framework, was reported (Scheme 1, path a).[20] In 2013, a visible-light-induced oxidative C−H functionalization was developed to realize the inter- and intramolecular cross-dehydrogenative coupling (CDC) reactions with palladium(II)−porphyrin as the catalyst (Scheme 1, path b).[21] Lately, an intramolecular C−N bond formation through the functionalization of the methylene group in diarylamines induced by tris(4-bromophenyl)aminium hexachloroantimonate ($TBPA^{\bullet+}SbCl_6^-$) was realized (Scheme 1, path c).[22] Herein, we disclose a novel hypervalent iodine(III) reagent mediated approach to access the tetrahydroisoquinoline framework via functionalization of the benzylic methylene group that is adjacent to the ring nitrogen atom (Scheme 1, path d).

We initiated our studies by using *N*-*tert*-butyl-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzamide **1a** as the model substrate to test out our postulate that by treating it with an appropriate hypervalent iodine reagent there would generate an iminium intermediate which, if captured by the neighboring amide group, would form tetrahydroisoquinolino[2,1-*a*]-quinazolinone **2a** through an intramolecular annulation. To our delight, the reaction took place as expected when **1a** was treated with 1.5 equiv of phenyliodine(III) diacetate (PIDA) in dichloroethane (DCE) at room temperature, and the desired cyclized product **2a** was formed, after 24 h, in a satisfactory yield of 69%, with 27% of the starting material recovered (Table 1, entry 1). When the more potent oxidant of phenyliodine(III) bis(trifluoroacetate) (PIFA, 1.5 equiv) was employed, no improvement was found, and there was still considerable amount of starting material left unreacted (Table 1, entry 2). A third oxidant, *o*-iodoxybenzoic acid (IBX[23]), was tested, but the result showed no reaction had occurred (Table 1, entry 3).

Our next study for improving the yield was to identify the appropriate additive, that would be effective in promoting the conversion. Three additives, namely $BF_3{\cdot}Et_2O$,[24] TMSOTf, and NaN_3, were chosen for their well-known ability to activate hypervalent iodine(III) reagents. However, results showed that

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Scheme 1. Direct C−Y (Y = C, N, O) Bond Formation via Activation of the Benzylic Methylene Group Adjacent to the Ring Nitrogen Atom in *N*-Aryltetrahydroisoquinolines

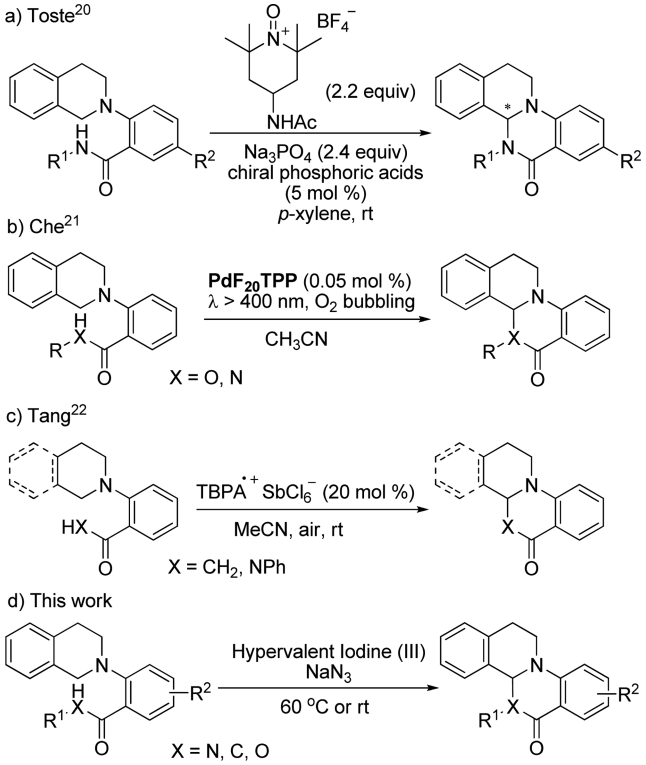
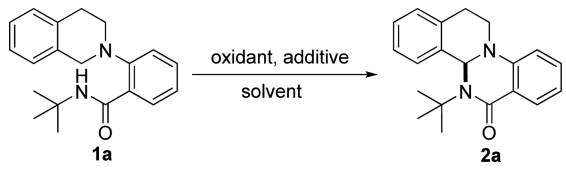


Table 1. Optimization of Reaction Conditions[a]



entry	oxidant	additive (equiv)	solvent	*T* (°C)	time (h)	yield[b] (%)
1	PIDA		DCE	rt	24	69[c]
2	PIFA		DCE	rt	24	71[d]
3	IBX		DCE	rt	24	NR
4	PIDA	TMSOTf (0.5)	DCE	60	1	63
5	PIDA	$BF_3{\cdot}Et_2O$ (0.5)	DCE	60	1	71
6	PIDA	NaN_3 (1.2)	DCE	60	1	82
7	**PIDA**	**NaN_3 (1.2)**	**MeOH**	**60**	**0.25**	**86**
8	PIDA	NaN_3 (1.2)	MeCN	60	0.5	83
9	PIDA	NaN_3 (1.2)	DMF	60	1	71
10	PIDA	NaN_3 (1.2)	toluene	60	1	49

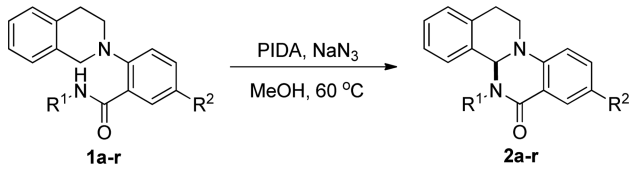
[a]All reactions were carried out with **1a** (0.5 mmol) and oxidant (1.5 equiv) in solvent (*c* = 0.05 M). [b]Isolated yield. [c]27% of the starting material was recovered. [d]24% of the starting material was recovered.

when $BF_3{\cdot}Et_2O$ or TMSOTf was used as additive accompanied by increasing the reaction temperature to 60 °C, the starting material was all consumed but the yield of **2a** remained essentially unchanged, nevertheless. Much to our delight, when 1.2 equiv of NaN_3 was added, the yield leapt to a satisfactory yield of 82%.

Solvent-screening study showed that MeOH was the best fit among all other solvents tested including DCE, MeCN, *N*,*N*-dimethylformamide (DMF), toluene, leading to the desired product in the highest yield of 86%. In addition, the reaction time was shortened to only 15 min.

Under the optimal reaction conditions (Table 1, entry 7),[25] we extended the methodology to a large variety of tetrahydroisoquinoline-*N*-benzamide derivatives. In general, the reactions proceeded well to afford the desired products in moderate to good yields. As shown in Table 2, when R^1 was a pure alkyl group, such as a *t*-Bu, cyclohexyl, or *n*-Bu group, the substrates gave the corresponding products in excellent yields and the reaction time was less than 30 min (Table 2, entries 1−3). For substrates where R^1 was a substituted alkyl group, attached with a furfuryl or an aryl group at the end, the substituent on the aromatic ring, whether it be an electron-donating (OMe, Me) or -withdrawing (F, Cl) group, did not show any profound effect on the reaction yield (Table 2, entries 4−11). However, the reaction yield dramatically decreased for substrates where R^1 was a phenyl group, with byproducts **2l′** and **2m′** being generated during the reaction, respectively (Table 2, entries 12 and 13, and Scheme 2).[26]

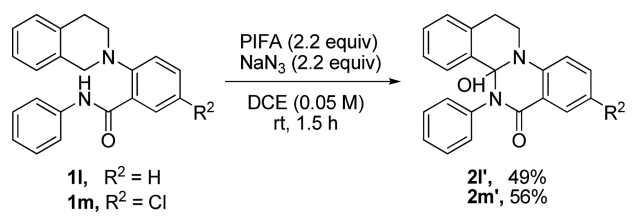
Table 2. PIDA-Mediated Cross-Coupling of Tetrahydroisoquinoline-*N*-benzamides[a]



entry	R^1	R^2	product **2**	time (h)	yield[b] (%)
1	*t*-Bu	H	**2a**	0.25	86
2	cyclohexyl	H	**2b**	0.5	85
3	*n*-Bu	H	**2c**	0.5	82
4	furfuryl	H	**2d**	4	58
5	Bn	H	**2e**	0.5	84
6	4-MeBn	H	**2f**	1	79
7	2-FBn	H	**2g**	1	63
8	$BnCH_2$	H	**2h**	1	76
9	2-$ClBnCH_2$	H	**2i**	1	72
10	3-$OMeBnCH_2$	H	**2j**	1	66
11	3,4-di$OMeBnCH_2$	H	**2k**	1	73
12[c]	Ph	H	**2l**	5	46
13[c]	Ph	Cl	**2m**	5	39
14	Bn	Cl	**2n**	2	83
15	furfuryl	Cl	**2o**	2	81
16	*t*-Bu	Cl	**2p**	3	56
17	$BnCH_2$	Cl	**2q**	4	39
18	cyclohexyl	CH_3	**2r**	1	88

[a]All reactions were carried out with **1** (0.5 mmol) in the presence of PIDA (1.5 equiv) and NaN_3 (1.2 equiv) in MeOH (c = 0.05 M) at 60 °C. [b]Isolated yield. [c]PIFA (2.2 equiv) and NaN_3 (2.2 equiv) were used in DCE at room temperature.

Scheme 2. PIFA-Mediated Cross-Coupling of 1l and 1m



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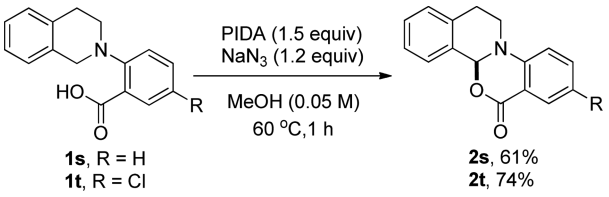
When the R^2 group was extended to other substituents, such as a chlorine atom, the corresponding benzamides could also be converted into the cyclized products **2n−q** in moderate to good yields under the described conditions (Table 2, entries 14−17). With R^2 being $-CH_3$, the sole example showed that the sizable substituent effect was minute, as the corresponding benzamide **1r** was cyclized into quinazolinone **2r** in excellent yield (Table 2, entry 18). To our disappointment, substrates with R^1 being a methoxyl group or a hydrogen atom gave no desired product (not shown).

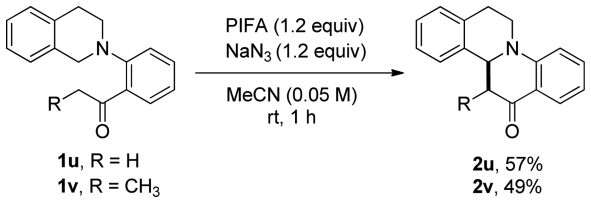
At the success of the above intramolecular oxidative C(sp^3)−N bond formation mediated by hypervalent iodine(III), we further investigated the application on the analogous substrates where the nitrogen in the acyl position was replaced by an O or a C atom. To our delight, tetrahydroisoquinoline-*N*-benzoic acid derivatives, namely the unsubstituted **1s** and the chloro-substituted **1t**, were both successfully converted to the desired lactones **2s** and **2t** in 61% and 74% yields, respectively, through the formation of a new C−O bond (Scheme 3, **2s**,**t**).

Scheme 3. PIDA-Mediated Intramolecular C−O Bond-Forming Reactions



When **1u** or **1v** was treated under the same optimized reaction conditions, no desired cyclized product was achieved, but when the more potent PIFA was employed instead, while keeping the same additive of NaN_3, the reaction proceeded in MeCN at room temperature and provided the desired product in moderate yields (Scheme 4, **2u−v**).

Scheme 4. PIFA-Mediated Intramolecular C−C Bond-Forming Reactions



On the basis of the previous reports in literature,[2] a plausible mechanistic pathway was proposed for this iodine(III)-mediated intramolecular oxidative C(sp^3)−X bond formation process, shown in Scheme 5. First, the highly reactive azidoiodinane, PhI(N_3)OAc, was formed as a result of an S_N2 reaction of PIDA by the azide anion.[27] A side reaction, during this initial stage, of PIDA reacting with 2 equiv of NaN_3 to give bis(azido)iodobenzene which then dissociated into one molecule of PhI and 3 equiv of N_2 gas was included in the mechanism scheme as step I′ to account for the observation of bubbles during the experiments.[28] This additional step is consistent with the fact that 1.5 equiv of PIDA was necessary for a complete consumption of the starting material. Then the reaction of **1a** with PhI(N_3)OAc offered the ammonium ion **A**. In the presence of the basic acetate anion, an E2 reaction occurred in **A** and furnished the iminium intermediate **B**,[29] along with the generation of one molecule of iodobenzene and acetic acid. The iminium intermediate **B** was attacked by the nearby nucleophilic N center,[30] with the abstract of a hydrazoic acid,[31] leading to the final product of **2a**. Furthermore, a control experiment involving the adding of 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) as additive showed neither the reaction rate nor the product yield was affected by this additive, suggesting that the reaction proceeds via an ionic mechanism.

In summary, we have demonstrated an efficient I(III)-mediated reaction for the synthesis of tetrahydroisoquinoline derivatives. The functionalization of the benzylic methylene group adjacent to the ring nitrogen atom was realized by forming the C(sp^3)−X (X = N, O, C) bond using the hypervalent iodine reagent. Advantages of this method include the ready availability of the starting materials, great functional-group tolerance, and the mild reaction conditions.

EXPERIMENTAL SECTION

I. General Information. ^1H and ^{13}C NMR spectra were recorded on a 600 or 400 MHz spectrometer at 25 °C. Chemical shifts values are given in ppm (parts per million) and referred to the internal standard TMS set as 0.00 ppm. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet). The coupling constants, *J*, are reported in hertz (Hz). High-resolution mass spectrometry (HRMS) was obtained on a Q-TOF micro spectrometer. Melting points were determined with a micromelting point apparatus. TLC plates were visualized by exposure to ultraviolet light. Reagents and solvents were purchased as reagent grade and were used without further purification. Flash column chromatography was performed over silica gel 200−300 mesh, and the eluent was a mixture of ethyl acetate (EA) and petroleum ether (PE).

II. Preparation of Substrates 1. *General Procedure A.*[20,32] All of the substrates **1a−v** were prepared adapted from a previously reported procedure with some modification. Known products **1a**,[20] **1b**,[20] **1e**,[20] **1f**,[20] **1l**,[20] **1s**,[32] **1u**,[33] and **1v**[33] were prepared in 80%, 63%, 76%, 42%, 71%, 75%, 70%, and 54% yields, respectively. The properties and ^1H NMR data of **1a**,**b**,**e**,**f**,**l**,**s**,**u**,**v** were consistent with those in the literature.

III. Construction of Products 2. *General Procedure B.* To a solution of substrate **1** (0.5 mmol) in MeOH (10 mL) were added PIDA (0.75 mmol, 241 mg) and NaN_3 (0.6 mmol, 39 mg). The mixture was stirred at 60 °C until total consumption of the substrate was reached. Saturated $NaHCO_3$ (20 mL) was then added to quench the reaction followed by extraction with EtOAc (3 × 20 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (PE/EA) on silica gel (for **2a−t**) to afford the desired product; the size of silica gel column was 10 × 300 mm.

General Procedure C. To a solution of substrate **1** (0.5 mmol) in DCE (10 mL) were added PIFA (1.1 mmol, 473 mg) and NaN_3 (1.1 mmol, 143 mg). The mixture was stirred at room temperature until total consumption of the substrate was reached. Saturated $NaHCO_3$ (20 mL) was then added to quench the reaction followed by extraction with EtOAc (3 × 20 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (PE/EA) on silica gel (for **2l**,**m**) to afford the desired product; the size of silica gel column was 10 × 300 mm.

General Procedure D. To a solution of substrate **1** (0.5 mmol) in MeCN (10 mL) were added PIFA (0.6 mmol, 258 mg) and NaN_3 (0.6 mmol, 39 mg). The mixture was stirred at room temperature until total consumption of the substrate was reached. Saturated $NaHCO_3$ (20 mL) was then added to quench the reaction, followed by extraction with EtOAc (3 × 20 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue

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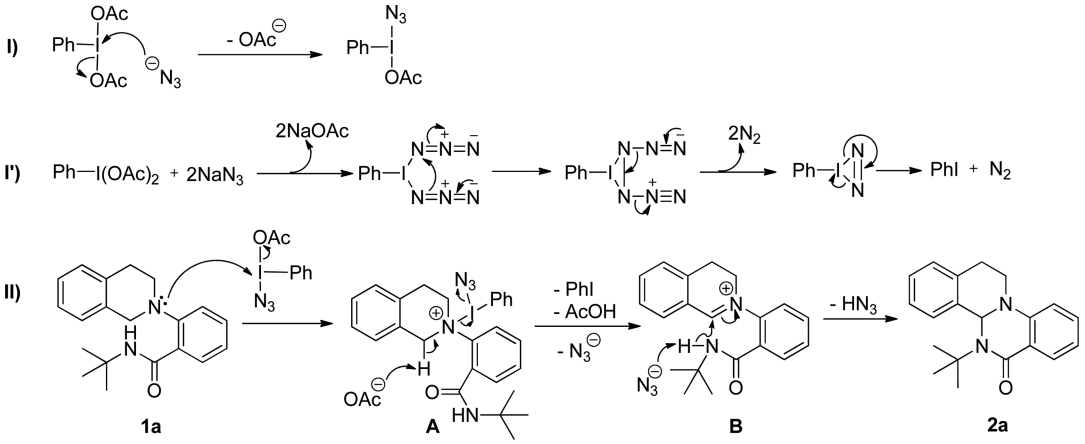
Scheme 5. Plausible Mechanistic Pathway



was purified by flash column chromatography (PE/EA) on silica gel (for **2u,v**) to afford the desired product; the size of silica gel column was 10 × 300 mm.

IV. Spectroscopic Data of 1c,d,g−k,m−r,t. *N-Butyl-2-(3,4-dihydroisoquinolin-2(1H)-yl)benzamide (**1c**).* Following general procedure A, **1c** was purified by silica gel chromatography (PE/EA = 9:1, V_{PE} = 1080 mL, V_{EA} = 120 mL): yield 33%, 1.65 mmol, 0.58 g, red liquid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.74 (s, 1H), 8.24 (s, 1H), 7.45 (t, J = 7.4 Hz, 1H), 7.25 (d, J = 7.4 Hz, 2H), 7.23−7.15 (m, 3H), 7.05 (d, J = 7.2 Hz, 1H), 4.11 (s, 2H), 3.37 (s, 2H), 3.31−3.29 (m, 2H), 3.07 (s, 2H), 1.20 (d, J = 6.8 Hz, 2H), 1.13−1.10 (m, 2H), 0.69 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.2, 151.1, 134.0, 133.4, 132.0, 131.6, 129.0, 128.2, 126.8, 126.4, 126.1, 125.0, 120.7, 56.9, 50.3, 39.2, 31.2, 29.5, 20.3, 13.7; HRMS (ESI) m/z calcd for $C_{20}H_{24}N_2NaO^+$ [M + Na^+] 331.1781, found 331.1783.

*2-(3,4-Dihydroisoquinolin-2(1H)-yl)-N-(furan-2-ylmethyl)-benzamide (**1d**).* Following general procedure A, **1d** was purified by silica gel chromatography (PE/EA = 8:2, V_{PE} = 960 mL, V_{EA} = 240 mL): yield 63%, 3.15 mmol, 1.05 g, white solid; mp 81−83 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.27 (d, J = 7.0 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.27 (dd, J = 8.4, 4.4 Hz, 2H), 7.22−7.16 (m, 2H), 7.13 (d, J = 7.2 Hz, 1H), 7.01 (d, J = 7.2 Hz, 1H), 6.96 (s,1H), 6.11 (s, 1H), 5.97 (s, 1H), 4.50 (s, 2H), 4.11 (s, 2H), 3.29 (s, 2H), 2.89 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.0, 151.3, 151.1, 141.9, 133.9, 133.5, 132.3, 131.6, 129.0, 127.8, 126.6, 126.4, 126.0, 125.2, 121.2, 110.2, 107.1, 56.2, 50.9, 36.6, 29.2; HRMS (ESI) m/z calcd for $C_{21}H_{20}N_2NaO_2^+$ [M + Na^+] 355.1417, found 355.1416.

*2-(3,4-Dihydroisoquinolin-2(1H)-yl)-N-(2-fluorobenzyl)-benzamide (**1g**).* Following general procedure A, **1g** was purified by silica gel chromatography (PE/EA = 9.5:0.5, V_{PE} = 1140 mL, V_{EA} = 60 mL): yield 73%, 3.65 mmol, 1.31 g, white solid; mp 97−99 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.27 (d, J = 7.0 Hz, 1H), 7.46 (t, J = 7.4 Hz, 1H), 7.28 (d, J = 7.4 Hz, 1H), 7.26 (d, J = 7.0 Hz, 1H), 7.20−7.17 (m, 1H), 7.17−7.09 (m, 3H), 7.07 (d, J = 7.4 Hz, 1H), 6.94 (d, J = 7.4 Hz, 1H), 6.87 (t, J = 7.2 Hz, 1H), 6.76 (t, J = 9.0 Hz, 1H), 4.54 (d, J = 4.3 Hz, 2H), 4.06 (s, 2H), 3.28 (s, 2H), 2.84 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.1, 160.8 (d, J = 244 Hz), 159.9, 151.3, 133.7, 133.3, 132.3, 131.6, 130.2 129.1 (d, J = 8.2 Hz), 127.9, 126.6, 126.2 (d, J = 22.0 Hz), 126.0, 125.0 (d, J = 4.3 Hz), 124.1, 121.3, 115.3, 115.1, 56.7, 50.3, 37.5, 29.2; HRMS (ESI) m/z calcd for $C_{23}H_{21}FN_2NaO^+$ [M + Na^+] 383.1530, found 383.1534.

*2-(3,4-Dihydroisoquinolin-2(1H)-yl)-N-phenethylbenzamide (**1h**).* Following general procedure A, **1h** was purified by silica gel chromatography (PE/EA = 9.5:0.5, V_{PE} = 950 mL, V_{EA} = 50 mL): yield 82%, 4.10 mmol, 1.46 g, yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.74 (s, 1H), 8.23 (s, 1H), 7.44 (t, J = 7.2 Hz, 1H), 7.27−7.16 (m, 6H), 7.16−7.11 (m, 2H), 7.04 (d, J = 7.4 Hz, 1H), 7.01 (d, J = 6.8 Hz, 2H), 4.06 (s, 2H), 3.58−3.61 (m, 2H), 3.24 (s, 2H), 2.82 (s, 2H), 2.62 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.4, 151.1, 139.0, 134.0, 133.5, 132.1, 131.5, 129.1, 128.5, 128.5, 128.0, 126.8, 126.4, 126.3, 126.1, 124.8, 120.9, 56.2, 50.5, 40.5, 35.2, 29.1; HRMS (ESI) m/z calcd for $C_{24}H_{24}N_2NaO^+$ [M + Na^+] 379.1781, found 379.1779.

*N-(2-Chlorophenethyl)-2-(3,4-dihydroisoquinolin-2(1H)-yl)-benzamide (**1i**).* Following general procedure A, **1i** was purified by silica gel chromatography (PE/EA = 8:2, V_{PE} = 800 mL, V_{EA} = 200 mL): yield 80%, 4 mmol, 1.56 g, yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.88 (s, 1H), 8.24 (d, J = 7.4 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.26−7.13 (m, 6H), 7.07 (s, 3H), 7.02 (d, J = 7.3 Hz, 1H), 4.08 (s, 2H), 3.60−3.57 (m, 2H), 3.26 (t, J = 5.1 Hz, 2H), 2.88 (s, 2H), 2.78 (t, J = 7.1 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.4, 151.0, 136.7, 134.1, 133.9, 133.3, 132.1, 131.6, 130.5, 129.5, 129.1, 128.0, 127.8, 126.9, 126.8, 126.4, 126.2, 125.0, 120.8, 56.2, 50.9, 38.9, 33.1, 29.2. HRMS (ESI) m/z calcd for $C_{24}H_{23}{}^{35}ClN_2NaO^+$ [M + Na^+] 413.1391, found 413.1390.

*2-(3,4-Dihydroisoquinolin-2(1H)-yl)-N-(3-methoxyphenethyl)-benzamide (**1j**).* Following general procedure A, **1j** was purified by silica gel chromatography (PE/EA = 8.5:1.5, V_{PE} = 850 mL, V_{EA} = 150 mL): yield 78%, 3.90 mmol, 1.50 g, yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.22 (d, J = 7.5 Hz, 1H), 7.43 (t, J = 7.4 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.22−7.16 (m, 3H), 7.14 (d, J = 7.2 Hz, 1H), 7.09 (t, J = 7.8 Hz, 1H), 7.03 (d, J = 7.3 Hz, 1H), 6.69 (d, J = 8.1 Hz, 1H), 6.62−6.54 (m, 2H), 4.06 (s, 2H), 3.72 (s, 3H), 3.62−3.55 (m, 2H), 3.23 (t, J = 5.3 Hz, 2H), 2.83 (s, 2H), 2.59 (t, J = 7.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.5, 159.6, 151.0, 140.7, 134.0, 133.5, 132.1, 131.6, 129.4, 129.1, 127.9, 126.8, 126.4, 126.1, 124.9, 120.8, 120.8, 114.0, 111.9, 56.3, 55.1, 50.6, 40.5, 35.2, 29.0. HRMS (ESI) m/z calcd for $C_{25}H_{26}N_2NaO_2^+$ [M + Na^+] 409.1886, found 409.1884.

*2-(3,4-Dihydroisoquinolin-2(1H)-yl)-N-(3,4-dimethoxyphenethyl)-benzamide (**1k**).* Following general procedure A, **1k** was purified by silica gel chromatography (PE/EA = 8:2, V_{PE} = 800 mL, V_{EA} = 200 mL): yield 75%, 3.75 mmol, 1.55 g, light yellow solid; mp 89−91 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.23 (d, J = 7.3 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.26−7.25 (t, J = 3.5 Hz, 1H), 7.22 (d, J = 7.7 Hz, 2H), 7.19 (d, J = 7.2 Hz, 1H), 7.15 (d, J = 7.4 Hz, 1H), 7.03 (d, J = 7.4 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.58−6.49 (m, 2H), 4.06 (s, 2H), 3.83 (s, 3H), 3.77 (s, 3H), 3.56 (d, J = 6.2 Hz, 2H), 3.26 (t, J = 5.7 Hz, 2H), 2.85 (t, J = 5.3 Hz, 2H), 2.57 (t, J = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.3, 151.0, 148.8, 147.4, 134.0, 133.4, 132.0, 131.6, 131.5, 129.0, 128.0, 126.7, 126.3, 126.0, 124.8, 120.7, 120.3, 111.6, 111.1, 56.3, 55.9, 55.7, 50.6, 40.6, 34.8, 29.2; HRMS (ESI) m/z calcd for $C_{26}H_{28}N_2NaO_3^+$ [M + Na^+] 439.1992, found 439.1990.

*5-Chloro-2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-phenylbenzamide (**1m**).* Following general procedure A, **1m** was purified by silica gel chromatography (PE/EA = 9:1, V_{PE} = 1080 mL, V_{EA} = 120 mL): yield 75%, 3.75 mmol, 1.36 g, white solid; mp 143−145 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.36 (s, 1H), 8.35 (s, 1H), 7.48 (d, J = 7.5 Hz, 1H), 7.30−7.28 (m, 5H), 7.19−7.15 (m, 3H), 7.06 (d, J = 7.0 Hz, 1H), 7.01 (d, J = 6.6 Hz, 1H), 4.19 (s, 2H), 3.43 (s, 2H), 3.17 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.4, 149.4, 138.4, 133.4, 133.0,

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J. Org. Chem. 2016, 81, 3372−3379

132.4, 131.7, 131.5, 129.7, 129.1, 129.0, 127.3, 126.8, 126.4, 123.9, 123.2, 119.6, 56.8, 51.1, 29.3; HRMS (ESI) m/z calcd for $C_{22}H_{19}{}^{35}ClN_2NaO^+$ [M + Na^+] 385.1078, found 385.1079.

*N-Benzyl-5-chloro-2-(3,4-dihydroisoquinolin-2(1H)-yl)benzamide (**1n**).* Following general procedure A, **1n** was purified by silica gel chromatography (PE/EA = 9:1, V_{PE} = 900 mL, V_{EA} = 100 mL): yield 81%, 4.05 mmol, 1.52 g, yellow solid; mp 94−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.25 (d, J = 2.3 Hz, 1H), 7.38−7.41 (m, 1H), 7.23−7.11 (m, 4H), 7.11−7.03 (m, 3H), 6.98 (d, J = 7.2 Hz, 3H), 4.46 (d, J = 2.4 Hz, 2H), 4.04 (s, 2H), 3.22 (t, J = 5.7 Hz, 2H), 2.75 (t, J = 5.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 149.6, 137.7, 133.2, 133.1, 132.0, 131.5, 131.0, 129.6, 129.0, 128.6, 127.9, 127.3, 126.9, 126.3, 122.6, 56.7, 50.5, 44.2, 29.1; HRMS (ESI) m/z calcd for $C_{23}H_{21}{}^{35}ClN_2NaO^+$ [M + Na^+] 399.1235, found 399.1238.

*5-Chloro-2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-(furan-2-ylmethyl)benzamide (**1o**).* Following general procedure A, **1o** was purified by silica gel chromatography (PE/EA = 9:1, V_{PE} = 900 mL, V_{EA} = 100 mL): yield 71%, 3.55 mmol, 1.32 g, white solid; mp 79−81 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.26 (s, 1H), 8.24 (s, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.23−7.16 (m, 3H), 7.12 (d, J = 7.1 Hz, 1H), 7.01 (d, J = 7.2 Hz, 1H), 6.96 (s, 1H), 6.12 (s, 1H), 5.99 (s, 1H), 4.50 (s, 2H), 4.08 (s, 2H), 3.26 (s, 2H), 2.88 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.6, 150.8, 149.7, 142.0, 133.5, 133.3, 132.0, 131.5, 131.0, 129.4, 129.0, 126.7, 126.3, 126.1, 122.8, 110.2, 107.2, 56.2, 51.0, 36.7, 29.0; HRMS (ESI) m/z calcd for $C_{21}H_{19}{}^{35}ClN_2NaO_2^+$ [M + Na^+] 389.1027, found 389.1025.

*N-tert-Butyl-5-chloro-2-(3,4-dihydroisoquinolin-2(1H)-yl)-benzamide (**1p**).* Following general procedure A, **1p** was purified by silica gel chromatography (PE/EA = 9:1, V_{PE} = 900 mL, V_{EA} = 100 mL): yield 83%, 4.15 mmol, 1.42 g, white solid; mp 139−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 8.16 (d, J = 2.5 Hz, 1H), 7.39−7.37 (m, 1H), 7.24−7.14 (m, 4H), 7.04 (d, J = 7.4 Hz, 1H), 4.04 (s, 2H), 3.38 (t, J = 5.9 Hz, 2H), 3.09 (t, J = 5.7 Hz, 2H), 1.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 149.1, 133.6, 133.3, 131.5, 131.3, 130.8, 130.7, 128.9, 127.1, 127.0, 126.3, 126.2, 122.1, 57.9, 50.8, 49.4, 29.5, 28.2; HRMS (ESI) m/z calcd for $C_{20}H_{23}{}^{35}ClN_2NaO^+$ [M + Na^+] 365.1391, found 365.1390.

*5-Chloro-2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-phenethylbenzamide (**1q**).* Following general procedure A, **1q** was purified by silica gel chromatography (PE/EA = 9:1, V_{PE} = 900 mL, V_{EA} = 100 mL): yield 82%, 4.10 mmol, 1.58 g, yellow solid; mp 115−116 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.65 (s, 1H), 8.19 (d, J = 7.0 Hz, 1H), 7.37 (dd, J = 8.5, 2.5 Hz, 1H), 7.24−7.17 (m, 4H), 7.14 (t, J = 6.2 Hz, 3H), 7.03 (d, J = 7.4 Hz, 1H), 7.00 (d, J = 7.3 Hz, 2H), 4.03 (s, 2H), 3.59 (dd, J = 12.6, 6.9 Hz, 2H), 3.19 (t, J = 5.8 Hz, 2H), 2.80 (t, J = 5.6 Hz, 2H), 2.62 (t, J = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.1, 149.4, 138.9, 133.6, 133.3, 131.8, 131.5, 130.7, 129.5, 129.1, 128.5, 128.4, 126.9, 126.4, 126.3, 122.4, 56.2, 50.7, 40.6, 35.1, 28.8 (One carbon signal was missing due to peak overlap); HRMS (ESI) m/z calcd for $C_{24}H_{23}{}^{35}ClN_2NaO^+$ [M + Na^+] 413.1391, found 413.1393.

*N-Cyclohexyl-2-(3,4-dihydroisoquinolin-2(1H)-yl)-5-methylbenzamide (**1r**).* Following general procedure A, **1r** was purified by silica gel chromatography (PE/EA = 9:1, V_{PE} = 1080 mL, V_{EA} = 120 mL): yield 71%, 3.55 mmol, 1.32 g, white solid; mp 79−81 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.06 (s, 1H), 7.24 (s, 1H), 7.23−7.10 (m, 4H), 7.03 (d, J = 7.2 Hz, 1H), 4.05 (s, 2H), 3.85 (s, 1H), 3.36 (s, 2H), 3.08 (s, 2H), 2.37 (s, 3H), 1.73 (d, J = 10.3 Hz, 2H), 1.45 (s, 3H), 1.27−1.19 (m, 2H), 0.91 (d, J = 9.6 Hz, 1H), 0.81 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.2, 148.6, 134.8, 134.2, 133.5, 132.4, 130.0, 128.9, 127.8, 126.8, 126.4, 126.0, 120.9, 57.6, 49.8, 47.9, 32.5, 29.6, 25.6, 24.6, 20.8; HRMS (ESI) m/z calcd for $C_{23}H_{29}N_2O^+$ [M + H^+] 349.2274, found 349.2276.

*5-Chloro-2-(3,4-dihydroisoquinolin-2(1H)-yl)benzoic acid (**1t**).* Following general procedure A without silica gel chromatography, **1t** was recrystallized from hot MeOH and H_2O: yield 75%, 3.75 mmol, 1.36 g, white solid; mp 178−179 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.43 (d, J = 8.5 Hz, 1H), 7.26 (t, J = 7.2 Hz, 1H), 7.22 (d, J = 7.0 Hz, 2H), 7.06 (d, J = 7.7 Hz, 1H), 4.21 (s, 2H), 3.36 (t, J = 5.5 Hz, 2H), 3.17 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.7, 149.1, 134.1, 133.8, 132.1, 132.1, 131.7, 129.1, 127.5, 126.9, 126.6, 126.5, 124.3, 55.9, 51.6, 28.9; HRMS (ESI) m/z calcd for $C_{16}H_{14}{}^{35}ClNO_2Na^+$[M + Na^+] 310.0605, found 310.0607.

V. Spectroscopic Data of 2a−v. *5-tert-Butyl-4b,5,12,13-tetrahydro-6H-isoquino[2,1-a]quinazoline-6-one (**2a**).* Following general procedure B, **2a** was purified by silica gel chromatography (PE/EA = 8:2, VPE = 320 mL, VEA = 80 mL): yield 86%, 0.43 mmol, 131 mg, white solid; mp 183−184 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, J = 7.7 Hz, 1H), 7.44−7.37 (m, 1H), 7.25 (dd, J = 10.0, 5.3 Hz, 1H), 7.14−7.07 (m, 2H), 6.99−6.94 (m, 1H), 6.86 (d, J = 8.3 Hz, 1H), 6.75 (t, J = 7.5 Hz, 1H), 5.94 (s, 1H), 4.24 (dd, J = 14.8, 7.3 Hz, 1H), 3.80−3.74 (m, 1H), 3.31−3.21 (m, 1H), 2.73 (dd, J = 17.3, 6.1 Hz, 1H), 1.71 (s, 9H); HRMS (ESI) m/z calcd for $C_{20}H_{23}N_2O^+$ [M + H^+] 307.1805, found 307.1803.

*5-Cyclohexyl-4b,5,12,13-tetrahydro-6H-isoquino[2,1-a]-quinazoline-6-one (**2b**).* Following general procedure B, **2b** was purified by silica gel chromatography (PE/EA = 9:1, V_{PE} = 350 mL, V_{EA} = 50 mL): yield 85%, 0.43 mmol, 141 mg, white solid; mp 202−203 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, J = 7.1 Hz, 1H), 7.34 (d, J = 7.4 Hz, 1H), 7.28−7.24 (m, 1H), 7.15−7.06 (m, 2H), 6.97 (d, J = 7.0 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 6.76 (t, J = 7.4 Hz, 1H), 5.65 (s, 1H), 4.66 (s, 1H), 4.22 (dd, J = 14.4, 7.1 Hz, 1H), 3.80−3.78 (m, 1H), 3.30−3.21 (m, 1H), 2.78 (dd, J = 17.2, 6.1 Hz, 1H), 2.17 (d, J = 10.9 Hz, 1H), 2.04 (d, J = 10.7 Hz, 1H), 1.87 (d, J = 12.8 Hz, 1H), 1.82 (d, J = 13.2 Hz, 1H), 1.69 (d, J = 13.1 Hz, 1H), 1.61−1.39 (m, 4H), 1.16−1.09 (m, 1H); HRMS (ESI) m/z calcd for $C_{22}H_{25}N_2O^+$ [M + H^+] 333.1961, found 333.1963.

*5-Butyl-4b,5,12,13-tetrahydro-6H-isoquino[2,1-a]quinazoline-6-one (**2c**).* Following general procedure B, **2c** was purified by silica gel chromatography (PE/EA = 8:2, V_{PE} = 320 mL, V_{EA} = 80 mL): yield 82%, 0.41 mmol, 125 mg, yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (dd, J = 7.7, 1.3 Hz, 1H), 7.33−7.27 (m, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.18−7.09 (m, 2H), 7.01 (d, J = 7.3 Hz, 1H), 6.87 (d, J = 8.3 Hz, 1H), 6.78 (t, J = 7.4 Hz, 1H), 5.67 (s, 1H), 4.51 (s, 1H), 4.14−4.17 (m, 1H), 3.72−3.61 (m, 1H), 3.29−3.19 (m, 1H), 3.11−3.01 (m, 1H), 2.71−2.75 (m, 1H), 1.71 (d, J = 6.8 Hz, 2H), 1.46−1.38 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.9, 147.0, 136.1, 134.4, 133.2, 129.3, 129.1, 128.1, 126.2, 125.6, 119.1, 118.6, 113.2, 72.7, 47.4, 44.7, 30.9, 24.0, 20.1, 13.9; HRMS (ESI) m/z calcd for $C_{20}H_{22}N_2NaO^+$ [M + Na^+] 329.1624, found 329.1620.

*5-(Furan-2-ylmethyl)-4b,5,12,13-tetrahydro-6H-isoquino[2,1-a]-quinazoline-6-one (**2d**).* Following general procedure B, **2d** was purified by silica gel chromatography (PE/EA = 17:3, V_{PE} = 425 mL, V_{EA} = 75 mL): yield 58%, 0.29 mmol, 86 mg, white solid; mp 185−186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 7.6 Hz, 1H), 7.39−7.32 (m, 2H), 7.24−7.19 (m, 1H), 7.17 (t, J = 7.0 Hz, 2H), 7.07 (d, J = 7.3 Hz, 1H), 6.93−6.84 (m, 2H), 6.32−6.29 (m, 2H), 5.82 (s, 1H), 5.45 (d, J = 7.3 Hz, 1H), 4.56 (d, J = 8.2 Hz, 1H), 4.07−4.02 (m, 1H), 3.67−3.57 (m, 1H), 3.23−3.14 (m, 1H), 2.82−2.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 150.7, 147.5, 142.4, 135.2, 134.7, 133.4, 129.4, 129.2, 128.2, 126.2, 125.9, 119.5, 118.6, 113.9, 110.5, 108.6, 71.9, 44.7, 42.7, 24.6; HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_2^+$ [M + H^+] 331.1441, found 331.1443.

*5-Benzyl-4b,5,12,13-tetrahydro-6H-isoquino[2,1-a]quinazoline-6-one (**2e**).* Following general procedure B, **2e** was purified by silica gel chromatography (PE/EA = 4:1, V_{PE} = 320 mL, V_{EA} = 80 mL): yield 84%, 0.42 mmol, 142 mg, white solid; mp 168−170 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, J = 7.7 Hz, 1H), 7.34 (dd, J = 11.3, 4.2 Hz, 1H), 7.29 (d, J = 6.0 Hz, 4H), 7.26 (d, J = 5.1 Hz, 2H), 7.21−7.14 (m, 2H), 7.02 (d, J = 7.2 Hz, 1H), 6.89 (d, J = 8.3 Hz, 1H), 6.85 (t, J = 7.4 Hz, 1H), 5.67 (s, 2H), 4.36 (d, J = 14.6 Hz, 1H), 4.00 (s, 1H), 3.56−3.45 (m, 1H), 3.10 (s, 1H), 2.71 (dd, J = 16.9, 4.2 Hz, 1H); HRMS (ESI) m/z calcd for $C_{23}H_{20}N_2NaO^+$ [M + Na^+] 363.1468, found 363.1465.

*5-(4-Methylbenzyl)-4b,5,12,13-tetrahydro-6H-isoquino[2,1-a]-quinazoline-6-one (**2f**).* Following general procedure B, **2f** was purified by silica gel chromatography (PE/EA = 4:1, V_{PE} = 320 mL, V_{EA} = 80 mL): yield 79%, 0.40 mmol, 140 mg, white solid; mp 184−186 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (d, J = 7.1 Hz, 1H), 7.34−7.30 (m, 1H), 7.27 (d, J = 7.4 Hz, 1H), 7.21−7.13 (m, 4H), 7.10 (d, J = 7.7 Hz, 2H), 7.01 (d, J = 7.2 Hz, 1H), 6.89−6.81 (m, 2H), 5.73

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(s, 1H), 5.65 (s, 1H), 4.28 (d, J = 15.0 Hz, 1H), 4.01 (d, J = 8.1 Hz, 1H), 3.55−3.47 (m, 1H), 3.12 (s, 1H), 2.72−2.66 (m, 1H), 2.32 (s, 3H); HRMS (ESI) m/z calcd for $C_{24}H_{23}N_2O^+$ [M + H$^+$] 355.1805, found 355.1805.

*5-(2-Fluorobenzyl)-4b,5,12,13-tetrahydro-6H-isoquino[2,1-a]-quinazoline-6-one (**2g**).* Following general procedure B, **2e** was purified by silica gel chromatography (PE/EA = 9:1, V_{PE} = 450 mL, V_{EA} = 50 mL): yield 63%, 0.32 mmol, 113 mg, white solid; mp 179−180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, J = 7.7, 1.3 Hz, 1H), 7.50 (t, J = 7.4 Hz, 1H), 7.36−7.30 (m, 1H), 7.22−7.25 (m, 2H), 7.20−7.12 (m, 2H), 7.10 (t, J = 7.5 Hz, 1H), 6.09−7.04 (m, 2H), 6.89 (d, J = 8.3 Hz, 1H), 6.82 (t, J = 7.4 Hz, 1H), 5.76 (s, 1H), 5.67 (d, J = 15.5 Hz, 1H), 4.48 (d, J = 15.6 Hz, 1H), 4.09 (dd, J = 14.4, 5.9 Hz, 1H), 3.58 (ddd, J = 14.4, 11.5, 5.7 Hz, 1H), 3.25−3.11 (m, 1H), 2.73 (dd, J = 17.0, 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 160.9 (d, J = 244.4 Hz), 159.7, 147.3, 135.5, 134.6, 133.5, 130.0 (d, J = 4.0 Hz), 129.1 (d, J = 4.0 Hz), 128.3, 126.3, 125.7, 124.5 (d, J = 3.5 Hz), 124.4, 124.2, 119.3, 118.3, 115.2 (d, J = 21.4 Hz), 113.5, 72.49, 44.67, 43.99, 24.29; HRMS (ESI) m/z calcd for $C_{23}H_{19}FN_2NaO^+$ [M + Na$^+$] 381.1374, found 381.1370.

*5-Phenethyl-4b,5,12,13-tetrahydro-6H-isoquino[2,1-a]-quinazoline-6-one (**2h**).* Following general procedure B, **2h** was purified by silica gel chromatography (PE/EA = 9:1, VPE = 360 mL, VEA = 40 mL): yield 76%, 134 mg, 0.38 mmol, white solid; mp 143−145 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (d, J = 7.0 Hz, 1H), 7.32 (t, J = 7.3 Hz, 1H), 7.28 (d, J = 6.6 Hz, 2H), 7.24−7.23 (m, 3H), 7.15 (s, 2H), 7.11 (d, J = 6.6 Hz, 1H), 7.01 (d, J = 6.2 Hz, 1H), 6.87 (d, J = 7.9 Hz, 1H), 6.83 (d, J = 6.6 Hz, 1H), 5.34 (s, 1H), 4.71 (s, 1H), 4.04 (d, J = 7.8 Hz, 1H), 3.39−3.34 (m, 1H), 3.21−3.18 (m, 2H), 2.99 (d, J = 8.0 Hz, 2H), 2.69 (d, J = 15.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.9, 147.1, 139.0, 134.4, 133.3, 129.3, 129.1, 129.1, 128.5, 128.2, 126.4, 126.2, 125.7, 119.3, 118.6, 113.3, 73.0, 49.5, 44.3, 35.3, 24.2 (one carbon signal was missing due to peak overlap); HRMS (ESI) m/z calcd for $C_{24}H_{22}N_2NaO^+$ [M + Na$^+$] 377.1624, found 377.1622.

*5-(2-Chlorophenethyl)-4b,5,12,13-tetrahydro-6H-isoquino[2,1-a]quinazoline-6-one (**2i**).* Following general procedure B, **2i** was purified by silica gel chromatography (PE/EA = 4:1, V_{PE} = 320 mL, V_{EA} = 80 mL): yield 72%, 0.36 mmol, 140 mg, white solid; mp 151−153 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (d, J = 7.6 Hz, 1H), 7.32−7.31 (m, 3H), 7.08−7.17 (m, 4H), 7.12−7.08 (m, 1H), 7.00 (d, J = 7.3 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.81 (t, J = 7.3 Hz, 1H), 5.37 (s, 1H), 4.68 (s, 1H), 4.05 (dd, J = 13.8, 5.6 Hz, 1H), 3.41−3.29 (m, 2H), 3.23−3.11 (m, 3H), 2.68 (dd, J = 16.8, 4.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.0, 147.1, 136.4, 134.3, 134.0, 133.3, 131.7, 129.4, 129.3, 129.1, 128.2, 128.1, 126.9, 126.3, 125.6, 119.2, 118.5, 113.2, 73.1, 47.4, 44.4, 33.0, 24.1 (One carbon signal was missing due to peak overlap); HRMS (ESI) m/z calcd for $C_{24}H_{21}{}^{35}ClN_2NaO^+$ [M + Na$^+$] 411.1235, found 411.1236.

*5-(3-Methoxyphenethyl)-4b,5,12,13-tetrahydro-6H-isoquino[2,1-a]quinazoline-6-one (**2j**).* Following general procedure B, **2j** was purified by silica gel chromatography (PE/EA = 4:1, V_{PE} = 400 mL, V_{EA} = 100 mL): yield 66%, 0.33 mmol, 127 mg, white solid; mp 132−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 7.6 Hz, 1H), 7.35 (s, 1H), 7.24−7.17 (m, 4H), 7.04 (d, J = 7.2 Hz, 1H), 6.91−6.83 (m, 3H), 6.84−6.81 (m, 2H), 5.32 (s, 1H), 4.76 (s, 1H), 4.08 (dd, J = 14.0, 6.1 Hz, 1H), 3.77 (s, 3H), 3.44−3.35 (m, 1H), 3.29−3.16 (m, 2H), 3.01 (d, J = 7.4 Hz, 2H), 2.71 (dd, J = 16.8, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 159.7, 147.2, 140.6, 135.7, 134.4, 133.3, 129.5, 129.3, 129.1, 128.2, 126.2, 125.6, 121.3, 119.2, 118.5, 114.2, 113.2, 112.5, 77.5, 77.4, 77.2, 73.1, 55.1, 49.6, 44.3, 35.4, 24.1; HRMS (ESI) m/z calcd for $C_{25}H_{24}N_2NaO_2^+$ [M + Na$^+$] 407.1730, found 407.1728.

*5-(3,4-Methoxyphenethyl)-4b,5,12,13-tetrahydro-6H-isoquino-[2,1-a]quinazoline-6-one (**2k**).* Following general procedure B, **2k** was purified by silica gel chromatography (PE/EA = 7:3, V_{PE} = 280 mL, V_{EA} = 120 mL): yield 73%, 0.37 mmol, 151 mg, white solid; mp 167−169 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (d, J = 7.6 Hz, 1H), 7.32 (t, J = 7.7 Hz, 1H), 7.15 (t, J = 7.1 Hz, 2H), 7.14−7.08 (m, 1H), 7.01 (d, J = 7.3 Hz, 1H), 6.87 (d, J = 8.2 Hz, 1H), 6.85−6.69 (m, 4H), 5.25 (s, 1H), 4.74 (s, 1H), 4.06−4.03 (m, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.37−3.32 (m, 1H), 3.25−3.13 (m, 2H), 2.94 (t, J = 6.2 Hz, 2H), 2.69−2.66 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.9, 148.7, 147.6, 147.1, 135.7, 134.4, 133.3, 131.7, 129.3, 129.0, 128.1, 126.1, 125.5, 120.7, 119.1, 118.5, 113.2, 112.5, 111.4, 73.1, 56.0, 55.6, 49.9, 44.2, 34.8, 24.1; HRMS (ESI) m/z calcd for $C_{26}H_{26}N_2NaO_3^+$ [M + Na$^+$] 437.1836, found 437.1835.

*5-Phenyl-4b,5,12,13-tetrahydro-6H-isoquino[2,1-a]quinazoline-6-one (**2l**).* Following general procedure C, **2l** was purified by silica gel chromatography (PE/EA = 4:1, V_{PE} = 400 mL, V_{EA} = 100 mL): yield 46%, 0.23 mmol, 75 mg, white solid; mp 135−136 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, J = 7.5 Hz, 1H), 7.49 (d, J = 7.6 Hz, 2H), 7.37 (t, J = 6.5 Hz, 3H), 7.34 (d, J = 7.5 Hz, 1H), 7.21 (t, J = 7.2 Hz, 1H), 7.15 (t, J = 7.2 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 7.5 Hz, 1H), 6.99 (d, J = 8.1 Hz, 1H), 6.88 (t, J = 7.3 Hz, 1H), 6.16 (s, 1H), 4.24 (dd, J = 14.2, 6.3 Hz, 1H), 3.76−3.69 (m, 1H), 3.33−3.26 (m, 1H), 2.84 (d, J = 16.9 Hz, 1H); HRMS (ESI) m/z calcd for $C_{22}H_{19}N_2O^+$ [M + H$^+$] 327.1492, found 327.1490.

*8-Chloro-5-phenyl-4b,5,12,13-tetrahydro-6H-isoquino[2,1-a]-quinazoline-6-one (**2m**).* Following general procedure C, **2m** was purified by silica gel chromatography (PE/EA= 9:1, V_{PE} = 450 mL, V_{EA} = 50 mL): yield 39%, 0.20 mmol, 70 mg, white solid; mp 213-215 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.47 (d, J = 6.9 Hz, 2H), 7.38 (s, 2H), 7.31 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 6.4 Hz, 1H), 7.16 (d, J = 6.6 Hz, 1H), 7.09 (d, J = 6.6 Hz, 1H), 7.05 (d, J = 6.8 Hz, 1H), 6.92 (d, J = 8.6 Hz, 1H), 6.14 (s, 1H), 4.18 (dd, J = 13.5, 5.3 Hz, 1H), 3.72 (d, J = 9.0 Hz, 1H), 3.26 (s, 1H), 2.84 (d, J = 16.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.7, 146.0, 141.4, 135.4, 134.2, 133.7, 129.4, 129.3, 129.0, 128.4, 127.1, 126.3, 126.1, 124.9, 124.8, 120.3, 115.6, 77.0, 75.4, 45.2, 24.4; HRMS (ESI) m/z calcd for $C_{22}H_{17}{}^{35}ClN_2NaO^+$ [M + Na$^+$] 383.0922, found 383.0925.

*5-Benzyl-8-chloro-4b,5,12,13-tetrahydro-6H-isoquino[2,1-a]-quinazoline-6-one (**2n**).* Following general procedure A, **2n** was purified by silica gel chromatography (PE/EA= 4:1, V_{PE} = 320 mL, V_{EA} = 80 mL): yield 83%, 0.42 mmol, 155 mg, white solid; mp 214−215 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.32−7.24 (m, 7H), 7.20−7.17 (m, 2H), 7.02 (d, J = 6.9 Hz, 1H), 6.82 (d, J = 8.6 Hz, 1H), 5.70 (s, 1H), 5.65 (s, 1H), 4.35 (d, J = 12.8 Hz, 1H), 3.95 (s, 1H), 3.51 (s, 1H), 3.07 (s, 1H), 2.75−2.68 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.4, 146.0, 136.9, 134.5, 133.3, 129.3, 129.1, 128.7, 128.5, 127.7, 127.6, 126.4, 125.9, 124.7, 119.7, 115.2, 71.7, 49.8, 44.7, 24.4; HRMS (ESI) m/z calcd for $C_{23}H_{19}{}^{35}ClN_2NaO^+$ [M + Na$^+$] 397.1078, found 397.1076.

*8-Chloro-5-(furan-2-ylmethyl)-4b,5,12,13-tetrahydro-6H-isoquino[2,1-a]quinazoline-6-one (**2o**).* Following general procedure B, **2o** was purified by silica gel chromatography (DCM, 350 mL): yield 81%, 0.41 mmol, 147 mg, white solid; mp 211−213 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.63 (s, 1H), 7.55 (s, 1H), 7.38 (d, J = 8.7 Hz, 1H), 7.22−7.15 (m, 2H), 7.11 (t, J = 7.3 Hz, 1H), 7.06 (d, J = 7.4 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.42 (s, 2H), 5.99 (s, 1H), 5.36 (d, J = 15.3 Hz, 1H), 4.57 (d, J = 15.5 Hz, 1H), 4.21−4.18 (m, 1H), 3.75−3.65 (m, 1H), 3.09−3.05 (m, 1H), 2.73 (dd, J = 17.5, 5.3 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.5, 150.4, 146.1, 142.9, 134.5, 133.1, 129.2, 127.9, 127.3, 125.8, 125.1, 122.5, 118.7, 116.2, 110.6, 108.8, 71.4, 43.8, 42.8, 23.0; HRMS (ESI) m/z calcd for $C_{21}H_{17}{}^{35}ClN_2NaO_2^+$ [M + Na$^+$] 387.0871, found 387.0872.

*5-tert-Butyl-8-chloro-4b,5,12,13-tetrahydro-6H-isoquino[2,1-a]-quinazoline-6-one (**2p**).* Following general procedure B, **2p** was purified by silica gel chromatography (PE/EA = 4:1, V_{PE} = 400 mL, V_{EA} = 100 mL): yield 56%, 0.28 mmol, 95 mg, white solid; mp 165−167 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.40−7.34 (m, 1H), 7.19 (d, J = 8.7 Hz, 1H), 7.16−7.10 (m, 2H), 6.98−6.94 (m, 1H), 6.80 (d, J = 8.7 Hz, 1H), 5.92 (s, 1H), 4.18 (dd, J = 14.8, 7.3 Hz, 1H), 3.83−3.74 (m, 1H), 3.28−3.18 (m, 1H), 2.75 (dd, J = 17.4, 6.0 Hz, 1H), 1.70 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.8, 145.3, 137.7, 133.9, 132.6, 129.2, 128.9, 127.9, 126.3, 126.1, 124.3, 122.1, 114.5, 70.7, 58.4, 45.5, 29.3, 23.5; HRMS (ESI) m/z calcd for $C_{20}H_{22}{}^{35}ClN_2O^+$ [M + H$^+$] 341.1415, found 341.1413.

*8-Chloro-5-phenethyl-4b,5,12,13-tetrahydro-6H-isoquino[2,1-a]-quinazoline-6-one (**2q**).* Following general procedure B, **2q** was

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J. Org. Chem. 2016, 81, 3372−3379

purified by silica gel chromatography (PE/EA = 4:1, V_{PE} = 400 mL, V_{EA} = 100 mL): yield 39%, 0.20 mmol, 76 mg, white solid; mp 199−201 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.28 (d, J = 6.7 Hz, 2H), 7.28−7.24 (m, 4H), 7.17−7.16 (m, 1H), 7.13 (s, 2H), 7.01 (d, J = 6.5 Hz, 1H), 6.80 (d, J = 8.5 Hz, 1H), 5.29 (s, 1H), 4.72 (s, 1H), 3.99 (d, J = 8.1 Hz, 1H), 3.38−3.32 (m, 1H), 3.22 (s, 1H), 3.17−3.14 (m, 1H), 2.99 (d, J = 8.0 Hz, 2H), 2.68 (d, J = 15.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.8, 145.7, 138.8, 135.4, 134.1, 133.1, 129.3, 129.1, 128.7, 128.5, 128.4, 126.5, 126.3, 125.5, 124.4, 119.7, 114.8, 73.0, 49.6, 44.4, 35.2, 24.0; HRMS (ESI) m/z calcd for $C_{24}H_{21}{}^{35}ClN_2NaO^+$ [M + Na^+] 411.1235, found 411.1230.

*5-Cyclohexyl-8-methyl-4b,5,12,13-tetrahydro-6H-isoquino[2,1-a]quinazoline-6-one (**2r**).* Following general procedure B, **2r** was purified by silica gel chromatography (PE/EA = 4:1, V_{PE} = 320 mL, V_{EA} = 80 mL): yield 88%, 0.44 mmol, 152 mg, white solid; mp 213-215 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.34 (d, J = 6.6 Hz, 1H), 7.10−7.06 (m, 3H), 6.96 (d, J = 5.9 Hz, 1H), 6.76 (d, J = 7.9 Hz, 1H), 5.63 (s, 1H), 4.67 (s, 1H), 4.18 (s, 1H), 3.76 (s, 1H), 3.27−3.22 (m, 1H), 2.75 (d, J = 12.5 Hz, 1H), 2.17 (s, 3H), 2.03 (d, J = 10.5 Hz, 1H), 1.87 (d, J = 11.6 Hz, 1H), 1.82 (d, J = 11.9 Hz, 1H), 1.69 (d, J = 12.1 Hz, 1H), 1.60−1.37 (m, 5H), 1.12 (d, J = 12.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.5, 144.7, 137.6, 134.4, 133.9, 129.5, 129.0, 128.3, 127.7, 126.5, 125.7, 119.4, 113.2, 68.8, 54.4, 44.8, 32.4, 30.8, 25.9, 25.5, 23.5, 20.3 (one carbon signal was missing due to peak overlap); HRMS (ESI) m/z calcd for $C_{23}H_{27}N_2O^+$ [M + H^+] 347.2118, found 347.2119.

*4b,13-Dihydro-6H,12H-isoquino[2,1-a][3,1]benzoxazin-6-one (**2s**).* Following general procedure B, **2s** was purified by silica gel chromatography (PE/EA = 17:3, V_{PE} = 340 mL, V_{EA} = 60 mL): yield 61%, 0.31 mmol, 76 mg, white solid; mp 142−144 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (d, J = 7.8 Hz, 1H), 7.57 (dd, J = 10.5, 4.3 Hz, 2H), 7.38−7.33 (m, 2H), 7.25 (d, J = 7.3 Hz, 1H), 7.16−7.10 (m, 2H), 6.21 (s, 1H), 3.75 (s, 1H), 3.51 (s, 1H), 3.11 (t, J = 5.8 Hz, 2H); HRMS (ESI) m/z calcd for $C_{16}H_{13}NNaO_2^+$ [M + Na^+] 274.0838, found 274.0837.

*8-Chloro-4b,13-dihydro-6H,12H-isoquino[2,1-a][3,1]benzoxazin-6-one (**2t**).* Following general procedure B, **2t** was purified by silica gel chromatography (DCM, 300 mL): yield 74%, 0.37 mmol, 105 mg, white solid; mp 208−209 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.59 (d, J = 7.3 Hz, 1H), 7.53 (d, J = 8.7 Hz, 1H), 7.43−7.31 (m, 2H), 7.25 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.7 Hz, 1H), 6.28 (s, 1H), 3.72 (s, 1H), 3.53 (s, 1H), 3.11 (t, J = 5.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.0, 148.4, 135.2, 134.6, 130.2, 129.6, 129.5, 128.6, 128.5, 127.4, 127.1, 118.9, 118.0, 85.9, 43.8, 28.8; HRMS (ESI) m/z calcd for $C_{16}H_{12}{}^{35}ClNNaO_2^+$ [M + Na^+] 308.0449, found 308.0446.

*6,7,11b,12-Tetrahydro-13H-dibenzo[a,f]quinolizin-13-one (**2u**).* Following general procedure D, **2u** was purified by silica gel chromatography (PE/EA = 9:1, V_{PE} = 450 mL, V_{EA} = 50 mL): yield 57%, 0.29 mmol, 71 mg, yellow solid; mp 122−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, J = 7.8, 1.6 Hz, 1H), 7.50−7.48 (m, 1H), 7.32−7.29 (m, 1H), 7.26 (d, J = 7.5 Hz, 1H), 7.25−7.20 (m, 2H), 7.03 (d, J = 8.6 Hz, 1H), 6.85 (t, J = 7.4 Hz, 1H), 4.77 (dd, J = 13.8, 2.6 Hz, 1H), 4.19−4.11 (m, 1H), 3.28−3.07 (m, 3H), 2.98−2.92 (m, 1H), 2.83−2.78 (m, 1H); HRMS (ESI) m/z calcd for $C_{17}H_{15}NNaO^+$ [M + Na^+] 272.1046, found 272.1045.

*6,7,11b,12-Tetrahydro-12-methyl-13H-dibenzo[a,f]quinolizin-13-one (**2v**).* Following general procedure D, **2v** was purified by silica gel chromatography (PE/EA = 9:1, V_{PE} = 450 mL, V_{EA} = 50 mL): yield 49%, 0.25 mmol, 64 mg, yellow solid; mp 142−144 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, J = 7.3 Hz, 1H), 7.40 (t, J = 7.1 Hz, 1H), 7.25 (s, 1H), 7.17 (s, 2H), 7.08 (s, 1H), 6.96 (d, J = 8.3 Hz, 1H), 6.73 (t, J = 7.0 Hz, 1H), 4.56 (d, J = 4.7 Hz, 1H), 4.27−4.18 (m, 1H), 3.47 (t, J = 12.1 Hz, 1H), 3.22−3.19 (m, 1H), 3.15−3.09 (m, 1H), 2.80 (d, J = 16.0 Hz, 1H), 1.34 (d, J = 6.9 Hz, 3H); HRMS (ESI) m/z calcd for $C_{18}H_{17}NNaO^+$ [M + Na^+] 286.1202, found 286.1200.

VI. Spectroscopic Data of 2l′ and 2m′. *4b-Hydroxy-5-phenyl-4b,5,12,13-tetrahydro-6H-isoquino[2,1-a]quinazoline-6-one (**2l′**).* Following general procedure C, **2l′** was purified by silica gel chromatography (PE/EA = 9:1, V_{PE} = 450 mL, V_{EA} = 50 mL): yield 49%, 0.25 mmol, 83 mg, gray solid; mp 178−179 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.36 (s, 1H), 7.85 (d, J = 7.2 Hz, 1H), 7.67 (t, J = 7.9 Hz, 3H), 7.61 (t, J = 7.2 Hz, 1H), 7.51−7.45 (m, 3H), 7.34 (t, J = 7.0 Hz, 2H), 7.28 (t, J = 7.8 Hz, 2H), 7.04 (t, J = 7.4 Hz, 1H), 3.98 (s, 2H), 3.14 (s, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.8, 163.2, 141.1, 139.4, 139.1, 135.2, 132.0, 131.0, 129.1, 128.6, 128.3, 127.7, 127.6, 127.3, 126.9, 126.7, 123.3, 119.6, 49.8, 27.6; HRMS (ESI) m/z calcd for $C_{22}H_{18}N_2NaO_2^+$ [M + Na^+] 365.1260, found 365.1263.

*8-Chloro-4b-hydroxy-5-phenyl-4b,5,12,13-tetrahydro-6H-isoquino[2,1-a]quinazoline-6-one (**2m′**).* Following general procedure C, **2m′** was purified by silica gel chromatography (PE/EA = 9:1, V_{PE} = 450 mL, V_{EA} = 50 mL): yield 56%, 0.28 mmol, 111 mg, white solid; mp 189−190 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.45 (s, 1H), 7.81 (s, 1H), 7.68 (m, 2H), 7.63 (s, 2H), 7.54 (d, J = 8.3 Hz, 1H), 7.50 (t, J = 7.2 Hz, 1H), 7.33 (d, J = 6.8 Hz, 2H), 7.27 (t, J = 7.2 Hz, 2H), 7.04 (t, J = 7.0 Hz, 1H), 3.95 (s, 2H), 3.13 (s, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.3, 163.2, 139.9, 139.2, 139.1, 136.7, 132.1, 131.1, 130.7, 129.7, 128.9, 128.6, 128.1, 127.6, 127.4, 126.8, 123.6, 119.7, 49.6, 27.5; HRMS (ESI) m/z calcd for $C_{22}H_{17}{}^{35}ClN_2NaO_2^+$ [M + Na^+] 399.0871, found 399.0870.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02443.

Spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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