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Synthesis of 3,4-dihydrobenzo[*g*]isoquinoline-1(2*H*)-ones and 3,4-dihydroisoquinoline-1(2*H*)-ones skeleton via intramolecular electrophilic cyclization

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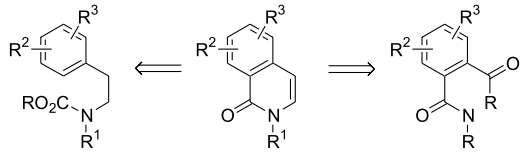
Abstract—An original alternative approach to isoquinolines based on the installation of a benzene nucleus on a performed heterocyclic ring. Synthesis of 3,4-dihydrobenzo[*g*]isoquinoline-1(2*H*)-ones and 3,4-dihydroisoquinoline-1(2*H*)-ones via intramolecular electrophilic cyclization of 3,4-disubstituted lactams is reported.

1. Introduction

The isoquinolone subunit is one of the most important pharmacophores that is widely found in biologically active molecules[1] and natural products.[2] This has encouraged the development of a number of approaches for the synthesis of the isoquinoline ring system and related heterocyclic compounds, including isoquinolones. Bischler–Napieralski,[3] Pictet–Spengler,[4] and Pomeranz–Fritsch[5] reactions have been powerful methods for the synthesis of isoquinolines. Other procedures like the Curtius rearrangement of cinnamic acids[6] or methanolysis of 2-alkynylbenzonitriles[7] to isoquinolones ring system were also reported. Although these classical methods have been frequently employed in the synthesis of isoquinoline or isoquinolone alkaloids, an electron-donating group on the aromatic ring was still required, such as alkoxy groups. Relatively strong acidic conditions were employed to cyclize β-phenethylamines or benzamide analog (Scheme 1). The substrates that lack of electron-donating groups often failed to cyclize or gave low yields.[8]



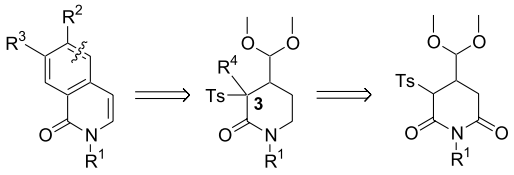
Scheme 1. Preparation of isoquinolone derivatives from β-phenethylamines and benzamide analog.

2. Result and discussion

Recently, we developed a facile stepwise [3+3] annulation reaction between *N*-benzyl-α-sulfonyl acetamide and different α- or β-, aryl- or alkyl- substituted acyclic α,β-unsaturated alkyl esters had lead to the corresponding glutarimides in good yields. This method has been used for the synthesis of natural products and potential biological drugs.[9]

2.1. Retrosynthesis of 3,4-dihydroisoquinoline-1(2*H*)-ones

Continuing our investigation on the application of the synthesis of alkaloids, we disclose our preliminary finding regarding a valuable alternative route for the preparation of 3,4-dihydrobenzo[*g*]isoquinoline-1(2*H*)-one and 3,4-dihydroisoquinoline-1(2*H*)-one analogues. The key step of the target structure construction was intramolecular electrophilic cyclization of a suitably substituted lactam (Scheme 2).



Scheme 2. Retrosynthesis of 3,4-dihydroisoquinoline-1(2*H*)-ones.

Keywords: Stepwise [3+3] annulation; 3,4-Dihydrobenzo[*g*]isoquinoline-1(2*H*)-ones and 3,4-dihydroisoquinoline-1(2*H*)-ones; Electrophilic cyclization.

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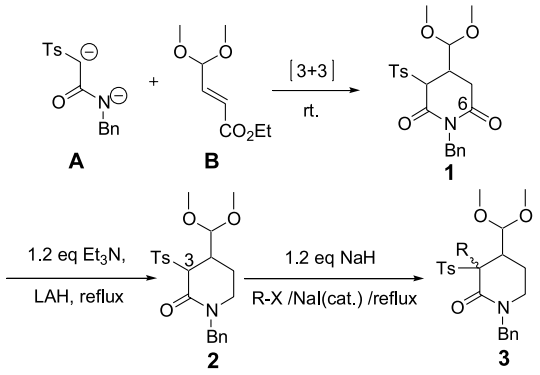
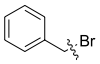
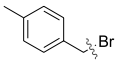
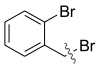
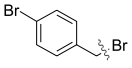
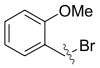
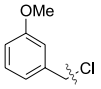
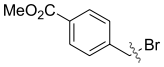
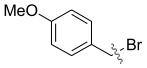
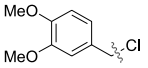
2.2. Synthesis of 3,4-disubstituted-δ-lactam

Our synthetic studies commenced with the construction of glutarimides **1**, which were easily prepared via stepwise [3+3] annulation of *N*-benzyl α-sulfonylacetamide A with α,β-unsaturated ester[9] B, followed by regioselective reduction[10] of C6 carbonyl (Scheme 3). Reaction of δ-lactam **2** with excess NaH and various alkyl halides provided alkylated products **3** (Table 1).



Scheme 3.

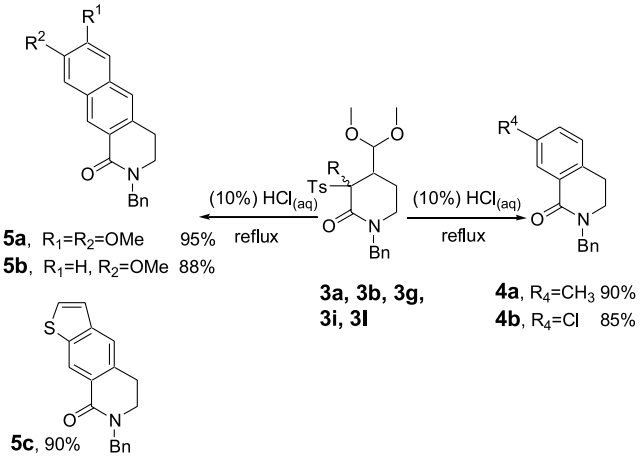
Table 1. Treatment of **2** with 1.5 equiv NaH and various alkyl halides

Entry	Alkyl halides (R–X)	Product (yield, %)
1		**3a** 87
2		**3b** 90
3		**3c** 90
4		**3d** 85
5		**3e** 80
6		**3f** 87
7		**3g** 86[a]
8		**3h** 81
9		**3i** 83
10		**3j** 75[a]
11		**3k** 86
12		**3l** 85

Reagents and conditions: Alkyl halides (1.5 equiv), NaH (1.2 equiv), solvent THF, reflux temperature.
[a] The compound decomposed during the separation on the silica gel. The yield was crude yield.

2.3. Synthesis of 3,4-dihydrobenzo[*g*]isoquinoline-1(2*H*)-ones and 3,4-dihydroisoquinoline-1(2*H*)-ones

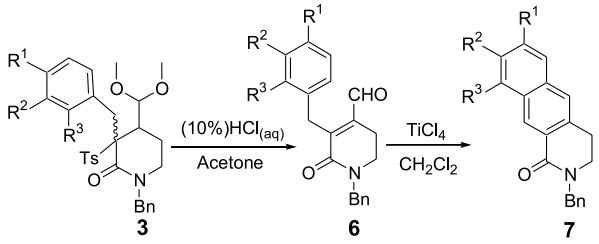
With the desired lactams **3** in hand, we started to focus on the intramolecular electrophilic cyclization. In the case of lactams **3a**, **3b**, **3g**, **3i**, **3l**, we accomplished the cyclization by dissolving the lactams in 10% aqueous hydrochloric acid and acetone followed by heating the resulting solution at reflux temperature. The corresponding 3,4-dihydroisoquinoline-1(2*H*)-ones **4a–b**, and 3,4-dihydrobenzo[*g*]isoquinoline-1(2*H*)-ones **5a–c** were obtained in good yield (Scheme 4).



Scheme 4. Intramolecular electrophilic cyclization.

For entries 1–7 (R_2=H), only hydrolyzed products **6** were found. However, treatment of compounds **6** with $TiCl_4$[11] in CH_2Cl_2 at reflux temperature for 4 h, the desired 3,4-dihydrobenzo[*g*]isoquinoline-1(2*H*)-one derivatives **7a–g** were obtained in good yield (Table 2). The structures of

Table 2. Hydrolysis of acetal and intramolecular electrophiliccyclization



Entry	Alkyl groups				Hydrolyzed product[a] (yield, %)[b]	Cyclized product[c] (yield, %)[b]
		R^1	R^2	R^3		
1	**3c**	H	H	H	**6a** (91)	**7a** (87)
2	**3d**	CH_3	H	H	**6b** (85)	**7b** (85)
3	**3e**	H	H	Br	**6c** (83)	**7c** (81)
4	**3f**	Br	H	H	**6d**[d] (85)	**7d**[d] (80)
5	**3h**	H	H	OMe	**6e** (87)	**7e** (83)
6	**3k**	OMe	H	H	**6f** (87)	**7f**[d] (82)
7	**3j**	CO_2Me	H	H	**6g** (90)	**7g**[d] (60)

[a] All reaction were carried out under reflux temperature of acetone.
[b] Isolated yields.
[c] Dichloromethane.
[d] The structures were confirmed by single crystal X-ray analysis.

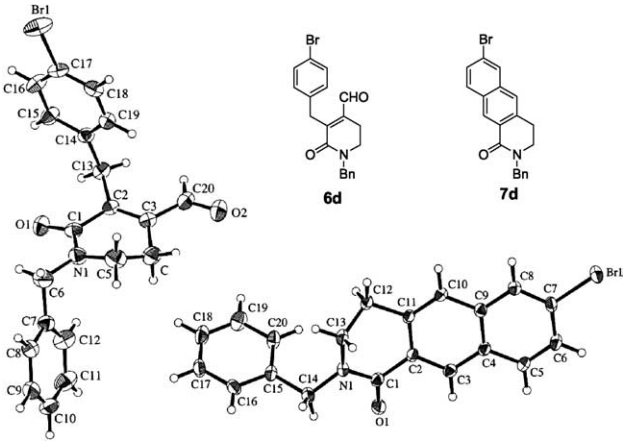
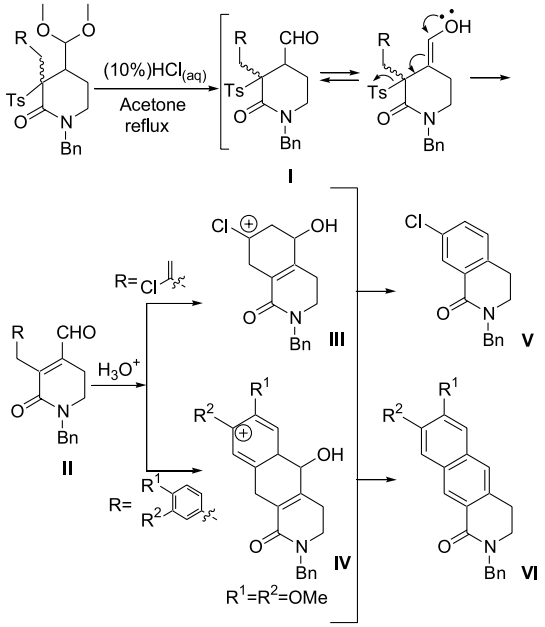


Figure 1. X-ray structures of **6d** and **7d**.

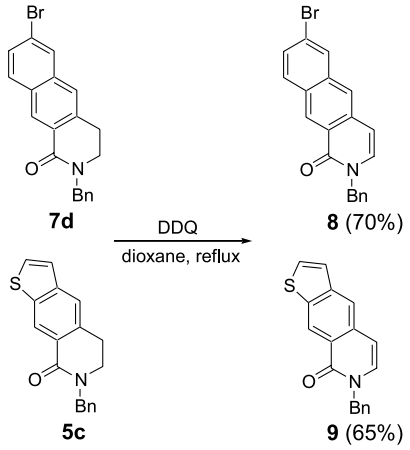
6d and **7d** were confirmed by single crystal X-ray analysis (Fig. 1).[12]

To account for these results, we propose a mechanism which involves (1) hydrolysis of the acetal to aldehyde **I**, (2) elimination of *p*-toluenesulfinic acid to the α?β-unsaturated lactam **II**, (3) intramolecular electrophilic cyclization forming the cation intermediates **III** or **IV** and (4) deprotonation and dehydration (Scheme 5). When R^2 substituents can stabilize the carbon cation either by electron donation or resonance, the target core structure would form easily in acidic aqueous solution. Otherwise, a Lewis acid has to be employed to promote the reaction (Scheme 5).



Scheme 5. Proposed mechanism for cyclization.

Finally, in the presence of DDQ,[13] **5c** and **7d** could be oxidized to the corresponding isoquinolones **8** and **9** in good yields (Scheme 6).



Scheme 6.

3. Conclusion

In conclusion, we developed an easy and alternative approach to synthesize substituted 3,4-dihydrobenzo[*g*]isoquinoline-1(2*H*)-one and 3,4-dihydroisoquinoline-1(2*H*)-one derivatives based on the construction of benzene ring on a preformed δ-lactam ring. This method is different from the traditional procedures, which start from a substituted benzene ring to the fused pyridine. It is noteworthy that in entry 7 (Table 2), the cyclization still occurred in the presence of a strong electron-withdrawing group (i.e. $-CO_2Me$) and provided **7g** in reasonable yield. Further application of this methodology in the synthesis of alkaloids is currently underway in our laboratory.

4. Experimental

4.1. General

Melting points were determined with Fargo micro melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on Varian unity INOVA-500 spectrometer. ^{1}H NMR spectra were recorded at indicated field strength as solution in $CDCl_3$ unless otherwise indicated. Chemical shifts are given in parts per million (ppm, δ) downfield from TMS and are reference to $CHCl_3$ (7.26 ppm) as internal standard. ^{13}C NMR spectra were recorded at indicated field strength as solution in $CDCl_3$ unless otherwise indicated. Mass spectra were recorded by Brucker APEX II. Elemental analyses were performed using a Perkin–Elmer 2400(II) CHN analyzer. Infrared spectra (IR) were measured with a Shimadzu IR-408 series FT-IR spectrophotometer. X-ray data were performed by Rigaku AFC6S diffractometer.

Tetrahydrofuran was distilled prior to use. All other reagents and solvents were obtained from commercial sources and were used without any further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Solutions of products in organic solvents were dried with anhydrous magnesium sulfate before concentration under vacuum.

4.2. Procedure for alkylation of lactam 2

A solution of lactam **2** (500 mg, 1.2 mmol) in THF (10 mL) was added to a rapidly stirred suspension of sodium hydride (96 mg, 2.4 mmol, 60%) in tetrahydrofuran (20 mL). After the reaction mixture was stirred at room temperature for 15 min, alkyl halides were added. The resulting mixtures were refluxed for 3–4 h, quenched with NH_4Cl (1 mL), filtered and concentrated under reduced pressure. The residue was diluted with water (10 ml) and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Chromatography on silica gel (hexane/ethyl acetate=3:1) afforded the pure products.

4.2.1. 1-Benzyl-4-dimethoxymethyl-3-(2-methyl allyl)-3-(toluene-4-sulfonyl)piperidin-2-one (3a). 90% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3012, 1635; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J=8.5 Hz, 2H), 7.36–7.24 (m, 7H), 5.16 (d, J=7.0 Hz, 1H),4.9 (d, J=15.0 Hz, 1H), 4.89 (s, 1H), 4.80 (s, 1H), 4.23 (d, J=15.0 Hz, 1H), 3.53 (s, 3H), 3.47–3.43 (m, 1H), 3.42 (s, 3H), 3.27 (dt, J=12.5, 4.5 Hz 1H), 3.19 (d, J=13.0 Hz, 1H), 2.92 (d, J=13.0 Hz, 1H), 2.8 (ddt, J=13.5, 13.0, 7.0 Hz, 1H), 2.59 (ddd, J=13.5, 10.0, 7.5 Hz 1H), 2.41 (s, 3H), 1.99 (ddt, J=14.0, 7.0, 3.0 Hz, 1H), 1.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.81, 144.35, 139.92, 136.37, 136.03, 130.66 (2C), 128.64 (2C), 128.69 (2C), 127.92 (2C), 127.42, 117.07, 104.72, 75.2, 56.04, 53.82, 51.49, 46.93, 42.36, 40.74, 23.61, 21.67, 20.88; HRMS m/z (ESI, $M^+ + 1$) calcd for $C_{26}H_{33}NO_5S$ 472.2079. Found 472.2106.

4.2.2. 1-Benzyl-3-(2-chloro allyl)-4-dimethoxymethyl-3-(toluene-4-sulfonyl)piperidin-2-one (3b). 90% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3012, 1635; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J=8.0 Hz, 2H), 7.36–7.25 (m, 7H), 5.33 (d, J=12.5 Hz, 1H), 5.18 (d, J=8.0 Hz, 1H), 4.89 (d, J=15.0 Hz, 1H), 4.23 (d, J=15.0 Hz, 1H), 3.57 (d, J=13.5 Hz, 1H), 3.54 (s, 3H), 3.44–3.4 (m, 2H), 3.39 (s, 3H), 3.32–3.25 (m, 2H), 2.74 (ddt, J=13.5, 13.0, 5.5 Hz, 1H), 2.64 (ddd, J=12.0, 8.0, 2.5 Hz 1H), 2.41 (s, 3H), 1.99 (ddt, J=11.5, 8.0, 2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.01, 144.65, 136.42, 136.37, 135.63, 130.56 (2C), 128.73 (2C), 128.43 (2C), 127.92 (2C), 127.32, 119.18, 104.63, 74.74, 55.81, 52.78, 51.54, 46.65, 42.23, 42.11, 21.67, 21.27; HRMS m/z (ESI, $M^+ + 1$) calcd for $C_{25}H_{31}NO_5SCl$ 492.1533. Found 492.1606.

4.2.3. 1,3-Dibenzyl-4-dimethoxymethyl-3-(toluene-4-sulfonyl)piperidin-2-one (3c). 90% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3014, 1641; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J=8.0 Hz, 2H), 7.30–7.25 (m, 7H), 7.19–7.14 (m, 5H), 5.31 (d, J=8.0 Hz, 1H), 4.60 (d, J=14.5 Hz, 1H), 4.48 (d, J=14.5 Hz, 1H), 3.78 (d, J=12.0 Hz, 1H), 3.65 (s, 3H), 3.52 (d, J=12.0 Hz, 1H), 3.35 (s, 3H), 3.22 (dd, J=5.5, 1.5 Hz, 1H), 2.9 (dt, J=12.0, 4.5 Hz, 1H), 2.71 (ddt, J=13.5, 13.0, 5.5 Hz, 1H), 2.43 (s, 3H), 2.44 (ddd, J=13.0, 8.0, 3.0 Hz, 1H), 1.86 (ddt, J=14.0, 7.5, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.38, 144.50, 136.20, 136.17, 135.33, 131.66 (2C), 130.73 (2C), 128.73 (2C), 128.52 (2C), 128.02 (2C), 127.68 (2C), 127.30, 126.77, 104.86, 77.44, 56.11, 52.88, 51.44, 46.65, 41.33, 38.61, 21.70, 21.07; HRMS m/z (ESI, $M^+ + 1$) calcd for $C_{29}H_{33}NO_5S$ 508.2079. Found 508.2064.

4.2.4. 1-Benzyl-3-(4-bromobenzyl)-4-dimethoxymethyl-3-(toluene-4-sulfonyl)piperidin-2-one (3f). 87% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3034, 1656; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J=9.0 Hz, 2H), 7.31–7.26 (m, 7H), 7.17 (d, J=9.0 Hz, 2H), 7.12 (d, J=7.0 Hz, 2H), 5.30 (d, J=8.0 Hz, 1H), 4.56 (d, 15.0 Hz, 1H), 4.50 (d, J=15.0 Hz, 1H), 3.76 (d, J=12.5 Hz, 1H), 3.66 (s, 3H), 3.42 (d, J=12.5 Hz, 1H), 3.37 (s, 3H), 3.21 (dd, J=8.0, 1.5 Hz, 1H), 2.89 (dt, J=12.5, 5.0 Hz 1H), 2.71 (ddt, J=13.5, 13.0, 5.0 Hz 1H), 2.46–2.41 (m, 1H), 2.44 (s, 3H), 1.88 (ddt, J=14.0, 12.5, 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.13, 144.68, 136.04, 135.91, 134.37, 133.54 (2C), 130.11 (2C), 130.74 (2C), 128.80 (2C), 128.58 (2C), 127.62 (2C), 127.42, 120.99, 105.01, 77.17, 56.23, 53.17, 51.54, 46.74, 41.33, 37.91, 21.72, 21.07; HRMS m/z (ESI, $M^+ + 1$) calcd for $C_{29}H_{32}NO_5SBr$ 586.1185. Found 586.1166.

4.2.5. 1-Benzyl-3-(2-bromobenzyl)-4-dimethoxymethyl-3-(toluene-4-sulfonyl)piperidin-2-one (3e). 80% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3012, 1635; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J=8.0 Hz, 2H), 7.51 (dd, J=8.0, 1.0 Hz, 1H), 7.40–7.33 (m, 7H), 6.95 (dt, J=7.5, 1.0 Hz, 1H), 6.87 (dt, J=7.5, 1.0 Hz, 1H), 6.61 (d, J=8.0 Hz, 1H), 5.19 (d, J=5.5 Hz, 1H), 4.79 (d, J=14.5 Hz, 1H), 4.61 (d, J=14.5 Hz, 1H), 4.12 (d, J=15.0 Hz, 1H), 3.56–3.53 (m, 1H), 3.50 (d, J=15.0 Hz, 1H), 3.38 (s, 3H), 3.34 (s, 3H), 3.33–3.27 (m, 1H), 2.86 (ddt, J=13.5, 13.0, 6.0 Hz, 1H), 2.51 (ddd, J=13.0, 6.0, 3.0 Hz, 1H), 2.43 (s, 3H), 1.92 (ddt, J=14.0, 6.0, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.01, 144.75, 136.14, 135.67, 135.58, 133.27, 130.97, 128.91 (2C), 128.83 (2C), 128.67 (2C), 128.52 (2C), 127.72, 127.66, 127.08, 126.25, 104.58, 75.61, 56.03, 55.15, 52.11, 47.07, 42.22, 38.44, 21.68, 20.01; HRMS m/z (ESI, $M^+ + 1$) calcd for $C_{29}H_{32}NO_5SBr$ 586.1185. Found 586.1179.

4.2.6. 1-Benzyl-4-dimethoxymethyl-3-(2-methoxy benzyl)-3-(toluene-4-sulfonyl)piperidin-2-one (3h). 81% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3016, 1628; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J=8.0 Hz, 2H), 7.39–7.24 (m, 9H), 7.14 (d, J=2.5 Hz, 1H), 6.69 (d, J=9.0 Hz, 1H), 5.16 (d, J=3.0 Hz, 1H), 4.95 (d, J=14.5 Hz, 1H), 4.35 (d, J=14.5 Hz, 1H), 3.92 (d, J=13.5 Hz, 1H), 3.78 (s, 3H), 3.52 (s, 3H), 3.42 (d, J=14.0 Hz, 1H), 3.38 (s, 3H), 3.37–3.32 (m, 1H), 3.08–3.04 (m, 1H), 2.83 (ddt, J=14.0, 13.5, 6.0 Hz, 1H), 2.42 (s, 3H), 2.27 (dt, J=12.5, 3.5 Hz, 1H), 1.84 (ddt, J=14.0, 6.0, 3.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.79, 156.8, 144.45, 136.39, 136.29, 133.55, 130.79(2C), 128.7 (2C), 128.64(2C), 128.56 (2C), 128.55, 127.65 (2C), 127.33, 126.22, 112.75, 112.12, 104.39, 57.17, 55.51, 51.31, 46.73, 44.19, 31.54, 21.65, 19.53; HRMS m/z (ESI, $M^+ + 1$) calcd for $C_{30}H_{36}NO_6S$ 538.2185. Found 538.2259.

4.2.7. 1-Benzyl-4-dimethoxymethyl-3-(3-methoxy benzyl)-3-(toluene-4-sulfonyl)piperidin-2-one (3i). 83% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3017, 1633; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J=8.5 Hz, 2H), 7.32–7.25 (m, 7H), 7.17 (d, J=7.0 Hz, 1H), 7.09 (t, J=8.0 Hz,

1H), 6.9 (s, 1H), 6.73 (d, J=8.0 Hz, 1H), 5.32 (d, J=8.0 Hz, 1H), 4.69 (d, J=14.5 Hz, 1H), 4.45 (d, J=14.5 Hz, 1H), 3.76 (d, J=12.5 Hz, 1H), 3.69 (s, 3H), 3.65 (s, 3H), 3.52 (d, J=12.5 Hz, 1H), 3.35 (s, 3H), 3.23 (dd, J=13.0, 5.0 Hz, 1H), 2.93 (dt, J=13.0, 5.0 Hz, 1H) 2.73 (ddt, J=13.5, 13.5, 5.0 Hz, 1H), 2.48 (ddd, J=8.5, 7.5, 2.5 Hz 1H), 2.44 (s, 3H), 1.86 (ddt, J=13.5, 7.5, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.41, 159.23, 144.45, 136.82, 136.27, 136.13, 130.66 (2C), 128.83, 128.73 (2C), 128.52 (3C), 127.51 (2C), 127.22, 124.01, 116.78, 112.7, 104.63, 56.04, 55.01, 52.68, 51.34, 46.55, 41.23, 38.61, 21.67, 21.07; HRMS m/z (ESI, $M^+ + 1$) calcd for $C_{30}H_{36}NO_6S$ 538.2185. Found 538.2263.

4.2.8. 4-[1-Benzyl-4-dimethoxymethyl-2-oxo-3-(toluene-4-sulfonyl)piperidin-3-ylmethyl]benzoic acid methyl ester (3j). 75% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3026, 1714, 1220; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J=8.0 Hz, 2H), 7.55 (d, J=8.0 Hz, 2H), 7.37 (d, J=8.0 Hz, 2H), 7.32–7.27 (m, 5H), 7.17 (d, J=8.0 Hz, 2H), 5.31 (d, J=8.5 Hz, 1H), 4.65 (d, J=15.0 Hz, 1H), 4.42 (d, J=15.0 Hz, 1H), 3.89 (s, 3H), 3.86 (d, J=12.0 Hz, 1H), 3.66 (s, 3H), 3.54 (d, J=12.0 Hz, 1H), 3.33 (s, 3H), 3.24 (dt, J=5.5, 4.0 Hz, 1H), 2.89 (dt, J=12.5, 5.0 Hz, 1H), 2.72 (ddt, J=13.5, 13.0, 5.5 Hz, 1H), 2.44 (s, 3H), 2.32 (ddd, J=11.5, 8.0, 3.0 Hz, 1H), 1.86 (ddt, J=13.5, 8.0, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.04, 164.18, 144.73, 141.01, 136.05, 135.88, 131.74 (2C), 130.76 (2C), 129.22 (2C), 128.82 (2C), 128.63, 128.59 (2C), 127.65 (2C), 127.45, 104.77, 77.17, 56.17, 52.68, 52.03, 51.53, 46.70, 41.32, 38.55, 21.74, 21.11.; HRMS m/z (ESI, $M^+ + 1$) calcd for $C_{31}H_{35}NO_7S$ 566.2134. Found ($M^+ + 1$) 566.2145.

4.2.9. 1-Benzyl-4-dimethoxymethyl-3-(4-methylbenzyl)-3-(toluene-4-sulfonyl)piperidin-2-one (3d). 85% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3030, 1656, 1223; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J=8.0 Hz, 2H), 7.31–7.27 (m, 5H), 7.19 (d, J=8.0 Hz, 2H), 7.16 (d, J=8.0 Hz, 2H), 6.98 (d, J=8.0 Hz, 2H), 5.32 (d, J=7.5 Hz, 1H), 4.62 (d, J=14.5 Hz, 1H), 4.49 (d, J=14.5 Hz, 1H), 3.74 (d, J=12.5 Hz, 1H), 3.66 (s, 3H), 3.48 (d, J=12.5 Hz, 1H), 3.37 (s, 3H), 3.22 (dd, J=5.5, 1.5 Hz, 1H), 2.90 (dt, J=12.5, 4.5 Hz, 1H), 2.72 (ddt, J=13.5, 13.0, 5.5 Hz, 1H), 2.46 (ddd, J=13.0, 8.0, 3.0 Hz, 1H), 2.44 (s, 3H), 2.29 (s, 3H), 1.87 (ddt, J=14.0, 7.5, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.42, 144.44, 136.27, 136.24 (2C), 132.09, 131.52 (2C), 130.73 (2C), 128.75 (2C), 128.71 (2C), 128.48 (2C), 127.69 (2C), 127.27, 104.85, 77.48, 56.13, 52.93, 51.40, 46.65, 41.32, 38.21, 21.70, 21.05, 21.00; HRMS m/z (ESI, $M^+ + 1$) calcd for $C_{30}H_{35}NO_5S$ 522.2236. Found ($M^+ + 1$) 522.2261.

4.2.10. 1-Benzyl-3-(3,4-dimethoxybenzyl)-4-dimethoxymethyl-3-(toluene-4-sulfonyl)piperidin-2-one (3l). 85% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3015, 1640, 1203; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J=8.0 Hz, 2H), 7.33–7.24 (m, 5H), 7.21 (d, J=8.0 Hz, 2H), 6.90 (dd, J=8.0, 2.0 Hz, 1H), 6.86 (d, J=2.0 Hz, 1H), 6.69 (d, J=8.0 Hz, 1H), 5.32 (d, J=8.0 Hz, 1H), 4.77 (d, J=15.0 Hz, 1H), 4.33 (d, J=15.0 Hz, 1H), 3.84 (s, 3H), 3.73 (s, 3H), 3.72 (d, J=12.0 Hz, 1H), 3.66 (s, 3H), 3.47 (d, J=12.0 Hz, 1H), 3.37 (s, 3H), 3.23 (dd, J=11.0, 4.5 Hz, 1H), 2.93 (dt, J=12.5, 5.0 Hz, 1H), 2.72 (ddt, J=13.5, 13.0, 5.5 Hz, 1H), 2.49 (ddd, J=13.0, 7.5, 2.5 Hz, 1H), 2.44 (s, 3H), 1.87 (ddt, J=13.5, 7.5, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.61, 148.24, 147.73, 144.49, 136.30, 136.09, 130.70 (2C), 128.79 (2C), 128.60 (2C), 127.59, 127.38 (2C), 127.33, 124.17, 114.55, 110.57, 104.89, 77.52, 56.06, 55.68, 55.65, 53.01, 51.28, 46.67, 41.33, 38.19, 21.73, 21.12.; HRMS m/z (ESI, $M^+ + 1$–$C_2H_6O_2$) calcd for $C_{30}H_{35}NO_5S$ 506.2236. Found ($M^+ + 1$) 506.2259.

4.3. Procedure for hydrolysis of lactam 3 to 1,2,3,4-tetrahydroisoquinoline derivatives 4 and 5

To a solution of lactam **3** (400 mg, 0.8 mmol) in acetone (20 mL) was added 10% aqueous HCl (1 mL). The resulting mixture was refluxed for 12 h and then evaporated. The residue was dissolved with dichloromethane and the mixture was basified with 2 N aqueous sodium hydroxide in an ice bath. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried, and evaporated to give crude product. Chromatography on silica gel (hexane/ethyl acetate=4:1) afforded the pure products.

4.3.1. 2-Benzyl-7-chloro-3,4-dihydro-2*H*-isoquinolin-1-one (4b). 85% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3030, 1656; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, J=2.5 Hz, 1H), 7.38 (dd, J=8.0, 2.5 Hz, 1H), 7.36–7.27 (m, 5H), 7.11 (d, J=8.0 Hz, 1H), 4.79 (s, 2H), 3.48 (t, J=6.5 Hz, 2H), 2.90 (t, J=6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.39, 137.10, 136.27, 133.15, 131.62, 130.89, 128.69 (2C), 128.47, 128.35, 128.06 (2C), 127.57, 50.54, 45.20, 27.51; HRMS m/z (ESI, $M^+ + 1$) calcd for $C_{16}H_{14}NOCl$ 272.0764. Found 272.0758.

4.3.2. 2-Benzyl-7-methyl-3,4-dihydro-2*H*-isoquinolin-1-one (4a). 90% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3022, 1652; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.33–7.27 (m, 5H), 7.23 (dd, J=6.5, 1.0 Hz, 1H), 7.05 (d, J=6.5 Hz, 1H), 4.79 (s, 2H), 3.46 (t, J=6.5 Hz, 2H), 2.89 (t, J=6.5 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.81, 137.47, 136.76, 135.05, 132.43, 129.08, 128.81, 128.60 (2C), 128.01 (2C), 127.38, 126.80, 50.45, 45.51, 27.67, 21.06; HRMS m/z (EI, M^+) calcd for $C_{17}H_{17}NO$ 251.1310. Found 251.1316.

4.3.3. 2-Benzyl-7,8-dimethoxy-3,4-dihydro-2*H*-benzo[*g*]isoquinolin-1-one (5a). 95% Yield; white solid; mp 189–191 °C; IR ($CHCl_3$, cm^{-1}) 3030, 1653, 1235; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.43 (s, 1H), 7.36–7.28 (m, 5H), 7.22 (s, 1H), 7.06 (s, 1H), 4.85 (s, 2H), 4.01 (s, 3H), 4.01 (s, 3H) 3.53 (t, J=6.5 Hz, 2H), 3.06 (t, J=6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.98, 151.18, 149.49, 137.52, 132.85, 131.15, 128.62 (2C), 128.03 (2C), 127.87, 127.78, 127.39, 125.75, 123.50, 107.34,105.38, 55.92, 55.89, 50.57, 45.72, 28.44; HRMS m/z (EI, M^+) calcd for $C_{22}H_{21}NO_3$ 347.1521. Found 347.1516. Compound **5a** was recrystallized from ethyl acetate.

4.3.4. 2-Benzyl-8-methoxy-3,4-dihydro-2*H*-benzo[*g*]isoquinolin-1-one (5b). 88% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3030, 1629, 1494; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.68 (d, J=9.0 Hz, 1H), 7.52 (s, 1H), 7.36–7.18 (m, 7H), 4.58 (s, 2H), 3.93 (s, 3H), 3.53 (t, J=6.3 Hz,

2H), 3.06 (t, J=6.3 Hz, 2H): ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.00, 158.79, 138.63, 134.48, 131.67, 129.84(2C), 129.59, 129.23(3C), 128.85, 128.62, 126.05, 122.14, 114.93, 107.97, 56.54, 51.78, 47.01, 29.55; HRMS *m/z* (EI, M^+) calcd for $C_{21}H_{19}NO_2$ 317.1416. Found 317.1409.

4.3.5. 7-Benzyl-6,7-dihydro-5*H*-1-thia-7-aza-cyclopenta[*b*]naphthalen-8-one (5c). 90% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3012, 1635; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.7 (s, 1H), 7.59 (s, 1H), 7.58 (s, 1H), 7.34–7.25 (m, 6H), 4.84 (s, 2H), 3.52 (t, J=6.5 Hz, 2H), 3.05 (t, J=6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.71, 141.95, 138.42, 137.45, 133.78, 130.02, 128.63 (2C), 128.02 (2C), 127.42, 125.93, 123.45, 123.21, 121.26, 50.52, 45.67, 28.55; HRMS *m/z* (EI, M^+) calcd for $C_{18}H_{15}NOS$ 239.0874. Found 239.871.

4.4. Procedure for hydrolysis of lactam 3 to 1-benzyl-3-substituted-2-oxo-1,2,5,6-tetrahydropyridine-4-carbaldehyde 6

To a solution of lactam **3** (400 mg, 0.8 mmol) in acetone (20 mL) was added 10% aqueous HCl (1 mL). The resulting mixture was refluxed for 12 h and then evaporated. The residue was dissolved with dichloromethane, and the mixture was basified with 2 N aqueous sodium hydroxide in an ice bath. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried, and evaporated to give the crude product. Chromatography on silica gel (hexane/ethyl acetate=4:1) afforded the pure products.

4.4.1. 1,3-Dibenzyl-2-oxo-1,2,5,6-tetrahydropyridine-4-carbaldehyde (6a). 91% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3022, 1635, 1220; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.37 (s, 1H), 7.31–7.19 (m, 10H), 4.66 (s, 2H), 4.29 (s, 2H), 3.31 (t, J=7.0 Hz, 2H), 2.54 (t, J=7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.43, 164.53, 145.48, 139.08, 138.68, 136.65, 128.77 (2C), 128.70 (2C), 128.50 (2C), 127.89 (2C), 127.63, 126.56, 50.87, 43.96, 30.27, 20.86; HRMS *m/z* (EI, M^+) calcd for $C_{20}H_{19}NO_2$ 305.1416. Found 305.3708.

4.4.2. 1-Benzyl-3-(4-methylbenzyl)-2-oxo-1,2,5,6-tetrahydropyridine-4-carbaldehyde (6b). 85% Yield; mp 126–128 °C; white solid; IR ($CHCl_3$, cm^{-1}) 3022, 1656; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.38 (s, 1H), 7.31–7.10 (m, 9H), 4.65 (s, 2H), 4.23 (s, 2H), 3.30 (t, J=7.0 Hz, 2H), 2.52 (t, J=7.0 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.52, 164.56, 145.73, 138.89, 136.70, 136.13, 135.60, 129.45 (2C), 128.68 (2C), 128.38 (2C), 127.90 (2C), 127.61, 50.84, 43.95, 29.85, 20.99, 20.84; HRMS *m/z* (EI, M^+) calcd for $C_{21}H_{21}NO_2$ 319.1572. Found 319.1569.

4.4.3. 1-Benzyl-3-(2-bromobenzyl)-2-oxo-1,2,5,6-tetrahydropyridine-4-carbaldehyde (6c). 83% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3022, 1663; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.25 (s, 1H), 7.56 (dd, J=8.0, 1.0 Hz, 1H), 7.31–7.20 (m, 7H), 7.11–7.08 (m, 1H), 4.67 (s, 2H), 4.36 (s, 2H), 3.55 (t, J=7.0 Hz, 2H), 2.55 (t, J=7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.42, 164.42, 143.91, 140.04, 138.17, 136.66, 132.99, 130.30, 128.70 (2C), 128.23, 127.92 (2C), 127.67 (2C), 124.25, 50.83, 43.96, 31.06, 21.09; HRMS *m/z* (EI) calcd for $C_{20}H_{18}BrNO_2$ 383.0521. Found (M^+) 383.0518.

4.4.4. 1-Benzyl-3-(4-bromo-benzyl)-2-oxo-1,2,5,6-tetrahydropyridine-4-carbaldehyde (6d). 85% Yield; white solid; IR ($CHCl_3$, cm^{-1}) 3030, 1655, 1227; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.36 (s, 1H), 7.42 (d, J=8.0 Hz, 2H), 7.31–7.18 (m, 5H), 7.14 (d, J=8.0 Hz, 2H), 4.65 (s, 2H), 4.22 (s, 2H), 3.31 (t, J=7.0 Hz, 2H), 2.54 (t, J=7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.07, 164.32, 144.88, 139.26, 137.62, 136.53, 131.82 (2C), 130.32 (2C), 128.74 (2C), 127.87 (2C), 127.72, 120.52, 50.89, 43.93, 29.81, 20.91; LRMS *m/z* (EI, 30 eV): 383 (M^+, 1%), 354 (2%), 288 (8%), 91 (100%). Anal. Calcd for $C_{20}H_{18}BrNO_2$: C, 62.51; H, 4.72; N, 3.65. Found: C, 62.45; H, 4.61; N, 4.05. Compound **6d** was recrystallized from ethyl acetate as a colorless prism.

Single-crystal X-ray diagram.[14] Crystals of **6d** were grown by slow diffusion of *n*-hexane into a solution of **6d** in ethyl acetate to yield colorless prism. The compound crystallizes in the monoclinic crystal system, space group $P2_1/n$(#14), a=14.142(3) Å, b=9.276(3) Å, c=19.066(4) Å, β=92.99(2)°, V=179.2(9) Å^3, Z=4, D_{calc}=1.425 g/cm^3, absorption coefficient 22.8 cm^{-1}, F(000)=784, 2θ range (8.8–13.8°).

4.4.5. 1-Benzyl-3-(2-methoxybenzyl)-2-oxo-1,2,5,6-tetrahydropyridine-4-carbaldehyde (6e). 87% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3022, 1663; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.43 (s, 1H), 7.36–7.18 (m, 7H), 6.92 (dd, J=0.5, 0.5 Hz, 1H), 6.83 (d, J=8.0 Hz, 1H) 4.65 (s, 2H), 4.25 (s, 2H), 3.76 (s, 3H) 3.24 (t, J=7.0 Hz, 2H), 2.48 (t, J=7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.30, 164.73, 157.06, 144.56, 138.18, 136.77, 130.91, 128.56 (2C), 127.88, 127.75 (2C), 127.44, 126.44, 120.67, 110.23, 54.84, 50.72, 43.95, 25.21, 20.72; HRMS *m/z* (EI, M^+) calcd for $C_{21}H_{21}NO_3$ 335.1521. Found 335.1517.

4.4.6. 1-Benzyl-3-(4-methoxybenzyl)-2-oxo-1,2,5,6-tetrahydropyridine-4-carbaldehyde (6f). 87% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3032, 1673; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.39 (s, 1H), 7.30–7.16 (m, 7H), 6.84 (d, J=8.5 Hz, 2H), 4.65 (s, 2H), 4.21 (s, 2H), 3.79 (s, 3H), 3.30 (t, J=7.0 Hz, 2H), 2.52 (t, J=7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.49, 164.58, 158.28, 145.87, 138.75, 136.67, 130.59, 129.57 (2C), 128.70 (2C), 127.88 (2C), 127.63, 114.17 (2C), 55.27, 50.86, 43.98, 29.42, 20.85; HRMS *m/z* (EI, M^+) calcd for $C_{21}H_{21}NO_3$ 335.1521. Found (M^+) 335.1519.

4.4.7. 4-(1-Benzyl-4-formyl-2-oxo-1,2,5,6-tetrahydropyridin-3-ylmethyl)benzoic acid methyl ester (6g). 90% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3030, 1683, 1652, 1611; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.37 (s, 1H), 7.97 (dd, J=7.0, 2.0 Hz, 2H), 7.33–7.28 (m, 5H), 7.19 (dd, J=7.0, 2.0 Hz, 2H), 4.65 (s, 2H), 4.33 (s, 2H), 3.91 (s, 3H), 3.32 (t, J=7.0 Hz, 2H), 2.55 (t, J=7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.04, 166.85, 164.30, 144.52, 144.05, 139.58, 136.52, 130.09 (2C), 128.75 (2C), 128.56, 128.52 (2C), 127.90 (2C), 127.74, 52.09, 50.90, 43.92,

30.40, 20.96; HRMS *m/z* (EI, M^+) calcd for $C_{22}H_{21}NO_4$ 363.1471. Found 363.1465.

4.5. Procedure for preparation of 1,2,3,4-tetrahydro-isoquinolone derivatives 7

To solution of lactam **6** (200 mg, 0.66 mmol) in CH_2Cl_2 (20 mL) was added $TiCl_4$ (124 mg, 0.66 mmol). The resulting mixture were refluxed for 12 h and then evaporated. The residue was dilute with water (10 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Chromatography on silica gel (hexane/ethyl acetate=4:1) afforded the pure products.

4.5.1. 2-Benzyl-3,4-dihydro-2*H*-benzo[*g*]isoquinolin-1-one (7a). 87% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3020, 1662, 1220; ^1H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.96 (dd, J=8.5, 2.0 Hz, 1H), 7.84 (d, J=9.0 Hz, 1H), 7.56 (dd, J=9.0, 2.0 Hz, 1H), 7.50 (s, 1H), 7.38–7.28 (m, 6H), 4.86 (s, 2H), 3.58 (t, J=6.5 Hz, 2H), 3.11 (t, J=6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.34, 137.19, 135.77, 135.58, 130.93, 130.59, 129.47 (2C), 129.16, 128.70 (2C), 128.08 (2C), 127.85, 127.55, 124.20, 122.25, 50.70, 45.48, 28.58; HRMS *m/z* (EI, M^+) calcd for $C_{20}H_{17}NO$ 287.1310. Found 287.1315.

4.5.2. 2-Benzyl-7-methyl-3,4-dihydro-2*H*-benzo[*g*]isoquinolin-1-one (7b). 85% Yield; white solid; mp 123–125 °C; IR ($CHCl_3$, cm^{-1}) 3022, 1656; ^1H NMR (500 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.86 (d, J=8.5 Hz, 1H), 7.55 (s, 1H), 7.48 (s, 1H), 7.36–7.30 (m, 6H), 4.86 (s, 2H), 3.53 (t, J=6.5 Hz, 2H), 3.09 (t, J=6.5 Hz, 2H), 2.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.87, 137.93, 137.42, 135.12, 134.35, 130.41, 129.30, 129.15, 128.64 (2C), 128.27, 128.05 (2C), 127.43, 126.59, 126.01, 124.37, 50.63, 45.65, 28.63, 21.91; HRMS *m/z* (EI, M^+) calcd for $C_{21}H_{19}NO$ 301.1467. Found 301.1462.

4.5.3. 2-Benzyl-9-bromo-3,4-dihydro-2*H*-benzo[*g*]isoquinolin-1-one (7c). 81% Yield; white solid; mp 146–148 °C; IR ($CHCl_3$, cm^{-1}) 3022, 1227; ^1H NMR (500 MHz, $CDCl_3$) δ 9.09 (s, 1H), 7.76 (dd, J=7.7, 1.0 Hz, 1H), 7.73 (d, J=8.5 Hz, 1H), 7.59 (s, 1H), 7.29–7.37 (m, 6H), 4.87 (s, 2H), 3.56 (t, J=6.0 Hz, 2H), 3.12 (t, J=6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.20, 137.25, 135.97, 135.33, 131.09, 130.01, 128.90, 128.73, 128.69 (2C), 128.11 (2C), 127.53, 126.53, 126.94, 125.71, 124.30, 50.77, 45.46, 28.37; HRMS *m/z* (EI, M^+) calcd for $C_{20}H_{16}NOBr$ 365.0415. Found 365.0408.

4.5.4. 2-Benzyl-7-bromo-3,4-dihydro-2*H*-benzo[*g*]isoquinolin-1-one (7d). 80% Yield; white solid; IR ($CHCl_3$, cm^{-1}) 3030, 1220; ^1H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.96 (d, J=2.0 Hz, 1H), 7.84 (d, J=9.0 Hz, 1H), 7.56 (dd, J=9.0, 2.0 Hz, 1H), 7.50 (s, 1H), 7.38–7.28 (m, 5H), 4.86 (s, 2H), 3.58 (t, J=6.5 Hz, 2H), 3.11 (t, J=6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.34, 137.19, 135.77, 135.58, 130.93, 130.59, 129.47 (2C), 129.16, 128.70 (2C), 128.08 (2C), 127.85, 127.55, 124.20, 122.25, 50.70, 45.48, 28.58; LRMS *m/z* (EI, 30 eV): 365 (M^+, 20%), 274 (9%), 91 (100%). Anal. Calcd for $C_{20}H_{16}BrNO$: C, 65.59; H, 4.40; N, 3.82. Found: C, 65.45; H, 4.36; N, 4.16. Compound **7d** was recrystallized from ethyl acetate as a colorless prism.

Single-crystal X-ray diagram.[14] Crystals of **7d** were grown by slow diffusion of *n*-hexane into a solution of **7d** in ethyl acetate to yield colorless prism. The compound crystallizes in the monoclinic crystal system, space group $P2_1/c$(#14), a=14.350(3) Å, b=7.859(2) Å, c=14.201(4) Å, β=99.34(2)°, V=1580.4(7) Å^3, Z=4, D_{calc}=1.539 g/cm^3, absorption coefficient 26.12 cm^{-1}, F(000)=744, 2θ range (8.63–14.15°).

4.5.5. 2-Benzyl-9-methoxy-3,4-dihydro-2*H*-benzo[*g*]isoquinolin-1-one (7e). 83% Yield; yellow oil; IR ($CHCl_3$, cm^{-1}) 3020,1232; ^1H NMR (500 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.51 (s, 1H), 7.43 (t, J=8.0 Hz, 1H), 7.31–7.25 (m, 6H), 6.01 (dd, J=8.0, 2.5 Hz, 1H), 4.86 (s, 2H), 4.00 (s, 3H), 3.52 (t, J=6.5 Hz, 2H), 3.08 (t, J=6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.82, 156.74, 137.52, 136.40, 135.94, 134.92, 128.61 (2C), 128.25, 128.09 (2C), 127.40, 126.65, 124.62, 124.25, 119.09, 103.74, 55.49, 50.68, 45.62, 28.59; HRMS *m/z* (EI, M^+) calcd for $C_{21}H_{19}NO_2$ 317.1416. Found 317.1418.

4.5.6. 2-Benzyl-7-methoxy-3,4-dihydro-2*H*-benzo[*g*]isoquinolin-1-one (7f). 82% Yield; white solid; IR ($CHCl_3$, cm^{-1}) 3030, 16215, 1220; ^1H NMR (500 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.85 (d, J=9.0 Hz, 1H), 7.46 (s, 1H), 7.37–7.26 (m, 5H), 7.14 (dd, J=9.0, 2.5 Hz, 1H), 7.07 (d, J=2.5 Hz, 1H), 4.85 (s, 2H), 3.92 (s, 3H), 3.53 (t, J=6.5 Hz, 2H), 3.08 (t, J=6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.89, 159.30, 137.49, 136.40, 135.02, 130.93, 129.34, 128.63 (2C), 128.06 (2C), 127.65, 127.41, 125.32, 123.85, 118.86, 105.01, 55.32, 50.59, 45.62, 28.67; HRMS *m/z* (EI, M^+) calcd for $C_{21}H_{19}NO_2$ 317.1416. Found 317.1409. Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.23; H, 6.39; N, 4.81. Compound **7f** was recrystallized from ethyl acetate as a colorless prism.

Single-crystal X-ray diagram.[14] Crystals of **7f** were grown by slow diffusion of *n*-hexane into a solution of **7f** in ethyl acetate to yield colorless prism. The compound crystallizes in the triclinic crystal system, space group *Pbca*, a=12.0504(16) Å, b=8.0388(11) Å, c=33.425(4) Å, α=90.00°, β=90.00°, γ=90.00°, Z=8, D_{calc}=1.302 g/cm^3, absorption coefficient 0.83 cm^{-1}, F(000)=1344.

4.5.7. 2-Benzyl-1-oxo-1,2,3,4-tetrahydro-benzo[*g*]isoquinoline-7-carboxylic acid methyl ester (7g). 60% Yield; yellow solid; mp 147–149 °C; IR ($CHCl_3$, cm^{-1}) 3018, 1721, 1629; ^1H NMR (500 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.55 (s, 1H), 8.06 (dd, J=8.5, 1.5 Hz, 1H), 8.01 (d, J=8.5 Hz, 1H), 7.70 (s, 1H), 7.36–7.29 (m, 5H), 4.87 (s, 2H), 3.99 (s, 3H), 3.57 (t, J=6.5 Hz, 2H), 3.13 (t, J=6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.99, 164.21, 137.13, 135.17, 134.17, 133.88, 130.03, 129.58, 129.47, 129.21, 129.14, 128.70 (2C), 128.07 (2C), 127.56, 126.54, 125.26, 52.36, 50.75, 45.50, 28.53; HRMS *m/z* (EI, M^+) calcd for $C_{22}H_{19}NO_3$ 345.1359, found 345.1366. Anal. Calcd for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.54; N, 4.06. Found: C, 76.20; H, 5.41; N, 4.48. Compound **7g** was recrystallized from ethyl acetate as a colorless prism.

Single-crystal X-ray diagram.[14] Crystals of **7g** were grown by slow diffusion of *n*-hexane into a solution of **7g** in ethyl acetate to yield colorless prism. The compound crystallizes in the triclinic crystal system, space group $P1(\#1)$, $a=8.818(4)$ Å, $b=12.692(4)$ Å, $c=8.517(3)$ Å, $\alpha=107.82(2)°$, $\beta=107.86(3)°$, $\gamma=82.04(3)°$, $V=862.7(5)$ Å^3, $Z=2$, $D_{calc}=1.330$ g/cm^3, absorption coefficient 0.88 cm^{-1}, $F(000)=364$, 2θ range (9.2–17.6°).

4.6. Procedure for preparation of isoquinolone derivatives 8 and 9

To a solution of **5c** (110 mg, 0.30 mmol) in 1,4-dioxane (15 mL) was added DDQ (275 mg, 1.2 mmol). The resulting mixture was refluxed for 24 h and then evaporated. The residue was dilute with water (10 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Chromatography on silica gel (hexane/ethyl acetate=4:1) afforded the pure products.

4.6.1. 2-Benzyl-7-bromo-2*H*-benzo[*g*]isoquinolin-1-one (8). 70% Yield; white solid; mp 170–172 °C; IR ($CHCl_3$, cm^{-1}) 3029, 1625, 1220; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.08 (d, $J=2.0$ Hz, 1H), 7.91 (d, $J=9.0$ Hz, 1H), 7.85 (s, 1H), 7.56 (dd, $J=9.0$, 2.0 Hz, 1H), 7.35–7.29 (m, 5H), 7.03 (d, $J=7.5$ Hz, 1H), 6.58 (d, $J=7.5$ Hz, 1H), 5.23 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.56, 136.77, 136.05, 133.86, 131.13, 130.92, 130.11, 129.54, 129.49, 129.41, 128.84 (2C), 127.96 (2C), 127.89, 124.98, 123.13, 122.66, 106.38, 51.53; HRMS *m/z* (EI, M$^+$) calcd for $C_{20}H_{14}NOBr$ 363.0259. Found 363.0255. Compound **8** was recrystallized from ethyl acetate.

4.6.2. 7-Benzyl-7,8-dihydrothieno[3,2-*g*]isoquinoline-8-one (9). 65% White solid; yield; mp 150–152 °C; IR ($CHCl_3$, cm^{-1}) 3030, 1640; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.95 (s, 1H), 7.68 (d, $J=5.0$ Hz, 1H), 7.42 (d, $J=5.0$ Hz, 1H), 7.35–7.29 (m, 5H), 7.04 (d, $J=7.5$ Hz, 1H), 6.59 (d, $J=7.5$ Hz, 1H), 5.26 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.36, 142.91, 138.74, 137.01, 132.99, 131.31, 129.95, 128.80 (2C), 127.92 (2C), 127.78, 123.35, 123.31, 122.80, 120.00, 106.79, 51.57; HRMS *m/z* (EI, M$^+$) calcd for $C_{18}H_{13}NOS$ 291.0718. Found 291.0712. Compound **9** was recrystallized from ethyl acetate

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Supplementary data

Experimental procedures and photocopies of spectral data for (^{1}H NMR in $CDCl_3$) were supported.

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