Article

Synthesis of 8-Alkoxy-5H-isochromeno[3,4-c]isoquinolines and 1-Alkoxy-4-arylisoquinolin-3-ols through Rh(III)-Catalyzed C-H Functionalization of Benzimidates with 4-Diazoisochroman-3-imines and 4-Diazoisoquinolin-3-ones

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c00283 • Publication Date (Web): 23 Mar 2020

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Synthesis of 8-Alkoxy-5*H*-isochromeno[3,4-*c*]isoquinolines and 1-Alkoxy-4-arylisoquinolin-3-ols through Rh(III)-Catalyzed C-H Functionalization of Benzimidates with 4-Diazoisochroman-3-imines and 4-Diazoisoquinolin-3-ones

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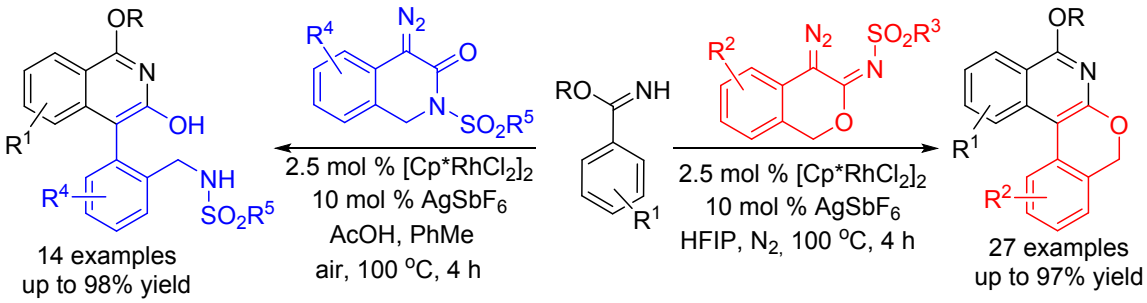
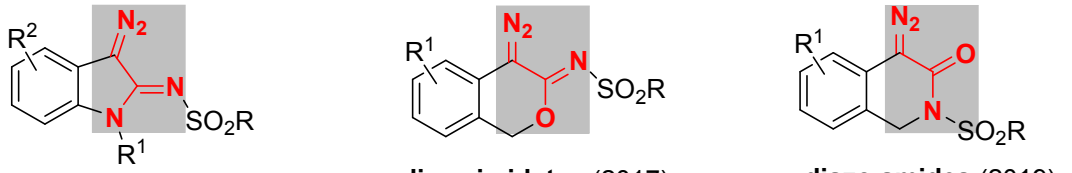


ABSTRACT: Rh(III)-catalyzed C-H activation/annulation of benzimidates with 4-diazoisochroman-3-imines furnished 8-alkoxy-5*H*-isochromeno[3,4-*c*]isoquinolines in moderate to excellent yields with a broad range of substrate scope. The reaction was carried out under mild reaction conditions and could be scaled up with practical usage. Similar reaction between benzimidates and 4-diazoisoquinolin-3-ones provided 1-alkoxy-4-arylisoquinolin-3-ols in excellent yields. Moreover, the synthesized products could be conveniently transformed to the corresponding heterocycles with a 1,8-naphthyridinone or isochromenopyridinone core, which are privileged structures in medicinal chemistry.

INTRODUCTION

Diazo compounds are valuable reagents in modern organic synthesis because they can be conveniently prepared and also be easily converted into more complicated compounds.[1] They are also versatile tools in chemical biology[2] and material chemistry.[3] By utilizing the copper(I)-catalyzed

reaction of 2-ethynylanilines with sulfonyl azides or the Huisgen-type cycloaddition of indoles with sulfonyl azides, we developed practical methods for thepreparation of 3-diazoindolin-2-imines in a single step in 2014 (Figure 1).[4] This class of cyclic α-diazo imidamides have been widely investigated by us and other groups and a variety of indole-containing heterocycles were thus conveniently synthesized.[4,5] Encouraged by this success, we further prepared 4-diazoisochroman-3-imines by the copper(I)-catalyzed reaction of (2-ethynylphenyl) methanols with sulfonyl azides in 2017.[6] 4-Diazoisochroman-3-imines contain a cyclic α-diazo imidate substructure and could be used as metal carbene precursors for cyclopropanation, transannulation[7] and C-H functionalization of *N*-methoxybenzamides[8] and *N*-alkylbenzamidines.[9] More significantly, we recently found that 4-diazoisochroman-3-imines could be converted to cyclic α-diazo amides via Dimorth rearrangement.[10] Thus, 4-diazoisoquinolin-3-ones appeared as more stable diazo reagents. In order to know the reactivity of 4-diazo- isochroman-3-imines and 4-diazoisoquinolin-3-ones and their potential applications in the synthesis of isochromans and isoquinolines which widely exist in the structures of nature products,[11] synthetic drugs,[12] and organic materials,[13] we studied the Rh(III)-catalyzed C-H activation/annulation reaction of these two class of diazo compounds with benzimidates.



α-diazo imidamides (2014)
3-diazoindolin-2-imines

α-diazo imidates (2017)
4-diazoisochroman-3-imines

α-diazo amides (2019)
4-diazoisoquinolin-3-ones

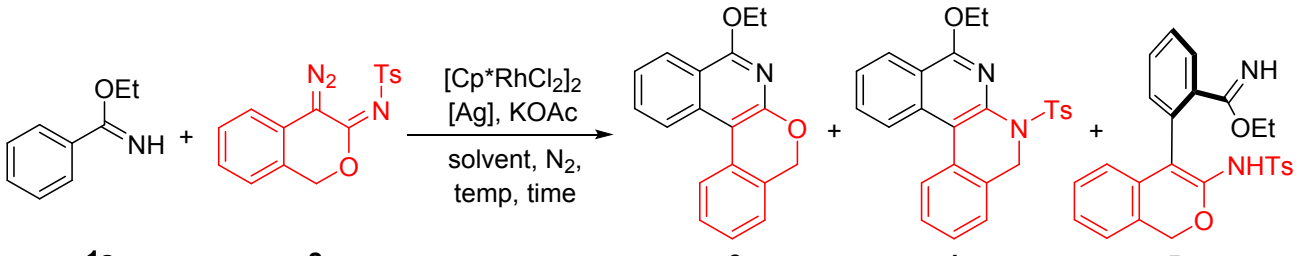
Figure 1. New Classes of Diazo Compounds Developed in Our Group

RESULTS AND DISCUSSION

Primarily, the reaction of ethyl benzimidate (**1a**) and diazo compound **2a** was selected for screening

the reaction conditions (Table 1). After the mixture of **1a** (0.12 mmol), **2a** (0.1 mmol), $[Cp^*RhCl_2]_2$ (0.0025 mmol), $AgSbF_6$ (0.01 mmol) and KOAc (0.02 mmol) in 1 mL of dichloroethane (DCE) reacted under air atmosphere at 100 °C for 12 h, **3a**, **4a**[14] and **5a** were isolated by column chromatograph in yields of 21%, 7% and 55%, respectively (Table 1, entry 1). Decreasing the reaction temperature and extending the reaction time reduced the yields of these products (Table 1, entry 2). The yield of **3a** was significantly improved by changing the reaction atmosphere to nitrogen. In this way, **3a** and **5a** were respectively isolated in 74% and 16% yields, while **4a** could only be detected by TLC (Table 1, entry 3). Then, several solvents, such as toluene, 1,4-dioxane, 2,2,2-trifluoroethanol (TFE), and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), were screened and HFIP gave the best yield of **3a** (Table 1, entries 4-7). The optimal reaction time and temperature were respectively determined to be 4 h and 100 °C (Table 1, entries 7-11). The reaction did not occur without the rhodium catalyst (Table 1, entry 12). Silver salt was indicated to be essential to complete the reaction with excellent selectivity (Table 1, entry 13). Higher yield of **3a** was obtained when the reaction was performed without base (Table 1, entry 14). When other silver salts were screened, no better results were observed (Table 1, entries 15-17). Considering the simplicity, entry 14 in Table 1 was selected as the optimal reaction conditions for the formation of **3a**. Many efforts have been paid to obtain **4a** in satisfactory yield were failed.

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3a** **4a** **5a**

entry	[Ag]	solvent	temp (°C)	time (h)	yield (%)[b] **3a**/**4a**/**5a**
1[c]	$AgSbF_6$	DCE	100	12	21/7/55

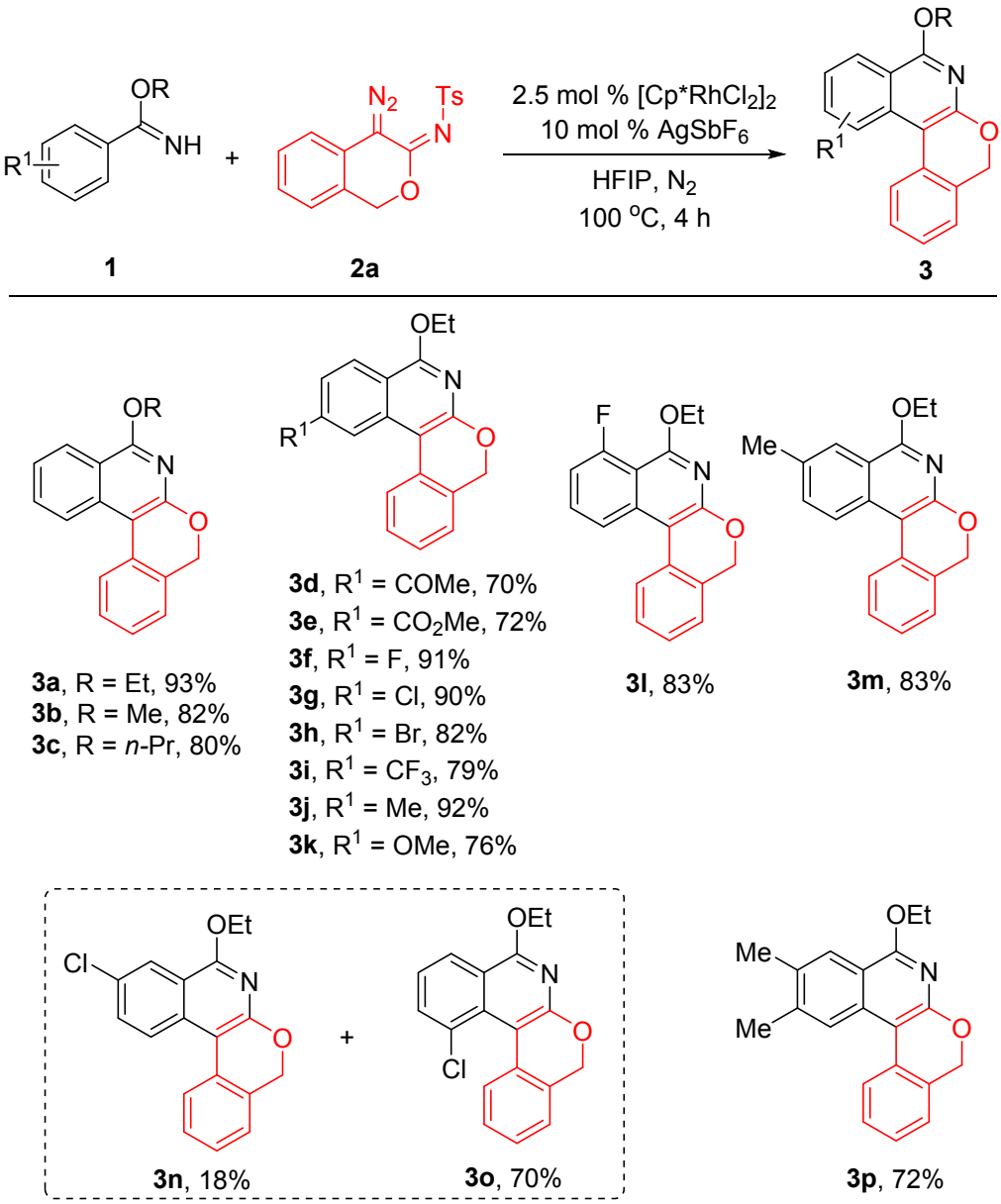
2[c]	$AgSbF_6$	DCE	60	16	7/2/48
3	$AgSbF_6$	DCE	100	12	74/trace/16
4	$AgSbF_6$	PhMe	100	12	46/trace/26
5	$AgSbF_6$	1,4-dioxane	100	12	68/0/20
6	$AgSbF_6$	TFE	100	12	80/0/12
7	$AgSbF_6$	HFIP	100	12	89/0/0
8	$AgSbF_6$	HFIP	100	4	94/0/0
9	$AgSbF_6$	HFIP	100	2	87/0/0
10	$AgSbF_6$	HFIP	80	18	85/0/trace
11	$AgSbF_6$	HFIP	120	4	90/0/0
12[d]	$AgSbF_6$	HFIP	100	4	NR
13	-	HFIP	100	4	79/trace/12
14[e]	$AgSbF_6$	HFIP	100	4	93/0/0
15[e]	AgOAc	HFIP	100	4	83/0/0
16[e]	$AgBF_4$	HFIP	100	4	84/0/0
17[e]	AgOTf	HFIP	100	4	80/0/0

[a] Reaction conditions: **1a** (0.12 mmol), **2a** (0.1 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), [Ag] (10 mol %), KOAc (20 mol %), solvent (1 mL), N_2. [b] Isolated yield. [c] Under air atmosphere. [d] Without $[Cp^*RhCl_2]_2$. [e] Without KOAc.

Subsequently, the scope of benzimidates **1** was studied (Scheme 1). Methyl benzimidate and propyl benzimidate provided **3b** and **3c** in 82% and 80%, respectively. The 4- position of benzimidate could either be electron-withdrawing group ($COCH_3$, CO_2CH_3, F, Cl, Br, CF_3) for **3d-i** and electron-donating group (CH_3, OCH_3) for **3j** and **3k**. Excellent yields were observed for those with mild electron-

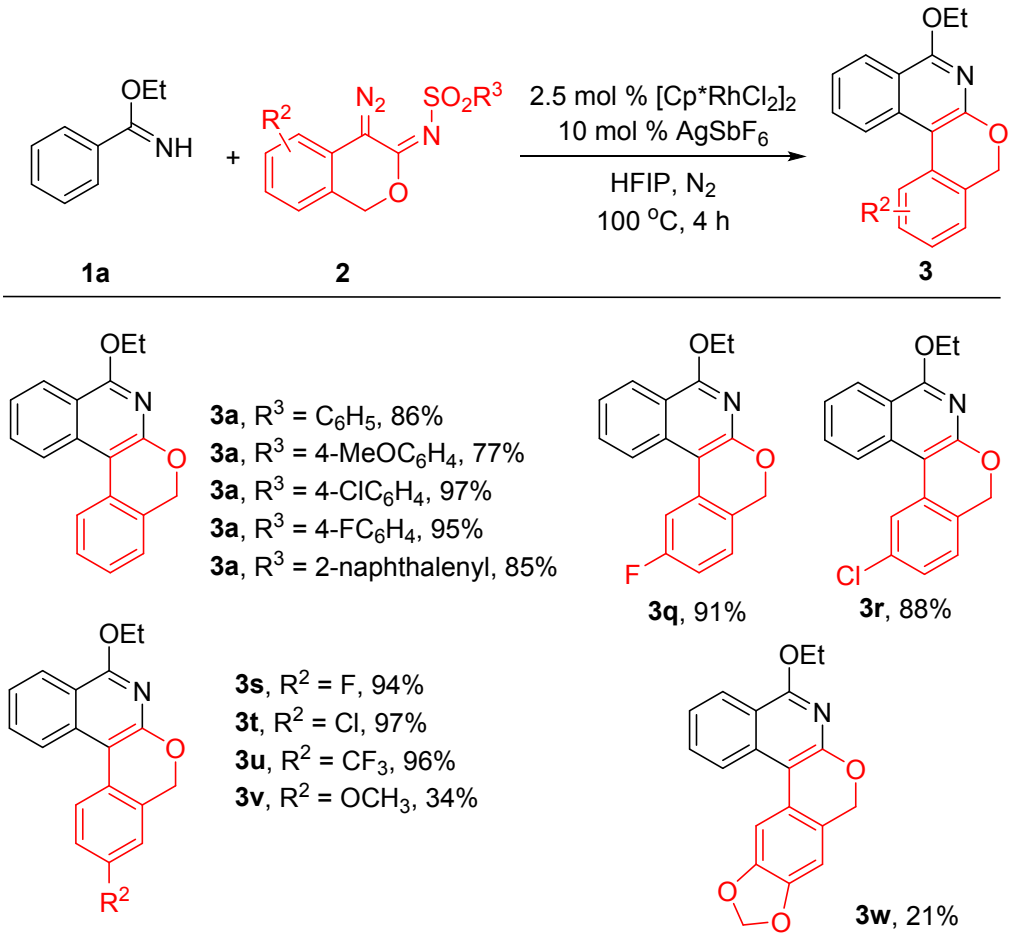
withdrawing (F, Cl) and mild electron-donating groups (CH_3). Both ethyl 2-fluorobenzimidate and ethyl 3-methylbenzimidate provided products **3l** and **3m** in 83% yield. When ethyl 3-chlorobenzimidate was used, isomers **3n** and **3o**[14] were separated by column chromatograph in 18% and 70% yields, respectively. The selectivity of more hindered **3o** could be contributed to the stronger acidity of 2-proton of 3-chlorobenzimidate, which is favored for the C−H bond activation. Ethyl 3,4-dimethylbenzimidate regioselectively gave **3p** in 72% yield.

Scheme 1. Scope of Benzimidates 1



The sulfonyl in **2** could be benzenesulfonyl, *p*-methoxybenzenesulfonyl, *p*-chlorobenzenesulfonyl, *p*-fluorobenzenesulfonyl and 2-naphthalenesulfonyl as well (Scheme 2). The highest yield (97%) of **3a** was obtained in the case where the sulfonyl is *p*-chlorobenzenesulfonyl. The 6-F-, 6-Cl-, 7-F-, 7-Cl-, and 7-CF_3-substituted 4-diazochroman-3-imines gave the corresponding products **3q-u** in excellent yields (88-97%), whereas 7-methoxy- and 6,7-methylenedioxy-substituted 4-diazochroman-3-imines provided **3v** (34%) and **3w** (21%) in much lower yields.

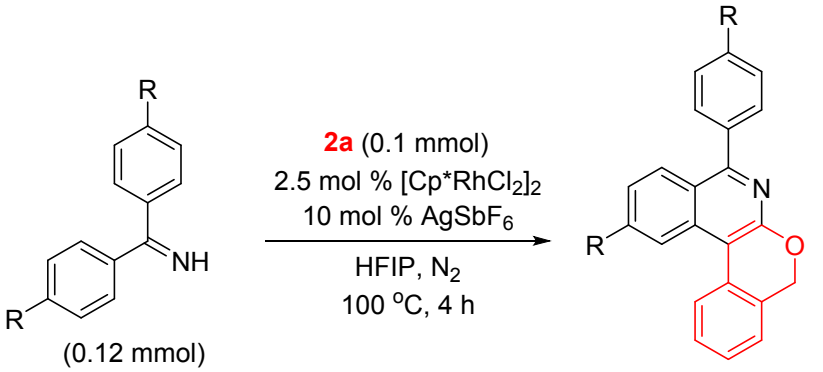
Scheme 2. Scope of Diazo Compounds 2



Imine-directed Rh(III)-catalyzed ortho C-H functionalization of diarylmethanimines was also comparatively investigated (Scheme 3). Under the same conditions for the preparation of **3** (Table 1,

entry 14), diphenylmethanimine (**6a**) reacted with **2a** to give 8-phenyl-5*H*-isochromeno[3,4-*c*]isoquinoline **7a** in 80% yield. In a similar way, **7b**,[14] **7c** and **7d** were obtained in 58-70% yields.

Scheme 3. Reactions of Diarylmethanimines



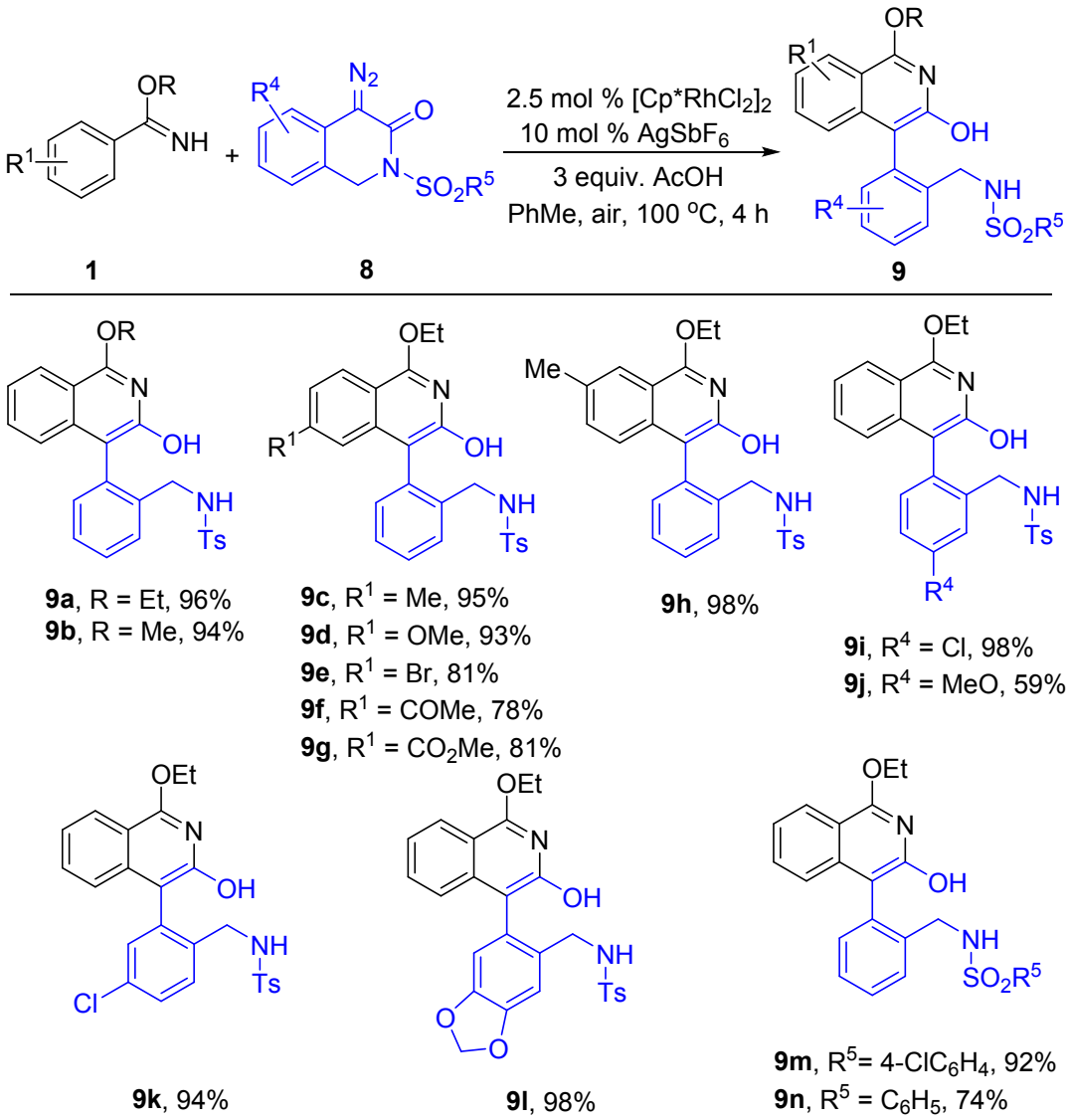
6a, R = H
6b, R = F
6c, R = Cl
6d, R = OCH_3

7a, R = H, 80%
7b, R = F, 59%
7c, R = Cl, 58%
7d, R = OCH_3, 70%

Delighted by these results, we then extended our method to the reaction of 4-diazoisoquinolinones **8**. By using **1a** and **8a** as the reaction components, **9a** was prepared in 75% yield.[14] Because of the structural unique and importance in medicinal chemistry,[15] we further optimized the reaction conditions in detail (Table S1, see Supporting Information). Optimal conditions were observed in the case where the reaction was performed at 100 °C in toluene using $[Cp^*RhCl_2]_2/AgSbF_6$/AcOH as catalyst system under air atmosphere (Table S1, entry 16). Under these conditions, we tested the scope of **1** (Scheme 4). Methyl benzimidate worked for the reaction and provided **9b** in 94% yield. The substituent on the 4-position of ethyl benzimidate could be methyl (**9c**, 95%), methoxy (**9d**, 93%), bromo (**9e**, 81%), acetyl (**9f**, 78%) and ester (**9g**, 81%). Ethyl 3-methylbenzimidate afforded **9h** in 98% yield. The substituent on the 7-posision of diazo component could be electron-withdrawing (Cl, **9i**,

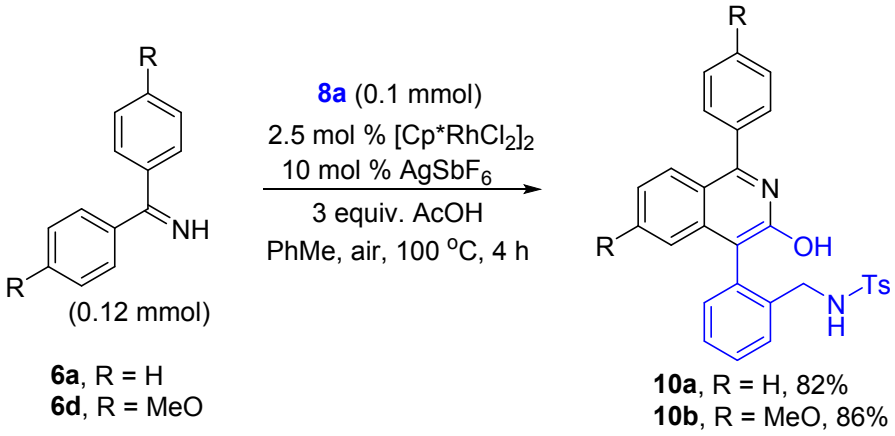
98%) or electron-donating (OMe, **9j**, 59%). Excellent yields were also observed for **9k** (94%) and **9l** (98%). Finally, **9m** (92%) and **9n** (74%) were prepared by changing the sulfonyl group.

Scheme 4. Scope of Benzimidates 1



The rhodium-catalyzed reaction of diphenylmethanimine **6a** with **8a** was also tested. In this case, **10a** was isolated in 82% yield (Scheme 5). Similar result was observed for the formation of **10b**.

Scheme 5. Reactions of Diarylmethane Imines



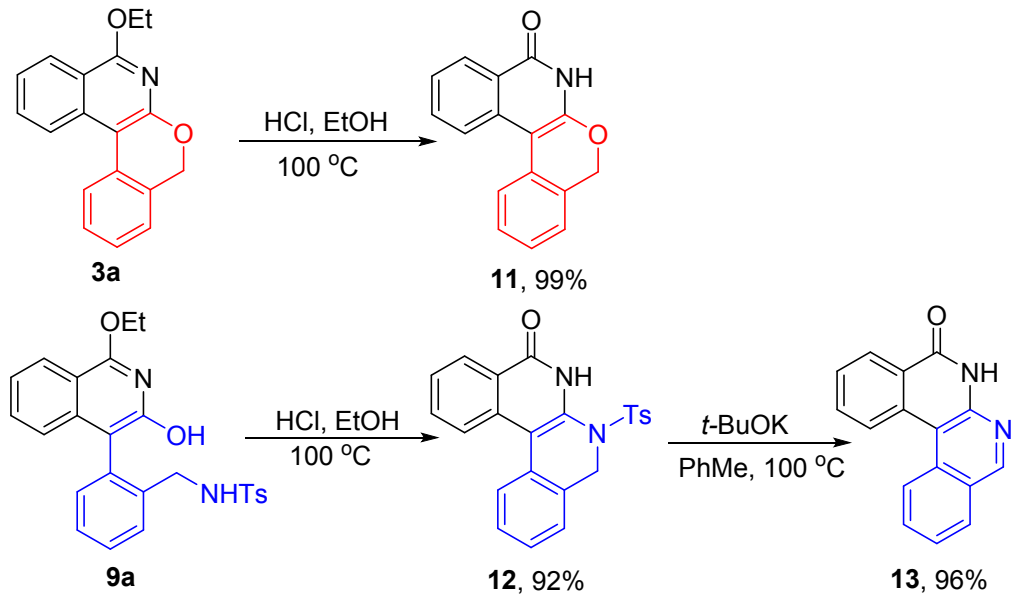
6a, R = H
6d, R = MeO

10a, R = H, 82%
10b, R = MeO, 86%

Our methods are of practical usage. In the presence of $[Cp^*RhCl_2]_2$ and $AgSbF_6$, 0.482 g of **3a** was obtained in 87% isolated yield when 2.4 mmol of **1a** and 2 mmol of **2a** were used. In this case, 0.311 g of $TsNH_2$ was simultaneously obtained in 91% yield after column chromatograph. Similarly, 0.399 g of **9a** was prepared in 89% yield when 1.2 mmol of **1a** and 1 mmol of **8a** were used.

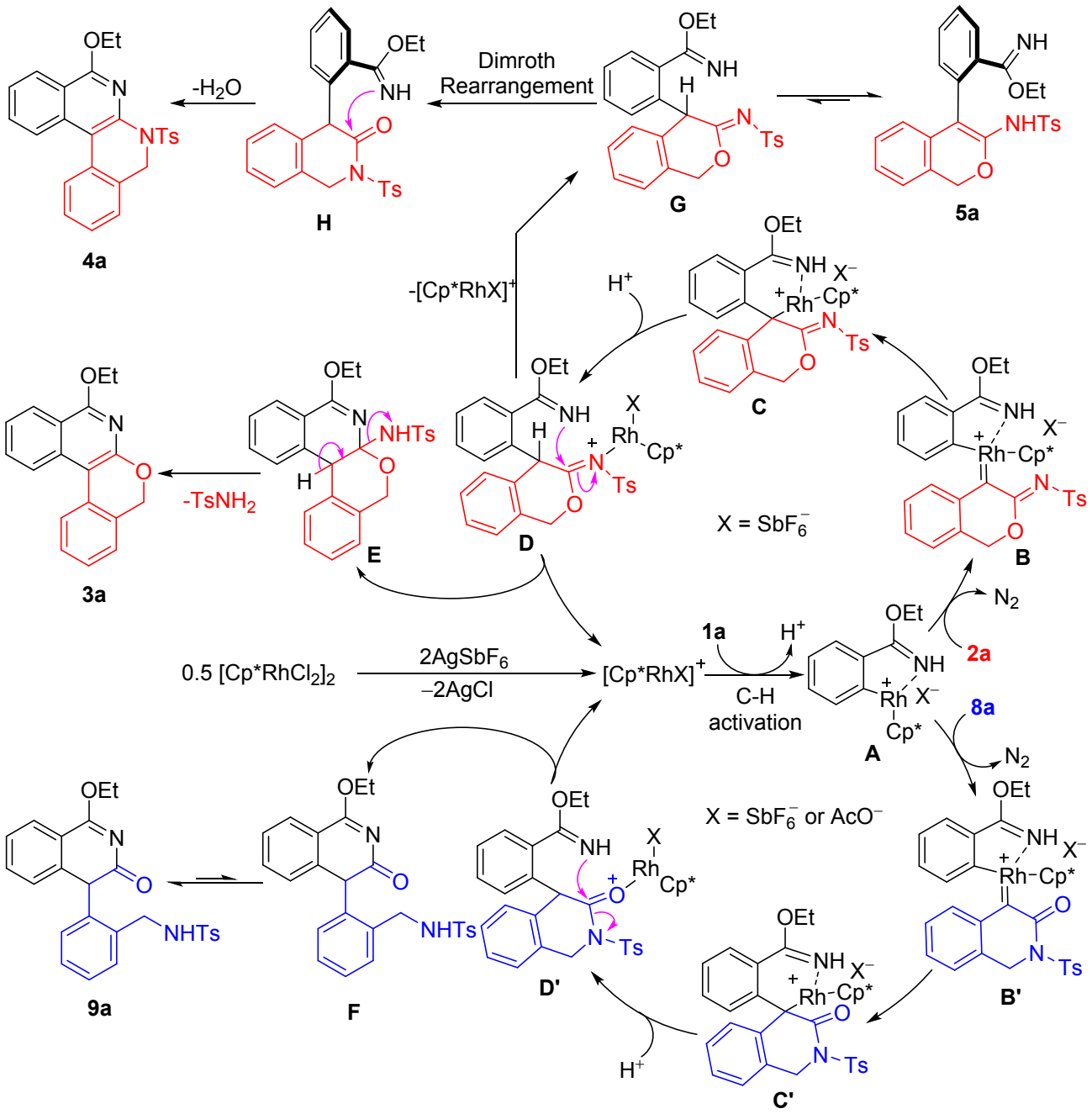
The further transformations of our products were also investigated. We demonstrated that the imidate substructure in **3** could be converted to amide through an acid-catalyzed hydrolysis.[16] As shown in Scheme 6, treatment of **3a** and **9a** with conc. HCl in methanol gave isochromenopyridinone **11** and dibenzo[1,8]naphthyridinone **12** in excellent yields, respectively. Further treatment of **12** with a strong base (e.g., potassium *tert*-butoxide)[17] at 100 °C furnished dibenzo[1,8]naphthyridinone **13** in almost quantitative yield.[14] In consideration of 1,8-naphthyridinones and isochromenopyridinones have been reported to possess strong pharmaceutical activities against cancer and inflammatory diseases,[18] our method should be valuable in medicinal chemistry.

Scheme 6. Further Transformation of 3a and 9a



Based on above results and literature reports,[5b,19] a possible mechanism is proposed for the formation of compounds **3a, 4a, 5a** and **9a** as shown in Scheme 7. Initially, **1a** coordinates with rhodium and C-H activation occurs to form intermediate **A**. The electron-deficient rhodium center reacts with **2a** to form Rh complex **B** along with the exclusion of nitrogen. A sequence of aryl migration/ligand exchange/protonation generates intermediate **D**. Subsequently, **D** undergoes nucleophilic addition to form **E**. Finally, aromatization furnishes **3a** by elimination of $TsNH_2$. The reaction of **8a** processes through a similar pathway to generate **D'**, which undergoes nucleophilic addition-elimination to form **F**. Tautomerism of **F** leads to a more stable product **9a**. The by-products **4a** and **5a** may be formed from intermediate **D** in the catalytic cycle. Thus, the release of the Rh (III) species from complex **D** generates intermediate **G**, which tautomerizes to more stable **5a**. On the other hand, **G** undergoes a Dimroth rearrangement and intramolecular condensation sequence to give **4a**.

Scheme 7. Possible Mechanism for the Formation of 3a, 4a, 5a and 9a



CONCLUSION

In conclusion, we have developed a facile and efficient protocol to construct 8-alkoxy-5*H*-isochromeno[3,4-*c*]isoquinolines through a Rh(III)-catalyzed reaction of benzimidates and 4-diazoisochroman-3-imines in moderate to excellent yields. Similar reaction between benzimidates and

4-diazoisoquinolin-3-ones furnished 1-alkoxy-4-arylisoquinolin-3-ols. When diarylmethanimines were used instead of benzimidates in these two transformations, 8-aryl-5*H*-isochromeno[3,4-*c*]isoquinoline and 1-aryl-4-arylisoquinolin-3-ols were prepared in excellent yields, accordingly. Furthermore, the synthesized isochromeno[3,4-*c*]isoquinolines and 4-arylisoquinolin-3-ols could be conveniently converted into the corresponding heterocycles with a 1,8-naphthyridinone or isochromenopyridinone core, which are privileged structures in medicinal chemistry.

EXPERIMENTAL SECTION

General Information. NMR spectra were obtained at ^{1}H 400 MHz and ^{13}C 100 MHz. ^{1}H NMR chemical shifts were quoted in parts per million (ppm) referenced to 0.0 ppm of TMS or the center line of a quintet at 2.50 ppm of DMSO-d_6. ^{13}C{^{1}H} NMR chemical shifts were reported in ppm referenced to the center line of a triplet at 77.00 ppm of $CDCl_3$ or the center line of a heptet at 39.52 ppm of DMSO-d_6. Some abbreviations such as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet) are used to describe peak patterns. *J* values were reported in Hz. HRMS data were recorded on ESI or EI mass spectrometer. Flash column chromatography was performed employing 300-400 mesh silica gel. Melting points were measured with a micro melting point apparatus without correction. Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and used as received.

Substrates **1** and **6** were prepared according to literature reports.[20,21] Diazo compounds **2** and **8** were synthesized by our previous methods.[6, 8]

Synthetic Procedures for Compounds 3 and 7. To an oven-dried Schlenk tube equipped with a magnetic stirring bar was added sequentially **1a** (0.12 mmol), **2a** (0.1 mmol), $[Cp^*RhCl_2]_2$ (0.0025 mmol), and $AgSbF_6$ (0.01mmol). After vacuuming and backfilling with N_2 three times, HFIP (1 mL)

was injected by syringe. The reaction mixture was stirred at 100 °C (oil bath) for 4 h. After cooling to room temperature, the resultant mixture was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 30:1, v/v) to give the products.

Synthetic Procedures for Compounds 9 and 10: To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added sequentially **1a** (0.12 mmol), **8a** (0.1 mmol), AcOH (0.3 mmol) and toluene (1 mL). The reaction mixture was stirred at 100 °C (oil bath) for 4 h. After cooling to room temperature, the resultant mixture was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1, v/v) to give the products.

Preparation of Compound 3a in 2 mmol Scale. To an oven-dried Schlenk tube equipped with a magnetic stirring bar was added sequentially **1a** (2.4 mmol), **2a** (2 mmol), $[Cp^*RhCl_2]_2$ (0.05 mmol), and $AgSbF_6$ (0.2 mmol). After vacuuming and backfilling with N_2 three times, HFIP (22 mL) was injected by syringe. The reaction mixture was stirred at 100 °C (oil bath) for 4 h. After cooling to room temperature, the resultant mixture was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 30:1, v/v) to give 0.482 g of pure **3a** (87% yield) and 0.311 g of $TsNH_2$ as byproduct.

Preparation of Compound 9a in 1 mmol Scale. To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added sequentially **1a** (1.2 mmol), **8a** (1 mmol), AcOH (3 mmol) and toluene (10 mL). The reaction mixture was stirred at 100 °C (oil bath) for 4 h. After cooling to room temperature, the resultant mixture was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1, v/v) to give0.399

g of pure **9a** (89% yield).

Synthetic Procedure for Compound 11. To a 25ml round bottom flask equipped with a magnetic stirring bar was added **3a** (0.1 mmol, 27.7 mg) and EtOH (3 mL). Hydrochloric acid (1 mL, 35%) was slowly added to the solution. Then, the reaction solution was stirred at 100 °C (oil bath) for 12 hours. After cooling down to room temperature, the mixture was washed with saturated aqueous $NaHCO_3$ solution and extracted by DCM (3×15 mL). The organic phase was combined and dried over sodium sulphate. The solvent was removed under reduced pressure and the residue was purified by recrystallized from dichloromethane/*n*-hexane = 4:1 (v/v) to give pure **11**.

Synthetic Procedure for Compound 12. To a 25 mL round bottom flask equipped with a magnetic stirring bar was added **9a** (0.1 mmol, 44.8 mg) and EtOH (3 mL). Hydrochloric acid (1 mL, 35%) was slowly added to the solution. Then, the solution was stirred at 100 °C (oil bath) for 12 hours. After cooling down to room temperature, the mixture was washed with saturated aqueous sodium bicarbonate and extracted by DCM (3×15 mL). The organic phase was combined and dried over sodium sulphate. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1, v/v) to give pure **12**.

Synthetic Procedure for Compound 13. To a 25 mL round bottom flask equipped with a magnetic stirring bar was added **12** (0.1 mmol, 40.2 mg), *t*-BuOK (4 equiv) and toluene (1 mL). The mixture was stirred at 100 °C (oil bath) for 1 hour. After cooling down to room temperature, the mixture was filtered through a pad of silica gel and washed with DCM. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate/methanol = 6:1:0.7, v/v/v) to give pure **13**.

8-Ethoxy-5H-isochromeno[3,4-c]isoquinoline (**3a**). White powder; petroleum ether /EtOAc (30/1)

as eluent; Yield: 25.8 mg, 93%; M.p. 99 – 100 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 8.4 Hz, 1H), 8.32 – 8.30 (m, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.72 – 7.68 (m, 1H), 7.45 – 7.40 (m, 2H), 7.3 – 7.29 (m, 2H), 5.19 (s, 2H), 4.61 (q, *J* = 7.1 Hz, 2H), 1.51 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.8, 157.4, 136.2, 131.3, 131.2, 130.6, 128.2, 126.3, 125.2, 125.1, 124.7, 124.0, 123.4, 117.6, 102.4, 69.7, 62.8, 14.5. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{18}H_{15}NO_2$ 277.1103; Found 277.1101. IR (film): 3069, 2978, 1735, 1695, 1619, 1588, 1571, 1509, 1424, 1379, 1346, 1263, 1163, 1060, 942, 823, 794 cm^{-1}.

8-Methoxy-5H-isochromeno[3,4-c]isoquinoline (**3b**). White powder; petroleum ether /EtOAc (30/1) as eluent; Yield: 21.6 mg, 82%; M.p. 160 – 161 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.8 Hz, 1H), 8.29 – 8.26 (m, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.71 – 7.67 (m, 1H), 7.44 – 7.39 (m, 2H), 7.30 – 7.28 (m, 2H), 5.19 (s, 2H), 4.16 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.1, 157.4, 136.2, 131.35, 131.26, 130.5,128.2, 126.3, 125.13, 125.09, 124.8, 124.1, 123.4, 117.5, 102.7, 69.7, 54.3. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{13}NO_2$ 263.0946; Found 263.0948. IR (film): 3075, 2994, 1620, 1588, 1572, 1509, 1458, 1376, 1331, 1265, 1204, 1098, 989, 773 cm^{-1}.

8-Propoxy-5H-isochromeno[3,4-c]isoquinoline (**3c**). Colorless liquid; petroleum ether /EtOAc (30/1) as eluent; Yield: 23.3 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.4 Hz, 1H), 8.31 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.71 – 7.66 (m, 1H), 7.44 – 7.38 (m, 1H), 7.29 – 7.27 (m, 2H), 5.18 (s, 2H), 4.50 (t, *J* = 6.6 Hz, 2H), 1.92 (h, *J* = 7.2 Hz, 2H), 1.10 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.9, 157.4, 136.2, 131.3, 131.2, 130.6, 128.2, 126.2, 125.14, 125.11, 124.7, 124.0, 123.4, 117.6, 102.4, 69.7, 68.5, 22.3, 10.6. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{19}H_{17}NO_2$ 291.1259; Found 291.1260. IR (film): 3070, 2966, 1619, 1588, 1571, 1508, 1425, 1360, 1329, 1290, 1264, 1203, 1163, 1097, 1061, 1026, 968, 945, 774 cm^{-1}.

1-(8-Ethoxy-5H-isochromeno[3,4-c]isoquinolin-11-yl)ethan-1-one (**3d**). Yellow powder; petroleum ether /EtOAc (30/1) as eluent; Yield: 22.3 mg, 70%; M.p. 146 – 147 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (d, *J* = 1.6 Hz, 1H), 8.36 (d, *J* = 8.4 Hz, 1H), 7.92 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.49 – 7.45 (m, 1H), 7.36 – 7.31 (m, 2H), 5.21 (s, 2H), 4.62 (q, *J* = 7.2 Hz, 2H), 2.73 (s, 3H), 1.53 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.2, 160.6, 158.0, 138.7, 135.8, 131.3, 130.1, 128.6, 126.7, 125.8, 125.4, 124.8, 124.6, 122.2, 119.4, 103.4, 69.8, 63.1, 27.0, 14.5. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{20}H_{17}NO_3$ 319.1208; Found 319.1209. IR (film): 2980, 1686, 1620, 1575, 1558, 1501, 1426, 1380, 1346, 1249, 1055, 950, 827, 789cm^{-1}.

Methyl 8-ethoxy-5H-isochromeno[3,4-c]isoquinoline-11-carboxylate (**3e**). Yellow powder; petroleum ether /EtOAc (30/1) as eluent; Yield: 24.1 mg, 72%; M.p. 199 – 200 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (d, *J* = 1.6 Hz, 1H), 8.34 (d, *J* = 8.8 Hz, 1H), 7.99 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.49 – 7.45 (m, 1H), 7.35 – 7.29 (m, 2H), 5.21 (s, 2H), 4.62 (q, *J* = 7.2 Hz, 2H), 4.00 (s, 3H), 1.52 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.9, 160.6, 157.9, 135.6, 132.3, 131.2, 130.1, 128.6, 126.6, 125.9, 125.5, 125.2, 124.9, 123.6, 119.5, 103.2, 69.8, 63.1, 52.5, 14.5. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{18}NO_4$ 336.1230; Found 336.1231. IR (film): 3062, 2985, 1726, 1624, 1576, 1558, 1504, 1425, 1379, 1347, 1329, 1252, 1188, 1110, 1059, 766cm^{-1}.

8-Ethoxy-11-fluoro-5H-isochromeno[3,4-c]isoquinoline (**3f**). White powder; petroleum ether /EtOAc (30/1) as eluent; Yield: 26.9 mg, 91%; M.p. 143 – 144 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 9.2, 6.4 Hz, 1H), 8.00 (dd, *J* = 11.2, 2.4 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.44 – 7.40 (m, 1H), 7.32 – 7.27 (m, 2H), 7.14 (ddd, *J* = 8.8, 7.6, 2.4 Hz, 1H), 5.18 (s, 2H), 4.59 (q, *J* = 7.1 Hz, 2H), 1.50 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.8 (d, *J* = 249.0 Hz), 160.7, 158.4, 137.8 (d, *J* = 10.6 Hz), 131.1, 130.2, 128.4, 128.2 (d, *J* = 10.3 Hz), 126.5, 125.2, 124.1, 114.5, 113.6

(d, J = 24.7 Hz), 107.8 (d, J = 23.2 Hz), 102.3 (d, J = 4.3 Hz), 69.7, 62.9, 14.5. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{18}H_{15}FNO_2$ 296.1081; Found 296.1081. IR (film): 3062, 2985, 1630, 1592, 1575, 1513, 1425, 1408, 1348, 1330, 1252, 1202, 1145, 1094, 865, 780cm^{-1}.

11-Chloro-8-ethoxy-5H-isochromeno[3,4-c]isoquinoline (**3g**). White powder; petroleum ether /EtOAc (30/1) as eluent; Yield: 28.0 mg, 90%; M.p. 152 – 153 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 1.6 Hz, 1H), 8.22 (d, J = 8.8 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.46 – 7.42 (m, 1H), 7.35 (dd, J = 8.8, 2.0 Hz, 1H), 7.33 – 7.26 (m, 2H), 5.18 (s, 2H), 4.59 (q, J = 7.6 Hz, 2H), 1.50 (t, J = 7.6 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.7, 158.3, 138.0, 137.1, 131.2, 130.0, 128.5, 126.9, 126.6, 125.2, 124.7, 124.4, 122.6, 115.8, 101.9, 69.7, 63.0, 14.5. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{18}H_{15}ClNO_2$ 312.0786; Found 312.0789. IR (film): 2980, 1615, 1587, 1570, 1498, 1416, 1380, 1344, 1284, 1248, 1190, 1102, 1056, 885, 776 cm^{-1}.

11-Bromo-8-ethoxy-5H-isochromeno[3,4-c]isoquinoline (**3h**). White powder; petroleum ether /EtOAc (30/1) as eluent; Yield: 29.1 mg, 82%; M.p. 154 – 155 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 1.6 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.49 (dd, J = 8.8, 1.6 Hz, 1H), 7.46 – 7.42 (m, 1H), 7.33 – 7.27 (m, 2H), 5.18 (s, 2H), 4.59 (q, J = 7.2 Hz, 2H), 1.50 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.8, 158.2, 137.4, 131.2, 130.0, 128.5, 127.3, 126.9, 126.7, 126.6, 125.8, 125.2, 124.4, 116.0, 101.8, 69.8, 63.0, 14.5. HRMS (EI) m/z: [M]$^+$ Calcd for $C_{18}H_{14}BrNO_2$ 355.0208; Found 355.0210. IR (film): 3075, 2979, 1611, 1586, 1567, 1496, 1429, 1415, 1380, 1345, 1284, 1265, 1189, 1100, 886, 781 cm^{-1}.

8-Ethoxy-11-(trifluoromethyl)-5H-isochromeno[3,4-c]isoquinoline (**3i**). Light yellow powder; petroleum ether /EtOAc (30/1) as eluent; Yield: 27.3 mg, 79%; M.p. 172 – 173 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.41 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.59 (dd, J = 8.8, 1.6

Hz, 1H), 7.49 – 7.45 (m, 1H), 7.36 – 7.30 (m, 2H), 5.21 (s, 2H), 4.63 (q, J = 7.2 Hz, 2H), 1.53 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.6, 158.3, 135.5, 132.6 (q, J =32.1 Hz), 131.3, 129.8, 128.7, 126.8, 126.5, 125.4, 124.5, 124.0 (q, J = 271.3 Hz), 120.9 (q, J = 4.4 Hz), 119.7 (q, J = 3.2 Hz), 118.9, 103.0, 69.8, 63.2, 14.4. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{15}F_3NO_2$ 346.1049; Found 346.1051. IR (film): 2985, 1579, 1555, 1509, 1434, 1408, 1380, 1349, 1314, 1286, 1251, 1111, 903, 832, 791 cm^{-1}.

8-Ethoxy-11-methyl-5H-isochromeno[3,4-c]isoquinoline (**3j**). White powder; petroleum ether /EtOAc (30/1) as eluent; Yield: 26.8 mg, 92%; M.p.85 – 86˚C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.17 (m, 2H), 7.91 (d, J = 7.6 Hz, 1H), 7.45 – 7.39 (m, 1H), 7.28 – 7.23 (m, 3H), 5.16 (s, 2H), 4.59 (q, J = 7.2 Hz, 2H), 2.54 (s, 3H), 1.50 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.7, 157.6, 141.6, 136.5, 131.3, 130.7, 128.1, 126.1, 126.0, 125.1, 125.0, 124.7, 122.7, 115.7, 102.0, 69.7, 62.6, 22.4, 14.5. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{18}NO_2$ 292.1332; Found 292.1333. IR (film): 2978, 1625, 1577, 1505, 1421, 1345, 1290, 1257, 1166, 1099, 1062, 827, 787 cm^{-1}.

8-Ethoxy-11-methoxy-5H-isochromeno[3,4-c]isoquinoline (**3k**). White powder; petroleum ether /EtOAc (30/1) as eluent; Yield: 23.3 mg, 76%; M.p. 167 – 168 ˚C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 9.2 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 2.4 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.30 – 7.27 (m, 2H), 7.03 (dd, J = 9.2, 2.4 Hz, 1H), 5.16 (s, 2H), 4.57 (q, J = 7.2 Hz, 2H), 3.95 (s, 3H), 1.49 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.1, 160.7, 158.2, 138.2, 131.3, 130.9, 128.2, 127.0, 126.1, 125.2, 123.9, 115.3, 112.4, 103.2, 102.1, 69.6, 62.6, 55.4, 14.6. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{19}H_{17}NO_3$ 307.1208; Found 307.1210. IR (film): 2988, 1620, 2590, 1579, 1508, 1422, 1381, 1345, 1261, 1225, 1151, 1062, 1026, 843, 781 cm^{-1}.

8-Ethoxy-9-fluoro-5H-isochromeno[3,4-c]isoquinoline (**3l**). White powder; petroleum ether

/EtOAc (30/1) as eluent; Yield: 24.5 mg, 83%; M.p. 165 – 166 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.44 – 7.37 (m, 2H), 7.32 – 7.28 (m, 2H), 7.04 (ddd, *J* = 8.8, 7.6, 0.8 Hz, 1H), 5.17 (s, 2H), 4.60 (q, *J* = 7.2 Hz, 2H), 1.51 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.4 (d, *J* = 259.4 Hz), 160.0 (d, *J* = 5.5 Hz), 157.7 (d, *J* = 1.1 Hz), 138.9 (d, *J* = 22.5 Hz), 131.5 (d, *J* = 9.7 Hz), 131.3, 130.6, 128.3, 126.5, 125.2, 124.7, 119.2 (d, *J* = 4.5 Hz), 110.0 (d, *J* = 21.8 Hz), 108.0 (d, *J* = 11.6 Hz), 102.0(d, *J* = 2.8 Hz), 69.7, 63.1, 14.4. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{15}FNO_2$ 296.1081; Found 296.1083. IR (film): 2976, 2899, 1626, 1573, 1506, 1426, 1376, 1330, 1132, 1074, 1050, 879, 806, 759 cm^{-1}.

8-Ethoxy-10-methyl-5H-isochromeno[3,4-c]isoquinoline (**3m**). Light yellow liquid; petroleum ether /EtOAc (30/1) as eluent; Yield: 24.2 mg, 83%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.4 Hz, 1H), 8.07 (s, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.52 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.42 – 7.38 (m, 1H), 7.28 – 7.27 (m, 2H), 5.16 (s, 2H), 4.60 (q, *J* = 6.8 Hz, 2H), 2.52 (s, 3H), 1.51 (t, *J* = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.3, 156.8, 134.3, 133.7, 133.2, 131.3, 130.7, 128.1, 126.1, 125.1, 124.7, 124.1, 123.3, 117.7, 102.4, 69.6, 62.7, 21.3, 14.5. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{18}NO_2$ 292.1332; Found 292.1335. IR (film): 3045, 2978, 1590, 1568, 1512, 1428, 1347, 1258, 1202, 1097, 1055, 1024, 944, 824, 760 cm^{-1}.

10-Chloro-8-ethoxy-5H-isochromeno[3,4-c]isoquinoline (**3n**). White powder; petroleum ether /EtOAc (30/1) as eluent; Yield: 5.6 mg, 18%; M.p. 134 – 135 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 9.2 Hz, 1H), 8.27 (d, *J* = 2.4 Hz, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.62 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.42 (ddd, *J* = 8.0, 6.0, 2.8 Hz, 1H), 7.33 – 7.28 (m, 2H), 5.19 (s, 2H), 4.60 (q, *J* = 7.2 Hz, 2H), 1.51 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.9, 157.6, 134.5, 131.9, 131.3, 130.1, 129.6, 128.3, 126.6, 125.3, 125.1, 124.6, 124.3, 118.4, 102.5, 69.7, 63.1, 14.5. HRMS (ESI) m/z: $[M + H]^+$

Calcd for $C_{18}H_{15}ClNO_2$ 312.0786; Found 312.0789. IR (film): 2980, 1587, 1567, 1501, 1429, 1378, 1345, 1256, 1124, 1052, 941, 881, 821 cm^{-1}.

12-Chloro-8-ethoxy-5H-isochromeno[3,4-c]isoquinoline (**3o**). Yellow powder; petroleum ether /EtOAc (30/1) as eluent; Yield: 21.8 mg, 70%; M.p. 150 – 151 ˚C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.75 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.39 – 7.35 (m, 1H), 7.34 – 7.30 (m, 1H), 7.27 – 7.20 (m, 3H), 5.30 (d, *J* = 12.0 Hz, 1H), 5.11 (d, *J* = 11.6 Hz, 1H), 7.66 – 7.54 (m, 2H), 1.50 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.8, 159.9, 134.0, 133.9, 130.5, 129.3, 128.7, 128.5, 126.9, 125.7, 124.3, 124.1, 124.0, 119.9, 101.3, 70.1, 63.3, 14.4. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{15}ClNO_2$ 312.0786; Found 312.0787. IR (film): 3080, 2980, 1603, 1566, 1549, 1496, 1422, 1377, 1347, 1257, 1176, 1050, 1025, 894, 773 cm^{-1}

8-Ethoxy-10,11-dimethyl-5H-isochromeno[3,4-c]isoquinoline (**3p**). White powder; petroleum ether /EtOAc (30/1) as eluent; Yield: 22.0 mg, 72%; M.p.175 – 177 ˚C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.02 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.28 – 7.27 (m, 1H), 7.29 – 7.24 (m, 2H), 5.15 (s, 2H), 4.58 (q, *J* = 7.2 Hz, 2H), 2.46 (s, 3H), 2.43 (s, 3H), 1.51 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.2, 156.9, 141.5, 134.9, 133.5, 131.3, 130.8, 128.1, 126.0, 125.0, 124.6, 124.5, 123.3, 116.2, 101.9, 69.6, 62.5, 20.9, 19.9, 14.6. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{20}NO_2$ 306.1489; Found 306.1492. IR (film): 2976, 2922, 1630, 1588, 1569, 1499, 1426, 1377, 1343, 1257, 1155, 1059, 791 cm^{-1}.

8-Ethoxy-2-fluoro-5H-isochromeno[3,4-c]isoquinoline (**3q**). White powder; petroleum ether /EtOAc (30/1) as eluent; Yield: 26.9 mg, 91%; M.p. 124 – 125 ˚C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.8 Hz, 1H), 7.24 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.74 – 7.70 (m, 1H), 7.60 (dd, *J* = 10.4, 2.4 Hz, 1H), 7.46 – 7.41 (m, 1H), 7.24 (dd, *J* = 8.0, 5.6 Hz, 1H), 6.97 (td, *J* = 8.4, 2.4 Hz, 1H), 5.14 (s, 2H),

4.61 (q, J = 7.2 Hz, 2H), 1.51 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.8 (d, J = 242.6 Hz), 161.3, 157.7, 136.0, 132.6 (d, J = 8.9 Hz), 131.6, 126.7 (d, J = 2.8 Hz), 126.5, 126.4, 125.3, 124.2, 122.9, 117.6, 112.7 (d, J = 21.9 Hz), 111.7 (d, J = 24.0 Hz), 101.7 (d, J = 2.2 Hz), 69.1, 62.9, 14.5. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{18}H_{14}FNO_2$ 295.1009; Found 295.1007. IR (film): 2916, 1618, 1591, 1573, 1508, 1427, 1346, 1221, 1165, 1108, 1064, 1030, 947, 878, 770 cm^{-1}.

2-Chloro-8-ethoxy-5H-isochromeno[3,4-c]isoquinoline (**3r**). White powder; petroleum ether /EtOAc (30/1) as eluent; Yield: 27.4 mg, 88%; M.p. 123 – 124 ˚C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 8.4 Hz, 1H), 7.87 (dd, J = 8.4, 0.8 Hz, 1H), 7.87 (d, J = 2.0 Hz, 1H), 7.75 – 7.71 (m, 1H), 7.46 – 7.42 (m, 1H), 7.26 – 7.24 (m, 1H), 7.21 (d, J = 8.0 Hz, 1H), 5.13 (s, 2H), 4.60 (q, J = 7.2 Hz, 2H), 1.51 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.3, 157.8, 135.9, 134.1, 132.4, 131.7, 129.4, 126.3, 126.0, 125.3, 124.5, 124.3, 123.0, 117.6, 101.5, 69.1, 62.9, 14.5. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{18}H_{14}ClNO_2$ 311.0713; Found 311.0714. IR (film): 3073, 2979, 1619, 1584, 1570, 1508, 1426, 1378, 1346, 1320, 1265, 1198, 1164, 1100, 1063, 1030, 944, 832, 805, 771 cm^{-1}.

8-Ethoxy-3-fluoro-5H-isochromeno[3,4-c]isoquinoline (**3s**). White powder; petroleum ether /EtOAc (30/1) as eluent; Yield: 27.7 mg, 94%; M.p. 139 – 140 ˚C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 – 8.27 (m, 2H), 7.85 (dd, J = 8.8, 5.2 Hz, 1H), 7.71 – 7.67 (m, 1H), 7.44 – 7.40 (m, 1H), 7.11 (td, J = 8.4, 2.8 Hz, 1H), 7.01 (dd, J = 8.0, 2.4 Hz, 1H), 5.14 (s, 2H), 4.60 (q, J = 7.1 Hz, 2H), 1.51 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.2 (d, J = 245.2 Hz), 160.6, 156.9 (d, J = 0.8 Hz), 135.9, 133.4 (d, J = 7.1 Hz), 131.3, 126.7 (d, J = 3.4 Hz), 126.1 (d, J = 7.7 Hz), 125.2, 124.1, 123.1, 117.6, 114.9 (d, J = 21.2 Hz), 112.4 (d, J = 22.2 Hz), 101.8, 69.1 (d, J = 2.2 Hz), 62.8, 14.5. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{18}H_{14}FNO_2$ 295.1009; Found 295.1008. IR (film): 3074, 2979, 1620, 1595, 1566, 1509, 1441, 1419, 1379, 1346, 1330, 1992, 1262, 1198, 1163, 1097, 1060, 965, 865, 771 cm^{-1}.

3-Chloro-8-ethoxy-5H-isochromeno[3,4-c]isoquinoline (**3t**). White powder; petroleum ether /EtOAc (30/1) as eluent; Yield: 30.2 mg, 97%; M.p. 169 – 170 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.8 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.37 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.28 (d, *J* = 1.6 Hz, 1H), 5.13 (s, 2H), 4.60 (q, *J* = 7.1 Hz, 2H), 1.51 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.0, 157.4, 136.0, 132.9, 131.7, 131.4, 129.2, 128.2, 125.8, 125.3, 124.2, 123.1, 117.9, 101.7, 69.0, 62.9, 14.5. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{18}H_{14}ClNO_2$ 311.0713; Found 311.0715. IR (film): 3071, 2980, 1618, 1585, 1570, 1508, 1432, 1417, 1377, 1345, 1265, 1199, 1163, 1102, 1060, 944, 872, 769 cm^{-1}.

8-Ethoxy-3-(trifluoromethyl)-5H-isochromeno[3,4-c]isoquinoline (**3u**). White powder; petroleum ether /EtOAc (30/1) as eluent; Yield: 33.1 mg, 96%; M.p. 123 – 124 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 – 8.31 (m, 2H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.74 – 7.70 (m, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.54 (s, 1H), 7.47 – 7.43 (m, 1H), 5.20 (s, 2H), 4.61 (q, *J* = 7.2 Hz, 2H), 1.52 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.7, 158.2, 136.1, 134.2, 131.7, 131.4, 127.9 (q, *J* = 32.5 Hz), 125.4, 125.2 (q, *J* =3.8 Hz), 124.6, 124.4, 124.1 (q, *J* = 270.0 Hz), 123.0, 122.0 (q, *J* = 3.6 Hz), 117.7, 101.5, 69.2, 63.1, 14.5. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{19}H_{14}F_3NO_2$ 345.0977; Found 345.0979. IR (film): 3075, 2982, 1617, 1590, 1572, 1512, 1421, 1381, 1329, 1290, 1263, 1198, 1166, 1121, 1076, 1009, 948, 887, 774 cm^{-1}.

8-Ethoxy-3-methoxy-5H-isochromeno[3,4-c]isoquinoline (**3v**). White powder; petroleum ether /EtOAc (30/1) as eluent; Yield: 10.4 mg, 34%; M.p. 138 – 139 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.8 Hz, 1H), 8.30 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.70 – 7.66 (m, 1H), 7.43 – 7.39 (m, 1H), 6.96 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.85 (d, *J* = 2.8 Hz, 1H), 5.15 (s, 2H), 4.60 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 1.51 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.0, 158.3,

156.5, 136.0, 133.1, 131.0, 126.0, 125.2, 123.9, 123.4, 123.3, 117.6, 113.5, 111.0, 102.4, 69.7, 62.7, 55.4, 14.5. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{18}NO_3$ 308.1281; Found 308.1283. IR (film): 2977, 1619, 1588, 1572, 1509, 1419, 1378, 1346, 1263, 1162, 1097, 1059, 1029, 952, 866, 770 cm^{-1}.

5-Ethoxy-8H-[1,3]dioxolo[4',5':6,7]isochromeno[3,4-c]isoquinoline (**3w**). Yellow powder; petroleum ether /EtOAc (30/1) as eluent; Yield: 6.7 mg, 21%; M.p. 144 – 146 ˚C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 – 8.28 (m, 2H), 7.70 – 7.66 (m, 1H), 7.43 – 7.39 (m, 2H), 6.79 (s, 1H), 6.02 (s, 2H), 5.07 (s, 2H), 4.59 (q, *J* = 7.2 Hz, 2H), 1.51 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.3, 156.7, 147.7, 145.9, 135.8, 131.1, 125.2, 124.9, 124.6, 123.9, 123.1, 117.5, 106.1, 105.8, 102.6, 101.2, 69.5, 62.7, 14.5. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{16}NO_4$ 322.1074; Found 322.1075. IR (film): 2979, 1621, 1567, 1506, 1486, 1427, 1377, 1322, 1237, 1162, 1106, 1042, 937, 885, 770 cm^{-1}.

8-Ethoxy-6-tosyl-5,6-dihydrodibenzo[c,f][1,8]naphthyridine (**4a**). White powder; petroleum ether /EtOAc (15/1) as eluent; Yield: 3.0 mg, 7%; M.p. 109 – 110 ˚C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.4 Hz, 1H), 8.29 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.69 – 7.65 (m, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.51 – 7.47 (m, 1H), 7.39 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.35 – 7.28 (m, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 4.95 (s, 2H), 4.47 (q, *J* = 7.8 Hz, 2H), 2.31 (s, 3H), 1.46 (t, *J* = 7.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.3, 143.7, 142.9, 138.1, 135.4, 133.4, 131.0, 130.6, 128.9, 127.5, 126.92, 126.87, 126.5, 126.0, 125.5, 124.9, 124.3, 118.6, 111.0, 63.0, 50.4, 21.4, 14.5. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{22}N_2NaO_3S$ 453.1243; Found 453.1246. IR (film): 3187, 2962, 1787, 1727, 1705, 1586, 1572, 1524, 1446, 1345, 1262, 1175, 1094, 1010, 802, 678 cm^{-1}.

Ethyl 2-(3-((4-methylphenyl)sulfonamido)-1H-isochromen-4-yl)benzimidate (**5a**). White powder; petroleum ether /EtOAc (5/1) as eluent; Yield: 24.6 mg, 55%; M.p. 105 – 106 ˚C; ^1H NMR (400 MHz,

$CDCl_3$) δ 8.17 – 8.14 (m, 1H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.55 – 7.52 (m, 1H), 7.49 – 7.46 (m, 1H), 7.46 – 7.42 (m, 1H), 7.32 – 7.36 (m, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.17 (dd, *J* = 7.6, 1.6 Hz, 1H), 6. 99 – 6.97 (m, 2H), 4.33 (s, 2H), 4.29 – 4.20 (m, 2H), 2.42 (s, 3H), 1.84 (s, 1H), 1.36 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.7, 143.4, 141.0, 140.8, 138.7, 138.4, 132.0, 131.6, 131.1, 129.5, 129.25, 129.16, 128.9, 127.5, 124.8, 124.4, 123.7, 116.4, 108.7, 63.0, 62.7, 21.5, 14.4. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{24}N_2NaO_4S$ 471.1349; Found 471.1347. IR (film): 3262, 3066, 2925, 1770, 1705, 1619, 1590, 1573, 1452, 1423, 1338, 1160, 1096, 1011, 814, 768 cm^{-1}.

8-Phenyl-5H-isochromeno[3,4-c]isoquinoline (**7a**). Yellow-green powder; petroleum ether /EtOAc (20/1) as eluent; Yield: 24.7 mg, 80%; M.p. 86 – 87 ˚C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 7.6 Hz, 1H), 7.80 – 7.76 (m, 2H), 7.72 – 7.68 (m, 2H), 7.55 – 7.48 (m, 3H), 7.46 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.43 – 7.40 (m, 1H), 7.39 – 7.36 (m, 1H), 7.34 (dd, *J* = 7.6, 2.0 Hz, 1H), 5.25 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.2, 157.8, 138.7, 135.4, 133.1, 130.7, 130.3, 129.9, 128.9, 128.8, 128.3, 128.2, 127.6, 126.3, 125.4, 124.8, 124.6, 124.0, 108.2, 69.5. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{16}NO$ 310.1226; Found 310.1227. IR (film): 3058, 2850, 1614, 1585, 1561, 1540, 1451, 1435, 1390, 1324, 1292, 1206, 1146, 1025, 941, 775 cm^{-1}.

11-Fluoro-8-(4-fluorophenyl)-5H-isochromeno[3,4-c]isoquinoline (**7b**). Light yellow solid; petroleum ether /EtOAc (20/1) as eluent; Yield: 20.4 mg, 59%; M.p. 225 – 227 ˚C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 10.8, 2.8 Hz, 1H), 8.11 (dd, *J* = 9.6, 6.0 Hz, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.78 – 7.73 (m, 2H), 7.52 – 7.48 (m, 1H), 7.43 – 7.34 (m, 2H), 7.24 – 7.17 (m, 3H), 5.26 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4 (d, *J* = 250.7 Hz), 163.4 (d, *J* = 247.8 Hz), 159.1, 158.5, 137.1 (d, *J* = 10.7 Hz), 134.5 (d, *J* = 3.5 Hz), 132.9, 132.1 (d, *J* = 8.2 Hz), 131.7 (d, *J* = 10.0 Hz),

129.5, 128.5, 127.9, 125.6, 125.5, 122.0, 115.4 (d, J = 21.6 Hz), 114.9, 108.1 (d, J = 5.1 Hz), 108.0 (d, J = 12.8 Hz), 69.5. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{14}F_2NO$ 346.1038; Found 346.1036. IR (film): 3054, 1625, 1566, 1544, 1509, 1439, 1404, 1321, 1280, 1252, 1225, 1199, 1157, 1054, 991, 845, 786, 737 cm^{-1}.

11-Chloro-8-(4-chlorophenyl)-5H-isochromeno[3,4-c]isoquinoline (**7c**). Yellow-green solid; petroleum ether /EtOAc (20/1) as eluent; Yield: 21.9 mg, 58%; M.p.225 – 227 ˚C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 2.0 Hz, 1H), 8.02 (d, J = 9.2 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.53 – 7.50 (m, 3H), 7.44 – 7.40 (m, 1H), 7.38 – 7.35 (m, 2H), 5.26 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.8, 158.5, 137.7, 136.7, 136.2, 135.4, 133.0, 131.5, 130.0, 129.2, 128.65, 128.64, 128.1, 126.0, 125.8, 125.6, 123.1, 122.9, 107.9, 69.6. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{14}Cl_2NO$ 378.0447; Found 378.0448. IR (film): 2920, 1609, 1553, 1537, 1493, 1398, 1320, 1285, 1182, 1088, 1049, 989, 844, 778 cm^{-1}.

11-Methoxy-8-(4-methoxyphenyl)-5H-isochromeno[3,4-c]isoquinoline (**7d**). Light-yellow powder; petroleum ether /EtOAc (20/1) as eluent; Yield: 25.8 mg, 70%; M.p. 187 – 189 ˚C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.8 Hz, 2H), 7.85 (d, J = 2.4 Hz, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.48 – 7.44 (m, 1H), 7.38 – 7.34 (m, 2H), 7.06 – 7.03 (m, 3H), 5.22 (s, 2H), 3.97 (s, 3H), 3.89 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.5, 160.3, 159.4, 158.5, 137.5, 133.0, 131.6, 131.3, 130.7, 130.4, 128.2, 127.2, 125.5, 125.1, 120.4, 116.7, 113.7, 107.0, 102.6, 69.4, 55.43, 55.37. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{24}H_{20}NO_3$ 370.1438; Found 370.1439. IR (film): 3062, 2934, 1619, 1565, 1542, 1514, 1452, 1399, 1323, 1288, 1249, 1225, 1178, 1058, 1031, 989, 840, 788 cm^{-1}.

N-(2-(1-ethoxy-3-hydroxyisoquinolin-4-yl)benzyl)-4-methylbenzenesulfonamide (**9a**). White powder; petroleum ether /EtOAc (4/1) as eluent; Yield: 43.0 mg, 96%; M.p. 151 – 152 ˚C; ^1H NMR

(400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.4 Hz, 1H), 7.47 – 7.44 (m, 1H), 7.42 – 7.35 (m, 5H), 7.29 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.18 – 7.16 (m, 1H), 7.02 (d, *J* = 7.6 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.46 (s, 1H), 4.86 (q, *J* = 7.5, 4.0 Hz, 1H), 4.57 – 4.46 (m, 2H), 3.90 (dd, *J* = 12.4, 7.6 Hz, 1H), 3.71 (dd, *J* = 12.4, 4.0 Hz, 1H), 2.33 (s, 3H), 1.53 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.1, 152.4, 142.9, 140.0, 136.1, 135.9, 134.2, 131.9, 131.2, 130.3, 129.3, 128.6, 128.5, 126.8, 124.4, 123.4, 122.9, 115.6, 102.8, 62.7, 45.9, 21.4, 14.5. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{25}H_{25}N_2O_4S$ 449.1530; Found 449.1525. IR (film): 3300, 2981, 2928, 1707, 1624, 1599, 1573, 1509, 1423, 1340, 1275, 1162, 1095, 1049, 941, 838, 771, 737, 676 cm^{-1}.

N-(2-(3-Hydroxy-1-methoxyisoquinolin-4-yl)benzyl)-4-methylbenzenesulfonamide (**9b**). Light yellow powder; petroleum ether /EtOAc (4/1) as eluent; Yield: 40.8 mg, 94%; M.p. 88 – 89 ˚C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.0 Hz, 1H), 7.47 – 7.38 (m, 6H), 7.32 – 7.28 (m, 1H), 7.18 – 7.16 (m, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.48 (s, 1H), 4.84 (dd, *J* = 7.6, 4.0 Hz, 1H), 4.11 (s, 3H), 3.90 (dd, *J* = 12.4, 7.2 Hz, 1H), 3.71 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.34 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.4, 152.4, 143.0, 140.0, 136.0, 135.9, 134.1, 131.9, 131.3, 130.4, 129.3, 128.7, 128.6, 126.8, 124.3, 123.6, 123.0, 115.6, 103.0, 54.2, 45.9, 21.4. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{22}N_2NaO_4S$ 457.1192; Found 457.1194. IR (film): 3301, 2949, 1626, 1599, 1573, 1509, 1463, 1448, 1379, 1351, 1277, 1211, 1115, 1095, 1006, 980, 814, 771, 672 cm^{-1}.

N-(2-(1-Ethoxy-3-hydroxy-6-methylisoquinolin-4-yl)benzyl)-4-methylbenzenesulf-onamide (**9c**). White powder; petroleum ether /EtOAc (4/1) as eluent; Yield: 43.9 mg, 95%; M.p. 205 – 207 ˚C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 1H), 7.48 – 7.46 (m, 1H), 7.43 – 7.37 (m, 4H), 7.18 – 7.16 (m, 1H), 7.12 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.73 (s, 1H), 6.07 (s, 1H), 4.83 (dd, *J* = 7.6, 4.0 Hz, 1H), 4.56 – 4.45 (m, 2H), 3.91 (dd, *J* = 12.4, 7.6 Hz, 1H), 3.71 (dd, *J* = 12.8, 4.0

Hz, 1H), 2.34 (s, 3H), 2.32 (s, 3H), 1.53 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.0, 152.5, 142.9, 141.8, 140.3, 136.1, 136.0, 134.4, 132.0, 130.3, 129.3, 128.6, 128.5, 126.8, 125.7, 124.2, 122.0, 113.8, 102.4, 62.5, 45.9, 22.1, 21.4, 14.6. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{26}N_2NaO_4S$ 485.1505; Found 485.1506. IR (film): 3300, 2980, 1626, 1576, 1501, 1423, 1382, 1339, 1264, 1161, 1096, 1048, 810, 738, 665 cm^{-1}.

N-(2-(1-ethoxy-3-hydroxy-6-methoxyisoquinolin-4-yl)benzyl)-4-methylbenzene-sulfonamide (**9d**). White powder; petroleum ether /EtOAc (4/1) as eluent; Yield: 44.5 mg, 93%; M.p. 84 – 85 ˚C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.8 Hz, 1H), 7.50 – 7.47 (m, 1H), 7.43 – 7.35 (m, 4H), 7.19 – 7.17 (m, 1H), 7.03 (d, J = 8.0 Hz, 2H), 6.90 (dd, J = 9.2, 2.4 Hz, 1H), 6.71 (s, 1H), 6.23 (d, J = 2.4 Hz, 1H), 4.89 (dd, J = 8.0, 4.0 Hz, 1H), 4.47 (q, J = 7.2 Hz, 2H), 3.92 (dd, J = 12.4, 7.6 Hz, 1H), 3.70 (dd, J = 12.4, 3.6 Hz, 1H), 3.64 (s, 3H), 2.33 (s, 3H), 1.50 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.0, 159.9, 153.2, 142.9, 142.2, 136.1, 135.9, 134.4, 131.8, 130.3, 129.3, 128.7, 128.5, 126.8, 126.3, 115.1, 110.5, 102.5, 102.1, 62.6, 55.2, 45.9, 21.4, 14.6. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{26}H_{27}N_2O_5S$ 479.1635; Found 479.1633. IR (film): 3288, 2981, 1621, 1582, 1504, 1422, 1340, 1235, 1158, 1027, 909, 813, 733, 672 cm^{-1}.

N-(2-(6-bromo-1-ethoxy-3-hydroxyisoquinolin-4-yl)benzyl)-4-methylbenzenesulf-onamide (**9e**). White powder; petroleum ether /EtOAc (4/1) as eluent; Yield: 42.6 mg, 81%; M.p. 205 – 206 ˚C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.44 – 7.36 (m, 4H), 7.16 – 7.12 (m, 2H), 7.08 (d, J = 8.0 Hz, 2H), 6.08 (s, 1H), 4.84 (dd, J = 7.6, 3.6 Hz, 1H), 4.52 (q, J = 7.2 Hz, 2H), 3.93 (dd, J = 12.8, 7.6 Hz, 1H), 3.72 (dd, J = 12.8, 3.6 Hz, 1H), 2.36 (s, 3H), 1.53 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.2, 153.3, 143.0, 141.3, 136.2, 136.1, 133.3, 131.9, 130.3, 129.3, 128.82, 128.76, 126.9, 126.7, 126.1, 125.2, 114.2, 102.1, 62.9, 45.7, 21.5, 14.5. HRMS

(ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{23}BrN_2NaO_4S$ 549.0454; Found 549.0437. IR (KBr): 3402, 3249, 2978, 1620, 1600, 1566, 1494, 1464, 1417, 1336, 1289, 1154, 1097, 1051, 872, 815, 778, 693 cm^{-1}.

N-(2-(6-acetyl-1-ethoxy-3-hydroxyisoquinolin-4-yl)benzyl)-4-methylbenzenesulf-onamide (**9f**). Yellow powder; petroleum ether /EtOAc (4/1) as eluent; Yield: 38.2 mg, 78%; M.p. 172 – 173 ˚C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.4 Hz, 1H), 7.80 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.59 (d, *J* = 1.6 Hz, 1H), 7.48 – 7.37 (m, 5H), 7.19 – 7.17 (m, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.28 (s, 1H), 4.95 (dd, *J* = 8.0, 3.6 Hz, 1H), 4.54 (q, *J* = 7.2 Hz, 2H), 3.94 (dd, *J* = 12.8, 8.0 Hz, 1H), 3.71 (dd, *J* = 12.8, 4.0 Hz, 1H), 2.48 (s, 3H), 2.35 (s, 3H), 1.54 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.2, 160.0, 153.3, 143.1, 139.7, 138.8, 136.1, 133.3, 131.9, 130.3, 129.3, 128.9, 128.7, 126.9, 125.1, 124.3, 121.6, 117.5, 103.8, 63.0, 45.7, 26.8, 21.5, 14.5. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{26}N_2NaO_5S$ 513.1455; Found 513.1453. IR (film): 3285, 2981, 1684, 1625, 1577, 1498, 1425, 1384, 1336, 1246, 1159, 1103, 911, 732, 672 cm^{-1}.

Methyl 1-ethoxy-3-hydroxy-4-(2-(((4-methylphenyl)sulfonamido)methyl)phenyl)-isoquinoline-6-carboxylate (**9g**). Light yellow powder; petroleum ether /EtOAc (4/1) as eluent; Yield: 41.0 mg, 81%; M.p. 185 – 186 ˚C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.8 Hz, 1H), 7.86 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.71 (d, *J* = 0.8 Hz, 1H), 7.47 – 7.37 (m, 5H), 7.18 – 7.15 (m, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.18 (s, 1H), 4.88 (dd, *J* = 7.5, 3.9 Hz, 1H), 4.54 (q, *J* = 7.0 Hz, 2H), 3.92 (dd, *J* = 12.6, 7.6 Hz, 1H), 3.87 (s, 3H), 3.71 (dd, *J* = 12.5, 3.8 Hz, 1H), 2.35 (s, 3H), 1.55 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.6, 159.9, 153.3, 143.0, 139.4, 135.97, 135.95, 133.4, 132.3, 131.9, 130.4, 129.3, 128.8, 128.7, 126.9, 125.3, 124.8, 122.9, 117.4, 103.7, 63.0, 52.4, 45.7, 21.4, 14.5. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{26}N_2NaO_6S$ 529.1404; Found 529.1403. IR (film): 3300, 2981, 1724, 1628, 1577, 1502, 1427, 1336, 1248, 1160, 1112, 1050, 814, 768, 668 cm^{-1}.

N-(2-(1-ethoxy-3-hydroxy-7-methylisoquinolin-4-yl)benzyl)-4-methylbenzenesulf-onamide (**9h**). White powder; petroleum ether /EtOAc (4/1) as eluent; Yield: 45.3 mg, 98%; M.p. 160 – 161 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 1.2 Hz, 1H), 7.46 – 7.44 (m, 1H), 7.41 – 7.34 (m, 4H), 7.25 (dd, *J* = 8.8, 2.0 Hz, 1H) (m, 1H), 7.17 – 7.15 (m, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.42 (s, 1H), 4.87 (s, 1H), 4.56 – 4.45 (m, 2H), 3.90 (dd, *J* = 12.4, 6.8 Hz, 1H), 3.70 (dd, *J* = 12.4, 3.2 Hz, 1H), 2.46 (s, 3H), 2.33 (s, 3H), 1.53 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.6, 151.7, 142.9, 138.2, 136.1, 136.0, 134.4, 133.3, 133.2, 131.9, 130.3, 129.2, 128.6, 128.5, 126.8, 123.3, 122.9, 115.7, 102.7, 62.6, 45.9, 21.4, 21.3, 14.6. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{26}N_2NaO_4S$ 485.1505; Found 485.1508. IR (film): 3299, 2980, 1629, 1615, 1599, 1570, 1427, 1332, 1280, 1206, 1160, 1024, 909, 814, 733, 668 cm^{-1}.

N-(5-chloro-2-(1-ethoxy-3-hydroxyisoquinolin-4-yl)benzyl)-4-methylbenzenesulf-onamide (**9i**). Light yellow powder; petroleum ether /EtOAc (4/1) as eluent; Yield: 47.2 mg, 98%; M.p. 92 – 93 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.4 Hz, 1H), 7.48 – 7.41 (m, 3H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.18 (d, *J* = 2.0 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.39 (s, 1H), 4.88 (dd, *J* = 7.6, 4.0 Hz, 1H), 4.57 – 4.48 (m, 2H), 3.87 (dd, *J* = 12.8, 7.6 Hz, 1H), 3.68 (dd, *J* = 12.8, 3.6 Hz, 1H), 2.34 (s, 3H), 1.53 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.4, 152.4, 143.1, 139.7, 136.1, 136.0, 134.8, 134.1, 131.8, 131.5, 129.3, 128.6, 126.9, 124.5, 123.7, 122.7, 115.7, 101.6, 62.8, 45.2, 21.4, 14.5. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{23}ClN_2NaO_4S$ 505.0959; Found 505.0958. IR (film): 3294, 2981, 1624, 1572, 1509, 1425, 1338, 1277, 1161, 1100, 1044, 909, 814, 771, 676 cm^{-1}.

N-(2-(1-ethoxy-3-hydroxyisoquinolin-4-yl)-5-methoxybenzyl)-4-methylbenzene-sulfonamide (**9j**). White powder; petroleum ether /EtOAc (4/1) as eluent; Yield: 28.2 mg, 59%; M.p. 188 – 189 ˚C; ^{1}H

NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.0 Hz, 1H), 7.44 – 7.40 (m, 3H), 7.30 – 7.26 (m, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 7.04 – 6.98 (m, 4H), 6.94 (dd, *J* = 8.3, 2.8 Hz, 1H), 6.42 (s, 1H), 4.90 (dd, *J* = 7.6, 4.4 Hz, 1H), 4.56 – 4.46 (m, 2H), 3.85 (dd, *J* = 12.6, 7.6 Hz, 1H), 3.81 (s, 3H), 3.68 (dd, *J* = 12.4, 4.0 Hz, 1H), 2.33 (s, 3H), 1.53 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.0, 159.5, 152.8, 142.9, 140.3, 137.4, 136.0, 133.0, 131.2, 129.3, 126.8, 125.9, 124.4, 123.4, 123.0, 115.7, 115.0, 114.7, 102.4, 62.7, 55.3, 46.0, 21.4, 14.5. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{26}N_2NaO_5S$ 501.1455; Found 501.1455. IR (film): 3331, 2979, 1624, 1606, 1573, 1511, 1422, 1339, 1237, 1199, 1161, 1051, 908, 815, 773, 667 cm^{-1}.

N-(4-chloro-2-(1-ethoxy-3-hydroxyisoquinolin-4-yl)benzyl)-4-methylbenzenesulf-onamide (**9k**). Light yellow powder; petroleum ether /EtOAc (4/1) as eluent; Yield: 45.3 mg, 94%; M.p. 84 – 85 ˚C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.8 Hz, 1H), 7.48 – 7.40 (m, 3H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.17 (d, *J* = 2.4 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.62 (s, 1H), 4.92 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.54 – 4.45 (m, 2H), 3.87 (dd, *J* = 12.6, 7.6 Hz, 1H), 3.68 (dd, *J* = 12.6, 4.0 Hz, 1H), 2.34 (s, 3H), 1.53 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.4, 152.5, 143.1, 139.7, 136.1, 136.0, 134.8, 134.1, 131.8, 131.5, 129.3, 128.5, 126.8, 124.5, 123.6, 122.7, 115.6, 101.6, 62.8, 45.2, 21.4, 14.5. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{23}ClN_2NaO_4S$ 505.0959; Found 505.0958. IR (film): 3295, 2982, 1624, 1573, 1509, 1425, 1338, 1277, 1161, 1101, 1012, 909, 814, 772, 732 cm^{-1}.

N-((6-(1-ethoxy-3-hydroxyisoquinolin-4-yl)benzo[d][1,3]dioxol-5-yl)methyl)-4-methylbenzenesulfonamide (**9l**). Light yellow powder; petroleum ether /EtOAc (4/1) as eluent; Yield: 48.2 mg, 98%; M.p. 97 – 98 ˚C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.6 Hz, 1H), 7.46 – 7.42 (m, 1H), 7.41 – 7.39 (m, 2H), 7.31 – 7.27 (m, 1H), 7.06 – 7.03 (m, 3H), 6.91 (s, 1H), 6.61 (s, 1H), 6.45

(s, 1H), 5.99 (dd, *J* = 16.8, 1.2 Hz, 2H), 4.84 (dd, *J* = 7.6, 4.0 Hz, 1H), 4.54 – 4.45 (m, 2H), 3.76 (dd, *J* = 12.4, 7.6 Hz, 1H), 3.57 (dd, *J* = 12.4, 4.0 Hz, 1H), 2.34 (s, 3H), 1.53 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 160.0, 152.7, 147.8, 147.7, 143.0, 140.1, 135.9, 131.3, 129.6, 129.3, 127.5, 126.8, 124.4, 123.5, 122.9, 115.7, 111.4, 110.3, 102.5, 101.4, 62.7, 45.7, 21.4, 14.5. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{24}N_2NaO_6S$ 515.1247; Found 515.1246. IR (film): 3301, 2981, 1624, 1573, 1507, 1486, 1418, 1380, 1334, 1160, 1074, 1038, 909, 814, 773, 730, 674 cm^{-1}.

4-Chloro-N-(2-(1-ethoxy-3-hydroxyisoquinolin-4-yl)benzyl)benzenesulfonamide (**9m**). Light yellow powder; petroleum ether /EtOAc (4/1) as eluent; Yield: 43.1 mg, 92%; M.p. 70 – 71 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 – 8.19 (m, 1H), 7.46 – 7.36 (m, 6H), 7.33 – 7.29 (m, 1H), 7.20 – 7.17 (m, 3H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.59 (s, 1H), 4.93 (dd, *J* = 7.2, 4.0 Hz, 1H), 4.50 (q, *J* = 7.2 Hz, 2H), 3.92 (dd, *J* = 12.4, 7.2 Hz, 1H), 3.75 (dd, *J* = 12.4, 3.6 Hz, 1H), 1.54 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 160.2, 152.4, 139.9, 138.7, 137.5, 135.6, 134.3, 132.0, 131.4, 130.3, 128.9, 128.8, 128.6, 128.2, 124.6, 123.6, 122.8, 115.6, 102.7, 62.8, 46.0, 14.5. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{21}ClN_2NaO_4S$ 491.0803; Found 491.0803. IR (film): 3300, 2981, 1623, 1572, 1509, 1423, 1340, 1277, 1163, 1095, 910, 827, 757, 677 cm^{-1}.

N-(2-(1-ethoxy-3-hydroxyisoquinolin-4-yl)benzyl)benzenesulfonamide (**9n**). Light yellow powder; petroleum ether /EtOAc (4/1) as eluent; Yield: 32.1 mg, 74%; M.p. 182 – 183 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.4 Hz, 1H), 7.55 – 7.53 (m, 2H), 7.45 – 7.34 (m, 5H), 7.32 – 7.25 (m, 3H), 7.18 (dd, *J* = 6.8, 2.0 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.35 (s, 1H), 4.93 (dd, *J* = 7.6, 4.0 Hz, 1H), 4.51 (q, *J* = 7.2 Hz, 2H), 3.93 (dd, *J* = 12.8, 7.2 Hz, 1H), 3.76 (dd, *J* = 12.8, 4.0 Hz, 1H), 1.53 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 160.1, 152.4, 140.0, 139.1, 136.0, 134.2, 132.2, 132.0, 131.3, 130.2, 128.7, 128.6, 128.5, 126.8, 124.5, 123.5, 122.9, 115.7, 102.8, 62.7, 45.8, 14.5. HRMS (ESI)

m/z: $[M + Na]^+$ Calcd for $C_{24}H_{22}N_2NaO_4S$ 457.1192; Found 457.1192. IR (film): 3301, 2981, 1623, 1572, 1509, 1447, 1422, 1340, 1161, 1095, 1050, 910, 754, 677 cm^{-1}.

N-(2-(3-hydroxy-1-phenylisoquinolin-4-yl)benzyl)-4-methylbenzenesulfonamide (**10a**). Yellow solid; petroleum ether /EtOAc (3/1) as eluent; Yield: 39.4 mg, 82%; M.p. 233 – 234 ˚C; ^1H NMR (400 MHz, $CDCl_3$) δ 13.21 (s, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.60 – 7.57 (m, 3H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.51 – 7.38 (m, 5H), 7.29 – 7.25 (m, 1H), 7.13 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.05 – 7.02 (m, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.21 (d, *J* = 9.2 Hz, 1H), 3.99 (dd, *J* = 11.6, 9.2 Hz, 1H), 3.50 (dd, *J* = 11.6, 1.6 Hz, 1H), 2.14 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.7, 152.8, 142.7, 141.6, 136.32, 136.28, 134.8, 132.6, 131.8, 131.4, 130.9, 130.3, 130.2, 129.4, 128.7, 128.4, 128.2, 128.1, 127.0, 123.9, 123.0, 117.9, 116.7, 46.5, 21.3. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{29}H_{24}N_2NaO_3S$ 503.1400; Found 503.1398. IR (KBr): 3289, 3063, 2885, 1614, 1554, 1460, 1402, 1369, 1328, 1259, 1162, 1094, 1055, 961, 898, 813, 793, 688 cm^{-1}.

N-(2-(3-hydroxy-6-methoxy-1-(4-methoxyphenyl)isoquinolin-4-yl)benzyl)-4-methylbenzenesulfonamide (**10b**). Yellow powder; petroleum ether /EtOAc (3/1) as eluent; Yield: 46.5 mg, 86%; M.p. 264 – 265 ˚C; ^1H NMR (400 MHz, $CDCl_3$) δ 13.87 (s, 1H), 7.63 – 7.60 (m, 4H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.44 (td, *J* = 7.6, 1.6 Hz, 2H), 7.39 (td, *J* = 7.6, 1.6 Hz, 2H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.84 (s, 1H), 6.62 (dd, *J* = 9.2, 2.4 Hz, 1H), 6.10 (d, *J* = 2.8 Hz, 1H), 4.03 (d, *J* = 11.6 Hz, 1H), 3.90 (s, 3H), 3.59 (s, 3H), 3.49 (d, *J* = 11.2 Hz, 1H), 2.13 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.2, 161.4, 159.7, 150.4, 144.5, 142.6, 136.6, 136.3, 135.7, 131.9, 131.4, 131.1, 130.3, 129.4, 128.3, 128.1, 127.0, 123.7, 117.3, 115.2, 114.3, 113.0, 99.9, 55.5, 55.2, 46.9, 21.3. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{31}H_{28}N_2NaO_5S$ 563.1611; Found 563.1612. IR (film): 3435, 2926, 1607, 1561, 1514, 1468, 1358, 1252, 1229, 1166, 1035, 812, 692

cm^{-1}.

5,7-Dihydro-8H-isochromeno[3,4-c]isoquinolin-8-one (**11**) Light-yellow powder; petroleum ether /EtOAc (4/1) as eluent; Yield: 24.7 mg, 99%; M.p. 248 – 249 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (s, 1H), 8.23 (dd, J = 8.0, 1.6 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.80 – 7.73 (m, 2H), 7.38 – 7.43 (m, 2H), 7.35 (dd, J = 7.6, 1.2 Hz, 1H), 7.24 (td, J = 7.6, 1.2 Hz, 1H), 5.21 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 161.4, 150.9, 135.2, 133.0, 129.3, 128.7, 128.6, 127.7, 125.5, 125.3, 124.3, 123.6, 123.3, 122.3, 92.8, 69.6. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{12}NO_2$ 250.0863; Found 250.0861. IR (KBr): 3069, 3036, 2851, 1640, 1621, 1553, 1519, 1485, 1473, 1342, 1289, 1268, 1205, 1152, 1056, 1025, 977, 907, 774 cm^{-1}.

7-Tosyl-7,8-dihydrodibenzo[c,f][1,8]naphthyridin-5(6H)-one (**12**). Light-yellow powder; petroleum ether /EtOAc (3/1) as eluent; Yield: 37.0 mg, 92%; M.p. 108 – 109 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.53 (dd, J = 8.0, 1.6 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7. 70 – 7.66 (m, 1H), 7.56 – 7.52 (m, 1H), 7. 27 – 7.25 (m, 1H), 7.20 – 7.09 (m, 5H), 6.77 (d, J = 8.0 Hz, 2H), 4.83 (s, 2H), 2.15 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.1, 144.1, 134.3, 133.5, 133.4, 132.8, 130.2, 128.92, 128.88, 128.6, 127.4, 126.9, 126.8, 126.5, 126.4, 126.3, 125.2, 124.7, 107.0, 50.8, 21.3. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{19}N_2O_3S$ 403.1111; Found 403.1110. IR (film): 3157, 3063, 2919, 1714, 1684, 1633, 1614, 1567, 1548, 1503, 1438, 1402, 1366, 1339, 1292, 1248, 1165, 1087, 1022, 930, 801, 776 cm^{-1}.

Dibenzo[c,f][1,8]naphthyridin-5(6H)-one (**13**). Yellow powder; petroleum ether /EtOAc/Methanol (6/1/0.7) as eluent; Yield: 23.6 mg, 96%; M.p. 273 – 274 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.26 (s, 1H), 9.28 (s, 1H), 8.89 – 8.84 (m, 2H), 8.46 (dd, J = 8.0, 1.6 Hz, 1H), 8.26 (dd, J = 8.0, 1.6 Hz, 1H), 8. 00 – 7.92 (m, 2H), 7.73 (t, J = 7.2 Hz, 1H), 7.67 (t, J = 7.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz,

DMSO-d_6) δ 161.3, 153.8, 145.1, 133.7, 132.9, 132.49, 132.46, 129.6, 127.9, 127.8, 127.0, 126.97, 126.1, 125.3, 123.9, 104.2. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{11}N_2O$ 247.0866; Found 247.0865. IR (KBr): 3432, 3058, 2919, 1671, 1620, 1589, 1521, 1403, 1352, 1329, 1160, 1141, 1027, 954, 881, 799 cm^{-1}.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Copies of ^1H NMR and ^{13}C NMR spectra for all new compounds; X-ray crystal structures and crystal data of compound **3o, 4a, 7b, 9a** and **13**. (PDF)

X-ray crystallographic data of **3o, 4a, 7b, 9a** and **13**. (CIF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was financially supported by NSFC (Nos. 21772169 and 21632003).

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