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Tf_2O-Mediated mild synthesis of 6*H*-chromeno[4,3-*b*]quinolines

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Dedicated to Prof. Léon Ghosez on the occasion of his 90th birthday

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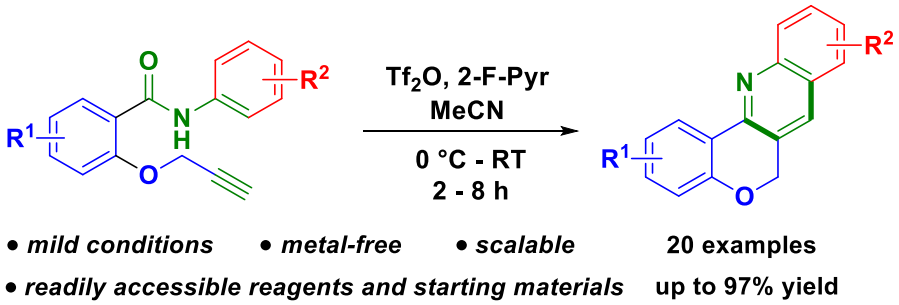
Abstract

A facile and versatile synthesis of 6*H*-chromeno[4,3-*b*]quinolines has been achieved through triflic anhydride/2-fluoropyridine (Tf_2O/2-F-Pyr)-promoting domino intramolecular cycloaddition reactions of salicylic-acid-derived *N*-phenyl-*ortho*-propynyloxy benzamides under mild, and metal-free conditions. This protocol is efficient, scalable, and well compatible with a broad scope of substrates bearing halogens, trifluoromethyl, and electron-donating groups.



Keywords: 6*H*-Chromeno[4,3-*b*]quinoline, amide activation, triflic anhydride, intramolecular cycloaddition, tandem reactions.

Introduction

6*H*-Chromeno[4,3-*b*]quinolines represent pharmacological-privileged chromene- and quinoline- fused scaffolds, exhibiting various biological activities.[1-4] Consequently, they are acknowledged as promising druggable molecules. For example, compounds **1** are selective estrogen-receptor beta (ERβ) ligands with high binding IC_{50} values of 3.3 nM (**1a**), 3.6 nM (**1b**), and 6.1 nM (**1c**), respectively.[3] Functional testing carried out on electron-withdrawing NO_2-substituted compound **2** showed good cytotoxicity against murine melanoma cell line B16F10 and female breast-cancer cell line MCF7 with IC_{50} values of 14.8 and 21.32 μM, respectively.[2] Similarly, the tri-methoxy-substituted compound **3** also displayed apoptotic effects on colon cancer cell line HT29 (IC_{50} = 2.61 μM).[1] Moreover, recent research indicated that 6*H*-chromeno[4,3-*b*]quinolines could be used as fluorescent probes for selective detection of diverse chemical and biological components,[5-8] such as thiols,[8] pH,[6,7] lysosomes,[6] and mitochondria.[5] For example, Ren and Liu demonstrated that chromenoquinoline **4**, exhibiting low-cytotoxicity, good photostability, and near-infrared emission, could efficiently stain mitochondria and zebrafish for bioimaging.[5] Lin and coworkers revealed that compound **5** is capable of ratiometric fluorescence, monitoring pH variations from 7.4 to 5.5 in live cells.[7] Hence, the synthesis of 6*H*-chromeno[4,3-*b*]quinolines has received continuous interest in the fields of organic and pharmaceutical chemistry for a long time.[9-17]

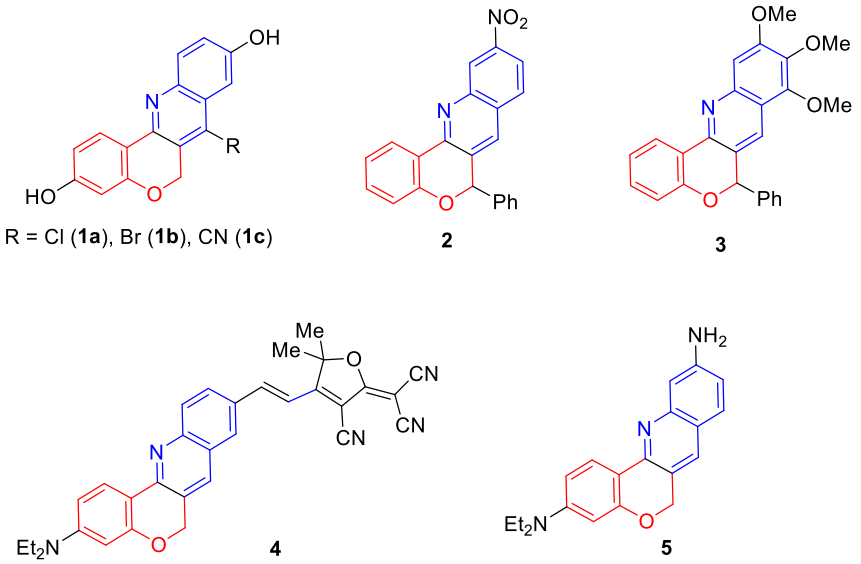
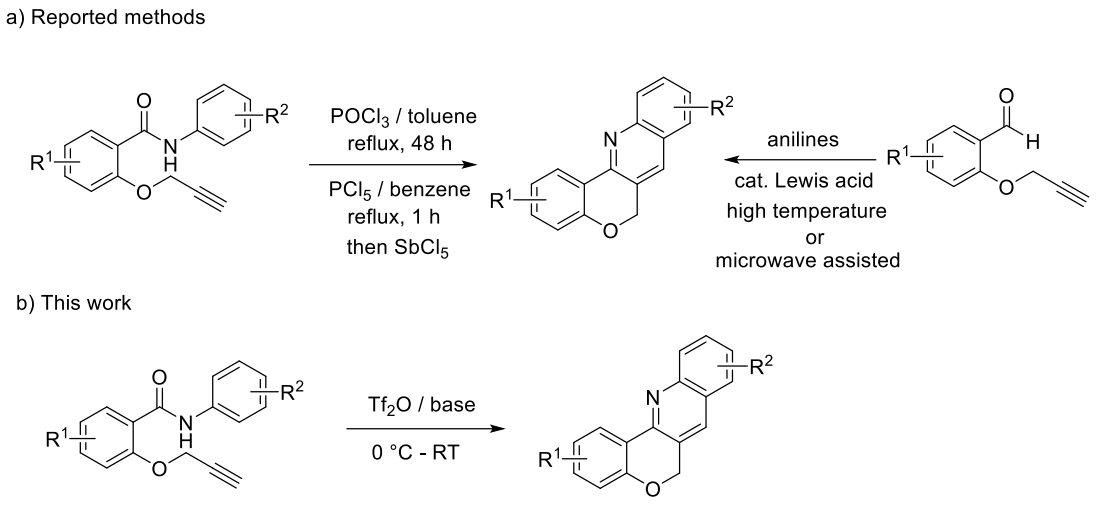


Figure 1. Some bioactive (upper) and luminescent (bottom) 6*H*-Chromeno[4,3-*b*]quinolines.

Among the developed methods, one-step construction of pyran and pyridine rings via intramolecular tandem cyclization reactions starting from readily available salicylic acid derivatives, also known as formal aza-Dies-Alder reactions or [4+2] cycloaddition reactions, stand out as an efficient and the most frequently employed strategy. In 1983, Miocque and coworkers synthesized 6*H*-chromeno[4,3-*b*]quinoline by subjecting *ortho*-propynyloxy benzamide to reflux conditions in toluene with $POCl_3$ for 48 hours (Scheme 1a).[15] This reaction involved an intramolecular cascade cycloaddition between the *in-situ* formed active nitrilium and a proximal alkyne. Alternatively, Ibrahim reported that the nitrilium intermediate was produced by treating *ortho*-propynyloxy benzamide with PCl_5 under reflux conditions in benzene to yield imidoyl chloride, followed by $SbCl_5$.[14] Also shown in Scheme 1a, the greener Lewis acid-catalyzed imine-alkyne intramolecular tandem

cyclization reaction of *ortho*-propynyloxy benzimines,[16] typically generated *in-situ* from condensation of *O*-propargylated salicylaldehydes and anilines,[5-7,9,10] represents a more broadly applicable protocol. However, due to relatively low nucleophilicity of the alkyne, the reaction often requires high-temperature conditions or microwave assistance.



Scheme 1. The representative synthetic strategy of 6*H*-chromeno[4,3-*b*]quinolines.

On the other hand, triflic anhydride (Tf_2O), an easily available mild electrophilic reagent, has been utilized to facilitate the conversions of diverse functional groups.[18] Pioneered by Ghosez,[19,20] direct transformations of amides have been extensively investigated and established as a robust method for selective synthesis.[21-48] Of particular interest is the utilization of an intermolecular alkyne-Tf_2O-activated amide cycloaddition for constructing ring structures. Ghosez's initial research demonstrated the smooth formation of cyclobutenones through Tf_2O/colidine-promoted [2+2]-cycloadditions of alkynes with tertiary amides under reflux conditions in $CHCl_3$.[19] Following this pioneering work, Yao treated an acetylenic aniline amide with Tf_2O/Ph_3PO to generate an imidate intermediate, initiating a cascade intramolecular annulation with an alkyne, to produce indolizinoquinolinones.[45] Huang and Liang, respectively, employed Tf_2O/2-fluoropyridine (2-F-Pyr) and Tf_2O/2,6-dichloropyridine (2,6-diCl-Pyr) as an activation system to promote the coupling reactions of secondary *N*-aryl secondary amides with alkynes, leading to the concise synthesis of quinolines.[46,47] It is worthy to note that the reactive nitrilium intermediate generated from Tf_2O/2-F-Pyr was identified by 2D NMR techniques.[46]

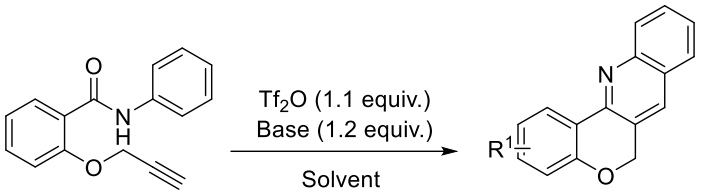
In light of the above-mentioned achievements, and in connection with our interest in developing a practical method for the direct transformation of amides,[25-32] we envisioned to develop a mild, efficient and versatile approach toward 6*H*-chromeno[4,3-*b*]quinoline through a Tf_2O-mediated amide-activation-triggered intramolecular-cascade alkyne-nitrilium cyclization reaction of salicylic-acid-derived *N*-phenyl *ortho*-propynyloxy benzamides (Scheme 1b above). Herein, we present the outcomes of our study.

Results and Discussion

We commenced our investigation by using *N*-phenyl-*ortho*-propynyloxy benzamide **6a** as a model compound to determine the optimal reaction conditions (Table 1). We first examined the conditions that we established previously for secondary amide activation.[48] The amide **6a** was treated with Tf_2O (1.1 equiv.) and 2-F-Pyr. (1.2 equiv.) in CH_2Cl_2 (0.1 M) at 0 °C for 15 min, then stirred at room temperature until the complete consumption of the substrate (monitored with TLC, ~8 h). To our delight, the desired product **7a** was afforded smoothly in 82% yield. Encouraged by this result, a screening of bases was conducted, however, the surveyed bases, including 2-Cl-Pyr., 2-Br-Pyr., 2,6-lutidine, 2,4,6-tri-tertbutylpyrimidine (TTBP), and pyridine (Pyr), all gave inferior results (entries 2-6). It is worth noting that **7a** could be generated in 50% yield under base-free conditions (entry 7). When running the reaction in 1,2-dichloroethane (DCE), **7a** was produced in the same yield (82%, entry 8). Changing the solvent to toluene resulted in a sharply reduced yield of 38% (entry 9). A slightly higher yield of 89% was obtained in the solvent CH_3CN (entry 10). Thus, CH_3CN was identified as the solvent of choice for subsequent optimization. Pleasingly, when increasing the concentration from 0.1 to 0.2 M (CH_3CN), **7a** was provided in an excellent isolated yield of 97% (entry 11). Further increase of the concentration to 0.5 M resulted in a loss of yield (90%, entry 12). Thus, the optimized conditions of the intramolecular tandem-cycloaddition reaction of *N*-phenyl *ortho*-propynyloxy benzamide **6a** were defined as follows: the amide **6a** was treated with Tf_2O (1.1 equiv.) and 2-F-Pyr. (1.2 equiv.) in CH_3CN (0.2 M) at 0 °C for 15 min, then stirred at room temperature for 8 h.

With optimized conditions in hand, the scope of amides was explored and the results are summarized in Table 2. For *N*-4-halogen-phenyl (F, Cl, Br, and I) benzamide **6b-e**, the corresponding 6*H*-chromeno[4,3-*b*]quinolines **7b-e** were afforded in good yields of 70%, 82%, 71%, and 87%, respectively. In the case of 3,4-dichloro-substituted **6f**, however, the product **7f** was provided in a modest yield of 27%. It is suggested that electron-withdrawing substituents at the *N*-phenyl moiety, therefore, have negative effects on the yield of the reaction, which was further demonstrated by the fact that the reaction of 4-CF_3-substituted **6g** produced the desired product **7g** in only 10% yield. The structure of **7g** was confirmed by single crystal X-ray diffraction analysis.

Table 1. Optimization of the Reaction Conditions[a]

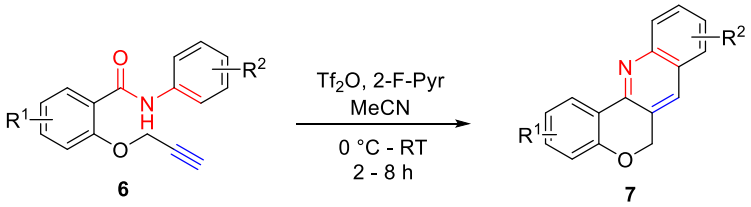


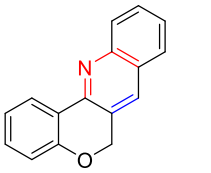
6a **7a**

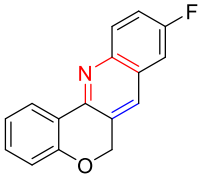
Entry	Base	Solvent	C(M)	Yield (%)[b]
1	2-F-Pyr	DCM	0.1	82%
2	2-Cl-Pyr	DCM	0.1	65%
3	2-Br-Pyr	DCM	0.1	45%
4	2,6-Lutidine	DCM	0.1	19%
5	TTBP[c]	DCM	0.1	32%
6	Pyr	DCM	0.1	22%
7	None	DCM	0.1	50%
8	2-F-Pyr	DCE	0.1	82%
9	2-F-Pyr	Toluene	0.1	38%
10	2-F-Pyr	CH_3CN	0.1	89%
11	**2-F-Pyr**	**CH_3CN**	**0.2**	**97%**[d]
12	2-F-Pyr	CH_3CN	0.5	90%

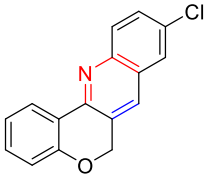
[a]Reaction conditions: To the mixture of amide **6a** (0.5 mmol), the base under investigation (0.60 mmol) in corresponding solvent Tf_2O (0.55 mmol) was added dropwise at 0 °C. After stirring at 0 °C for 15 minutes, the reaction was allowed to warm to room temperature and stirred until the complete consumption of the substrate (monitored with TLC, ~8 h). [b]Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c]TTBP=2,4,6-tri-*tert*-butylpyrimidine, 0.30 mmol. [d]Isolated yield.

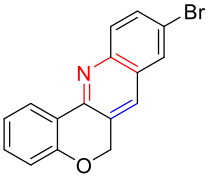
Table 2. Scope of Amides **6**

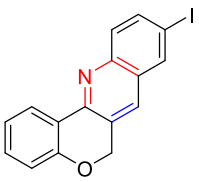


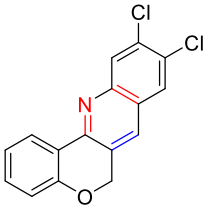

7a (97%)

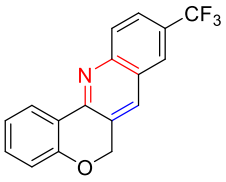

7b (70%)

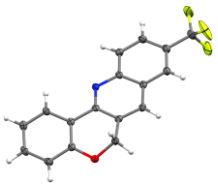

7c (82%)


7d (71%)


7e (87%)


7f (27%)


7g (10%[a]) (27%[b])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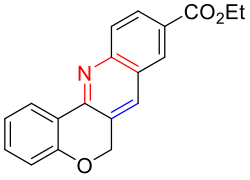
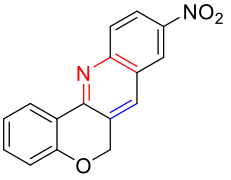
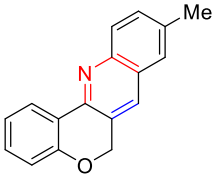
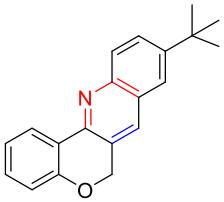
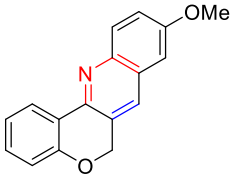
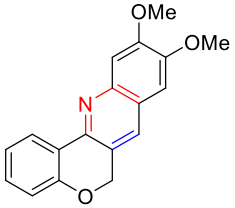

7h (ND[a, b])

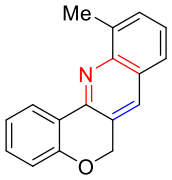

7i (ND[a, b])

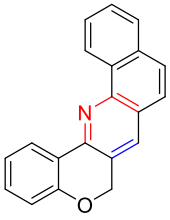

7j (76%)

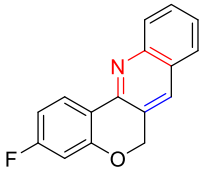

7k (75%)

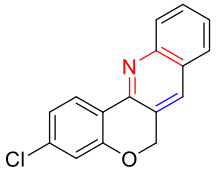

7l (94%)

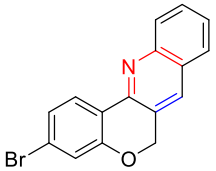

7m (57%)

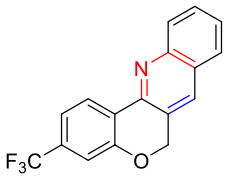

7n (62%)

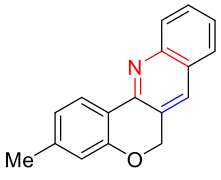

7o (37%)

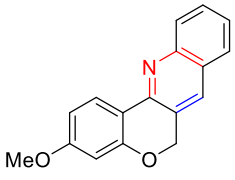

7p (65%)

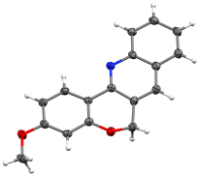

7q (79%)


7r (82%)


7s (50%[b])


7t (87%)


7u (95%[a]) (95%[c])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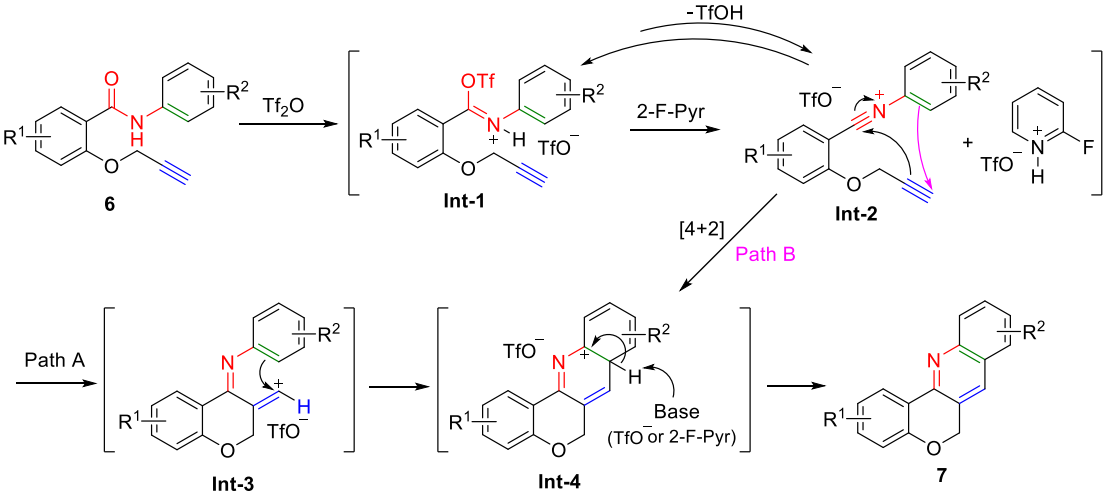
[a]Reaction conditions: To the mixture of amide **6** (0.5 mmol), 2-F-Pyr (0.60 mmol) in CH_3CN (2.5 mL) Tf_2O (0.55 mmol) was added dropwise at 0 °C. After stirring for 15 minutes at 0 °C, the reaction was allowed to warm to room temperature and stirred until the complete consumption of the substrate (monitored with TLC, 2~8 h). [b]80 °C, overnight. [c]Performed on the 6.0 mmol scale, 1.50 g of **7u** was obtained.

When raising the reaction temperature to 80 °C, and prolonging the reaction time to overnight, the yield of **7g** was slightly increased to 27%. Furthermore, no cycloaddition products **7h** and **7i** were observed in the reactions of the stronger electron-withdrawing methoxycarbonyl (CO_2Et) and nitro (NO_2) substituted benzamides **6h** and **6i** under standard conditions or at 80 °C overnight conditions. Comparatively, the reactions of 4-methyl and 4-*t*-butyl substituted **6j** and **6k** proceeded smoothly to afford the corresponding products **7j** and **7k** in good yields of 76% and 75%, respectively. In the case of the electron-rich 4-methoxy substituted **6l**, the corresponding chromenoquinoline **7l** was produced in an excellent yield of 94%. Unexpectedly, the cycloaddition of 3,4-dimethoxy substituted **6m** resulted in the corresponding product **7m** only in a moderate yield of 57% maybe owing to steric-hindrance. In addition, the reaction was well compatible with the sterically hindered *N*-2-methyl-phenyl benzamide **6n** to yield product **7n** in a slightly lower yield of 62%. For *N*-naphthyl benzamide **6o**, the reaction provided the cycloadduct **7o** in 37% yield. Next, the *N*-phenyl substituted benzamides were examined. Similarly, the reactions of *N*-phenyl 4-halogen (F, Cl, Br) substituted benzamides **6p**-**6r** gave the corresponding cycloadducts **7p**-**7r** in good yields of 65%, 79%, 82%, respectively. Delightfully, for 4-CF_3-substituted substrate **6s**, the product 7**s** was obtained in a moderate yield of 50% under the standard conditions. Expectedly, the benzamides (**6t** and **6u**) bearing an electron-donating methyl or methoxy group at the *para*-position provided corresponding cycloadducts **7t** and **7u** in excellent yields of 87% and 95%, respectively. The structure of **7u** has been determined by single crystal X-ray diffraction analysis. Additionally, the 6.0 mmol scale reaction of **6u** proceeded smoothly to give chromenoquinoline **7u** (1.50 g) in same yield of 95%.

Based on these results and previous NMR studies,[46] a plausible mechanism for the Tf_2O/2-F-Pyr-promoting domino intramolecular cycloaddition reaction of *N*-phenyl-*ortho*-propynyloxy benzamide is depicted in Scheme 2. Upon the amide **6** treatment with Tf_2O, the imidate **Int-1** and nitrilium **Int-2** were formed. And the presence of 2-F-Pyr facilitates the complete conversion of **Int-1** into **Int-2**. The highly electrophilic nitrilium **Int-2** couples with alkyne group to give an alkenyl cation intermediate **Int-3**,[46,49] which is prone to be captured by the proximal *N*-phenyl group to produce, via a Friedel-Crafts cyclization, 6*H*-chromeno[4,3-*b*]quinoline **7** (Path A). Alternatively, **Int-2** has the potential to undergo a [4+2] cycloaddition process to form **Int-4**, ultimately leading to the formation of chromenoquinoline **7** (Path B).



Scheme 2. Plausible mechanism.

Conclusions

In summary, we have disclosed a facile and efficient approach towards bio-important and fluorescent 6*H*-chromeno[4,3-*b*]quinolines, via Tf_2O-mediated tandem intramolecular cycloaddition reactions of the easily accessible *N*-phenyl *ortho*-propynyloxy benzamides. This method features good yields, good substrate scope, mild and metal-free reaction conditions, and scalability, thereby providing a viable alternative for the preparation of functionalized chromenoquinolines from amides without the use of toxic/sensitive reagents such as $POCl_3$ and PCl_5.

Experimental Section

General. Melting points were determined by a Switzerland Büchi M-560 automatic melting point apparatus. Infrared spectra were measured with a Nicolet Avatar 330 FT-IR spectrometer using film KBr pellet techniques. ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 MHz spectrometer with $CDCl_3$ as solvent. Chemical shifts (δ) are reported in ppm and respectively referenced to either the internal standard Me_4Si (TMS) or solvent signals (Me_4Si at 0 ppm for ^{1}H NMR, and $CDCl_3$ at 77.0 ppm for ^{13}C NMR). HRMS spectra were recorded on a Bruker Dalton Esquire 3000 plus mass spectrometer by the ESI method. Unless otherwise stated, reactions were performed in oven-dried glassware under a nitrogen atmosphere using standard Schlenk techniques. Flash-column chromatography was performed with silica gel (300-400 mesh), eluting with EtOAc/petroleum ether. Triflic anhydride (Tf_2O) was distilled over phosphorous pentoxide and was stored under 0 °C for no more than a week before use. All other commercially available compounds were used as received.

General procedure for the synthesis of 6*H*-chromeno[4,3-*b*]quinolines. To a flame-dried Schlenk tube were added sequentially an amide (0.5 mmol, 1.0 equiv), 2-F-Pyr (0.60 mmol, 1.2 equiv) and MeCN (2.5 mL) at room temperature, then trifluoromethanesulfonic anhydride (Tf_2O, 0.55 mmol, 1.1 equiv) was added dropwise at 0 °C. After stirring for 15 minutes at 0 °C, the mixture was allowed to warm to room temperature and stirred until the complete consumption of the substrate (monitored with TLC, 2~8 h). The the reaction was then quenched with a saturated aqueous $NaHCO_3$ solution (1.0 mL). The reaction mixture was extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (elution EtOAc/petroleum ether) on silica gel to afford the desired product.

6*H*-Chromeno[4,3-*b*]quinoline (7a). Following the general procedure, the reaction of **6a** (125.5 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/petroleum ether = 1:20), compound **7a** as a white floppy solid (113mg, yield: 97%). Mp: 125-127 °C (lit.[16] Mp 64-66 °C ; lit.[50] Mp 126 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (dd, *J* 7.7, 1.7 Hz, 1H), 8.13 (d, *J* 8.4 Hz, 1H), 7.87 (s, 1H), 7.77 (d, *J* 8.2 Hz, 1H), 7.73 –7.64 (m, 1H), 7.50 (t, *J* 7.5 Hz, 1H), 7.42 –7.33 (m, 1H), 7.17 (t, *J*7.4 Hz, 1H), 7.02 (d, *J* 8.2 Hz, 1H), 5.36 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.65, 149.27, 148.59, 132.11, 131.17, 129.77, 129.66, 127.82, 127.66, 126.52, 125.79, 125.48, 123.50, 122.79, 117.57, 68.65 ppm; HRMS (ESI) *m/z*: calcd for $C_{16}H_{12}NO^+$ $[M + H]^+$: 234.0913, found: 234.0913.

9-Fluoro-6*H*-chromeno[4,3-*b*]quinoline (7b). Following the general procedure, the reaction of **6b** (134.5 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/petroleum ether = 1:20), compound **7b** as a white floppy solid (88 mg, yield: 70%). Mp: 118-121 °C (lit.[50] Mp 99-101 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (dd, *J* 7.8, 1.9 Hz, 1H), 8.11 (dd, *J* 9.2, 5.4 Hz, 1H), 7.79 (s, 1H), 7.45 (td, *J* 8.8, 2.7 Hz, 1H), 7.41 –7.33 (m, 2H), 7.16 (t, *J* 7.5 Hz, 1H), 7.02 (d, *J* 8.2 Hz, 1H), 5.34 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.58 (d, $J_{C\text{-}F}$= 248.0 Hz), 157.51,

148.72, 145.63, 132.15 (d, $J_{C\text{-}F}$= 4.5 Hz), 132.00, 130.47 (d, $J_{C\text{-}F}$= 5.3 Hz), 128.34 (d, $J_{C\text{-}F}$= 9.9 Hz), 126.31, 125.60, 123.24, 122.84, 119.87 (d, $J_{C\text{-}F}$= 25.6 Hz), 117.59, 110.79 (d, $J_{C\text{-}F}$= 21.9 Hz), 68.51 ppm; HRMS (ESI) *m/z*: calcd for $C_{16}H_{11}FNO^+$ [M + H]$^+$: 252.0819, found: 252.0819.

9-Chloro-6*H*-chromeno[4,3-*b*]quinoline (7c). Following the general procedure, the reaction of **6c** (142.5 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/petroleum ether = 1:20), compound **7c** as a pale-yellow crystalline solid (109 mg, yield: 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, *J* 7.8, 1.7 Hz, 1H), 8.02 (d, *J* 9.0 Hz, 1H), 7.72 –7.65 (m, 2H), 7.59 (dd, *J* 9.0, 2.3 Hz, 1H), 7.41 –7.33 (m, 1H), 7.15 (t, *J* 7.4 Hz, 1H), 7.00 (d, *J* 8.1 Hz, 1H), 5.30 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.58, 149.47, 146.87, 132.33, 132.07, 131.15, 130.58, 130.09, 128.29, 126.33, 126.29, 125.71, 123.08, 122.82, 117.59, 68.41 ppm; HRMS (ESI) *m/z*: calcd for $C_{16}H_{11}ClNO^+$ [M + H]$^+$: 268.0524, found: 268.0522.

9-Bromo-6*H*-chromeno[4,3-*b*]quinoline (7d). Following the general procedure, the reaction of **6d** (164.5 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/petroleum ether = 1:15), compound **7d** as a yellow floppy solid (110 mg, yield: 71%). Mp: 142-144 °C (lit.[16] Mp 137-139 °C ; lit.[50] Mp 138 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, *J* 7.8, 1.7 Hz, 1H), 7.95 (d, *J* 8.9 Hz, 1H), 7.86 (d, *J* 2.2 Hz, 1H), 7.74 –7.66 (m, 2H), 7.39 –7.35 (m, 1H), 7.15 (td, *J* 7.5, 1.2 Hz, 1H), 7.00 (dd, *J* 8.2, 1.1 Hz, 1H), 5.30 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.62, 149.60, 147.07, 133.13, 132.39, 131.26, 130.01, 129.63, 128.82, 126.32, 125.76, 123.06, 122.83, 120.24, 117.61, 68.41 ppm; HRMS (ESI) *m/z*: calcd for $C_{16}H_{11}BrNO^+$ [M + H]$^+$: 312.0019, found: 312.0019.

9-Iodo-6*H*-chromeno[4,3-*b*]quinoline (7e). Following the general procedure, the reaction of **6e** (188.5 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/petroleum ether = 1:15), compound **7e** as a pale-yellow crystalline solid (156 mg, yield: 87%). Mp: 138-141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (dd, *J* 7.8, 1.5 Hz, 1H), 8.08 (t, *J* 1.5 Hz, 1H), 7.87 (dt, *J* 8.9, 1.6 Hz, 1H), 7.79 (d, *J* 8.9 Hz, 1H), 7.64 (s, 1H), 7.40 –7.33 (m, 1H), 7.14 (t, *J* 7.5 Hz, 1H), 6.99 (d, *J* 8.2 Hz, 1H), 5.28 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.62, 149.69, 147.38, 138.39, 136.28, 132.43, 131.18, 129.78, 129.37, 126.13, 125.79, 123.00, 122.82, 117.60, 91.83, 68.39 ppm; HRMS (ESI) *m/z*: calcd for $C_{16}H_{11}INO^+$ [M + H]$^+$: 359.9880, found: 359.9878.

9,10-Dichloro-6*H*-chromeno[4,3-*b*]quinoline (7f). Following the general procedure, the reaction of **6f** (159.5 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/petroleum ether = 1:50), compound **7f** as a white solid (41 mg, yield: 27%). Mp: 166-168 °C; IR (film) ν_{max}: 2917, 1607, 1580, 1471, 1239, 1150, 1037, 915, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (dd, *J* 7.8, 1.8 Hz, 1H), 8.22 (s, 1H), 7.84 (s, 1H), 7.73 (s, 1H), 7.42 –7.37 (m, 1H), 7.16 (t, *J* 7.6 Hz, 1H), 7.01 (d, *J* 8.2 Hz, 1H), 5.32 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.74, 150.46, 147.16, 134.11, 132.72, 130.81, 130.66, 129.84, 128.08, 126.78, 126.54, 125.86, 122.92, 122.81, 117.68, 68.37 ppm; HRMS (ESI) *m/z*: calcd for $C_{16}H_{10}Cl_2NO^+$ [M + H]$^+$: 302.0134, found: 302.0134.

9-(Trifluoromethyl)-6*H*-chromeno[4,3-*b*]quinoline (7g). Following the general procedure, the reaction of **6g** (159.5 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/petroleum ether = 1:20), compound **7g** as a pale-yellow solid (15 mg, yield: 10%; 41 mg, yield: 27% obtained at 80 °C overnight conditions). Mp: 147-149 °C (lit.[16] Mp 122-124 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* 7.8 Hz, 1H), 8.16 (d, *J* 8.8 Hz, 1H), 8.00 (s, 1H), 7.82 –7.80 (m, 2H), 7.38 (t, *J* 7.6 Hz, 1H), 7.15 (t, *J* 7.5 Hz, 1H), 7.00 (d, *J* 8.2 Hz, 1H), 5.30 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.85, 151.24, 149.47, 132.83, 131.68, 130.66, 128.06 (q, $J_{C\text{-}F}$= 32.0 Hz), 126.63, 125.61, 125.99, 125.50 (q, $J_{C\text{-}F}$= 5.0 Hz) , 125.37, 125.33, 124.26 (q, $J_{C\text{-}F}$= 271.0 Hz) 122.87, 117.67, 68.32 ppm; HRMS (ESI) *m/z*: calcd for $C_{17}H_{11}F_3NO^+$ [M + H]$^+$: 302.0787, found: 302.0787.

9-Methyl-6*H*-chromeno[4,3-*b*]quinoline (7j). Following the general procedure, the reaction of **6j** (132.5 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/petroleum ether = 1:15), compound **7j** as a brown-yellow floppy solid (94 mg, yield: 76%). Mp: 125-127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (dd, *J* 7.8, 1.6 Hz, 1H), 8.00 (d, *J* 8.5 Hz, 1H), 7.68 (s, 1H), 7.54 –7.41 (m, 2H), 7.39 –7.29 (m, 1H), 7.18 –7.11 (m, 1H), 7.00 (d, *J* 8.1 Hz, 1H), 5.28 (s, 2H), 2.49 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.43, 148.32, 147.09, 136.36, 131.97, 131.78,

130.43, 129.26, 127.77, 126.54, 125.57, 125.35, 123.57, 122.68, 117.46, 68.62, 21.75 ppm; HRMS (ESI) *m/z*: calcd for $C_{17}H_{14}NO^+$ $[M + H]^+$: 248.1070, found: 248.1070.

9-(*tert*-Butyl)-6*H*-chromeno[4,3-*b*]quinoline (7k). Following the general procedure, the reaction of **6k** (153.5 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/petroleum ether = 1:15), compound **7k** as a brown-yellow solid (108 mg, yield: 75%). Mp: 143-146 °C; IR (film) ν_{max}: 3048, 2978, 2897, 2867, 1584, 1465, 1236, 917, 838, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (dd, *J* 7.8, 1.7 Hz, 1H), 8.05 (d, *J* 8.9 Hz, 1H), 7.82 –7.72 (m, 2H), 7.66 (d, *J* 2.2 Hz, 1H), 7.40 –7.30 (m, 1H), 7.15 (t, *J* 7.4 Hz, 1H), 7.01 (d, *J* 8.1 Hz, 1H), 5.32 (s, 2H), 1.42 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.46, 149.38, 148.58, 147.12, 131.78, 131.10, 129.15, 128.66, 127.50, 125.65, 125.31, 123.68, 122.70, 122.67, 117.48, 68.68, 35.11, 31.40 ppm; HRMS (ESI) *m/z*: calcd for $C_{20}H_{20}NO^+$ $[M + H]^+$: 290.1539, found: 290.1539.

9-Methoxy-6*H*-chromeno[4,3-*b*]quinoline (7l). Following the general procedure, the reaction of **6l** (140.5 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/petroleum ether = 1:4), compound **7l** as a brown-yellow solid (124 mg, yield: 94%). Mp: 140-143 °C (lit.[50] Mp 125 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (dd, *J* 7.8, 1.7 Hz, 1H), 8.02 (d, *J* 9.2 Hz, 1H), 7.72 (s, 1H), 7.38 –7.30 (m, 2H), 7.19 –7.11 (m, 1H), 7.04 –6.96 (m, 2H), 5.31 (s, 2H), 3.92 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.92, 157.21, 146.94, 144.59, 131.53, 131.06, 129.92, 128.79, 125.72, 125.35, 123.65, 122.73, 122.29, 117.44, 105.40, 68.65, 55.74 ppm; HRMS (ESI) *m/z*: calcd for $C_{17}H_{14}NO_2^+$ $[M + H]^+$: 264.1019, found: 264.1019.

9,10-Dimethoxy-6*H*-chromeno[4,3-*b*]quinoline (7m). Following the general procedure, the reaction of **6m** (155.5 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/petroleum ether = 1:15), compound **7m** as a white solid (84 mg, yield: 57%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (dd, *J* 7.8, 1.7 Hz, 1H), 7.71 (s, 1H), 7.47 (s, 1H), 7.37 –7.30 (m, 1H), 7.15 (t, *J* 7.5 Hz, 1H), 7.01 (d, *J* 6.6 Hz, 2H), 5.32 (s, 2H), 4.06 (s, 3H), 4.02 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.17, 152.68, 149.94, 147.14, 145.56, 131.44, 129.56, 125.18, 123.80, 123.58, 123.32, 122.68, 117.44, 108.38, 105.25, 68.66, 56.39, 56.27 ppm; HRMS (ESI) *m/z*: calcd for $C_{18}H_{16}NO_3^+$ $[M + H]^+$: 294.1125, found: 294.1124.

11-Methyl-6*H*-chromeno[4,3-*b*]quinoline (7n). Following the general procedure, the reaction of **6n** (132.5 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/petroleum ether = 1:20), compound **7n** as a yellow floppy solid (76 mg, yield: 62%). Mp: 92-95 °C (lit.[16] Mp 72-74 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (dd, *J* 7.8, 1.8 Hz, 1H), 7.81 (s, 1H), 7.59 (d, *J* 8.1 Hz, 1H), 7.53 (d, *J* 7.0 Hz, 1H), 7.39 –7.34 (m, 2H), 7.16 (t, *J* 7.4 Hz, 1H), 7.01 (d, *J* 8.1 Hz, 1H), 5.36 (s, 2H), 2.88 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.53, 147.82, 147.47, 137.70, 131.83, 131.27, 129.81, 127.73, 126.25, 125.74, 125.58, 124.92, 123.91, 122.65, 117.48, 68.62, 18.11 ppm; HRMS (ESI) *m/z*: calcd for $C_{17}H_{14}NO^+$ $[M + H]^+$: 248.1070, found: 248.1070.

6*H*-Benzo[h]chromeno[4,3-*b*]quinoline (7o). Following the general procedure, the reaction of **6o** (150.5 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/petroleum ether = 1:15), compound **7o** as a white floppy solid (52 mg, yield: 37%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.55 (d, *J* 8.0 Hz, 1H), 8.49 (d, *J* 8.0 Hz, 1H), 8.05 –7.90 (m, 3H), 7.69 –7.60 (m, 2H), 7.41 –7.34 (m, 1H), 7.18 (t, *J* 7.5 Hz, 1H), 7.03 (d, *J* 8.1 Hz, 1H), 5.46 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.34, 148.66, 148.46, 131.95, 131.83, 131.04, 129.78, 129.00, 128.50, 127.37, 127.28, 126.38, 125.48, 125.06, 124.80, 123.42, 122.78, 122.68, 117.46, 68.83 ppm; HRMS (ESI) *m/z*: calcd for $C_{20}H_{14}NO^+$ $[M + H]^+$: 284.1070, found: 284.1070.

3-Fluoro-6*H*-chromeno[4,3-*b*]quinoline (7p). Following the general procedure, the reaction of **6p** (134.5 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/petroleum ether = 1:70), compound **7p** as a pale-yellow floppy solid (82 mg, yield: 65%). Mp: 115-118 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 –8.41 (m, 1H), 8.09 (d, *J* 8.5 Hz, 1H), 7.83 (s, 1H), 7.75 (d, *J* 8.1 Hz, 1H), 7.69 (t, *J* 7.7 Hz, 1H), 7.48 (t, *J* 7.5 Hz, 1H), 6.87 (td, *J* 8.5, 2.5 Hz, 1H), 6.72 (dd, *J* 9.8, 2.5 Hz, 1H), 5.35 (s, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.23 (d, $J_{C\text{-}F}$= 250.3 Hz), 158.85 (d, $J_{C\text{-}F}$= 12.4 Hz), 148.54, 148.51, 131.24, 129.88, 129.52, 127.69, 127.67, 127.49 (d, $J_{C\text{-}F}$= 10.4 Hz), 126.50, 124.52,

119.86 (d, J_{C-F}= 2.7 Hz), 110.30 (d, J_{C-F}= 22.2 Hz), 104.87 (d, J_{C-F}= 24.7 Hz), 68.96 ppm; MS (ESI) *m/z*: calcd for $C_{16}H_{11}FNO^+$ [M + H]$^+$: 252.0819, found: 252.0819.

3-Chloro-6*H*-chromeno[4,3-*b*]quinoline (7q). Following the general procedure, the reaction of **6q** (142.5 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/petroleum ether = 1:70), compound **7q** as a white floppy solid (105 mg, yield: 79%). Mp: 138-139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.40 (d, *J* 8.4 Hz, 1H), 8.10 (d, *J* 8.5 Hz, 1H), 7.83 (s, 1H), 7.75 (d, *J* 8.2 Hz, 1H), 7.71 –7.67 (m, 1H), 7.51 –7.47 (m, 1H), 7.12 (dd, *J* 8.4, 2.0 Hz, 1H), 7.02 (d, *J* 2.0 Hz, 1H), 5.34 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 158.00, 148.52, 148.31, 137.34, 131.27, 129.94, 129.59, 127.82, 127.68, 126.83, 126.69, 124.79, 123.16, 122.05, 117.85, 68.83 ppm; HRMS (ESI) *m/z*: calcd for $C_{16}H_{11}ClNO^+$ [M + H]$^+$: 268.0524, found: 268.0524.

3-Bromo-6*H*-chromeno[4,3-*b*]quinoline (7r). Following the general procedure, the reaction of **6r** (164.5 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/petroleum ether = 1:70), compound **7r** as a white floppy solid (127 mg, yield: 82%). Mp: 150-152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.30 (d, *J* 8.4 Hz, 1H), 8.07 (d, *J* 8.4 Hz, 1H), 7.76 (s, 1H), 7.73 –7.64 (m, 2H), 7.47 (t, *J* 7.3 Hz, 1H), 7.25 (dd, *J* 8.3, 2.0 Hz, 1H), 7.16 (d, *J* 1.9 Hz, 1H), 5.29 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 157.96, 148.46, 148.26, 131.21, 129.90, 129.55, 127.79, 127.65, 126.96, 126.67, 125.96, 125.41, 124.75, 122.41, 120.75, 68.76 ppm; HRMS (ESI) *m/z*: calcd for $C_{16}H_{11}BrNO^+$ [M + H]$^+$: 312.0019, found: 312.0018.

3-(Trifluoromethyl)-6*H*-chromeno[4,3-*b*]quinoline (7s). Following the general procedure, the reaction of **6s** (159.5 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/petroleum ether = 1:80), compound **7s** as a pale-yellow solid (75 mg, yield: 50%). Mp: 138-140 °C; IR (film) ν_{max}: 3077, 2924, 1582, 1496, 1450, 1327, 1164, 1118, 880, 763 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.55 (d, *J* 8.1 Hz, 1H), 8.11 (d, *J* 8.5 Hz, 1H), 7.81 (s, 1H), 7.76 – 7.67 (m, 2H), 7.52 –7.48 (m, 1H), 7.36 (dd, *J* 8.2, 1.7 Hz, 1H), 7.25 (s, 1H), 5.35 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 157.34, 148.51, 147.65, 133.44 (q, J_{C-F}= 33.0 Hz), 131.41, 130.05, 129.78, 128.04, 127.69, 127.09, 126.37, 125.27, 125.06, 123.92 (q, J_{C-F}= 271.0 Hz), 119.11 (q, J_{C-F}= 3.8 Hz), 114.94 (q, J_{C-F}= 4.0 Hz), 68.67 ppm; HRMS (ESI) *m/z*: calcd for $C_{17}H_{11}F_3NO^+$ [M + H]$^+$: 302.0787, found: 302.0787.

3-Methyl-6*H*-chromeno[4,3-*b*]quinoline (7t). Following the general procedure, the reaction of **6t** (132.5 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/petroleum ether = 1:80), compound **7t** as a pale-yellow floppy solid (107 mg, yield: 87%). Mp: 101-103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.31 (d, *J* 7.9 Hz, 1H), 8.05 (d, *J* 8.7 Hz, 1H), 7.62 –7.56 (m, 3H), 7.38 –7.33 (m, 1H), 6.92 (d, *J* 7.9 Hz, 1H), 6.77 (s, 1H), 5.17 (s, 2H), 2.32 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 157.42, 149.20, 148.36, 142.66, 130.77, 129.45, 129.33, 127.50, 127.48, 126.01, 125.47, 125.07, 123.66, 120.65, 117.71, 68.42, 21.73 ppm; HRMS (ESI) *m/z*: calcd for $C_{17}H_{14}NO^+$ [M + H]$^+$: 248.1070, found: 248.1069.

3-Methoxy-6*H*-chromeno[4,3-*b*]quinoline (7u). Following the general procedure, the reaction of **6u** (140.5 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/petroleum ether = 1:70), compound **7u** as a pale-yellow solid (125 mg, yield: 95%). Mp: 119-122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.36 (d, *J* 8.7 Hz, 1H), 8.05 (d, *J* 8.4 Hz, 1H), 7.68 (s, 1H), 7.66 –7.59 (m, 2H), 7.42 –7.37 (m, 1H), 6.70 (dd, *J* 8.7, 2.5 Hz, 1H), 6.50 (d, *J* 2.5 Hz, 1H), 5.24 (s, 2H), 3.80 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 163.06, 158.95, 149.24, 148.49, 130.81, 129.54, 129.23, 127.56, 127.34, 126.92, 125.86, 124.54, 116.41, 109.81, 101.87, 68.78, 55.59 ppm; HRMS (ESI) *m/z*: calcd for $C_{17}H_{14}NO_2^+$ [M + H]$^+$: 264.1019, found: 264.1019.

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Supplementary Material

Experimental procedures for the synthesis of the amides, and copies of ^{1}H and ^{13}C NMR spectra of compounds **6d-6h**, **6p-6u, 7a-7g**, **7j-7u**, and X-ray crystallographic data of compounds **7g**, **7u** (CCDC 2335879, 2335878) are presented in the Supplementary Material associated with this paper.

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