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Note

Intramolecular Povarov Reactions for the Synthesis of Chromenopyridine Fused 2-Pyridone Polyheterocycles Binding to α-Synuclein and Amyloid-β Fibrils

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ABSTRACT: A $BF_3 \cdot OEt_2$ catalyzed intramolecular Povarov reaction was used to synthesize 15 chromenopyridine fused thiazolino-2-pyridone peptidomimetics. The reaction works with several O-alkylated salicylaldehydes and amino functionalized thiazolino-2-pyridones, to generate polyheterocycles with diverse substitution. The synthesized compounds were screened for their ability to bind α-synuclein and amyloid β fibrils *in vitro*. Analogues substituted with a nitro group bind to mature amyloid fibrils, and the activity moreover depends on the positioning of this functional group.
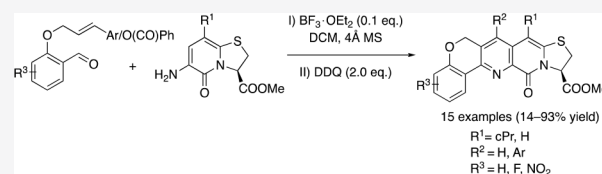
The thiazolino fused 2-pyridone represents a privileged scaffold which can be modified to display various biological activities.[1] It was initially designed as a peptidomimetic to combat the virulence of uropathogenic *E. coli* by inhibiting the formation of pili.[1a] With alternative substitution patterns, compounds based on this scaffold have also demonstrated activity against *Chlamydia trachomatis*,[1b] *Listeria monocytogenes*,[1c] and *Mycobacterium tuberculosis*.[1d] Rigidifying the scaffold by equipping it with sterically demanding aryl groups provides compounds with the ability to modulate formation of bacterial and human amyloid fibrils.[2] Extension of the bicyclic thiazolino fused 2-pyridone with nitrogen containing aromatic heterocycles offers another way of rigidifying the peptidomimetic scaffold,[3] as exemplified by compounds 1−4 (Figure 1A). These analogues are able to modulate α-synuclein amyloid fibril formation, which is associated with Parkinson's disease, a human neurodegenerative disorder,[2a,3a,b] or bind to mature α-synuclein fibrils.[3c]

Chromenopyridine is a versatile structural motif present in a variety of polyheterocycles with applications in biology as estrogenic, antibacterial, and anticancer agents and biosensors (compounds 5−8, respectively, Figure 1B).[4] Recently, the merging of two different active fragments to develop scaffolds with improved biological properties has received considerable attention.[5] As mentioned above, annulation of bicyclic thiazolino fused 2-pyridone with different heterocycles has resulted in scaffolds capable of modulating amyloid fibrils.[3] We envisaged that fusing thiazolino 2-pyridone and chromenopyridine, by combining units 9 and 10, could afford scaffolds with the ability to target amyloid structures (Figure 1B) and, in addition, constitute a new central fragment with great potential for drug discovery in general.

Since its discovery, the Povarov reaction[6] has been used widely for the synthesis of nitrogen containing, six-membered heterocycles with biological relevance.[7] Recently, we utilized the Lewis acid catalyzed Povarov reaction to construct a tricyclic pyridine fused 2-pyridone peptidomimetic scaffold,[3c] whose analogues have been shown to bind α-synuclein and Aβ fibrils by ThT displacement[8] *in vitro* (e.g., compound 4, Figure 1A). We envisioned that performing the Povarov reaction in an intramolecular fashion[9] could result in the desired chromenopyridine annulated 2-pyridones 11 in a single operation (Figure 1B). The new scaffold 11 being equipped with the tetrahedral carbon, and the oxygen, could decrease planarity of the structures and enable increased hydrogen bonding, respectively.[10] In addition, these features could potentially confer selectivity between different amyloid structures, a very desired property in diagnostic and therapeutic applications of amyloid binding small molecules.[11]

We perceived that chromenopyridine ring fused 2-pyridone scaffold 11 would be accessible from amino 2-pyridone 9 and O-alkylated salicylaldehyde 10. Hence, we began our work by investigating the feasibility of the reaction between 9a and O-cinnamyl salicylaldehyde 10a in an intramolecular Povarov setup using $BF_3 \cdot OEt_2$ as catalyst, followed by oxidation with DDQ (Scheme 1).[3c] As hypothesized, the intramolecular reaction worked smoothly, and the desired product 11a was
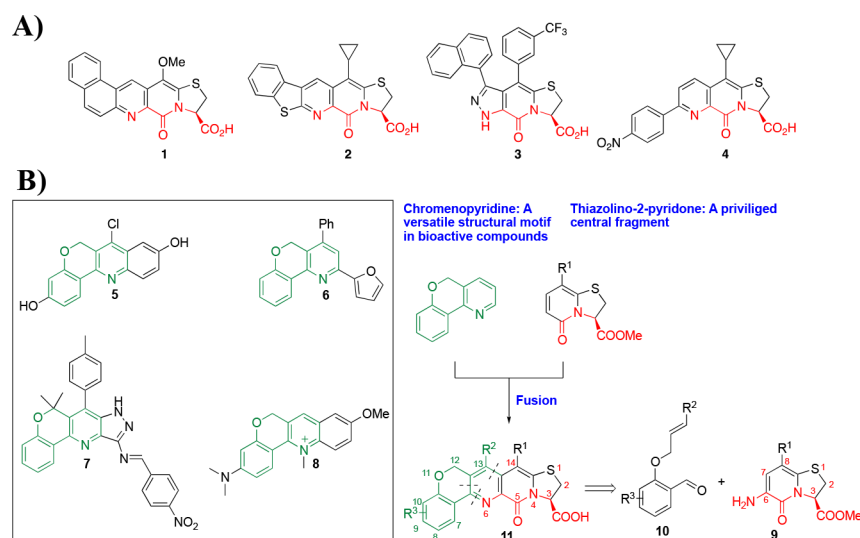
**Figure 1.** (A) Bicyclic 2-pyridones capable of modulating (compounds **1−3**) and binding (compound **4**) to α-synuclein and amyloid β fibrils. (B) Chromenopyridine containing bioactive polyheterocycles **5−8** and retrosynthetic strategy devised for construction of chromenopyridine fused 2-pyridone polyheterocycle **11**.

**Scheme 1. Synthesis of 2-Pyridone Based Polyheterocycles 11a−k**
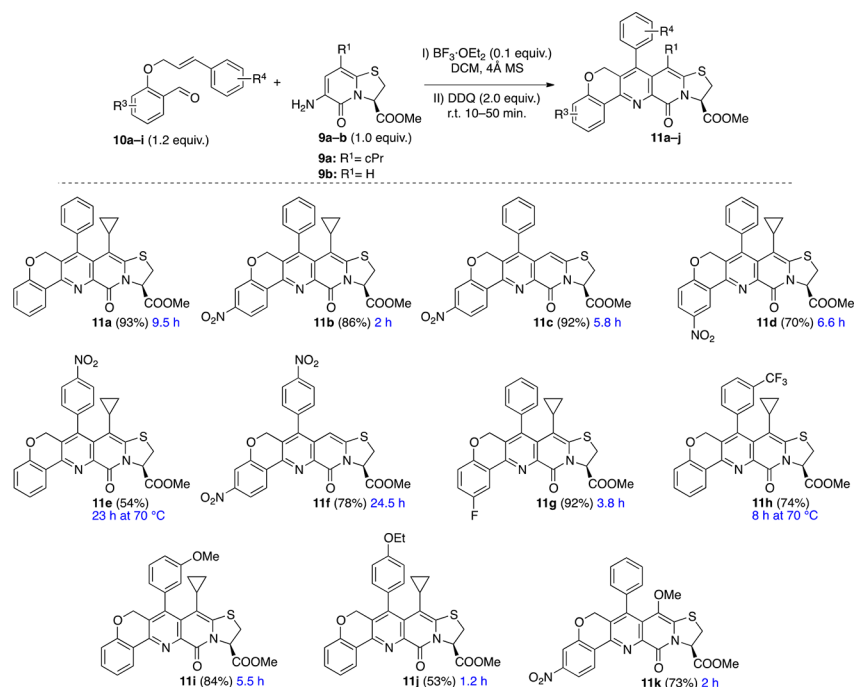
isolated in excellent yield. To explore the substrate scope of the reaction, substituted *O*-cinnamyl salicylaldehydes **10b−i** (Schemes S1 and S2) were allowed to react with 6-amino-2-pyridones **9a,b** to construct **11b−k** in good to excellent yields (Scheme 1).

Aware of the importance of the 4-nitrophenyl substituent for amyloid binding activity of the tricyclic scaffold **4**,[3c] we prepared **11b−f** and **11k** with nitro groups in various positions. Notably, salicylaldehydes with electron withdrawing R^3 substituents underwent faster Povarov reaction due to lowering of LUMO in the electrophilic imine intermediate, providing **11b−d**, **11g**, and **11k**.[12] Electron donating R^4 substituents rendered the alkene more nucleophilic and likewise decreased the reaction times, while electron with-

drawing R^4 substituents increased them. Heating was required to achieve synthetically useful reaction times for synthesis of **11e** and **11h**, where, in the former case, the moderate yield reflects a less clean conversion. In the preparation of **11f**, the effect of the electron withdrawing R^3 substituent compensated for poor nucleophilicity of the alkene moiety, and heating was not required to complete the reaction in 1 day. To test the scalability, **11b** was also prepared from 1.6 mmol of **9a**. The yield (88%) is comparable to that at 0.4 mmol scale (86%).

Next, we turned our attention toward the synthesis of C-13 unsubstituted target molecules **13** (Scheme 2). SAR from our previous study suggested that the best amyloid binding properties are achieved when the corresponding position is unsubstituted.[3c] It was approached by Povarov reaction

Scheme 2. Unsuccessful Attempt to Synthesize C-13 Unsubstituted Compound 13a
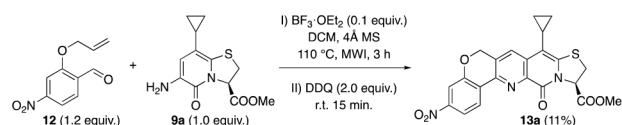
between **9a** and *O*-allyl salicylaldehyde **12**. To our dismay, we were only able to isolate small amounts (7%) of the desired product **13a**, from the complex reaction mixture after 4 days at 70 °C. Microwave irradiation, 120 °C for 3 h, shared the same lack of success, and **13a** was isolated in only 11% yield. Though fruitful results are reported,[9e] attempts with terminal allyl moieties often suffer from low yields.[7a,9a,12a,b]

Familiar with the mechanistic features of the Lewis acid catalyzed Povarov reaction,[7a,d,e,12c,13] we realized that use of the terminal allyl group as alkene components would require the reaction to go via high energy carbocations or operate via an alternative mechanism.[9a,b,d,14] With our previous strives in mind where we had made use of ethyl vinyl ether as alkene component, for synthesis of unsubstituted tricyclic analogues **4**,[3c] we naturally thought of employing a vinyl ester moiety as electron donating auxiliary. With 3-bromopropenyl benzoate,[15] we were able to alkylate salicylic aldehydes to synthesize the required intermediates **14a–d** (Schemes 3 and S3). With the

Scheme 3. Synthesis of C-13 Unsubstituted Compounds 13a–e[a]
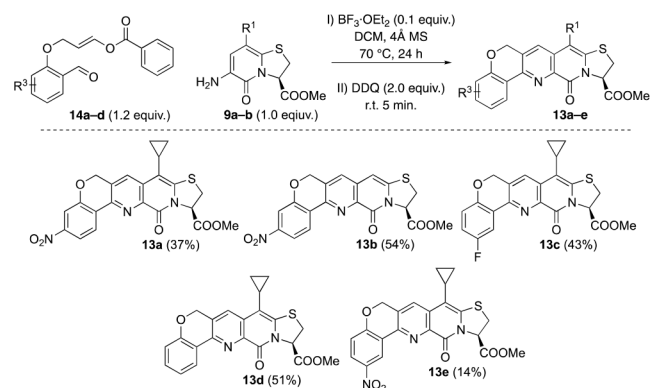
[a]The benzoate functionality was eliminated during oxidation to provide the desired products.

alkene component now armed with an ester group, capable of mesomeric contributions, we attempted Povarov reactions between **14a–d** and **9a,b**. Still, heating the reaction mixtures to 70 °C was required to achieve reasonable reaction times.

The desired compounds **13a–e** were isolated in low to moderate yields after 24 h of heating, followed by oxidation with DDQ at room temperature. The unusually low yield of **13e** results from the formation of side products, which complicated the purification. The low to moderate yields motivated us to try a slightly different approach, using CuBr$_2$ catalysis and *O*-propargyl salicylaldehyde (Scheme S4).[7b,c,f,9a] Unfortunately, the method suffered from undesired side reactions and **13a** was only isolated in 31% yield.

Having both sets of compounds in hand, we hydrolyzed the methyl ester to deprotect the carboxylic acid and reveal the peptidomimetic (Scheme 4). The limited solubility of **16a–e**

in organic solvents complicated handling, and these compounds were thus obtained in lower yields.

**Scheme 4. Deprotection of Methyl Esters through Saponification of 11a–k and 13a–e**
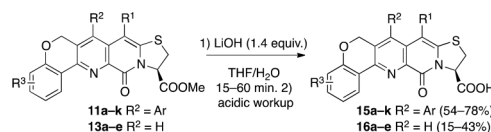
The carboxylic acids **15a–k** and **16a–e** were initially screened in an α-synuclein fibrilization assay with Thioflavin T (ThT) to probe for fibril binding and modulation of amyloid fibril formation (Figure 2A and Figure S1).[8,16] Compounds **15b,c, 15e,f, 15k, 16a,b**, and **16e** bind to the α-synuclein fibrils and had a significant effect on the fluorescence intensity, by competing with ThT for binding. In addition, compound **15e** has a mild inhibitory effect upon the fibril formation, as the lag phase was slightly extended. In order to verify that amyloid fibrils were indeed present, samples were taken upon the end point of the assay and visualized with transmission electron microscopy (TEM) (Figure S2). No visible difference was observed between the control experiment (black trace) and the mixture with **16a** (green trace) (Figures 2B and S2).

In a similar assay, compounds (**15a–c, 15e,f, 15k, 16a–c, 16e**) were added after 70 h, when the fluorescence traces had reached the plateau phase (Figures 3A and S3). The compounds were observed to bind to the mature α-synuclein fibrils and displace bound ThT, indicated by reduction of the ThT fluorescence, to varying degrees (Figures 3B and S4).

Interestingly, all compounds equipped with a nitro group except **15d** showed binding activity. The strongest binding was observed for compounds with the nitro group situated in position C-9 (**15b, 15c, 16a**, and **16b**). Moving the nitro group to position C-8 (**16e**) or to the 4′ position of the C-13 aryl group (**15e,f**) is accompanied by a decrease in fibril binding ability. Notably, the presence of the C-13 phenyl group abolishes all binding activity rendered by the nitro group in position C-8 (**15d vs 16e**) but not C-9 (**15b vs 16a**, Figure S3). The cyclopropyl group appears to be the favored C-14 substituent, over methoxy and proton (**15b vs 15c and 15k**, and **16a vs 16b**). This observation is in agreement with the SAR on scaffold **4**, where cyclopropyl as R^1 substituent was found somewhat superior to phenyl, hydrogen, and methoxy substituents.[3c] Taken together, these observations fit with the hypothesis that binding sites on amyloid fibrils are made up of shallow hydrophobic clefts flanked by polar groups, situated between the rows of side chains and running parallel to the fiber axis.[11a,c,e]

Compounds were also evaluated against Aβ40 in a similar manner (Figure 4 and Figures S5–S7). Compounds **15b,c, 15f**, and **16a**, which bind strongly to α-synuclein fibrils, were found to bind mature Aβ fibrils as well, indicated by reduced ThT fluorescence, compared to the control experiments.

In summary, we have developed methods to fuse two privileged scaffolds, namely, chromenopyridines and thiazolino 2-pyridones. These new peptidomimetic polyheterocycles constitute a new scaffold with potential for diverse substitution patterns. The intramolecular Povarov reaction between *O*-alkylated salicylaldehydes and amino functionalized thiazolino-2-pyridones afforded chromenopyridine fused 2-pyridone polyheterocycles in moderate to excellent yields. Rewardingly,
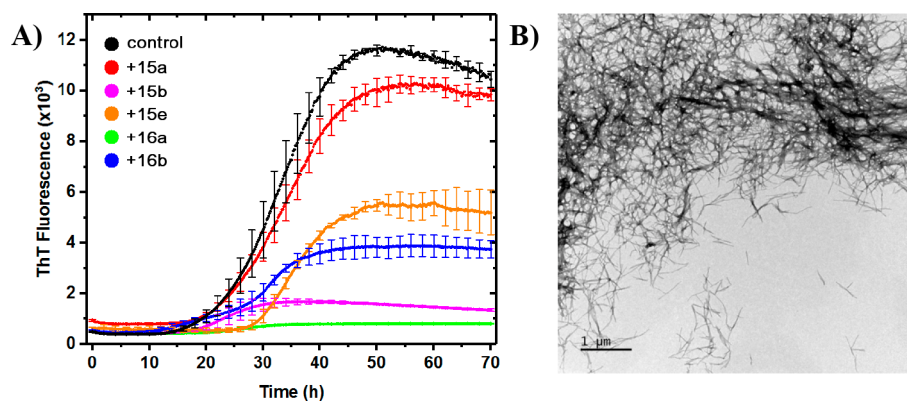
Figure 2. (A) Representative selection of ThT fluorescence traces. Each experiment was performed in triplicate (Figure S1) and normalized to the average. Compounds **15b** and **16a** appear to bind fibrils strongly, whereas **15a** does not seem to bind to any significant extent. **15e** and **16b** are borderline. (B) TEM picture of fibrils formed in the presence of compound **16a** (green trace).
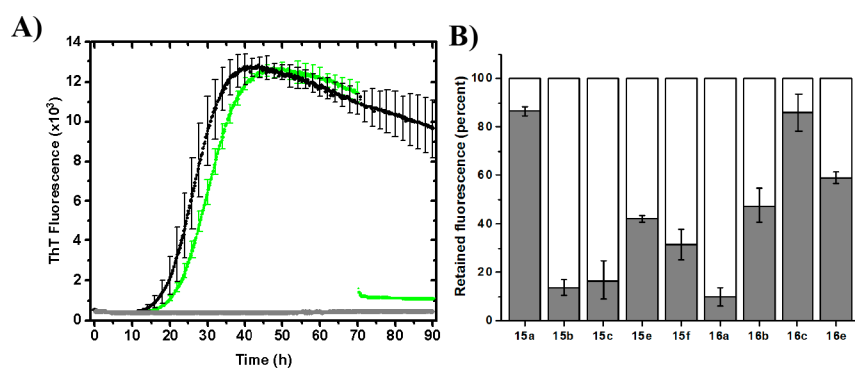
Figure 3. (A) ThT trace for compound **16a** added after 70 h (green), α-Syn control (black), and ThT background fluorescence (gray). (B) Retained ThT fluorescence 5 h after addition of compounds **15a–c**, **15e,f**, **15k**, **16a–c**, and **16e** to mature α-synuclein fibrils, compared to the fluorescence intensity 1 h before addition. For comparison, **15a** and **16c** were also included.
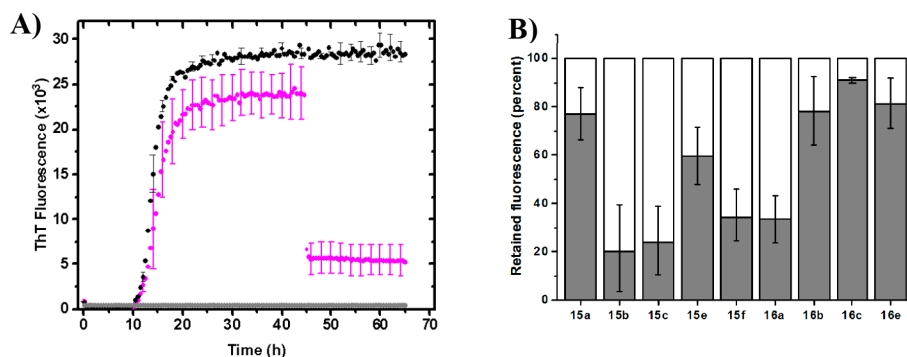
Figure 4. Retained ThT fluorescence after addition of selected compounds to mature Aβ40 fibrils *in vitro*. (A) ThT fluorescence trace for addition of compound **15b** (magenta), α-Syn control (black), and ThT background fluorescence (gray). (B) Bar chart representation of the retained fluorescence (60 h), compared to the intensity before compound addition (40 h).

biological evaluation of chromenopyridine fused thiazolino 2-pyridones revealed compounds capable of binding to α-synuclein and Aβ40 amyloid fibrils *in vitro*. An interesting SAR was observed with respect to groups at position C-9. The polyheterocycles equipped with a nitro group at position C-9 showed the strongest binding to α-synuclein and Aβ40 amyloid fibrils. However, changing the position of the nitro group resulted in decreased binding ability versus both amyloid fibrils. As binding to mature amyloid fibrils is a property of pharmacological relevance,[11] we intend to investigate these promising compounds further in future biological studies.

■ EXPERIMENTAL SECTION

General. Unless otherwise stated, purchased reactants and reagents were used as received from commercial suppliers. Molecular sieves and LiCl were dried at 300 °C under high vacuum for 4 h prior to use. Acetonitrile was dried over activated 3 Å molecular sieves (5% w/v) for 48 h, then transferred via syringe to new 3 Å molecular sieves (5% w/v) for storage until use. DMF, THF, and diethyl ether were dried using an SG Water solvent drying tower according to the manufacturer's instructions and stored over activated 3 Å (DMF) or 4 Å (THF and diethyl ether) MS for 48 h or more before use. Amberlyst was rinsed prior to use with THF/MeOH 1:1 in a cylindrical sintered funnel until the filtrate was transparent, then dried briefly by passing air through. Microwave reactions were performed in

sealed vessels using a Biotage Initiator microwave synthesizer, temperatures were monitored by an internal IR probe, and stirring was mediated magnetically. TLC was performed on purchased aluminum backed silica gel plates (median pore size 60 Å, fluorescent indicator 254 nm) and detected with UV light at 254 and 366 nm. Flash column chromatography was performed using silica gel (0.063−0.200 mesh). Automated flash column chromatography was performed using a Biotage Isolera One system and purchased prepacked silica gel cartridges (Biotage SNAP Cartridge, KP-Sil). Preparative HPLC was performed on a Gilson instrument with a Phenomenex column (250 × 21.2 mm; Gemini 5 μm NX-C18, 110 Å). MeCN/water, with 0.75% HCOOH in the mobile phase. 30−100% MeCN in water over 30 min with a flow rate of 20 mL/min. The elution was monitored with UV-abs. at 254 nm. Freeze-drying was accomplished by freezing the diluted MeCN/water solutions in liquid nitrogen and then employing a Scanvac CoolSafe freeze-dryer connected to an Edwards 28 rotary vane oil pump. Optical rotation was measured with a Rudolph Autopol IV polarimeter 343 at 22 °C and 589 nm. [α] is reported in deg·mL·g^{-1}·dm^{-1}; concentrations (c) are given in g/100 mL. IR spectra were recorded on a Bruker Alpha-t spectrometer. The samples were prepared as KBr pellets or between NaCl plates; absorbances are given in reciprocal cm. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer with a BBO-F/H Smartprobe or a Bruker Avance III HD 600 MHz spectrometer with a CP BBO-H/F, 5 mm cryoprobe, at 298 K, unless another temperature is given. All spectrometers were operated by Topspin 3.5. Resonances are given in ppm relative to TMS, and calibrated to solvent residual signals [CDCl$_3$: δ_H = 7.26 ppm; δ_C = 77.16 ppm. (CD$_3$)$_2$SO: δ_H = 2.50 ppm; δ_C = 39.51 ppm. (CD$_3$)CO δ_H = 2.05 ppm; δ_C = 29.84 ppm]. The following abbreviations are used to indicate splitting patterns: s = singlet; d = doublet; dd = double doublet; t = triplet; m = multiplet; bs = broad singlet. LC-MS was conducted on a Micromass ZQ mass spectrometer with ES$^+$ and ES$^-$ ionization. HRMS was performed on a mass spectrometer with ESI-TOF (ES$^+$/ES$^-$). Human wild-type α-synuclein was expressed and purified as described previously,[3c] expressed and purified Aβ40 was supplied by Alexotech AB.

General Procedure for Synthesis of O-Alkylated Salicylaldehydes 10a−i. Salicylaldehydes were O-alkylated according to established procedures with modifications.[17] Under an atmosphere of nitrogen, cinnamyl bromide **II** (2.34 mmol, 1.30 equiv) was dissolved in DMF (1.0 mL) and transferred with a syringe to a mixture of salicylaldehyde **I** (1.80 mmol, 1.00 equiv) and K$_2$CO$_3$ (496 mg, 2.00 equiv) under nitrogen. The reaction mixture was stirred at r.t. until completion was indicated by TLC analysis. The mixture was then transferred to a beaker of ice-cold water (60 mL) while stirring; the resulting precipitate was filtered off and washed with water (5 mL). The precipitate was then dissolved in EtOAc (50 mL) and washed with brine (5 × 25 mL), dried with sodium sulfate, filtered, and evaporated. Unless otherwise stated, the compounds were used in the following synthetic step without further purification.

2-(Cinnamyloxy)benzaldehyde (10a). The compound was prepared by following the general procedure. The mixture was stirred for 6.5 h. The crude product was purified with automated flash column chromatography (25 g cartridge, 10−20% EtOAc in heptane). White, low melting solid (373 mg, 87.2%). IR (KBR): ν 3028, 2862, 1684, 1598, 1580, 1481, 1455, 1375, 1286, 1236 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 10.58 (s, 1H), 7.86 (dd, J = 7.9, 1.8 Hz, 1H), 7.55 (td, J = 8.0, 1.8 Hz, 1H), 7.43 (d, J = 7.0 Hz, 2H), 7.35 (t, J = 7.6 Hz, 2H), 7.31−7.27 (m, 1H), 7.05 (dt, J = 7.5, 3.2 Hz, 2H), 6.77 (d, J = 16.0 Hz, 1H), 6.43 (dt, J = 16.0, 5.7 Hz, 1H), 4.84 (dd, J = 5.7, 1.4 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 189.9, 161.1, 136.2, 136.0, 133.7, 128.8, 128.7, 128.3, 126.8, 125.3, 123.6, 121.1, 113.1, 69.3. HRMS (ESI-TOF) m/z: [M − H]$^-$ Calcd for C$_{16}$H$_{13}$O$_2^-$ 237.0921; Found 237.0917.

2-(Cinnamyloxy)-4-nitrobenzaldehyde (10b). The compound was prepared by following the general procedure. The reaction mixture was stirred for 5 h. Light yellow solid (425 mg, 83.6%). IR (KBr): ν 3116, 3042, 2903, 2864, 1693, 1612, 1592, 1527, 1480, 1428, 1408, 1386, 1347, 1301, 1208, 1182, 971 cm^{-1}. ^{1}H NMR (400 MHz,

CDCl$_3$): δ 10.60 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.92 (s, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 7.7 Hz, 2H), 7.36 (t, J = 7.5 Hz, 2H), 7.31 (t, J = 7.3 Hz, 1H), 6.83 (d, J = 15.9 Hz, 1H), 6.43 (dt, J = 15.9, 6.0 Hz, 1H), 4.95 (d, J = 5.9 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 188.4, 161.0, 152.3, 135.8, 135.3, 129.8, 129.0, 128.9, 128.7, 126.9, 122.0, 115.9, 108.5, 70.2. HRMS (ESI-TOF) m/z: [M − H]$^-$ Calcd for C$_{16}$H$_{12}$NO$_4^-$ 282.0772; Found 282.0774.

2-(Cinnamyloxy)-5-nitrobenzaldehyde (10c). The compound was prepared by following the general procedure. The reaction mixture was stirred for 2.75 h. Light yellow solid (446 mg; 87.7%). IR (KBr): ν 3075, 2908, 1688, 1610, 1588, 1516, 1487, 1450, 1429, 1391, 1340, 1274, 1177, 1157, 1141, 1078, 1063 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 10.53 (s, 1H), 8.73 (d, J = 2.9 Hz, 1H), 8.43 (dd, J = 9.2, 2.9 Hz, 1H), 7.48−7.41 (m, 2H), 7.41−7.28 (m, 3H), 7.18 (d, J = 9.2 Hz, 1H), 6.85−6.76 (m, 1H), 6.42 (dt, J = 15.9, 6.0 Hz, 1H), 4.97 (dd, J = 6.0, 1.5 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 187.6, 164.8, 141.8, 135.7, 135.3, 130.7, 129.0, 128.9, 126.9, 125.0, 124.9, 121.8, 113.5, 70.4. HRMS (ESI-TOF) m/z: [M − H]$^-$ Calcd for C$_{16}$H$_{12}$NO$_4^-$ 282.0772; Found 282.0767.

2-(Cinnamyloxy)-5-fluorobenzaldehyde (10d). The compound was prepared by following the general procedure starting from 5-fluoro-2-hydroxybenzaldehyde (251 mg, 1.79 mmol). The reaction was stirred for 4.5 h, and the product was purified with automated flash column chromatography (50 g cartridge, 3−20% EtOAc in n-heptane) as white solid in 84% yield (388 mg, 1.51 mmol). IR (KBr): ν 3415, 3339, 3065, 3030, 2940, 2868, 2054, 1976, 1883, 1780, 1679, 1610, 1580, 1485, 1461 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 10.54 (d, J = 3.1 Hz, 1H), 7.56 (dd, J = 8.3, 3.3 Hz, 1H), 7.47−7.41 (m, 2H), 7.41−7.34 (m, 2H), 7.34−7.24 (m, 3H), 7.04 (dd, J = 9.1, 3.9 Hz, 1H), 6.78 (dd, J = 16.0, 1.6 Hz, 1H), 6.43 (dt, J = 16.0, 5.8 Hz, 1H), 4.84 (dd, J = 5.8, 1.5 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 188.7, 188.6, 135.9, 133.8, 128.7, 128.2, 126.6, 126.0, 125.9, 123.1, 122.5, 122.3, 114.7, 114.6, 114.2, 114.0, 77.3, 77.0, 76.7, 69.9. ^{19}F{^{1}H} NMR (376 MHz, CDCl$_3$) δ −122.14. HRMS (ESI-TOF) m/z: [M − H]$^-$ Calcd for C$_{16}$H$_{12}$FO$_2^-$ 255.0827; Found 255.0819.

(E)-4-Nitro-2-((3-(4-nitrophenyl)allyl)oxy)benzaldehyde (10e). The compound was prepared by following the general procedure but with 1.8 equiv of alkyl bromide. The reaction mixture was stirred overnight. During workup, the precipitate was dissolved in DCM instead of EtOAc. The crude product was purified with flash column chromatography (30 × 70 mm silica gel, DCM). Light yellow solid (431 mg, 73.1%). IR (KBr): ν 3113, 1692, 1596, 1526, 1511, 1391, 1345, 1309, 1248, 1183, 1109 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 10.61 (d, J = 0.7 Hz, 1H), 8.23 (d, J = 8.8 Hz, 2H), 8.03 (d, J = 8.3 Hz, 1H), 7.92 (dt, J = 11.4, 1.5 Hz, 2H), 7.58 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 16.1 Hz, 1H), 6.61 (dt, J = 16.0, 5.5 Hz, 1H), 5.00 (dd, J = 5.5, 1.6 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 188.1, 160.6, 152.3, 147.7, 142.1, 132.2, 130.1, 129.0, 127.5, 126.9, 124.3, 116.3, 108.3, 69.4. HRMS (ESI-TOF) m/z: [M − H]$^-$ Calcd for C$_{16}$H$_{11}$N$_2$O$_6^-$ 327.0622; Found 327.0622.

(E)-2-((3-(4-Nitrophenyl)allyl)oxy)benzaldehyde (10f). The compound was prepared by following the general procedure but with 1.8 equiv of crude alkyl bromide. The reaction mixture was stirred overnight. The crude product was purified with automated flash column chromatography (25 g cartridge, 8−25% EtOAc in heptane. Off white solid (311 mg, 61.1%). IR (KBr): ν 3106, 3078, 2869, 1688, 1597, 1513, 1484, 1458, 1450, 1340, 1284, 1251, 1235, 1189, 1165, 1105, 1072, 1041, 1002 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 10.58 (d, J = 0.7 Hz, 1H), 8.21 (d, J = 8.8 Hz, 2H), 7.88 (dd, J = 7.7, 1.8 Hz, 1H), 7.62−7.51 (m, 3H), 7.12−6.99 (m, 2H), 6.86 (d, J = 16.1 Hz, 1H), 6.61 (dt, J = 16.1, 5.2 Hz, 1H), 4.89 (dd, J = 5.2, 1.7 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 189.6, 160.7, 147.4, 142.7, 136.1, 130.8, 129.0, 128.6, 127.3, 125.3, 124.3, 121.5, 112.9, 68.5. HRMS (ESI-TOF) m/z: [M − H]$^-$ Calcd for C$_{16}$H$_{12}$NO$_4^-$ 282.0772; Found 282.0767.

(E)-2-((3-(3-(Trifluoromethyl)phenyl)allyl)oxy)benzaldehyde (10g). The compound was prepared by following the general procedure but with 1.8 equiv of crude alkyl bromide. The reaction mixture was stirred overnight. The crude product was purified with automated flash column chromatography (50 g cartridge, 3−10%

EtOAc in heptane). White, low melting solid (434 mg, 78.8%). IR (KBr): ν 3071, 2936, 2878, 2770, 1682, 1598, 1484, 1459, 1441, 1404, 1378, 1322, 1306, 1287, 1243, 1201, 1164, 1122, 1075, 1041, 1007 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 10.58 (d, J = 0.8 Hz, 1H), 7.87 (dd, J = 7.7, 1.9 Hz, 1H), 7.66 (s, 1H), 7.62–7.50 (m, 3H), 7.47 (t, J = 7.7 Hz, 1H), 7.10–7.00 (m, 2H), 6.81 (d, J = 16.1 Hz, 1H), 6.51 (dt, J = 15.9, 5.4 Hz, 1H), 4.86 (dd, J = 5.5, 1.6 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 189.8, 160.9, 137.1, 136.1, 131.9, 131.3 (q, J = 32.2 Hz), 129.9 (d, J = 1.5 Hz), 129.3, 128.8, 125.7, 125.3, 124.8 (q, J = 3.8 Hz), 124.2 (q. J = 272.4 Hz), 123.4 (q, J = 3.8 Hz), 121.3, 113.0, 68.8. ^{19}F NMR (376 MHz, CDCl$_3$): δ −62.79. HRMS (ESI-TOF) m/z: [M − H]$^-$ Calcd for C$_{17}$H$_{12}$F$_3$O$_2$$^-$ 305.0795; Found 305.0782.

(E)-2-((3-(3-Methoxyphenyl)allyl)oxy)benzaldehyde (10h). The compound was prepared by following the general procedure but with 1.8 equiv of crude alkyl bromide. The reaction mixture was stirred overnight. The crude product was purified with automated flash column chromatography (50 g cartridge, 5−20% diethyl ether in heptane). The fractions containing the pure desired product were combined and evaporated. The residue was then co-evaporated with chloroform twice. White, low melting solid (446 mg, 93%) calculated from 494 mg containing chloroform. IR (KBr): ν 3003, 2967, 2876, 2839, 1683, 1600, 1575, 1484, 1464, 1435, 1375, 1308, 1290, 1244, 1155, 1048, 1002, 972 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 10.57 (d, J = 0.7 Hz, 1H), 7.86 (dd, J = 8.0, 1.9 Hz, 1H), 7.55 (ddd, J = 8.3, 7.4, 1.9 Hz, 1H), 7.30−7.21 (m, 1H), 7.09−6.98 (m, 3H), 6.95 (t, J = 2.1 Hz, 1H), 6.84 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 6.74 (d, J = 15.9 Hz, 1H), 6.42 (dt, J = 16.0, 5.7 Hz, 1H), 4.83 (dd, J = 5.7, 1.6 Hz, 2H), 3.83 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 189.9, 161.1, 160.0, 137.7, 136.0, 133.5, 129.8, 128.7, 125.3, 123.9, 121.1, 119.4, 114.0, 113.1, 112.1, 69.2, 55.4. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for C$_{16}$H$_{16}$NaO$_3$$^+$ 291.0997; Found 291.1003.

(E)-2-((3-(4-Ethoxyphenyl)allyl)oxy)benzaldehyde (10i). The compound was prepared by following the general procedure but with 1.8 equiv of crude alkyl bromide. The reaction mixture was stirred overnight. Only about 50% conversion of salicylaldehyde was indicated by TLC, but the alkyl bromide was consumed. The crude product was purified with automated flash column chromatography (25 g cartridge, 5−20% diethyl ether in heptane). Off white solid (124 mg, 24.5%). IR (KBr): ν 2980, 2934, 2879, 1681, 1599, 1512, 1485, 1455, 1388, 1287, 1239, 1179, 1047, 978, cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 10.59 (s, 1H), 7.88 (dd, J = 8.0, 1.8 Hz, 1H), 7.60−7.52 (m, 1H), 7.37 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 6.73 (d, J = 16.0 Hz, 1H), 6.31 (dt, J = 15.9, 5.9 Hz, 1H), 4.83 (dd, J = 6.0, 1.5 Hz, 2H), 4.07 (q, J = 7.0 Hz, 2H), 1.44 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 190.0, 161.3, 159.2, 136.0, 133.6, 128.8, 128.6, 128.0, 125.3, 121.1, 121.0, 114.8, 113.1, 69.6, 63.7, 15.0. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for C$_{18}$H$_{18}$NaO$_3$$^+$ 305.1154; Found 305.1160.

General Procedure for Synthesis of C-13 Aryl Substituted Povarov Reaction Products 11a−j. The 6-amino thizolo-2-pyridone **9** (0.40 mmol, 1.00 equiv) and 2-(cinnamyloxy)-benzaldehyde **10** (0.48 mmol, 1.20 equiv) were weighed up in a Biotage Microwave reaction tube and dissolved in DCM (4 mL). 4 Å MS (8−10 pellets) was added, followed by BF$_3$·OEt$_2$ (10.8 μL; 0.100 equiv), whereupon the tube was sealed and left stirring at r.t. The reaction was monitored with TLC until complete consumption of **1**, and the corresponding imine intermediate, was indicated. The tube was then opened and DDQ (182 mg; 2.00 equiv) was added. The reaction mixture was stirred until complete oxidation was visible by TLC, then transferred to a separation funnel and diluted with DCM (25 mL). The mixture was washed with saturated aqueous bicarbonate solution (2 × 10 mL), followed by brine (10 mL). The aq. phases were re-extracted once each with DCM (3 mL). The organic phase was dried over sodium sulfate, filtered, and evaporated to dryness. The crude residue was redissolved in DCM and purified with automated flash column chromatography. The fractions containing pure desired product were combined, evaporated, and co-evaporated with distilled chloroform twice. The residue was put under high vacuum for several hours before storage at −20 °C. The

yield was calculated from the ^{1}H NMR spectrum recorded in d6-DMSO.

Methyl (R)-8-Cyclopropyl-13-oxo-7-phenyl-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylate (11a). The compound was prepared by following the general procedure. The reaction was finished by TLC analysis after 9.5 h. DDQ was added, and the mixture was stirred for 25 min. The crude product was purified with automated flash column chromatography (25 g cartridge, 25−75% EtOAc in heptane). Yellow-orange solid (185 mg, 93%). The compound contained chloroform; yield calculated from ^{1}H NMR sample in (CD$_3$)$_2$SO. [α]$_D$ −226° (c 0.35, CHCl$_3$). IR (KBr): ν 3451, 1001, 2950, 1753, 1666, 1579, 1461, 1436, 1382, 1300, 1258, 1220, 1183, cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.51 (dd, J = 7.8, 1.7 Hz, 1H), 7.43 (dq, J = 4.7, 3.2, 2.5 Hz, 3H), 7.37−7.28 (m, 2H), 7.12 (td, J = 7.5, 1.1 Hz, 1H), 6.91 (dd, J = 8.1, 1.1 Hz, 1H), 5.73 (dd, J = 8.2, 2.6 Hz, 1H), 5.12−4.98 (m, 2H), 3.81 (s, 3H), 3.69 (dd, J = 11.6, 8.2 Hz, 1H), 3.50 (dd, J = 11.6, 2.6 Hz, 1H), 1.01−0.89 (m, 1H), 0.34−0.11 (m, 4H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 168.8, 159.6, 156.4, 146.9, 143.5, 142.3, 140.8, 137.5, 133.6, 131.8, 130.0, 129.9, 129.5, 128.4, 128.0, 126.5, 123.0, 122.7, 116.6, 109.5, 66.6, 63.5, 53.5, 31.6, 15.7, 11.6, 11.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{28}$H$_{23}$N$_2$O$_4$S$^+$ 483.1373; Found 483.1379.

Methyl 8-Cyclopropyl-3-nitro-13-oxo-7-phenyl-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylate (11b). The compound was prepared by following the general procedure. Upon addition of boron trifluoride, the stirred solution turned dark purple and a precipitate emerged within a few minutes. The resulting suspension thickened so that the stirring was compromised. The tube was shaken manually with regular intervals for 20 min until the suspension was lighter and the magnetic stirring could be continued. The precipitate eventually dissolved completely, and the reaction was then followed with TLC until complete consumption of **9a** was indicated, after 2 h reaction time. DDQ (197 mg, 2.17 equiv) was added and stirred for 50 min. The residue was purified with automated flash column chromatography (25 g SNAP Cartridge, 20−65% EtOAc in heptane). Yellow solid (181 mg, 85.8%) The compound contained chloroform; yield calculated from ^{1}H NMR sample in (CD$_3$)$_2$SO. **11b** (746 mg, 88.4%) was also prepared at 1.6 mmol scale, according to the general procedure. The reaction was complete after 3 h. [α]$_D$ −228° (c 0.289, CHCl$_3$); IR (KBr): ν 3452, 1752, 1668, 1573, 1526, 1433, 1342, 1227 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.65 (d, J = 8.6 Hz, 1H), 7.95 (dd, J = 8.6, 2.2 Hz, 1H), 7.76 (d, J = 2.2 Hz, 1H), 7.49−7.42 (m, 3H), 7.36−7.30 (m, 1H), 7.24−7.29 (m, 1H), 5.74 (dd, J = 8.3, 2.7 Hz, 1H), 5.22−5.07 (m, 2H), 3.83 (s, 3H), 3.71 (dd, J = 11.7, 8.3 Hz, 1H), 3.52 (dd, J = 11.6, 2.6 Hz, 1H), 1.03−0.90 (m, 1H), 0.36−0.23 (m, 2H), 0.23−0.14 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 168.6, 159.4, 156.3, 149.7, 145.3, 144.5, 142.7, 141.2, 137.0, 134.6, 129.9, 129.8, 129.6, 128.74, 128.65, 128.2, 127.1, 117.5, 112.5, 109.4, 67.1, 63.6, 53.5, 31.6, 15.7, 11.68, 11.60. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{28}$H$_{22}$N$_3$O$_6$S$^+$ 528.1224; Found 528.1229.

Methyl (R)-3-Nitro-13-oxo-7-phenyl-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylate (11c). The compound was prepared by following the general procedure. A precipitate emerged after 10 min stirring upon addition of boron trifluoride. The magnetic stirring was compromised as the mixture got viscous, and the tube was shaken manually for 10 min, until the viscosity had decreased to a point where magnetic stirring was possible. The reaction was finished after 5.8 h. DDQ was added, and the mixture was stirred for 10 min. The crude product was dissolved in a larger volume of DCM and loaded onto a column (30 × 80 mm silica gel, equilibrated with DCM) and purified with flash column chromatography (0−70% EtOAc in heptane). Yellow solid (179 mg, 92%). The compound contained chloroform; yield was calculated from ^{1}H NMR spectrum recorded in (CD$_3$)$_2$SO. [α]$_D$ −256° (c 0.55, CHCl$_3$). IR (KBr): ν 3443, 1754, 1680, 1595, 1535, 1514, 1451, 1432, 1342, 1322, 1222, 1179, 1041 cm^{-1}. ^{1}H NMR [400 MHz, (CD$_3$)$_2$SO]: δ 8.48 (d, J = 8.6 Hz, 1H), 8.06 (dd, J = 8.6, 2.3 Hz, 1H), 7.79 (d, J = 2.2 Hz, 1H), 7.66−7.53 (m, 3H), 7.37 (ddt, J =

13.3, 7.8, 1.7 Hz, 2H), 6.02 (s, 1H), 5.75 (dd, J = 8.7, 2.0 Hz, 1H), 5.20 (d, J = 3.4 Hz, 2H), 3.94 (dd, J = 11.9, 8.7 Hz, 1H), 3.75 (s, 3H), 3.66 (dd, J = 11.9, 2.0 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 168.4, 159.8, 156.4, 149.8, 145.2, 142.6, 142.3, 139.6, 133.9, 133.5, 129.5, 129.5, 129.4, 129.0, 128.8, 128.5, 128.5, 127.1, 117.5, 112.7, 96.1, 66.9, 63.0, 53.6, 32.4. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{25}$H$_{18}$N$_3$O$_6$S$^+$ 488.0911; Found 488.0901.

Methyl (R)-8-Cyclopropyl-2-nitro-13-oxo-7-phenyl-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylate (11d). The compound was prepared by following the general procedure. The reaction was finished after 6.6 h. DDQ was added, and the mixture was stirred for 20 min. The crude product was purified with automated flash column chromatography (25 g cartridge, 15−55% EtOAc in heptane). Yellow solid (148 mg, 70%). The compound contained chloroform; yield was calculated from ^{1}H NMR spectrum recorded in (CD$_3$)$_2$SO. [α]$_D$ −197° (c 0.29, CHCl$_3$). IR (KBr): ν 3444, 3001, 2953, 1753, 1669, 1618, 1580, 1549, 1518, 1494, 1482, 1459, 1443, 1384, 1340, 1299, 1250, 1229, 1088, 1022 cm^{-1}; ^{1}H NMR [400 MHz, (CD$_3$)$_2$SO]: δ 8.99 (d, J = 2.9 Hz, 1H), 8.26 (dd, J = 9.0, 2.9 Hz, 1H), 7.55−7.44 (m, 3H), 7.36 (dt, J = 5.4, 2.9 Hz, 1H), 7.22 (d, J = 9.0 Hz, 1H), 5.72 (dd, J = 8.8, 2.6 Hz, 1H), 5.39−5.14 (m, 2H), 3.86 (dd, J = 11.8, 8.8 Hz, 1H), 3.76 (s, 3H), 3.58 (dd, J = 11.8, 2.6 Hz, 1H), 0.87 (m, 1H), 0.32−-0.02 (m, 4H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 168.6, 160.8, 159.3, 145.0, 144.4, 143.4, 142.6, 141.2, 137.0, 134.4, 129.8, 129.7, 128.7, 128.4, 128.2, 126.8, 123.3, 122.4, 117.6, 109.2, 67.3, 63.5, 53.5, 31.6, 15.7, 11.7, 11.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{28}$H$_{22}$N$_3$O$_6$S$^+$ 528.1224; Found 528.1216.

Methyl (R)-8-Cyclopropyl-7-(4-nitrophenyl)-13-oxo-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylate (11e). The compound was prepared by following the general procedure, but the mixture was heated in an oil bath at 70 °C for 23 h. DDQ was added, and the mixture was stirred at room temperature for 15 min. The crude product was purified with automated flash column chromatography (25 g cartridge, 15−60% EtOAc in heptane). Yellow solid (114 mg, 54%). The compound contained chloroform; yield was calculated from ^{1}H NMR spectrum recorded in (CD$_3$)$_2$SO. [α]$_D$ −163° (c 0.21, CHCl$_3$). IR (KBr): ν 2999, 2953, 2848, 1752, 1667, 1579, 1552, 1519, 1491, 1462, 1438, 1381, 1347, 1299, 1258, 1220, 1179, 1149, 1107, 1070, 1035, 1005 cm^{-1}. ^{1}H NMR [400 MHz, (CD$_3$)$_2$SO]: δ 8.33 (dt, J = 6.4, 2.3 Hz, 2H), 8.21 (dd, J = 7.7, 1.7 Hz, 1H), 7.79 (dd, J = 8.7, 2.0 Hz, 1H), 7.69 (dd, J = 8.7, 2.0 Hz, 1H), 7.41 (td, J = 7.7, 1.7 Hz, 1H), 7.20 (td, J = 7.5, 1.1 Hz, 1H), 7.00 (dd, J = 8.2, 1.1 Hz, 1H), 5.73 (dd, J = 8.7, 2.5 Hz, 1H), 5.20−4.97 (m, 2H), 3.86 (dd, J = 11.9, 8.8 Hz, 1H), 3.76 (s, 3H), 3.58 (dd, J = 11.9, 2.6 Hz, 1H), 0.92−0.80 (m, 1H), 0.34−0.17 (m, 3H), 0.07 (q, J = 7.2, 6.1 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 168.6, 159.3, 156.3, 147.8, 147.1, 145.0, 144.4, 141.0, 139.3, 133.2, 132.1, 131.1, 131.1, 128.9, 126.5, 123.3, 122.9, 122.7, 116.7, 108.3, 66.2, 63.6, 53.5, 31.6, 16.0, 12.3, 12.2. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{28}$H$_{22}$N$_3$O$_6$S$^+$ 528.1224; Found 528.1228.

Methyl (R)-3-Nitro-7-(4-nitrophenyl)-13-oxo-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylate (11f). The compound was prepared by following the general procedure. A red precipitate emerged upon addition of boron trifluoride. The mixture got thick, so the tube was sonicated in an ultrasonic water bath at room temperature for 5 min, then shaken manually with regular intervals during several hours, until the viscosity had decreased to a point where magnetic stirring was no longer compromised. The reaction was finished after 24.5 h. DDQ was added, and the mixture was stirred for 10 min. The crude product was purified with flash column chromatography (80 × 30 mm SiO$_2$, 0−17% EtOAc in DCM. Orange solid (167 mg, 78.5%). The compound contained chloroform; yield was calculated from ^{1}H NMR spectrum recorded in (CD$_3$)$_2$SO. [α]$_D$ −239° (c 0.28, CHCl$_3$). IR (KBr): ν 3447, 1756, 1670, 1595, 1532, 1433, 1348, 1227, 1042 cm^{-1}. ^{1}H NMR [400 MHz, (CD$_3$)$_2$SO]: δ 8.51−8.40 (m, 3H), 8.07 (dd, J = 8.7, 2.3 Hz, 1H), 7.80 (d, J = 2.3 Hz, 1H), 7.75−7.66 (m, 2H), 6.06 (s, 1H), 5.79−5.72 (m, 1H), 5.22 (d, J = 1.6 Hz, 2H), 3.94 (dd, J =

11.9, 8.8 Hz, 1H), 3.76 (s, 3H), 3.66 (dd, J = 11.8, 2.0 Hz, 1H). ^{13}C{^{1}H} NMR [151 MHz, (CD$_3$)$_2$SO]: δ 168.6, 158.3, 155.9, 149.1, 147.9, 144.7, 143.5, 139.9, 139.6, 138.6, 133.1, 130.8, 130.6, 128.3, 128.1, 125.9, 124.3 (2C), 117.5, 112.3, 94.2, 79.2, 66.3, 62.5, 53.1, 31.5. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{25}$H$_{17}$N$_4$O$_8$S$^+$ 533.0762; Found 533.0748.

Methyl (R)-8-Cyclopropyl-2-fluoro-13-oxo-7-phenyl-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylate (11g). The compound was prepared by following the general procedure starting from 9a (106 mg, 0.40 mmol). The reaction was stirred for 4.5 h, and the product was purified with automated flash column chromatography (50 g cartridge, 10−70% EtOAc in n-heptane) in 92% yield as a light-yellow powder (170 mg, 0.36 mmol). [α]$_D$ −160° [c 0.33, (CD$_3$)$_2$SO]. IR (KBr): ν 3548, 3473, 3414, 3081, 3000, 2953, 2844, 2041, 1752, 1665, 1617, 1578, 1550, 1520, 1494, 1483, 1461, 1429 cm^{-1}. ^{1}H NMR [400 MHz, (CH$_3$)$_2$SO] δ 7.66 (dd, J = 9.0, 3.2 Hz, 1H), 7.27 (ttd, J = 7.7, 5.6, 5.1, 3.0 Hz, 4H), 7.15 (dt, J = 5.6, 3.0 Hz, 1H), 7.05 (td, J = 8.6, 3.2 Hz, 1H), 6.84 (dd, J = 8.9, 4.5 Hz, 1H), 5.50 (dd, J = 8.8, 2.5 Hz, 1H), 4.99−4.75 (m, 2H), 3.65 (dd, J = 11.8, 8.8 Hz, 1H), 3.55 (s, 3H), 3.36 (dd, J = 11.9, 2.6 Hz, 1H), 0.72−0.61 (m, 1H), 0.10 to −0.08 (m, 3H), −0.12 to −0.24 (m, 1H). ^{13}C{^{1}H} NMR [100 MHz, (CD$_3$)$_2$SO] δ 169.2, 158.5, 152.5, 145.9, 144.6, 142.4, 140.4, 137.0, 134.2, 130.3, 130.2, 129.4, 128.8, 128.3, 128.2, 119.1, 119.0, 108.0, 79.6, 66.63, 63.64, 53.4, 31.1, 15.7, 11.5, 11.4. ^{19}F{^{1}H} NMR [376 MHz, (CD$_3$)$_2$SO] δ −120.83. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{28}$H$_{22}$FN$_2$O$_4$S$^+$ 501.1279; Found 501.1287.

Methyl (R)-8-Cyclopropyl-13-oxo-7-(3-(trifluoromethyl)phenyl)-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]-naphthyridine-11-carboxylate (11h). The compound was prepared by following the general procedure, but the mixture was heated in an oil bath at 70 °C for 8 h. DDQ was added, and the mixture was stirred at room temperature for 10 min. The crude product was purified with automated flash column chromatography (25 g cartridge, 20−65% EtOAc in heptane). Yellow solid (163 mg, 74%). The compound contained chloroform; yield was calculated from ^{1}H NMR spectrum recorded in (CD$_3$)$_2$SO. [α]$_D$ −165° (c 0.37, CHCl$_3$). IR (KBr): ν 3552, 3475, 3414, 3236, 3002, 2955, 1753, 1668, 1611, 1580, 1553, 1518, 1489, 1464, 1437, 1382, 1329, 1296, 1257, 1221, 1178, 1168, 1126, 1108, 1073, 1046 cm^{-1}. ^{1}H NMR [400 MHz, (CD$_3$)$_2$SO]: δ 8.21 (dd, J = 7.8, 1.7 Hz, 1H), 7.96−7.64 (m, 4H), 7.40 (td, J = 7.7, 1.7 Hz, 1H), 7.19 (td, J = 7.6, 1.1 Hz, 1H), 6.99 (d, J = 8.1 Hz, 1H), 5.71 (d, J = 8.7 Hz, 1H), 5.20−4.89 (m, 2H), 3.86 (ddd, J = 11.9, 8.7, 6.4 Hz, 1H), 3.75 (s, 3H), 3.57 (ddd, J = 11.8, 4.0, 2.6 Hz, 1H), 0.77 (m, 1H), 0.39 to −0.16 (m, 4H). ^{13}C{^{1}H} NMR [100 MHz, (CD$_3$)$_2$SO, 343 K]: δ 168.4 (d, J = 3.3 Hz), 157.8, 155.5, 145.1, 144.8, 139.9, 139.7, 137.6, 133.6 (d, J = 10.1 Hz), 132.9 (d, J = 6.0 Hz), 131.4, 128.7 (d, J = 7.5 Hz), 128.6 (d, J = 2.7 Hz), 126.26−125.97 (m), 124.6, 124.6 (d, J = 4.0 Hz), 122.1 (d, J = 7.4 Hz), 116.4, 106.7 (d, J = 7.2 Hz), 78.8, 65.6, 63.0 (d, J = 4.7 Hz), 52.5, 30.3 (d, J = 4.2 Hz), 14.9 (d, J = 5.7 Hz), 11.0, 10.9. *The multiplets in the^{13}C NMR spectrum are caused by atropoisomers.* ^{19}F NMR (376 MHz, CDCl$_3$) δ −62.68. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{29}$H$_{22}$F$_3$N$_2$O$_4$S$^+$ 551.1247; Found 551.1249.

Methyl (R)-8-Cyclopropyl-7-(3-methoxyphenyl)-13-oxo-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]-naphthyridine-11-carboxylate (11i). The compound was prepared by following the general procedure. The reaction was finished after 5.5 h. DDQ was added, and the mixture was stirred for 10 min. The crude product was purified with automated flash column chromatography (25 g cartridge, 20−70% EtOAc in heptane). Yellow solid (172 mg, 83.7%). The compound contained chloroform; yield was calculated from ^{1}H NMR spectrum recorded in (CD$_3$)$_2$SO. [α]$_D$ −160° (c 0.31, CHCl$_3$). IR (KBr): ν 3442, 3000, 2953, 2837, 1753, 1667, 1606, 1579, 1552, 1517, 1489, 1463, 1436, 1381, 1371, 1298, 1284, 1260, 1217, 1180, 1149, 1107, 1071, 1035 cm^{-1}. ^{1}H NMR [400 MHz, (CD$_3$)$_2$SO, 343 K]: δ 8.23 (dd, J = 7.8, 1.7 Hz, 1H), 7.45−7.33 (m, 2H), 7.17 (td, J = 7.5, 1.1 Hz, 1H), 7.07−6.94 (m, 3H), 6.94−6.87 (m, 1H), 5.68 (dt, J = 8.7, 3.1 Hz, 1H), 5.19−4.95 (m, 2H), 3.89−3.79 (m, 4H), 3.76 (s, 3H), 3.54 (dd, J = 11.8, 2.8 Hz, 1H), 1.02−

0.93 (m, 1H), 0.30 (m, 3H), 0.21−0.09 (m, 1H). ^{13}C{^{1}H} NMR [100 MHz, (CD$_3$)$_2$SO, 343 K]: 168.4, 158.4 (d, J = 7.5 Hz), 157.9, 155.6, 144.8, 144.3, 141.4, 139.9, 137.8, 133.0, 131.3, 128.7 (d, J = 7.9 Hz), 128.5, 124.6, 122.3, 122.0, 121.9, 116.4, 115.4 (d, J = 13.4 Hz), 113.6, 107.3, 78.8, 65.8, 62.9, 55.1, 52.5, 30.3, 14.7, 10.83−10.45 (m). *The multiplets in the* ^{13}*C NMR spectrum are caused by atropoisomers.* HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for C$_{29}$H$_{25}$N$_2$O$_5$S$^+$ 513.1479; Found 513.1476.

Methyl (R)-8-Cyclopropyl-7-(4-ethoxyphenyl)-13-oxo-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylate (11j). The compound was prepared by following the general procedure. The reaction was finished after 70 min. DDQ was added, and the mixture was stirred for 10 min. The crude product was purified with automated flash column chromatography (25 g cartridge, 20−60% EtOAc in heptane). The column was colored orange as the desired product eluted; we are hence suspecting that the compound binds to or breaks down on silica gel. Yellow solid (112 mg, 53.0%). The compound contained chloroform; yield was calculated from ^{1}H NMR spectrum recorded in (CD$_3$)$_2$SO. [α]$_D$ −188° (*c* 0.32, CHCl$_3$). IR (KBr): ν 3443, 2979, 1753, 1666, 1607, 1581, 1507, 1437, 1381, 1245, 1176, 1108, 1044 cm^{-1}. ^{1}H NMR [400 MHz, (CD$_3$)$_2$SO]: δ 8.19 (dd, J = 7.8, 1.7 Hz, 1H), 7.43−7.30 (m, 2H), 7.24 (dd, J = 8.7, 2.3 Hz, 1H), 7.18 (td, J = 7.5, 1.1 Hz, 1H), 7.05−6.95 (m, 3H), 5.69 (dd, J = 8.7, 2.5 Hz, 1H), 5.22−5.00 (m, 2H), 4.09 (d, J = 7.0 Hz, 2H), 3.85 (dd, J = 11.8, 8.7 Hz, 1H), 3.75 (s, 3H), 3.56 (dd, J = 11.8, 2.6 Hz, 1H), 1.37 (t, J = 6.9 Hz, 3H), 0.98−0.84 (m, 1H), 0.40−0.26 (m,1H), 0.26−0.03 (m, 3H). ^{13}C{^{1}H} NMR [100 MHz, (CD$_3$)$_2$SO]: δ 168.8, 158.4, 158.3, 155.8, 145.1, 144.6, 141.8, 140.0, 133.6, 131.7, 131.1, 129.1, 128.7, 125.0, 122.8, 122.5, 116.8, 113.7, 113.5, 107.8, 79.2, 66.0, 63.1, 52.9, 30.6, 15.1, 14.6, 10.9, 10.9. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for C$_{30}$H$_{27}$N$_2$O$_5$S$^+$ 527.1635; Found 527.1632.

(R)-Methyl 8-Methoxy-3-nitro-13-oxo-7-phenyl-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylate (11k). The compound was prepared by following the general procedure. The reaction was finished after 2 h. DDQ was added, and the mixture was stirred for 10 min. The crude product was purified with automated flash column chromatography (25 g cartridge, 0−100% EtOAc in heptane). Yellow solid (155 mg, 73%). [α]$_D^{25}$ −241 (*c* 0.4, CHCl$_3$). IR (KBr): ν 3468, 3000, 1742, 1667, 1592, 1552, 1531, 1494, 1456, 1410, 1375, 1226, 922, 799, 740, 705 cm^{-1}. ^{1}H NMR (600 MHz, CDCl$_3$): δ 8.68 (d, J = 8.3 Hz, 1H), 7.94 (d, J = 7.3 Hz, 1H), 7.75 (d, J = 2.0 Hz, 1H), 7.52−7.43 (m, 3H), 7.28 (d, J = 6.5 Hz, 2H), 5.78 (d, J = 6.2 Hz, 1H), 5.03 (q, J = 15.0 Hz, 2H), 3.83 (s, 3H), 3.81−3.76 (m, 1H), 3.61 (d, J = 11.1 Hz, 1H), 2.98 (s, 3H). ^{13}C NMR (151 MHz, CDCl$_3$): δ 168.2, 158.4, 156.4, 149.8, 145.0, 140.9, 140.4, 135.8, 135.7, 132.5, 130.0, 129.9, 128.5, 128.2, 128.2, 128.2, 128.1, 127.1, 117.4, 112.6, 66.8, 63.4, 60.1, 53.6, 32.0. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for C$_{26}$H$_{20}$N$_3$O$_7$S$^+$ 518.1016; Found 518.1016.

2-(Allyloxy)-4-nitrobenzaldehyde (12). Under an atmosphere of nitrogen, 2-hydroxy-4-nitrobenzaldehyde **Ib** (300 mg, 1.00 equiv) and K$_2$CO$_3$ (498 mg, 2.01 equiv) were suspended in DMF (1.5 mL). While stirring at r.t., allyl bromide (198 μL, 1.30 equiv) was added. The reaction mixture was stirred for 3:40 h at r.t. until completion was indicated by TLC analysis. The mixture was transferred to a beaker of ice-cold water (60 mL) while stirring; the resulting precipitate was filtered off and washed with water (5 mL). The precipitate was then dissolved in EtOAc (50 mL) and washed with brine (5 × 25 mL), dried with sodium sulfate, filtered, and evaporated. Yellow solid (326 mg, 87.7%). IR (KBr): ν 3102, 3086, 2886, 1689, 1614, 1590, 1532, 1482, 1433, 1420, 1395, 1369, 1350, 1308, 1270, 1246, 1184, 1111, 1087, 995, 937, 88, 815, 747 cm^{-1}. ^{1}H NMR (600 MHz, CDCl$_3$): δ 10.57 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.85 (s, 1H), 6.09 (ddt, J = 16.6, 10.6, 5.3 Hz, 1H), 5.51 (d, J = 17.3 Hz, 1H), 5.42 (d, J = 10.5 Hz, 1H), 4.78 (d, J = 4.7 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$): δ 188.4, 160.9, 152.2, 131.3, 129.7, 129.0, 119.6, 115.8, 108.5, 70.2. HRMS (ESI-TOF) *m/z*: [M − H]$^-$ Calcd for C$_{10}$H$_8$NO$_4^-$ 206.0459; Found 206.0465.

General Procedure for Synthesis of Povarov Reaction Products 13a−e.

The 6-amino thizolo-2-pyridone **9** (0.40 mmol, 1.00 equiv) and *O*-(propenyl benzoate)-salicylaldehyde **14** (0.48 mmol, 2.00 equiv) were weighed up in a Biotage Microwave reaction tube and dissolved in DCM (4 mL). 4 Å MS (8−10 pellets) was added, followed by BF$_3$·OEt$_2$ (10.8 μL; 0.10 equiv), whereupon the tube was sealed and left stirring in an oil bath at 70 °C. The reaction was monitored with TLC until complete consumption of **9** was indicated. The tube was then cooled down to r.t., opened, and DDQ (182 mg; 2.00 equiv) was added. The reaction mixture was stirred for 5 min; complete oxidation was indicated by TLC. Then it was transferred to a separation funnel and diluted with DCM (25 mL). The mixture was washed with saturated aqueous bicarbonate solution (2 × 10 mL), followed by brine (10 mL). The aq. phases were re-extracted once each with DCM (3 mL). The organic phase was dried over sodium sulfate, filtered, and evaporated to dryness. The crude residue was redissolved in DCM and purified with automated flash column chromatography. The fractions containing pure desired product were combined, evaporated, and co-evaporated with distilled chloroform twice. The residue was put under high vacuum for several hours before storage at −20 °C. The yield was calculated from ^{1}H NMR spectrum recorded in d6-DMSO.

Methyl 8-Cyclopropyl-3-nitro-13-oxo-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylate (13a). The compound was prepared by following the general procedure starting from **9a** (106 mg, 0.40 mmol). The reaction mixture was stirred for 24 h, and the product was purified on automated flash column chromatography (50 g cartridge, 10−75% EtOAc in *n*-heptane) in 37% yield (66 mg, 0.146 mmol), isolated as a light yellow solid. [α]$_D$ −235° (*c* 0.264, CHCl$_3$); IR (KBr): ν 3086, 6005, 2955, 2924, 2852, 1754, 1670, 1577, 1531, 1460, 1343, 1237, 1032, 918, 805, 738 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$): δ 8.64 (d, J = 8.6 Hz, 1H), 8.09 (s, 1H), 7.96−7.91 (m, 1H), 7.84−7.80 (m, 1H), 5.77 (dd, J = 8.2, 1.8 Hz, 1H), 5.45 (s, 2H), 3.80 (s, 3H), 3.76 (dd, J = 11.5, 8.4 Hz, 1H), 3.58 (d, J = 11.6 Hz, 1H), 1.79−1.73 (m, 1H), 1.15−1.04 (m, 2H), 0.76−0.68 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$): δ 168.6, 159.5, 156.6, 149.7, 144.9, 143.3, 140.2, 135.9, 130.4, 128.2, 127.3, 126.8, 117.5, 112.9, 108.1, 68.6, 63.1, 53.5, 31.8, 10.1, 7.7, 7.6. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for C$_{22}$H$_{18}$N$_3$O$_6$S$^+$ 452.0911; Found 452.0911.

Methyl (R)-3-Nitro-13-oxo-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylate (13b). The compound was prepared by following the general procedure starting from **9a** (106 mg, 0.40 mmol). The reaction mixture was stirred for 24 h, and the product was purified on automated flash column chromatography (50 g cartridge, 10−50% EtOAc in *n*-heptane) in 54% yield (89 mg, 0.216 mmol) as a yellow powder. [α]$_D$ −216° [*c* 0.16, (CH$_3$)$_2$SO]. IR (KBr): ν 3548, 3415, 3083, 3006, 2955, 2851, 1749, 1672, 1605, 1589, 1533, 1514, 1457, 1433 cm^{-1}. ^{1}H NMR [400 MHz, (CD$_3$)$_2$SO] δ 8.38 (d, J = 8.6 Hz, 1H), 8.01 (dd, J = 8.6, 2.3 Hz, 1H), 7.87 (d, J = 1.1 Hz, 1H), 7.79 (d, J = 2.3 Hz, 1H), 6.71 (s, 1H), 5.73 (dd, J = 8.7, 2.0 Hz, 1H), 5.54 (s, 2H), 3.98 (dd, J = 11.8, 8.7 Hz, 1H), 3.75 (s, 3H), 3.69 (dd, J = 11.9, 2.0 Hz, 2H). ^{13}C{^{1}H} NMR [100 MHz, (CD$_3$)$_2$SO] δ 169.1, 156.6, 149.4, 144.0, 138.9, 135.2, 131.5, 130.1, 117.8, 112.8, 97.2, 68.0, 62.9, 53.5, 32.0. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for C$_{19}$H$_{13}$N$_3$NaO$_6$S$^+$ 434.0423; Found 434.0428.

Methyl (R)-8-Cyclopropyl-2-fluoro-13-oxo-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylate (13c). The compound was prepared by following the general procedure starting from **9a** (106 mg, 0.40 mmol). The reaction mixture was stirred for 24 h, and the product was purified on automated flash column chromatography (50 g cartridge, 10−50% EtOAc in *n*-heptane) isolated in 43% yield (73 mg, 0.172 mmol) as a light-yellow powder. [α]$_D$ −200° [*c* 0.33, (CH$_3$)$_2$SO]. IR (KBr): ν 3549, 3473, 3415, 3004, 2247, 1753, 1663, 1606, 1582, 1523, 1490, 1470 cm^{-1}. ^{1}H NMR [600 MHz, (CD$_3$)$_2$SO] δ 8.29 (s, 1H), 7.90−7.79 (m, 1H), 7.26 (d, J = 3.3 Hz, 1H), 7.09 (dd, J = 8.9, 4.5 Hz, 1H), 5.71 (dd, J = 8.9, 2.1 Hz, 1H), 5.52−5.42 (m, 2H), 3.88 (dd, J = 11.8, 8.9 Hz, 1H), 3.74 (s, 3H), 3.62 (dd, J = 11.8, 2.2 Hz, 1H), 1.83−1.74

(m, 1H), 1.13−0.99 (m, 2H), 0.70−0.55 (m, 2H). $^{13}C\{^1H\}$ NMR [151 MHz, $(CD_3)_2SO$] δ 169.3, 158.7, 158.7, 157.1, 153.1, 145.2, 145.2, 143.2, 139.2, 135.5, 130.8, 128.1, 124.0, 124.0, 119.4, 119.4, 118.9, 118.7, 110.5, 110.3, 107.2, 67.9, 63.0, 53.4, 31.2, 10.2, 7.9, 7.7. ^{19}F NMR [565 MHz, $(CD_3)_2SO$] δ −120.86 (td, J = 8.8, 8.3, 4.4 Hz). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{18}FN_2O_4S^+$ 425.0966; Found 425.0972.

Methyl (R)-8-Cyclopropyl-13-oxo-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylate (13d). The compound was prepared by following the general procedure starting from **9a** (106 mg, 0.40 mmol). The reaction mixture was stirred for 24 h, and the product was purified with automated flash column chromatography (50 g cartridge, 20−80% EtOAc in n-heptane) isolated in 51% yield (85 mg, 0.20 mmol) as a yellow powder. $[\alpha]_D$ −135° [c 0.33, $(CH_3)_2SO$]. IR (KBr): ν 3415, 3082, 3003, 2953, 2927, 2844, 1747, 1663, 1603, 1588, 1578, 1519, 1493, 1461 cm^{-1}. ^1H NMR [600 MHz, $(CD_3)_2SO$] δ 8.27 (s, 1H), 8.21 (dd, J = 7.8, 1.7 Hz, 1H), 7.41 (td, J = 7.7, 1.7 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.04 (d, J = 8.1 Hz, 1H), 5.71 (dd, J = 8.8, 2.2 Hz, 1H), 5.50−5.45 (m, 2H), 3.89 (dd, J = 11.8, 8.8 Hz, 1H), 3.74 (s, 3H), 3.62 (dd, J = 11.8, 2.2 Hz, 1H), 1.85−1.75 (m, 1H), 1.10−1.05 (m, 2H), 0.71−0.56 (m, 2H). $^{13}C\{^1H\}$ NMR [151 MHz, $(CD_3)_2SO$] δ 169.3, 158.8, 156.9, 146.2, 142.6, 139.3, 135.0, 132.2, 130.8, 127.9, 125.0, 122.8, 122.8, 117.6, 107.2, 67.8, 63.0, 53.4, 31.2, 10.2, 7.9, 7.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{19}N_2O_4S^+$ 407.1060; Found 407.1063.

Methyl (R)-8-Cyclopropyl-2-nitro-13-oxo-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylate (13e). The compound was prepared by following the general procedure starting from **9a** (106 mg, 0.40 mmol). The reaction mixture was stirred for 24 h, and the product was purified with automated flash column chromatography (50 g cartridge, 10−50% EtOAc in n-heptane) in 14% yield (25 mg, 0.05 mmol) as a yellow powder. $[\alpha]_D$ −83° [c 0.12, $(CH_3)_2SO$]. IR (KBr): ν 3417, 3082, 30009, 2954, 2852, 2247, 1753, 1665, 1617, 1606, 1592, 1578, 1520, 1488, 1467 cm^{-1}. ^1H NMR [600 MHz, $(CD_3)_2SO$] δ 8.98 (d, J = 2.9 Hz, 1H), 8.34 (s, 1H), 8.27 (dd, J = 9.0, 2.9 Hz, 1H), 7.27 (d, J = 9.0 Hz, 1H), 5.78−5.67 (m, 3H), 3.91 (dd, J = 11.8, 8.9 Hz, 1H), 3.75 (s, 3H), 3.64 (dd, J = 11.8, 2.2 Hz, 1H), 1.85−1.78 (m, 1H), 1.15−1.05 (m, 2H), 0.73−0.60 (m, 2H). $^{13}C\{^1H\}$ NMR [151 MHz, $(CD_3)_2SO$] δ 169.2, 161.6, 158.6, 143.8, 143.8, 142.7, 139.4, 135.8, 130.1, 128.4, 127.3, 122.8, 120.4, 119.0, 107.2, 68.6, 63.0, 53.4, 31.2, 10.2, 7.9, 7.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{17}N_3NaO_6S^+$ 474.0736; Found 474.0714.

General Procedure for Synthesis of O-Alkylated Salicylaldehydes 14a−d. Under an atmosphere of nitrogen, 3-bromopropenyl benzoate (868 mg, 3.60 mmol, 1.80 equiv) was dissolved in DMF (2.0 mL) and transferred with a syringe to a mixture of salicylaldehyde **I** (2.00 mmol, 1.00 equiv) and K_2CO_3 (553 mg, 2.00 equiv) under nitrogen. The reaction mixture was stirred at r.t. until completion was indicated by TLC analysis. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with brine (5 × 50 mL), filtered through sodium sulfate, and evaporated. The crude product was purified with automated flash column chromatography.

(E)-3-(2-Formyl-4-nitrophenoxy)prop-1-en-1-yl Benzoate (14a). The compound was prepared by following the general procedure starting from 5-nitro-2-hydroxybenzaldehyde (334 mg, 2.00 mmol). The reaction mixture was stirred for 1.0 h, and the product was purified with automated flash column chromatography (50 g cartridge, 5−85% EtOAc in n-heptane) in 61% yield (400 mg, 1.22 mmol) as a white powder. (E)-3-Bromoprop-1-en-1-yl benzoate was prepared according to literature reports and crystallized from heptane.[15a] IR (KBr): ν 3412, 3111, 3069, 2947, 2898, 2631, 1718, 1687, 1609, 1588, 1526, 1481, 1451, 1428, 1406 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 10.51 (s, 1H), 8.75 (d, J = 2.9 Hz, 1H), 8.47 (dd, J = 9.1, 2.9 Hz, 1H), 8.18−8.10 (m, 2H), 7.83 (d, J = 12.4 Hz, 1H), 7.67 (t, J = 7.5 Hz, 1H), 7.53 (t, J = 7.8 Hz, 2H), 7.19 (d, J = 9.1 Hz, 1H), 5.95 (dt, J = 12.5, 7.1 Hz, 1H), 4.89 (d, J = 7.1 Hz, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 187.3, 164.3, 163.2, 141.8, 141.1, 130.5, 130.1, 130.1, 128.7, 128.5, 128.3, 128.2, 127.0, 124.9, 124.8, 113.0,

107.7, 66.6. HRMS (ESI-TOF) m/z: $[M − H]^−$ Calcd for $C_{17}H_{12}NO_6^−$ $[M − H]^−$ 326.0670; Found 326.0657.

(E)-3-(2-Formyl-5-nitrophenoxy)prop-1-en-1-yl Benzoate (14b). The compound was prepared by following the general procedure starting from 4-nitro-2-hydroxybenzaldehyde (334 mg, 2.00 mmol). The reaction mixture was stirred for 2.0 h, and the product was purified with automated flash column chromatography (50 g cartridge, 10−90% EtOAc in n-heptane) in 68% yield (450 mg, 1.37 mmol) as a white powder. (E)-3-Bromoprop-1-en-1-yl benzoate was prepared according to literature reports and crystallized from heptane.[15a] IR (KBr): ν 3420, 3098, 3086, 3036, 2953, 2868, 2756, 1730, 1694, 1613, 1601, 1586, 1523, 1493, 1477, 1452, 1428 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 10.58 (s, 1H), 8.15 (dt, J = 8.2, 0.9 Hz, 2H), 8.03 (d, J = 8.9 Hz, 1H), 7.93 (dq, J = 5.0, 2.0 Hz, 2H), 7.83 (dd, J = 12.5, 1.2 Hz, 1H), 7.70−7.59 (m, 1H), 7.52 (t, J = 7.7 Hz, 2H), 5.96 (dt, J = 12.6, 7.0 Hz, 1H), 4.87 (d, J = 7.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 188.1, 163.2, 160.5, 140.9, 134.0, 130.1, 129.7, 128.8, 128.6, 128.2, 115.9, 108.1, 107.9, 66.4. HRMS (ESI-TOF) m/z: $[M − H]^−$ Calcd for $C_{17}H_{12}NO_6^−$ 326.0670; Found 326.0668.

(E)-3-(4-Fluoro-2-formylphenoxy)prop-1-en-1-yl Benzoate (14c). The compound was prepared by following the general procedure starting from 5-fluoro-2-hydroxybenzaldehyde (251 mg, 1.79 mmol). The reaction mixture was stirred for 2.5 h, and the product was purified with automated flash column chromatography (50 g cartridge, 2−50% EtOAc in n-heptane) as a white powder in 84% yield (388 mg, 1.51 mmol). (E)-3-Bromoprop-1-en-1-yl benzoate was prepared according to literature reports and crystallized from heptane.[15a] IR (KBr): ν 3548, 3415, 3091, 3059, 2946, 2892, 2870, 2766, 1727, 1685, 1614, 1599, 1584, 1495, 1452 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 10.48 (s, 1H), 8.18−8.09 (m, 2H), 7.76 (dd, J = 12.5, 1.3 Hz, 1H), 7.70−7.62 (m, 1H), 7.56 (dd, J = 8.2, 3.3 Hz, 1H), 7.52 (t, J = 7.8 Hz, 2H), 7.31−7.27 (m, 3H), 7.04 (dd, J = 9.1, 3.9 Hz, 1H), 5.92 (dt, J = 12.5, 7.0 Hz, 1H), 4.74 (dd, J = 7.0, 1.2 Hz, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 188.58, 188.57, 163.3, 157.9, 156.98, 156.97, 156.3, 140.2, 133.9, 130.10, 128.6, 128.4, 122.5, 122.3, 114.68, 114.63, 114.3, 114.1, 108.9. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −121.79. HRMS (ESI-TOF) m/z: $[M − H]^−$ Calcd for $C_{17}H_{12}FO_4^−$ 299.0725; Found 299.0725.

3-(2-Formylphenoxy)prop-1-en-1-yl Benzoate (14d). The compound was prepared by following the general procedure starting from 2-hydroxybenzaldehyde (244 mg, 2.00 mmol). The reaction mixture was stirred for 1.5 h, and the product was purified with automated flash column chromatography (50 g cartridge, 2−25% EtOAc in n-heptane) in 79% yield as a white powder (450 mg, 1.59 mmol). 3-Bromoprop-1-en-1-yl benzoate was prepared by following literature reports.[15a] Instead of recrystallization, it was purified on automated flash column chromatography (50 g cartridge, 0−10% EtOAc in n-heptane) and isolated as a mixture of E and Z isomers. Thus, the alkylated salicylaldehyde was also isolated as a mixture of E and Z isomers. IR (KBr): ν 3415, 3093, 3067, 2941, 2859, 2761, 1734, 1691, 1599, 1582, 1482, 1453, 1400 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 10.55 (s, 1H), 10.25 (s, 1H), 8.30−8.23 (m, 1H), 8.19−8.09 (m, 2H), 8.00−7.98 (m, 1H), 7.90−7.87 (m, 1H), 7.80−7.42 (m, 9H), 7.37−7.35 (m, 1H), 7.12−7.02 (m, 2H), 5.98−5.91 (m, 1H), 5.42−5.37 (m, 1H), 5.03−5.01 (m, 1H), 4.77−4.75 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 189.7, 189.6, 188.4, 164.9, 163.3, 162.8, 160.7, 152.3, 140.0, 137.1, 135.8, 135.8, 135.3, 134.0, 134.0, 133.9, 130.3, 130.2, 130.1, 130.0, 128.7, 128.7, 128.6, 128.6, 128.6, 128.5, 128.4, 128.3, 126.5, 125.2, 125.2, 123.5, 121.1, 121.0, 112.8, 112.7, 109.2, 108.7, 65.4, 62.2. HRMS (ESI-TOF) m/z: $[M − H]^−$ Calcd for $C_{17}H_{13}O_4^−$ 281.0819; Found 281.0819.

General Procedure for Hydrolysis of Methyl Esters. Synthesis of 15a−j and 16a−e. The methyl ester was dissolved in THF (4 mL), and LiOH (0.10 M, 1.40 equiv) was added to the stirred solution. The hydrolysis was monitored with TLC. Upon completion, HCl (1.00 M, 1.50 equiv) was added. The resulting mixture was stirred for 5 min, then concentrated partially, until most of the THF was removed. The residue was partitioned between water and $CHCl_3$/MeOH 9:1 (10 mL). The phases were separated, and the

aqueous phase was extracted once more (5 mL). The combined organic extracts were dried with sodium sulfate, filtered, and evaporated. The residue was redissolved in DMSO (1−3 mL) and purified with preparative HPLC. The fractions containing the pure desired product were combined, diluted with water, and freeze-dried.

(R)-8-Cyclopropyl-13-oxo-7-phenyl-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylic Acid (15a). The compound was prepared by following the general procedure. 50 mg of **11a** was hydrolyzed. The reaction was finished after 42 min. Orange solid (32.6 mg, 67.2%). $[\alpha]_D$ −90.40 [c 0.20, (CD$_3$)$_2$SO]; IR (KBr): ν 3441, 3003, 1743, 1648, 1610, 1576, 1519, 1493, 1463, 1437, 1382, 1299, 1253, 1221, 1182, 1036 cm^{-1}. ^{1}H NMR [600 MHz, (CD$_3$)$_2$SO]: δ 13.52 (s, 1H), 8.21 (dd, J = 7.7, 1.6 Hz, 1H), 7.55−7.31 (m, 6H), 7.19 (t, J = 7.5 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 5.60 (dd, J = 8.7, 1.9 Hz, 1H), 5.13 (d, J = 14.7 Hz, 1H), 5.00 (d, J = 14.6 Hz, 1H), 3.83 (dd, J = 11.7, 8.7 Hz, 1H), 3.54 (dd, J = 11.9, 1.9 Hz, 1H), 0.85−0.75 (m, 1H), 0.30 to −0.01 (m, 4H). ^{13}C{^{1}H} NMR [151 MHz, (CD$_3$)$_2$SO] δ 169.6, 158.2, 155.8, 145.1, 145.0, 141.7, 140.1, 136.8, 133.3, 131.7, 129.9, 129.8, 128.7, 128.3, 127.8, 127.7, 125.0, 122.7, 122.5, 116.8, 107.3, 66.0, 63.2, 30.9, 15.2, 11.2, 11.0. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{27}$H$_{21}$N$_2$O$_4$S$^+$ 469.1217; Found 469.1228.

8-Cyclopropyl-3-nitro-13-oxo-7-phenyl-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylic Acid (15b). The compound was prepared by following the general procedure. 62 mg of methyl ester **11b** was hydrolyzed. The reaction was found complete after 50 min. Yellow solid (30.9 mg, 51.2%). $[\alpha]_D$ −122.3° [c 0.308, (CD$_3$)$_2$SO]; IR (KBr): ν 3448, 1638, 1573, 1530, 1438, 1343, 1226, 1042, 741 cm^{-1}. ^{1}H NMR [600 MHz, (CD$_3$)$_2$SO]: δ 13.63 (bs, 1H), 8.42 (dd, J = 8.6, 1.8 Hz, 1H), 8.05 (dd, J = 8.6, 2.2 Hz, 1H), 7.76 (d, J = 2.2 Hz, 1H), 7.54−7.41 (m, 4H), 7.40−7.33 (m, 1H), 5.61 (d, J = 8.7 Hz, 1H), 5.31−5.09 (m, 2H), 3.84 (dd, J = 11.7, 8.7 Hz, 1H), 3.56 (dd, J = 11.7, 1.9 Hz, 1H), 0.90−0.82 (m, 1H), 0.30−0.15 (m, 3H), 0.12−0.00 (m, 1H). ^{13}C{^{1}H} NMR [151 MHz, (CD$_3$)$_2$SO]: δ 169.5, 157.9, 155.7, 149.1, 146.7, 142.7, 142.1, 140.4, 136.4, 134.3, 129.8, 129.7, 129.2, 128.5, 128.4, 127.9, 127.8, 126.0, 117.5, 112.0, 107.3, 66.7, 63.3, 31.1, 15.2, 11.2, 11.1. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{27}$H$_{20}$N$_3$O$_6$S$^+$ 514.1068; Found 514.1062.

(R)-3-Nitro-13-oxo-7-phenyl-6,10,11,13-tetrahydrochromeno-[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylic Acid (15c). The compound was prepared by following the general procedure but with 1.60 equiv of LiOH. 50 mg of **11c** was hydrolyzed. The reaction was finished after 2 h, whereupon 1.72 equiv of HCl was added. The mixture was partitioned between DCM/n-BuOH (2:1) and brine/water (1:1). Yellow solid (38 mg, 78%). $[\alpha]_D$ −6.79 [c 0.18, (CD$_3$)$_2$SO]. IR (KBr): ν 3440, 3082, 2935, 1754, 1666, 1623, 1592, 1577, 1536, 1517, 1226, 1043 cm^{-1}. ^{1}H NMR [400 MHz, (CD$_3$)$_2$SO, 343 K]: δ 8.50 (d, J = 8.6 Hz, 1H), 8.02 (dd, J = 8.6, 2.3 Hz, 1H), 7.74 (d, J = 2.3 Hz, 1H), 7.65−7.55 (m, 3H), 7.40−7.32 (m, 2H), 5.95 (s, 1H), 5.62 (dd, J = 8.5, 1.8 Hz, 1H), 5.19 (s, 2H), 3.93 (dd, J = 11.8, 8.5 Hz, 1H), 3.62 (dd, J = 11.7, 1.8 Hz, 1H). ^{13}C{^{1}H} NMR [100 MHz, (CD$_3$)$_2$SO, 343 K]: δ 168.9, 158.1, 155.6, 148.9, 144.0, 143.1, 141.3, 138.6, 133.2, 132.8, 128.82, 128.79, 128.75, 128.5, 128.4, 128.1, 127.7, 125.6, 116.9, 111.8, 93.6, 66.3, 62.6, 31.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{24}$H$_{16}$N$_3$O$_6$S$^+$ 474.0755; Found 474.0757.

(R)-8-Cyclopropyl-2-nitro-13-oxo-7-phenyl-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylic Acid (15d). The compound was prepared by following the general procedure. 50 mg of **11d** was hydrolyzed. The reaction was finished after 40 min. Yellow solid (36.9 mg, 75.8%). $[\alpha]_D$ −92.47 [c 0.23, (CH$_3$)$_2$SO]. IR (KBr): ν 3442, 3082, 3002, 1743, 1631, 1589, 1574, 1550, 1518, 1494, 1481, 1460, 1443, 1385, 1341, 1297, 1251, 1201, 1091, 1023 cm^{-1}. ^{1}H NMR [600 MHz, (CD$_3$)$_2$SO]: δ 13.62 (s, 1H), 9.00 (d, J = 2.9 Hz, 1H), 8.25 (dd, J = 8.9, 2.5 Hz, 1H), 7.47 (dd, J = 17.9, 4.9 Hz, 4H), 7.36 (d, J = 5.2 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 5.62 (d, J = 8.5 Hz, 1H), 5.27 (dd, J = 87.1, 14.9 Hz, 2H), 3.84 (dd, J = 11.7, 8.7 Hz, 1H), 3.56 (d, J = 11.6 Hz, 1H), 0.86 (s, 1H), 0.30−0.15 (m, 3H), 0.10−0.00 (m, 1H). ^{13}C{^{1}H} NMR [151

MHz, (CD$_3$)$_2$SO]: δ 169.5, 160.6, 158.0, 146.3, 142.5, 142.4, 142.2, 140.2, 136.4, 134.1, 129.7, 129.7, 128.5, 128.0, 127.9, 127.8, 126.9, 122.6, 120.2, 118.2, 107.2, 66.9, 63.4, 31.0, 15.2, 11.2, 11.1. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{27}$H$_{20}$N$_3$O$_6$S$^+$ 514.1068; Found 514.1088.

(R)-8-Cyclopropyl-7-(4-nitrophenyl)-13-oxo-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylic Acid (15e). The compound was prepared by following the general procedure. 50 mg of **11e** was hydrolyzed. The reaction was finished after 30 min. Yellow solid (34.5 mg, 70.9%). $[\alpha]_D$ −94.72° [c 0.26, (CD$_3$)$_2$SO]. IR (KBr): ν 3442, 3075, 3002, 2850, 2578, 1758, 1665, 1605, 1561, 1519, 1491, 1464, 1442, 1385, 1348, 1298, 1258, 1225, 1183, 1109, 1045 cm^{-1}. ^{1}H NMR [600 MHz, (CD$_3$)$_2$SO]: δ 13.58 (s, 1H), 8.37−8.27 (m, 2H), 8.21 (d, J = 7.7 Hz, 1H), 7.78 (d, J = 7.7 Hz, 1H), 7.68 (d, J = 7.9 Hz, 1H), 7.40 (t, J = 7.7 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.00 (d, J = 8.1 Hz, 1H), 5.62 (d, J = 8.6 Hz, 1H), 5.17−4.97 (m, 2H), 3.89−3.78 (m, 1H), 3.55 (d, J = 11.6 Hz, 1H), 0.89−0.82 (m, 1H), 0.32−0.17 (m, 3H), 0.10−0.03 (m, 1H). ^{13}C{^{1}H} NMR [151 MHz, (CD$_3$)$_2$SO]: δ 169.5, 158.0, 155.8, 147.2, 146.1, 144.9, 143.7, 140.1, 139.4, 133.0, 131.8, 131.4, 131.3, 128.5, 125.0, 123.0, 122.9, 122.6, 122.5, 116.8, 106.7, 65.8, 63.3, 31.0, 15.5, 11.8, 11.7. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{27}$H$_{20}$N$_3$O$_6$S$^+$ 514.1068; Found 514.1072.

(R)-3-Nitro-7-(4-nitrophenyl)-13-oxo-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylic Acid (15f). The compound was prepared by following the general procedure but with 1.60 equiv of LiOH. 50 mg of **11f** was hydrolyzed. The reaction was finished after 2 h, whereupon 1.72 equiv of HCl was added. The mixture was partitioned between DCM/n-BuOH (1:1) and brine/water (1:1). Yellow solid (26.1 mg, 53.6%) $[\alpha]_D$ −3.55 [c 0.51, (CD$_3$)$_2$SO]. IR (KBr): ν 3435, 3107, 1748, 1666, 1592, 1566, 1533, 1453, 1431, 1384, 1346, 1227, 1180, 1043 cm^{-1}. ^{1}H NMR [400 MHz, (CD$_3$)$_2$SO]: δ 13.74 (s, 1H), 8.54−8.35 (m, 3H), 8.04 (dd, J = 8.7, 2.3 Hz, 1H), 7.77 (d, J = 2.3 Hz, 1H), 7.73−7.67 (m, 1H), 5.98 (s, 1H), 5.62 (dd, J = 8.6, 1.5 Hz, 1H), 5.20 (s, 2H), 3.90 (dd, J = 11.8, 8.6 Hz, 1H), 3.62 (dd, J = 11.8, 1.6 Hz, 1H). ^{13}C{^{1}H} NMR [100 MHz, (CD$_3$)$_2$SO]: δ 169.4, 158.3, 155.8, 149.0, 147.9, 144.9, 143.2, 140.0, 139.5, 138.6, 133.1, 130.8, 130.6, 128.1, 128.0, 125.8, 124.3, 117.5, 112.2, 93.9, 66.3, 62.8, 31.9. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{24}$H$_{15}$N$_4$O$_8$S$^+$ 519.0605; Found 519.0612.

(R)-8-Cyclopropyl-2-fluoro-13-oxo-7-phenyl-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylic Acid (15g). The compound was prepared by following the general procedure starting from **11g** (50 mg, 0.09 mmol). The reaction mixture was stirred for 4 h, and the product was isolated as a yellow powder in 38% yield (38 mg, 0.07 mmol). $[\alpha]_D$ −113° [c 0.12, (CH$_3$)$_2$SO]. IR (KBr): ν 3415, 3081, 3001, 2921, 2852, 1713, 1656, 1619, 1575, 1550, 1520, 1494, 1482, 1462, 1429 cm^{-1}. ^{1}H NMR [600 MHz, (CD$_3$)$_2$SO] δ 7.67 (dd, J = 9.0, 3.2 Hz, 1H), 7.31−7.19 (m, 5H), 7.14 (dt, J = 6.8, 2.4 Hz, 1H), 7.03 (td, J = 8.6, 3.2 Hz, 1H), 6.83 (dd, J = 8.9, 4.5 Hz, 1H), 5.25 (t, J = 7.8 Hz, 1H), 4.94−4.76 (m, 2H), 3.54 (dd, J = 11.3, 8.4 Hz, 1H), 3.33 (dt, J = 11.5, 2.9 Hz, 1H), 0.70−0.55 (m, 1H), 0.15 to −0.10 (m, 3H), −0.13 to −0.25 (m, 1H). ^{13}C{^{1}H} NMR [151 MHz, (CD$_3$)$_2$SO] δ 169.5, 158.8, 158.46, 158.44, 157.2, 152.4, 146.8, 144.0, 142.0, 140.7, 140.6, 137.2, 134.06, 134.04, 130.3, 130.25, 130.22, 128.9, 128.7, 128.2, 128.16, 128.12, 124.6, 124.5, 119.0, 118.9, 118.6, 118.5, 110.8, 110.7, 107.1, 66.64, 66.62, 64.8, 32.1, 15.67, 15.65, 11.6, 11.5. ^{19}F NMR [565 MHz, (CD$_3$)$_2$SO] δ −120.83 HRMS (ESI) m/z: [M + H]$^+$ Calcd for C$_{27}$H$_{20}$FN$_2$O$_4$S$^+$ 487.1123; Found 487.1103.

(R)-8-Cyclopropyl-13-oxo-7-(3-(trifluoromethyl)phenyl)-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]-naphthyridine-11-carboxylic Acid (15h). The compound was prepared by following the general procedure, but upon complete saponification, the mixture was neutralized with Amberlyst 15 until around pH = 6 by pH paper, then filtered through a pad of THF-wet Celite. The amberlyst and Celite were rinsed with MeOH until the filtrate was transparent. The filtrate was evaporated and extracted according to the general procedure. The residue was triturated with

Et$_2$O (0.5 mL) and filtered. The solid was washed with more Et$_2$O (0.5 mL) and dried under vacuum overnight. 25 mg of **11h** was hydrolyzed to provide **15h** (15.45 mg, 63.4%) as a yellow solid. $[\alpha]_D$ −51.71° [c 0.29, (CD$_3$)$_2$SO]. IR (KBr): ν 3442, 3082, 3003, 1734, 1629, 1577, 1518, 1490, 1446, 1382, 1330, 1169, 1127 cm^{-1}. ^{1}H NMR [600 MHz, (CD$_3$)$_2$SO, 343 K]: δ 8.25 (dd, J = 7.7, 1.8 Hz, 1H), 7.85−7.65 (m, 4H), 7.37 (td, J = 7.8, 1.7 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H), 6.96 (d, J = 8.1 Hz, 1H), 5.38 (d, J = 8.2 Hz, 1H), 5.14−4.92 (m, 2H), 3.68 (dt, J = 10.0, 7.3 Hz, 1H), 3.55 (d, J = 10.9 Hz, 1H), 0.80−0.70 (m, 1H), 0.34 to −0.07 (m, 4H). ^{13}C{^{1}H} NMR [151 MHz, (CD$_3$)$_2$SO, 343 K]: δ 168.4, 157.7, 155.4, 146.6, 144.0, 140.3, 137.9, 133.6, 132.6 (d, J = 13.3 Hz), 131.0, 128.6 (d, J = 9.9 Hz), 127.8, 126.1, 124.7, 124.6, 124.3, 122.9, 122.5, 122.0, 116.3, 105.3, 65.6, 65.1, 31.8 (d, J = 8.3 Hz), 14.8 (d, J = 9.5 Hz), 11.2−0.9 (m). *The multiplets in the ^{13}C NMR spectrum are caused by atropoisomerism.* ^{19}F NMR [565 MHz, (CD$_3$)$_2$SO, 343 K]: δ −61.20. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{28}$H$_{20}$F$_3$N$_2$O$_4$S$^+$ 537.1091; Found 537.1094.

(R)-8-Cyclopropyl-7-(3-methoxyphenyl)-13-oxo-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylic Acid (15i). The compound was prepared by following the general procedure, but upon complete saponification, the mixture was neutralized with Amberlyst 15 until around pH = 6 by pH paper, then filtered through a pad of THF-wet Celite. The amberlyst and Celite were rinsed with MeOH until the filtrate was transparent. The filtrate was evaporated and extracted according to the general procedure. The residue was triturated in Et$_2$O (0.5 mL) and filtered. The solid was washed with more Et$_2$O (0.5 mL) and dried under vacuum overnight. 25 mg of **11i** was converted to **15i** (17.5 mg, 72%) isolated as a yellow solid. $[\alpha]_D$ −91.56° [c 0.21, (CD$_3$)$_2$SO]. IR (KBr): ν 3442, 3390, 2941, 2836, 1757, 1646, 1608, 1577, 1519, 1463, 1439, 1439, 1218, 1038 cm^{-1}. ^{1}H NMR [600 MHz, (CD$_3$)$_2$SO, 343 K]: δ 8.24 (dd, J = 7.8, 1.7 Hz, 1H), 7.44−7.33 (m, 2H), 7.16 (td, J = 7.5, 1.1 Hz, 1H), 7.03 (dd, J = 8.2, 2.5 Hz, 1H), 7.00−6.87 (m, 3H), 5.51−5.45 (m, 1H), 5.17−4.96 (m, 2H), 3.82 (d, J = 8.6 Hz, 3H), 3.78−3.71 (m, 1H), 3.53 (dd, J = 11.3, 2.0 Hz, 1H), 0.99−0.92 (m, 1H), 0.34−0.21 (m, 3H), 0.20−0.09 (m, 1H). ^{13}C{^{1}H} NMR [151 MHz, (CD$_3$)$_2$SO, 343 K]: δ 168.7, 158.4 (d, J = 9.2 Hz), 157.8, 155.5, 145.2, 144.3, 141.0, 140.1, 138.0, 132.8, 131.1, 128.6 (d, J = 10.8 Hz), 128.0, 124.6, 122.5, 121.9, 116.3, 115.4 (d, J = 12.2 Hz), 113.5, 106.4, 65.8, 64.1, 55.1, 31.2, 14.6, 11.14−10.10 (m). *The multiplets in the ^{13}C NMR spectrum are caused by atropoisomerism.* HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{28}$H$_{22}$N$_2$O$_5$S$^+$ 499.1322; Found 499.1326.

(R)-8-Cyclopropyl-7-(4-ethoxyphenyl)-13-oxo-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylic Acid (15j). The compound was prepared by following the general procedure. 50 mg of **11j** was hydrolyzed. The reaction was finished after 65 min. Yellow powder (35.5 mg, 72.9%). $[\alpha]_D$ −78.30° [c 0.19, (CD$_3$)$_2$SO]. IR (KBr): ν 3413, 2980, 1745, 1640, 1608, 1577, 1508, 1463, 1441, 1283, 1299, 1283, 1245, 1223, 1178, 1111, 1045 cm^{-1}. ^{1}H NMR [600 MHz, (CD$_3$)$_2$SO] δ 13.52 (s, 1H), 8.19 (d, J = 7.8 Hz, 1H), 7.39 (t, J = 7.7 Hz, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.24 (d, J = 8.2 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.07−6.95 (m, 3H), 5.59 (d, J = 8.7 Hz, 1H), 5.21−5.01 (m, 2H), 4.09 (q, J = 6.8 Hz, 2H), 3.86−3.78 (m, 1H), 3.53 (d, J = 11.6 Hz, 1H), 1.37 (t, J = 6.9 Hz, 3H), 1.00−0.90 (m, 1H), 0.36−0.08 (m, 4H). ^{13}C{^{1}H} NMR [151 MHz, (CD$_3$)$_2$SO] δ 169.6, 158.4, 158.2, 155.8, 144.9, 144.9, 141.7, 140.1, 133.5, 131.6, 131.1, 129.0, 128.8, 125.0, 122.8, 122.4, 116.8, 113.6, 113.5, 107.5, 66.0, 63.2, 63.1, 30.9, 15.0, 14.6, 11.0, 10.9. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{29}$H$_{25}$N$_2$O$_5$S$^+$ 513.1479; Found 513.1496.

(R)-8-Methoxy-3-nitro-13-oxo-7-phenyl-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylic Acid (15k). The compound was prepared by following the general procedure. Compound precipitated during the workup and was filtered through a sintered funnel and dried. The compound was redissolved in DMSO (3 mL) and purified with preparative HPLC. 105 mg of **11k** was hydrolyzed. The reaction was finished after 16 h. Yellow powder (66 mg, 64.6%). $[\alpha]_D$ −52° [c 0.4, (CD$_3$)$_2$SO]. IR (KBr): ν 3449, 3057, 1740, 1665, 1635, 1583, 1556, 1533, 1515,

1458, 1430, 1382, 1229, 1181, 925, 820, 740, 707 cm^{-1}. ^{1}H NMR [600 MHz, (CD$_3$)$_2$SO] δ 8.51−8.37 (m, 1H), 8.04 (dd, J = 8.6, 2.2 Hz, 1H), 7.75 (d, J = 2.2 Hz, 1H), 7.49−7.48 (m, 3H), 7.39−7.36 (m, 2H), 5.63 (d, J = 8.5 Hz, 1H), 5.10−5.01 (m, 2H), 3.90 (dd, J = 11.6, 8.6 Hz, 1H), 3.64 (d, J = 11.3 Hz, 1H), 2.88 (s, 3H). ^{13}C{^{1}H} NMR [151 MHz, (CD$_3$)$_2$SO] δ 169.2, 157.1, 155.7, 149.0, 143.0, 140.1, 139.6, 137.2, 135.5, 130.6, 129.6, 129.4, 128.3, 128.1, 128.0, 127.7, 127.6, 125.9, 117.4, 112.1, 66.3, 63.4, 59.4, 31.7. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{25}$H$_{18}$N$_3$O$_7$S$^+$ 504.0860; Found 504.0842.

8-Cyclopropyl-3-nitro-13-oxo-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylic Acid (16a). The compound was prepared by following the general procedure. 33 mg of **13a** was hydrolyzed. The reaction was finished after 40 min. Orange solid (9.1 mg, 28.5%). $[\alpha]_D$ −162.3° [c 0.186, (CD$_3$)$_2$SO]; IR (KBr): ν 3438, 1731, 1652, 1578, 1531, 1432, 1345, 1238, 1034, 919, 739 cm^{-1}. ^{1}H NMR [600 MHz, (CD$_3$)$_2$SO]: δ 8.38 (dd, J = 8.6, 2.1 Hz, 1H), 8.29 (s, 1H), 8.01 (dd, J = 8.6, 2.3 Hz, 1H), 7.80 (d, J = 2.2 Hz, 1H), 5.63−5.60 (m, 3H), 3.86 (dd, J = 11.7, 8.7 Hz, 1H), 3.61 (dd, J = 11.7, 1.6 Hz, 1H), 1.80−1.74 (m, 1H), 1.12−1.02 (m, 2H), 0.68−0.63 (m, 1H), 0.56−0.51 (m, 1H). ^{13}C{^{1}H} NMR [151 MHz, (CD$_3$)$_2$SO]: δ 169.6, 158.2, 156.3, 148.9, 144.1, 143.3, 139.6, 135.5, 130.6, 128.2, 127.7, 125.6, 117.3, 112.3, 106.5, 67.9, 62.8, 31.3, 9.7, 7.5, 7.3. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{21}$H$_{16}$N$_3$O$_6$S$^+$ 438.0755; Found 438.0769.

(R)-3-Nitro-13-oxo-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylic Acid (16b). The compound was prepared by following the general procedure starting from **13b** (28 mg, 0.07 mmol). The reaction mixture was stirred for 0.5 h, and the product was isolated as a yellow powder in 15% yield (4.200 mg, 0.01 mmol). $[\alpha]_D$ −100° [c 0.10, (CD$_3$)$_2$SO]. IR (KBr): ν 3418, 3085, 2927, 2597, 1742, 1642, 1614, 1584, 1535, 1516, 1456 cm^{-1}. ^{1}H NMR [600 MHz, (CD$_3$)$_2$SO] δ 8.41 (d, J = 8.6 Hz, 1H), 8.03 (dd, J = 8.6, 2.3 Hz, 1H), 7.87 (s, 1H), 7.81 (d, J = 2.2 Hz, 1H), 6.68 (s, 1H), 5.55 (d, J = 17.8 Hz, 3H), 3.93 (dd, J = 11.5, 8.5 Hz, 1H), 3.66 (d, J = 11.4 Hz, 1H). ^{13}C{^{1}H} NMR [151 MHz, (CD$_3$)$_2$SO] δ 169.3, 158.5, 156.2, 148.9, 144.0, 143.5, 138.7, 134.7, 130.8, 129.5, 128.2, 125.6, 117.3, 112.3, 96.3, 67.6, 63.0, 32.1. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{18}$H$_{12}$N$_3$O$_6$S$^+$ 398.0442; Found 398.0439.

(R)-8-Cyclopropyl-2-fluoro-13-oxo-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylic Acid (16c). The compound was prepared by following the general procedure starting from **13c** (47 mg, 0.11 mmol). The reaction mixture was stirred for 1 h, and the product was isolated as a yellow powder in 43% yield (20 mg, 0.04 mmol). $[\alpha]_D$ −145° [c 0.22, (CD$_3$)$_2$SO]. IR (KBr): ν 3415, 3070, 3002, 2846, 1744, 1626, 1601, 1569, 1525, 1473 cm^{-1}. ^{1}H NMR [400 MHz, (CD$_3$)$_2$SO] δ 13.49 (s, 1H), 8.27 (s, 1H), 7.85 (dd, J = 9.0, 3.2 Hz, 1H), 7.26 (td, J = 8.6, 3.2 Hz, 1H), 7.09 (dd, J = 8.9, 4.6 Hz, 1H), 5.61 (dd, J = 8.8, 1.6 Hz, 1H), 5.47 (s, 2H), 3.86 (dd, J = 11.8, 8.7 Hz, 1H), 3.60 (dd, J = 11.8, 1.7 Hz, 1H), 1.85−1.70 (m, 1H), 1.13−1.02 (m, 2H), 0.70−0.54 (m, 2H). ^{13}C{^{1}H} NMR [100 MHz, (CD$_3$)$_2$SO] δ 170.1, 159.1, 158.7, 156.7, 153.0, 145.0, 143.5, 139.4, 135.4, 130.6, 127.9, 124.1, 124.0, 119.4, 119.3, 118.8, 118.6, 110.5, 110.3, 106.9, 67.9, 63.2, 31.6, 10.2, 7.9, 7.7. ^{19}F{^{1}H} NMR [376 MHz, (CD$_3$)$_2$SO] δ −120.90. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{21}$H$_{16}$FN$_2$O$_4$S$^+$ 411.0810; Found 411.0801.

(R)-8-Cyclopropyl-13-oxo-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylic Acid (16d). The compound was prepared by following the general procedure starting from **13d** (47 mg, 0.11 mmol). The reaction mixture was stirred for 2 h, and the product was isolated as a white powder in 28% yield (13 mg, 0.03 mmol). $[\alpha]_D$ −60° [c 0.16, (CD$_3$)$_2$SO]. IR (KBr): ν 3432, 3001, 2548, 1742, 1625, 1599, 1582, 1565, 1524, 1493, 1467 cm^{-1}. ^{1}H NMR [600 MHz, (CD$_3$)$_2$SO] δ 8.26 (s, 1H), 8.21 (dd, J = 7.8, 1.7 Hz, 1H), 7.40 (td, J = 7.7, 1.7 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.04 (d, J = 8.1 Hz, 1H), 5.61 (dd, J = 8.8, 1.6 Hz, 1H), 5.47 (d, J = 1.5 Hz, 2H), 3.86 (dd, J = 11.7, 8.7 Hz, 1H), 3.59 (dd, J = 11.7, 1.6 Hz, 1H), 1.83−1.74 (m, 1H), 1.13−1.02 (m, 2H), 0.70−0.54 (m, 2H). ^{13}C{^{1}H} NMR [151 MHz, (CD$_3$)$_2$SO] δ 168.0, 156.7, 154.7, 143.9,

140.7, 137.3, 132.9, 130.0, 128.5, 125.6, 122.9, 120.75, 120.73, 115.5, 104.8, 65.7, 61.0, 29.4, 8.1, 5.7, 5.6. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{21}H_{16}N_2NaO_4S^+$ 415.0729; Found 415.0712.

(R)-8-Cyclopropyl-2-nitro-13-oxo-6,10,11,13-tetrahydrochromeno[4,3-b]thiazolo[2,3-g][1,7]naphthyridine-11-carboxylic Acid (16e). The compound was prepared by following the general procedure starting from **13e** (20.76 mg, 0.046 mmol). The reaction was stirred for 1.5 h, and the product was isolated as yellow powder in 20% yield (4.200 mg, 0.009 mmol). $[\alpha]_D$ −198° [c 0.10, $(CD_3)_2SO$]. IR (KBr): ν 3550, 3475, 3414, 3236, 3079, 2844, 2497, 1754, 1634, 1617, 1587 cm^{-1}. ^{1}H NMR [600 MHz, $(CD_3)_2SO$] δ 8.95 (d, J = 2.8 Hz, 1H), 8.24 (dd, J = 9.0, 2.9 Hz, 1H), 7.25 (d, J = 9.0 Hz, 1H), 5.69−5.59 (m, 4H), 3.87−3.84 (m, 1H), 3.61 (dd, J = 11.6, 1.7 Hz, 1H), 1.79−1.75 (m, 1H), 1.11−1.03 (m, 2H), 0.68−0.56 (m, 2H). ^{13}C{^{1}H} NMR [151 MHz, $(CD_3)_2SO$] δ 169.5, 161.1, 158.2, 143.7, 143.0, 142.2, 139.0, 135.2, 129.3, 127.7, 126.7, 122.3, 119.8, 118.5, 106.3, 68.1, 62.9, 31.2, 9.7, 7.4, 7.2. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{21}H_{16}N_3O_6S^+$ 438.0755; Found 438.0766.

2-(Hydroxymethyl)-5-nitrophenol. The compound was prepared from 2-hydroxy-4-nitro-benzoic acid by following a published procedure[18] but with only 3 equiv of BH$_3$·SMe$_2$. 10.00 g was converted to 8.39 g (91%) after purification. NMR data were in agreement with published data.

2-Hydroxy-4-nitrobenzaldehyde (Ib). 2-(Hydroxymethyl)-5-nitrophenol (8.20 g, 1.00 equiv) was dissolved in THF (100 mL). (Diacetoxyiodo)benzene (17.27 g, 1.11 equiv) and TEMPO (158 mg, 0.02 equiv) were weighed up and added. The resulting suspension was stirred at r.t. After 30 min, a clear solution remained, but TLC indicated some remaining acid. No further progress was indicated after 65 min, whereupon (diacetoxyiodo)benzene (3.14 g, 0.20 equiv) was added. After 50 min of stirring, the reaction was found complete by TLC. Saturated aqueous sodium thiosulfate solution (100 mL) was added, and the mixture was stirred for 5 min, then transferred to a separation funnel and extracted with EtOAc (150 + 50 + 50 mL). The organic phases were combined, washed with brine (200 mL), and evaporated. The residue was redissolved in chloroform (300 mL) and extracted with aqueous potassium hydroxide solution (5% w/v, 3 × 200 mL). The combined extracts were cooled in an ice-water bath and neutralized with HCl (12 M, 44 mL). The precipitate was filtered off and dissolved in EtOAc, dried with sodium sulfate, filtered, and evaporated. The residue was redissolved in DCM/MeOH (99:1) and purified with flash column chromatography (70 × 120 mm silica gel, DCM/MeOH 99:1). 5.23 g (64.5%) isolated as a light-yellow powder. NMR data recorded in $(CD_3)_2CO$ are in close agreement with published data,[18] and the phenolic proton is visible as well. ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 11.06 (s, 1H), 10.27 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.93−7.81 (m, 1H), 7.76 (s, 1H). IR (KBr): ν 3452, 3224, 3110, 3046, 2885, 1676, 1537, 1476, 1353, 1299, 1219, 1172, 1116, 958, 882, 827, 793, 740 cm^{-1}. ^{1}H NMR (600 MHz, CDCl$_3$): δ 11.16 (s, 1H), 10.08 (s, 1H), 7.79−7.89 (m, 3H). ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$): δ 196.1, 162.0, 152.6, 134.9, 123.8, 114.5, 113.6. HRMS (ESI-TOF) m/z: [M − H]$^-$ Calcd for $C_7H_4NO_4^-$ 166.0146; Found 166.0145.

General Procedure for Synthesis of Cinnamyl Esters IVa–c. The cinnamyl esters were synthesized according to a literature procedure with slight modifications.[19] LiCl (509 mg; 12 mmol, 1.2 equiv) was weighed up in an oven-dried 100 mL round-bottom flask and put under vacuum. The flask was heated with a hot air gun for several minutes and allowed to cool down to room temperature, then back-filled with nitrogen. The flask was put under vacuum and back-filled with nitrogen twice more. Dried MeCN (30 mL) was added with a syringe, and the resulting suspension was cooled to 0 °C in an ice-water bath. Triethylphosphonoacetate (2.4 mL, 12 mmol, 1.2 equiv) was added with a syringe while stirring. After 20 min was added benzaldehyde **III** (10 mmol, 1.0 equiv), followed by DBU (1.8 mL, 12 mmol, 1.2 equiv) dropwise. The resulting reaction mixture was allowed to warm up to room temperature and stirred until completion was indicated by TLC analysis. Upon complete consumption of the aldehyde, the mixture was concentrated under reduced pressure and partitioned between diethyl ether (30 mL) and

NH$_4$Cl solution (sat. aq.) (40 mL). The aq. phase was extracted with diethyl ether (2 × 30), and the combined organic phase was dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was redissolved in DCM and purified with automated flash column chromatography.

Ethyl (E)-3-(3-Methoxyphenyl)acrylate (IVa). The compound was prepared by following the general procedure. The reaction was finished after 3.5 h. The crude product was purified with automated flash column chromatography (50 g cartridge, 5−15% EtOAc in heptane). Transparent oil (1.94 g, 94%). IR (KBr): ν 2981, 2940, 2906, 2837, 1712, 1638, 1581, 1490, 1466, 1434, 1367, 1311, 1293, 1261, 1179, 1041, 982 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.65 (d, J = 16.0 Hz, 1H), 7.30 (t, J = 7.9 Hz, 1H), 7.12 (dt, J = 7.7, 1.2 Hz, 1H), 7.04 (s, 1H), 6.93 (ddd, J = 8.3, 2.5, 0.9 Hz, 1H), 6.42 (d, J = 16.0 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 167.1, 160.0, 144.6, 136.0, 130.0, 120.9, 118.7, 116.3, 113.0, 60.7, 55.4, 14.5. The NMR data are in agreement with published data for this compound.[20a]

Ethyl (E)-3-(3-(Trifluoromethyl)phenyl)acrylate (IVb). The compound was prepared by following the general procedure. The reaction was finished after 1.3 h. The crude product was purified with automated flash column chromatography (50 g cartridge, 5% EtOAc in heptane). Colorless oil that crystallizes at room temperature (1.20 g, 89%). IR (KBr): ν 3048, 2986, 2912, 1715, 1675, 1642, 1478, 1441, 1367, 1335, 1308, 1281, 1202, 1157, 1125, 1098, 1079, 1035, 996 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.77 (s, 1H), 7.74−7.66 (m, 2H), 7.63 (d, J = 7.8 Hz, 0H), 7.52 (t, J = 7.8 Hz, 1H), 6.50 (d, J = 16.0 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 166.6, 142.9, 135.4, 131.6 (q, J = 32.5 Hz), 131.2 (d, J = 1.4 Hz), 129.6, 126.7 (q, J = 3.7 Hz), 124.7 (q, J = 3.8 Hz), 123.9 (q, J = 272.5 Hz), 120.4, 60.9, 14.4. ^{19}F NMR (376 MHz, CDCl$_3$) δ −62.9. The NMR data are in agreement with published data for this compound.[20b]

Ethyl (E)-3-(4-Ethoxyphenyl)acrylate (IVc). The compound was prepared by following the general procedure but at 15 mmol scale. The reaction was finished after 2.2 h. The crude product was purified with automated flash column chromatography (50 g cartridge, 5% EtOAc in heptane). White solid (3.03 g, 91%). IR (KBr): ν 3395, 2988, 2932, 1710, 1631, 1604, 1573, 1482, 1425, 1394, 1364, 1289, 1253, 1168, 1043 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.64 (d, J = 15.9 Hz, 1H), 7.46 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.8 Hz 2H), 6.30 (d, J = 15.9 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 4.06 (q, J = 7.0 Hz, 2H), 1.43 (t, J = 7.0 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 167.5, 160.9, 144.5, 129.8, 127.2, 115.8, 114.9, 63.8, 60.5, 14.9, 14.52.

General Procedure for Synthesis of Cinnamyl Alcohols Va–d. The cinnamyl alcohols were synthesized according to a literature procedure.[19c] The cinnamyl ester **IV** (10 mmol, 1.0 equiv) was weighed up in an oven-dried 100 mL round-bottom flask, put under nitrogen, and dissolved in dried THF (30 mL). The reaction mixture was cooled to −78 °C in a dry ice/acetone bath, and DiBAl-H (1 M in toluene, 24 mL, 24 mmol. 2.4 equiv) was added slowly with a syringe. The mixture was stirred at −78 °C while the reaction was monitored with TLC. Upon complete consumption of the cinnamyl ester, saturated Rochelle salt solution (20 mL) was added to the mixture at −78 °C. The mixture was allowed to warm up to room temperature, transferred to a separation funnel, and extracted with EtOAc (5 × 40 mL). The organic phases were combined, dried over sodium sulfate, filtered through a pad of EtOAc-wet Celite, and concentrated by rotary evaporation.

(E)-3-(3-Methoxyphenyl)prop-2-en-1-ol (Va). The compound was prepared at 9.30 mmol scale by following the general procedure. The reaction was finished after 1 h. Transparent liquid (1.54 g, quant.). IR (KBr): ν 3361, 2939, 2836, 1599, 1580, 1490, 1465, 1454, 1433, 1289, 1257, 1156, 1046, 1011, 970 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.27−7.20 (m, 1H), 7.02−6.96 (m, 1H), 6.93 (t, J = 2.1 Hz, 1H), 6.81 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 6.59 (d, J = 15.9 Hz, 1H), 6.36 (dt, J = 15.9, 5.7 Hz, 1H), 4.33 (dd, J = 5.7, 1.5 Hz, 2H), 3.82 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 159.9, 138.3,

131.1, 129.7, 129.0, 119.3, 113.5, 111.9, 63.8, 55.4. The NMR data are in agreement with published data for this compound.[20c]

(E)-3-(3-(Trifluoromethyl)phenyl)prop-2-en-1-ol (Vb). The compound was prepared at 8.89 mmol scale by following the general procedure. The reaction was complete after 1 h. Transparent liquid (1.76 g, quant.). IR (KBr): ν 3345, 2869, 1487, 1441, 1334, 1270, 1199, 1165, 1125, 1099, 1072, 1011, 967 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.63 (s, 1H), 7.55 (d, J = 7.4 Hz, 1H), 7.52−7.39 (m, 2H), 6.71−6.61 (m, 1H), 6.44 (dt, J = 15.9, 5.4 Hz, 1H), 4.36 (dd, J = 5.4, 1.6 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 137.6, 131.2, (q, J = 32.3 Hz), 130.7, 129.7 (d, J = 1.4 Hz), 129.5, 129.2, 124.3 (q, J = 3.8 Hz), 124.2 (q, J = 136.2 Hz), 123.2 (q, J = 3.8 Hz), 63.5. ^{19}F NMR (376 MHz, CDCl$_3$): δ −62.81. The NMR data are in agreement with published data for this compound.[20d]

(E)-3-(4-Ethoxyphenyl)prop-2-en-1-ol (Vc). The compound was prepared at 8.57 mmol scale by following the general procedure. The reaction was complete after 2 h. White solid (1.52 g, quant.). IR (KBr): ν 3363, 3274, 2979, 2931, 1605, 1512, 1476, 1447, 1397, 1305, 1269, 1246, 1175, 1114, 1087, 1048, 1007, 970 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.38−7.29 (m, 2H), 6.92−6.80 (m, 2H), 6.62−6.48 (m, 1H), 6.23 (dt, J = 15.9, 6.0 Hz, 1H), 4.35−4.27 (m, 2H), 4.04 (q, J = 7.0 Hz, 2H), 1.41 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 158.9, 131.2, 129.4, 127.8, 126.2, 114.7, 64.1, 63.6, 15.0. The NMR data are in agreement with published data for this compound.[20e]

(E)-3-(4-Nitrophenyl)prop-2-en-1-ol (Vd). The compound was prepared at 10.4 mmol scale by following the general procedure. The reaction was finished after 1 h. Light yellow solid (1.89 g, quant.). IR (KBr): ν 3508, 3108, 3080, 1652, 1596, 1504, 1455, 1411, 1338, 1101, 972, 958 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.23−8.10 (m, 2H), 7.59−7.44 (m, 2H), 6.72 (dt, J = 16.0, 1.8 Hz, 1H), 6.54 (dt, J = 16.0, 5.1 Hz, 1H), 4.40 (dd, J = 5.1, 1.7 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 147.1, 143.4, 133.7, 128.4, 127.1, 124.2, 63.3. The NMR data are in agreement with published data for this compound.[20f]

General Procedure for Synthesis of Cinnamyl Bromides IIa−d. The cinnamyl bromides were synthesized according to a literature procedure with slight modifications.[19c] The cinnamyl alcohol **V** (2.0 mmol, 1.0 equiv) was weighed up in an oven-dried Biotage microwave reaction tube and put under nitrogen. Dried diethyl ether (4 mL) was added, and the resulting suspension was cooled to 0 °C in an ice/water bath. PBr$_3$ (0.20 mL, 2.0 mmol, 1.0 equiv) was added dropwise with a syringe. The resulting mixture was stirred at 0 °C until complete consumption of the starting material was indicated by TLC. The reaction was quenched at 0 °C by slow and careful addition of a concentrated phosphate buffer at pH 7.4 (4 mL). The reaction mixture was transferred to a separation funnel, and the phases were separated. The aq. phase was extracted with diethyl ether (2 × 5 mL). The combined organic phases were dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The crude cinnamyl bromide was used for the next step without further purification or storage.

(E)-1-(3-Bromoprop-1-en-1-yl)-3-methoxybenzene (IIa). The compound was prepared at 4.45 mmol scale by following the general procedure but with 0.915 equiv of PBr$_3$ used. The reaction was complete after 5 min. Transparent liquid (0.938 g, 92.8% crude yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.25 (t, J = 7.9 Hz, 1H), 6.98 (dt, J = 7.6, 1.2 Hz, 1H), 6.92 (t, J = 2.1 Hz, 1H), 6.86−6.80 (m, 1H), 6.62 (d, J = 15.5 Hz, 1H), 6.39 (dt, J = 15.5, 7.7 Hz, 1H), 4.16 (dd, J = 7.8, 1.0 Hz, 2H), 3.82 (s, 3H). The NMR data are in agreement with published data for this compound.[20g]

(E)-1-(3-Bromoprop-1-en-1-yl)-3-(trifluoromethyl)benzene (IIb). The compound was prepared at 3.98 mmol scale by following the general procedure. The reaction was complete after 25 min. Off white solid (0.977 g, 92.6% crude yield). ^{1}H NMR (600 MHz, CDCl$_3$): δ 7.63 (s, 1H), 7.54 (ddd, J = 19.3, 7.7, 1.7 Hz, 2H), 7.45 (t, J = 7.7 Hz, 1H), 6.67 (d, J = 15.6 Hz, 1H), 6.47 (dt, J = 15.5, 7.7 Hz, 1H), 4.15 (dd, J = 7.7, 1.1 Hz, 2H). The NMR data are in agreement with published data for this compound.[20h]

(E)-1-(3-Bromoprop-1-en-1-yl)-4-ethoxybenzene (IIc). The compound was prepared at 5.03 mmol scale by following the general procedure. The reaction was finished after 5 min. White solid (1.10 g, 91% crude yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.31 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 6.59 (d, J = 15.6 Hz, 1H), 6.26 (dt, J = 15.6, 7.9 Hz, 1H), 4.17 (dd, J = 7.9, 1.0 Hz, 2H), 4.04 (q, J = 7.0 Hz, 2H), 1.41 (t, J = 7.0 Hz, 3H). This compound is unstable and has to be used in the next step immediately.

(E)-1-(3-Bromoprop-1-en-1-yl)-4-nitrobenzene (IId). The compound was prepared at 6.0 mmol scale by following the general procedure but with DCM as solvent and 1.22 equiv of PBr$_3$ used. The reaction was complete after 40 min. Light yellow solid (1.39 g, 96% crude yield). IR (KBr): ν 1595, 1515, 1341, 1197, 1107, 971 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.20 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H), 6.71 (d, J = 15.7 Hz, 1H), 6.61−6.51 (m, 1H), 4.16 (dd, J = 7.5, 0.9 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 147.5, 142.3, 132.2, 130.0, 127.4, 124.2, 32.0. The NMR data are in agreement with published data for this compound.[20i]

2-(Prop-2-yn-1-yloxy)benzaldehyde (VI). Under an atmosphere of nitrogen, salicylaldehyde **Ia** (1.07 mL, 1.00 equiv) and K$_2$CO$_3$ (2.76 g, 2.00 equiv) were suspended in DMF (5.0 mL). While stirring at r.t., propargyl bromide (80% w/w in toluene, 1.45 mL, 1.30 equiv) was added. The reaction mixture was stirred for 2.5 h at r.t. until completion was indicated by TLC analysis, then diluted with DCM (100 mL) and washed with water (50 mL), followed by brine (3 × 50 mL). The organic phase was dried, filtered, and concentrated. The crude product was purified with automated flash column chromatography (50 g cartridge, 0−4% EtOAc in heptane). Off white solid (1.50 g, 94%). NMR spectra were in agreement with published data.[21]

(R)-8-Cyclopropyl-6-nitro-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]-pyridine-3-carboxylic Acid (VII). The ester (methyl (R)-8-cyclopropyl-6-nitro-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylate, 50 mg, 0.169 mmol, 1.0 equiv) was dissolved in THF (4 mL) and put under stirring at r.t. LiOH solution (2.36 mL, 0.1M, 1.4 equiv) was added. TLC after 70 min indicated complete conversion. HCl (1 M aq., 253 µL, 1.5 equiv) was added. After 5 min stirring, the mixture was evaporated to water, diluted with brine (3 mL), and extracted with CHCl$_3$/IPA 9:1 (10 + 5 mL). The organic phases were combined, dried, filtered, and evaporated (47.4 mg). The residue was trituated with diethyl ether (2 × 2,5 mL) and dried under vacuum. Yellow solid (35 mg, 74%). $[\alpha]_D$ −1.3° [c 0.15, (CD$_3$)$_2$SO]. IR (KBr): ν 3393, 3010, 1738, 1679, 1496, 1391, 1313, 1266, 1240, 1008 cm^{-1}. ^{1}H NMR [600 MHz, (CD$_3$)$_2$SO] δ 13.84 (s, 1H), 8.13 (s, 1H), 5.67 (dd, J = 9.6, 1.9 Hz, 1H), 4.03 (dd, J = 12.1, 9.6 Hz, 1H), 3.75 (dd, J = 12.1, 1.9 Hz, 1H), 1.63 (tt, J = 8.3, 5.1 Hz, 1H), 0.92−0.84 (m, 2H), 0.73−0.66 (m, 1H), 0.66−0.60 (m, 1H). ^{13}C{^{1}H} NMR [151 MHz, (CD$_3$)$_2$SO] δ 168.8, 161.1, 152.2, 138.7, 132.1, 112.2, 64.2, 32.3, 11.9, 6.4, 6.2. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for C$_{11}$H$_{10}$N$_2$NaO$_5$S$^+$ 305.0208; Found 305.0198.

■ ASSOCIATED CONTENT

ⓈSupporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01699.

Schemes S1−S4; ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra for all new compounds; and fibrils binding results for carboxylic acids **15a−k** and **16a−e** (PDF)

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Notes
The authors declare no competing financial interest.

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