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Pyridine fused 2-pyridones *via* Povarov and A^3 reactions: rapid generation of highly functionalized tricyclic heterocycles capable of amyloid fibril binding

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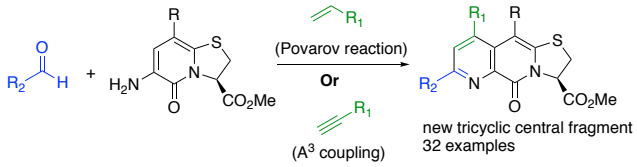
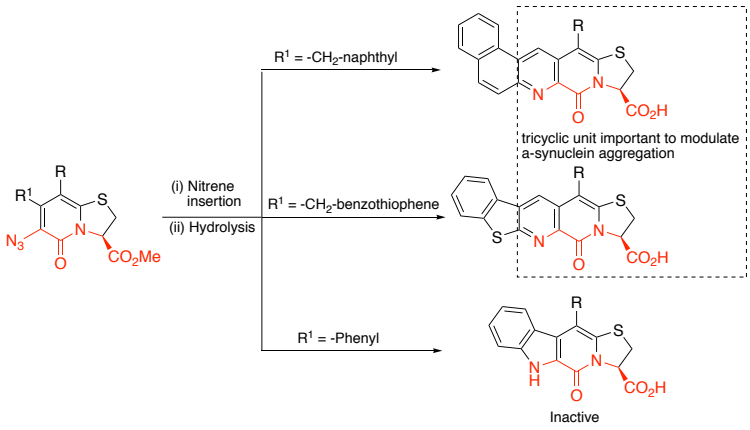


ABSTRACT: We here describe the use of three component reactions to synthesize tricyclic pyridine ring-fused 2-pyridones. The developed protocols have wide substrate scope and allow the installation of diverse chemical functionalities on the tricyclic central fragment. Several of these pyridine-fused rigid polyheterocycles are shown to bind to Aβ and α-synuclein fibrils, which are associated with neurodegenerative diseases.

INTRODUCTION

The ring-fused 2,3-dihydrothiazolo-2-pyridone unit has received considerable attention as a scaffold which can be modified to demonstrate varied biological activities.[1,2a–f] Particular substitution patterns show activity against specific bacterial infections,[1] while others modulate the formation of amyloids associated with neurological disorders.[2a–f] Rigidification of the bicyclic 2-pyridone, either by decoration with sterically demanding aryl groups[2a–d] or by annulation with nitrogen heterocycles[2e] offers a route to modulators of amyloid formation. Recently, we reported a nitrene insertion approach for facile synthesis of fluorescent multi ring-fused 2-pyridone polyheterocycles (**Figure 1a**).[2f] The benzoquinoline and benzothienopyridine annulated polyheterocycles modulated α-synuclein amyloid formation, while indole annulated 2-pyridones were ineffective. These results motivated us to synthesize diverse tricyclic pyridine ring-fused 2-pyridone scaffolds and identify leads with improved physico-chemical and biological properties. We perceived that multicomponent coupling reactions of bicyclic 6-amino-2-pyridones could allow rapid construction of analogues containing a highly functionalized pyridine fused tricyclic central fragment with the same hydrogen bond donor-acceptor configurations as in the previously reported polyheterocycles (**Figure 1b**).

a. Previous work: Intramolecular nitrene insertion of 6-azido-2-pyridones



b. This work: A^3 and Povarov reactions of 6-amino-2-pyridones

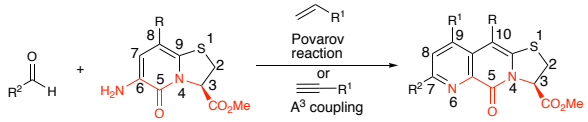


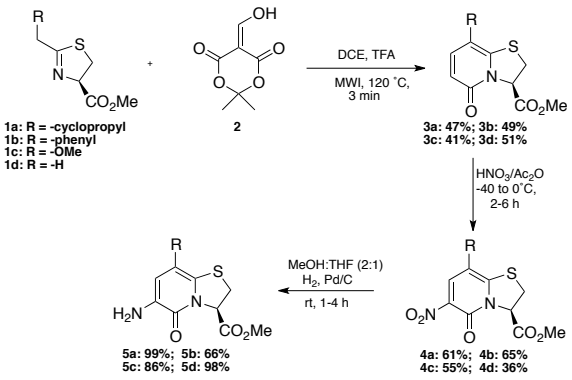
Figure 1. Synthesis of ring-fused 2-pyridone polyheterocycles

Multicomponent reactions are a powerful tool for facile assembly of diverse and complex ring-fused nitrogen heterocycles.[3] In particular, transition metal catalyzed three component couplings of amines, aldehydes and alkynes (A^3) and Lewis acid catalyzed three component Povarov reactions have been widely used for the construction of highly functionalized, biologically important heterocycles.[4,5]

Motivated by our interest in the synthesis of thiazolo ring fused 2-pyridone based heterocycles,[2f,6] we herein present A^3 and Povarov reactions of 6-amino-2-pyridones for the efficient synthesis of complex, diversely functionalized pyridine ring-fused 2-pyridones. Preliminary investigation into the fibril binding of analogues containing these scaffolds suggest they are capable of binding to amyloid β (Aβ 1–40) and α-synuclein fibrils, which are associated with Alzheimer's and Parkinson's disease respectively.

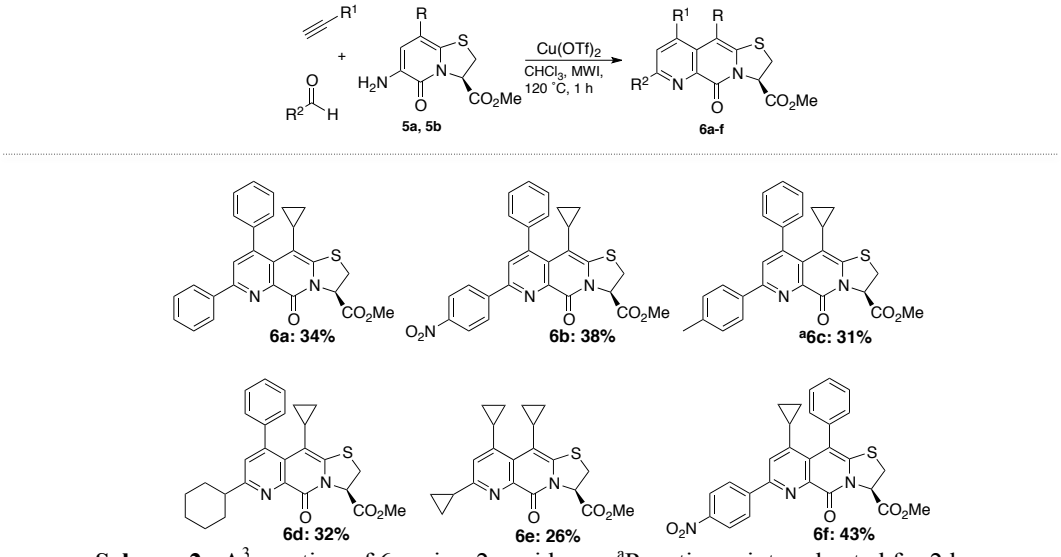
RESULTS AND DISCUSSION

Our studies began with the synthesis of C-7 unsubstituted bicyclic 6-amino-2-pyridones **5a–d** as substrates. An acyl ketene-imine cyclocondensation between thiazolines[7a–b] **1a–d** and Meldrum's acid derivative **2**[7c] afforded thiazolo-2-pyridones **3a–d**. Subsequent nitration of **3a–d** was followed by reduction to give 6-amino-2-pyridones **5a–d** in good yields (**Scheme 1**).



Scheme 1. Synthesis of 6-amino-2-pyridones **5a**-**5d**

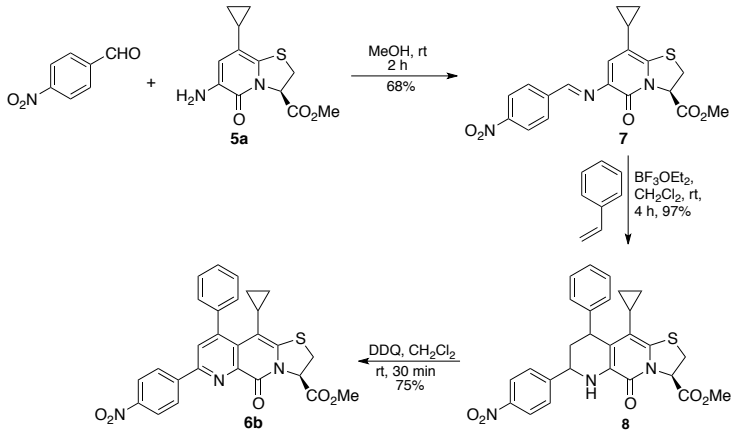
Initial investigations of the A^3 reaction employed amino-2-pyridone **5a**, benzaldehyde and phenyl acetylene as reactants alongside catalytic copper (II) triflate. The desired pyridine fused 2-pyridone **6a** was attained in 34% yield (**Scheme 2**). The reaction worked with both aromatic (**6a**–**c** and **6f**) and aliphatic (**6d**–**e**) aldehydes, and also with aromatic (**6a**–**d**) and aliphatic (**6e**–**f**) alkynes. The electronic nature of the reactants did not have a pronounced effect on the yields, however reaction with *p*-tolyl benzaldehyde was noticeably slower. The A^3 route allowed rapid construction of a diversely functionalized molecular framework, diversifying the tricyclic central fragment in three positions simultaneously.



Scheme 2. A^3 reaction of 6-amino-2-pyridones. [a]Reaction mixture heated for 2 hours

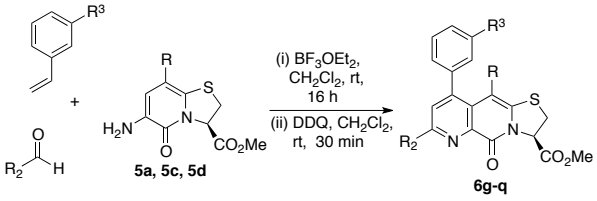
We were encouraged by the A^3 results, however the utility of this method was limited by harsh conditions, sometimes leading to complex reaction mixtures and moderate yields. As an alternative we considered the $BF_3{\cdot}OEt_2$ catalyzed Povarov reaction of 6-amino-2-pyridones, aiming to synthesize the tricyclic scaffold under milder conditions.

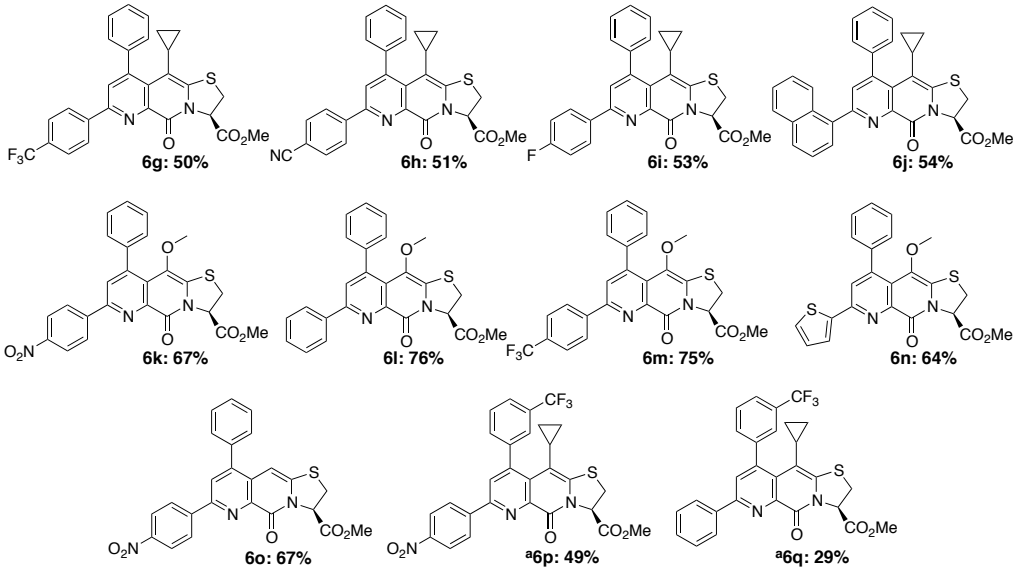
For the initial study of the Povarov reaction, 2-pyridone fused aza-diene **7** (**Scheme 3**) was synthesized by stirring 6-amino-2-pyridone **5a** with *p*-nitrobenzaldehyde in methanol. Imine **7** then underwent a Povarov reaction with styrene, in the presence of 10 mole percent of $BF_3{\cdot}OEt_2$ in DCM at room temperature. Povarov adduct **8** was obtained, and DDQ used to expedite the slow aerobic oxidation to polyaromatic heterocycle **6b**.



Scheme 3. Stepwise Povarov reaction with styrene

We next investigated the scope of the Povarov reaction in a multicomponent procedure. Thus, 6-amino-2-pyridones **5a**–**d** carrying different substituents on C-8 were reacted with various aldehydes and styrene to establish the substrate scope and prepare suitable analogues for biological testing (**Scheme 4**). Gratifyingly, the reaction worked with all aldehydes and 6-amino-2-pyridones tested. Povarov adducts were oxidized with DDQ to afford pyridine ring-fused 2-pyridones **6g**–**o** in 50–76% yields. The Povarov reaction proved slow with *m*-CF_3-styrene, requiring elevated temperature and longer reaction time to obtain moderate yields of products **6p** and **6q** respectively.

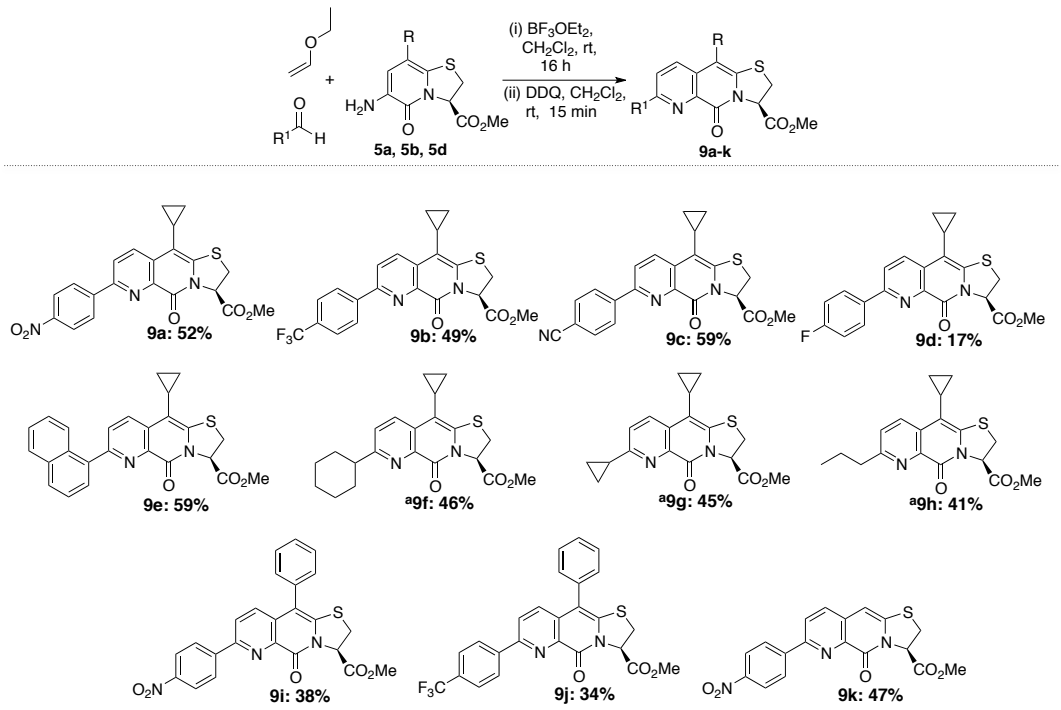




Scheme 4. Three component Povarov reaction with styrenes, [a]Heated to 50 °C for 4 days

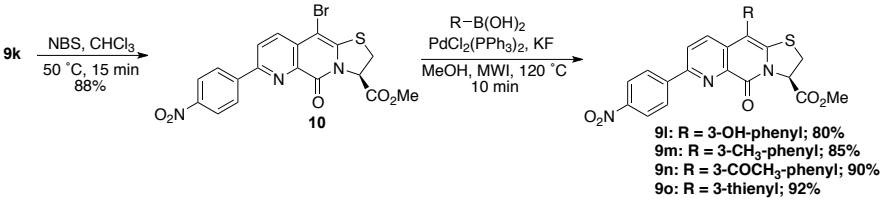
To expand the scope of the reaction and investigate the structure activity relationship of this fragment, we envisioned using ethyl vinyl ether as a dienophile to access a C-9 unsubstituted and less hydrophobic scaffold. 6-amino-2-pyridones **5a**, **5b**, **5d** reacted with different aldehydes and ethyl vinyl ether to furnish the desired scaffold **9a**–**k** in 17–59% yield (**Scheme 5**). The

synthesis of **9k** was tested on a 1.2 gram (5.30 mmol) scale to confirm the scalability of the procedure, with the resulting 44% yield comparable to that achieved previously (47%, 0.39 mmol).



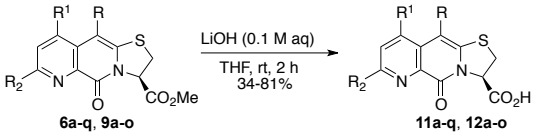
Scheme 5. Three component Povarov reaction with ethyl vinyl ether,
a: Povarov adduct oxidized spontaneously

Observing that the C-10 unsubstituted **9k** presented opportunities for late functionalization and efficient library synthesis, we explored a regioselective halogenation and transition metal coupling approach. Selective bromination of **9k** gave brominated tricyclic intermediate **10**, which underwent Suzuki coupling to furnish products **9l**–**o** in good yields (**Scheme 6**)



Scheme 6. Bromination and Suzuki coupling

Finally, hydrolysis of the methyl esters **6a**–**q and 9a**–**o** gave carboxylic acids **11a**–**q** and **12a**–**o** respectively (**Scheme 7**).



Scheme 7. Hydrolysis of methyl esters

The carboxylic acids were evaluated for their ability to modulate α-synuclein amyloid formation by a fluorescence assay with amyloidophilic dye Thioflavin T (ThT), which produces enhanced fluorescent emission on binding to fibril structures.[8] We postulated that the complexity and diverse substitution of the analogues may allow selective interaction with amyloidogenic proteins, as previously observed with related structures.[2e,f] Even though ThT flourescence signals were low in assays including these

compounds (**Figure S1**), TEM images subsequently showed these samples to contain fibrils indistinguishable from the control by appearance or seeding behaviour (**Figure 2b** and **S2**, **S3**). Further, the observed lag phase and results from DLS experiments with **12a** (**Figure S4**) did not suggest modulatory activity. Given the relatively planar core scaffold, we hypothesized that these analogues instead competed with ThT binding to fibrils. We conducted a preliminary screen for amyloid binding using carboxylic acids **11a–q** and **12a–o** and displacement of ThT bound to α-synuclein and Aβ (1–40) fibrils as a proxy for binding **(Figure S5–7)**.[9] Compounds **11b**, **11f**, **11o**, **11p**, **12a**, **12i**, **12k–o** with a *p*-nitrophenyl at position C-7 of the tricyclic skeleton bound to both fibril structures, indicated by reduction of the ThT derived fluorescence (**Figure 2a and S5–7**).

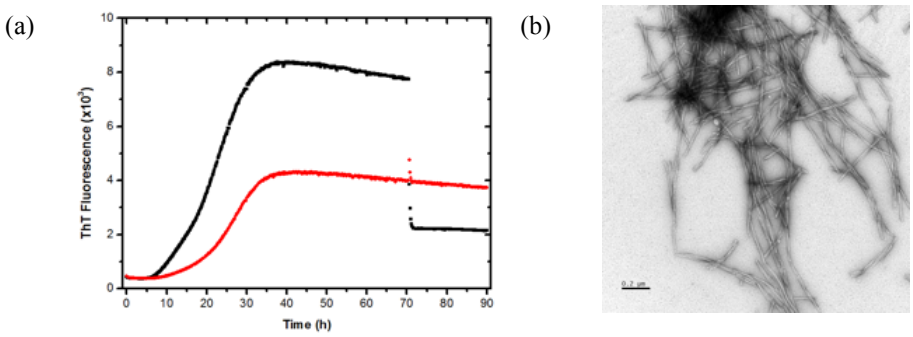
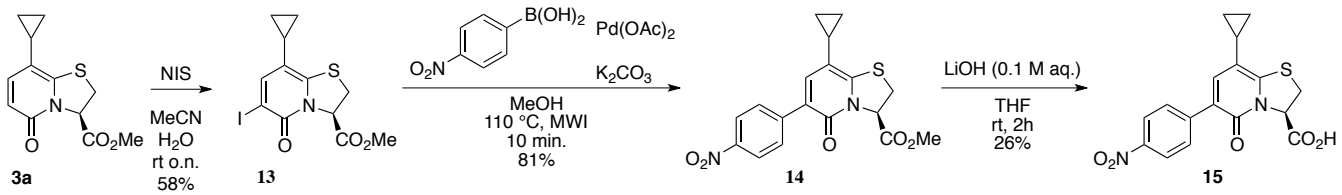


Figure 2. Binding of compounds interferes with Thioflavin T. (a) Black trace show α-syn monomers incubated for 70 hours, forming mature fibers. Then, 100 μM of **11b** was added, followed by further incubation, and a loss of fluorescence signal. In red, **11b** was added at time zero. This procedure was repeated for all compounds. (b) Transmission electron microscopy pictures of α-synuclein fibers formed in the presence of selected compound 11b.

A similar structure activity relationship was observed for both Aβ and α-synuclein fibrils. The apparent requirement for a C4' nitro substituent may reflect a polar interaction, as analogues with alternative electron withdrawing groups were not active (**11g** and **11h**). A C-10 electron releasing methoxy substituent appears unfavorable, as evidenced by lower binding compared to analogues with both larger and smaller substituents (**11k** vs **11b** and **11o**). Although concurrent C-9 and C-10 substitution was tolerated, placement of the larger substituent in C-10 appears favored (**11b** vs **11k**). A range of C-10 aryl substituents were tolerated, at least where C-9 is unsubstituted (**12l–12o**). Since all compounds that was shown to bind amyloid fibrils was equipped with a 4-nitrophenyl substituent, we prepared and tested the fibril binding activity of bicyclic 2-pyridone **15** (**Scheme 8**) substituted with a 4-nitrophenyl ring at position C-6. No significant binding to α-synuclein fibrils was observed upon evaluation (**Figure S1**). This result further consolidates that the fused pyridine ring present in the tricyclic scaffold is important for fibril binding activity.



Scheme 8. Synthesis of bicyclic 2-pyridone **15** equipped with a 4-nitrophenyl substituent.

CONCLUSION

In summary, we have synthesized C-7 unsubstituted 6-amino-2-pyridones, and used them in A^3 and Povarov reactions, allowing synthesis of diversely functionalized pyridine ring-fused 2-pyridone polyheterocycles. Both methods permit rapid ring construction of new complex heterocycles with multiple points of variation. The milder Povarov approach proved effective for accessing compact, less hydrophobic central fragments. The preliminary *in-vitro* biological evaluation suggested that eight of the thirty-two tricyclic 2-pyridones tested were able to bind Aβ and α-synuclein amyloid fibrils. Annulation of bicyclic 2-pyridones with functionalized pyridine rings therefore provides a straightforward synthetic route to novel tricyclic 2-pyridone peptidomimetics capable of binding to amyloid fibrils. To build on these promising results we intend to undertake more detailed appraisal of analogue binding selectivity, properties and structure activity relationships. Selective binding to mature fibrils is a property of potential diagnostic and therapeutic value,[10] and further development of these molecules as modulators or probes for neurodegenerative disease may facilitate application in chemical biology or as clinical diagnostic tools such as PET probes.

EXPERIMENTAL SECTION

General information: Unless stated, all reagents and solvents were used as received from commercial suppliers. All reactions were carried out under an inert atmosphere with dry solvents under anhydrous conditions, unless otherwise indicated. 4 Å MS were activated at 300 °C under vacuum for 4 h. Microwave reactions were performed in sealed vessels using a Biotage® Initiator microwave synthesizer; temperatures were monitored by an internal IR probe. TLC was performed on purchased aluminium 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 pre-packed silica gel cartridges (Biotage® SNAP Cartridge, KP-Sil). Preparative HPLC was performed with a Gilson instrument using a Nucleodur C18 HTec column (25 cm x 21.5 mm; particle size 5 μm). Optical rotation was measured with a Perkin Elmer polarimeter 343 at 25 °C and 589 nm. 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^{TM}, a Bruker Avance III HD 600 MHz spectrometer with a CP BBO-H/F, 5 mm cryoprobe, or a Bruker Avance III HD 850 MHz spectrometer with a CP TCI HCN, 5 mm cryoprobe, at 298 K, unless other temperature is given. All spectrometers were operated by Topspin 3.5.7. 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. $(CD_3)_2SO$: δ_H = 2.50 ppm; δ_C = 39.51 ppm. CD_3OD δ_H = 3.31 ppm; δ_C = 49.00 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 using ES^+ ionization unless otherwise stated. HRMS was performed on a mass spectrometer with ESI-TOF (ES^+). Amyloid formation was probed by thioflavin T (ThT) fluorescence, with a Fluorostar Omega instrument (BMG Labtech, Germany), using excitation and emission filters of 440 and 480 nm, respectively.

Meldrum's acid derivative (2) was prepared following a published experimental procedure[2] with some modifications: Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) (60.0 g; 0.42 mol) was placed in a round bottomed flask and triethyl orthoformate (195 ml; 1.17 mol) was added. The mixture was heated with an oil bath at 85 °C, while stirring. The reaction was followed with TLC

($CHCl_3$/MeOH 9:1) and confirmed to be finished after 2 h. The excess triethyl orthoformate was removed with rotary evaporation. $HCl_{(aq)}$ (2 M; 800 ml) was added to the yellow oily residue while stirring. A precipitate formed soon after the addition. The mixture was stirred at r.t. for 30 min. and then filtered. The solid was dissolved in DCM (500 ml) and washed with brine (2 x 250 ml). The organic phase was dried, filtered and evaporated to give a bright yellow solid (48.3 g, 67%). The aqueous phase was combined with the filtrate and extracted with DCM (3 x 150 ml). The organic phases were combined, dried, filtered and evaporated to give a yellow–orange solid (16.4 g; 29%). Total yield (64.7 g, 90%). IR (KBr): ν 1747, 1683, 1592, 1419, 1277, 1259, 1184 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.76 (s, 6H), 8.54 (s, 1H); $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ 27.4, 95.6, 107.2, 160.7, 168.2, 177.1; LC-MS (ESI–): m/z = 171.2 $[M-H]^-$, $C_7H_7O_5^-$ requires 172.1.

General procedure for synthesis of 3a–d: In a microwave reaction tube equipped with a magnetic stirrer, thiazoline (1.0 mmol, 1.0 eq.) and Meldrum's acid derivative (0.60 g, 3.5 mmol, 3.5 eq.) was dissolved in 1,2-dichloroethane (10ml). TFA (150 µl, 2.0 mmol, 2.0 eq.) was added, the tube was sealed and heated to 120 °C under microwave irradiations for 3 min. The reaction mixture was cooled to room temperature diluted with DCM (8 ml) and washed with saturated aqueous sodium bicarbonate solution (4 ml) followed by brine (4 ml). The aqueous phases were re-extracted with DCM (2 ml each). The organic phases were combined, dried, filtered and evaporated. The compound was purified with flash column chromatography.

(R)-Methyl 8-cyclopropyl-5-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyridine-3-carboxylate (3a): Prepared by following the general procedure. The product was purified with automated flash column chromatography (50 g SNAP Cartridge; ethyl acetate in heptane, 20–100% in 8 CV). Brown solid, 1426 mg (47%); $[\alpha]_D^{25}$ −150 (*c* 0.52, MeOH). IR (KBr): ν 1753, 1651, 1582, 1502, 1362, 1212, 1007, 822 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.53–0.59 (m, 2H), 0.80–0.87 (m, 2H), 1.53–1.59 (m, 2H), 3.54 (dd, *J* = 1.9, 11.7 Hz, 1H), 3.69 (dd, *J* = 8.4, 11.5 Hz, 1H), 3.79 (s, 3H), 5.60 (dd, *J* = 1.9, 8.5 Hz, 1H), 6.22 (d, *J* = 9.2 Hz, 1 H), 7.07 (d, *J* = 9.2 Hz, 1H); $^{13}C\{^1H\}$-NMR (151 MHz, $CDCl_3$): δ 6.1, 6.3, 12.4, 31.8, 53.4, 63.4, 114.5, 115.2, 141.1, 146.6, 161.6, 168.6; LC-MS: *m/z* = 252.1 $[M+H]^+$, $C_{12}H_{14}NO_3S^+$ requires 252.2.

(R)-Methyl 5-oxo-8-phenyl-3,5-dihydro-2H-thiazolo[3,2-a]pyridine-3-carboxylate (3b): Prepared by following the general procedure. The product was purified with automated flash column chromatography (50 g SNAP Cartridge; ethyl acetate in heptane, 20–100%). Brown solid, 900 mg (49%); $[\alpha]_D^{25}$ −83 (*c* 0.31, $CHCl_3$); IR ($CHCl_3$): ν 1752, 1657, 1586, 1490, 1442, 1370, 1216, 1167, 1068, 821, 767, 701 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.53 (dd, *J* = 2.0, 11.6 Hz, 1H), 3.66 (dd, *J* = 8.4, 11.6 Hz, 1H), 3.83 (s, 3H), 5.70 (dd, *J* = 2.0, 8.4 Hz, 1H), 6.40 (d, *J* = 9.2 Hz, 1H), 7.31–7.44 (m, 6H); $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ 31.6, 53.4, 63.3, 115.7, 116.1, 127.7 (2C), 128.9, 137.5, 142.3, 145.4, 161.4, 168.5; LC-MS: *m/z* = 288 $[M+H]^+$, $C_{15}H_{14}NO_3S^+$ requires 288.

(R)-Methyl 8-methoxy-5-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyridine-3-carboxylate(3c): Prepared by following the general procedure. The product was purified with automated flash column chromatography (50 g SNAP Cartridge; ethyl acetate in heptane, 20–100%). Brown solid, 263 mg (47%); $[\alpha]_D^{25}$ −62 (*c* 0.42, $CHCl_3$); IR ($CHCl_3$): ν 1751, 1664, 1578, 1505, 1440, 1412, 1379, 1278, 1215, 1174, 1068, 816, 729 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.57 (dd, *J* = 2.4, 12.0 Hz, 1H), 3.74 (dd, *J* = 8.4, 12.0 Hz, 1H), 3.75 (s, 3H), 3.79 (s, 3H), 5.60 (dd, *J* = 2.0, 8.4 Hz, 1H), 6.27 (d, *J* = 10.0 Hz, 1H), 7.26 (d, *J* = 9.6 Hz, 1H); $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ 32.3, 53.4, 59.1, 63.5, 115.5, 133.2, 135.7, 137.8, 160.3, 168.3; LC-MS: *m/z* = 242 $[M+H]^+$, $C_{10}H_{12}NO_4S^+$ requires 242.

(R)-Methyl 5-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyridine-3-carboxylate (3d): Prepared by following the general procedure. The product was purified with automated flash column chromatography (50 g SNAP Cartridge; ethyl acetate in heptane, 20–100%). Brown solid, 344 mg (51%); $[\alpha]_D^{25}$ −170 (*c* 5.92, $CHCl_3$); IR ($CHCl_3$): ν 1750, 1658, 1572, 1513, 1437, 1215, 783 cm^{-1} ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.54 (dd, *J* = 2.4, 11.6 Hz, 1H), 3.73 (dd, *J* = 8.4, 12.0 Hz, 1H), 3.80 (s, 3H), 5.60 (dd, *J* = 2.0, 8.4 Hz, 1H), 6.12 (dd, *J* = 0.8, 7.2 Hz, 1H), 6.27 (dd, *J* = 0.8, 8.8 Hz, 1H), 7.27 (dd, *J* = 7.2, 9.2 Hz, 1H); $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ 31.9, 53.4, 63.0, 100.6, 115.3, 140.7, 147.5, 162.2, 168.4; LC-MS: *m/z* = 212 $[M+H]^+$, $C_9H_{10}NO_3S^+$ requires 212.

*General procedure for preparation of 6-nitro-2-pyridones 4a–d:*The 2-pyridone of general structure **3** (1.0 mmol, 1.0 eq.) was dissolved in acetic anhydride (3.4 ml) and cooled to −40 °C. Acetic anhydride (1.7 ml) was cooled on ice and HNO_3 (65% aq.) (0.10 ml, 1.5 mmol, 1.5 eq.) was added slowly. The diluted acid was transferred to a dropping funnel and added slowly to the stirred solution. The reaction mixture was allowed to warm to 0 °C and stirred until completion was indicated by TLC (EtOAc). The reaction mixture was then quenched with methanol (10 ml) at 0 °C, transferred to a separation funnel with ice-cold $NaHCO_3$ (sat. aq.) (10 ml) and EtOAc (10 ml). The phases were separated and the aqueous phase was extracted once more with EtOAc (10 ml). The organic phases were combined, dried over anhydrous sodium sulphate, filtered and evaporated. The crude product was purified with flash column chromatography.

(R)-Methyl 8-cyclopropyl-6-nitro-5-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyridine-3-carboxylate (4a): Prepared by following the general procedure. The reaction was finished after 105 min. Purified with flash column chromatography (40 x 120 mm silica; ethyl acetate in heptane, 25–70%). Yellow solid, 1.01 g (61%); $[\alpha]_D^{25}$ −387 (*c* 0.40, $CHCl_3$); IR (KBr): ν 1752, 1677, 1496, 1313, 1263, 1219, 1002, 772 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.62–0.72 (m, 2H), 0.91–1.01 (m, 2H), 1.60–1.68 (m, 1H), 3.67 (dd, *J* = 2.3, 12.0 Hz, 1H), 3.83 (s, 3H), 3.88 (dd, *J* = 9.2, 12.0 Hz, 1H), 5.78 (dd, *J* = 2.3, 9.2 Hz, 1H), 8.25 (s, 1H); $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ 6.5, 6.7, 12.4, 32.3, 53.9, 64.3, 113.4, 133.0, 140.4, 153.3, 159.8, 167.6; LC-MS: *m/z* = 297 $[M+H]^+$, $C_{12}H_{13}N_2O_5S^+$ requires 297.

(R)-Methyl 6-nitro-5-oxo-8-phenyl-3,5-dihydro-2H-thiazolo[3,2-a]pyridine-3-carboxylate (4b): Prepared by following the general procedure (1 mmol of HNO_3 was used). The reaction was finished after 2 hours. Purified with automated flash column chromatography (50 g SNAP Cartridge; ethyl acetate in heptane, 20-100%). Yellow solid, 735 mg (65%); $[\alpha]_D^{25}$ −184 (*c* 0.52, $CHCl_3$); IR ($CHCl_3$): ν 1751, 1682, 1599, 1487, 1441, 1379, 1327, 1260, 1219, 1150, 751, 701 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.66 (dd, *J* = 2.0, 12.0 Hz, 1H), 3.84–3.89 (m, 4H), 5.86 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.39–7.46 (m, 5H) 8.52 (s, 1H); $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ 32.2, 53.9, 64.4, 114.1, 127.9, 128.9, 129.3, 133.8, 135.3, 141.1, 153.0, 157.4, 167.5; LC-MS: *m/z* = 333 $[M+H]^+$, $C_{15}H_{13}N_2O_5S^+$ requires 333.

(R)-Methyl 8-methoxy-6-nitro-5-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyridine-3-carboxylate (4c): Prepared by following the general procedure. The reaction was finished after 2 hours. Purified with automated flash column chromatography (50 g SNAP Cartridge; ethyl acetate in heptane, 20-100%). Yellow solid, 665 mg (55%); $[\alpha]_D^{25}$ −187 (*c* 0.42, $CHCl_3$) IR ($CHCl_3$): ν 1751, 1677, 1586, 1511, 1401, 1308, 1259, 1220, 1144, 1089, 935, 765 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 3.76 (s, 3H), 3.82 (dd, *J* = 2.0, 12.0 Hz, 1H), 3.86 (s, 3H), 4.05 (dd, *J* = 9.6, 12.0 Hz, 1H), 3.83 (s, 3H), 5.81 (dd, *J* = 2.0, 9.6 Hz, 1H), 8.46 (s, 1H); $^{13}C\{^1H\}$-NMR (100 MHz, $(CD_3)_2SO$): δ 32.1, 53.2, 58.2, 64.2, 127.6, 130.1, 134.4, 151.0, 151.9, 167.8; LC-MS: *m/z* = 287 $[M+H]^+$, $C_{10}H_{11}N_2O_6S^+$ requires 287.

(R)-Methyl 6-nitro-5-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyridine-3-carboxylate (4d): Prepared by following the general procedure. The reaction was finished after 6 hours. Purified with automated

flash column chromatography (50 g SNAP Cartridge; ethyl acetate in heptane, 20-100%). Yellow solid, 457 mg (36%); $[\alpha]_D^{25}$ −137 (*c* 1.6, $CHCl_3$); IR ($CHCl_3$): ν 1749, 1677, 1515, 1439, 1309, 1166, 1219 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.69 (dd, *J* = 2.0, 12.0 Hz, 1H), 3.83 (s, 3H), 3.92 (dd, *J* = 9.2, 12.0 Hz, 1H), 5.75 (dd, *J* = 2.0, 9.2 Hz, 1H), 6.25 (d, *J* = 8.4 Hz, 1H), 8.43 (dd, *J* = 8.4 Hz, 1H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 32.7, 53.9, 63.9, 98.6, 133.5, 140.8, 153.6, 159.0, 167.3; LC-MS: *m/z* = 257 $[M+H]^+$, $C_9H_9N_2O_5S^+$ requires 257.

*General procedure for preparation of 6-amino-2-pyridones 5a–d***:** Pd/C-10 (53 mg, 50 μmol, 0.050 eq.) was placed in a round bottomed flask. The flask was evacuated and back-filled with nitrogen thrice. MeOH (6 ml) and THF (3 ml) was added. The flask was placed under vacuum until the solvent started boiling and back-filled with hydrogen. The 6-nitro-2-pyridone of general structure **4** (1 mmol, 1.0 eq.) was dissolved in MeOH (6 ml) and added to the round bottomed flask while stirring. The reaction mixture was then stirred vigorously at room temperature. When TLC (EtOAc) indicated completion, chloroform (3 ml) was added. The solution was filtered through a pad of Celite® and evaporated.

(R)-Methyl 6-amino-8-cyclopropyl-5-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyridine-3-carboxylate: (5a): Prepared following the general procedure. The reaction was finished after 100 min. Dark brown solid, 0.89 g (99%); $[\alpha]_D^{25}$ −151 (*c* 0.19, DMSO). IR (KBr): ν 3448, 3346, 1748, 1643, 1592, 1519, 1292, 1217, 1005, 766 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.52–0.57 (m, 2H), 0.77–0.83 (m, 2H), 1.50–1.58 (m, 1H), 3.53 (dd, *J* = 2.2, 11.7 Hz, 1H), 3.68 (dd, *J* = 8.0, 11.7 Hz, 1H), 3.79 (s, 3H), 5.58 (dd, *J* = 2.2, 8.2 Hz, 1H), 6.31 (s, 1H); ^{13}C{^{1}H}-NMR (151 MHz, $CDCl_3$): δ 6.2, 6.4, 12.8, 32.4, 53.3, 63.3, 114.9, 115.2, 130.5, 134.0, 157.0, 168.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{15}N_2O_3S^+$ 267.0798; Found 267.0790.

(R)-Methyl 6-amino-5-oxo-8-phenyl-3,5-dihydro-2H-thiazolo[3,2-a]pyridine-3-carboxylate (5b): Prepared by following the general procedure. The reaction was finished after 1.5 hours. Purified with automated flash column chromatography (25 g SNAP Cartridge; ethyl acetate in heptane, 0–60%). Grey solid, 240 mg (66%); $[\alpha]_D^{25}$ −88 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$): ν 3454, 3336, 3007, 2954, 1750, 1643, 1596, 1522, 1493, 1442, 1351, 1217, 1156, 1013, 765, 701 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.52 (dd, *J* = 2.0, 11.6 Hz, 1H), 3.64 (dd, *J* = 8.0, 11.6 Hz, 1H), 3.83 (s, 3H), 5.68 (dd, *J* = 2.4, 8.0 Hz, 1H), 6.72 (s, 1H), 7.28–7.41(m, 5H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 32.2, 53.4, 63.3, 115.5, 116.3, 127.5, 127.7, 128.7, 129.9, 134.5, 138.2, 157.1, 168.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{15}N_2O_3S^+$ 303.0798; Found 303.0802.

(R)-Methyl 6-amino-8-methoxy-5-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyridine-3-carboxylate (5c): Prepared following the general procedure. The reaction was finished after 3 hours. Black solid, 398 mg (86%); $[\alpha]_D^{25}$ −8 (*c* 0.062, $CHCl_3$); IR (KBr): 3549, 2956, 1746, 1638, 1617, 1585, 1524, 1452, 1311, 1260, 1217, 1173, 760, 620 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$)): δ 3.55 (dd, *J* = 2.4, 12.0 Hz, 1H), 3.68 (dd, *J* = 8.0, 11.6 Hz, 1H), 3.72 (s, 3H), 3.80 (s, 3H), 4.12 (bs, 1H), 5.59 (dd, *J* = 2.4, 8.0 Hz, 1H), 6.56 (s, 1H); ^{13}C{^{1}H}-NMR (100 MHz, $(CD_3)_2SO$)): δ 32.8, 53.4, 59.0, 63.4, 127.6, 130.1, 134.4, 151.0, 151.9, 167.8; HRMS (ESI-TOF) *m/z*: $[M]^+$ Calcd for $C_{10}H_{12}N_2O_4S^+$ 256.0518; Found 256.0518.

(R)-Methyl 6-amino-5-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyridine-3-carboxylate (5d): Prepared following the general procedure. The reaction was finished after 4 hours. Black solid, 190 mg (98%); $[\alpha]_D^{25}$ −13 (*c* 7.4, $CHCl_3$); IR ($CHCl_3$): ν 3440, 3327, 1746, 1644, 1592, 1437, 1218, 1179 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.54 (dd, *J* = 2.0, 11.6 Hz, 1H), 3.71 (dd, *J* = 8.0, 11.6 Hz, 1H), 3.79 (s, 3H), 4.00 (bs, 3H), 5.75 (dd, *J* = 2.0, 8.0 Hz, 1H), 6.00 (d, *J* = 7.6 Hz, 1H), 6.53 (d, *J* = 7.6 Hz, 1H);

$^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ 32.7, 53.3, 63.0, 101.0, 114.6, 131.7, 134.1, 157.7, 168.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_9H_{11}N_2O_3S^+$ 227.0485; Found 227.0492.

General procedure of the A³-reaction: Preparation of compounds 6a–f : Under air, 6-amino-2-pyridones of general structure **5** (0.38 mmol, 1.0 eq.) was placed in a 5 ml microwave reaction tube equipped with a magnetic stirrer and dissolved in chloroform (4 ml). The aldehyde (0.64 mmol, 1.7 eq.) was added, followed by the acetylene (1.13 mmol, 3.0 eq.) and copper trifluoromethanesulfonate (41 mg, 0.11 mmol, 0.30 eq.). The tube was sealed and heated to 120 °C for 1 h. The tube was opened and the reaction progress was checked with TLC (ethyl acetate in heptane, 50%) and LC-MS. When no 6-amino-2-pyridone was left, the mixture was transferred to a separating funnel, diluted with DCM (5 ml) and washed with $NaHCO_3$ (sat. aq.) (3 ml) followed by brine (3 ml). Then dried over anhydrous sodium sulphate, filtered and evaporated. The crude residue was purified with flash column chromatography.

(R)-Methyl 10-cyclopropyl-5-oxo-7,9-diphenyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (6a): The compound was prepared following the general procedure. Purified with flash column chromatography (20 x 120 mm silica; ethyl acetate in toluene, 5–50%). 101 mg of **5a** was converted to 58 mg (34%) of **6a**, isolated as a light brown solid. $[\alpha]_D^{25}$ −134 (*c* 0.22, $CHCl_3$); IR (NaCl): ν 1752, 1663, 1591, 1512, 1491, 1459, 1439, 1380, 1214, 1180, 751, 698 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.16–0.25 (m, 4H), 1.14–1.22 (m, 1H), 3.52 (dd, *J* = 2.7, 11.6 Hz, 1H), 3.72 (dd, *J* = 8.3, 11.6 Hz, 1H), 3.81 (s, 3H), 5.76 (dd, *J* = 2.5, 8.3 Hz, 1H), 7.37–7.52 (m, 8H), 7.88 (s, 1H), 8.17–8.24 (m, 2H); $^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ 10.7, 10.8, 16.1, 31.6, 53.4, 63.5, 109.0, 126.6, 127.4, 127.9, 128.0, 128.8, 129.3, 129.5, 132.7, 138.2, 141.4, 141.8, 143.6, 147.5, 154.4, 159.8, 168.8; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{27}H_{23}N_2O_3S^+$ 455.1423; Found 455.1427.

(R)-Methyl 10-cyclopropyl-7-(4-nitrophenyl)-5-oxo-9-phenyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (6b): The compound was prepared following the general procedure. Purified with flash column chromatography (20 x 120 mm silica; ethyl acetate in toluene, 5–50%). 100 mg of **5a** was converted to 72 mg (38%) of **6b**, isolated as a yellow-brown solid. $[\alpha]_D^{25}$ −138 (*c* 0.27, $CHCl_3$); IR ($CHCl_3$): ν 1751, 1665, 1590, 1552, 1520, 1344, 1216, 752 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.16–0.26 (m, 4H), 1.15–1.23 (m, 1H), 3.55 (dd, *J* = 2.6, 11.7 Hz, 1H), 3.75 (dd, *J* = 8.2, 11.6 Hz, 1H), 3.83 (s, 1H), 5.77 (dd, *J* = 2.6, 8.3 Hz, 1H), 7.39–7.53 (m, 5H), 7.93 (s, 1H), 8.30 (d, *J* = 9.0 Hz, 2H), 8.38 (d, *J* = 8.9 Hz, 2H); $^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ 10.8, 10.9, 16.1, 31.6, 53.5, 63.6, 109.0, 124.1, 127.0, 128.1, 128.3, 129.3, 133.7, 141.3, 141.5, 144.1, 145.2, 148.0, 148.4, 151.5, 159.5, 168.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{27}H_{22}N_3O_5S^+$ 500.1275; Found 500.1295.

(R)-Methyl 10-cyclopropyl-5-oxo-9-phenyl-7-(p-tolyl)-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (6c): The compound was prepared following the general procedure but the reaction mixture was heated for 2 h. Purified with flash column chromatography (20 x 110 mm silica; ethyl acetate in toluene 5–40%). 101 mg of **5a** was converted to 56 mg (31%) of **6c**, isolated as a light brown solid. $[\alpha]_D^{25}$ −141 (*c* 0.23, $CHCl_3$). IR ($CHCl_3$): ν 1752, 1664, 1591, 1456, 1441, 1214, 1181, 751, 701, 664 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.15–0.25 (m, 4H), 1.14–1.22 (m, 1H), 2.40 (s, 3H), 3.52 (dd, *J* = 2.6, 11.6 Hz, 1H), 3.72 (dd, *J* = 8.3, 11.6 Hz, 1H), 3.81 (s, 3H), 5.76 (dd, *J* = 2.6, 8.2 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 2H), 7.38–7.52 (m, 5H), 7.86 (s, 1H), 8.12 (d, *J* = 8.2 Hz, 2H); $^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ 10.7, 10.8, 16.1, 21.5, 31.6, 53.4, 63.5, 109.1, 126.3, 127.3, 128.0, 129.4, 129.5, 132.5, 135.4, 139.6, 141.3, 141.9, 143.3, 147.4, 154.5, 159.8, 168.9; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{28}H_{25}N_2O_3S^+$ 469.1579; Found 469.1584.

(R)-Methyl 7-cyclohexyl-10-cyclopropyl-5-oxo-9-phenyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (6d): The compound was prepared following the general procedure. Purified with flash column chromatography (20 x 110 mm silica; ethyl acetate in toluene, 20–60%). 100 mg of **5a** was converted to 55 mg (32%) of **6d**, isolated as a yellow solid. $[\alpha]_D^{25}$ −115 (*c* 0.24, $CHCl_3$) IR ($CHCl_3$): ν 2926, 2852, 1753, 1663, 1593, 1459, 1214, 753 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.14–0.21 (m, 4H), 1.12–1.18 (m, 1H), 1.23–1.31 (m, 1H), 1.37–1.47 (m, 2H), 1.50–1.59 (m, 2H), 1.72–1.77 (m, 1H), 1.78–1.87 (m, 2H), 2.00–2.06 (m, 2H), 2.97–3.04 (m, 1H), 3.50 (dd, *J* = 2.8, 11.6 Hz, 1H), 3.67 (dd, *J* = 8.2, 11.6 Hz, 1H), 3.80 (s, 3H), 5.72 (dd, *J* = 2.8, 8.7 Hz, 1H), 7.31 (s, 1H), 7.35–7.44 (m, 5H); ^{13}C{^{1}H}-NMR (151 MHz, $CDCl_3$): δ 10.7, 10.8, 16.2, 26.1, 26.6, 31.6, 33.0, 33.1, 46.5, 53.4, 63.5, 109.0, 127.2, 127.8 (2C), 129.4, 132.1, 140.7, 142.0, 142.6, 147.1, 159.8, 164.5, 169.0; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{27}H_{28}N_2NaO_3S^+$ 483.1713; Found 483.1714.

(R)-Methyl 7,9,10-tricyclopropyl-5-oxo-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (6e): Prepared by following the general procedure. Purified with flash column chromatography (20 x 120 mm silica; ethyl acetate in heptane, 10–80%). 96 mg of **5a** was converted to 37 mg (26%) of **6e**, isolated as a light yellow solid. $[\alpha]_D^{25}$ −202 (*c* 0.22, $CHCl_3$); IR (KBr): ν 1754, 1656, 1594, 1454, 1379, 1306, 1212, 1022, 972, 838 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.62-0.71 (m, 2H), 0.71-0.80 (m, 2H), 0.96-1.07 (m, 8H), 2.11-2.19 (m, 2H), 2.84-2.91 (m, 1H), 3.47 (dd, *J* = 2.4, 11.6 Hz, 1H), 3.65 (dd, *J* = 8.4, 11.6 Hz, 1H), 3.77 (s, 3H), 5.66 (dd, *J* = 2.4, 8.0 Hz, 1H), 6.87 (s, 1H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 10.2, 10.3, 10.4, 10.6, 10.9, 11.0, 15.0, 15.6, 17.6, 31.5, 53.3, 63.3, 109.5, 121.8, 134.2, 140.3, 141.4, 149.0, 159.8, 161.2, 169; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{22}N_2NaO_3S^+$ 405.1243; Found 405.1248.

(R)-Methyl 9-cyclopropyl-7-(4-nitrophenyl)-5-oxo-10-phenyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (6f): Prepared by following the general procedure**,** purified by automated flash column chromatography (25 g SNAP Cartridge) eluting with 0–30% ethyl acetate in dichloromethane. 80 mg of **5b** was converted to 57 mg (43%) of **6f**, isolated as a yellow solid. $[\alpha]_D^{25}$ −122 (*c* 0.31, $CHCl_3$); IR (KBr): ν 1752, 1667, 1592, 1554, 1521, 1493, 1451, 1410, 1344, 1217, 1176, 927, 855, 733, 699 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.39–0.47 (m, 2H), 0.52–0.59 (m, 2H), 1.34–1.41 (m, 1H), 3.41 (d, *J* = 10.0 Hz, 1H), 3.61 (dd, *J* = 8.8, 11.2 Hz, 1H), 3.77 (s, 3H), 5.80 (d, *J* = 6.8 Hz, 1H), 7.19–7.42 (m, 5H), 7.53(s, 1H), 8.24 (s, 4H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 10.3, 10.8, 17.3, 31.4, 53.5, 63.9, 110.6, 122.2, 124.0, 128.0, 128.3, 128.6, 128.7, 130.5, 130.6, 133.9, 139.7, 140.8, 143.5, 144.4, 148.3, 150.0, 152.4, 159.6, 168.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{27}H_{22}N_3O_5S^+$ 500.1275; Found 500.1273.

(R,E)-Methyl 8-cyclopropyl-6-(4-nitrostyryl)-5-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyridine-3-carboxylate (7): 6-Amino-2-pyridone **5a** (200 mg, 0.75 mmol, 1.0 eq.) and 4-Nitrobenzaldehyde (136.2 mg, 0.90 mmol, 1.2 eq.) were dissolved in dry methanol (6 mL). A precipitate was formed after stirring at room temperature for 4 hours. The precipitate was filtered through sintered funnel, washed with heptane and dried under vacuum to yield compound **7** (205 mg, 68 %) as a red solid. $[\alpha]_D^{25}$ −55 (*c* 0.26, DMSO); IR (KBr): ν 3417, 2958, 1749, 1629, 1565,1518, 1486, 1399, 1385, 1342, 1272, 1223, 1144, 1105, 842, 992, 622. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$, 343K): δ 0.67–0.70 (m, 2H), 0.88–0.90 (m, 2H), 1.62 (broad s, 1H), 3.70 (d, *J* = 12.4 Hz, 1H), 3.76 (s, 3H), 4.00 (dd, *J* = 9.6, 11.6 Hz, 1H), 5.68 (d, *J* = 7.6 Hz, 1H), 7.31 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 2H), 8.30 (d, *J* = 8.4 Hz, 2H), 9.60 (s, 1H); ^{13}C{^{1}H}-NMR (100 MHz, $(CD_3)_2SO$): δ 5.6, 5.8, 11.8, 30.9, 52.5, 63.0, 113.1, 123.5, 128.5, 131.9, 135.8, 142.4, 145.9, 148.2, 156.0, 156.8, 168.1.

(3R)-Methyl 10-cyclopropyl-7-(4-nitrophenyl)-5-oxo-9-phenyl-3,5,6,7,8,9-hexahydro-2H-

thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (8): Compound **7** (100 mg, 0.25 mmol, 1.0 eq.) was dissolved in dry DCM (4 ml) and styrene (34 µL, 0.30 mmol, 1.2 eq.) was added, followed by $BF_3{\cdot}OEt_2$ (3.1 µL, 0.025 mmol, 0.10 eq.) at room temperature. The reaction mixture was stirred at room temperature for 4 h, diluted with DCM (15 ml) and washed with water (2x10 ml). The combined aqueous phase was re-extracted with DCM (15 ml). The organic phases were combined, dried over anhydrous sodium sulphate and evaporated under reduced pressure to yield the crude product. The product was purified with automated flash column chromatography (25 g SNAP Cartridge) eluting with 0–80% ethyl acetate in heptane to yield 123 mg (97%) of **8** as a yellow solid. $[\alpha]_D^{25}$ −210 (*c* 0.2, $CHCl_3$); IR (KBr): ν 3001, 2952, 1755, 1638, 1590, 1518, 1490, 1462, 1401, 1346, 1252, 1211, 1182, 854, 699 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.49–0.66 (m, 5H), 2.07–2.16 (m, 1H), 2.44–2.50 (m, 1H), 3.47 (dd, *J* = 2.0, 11.6 Hz, 1H), 3.68 (dd, *J* = 8.0, 11.6 Hz, 1H), 3.68 (s, 1H), 4.42–4.48 (m, 2H), 5.65 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.08–7.12 (m, 3H), 7.15–7.26 (m, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 8.11 (dd, *J* = 2.0, 8.8 Hz, 2H); $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ 7.5, 9.1, 13.0, 32.0, 42.2, 44.1, 53.3, 55.5, 63.1, 114.6, 123.8, 126.3, 127.5, 128.5 (2C), 132.4, 133.4, 144.9, 147.3, 150.5, 156.4, 168.7; LC-MS: *m/z* = 504 $[M+H]^+$, $C_{27}H_{26}N_3O_5S^+$ requires 504.

*Synthesis of compound 6b from Povarov adduct 8***:** To a solution of Povarov adduct **8** (100 mg, 0.198 mmol, 1.0 eq.) in DCM (4 ml) was added DDQ (45.0 mg, 0.198 mmol, 1.0 eq.) and the reaction mixture was stirred at room temperature for 30 minutes. After completion, the mixture was diluted with DCM (20 ml) and washed with water (5x15 ml). The organic phase was dried over anhydrous sodium sulphate and evaporated under reduced pressure. The crude product was purified by automated flash column chromatography (25 g SNAP Cartridge) eluting with 0–100% ethyl acetate in heptane to yield 74 mg (75%) of **8** as a yellow solid. The data is the same as for the product prepared via the A^3 coupling reaction.

General procedure for the three component Povarov reaction using styrene as dienophile: Preparation of compounds 6g–q. Procedure A : Under an atmosphere of nitrogen, 6-aminopyridone of general structure **5** (0.35 mmol, 1.0 eq.) was placed in an oven dried 5 ml microwave reaction tube or round bottom flask equipped with a magnetic stirrer, and dissolved in DCM (4 ml). The aldehyde (0.70 mmol, 2.0 eq.) was added while stirring, followed by the styrene (0.70 mmol, 2.0 eq.) and $BF_3{\cdot}OEt_2$ (9.4 µl, 0.035 mmol, 0.10 eq.). The tube was sealed with a cap and stirred at room temperature for 16 h. The reaction was monitored by TLC and LC-MS. When no starting material remained, DDQ (79 mg, 0.35 mmol, 1.0 eq.) was added and the mixture was stirred for 30 min. Upon completion, the mixture was diluted with DCM (5 ml), washed with $NaHCO_3$ (sat. aq.) (3 ml) followed by brine (3 ml), dried over anhydrous sodium sulphate, filtered and evaporated. The desired product was purified with flash column chromatography.

Procedure B: Under air, 6-aminopyridone of general structure **5** (0.35 mmol, 1.0 eq.) was placed in an oven dried 5 ml microwave reaction tube or round bottom flask equipped with a magnetic stirrer, and dissolved in DCM (4 ml). The aldehyde (0.42 mmol, 1.2 eq.) was added while stirring, followed by 5–10 rods of activated 4Å MS. The styrene (0.42 mmol, 1.2 eq.) and $BF_3{\cdot}OEt_2$ (9.4 µl, 0.035 mmol, 0.1 eq.) was subsequently added. The tube was sealed with a cap and stirred at room temperature for 16 h. The reaction was checked with TLC and LC-MS. When no starting material remained, DDQ (79 mg, 0.35 mmol, 1.0 eq.) was added and the mixture was stirred for 30 min. Upon completion, the mixture was diluted with DCM (5 ml), washed with $NaHCO_3$ (sat. aq.) (3 ml) followed by brine (3 ml), dried over anhydrous sodium sulphate, filtered and evaporated. The desired product was purified with flash column chromatography.

(R)-Methyl 10-cyclopropyl-5-oxo-9-phenyl-7-(4-(trifluoromethyl)phenyl)-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (6g): The compound was prepared following general procedure B. Purified with flash column chromatography (20 x 130 mm silica; ethyl acetate in toluene, 5–30%). 100 mg of **5a** was converted to 98 mg (50%) of **6g**, isolated as a yellow solid. $[\alpha]_D$ −100° (*c* 0.18, $CHCl_3$); IR (KBr): ν 1750, 1667, 1591, 1458, 1324, 1165, 1123, 1068 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.17–0.24 (m, 4H), 1.14–1.22 (m, 1H), 3.53 (dd, *J* = 2.6, 11.6 Hz, 1H), 3.74 (dd, *J* = 8.3, 11.6 Hz, 1H), 3.82 (s, 3H), 5.76 (dd, *J* = 2.6, 8.3 Hz, 1H), 7.38–7.53 (m, 5H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.90 (s, 1H), 8.32 (d, *J* = 8.2 Hz, 2H); ^{13}C{^{1}H}-NMR (151 MHz, $CDCl_3$): δ 10.8, 10.9, 16.1, 31.7, 53.5, 63.6, 109.0, 124.3 (q, J = 272 Hz), 125.75 (d, *J* = 3 Hz), 126.7, 127.7, 128.1 (d, *J* = 7 Hz), 128.2, 129.3, 131.2 (q, J = 32 Hz), 133.3, 141.5, 141.6, 144.6, 147.9, 152.7, 159.6, 168.7; ^{19}F-NMR (564 MHz, $CDCl_3$): δ −62.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{28}H_{22}F_3N_2O_3S^+$ 523.1298; Found 523.1295.

(R)-Methyl 7-(4-cyanophenyl)-10-cyclopropyl-5-oxo-9-phenyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (6h): The compound was prepared following general procedure B. Purified with flash column chromatography (20 x 120 mm silica; ethyl acetate in heptane, 20–65%). 100 mg of **5a** was converted to 92 mg (51%) of **6h**, isolated as a yellow solid. $[\alpha]_D^{25}$ −138 (*c* 0.27, $CHCl_3$); IR ($CHCl_3$): ν 2226, 1752, 1665, 1590, 1553, 1457, 1441, 1216, 1180, 749 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.18–0.25 (m, 4H), 1.16–1.22 (m, 1H), 3.54 (dd, *J* = 2.6, 11.6 Hz, 1H), 3.74 (dd, *J* = 8.3, 11.6 Hz, 1H), 3.83 (s, 3H), 5.76 (dd, *J* = 2.6, 8.3 Hz, 1H), 7.40–7.51 (m, 5H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.90 (s, 1H), 8.33 (d, *J* = 8.6 Hz, 2H); ^{13}C{^{1}H}-NMR (151 MHz, $CDCl_3$): δ 10.8, 10.9, 16.1, 31.6, 53.5, 63.6, 109.0, 112.8, 119.0, 126.7, 127.9, 128.1 (2C), 128.3, 129.3, 132.7, 133.6, 141.46, 141.54, 142.3, 145.0, 148.0, 151.9, 159.5, 168.7; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{28}H_{21}N_3NaO_3S^+$ 502.1195; Found 502.1196.

(R)-Methyl 10-cyclopropyl-7-(4-fluorophenyl)-5-oxo-9-phenyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (6i): The compound was prepared following general procedure B. Purified with flash column chromatography (20 x 100 mm silica; ethyl acetate in toluene, 5–40%). 100 mg of **5a** was converted to 94 mg (53%) of **6i**, isolated as a light brown solid. $[\alpha]_D^{25}$ −135 (*c* 0.41, $CHCl_3$); IR ($CHCl_3$): ν 1753, 1663, 1592, 1459, 1221, 751 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.16–0.24 (m, 4H), 1.14–1.22 (m, 1H), 3.53 (dd, *J* = 2.6, 11.6 Hz, 1H), 3.73 (dd, *J* = 8.4, 11.6 Hz, 1H), 3.81 (s, 3H), 5.76 (dd, *J* = 2.6, 8.2 Hz, 1H), 7.14 (apparent triplet, *J* = 8.8 Hz, 2H), 7.39–7.51 (m, 5H), 7.83 (s, 1H), 8.20 (dd, *J* = 5.5, 8.9 Hz, 2H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 10.6, 10.9, 16.1, 31.6, 53.4, 63.5, 109.0, 115.8 (d, *J* = 22 Hz), 126.3, 128.0, 128.1, 129.3 (2C; d, *J* = 8 Hz), 132.7, 134.4 (d, *J* = 3 Hz), 141.3, 141.8, 143.7, 147.7, 153.4, 159.8, 163.9 (d, *J* = 249 Hz), 168.8; ^{19}F{^{1}H}-NMR (376 MHz, $CDCl_3$): δ −112.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{27}H_{22}FN_2O_3S^+$ 473.1329; Found 473.1328.

(R)-Methyl 10-cyclopropyl-7-(naphthalen-1-yl)-5-oxo-9-phenyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (6j): Prepared by following general procedure A**,** purified by automated flash column chromatography (25 g SNAP Cartridge) eluting with 0–70% ethyl acetate in heptane. 70 mg of **5a** was converted to 72 mg (54%) of **6j**, isolated as an off white solid. $[\alpha]_D^{25}$ −156 (*c* 0.22, $CHCl_3$); IR (KBr): ν 1751, 1666, 1588, 1555, 1510, 1468, 1439, 1379, 1213, 1148, 1074, 778, 702, 616 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.22–0.28 (m, 4H), 1.20–1.27 (m, 1H), 3.54 (dd, *J* = 2.8, 11.6 Hz, 1H), 3.72 (dd, *J* = 8.4, 11.6 Hz, 1H), 3.81 (s, 3H), 5.79 (dd, *J* = 2.4, 8.0 Hz, 1H), 7.39-7.42 (m, 3H), 7.46–7.55 (m, 5H), 7.77–7.78 (m, 2H), 7.88–7.90 (m, 2H), 8.31–8.33 (m, 1H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 10.8, 10.9, 16.1, 31.6, 53.4, 63.5, 108.8, 125.3, 125.7, 125.9, 126.8, 127.9, 128.0,

128.4, 129.3, 129.4, 131.1, 131.4, 132.5, 134.0, 137.4, 141.4, 141.5, 143.9, 146.9, 156.4, 159.6, 168.8; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{25}N_2O_3S^+$ 505.1580; Found 505.1583.

(R)-Methyl 10-methoxy-7-(4-nitrophenyl)-5-oxo-9-phenyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (6k): Prepared by following general procedure A**,** purified by automated flash column chromatography (25 g SNAP Cartridge) eluting with 0–100% ethyl acetate in heptane. 90 mg of **5c** was converted to 115 mg (67%) of **6k**, isolated as a yellow solid. $[\alpha]_D^{25}$ −174 (*c* 0.22, $CHCl_3$); IR (KBr): ν 1743, 1665, 1595, 1558, 1522, 1462, 1442, 1343, 1229, 1147, 1070 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 2.96 (s, 3H), 3.62 (dd, *J* = 1.8, 11.4 Hz, 1H), 3.79 (dd, *J* = 7.8, 11.4 Hz, 1H), 3.83 (s, 3H), 5.80 (dd, *J* = 1.8, 8.4 Hz, 1H), 7.45–7.48 (m, 5H), 7.91 (s, 1H), 8.31 (d, *J* = 9.0 Hz, 2H), 8.38 (d, *J* = 8.4 Hz, 2H); ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$): δ 31.9, 53.6, 60.0, 63.5, 124.1, 126.8, 127.6, 128.1, 128.4, 128.7, 129.2, 132.0, 135.4, 139.1, 141.3, 143.9, 146.2, 148.5, 152.1, 158.6, 168.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{20}N_3O_6S^+$ 490.1067; Found 490.1064.

(R)-Methyl 10-methoxy-5-oxo-7,9-diphenyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (6l): Prepared by following general procedure A**,** purified by automated flash column chromatography (25 g SNAP Cartridge) eluting with 0–100% ethyl acetate in heptane. 85 mg of **5c** was converted to 122 mg (76%) of **6l**, isolated as a light yellow solid. $[\alpha]_D^{25}$ −171 (*c* 0.21, $CHCl_3$); IR (KBr): ν 1747, 1666, 1606, 1563, 1442, 1362, 1222, 1183, 1076, 1013, 697 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 2.95 (s, 3H), 3.59 (dd, *J* = 1.8, 11.4 Hz, 1H), 3.76 (dd, *J* = 8.4, 11.4 Hz, 1H), 3.82 (s, 3H), 5.80 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.42–7.48 (m, 8H), 7.86 (s, 1H), 8.21 (dd, *J* = 1.2, 7.8 Hz, 2H); ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$): δ 31.9, 53.5, 59.9, 63.4, 126.4, 127.4, 127.8, 128.0, 128.8, 129.3, 129.6, 132.2, 133.7, 138.0, 139.6, 141.2, 145.6, 155.1, 158.9, 168.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{21}N_2O_4S^+$ 445.1217; Found 445.1231.

(R)-Methyl 10-methoxy-5-oxo-9-phenyl-7-(4-(trifluoromethyl)phenyl)-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (6m): Prepared by following general procedure A, purified by automated flash column chromatography (25 g SNAP Cartridge) eluting with 0–100% ethyl acetate in heptane. 92 mg of **5c** was converted to 138 mg (75%) of **6m**, isolated as a yellow solid. $[\alpha]_D^{25}$ −135 (*c* 0.12, $CHCl_3$); IR (KBr): ν 1746, 1667, 1604,1562, 1454, 1324, 1230, 1066, 854, 744, 702 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 2.96 (s, 3H), 3.61 (dd, *J* = 1.8, 11.4 Hz, 1H), 3.79 (dd, *J* = 8.4, 12.0 Hz, 1H), 3.83 (s, 3H), 5.80 (dd, *J* = 1.2, 7.8 Hz, 1H), 7.44–7.48 (m, 5H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.88 (s, 1H), 8.32 (d, *J* = 8.4 Hz, 2H); ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$): δ 31.9, 53.5, 59.9, 63.5, 123.3 (q, *J* = 270.4 Hz) 125.8 (q, *J* = 3.7 Hz), 126.5, 127.5, 127.7, 128.2, 128.4, 129.2, 131.2 (q, *J* = 32.2 Hz), 132.1, 134.7, 139.3, 141.2, 141.3, 146.0, 153.3, 158.7, 168.4; ^{19}F-NMR: (376 MHz, $(CD_3)_2SO$): δ −62.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{20}F_3N_2O_4S^+$ 513.1090; Found 513.1111.

(R)-Methyl 10-methoxy-5-oxo-9-phenyl-7-(thiophen-2-yl)-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (6n): Prepared by following general procedure A**,** purified by automated flash column chromatography (25 g SNAP Cartridge) eluting with 0–100% ethyl acetate in heptane. 84 mg of **5c** was converted to 95 mg (64%) of **6n**, isolated as a light yellow solid. $[\alpha]_D^{25}$ −79 (*c* 0.23, $CHCl_3$); IR (KBr): ν 1744, 1663, 1599, 1562, 1531, 1462, 1443, 1352, 1224, 1145, 1071, 748, 701, 617 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.94 (s, 3H), 3.58 (dd, *J* = 2.0, 11.6 Hz, 1H), 3.76 (dd, *J* = 8.0, 11.6 Hz, 1H), 3.81 (s, 3H), 5.77 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.11 (dd, *J* = 4.0, 5.2 Hz, 1H), 7.42–7.48 (m, 6H), 7.71–7.73 (m, 2H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 32.0, 53.5, 59.9, 63.4, 125.2, 126.1, 127.5, 127.7, 128.1(2C), 129.2, 132.3, 133.5, 139.4, 141.0, 143.9, 145.6, 150.6, 158.5, 168.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{19}N_2O_4S_2^+$ 451.0781; Found 451.0794.

(R)-Methyl 7-(4-nitrophenyl)-5-oxo-9-phenyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (6o): Prepared by following general procedure A**,** purified by automated flash column chromatography (10 g SNAP Cartridge) eluting with 0–70% ethyl acetate in heptane. 50 mg of **5d** was converted to 68 mg (67%) of **6o**, isolated as a yellow solid. $[\alpha]_D^{25}$ −177 (*c* 0.28, $CHCl_3$); IR (KBr): ν 1747, 1669, 1596, 1565, 1522, 1461, 1440, 1411, 1344, 1215, 849, 729, 701, 620 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.62 (d, *J* = 11.2 Hz, 1H), 3.80–3.85 (m, 4H), 5.77 (d, *J* = 7.2 Hz, 1H), 6.45 (s, 1H), 7.45–7.56 (m, 5H), 7.94 (s, 1H) 8.30–8.38 (m, 4H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 32.4, 53.6, 63.0, 95.6, 124.1, 124.5, 128.1, 129.1, 129.2, 132.3, 137.0, 140.2, 142.4, 144.2, 147.5, 148.4, 152.5, 159.9, 168.4; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{18}N_3O_5S^+$ 460.0962; Found 460.0963.

(R)-Methyl 10-cyclopropyl-7-(4-nitrophenyl)-5-oxo-9-(3-(trifluoromethyl)phenyl)-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (6p): The compound was prepared following general procedure B but the reaction mixture was stirred at r.t. for 4 d., followed by addition of DDQ. Purified with flash column chromatography (20 x 120 mm silica; ethyl acetate in toluene, 10–60%). 100 mg of **5a** was converted to 35 mg (16%) of **6p**, isolated as a yellow solid. The compound was also prepared following general procedure B but with stirring at 50 °C for 4 d. followed by addition of DDQ at room temperature. Purified with flash column chromatography (20 x 120 mm silica; toluene/EtOAc 5-30%). 105 mg of **5a** was converted to 110 mg (49%) of **6p**, isolated as a yellow solid. $[\alpha]_D^{25}$ −133 (*c* 0.17, $CHCl_3$). IR ($CHCl_3$): ν 1753, 1667, 1589, 1552, 1522, 1458, 1343, 1327, 1167, 1126 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$, 343 K): δ −0.04–0.31 (m, 4H), 1.00–1.09 (m, 1H), 3.60 (dd, *J* = 2.8, 11.8 Hz, 1H), 3.77 (s, 3H), 3.91 (dd, *J* = 8.9, 11.8 Hz, 1H), 5.74 (dd, *J* = 2.8, 8.8 Hz, 1H), 7.68–7.75 (m, 1H), 7.78–7.83 (m, 1H), 7.83–7.89 (m, 1H), 7.95 (bs, 1H), 8.29 (s, 1H), 8.35 (d, *J* = 9 Hz, 2H), 8.55 (d, *J* = 9 Hz, 2H); ^{13}C{^{1}H}-NMR (151 MHz, $(CD_3)_2SO$, 343 K): δ 10.2, 10.4, 15.2, 30.4, 52.5, 63.0, 78.8, 106.2, 123.5, 123.9 (q, *J* = 272 Hz) 124.2, 125.4, 126.5, 127.7, 128.4 (q, *J* = 32 Hz) 128.5, 132.8, 133.1, 140.4, 141.4, 143.2, 145.1, 146.6, 147.7, 150.0, 157.8, 168.3; ^{19}F-NMR (376 MHz; $(CD_3)_2SO$, 343 K): δ −61.1; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{28}H_{20}F_3N_3NaO_5S^+$ 590.0969; Found 590.0963.

(R)-Methyl 10-cyclopropyl-5-oxo-7-phenyl-9-(3-(trifluoromethyl)phenyl)-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (6q): The compound was prepared following general procedure B but the reaction mixture was stirred at r.t. for 11 d., followed by oxidation with DDQ. Purified with flash column chromatography (20 x 120 mm silica; ethyl acetate in toluene, 10–35%). 100 mg of **5a** was converted to 8 mg (4%) of **6q**, isolated as a yellow solid. The compound was also prepared with stirring at 50 °C for 4 d. followed by addition of DDQ at room temperature. Purified with flash column chromatography (20 x 120 mm silica; ethyl acetate in toluene, 5–30%). 105 mg of **5a** was converted to 60 mg (29%) of **6q**, isolated as a yellow solid. $[\alpha]_D^{25}$ −122 (*c* 0.18, $CHCl_3$); IR ($CHCl_3$): ν 1753, 1666, 1591, 1460, 1441, 1325, 1216, 1166, 1125, 1073, 752 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$, 343 K): δ −0.06–0.27 (m, 4H), 0.99–1.08 (m, 1H), 3.58 (dd, *J* = 2.8, 11.8 Hz, 1H), 3.78 (s, 3H), 3.90 (dd, *J* = 8.7, 11.8 Hz, 1H), 5.72 (dd, *J* = 2.8, 8.7 Hz, 1H), 7.44–7.55 (m, 3H), 7.67–7.73 (m, 1H), 7.77–7.81 (m, 1H), 7.81–7.88 (m, 1H), 7.92 (bs, 1H), 8.11 (s, 1H), 8.22–8.29 (m, 2H); ^{13}C{^{1}H}-NMR (151 MHz, $(CD_3)_2SO$, 343 K): δ 10.2, 10.4, 15.3, 30.4, 52.5, 63.0, 106.2, 123.9 (q, *J* = 272 Hz) 124.1, 125.4, 125.7, 126.6, 128.4, 128.5, 129.1, 131.9, 133.1, 137.3, 140.3, 141.8, 144.8, 145.2, 152.6, 158.0, 168.4; ^{19}F-NMR (376 MHz; $(CD_3)_2SO$, 343 K): δ −61.1; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{28}H_{22}F_3N_2O_3S^+$ 523.1298; Found 523.1283.

General procedure for preparation of 9a–k: Procedure A: 6-amino-2-pyridones of general structure **5** (0.33 mmol, 1.0 eq.) was placed in an oven dried 5 ml microwave reaction tube or 10 ml round bottom flask equipped with a magnetic stirrer, and dissolved in dry DCM (4 ml). The aldehyde (0.40 mmol, 1.2 eq.) was added while stirring, and $BF_3{\cdot}OEt_2$ (8.9 μl, 0.033 mmol, 0.10 eq.). The tube was sealed and the mixture stirred for 1 h at room temperature. Ethyl vinyl ether (0.40 mmol, 1.2 eq.) was added and the mixture was stirred at room temperature until completion of the reaction (16 h). The reaction was checked with TLC and LC-MS. When no starting material remained, the mixture was diluted with DCM (5 ml), washed with $NaHCO_3$ (sat. aq.) (3 ml) followed by brine (3 ml), dried, filtered and evaporated. Crude material was dissolved in DCM (5 ml), DDQ (75 mg, 0.33 mmol, 1.0 eq.) was added and stirred for 30 minutes. Upon completion, the mixture was diluted with DCM (5 ml), washed with $NaHCO_3$ (sat. aq.) (3 ml) followed by brine (3 ml), dried, filtered and evaporated. The desired product was purified with flash column chromatography.

General Procedure B: 6-amino-2-pyridones of general structure **5** (0.33 mmol, 1.0 eq.) was placed in an oven dried 5 ml microwave reaction tube or 10 ml round bottom flask equipped with a magnetic stirrer, and dissolved in dry DCM (4 ml). The aldehyde (0.40 mmol, 1.2 eq.) was added while stirring, and $BF_3{\cdot}OEt_2$ (8.9 μl, 0.033 mmol, 0.10 eq.). The tube was sealed and the mixture stirred for 1 h at room temperature. Ethyl vinyl ether (0.40 mmol, 1.2 eq.) was added and the mixture was stirred at room temperature under air balloon until completion of the reaction (16 h). The reaction was monitored by TLC and LC-MS. When no starting material remained, the mixture was diluted with DCM (5 ml), washed with $NaHCO_3$ (sat. aq.) (3 ml) followed by brine (3 ml), dried, filtered and evaporated. The desired product was purified with flash column chromatography.

(R)-Methyl 10-cyclopropyl-7-(4-nitrophenyl)-5-oxo-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (9a): Prepared by following the general procedure A**,** purified by automated flash column chromatography (25 g SNAP Cartridge) eluting with 0–80% ethyl acetate in heptane. 70 mg of **5a** was converted to 52 mg (52%) of **9a**, isolated as yellow solid. $[\alpha]_D^{25}$ −120 (*c* 0.24, $CHCl_3$); IR (KBr): ν 1747, 1665, 1599, 1573, 1525, 1510, 1469, 1411, 1337, 1215, 1179, 852, 835, 726 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.69–0.76 (m, 2H), 1.04–1.15 (m. 2H), 1.75–1.82 (m, 1H), 3.58 (dd, *J* = 2.0, 11.6 Hz, 1H), 3.75 (dd, *J* = 8.4, 11.6 Hz, 1H), 3.80 (s, 3H), 5.78 (dd, *J* = 2.0, 8.4 Hz, 1H), 8.07 (d, *J* = 8.8 Hz, 1H), 8.31–8.36 (m, 4H), 8.46 (dd, *J* = 1.6, 8.4 Hz, 1H); $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ 7.5(2C), 10.0, 31.7, 53.4, 63.0, 108.1, 123.9, 124.0, 128.0, 132.8, 135.0, 140.0, 142.8, 144.2, 148.3, 152.3, 159.7, 168.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{18}N_3O_5S^+$ 424.0962; Found 424.0963.

(R)-Methyl 10-cyclopropyl-5-oxo-7-(4-(trifluoromethyl)phenyl)-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (9b): Prepared by following the general procedure A**,** purified by automated flash column chromatography (10 g SNAP Cartridge) eluting with 0–80% ethyl acetate in heptane. 50 mg of **5a** was converted to 41 mg (49%) of **9b**, isolated as an off white solid. $[\alpha]_D^{25}$ −147 (*c* 0.13, $CHCl_3$); IR ($CHCl_3$): ν 1753, 1666, 1600, 1511, 1473, 1412, 1325, 1216, 1167, 1014, 833, 753, 722 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.67–0.75 (m, 2H), 1.02–1.13 (m. 2H), 1.74–1.80 (m, 1H), 3.56 (dd, *J* = 2.0, 11.6 Hz, 1H), 3.76 (dd, *J* = 8.4, 11.6 Hz, 1H), 3.79 (s, 3H), 5.77 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 8.04 (d, *J* = 8.8 Hz, 1H), 8.29 (d, *J* = 8.0 Hz, 2H), 8.43 (d, *J* = 8.8 Hz, 1H); $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ 7.4, 7.5, 10.0, 31.7, 53.4, 62.9, 108.1, 122.9 (q, *J* = 270 Hz), 123.7, 125.7 (q, *J* = 3.6 Hz), 127.6, 130.9 (q, *J* = 32.3 Hz), 132.7, 134.7, 140.0, 141.7, 142.1, 153.5, 159.8, 168.7; ^{19}F-NMR (376 MHz, $(CD_3)_2SO$): δ −62.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{18}F_3N_2O_3S^+$ 447.0985; Found 447.0992.

(R)-Methyl 7-(4-cyanophenyl)-10-cyclopropyl-5-oxo-3,5-dihydro-2H-thiazolo[2,3-

g][1,7]naphthyridine-3-carboxylate (9c): Prepared by following the general procedure A**,** purified by automated flash column chromatography (25 g SNAP Cartridge) eluting with 0–80% ethyl acetate in heptane. 90 mg of **5a** was converted to 80 mg (59%) of **9c**, isolated as an off white solid. $[\alpha]_D^{25}$ −177 (*c* 0.2, $CHCl_3$); IR ($CHCl_3$): ν 2225, 1752, 1665, 1599, 1578, 1527, 1471, 1365, 1216, 832, 747 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.67–0.76 (m, 2H), 1.03–1.14 (m, 2H), 1.74–1.81 (m, 1H), 3.57 (dd, *J* = 2.0, 11.6 Hz, 1H), 3.74 (dd, *J* = 8.4, 11.6 Hz, 1H), 3.79 (s, 3H), 5.77 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.75 (dd, *J* = 2.0, 6.8 Hz, 2H), 8.03 (d, *J* = 8.4 Hz, 1H), 8.29 (dd, *J* = 1.6, 6.8 Hz, 2H), 8.44 (d, *J* = 8.4 Hz, 1H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 7.5(2C), 10.0, 31.7, 53.4, 62.9, 108.1, 112.7, 118.9, 123.7, 127.8, 132.6, 132.8, 134.9, 140.0, 142.5, 142.6, 152.8, 159.7, 168.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{18}N_3O_3S^+$ 404.1063; Found 404.1065.

(R)-Methyl 10-cyclopropyl-7-(4-fluorophenyl)-5-oxo-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (9d): The compound was prepared following general procedure A. Purified with flash column chromatography (20 x 115 mm silica; ethyl acetate in toluene, 5–40%). 101 mg of **5a** was converted to 25 mg (17%) of **9d**, isolated as a light yellow solid. $[\alpha]_D^{25}$ −223 (*c* 0.26, $CHCl_3$). IR ($CHCl_3$) : ν 1752, 1665, 1602, 1473, 1221, 1156, 833, 746 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.65–0.74 (m, 2H), 1.00–1.12 (m, 2H), 1.71–1.79 (m, 1H), 3.54 (dd, *J* = 2.1, 11.7 Hz, 1H), 3.74 (dd, *J* = 8.3, 11.7 Hz, 1H), 3.78 (s, 3H), 5.76 (dd, *J* = 2.1, 8.3 Hz, 1H), 7.14 (apparent triplet, *J* = 8.7 Hz, 2H), 7.96 (d, *J* = 8.7 Hz, 1H), 8.17 (dd, *J* = 5.5, 8.8 Hz, 2H), 8.37 (d, *J* = 8.8 Hz); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 7.4, 7.5, 10.1, 31.8, 53.4, 63.0, 108.2, 115.7 (d, *J* = 22 Hz), 123.3, 129.3 (d, *J* = 9 Hz), 132.5, 134.0, 134.7 (d, *J* = 3 Hz), 139.8, 141.3, 154.2, 159.9, 163.9 (d, *J* = 249 Hz), 168.8; ^{19}F{^{1}H}-NMR (376 MHz, $CDCl_3$): δ −112.4; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{18}FN_2O_3S^+$ 397.1016; Found 397.1017.

(R)-Methyl 10-cyclopropyl-7-(naphthalen-1-yl)-5-oxo-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (9e): Prepared by following the general procedure A**,** purified by automated flash column chromatography (25 g SNAP Cartridge) eluting with 0–20% ethyl acetate in DCM. 70 mg of **5a** was converted to 67 mg (59%) of **9e**, isolated as an off white solid. $[\alpha]_D^{25}$ −226 (*c* 0.22, $CHCl_3$); IR (KBr): ν 1748, 1669, 1602, 1579, 1514, 1477, 1322, 1221, 1150, 852, 748, 665 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.76–0.77 (m, 2H), 1.05–1.13 (m. 2H), 1.81–1.84 (m, 1H), 3.57 (d, *J* = 11.6 Hz, 1H), 3.72 (dd, *J* = 8.4, 11.2 Hz, 1H), 3.79 (s, 3H), 5.79 (d, *J* = 6.8 Hz, 1H), 7.47–7.56 (m, 3H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.86–7.91 (m, 3H), 8.19 (d, *J* = 8.4 Hz, 1H), 8.46 (d, *J* = 8.8 Hz, 1H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 7.5(2C), 10.1, 31.8, 53.4, 62.9, 108.1, 125.4, 125.6, 125.9, 126.7, 128.4, 129.2, 131.3, 131.8, 133.9, 134.0, 137.8, 140.0, 141.5, 157.3, 159.8, 168.9; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{21}N_2O_3S^+$ 429.1267; Found 429.1262.

(R)-Methyl 7-cyclohexyl-10-cyclopropyl-5-oxo-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (9f): Prepared by following the general procedure B**,** purified by automated flash column chromatography (10 g SNAP Cartridge) eluting with 0–85% ethyl acetate in heptane. 70 mg of **5a** was converted to 47 mg (47%) of **9f**, isolated as a light yellow solid. $[\alpha]_D^{25}$ −148 (*c* 0.36, $CHCl_3$); IR ($CHCl_3$): ν 2926, 2852, 1753, 1666, 1604, 1585, 1523, 1478, 1448, 1389, 1364, 1323, 1213, 840, 732 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.62-0.71 (m, 2H), 0.97–1.08 (m, 2H), 1.22–1.33 (m, 1H), 1.35–1.46 (m, 2H), 1.48–1.58 (m, 2H), 1.69–1.76 (m, 2H), 1.81–1.85 (m, 2H), 1.97–2.00 (m, 2H), 2.94–3.02 (m, 1H), 3.51 (dd, *J* = 2.4, 11.6 Hz, 1H), 3.67 (dd, *J* = 8.4, 11.6 Hz, 1H), 3.75 (s, 3H), 5.72 (dd, *J* = 2.0. 8.0 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 1H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 7.3, 7.4, 10.0, 26.1, 26.5, 31.7, 32.9, 33.0, 46.8, 53.3, 62.8, 108.2, 124.4, 132.0, 133.5, 139.3, 140.1, 160.1, 165.4, 168.9; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for

$C_{21}H_{25}N_2O_3S^+$ 385.1580; Found 385.1585.

(R)-Methyl 7,10-dicyclopropyl-5-oxo-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (9g): Prepared by following the general procedure B**,** purified by automated flash column chromatography (25 g SNAP Cartridge) eluting with ethyl acetate in heptane, 0–85%. 80 mg of **5a** was converted to 46 mg (45%) of **9g**, isolated as light brown solid. $[\alpha]_D^{25}$ −155 (*c* 0.28, $CHCl_3$); IR ($CHCl_3$): ν 1753, 1663, 1604, 1585, 1482, 1326, 1212, 886, 836, 752 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.63–0.67 (m, 2H), 0.97–1.12 (m, 6H), 1.68–1.74 (m, 1H), 2.23–2.28 (m, 1H), 3.51 (dd, *J* = 2.0, 11.6 Hz, 1H), 3.74 (dd, *J* = 8.4, 11.6 Hz, 1H), 3.76 (s, 3H), 5.71 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 8.8 Hz, 1H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 7.3, 7.4, 10.0, 10.5, 10.6, 17.9, 31.7, 53.5, 62.8, 108.3, 123.7, 131.6, 133.1, 139.4, 139.6, 159.9, 162.0, 168.9; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{19}N_2O_3S^+$ 343.1111; Found 343.1111.

(R)-Methyl 10-cyclopropyl-5-oxo-7-propyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (9h): Prepared by following the general procedure A**,** purified by automated flash column chromatography (25 g SNAP Cartridge) eluting with 0–80% ethyl acetate in heptane. 80 mg of **5a** was converted to 42 mg (41%) of **9h**, isolated as an off white solid. $[\alpha]_D^{25}$ −142 (*c* 0.32, $CHCl_3$); IR ($CHCl_3$): ν 1753, 1663, 1603, 1481, 1213, cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.65–0.71 (m, 2H), 0.98 (t, *J* = 7.2 Hz, 3H), 1.00–1.06 (m, 2H), 1.74–1.84 (m, 3H), 2.92–2.95 (m, 2H), 3.52 (dd, *J* = 2.4, 11.6 Hz, 1H), 3.69 (dd, *J* = 8.4, 11.6 Hz, 1H), 3.76 (s, 3H), 5.71 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 8.25 (d, *J* = 8.4 Hz, 1H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 7.4 (2C), 10.0, 14.1, 23.3, 31.7, 40.6, 53.3, 62.9, 108.3, 126.4, 131.8, 133.4, 139.6, 140.2, 160.0, 161.3, 168.9; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{21}N_2O_3S^+$ 345.1267; Found 345.1273.

(R)-Methyl 7-(4-nitrophenyl)-5-oxo-10-phenyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (9i): Prepared by following the general procedure A**,** purified by automated flash column chromatography (25 g SNAP Cartridge) eluting with 0–20% ethyl acetate in DCM. 100 mg of **5b** was converted to 58 mg (38%) of **9i**, isolated as a yellow solid. $[\alpha]_D^{25}$ −79 (*c* 0.23, $CHCl_3$); IR ($CHCl_3$): ν 1752, 1671, 1599, 1572, 1525, 1493, 1468, 1343, 1217, 726, 704 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.56 (dd, *J* = 2.0, 11.6 Hz, 1H), 3.76 (dd, *J* = 8.4, 11.6 Hz, 1H), 3.84 (s, 3H), 5.88 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.36–7.47 (m, 2H), 7.49–7.54 (m, 3H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 8.39–8.35 (m, 4H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 31.8, 53.6, 63.7, 110.8, 124.1, 124.2, 128.1, 128.8, 129.2, 129.4, 130.1, 130.5, 133.3, 133.9, 135.0, 139.9, 141.8, 144.1, 148.4, 152.7, 159.5, 168.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{18}N_3O_5S^+$ 460.0962; Found 460.0956.

(R)-Methyl 5-oxo-10-phenyl-7-(4-(trifluoromethyl)phenyl)-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (9j): Prepared by following the general procedure A**,** purified by automated flash column chromatography (25 g SNAP Cartridge) eluting with 0–20% ethyl acetate in DCM. 100 mg of **5b** was converted to 55 mg (34%) of **9j**, isolated as a light brown solid. $[\alpha]_D^{25}$ –93 (*c* 0.32, $CHCl_3$); IR ($CHCl_3$): ν 1753, 1670, 1597, 1583, 1510, 1493, 1443, 1412, 1374, 1326, 1217, 834, 754, 723, 702 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.54 (dd, *J* = 2.0, 11.6 Hz, 1H), 3.74 (dd, *J* = 8.4, 11.6 Hz, 1H), 3.84 (s, 3H), 5.87 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.36–7.42 (m, 2H), 7.44–7.54 (m, 3H), 7.70–7.73 (m, 3H), 7.91 (d, *J* = 8.8 Hz, 1H), 8.28 (d, *J* = 8.8 Hz, 2H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 31.8, 53.5, 63.8, 110.9, 122.9, 123.9, 125.7 (d, J = 3.7 Hz), 127.6, 128.7, 129.2, 129.4, 130.2, 130.5, 133.0 (d, *J* = 31.9 Hz), 133.1, 133.6, 135.2, 139.8, 141.0, 141.6, 153.9, 159.7, 168.6; ^{19}F-NMR (376 MHz, $(CD_3)_2SO$): δ −62.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{18}F_3N_2O_3S^+$ 483.0985; Found 483.0983.

(R)-Methyl 7-(4-nitrophenyl)-5-oxo-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (9k): Prepared by following the general procedure A**,** purified by automated flash column chromatography (50 g SNAP Cartridge) eluting with 0–50% ethyl acetate in DCM. 1200 mg of **5d** was converted to 895 mg (44%) of **9k**, isolated as a yellow solid. $[\alpha]_D^{25}$ –140 (*c* 0.27, $CHCl_3$). IR (KBr): ν 1747, 1667, 1598, 1582, 1526, 1470, 1439, 1346, 1222, 1066, 847, 723 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.64 (dd, *J* = 2.0, 11.6 Hz, 1H), 3.81 (s, 3H), 3.84 (dd, *J* = 8.4, 11.6 Hz, 1H), 5.76 (dd, *J* = 2.0, 8.0 Hz, 1H), 6.41 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 8.29–8.35 (m, 4H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 32.4, 53.5, 62.9, 97.5, 124.1, 124.4, 128.1, 133.9, 134.5, 139.6, 142.7, 144.2, 148.4, 152.9, 159.9, 168.4; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{14}N_3O_5S^+$ 384.0649; Found 384.0651.

(R)-methyl 10-bromo-7-(4-nitrophenyl)-5-oxo-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (10): Compound **9k** (800 mg, 2.09 mmol, 1.00 eq.) was dissolved in chloroform (30 ml), *N*-bromosuccinimide (371.4 mg, 2.09 mmol, 1.00 eq.) was added and the reaction mixture was heated at 50 °C for 15 minutes. Completion was confirmed by TLC (80% ethyl acetate in heptane). The reaction was allowed to reach room temperature and then quenched with a saturated aqueous sodium thiosulphate solution. Saturated aqueous sodium hydrogen carbonate solution was added, the phases were separated and the aqueous phase was extracted with dichloromethane (2 x 20 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was recrystallized from dichloromethane and heptane to yield compound **10** (756.0 mg, 1.64 mmol, 78 %) as a yellow solid. $[\alpha]_D^{25}$ –202 (*c* 0.35, $CHCl_3$); IR ν 1740, 1667, 1574, 1526, 1460, 1338, 1239, 853, 833 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* 3.66 (dd, *J* = 11.7, 1.9 Hz, 1H), 3.83 (s, 3H), 3.90 (dd, *J* = 11.7, 8.3 Hz, 1H), 5.93 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.14 (m, 2H), 8.35 (m, 4H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): *δ* 31.9, 53.8, 64.9, 64.9, 91.0, 124.2 (2C), 125.0, 128.3 (2C), 133.1, 134.2, 139.6, 143.6, 144.1, 148.7, 153.5, 158.9, 168.2 ppm; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{13}BrN_3O_5S^+$ 461.9754; Found 461.9753.

General procedure for the synthesis of compound 9l–9o: Compound **10** (0.13 mmol, 1.0 eq.) was dissolved in methanol (5 mL). Under a nitrogen atmosphere, boronic acid (0.26 mmol, 2.0 eq.), KF (0.25 mmol, 1.8 eq.) and lastly $Pd(PPh_3)_2Cl_2$ (0.013 mmol, 0.1 eq.) were added. The reaction was heated to 120 °C under MWI for 10 minutes. Completion was confirmed by LC-MS. The reaction mixture was diluted with DCM and washed with brine (5 mL). The aqueous phase was extracted with DCM (2 x 15 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash column chromatography.

(R)-methyl 10-(3-hydroxyphenyl)-7-(4-nitrophenyl)-5-oxo-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (9l): Prepared by following the general procedure**,** purified by flash column chromatography (ethyl acetate in DCM, 80–100%) and recrystallization from DCM and heptane. 60 mg of **10** was converted to 41 mg (79%) of **9l**, isolated as a yellow solid. $[\alpha]_D^{25}$ –122 (*c* 0.22, DMSO); IR: ν 3224, 1747, 1648, 1574, 1523, 1470, 1339, 1220, 750, 725 621 cm^{-1}; ^{1}H-NMR (600 MHz, $(CD_3)_2SO$): *δ* 3.61 (broad d, *J* = 11.5 Hz, 1H), 3.79 (s, 3H), 3.91 (m, 1H), 5.85 (d, *J* = 8.3 Hz, 1H), 6.79 (m, 2H), 6.89 (broad t, *J* = 7.2 Hz, 1H), 7.37 (broad t, *J* = 8.3 Hz, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 8.42 (m, 5H), 9.72 (s, 1H); ^{13}C{^{1}H}-NMR (151 MHz, $(CD_3)_2SO$): *δ* 30.9, 53.1, 63.3, 109.1, 115.7, 116.8, 120.5, 124.2 (2C), 124.8, 127.8 (2C), 130.4, 132.9, 133.4, 135.9, 138.9, 142.5, 143.6, 147.9, 151.4, 157.9, 158.2, 168.8; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{18}N_3O_6S^+$ 476.0916; Found 476.0912.

(R)-methyl 7-(4-nitrophenyl)-5-oxo-10-(m-tolyl)-3,5-dihydro-2H-thiazolo[2,3-

g][1,7]naphthyridine-3-carboxylate (9m): Prepared by following the general procedure**,** purified by flash column chromatography (ethyl acetate in DCM, 0–50%) and recrystallization from MeOH. 44.4 mg of **10** was converted to 38.5 mg (85%) of **9m**, isolated as an orange solid. $[\alpha]_D^{25}$ −115 (*c* 0.36, $CHCl_3$); IR: ν 2955, 1752, 1669, 1600, 1575, 1513, 1468, 1344, 1216, 839, 753 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* 2.45 (s, 3H), 3.55 (dd, *J* = 11.61, 1.74 Hz, 1H), 3.75 (dd, *J* = 11.57, 8.25 Hz, 1H), 3.84 (s, 3H), 5.87 (dd, *J* = 7.97, 1.40 Hz, 1H), 7.30 (m, 4H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 8.6 Hz, 1H), 8.31 (d, *J* = 8.9 Hz, 2H), 8.35 (d, *J* = 8.9 Hz, 2H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): *δ* 21.5, 31.8, 53.6, 63.7, 110.8, 124.1 (3C), 128.2 (2C), 129.9, 130.0, 130.2, 130.4, 132.0, 133.4, 134.1, 138.8, 139.9, 141.7, 144.2, 148.4, 152.7, 159.6, 168.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{20}N_3O_5S^+$ 474.1124; Found 474.1121.

(R)-methyl 10-(3-acetylphenyl)-7-(4-nitrophenyl)-5-oxo-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (9n): Prepared by following the general procedure**,** purified by flash column chromatography (ethyl acetate in DCM, 80–100%) and recrystallization from DCM and heptane. 47 mg of **10** was converted to 46 mg (90%) of **9n**, isolated as an orange solid. $[\alpha]_D^{25}$ −100 (*c* 0.25, DMSO); IR ν 3016, 2956, 1752, 1673, 1601, 1573, 1526, 1468, 1343,1217, 840, 753 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$, 343 K): *δ* 2.63 (s, 3H), 3.62 (dd, *J* = 11.7, 1.8 Hz, 1H), 3.80 (s, 3H), 3.94 (dd, *J* = 11.7, 8.9 Hz, 1H), 5.85 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.71 (m, 3H), 7.97 (s, 1H), 8.09 (m, 1H), 8.32 (d, *J* = 9.2 Hz, 1H), 8.37 (d, *J* = 8.7 Hz, 1H), 8.45 (d, *J* = 8.7 Hz, 1H); ^{13}C{^{1}H}-NMR (100 MHz, $(CD_3)_2SO$, 343 K): *δ* 26.4, 30.8, 52.6, 62.2, 108.0, 123.7 (2C), 124.5, 127.6, (2C), 128.0, 129.4, 129.5, 132.4, 133.0, 134.5, 135.1, 137.6, 138.8, 142.9, 143.4, 147.8, 151.3, 157.9, 168.3, 197.1; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{20}N_3O_6S^+$ 502.1073; Found 502.1079.

(R)-methyl 7-(4-nitrophenyl)-5-oxo-10-(thiophen-3-yl)-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylate (9o): Prepared by following the general procedure**,** purified by flash column chromatography (ethyl acetate in heptane, 0–20%) and recrystallization from DCM and heptane. 61.2 mg of **10** was converted to 56.6 mg (92%) of **9o**, isolated as an orange solid. $[\alpha]_D^{25}$ −127 (*c* 0.28, $CHCl_3$) IR: ν 2955, 1752, 1669, 1600, 1575, 1513, 1468, 1344, 1216, 839, 753 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* 3.55 (dd, *J* = 11.6, 1.9 Hz, 1H), 3.77 (m, 1H), 3.83 (s, 3H), 5.86 (dd *J* = 8.2, 1.9 Hz, 1H), 7.13 (dd, *J* = 4.8, 1.1 Hz, 1H), 7.39 (dd, *J* = 2.9, 1.1 Hz, 1H), 7.52 (dd, *J* = 4.8, 2.9 Hz, 1H), 7.81 (d, *J* = 8.6 Hz, 1H), 7.96 (d, *J* = 8.6 Hz, 1H), 8.31 (m, 4H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): *δ* 31.6, 53.6, 63.8, 105.9, 124.1, 124.2 (2C), 125.9, 127.0, 128.1 (2C), 128.7, 133.3, 134.0, 134.8, 139.8, 142.4, 144.1, 148.4, 152.7, 159.4, 168.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{16}N_3O_5S_2^+$ 466.0531; Found 466.0527.

General procedure for preparation of acids 11a–q and 12a–o: Procedure A. The ester was dissolved in THF (2 ml) and LiOH (0.1 M aq.; 1.4 eq.) was added while stirring. The reaction mixture was left stirring at r.t. while monitored with TLC (EtOAc). Upon completion, the reaction was quenched with HCl (1 M aq.; 1.5 eq.). The mixture was evaporated and the watery residue was partioned between chloroform (10 ml) and brine (5 ml). The phases were separated and the aqueous phase was extracted with another portion of $CHCl_3$ (10 ml). The organic phases were combined, dried, filtered and evaporated. The residue was re-dissolved in DMSO (1 ml) and purified with preparative HPLC (H_2O/MeCN + 0.75% HCOOH; 30–100% in 25 min., 100% for 10 min.) The fraction containing the desired product was diluted with H_2O (1:1) and freeze-dried.

General Procedure B. The ester was dissolved in THF (2 ml) and LiOH (0.1 M aq.; 1.4 eq.) was added while stirring. The reaction mixture was left stirring at r.t. while monitored with TLC (EtOAc). Upon completion, the reaction was quenched with HCl (1 M; 1.5 eq.). The mixture was diluted with EtOAc (15 ml) and washed with brine (10 ml). The aqueous phase was extracted with EtOAc (10 ml). The organic phases were combined, dried, filtered and evaporated. The residue was re-dissolved in DMSO (1 ml) and purified with preparative HPLC (H_2O/MeCN + 0.75% HCOOH; 30–100% in 25 min., 100% for 10 min.) The fraction containing the desired product was diluted with H_2O (1:1) and freeze-dried.

General Procedure C. Upon complete saponification the reaction mixture was neutralised with prewashed* Amberlyst® 15 until around pH = 6 by pH-paper, then filtered through a pad of wet (THF) Celite®. The amberlyst and Celite® was rinsed with MeOH until the filtrate was transparent. The filtrate was evaporated and extracted according to the general procedure. The residue was trituated in Et_2O (2 ml) and filtered through a cotton-plug in a Pasteur pipet. The solid was washed with more Et_2O (2 ml) and dried under vacuum o.n.

* The 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 the funnel.

(R)-10-Cyclopropyl-5-oxo-7,9-diphenyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (11a): The compound was prepared and purified according to general procedure C. 50 mg of **6a** was converted to 26 mg (53%) of **11a**, isolated as a dark yellow solid. $[\alpha]_D^{25}$ –36 (*c* 0.17, DMSO); IR (KBr): ν 1622, 1588, 1557, 1462, 1442, 1382, 1134, 701 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3OD (+ $CDCl_3$)): δ 0.12–0.27 (m, 4H), 1.15–1.23 (m, 1H), 3.62 (dd, *J* = 1.0, 11.3 Hz, 1H), 3.79 (dd, *J* = 8.5, 11.3 Hz, 1H), 5.65 (dd, *J* = 0.9, 8.1 Hz, 1H), 7.39–7.59 (m, 8H), 7.93 (s, 1H), 8.21 (d, *J* = 7.3 Hz, 2H); ^{13}C{^{1}H}-NMR (100 MHz, CD_3OD): δ 11.4, 11.5, 17.0, 32.4, 65.1, 110.6, 127.8, 128.4, 129.0, 129.1, 129.8, 130.5 (2C), 134.0, 139.4, 141.8, 142.9, 146.2, 149.4, 155.8, 161.8, 171.2; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{21}N_2O_3S^+$ 441.1266; Found 441.1265.

(R)-10-Cyclopropyl-7-(4-nitrophenyl)-5-oxo-9-phenyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (11b): Prepared by following the general procedure B**,** 49 mg of **6b** was converted to 20 mg (49%) of **11b**, isolated as a yellow solid. $[\alpha]_D^{25}$ –28 (*c* 0.21, $CHCl_3$); IR (KBr): ν 3434, 3097, 1742, 1635, 1585, 1553, 1521, 1460, 1442, 1410, 1342, 1229, 830, 735, 702, 621 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 0.04–0.22 (m, 4H), 1.10–1.17 (m, 1H), 3.49 (dd, *J* = 2.0, 11.6 Hz, 1H), 3.82 (dd, *J* = 8.8, 11.6 Hz, 1H), 5.74 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.46–7.58 (m, 5H) 8.24 (s, 1H), 8.37 (d, *J* = 8.8 Hz, 2H), 8.50 (d, *J* = 8.8 Hz, 2H), 13.57 (s, 1H); ^{13}C{^{1}H}-NMR (100 MHz, $(CD_3)_2SO$): δ 10.3, 10.4, 15.6, 31.0, 63.3, 106.7, 123.9, 126.5, 127.7, 127.9, 129.2, 133.1, 140.6, 140.8, 143.6, 146.6, 147.1, 147.7, 149.9, 158.1, 169.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{20}N_3O_5S^+$ 486.1118; Found 486.1114.

(R)-10-Cyclopropyl-5-oxo-9-phenyl-7-(p-tolyl)-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (11c): The compound was prepared according to general procedure A. 25 mg of **6c** was converted to 14.3 mg (59%) of **11c**, isolated as a bright yellow powder. $[\alpha]_D^{25}$ –44 (*c* 0.25, DMSO). IR (KBr): ν 1626, 1589, 1556, 1509, 1490, 1460, 1442, 1380, 1278, 823, 735, 701 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 0.02–0.22 (m, 4H), 1.08–1.16 (m, 1H), 2.38 (s, 3H), 3.56 (dd, *J* = 1.9, 11.9 Hz, 1H), 3.86 (dd, *J* = 8.8, 11.8 Hz, 1H), 5.63 (dd, *J* = 1.8, 8.7 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.40–7.60 (m, 5H), 8.02 (s, 1H), 8.16 (d, *J* = 8.3 Hz, 2H). 13.55 (bs, 1H). ^{13}C{^{1}H}-NMR (151 MHz, $(CD_3)_2SO$): δ 10.3, 10.5, 15.7, 20.9, 31.0, 63.2, 106.8, 125.4, 126.8, 127.7, 127.8, 129.2,

129.3, 129.4, 132.1, 134.9, 139.1, 140.5, 141.2, 144.9, 146.9, 152.6, 158.4, 169.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{27}H_{23}N_2O_3S^+$ 455.1423; Found 455.1424.

(R)-7-Cyclohexyl-10-cyclopropyl-5-oxo-9-phenyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (11d): The compound was prepared and purified according to general procedure C. 60 mg of **6d** was converted to 23 mg (39%) of **11d**, isolated as a dark yellow solid. $[\alpha]_D^{25}$ −67 (*c* 0.90, DMSO). IR ($CHCl_3$): ν 2928, 2853, 1740, 1662, 1590, 1557, 1513, 1463, 1443, 1388, 1265, 737, 703 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3OD): δ 0.11–0.22 (m, 4H), 1.13–1.22 (m, 1H), 1.28–1.41 (m, 1H), 1.41–1.55 (m, 2H), 1.57–1.72 (m, 2H), 1.72–1.81 (m, 1H), 1.83–1.92 (m, 2H), 1.93–2.02 (m, 2H), 2.88–2.98 (m, 1H), 3.60 (d, *J* = 11.3 Hz, 1H), 3.81 (dd, *J* = 8.5, 11.3 Hz, 1H), 5.70 (d, *J* = 7.9 Hz, 1H), 7.37–7.52 (m, 5H); $^{13}C\{^1H\}$-NMR (100 MHz, CD_3OD): δ 10.4, 10.5, 15.7, 25.5, 26.0, 31.5, 32.1, 32.2, 45.4, 64.2, 106.1, 126.8, 127.5, 127.6, 127.7, 129.0, 129.1, 131.4, 140.2, 141.4, 144.6, 146.1, 158.4, 162.5, 169.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{27}N_2O_3S^+$ 447.1737; Found 447.1737.

(R)-7,9,10-Tricyclopropyl-5-oxo-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (11e): The compound was prepared according to general procedure A. 45 mg of **6e** was converted to 16 mg (37%) of **11e**, isolated as a yellow powder. $[\alpha]_D^{25}$ −113 (*c* 0.19, $CHCl_3$). IR (KBr): ν 3413, 1735, 1655, 1593, 1530, 1472, 1386, 1222, 1031, 959, 886, 809, 732 cm^{-1}; ^{1}H-NMR (600 MHz, $(CD_3)_2SO$): δ 0.45–0.50 (m, 1H), 0.54–0.59 (m, 1H), 0.81–0.90 (m, 2H), 0.95 (d, *J* = 6.0 Hz, 4H), 0.97–1.60 (m, 2H), 1.10 (dd, *J* = 2.2, 8.4 Hz, 2H), 2.11–2.17 (m, 2H), 2.88–2.93 (m, 1H), 3.50 (dd, J = 2.4, 11.7 Hz, 1H), 3.79 (dd, *J* = 8.7, 11.6 Hz, 1H), 5.49 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.11 (s, 1H), 13.44 (bs, 1H); $^{13}C\{^1H\}$-NMR (151 MHz, $(CD_3)_2SO$): δ 9.9, 10.0, 10.6, 10.7, 10.9, 11.0, 14.6, 15.0, 16.6, 30.8, 63.0, 107.6, 121.6, 133.4, 139.6, 142.4, 148.9, 158.3, 159.7, 169.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{20}N_2NaO_3S^+$ 391.1087; Found 391.1088.

(R)-9-Cyclopropyl-7-(4-nitrophenyl)-5-oxo-10-phenyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (11f): Prepared by following the general procedure B**,** 48 mg of **6f** was converted to 23 mg (42%) of **11f**, isolated as a yellow solid. $[\alpha]_D^{25}$ −97 (*c* 0.22, DMSO); IR (KBr): ν 3429, 2863, 1752, 1616, 1579, 1554, 1521, 1493, 1466, 1411, 1344, 1218, 854, 732, 701, cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 0.35–0.40 (m, 2H), 0.80–0.84 (m, 2H), 1.33-1.40 (m, 1H), 3.49 (dd, *J* = 1.6, 11.6 Hz, 1H), 3.82 (dd, *J* = 8.8, 11.6 Hz, 1H), 5.74 (dd, *J* = 1.6, 8.8 Hz, 1H), 7.38–7.54 (m, 5H) 7.46 (s, 1H), 8.37 (dd, *J* = 2.0, 9.7 Hz, 2H), 8.50 (d, *J* = 2.0, 9.7 Hz, 2H); $^{13}C\{^1H\}$-NMR (100 MHz, $(CD_3)_2SO$): δ 10.1, 10.6, 16.9, 30.8, 63.7, 108.7, 121.5, 123.8, 127.9, 128.4, 130.3, 130.5, 133.3, 139.5, 139.9, 143.8, 144.6, 147.7, 149.4, 150.8, 158.2, 169.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{20}N_3O_5S^+$ 486.1118; Found 486.1114.

(R)-10-Cyclopropyl-5-oxo-9-phenyl-7-(4-(trifluoromethyl)phenyl)-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (11g): The compound was prepared and purified according to general procedure C. 60 mg of **6g** was converted to 26 mg (44%) of **11g**, isolated as a dark yellow solid. $[\alpha]_D^{25}$ −43 (*c* 0.24, DMSO). IR ($CHCl_3$): ν 1741, 1637, 1587, 1556, 1464, 1325, 1170, 1123, 1068, 737 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 0.05–0.25 (m, 4H), 1.06–1.22 (m, 1H), 3.57 (d, *J* = 11.3, 1H), 3.88 (dd, *J* = 8.9, 11.1 Hz, 1H), 5.64 (d, *J* = 7.6 Hz, 1H), 7.40–7.64 (m, 5H), 7.86 (d, *J* = 7.8 Hz, 2H), 8.14 (s, 1H), 8.48 (d, *J* = 7.8 Hz, 2H), 13.26 (bs, 1H); $^{13}C\{^1H\}$-NMR: (100 MHz, $(CD_3)_2SO$): δ 10.3, 10.5, 15.7, 31.0, 63.2, 106.8, 125.66, 125.68, 126.2, 127.5, 127.7, 127.9, 129.3, 132.9, 140.6, 140.9, 141.4, 146.0, 147.2, 150.8, 158.2, 169.6; $^{19}F\{^1H\}$-NMR (376 MHz, $(CD_3)_2SO$): δ −61.0; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{27}H_{20}F_3N_2O_3S^+$ 509.1141; Found 509.1140.

(R)-7-(4-Cyanophenyl)-10-cyclopropyl-5-oxo-9-phenyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (11h): The compound was prepared and purified according to general procedure C but extracted with $CHCl_3$/IPA 10:1. 50 mg of **6h** was converted to 29 mg (60%) of **11h**, isolated as a dark yellow solid. $[\alpha]_D^{25}$ −106 (*c* 0.67, DMSO). IR ($CHCl_3$): ν 3467, 3058, 3003, 2227, 1736, 1658, 1588, 1553, 1490, 1461, 1382, 1266, 848, 734, 702 cm^{-1}; ^{1}H-NMR (400 MHz, CH_3OD (+ $CDCl_3$)): δ 0.17–0.25 (m, 4H), 1.16–1.24 (m, 1H), 3.63 (dd, *J* = 1.6, 11.6 Hz, 1H), 3.81 (dd, *J* = 8.5, 11.6 Hz, 1H), 5.73 (dd, *J* = 1.4, 8.2 Hz, 1H), 7.38–7.56 (m, 5H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.98 (s, 1H), 8.38 (d, *J* = 8.3 Hz, 2H); ^{13}C{^{1}H}-NMR (151 MHz, CH_3OD (+ $CDCl_3$)): δ 11.1, 11.2, 16.4, 32.3, 109.8, 112.8, 119.2, 127.5, 128.4, 128.50, 128.52, 128.7, 129.7, 133.1, 134.2, 141.4, 141.7, 143.1, 146.8, 148.8, 152.5, 161.0; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{27}H_{20}N_3O_3S^+$ 466.1219; Found 466.1214.

(R)-10-Cyclopropyl-7-(4-fluorophenyl)-5-oxo-9-phenyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (11i): The compound was prepared and purified according to general procedure C but extracted with $CHCl_3$/IPA 10:1. 44 mg of **6i** was converted to 22 mg (52%) of **11i**, isolated as a dark yellow solid. $[\alpha]_D^{25}$ −104 (*c* 0.53, DMSO). IR ($CHCl_3$): ν 1737, 1635, 1589, 1559, 1518, 1464, 1442, 1413, 1229, 1163, 739 cm^{-1}; ^{1}H-NMR (400 MHz, CH_3OD + $CDCl_3$): δ 0.10–0.24 (m, 4H), 1.12–1.20 (m, 1H), 3.57 (dd, *J* = 1.6, 11.7 Hz, 1H), 3.73 (dd, *J* = 8.3, 11.5 Hz, 1H), 5.72 (dd, *J* = 1.9, 8.2 Hz, 1H), 7.13 (apparent triplet, *J* = 8.7, 2H), 7.32–7.49 (m, 5H), 7.82 (s, 1H), 8.18 (dd, *J* = 5.4, 8.7 Hz, 2H); ^{13}C{^{1}H}-NMR (100 MHz, CD_3OD): δ 11.5 (2C), 17.0, 33.6, 67.6, 110.0, 116.5 (d, *J* = 22 Hz), 127.3, 128.95, 129.01, 130.4, 130.6 (d, *J* = 8 Hz), 134.0, 136.1 (d, *J* = 2 Hz), 142.0, 143.1, 147.3, 149.2, 154.3, 161.8, 165.1 (d, *J* = 248 Hz) 174.3; ^{19}F{^{1}H}-NMR (376 MHz, $(CD_3)_2SO$): δ −112.5; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{26}H_{19}FN_2NaO_3S^+$ 481.0992; Found 481.0991.

(R)-10-Cyclopropyl-7-(naphthalen-1-yl)-5-oxo-9-phenyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (11j): Prepared by following the general procedure B**,** 33 mg of **6j** was converted to 18 mg (56%) of **11j**, isolated as a yellow solid. $[\alpha]_D^{25}$ −24 (*c* 0.13, DMSO); IR (KBr): ν 3055, 3003, 1740, 1663, 1587, 1558, 1510, 1470, 1440, 1398, 1294, 1238, 864, 779, 702, 616 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 0.02–0.28 (m, 4H), 1.12–1.21 (m, 1H), 3.58 (dd, *J* = 1.6, 11.6 Hz, 1H), 3.87 (dd, *J* = 8.4, 11.6 Hz, 1H), 5.64 (dd, *J* = 1.6, 8.8 Hz, 1H), 7.43–7.46 (m, 3H), 7.52–7.59 (m, 4H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.76–7.80 (m, 2H), 8.04 (t, *J* = 7.6 Hz, 2H), 8.30 (dd, *J* = 0.8, 8.8 Hz, 1H); ^{13}C{^{1}H}-NMR (100 MHz, $(CD_3)_2SO$): δ 10.3, 10.5, 15.7, 31.0, 63.3, 106.6, 125.4, 125.5, 126.0, 126.7, 127.8, 128.0, 128.3, 129.1, 130.1, 130.5, 132.0, 133.4, 136.7, 140.4, 140.9, 145.5, 146.5, 154.9, 158.3, 169.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{30}H_{23}N_2O_3S^+$ 491.1424; Found 491.1423.

(R)-10-Methoxy-7-(4-nitrophenyl)-5-oxo-9-phenyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (11k): Prepared by following the general procedure C**,** 70 mg of **6k** was converted to 52 mg (76%) of **11k**, isolated as a light yellow solid. $[\alpha]_D^{25}$ −4 (*c* 0.2, DMSO); IR (KBr): ν 2932, 2589, 1742, 1639, 1591, 1560, 1522, 1491, 1467, 1443, 1410, 1343, 1228, 886, 754, 735, 698 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 2.98 (s, 3H), 3.66 (d, *J* = 11.6 Hz, 1H), 3.93 (dd, *J* = 8.4, 11.6 Hz, 1H), 5.70 (d, *J* = 7.2 Hz, 1H), 7.46–7.55 (m, 5H), 8.23 (s, 1H), 8.37 (d, *J* = 8.8 Hz, 2H), 8.37 (d, *J* = 8.8 Hz, 2H); ^{13}C{^{1}H}-NMR (100 MHz, $(CD_3)_2SO$): δ 31.4, 59.3, 63.2, 123.9, 126.5, 127.1, 127.8, 128.0, 128.1, 129.2, 130.3, 136.6, 138.8, 140.3, 143.4, 145.3, 147.8, 150.5, 157.3, 169.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{18}N_3O_6S^+$ 476.0911; Found 476.0910.

(R)-10-Methoxy-5-oxo-7,9-diphenyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (11l): Prepared by following the general procedure B**,** 73 mg of **6l** was converted to 36 mg (51%) of **11l**, isolated as a light yellow solid. $[\alpha]_D^{25}$ −20 (*c* 0.25, DMSO); IR (KBr): ν 3055, 2929,

2591, 1740, 1649, 1592, 1514, 1491, 1467, 1444, 1383, 1362, 1280, 1228, 887, 752, 735, 699 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 2.84 (s, 3H), 3.64 (dd, *J* = 1.6, 12.0 Hz, 1H), 3.91 (dd, *J* = 8.4, 11.6 Hz, 1H), 5.67 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.42–7.54 (m, 8H), 8.02 (s, 1H), 8.25 (dd, *J* = 1.2, 8.0 Hz, 2H); $^{13}C\{^1H\}$-NMR (100 MHz, $(CD_3)_2SO$): δ 31.4, 59.2, 63.2, 125.6, 126.9, 127.1, 127.3, 127.7, 128.8, 129.1, 129.5, 130.4, 135.1, 137.5, 139.1, 140.3, 145.0, 153.1, 157.5, 169.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{19}N_2O_4S^+$ 431.1060; Found 431.1058.

(R)-10-Methoxy-5-oxo-9-phenyl-7-(4-(trifluoromethyl)phenyl)-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (11m): Prepared by following the general procedure B**,** purified by recrystallization from methanol (2 ml). 60 mg of **6m** was converted to 38 mg (65%) of **11m**, isolated as a light yellow solid. $[\alpha]_D^{25}$ −4 (*c* 0.19, DMSO); IR: ν 3434, 1741, 1651, 1595, 1491, 1468, 1412, 1324, 1230, 168, 1126, 1066, 886, 746, 701, 620 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 2.86 (s, 3H), 3.66 (d, *J* = 11.6 Hz, 1H), 3.93 (dd, *J* = 8.4, 11.6 Hz, 1H), 5.69 (d, *J* = 8.4 Hz, 1H), 7.47–7.53 (m, 5H), 7.89 (d, *J* = 8.0 Hz, 2H), 8.17 (s, 1H), 8.50 (d, *J* = 8.0 Hz, 2H), 13.67 (bs, 1H); $^{13}C\{^1H\}$-NMR (100 MHz, $(CD_3)_2SO$): δ 31.9, 59.7, 63.6, 126.2, 126.7, 127.6, 128.1, 128.3, 128.4, 129.7, 130.1, 130.8, 136.5, 139.4, 140.8, 141.8, 145.7, 151.9, 157.8, 169.9; ^{19}F-NMR (376 MHz, $(CD_3)_2SO$): δ −61.0; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{18}F_3N_2O_4S^+$ 499.0934; Found 499.0938.

(R)-10-Methoxy-5-oxo-9-phenyl-7-(thiophen-2-yl)-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (11n): Prepared by following the general procedure B**,** 73 mg of **6n** was converted to 34 mg (48%) of **11n**, isolated as light yellow solid. $[\alpha]_D^{25}$ −25 (*c* 0.27, DMSO); IR (KBr): ν 3435, 3101, 1743, 1640, 1592, 1506, 1468, 1327, 1223, 846, 738, 699, 616 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 2.84 (s, 3H), 3.63 (dd, *J* = 2.0, 12.0 Hz, 1H), 3.92 (dd, *J* = 8.8, 11.6 Hz, 1H), 5.64 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.18 (dd, *J* = 4.0, 7.8 Hz, 1H) 7.43–7.50 (m, 5H), 7.71 (dd, *J* = 1.2, 7.8 Hz, 1H), 8.00 (dd, *J* = 1.2, 4.0 Hz, 1H), 8.02 (s, 1H); $^{13}C\{^1H\}$-NMR (100 MHz, $(CD_3)_2SO$): δ 31.3, 59.2, 63.1, 124.4, 126.8, 127.1, 127.2, 127.7, 128.5, 129.0, 129.5, 130.5, 134.8, 138.9, 139.9, 143.6, 144.9, 149.4, 157.1, 169.4; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{17}N_2O_4S_2^+$437.0624; Found 437.0634.

(R)-7-(4-Nitrophenyl)-5-oxo-9-phenyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid 11o): Prepared by following the general procedure B**,** 27 mg of **6o** was converted to 11 mg (42%) of **11o**, isolated as a yellow solid. $[\alpha]_D^{25}$ −3 (*c* 0.4, DMSO). IR (KBr): ν 3471, 3414, 2950, 1740, 1642, 1594, 1567, 1519, 1464, 1442, 1406, 1342, 1218, 862, 728, 702, 621 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 3.65 (d, *J* = 11.6 Hz, 1H), 3.93 (dd, *J* = 8.4, 11.6 Hz, 1H), 5.62 (d, *J* = 8.4 Hz, 1H), 6.41 (s, 1H), 7.54-7.62 (m, 5H), 8.30 (s, 1H), 8.37 (d, *J* = 8.8 Hz, 2H), 8.56 (d, *J* = 9.2 Hz, 2H); $^{13}C\{^1H\}$-NMR (100 MHz, $(CD_3)_2SO$): δ 31.0, 62.9, 93.4, 123.9, 124.4, 127.9, 128.8, 129.2, 131.8, 136.6, 139.4, 143.8, 144.1, 146.4, 147.7, 150.8, 158.6,169.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{16}N_3O_5S^+$ 446.0805; Found 446.0805.

(R)-10-Cyclopropyl-7-(4-nitrophenyl)-5-oxo-9-(3-(trifluoromethyl)phenyl)-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (11p): The compound was prepared and purified according to general procedure C but extracted with $CHCl_3$/IPA 10:1. 36 mg of **6p** was converted to 15 mg (43%) of **11p**, isolated as a dark yellow solid. $[\alpha]_D^{25}$ −83 (*c* 0.32, DMSO); IR ($CHCl_3$): ν 1751, 1618, 1580, 1553, 1520, 1340, 1326, 1122 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$, 343 K): δ −0.02–0.3 (m, 4H), 0.99–1.09 (m, 1H), 3.59 (dd, *J* = 2.0, 11.8 Hz, 1H), 3.90 (dd, *J* = 8.8, 11.7, 1H), 5.66 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.67–7.76 (m, 1H), 7.77–7.89 (m, 2H), 7.90–8.00 (m, 1H), 8.28 (s, 1H), 8.36 (d, *J* = 8.8 Hz, 2H), 8.56 (d, *J* = 8.8 Hz, 2H); $^{13}C\{^1H\}$-NMR (100 MHz, $(CD_3)_2SO$, 343 K): δ 10.2, 10.4, 15.2, 30.8, 63.1, 106.0, 123.5, 123.9 (q, *J* = 273 Hz), 124.8, 125.4, 126.4, 127.7, 128.5, 132.8, 133.1, 140.5,

141.5, 143.3, 145.0, 146.9, 147.7, 149.9, 157.7, 169.0. ^{19}F-NMR (376 MHz, $(CD_3)_2SO$): δ −61; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{27}H_{19}F_3N_3O_5S^+$ 554.0992; Found 554.0979.

(R)-10-Cyclopropyl-5-oxo-7-phenyl-9-(3-(trifluoromethyl)phenyl)-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (11q): The compound was prepared and purified according to general procedure C but extracted with $CHCl_3$/IPA 10:1. 39 mg of **6q** was converted to 22.6 mg (60%) of **11q**, isolated as a dark yellow solid. $[\alpha]_D^{25}$ −119 (*c* 0.31, DMSO); IR ($CHCl_3$): ν 1735, 1660, 1623, 1587, 1443, 1381, 1326, 1167, 1126, 704 cm^{-1}; ^{1}H-NMR (600 MHz, $(CD_3)_2SO$, 333 K: δ −0.04–0.24 (m, 4H), 0.96–1.02 (m, 1H), 3.58 (d, *J* = 10.8 Hz, 1H), 3.70–3.76 (m, 1H), 5.43 (d, *J* = 7.9 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 7.5, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.83 (d, *J* = 7.1 Hz, 1H), 7.90 (s, 1H), 8.06 (s, 1H), 8.26 (d, *J* = 7.5 Hz, 1H); ^{13}C{^{1}H}-NMR (151 MHz, $(CD_3)_2SO$, 333 K): δ 10.4, 10.5, 15.3, 31.8, 64.9, 104.9, 123.9 (d, *J* = 3 Hz), 124.0 (q, *J* = 272 Hz), 125.2, 125.4 (d, *J* = 3 Hz), 126.6, 128.3, 128.4, 128.5, 128.9, 131.8, 133.1 (d, *J* = 1.4 Hz), 137.7, 140.7, 142.1, 144.4, 146.6, 151.9, 157.9, 168.5; ^{19}F-NMR (564 MHz, $(CD_3)_2SO$): δ −61.0; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{27}H_{20}F_3N_2O_3S^+$ 509.1141;Found 509.1148.

(R)-10-Cyclopropyl-7-(4-nitrophenyl)-5-oxo-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (12a): Prepared by following the general procedure B**,** purified by recrystallization from methanol (2 ml), 27 mg of **9a** was converted to 17 mg (65%) of **12a**, isolated as yellow solid. $[\alpha]_D^{25}$ −64 (*c* 0.16, DMSO); IR (KBr): ν 3417, 2921, 2851, 1740, 1638, 1596, 1573, 1472, 1412, 1384, 1337, 1232, 853, 726, 623 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 0.59–0.64 (m, 2H), 1.08 (m, 2H), 1.82 (m, 1H), 3.61 (d, *J* = 11.6 Hz, 1H), 3.87 (dd, *J* = 9.2, 11.6 Hz, 1H), 5.64 (d, *J* = 8.0 Hz, 1H), 8.38–8.51 (m, 6H), 13.60 (s, 1H); ^{13}C{^{1}H}-NMR (100 MHz, $(CD_3)_2SO$): δ 7.1, 7.3, 9.6, 31.1, 62.7, 106.3, 124.0, 124.2, 127.7, 132.8, 134.6, 139.2, 143.6, 143.8, 147.7, 150.8, 158.3, 169.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{16}N_3O_5S^+$ 410.0805; Found 410.805.

(R)-10-Cyclopropyl-5-oxo-7-(4-(trifluoromethyl)phenyl)-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (12b): Prepared by following the general procedure B **,** 24 mg of **9b** was converted to 13 mg (56%) of **12b**, isolated as a light yellow solid. $[\alpha]_D^{25}$ −38 (*c* 0.06, DMSO); IR (KBr): ν 3435, 1743, 1635, 1574, 1514, 1479, 1385, 1325, 1231, 1170, 1124, 1068, 834, 753 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 0.57–0.67 (m, 2H), 1.07–1.11 (m, 2H), 1.79–1.86 (m, 1H), 3.61 (dd, *J* = 1.2, 11.6 Hz, 1H), 3.87 (dd, *J* = 8.8, 12.0 Hz, 1H), 5.64 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 2H), 8.42 (d, *J* = 8.4 Hz, 3H), 8.49 (d, *J* = 8.4 Hz, 1H); ^{13}C{^{1}H}-NMR (100 MHz, $(CD_3)_2SO$): δ 7.1, 7.3, 9.6, 31.1, 62.6, 106.3, 122.9 (q, *J* = 270 Hz), 123.9, 125.7 (d, *J* = 3.6 Hz), 127.3, 129.1 (d, *J* = 31.1 Hz), 132.7, 134.4, 139.1, 141.6, 143.1, 151.7, 158.4, 169.6; ^{19}F-NMR: (376 MHz, $(CD_3)_2SO$): δ −61.0; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{16}F_3N_2O_3S^+$ 433.0828; Found 433.0840.

(R)-7-(4-Cyanophenyl)-10-cyclopropyl-5-oxo-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (12c): Prepared by following the general procedure C**,** 17 mg of **9c** was converted to 13 mg (81%) of **12c**, isolated as a yellow solid. $[\alpha]_D^{25}$ −168 (*c* 0.17, DMSO); IR (KBr): ν 3431, 2226, 1759, 1654, 1625, 1577, 1524, 1476, 1408, 1300, 1216, 834, 763 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 0.56–0.68 (m, 2H), 1.03–1.11 (m, 2H), 1.79–1.84 (m, 1H), 3.61 (dd, *J* = 1.2, 11.6 Hz, 1H), 3.85 (dd, *J* = 8.8, 12.0 Hz, 1H), 5.62 (dd, *J* = 1.6, 8.8 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 2H), 8.40 (d, *J* = 8.4 Hz, 2H), 8.44 (d, *J* = 8.4 Hz, 1H), 8.49 (d, *J* = 8.8 Hz, 1H); ^{13}C{^{1}H}-NMR (100 MHz, $(CD_3)_2SO$): δ 7.1, 7.3, 9.6, 31.2, 62.7, 106.2, 111.5, 118.7, 124.0, 127.3, 132.7, 132.8, 134.5, 139.1, 142.0, 143.4, 151.2, 158.4, 169.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{16}N_3O_3S^+$ 390.0907; Found 390.0908.

(R)-10-Cyclopropyl-7-(4-fluorophenyl)-5-oxo-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (12d): The compound was prepared and purified according to general procedure C but was extracted with $CHCl_3$/IPA 10:1. 29 mg of **9d** was converted to 9.4 mg (34%) of **12d**, isolated as a dark yellow solid. $[\alpha]_D^{25}$ −58 (*c* 0.34, DMSO); IR (NaCl): ν 1743, 1628, 1590, 1576, 1474, 1221, 1181, 1135 cm^{-1}; ^{1}H-NMR (600 MHz, $(CD_3)_2SO$): δ 0.55–0.61 (m, 1H), 0.62–0.67 (m, 1H), 1.02–1.12 (m, 2H), 1.79–1.85 (m, 1H), 3.59 (dd, J = 1.1, 11.6 Hz, 1H), 3.83 (dd, J = 8.7, 11.7 Hz, 1H), 5.58 (d, J = 8.2 Hz, 1H), 7.38 (apparent triplet, J = 8.8 Hz, 2H), 8.26 (dd, J = 5.6, 8.7 Hz, 2H), 8.32 (d, J = 8.6 Hz, 1H), 8.44 (d, J =8.6 Hz, 1H); $^{13}C\{^1H\}$-NMR (151 MHz, $(CD_3)_2SO$): δ 7.1, 7.3, 9.6, 31.3, 62.9, 106.2, 115.7 (d, J = 22 Hz), 123.3, 128.9 (d, J = 8 Hz), 132.5, 133.7, 134.5, 139.1, 142.5, 152.4, 158.6, 163.0 (d, J = 247 Hz), 169.6; $^{19}F\{^1H\}$-NMR (376 MHz, $(CD_3)_2SO$): δ −112.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{16}FN_2O_3S^+$ 383.0860; Found 383.0868.

(R)-10-Cyclopropyl-7-(naphthalen-1-yl)-5-oxo-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (12e): Prepared by following the general procedure B**,** 25 mg of **9e** was converted to 17 mg (70%) of **12e**, isolated as a light yellow solid. $[\alpha]_D^{25}$ −47 (*c* 0.13, DMSO); IR (KBr): ν 3414, 1737, 1617, 1580, 1516, 1481, 1398, 1384, 1244, 803, 778, 620 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 0.26–0.72 (m, 2H), 1.07–1.18 (m. 2H), 1.83–1.90 (m, 1H), 3.61 (dd, *J* = 1.2, 11.6 Hz, 1H), 3.84 (dd, *J* = 8.4, 11.6 Hz, 1H), 5.60 (d, *J* = 7.6 Hz, 1H), 7.51–7.60 (m, 2H), 7.64–7.71 (m, 2H), 8.02–8.07 (m, 3H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.54 (d, *J* = 8.8 Hz, 1H); $^{13}C\{^1H\}$-NMR (100 MHz, $(CD_3)_2SO$): δ 7.1, 7.2, 9.6, 31.2, 62.7, 106.3, 125.4, 126.0, 126.6, 127.7, 128.1, 128.3, 129.0, 130.5, 132.1, 133.4, 133.6, 137.3, 139.0, 142.5, 155.9, 158.6, 169.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{19}N_2O_3S^+$ 415.1111; Found 415.1114.

(R)-7-Cyclohexyl-10-cyclopropyl-5-oxo-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (12f): Prepared by following the general procedure B**,** 36 mg of **9f** was converted to 20 mg (58%) of **12f**, isolated as a light yellow solid. $[\alpha]_D^{25}$ −77 (*c* 0.17, DMSO); IR (KBr): ν 3434, 2927, 2850, 1738, 1665, 1601, 1583, 1524, 1482, 1448, 1390, 1326, 1223, 852, 623 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 0.55–0.58 (m, 2H), 1.02 (m, 2H), 1.25–1.44 (m, 3H), 1.54–1.57 (m, 2H), 1.71–1.88 (m, 6H), 2.77–2.83 (m, 1H), 3.55 (d, *J* = 11.6 Hz, 1H), 3.81 (dd, *J* = 9.2, 10.8 Hz, 1H), 5.56 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 8.30 (d, *J* = 8.4 Hz, 1H); $^{13}C\{^1H\}$-NMR (100 MHz, $(CD_3)_2SO$): δ 7.0, 7.2, 9.6, 25.5, 25.9, 31.0, 32.1, 32.2, 45.7, 62.5, 106.3, 124.8, 131.8, 133.1, 138.5, 141.0, 158.6, 163.7, 169.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{23}N_2O_3S^+$ 371.1424; Found 371.1427.

(R)-7,10-Dicyclopropyl-5-oxo-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (12g): Prepared by following the general procedure B**,** 30 mg of **9g** was converted to 15 mg (52%) of **12g**, isolated as a light yellow solid. $[\alpha]_D^{25}$ −208 (*c* 0.18, DMSO); IR (KBr): ν 3416, 2924, 2851, 1728, 1673, 1635, 1542, 1526, 1403, 1362, 1315, 1224, 845, 631 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 0.51–0.60 (m, 2H), 0.99–1.03 (m, 6H), 1.72–1.78 (m, 1H), 2.21–2.26 (m, 1H), 3.54 (dd, *J* = 1.2, 12.0 Hz, 1H), 3.80 (dd, *J* = 8.4, 11.6 Hz, 1H), 5.25 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H); $^{13}C\{^1H\}$-NMR (100 MHz, $(CD_3)_2SO$): δ 7.0, 7.2, 9.6, 10.1, 10.2, 17.0, 31.0, 62.6, 106.3, 124.7, 131.3, 132.7, 138.8, 140.5, 158.4, 160.5, 169.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{17}N_2O_3S^+$ 329.0954; Found 329.0953.

(R)-10-Cyclopropyl-5-oxo-7-propyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (12h): Prepared by following the general procedure B**,** 28 mg of **9h** was converted to 12 mg (45%) of **12h**, isolated as a light yellow solid. $[\alpha]_D^{25}$ −27 (*c* 0.21, DMSO); IR (KBr): ν 3432, 3082, 2961, 2930, 1735, 1655, 1600, 1583, 1525, 1485, 1388, 1332, 1286, 1223, 1185, 853, 616 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 0.51–0.63 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H), 0.99–1.08 (m, 2H), 1.68–

1.80 (m, 3H), 2.83 (t, *J* = 7.6 Hz, 2H) 3.56 (dd, *J* = 1.6, 11.6 Hz, 1H), 3.82 (dd, *J* = 8.8, 11.6 Hz, 1H), 5.58 (dd, *J* = 1.6, 8.8 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 8.31 (d, *J* = 8.4 Hz, 1H); $^{13}C\{^{1}H\}$-NMR (100 MHz, $(CD_3)_2SO$): δ 7.0, 7.2, 9.6, 13.6, 22.5, 31.0, 38.8, 62.5, 106.3, 126.4, 131.7, 133.0, 138.6, 141.1, 158.5, 159.8, 169.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{19}N_2O_3S^+$ 331.1111; Found 331.1136.

(R)-7-(4-Nitrophenyl)-5-oxo-10-phenyl-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (12i): Prepared by following the general procedure B**,** 30 mg of **9i** was converted to 18 mg (62%) of **12i**, isolated as a yellow solid. $[\alpha]_D^{25}$ −58 (*c* 0.22, DMSO); IR (KBr): ν 1740, 1652, 1577, 1524, 1493, 1470, 1443, 1411, 1372, 1343, 1223, 854, 839, 777 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 3.59 (dd, *J* = 1.4, 12.2 Hz, 1H), 3.89 (dd, *J* = 8.6, 11.6 Hz, 1H), 5.75 (dd, *J* = 1.4, 8.6 Hz, 1H), 7.37–7.43 (m, 2H), 7.45–7.59 (m, 3H), 7.64 (d, *J* = 8.8 Hz, 1H) 8.35–8.47 (m, 5H); $^{13}C\{^{1}H\}$-NMR (100 MHz, $(CD_3)_2SO$): δ 31.3, 63.4, 108.8, 124.1, 124.6, 127.7, 128.5, 129.2, 130.1, 132.7, 133.3, 134.8, 139.0, 142.9, 143.6, 147.8, 151.2, 158.2, 169.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{16}N_3O_5S^+$ 446.0805; Found 446.0808.

(R)-5-Oxo-10-phenyl-7-(4-(trifluoromethyl)phenyl)-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (12j): Prepared by following the general procedure B**,** purified by recrystallization from methanol (2ml), 27 mg of **9j** was converted to 14 mg (53%) of **12j**, isolated as a light yellow solid. $[\alpha]_D^{25}$ −46 (*c* 0.20, DMSO); IR (KBr): ν 3449, 1743, 1658, 1618, 1584, 1493, 1325, 1243, 1167, 1123, 1067, 1014, 860, 703 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 3.57 (d, *J* = 11.6 Hz, 1H), 3.90 (t, *J* = 9.2, 11.2 Hz, 1H), 5.74 (d, *J* = 7.6 Hz, 1H), 7.42–7.68 (m, 6H), 7.89 (d, *J* = 8.4 Hz, 2H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.40 (d, *J* = 7.2 Hz, 2H); $^{13}C\{^{1}H\}$-NMR (100 MHz, $(CD_3)_2SO$): δ 31.2, 63.3, 108.8, 124.3, 125.6, 125.8, 127.4, 128.4, 129.2, 129.5, 130.1, 132.7, 133.1, 134.9, 138.9, 141.5, 142.4, 152.0, 158.3, 169.6; ^{19}F-NMR (376 MHz, $(CD_3)_2SO$): δ −61.0; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{16}F_3N_2O_3S^+$ 469.0828; Found 469.0835.

(R)-7-(4-Nitrophenyl)-5-oxo-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (12k): Prepared by following the general procedure B but was extracted with $CHCl_3$/IPA 10:1. 50 mg of **9k** was converted to 17 mg (58%) of **12k**, isolated as yellow solid. $[\alpha]_D^{25}$ −10 (*c* 0.08, DMSO); IR (KBr): ν 3416, 1747, 1654, 1578, 1510, 1471, 1401, 1375, 1343, 1226, 851, 818, 622 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 3.67 (d, *J* = 11.5 Hz, 1H), 3.97 (dd, *J* = 11.4, 8.9 Hz, 1H), 5.63 (d, *J* = 8.1 Hz, 1H), 6.72 (s, 1H), 8.12 (d, 1H), 8.43 (m, 5H); $^{13}C\{^{1}H\}$-NMR (400 MHz, $(CD_3)_2SO$): δ 31.9, 62.6, 96.4, 124.1 (2C), 124.7, 127.8 (2C), 134.0, 134.9, 138.6, 143.5, 143.9, 147.8, 151.3, 158.8, 169.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{12}N_3O_5S^+$ 370.0498; Found 379.0504.

(R)-10-(3-hydroxyphenyl)-7-(4-nitrophenyl)-5-oxo-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (12l): The compound was prepared according to general procedure B but extracted with $CHCl_3$/IPA 7:3. Purified by recrystallization from methanol. 31.2 mg of **9l** was converted to 18.3 mg (60%) of **12l**, isolated as an orange solid. $[\alpha]_D^{25}$ −3 (*c* 0.29, DMSO); IR: ν 3019, 1728, 1648, 1571, 1512, 1466, 1442, 1411, 1335, 1213, 914, 752, 709 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$, 343 K): *δ* 3.57 (dd, *J* = 11.5, 1.6 Hz, 1H), 3.84 (dd, *J* = 11.6, 8.5 Hz, 1H), 5.66 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.78 (m, 2H), 6.8 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.34 (t, *J* = 8.7 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 8.29 (d, *J* = 8.7 Hz, 1H), 8.36 (m, 2H), 8.45 (m, 2H); $^{13}C\{^{1}H\}$-NMR (100 MHz, $(CD_3)_2SO$, 343 K): *δ* 31.3, 63.9, 108.4, 115.2, 116.7, 120.3, 123.7 (2C), 124.0, 127.5 (2C), 129.9, 132.4, 133.1, 135.9, 138.9, 142.8, 143.7, 147.7, 150.8, 157.7, 157.9, 168.9; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{16}N_3O_6S^+$ 462.0760; Found 462.0764.

(R)-7-(4-nitrophenyl)-5-oxo-10-(m-tolyl)-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-

carboxylic acid (12m): The compound was prepared according to general procedure B but extracted with $CHCl_3$/IPA 7:3. Purified by recrystallization from methanol. 42.5 mg of **9m** was converted to 21.2 mg (52%) of **12m**, isolated as an orange solid. $[\alpha]_D^{25}$ –47 (*c* 0.04, DMSO); IR: ν 1747, 1634, 1578, 1510, 1471, 1401, 1343, 1226, 851, 725 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): *δ* 2.41 (s, 3H), 3.58 (dd, *J* = 11.8, 1.3, 1H), 3.89 (dd, *J* = 11.8, 8.6 Hz, 1H), 5.75 (dd, *J* = 8.7, 1.3 Hz, 1H), 7.31 (m, 4H), 7.68 (d, *J* = 8.7 Hz, 1H), 8.34 (d, *J* = 8.7 Hz, 1H), 8.39 (d, *J* = 9.0 Hz, 2H), *δ* 8.44 (d, *J* = 9.0 Hz, 2H); ^{13}C{^{1}H}-NMR (100 MHz, $(CD_3)_2SO$): *δ* 20.9, 31.2, 63.4, 108.8, 124.1 (2C), 124.6, 127.8 (2C), 129.8 (2C), 130.0 (2C), 131.9, 132.8, 133.5, 137.9, 139.1, 142.9, 143.7, 147.8, 151.2, 158.2, 169.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{18}N_3O_5S^+$ 460.0967; Found 460.0962.

(R)-10-(3-acetylphenyl)-7-(4-nitrophenyl)-5-oxo-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (12n): The compound was prepared according to general procedure B but extracted with $CHCl_3$/IPA 7:3. Purified by recrystallization from methanol. 41.6 mg of **9n** was converted to 18.1 mg (45%) of **12n**, isolated as an orange solid. $[\alpha]_D^{25}$ –6 (*c* 0.3, DMSO); IR: ν 1760, 1679, 1599, 1572, 1525, 1470, 1412, 1343 1259, 839, 754 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$, 343 K): *δ* 2.63 (s, 3H), 3.60 (dd, *J* = 11.6, 1.5 Hz, 1H), 3.89 (dd, *J* = 11.7, 8.5 Hz, 1H), 5.73(dd, *J* = 8.5, 1.4 Hz, 1H), 7.71 (m, 3H), 7.96 (broad s, 1H), 8.07 (m, 1H), 8.29 (d, *J* = 8.8 Hz, 1H), 8.36 (d, *J* = 8.9 Hz, 2H), 8.45 (d, *J* = 8.9 Hz, 2H); ^{13}C{^{1}H}-NMR (100 MHz, $(CD_3)_2SO$, 343 K): *δ* 26.4, 31.3, 63.6, 107.6, 123.7 (2C), 124.3, 127.6 (2C), 127.9, 129.4, 129.5, 132.2, 132.9, 134.6, 135.3, 137.6, 138.9, 143.3, 143.5, 147.7, 151.1, 157.9, 168.9, 197.2; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{18}N_3O_6S^+$ 488.0916; Found 488.0911.

(R)-7-(4-nitrophenyl)-5-oxo-10-(thiophen-3-yl)-3,5-dihydro-2H-thiazolo[2,3-g][1,7]naphthyridine-3-carboxylic acid (12o): The compound was prepared according to general procedure B but extracted with $CHCl_3$/IPA 7:3. Purified by recrystallization from methanol. 60.6 mg of **9o** was converted to 56.2 mg (96%) of **12o**, isolated as an orange solid. $[\alpha]_D^{25}$ –75 (*c* 0.08, DMSO); IR: ν 1741, 1636, 1576, 1470, 1339, 851, 725 cm^{-1}; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): *δ* 3.59 (dd, *J* = 11.6, 1.2 Hz, 1H), 3.89 (dd, *J* = 11.7, 8.7 Hz, 1H), 5.74 (dd, *J* = 8.9, 1.3 Hz, 1H), 7.22 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.69 (dd, *J* = 2.8, 1.2 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.80 (dd, *J* = 5.0, 2.8 Hz, 1H), 8.39 (d, *J* = 8.8 Hz, 1H), 8.42 (m, 4H); ^{13}C{^{1}H}-NMR (100 MHz, $(CD_3)_2SO$): *δ* 31.2, 63,5, 104.1, 124.1 (2C), 124.7, 126.2, 127.4, 127.8 (2C), 128.8, 132.9, 133.5, 134.5, 138.9, 143.4, 143.6, 147.8, 151.2, 158.1, 169.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{14}N_3O_5S_2^+$ 452.0369; Found 452.0377.

Methyl (R)-8-cyclopropyl-6-iodo-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylate (13): 2-pyridone **3a** (4.8 g, 19 mmol, 1.0 eq.) was dissovled in acetonitrile (190 ml) in a round bottomed flask. N-iodosuccinimide (5.2 g, 23 mmol, 1.2 eq.) was added while stirring. Water (41 µl, 2.3 mmol, 0.12 eq.) was added, the flask was covered with a septum and the reaction mixture was stirred at r.t. The reaction was followed with TLC (80% ethyl acetate in heptane) and found complete after stirring over night. Upon completion, saturated aqueous sodium thiosulfate solution (80 ml) was added and the resulting mixture was stirred for 5 min. The mixture was subsequently partitioned between ethyl acetate (350 ml) and brine (200 ml). The organic phase was dried over anhydrous sodium sulfate, filtered and evaporated. The product was purified with automated flash column chromatography (100 g cartridge; 15–35% ethyl acetate in heptane) to provide 4.2 g (58%) of the title compound **13** as a light yellow solid. $[\alpha]_D^{25}$ –234 (*c* 0.665, $CHCl_3$). IR (KBr cm^{-1}): ν 3012, 2953, 1738, 1715, 1649, 1578, 1482, 1436, 1370, 1353, 1330, 1265, 1244, 1218, 1180, 1149, 1017. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.61–0.54 (m, 2H), 0.89–0.82 (m, 2H), 1.59–1.53 (m, 1H), 3.52 (dd, *J* = 2.4, 11.6 Hz, 1H), 3.73 (dd, *J* = 8.6, 11.6 Hz, 1H), 3.80 (s, 3H), 5.61 (dd, 2.4, 8.8 Hz, 1H), 7.66 (s, 1H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 6.2, 6.5, 12.3, 32.1, 53.5, 64.7, 84.4, 116.2, 148.3, 149.7, 158.7, 168.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{13}INO_3S^+$ 377.9655; Found 377.9661.

(R)-methyl 8-cyclopropyl-6-(4-nitrophenyl)-5-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyridine-3-carboxylate (14): 6-iodo-2-pyridone **13** (0.86 mmol, 1.0 eq.) and boronic acid (1.3 mmol, 1.2 eq.) was dissolved in methanol (5 ml) in a Biotage microwave reaction tube. The tube was selaed with a septum. While stirring, the solution was bubbled with a stream of nitrogen for 5 min. Potassium carbonate (215 mg, 1.6 mmol, 1.8 eq.) and palladium(II) acetate (19 mg, 0.8 mmol, 0.1 eq.) was added. The tube was sealed and degassed anew for 1 min., then heated to 110 °C for 10 min. under microwawe irradiation. The vial was opened and found complete by TLC. The reaction mixture was partitioned between DCM (30 ml) and water (15 ml). The aqueous phase was re-extracted with DCM (3 ml). The organic phase was dried over anhydrous sodium sulfate, filtered and evaporated. The crude product was purified with automated flash column chromatography (25 g cartridge; 0–100% ethyl acetate in heptane) 260 mg of **14** (81%) was isolated as a yellow solid. $[\alpha]_D^{25}$ −57 (*c* 0.5, $CHCl_3$). IR (KBr cm^{-1}): ν 2999, 1750, 1636, 1590, 1508, 1434, 1390, 1276, 1218, 1172, 1146. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.68–0.60 (m, 2H), 0.95–0.86 (m, 2H), 1.69–1.62 (m, 1H), 3.59 (dd, *J* = 2.5, 11.7 Hz, 1H), 3.79 (dd, *J* = 8.8, 11.7 Hz, 1H), 3.82 (s, 3H), 5.68 (dd, *J* = 2.5, 8.7 Hz, 1H), 7.39 (s, 1H), 7.87 (d, *J* = 8.9 Hz, 2H), 8.19 (d, *J* = 8.9 Hz, 2H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 6.2, 6.4, 12.5, 31.8, 53.5, 63.9, 114.8, 123.3, 123.4, 128.9, 140.6, 143.1, 146.6, 148.9, 159.7, 168.4. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{17}N_2O_5S^+$ 373.0853; Found 373.0865.

(R)-8-cyclopropyl-6-(4-nitrophenyl)-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (15): The methyl ester **14** (18 mg, 48 μmol, 1.0 eq.) was dissolved in THF (2.5 ml). LiOH (0.1 M aq.; 0.68 ml, 68 μmol, 1.4 eq.) was added dropwise while stirring. The reaction was found complete by TLC after 50 min. HCl (1 M aq.; 72 μl, 72 μmol, 1.5 eq.) was added while stirring. The reaction mixture was evaporated until only water remained, diluted with brine (2 ml) and extracted with chloroform/isopropanol 10:1 (2 x 7 ml). The organic phase was dried over anhydrous sodium supfate, filtered and evaporated. The residue was trituated with diethyl ether (1 + 0.2 ml) and dried under vacuum to afford 4.5 mg (26%) of **15** as a yellow solid. $[\alpha]_D^{25}$ −2 [c 0.2, $(CH_3)_2SO$]. IR (KBr cm^{-1}): ν 3419, 1740, 1617, 1592, 1565, 1507, 1401, 1385, 1341, 1266, 1250. ^{1}H-NMR [600 MHz, $(CD_3)_2SO$]: δ 0.81–0.64 (m, 2H), 0.85 (dh, *J* = 9.1, 2.4 Hz, 2H), 1.60 (tt, *J* = 8.4, 5.1 Hz, 1H), 3.66 (dd, *J* = 11.9, 1.9 Hz, 1H), 3.96 (dd, *J* = 11.9, 9.2 Hz, 1H), 5.59 (dd, *J* = 9.2, 1.8 Hz, 1H), 7.52 (s, 1H), 8.14–8.01 (m, 2H), 8.27–8.17 (m, 2H), 13.55 (s, 1H). ^{13}C{^{1}H}-NMR [151 MHz, $(CD_3)_2SO$]: δ 6.1, 6.3, 12.3, 31.6, 63.7, 113.5, 121.3, 123.1, 128.8, 139.4, 143.3, 145.7, 149.6, 158.7, 169.4; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{15}N_2O_5S^+$ 359.0696; Found 359.0701.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. ^{1}H-NMR, ^{13}CNMR, 19F-NMR for all new compounds and fibrils binding assay for carboxylic acids (PDF)

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