Tandem Ring Opening/Intramolecular [2 + 2] Cycloaddition Reaction for the Synthesis of Cyclobutane Fused Thiazolino-2-Pyridones

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ABSTRACT: Reaction of thiazoline fused 2-pyridones with alkyl halides in the presence of cesium carbonate opens the thiazoline ring via S-alkylation and generates N-alkenyl functionalized 2-pyridones. In the reaction with propargyl bromide, the thiazoline ring opens and subsequently closes via a [2 + 2] cycloaddition between an in situ generated allene and the α,β-unsaturated methyl ester. This method enabled the synthesis of a variety of cyclobutane fused thiazolino-2-pyridones, of which a few analogues inhibit amyloid β1−40 fibril formation. Furthermore, other analogues were able to bind mature α-synuclein and amyloid β1−40 fibrils. Several thiazoline fused 2-pyridones with biological activity tolerate this transformation, which in addition provides an exocyclic alkene as a potential handle for tuning bioactivity.

INTRODUCTION

The direct modification of an existing bioactive scaffold rather than the positioning of substituents is an important strategy to develop compounds with diverse shapes and properties.1 Cyclobutanes are an important class of rigid motifs present in a variety of natural products and other biologically important molecules.2 A plethora of reactions like [2 + 2] cycloadditions2c−e,3 and rearrangements4 have been developed to construct structurally diverse cyclobutane containing scaffolds. Due to their rigid architecture, annulation of a cyclobutane ring with biologically relevant scaffolds like 2-pyridones,5 quinolones,6 and indoles2c has recently become popular (Figure 1).

Thiazoline fused 2-pyridones have found various applications in developing biologically active compounds against Escherichia coli, Chlamydia trachomatis, Listeria monocytogenes, and Mycobacterium tuberculosis infections.7 We have also demonstrated that rigidification, either by functionalizing the compounds with sterically demanding aryl groups or annulation with heterocycles, has resulted in ring fused 2-pyridones capable of modulating or binding amyloid fibrils.8 In a recent report, we demonstrated that the thiazoline ring can be opened by reaction with an aryne to generate N-alkenyl-2-pyridones (Scheme 1).8e Knowing that ring opening results in the formation of a Michael acceptor, we envisaged that reaction of thiazolino-2-pyridones with alkyl halides would generate N-alkenyl-S-alkyl-2-pyridones, which could be used as synthons to build structurally diverse scaffolds.

We further envisioned that annulation of the thiazolino-2-pyridone scaffold with a cyclobutane ring would help in fine-tuning biological activity and may result in improved amyloid binding/modulating properties of the resulting compounds. Intramolecular [2 + 2] cycloadditions of allenes with alkene constitute a versatile method to synthesize cyclobutane

Figure 1. Selected bioactive compounds containing a fused cyclobutane motif.

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containing rigid bicyclic frameworks. Since allenes can be prepared from S-propargyls, we planned to open the thiazoline ring with propargyl halides. The resulting N-alkenyl-S-propargyl-2-pyridone could then be used as a building block to construct a cyclobutane fused thiazolino-2-pyridone via formation of an allene and a subsequent intramolecular [2 + 2] cycloaddition.

**RESULTS AND DISCUSSION**

To develop the thiazoline ring opening reaction, we commenced our studies by investigating the reaction of 1a with simple alkyl halides such as methyl iodide. A few bases and solvents were screened to open the ring with methyl iodide (Scheme S1, Supporting Information). Under established conditions, ring opened product 2a could be obtained in 88% yield by using Cs₂CO₃ in THF at 60°C for 24 h (Scheme 2). To further extend the scope, different alkyl halides and substituted 2-pyridones 1a–d and 3a were tested under these standardized conditions to give ring opened 2-pyridones 2a–g and 4.

Next, we attempted ring opening of 1a with propargyl bromide (Scheme 3). Pleasingly, cyclobutane fused thiazolino-2-pyridone 5a was formed in 44% yield (as a mixture of enantiomers) together with ring opened product 2h in 20% yield. To our delight, prolonged heating and use of 3 equiv of Cs₂CO₃ gave 5a exclusively, in 69% yield (Scheme 4). Only starting material was recovered when the reaction was performed in the presence of Na₂CO₃ or DIPEA (Scheme S3, Supporting Information). Purified 2h, when treated with Cs₂CO₃ in THF, provided 5a, which confirms the intermediacy of 2h.

To evaluate the effect of substituents on the outcome of the reaction, a series of substituted bicyclic thiazolino-2-pyridones was prepared and investigated for their reaction with propargyl bromide (Scheme 4). Compound 5a–d was provided in moderate to good yield. Substrates equipped with an aryl/heteroaryl group as R₃ substituents reacted smoothly with propargyl bromide to afford 2-pyridones 5e–h in good yields. In line with our previous study, low to moderate yields were obtained of Si–I, with CH₃-naphthyl groups as R³ substituents.

A single crystal X-ray diffraction analysis of analogue 5e verified the structure elucidated by NMR spectroscopy (Scheme 4). When propargyl bromide was replaced with 3-bromo-1-butynyl or 4-bromo-1-butynyl, no ring opening was triggered. With 1-bromo-2-butynyl, only the ring opened product 2i was provided; no further ring closing was observed (Scheme S4, Supporting Information).

Mechanistically, we propose that nucleophilic attack by the sulfur on propargyl bromide results in the formation of intermediate A (Scheme 6) which upon deprotonation by base gives ring opened product 2h. The intermediate 2h was isolated and characterized by NMR spectroscopy. Since 5-
propargyls are known to form allene under basic conditions, it is likely that base promoted abstraction of methylene protons generates allene B, which undergoes intramolecular [2 + 2] cycloaddition with the alkene to furnish cyclobutane fused thiazolino-2-pyridone 5a.

Knowing that bicyclic and tricyclic thiazolino-2-pyridones have the potential to modulate and bind amyloid fibrils, respectively, cyclobutane fused compounds 5i–k and ring opened 2-pyridones 2c, 2f, and 4 were hydrolyzed to their corresponding acids 6a–c, 9a–b, and 7, respectively (Scheme 7).

Scheme 7. Hydrolysis of Methyl Esters

Tricyclic thiazolino-2-pyridones are of therapeutic and diagnostic interest because they have been shown to bind mature α-synuclein and Aβ fibrils. Reaction of tricyclic compounds with propargyl bromide (Scheme 8), however, resulted in complex mixtures and the desired cyclobutane fused products were isolated as mixtures of propargyl and methyl esters (perhaps by methyl ester hydrolysis followed by re-esterification with propargyl alcohol). Thus, the mixed esters were saponified directly, using lithium hydroxide, to give 10a–e, in 13–26% yield over two steps.

Scheme 8
Compounds 8a−b (Figure 2), 9a−b (Figures S9−S12, Supporting Information), and 10a−e (Figure 3) were evaluated for their ability to modulate/bind to α-synuclein and amyloid β_{1−40} fibrils in vitro. In this assay, the effects on fibril formation are observed as changes of the lag phase duration. Further, the ability to bind α-Syn fibrils and displace fibril bound ThT is indicated by a reduced ThT fluorescence amplitude in comparison to the control experiments, where no peptidomimetic compound is included. Interestingly, both 8a and 8b were found to accelerate α-synuclein fibril formation, as indicated by reduction of the lag time (Figure 2A). Compound 8b, like its parent compound C10, showed strong acceleration of fibril formation, and amyloid β_{1−40} fibril formation (Figure 3B), compounds 10a−b turned out, contrary to their parent compounds which are inactive, to be inhibitors.8d

All of the cyclobutane fused thiazolino-2-pyridones were tested as racemates. To investigate the effect of each enantiomer on fibril formation, racemic 6b was separated to its pure enantiomers using chiral HPLC. When evaluated for their effect on fibril formation in vitro, the pure enantiomers were found to modulate α-synuclein and Aβ fibrils equally, to a similar extent as the racemic mixture (Figures S13 and S14, Supporting Information).

CONCLUSION

In conclusion, we have prepared N-alkenyl 2-pyridones via a thiazoline ring opening reaction with alkyl halides. Reaction of thiazolino-2-pyridones with propargyl bromide gave cyclobutane fused thiazolino-2-pyridones via sequential ring opening, in situ allene formation, and intramolecular [2 + 2] cycloaddition. The methodology was also successfully applied to functionalize bioactive tricyclic pyridine fused thiazolino-2-pyridones. The developed methodology transformed inactive compounds to inhibitors of amyloid β_{1−40} fibril formation. Selective modulation of amyloid fibrils by small molecules provides a possible approach in the diagnosis and/or treatment of neurodegenerative diseases,11 justifying the importance of such late-stage transformations on thiazolino-2-pyridone peptidomimetic scaffolds for tuning their biological activity. Further advanced structural modifications on these compounds will become a subject for future investigations in order to find new diagnostic/therapeutic agents for neurodegenerative diseases.

EXPERIMENTAL SECTION

General Information. All reagents were purchased from commercial suppliers and used as received, unless otherwise stated. Molecular sieves were dried at 300 °C under a high vacuum for 4 h prior to use. DMF and THF were dried using an SG Water solvent drying tower, according to the manufacturer’s instructions, and stored over activated 3 Å (DMF) or 4 Å (THF) molecular sieves (5% w/v) for 48 h or more before use. Cs2CO3 was used as purchased from Sigma-Aldrich (i.e., without further drying). Microwave reactions were performed in sealed vessels using a Biotage Initiator microwave synthesizer, temperatures were monitored by an internal IR probe, and stirring was mediated magnetically. TLC was performed on purchased aluminum backed silica gel plates (median pore size 60 Å, fluorescent indicator 254 nm) and detected with UV light at 254 and 366 nm. Flash column chromatography was performed using silica gel (0.063–0.200 mesh). Automated flash column chromatography was performed using a Biotage Isolera One system and purchased prepacked silica gel cartridges (Biotage SNAP cartridge, KP-Sil or Biotage Silica D, Duo 60 μm, cartridge). Preparative HPLC was performed on a Gilson instrument with a Phenomenex column (250 × 21.2 mm²; Gemini 5 μm C18, 110 Å). MeCN/water, with 0.1% HCOOH, was used as mobile phase. A gradient from 30−100% MeCN in water was run over 30 min with a flow rate of 20 mL/min. The elution was monitored with UV-abs. at 254 nm. Freeze-drying was accomplished by freezing the diluted MeCN/water solutions in liquid nitrogen and then employing a Scanvac CoolSafe freeze-dryer connected to an Edwards 28 rotary vane oil pump. IR spectra were measured by thin film (100 μg) on a Bruker Alpha FTIR.

Compounds 10a−e were tested for their effect against α-synuclein and amyloid β_{1−40} fibril formation (Figure 3). 4-
recorded on a Bruker Alpha-3 spectrometer. The samples were prepared as KBr pellets or between NaCl plates; absorbances are given in reciprocal cm. 1H and 13C NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer with a BBO-F/H Smartprobe or a Bruker Avance III HD 600 MHz spectrometer with a CP BBO-H/F, 5 mm cryoprobe, at 298 K, unless another temperature is given. All spectrometers were operated by Topspin 3.5.7. Spectra were then processed by MestReNova v. 10. Resonances are given in ppm relative to TMS and calibrated to 6.77 ppm for 1H, 77.16 ppm for 13C. The following abbreviations are used to indicate splitting patterns: s = singlet; d = doublet; dd = double doublet; t = triplet; br = broad singlet. LC-MS was conducted on a Micromass QqQ mass spectrometer with ESI-TOF (ES +/ES −) and a Bruker Avance III HD 600 MHz spectrometer. HRMS was performed on a mass spectrometer with ESI-TOF (ES +/ES −). The compound was prepared from 1a (148 mg, 0.5 mmol) following the general procedure, using 4.2 eq. of methyl iodide (131 μL, 2.1 mmol). The reaction was complete to TLC analysis after 21 h. The crude product was purified with automated flash column chromatography (10 g Sfar cartridge, 10–50% EtOAc in heptane) to give pure 2b as a yellow solid (75 mg, 0.240 mmol, 48%). IR (KBr): ν 3044, 2999, 2951, 1734, 1663, 1583, 1510, 1482, 1437, 1404, 1358, 1331, 1281, 1204, 1178, 1134 cm −1. 1H NMR (400 MHz, (CD3)2SO, 343 K) δ 7.93 (s, 1H), 7.50 (d, J = 1.2 Hz, 1H), 5.89 (d, J = 1.2 Hz, 1H), 3.84 (s, 3H), 2.44 (s, 3H), 2.30–2.20 (m, 1H), 1.17–1.05 (m, 2H), 0.78–0.70 (m, 2H). 13C{1H} NMR (100 MHz, CDCl3) δ 162.5, 154.0, 152.4, 138.3, 136.9, 135.9, 128.3, 124.0, 53.3, 19.8, 13.0, 8.8, 8.1. HRMS (ESI-TOF) m/z: [M + H]+ calculated for C13H14NO3S+ 266.0845; observed 266.0846.

**Methyl 2-(5-Cyclopropyl-6-(methylthio)-2-oxopyridin-1(2H)-yl)acrylate (2b)**. The compound was prepared from 1b (148 mg, 0.5 mmol) following the general procedure, using 4.2 eq. of methyl iodide (131 μL, 2.1 mmol). The reaction was complete to TLC analysis after 21 h. The crude product was purified with automated flash column chromatography (10 g Sfar cartridge, 10–50% EtOAc in heptane) to give pure 2b as a yellow bright solid (75 mg, 0.240 mmol, 48%). IR (KBr): ν 3044, 2999, 2951, 1734, 1663, 1583, 1510, 1482, 1437, 1404, 1358, 1331, 1281, 1204, 1178, 1134 cm −1. 1H NMR (400 MHz, (CD3)2SO, 343 K) δ 7.93 (s, 1H), 7.50 (d, J = 1.2 Hz, 1H), 5.89 (d, J = 1.2 Hz, 1H), 3.84 (s, 3H), 2.44 (s, 3H), 2.30–2.20 (m, 1H), 1.17–1.05 (m, 2H), 0.78–0.70 (m, 2H). 13C{1H} NMR (100 MHz, CDCl3) δ 162.5, 154.0, 152.4, 138.3, 136.9, 135.9, 128.3, 124.0, 53.3, 19.8, 13.0, 8.8, 8.1. HRMS (ESI-TOF) m/z: [M + H]+ calculated for C13H14NO3S+ 266.0845; observed 266.0846.

**Methyl 2-(5-Cyclopropyl-6-(methylthio)-3-nitro-2-oxopyridin-1(2H)-yl)acrylate (2b)**. The compound was prepared from 1a (126 mg, 0.5 mmol) following the general procedure, using 3.0 equiv of butyl iodide (171 μL, 1.5 mmol). The reaction was complete to TLC analysis after 47 h. The crude product was purified with automated flash column chromatography (10 g Sfar cartridge, 10–70% EtOAc in heptane) to give pure 2e as a yellow solid (93 mg, 0.303 mmol 61%).
IR (KBr): ν 2957, 1736, 1671, 1593, 1498, 1438, 1363, 1327, 1303, 1249, 1200, 1171, 1088 cm⁻¹. 1H NMR (600 MHz, CDCl₃) δ 6.68 (d, J = 9.6 Hz, 1H), 1.76 (s, 1H), 0.62 (d, J = 9.6 Hz, 1H), 3.82 (d, J = 0.7 Hz, 1H), 3.80 (s, 3H), 2.71 (q, J = 7.3 Hz, 2H), 2.35 (t, J = 8.5, 5.2 Hz, 1H), 1.58—1.48 (m, 2H), 1.42—1.34 (m, 2H), 1.01—0.94 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H), 0.68—0.61 (m, 1H). 13C{1H} NMR (151 MHz, CDCl₃) δ 163.4, 162.4, 140.0, 137.1, 136.3, 127.6, 127.2, 122.0, 52.9, 36.3, 31.2, 23.1, 12.7, 7.9, 7.8. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C₁₅H₁₈NO₃S + 292.1002; observed 292.1011.

**2-Methyl-2-(6-(But-2-yn-1-ylthio)-5-cyclopropyl-2-oxopyridin-1(2H)-yl)acrylate (2h).** The compound was prepared from 1a (126 mg, 0.5 mmol) following the general procedure, using propargyl bromide (225 µL, 2.10 mmol, 4.2 equiv). The crude product was purified with automated flash column chromatography (50 g Siar cartridge, 10—80% EtOAc in hexane) to give pure 2h as a light brown syrup (30 mg, 0.10 mmol, 20%) and 5a as a light brown powder (65 mg, 0.22 mmol, 44%). IR (KBr): ν 3437, 3288, 3082, 3002, 2953, 1733, 1666, 1590, 1498, 1438, 1364, 1327, 1303, 1250, 1200, 1171 cm⁻¹. 1H NMR (400 MHz, CDCl₃) δ 6.85 (d, J = 9.7 Hz, 1H), 6.76 (s, 1H), 6.67—6.57 (m, 1H), 5.88 (s, 1H), 3.81 (s, 3H), 3.49 (dd, J = 16.0, 2.6 Hz, 1H), 3.39 (dd, J = 16.0, 2.6 Hz, 1H), 2.45—2.38 (m, 1H), 1.10—0.90 (m, 2H), 0.68—0.65 (m, 2H). 13C{1H} NMR (100 MHz, CDCl₃) δ 163.4, 162.1, 137.2, 136.1, 128.9, 127.7, 123.8, 77.7, 77.4, 71.7, 68.6, 53.3, 53.0, 24.8, 12.9, 8.26, 8.20. HRMS (ESI-TOF) m/z: [M + H]+ calcld for C₁₅H₁₈NO₃S + 290.0845; observed 290.0848.

**Methyl 4-Cyclopropyl-2-methylene-7-oxo-2,2a-dihydro-7H-cyclobuta[4,5]thiazolo[3,2-a]pyridine-8a(1H)-carboxylate (5a).** The compound was prepared following the procedure described above. Brown powder, 100 mg, 66% yield. IR (KBr): ν 3437, 3083, 2349, 1744, 1657, 1585, 1498, 1436, 1303 cm⁻¹. 1H NMR (400 MHz, CDCl₃) δ 7.10 (d, J = 9.2 Hz, 1H), 6.22 (d, J = 9.2 Hz, 1H), 5.31—5.24 (m, 1H), 5.20—5.13 (m, 1H), 4.80 (q, J = 2.5 Hz, 1H), 4.01 (d, J = 17.3, 2.9 Hz, 1H), 3.11 (dd, J = 17.3, 2.5 Hz, 1H), 1.60—1.51 (m, 1H), 0.89—0.87 (m, 2H), 2.62—0.53 (m, 5H). 13C{1H} NMR (100 MHz, CDCl₃) δ 168.12, 161.1, 149.29, 145.15, 141.72, 115.25, 114.69, 113.13, 74.33, 53.41, 51.60, 41.17, 12.49, 6.54, 6.17. HRMS (ESI-TOF) m/z: [M + H]+ calcld for C₁₅H₁₄NO₃S + 293.0945; observed 293.0948.
Methyl 2-Methylene-7-oxo-2,2a-dihydro-7-cyclobuta[4,5]thiazolo[3,2-a]pyridine-8a(1H)-carboxylate (5b). Sb was prepared following the general procedure described above. Brown syrup, 60 mg, 48%. IR (KBr): v 1742, 1639, 1570, 1511, 1302, 1221 cm⁻¹. ¹H NMR [600 MHz, (CD₃)₂SO] δ 7.43 (dd, J = 9.0, 7.2 Hz, 1H), 6.31 (dd, J = 7.2, 1.0 Hz, 1H), 6.13 (dd, J = 9.0, 1.0 Hz, 1H), 5.34–5.25 (m, 2H), 5.19 (t, J = 2.0 Hz, 1H), 3.81–3.77 (m, 1H), 3.69 (s, 3H), 2.94 (dd, J = 17.1, 2.5 Hz, 1H). ¹³C{¹H} NMR [151 MHz, (CD₃)₂SO] δ 167.3, 150.2, 141.8, 141.2, 128.6, 117.6, 117.5, 117.4, 111.9, 109.8, 105.8 cm⁻¹. ¹H NMR [600 MHz, (CD₃)₂SO] δ 7.60 (d, J = 9.7 Hz, 1H), 6.13 (d, J = 9.7 Hz, 1H), 5.39–5.26 (m, 2H), 5.24–5.15 (m, 1H), 3.77 (dt, J = 17.2, 2.8 Hz, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 2.97–2.92 (m, 1H). ¹³C{¹H} NMR [151 MHz, (CD₃)₂SO] δ 167.2, 158.4, 145.2, 137.4, 135.6, 112.9, 73.5, 53.9, 51.3, 51.8. HRMS (ESI-TOF) m/z: [M + H]⁺ calc'd for C₂₃H₂₂NO₃S⁺ 380.1352; observed 380.1354.

Methyl 4-Methoxy-2-methylene-7-oxo-2,2a-dihydro-7-cyclobuta[4,5]thiazolo[3,2-a]pyridine-8a(1H)-carboxylate (5c). Sb was prepared following the general procedure described above. Brown syrup, 80 mg, 57%. IR (KBr): v 3346, 2952, 2837, 1744, 1663, 1579, 1503, 1453, 1435, 1411, 1351, 1303, 1268, 1178, 1150, 1080, 1051 cm⁻¹. ¹H NMR [600 MHz, (CD₃)₂SO] δ 7.60 (d, J = 9.7 Hz, 1H), 6.13 (d, J = 9.7 Hz, 1H), 5.39–5.26 (m, 2H), 5.24–5.15 (m, 1H), 3.77 (dt, J = 17.3, 2.8 Hz, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 2.97–2.92 (m, 1H). ¹³C{¹H} NMR [151 MHz, (CD₃)₂SO] δ 167.4, 158.2, 146.5, 143.6, 135.6, 125.8, 125.1, 123.1, 119.9, 113.5, 112.8, 73.7, 53.0, 51.1, 40.6, 40.9, 39.9, 39.6, 39.6, 39.5, 39.3, 39.2, 39.1, 39.1, 39.4, 6.4, 6.2. HRMS (ESI-TOF) m/z: [M + H]⁺ calc'd for C₂₃H₂₆NO₅S⁺ 372.0723; observed 372.0724.

Methyl 2-Methylene-7-oxo-2,2a-dihydro-7-cyclobuta[4,5]thiazolo[3,2-a]pyridine-8a(1H)-carboxylate (5f). The compound was prepared following the general procedure described above, but after addition of Cs₂CO₃ (325 mg, 1 mmol), the reaction mixture was stirred for 2 h. White powder, 105 mg, 49%. IR (KBr): v 3087, 3004, 2952, 1745, 1652, 1577, 1488, 1428, 1398, 1363, 1331, 1302, 1290, 1264, 1166, 1092, 1067, 1030 cm⁻¹. ¹H NMR [600 MHz, (CD₃)₂SO] δ 8.00–7.94 (m, 1H), 7.94–7.85 (m, 2H), 7.56–7.47 (m, 3H), 7.41 (dd, J = 7.0, 1.2 Hz, 1H), 5.32–5.11 (m, 2H), 5.20–5.17 (m, 1H), 5.17–5.16 (m, 1H), 4.51–4.42 (m, 2H), 3.73 (dt, J = 17.1, 2.9 Hz, 1H), 3.62 (dd, J = 18.4, 3.8 Hz, 2.85 (dq, J = 17.1, 2.6 Hz, 1H), 1.80–1.74 (m, 1H), 0.99–0.90 (m, 2H), 0.83–0.69 (m, 2H). ¹³C{¹H} NMR [151 MHz, (CD₃)₂SO] δ 167.5, 150.4, 148.4, 144.4, 144.1, 115.3, 113.0, 84.6, 74.2, 53.1, 51.4, 11.9, 6.4, 6.1. HRMS (ESI-TOF) m/z: [M + H]⁺ calc'd for C₂₃H₂₆NO₅S+F⁺ 430.1471; observed 430.1467.

Methyl 2-Methylene-5-(naphthalen-1-ylmethyl)-7-oxo-2,2a-dihydro-7-cyclobuta[4,5]thiazolo[3,2-a]pyridine-8a(1H)-carboxylate (5j). The compound was prepared following the general procedure described above, but after addition of Cs₂CO₃ (325 mg, 1 mmol), the reaction mixture was stirred for 2 h. White powder, 105 mg, 49%. IR (KBr): v 3087, 3004, 2952, 1745, 1652, 1577, 1488, 1428, 1398, 1363, 1331, 1302, 1290, 1264, 1166, 1092, 1067, 1030 cm⁻¹. ¹H NMR [600 MHz, (CD₃)₂SO] δ 8.00–7.94 (m, 1H), 7.94–7.85 (m, 2H), 7.56–7.47 (m, 3H), 7.41 (dd, J = 7.0, 1.2 Hz, 1H), 5.32–5.11 (m, 2H), 5.20–5.17 (m, 1H), 5.17–5.16 (m, 1H), 4.51–4.42 (m, 2H), 3.73 (dt, J = 17.1, 2.9 Hz, 1H), 3.62 (dd, J = 18.4, 3.8 Hz, 2.85 (dq, J = 17.1, 2.6 Hz, 1H), 1.80–1.74 (m, 1H), 0.99–0.90 (m, 2H), 0.83–0.69 (m, 2H). ¹³C{¹H} NMR [151 MHz, (CD₃)₂SO] δ 167.5, 150.4, 148.4, 144.4, 144.1, 115.3, 113.0, 84.6, 74.2, 53.1, 51.4, 11.9, 6.4, 6.1. HRMS (ESI-TOF) m/z: [M + H]⁺ calc'd for C₂₃H₂₆NO₅S+F⁺ 430.1471; observed 430.1467.
late (5f). White powder, 81 mg, 41%. IR (KBr): ν 2952, 1743, 1656, 1573, 1506, 1345, 1396, 1306, 1222, 1156, 1090, 1068, 1018 cm⁻¹.
1H NMR (400 MHz, CDCl3) δ 8.08–8.03 (m, 1H), 7.95 (dd, J = 7.3, 2.1 Hz, 1H), 7.90–7.83 (m, 1H), 7.59–7.46 (m, 4H), 6.23 (d, J = 1.4 Hz, 1H), 5.88 (d, J = 1.4 Hz, 1H), 5.26 (q, J = 2.6 Hz, 2H), 5.14 (q, J = 2.0 Hz, 1H), 4.25 (s, 2H), 3.73 (dt, J = 17.1, 2.7 Hz, 1H), 3.65 (s, 3H), 2.88 (dq, J = 17.2, 2.6 Hz, 1H). 13C{1H} NMR [100 MHz, CDCl3] δ 167.3, 160.1, 156.0, 149.9, 145.1, 134.2, 132.3, 131.4, 128.6, 127.8, 127.4, 126.3, 125.8, 124.0, 112.8, 112.7, 101.5, 72.4, 52.9, 51.3, 37.4. HRMS (ESI-TOF) m/z: [M + H]+ calc for C25H22NO3S+: 416.1315; observed 416.1319.

Preparation of Imidazolium Carboxylate Salts 8a–b. Caboxycilic acid 6a (8.00 mg, 0.019 mmol, 1.0 equiv) dissolved in THF (1 mL) and showed complete in 3 h. Colorless powder, 8 mg, 41%. IR (KBr): ν 3437, 2925, 2854, 2828, 2786, 1726, 1622, 1531, 1480, 1412, 1293, 1216 cm⁻¹. 1H NMR [400 MHz, CD3OD] δ 8.10–8.01 (m, 1H), 7.93–7.85 (m, 1H), 7.61–7.51 (m, 2H), 7.39–7.29 (m, 2H), 5.28 (s, J = 2.7 Hz, 1H), 5.19 (d, J = 1.1 Hz, 1H), 5.13 (dd, J = 11.6, 2.7 Hz, 2H), 4.28 (s, 2H), 3.72–3.60 (m, 1H), 2.86 (d, J = 2.6 Hz, 1H), 2.75 (s, 6H), 2.66 (s, 3H). 13C{1H} NMR [151 MHz, CD3OD] δ 168.9, 159.3, 157.4, 149.4, 133.6, 132.9, 132.0, 128.0, 126.7, 126.5, 126.1, 125.5, 125.3, 125.0, 113.6, 112.7, 51.8, 45.2, 43.2, 34.9. HRMS (ESI-TOF) m/z: [M + H]+ calc for C25H34NO3S+ 433.5800; observed 433.5802.

General Procedure for Synthesis of 9a–b and 7. The methyl ester (0.1 mmol, 1.0 equiv) and LiOH (0.06 mmol, 6 equiv) was added in THF/H2O 3:1 (5 mL) and stirred at room temperature until complete or almost complete hydrolysis of the methyl ester was indicated by TLC analysis. Then, 1 M HCl (0.7 mmol, 7.0 equiv) was added, and the resulting mixture was stirred for 1 min or until no further color change was seen. The mixture was evaporated partially (THF) and partitioned between brine (5 mL) and DCM/MeOH 9:1 (2 × 10 mL). The organic phase was dried, filtered, and evaporated. The residue was dissolved in DMSO (1–2 mL), filtered through a 0.45 µm syringe filter, and purified with preparative reverse phase chromatography. The fractions containing the pure desired product were combined and concentrated partially and then redissolved by addition of a small amount of MeCN. The solution was diluted by quick addition of water, frozen in liquid nitrogen, and freeze-dried. Note: The hydrazine of the ring opened products 2 was slower and lower yielding, and the conversion was much less clean compared to general thiazoline fused 2-pyridines and the ring closed compounds S.

Preparation of 9-(4-Methylthio)imidazolium-2-carboxylate 9a. The compound was purified from 2c (52 mg, 0.128 mmol) following the general procedure. The reaction was finished after 2.5 h, and the product was subsequently isolated as a white powder (11 mg, 0.028 mmol, 22%). IR (KBr): ν 3431, 3063, 3050, 2925, 1718, 1617, 1598, 1556, 1481, 1409, 1277, 1194, 1140, 781 cm⁻¹. 1H NMR [600 MHz, CD3OD] δ 13.14 (1s, 1H), 8.03–7.94 (m, 1H), 7.89 (s, J = 8.4 Hz, 2H), 7.60–7.47 (m, 3H), 7.41 (d, J = 6.9 Hz, 1H), 6.46 (s, 1H), 5.79 (s, 1H), 5.47 (s, 1H), 4.61–4.44 (m, 2H), 2.39 (s, 3H), 1.83 (dd, J = 13.9, 8.1, 5.8 Hz, 1H), 1.23–1.13 (m, 1H), 1.13–1.06 (m, 1H), 0.97 (dd, J = 9.6, 4.5 Hz, 1H), 0.80–0.70 (m, 1H). 13C{1H} NMR [151 MHz, CD3OD] δ 163.8, 160.7, 156.4, 144.8, 134.3, 133.5, 131.6, 128.7, 127.8, 126.4, 125.9, 125.7, 124.0, 121.3, 118.1, 35.6, 19.9, 11.3, 10.8, 9.0. HRMS (ESI-TOF) m/z: [M + H]+ calc for C25H34NO3S+: 432.1315; observed 432.1324.

Preparation of 8-(4-Methylthio)-2-(4-nitrophenyl)-8-oxo-pyrindin-2(1H)-ylcarboxylate Acid 9b. The compound was prepared from 4 (50 mg, 0.097 mmol) following the general procedure. The reaction was finished after 2.5 h, and the product was subsequently isolated as a yellow powder (14 mg, 0.028 mmol, 29%). IR (KBr): ν 3433, 3001, 2905, 1731, 1649, 1584, 1520, 1455, 1440, 1410, 1345, 1312, 1258, 1165, 1144, 854, 736 cm⁻¹. 1H NMR [600 MHz, CD3OD] δ 13.30 (bs, 1H), 8.59 (d, J = 8.9 Hz, 2H), 8.46–8.29 (m, 3H), 7.82–7.39 (m, 3H), 6.66 (s, 1H), 6.07 (s, 1H), 2.45 (s, 3H), 1.18 (dd, J = 13.9, 7.6, 6.0 Hz, 1H), 0.52–0.01 (m, 1H). 13C{1H} NMR [151 MHz, CD3OD] δ 164.0, 159.3, 151.7, 148.6, 148.0, 144.5, 134.5, 142.4, 140.7, 137.0, 133.3, 129.2, 128.3, 128.2, 128.0, 127.2, 126.4, 120.8, 118.8, 19.7, 16.5, 13.1, 12.1. HRMS (ESI-TOF) m/z: [M + H]+ calc for C24H26NO3S2: 392.1315; observed 392.1312.
reported as overall yields for the two steps.

2-(6-(Butythio)-5-cyclopentyl-4-(napthalen-1-ylmethyl)-2-oxopyridin-1(2H)-yl)acrylic Acid (9b). The compound was prepared from 2f (44 mg, 0.009 mmol) following the general procedure. The reaction was finished after 3 h, and the product was subsequently isolated as a white powder (12 mg, 0.008 mmol, 28%). IR (KBr): ν 3045, 3004, 2985, 2931, 2871, 1720, 1646, 1598, 1409, 1274, 1179, 1141, 793, 781 cm⁻¹. 1H NMR (600 MHz, (CD3)2SO) δ 13.13 (bs, 1H), 8.04–7.93 (m, 1H), 7.89 (dd, J = 8.7, 4.2 Hz, 2H), 7.61–7.45 (m, 3H), 7.39 (dd, J = 7.0, 1.1 Hz, 4H), 6.65 (s, 1H), 5.75 (s, 1H), 5.58–5.64 (2H, 1H), 2.87 (s, 2H), 1.72 (dd, J = 13.8, 8.1, 5.6 Hz, 1H). 14C (1H) NMR [151 MHz, (CD3)2SO] δ 163.7, 160.8, 155.7, 143.5, 143.6, 133.5, 131.5, 128.7, 127.5, 127.4, 126.4, 125.9, 125.7, 123.9, 123.5, 118.2, 99.5, 79.2, 35.8, 35.6, 30.7, 21.2, 13.5, 11.4, 11.0, 9.2. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C36H29NO3S+ 621.1382.

General Procedure for Synthesis of 10a–e. Thiabalone fused 2-pyridone 3a–e (0.25 mmol, 1.0 equiv) and cesium carbonate (0.5 mmol, 2.0 equiv) were weighed together in a 2–5 mL microwave reaction tube and flushed with nitrogen. Dry THF (1.5 mL) and propargyl bromide (0.76 mmol, 4.2 equiv) were added. After 24 h, additional cesium carbonate and propargyl bromide were added, as specified below, and the reaction mixture was left stirring for 1–3 h more until reaction completion. THF was removed on a rotary evaporator, and the remaining mixture was partitioned between DCM (50 mL) and brine (30 mL). The organic phase was filtered, concentrated, and purified with automated flash chromatography using a 50 g Sfar cartridge. Because of partial transesterification from methyl ester to propargyl ester and difficulty in their separation by column chromatography, the mixture of both esters was proceeded for ester hydrolysis using LiOH.

General Procedure for Ester Hydrolysis. The obtained mixture of esters was distilled in THF (3 mL), and LiOH (0.10 M, 10.0 equiv) was added. Upon completion, HCl (1.00 M, 11.0 equiv) was added. The mixture was stirred for 1 min and concentrated on a rotary evaporator. The residue was dissolved in EtOAc (50 mL) and washed with brine (30 mL). The organic phase was filtered, concentrated, and purified with preparative HPLC. 10a and 10c were instead purified with normal phase chromatography using 5–30% MeOH in DCM. The yields are reported as overall yields for the two steps.

5-Cyclopentyl-7-methylene-2-(4-nitrophenyl)-10-oxo-4-phenyl-7,8-dihydro-10H-cyclobuta[4,5]thiazolo[2,3-g][1,7]naphthyridine-8a(6H)-carboxylic Acid (10a). After 24 h, Cs2CO3 (81 mg, 0.25 mmol, 1.0 equiv) and propargyl bromide (56 µL, 0.50 mmol, 2.0 equiv) were added and the mixture was stirred for 1 h more; the reaction completed in 25 h in total. Reaction residue was purified by automated flash column chromatography (50 g Sfar cartridge, 10–80% EtOAc in heptane) to give a mixture of esters as a yellow syrup which was subjected to ester hydrolysis by LiOH in 7 h, as described above. Light yellow powder, 20 mg, 16%. IR (KBr): ν 3358, 1728, 1644, 1588, 1554, 1488, 1459, 1441, 1378, 1275, 1125, 1139, 1032 cm⁻¹. 1H NMR [600 MHz, (CD3)2SO] δ 8.16 (s, 1H), 8.03 (s, 1H), 7.55 (s, 1H), 7.54 (s, 1H), 7.47–7.43 (m, 4H), 7.33 (s, 1H), 7.32 (s, 1H), 5.30 (s, 1H), 5.22–5.13 (2H, 1H), 3.83 (dt, J = 17.0, 2.7 Hz, 1H), 3.10 (dt, J = 17.0, 2.7 Hz, 1H), 2.37 (s, 7H), 1.14–1.10 (11H, 0.16–0.11 (m, 4H). 13C (1H) NMR [151 MHz, (CD3)2SO] δ 168.8, 157.8, 152.9, 147.0, 145.7, 140.1, 139.1, 134.8, 132.4, 129.8, 127.7, 126.7, 125.5, 112.2, 107.2, 73.5, 50.8, 10.8, 10.7. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C26H25N2O5S+ 455.1582; observed 455.1578.

2-(4-Fluorophenyl)-7-methylene-10-oxo-5-phenyl-7,8-dihydro-10H-cyclobuta[4,5]thiazo[2,3-g][1,7]naphthyridine-8a(6H)-carboxylic Acid (10c). After 24 h, Cs2CO3 (162 mg, 0.5 mmol, 2.0 equiv) and propargyl bromide (113 µL, 1.0 mmol, 4.0 equiv) were added and the reaction mixture was stirred for 3 h more; the reaction completed in 27 h in total. The crude product was purified by automated flash column chromatography (50 g Sfar cartridge, 10–80% EtOAc in heptane) to give a mixture of esters as a yellow syrup which was subjected to ester hydrolysis by LiOH in 7 h, as described above. Light yellow powder, 20 mg, 16%. IR (KBr): ν 3358, 1728, 1644, 1588, 1554, 1488, 1459, 1441, 1378, 1275, 1125, 1139, 1032 cm⁻¹. 1H NMR [600 MHz, (CD3)2SO] δ 8.16 (s, 1H), 8.03 (s, 1H), 7.55 (s, 1H), 7.54 (s, 1H), 7.47–7.43 (m, 4H), 7.33 (s, 1H), 7.32 (s, 1H), 5.30 (s, 1H), 5.22–5.13 (2H, 1H), 3.83 (dt, J = 17.0, 2.7 Hz, 1H), 3.10 (dt, J = 17.0, 2.7 Hz, 1H), 2.37 (s, 7H), 1.14–1.10 (11H, 0.16–0.11 (m, 4H). 13C (1H) NMR [151 MHz, (CD3)2SO] δ 168.8, 157.8, 152.9, 147.0, 145.7, 140.1, 139.1, 134.8, 132.4, 129.8, 127.7, 126.7, 125.5, 112.2, 107.2, 73.5, 50.8, 10.8, 10.7. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C26H25N2O5S+ 455.1582; observed 455.1578.
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