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Diverse Functionalization of Thiazolo Ring-Fused 2-Pyridones

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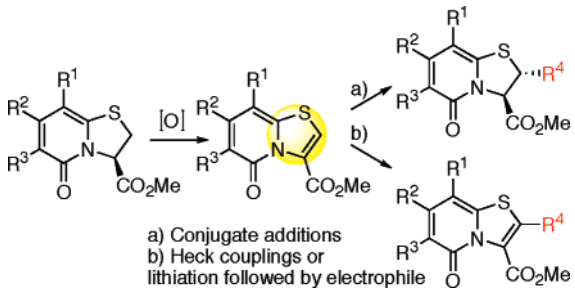

Thiazolo ring-fused 2-pyridones have proven to be highly interesting scaffolds for the development of biologically active compounds. Many methods are today available to introduce a variety of substituents in the 2-pyridone part of the heterocycle. Herein we disclose how a diverse set of substituents can be introduced in the thiazolo ring, with possibilities to vary also the spatial arrangement of the substituents. A key intermediate is the oxidized framework **9** for which an effective synthesis is described. The thiazolo part of this system can be substituted either via conjugate additions, resulting in trans selectivity, or via microwave-assisted Heck couplings that result in unsaturated aryl-substituted analogues. The scaffold can also be lithiated followed by the addition of various electrophiles, which increases the diversification potential substantially, as exemplified with the introduction of halogens, alkyl, acyl, and amide substituents.

Introduction

Ring-fused 2-pyridones can be found in many biologically active compounds and natural products ranging from the multi-ring-fused natural product Nauclefine[1] **1** and Camptothecin **2**, where the latter has proven to be a potent anticancer drug,[2] to bicyclic systems where the 2-pyridone acid A58365A **3** has been found to be an ACE inhibitor at nanomolar concentrations[3−5] (Figure 1). The rigidity of these systems has also attracted researchers to construct peptidomimetics in order to probe conformation−activity relationships in peptide science.[6,7] In addition, we have shown that thiazolo ring-fused 2-pyridones are highly interesting as scaffolds for the development of compounds that inhibit protein−protein interactions.[8−10] Hence, both novel antibacterial agents, termed pilicides, that target the molecular machinery of pilus assembly in uropathogenic *Escherichia coli*,[9] as well as compounds that inhibit amyloid formation,[11] have been developed (e.g., pilicide **4** and amyloid inhibitor **5**, Figure 1).

Due to the great interest in these systems, several synthetic methodologies have been developed through the years, and two of these, a cyclobutenedione-based method developed in the Liebeskind laboratories[12] and an isomünchnone-based method

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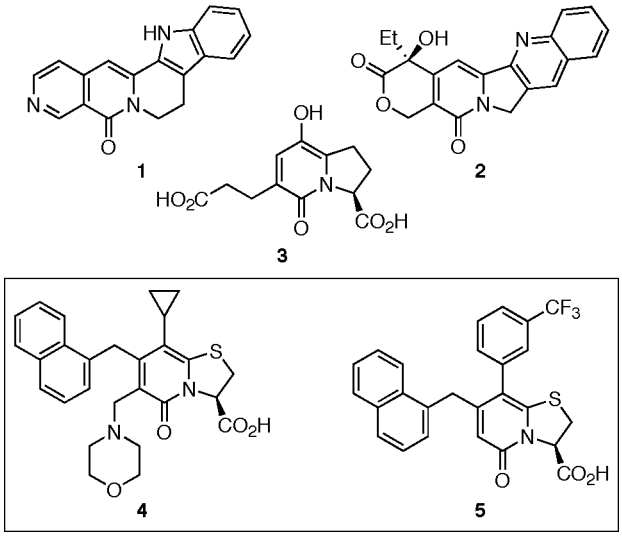

FIGURE 1. Ring-fused 2-pyridones can be found in biologically active compounds and natural products. Thiazolo-fused 2-pyridones have proven to be interesting scaffolds for the development of novel antibacterial agents, *pilicides*, as well as amyloid inhibitors (**4** and **5**, respectively).

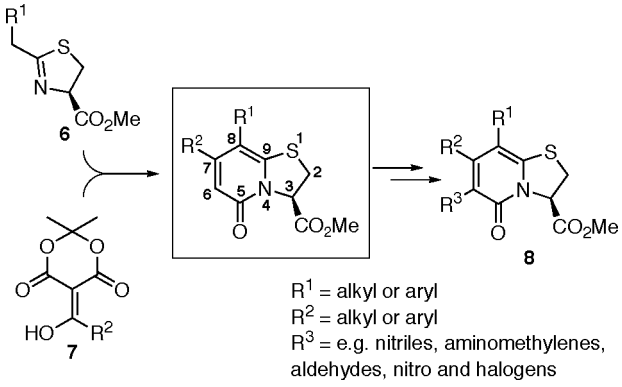

FIGURE 2. Synthesis of the thiazolo ring-fused 2-pyridone scaffold via Meldrum's acid derivatives (**7**) and Δ^2-thiazolines (**6**). Methods to introduce substituents in position 6 (R^3) on the scaffold have been developed using different electrophilic reagents.[15−17]

developed by Padwa and co-workers,[13] are attractive examples that result in highly substituted ring-fused 2-pyridones. Our contribution to the synthesis of ring-fused 2-pyridones is based upon an acyl ketene imine cyclocondensation. The synthesis starts with Δ^2-thiazolines **6** and Meldrum's acid derivatives **7** derived from commercially available nitriles and carboxylic acids[14] (Figure 2).

Besides being fairly mild and scalable, this methodology also allows substituents to be introduced independent of each other

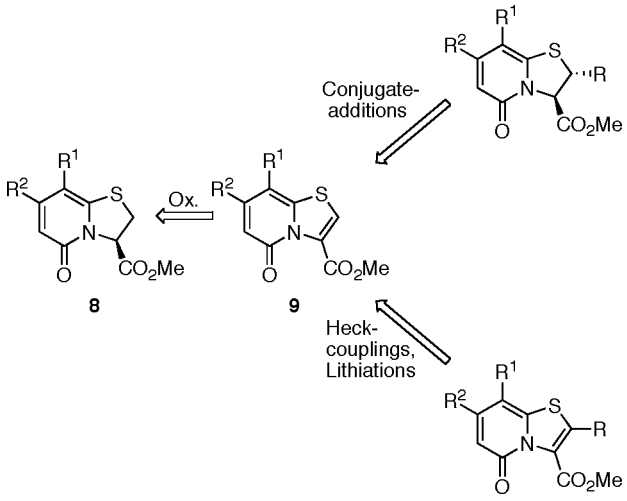

FIGURE 3. Synthetic outline.

at positions 7 and 8 directly in the 2-pyridone forming step (Figure 2). This methodology has been modified and transferred to solid phase chemistry[18] and also proven to be ideal for microwave-assisted synthesis,[19] which substantially shortens the reaction times. In addition, the use of imines other than thiazolines has proven to work well, resulting in multi-ring-fused 2-pyridones in high yields.[20] Furthermore, position 6 in this scaffold can be substituted with a variety of substituents by using electrophilic reagents and efficient methods to introduce functional groups, such as nitriles, aminomethylenes, aldehydes, nitro groups, and halogens have been developed.[15−17]

The highly interesting biological activity seen for the ring-fused 2-pyridones **4** and **5** (Figure 1) and their more general use as scaffolds for development of peptidomimetics motivated further studies to develop efficient methods to introduce diverse substituents also in the thiazolo part of the framework. Indeed, tools to fine-tune the substitution pattern, also in the previously never varied thiazolo part of the scaffold, would be important to gain further knowledge about underlying molecular mechanisms and structure−activity relationships. Besides the need for methods to introduce diverse substituents, it is also important to be able to study the effect of the spatial arrangement of the substituents. Herein we now present methods to introduce substituents in a new position on biologically active thiazolo ring-fused 2-pyridones. Pivotal to the work is the formation of an α,β-unsaturated methyl ester to which substituents are introduced via either conjugate additions, microwave-accelerated Heck couplings, or lithiation followed by reaction with a diverse set of electrophiles (Figure 3), thus making it possible to independently vary all positions in the core structure. Furthermore, the displayed methods for substitution presented in this work open up possibilities for future design and development of both pilicides and amyloid aggregation inhibitors.

Results and Discussion

With the aim to introduce a diverse set of substituents in the thiazolo part of the scaffold and also to be able to vary the spatial

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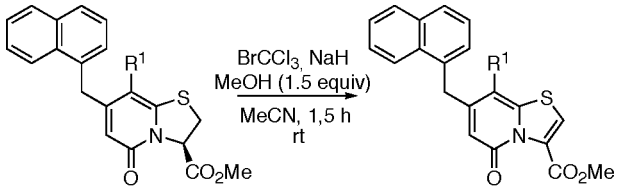
SCHEME 1

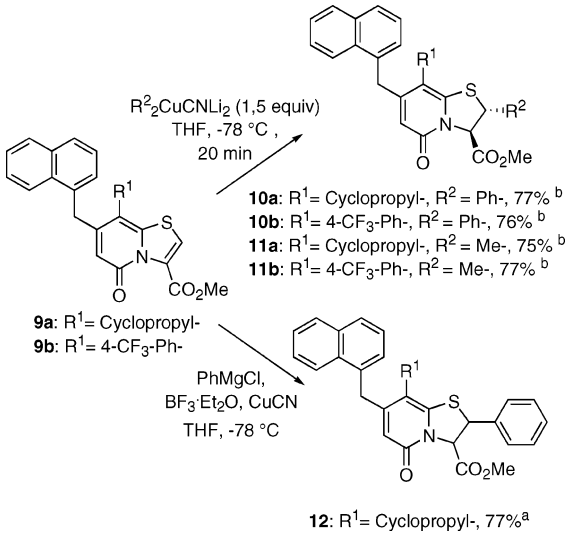


8a: R^1= Cyclopropyl-
8b: R^1= 4-CF_3-Ph-

9a: R^1= Cyclopropyl-, 89%
9b: R^1= 4-CF_3-Ph-, 83%

arrangement of these substituents, an oxidized intermediate **9** appeared attractive. The α,β-unsaturated methyl ester thus obtained could serve as a handle to perform conjugate additions with different nucleophiles onto the scaffold. Thus compounds substituted α to the sulfur with an sp^3 hybridization would be accessible. Furthermore, transition-metal-catalyzed reactions, such as the Heck reaction, using the same intermediate would result in substituted compounds with the sp^2 hybridization intact. As a complement to these two approaches, intermediate **9** could also potentially be lithiated and used as a nucleophile with various electrophiles, thus increasing the diversification power substantially. Consequently, it was crucial to find a convenient and high yielding reaction to convert the dihydro thiazolo-fused 2-pyridone **8** to its unsaturated counterpart **9**. To our knowledge, there are no methods reported for this transformation on this system in the literature, although there are several methods reported for the preparation of α,β-unsaturated esters on similar substrates. The most frequently used methods to oxidize thiazolines or imidazolines are using MnO_2[21−23] or a combination of $BrCCl_3$ and DBU[23−25] that both successfully have given the dehydrogenated analogues in high yields. Somewhat surprising, the use of MnO_2 gave no reaction and the use of $BrCCl_3$ and DBU gave only low yields with poor consumption of starting material when applied to our ring-fused systems. Nevertheless, efforts to improve the $BrCCl_3$/DBU method by varying base strength (NaOMe, *t*-BuOK, NaH, and LDA) were performed, giving NaH as the base of choice. Still, the conversion of starting material was not yet satisfactory, and hydrolysis of the methyl ester during the reaction was significant. Hence, different solvents, such as THF, MeCN, DCE, and MeOH, and combinations thereof were investigated. By using acetonitrile as solvent, the hydrolysis problem was substantially suppressed, but the conversion of starting material was still low. After further fine-tuning of the conditions, this could finally be circumvented by the addition of MeOH to the reaction; higher amounts of MeOH gave considerable amounts of hydrolysis, but with the addition of 1.5 equiv of MeOH, the 2-pyridones **9a** and **9b** could be isolated in 89 and 83% yields, respectively (Scheme 1).With the oxidation reaction to the key intermediate **9** in hand, the attention was then directed toward further substitution of the scaffold. No methods for conjugate addition to this type of ring-fused heterocycle could be found in the literature, but a method for addition to α,β-unsaturated

SCHEME 2[a]



10a: R^1= Cyclopropyl-, R^2 = Ph-, 77% [b]
10b: R^1= 4-CF_3-Ph-, R^2 = Ph-, 76% [b]
11a: R^1= Cyclopropyl-, R^2 = Me-, 75% [b]
11b: R^1= 4-CF_3-Ph-, R^2 = Me-, 77% [b]

12: R^1= Cyclopropyl-, 77%[a]

[a] As diastereoisomeric mixture. [b] Pure trans diastereomer.

thiazolines attracted us. Here, Seebach and co-workers reported the use of higher order cuprates, in attempts to perform stereoselective C-alkylation of cysteine.[26] This strategy demanded BF_3•Et_2O activation of the cuprate and prolonged reaction times to give the desired product. Unfortunately, the yield was poor, probably due to problems with β-elimination of the sulfur.

Our initial attempts were based upon this method, and the first screen showed that in our system the reaction did not require any BF_3•Et_2O activation. Instead a nice conversion was observed within 15 min by using the in situ prepared $Ph_2CuCNLi_2$ reagent, and the 2-phenyl-substituted ring-fused 2-pyridones **10a** and **10b** were obtained in 77 and 76% isolated yields, respectively, as the pure trans stereoisomers (Scheme 2). Also, an alkyl substituent could be efficiently and stereoselectively introduced via this method, resulting in the methyl-substituted analogues **11a** and **11b** in 75 and 77% isolated yields.

Copper-catalyzed Grignard reagents are also known to react in conjugate additions, but although the yield of conjugate addition remained high (77% yield), the stereoselectivity was very low and 2-pyridone **12** was obtained as a 1:1 mixture of cis and trans stereoisomers[27] (Scheme 2). The higher order cuprate reagents proceeded with complete trans selectivity for the transfer of both aryl and alkyl substituents, and thus sp^3−sp^2 as well as sp^3−sp^3 carbon−carbon bonds are available via this method.

In fine-tuning biological activity, the introduction of heteroatoms obviously can play an important role via their ability to act as hydrogen bond acceptors, and fortunately, methoxy-substituted analogues were obtained by the use of LiOMe in THF/MeOH (3:1). Also, in this case, the pure trans products were obtained; however, the products were also hydrolyzed during the reaction to afford carboxylic acids **13a** and **13b** (Scheme 3). This was consistent with what had earlier been observed in the oxidation to the unsaturated methyl ester, where the use of higher amounts of MeOH in basic con-

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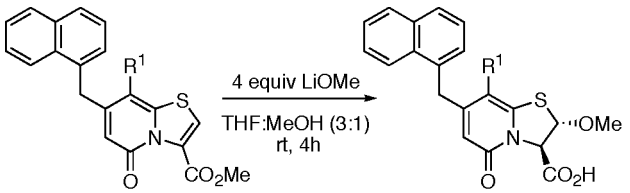
SCHEME 3[a]

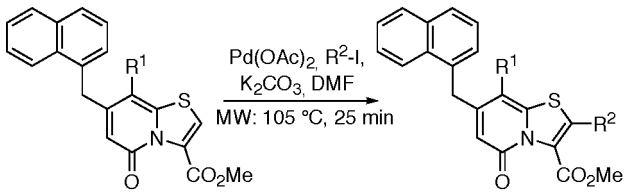


9a: R^1= Cyclopropyl-
9b: R^1= 4-CF_3-Ph-

13a: R^1= Cyclopropyl-, 75% [a]
13b: 4-CF_3-Ph-, 77% [a]

[a] Pure trans diastereomer.

SCHEME 4



9a: R^1= Cyclopropyl-
9b: R^1= 4-CF_3-Ph-

14a: R^1= Cyclopropyl-, R^2 = Ph-, 83%
14b: R^1= 4-CF_3-Ph-, R^2 = 4-MeO-Ph-, 82%
15a: R^1= Cyclopropyl-, R^2 = Ph-, 82%
15b: R^1= 4-CF_3-Ph-, R^2 = 4-MeO-Ph-, 81%

ditions gave hydrolysis. However, in the conjugate addition reaction, the use of higher amounts of MeOH is crucial for the LiOMe to dissolve properly. Still, taking into consideration that the carboxylic acids are the active species in both the pilicide and the amyloid inhibitor projects, this is not a major problem. Typically, by using 4 equiv of LiOMe, the 2-pyridones **13a** and **13b** were obtained in 75 and 77% yields, respectively (Scheme 3).

At this point, all reactions employed have resulted in the saturated product and thereby the formation of two new stereocenters. To further increase the structural diversity, we wished to introduce substituents α to the sulfur while keeping the double bond intact. Although palladium-catalyzed Heck couplings[28] to α,*β*-unsaturated carboxylic esters are well established in the literature,[13,29−31] more sophisticated examples with *β*-sulfide substituents and other heteroatoms in the vicinity are rare. To the best of our knowledge, no examples where Heck couplings have been performed on structures like ours in the intended position have been published. We had previously experienced problems when applying transition-metal-catalyzed reactions at position 6 on this scaffold,[15] and we were therefore not surprised when our initial trials were unsuccessful. The reaction demanded the extensive study of the choice of reaction conditions. Conventional heating using $Pd(OAc)_2$ and Na_2CO_3 in DMF resulted in low yield of the desired product after prolonged reaction times (24 h). Microwave-assisted organic synthesis (MAOS) has been shown to often improve transition-metal-catalyzed reactions,[29,31−33] and since we have had very good experience in many other reactions with these heterocycles performed under MAOS conditions,[15,19] it was also applied this time. The microwave-accelerated reaction was improved by changing to different solvents (NMP, DMF, toluene, MeCN), catalysts ($Pd(OAc)_2$, $Pd_2(dba)_3$, tetrakis(triphenylphosphine)palladium-(0)), ligands (PPh_3, BINAP), bases (TEA, Na_2CO_3, K_2CO_3), temperatures (80−150 °C), and reaction times (5−60 min). The best conversion and yield was obtained by using 9 mol % of $Pd(OAc)_2$ without any catalyst precursors. Lowering the $Pd(OAc)_2$ loading to 4 mol % significantly reduced the yield, from 83 to 53%, leaving considerable amounts of unconsumed starting material. The base of choice proved to be K_2CO_3, the solvent DMF, and the best temperature and time was found to be 105 °C for 25 min. Applying these conditions to **9a**,**b** resulted in the formation of aryl-substituted 2-pyridones **14a**,**b** and **15a**,**b** in high yields (Scheme 4).

In a recent report, the possibility of direct lithiation[34] of thiazoles, followed by reaction with different electrophiles, was described.[35] To be able to introduce a more diverse set of substituents to our system, this approach would be an excellent complement to the Heck reaction. However, in the thiazolo-fused 2-pyridone system, there are several positions that potentially can be lithiated (e.g., position 6 and the naphthyl linkage). This was experienced with a decarboxylated analogue that gave a complex mixture of products when reacted with LDA followed by methyl iodide. Nevertheless, with the ester functionality intact, the acidity of the *β*-hydrogen at the desired 2-position is substantially lower, and indeed, treating **9a** or **9b** in THF at −78 °C with 1.05 equiv of LDA gave exclusively 2-pyridones lithiated in the desired position. These could be reacted with bromotrichloromethane to give brominated 2-pyridones **16a** and **16b** in good to excellent yields (Table 1, entries 1 and 2).

Introduction of halogens has previously been performed by methods other than direct lithiation on thiazoles by using halogenating agents.[36,37] However, looking at our system, there are other feasible positions able to react with halogenating agents, which also was confirmed when the lithiated 2-pyridones were reacted with bromine as electrophile, giving mixtures of brominated products. This problem was easily circumvented by exchanging the bromine source with bromotrichloromethane. These brominated compounds together with the chlorinated compounds **17a** and **17b** (entries 3 and 4), formed by reaction with benzenesulfonyl chloride, are also interesting as substrates for further transition-metal-catalyzed cross-coupling reactions. In addition to the halogenated products, the incorporation of a methyl substituent proved to work well, giving **18a** and **18b**. Furthermore, acylations turned out to be straightforward, as exemplified with benzoyl chloride as acylating agent, which resulted in **19a** and **19b** (entries 7 and 8). Finally, the

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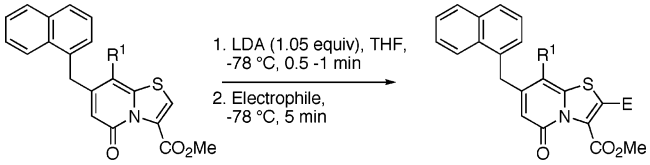
TABLE 1. Lithiation Followed by Reaction with Different Electrophiles



9a, **b** **16a**, **b** to **20a**, **b**

entry	R^1	electrophile	E	product	yield (%)[a]
1	cyclopropyl-	$BrCCl_3$	-Br	**16a**	93
2	4-CF_3-Ph-	$BrCCl_3$	-Br	**16b**	87
3	cyclopropyl-	$PhSO_2Cl$	-Cl	**17a**	75
4	4-CF_3-Ph-	$PhSO_2Cl$	-Cl	**17b**	76
5	cyclopropyl-	Me−I	-Me	**18a**	90[b]
6	4-CF_3-Ph-	Me−I	-Me	**18b**	65[b]
7	cyclopropyl-	PhCOCl	-COPh	**19a**	72
8	4-CF_3-Ph-	PhCOCl	-COPh	**19b**	74
9	cyclopropyl-	Ph−NCO	-CONHPh	**20a**	78
10	4-CF_3-Ph-	Ph−NCO	-CONHPh	**20b**	75

[a] Isolated yield. [b] Prolonged reaction time to 15 min.

reaction with isocyanates gave the amides **20a** and **20b** in good yields (entries 9 and 10).

Conclusion

In summary, methods to introduce a diverse set of substituents onto the thiazolo part of biologically active ring-fused 2-pyridones have been developed. The methods have been chosen to complement each other regarding the spatial arrangement of the obtained products as well as their diversifying potential. The key intermediate for all of these transformations is an α,β-unsaturated methyl ester **9** obtained from the dihydro thiazolo-fused pyridone **8** in a bromination−elimination reaction. To this intermediate were introduced a variety of substituents in the desired position. Conjugate addition using higher order cuprates or lithium methoxide resulted in saturated products, microwave-accelerated Heck couplings, and lithiations followed by reactions with different electrophiles that gave unsaturated products. The compounds obtained in this study will be biologically evaluated in due course, and the generated structure activity data together with the synthetic methods described in this article will constitute an important platform in future design and development of pilicides and inhibitors of Alzheimer amyloids.

Experimental Section

2-Pyridonecarboxylic Acid Methyl Esters (8a and 8b). These were prepared according to previously published procedures.[11,19]

8-Cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (9a). NaH (36.8 mg, 1.53 mmol, washed with *n*-pentane) was added to **8a** (300 mg, 0.77 mmol) dissolved in 6 mL of dry MeCN at 0 °C while stirring. After 10 min, $BrCCl_3$ (0.076 mL, 0.76 mmol) was added, and the mixture was allowed to attain rt and was stirred for an additional 10 min followed by the addition of dry MeOH (0.047 mL, 1.15 mmol). After approximately 1.5 h of stirring at rt, the reaction was quenched by dropwise addition of 2% aqueous $KHSO_4$ (the reaction was carefully monitored with TLC, and one could also observe a color change from pale yellow to yellow-orange upon completion). The mixture was acidified and then extracted three times with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by silica gel chromatography (heptane/EtOAc, 1/1) gave **9a** as a white foam (266 mg, 89%): mp 170−171 °C; IR (neat) 3003, 2942, 1719, 1649, 1464, 1248, and 780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.73−0.79 (m, 2H), 1.00−1.07 (m, 2H), 1.74−1.83 (m, 1H), 3.92 (s, 3H), 4.54 (s, 2H), 5.93 (s, 1H), 7.07 (s, 1H), 7.12−7.25 (m, 1H), 7.36−7.43 (m, 1H), 7.43−7.50 (m, 2H), 7.75−7.90 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8 (2C), 10.9, 36.2, 53.2, 111.8, 112.2, 113.8, 123.6, 125.5, 125.7, 126.2, 127.3, 127.6, 128.8, 131.5, 131.9, 133.9, 134.1, 147.2, 153.8, 159.0, 161.1; HRMS (FAB) calcd for $[M + H]^+$ $C_{23}H_{19}NO_3S$ 390.1164, obsd 390.1174.

7-Naphthalen-1-ylmethyl-5-oxo-8-(3-trifluoromethylphenyl)-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (9b). By following the procedure described for the preparation of **9a** from **8a**, **8b** (126 mg, 0.255 mmol) gave **9b**, after purification by silica gel chromatography (heptane/EtOAc, 3/2), as a white foam (105 mg, 83%): mp 100−102 °C; IR (neat) 3058, 2949, 1738, 1654, 1467, 1119, and 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 3H), 4.10 (s, 2H), 6.14 (s, 1H), 7.02 (s, 1H), 7.12−7.17 (m, 1H), 7.31−7.49 (m, 4H), 7.50−7.65 (m, 4H), 7.70−7.74 (m, 1H), 7.79−7.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.7, 53.4, 111.9, 113.5, 113.8, 123.3, 125.3, 125.58 (q, J = 3.70 Hz), 125.64, 126.2, 126.3 (q, J = 272.55 Hz) 126.8 (q, J = 3.70 Hz), 127.7, 127.8, 128.8, 130.1, 131.5, 131.7, 131.9 (q, J = 32.76 Hz), 133.4, 133.6, 133.8, 136.5, 147.4, 151.2, 158.9, 160.6; HRMS (FAB) calcd for $[M + H]^+$ $C_{27}H_{18}F_3NO_3S$ 494.1038, obsd 494.1038.

General Procedure for the Preparation of 10a,b and 11a,b. Preparation of cuprate: A solution of RLi (R = Ph for **10** (2.0 M in dibutyl ether, 0.5 mL, 1.0 mmol) and R = Me for **11** (1.6 M in diethyl ether, 0.625 mL, 1.0 mmol)) was added dropwise to CuCN (45 mg, 0.50 mmol) in 2 mL of THF at −78 °C. The mixture was stirred at −78 °C for 10 min before being warmed to 0 °C and was stirred there for 10 min before the clear solution was again cooled to −78 °C.

Cuprate (1.5 equiv) ($Ph_2CuCNLi_2$, 0.2 M for **10**, $Me_2CuCNLi_2$, 0.19 M for **11**) was added to **9** in 2 mL of THF at −78 °C. After stirring for 20 min, the reaction was quenched with aqueous saturated NH_4Cl, and the solution was extracted three times with DCM. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated; the residue was purified by column chromatography (heptane/EtOAc, 3/2 for **10**, 2/3 for **11**) giving **10** or **11**.

8-Cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-2-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (10a). 9a (40 mg, 0.103 mmol) gave **10a** as a foam (37.0 mg, 77%): mp 90−91 °C; IR (neat) 3063, 2952, 1746, 1648, 1481, 1208, and 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.71−0.82 (m, 2H), 0.87−1.01 (m, 2H), 1.64−1.72 (m, 1H), 3.82 (s, 3H), 4.40−4.52 (m, 2H), 4.99 (d, J = 2.88 Hz, 1H), 5.58 (d, J = 2.88 Hz, 1H), 5.77 (s, 1H), 7.27−7.52 (m, 9H), 7.76−7.91 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.5, 7.9, 11.2, 36.3, 50.6, 53.3, 69.8, 113.2, 115.7, 123.8, 125.5, 125.7, 126.2, 126.6 (2C), 127.6, 127.7, 128.7, 128.8, 129.2 (2C), 132.0, 133.9, 134.0, 139.2, 146.5, 156.9, 161.2, 168.3; HRMS (FAB) calcd for $[M + H]^+$ $C_{29}H_{25}NO_3S$ 468.1633, obsd 468.1636.

7-Naphthalen-1-ylmethyl-5-oxo-2-phenyl-8-(3-trifluoromethylphenyl)-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (10b). 9b (40 mg, 0.081 mmol) gave **10b** as a foam (35.0 mg, 76%): mp 98−99 °C; IR (neat) 3044, 2956, 1748, 1652, 1482, 1330, 1119, and 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 4.00 (s, 2H), 5.00 (d, J = 3.34 Hz, 1H), 5.60−5.66 (m, 1H), 5.98 (s, 1H), 7.18−7.23 (m, 1H), 7.28−7.52 (m, 10H), 7.54−7.66 (m, 3H), 7.72−7.77 (m, 1H), 7.80−7.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.8, 51.0, 53.5, 70.8, 114.2, 116.1, 123.5, 123.8 (q, J = 272.55 Hz), 125.2 (q, J = 3.73 Hz), 125.4, 125.7, 126.2, 126.6 (broad), 127.1 (broad split), 127.8, 127.9, 128.8, 129.0, 129.3 (2C), 129.5, 131.4 (q, J = 32.64 Hz), 131.7, 133.3, 133.5 (d, J = 29.33 Hz), 133.9, 136.9, 138.3, 146.8, 154.1, 161.1, 168.1 (broad and split, J = 4.26 Hz); HRMS (FAB) calcd for $[M + H]^+$ $C_{33}H_{24}F_3NO_3S$ 572.1507, obsd 572.1506.

8-Cyclopropyl-2-methyl-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (11a). 9a (20 mg, 0.051 mmol) gave **11a** as a foam (15.5 mg, 75%): mp 84−85 °C; IR (neat) 3042, 2948, 1720, 1649, 1477, 1431, 1204, and 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.70−0.76 (m, 2H), 0.86−1.00 (m, 2H), 1.57 (d, J = 6.93 Hz, 3H), 1.60−1.68 (m, 1H), 3.77 (s, 3H), 3.96 (dq, J = 2.32, 6.93 Hz, 1H), 4.35−4.51 (m, 2H), 5.21 (d, J = 2.32 Hz, 1H), 5.74 (s, 1H), 7.25−7.31 (m, 1H), 7.38−7.51 (m, 3H), 7.75−7.84 (m, 2H), 7.84−7.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.5, 7.9, 11.1, 23.1, 36.3, 42.9, 53.1, 69.3, 113.5, 115.3, 123.8, 125.6, 125.7, 126.2, 127.6, 127.7, 128.8, 132.0, 133.97, 133.99, 146.5, 156.8, 161.6, 168.4; HRMS (FAB) calcd for $[M + H]^+$ $C_{24}H_{23}NO_3S$ 406.1477, obsd 406.1482.

2-Methyl-7-naphthalen-1-ylmethyl-5-oxo-8-(3-trifluoromethylphenyl)-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (11b). 9b (40 mg, 0.081 mmol) gave **11b** as a foam (31.8 mg, 77%): mp 88−89 °C; IR (neat) 3040, 2955, 1750, 1654, 1482, 1330, 1121, and 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.56 (d, J = 6.73 Hz, 3H), 3.81 (s, 3H), 3.89−4.05 (m, 3H), 5.28 (d, J = 2.58 Hz, 1H), 5.94 (s, 1H), 7.16−7.22 (m, 1H), 7.32−7.52 (m, 5H), 7.53−7.64 (m, 3H), 7.71−7.76 (m, 1H), 7.79−7.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 36.8, 43.3, 53.2, 70.2, 114.5, 115.6, 123.4, 123.8 (q, J = 272.50 Hz), 125.1 (m, J = 3.87 Hz), 125.3, 125.6, 126.2, 126.9 (broad and split, J = 24.20 Hz), 127.7, 127.8, 128.7, 129.4, 131.3 (q, J = 32.79 Hz), 131.6, 133.3, 133.5 (broad and split, J = 28.18 Hz), 133.8, 137.0, 146.8, 153.9, 161.4, 168.1; HRMS (FAB) calcd for $[M + H]^+$ $C_{28}H_{22}F_3NO_3S$ 510.1351, obsd 510.1349.

8-Cyclopropyl-2-methoxy-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid (13a). LiOMe (7.7 mg, 0.204 mmol) was added to **9a** (20 mg, 0.051 mmol) dissolved in 0.6 mL of THF and 0.2 mL of MeOH at rt while stirring. The solution was stirred for 4 h at rt before being concentrated. Purification by silica gel chromatography (DCM/MeOH/AcOH, 95/4/1) gave **13a** as a white solid (15.6 mg, 75%): mp 138−140 °C; IR (neat) 3005, 2947, 1719, 1648, 1466, 1247, and 780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.71−0.83 (m, 2H), 0.93−1.08 (m, 2H), 1.71−1.81 (m, 1H), 3.46 (s, 3H), 4.47−4.62 (m, 2H), 5.52 (s, 1H), 5.63−5.66 (m, 2H), 7.32−7.36 (m, 1H), 7.43−7.53 (m, 3H), 7.80−7.94 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.0, 7.2, 10.7, 35.9, 55.4, 70.4, 87.8, 114.0, 115.4, 123.7, 125.3, 125.5, 126.1, 127.5 (2C), 128.5, 132.0, 134.1, 134.2, 146.6, 158.5, 162.2, 167.0; HRMS (FAB) calcd for $[M + H]^+$ $C_{23}H_{21}NO_4S$ 408.1270, obsd 408.1264.

2-Methoxy-7-naphthalen-1-ylmethyl-5-oxo-8-(3-trifluoromethylphenyl)-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid (13b). By following the procedure described for the preparation of **13a** from **9a**, **9b** (20 mg, 0.041 mmol) gave **13b** as a white solid (15.9 mg, 77%): mp 137−138 °C; IR (neat) 2927, 1736, 1639, 1485, 1334, 1087, and 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.38 (s, 3H), 4.01−4.15 (m, 2H), 5.60−5.67 (m, 2H), 5.98 (d, J = 6.26 Hz, 1H), 7.20−7.26 (m, 1H), 7.34−7.46 (m, 3H), 7.49−7.63 (m, 4H), 7.63−7.70 (m, 1H), 7.72−7.78 (m, 1H), 7.80−7.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.2, 55.5, 71.4, 88.7, 114.6, 114.7, 116.2, 123.3, 124.0 (q, J = 272.49 Hz), 124.9 (broad), 125.1, 125.4, 125.9, 126.6 (broad), 126.9 (broad), 127.5, 128.4, 129.6, 130.9 (q, J = 31.57 Hz), 131.6, 133.6, 133.7, 134.0, 137.1 (d, J = 6.70 Hz), 146.9, 155.3, 162.2; HRMS (FAB) calcd for $[M + H]^+$ $C_{27}H_{20}F_3NO_4S$ 512.1143, obsd 512.1144.

General Procedure for the Preparation of 14a,b and 15a,b. X (iodobenzene for the preparation of **14** and 4-iodoanisole for the preparation of **15**) was added to **9** (0.061 mmol), K_2CO_3 (17 mg, 0.12 mmol), and $Pd(OAc)_2$ (1.2 mg, 0.0055 mmol) in 1.2 mL of DMF. N_2(g) was led through the reaction mixture for 1 min followed by heating using microwave irradiation for 25 min at 105 °C. The mixture was cooled to rt, filtered through a plug of Celite, and rinsed three times with EtOAc. The combined organic phases were washed two times with water/brine (50/50), dried (Na_2SO_4), filtered, and concentrated; the residue was purified by column chromatography (DCM/EtOAc 95/5) giving **14** or **15**.

8-Cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-2-phenyl-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (14a). 9a (24 mg, 0.061 mmol), X = iodobenzene (0.013 mL, 0.12 mmol), gave **14a** as a foam (23.7 mg, 83%): mp 117−118 °C; IR (neat) 3003, 2946, 1731, 1650, and 1466 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.76−0.86 (m, 2H), 1.00−1.11 (m, 2H), 1.76−1.88 (m, 1H), 3.89 (s, 3H), 4.56 (s, 2H), 5.95 (s, 1H), 7.21−7.26 (m, 1H), 7.38−7.52 (m, 6H), 7.57−7.63 (m, 2H), 7.77−7.81 (m, 1H), 7.81−7.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8 (2C), 10.8, 36.1, 53.2, 111.6, 111.8, 123.5, 125.4, 125.5, 125.6, 126.1, 127.2, 127.5, 128.4 (2C), 128.59, 128.64, 128.7, 129.1 (2C), 129.8, 131.8, 133.8, 134.1, 146.2, 153.3, 158.8, 161.6; HRMS (FAB) calcd for $[M + H]^+$ $C_{29}H_{23}NO_3S$ 466.1477, obsd 466.1479.

7-Naphthalen-1-ylmethyl-5-oxo-2-phenyl-8-(3-trifluoromethylphenyl)-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (14b). 9b (30 mg, 0.061 mmol), X = iodobenzene (0.013 mL, 0.12 mmol), gave **14b** as a foam (28.3 mg, 82%): mp 114−115 °C; IR (neat) 3042, 2963, 1747, 1650, 1330, 1120, and 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 4.12 (s, 2H), 6.16 (s, 1H), 7.14−7.19 (m, 1H), 7.31−7.46 (m, 6H), 7.46−7.57 (m, 4H), 7.57−7.66 (m, 3H), 7.71−7.76 (m, 1H), 7.79−7.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.7, 53.5, 111.8, 113.3, 123.4, 123.7 (q, J = 272.88 Hz), 125.3, 125.6 (q, J = 3.62 Hz), 125.7, 126.2, 126.8 (q, J = 3.66 Hz), 127.7, 127.8, 128.2, 128.4 (2C), 128.8, 128.9, 129.2 (2C), 130.09, 130.14, 131.5, 131.9 (q, J = 32.58 Hz), 133.4 (broad), 133.6, 133.8, 136.6, 146.5, 150.8, 158.8, 161.4; HRMS (FAB) calcd for $[M + H]^+$ $C_{33}H_{22}F_3NO_3S$ 570.1351, obsd 570.1350.

8-Cyclopropyl-2-(4-methoxyphenyl)-7-naphthalen-1-ylmethyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (15a). 9a (24 mg, 0.061 mmol), X = 4-iodoanisole (29 mg, 0.12 mmol), gave **15a** as a foam (24.9 mg, 82%): mp 106−108 °C; IR (neat) 1731, 1649, 1465, and 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.75−0.84 (m, 2H), 1.01−1.08 (m, 2H), 1.75−1.84 (m, 1H), 3.85 (s, 3H), 3.88 (s, 3H), 4.54 (s, 2H), 5.93 (s, 1H), 6.93−6.99 (m, 2H), 7.21−7.25 (m, 1H), 7.37−7.43 (m, 1H), 7.44−7.51 (m, 2H), 7.51−7.57 (m, 2H), 7.75−7.80 (m, 1H), 7.81−7.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.0 (broad), 11.0, 11.1, 36.3, 53.4, 55.5, 111.8, 112.0, 114.7, 121.0, 123.7, 123.8, 124.8, 125.6, 125.8, 126.3, 127.4, 127.7, 127.8, 128.9, 129.0, 130.0, 132.0, 134.0, 134.4, 146.3, 153.3, 159.0, 161.0, 162.0; HRMS (FAB) calcd for $[M + H]^+$ $C_{30}H_{25}NO_4S$ 496.1583, obsd 496.1587.

2-(4-Methoxyphenyl)-7-naphthalen-1-ylmethyl-5-oxo-8-(3-trifluoromethylphenyl)-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (15b). 9b (30 mg, 0.061 mmol), X = 4-iodoanisole (29 mg, 0.12 mmol), gave **15b** as a foam (29.6 mg, 81%): mp 200−202 °C; IR (neat) 3060, 2955, 1738, 1652, 1472, 1119, and 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.91 (s, 3H), 4.11 (s, 2H), 6.14 (s, 1H), 6.88−6.94 (m, 2H), 7.14−7.18 (m, 1H), 7.31−7.65 (m, 10H), 7.71−7.75 (m, 1H), 7.79−7.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.8, 53.4, 55.4, 111.8, 113.1, 114.6 (2C), 120.3, 123.4, 123.7 (q, J = 272.64 Hz), 124.8, 125.3, 125.5 (q, J = 3.64 Hz), 125.7, 126.2, 126.9 (q, J = 3.65 Hz), 127.7, 127.8, 128.8, 129.1, 129.9 (2C), 130.1, 131.6, 131.9 (q, J = 32.58 Hz), 133.4, 133.7, 133.9, 136.7, 146.4, 150.6, 158.8, 161.1, 161.6; HRMS (FAB) calcd for $[M + H]^+$ $C_{34}H_{24}F_3NO_4S$ 600.1456, obsd 600.1450.

General Procedure for the Preparation of 16a,b to 20a,b. To a solution of **9** in 1.5 mL of THF at −78 °C was rapidly added freshly prepared LDA (1.05 equiv). After stirring for 30−60 s at −78 °C, the electrophile was added and the solution was left stirring for 2−15 min at −78 °C before quenching with 2% aqueous $KHSO_4$. The solution was extracted three times with DCM, and the combined organic layers were dried (Na_2SO_4), filtered, and

concentrated; the residue was purified by column chromatography (heptane/EtOAc, 5/2 for **16**, **17**, and **18**, 2/1 for **19** and **20**) giving **16**−**20**.

2-Bromo-8-cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (16a). **9a** (24 mg, 0.061 mmol), electrophile = bromotrichloromethane (0.015 mL, 0.153 mmol), gave **16a** as a foam (26.7 mg, 93%): mp 99−100 °C; IR (neat) 3009, 1740, 1655, 1468, and 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.72−0.78 (m, 2H), 1.00−1.07 (m, 2H), 1.71−1.80 (m, 1H), 3.96 (s, 3H), 4.51 (s, 2H), 5.90 (s, 1H), 7.19−7.23 (m, 1H), 7.37−7.51 (m, 3H), 7.75−7.81 (m, 2H), 7.84−7.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8 (2C), 10.9, 36.2, 53.5, 103.5, 112.1, 112.2, 123.5, 125.5, 125.8, 126.3, 127.3, 127.7, 128.9, 130.6, 131.8, 133.8, 133.9, 146.6, 153.9, 158.0, 160.0; HRMS (FAB) calcd for $[M + H]^+$ $C_{23}H_{18}BrNO_3S$ 468.0269, obsd 468.0260.

2-Bromo-7-naphthalen-1-ylmethyl-5-oxo-8-(3-trifluoromethylphenyl)-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (16b). **9b** (30 mg, 0.061 mmol), electrophile = bromotrichloromethane (0.015 mL, 0.153 mmol), gave **16b** as a foam (30.4 mg, 87%): mp 100−102 °C; IR (neat) 3051, 2954, 1740, 1657, 1469, 1121, and 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.00 (s, 3H), 4.08 (s, 2H), 6.12 (s, 1H), 7.11−7.16 (m, 1H), 7.30−7.47 (m, 4H), 7.50−7.58 (m, 3H), 7.61−7.65 (m, 1H), 7.70−7.75 (m, 1H), 7.79−7.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.8, 53.7, 103.3, 112.3, 113.3, 123.2, 123.5 (q, J = 272.63 Hz), 125.3, 125.7, 125.8 (q, J = 3.65 Hz), 126.2, 126.6 (q, J = 3.75 Hz), 127.7, 127.9, 128.8, 130.2, 130.7, 131.5, 132.1 (q, J = 32.61 Hz), 133.2, 133.3, 133.8, 136.0, 146.9, 151.3, 157.9, 159.6; HRMS (FAB) calcd for $[M + H]^+$ $C_{27}H_{17}BrF_3NO_3S$ 572.0143, obsd 572.0129.

2-Chloro-8-cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (17a). **9a** (24 mg, 0.061 mmol), electrophile = benzenesulfonyl chloride (0.020 mL, 0.153 mmol), gave **17a** as a foam (19.4 mg, 75%): mp 94−95 °C; IR (neat) 3002, 2949, 1738, 1654, 1469, and 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.72−0.79 (m, 2H), 1.00−1.08 (m, 2H), 1.71−1.81 (m, 1H), 3.96 (s, 3H), 4.51 (s, 2H), 5.91 (s, 1H), 7.19−7.24 (m, 1H), 7.37−7.52 (m, 3H), 7.75−7.82 (m, 2H), 7.85−7.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8 (2C), 10.9, 36.3, 53.6, 112.2, 112.4, 120.0, 123.6, 125.5, 125.8, 126.3, 127.4, 127.8, 128.1, 128.9, 131.8, 133.8, 134.0, 144.9, 153.9, 158.1, 159.5; HRMS (FAB) calcd for $[M + H]^+$ $C_{23}H_{18}ClNO_3S$ 424.0774, obsd 424.0778.

2-Chloro-7-naphthalen-1-ylmethyl-5-oxo-8-(3-trifluoromethylphenyl)-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (17b). **9b** (30 mg, 0.061 mmol), electrophile = benzenesulfonyl chloride (0.020 mL, 0.153 mmol), gave **17b** as a foam (24.4 mg, 76%): mp 99−100 °C; IR (neat) 3022, 2945, 1741, 1663, 1470, and 1120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.99 (s, 3H), 4.08 (s, 2H), 6.13 (s, 1H), 7.11−7.16 (m, 1H), 7.30−7.48 (m, 4H), 7.50−7.59 (m, 3H), 7.61−7.66 (m, 1H), 7.71−7.75 (m, 1H), 7.79−7.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.8, 53.7, 112.5, 113.4, 119.9, 123.2, 123.6 (q, J = 272.56 Hz), 125.3, 125.7, 125.9 (q, J = 3.70 Hz), 126.3, 126.6 (q, J = 3.67 Hz), 127.7, 127.9, 128.3, 128.8, 130.3, 131.5, 132.1 (q, J = 32.59 Hz), 133.16, 133.23, 133.8, 135.9, 145.2, 151.4, 158.0, 159.1; HRMS (FAB) calcd for $[M + H]^+$ $C_{27}H_{17}ClF_3NO_3S$ 528.0648, obsd 528.0651.

8-Cyclopropyl-2-methyl-7-naphthalen-1-ylmethyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (18a). **9a** (24 mg, 0.061 mmol), electrophile = iodomethane (0.0095 mL, 0.153 mmol), gave **18a** as a foam (22.2 mg, 90%): mp 184−185 °C; IR (neat) 1731, 1646, 1465, and 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.71−0.78 (m, 2H), 0.97−1.05 (m, 2H), 1.71−1.80 (m, 1H), 2.37 (s, 3H), 3.92 (s, 3H), 4.52 (s, 2H), 5.90 (s, 1H), 7.19−7.24 (m, 1H), 7.36−7.42 (m, 1H), 7.43−7.50 (m, 2H), 7.74−7.79 (m, 1H), 7.80−7.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8 (2C), 10.9, 11.8, 36.1, 53.1, 111.7, 111.9, 123.6, 125.5, 125.7, 126.2, 126.3, 127.0, 127.3, 127.6, 128.8, 131.9, 133.9, 134.3, 146.5, 153.1, 158.6, 161.5; HRMS (FAB) calcd for $[M + H]^+$ $C_{24}H_{21}NO_3S$ 404.1320, obsd 404.1313.

2-Methyl-7-naphthalen-1-ylmethyl-5-oxo-8-(3-trifluoromethylphenyl)-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (18b). **9b** (30 mg, 0.061 mmol), electrophile = iodomethane (0.0095 mL, 0.153 mmol), gave **18b** as a foam (20.0 mg, 65%): mp 107−108 °C; IR (neat) 3042, 2950, 1734, 1656, 1470, 1120, and 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.96 (s, 3H), 4.09 (s, 2H), 6.11 (s, 1H), 7.12−7.17 (m, 1H), 7.30−7.64 (m, 8H), 7.70−7.75 (m, 1H), 7.79−7.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 36.7, 53.3, 111.9, 113.1, 123.4, 123.7 (q, J = 272.45 Hz), 125.3, 125.5 (q, J = 3.80 Hz), 125.6, 126.2, 126.5, 126.8 (q, J = 3.66 Hz), 127.7, 127.8, 128.8, 130.0, 131.6, 131.9 (q, J = 32.61 Hz), 133.4 (broad), 133.7, 133.9, 136.7, 146.7, 150.5, 158.6, 161.0; HRMS (FAB) calcd for $[M + H]^+$ $C_{28}H_{20}F_3NO_3S$ 508.1194, obsd 508.1191.

2-Benzoyl-8-cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (19a). **9a** (24 mg, 0.061 mmol), electrophile = benzoyl chloride (0.018 mL, 0.153 mmol), gave **19a** as a foam (21.7 mg, 72%): mp 100−102 °C; IR (neat) 1747, 1666, 1241, 1003, and 713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.76−0.83 (m, 2H), 1.04−1.12 (m, 2H), 1.76−1.85 (m, 1H), 3.71 (s, 3H), 4.55 (s, 2H), 5.92 (s, 1H), 7.21−7.26 (m, 1H), 7.38−7.56 (m, 5H), 7.62−7.68 (m, 1H), 7.76−7.91 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.0 (2C), 10.9, 36.4, 53.3, 112.0, 112.1, 123.6, 125.5, 125.7, 125.8, 126.3, 127.4, 127.8, 128.6 (2C), 128.8 (2C), 128.9, 131.8, 133.6, 133.8, 134.0, 134.8, 136.8, 146.4, 155.4, 159.1, 160.2, 186.5; HRMS (FAB) calcd for $[M + H]^+$ $C_{30}H_{23}NO_4S$ 494.1426, obsd 494.1424.

2-Benzoyl-7-naphthalen-1-ylmethyl-5-oxo-8-(3-trifluoromethylphenyl)-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (19b). **9b** (30 mg, 0.061 mmol), electrophile = benzoyl chloride (0.018 mL, 0.153 mmol), gave **19b** as a foam (27.0 mg, 74%): mp 114−115 °C; IR (neat) 3057, 2951, 1740, 1662, 1470, 1258, and 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 4.10 (s, 2H), 6.14 (s, 1H), 7.13−7.17 (m, 1H), 7.32−7.65 (m, 11H), 7.72−7.85 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.0, 53.5, 112.2, 113.3, 123.2, 123.6 (q, J = 272.73 Hz), 125.3, 125.5, 125.7, 125.9 (q, J = 3.72 Hz), 126.3, 126.7 (q, J = 3.46 Hz), 127.7, 128.0, 128.6 (2C), 128.7 (2C), 128.8, 130.3, 131.5, 132.1 (q, J = 32.54 Hz), 133.2, 133.3, 133.7, 133.9, 134.8, 136.0, 136.5, 146.6, 152.7, 159.0, 159.9, 185.9; HRMS (FAB) calcd for $[M + H]^+$ $C_{34}H_{22}F_3NO_4S$ 598.1300, obsd 598.1296.

8-Cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-2-phenylcarbamoyl-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (20a). **9a** (24 mg, 0.061 mmol), electrophile = phenyl isocyanate (0.017 mL, 0.153 mmol), gave **20a** as a foam (24.2 mg, 78%): mp 138−139 °C; IR (neat) 3009, 2950, 1742, 1654, 1467, 1435, 1245, and 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.79−0.85 (m, 2H), 1.07−1.14 (m, 2H), 1.79−1.88 (m, 1H), 3.98 (s, 3H), 4.55 (s, 2H), 5.90 (s, 1H), 7.16−7.22 (m, 1H), 7.24−7.28 (m, 1H), 7.34−7.52 (m, 5H), 7.60−7.65 (m, 2H), 7.77−7.82 (m, 2H), 7.86−7.91 (m, 1H), 9.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.0 (2C), 10.9, 36.4, 54.2, 111.7, 112.4, 120.1 (2C), 123.6, 125.4, 125.5, 125.8, 126.3, 127.6, 127.8, 128.2, 128.8, 128.9, 129.2 (2C), 131.9, 133.8, 134.0, 137.0, 145.8, 155.2, 156.6, 159.3, 162.7; HRMS (FAB) calcd for $[M + H]^+$ $C_{30}H_{24}N_2O_4S$ 509.1535, obsd 509.1528.

7-Naphthalen-1-ylmethyl-5-oxo-2-phenylcarbamoyl-8-(3-trifluoromethylphenyl)-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic Acid Methyl Ester (20b). **9b** (30 mg, 0.061 mmol), electrophile = phenyl isocyanate (0.017 mL, 0.153 mmol), gave **20b** as a foam (28.1 mg, 75%): mp 139−140 °C; IR (neat) 3047, 1735, 1657,

1468, 1326, 1255, and 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.02 (s, 3H), 4.11 (s, 2H), 6.12 (s, 1H), 7.14−7.21 (m, 2H), 7.32−7.69 (m, 12H), 7.73−7.78 (m, 1H), 7.81−7.86 (m, 1H), 9.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.9, 54.4, 111.9, 113.6, 120.1 (2C), 123.3, 123.6 (q, J = 272.75 Hz), 125.4, 125.5, 125.8, 125.9 (q, J = 3.69 Hz), 126.3, 126.8 (q, J = 3.67 Hz), 127.9, 128.0, 128.2, 128.9, 129.2, 129.3 (2C), 130.4, 131.5, 132.2 (q, J = 32.89 Hz), 133.25, 133.30, 133.9, 135.9, 136.8, 146.1, 152.6, 156.0, 159.2, 162.3; HRMS (FAB) calcd for $[M + H]^+$ $C_{34}H_{23}F_3N_2O_4S$ 613.1409, obsd 613.1417.

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra of **9a**,**b**−**20a**,**b**. Temperature, pressure, and power graphs for microwave heating of **14a**,**b** and **15a**,**b**. General experimental section. This material is available free of charge via the Internet at http://pubs.acs.org.

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