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Original article

Synthesis and application of a bromomethyl substituted scaffold to be used for efficient optimization of anti-virulence activity

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ABSTRACT

Pilicides are a class of compounds that attenuate virulence in Gram negative bacteria by blocking the chaperone/usher pathway in *Escherichia coli*. It has also been shown that compounds derived from the peptidomimetic scaffold that the pilicides are based on can prevent both Aβ aggregation and curli formation. To facilitate optimizations towards the different targets, a new synthetic platform has been developed that enables fast and simple introduction of various substituents in position C-7 on the peptidomimetic scaffold. Importantly, this strategy also enables introduction of previously unattainable heteroatoms in this position. Pivotal to the synthetic strategy is the synthesis of a C-7 bromomethyl substituted derivative of the ring-fused dihydrothiazolo 2-pyridone pilicide scaffold. From this versatile and reactive intermediate various heteroatom-linked substituents could be introduced on the scaffold including amines, ethers, amides and sulfonamides. In addition, carbon-carbon bonds could be introduced to the sp^3-hybridized bromomethyl substituted scaffold by Suzuki–Miyaura cross couplings. Evaluation of the 24 C-7 substituted compounds in whole-bacterial assays provided important structure–activity data and resulted in the identification of a number of new pilicides with activity as good or better than those developed previously.

1. Introduction

Anti-virulence strategies are one potential way to meet the immense need for new antibacterial drugs with new modes of action that arise in the wake of the global spread of bacterial resistance [1,2]. Pilicides constitute a class of low molecular weight compounds that target bacterial virulence in Gram negative bacteria, thus rendering the bacteria unable to cause disease but still fully viable [3,4]. In theory, this should result in a reduced selective pressure on resistant bacteria and simultaneously be more benign to the human microbiota.

The pilicides prevent assembly of extracellular proteinaceous fibres, pili or fimbriae, important in many stages of bacterial infections, by targeting the chaperone/usher pathway (demonstrated for uropathogenic *Escherichia coli*) [4]. In the chaperone/usher pathway the pilus subunits are incorporated in the growing pilus fiber via an outer membrane assembly site called the usher [5–7]. Partial folding and transportation of the pilus subunits from the bacterial inner membrane through the periplasm to the usher is accomplished by the chaperone [8–10]. The pilicides have been shown to bind to the same residues on the chaperone as the usher and thereby block binding of chaperone-subunit complexes to the usher [4,11]. Hence, by interfering with the chaperone/usher pathway the pilicides block pilus assembly. Considering that this assembly pathway is highly conserved [12], the pilicides could potentially be applicable towards many bacterial strains.

The peptidomimetic pilicide scaffold (**3**) is synthesized via an acyl-ketene imine cyclocondensation from Meldrum's acid derivatives (**1**) and Δ^2-thiazolines (**2**) (Fig. 1) [13–15]. In this reaction the substituents from the Δ^2-thiazolines and Meldrum's acid derivatives are introduced in position C-7 and C-8, respectively.

An early study of the pilicide scaffold **3** based on seven aryl and alkyl C-7 substituents and *in vitro* assay data suggested that a naphthyl substituent in position C-7 on the scaffold is beneficial for pilicide activity (e.g. pilicide **5** and **6**, Fig. 2) [16]. As a result, the

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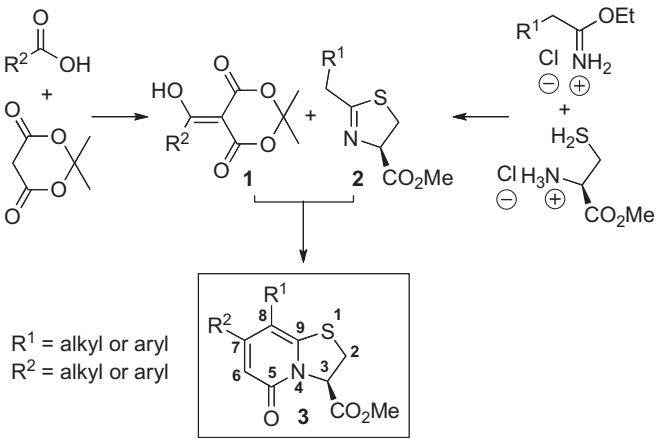


Fig. 1. From Meldrum's acid derivatives (**1**) and Δ^2-thiazolines (**2**) the ring-fused dihydrothiazolo 2-pyridone scaffold (**3**) is synthesized via an acyl-ketene imine cyclocondensation [13,14].

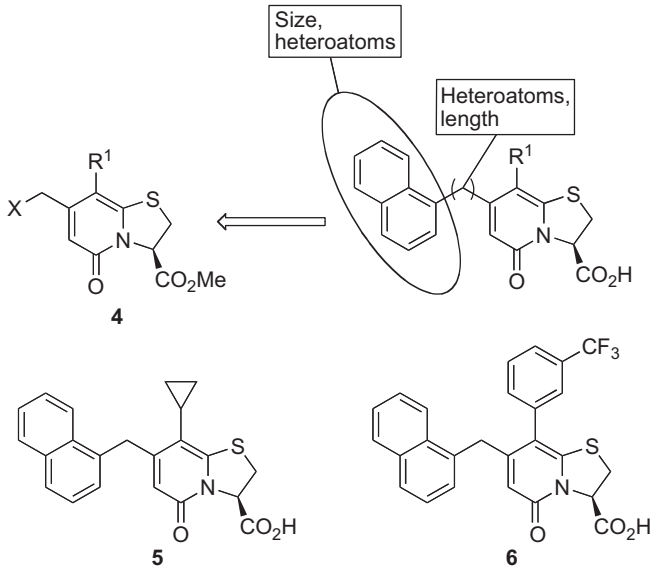


Fig. 2. Synthesis of a scaffold with a reactive C-7 group (**4**) for efficient introduction of various C-7 substituents. Known pilicides with CH_2-1-naphthyl substituent in C-7 (R^2) and a cyclopropyl (**5**) or 3-CF_3-phenyl (**6**) C-8 (R^1) substituent [16–18].

C-7-naphthyl substituent has been used in all of the following studies of the pilicides. The lack of more comprehensive C-7 SAR including heteroatoms can mainly be explained by the synthetic method's inherent restrictions both in terms of possible substituents in the synthesis of acyl Meldrum's acid derivatives but also in the subsequent acyl-ketene imine cyclocondensation. Furthermore, the synthesis of a diverse set of C-7 substituted analogues via the original synthesis, by synthesis of a new Meldrum's acid derivative for every compound, is both ineffective and time-consuming. As a consequence, we wanted to develop a synthetic platform that enable introduction of various C-7 substituents by fast and simple transformations. The strategy is to synthesize a large amount of the scaffold with a reactive C-7 "handle" for late introduction of the various substituents.

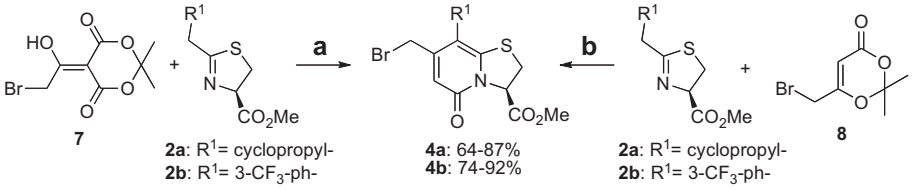
Here we describe the synthesis of the bromomethyl-substituted pilicide scaffold **4a** and **4b** and the efficient use of these versatile scaffolds for introduction of various C-7 substituents. The two C-8 (R^1) substituents with different size were selected from previously reported pilicides **5** and **6** (Fig. 2) [16–18]. From the two brominated compounds (**4a** and **4b**) C-7 substituents were introduced by reactions with amines or alcohols. Primary amines were also prepared via substitution with azide followed by reduction, and these were reacted further to generate amides and sulfonamides. In addition, the versatility of this reactive scaffold was further expanded to include carbon–carbon bonds that were introduced via Suzuki–Miyaura cross couplings on the sp^3-hybridized carbon. All generated compounds as carboxylic acids were biologically evaluated in biofilm and HA-titer assays.

2. Results and discussion

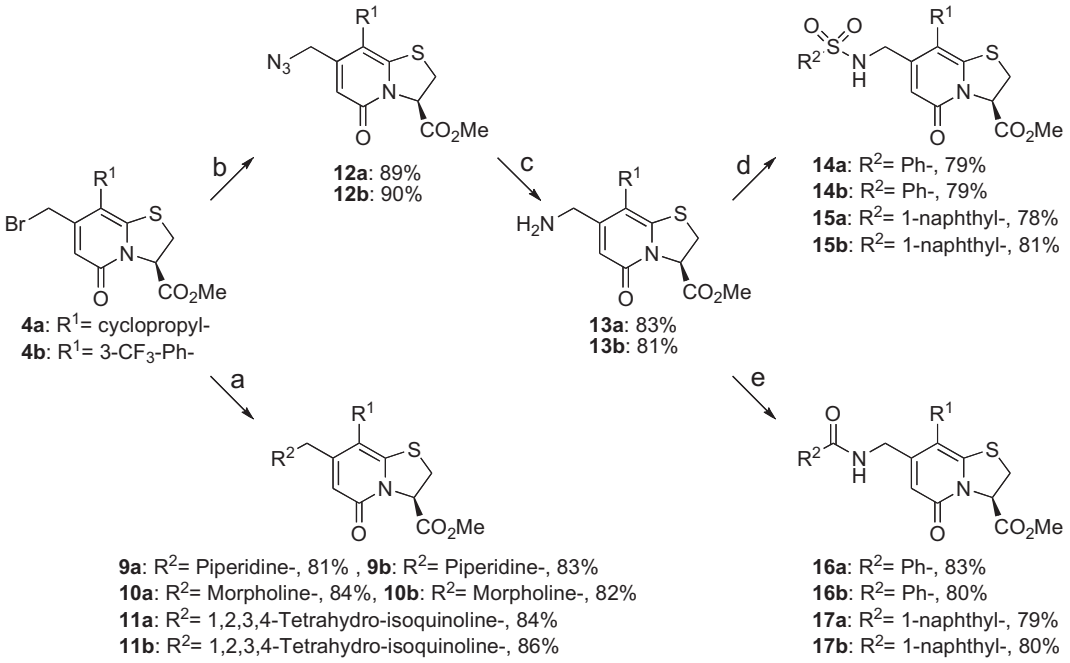
2.1. Synthesis

The common starting point for introduction of C-7 substituents in this paper is the bromomethyl-substituted scaffold **4a** and **4b** (Scheme 1). To obtain these compounds, the corresponding brominated Meldrum's acid derivative (**7**) was desired. By slightly modifying the standard conditions, Meldrum's acid derivative (**7**) could be synthesized by coupling Meldrum's acid with bromoacetic acid. Reacting **7** with the Δ^2-thiazolines **2a** and **2b** generated the target compounds **4a** and **4b** in high yields (Scheme 1). However, the purity of **7** proved to be important and repeated recrystallizations were necessary to obtain high and reproducible yields. As a consequence, an alternative approach to generate the key compounds **4a** and **4b** was also developed using a different acyl-ketene source (**8**). Synthesis of **8** could be accomplished by starting from the corresponding γ-brominated β-keto acid, obtained by a previously described procedure for similar compounds [19]. Subsequent ring closure of the γ-brominated β-keto acid using conc. H_2SO_4, Ac_2O, and acetone gave the desired bromo-dioxinone **8**. Using this acyl-ketene source in the cyclocondensation with the Δ^2-thiazolines gave reproducible yields of **4a** and **4b** (64% and 74%, respectively) (Scheme 1).

Having established robust methods for the synthesis of these compounds, introduction of various C-7 substitutents was next attempted. Introduction of amines was straightforward. Reactions of **4a** and **4b** with piperidine, morpholine or 1,2,3,4-tetrahydroisoquinoline in DMF resulted in high yields of **9a**, **b**–**11a**, **b** (Scheme 2). Synthesis of primary amines was accomplished in a two-step process. First sodium azide was added to **4a** or **4b** giving **12a** and **12b** in 89% and 90% yields, respectively. This was followed by reduction using zinc and ammonium chloride to give **13a** and **13b** in 83% and 81% yields, respectively (Scheme 2). From these



Scheme 1. (a) TFA, dichloroethane, MWI: 140 °C, 2.5 min (**4a** and **4b**: 87% and 92%, respectively); (b) TFA, dichloroethane, microwave irradiation: 140 °C, 2 min (**4a** and **4b**: 64% and 74%, respectively).



Scheme 2. (a) Amine (piperidine, morpholine or 1,2,3,4-tetrahydroisoquinoline), DMF, rt, 30 min (**9a**: 81%, **9b**: 83%, **10a**: 84%, **10b**: 82%, **11a**: 84%, **11b**: 86%); (b) NaN_3, DMF, rt, 15 min (**12a**,**b**: 89% and 90%, respectively); (c) Zn, NH_4Cl, EtOH:H_2O (3:1), rt, 20 min (**13a**,**b**: 83% and 81%, respectively); (d) benzenesulfonyl chloride or 1-naphthalenesulfonyl chloride, NEt_3, CH_2Cl_2, rt, o.n. (**14a**: 79%, **14b**: 79%, **15a**: 78%, **15b**: 81%); (e) benzoyl chloride or 1-naphthoyl chloride, NEt_3, CH_2Cl_2, rt, o.n. (**16a**: 83%, **16b**: 80%, **17a**: 79%, **17b**: 80%).

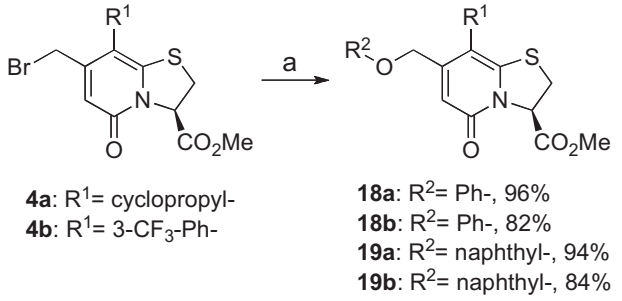
primary amines, compounds with C-7 amide and sulfonamide substituents could be synthesized. Sulfonamides were prepared by reacting amines **13a** or **13b** with phenylsulfonyl or 1-naphthylsulfonyl chloride to give **14a**, **b** and **15a**, **b** in 78–81% yields. The amides were generated in a similar manner by reacting **13a** or **13b** with benzoyl or 1-naphthoyl chloride to give **16a**, **b** and **17a**, **b** in 79–83% yields (Scheme 2).

After successful use of **4a** and **4b** to introduce a C–N linkage (e.g. amines, amides and sulfonamides) the possibilities to use the same substrates for introduction of a C–O linkage were investigated. The presence of both a stereogenic centrum and a methyl ester in **4a** and **4b** made the choice of proper reaction conditions crucial to avoid epimerization and re-esterification. Fortunately, the use of Cs_2CO_3 in combination with phenol or naphthol in DMF at 0 °C gave **18a**, **b**–**19a**, **b** in high yields (82–96%, Scheme 3).

To further expand the use of the bromomethyl substituted scaffold for C-7 derivatization, by late introduction of various substituents, the possibility to introduce carbon-carbon bonds was investigated. Because CH_2-aryl substituents in position C-7 previously was shown to result in interesting pilicide properties, the use of Suzuki–Miyaura cross couplings for introduction of various aryl substituents was applied. However, directly applying previously developed methods for Suzuki–Miyaura couplings of **4a** and **4b** gave poor conversion (Table 1, entry 1) [11]. To improve the reaction conditions for use on the bromomethyl substituted scaffold three different Pd-catalysts were tested ($Pd(PPh_3)_2Cl_2$, Pd-NHC ([1,3-Bis(2,6-Diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichlorid), and $Pd(PPh_3)_4$). The results are summarized in Table 1.

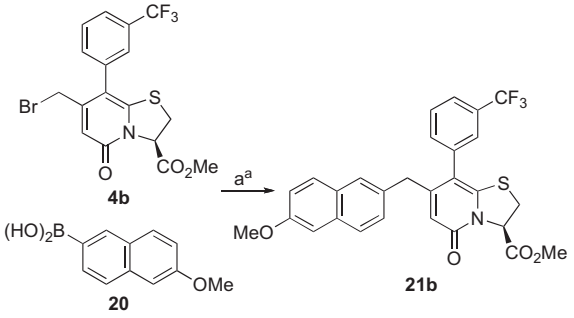
The yields were significantly improved at lower catalyst loadings by the use of $Pd(PPh_3)_2Cl_2$ (Table 1, entry 2). Using these conditions, three different boronic acids were coupled to the two bromomethyl substituted scaffolds **4a** and **4b** (Table 2).

In all cases the method generated the desired products in acceptable yields. The methoxynaphthyl and indole boronic acids



Scheme 3. (a) Phenol or naphthol, DMF, Cs_2CO_3, 3A MS, 0 °C, 3 h (**18a**: 96%, **18b**: 82%, **19a**: 94%, **19b**: 84%).

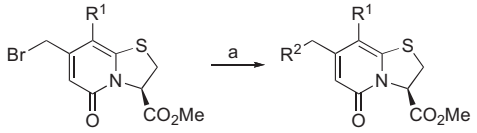
Table 1
Testing different Pd-catalysts for Suzuki–Miyaura cross couplings.[a]



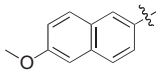
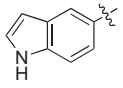
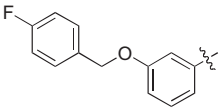
Entry	Pd-catalyst	Amount catalyst (mol%)	Yield[b] (%)
1	$Pd(OAc)_2$	10	11
2	$Pd(PPh_3)_2Cl_2$	5	84
3	Pd-NHC	5	50
4	$Pd(PPh_3)_4$	5	65

[a] KF, MeOH, microwave irradiation: 110 °C, 10 min.
[b] Isolated yields.

Table 2
Synthesis of C-7 CH_2-aryl substituents by Suzuki–Miyaura cross couplings.



4a: R^1= cyclopropyl-
4b: R^1= 3-CF_3-Ph-

Entry	R^1	Compound	R^2	Yield[a] (%)
1	Cyclopropyl-	**21a**		72
2	3-CF_3-Ph-	**21b**		84
3	Cyclopropyl-	**22a**		77
4	3-CF_3-Ph-	**22b**		88
5	Cyclopropyl-	**23a**		56
6	3-CF_3-Ph-	**23b**		61

[a] Isolated yields.

gave best results (Entries 1–4, Table 2) while the p-fluorobenzyloxy substituted phenyl gave slightly lower yields (Entries 5–6, Table 2).

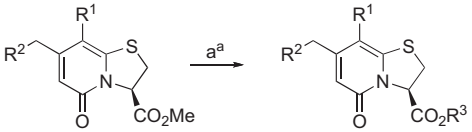
2.2. Biological evaluation

A previous study has shown that a free carboxylic acid or lithium carboxylate is important for a retained pilicide activity [16,17]. As a consequence, the methyl ester functionality in each of the C7-substitued derivatives of the pilicide scaffold described above was hydrolyzed before being evaluated for their ability to prevent biofilm formation (Table 3). The biofilm formation assay is based on the ability of *E. coli* to form type 1 pilus-dependent biofilms on PVC surfaces [20]. Blocking type 1 pili formation in this assay also prevents the ability of the bacteria to form biofilm and the amount of biofilm that is formed in the presence of pilicide is thus related to the potency of the compound in blocking pili formation. This assay is based on whole bacteria and, thus, generates more relevant biological information than elementary *in vitro* binding assays.

First, all compounds were screened for their ability to prevent biofilm formation at 200 μM. Compounds having a 60% or higher inhibition of biofilm formation at this concentration was considered interesting and were further diluted to generate EC_{50}-values. The results are summarized in Table 3.

We found that proper substitution of position C-7 on the pilicide scaffold was highly important for the biological response

Table 3
Biological evaluation of the compounds ability to prevent biofilm formation.[a]



9a,b-11a,b
14a,b-19a,b
21a,b-23a,b

24a,b-35a,b

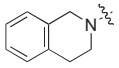
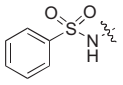
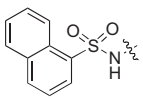
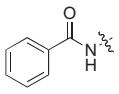
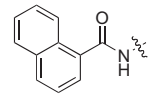
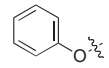
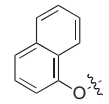
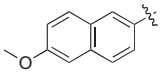
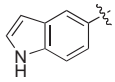
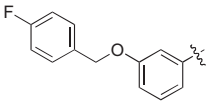
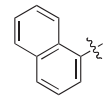
Entry	Substrate	Prod	R^1	R^2	R^3	200 μM	EC_{50} (μM)[b]
1	**9a**	**24a**	Cyclopropyl-		Li	NA[c]	–
2	**9b**	**24b**	3-CF_3-Ph-		Li	30%	–
3	**10a**	**25a**	Cyclopropyl-		Li	NA[c]	–
4	**10b**	**25b**	3-CF_3-Ph-		Li	NA[c]	–
5	**11a**	**26a**	Cyclopropyl-		Li	NA[c]	–
6	**11b**	**26b**	3-CF_3-Ph-		Li	84%	130
7	**14a**	**27a**	Cyclopropyl-		H	NA[c]	–
8	**14b**	**27b**	3-CF_3-Ph-		H	48%	–
9	**15a**	**28a**	Cyclopropyl-		H	NA[c]	–
10	**15b**	**28b**	3-CF_3-Ph-		H	91%	38
11	**16a**	**29a**	Cyclopropyl-		H	NA[c]	–
12	**16b**	**29b**	3-CF_3-Ph-		H	NA[c]	–

Table 3 (*continued*).

Entry	Substrate	Prod	R^1	R^2	R^3	200 μM	EC_{50} (μM)[b]
13	**17a**	**30a**	Cyclopropyl-		H	NA[c]	–
14	**17b**	**30b**	3-CF_3-Ph-		H	65%	130
15	**18a**	**31a**	Cyclopropyl-		H	43%	–
16	**18b**	**31b**	3-CF_3-Ph-		H	80%	21
17	**19a**	**32a**	Cyclopropyl-		H	96%	32
18	**19b**	**32b**	3-CF_3-Ph-		H	72%	37
21	**21a**	**33a**	Cyclopropyl-		H	NA[c]	–
22	**21b**	**33b**	3-CF_3-Ph-		H	93%	9
23	**22a**	**34a**	Cyclopropyl-		H	37%	–
24	**22b**	**34b**	3-CF_3-Ph-		H	97%	30
25	**23a**	**35a**	Cyclopropyl-		H	76%	43
26	**23b**	**35b**	3-CF_3-Ph-		H	75%	(3)[d]
27	–	**5**	Cyclopropyl-		H	54%	189
28	–	**6**	3-CF_3-Ph-		H	92%	17

[a] LiOH, THF, rt, 4–24 h, (for **27a-35b**: acidic work up), yields normally over 90%, see Section 4 for details.
[b] Estimated from triplicates on every concentration.
[c] Not active.
[d] Never reached higher than 80% inhibition even at 200 μM.

and that it was possible to improve activity over the parent naphthyl substituent in **5** and **6** by varying this position. In general, the cyclopropyl series of compounds did not show as high activity as the 3-CF_3-phenyl series (Table 3, **24**–**35a** vs. **24**–**35b**). However, the 1-naphthoxy substituent in **32a** is noteworthy as it has a 6-fold increased potency compared to the parent 1-naphthyl substituent in **5** (Table 3, entry 17 vs. 27). Nevertheless, best of all compounds was **33b** carrying the 6-methoxy-2-naphthyl substituent with an estimated EC_{50} of 9 μM (Table 3, entry 22). Compound **35b** also displayed interesting properties, although it never completely inhibited the biofilm formation even at higher concentrations, it reached 50% biofilm inhibition at as low as 3 μM, again showing on the potential of varying this position (Table 3, entry 26).

Exchange of the 1-naphthyl substituent in **6** to a 1-naphthyl sulfonamide as in **28b** retained much of the pilicide activity and proved to be preferable compared to the 1-naphthyl amide in **30b** (Table 3, entries 10, 14 and 28). All smaller substituents resulted in inactive compounds except for the phenoxy substituent in **31b** that quite unexpectedly showed activity in the same range as the parent pilicide **6** (Table 3, entries 1–4, 7, 8, 11, 12, 15 and 16). It should also be noted that none of the compounds showed any effect on bacterial growth at 200 μM (Fig. S1 in Supporting Information). Furthermore, the best compounds were evaluated in a hemagglutination (HA) titer assay (Table S1 in Supporting Information) to verify that the observed biofilm inhibition is a result of reduced pili formation. In this assay, the degree of piliation of the culture is related to the HA titer. Thus, after growth in the presence of pilicide, the HA titers are determined to evaluate the potencies of the compounds in blocking pilus formation. Gratifyingly this correlated well with the observed biofilm inhibition and showed that these compounds did indeed prevent pili formation. Finally, an initial study of the cytotoxic properties of **28b**, **31b**, **32a,b**, **33b**, **34b**, **35a**, **b**, **5**, and **6** against HeLa cells was performed as a control experiment. This showed that none of the tested compounds displayed toxicity close to the estimated EC_{50} concentrations (Fig. S2 in Supporting Information).

3. Conclusion

A synthetic platform has been developed that gave access to analogues carrying various C-7 substituents, including some that previously were unattainable, by simple and fast transformations. Central to the strategy is the synthesis of a C-7 bromomethyl substituted scaffold onto which substituents were introduced by different methods. First, amines and ethers were introduced in a straightforward manner by substitution reactions. Secondly, introduction of amides and sulfonamides were realized via the free amine. Finally, the scaffold could further be used to introduce carbon-carbon bonds via Suzuki–Miyaura couplings. After ester

hydrolysis, all compounds were evaluated in a biofilm assay and, to verify pilicide activity, also further tested in a HA titer assay. From this we learned that the nature of the substituents at the C-7 position is highly important for pilicide activity. It should be possible to further improve and fine-tune the activity by substituent variation at this position. In general, sterically more demanding substituents seem to be favorable, the heteroatom-linked ethers and Suzuki–Miyaura coupled aryl substituents being most promising. Interestingly, the basic amine substituents and the smaller amide- and sulfonamide-linked substituents mainly resulted in inactive compounds.

The herein developed synthetic platform is not only beneficial in the optimization process of the pilicides but will in the future also be highly useful in the design of peptidomimetics towards other biological targets.

4. Experimental

4.1. General synthesis

All reactions were carried out under inert atmosphere, with dry solvents and anhydrous conditions, unless otherwise stated. DMF was distilled from P_2O_5 and dried over 3 Å molecular sieves. EtOH, MeOH was dried over 3 Å molecular sieves. Zinc dust was activated by stirring in 10% HCl for 2 min and then filtered and washed with water and acetone. HCl (g) was passed through concentrated H_2SO_4 prior to use. TLC was performed on Silica Gel 60 F254 (Merck) using UV light detection. Flash column chromatography employed normal phase silica gel (Matrex, 60 Å, 35–70 μm, Grace Amicon). ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 or a Bruker DRX-360 in $CDCl_3$ [residual $CHCl_3$ (δ_H 7.26 ppm) or $CDCl_3$ (δ_C 77.0 ppm) as internal standard], CD_3OD [residual CD_3OD (δ_H 3.31 ppm) or CD_3OD (δ_C 49.0 ppm) as internal standard], DMSO-d_6 [residual DMSO (δ_H 2.50 ppm) or DMSO-d_6 (δ_C 40.0 ppm) as internal standard] at 298 K. Microwave reactions were carried out using a monomode reactor (Smith Creator, Biotage AB) in Teflon septa capped 0.5–2 mL or 2–5 mL Smith TM process vials with stirring. Reaction times refer to irradiation time at target temperature, as measured by IR sensor. IR spectra were recorded on an FTIR spectrometer. Melting points are uncorrected.

4.2. Synthesis of **2a** and **2b**

2a and **2b** were synthesized according to previously published procedures. Data in agreement with published data [15,21].

4.3. 4-Bromo-3-oxo-butyric acid

Tert-butyl acetoacetate (2.0 mL, 12 mmol) was dissolved in $CHCl_3$ (6 mL) and cooled to 0 °C. Br_2 (0.62 mL, 12 mmol) dissolved in $CHCl_3$ (3 mL) was added dropwise over 45 min, and the reaction was stirred for 17 h (0 °C → rt). For the last 2 h, air was bubbled through the solution. The crude reaction mixture was purified by column chromatography on silca gel (heptane:EtOAc:AcOH 80:19:1). 1.5 g of the desired product was isolated as a colourless solid (69% yield). ^1H NMR (400 MHz, $CDCl_3$) δ (Keto form) 3.79 (s, 2H), 4.05 (s, 2H), (Enol form) 3.87 (s, 2H), 5.35 (s, 1H), 11.61 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 33.8, 45.5, 91.0, 172.1, 173.5, 176.2, 194.4.

4.4. 6-Bromomethyl-2,2-dimethyl-[1,3]dioxin-4-one (**8**)

4-Bromo-3-oxo-butyric acid (1.00 g, 5.53 mmol) was dissolved in acetone (0.81 mL, 11 mmol) and Ac_2O (1.57 mL, 16.6 mmol) and cooled to 0 °C. Conc. H_2SO_4 (0.10 mL, 1.8 mmol) was added and the reaction was stirred for 3 h. The reaction was quenched with saturated $NaHCO_3$ (aq) and extracted with CH_2Cl_2. The solvent was dried (Na_2SO_4), filtered and concentrated to give a brown oil. The crude product was used in the next step without purification. ^1H NMR (400 MHz, $CDCl_3$) δ 1.72 (s, 6H), 3.88 (s, 2H), 5.53 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9 (2C), 27.0, 95.9, 107.7, 160.6, 164.5.

4.5. (3R)-7-Bromomethyl-8-cyclopropyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (**4a**)

4.5.1. Using **7**

*4.5.1.1. Synthesis of **7**.* Bromoacetic acid (5.00 g, 36.0 mmol, 1 eq), DMAP (4.84 g, 39.6 mmol, 1.1 eq) and Meldrum's acid (5.70 g, 39.6 mmol, 1.1 eq) were dissolved in 350 mL CH_2Cl_2 at 0 °C. DCC (8.54 g, 41.4 mmol, 1.15 eq) dissolved in 50 mL CH_2Cl_2 was added dropwise to the solution over 10 minutes. The reaction mixture was then left at room temperature over night. The reaction was quenched with 6% (aq.) $KHSO_4$ and the resulting precipitate was filtered off. The filtrate was then washed twice with 6% $KHSO_4$, dried with $NaSO_4$, filtrated, and concentrated giving **7** as an oil (6.77 g, 71% yield) that was used without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 1.74 (s, 6H), 4.65 (s, 2H).

*4.5.1.2. Synthesis of **4a**.* **7** (1.33 g, 5.02 mmol) and **2a** (0.76 g, 2.51 mmol, 1 eq) were dissolved in 8 mL 1,2-dichloroethane. TFA (0.194 mL, 2.51 mmol) was added to the stirring solution and the reaction vessel was sealed and heated for 140 seconds at 120 °C using microwave irradiation. The solution was diluted with CH_2Cl_2 and washed with water, $NaHCO_3$ (aq. saturated), and brine followed by drying with Na_2SO_4, filtration, and concentration. Purification by column chromatography (heptane:ethylacetate 1:6) gave **4a** as a foam (0.75 g, 87%).

4.5.2. Using **8**

2a (0.54 g, 2.7 mmol) and **8** (1.5 g, 6.8 mmol) was dissolved in 1,2-dichloroethane (4 mL) and TFA (0.21 mL, 2.7 mmol) was added. The reaction was heated in the microwave oven at 140 °C for 2 min. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ (aq), the organic phase was dried (Na_2SO_4), filtered and concentrated. The crude product was purified by column chromatography on silica gel (heptane:EtOAc 50:50 → 30:70). The desired product was isolated as a foam (0.6 g, 64% yield). $[\alpha]_D = -106$ (c 0.5, $CHCl_3$). IR (ν cm^{-1}) 1746, 1648, 1577, 1481, and 1425. HRMS (ES^+) calcd $[M + H^+]$ for $C_{13}H_{14}BrNO_3S$ 343.9956 obsd 343.9962. ^1H NMR (400 MHz, $CDCl_3$) δ, 0.60–0.72 (m, 2H), 0.87–1.01 (m, 2H), 1.66–1.76 (m, 1H), 3.49 (dd, $J = 2.4$, 11.8 Hz, 1H), 3.65 (dd, $J = 8.6$, 11.8 Hz, 1H), 3.77 (s, 3H), 4.31–4.52 (m, 2H), 5.56 (dd, $J = 2.4$, 8.6 Hz, 1H), 6.32 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.1, 7.4, 10.5, 29.1, 31.8, 53.4, 62.9, 112.7, 116.3, 148.7, 152.6, 161.0, 168.4.

4.6. (3R)-7-Bromomethyl-5-oxo-8-(3-trifluoromethyl-phenyl)-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (**4b**)

4.6.1. Using **7**

Prepared according to the procedure described for compound **4a** starting from **7** (1.33 g, 5.02 mmol) and **2b** (0.760 g, 2.51 mmol). Giving **4b** as a foam (1.03 g, 92%).

4.6.2. Using **8**

Prepared according to the procedure described for compound **4a** starting from **8** (0.910 g, 4.13 mmol), **2b** (0.500 g, 1.65 mmol) 1,2-dichloroethane (4 mL) and TFA (0.13 mL, 1.7 mmol). The crude product was purified by column chromatography on silica gel

(heptane:EtOAc 40:60) giving **4b** as a foam (0.55 g, 74% yield). $[\alpha]_D = -124$ (*c* 0.5, $CHCl_3$). IR (ν cm^{-1}) 1748, 1653, 1579, 1482, 1435, and 1327. HRMS (ES^+) calcd $[M+H^+]$ for $C_{17}H_{13}BrF_3NO_3S$ 447.9830 obsd 447.9841. ^1H NMR (400 MHz, $CDCl_3$) δ 3.47–3.53 (m, 1H), 3.66–3.75 (m, 1H), 3.84 (s, 3H), 3.89–4.04 (m, 2H), 5.66 (dd, $J = 2.4$, 8.6 Hz, 1H), 6.47 (s, 1H), 7.51-7.71 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7, 32.0, 53.6, 63.8, 113.5, 116.6, 123.9 (q, $J = 271$ Hz, 1C), 125.7, 127.1 and 127.3 (1C), 129.7, 131.5 (splitted q, $J = 33$ Hz, 1C), 133.6 and 133.9 (1C), 135.9, 148.7, 149.9, 161.0, 168.2.

4.7. General procedure for the preparation of **9a**, **b**–**11a**, **b**

Amine (piperidine or morpholine or 1,2,3,4-tetrahydroisoquinoline, 2 mmol) was added dropwise to a stirred solution of **4a** or **4b** (1 mmol) in dry DMF (8 mL) at rt under nitrogen atmosphere. After being stirred for 30 min or till disappearance of starting material, the reaction was quenched with aqueous saturated NH_4Cl, and the solution was extracted with dichloromethane, dried over Na_2SO_4, and concentrated. Purification by silica gel chromatography (heptane:EtOAc, 1:9) gave **9a**, **b**–**11a**, **b**.

4.7.1. (3R)-8-cyclopropyl-7-piperidino-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid methyl ester (**9a**)

From **4a** (0.065 g, 0.19 mmol) and piperidine (0.037 mL, 0.38 mmol) was prepared **9a** (0.053 g, 81%) as an oil. $[\alpha]_D = -107$ (*c* 0.5, $CHCl_3$). IR (ν cm^{-1}) 1754, 1650, 1583, 1494, and 1206. HRMS (ES^+) calcd $[M+H^+]$ for $C_{18}H_{25}N_2O_3S$ 349.1586 obsd 389.1611. ^1H NMR (400 MHz, $CDCl_3$) δ 0.54–0.63 (m, 2H), 0.80–0.92 (m, 2H), 1.37–1.48 (m, 2H), 1.51–1.68 (m, 5H), 2.34–2.47 (m, 4H), 3.28–3.52 (m, 3H), 3.63 (dd, $J_1 = 8.54$ Hz, $J_2 = 11.67$ Hz, 1H), 3.78 (s, 3H), 5.57 (dd, $J_1 = 2.30$ Hz, $J_2 = 8.50$ Hz, 1H), 6.46 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.2, 7.5, 10.8, 24.3, 26.1 (2C), 31.6, 53.1, 54.9 (2C), 60.2, 62.7, 113.5, 114.3, 146.4, 155.0, 161.5, 168.8.

4.7.2. (3R)-8-cyclopropyl-7-morpholino-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid methyl ester (**10a**)

From **4a** (0.052 g, 0.15 mmol) and morpholine (0.026 mL, 0.30 mmol) was prepared **10a** (0.044 g, 84%) as a foam, m.p. 153–154 °C. $[\alpha]_D = -27$ (*c* 0.5, $CHCl_3$). IR (ν cm^{-1}) 1752, 1652, 1581, 1490, and 1208. HRMS (ES^+) calcd $[M+H^+]$ for $C_{17}H_{23}N_2O_4S$ 351.1379 obsd 351.1376. ^1H NMR (400 MHz, $CDCl_3$) δ 0.55–0.64 (m, 2H), 0.81–0.94 (m, 2H), 1.59–1.69 (m, 1H), 2.43–2.54 (m, 4H), 3.39–3.55 (m, 3H), 3.58–3.74 (m, 5H), 3.78 (s, 3H), 5.57 (dd, $J_1 = 2.34$ Hz, $J_2 = 8.54$ Hz, 1H), 6.44 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.3, 7.4, 10.7, 31.6, 53.2, 53.8 (2C), 59.7, 62.7, 67.0 (2C), 113.4, 114.4, 147.0, 153.8, 161.4, 168.6.

4.7.3. (3R)-8-cyclopropyl-7-tetrahydroisoquinolino-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid methyl ester (**11a**)

From **4a** (0.100 g, 0.290 mmol) and 1,2,3,4-tetrahydroisoquinoline (0.073 mL, 0.58 mmol) was prepared **11a** (0.096 g, 84%), as an oil. $[\alpha]_D = -83$ (*c* 0.5, $CHCl_3$). IR (ν cm^{-1}) 1749, 1649, 1577, 1488, 1434, and 1209. HRMS (ES^+) calcd $[M+H^+]$ for $C_{22}H_{25}N_2O_3S$ 397.1586 obsd 397.1585. ^1H NMR (400 MHz, $CDCl_3$) δ 0.58–0.68 (m, 2H), 0.81–0.96 (m, 2H), 1.66–1.75 (m, 1H), 2.72–2.84 (m, 2H), 2.88–2.94 (m, 2H), 3.49 (dd, $J_1 = 2.33$ Hz, $J_2 = 11.71$ Hz, 1H), 3.56–3.76 (m, 5H), 3.80 (s, 3H), 5.59 (dd, $J_1 = 2.31$ Hz, $J_2 = 8.52$ Hz, 1H), 6.49 (s, 1H), 6.97–7.02 (m, 1H), 7.07–7.16 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.2, 7.4, 10.8, 29.3, 31.6, 51.1, 53.2, 56.2, 59.5, 62.7, 113.6, 114.5, 125.5, 126.1, 126.4, 128.6, 134.3, 134.7, 146.9, 154.3, 161.4, 168.7.

4.7.4. (3R)-8-(3-Trifluoromethyl)phenyl-7-piperidino-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid methyl ester (**9b**)

From **4b** (0.012 g, 0.27 mmol) and piperidine (0.052 mL, 0.53 mmol) was prepared **9b** (0.100 g, 83%) as an oil. $[\alpha]_D = -52$ (*c* 0.5, $CHCl_3$). IR (ν cm^{-1}) 2936, 1753, 1656, 1583, 1485, 1437, and 1329. HRMS (ES^+) calcd $[M+H^+]$ for $C_{22}H_{24}F_3N_2O_3S$ 453.1460 obsd 453.1461. ^1H NMR (400 MHz, $CDCl_3$) δ 1.29–1.47 (m, 6H), 2.08–2.31 (m, 4H), 2.86–3.02 (m, 2H), 3.46 (dd, $J_1 = 2.25$ Hz, $J_2 = 11.70$ Hz, 1H), 3.67 (dd, $J_1 = 8.55$ Hz, $J_2 = 11.69$ Hz, 1H), 3.83 (s, 3H), 5.65 (dd, $J_1 = 2.31$ Hz, $J_2 = 8.51$ Hz, 1H), 6.44 (s, 1H), 7.41–7.71 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 25.8 (2C), 31.7, 53.3, 54.3 (2C), 60.6, 63.5, 114.8 (broad), 115.3 (broad), 123.9 (q, $J = 272.3$ Hz), 124.8 (broad and split $J = 3.60$ Hz), 127.2 (q, $J = 3.70$ Hz), 128.9, 130.8 (q, $J = 31.17$ Hz), 133.4, 137.2, 146.8, 151.9 (broad), 161.3, 168.4.

4.7.5. (3R)-8-(3-Trifluoromethyl)phenyl-7-morpholino-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid methyl ester (**10b**)

From **4b** (0.23 g, 0.51 mmol) and morpholine (0.089 mL, 1.0 mmol) was prepared **10b** (0.19 g, 82%), as an oil. $[\alpha]_D = -64$ (*c* 0.5, $CHCl_3$). IR (ν cm^{-1}) 1753, 1656, 1583, 1485, 1436, and 1330. HRMS (ES^+) calcd $[M+H^+]$ for $C_{21}H_{22}F_3N_2O_4S$ 455.1252 obsd 455.1251. ^1H NMR (400 MHz, $CDCl_3$) δ 2.11–2.34 (m, 4H), 2.89–3.03 (m, 2H), 3.43 (dd, $J_1 = 2.26$ Hz, $J_2 = 11.79$ Hz, 1H), 3.46–3.54 (m, 4H), 3.64 (dd, $J_1 = 8.51$ Hz, $J_2 = 11.78$ Hz, 1H), 3.77 (s, 3H), 5.60 (dd, $J_1 = 2.17$ Hz, $J_2 = 8.51$ Hz, 1H), 6.36 (s, 1H), 7.38–7.67 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.7, 53.2 (2C), 53.4, 60.1, 63.5, 66.8 (2C), 114.5 (broad), 115.6 (broad), 123.9 (q, $J = 272.3$ Hz), 124.9 (broad), 127.2 (broad), 129.0, 130.9 (q, $J = 34.7$ Hz), 133.4 (broad), 137.0, 147.3, 150.6 (broad), 161.1, 168.3.

4.7.6. (3R)-8-(3-Trifluoromethyl)phenyl-7-tetrahydroisoquinolino-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid methyl ester (**11b**)

From **4b** (0.078 g, 0.17 mmol) and 1,2,3,4-tetrahydroisoquinoline (0.043 mL, 0.35 mmol) was prepared **11b** (0.075 g, 86%) as a foam, m.p. 70–72 °C. $[\alpha]_D = -77$ (*c* 0.5, $CHCl_3$). IR (ν cm^{-1}) 1751, 1655, 1582, 1484, 1436, and 1327. HRMS (ES^+) calcd $[M+H^+]$ for $C_{26}H_{24}F_3N_2O_3S$ 501.1460 obsd 501.1456. ^1H NMR (400 MHz, $CDCl_3$) δ 2.51–2.68 (m, 2H), 2.74–2.84 (m, 2H), 3.13–3.28 (m, 2H), 3.44–3.58 (m, 3H), 3.68 (dd, $J_1 = 8.59$ Hz, $J_2 = 11.62$ Hz, 1H), 3.85 (s, 3H), 5.67 (dd, $J_1 = 2.16$ Hz, $J_2 = 8.51$ Hz, 1H), 6.55 (s, 1H), 6.90–6.97 (m, 1H), 7.03–7.15 (m, 3H), 7.46–7.72 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.0, 31.7, 50.8, 53.3, 55.5, 59.6, 63.5, 114.5 (broad), 115.2 (broad), 123.8 (q, $J = 272.5$ Hz), 124.9 (broad), 125.5, 126.0, 126.3, 127.0 (broad), 128.5, 129.0, 130.9 (q, $J = 33.71$ Hz), 133.6 (broad), 134.0, 134.3, 136.9, 147.1, 151.2, 161.2, 168.3.

4.8. General procedure for the preparation of **12a**, **b**

To a stirred solution of **4a** or **4b** (1 mmol) in dry DMF (5 mL) was added sodium azide (1.6 mmol) and the mixture was stirred under nitrogen atmosphere at rt for 15 min or till disappearance of starting material. The reaction mixture was diluted with water and extracted with dichloromethane, dried over Na_2SO_4, and concentrated. Purification by silica gel chromatography (heptane:EtOAc, 1:9) gave **12a** or **12b.**

4.8.1. (3R)-8-cyclopropyl-7-azido-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid methyl ester (**12a**)

From **4a** (1.20 g, 3.49 mmol) and sodium azide (0.379 g, 5.58 mmol) was prepared **12a** (0.95 g, 89%) an oil. $[\alpha]_D = -179$ (*c* 0.5, $CHCl_3$). IR (ν cm^{-1}) 2103, 1750, 1653, 1583, 1490, and 1433. ^1H NMR (400 MHz, $CDCl_3$) δ 0.47–0.56 (m, 2H), 0.74–0.91 (m, 2H),

1.43–1.53 (m, 1H), 3.40 (dd, $J_1 = 2.19$ Hz, $J_2 = 11.78$ Hz, 1H), 3.59 (dd, $J_1 = 8.70$ Hz, $J_2 = 11.74$ Hz, 1H), 3.68 (s, 3H), 4.27–4.38 (m, 2H), 5.47 (dd, $J_1 = 2.13$ Hz, $J_2 = 8.63$ Hz, 1H), 6.20 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.87, 6.95, 9.9, 31.3, 51.4, 52.9, 62.4, 111.3, 113.3, 148.0, 150.6, 160.5, 168.1.

4.8.2. (3R)-8-(3-Trifluoromethyl)phenyl-7-azido-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid methyl ester (**12b**)

From **4b** (0.50 g, 1.1 mmol) and sodium azide (0.120 g, 1.79 mmol) was prepared **12b** (0.41 g, 90%) as a foam, m.p. 142–143 °C. $[\alpha]_D = 0$ (*c* 0.5, $CHCl_3$). IR (ν cm^{-1}) 2116, 1755, 1655, 1501, 1480, 1338, and 1312. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (dd, $J_1 = 1.96$ Hz, $J_2 = 11.79$ Hz, 1H), 3.70 (dd, $J_1 = 8.89$ Hz, $J_2 = 11.48$ Hz, 1H), 3.82 (s, 3H), 3.89–4.00 (m, 2H), 5.66 (dd, $J_1 = 2.24$ Hz, $J_2 = 8.58$ Hz, 1H), 6.43 (s, 1H), 7.43–7.50 (m, 1H), 7.51–7.62 (m, 2H), 7.64–7.69 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8, 51.8, 53.4, 63.5, 112.6, 114.5, 123.6 (q, $J = 272.6$ Hz), 125.5 (q, $J = 3.7$ Hz), 126.7 (broad), 129.7, 131.5 (q, $J = 35.6$ Hz), 133.3 (broad and split $J = 33.4$ Hz), 135.8, 147.9, 148.2, 160.7, 168.0.

4.9. General procedure for the preparation of **13a**, **b**

To a stirred solution of **12a** or **12b** (1 mmol) in a mixture of ethanol and water (3:1, 8 mL) was added activated zinc (6 mmol) and ammonium chloride (6 mmol) and the mixture was stirred at rt for 20 min or till complete disappearance of starting material. The reaction mixture was filtered (the residue was washed with ethanol), and the solvent was removed under reduced pressure. The obtained solid mass was dissolved in CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated to give **13a** or **13b** as a light yellow solid. Used for the next step without further purification.

4.9.1. (3R)-8-cyclopropyl-7-amino-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid methyl ester (**13a**)

From **12a** (1.00 g, 3.26 mmol), zinc (1.27 g, 19.5 mmol) and ammonium chloride (1.04 g, 19.5 mmol) was prepared **13a** (0.76 g, 83%) as an oil, m.p. 157–159 °C. $[\alpha]_D = -174$ (*c* 0.5, MeOH). IR (ν cm^{-1}) 1742, 1642, 1550, 1491, and 1438. ^{1}H NMR (400 MHz, MeOD) δ 0.58–0.74 (m, 2H), 0.88–1.08 (m, 2H), 1.63–1.74 (m, 1H), 3.62 (dd, $J_1 = 2.09$ Hz, $J_2 = 12.05$ Hz, 1H), 3.78 (s, 3H), 3.86 (dd, $J_1 = 8.99$ Hz, $J_2 = 12.05$ Hz, 1H), 4.20–4.38 (m, 2H), 5.66 (dd, $J_1 = 2.06$ Hz, $J_2 = 8.98$ Hz, 1H), 6.28 (s, 1H).

4.9.2. (3R)-8-(3-Trifluoromethyl)phenyl-7-amino-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid methyl ester (**13b**)

From **12b** (0.500 g, 0.122 mmol), zinc (0.047 g, 0.73 mmol) and ammonium chloride (0.039 g, 0.73 mmol) was prepared **13b** (0.034 g, 81%) as an oil, m.p. 185–187 °C. $[\alpha]_D = -23$ (*c* 0.5, $CHCl_3$). IR (ν cm^{-1}) 1746, 1646, 1560, 1484, 1437, and 1328. ^{1}H NMR (400 MHz, MeOD) δ 3.58–3.67 (m, 1H), 3.72–3.86 (m, 5H), 3.87–3.99 (m, 1H), 5.73–5.80 (m, 1H), 6.49 (s, 1H), 7.57–7.66 (m, 1H), 7.67–7.81 (m, 3H).

4.10. General procedure for the preparation of **14a**, **b**–**17a**, **b**

To a stirred solution of **13a** or **13b** (1 mmol) and triethylamine (3 mmol) in CH_2Cl_2 (8 mL) was added acylating agent (benzoyl chloride or 1-naphthoyl chloride, 1.5 mmol) or sulfonylating agent (benzenesulfonyl chloride or 1-naphthalenesulfonyl chloride, 1.5 mmol) dropwise and the mixture was stirred under nitrogen atmosphere at rt over night. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and aqueous $KHSO_4$ (2%), dried over Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography (heptane:EtOAc, 1:9 to 0:1) gave **14a**, **b**–**17a**, **b**.

4.10.1. (3R)-8-cyclopropyl-7-benzenesulfonamido-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid methyl ester (**14a**)

From **13a** (0.050 g, 0.18 mmol), 1-benzenesulphonyl chloride (0.034 mL, 0.27 mmol) and triethylamine (0.069 mL, 0.53 mmol) was prepared **14a** (0.059 g, 79%) as a foam, m.p. 108–110 °C. $[\alpha]_D = -170$ (*c* 0.5, $CHCl_3$). IR (ν cm^{-1}) 1751, 1655, 1568, 1498, and 1321. HRMS (ES^+) calcd $[M + H^+]$ for $C_{19}H_{21}N_2O_5S_2$ 421.0892 obsd 421.0895. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.48–0.61 (m, 2H), 0.74–0.92 (m, 2H), 1.43–1.52 (m, 1H), 3.44–3.52 (m, 1H), 3.62–3.72 (m, 1H), 3.75 (s, 3H), 4.04–4.25 (m, 2H), 5.71–5.78 (m, 1H), 6.31 (s, 1H), 6.64–6.70 (m, 1H), 7.45–7.58 (m, 3H), 7.84–7.92 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.2, 7.4, 10.2, 31.7, 43.8, 53.3, 62.9, 112.9, 113.0, 126.9 (2C), 129.0 (2C), 132.5, 140.1, 148.1, 153.3, 161.4, 168.4.

4.10.2. (3R)-8-cyclopropyl-7-naphthalenesulfonamido-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid methyl ester (**15a**)

From **13a** (0.065 g, 0.23 mmol), 1-naphthalenesulfonyl chloride (0.079 mL, 0.35 mmol) and triethylamine (0.090 mL, 0.70 mmol) was prepared **15a** (0.085 g, 78%) as a foam, m.p. 102–104 °C. $[\alpha]_D = -152$ (*c* 0.5, $CHCl_3$). IR (ν cm^{-1}) 1749, 1648, 1570, 1493, and 1322. HRMS (ES^+) calcd $[M + H^+]$ for $C_{23}H_{23}N_2O_5S_2$ 471.1048 obsd 471.1052. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.39–0.48 (m, 2H), 0.61–0.72 (m, 2H), 1.28–1.37 (m, 1H), 3.44 (dd, $J_1 = 1.99$ Hz, $J_2 = 11.75$ Hz, 1H), 3.61 (dd, $J_1 = 8.63$ Hz, $J_2 = 11.71$ Hz, 1H), 3.74 (s, 3H), 4.01–4.22 (m, 2H), 5.65 (dd, $J_1 = 1.95$ Hz, $J_2 = 8.54$ Hz, 1H), 6.23 (s, 1H), 6.64–6.69 (m, 1H), 7.44–7.66 (m, 3H), 7.89–7.95 (m, 1H), 8.02–8.07 (m, 1H), 8.24–8.29 (m, 1H), 8.72–8.77 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.0, 7.3, 10.1, 31.7, 43.9, 53.2, 62.8, 112.5, 113.6, 124.0, 124.6, 126.9, 128.2, 128.3, 128.8, 129.4, 134.2 (2C), 135.0, 147.9, 152.8, 161.1, 168.4.

4.10.3. (3R)-8-cyclopropyl-7-benzamido-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid methyl ester (**16a**)

From **13a** (0.073 g, 0.26 mmol), benzoyl chloride (0.055 mL, 0.39 mmol) and triethylamine (0.102 mL, 0.783 mmol) was prepared **16a** (0.083 g, 83%) as a foam, m.p. 88–90 °C. $[\alpha]_D = -158$ (*c* 0.5, $CHCl_3$). IR (ν cm^{-1}) 3290, 1749, 1641, 1582, and 1488. HRMS (ES^+) calcd $[M + H^+]$ for $C_{20}H_{21}N_2O_4S$ 385.1222 obsd 385.1224. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.58–0.70 (m, 2H), 0.83–1.00 (m, 2H), 1.51–1.62 (m, 1H), 3.42–3.52 (m, 1H), 3.59–3.68 (m, 1H), 3.75 (s, 3H), 4.45–4.84 (m, 2H), 5.47–5.58 (m, 1H), 6.20 (s, 1H), 7.30–7.36 (bs, 1H), 7.35–7.54 (m, 3H), 7.81–7.90 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.3, 7.5, 10.3, 31.7, 40.8, 53.2, 62.7, 111.9, 112.7, 127.1 (2C), 128.5 (2C), 131.6, 133.8, 147.6, 154.7, 161.3, 167.5, 168.5.

4.10.4. (3R)-8-cyclopropyl-7-naphthalamido-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid methyl ester (**17a**)

From **13a** (0.052 g, 0.19 mmol), 1-naphthoyl chloride (0.042 mL, 0.28 mmol) and triethylamine (0.072 mL, 0.56 mmol) was prepared **17a** (0.063 g, 79%) as a foam, m.p. 82–84 °C. $[\alpha]_D = -144$ (*c* 0.5, $CHCl_3$). IR (ν cm^{-1}) 3270, 1749, 1641, and 1492. HRMS (ES^+) calcd $[M + H^+]$ for $C_{24}H_{23}N_2O_4S$ 435.1379 obsd 435.1383. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.62–0.71 (m, 2H), 0.84–1.03 (m, 2H), 1.55–1.66 (m, 1H), 3.44 (dd, $J_1 = 2.08$ Hz, $J_2 = 11.81$ Hz, 1H), 3.58 (dd, $J_1 = 8.60$ Hz, $J_2 = 11.72$ Hz, 1H), 3.74 (s, 3H), 4.58–4.83 (m, 2H), 5.39–5.45 (m, 1H), 6.28 (s, 1H), 6.90 (s, 1H), 7.36–7.43 (m, 1H), 7.46–7.55 (m, 2H), 7.63–7.69 (m, 1H), 7.81–7.91 (m, 2H), 8.28–8.33 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.4, 7.5, 10.4, 31.6, 40.7, 53.2,

62.7, 111.8, 112.5, 124.6, 125.2, 125.4, 126.4, 127.2, 128.2, 130.1, 130.7, 133.6, 133.7, 147.7, 154.3, 161.2, 168.4, 169.6.

4.10.5. (3R)-8-(3-Trifluoromethyl)phenyl-7-benzenesulfonamido-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid methyl ester (**14b**)

From **13b** (0.027 g, 0.073 mmol), 1-benzenesulfonyl chloride (0.014 mL, 0.11 mmol) and triethylamine (0.029 mL, 0.21 mmol) was prepared **14b** (0.029 g, 79%) as a foam, m.p. 184–186 °C. $[\alpha]_D = -65$ (*c* 0.5, $CHCl_3$). IR (ν cm^{-1}) 3109, 1755, 1657, 1572, 1503, 1486, 1441, and 1321. HRMS (ES^+) calcd $[M+H^+]$ for $C_{23}H_{20}F_3N_2O_5S_2$ 525.0766 obsd 525.0769. ^1H NMR (400 MHz, $CDCl_3$) δ 3.45–3.52 (m, 1H), 3.65–3.78 (m, 3H), 3.80–3.84 (m, 3H), 5.75–5.83 (m, 1H), 6.09–6.24 (m, 1H), 6.43–6.48 (m, 1H), 7.37–7.57 (m, 6H), 7.62–7.67 (m, 1H), 7.72–7.78 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8, 44.3, 53.4, 63.7, 113.4 (broad), 113.6 (broad), 123.7 (q, $J = 272.7$ Hz), 125.5 (broad), 126.8 (broad, 3C), 129.1 (2C), 129.7, 131.4 (q, $J = 31.7$ Hz), 132.6, 133.4 (broad and split, $J = 33.4$ Hz), 135.6 (broad), 139.8, 148.1, 150.3, 161.3, 168.1.

4.10.6. (3R)-8-(3-Trifluoromethyl)phenyl-7-naphthale nesulfonamido-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid methyl ester (**15b**)

From **13b** (0.043 g, 0.11 mmol), 1-naphthalenesulfonyl chloride (0.037 mL, 0.17 mmol) and triethylamine (0.043 mL, 0.33 mmol) was prepared **15b** (0.052 g, 81%) as a foam, m.p. 112–114 °C. $[\alpha]_D = -53$ (*c* 0.5, $CHCl_3$). IR (ν cm^{-1}) 1751, 1653, 1576, 1486, 1437, and 1323. HRMS (ES^+) calcd $[M+H^+]$ for $C_{27}H_{22}F_3N_2O_5S_2$ 575.0922 obsd 575.0918. ^1H NMR (400 MHz, $CDCl_3$) δ 3.44 (dd, $J_1 = 1.84$ Hz, $J_2 = 11.77$ Hz, 1H), 3.62–3.73 (m, 3H), 3.80 (s, 3H), 5.68–5.78 (m, 1H), 5.82–5.99 (m, 1H), 6.41 (s, 1H), 7.27–7.32 (m, 1H), 7.33–7.50 (m, 3H), 7.53–7.68 (m, 3H), 7.91–7.96 (m, 1H), 8.01–8.06 (m, 1H), 8.10–8.15 (m, 1H), 8.59–8.65 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8, 44.3, 53.4, 63.6, 113.0, 114.0, 123.6 (q, $J = 272.6$ Hz), 124.1, 124.4, 125.4 (broad), 126.6 (broad and split, $J = 30.8$ Hz), 127.0, 128.0, 128.5, 129.1, 129.5, 129.6, 131.4 (q, $J = 32.5$ Hz), 133.3 (broad and split, $J = 39.5$ Hz), 134.3, 134.4 (2C), 135.6, 148.0, 149.8, 161.0, 168.1.

4.10.7. (3R)-8-(3-Trifluoromethyl)phenyl-7-benzamido-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid methyl ester (**16b**)

From **13b** (0.043 g, 0.11 mmol), benzoyl chloride (0.019 mL, 0.17 mmol) and triethylamine (0.042 mL, 0.33 mmol) was prepared **16b** (0.043 g, 80%) as a foam, m.p. 104–106 °C. $[\alpha]_D = -9$ (*c* 0.5, $CHCl_3$). IR (ν cm^{-1}) 3308, 1751, 1647, 1484, and 1324. HRMS (ES^+) calcd $[M+H^+]$ for $C_{24}H_{20}F_3N_2O_4S$ 489.1096 obsd 489.1099. ^1H NMR (400 MHz, $CDCl_3$) δ 3.42–3.50 (m, 1H), 3.61–3.71 (m, 1H), 3.77 (s, 3H), 3.94–4.44 (m, 2H), 5.59 (dd, $J_1 = 2.15$ Hz, $J_2 = 8.56$ Hz, 1H), 6.34 (s, 1H), 7.31–7.66 (m, 7H), 7.73–7.81 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.6 (broad), 41.2, 53.3, 63.5, 112.3, 113.5, 123.7 (q, $J = 272.7$ Hz), 125.4 (broad and split, $J = 3.6$ Hz), 126.7 (broad), 127.1 (2C), 128.4 (2C), 129.7 (broad), 131.3 (broad and split, $J = 33.1$ Hz), 131.6, 133.4 (broad and split, $J = 10.2$ Hz), 133.6 (broad), 136.0 (broad and split, $J = 6.6$ Hz), 147.6, 152.0, 161.2, 167.4 (broad and split, $J = 6.9$ Hz), 168.1.

4.10.8. (3R)-8-(3-Trifluoromethyl)phenyl-7-naphthalamido-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid methyl ester (**17b**)

From **13b** (0.026 g, 0.067 mmol), 1-naphthoyl chloride (0.015 mL, 0.10 mmol) and triethylamine (0.026 mL, 0.20 mmol) was prepared **17b** (0.028 g, 78%) as a foam, m.p. 124–127 °C. $[\alpha]_D = -3$ (*c* 0.5, $CHCl_3$). IR (ν cm^{-1}) 1751, 1648, 1484, and 1324. HRMS (ES^+) calcd $[M+H^+]$ for $C_{28}H_{22}F_3N_2O_4S$ 539.1252 obsd 539.1255. ^1H NMR (400 MHz, $CDCl_3$) δ 3.40–3.49 (m, 1H), 3.61 (dd, $J_1 = 8.60$ Hz, $J_2 = 11.70$ Hz, 1H), 3.80 (s, 3H), 4.08–4.47 (m, 2H), 5.47 (dd, $J_1 = 8.27$ Hz, $J_2 = 22.67$ Hz, 1H), 6.38 (s, 1H), 6.64–6.75 (m, 1H), 7.37–7.45 (m, 1H), 7.47–7.70 (m, 7H), 7.81–7.86 (m, 1H), 7.87–7.92 (m, 1H), 8.17–8.24 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.7, 41.3, 53.4, 63.4, 112.5 (broad and split, $J = 7.1$ Hz), 113.1, 123.7 (q, $J = 272.8$ Hz), 124.6, 125.1, 125.3, 125.5 (broad and split, $J = 73.6$ Hz), 126.5, 126.8 (broad), 127.2, 128.2, 129.8, 130.0, 130.9, 131.5 (q, $J = 32.7$ Hz), 133.6 (broad, 3C), 136.1 (broad and split, $J = 11.2$ Hz), 147.8, 151.4 (broad), 161.0, 168.1, 169.4.

4.10.9. (3R)-8-cyclopropyl-7-phenoxymethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (**18a**)

The procedure described for **18a** is representative.

A solution of **4a** (180 mg, 0.52 mmol) in dried DMF (10 mL) was stirred with 3 Å MS at 0 °C. After 5 min was added phenol (73 mg, 0.78 mmol) and cesium carbonate (254 mg, 0.78 mmol) and the reaction was stirred for 3 h at 0 °C. The reaction mixture was filtrated and was diluted with EtOAc and washed with water three times, and with brine. The organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude product was purified with column chromatography on silica gel (EtOAc:heptane, 5:1) to give **18a** (178 mg, 96%) as a white solid. $[\alpha]_D = -51$ (c 0.5, $CHCl_3$). IR (ν cm^{-1}) (neat) 1750, 1655, 1586, 1484, 1213 and 1117. HRMS (ES^+) calcd $[M+H^+]$ for C19H19NO4S 358.1113, obsd 358.1117. ^1H NMR (400 MHz, $CDCl_3$) δ 0.65–0.70 (m, 2H), 0.88–0.98 (m, 2H), 1.61–1.69 (m, 1H), 3.49–3.56 (m, 1H), 3.64–3.73 (m, 1H), 3.81 (s, 3H), 5.1 (s, 2H), 5.58–5.64 (m, 1H), 6.55 (s, 1H), 6.92–7.2 (m, 3H), 7.27–7.35 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.1, 7.2, 10.2, 31.8, 53.3, 62.8, 66.4, 77.4, 111.4, 114.7, 121.4, 129.6, 147.5, 152.5, 158.2, 161.3, 168.6.

4.10.10. (3R)-8-cyclopropyl-7-(naphthalen-1-yloxymethyl)-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (**19a**)

Prepared according to the procedure described for compound **18a** starting from **4a** (167 mg, 0.48 mmol). Purification by silica gel chromatography (EtOAc:heptane, 5:1) gave **19a** as a foam (183 mg, 94%). $[\alpha]_D = -50$ (c 0.5, $CHCl_3$). IR (ν cm^{-1}) (neat) 1749, 1652, 1549, 1493, 1268 and 1177. HRMS (ES^+) calcd $[M+H^+]$ for C23H21NO4S 408.1270, obsd 408.1281. ^1H NMR (400 MHz, $CDCl_3$) δ 0.65–0.70 (m, 2H), 0.88–0.96 (m, 2H), 1.61–1.69 (m, 1H), 3.47–3.54 (m, 1H), 3.61–3.67 (m, 1H), 3.80 (s, 3H), 5.2 (s, 2H), 5.58–5.64 (m, 1H), 6.71 (s, 1H), 6.80–6.84 (m, 1H), 7.25–7.37 (m, 1H), 7.44–7.52 (m, 3H), 7.78–7.83 (m, 1H), 8.33–8.38 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.2, 7.2, 10.3, 31.8, 53.4, 62.9, 66.5, 77.4, 105.0, 111.5, 112.8, 121.0, 122.1, 125.6, 125.7, 126.7, 127.5, 134.6, 147.6, 152.5, 153.9, 161.4, 168.7.

4.10.11. 5-Oxo-7-phenoxymethyl-8-(3-trifluoromethyl-phenyl)-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (**18b**)

Prepared according to the procedure described for compound **18a** starting from **4a** (111 mg, 0.25 mmol). Purification by silica gel chromatography (EtOAc:heptane, 5:1) gave **18b** as a foam (95 mg, 82%). $[\alpha]_D = -25$ (c 0.5, $CHCl_3$). IR (ν cm^{-1}) (neat) 1749, 1655, 1586, 1484, 1213 and 1117. HRMS (ES^+) calcd $[M+H^+]$ for C23H18F3NO4S 462.0987 obsd 462.0992. ^1H NMR (400 MHz, $CDCl_3$) δ 3.49–3.57 (m, 1H), 3.66–3.78 (m, 1H), 3.86 (s, 3H), 4.63 (s, 2H), 5.67–5.75 (m, 1H), 6.67 (s, 1H), 6.74–6.81 (m, 2H), 6.92–7.00 (m, 1H), 7.20–7.31 (m, 2H), 7.49–7.71 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.0, 53.6, 63.7, 66.8, 77.3, 112.5, 114.1, 114.8, 121.7, 123.9 (q, $J = 277.50$ Hz), 125.6, 126.9 (d, $J = 19.50$ Hz), 129.6, 129.7, 131.6 (q, $J = 41.94$ Hz), 133.3 (d, $J = 40.6$ Hz), 136.1, 147.8, 149.7, 157.9, 161.3, 168.4.

*4.10.12. 5-Oxo-7-(naphtalen-1-yloxymethyl)–8-(3-trifluoromethyl-phenyl)-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (**19b**)*

Prepared according to the procedure described for compound **18a** starting from **4a** (100 mg, 0.22 mmol). Purification by silica gel chromatography (EtOAc:heptane, 5:1) gave **19b** as a foam (95 mg, 84%). $[\alpha]_D$ = = −40 (c 0.5, $CHCl_3$). IR (ν cm^{-1}) (neat) 1749, 1657, 1584, 1481, 1209 and 1116. HRMS (ES^+) calcd $[M+H^+]$ for C27H20F3NO4S 512.1143 obsd 512.1151. ^1H NMR (400 MHz, $CDCl_3$) δ 3.50–3.56 (m, 1H), 3.67–3.77 (m, 1H), 3.87 (s, 3H), 4.80 (s, 2H), 5.70–5.75 (m, 1H), 6.54–6.59 (m, 1H), 6.83 (s, 1H), 7.24–7.31 (m, 1H), 7.40–7.45 (m, 1H), 7.46–7.53 (m, 2H), 7.53–7.58 (m, 2H), 7.62–7.69 (m, 2H), 7.76–7.81 (m, 1H), 8.20–8.26 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.0, 53.6, 63.8, 66.8, 105.0, 112.5, 113.9, 114.8, 121.3, 122.0, 123.9 (q, J = 32.70 Hz), 125.6, 125.7, 126.8, 126.8 (d, J = 25.54 Hz), 127.6, 129.7, 129.8, 131.7 (q, J = 275.83 Hz), 133.3 (d, J = 38.29 Hz), 134.6, 147.9, 149.7, 153.5, 161.3, 168.4.

*4.10.13. (3R)-8-cyclopropyl-7-(6-methoxy-naphthalen-2-ylmethyl)-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (**21a**)*

The procedure described for **21a** is representative for all Suzuki–Miyaura cross couplings.

4a (132 mg, 0.38 mmol), 6-methoxy-2-naphthaleneboronic acid (115 mg, 0.57 mmol), $Pd(PPh_3)_2Cl_2$ (13 mg, 0.019 mmol) and KF (44 mg, 0.76 mmol) was dissolved in dry MeOH (3 mL, dried over 3Å MS) and the reaction was heated by microwave irradiation at 110 °C for 10 min. The reaction mixture was diluted with saturated $NaHCO_3$ (aq) and extracted with EtOAc, the organic phase was dried (Na_2SO_4), filtered and concentrated. The crude product was purified by column chromatography on silica gel (heptane:EtOAc 50:50 → 20:80) giving **21a** as a colorless foam (115 mg, 72% yield). $[\alpha]_D$ = −132 (c 0.5, $CHCl_3$). IR (ν cm^{-1}) 1750, 1651, 1605, 1577, 1482. HRMS (ES^+) calcd $[M+H^+]$ for $C_{24}H_{23}NO_4S$ 422.1426 obsd 422.1422. ^1H NMR (400 MHz, $CDCl_3$) δ 0.59–0.70 (m, 2H), 0.80–0.97 (m, 2H), 1.36–1.45 (m, 1H), 3.46 (dd, J = 2.2, 11.8 Hz, 1H), 3.61 (dd, J = 8.5, 11.8 Hz, 1H), 3.78 (s, 3H), 3.89 (s, 3H), 4.00–4.17 (m, 2H), 5.58 (dd, J = 2.2, 8.5 Hz, 1H), 6.08 (s, 1H), 7.08–7.14 (m, 2H), 7.24–7.28 (m, 1H), 7.54 (s, 1H), 7.65 (t, J = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.7, 8.0, 11.3, 31.7, 39.3, 53.3, 55.3, 62.8, 105.7, 113.9, 115.7, 119.0, 127.1, 127.5, 128.0, 129.0, 129.1, 133.2, 133.4, 147.4, 157.1, 157.5, 161.4, 168.7.

*4.10.14. (3R)-8-cyclopropyl-7-(1H-indol-5-ylmethyl)-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (**22a**)*

Prepared according to the procedure described for compound **21a** starting from **4a** (132 mg, 0.38 mmol). Purification by silica gel chromatography (heptane:EtOAc 50:50 → 10:90) gave **22a** as a colorless foam (112 mg, 77% yield). $[\alpha]_D$ = −134 (c 0.5, $CHCl_3$). IR (ν cm^{-1}) 3224, 1745, 1640, 1564, 1486, 1422. HRMS (ES^+) calcd $[M+H^+]$ for $C_{21}H_{20}N_2O_3S$ 381.1273 obsd 381.1274. ^1H NMR (400 MHz, $CDCl_3$) δ 0.61–0.71 (m, 2H), 0.82–0.99 (m, 2H), 1.42–1.51 (m, 1H), 3.44 (dd, J = 2.0, 11.7 Hz, 1H), 3.58 (dd, J = 8.6, 11.7 Hz, 1H), 3.73 (s, 3H), 3.98–4.14 (m, 2H), 5.57 (dd, J = 2.0, 8.6 Hz, 1H), 6.14 (s, 1H), 6.40–6.44 (m, 1H), 6.91–6.96 (m, 1H), 7.12–7.16 (m, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.40–7.44 (m, 1H), 9.13 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.7, 8.0, 11.3, 31.6, 39.5, 53.2, 62.8, 101.7, 111.5, 114.5, 115.3, 120.8, 123.0, 125.0, 128.1, 128.7, 134.9, 147.2, 158.8, 161.6, 168.8.

*4.10.15. (3R)-8-cyclopropyl-7-[3-(4-fluoro-benzyloxy)-benzyl]-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (**23a**)*

Prepared according to the procedure described for compound **21a** starting from **4a** (150 mg, 0.44 mmol). Purification by HPLC (C_{18} 250 × 21.2 mm 5 μm, H_2O:MeCN 70:30 → 0:100 over 1 h, the eluent contained 0.1% TFA) gave **23a** as a colorless foam (115 mg, 56% yield). $[\alpha]_D$ = −130 (c 0.5, $CHCl_3$). IR (ν cm^{-1}) 1750, 1652, 1580, 1486. HRMS (ES^+) calcd $[M+H^+]$ for $C_{26}H_{24}FNO_4S$ 466.1488 obsd 466.1496. ^1H NMR (400 MHz, $CDCl_3$) δ 0.57–0.66 (m, 2H), 0.78–0.92 (m, 2H), 1.32–1.42 (m, 1H), 3.47 (dd, J = 2.3, 11.8 Hz, 1H), 3.63 (dd, J = 8.6, 11.8 Hz, 1H), 3.78 (s, 3H), 3.86–4.02 (m, 2H), 4.98 (s, 2H), 5.58 (dd, J = 2.3, 8.6 Hz, 1H), 6.04 (s, 1H), 6.74–6.85 (m, 3H), 7.02–7.09 (m, 2H), 7.18–7.23 (m, 1H), 7.35–7.41 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.7, 8.0, 11.3, 31.7, 39.3, 53.3, 62.8, 69.3, 112.9, 113.8, 115.4, 115.6, 115.7, 115.8, 122.0, 129.4, 129.5, 129.7, 132.8, 139.8, 147.4, 156.7, 158.9, 161.4, 162.5 (d, J = 245 Hz, 1C), 168.7.

*4.10.16. (3R)-7-(6-Methoxy-naphthalen-2-ylmethyl)-5-oxo-8-(3-trifluoromethyl-phenyl)-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (**21b**)*

Prepared according to the procedure described for compound **21a** starting from **4a** (22 mg, 0.05 mmol). Purification by silica gel chromatography (heptane:EtOAc 50:50 → 20:80) gave **21b** as a colorless foam (22 mg, 84% yield). $[\alpha]_D$ = −45 (c 0.5, $CHCl_3$). IR (ν cm^{-1}) 1750, 1652, 1606, 1579, 1481, 1435. HRMS (ES^+) calcd $[M+H^+]$ for $C_{28}H_{22}F_3NO_4S$ 526.1300 obsd 526.1305. ^1H NMR (400 MHz, $CDCl_3$) δ 3.44–3.50 (m, 1H), 3.63–3.71 (m, 3H), 3.84 (s, 3H), 3.90 (s, 3H), 5.66 (dd, J = 2.4, 8.6 Hz, 1H), 6.27 (s, 1H), 6.93–6.99 (m, 1H), 7.05–7.12 (m, 2H), 7.15 (s, 1H), 7.20–7.49 (m, 3H), 7.50–7.63 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.9, 39.8, 53.4, 55.3, 63.6, 105.6, 114.9, 115.9, 119.0, 123.8 (q, J = 272 Hz, 1C), 125.1, 127.1, 127.3, 127.5, 128.8, 129.0, 129.2 and 129.3 (1C), 131.2 (splitted q, J = 35 Hz, 1C), 132.3, 133.3, 133.6, 133.9, 137.0, 147.4, 154.2, 157.6, 161.3, 168.4.

*4.10.17. (3R)-7-Bromomethyl-5-oxo-8-(3-trifluoromethyl-phenyl)-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (**22b**)*

Prepared according to the procedure described for compound **21a** starting from **4a** (130 mg, 0.29 mmol). Purification by silica gel chromatography (heptane:EtOAc 50:50 → 20:80) gave **22b** as a colorless foam (124 mg, 88% yield). $[\alpha]_D$ = −50 (c 0.5, $CHCl_3$). IR (ν cm^{-1}) 3239, 1748, 1644, 1570, 1480, 1435, 1328. HRMS (ES^+) calcd $[M+H^+]$ for $C_{25}H_{19}F_3N_2O_3S$ 485.1147 obsd 485.1153. ^1H NMR (400 MHz, $CDCl_3$) δ 3.41–3.48 (m, 1H), 3.60–3.67 (m, 3H), 3.79 (s, 3H), 5.65 (dd, J = 2.3, 8.6 Hz, 1H), 6.27 (s, 1H), 6.37 (s, 1H), 6.63–6.72 (m, 1H), 7.06 (s, 1H), 7.12–7.20 (m, 2H), 7.27–7.49 (m, 3H), 7.58–7.64 (m, 1H), 8.71 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8, 40.0, 53.4, 63.7, 102.1, 111.3, 115.2, 115.7, 120.9, 122.9, 123.9 (q, J = 272 Hz, 1C), 124.9, 125.1, 127.2 and 127.4 (1C), 128.2, 129.3, 131.1 (splitted q, J = 32 Hz, 1C), 133.7, 134.0, 134.9, 137.2, 147.1, 155.6, 161.6, 168.5.

*4.10.18. (3R)-7-[3-(4-Fluoro-benzyloxy)-benzyl]-5-oxo-8-(3-trifluoromethyl-phenyl)-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (**23b**)*

Prepared according to the procedure described for compound **21a** starting from **4a** (130 mg, 0.29 mmol). Purification by HPLC (C_{18} 250 × 21.2 mm 5 μm, H_2O:MeCN 70:30 → 0:100 over 1 h, the eluent contained 0.1% TFA) gave **23b** as a colorless foam (100 mg, 61% yield). $[\alpha]_D$ = −39 (c 0.5, $CHCl_3$). IR (ν cm^{-1}) 1750, 1654, 1583, 1484. HRMS (ES^+) calcd $[M+H^+]$ for $C_{30}H_{23}F_4NO_4S$ 570.1362 obsd 570.1362. ^1H NMR (400 MHz, $CDCl_3$) δ 3.42–3.56 (m, 3H), 3.63–3.73 (m, 1H), 3.84 (s, 3H), 4.91 (s, 2H), 5.66 (d, J = 8.0 Hz, 1H), 6.20–6.24 (m, 1H), 6.37–6.49 (m, 2H), 6.75 (dd, J = 1.9, 8.2 Hz, 1H), 7.02–7.10 (m, 3H), 7.21–7.40 (m, 4H), 7.45 (t, J = 7.5 Hz, 1H), 7.55–7.62 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8, 39.9, 53.5, 63.7, 69.2, 113.1, 114.7, 115.4, 115.5, 115.6, 116.1, 121.7 (splitted), 123.9 (q, J = 271 Hz, 1C), 125.1, 127.2 and 127.3 (1C), 129.3, 129.4, 129.5, 129.6, 131.1 (dq, J = 11, 32 Hz, 1C), 132.8, 133.7 (d, J = 26 Hz, 1C), 137.0 (splitted), 139.0, 147.5 (splitted), 153.7, 158.8, 161.3, 162.5 (d, J = 245 Hz, 1C), 168.4.

General hydrolysis method 1: 0.10 M LiOH(aq) or 1.0 M LiOH(aq) (1.0 equiv) was added to the substrate in THF (42 mL/mmol) at rt. The reaction mixture was stirred for approximately 12 h before being concentrated. The crude products were filtered through a C_{18} column [MeCN:H_2O].

General hydrolysis method 2: 0.10 M LiOH(aq) (1.05 equiv) was added to the substrate in THF (42 mL/mmol) at rt. The reaction mixture was stirred for approximately 12 h before being concentrated. The crude products were purified by column chromatography on silica gel [CH_2Cl_2:MeOH 97:3 → CH_2Cl_2:MeOH 95:5 and 1% AcOH].

General hydrolysis method 3: 1.0 M LiOH(aq) (2 equiv) was added to the substrate in THF (42 mL/mmol) at rt and the reaction mixture was stirred for 1 h. The reaction mixture was diluted with water and pH was set to approx 1 with 1 M HCl (aq), and extracted with EtOAc. The organic phase was dried (Na_2SO_4), filtered and concentrated. The crude products were purified by column chromatography on silica gel (CH_2Cl_2:MeOH:AcOH).

*4.10.19. (3R)-8-cyclopropyl-7-piperidino-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-lithium carboxylate (**24a**)*

By following general hydrolysis method 1 and using 0.10 M LiOH (aq), **9a** (43 mg, 0.12 mmol) gave **24a** (40 mg, 95% yield) as a solid. $[\alpha]_D = -43$ (*c* 0.5, MeOH). IR (ν cm^{-1}) 1631, 1568, 1490, and 1395. HRMS (ES^+) calcd $[M+H^+]$ for $C_{17}H_{21}LiN_2O_3S$ 341.1506 obsd 341.1494. ^{1}H NMR (360 MHz, MeOD) δ 0.54–0.70 (m, 2H), 0.79–0.98 (m, 2H), 1.41–1.53 (m, 2H), 1.54–1.71 (m, 5H), 2.39–2.53 (m, 4H), 3.44–3.62 (m, 3H), 3.71 (dd, $J_1 = 8.60$ Hz, $J_2 = 11.32$ Hz, 1H), 5.40 (dd, $J_1 = 1.35$ Hz, $J_2 = 8.53$ Hz, 1H), 6.41 (s, 1H). ^{13}C NMR (90 MHz, MeOD) δ 8.0, 8.4, 11.7, 25.4, 27.1 (2C), 33.9, 56.0 (2C), 61.1, 67.2, 114.0, 115.8, 150.8, 156.2, 163.9, 174.1.

*4.10.20. (3R)-8-cyclopropyl-7-morpholino-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-lithium carboxylate (**25a**)*

By following general hydrolysis method 1 and using 0.10 M LiOH(aq), **10a** (25 mg, 0.072 mmol) gave **25a** (23 mg, 92% yield) as a solid. $[\alpha]_D = -33$ (*c* 0.5, MeOH). IR (ν cm^{-1}) 1731, 1632, 1566, 1490, and 1394. HRMS (ES^+) calcd $[M+H^+]$ for $C_{16}H_{19}LiN_2O_4S$ 343.1298 obsd 343.1291. ^{1}H NMR (400 MHz, D_2O) δ 0.56–0.68 (m, 2H), 0.87–1.09 (m, 2H), 1.62–1.72 (m, 2H), 2.68–2.82 (m, 4H), 3.55 (d, $J = 11.73$ Hz, 1H), 3.74–3.87 (m, 7H), 5.41 (d, $J = 8.62$ Hz, 1H), 6.36 (s, 1H). ^{13}C NMR (100 MHz, D_2O) δ 7.1, 7.5, 10.4, 32.6, 53.1 (2C), 58.2, 65.95 (2C), 61.02, 112.9, 116.4, 150.7, 152.9, 162.4, 174.2.

*4.10.21. (3R)-8-cyclopropyl-7-tetrahydroisoquinolino-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-lithium carboxylate (**26a**)*

By following general hydrolysis method 1 and using 0.10 M LiOH (aq), **11a** (22 mg, 0.056 mmol) gave **26a** (20 mg, 92% yield) as a solid. $[\alpha]_D = -42$ (*c* 0.5, MeOH). IR (ν cm^{-1}) 1629, 1565, 1490, and 1393. HRMS (ES^+) calcd $[M+H^+]$ for $C_{21}H_{21}LiN_2O_3S$ 389.1506 obsd 389.1494. ^{1}H NMR (400 MHz, MeOD) δ 0.58–0.72 (m, 2H), 0.81–0.99 (m, 2H), 1.64–1.73 (m, 1H), 2.73–2.86 (m, 2H), 2.87–2.94 (m, 2H), 3.58 (dd, $J_1 = 1.30$ Hz, $J_2 = 11.31$ Hz, 1H), 3.66–3.82 (m, 5H), 5.41 (dd, $J_1 = 1.19$ Hz, $J_2 = 8.44$ Hz, 1H), 6.47 (s, 1H), 6.96–7.03 (m, 1H), 7.04–7.13 (m, 3H). ^{13}C NMR (90 MHz, MeOD) δ 8.0, 8.4, 11.7, 30.2, 33.9, 52.3, 57.4, 60.1, 67.2, 113.9, 115.7, 126.7, 127.2, 127.5, 129.6, 135.3, 135.9, 151.0, 155.9, 163.9, 174.1.

*4.10.22. (3R)-8-cyclopropyl-7-benzenesulfonamido-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid (**27a**)*

By following general hydrolysis method 2, **14a** (50 mg, 0.12 mmol) gave **27a** (45 mg, 93% yield) as a solid. $[\alpha]_D = -132$ (*c* 0.5, MeOH). IR (ν cm^{-1}) 1734, 1639, 1556, 1493, and 1324. HRMS (ES^+) calcd $[M+H^+]$ for $C_{18}H_{18}N_2O_5S_2$ 407.0730 obsd 407.0720. ^{1}H NMR (400 MHz, MeOD) δ 0.48–0.64 (m, 2 h), 0.76–0.96 (m, 2H), 1.48–1.62 (m, 1H), 3.58 (d, $J = 11.82$ Hz, 1H), 3.77 (dd, $J_1 = 8.76$ Hz, $J_2 = 11.81$ Hz, 1H), 4.09–4.28 (m, 2H), 5.54 (d, $J = 8.74$ Hz, 1H), 6.28 (s, 1H), 7.52–7.70 (m, 3H), 7.83–7.94 (m, 2H). ^{13}C NMR (100 MHz, MeOD) δ 8.0, 8.2, 11.1, 32.7, 44.8, 64.7, 113.7, 114.6, 127.9 (2H), 130.2 (2H), 133.7, 141.9, 150.6, 155.3, 163.4, 171.0.

*4.10.23. (3R)-8-cyclopropyl-7-naphthalenesulfonamido-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid (**28a**)*

By following general hydrolysis method 2, **15a** (39 mg, 0.082 mmol) gave **28a** (34 mg, 91% yield) as a solid. $[\alpha]_D = -144$ (*c* 0.5, MeOH). IR (ν cm^{-1}) 1732, 1639, 1561, 1493, and 1321. HRMS (ES^+) calcd $[M+H^+]$ for $C_{22}H_{20}N_2O_5S_2$ 457.0886 obsd 457.0883. ^{1}H NMR (400 MHz, MeOD) δ 0.34–0.46 (m, 2H), 0.58–0.79 (m, 2H), 1.26–1.36 (m, 1H), 3.52 (dd, $J_1 = 1.56$ Hz, $J_2 = 11.89$ Hz, 1H), 3.68 (dd, $J_1 = 8.72$ Hz, $J_2 = 11.83$ Hz, 1H), 4.04–4.28 (m, 2H), 5.42 (dd, $J_1 = 1.45$ Hz, $J_2 = 8.77$ Hz, 1H), 6.12 (s, 1H), 7.53–7.72 (m, 3H), 7.98–8.04 (m, 1H), 8.10–8.22 (m, 2H), 8.67–8.73 (m, 1H). ^{13}C NMR (100 MHz, MeOD) δ 7.6, 8.1, 11.0, 32.8, 44.7, 64.6, 114.4, 114.7, 125.2, 125.8, 128.1, 129.1, 129.4, 130.0, 130.4, 135.3, 135.7, 136.9, 150.5, 154.5, 163.1, 171.0.

*4.10.24. (3R)-8-cyclopropyl-7-benzamido-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid (**29a**)*

By following general hydrolysis method 2, **16a** (41 mg, 0.11 mmol) gave **29a** (37 mg, 94% yield) as a solid. $[\alpha]_D = -92$ (*c* 0.5, MeOH). IR (ν cm^{-1}) 1737, 1636, 1538, and 1489. HRMS (ES^+) calcd $[M+H^+]$ for $C_{19}H_{18}N_2O_4S$ 371.1060 obsd 371.1056. ^{1}H NMR (360 MHz, MeOD) δ 0.64–0.76 (m, 2H), 0.90–1.08 (m, 2H), 1.64–1.76 (m, 1H), 3.62 (dd, $J_1 = 1.36$ Hz, $J_2 = 11.92$ Hz, 1H), 3.82 (dd, $J_1 = 8.96$ Hz, $J_2 = 11.90$ Hz, 1H), 4.60–4.76 (m, 2H), 5.60 (dd, $J_1 = 1.33$ Hz, $J_2 = 8.76$ Hz, 1H), 6.22 (s, 1H), 7.45–7.60 (m, 3H), 7.87–7.94 (m, 2H). ^{13}C NMR (90 MHz, MeOD) δ 8.1, 8.3, 11.2, 32.8, 41.8, 64.6, 111.1, 115.3, 128.4 (2C), 129.7 (2C), 133.0, 135.1, 150.9, 157.5, 163.4, 170.3, 170.7.

*4.10.25. (3R)-8-cyclopropyl-7-naphthalamido-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid (**30a**)*

By following general hydrolysis method 2, **17a** (31 mg, 0.072 mmol) gave **30a** (27 mg, 90% yield) as a solid. $[\alpha]_D = -86$ (*c* 0.5, MeOH). IR (ν cm^{-1}) 1735, 1637, 1531, and 1493. HRMS (ES^+) calcd $[M+H^+]$ for $C_{23}H_{20}N_2O_4S$ 421.1217 obsd 421.1209. ^{1}H NMR (360 MHz, MeOD) δ 0.66–0.78 (m, 2H), 0.92–1.10 (m, 2H), 1.66–1.79 (m, 1H), 3.61 (d, $J = 11.83$ Hz, 1H), 3.82 (dd, $J_1 = 8.94$ Hz, $J_2 = 11.74$ Hz, 1H), 4.66–4.82 (m, 2H), 5.60 (d, $J = 8.24$ Hz, 1H), 6.35 (s, 1H), 7.49–7.64 (m, 3H), 7.71–7.80 (m, 1H), 7.88–8.06 (m, 2H), 8.20–8.31 (m, 1H). ^{13}C NMR (90 MHz, MeOD) δ 8.2, 8.3, 11.3, 32.7, 41.7, 64.6, 111.7, 114.8, 125.9, 126.3, 126.5, 127.5, 128.1, 129.5, 131.5, 131.8, 135.1, 135.2, 150.7, 157.0, 163.7, 170.8, 172.6.

*4.10.26. (3R)-8-CYCLOPROPYL-7-phenoxymethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (**31a**)*

By following general hydrolysis method 2, **18a** (71 mg, 0.20 mmol) gave **31a** (66 mg, quant.) as a solid. $[\alpha]_D = -28$ (c 0.5, DMSO). IR (ν cm^{-1}) (neat) 1634, 1558, 1491, 1397, 1236 and 1026. HRMS (ES^+) calcd $[M+H^+]$ for $C_{18}H_{17}NO_4S$ 344.0951 obsd 344.0953. ^{1}H NMR (400 MHz, d_6-DMSO) δ 0.51–0,70 (m, 2H), 0.78–0.91 (m, 2H), 1.61–1.73 (m, 1H), 3.51–3.58 (m, 1H), 3.66–3.76 (m, 1H), 509–5.21 (m, 2H), 5.27–5.35 (m, 1H), 6.14 (s, 1H), 6.93–7.07 (m, 3H), 7.29–7.37 (m, 2H).^{13}C NMR (100 MHz, d_6-DMSO) δ 7.1, 7.2, 24.4, 33.3, 65.8, 66.4, 79.7, 109,9, 111,9, 115,1, 121,5, 130,1, 149,6, 121,1, 158,5, 160,8, 171,2.

*4.10.27. (3R)-8-cyclopropyl-7-(naphthalen-1-yloxymethyl)-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (**32a**)*

By following general hydrolysis method 2, **19a** (102 mg, 0.25 mmol) gave **32a** (95 mg, quant.) as a solid. $[\alpha]_D = -35$ (c 0.5, DMSO). IR (ν cm^{-1}) (neat) 1624, 1567, 1496, 1397, 1268 and 1103. HRMS (ES$^+$) calcd [M + H$^+$] for $C_{22}H_{19}NO_4S$ 394.1108 obsd 394.1102. ^{1}H NMR (400 MHz, d_6-DMSO) δ 0.52–0.74 (m, 2H), 0.78–0.93 (m, 2H), 1.65–1.78 (m, 1H), 3.48–3.60 (m, 1H), 3.67–3.79 (m, 1H), 5.28–5.42 (m, 3H), 6.30 (s, 1H), 7.00–7.09 (m, 1H), 7.40–7.49 (m, 1H), 7.49–7.61 (m, 3H), 7.86–7.94 (m, 1H), 8.20–8.30 (m, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 6.7, 9.9, 31.3, 62.5, 66.1, 105.6, 110.1, 111.0, 120.5, 121.3, 124.8, 125.7, 126.1, 126.6, 127.6, 134.1, 148.5, 152.1, 153.1, 160.0, 169.6.

*4.10.28. (3R)-8-cyclopropyl-7-(6-methoxy-naphthalen-2-ylmethyl)-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (**33a**)*

By following general hydrolysis method 3, **21a** (110 mg, 0.26 mmol) gave **33a**, after purification by column chromatography on silica gel (CH_2Cl_2:MeOH:AcOH 95:4:1), as a colourless foam (100 mg, 94% yield). $[\alpha]_D = -25$ (c 0.25, $CHCl_3$:MeOH 9:1). IR (ν cm^{-1}) 1733, 1633, 1605, 1482. HRMS (ES$^+$) calcd [M + H$^+$] for $C_{23}H_{21}NO_4S$ 408.1264 obsd 408.1270. ^{1}H NMR (400 MHz, d_6-DMSO) δ 0.50–0.68 (m, 2H), 0.80–0.97 (m, 2H), 1.38–1.47 (m, 1H), 3.49 (d, J = 11.7 Hz), 3.75 (dd, J = 9.5, 11.7 Hz, 1H), 3.86 (s, 3H), 4.02–4.15 (m, 2H), 5.35–5.42 (m, 1H), 5.79 (s, 1H), 7.14 (dd, J = 2.1, 9.0 Hz, 1H), 7.27–7.36 (m, 1H), 7.66 (s, 1H), 7.74–7.80 (m, 2H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 7.5, 7.7, 10.9, 31.3, 38.2, 55.2, 62.6, 105.8, 111.9, 114.1, 118.7, 126.9, 127.2, 128.1, 128.5, 129.0, 133.0, 133.7, 148.3, 156.5, 157.0, 160.1, 169.7.

*4.10.29. (3R)-8-cyclopropyl-7-(1H-indol-5-ylmethyl)-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (**34a**)*

By following general hydrolysis method 3, **22a** (110 mg, 0.29 mmol) gave **34a**, after purification by column chromatography on silica gel (CH_2Cl_2:MeOH:AcOH 90:9:1), as a colourless foam (100 mg, 94% yield). $[\alpha]_D = -39$ (c 0.25, DMSO). IR (ν cm^{-1}) 3259, 1627, 1547, 1486, 1394. HRMS (ES$^+$) calcd [M + H$^+$] for $C_{20}H_{18}N_2O_3S$ 367.1111 obsd 367.1099. ^{1}H NMR (400 MHz, d_6-DMSO) δ 0.50–0.69 (m, 2H), 0.81–0.97 (m, 2H), 1.40–1.50 (m, 1H), 3.44–3.52 (m, 1H), 3.72–3.81 (m, 1H), 3.95–4.09 (m, 2H), 5.36–5.42 (m, 1H), 5.77 (s, 1H), 6.35–6.39 (m, 1H), 6.92–6.98 (m, 1H), 7.28–7.40 (m, 3H), 11.05 (bs, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 7.5, 7.7, 10.9, 31.2, 38.5, 62.4, 100.8, 111.4, 112.2, 114.0, 120.2, 122.5, 125.5, 127.9, 128.5, 134.7, 147.9, 157.8, 160.1, 169.7.

*4.10.30. (3R)-8-cyclopropyl-7-[3-(4-fluoro-benzyloxy)-benzyl]-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (**35a**)*

By following general hydrolysis method 3, **23a** (110 mg, 0.24 mmol) gave **35a**, after purification by column chromatography on silica gel (CH_2Cl_2:MeOH:AcOH 95:4:1), as a colourless foam (100 mg, 92% yield). $[\alpha]_D = -12$ (c 0.25, $CHCl_3$:MeOH 9:1). IR (ν cm^{-1}) 1732, 1605, 1540, 1487. HRMS (ES$^+$) calcd [M + H$^+$] for $C_{25}H_{22}FNO_4S$ 452.1326 obsd 452.1329. ^{1}H NMR (400 MHz, d_6-DMSO) δ 0.46–0.63 (m, 2H), 0.76–0.91 (m, 2H), 1.30–1.40 (m, 1H), 3.46–3.52 (m, 1H), 3.75 (dd, J = 9.2, 11.6 Hz, 1H), 3.87–3.99 (m, 2H), 5.06 (s, 2H), 5.36–5.41 (m, 1H), 5.79 (s, 1H), 6.79–6.91 (m, 3H), 7.16–7.27 (m, 3H), 7.45–7.52 (m, 2H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 7.4, 7.6, 10.8, 31.3, 38.2, 62.6, 68.4, 111.8, 112.7, 114.1, 115.1, 115.3, 115.6, 121.6, 129.5, 129.9, 130.0, 133.3, 140.2, 148.2, 156.1, 158.3, 160.1, 162.2 (d, J = 243 Hz, 1C), 170.2.

*4.10.31. (3R)-8-(3-Trifluoromethyl)phenyl-7-piperidino-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-lithium carboxylate (**24b**)*

By following general hydrolysis method 1 and using 1.0 M LiOH (aq), **9b** (93 mg, 0.21 mmol) gave **24b** (83 mg, 91% yield) as a solid. $[\alpha]_D = -4$ (c 0.5, MeOH). IR (ν cm^{-1}) 1626, 1568, 1487, 1437, 1405, and 1330. HRMS (ES$^+$) calcd [M + H$^+$] for $C_{21}H_{20}F_3LiN_2O_3S$ 445.1380 obsd 445.1373. ^{1}H NMR (400 MHz, MeOD) δ 1.33–1.43 (m, 2H), 1.44–1.56 (m, 4H), 2.22–2.44 (m, 4H), 3.04–3.24 (m, 2H), 3.58 (dd, J_1 = 1.39 Hz, J_2 = 11.39 Hz, 1H), 3.76 (dd, J_1 = 8.92 Hz, J_2 = 11.02 Hz, 1H), 5.49 (dd, J_1 = 1.39 Hz, J_2 = 8.61 Hz, 1H), 6.46 (s, 1H), 7.55–7.74 (m, 4H). ^{13}C NMR (100 MHz, MeOD) δ 24.8, 26.5 (2C), 34.1, 55.2 (2C), 60.9, 68.1, 115.3 (broad), 116.6, 125.5 (q, J = 271.9 Hz), 125.8 (broad and split J = 3.43 Hz), 128.5 (d, J = 31.6 Hz), 130,5, 131.8 (q, J = 34.1 Hz), 135.3 (d, J = 31.0 Hz), 139.0, 151.1, 151.9, 163.7, 173.9.

*4.10.32. (3R)-8-(3-Trifluoromethyl)phenyl-7-morpholino-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-lithium carboxylate (**25b**)*

By following general hydrolysis method 1 and using 1.0 M LiOH (aq), **10b** (149 mg, 0.328 mmol) gave **25b** (141 mg, 96% yield) as a solid. $[\alpha]_D = -21$ (c 0.5, MeOH). IR (ν cm^{-1}) 1622, 1570, 1486, 1400, and 1331. HRMS (ES$^+$) calcd [M + H$^+$] for $C_{20}H_{18}F_3LiN_2O_4S$ 447.1172 obsd 447.1158. ^{1}H NMR (400 MHz, MeOD) δ 2.15–2.36 (m, 4H), 3.01–3.18 (m, 2H), 3.47–3.60 (m, 5H), 3.75 (dd, J_1 = 8.67 Hz, J_2 = 11.38 Hz, 1H), 5.49 (dd, J_1 = 1.39 Hz, J_2 = 8.57 Hz, 1H), 6.40 (s, 1H), 7.57–7.74 (m, 4H). ^{13}C NMR (100 MHz, MeOD) δ 34.1, 54.2 (2C), 61.0, 67.8 (2C), 68.0, 115.3 (broad), 116.6, 125.5 (q, J = 271.9 Hz), 125.7 (broad and split J = 3.7 Hz), 128.4 (d, J = 40.2 Hz), 130,4, 131.7 (q, J = 32.1 Hz), 135.1 (d, J = 42.1 Hz), 139.1, 150.9, 152.1 (broad), 163.7, 173.9.

*4.10.33. (3R)-8-(3-Trifluoromethyl)phenyl-7-tetrahydroisoquinolino-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-lithium carboxylate (**26b**)*

By following general hydrolysis method 1 and using 1.0 M LiOH (aq), **11b** (60 mg, 0.12 mmol) gave **26b** (56 mg, 94% yield) as a solid. $[\alpha]_D = -5$ (c 0.5, MeOH). IR (ν cm^{-1}) 1621, 1572, 1488, and 1331. HRMS (ES$^+$) calcd [M + H$^+$] for $C_{25}H_{20}F_3LiN_2O_3S$ 493.1380 obsd 493.1370. ^{1}H NMR (400 MHz, MeOD) δ 2.53–2.67 (m, 2H), 2.72–2.80 (m, 2H), 3.23–3.38 (m, 2H), 3.49 (s, 2H), 3.56 (dd, J_1 = 1.40 Hz, J_2 = 11.41 Hz, 1H), 3.70–3.80 (m, 1H), 5.50 (dd, J_1 = 1.37 Hz, J_2 = 8.57 Hz, 1H), 6.52 (s, 1H), 6.88–6.94 (m, 1H), 6.99–7.10 (m, 3H), 7.54–7.72 (m, 4H). ^{13}C NMR (100 MHz, MeOD) δ 29.9, 34.2, 51.9, 56.6, 60.3, 68.0, 114.7 (broad), 116.5, 125.5 (q, J = 271.7 Hz), 125.8 (broad and split J = 3.8 Hz), 126.6, 127.2, 127.4, 128.4 (d, J = 38.3 Hz), 129.5, 130.5, 131.9 (q, J = 33.4 Hz), 135.1, 135.3 (d, J = 33.0 Hz), 135.4, 139.0, 151.0, 152.5, 163.8, 173.9.

*4.10.34. (3R)-8-(3-Trifluoromethyl)phenyl-7-benzenesulfonamido-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid (**27b**)*

By following general hydrolysis method 3, **14b** (25 mg, 0.047 mmol) gave **27b** (22 mg, 93% yield) as a solid. $[\alpha]_D = -5$ (c 0.5, MeOH). IR (ν cm^{-1}) 1735, 1643, 1564, 1486, 1446, and 1326. HRMS (ES$^+$) calcd [M + H$^+$] for $C_{22}H_{17}F_3N_2O_5S_2$ 511.0604 obsd 511.0601. ^{1}H NMR (400 MHz, MeOD) δ 3.55–3.73 (m, 3H), 3.78–3.89 (m, 1H), 5.59–5.70 (m, 1H), 6.42 (s, 1H), 7.41–7.65 (m, 6H), 7.66–7.78 (m, 3H). ^{13}C NMR (100 MHz, MeOD) δ 33.1, 44.9, 65.8, 114.1, 115.1, 125.4 (q, J = 271.5 Hz), 126.4 (broad), 127.8 (broad, 3C), 130.2 (2C), 131.0, 132.3 (q, J = 32.6 Hz), 133.8, 135.1 (d, J = 27.2 Hz), 137.7, 141.4, 150.7, 152.3, 163.4, 171.4 (broad).

*4.10.35. (3R)-8-(3-Trifluoromethyl)phenyl-7-naphthalenesulfonamido-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid (**28b**)*

By following general hydrolysis method 3, **15b** (35 mg, 0.060 mmol) gave **28b** (31 mg, 93% yield) as a solid. $[\alpha]_D = -4$ (c 0.5, MeOH). IR (ν cm^{-1}) 1733, 1642, 1568, 1485, 1436, and 1325. HRMS (ES$^+$) calcd [M + H$^+$] for $C_{26}H_{19}F_3N_2O_5S_2$ 561.0760 obsd 561.0769.

^{1}H NMR (400 MHz, MeOD) δ 3.53 (d, $J = 11.91$ Hz, 1H), 3.58–3.71 (m, 2H), 3.72–3.84 (m, 1H), 5.57 (d, $J = 8.46$ Hz, 1H), 6.37 (s, 1H), 7.25–7.74 (m, 7H), 7.94–8.15 (m, 3H), 8.58–8.66 (m, 1H). ^{13}C NMR (100 MHz, MeOD) δ 33.1, 44.7, 65.7 (broad), 114.3, 115.0, 125.1, 125.3 (q, $J = 272.2$ Hz), 125.7, 126.3 (broad), 128.0 (broad, 2C), 129.2, 129.3, 130.1, 130.2, 130.9, 132.2 (q, $J = 31.9$ Hz), 135.0 (d, $J = 29.7$ Hz), 135.4, 135.7, 136.2 (broad), 137.5, 150.5, 152.2, 163.3, 171.3 (broad).

*4.10.36. (3R)-8-(3-Trifluoromethyl)phenyl-7-benzamido-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid (**29b**)*

By following general hydrolysis method 3, **16b** (36 mg, 0.073 mmol) gave **29b** (33 mg, 96% yield) as a solid. $[\alpha]_D = -0$ (*c* 0.5, MeOH). IR (ν cm^{-1}) 1632, 1536, 1485, and 1328. HRMS (ES$^+$) calcd [M + H$^+$] for $C_{23}H_{17}F_3N_2O_4S$ 475.0934 obsd 475.0940. ^{1}H NMR (400 MHz, MeOD) δ 3.58 (dd, $J_1 = 1.38$ Hz, $J_2 = 11.42$ Hz, 1H), 3.71–3.85 (m, 1H), 4.06–4.34 (m, 2H), 5.50 (dd, $J_1 = 1.37$ Hz, $J_2 = 8.60$ Hz, 1H), 6.30 (s, 1H), 7.40–7.58 (m, 3H), 7.60–7.84 (m, 6H). ^{13}C NMR (100 MHz, MeOD) δ 34.1, 42.4, 67.8, 112.6 (broad and split $J = 14.6$ Hz), 115.1, 125.4 (q, $J = 271.9$ Hz), 126.2 (broad and split $J = 3.7$ Hz), 128.2 (d, $J = 35.4$ Hz), 128.3 (2C), 129.5 (2C), 131.0, 132.3 (q, $J = 32.3$ Hz), 132.9, 135.0, 135.2 (d, $J = 47.0$ Hz), 138.4 (broad), 151.2, 152.8, 163.8, 170.0, 173.5, 173.6 (d, $J = 12.4$ Hz).

*4.10.37. (3R)-8-(3-Trifluoromethyl)phenyl-7-naphthalamido-1-ylmethyl-5-oxo-2,3-dihydro-5-H-thiazolo [3,2-a]pyridin-3-carboxylic acid (**30b**)*

By following general hydrolysis method 3, **17b** (21 mg, 0.040 mmol) gave **30b** (19 mg, 92% yield) as a solid. $[\alpha]_D = -0$ (*c* 0.5, MeOH). IR (ν cm^{-1}) 1725, 1638, 1486, and 1327. HRMS (ES$^+$) calcd [M + H$^+$] for $C_{27}H_{19}F_3N_2O_4S$ 525.1090 obsd 525.1074. ^{1}H NMR (400 MHz, MeOD) δ 3.60 (d, $J = 11.69$ Hz, 1H), 3.78–3.91 (m, 1H), 4.16–4.39 (m, 2H), 5.63 (d, $J = 8.54$ Hz, 1H), 6.45 (s, 1H), 7.46–7.84 (m, 8H), 7.87–7.94 (m, 1H), 7.97 (d, 8.19 Hz, 1H), 8.10–8.17 (m, 1H). ^{13}C NMR (100 MHz, MeOD) δ 33.38, 42.3, 66.3 (broad), 112.7 (d, $J = 12.8$ Hz), 115.3, 125.4 (q, $J = 271.5$ Hz), 125.8, 126.3, 236.5 (2C), 127.5, 128.1 (2C), 129.4, 131.1, 131.4, 131.8, 132.4 (q, $J = 32.7$ Hz), 134.8, 135.1, 135.2 (d, $J = 32.3$ Hz), 138.1 (d, $J = 8.5$ Hz), 151.0, 153.3, 163.6, 171.9 (broad), 172.3.

*4.10.38. 5-Oxo-7-phenoxymethyl-8-(3-trifluoromethyl-phenyl)-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (**31b**)*

By following general hydrolysis method 2, **18b** (63 mg, 0.12 mmol) gave **31b** (53 mg, quant.) as a solid. $[\alpha]_D = -24$ (c 0.5, DMSO). IR (ν cm^{-1}) (neat) 1642, 1568, 1486, 1326 1164 and 1118. HRMS (ES$^+$) calcd [M + H$^+$] for $C_{22}H_{16}F_3NO_4S$ 448.0825 obsd 448.0824. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49–3.57 (m, 1H), 3.82–3.92(m, 1H), 4.73 (s, 2H), 5.50–5.58 (m, 1H), 6.37 (s, 1H), 6.74–6.82 (m, 2H), 6.87–6.94 (m, 1H), 7.18–7.27 (m, 2H), 7.57–7.84 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.0, 63.9, 66.8, 111.8, 113.5, 115.0, 121.6, 124.5 (q, $J = 275.06$ Hz), 125.5 (d, $J = 3.95$ Hz), 126.9 (d, $J = 3.40$ Hz), 129.9, 130.0 (q, $J = 29.68$ Hz), 130.4, 134.5, 137.0, 149.4, 157.9, 160.5, 169.9.

*4.10.39. 5-Oxo-7-(naphtalen-1-yloxymethyl)-8-(3-trifluoromethyl-phenyl)-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (**32b**)*

By following general hydrolysis method 2, **19b** (95 mg, 0.19 mmol) gave **32b** (94 mg, quant.) as a solid. $[\alpha]_D = -28$ (c 0.5, DMSO). IR (ν cm^{-1}) (neat) 1634, 1485, 1326, 1238, 1120 and 1072. HRMS (ES$^+$) calcd [M + H$^+$] for $C_{26}H_{18}F_3NO_4S$ 498.0981 obsd 498.0975. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.50–3.61 (m, 1H), 3.81–3.95 (m, 1H), 5.00 (s, 2H), 5.52–5.63 (m, 1H), 6.53 (s, 1H), 6.75–6.84 (m, 1H), 7.28–7.37 (m, 1H), 7.40–7.55 (m, 3H), 7.57–7.88 (m, 5H), 7.89–7.98 (m, 1H.). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.1, 64.0, 67.1, 105.8, 111.8, 113.6, 121.0, 124.4 (q, $J = 275.78$ Hz), 125.1, 125.4, 125.9, 126.4, 126.8, 127.0, 130.0 (q, $J = 35.23$ Hz), 130.40, 134.4, 137.2, 133.3, 149.3, 149.6, 153.3, 160.5, 169.9.

*4.10.40. (3R)-7-(6-Methoxy-naphthalen-2-ylmethyl)-5-oxo-8-(3-trifluoromethyl-phenyl)-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (**33b**)*

By following general hydrolysis method 3, **21b** (38 mg, 0.07 mmol) gave **33b**, after purification by column chromatography on silica gel (CH_2Cl_2:MeOH:AcOH 85:14:1), as a colourless foam (35 mg, 98% yield). $[\alpha]_D = -2$ (*c* 0.5, $CHCl_3$). IR (ν cm^{-1}) 1733, 1634, 1606, 1550, 1482. HRMS (ES$^+$) calcd [M + H$^+$] for $C_{27}H_{20}F_3NO_4S$ 512.1138 obsd 512.1141. ^{1}H NMR (400 MHz, d_6-DMSO) δ 3.44–3.51 (m, 1H), 3.68–3.84 (m, 3H), 3.84 (s, 3H), 5.42–5.48 (m, 1H), 6.05 (s, 1H), 6.98–7.02 (m, 1H), 7.09 (dd, $J = 2.4$, 8.9 Hz, 1H), 7.17 (s, 1H), 7.21–7.25 (m, 1H), 7.31–7.41 (m, 1H), 7.47–7.56 (m, 1H), 7.56–7.66 (m, 3H), 7.67–7.75 (m, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 31.8, 38.6, 55.1, 63.8, 105.7, 112.8, 114.5, 118.6, 123.9, (q, $J = 271$ Hz, 1C), 124.7 (broad), 126.9, 126.8 (broad), 126.9, 127.5, 128.3, 128.7, 129.3 (q, $J = 32$ Hz, 1C), 129.8, 132.9 (splitted, 2C), 134.4, 137.4, 148.5, 153.1, 157.0, 160.1, 169.5.

*4.10.41. (3R)-7-(1H-Indol-5-ylmethyl)-5-oxo-8-(3-trifluoromethyl-phenyl)-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (**34b**)*

By following general hydrolysis method 3, **22b** (120 mg, 0.25 mmol) gave **34b**, after purification by column chromatography on silica gel (CH_2Cl_2:MeOH:AcOH 85:14:1), as a colourless foam (110 mg, 93% yield). $[\alpha]_D = 7$ (*c* 0.25, $CHCl_3$). IR (ν cm^{-1}) 3242, 1732, 1634, 1558, 1482, 1332. HRMS (ES$^+$) calcd [M + H$^+$] for $C_{24}H_{17}F_3N_2O_3S$ 471.0985 obsd 471.0987. ^{1}H NMR (400 MHz, d_6-DMSO) δ 3.43–3.53 (m, 1H), 3.57–3.68 (m, 2H), 3.77–3.90 (m 1H), 5.43–5.53 (m, 1H), 5.98 (s, 1H), 6.24–6.29 (m, 1H), 6.56–6.63 (m, 1H), 6.99 (s, 1H), 7.21 (d, $J = 8.1$ Hz, 1H), 7.25–7.30 (m, 1H), 7.32–7.43 (m, 1H), 7.48–7.60 (m, 1H), 7.65 (t, $J = 7.8$ Hz, 1H), 7.71–7.79 (m, 1H), 10.99 (bs, 1H), 13.45 (bs, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 31.7, 38.8, 63.5, 100.7, 111.2, 113.0, 114.2, 120.0, 122.1, 124.0 (q, $J = 272$ Hz, 1C), 124.7, 125.5, 126.9, 127.7, 127.9, 129.4 (q, $J = 31$ Hz, 1C), 129.8, 134.4, 134.6, 137.5, 148.1, 154.5, 160.2, 169.5.

*4.10.42. (3R)-7-[3-(4-Fluoro-benzyloxy)-benzyl]-5-oxo-8-(3-trifluoromethyl-phenyl)-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (**35b**)*

By following general hydrolysis method 3, **23b** (95 mg, 0.17 mmol) gave **35b**, after purification by column chromatography on silica gel (CH_2Cl_2:MeOH:AcOH 95:4:1), as a colourless foam (85 mg, 90% yield). $[\alpha]_D = 6$ (*c* 0.25, $CHCl_3$). IR (ν cm^{-1}) 1731, 1626, 1544, 1484, 1440, 1334. HRMS (ES$^+$) calcd [M + H$^+$] for $C_{29}H_{21}F_4NO_4S$ 556.1200 obsd 556.1194. ^{1}H NMR (400 MHz, d_6-DMSO) δ 3.46–3.63 (m, 3H), 3.77–3.87 (m, 1H), 4.95 (s, 2H), 5.48–5.55 (m, 1H), 6.06 (s, 1H), 6.39–6.45 (m, 1H), 6.48 (s, 1H), 6.75–6.81 (m, 1H), 7.04–7.12 (m, 1H), 7.16–7.24 (m, 2H), 7.26–7.36 (m, 1H), 7.40–7.54 (m, 3H), 7.58–7.66 (m, 1H), 7.67–7.75 (m, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 31.7, 38.6, 63.6, 68.3, 112.7, 112.9, 114.6, 115.1 (splitted, 2C), 115.3, 121.2, 123.9 (q, $J = 271$ Hz, 1C), 124.7 (broad), 126.8 (broad and splitted), 129.3, 129.4 (q, $J = 32$ Hz, 1C), 129.8 (splitted, 3C), 133.2 (splitted), 134.3, 137.3, 139.5, 148.4, 153.0, 158.2, 160.1, 161.7 (d, $J = 243$ Hz, 1C), 169.5.

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Appendix A. Supplementary data

Supplementary data (Bacterial Growth for all biologically evaluated compounds, HA-titer assay results for **33b**, **34b**, **32a**, **32b**, **5**, and **6**, cytotoxic properties of **28b**, **31b**, **32a,b**, **33b**, **34b**, **35a,b**, **5**, and **6**, NMR spectra for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2011.01.025.

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