Original article

Design, synthesis and evaluation of triazole functionalized ring-fused 2-pyridones as antibacterial agents

Christoffer Bengtsson [a], Anders E.G. Lindgren [a], Hanna Uvell [b], Fredrik Almqvist [a,b,c,*]

[a] Department of Chemistry, Umeå University, Linnaeus väg 10, SE-90187 Umeå, Sweden
[b] Laboratories for Chemical Biology Umeå LCBU, Umeå University, SE-90187 Umeå, Sweden
[c] Umeå Center for Microbial Research UCMR, Umeå University, SE-90187 Umeå, Sweden

ARTICLE INFO

ABSTRACT

Antibacterial resistance is today a worldwide problem and the demand for new classes of antibacterial agents with new mode of action is enormous. In the strive for new antibacterial agents that inhibit pilus assembly, an important virulence factor, routes to introduce triazoles in position 8 and 2 of ring-fused bicyclic 2-pyridones have been developed. This was made via Sonogashira couplings followed by Huisgen 1,3-dipolar cycloadditions. The method development made it possible to introduce a diverse series of substituted triazoles and their antibacterial properties were tested in a whole cell pili-dependent biofilm assay. Most of the twenty four candidates tested showed low to no activity but interestingly three compounds, one 8-substituted and two 2-substituted, showed promising activities with EC_{50}'s between 9 and 50 μM.

1. Introduction

Considering the ever growing antibiotic resistance developed by many bacteria, there is an immense need for new compounds with new mode of actions, for treatment of bacterial infections. Bicyclic 2-pyridones, named pilicides, have been designed and synthesized to inhibit the pili assembly machinery in uropathogenic *Escherichia coli* by inhibition of the chaperone/usher pathway [1]. Furthermore it has been shown that a carboxylic acid [2,3] or a carboxylic acid isostere [4] in position 3 is essential for biological activity. Pili are important virulence factors for the bacteria and they need these organelles to attach to the host cell, to withstand shear forces (in the urinary tract), to invade the host and to establish biofilm like colonies [5]. Bacterial biofilms are complex structures and are involved in many serious bacterial infections such as urinary tract infection (UTI). UTI by it's own is responsible for infecting more than 900 000 women and men, several times per year in U.S. alone! [6]. Depending on the substitution pattern on the bicyclic 2-pyridones, particularly in position 8 (Fig. 1), the biological target can be switched from inhibition of pilus assembly to inhibition of curli formation. In the latter example this is achieved by preventing polymerization of the major curli subunit protein, CsgA, into a functional amyloid fibre [2,7]. The bicyclic 2-pyridones are synthesized via an acid induced acylketene/imine cyclocondensation between an acyl Meldrum's acid derivative and a Δ^2-thiazoline, either via conventional heating [8] or more convenient under microwave irradiation to yield the 7 and 8 substituted bicyclic 2-pyridones [9] (Fig. 1).

Previous biological data has revealed that small heterocycles i.e. thiophenes and furanes can be beneficial substituents in position 8 (**1**) and 2 (**2**) of the ring-fused bicyclic 2-pyridones (Fig. 2), resulting in increased biological activity [6,10].

These results encouraged us also to investigate other small heterocycles like triazoles, which ultimately would allow the introduction of a diverse set of substituted heterocycles to gain further knowledge in structure activity relationships. Substituted triazoles are scarcely commercially available as their boronic acid/ester counterparts, which considerably limit the Suzuki–Miyaura coupling as an alternative for library synthesis in this case. However, triazoles can be synthesized via the Huisgen 1,3-dipolar cycloaddition often referred to as "click chemistry". This reaction allows late introduction of diverse substituents, which is advantageous in library synthesis. Triazoles are widely used as mimetics in different occasions, most well known as peptide bond mimetics [11] but they have also served as double bond- [12] and furan substitutes [13].

* Corresponding author. Department of Chemistry, Umeå University, Linnaeus väg 10, SE-90187 Umeå, Sweden. Tel.: +46 90 7866925; fax: +46 90 7867655.
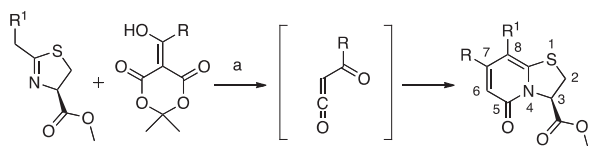E-mail address: fredrik.almqvist@chem.umu.se (F. Almqvist).

Fig. 1. Schematic view over the acylketene/imine cyclocondensation to the 7- and 8 substituted thiazolino ring-fused bicyclic 2-pyridones. Reaction conditions: (a) TFA, DCM, MWI 140 °C for 2 min.
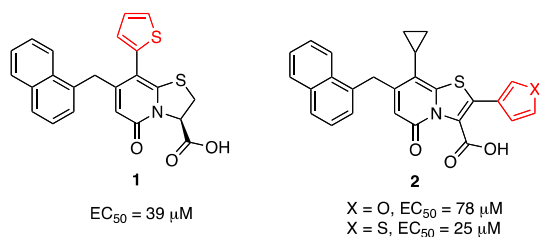

Fig. 2. Examples of biologically active, heterocycle functionalized bicyclic 2-pyridones, the heterocycles are highlighted in red. Their respective effective concentration with 50% inhibition (EC$_{50}$) of pilus dependent biofilm formation is shown. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 3. Retrosynthetic scheme over the triazole functionalizations of position 8 (A) and 2 (B).

The halogenated compounds **3** and **4** have previously been synthesized and successfully used in Pd-catalyzed cross couplings (i.e. Su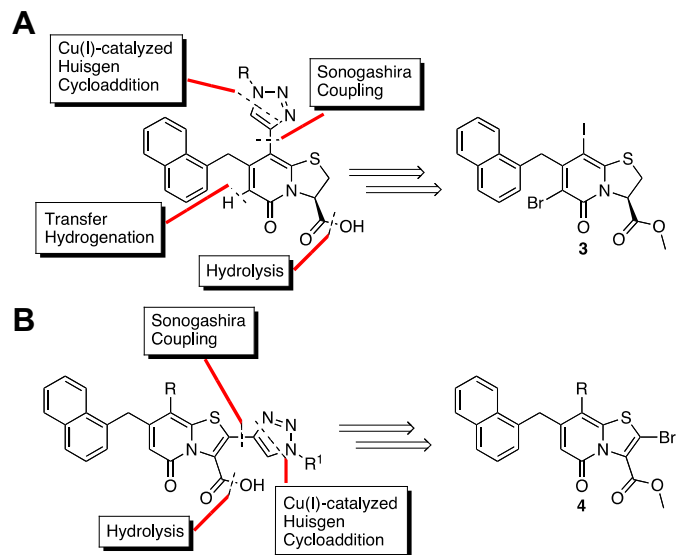zuki–Miyaura [14], and Sonogashira couplings [15]). These compounds were considered to be key intermediates for the introduction of substituted triazoles in the 8- and 2 positions respectively as outlined in the retrosynthetic scheme (Fig. 3).

Table 1
Selective Sonogashira coupling of the bromo-iodo-bicyclic 2-pyridone **3** followed by Huisgen 1,3-dipolar cycloadditions.
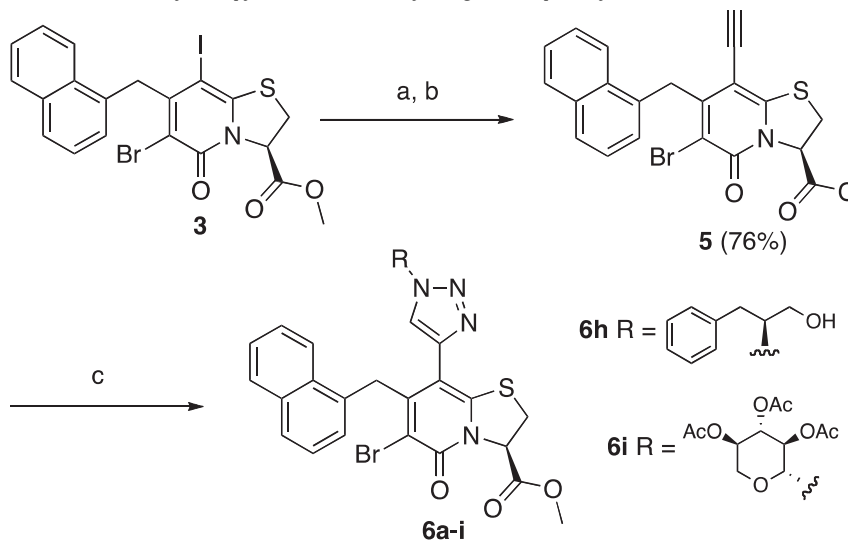
Reaction conditions: (a) Pd(PPh$_3$)$_2$Cl$_2$, CuI, TMSA, TEA, DMF (b) K$_2$CO$_3$ MeOH:THF 4:1 (c) CuSO$_4$, Na-ascorbate, NaN$_3$, R-X, DMF:H$_2$O 1:1

R	X	Product	Yield (%)
H	N$_3$[a]	**6a**	42
Me	I	**6b**	79
Et	I	**6c**	78
cPrCH2	Br	**6d**	54
Bn	Br	**6e**	70
pMeBn	Br	**6f**	82
pNO$_2$Bn	Br	**6g**	84
	N$_3$[b]	**6h**	66
	N$_3$	**6i**	95

[a] TMSN$_3$ was used in the reaction instead of NaN$_3$.
[b] The azido alcohol was made from the corresponding commercial available amino alcohol via a diazo-transfer reaction with TfN$_3$ according to published procedures [16].

Table 2
Hydrolysis of the 8-position triazole functionalized bicyclic 2-pyridones followed by reductive dehalogenation.

Reaction conditions: (a) LiOH (aq), THF (b) Ammoniumformate, Pd/C, MeOH
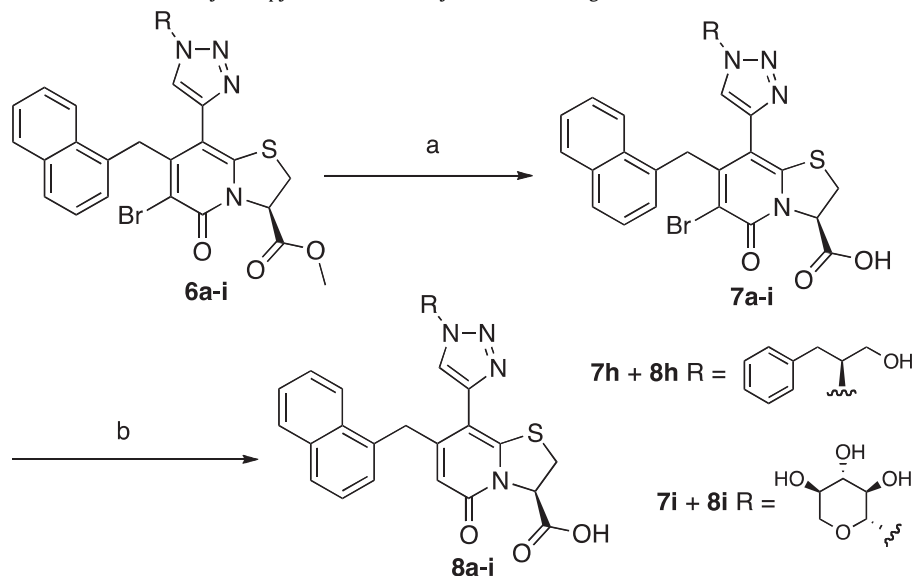
R	Product	Yield (%)	EC$_{50}$[a] (μM)	Product	Yield (%)	EC$_{50}$[a] (μM)
H	**7a**	72	>200	**8a**	73	>200
Me	**7b**	73	>200	**8b**	85	>200
Et	**7c**	87	>200	**8c**	69	>200
cPrCH$_2$	**7d**	93	>200	**8d**	72	>200
Bn	**7e**	85	100	**8e**	67	100
pMeBn	**7f**	82	200	**8f**	92	75
pNO$_2$Bn	**7g**	63	35	**8g**[b]	82	>200
	7h	77	150	**8h**	88	>200
	7i	79	>200	**8i**	74	>200

[a] Experiments were performed in triplicates and compared to DMSO-treated controls. The biofilm formation was studied under type-1 pili inducing conditions [5a].
[b] The nitro group was reduced to the corresponding aniline.

2. Results and discussion

2.1. Functionalization of the 8-position

Triazole functionalization of the 8-position started by a regioselective Sonogashira coupling on the 6-bromo-8-iodo bicyclic 2-pyridone **3** [14] with trimethylsilylacetylene (TMSA). The trimethylsilyl (TMS) group was then deprotected by K$_2$CO$_3$ in THF:MeOH 1:4 to give the terminal acetylene **5** in 76% yield. The terminal alkyne was then exposed to a Cu(I) catalyzed Huisgen 1,3-dipolar cycloaddition with a variety of azides (either as presynthesized azides or by in situ generation via NaN$_3$ and alkyl halides) (Table 1).

LiOH mediated hydrolysis furnished the 6-bromo substituted carboxylic acid intermediates **7a–i** in 63–93% yields (Table 2). The following dehalogenation by ammoniumformate and Pd/C in refluxing methanol [14] gave the final 8-triazole functionalized bicyclic 2-pyridones **8a–i** in 67–92% yields (Table 2) without any debenzylation detected (i.e. **8f** and **8g**, Table 2).
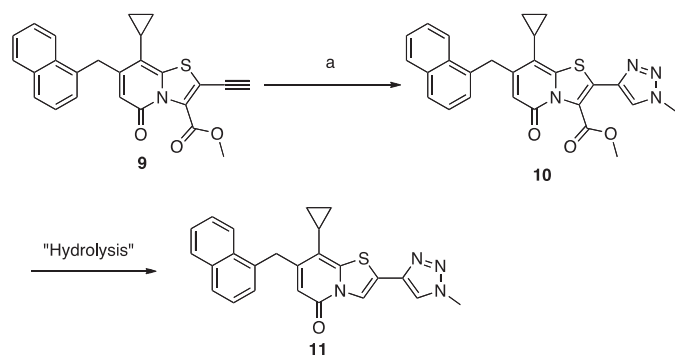
The compounds (**7a–7i** and **8a–8i**) were evaluated for their ability to inhibit the formation of pili in an uropathogenic E. coli strain (the clinical isolate UTI89). The assay is a whole cell based assay where the bacteria are grown under conditions where they form a bacterial biofilm, which is dependent upon pilus assembly. The efficacy as a whole of the compounds is not only dependent on there direct interaction with the target (Chaperone-Usher pathway) but also upon their ability to enter the bacteria. Hence, it is hard to foresee and predict if a substitution pattern will be good or bad for antibacterial activity. In the series of 8-triazolo substituted pilicides only five out of eighteen tested compounds had an activity with an EC$_{50}$ below 200 μM (i.e. **7e**, **7g**, **7h**, **8e** and **8f**). However, the best pilicide in this collection, **7g**, was active in the lower μM range (EC$_{50}$ at 35 μM), which is comparable to the thiophene analogue **1** with an EC$_{50}$ of 39 μM. Interestingly, the analogues most similar to pilicide **1** in size (i.e. **8a** and **8b**) both had EC$_{50}$'s higher than 200 μM.

2.2. Functionalization of the 2-position

Triazole functionalization of the 2-position turned out to be more demanding. Our first attempt was made with the previously published alkyne functionalized bicyclic 2-pyridone methyl ester **9** [15]. The Huisgen 1,3-dipolar cycloaddition proceeded in 71%, however the methyl ester **10** was shown to be very difficult to hydrolyze and only generated the decarboxylated compound **11**, even when using the hydrolysis method previously developed for thiophene and furane substituted compounds (i.e. **2**) (Scheme 1).

The starting material was exchanged for the corresponding alkyne functionalized trimethylsilyl ethyl ester (TMSE) **12** [15], which can be deprotected under milder conditions. Due to higher lipophilicity of these compounds DMSO:H$_2$O 1:1 could not be used as solvent for the Huisgen 1,3-dipolar cycloaddition. Instead the DMSO content was increased to DMSO:H$_2$O 9:1 and after subsequent TBAF·3H$_2$O deprotection of the TMSE ester in THF at room temperature the 2-position triazole functionalized bicyclic 2-

Scheme 1. Synthesis of triazole substituted methyl ester and attempted hydrolysis. Reaction conditions: (a) CuSO$_4$, Na-ascorbate, NaN$_3$, MeI, DMSO:H$_2$O 1:1, 71%.

3. Conclusion

Herein we present a synthetic route to functionalize the ring-fused bicyclic 2-pyridones in position 8 and 2 with triazoles. This was made via a Sonogashira coupling followed by a Huisgen 1,3-dipolar cycloaddition. In the 8-position this strategy was effective for a wide range of azides, both in situ generated (**6b**–**g**), commercially available (**6a** and **6i**) and synthesized (**6h**). The 2-position triazole functionalized methyl ester was proven to be hard to hydrolyze this problem was circumvented by using the previously developed TMSE esters **12a**–**b** [15], which could be deprotected under mild conditions with TBAF in THF at room temperature without any decarboxylation observed. All together this gave a collection of twenty-four potential pilus dependent biofilm inhibitors. The evaluation showed that the 8-position was difficult to vary without affecting the biofilm inhibition capacity negatively. Here only one out of eighteen pilicides gave an EC$_{50}$ below 50 μM. However, in the 2 position it was shown that substituted triazoles can be a very attractive substituent for the future, with the best pilicide **13e** showing EC$_{50}$ values below 10 μM. Both small (methyl, **13e**) and larger (benzyl, **13f**) groups in the triazolo substituent were allowed indicating that further fine-tuning of the substitution pattern in this position have potential to result in more potent pilicides. The methodologies developed in this study are general and robust, which is a prerequisite to enable such studies in the future.

4. Experimental section

4.1. General synthesis

Unless stated otherwise, all reagents and solvents were used as received from commercial suppliers. CuI was purified by refluxing with DCM for 20 h in a Soxhlet apparatus and stored under dark and dry conditions. DMF was distilled under vaccum and stored over 3 Å

pyridone acids **13a**–**f** could be isolated in 54–69% yields over two steps (Table 3) without any decarboxylation detected.

Four out of six analogues showed 50% effective concentrations lower than 200 μM (Table 3). As pointed out earlier, the assay in this case is a whole cell assay, which will reflect not only the direct interaction with the potential target but also will take into account uptake and distribution within the bacteria, a clear structure activity can be hard to predict. The trend is that a larger substituent in position eight (e.g. R = mCF$_3$Ph) is better than a smaller (e.g. R = cPr) but interesting differences can be seen when the triazolo substituent is taken into account. Here R^1 = H is better in combination with a cyclopropyl substituent compared to a meta CF$_3$-phenyl substituent (compare **13a** with **13d**) and the opposite is seen for R^1 = Bn (compare **13c** with **13f**). Pilicide **13e** was the most potent analogue in this study and had an EC$_{50}$ of 9 μM, which is very promising. Among the pilicides tested the past two years (approx. 120) [6,10,17] only sixteen of them have shown EC$_{50}$ below 10 μM with the best being a pilus dependent biofilm inhibitor with an EC$_{50}$ of 400 nM [10].

Table 3
Huisgen 1,3-dipolar cycloaddition in position 2 of the thiazolo ring-fused bicyclic 2-pyridones followed by TBAF deprotection of the TMSE ester.

12a R = cPr
12b R = mCF$_3$Ph

13a-f
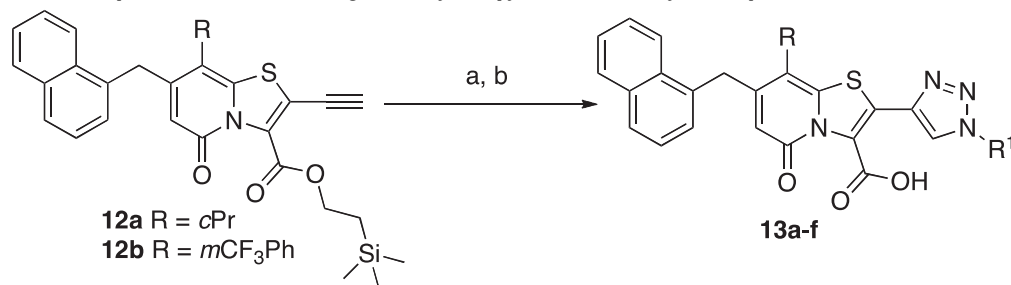
Reaction conditions: (a) CuSO$_4$/Na-ascorbate or CuTC, NaN$_3$, R^1-X, DMSO:H$_2$O 9:1
(b) TBAF*3H$_2$O, THF

Product	R	R^1	X	Yield (%)	EC$_{50}$ (μM)[f]
13a	cPr	H		56	75
13b	cPr	Me	I	69[a]	150
13c	cPr	Bn	Br	54[b]	>200
13d	mCF$_3$Ph	H		61	>200
13e	mCF$_3$Ph	Me	I	61[c,d]	9
13f	mCF$_3$Ph	Bn	Br	55[e]	50

[a] Approx 5% of **13a** was formed.
[b] Approx 10% of **13a** was formed.
[c] Approx 5% of **13d** was formed.
[d] CuTC was used instead of CuSO$_4$/Na-ascorbate.
[e] Approx 10% of **13d** was formed.
[f] Experiments were performed in triplicates and compared to DMSO-treated controls. The biofilm formation was studied under type-1 pili inducing conditions [5a].

molecular sieves. All HPLC was performed on a C18 reversed-phase column with H_2O:MeCN mixtures as eluent. TLC was performed on silica gel detected with UV-light. Column chromatography was employed on normal phase silica gel (eluents given in brackets). Optical rotation was measured with a polarimeter at 20 °C and 589 nm. IR was recorded on a spectrometer equipped with an ATR device. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz or a 500 MHz spectrometer at 298 K and calibrated using the residual peak of solvent as internal standard [CDCl$_3$ (CHCl$_3$ δ_H 7.26 ppm, CDCl$_3$ δ_C 77.16 ppm), d_6-DMSO (d_5-DMSO δ_H 2.49 ppm, d_6-DMSO δ_C 39.5 ppm), d_3-AcOD (d_2-AcOD δ_H 2.00 ppm and 11.70 ppm, d_3-AcOD δ_C 20.0 ppm and 180.0 ppm)]. HRMS was performed using a mass spectrometer with electrospray ionization (ES$^+$), sodiumformate was used as calibration chemical. $E.\ coli$, UTI89, was inoculated in LB over night at 37 °C. The next day the culture was diluted 1:1000 in LB and plated into 96-well PVC plates (Falcon #353911), 100 μl per well. Compounds were added to the wells to desired concentration, the DMSO concentration was kept constant. The plates were incubated for 24 h in humid boxes at 26 °C. The plates were washed extensively with water and air dried before 125 μl/well of 1% crystal violet (Sigma C3886) was added. The plates were incubated with crystal violet for 10 min at room temperature, washed extensively with water and then air dried. 150 μl/well of 33% acetic acid was added, 100 μl from each well was transferred to a new clear bottom 96-well plates (Nunc #167008). Absorbance was read at 600 nm. Growth was monitored in separate sterile clear bottom 96-well plates. All experiments were performed in triplicates.

Compounds **3** [14], **4** [6], **9** [15] and **12** [15] were synthesized according to published procedures. Data in agreement with published data.

4.1.1. (3R)-6-Bromo-7-naphthalen-1-ylmethyl-5-oxo-8-ethynyl-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (5)

3 (1.5 g, 2.7 mmol), CuI (51.4 mg, 0.27 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (94.7 mg, 0.135 mmol) and TEA (0.75 ml, 5.4 mmol) in DMF (25 ml, degassed before use) was stirred for 5 min and TMSA (1.14 ml, 8.1 mmol) in DMF (7 ml) was added dropwise over 5 min. The flask was sealed and stirred at room temperature under nitrogen atmosphere for 20 h. The reaction mixture was diluted with EtOAc and washed with brine. The organic layer was dried (Na$_2$SO$_4$), filtered and concentrated. The crude material was dissolved in THF/MeOH 1:4 (70 ml) and K$_2$CO$_3$ (746 mg, 5.4 mmol) was added, the reaction was stirred at room temperature for 15 min. The reaction mixture was diluted with EtOAc and washed with brine. The organic layer was dried (Na$_2$SO$_4$), filtered and concentrated. Purification by column chromatography on silica gel (Heptane:EtOAc 65:35) gave **5** (931 mg, 76%). [α]$_D$ −1 (c 0.50, CHCl$_3$); IR 3226, 2952, 2361, 1747, 1642, 1576, 1473, 1212, 999, 771 cm^{-1}; ^{1}H NMR, (400 MHz, CDCl$_3$) δ 8.13 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.62–7.57 (m, 1H), 7.56–7.51 (m, 1H), 7.35 (t, J = 7.6 Hz, 1H), 6.94 (dd, J = 7.2, 0.8 Hz, 1H), 5.74 (dd, J = 8.8, 2.4 Hz, 1H), 4.69 (s, 2H), 3.87 (s, 3H), 3.85–3.81 (m, 1H), 3.62 (dd, J = 12.0, 2.4 Hz, 1H), 3.15 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 167.9, 157.2, 153.4, 152.8, 133.9, 132.0, 131.8, 129.0, 127.4, 126.3, 125.9, 125.7, 124.0, 123.1, 113.7, 98.4, 85.3, 65.4, 53.8, 38.0, 32.0; LRMS (ES) calcd [M + H] for C$_{22}$H$_{17}$BrNO$_3$S 455, obsd 455.

4.2. Typical procedure for the Huisgen 1,3-dipolar cycloaddition in the 8-position (compounds 6a–i)

4.2.1. (3R)-6-Bromo-8-(1-methyl-1H-[1,2,3]triazol-4-yl)-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (6b)

NaN$_3$ (25.8 mg, 0.40 mmol), Na-ascorbate (5.9 mg, 0.03 mmol) and CuSO$_4$ (1.6 mg, 0.01 mmol) were dissolved in water (0.75 ml).

The mixture was stirred for 5 min at room temperature and DMF (0.75 ml), MeI (6 μl, 0.10 mmol) and **5** (30 mg, 0.066 mmol) were added. The reaction mixture was stirred at 70 °C for 16 h (oil bath). Diluted with EtOAc and washed with brine. The organic layer was dried (Na$_2$SO$_4$), filtered and concentrated. The crude product was purified by column chromatography on silica gel (heptane:EtOAc 80:20 → 0:100) gave **6b** (26.6 mg, 79%).[α]$_D$ 0 (c 0.50, CDCl$_3$); IR 1740, 1652, 1472, 1212, 988, 792 cm^{-1}; ^{1}H NMR, (400 MHz, CHCl$_3$) δ 7.89–7.80 (m, 2H), 7.75 (d, J = 8.3 Hz, 1H), 7.54–7.49 (m, 2H), 7.35 (t, J = 7.5 Hz, 1H), 7.03 (dd, J = 7.1, 0.9 Hz, 1H), 6.64 (s, 1H), 5.76 (dd, J = 8.6, 2.5 Hz, 1H), 4.57–4.40 (m, 2H), 3.86 (s, 3H), 3.74–3.67 (m, 4H), 3.53 (dd, J = 11.8, 2.5 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.2, 157.6, 152.0, 148.6, 142.1, 133.8, 132.7, 131.5, 128.9, 127.5, 126.5, 126.1, 125.7, 124.7, 123.7, 123.0, 114.8, 106.5, 64.9, 53.7, 37.4, 36.7, 31.9; LRMS (ES) calcd [M + H] for C$_{23}$H$_{20}$BrN$_4$O$_3$S 512, obsd 512.

4.2.2. (3R)-6-Bromo-7-naphthalen-1-ylmethyl-5-oxo-8-(1H-[1,2,3] triazol-4-yl)-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (6a)

From **5** (40 mg, 0.088 mmol) was prepared **6a** (19 mg, 42% yield) after purification by column chromatography on silica gel heptane:EtOAc 30:70; [α]$_D$ −1 (c 0.50, DMSO); IR 2355, 1744, 1622, 1473, 1155, 975, 792; ^{1}H NMR, (400 MHz, d_6-DMSO) δ 8.08–8.01 (m, 1H), 7.97–7.91 (m, 1H), 7.79 (d, J = 8.3 Hz, 1H), 7.59–7.51 (m, 2H), 7.40 (t, J = 7.7 Hz, 1H), 7.24 (s, 1H), 6.92 (d, J = 7.2 Hz, 1H), 5.77 (dd, J = 10.4, 1.7 Hz, 1H), 4.57–4.36 (m, 2H), 3.87 (dd, J = 12.1, 9.4 Hz, 1H), 3.80 (s, 3H), 3.56 (dd, J = 12.1, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 168.5, 156.3, 151.1, 148.7, 139.7, 133.3, 132.6, 131.1, 128.7, 128.6, 126.8, 126.3, 125.9, 125.5, 123.6, 123.1, 113.0, 107.1, 64.4, 53.1, 37.1, 30.9; LRMS (ES) calcd [M + H] for C$_{22}$H$_{18}$BrN$_4$O$_3$S 498, obsd 498.

4.2.3. (3R)-6-Bromo-8-(1-ethyl-1H-[1,2,3]triazol-4-yl)-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (6c)

From **5** (100 mg, 0.22 mmol) was prepared **6c** (90 mg, 78% yield) after purification by column chromatography on silica gel heptane:EtOAc 80:20 → 0:100; [α]$_D$ 2 (c 0.50, CHCl$_3$); IR 1747, 1646, 1472, 1213, 1174, 792 cm^{-1}; ^{1}H NMR, (400 MHz, CDCl$_3$) δ 7.89–7.79 (m, 2H), 7.74 (d, J = 8.2 Hz, 1H), 7.53–7.46 (m, 2H), 7.35 (t, J = 8.0 Hz, 1H), 7.04 (d, J = 7.1 Hz, 1H), 6.54 (s, 1H), 5.76 (dd, J = 8.5, 2.3 Hz, 1H), 4.55–4.39 (m, 2H), 3.97 (dq, J = 2.1, 8.5 Hz, 2H), 3.86 (s, 3H), 3.71 (dd, J = 11.8, 8.6 Hz, 1H), 3.52 (dd, J = 11.8, 2.4 Hz, 1H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.2, 157.6, 152.1, 148.6, 141.8, 133.9, 132.7, 131.4, 128.9, 127.5, 126.5, 126.1, 125.7, 124.7, 123.0, 122.1, 114.9, 106.5, 64.9, 53.7, 45.2, 37.5, 31.9, 14.7; LRMS (ES) calcd [M + H] for C$_{24}$H$_{22}$BrN$_4$O$_3$S 526, obsd 526.

4.2.4. (3R)-6-Bromo-8-(1-cyclopropylmethyl-1H-[1,2,3]triazol-4-yl)-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a] pyridine-3-carboxylic acid methyl ester (6d)

From **5** (40 mg, 0.088 mmol) was prepared **6d** (26 mg, 54% yield) after purification by column chromatography on silica gel heptane:EtOAc 80:20 → 0:100; [α]$_D$ −1 (c 0.50, CHCl$_3$); IR 1738, 1646, 1472, 1432, 1212, 1170, 791 cm^{-1}; ^{1}H NMR, (400 MHz, CDCl$_3$) δ 7.90–7.83 (m, 2H), 7.76 (d, J = 8.2 Hz, 1H), 7.53–7.47 (m, 2H), 7.37 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 6.9 Hz, 1H), 6.71 (s, 1H), 5.78 (dd, J = 8.5, 2.2 Hz, 1H), 4.58–4.41 (m, 2H), 3.87 (s, 3H), 3.85–3.75 (m, 2H), 3.75–3.67 (m, 1H), 3.54 (dd, J = 11.8, 2.3 Hz, 1H), 0.61–0.50 (m, 1H), 0.19–0.06 (m, 2H), −0.12–0.19 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.2, 157.6, 151.6, 148.5, 141.7, 134.0, 132.5, 131.4, 128.9, 127.5, 126.6, 126.1, 125.8, 124.6, 123.0, 122.1, 115.0, 106.7, 64.9, 54.9, 53.7, 37.8, 32.0, 10.2,

3.8, 3.7; LRMS (ES) calcd [M + H] for $C_{26}H_{24}BrN_4O_3S$ 552, obsd 552.

4.2.5. (3R)-8-(1-Benzyl-1H-[1,2,3]triazol-4-yl)-6-bromo-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (6e)

From 5 (40 mg, 0.088 mmol) was prepared 6e (36 mg, 70% yield) after purification by column chromatography on silica gel heptane:EtOAc 90:10 → 20:80; $[\alpha]_D$ −4 (c 0.25, DMSO); IR 1750, 1646, 1598, 1474, 1212, 792, 725 cm^{-1}; ^{1}H NMR, (400 MHz, d_6-DMSO) δ 8.03−7.93 (m, 2H), 7.83 (s, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.57−7.53 (m, 2H), 7.36 (t, J = 7.4 Hz, 1H), 7.17 (t, J = 7.2 Hz, 1H), 7.05 (t, J = 7.3 Hz, 2H), 6.88 (d, J = 7.1 Hz, 1H), 6.77 (t, J = 7.7 Hz, 2H), 5.79 (d, J = 9.0 Hz, 1H), 5.40 (s, 2H), 4.58−4.34 (m, 2H), 3.95−3.86 (m, 1H), 3.79 (s, 3H), 3.65−3.58 (m, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 168.4, 156.4, 151.3, 149.7, 141.2, 135.5, 133.2, 132.1, 131.0, 128.6, 128.5 (2C), 127.8, 126.9, 126.9 (2C), 126.3, 125.9, 125.5, 124.3, 123.6, 123.0, 113.1, 105.3, 64.5, 53.2, 52.6, 36.8, 31.1; LRMS (ES) calcd [M + H] for $C_{29}H_{24}BrN_4O_3S$ 588, obsd 588.

4.2.6. (3R)-6-Bromo-8-[1-(4-methyl-benzyl)-1H-[1,2,3]triazol-4-yl]-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (6f)

From 5 (60 mg, 0.132 mmol) was prepared 6f (65 mg, 82% yield) after purification by column chromatography on silica gel heptane:EtOAc 85:15 → 0:100; $[\alpha]_D$ 1 (c 0.50, CHCl$_3$); IR 1748, 1645, 1472, 1212, 1156, 792, 770 cm^{-1}; ^{1}H NMR, (400 MHz, CDCl$_3$) δ 7.89 (dd, J = 9.2, 1.3 Hz, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.57−7.47 (m, 2H), 7.26 (t, J = 7.7 Hz, 1H), 6.94 (dd, J = 8.0, 0.9 Hz, 1H), 6.85 (d, J = 7.8 Hz, 2H), 6.61 (d, J = 8.0 Hz, 2H), 6.55 (s, 1H), 5.75 (dd, J = 8.6, 2.4 Hz, 1H), 5.1 (s, 2H), 4.53−4.35 (m, 2H), 3.85 (s, 3H), 3.69 (dd, J = 11.8, 8.6 Hz, 1H), 3.51 (dd, J = 11.8, 2.4 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.1, 157.5, 151.7, 148.4, 142.0, 138.5, 133.8, 132.3, 131.3, 130.5, 129.6 (2C), 128.9, 127.9 (2C), 127.4, 126.5, 126.0, 125.6, 124.4, 123.0, 122.6, 114.9, 106.5, 64.8, 53.9, 53.7, 37.6, 31.9, 21.2; LRMS (ES) calcd [M + H] for $C_{30}H_{26}BrN_4O_3S$ 603, obsd 603.

4.2.7. (3R)-6-Bromo-7-naphthalen-8-[1-(4-nitro-benzyl)-1H-[1,2,3]triazol-4-yl]-1-ylmethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (6g)

From 5 (40 mg, 0.088 mmol) was prepared 6g (49 mg, 84% yield) after purification by column chromatography on silica gel heptane:EtOAc 80:20 → 0:100; $[\alpha]_D$ 1 (c 0.50, CHCl$_3$); IR 1747, 1644, 1416, 1472, 1342, 1213, 725 cm^{-1}; ^{1}H NMR, (400 MHz, CDCl$_3$) δ 7.88−7.81 (m, 3H), 7.76 (d, J = 8.3 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.57−7.44 (m, 2H), 7.26 (t, J = 7.7 Hz, 1H), 6.95 (d, J = 7.1 Hz, 1H). 6.78 (d, J = 8.8 Hz, 2H), 6.64 (s, 1H), 5.76 (dd, J = 8.6, 2.4 Hz, 1H), 5.30−5.19 (m, 2H), 4.52−4.33 (m, 2H), 3.86 (s, 3H), 3.73 (dd, J = 11.8, 8.6 Hz, 1H), 3.54 (dd, J = 11.8, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.1, 157.5, 151.3, 148.6, 147.9, 142.7, 140.5, 133.8, 132.1, 131.2, 128.9, 128.3 (2C), 127.5, 126.6, 126.3, 125.6, 124.2 (2C), 124.2, 122.9, 122.8, 115.0, 105.9, 64.8, 53.7, 53.0, 37.7, 32.0; LRMS (ES) calcd [M + H] for $C_{29}H_{23}BrN_5O_5S$ 633, obsd 633.

4.2.8. (3R)-8-((S)-1-Benzyl-2-hydroxy-ethyl)-1H-[1,2,3]triazol-4-yl)-6-bromo-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (6h)

From 5 (100 mg, 0.22 mmol) was prepared 6h (92 mg, 66% yield) after purification by column chromatography on silica gel heptane:EtOAc 75:25 → 0:100; $[\alpha]_D$ −222 (c 0.10, DMSO); IR 1744, 1636, 1591, 1475, 1220, 1158, 987, 791 cm^{-1}; ^{1}H NMR, (400 MHz, d_6-DMSO) δ 8.11−7.99 (m, 1H), 7.98−7.90 (m, 1H), 7.87−7.77 (m, 2H), 7.64−7.52 (m, 2H), 7.45−7.37 (m, 1H), 7.02−6.84 (m, 4H), 6.75−6.66 (m, 2H), 5.84−5.77 (m, 1H), 5.04 (s, 1H, broad), 4.67−4.24 (m, 3H), 3.95−3.84 (m, 1H), 3.84 (s, 3H), 3.66−3.53 (m, 3H), 3.05−2.64 (m, 2H); ^{13}C NMR

(100 MHz, d_6-DMSO) δ 168.4 (splitted, 1C), 156.4, 151.5 + 151.4 (1C), 149.6, 140.8 + 140.6 (1C), 136.9, 133.3 (splitted, 1C), 132.5 (splitted, 1C), 131.1 (splitted, 1C), 128.6 (splitted, 1C), 128.5 (splitted, 1C), 128.5 (splitted, 1C), 128.1 (splitted, 2C), 126.8 (splitted, 1C), 126.3 + 126.2 (2C), 125.9 (splitted, 1C), 125.5 (splitted, 1C), 123.8 (splitted, 1C), 123.3 + 123.1 (1C), 123.1 + 122.9 (1C), 113.0 + 113.0 (1C), 105.8 + 105.7 (1C), 64.6 + 64.5 (2C), 62.8 + 62.7 (1C), 53.1 (splitted, 1C), 36.9 (splitted, 1C), 36.6 + 36.5 (1C), 31.1 + 31.0 (1C); LRMS (ES) calcd [M + H] for $C_{31}H_{28}BrN_4O_4S$ 633, obsd 633.

4.2.9. (3R)-6-Bromo-7-naphthalen-1-ylmethyl-5-oxo-8-[1-(2,3,4-tri-O-acetyl-ß-D-xylopyranosyl)-1H-[1,2,3]triazol-4-yl]-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (6i)

From 5 (50 mg, 0.11 mmol) was prepared 6i (79 mg, 95% yield) after purification by column chromatography on silica gel heptane:EtOAc 85:15 → 0:100; $[\alpha]_D$ −2 (c 0.50, CHCl$_3$); IR 1740, 1646, 1473, 1365, 1207, 1033, 746 cm^{-1}; ^{1}H NMR, (400 MHz, CDCl$_3$) δ 8.04−7.84 (m, 2H), 7.76 (t, J = 7.8 Hz, 1H), 7.59−7.46 (m, 2H), 7.38−7.32 (m, 1H), 7.02 (t, J = 7.1 Hz, 1H), 6.97, 6.86 (s, 1H), 5.79−5.71 (m, 1H), 5.45 (dd, J = 8.9, 6.3 Hz, 1H), 5.22 (dt, J = 9.4, 1.1 Hz, 1H), 4.85−4.62 (m, 2H), 4.58−4.35 (m, 2H), 3.98−3.87 (m, 1H), 3.84, 3.83 (s, 3H), 3.76−3.64 (m, 1H), 3.54−3.48 (m, 1H), 3.38−3.28 (m, 1H), 2.05−1.97 (m, 6H), 1.71, 1.59 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 169.7 (splitted, 1C), 169.7, 168.8 + 168.7 (1C), 168.1 + 168.0 (1C), 157.5 + 157.4 (1C), 151.9 + 151.6 (1C), 148.8 + 148.6 (1C), 142.6 + 142.5 (1C), 134.0 + 133.9 (1C), 132.3 + 132.2 (1C), 131.4 + 131.3 (1C), 129.0 + 128.9 (1C), 127.6 + 127.5 (1C), 126.5 + 126.4 (1C), 126.1 + 125.9 (1C), 125.8 + 125.7 (1C), 124.5 + 124.4 (1C), 123.4 + 123.2 (1C), 121.3 + 121.0 (1C), 115.2 + 114.9 (1C), 106.0 + 105.8 (1C), 86.3 + 86.2 (1C), 71.4 + 71.3 (1C), 70.9 + 70.4 (1C), 68.2 + 68.1 (1C), 65.2, 65.0 + 64.7 (1C), 53.6 (splitted, 1C), 37.3 + 37.2 (1C), 32.0 + 31.9 (1C), 20.7, 20.6 (splitted, 1C), 20.0 + 19.8 (1C); LRMS (ES) calcd [M + H] for $C_{33}H_{32}BrN_4O_{10}S$ 757, obsd 757.

4.3. Typical procedure for hydrolysis of the 8-position triazole functionalized bicyclic 2-pyridones (compounds 7a−i)

4.3.1. (3R)-6-Bromo-7-naphthalen-1-ylmethyl-5-oxo-8-(1H-[1,2,3]triazol-4-yl)-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (7a)

6a (29.0 mg, 0.058 mmol) was dissolved in THF (5 ml) and 1 M LiOH (0.174 ml) was added. The mixture was stirred at room temperature for 17 h. The suspension was diluted with EtOAc and brine was added. 1 M HCl was added until pH = 1. The organic phase was dried (Na$_2$SO$_4$), filtered and concentrated. Purification by HPLC gave 7a (20.1 mg, 72%). $[\alpha]_D$ −1 (c 0.10, DMSO); IR 2936, 1722, 1619, 1472, 1390, 1158, 1139, 977, 792 cm^{-1}; ^{1}H NMR, (400 MHz, d_6-DMSO) δ 15.05 (broad s, 1H), 8.05−7.99 (m, 1H), 7.97−7.91 (m, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.58−7.53 (m, 2H), 7.40 (t, J = 7.4 Hz, 1H), 7.33 (s, 1H, broad), 6.93 (d, J = 6.9 Hz, 1H), 5.68 (dd, J = 9.0, 1.3 Hz, 1H), 4.55−4.32 (m, 2H), 3.89 (dd, J = 11.9, 9.3 Hz, 1H), 3.59 (dd, J = 11.9, 4.7 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.2, 156.4, 150.8 (broad), 149.6, 141.6 (broad), 133.3, 132.7 (broad), 132.4, 131.0, 128.6, 126.9, 126.4, 125.9, 125.5, 123.7, 123.0, 113.3, 105.2 (broad), 64.7, 37.0, 31.5; HRMS (ES) calcd [M + Na] for $C_{21}H_{15}BrN_4NaO_3S$ 504.9946, obsd 504.9934.

4.3.2. (3R)-6-Bromo-8-(1-methyl-1H-[1,2,3]triazol-4-yl)-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (7b)

From 6b (60 mg, 0.116 mmol) was prepared 7b (42 mg, 73% yield) after purification by column chromatography on silica gel DCM:MeOH:AcOH 91:7:2; $[\alpha]_D$ −5 (c 0.10, DMSO); IR 1779, 1693, 1606, 1531, 1307, 1127, 886, 818 cm^{-1}; ^{1}H NMR, (400 MHz, d_6-DMSO) δ 8.01 (d, J = 7.9 Hz, 1H), 7.92 (d, J = 6.8 Hz, 1H), 7.82−7.73 (m, 2H), 7.59−7.49 (m, 2H), 7.39 (t, J = 7.1 Hz, 1H), 6.91 (d, J = 6.9 Hz, 1H), 5.67 (d, J = 8.8 Hz, 1H), 4.56−4.33 (m, 2H), 3.89 (dd, J = 11.2,

9.7 Hz, 1H), 3.82 (s, 3H), 3.58 (d, $J = 11.2$ Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.2, 156.4, 151.4, 149.7, 141.2, 133.2, 132.7, 131.1, 128.6, 126.9, 126.3, 125.8, 125.5, 124.7, 123.8, 123.1, 113.0, 105.4, 64.7, 36.5, 36.3, 31.5; HRMS (ES) calcd [M + Na] for $C_{22}H_{17}BrN_4NaO_3S$ 519.0102, obsd 519.0098.

4.3.3. (3R)-6-Bromo-8-(1-ethyl-1H-[1,2,3]triazol-4-yl)-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (7c)

From **6c** (88 mg, 0.167 mmol) was prepared **7c** (74 mg, 87% yield) after purification by HPLC; $[\alpha]_D$ −2 (c 0.10, DMSO); IR 1725, 1617, 1475, 1167, 768, 719 cm^{-1}; ^{1}H NMR, (400 MHz, d_6-DMSO) δ 8.02–7.96 (m, 1H), 7.96–7.88 (m, 1H), 7.78 (d, $J = 8.0$ Hz, 1H), 7.67 (s, 1H), 7.58–7.48 (m, 2H), 7.39 (t, $J = 7.6$ Hz, 1H), 6.92 (d, $J = 6.9$ Hz, 1H), 5.68 (d, $J = 8.9$ Hz, 1H), 4.57–4.33 (m, 2H), 4.16–4.06 (m, 2H), 3.88 (dd, $J = 11.4$, 9.8 Hz, 1H), 3.57 (d, $J = 11.4$ Hz, 1H), 1.03 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.4, 156.6, 151.6, 149.9, 141.3, 133.4, 132.8, 131.2, 128.8, 127.1, 126.5, 126.0, 125.7, 124.1, 123.4, 123.2, 113.4, 105.5, 64.9, 44.7, 36.7, 31.7, 15.1; HRMS (ES) calcd [M + Na] for $C_{23}H_{19}BrN_4NaO_3S$ 533.0259, obsd 533.0255.

4.3.4. (3R)-6-Bromo-8-(1-cyclopropylmethyl-1H-[1,2,3]triazol-4-yl)-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (7d)

From **6d** (55 mg, 1 mmol) was prepared **7d** (51 mg, 93% yield) after purification by column chromatography on silica gel DCM:MeOH:AcOH 91:7:2; $[\alpha]_D$ −2 (c 0.10, DMSO); IR 1634, 1474, 1396, 1179, 791, 768 cm^{-1}; ^{1}H NMR, (400 MHz, d_6-DMSO) δ 8.04–7.97 (m, 1H), 7.95–7.89 (m, 1H), 7.79 (d, $J = 8.1$ Hz, 1H), 7.58 (s, 1H), 7.56–7.49 (m, 2H), 7.40 (t, $J = 7.9$ Hz, 1H), 6.93 (d, $J = 7.0$ Hz, 1H), 5.56 (d, $J = 8.7$ Hz, 1H), 4.55–4.31 (m, 2H), 4.03–3.91 (m, 2H), 3.81 (dd, $J = 11.4$, 9.4 Hz, 1H), 3.58 (d, $J = 11.4$ Hz, 1H), 0.83–0.71 (m, 1H), 0.20–0.06 (m, 2H), 0.04–0.07 (m, 2H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.4, 156.7, 150.6, 150.1, 141.4, 133.5, 132.8, 131.2, 128.7, 127.1, 126.5, 126.0, 125.7, 124.0, 123.4, 123.3, 113.5, 105.1, 66.2, 53.7, 37.0, 32.4, 11.0, 3.4 (splitted, 2C); HRMS (ES) calcd [M + Na] for $C_{25}H_{21}BrN_4NaO_3S$ 559.0415, obsd 559.0420.

4.3.5. (3R)-8-(1-Benzyl-1H-[1,2,3]triazol-4-yl)-6-bromo-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (7e)

From **6e** (79 mg, 0.135 mmol) was prepared **7e** (66 mg, 85% yield) after purification by HPLC; $[\alpha]_D$ −11 (c 0.10, DMSO); IR 1750, 1614, 1474, 1201, 714 cm^{-1}; ^{1}H NMR, (400 MHz, d_6-DMSO) δ 8.04–7.92 (m, 2H), 7.83 (s, 1H), 7.78 (d, $J = 8.3$ Hz, 1H), 7.61–7.52 (m, 2H), 7.36 (t, $J = 7.6$ Hz, 1H), 7.17 (t, $J = 7.3$ Hz, 1H), 7.05 (t, $J = 7.4$ Hz, 2H), 6.89 (d, $J = 6.9$ Hz, 1H), 6.77 (d, $J = 7.4$ Hz, 2H), 5.68 (d, $J = 8.9$ Hz, 1H), 5.40 (s, 2H), 4.57–4.32 (m, 2H), 3.89 (t, $J = 10.4$ Hz, 1H), 3.59 (d, $J = 5.8$ Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.2, 156.4, 151.0, 149.7, 141.3, 135.5, 133.2, 132.2, 131.0, 128.6, 128.5 (2C), 127.8, 126.9, 126.9 (2C), 126.3, 125.9, 125.5, 124.3, 123.6, 123.0, 113.2, 105.2, 64.7, 52.6, 36.8, 31.6; HRMS (ES) calcd [M + Na] for $C_{28}H_{21}BrN_4NaO_3S$ 595.0415, obsd 595.0410.

4.3.6. (3R)-6-Bromo-8-[1-(4-methyl-benzyl)-1H-[1,2,3]triazol-4-yl]-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (7f)

From **6f** (93 mg, 0.153 mmol) was prepared **7f** (74 mg, 82% yield) after purification by HPLC; $[\alpha]_D$ −6 (c 0.10, DMSO); IR 1748, 1612, 1474, 1199, 1120, 788, 762 cm^{-1}; ^{1}H NMR, (400 MHz, d_6-DMSO) δ 7.99 (t, $J = 8.8$ Hz, 2H), 7.82–7.75 (m, 2H), 7.63–7.53 (m, 2H), 7.37 (t, $J = 7.7$ Hz, 1H), 6.89 (d, $J = 7.1$ Hz, 1H), 6.83 (d, $J = 7.8$ Hz, 2H), 6.68 (d, $J = 7.9$ Hz, 2H), 5.69 (d, $J = 8.9$ Hz, 1H), 5.34 (s, 2H), 4.55–4.31 (m, 2H), 3.89 (dd, $J = 11.9$, 9.4 Hz, 1H), 3.60 (d, $J = 11.9$ Hz, 1H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.4, 156.6, 151.2, 149.9, 141.5, 137.3, 133.5,

132.6, 132.4, 131.2, 129.2 (2C), 128.8, 127.3 (2C), 127.1, 126.5, 126.1, 125.7, 124.3, 123.8, 123.2, 113.4, 105.4, 64.9, 52.6, 37.0, 31.8, 20.8; HRMS (ES) calcd [M + Na] for $C_{29}H_{23}BrN_4NaO_3S$ 609.0572, obsd 609.0576.

4.3.7. (3R)-6-Bromo-7-naphthalen-8-[1-(4-nitro-benzyl)-1H-[1,2,3]triazol-4-yl]-1-ylmethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (7g)

From **6g** (67 mg, 0.106 mmol) was prepared **7g** (41 mg, 63% yield) after purification by HPLC; $[\alpha]_D$ −4 (c 0.10, DMSO); IR 1734, 1592, 1521, 1476, 1344, 1160, 1111, 798, 777, 731 cm^{-1}; ^{1}H NMR, (400 MHz, d_6-DMSO) δ 7.99–7.94 (m, 1H), 7.93–7.89 (m, 1H), 7.88 (s, 1H), 7.83 (d, $J = 8.7$ Hz, 2H), 7.76 (d, $J = 8.2$ Hz, 1H), 7.55–7.48 (m, 2H), 7.36 (t, $J = 7.9$ Hz, 1H), 6.95 (d, $J = 8.6$ Hz, 1H), 6.87 (d, $J = 7.1$ Hz, 1H), 5.69 (dd, $J = 7.8$, 1.0 Hz, 1H), 5.59 (s, 2H), 4.54–4.31 (m, 2H), 3.91 (dd, $J = 11.7$, 9.1 Hz, 1H), 3.60 (dd, $J = 11.7$, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.4, 156.6, 151.1, 150.0, 147.0, 143.2, 141.8, 133.4, 132.3, 131.1, 128.7, 128.2 (2C), 127.1, 126.5, 126.1, 125.7, 124.8, 123.8 (2C), 123.7, 123.2, 113.4, 105.1, 64.9, 51.9, 37.0, 31.8; HRMS (ES) calcd [M + Na] for $C_{28}H_{20}BrN_5NaO_5S$ 640.0266, obsd 640.0270.

4.3.8. (3R)-8-((S)-1-Benzyl-2-hydroxy-ethyl)-1H-[1,2,3]triazol-4-yl)-6-bromo-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (7h)

From **6h** (80 mg, 0.126 mmol) was prepared **7h** (60 mg, 77% yield) after purification by HPLC; $[\alpha]_D$ −104 (c 0.10, DMSO); IR 1776, 1622, 1532, 1475, 1308, 1163, 1018, 792, 701 cm^{-1}; ^{1}H NMR, (400 MHz, d_6-DMSO) δ 8.09–7.99 (m, 1H), 7.97–7.93 (m, 1H), 7.84–7.78 (m, 2H), 7.61–7.52 (m, 2H), 7.43–7.37 (m, 1H), 6.98–6.85 (m, 4H), 6.72–6.67 (m, 2H), 5.67 (d, $J = 9.0$ Hz, 1H), 4.66–4.24 (m, 3H), 3.94–3.83 (m, 1H), 3.62–3.50 (m, 3H), 3.03–2.89 (m, 1H), 2.80–2.63 (m, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.2 (splitted, 1C), 156.4, 151.2 + 151.1 (1C), 149.7, 140.9 + 140.7 (1C), 136.9, 133.3 (splitted, 1C), 132.6 (splitted, 1C), 131.1 (splitted, 1C), 128.6 (splitted, 1C), 128.5 (splitted 2C), 128.1 (2C), 126.8 (splitted, 1C), 126.3 + 126.2 (1C), 125.9 (splitted, 1C), 125.5 (splitted, 1C), 123.8, 123.3, 123.1, 122.9, 113.1 + 113.0 (1C), 105.6 (splitted, 1C), 64.7 (splitted, 1C), 64.6 + 64.5 (splitted, 1C), 62.8 + 62.7 (1C), 36.9, 36.6 + 36.5 (splitted, 1C), 31.5 + 31.4 (splitted, 1C); HRMS (ES) calcd [M + Na] for $C_{30}H_{25}BrN_4NaO_4S$ 639.0678, obsd 639.0680.

4.3.9. (3R)-6-Bromo-7-naphthalen-1-ylmethyl-5-oxo-8-[1-(2,3,4-tri-hydroxy-ß-D-xylopyranosyl)-1H-[1,2,3]triazol-4-yl]-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (7i)

From **6i** (72 mg, 0.095 mmol) was prepared **7i** (46 mg, 79% yield) after purification by HPLC; $[\alpha]_D$ −21 (c 0.10, DMSO); IR 3351, 1722, 1621, 1473, 1310, 1039, 991, 792 cm^{-1}; ^{1}H NMR, (400 MHz, d_6-DMSO) δ 8.09–8.04 (m, 1H), 8.00 (d, $J = 15.2$ Hz, 1H), 7.96–7.91 (m, 1H), 7.79 (d, $J = 8.2$ Hz, 1H), 7.59–7.51 (m, 2H), 7.40 (dt, $J = 0.7$, 7.7 Hz, 1H), 6.94 (d, $J = 7.2$ Hz, 1H), 5.68 (dd, $J = 9.1$, 1.1 Hz, 1H), 5.34 (dd, $J = 9.2$, 1.5 Hz, 1H), 4.54–4.30 (m, 2H), 3.94–3.85 (m, 1H), 3.74–3.66 (m, 1H), 3.61–3.47 (m, 2H), 3.36–3.18 (m, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.2, 156.4, 151.2 + 151.1 (1C), 150.0 + 149.9 (1C), 141.1, 133.3, 132.6, 131.2, 128.6, 126.9, 126.4 + 126.3 (1C), 125.9 + 125.9 (1C), 125.6, 123.9, 123.3, 123.1, 113.2 + 113.1 (1C), 105.3, 88.0 + 87.9 (1C), 76.9, 71.9 + 71.8 (1C), 69.0, 68.2 + 68.1 (1C), 64.7, 36.7 + 36.6 (1C), 31.5; HRMS (ES) calcd [M + Na] for $C_{26}H_{23}BrN_4NaO_7S$ 637.0369, obsd 637.0357.

4.4. Typical procedure for the dehalogenation of the 8-position triazole functionalized bicyclic 2-pyridones (compounds 8a–i)

4.4.1. (3R)-7-Naphthalen-1-ylmethyl-5-oxo-8-(1H-[1,2,3]triazol-4-yl)-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (8a)

7a (10.1 mg, 0.0209 mmol), ammoniumformate (19.7 mg, 0.313 mmol) and 10% Pd/C (5.0 mg) were dissolved in MeOH (2 ml).

The mixture was refluxed for 4 h after which the solvent was evaporated. The residue was dissolved in DMSO and Pd/C was filtered off. Purification by HPLC gave **8a** (6.2 mg, 73%). $[\alpha]_D$ 5 (*c* 0.25, DMSO); IR 1733, 1634, 1483, 1178, 780 cm^{-1}; ^{1}H NMR, (400 MHz, d_6-DMSO) δ 8.02 (s, 1H, broad), 7.99–7.92 (m, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.83–7.78 (m, 1H), 7.56–7.49 (m, 2H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.29 (d, *J* = 7.0 Hz, 1H), 5.51–5.42 (m, 2H), 4.34–4.10 (m, 2H), 3.81 (dd, *J* = 12.0, 9.1 Hz, 1H), 3.50 (dd, *J* = 12.0, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 169.4, 159.7, 158.1 + 157.8 (1C), 153.7, 149.7, 134.0, 133.4, 131.3, 128.6, 127.5, 127.4, 126.4, 125.9, 125.6, 123.9, 113.9 (splitted, 2C), 104.3, 63.1, 35.8, 31.2; HRMS (ES) calcd [M + Na] for $C_{21}H_{16}N_4NaO_3S$ 427.0841, obsd 427.0836.

4.4.2. (3R)-8-(1-Methyl-1H-[1,2,3]triazol-4-yl)-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (8b)

From **7b** (20 mg, 0.040 mmol) was prepared **8b** (14 mg, 85% yield) after purification by HPLC; $[\alpha]_D$ −3 (*c* 0.10, DMSO); IR 1734, 1622, 1566, 1492, 1441, 1183, 782 cm^{-1}; ^{1}H NMR, (400 MHz, d_6-DMSO) δ 8.31 (s, 1H), 7.99–7.92 (m, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.83–7.75 (m, 1H), 7.56–7.43 (m, 3H), 7.33 (d, *J* = 6.7 Hz, 1H), 5.44 (d, *J* = 8.7 Hz, 1H), 5.38 (s, 1H), 4.36–4.10 (m, 2H), 4.07 (s, 3H), 3.79 (dd, *J* = 11.2, 9.5 Hz, 1H), 3.49 (d, *J* = 11.2 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.4, 159.7, 153.9, 149.6, 141.2, 134.0, 133.4, 131.4, 128.6, 127.8, 127.4, 126.3, 125.8, 125.6, 125.2, 123.9, 113.6, 104.5, 63.1, 36.4, 35.8, 31.2; HRMS (ES) calcd [M + Na] for $C_{22}H_{18}N_4NaO_3S$ 441.0997, obsd 441.1003.

4.4.3. (3R)-8-(1-Ethyl-1H-[1,2,3]triazol-4-yl)-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (8c)

From **7c** (38 mg, 0.075 mmol) was prepared **8c** (22 mg, 69% yield) after purification by HPLC; $[\alpha]_D$ −11 (*c* 0.10, DMSO); IR 1731, 1627, 1563, 1491, 1443, 1220, 1197, 1168, 781 cm^{-1}; ^{1}H NMR, (400 MHz, d_6-DMSO) δ 8.32 (s, 1H), 7.97–7.92 (m, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.83–7.78 (m, 1H), 7.54–7.48 (m, 2H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 7.0 Hz, 1H), 5.46–5.41 (m, 2H), 4.38 (q, *J* = 7.3 Hz, 2H), 4.35–4.12 (m, 2H), 3.78 (dd, *J* = 11.8, 9.4 Hz, 1H), 3.49 (d, *J* = 11.8 Hz, 1H), 1.38 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.5, 159.7, 153.7, 149.6, 141.2, 134.0, 133.4, 131.4, 128.6, 127.7, 127.4, 126.3, 125.8, 125.6, 123.9, 123.7, 113.8, 104.6, 63.1, 44.7, 35.7, 31.3, 15.2; HRMS (ES) calcd [M + Na] for $C_{23}H_{20}N_4NaO_3S$ 455.1154, obsd 455.1148.

4.4.4. (3R)-8-(1-Cyclopropylmethyl-1H-[1,2,3]triazol-4-yl)-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (8d)

From **7d** (44 mg, 0.082 mmol) was prepared **8d** (26 mg, 72% yield) after purification by HPLC; $[\alpha]_D$ 9 (*c* 0.10, DMSO); IR 1731, 1621, 1489, 1444, 1197, 1167, 782 cm^{-1}; ^{1}H NMR, (400 MHz, d_6-DMSO) δ 8.28 (s, 1H), 7.97–7.92 (m, 1H), 7.88–7.80 (m, 2H), 7.54–7.49 (m, 2H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.29 (d, *J* = 7.0 Hz, 1H), 5.50 (s, 1H), 5.46 (dd, *J* = 8.8, 1.2 Hz, 1H), 4.37–4.14 (m, 2H), 4.22 (d, *J* = 7.2 Hz, 2H), 3.80 (dd, *J* = 11.9, 9.3 Hz, 1H), 3.50 (dd, *J* = 11.9, 1.1 Hz, 1H), 1.25–1.13 (m, 1H), 0.50–0.44 (m, 2H), 0.36–0.31 (m, 2H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.5, 159.7, 153.6, 149.6, 141.1, 134.1, 133.4, 131.3, 128.6, 127.5, 127.4, 126.3, 125.8, 125.6, 123.8 (2C), 113.9, 104.6, 63.0, 53.8, 35.8, 31.2, 11.2, 3.6 (splitted, 2C); HRMS (ES) calcd [M + Na] for $C_{25}H_{22}N_4NaO_3S$ 481.1310, obsd 481.1319.

4.4.5. (3R)-8-(1-Benzyl-1H-[1,2,3]triazol-4-yl)-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester (8e)

From **7e** (34 mg, 0.059 mmol) was prepared **8e** (20 mg, 67% yield) after purification by HPLC; $[\alpha]_D$ −4 (*c* 0.10, DMSO); IR 1723, 1615, 1488, 1442, 1158, 718 cm^{-1}; ^{1}H NMR, (400 MHz, d_6-DMSO) δ 8.41 (s, 1H), 7.98–7.93 (m, 1H), 7.87–7.79 (m, 2H), 7.55–7.47 (m, 2H), 7.46–7.39 (m, 1H), 7.33–7.24 (m, 4H), 7.21–7.16 (m, 2H), 5.62 (s, 2H), 5.49 (s, 1H), 5.45 (dd, *J* = 8.9, 1.4 Hz, 1H), 4.38–4.13 (m, 2H), 3.79 (dd, *J* = 9.2, 2.7 Hz, 1H), 3.49 (dd, *J* = 11.9, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.4, 159.7, 153.5, 149.7, 141.4, 135.9, 133.9, 133.4, 131.3, 128.7 (2C), 128.6, 128.0, 127.5 (2C), 127.5, 127.4, 126.3, 125.8, 125.6, 124.6, 123.8, 113.9, 104.4, 63.0, 52.9, 35.7, 31.2; HRMS (ES) calcd [M + Na] for $C_{28}H_{22}N_4NaO_3S$ 517.1310, obsd 517.1303.

4.4.6. (3R)-8-[1-(4-Methyl-benzyl)-1H-[1,2,3]triazol-4-yl]-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (8f)

From **7f** (31 mg, 0.053 mmol) was prepared **8f** (25 mg, 92% yield) after purification by HPLC; $[\alpha]_D$ −3 (*c* 0.10, DMSO); IR 1727, 1621, 1563, 1488, 1442, 1158, 783 cm^{-1}; ^{1}H NMR, (400 MHz, d_6-DMSO) δ 8.36 (s, 1H), 7.95 (d, *J* = 7.9 Hz, 1H), 7.88–7.78 (m, 2H), 7.56–7.47 (m, 2H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.29–7.23 (m, 1H), 7.10 (s, 4H), 5.55 (s, 2H), 5.48 (s, 1H), 5.45 (d, *J* = 8.9 Hz, 1H), 4.36–4.11 (m, 2H), 3.83–3.74 (m, 1H), 3.49 (d, *J* = 11.8 Hz, 1H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.4, 159.7, 153.5, 149.6, 141.4, 137.4, 134.0, 133.4, 132.9, 131.3, 129.2 (2C), 128.6, 127.6 (2C), 127.5, 127.4, 126.3, 125.8, 125.6, 124.5, 123.8, 113.9, 104.5, 63.0, 52.7, 35.7, 31.2, 20.7; HRMS (ES) calcd [M + Na] for $C_{29}H_{24}N_4NaO_3S$ 531.1467, obsd 531.1463.

4.4.7. (3R)-8-[1-(4-Amino-benzyl)-1H-[1,2,3]triazol-4-yl]-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (8g)

From **7g** (32 mg, 0.052 mmol) was prepared **8g** (22 mg, 82% yield) after purification by HPLC; $[\alpha]_D$ −11 (*c* 0.10, DMSO); IR 1681, 1622, 1490, 1444, 1198 cm^{-1}; ^{1}H NMR, (400 MHz, d_6-DMSO) δ 8.34 (s, 1H), 7.98–7.93 (m, 1H), 7.88–7.78 (m, 2H), 7.55–7.47 (m, 2H), 7.46–7.40 (m, 11H), 7.27 (d, *J* = 7.0 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.3 Hz, 2H), 5.49 (s, 2H), 5.47–5.42 (m, 2H), 4.36–4.12 (m, 2H), 3.78 (dd, *J* = 11.9, 9.2 Hz, 1H), 3.48 (dd, *J* = 11.9, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.4, 159.7, 153.6, 149.6, 141.6 (broad), 141.4, 134.0, 133.4, 131.3, 129.0 (2C), 128.6, 128.1 (broad), 127.6, 127.4, 126.3, 125.8, 125.6, 124.3, 123.9, 117.8 (2C), 113.9, 104.5, 63.0, 52.7, 35.7, 31.2; HRMS (ES) calcd [M + Na] for $C_{28}H_{23}N_5NaO_3S$ 532.1419, obsd 532.1409.

4.4.8. (3R)-8-((S)-1-Benzyl-2-hydroxy-ethyl)-1H-[1,2,3]triazol-4-yl)-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (8h)

From **7h** (34 mg, 0.056 mmol) was prepared **8h** (27 mg, 88% yield) after purification by HPLC; $[\alpha]_D$ −154 (*c* 0.10, DMSO); IR 1731, 1645, 1489, 1439, 1196, 1022, 996, 782, 700 cm^{-1}; ^{1}H NMR, (400 MHz, d_6-DMSO) δ 8.35 (d, *J* = 16.4 Hz, 1H), 8.00–7.95 (m, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.81–7.71 (m, 1H), 7.57–7.46 (m, 3H), 7.33 (d, *J* = 6.9 Hz, 1H), 7.15–6.97 (m, 5H), 5.47–5.41 (m, 1H), 5.33 (d, *J* = 14.5 Hz, 1H), 4.90–4.79 (m, 1H), 4.28–3.94 (m, 3H), 3.92–3.83 (m, 2H), 3.83–3.75 (m, 1H), 3.53–3.47 (m, 1H), 3.27–3.18 (m, 1H), 3.14–3.04 (m, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.5, 159.7, 153.9 + 153.8 (1C), 149.5 (splitted, 1C), 140.6 + 140.5 (1C), 137.2 + 137.1 (1C), 134.0 (splitted, 1C), 133.5, 131.4 + 131.3 (1C), 128.8 (splitted, 2C), 128.6, 128.2 (2C), 127.9 + 127.8 (1C), 127.5 (splitted, 1C), 126.3 (splitted, 2C), 125.8, 125.7, 124.0 (splitted, 1C), 124.0 + 123.7 (1C), 113.5 + 113.4 (1C), 104.6, 64.8 (splitted, 1C), 63.1 (splitted, 1C), 63.0, 37.1 + 37.0 (1C), 35.8 (splitted, 1C), 31.2; HRMS (ES) calcd [M + Na] for $C_{30}H_{26}N_4NaO_4S$ 561.1572, obsd 561.1580.

4.4.9. (3R)-7-Naphthalen-1-ylmethyl-5-oxo-8-[1-(2,3,4-tri-hydroxy-ß-D-xylopyranosyl)-1H-[1,2,3]triazol-4-yl]-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (8i)

From **7i** (38 mg, 0.062 mmol) was prepared **8i** (24 mg, 74% yield) after purification by HPLC; $[\alpha]_D$ −22 (*c* 0.10, DMSO); IR 1716, 1633,

1490, 1416, 1064, 781 cm^{-1}; ^{1}H NMR, (400 MHz, d_6-DMSO) δ 13.49 (broad s, 1H) 8.66 (d, J = 4.0 Hz, 1H), 7.99–7.94 (m, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.81–7.76 (m, 1H), 7.55–7.46 (m, 3H), 7.37 (d, J = 6.7 Hz, 1H), 5.56 (d, J = 9.2 Hz, 1H), 5.43 (d, J = 8.5 Hz, 1H), 5.26 (d, J = 10.0 Hz, 1H), 4.36 (d, J = 17.3 Hz, 1H), 4.16–4.07 (m, 1H), 3.90–3.74 (m, 3H), 3.53–3.45 (m, 2H), 3.43–3.33 (m, 2H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.4, 159.6, 153.8 + 153.7 (1C), 149.7, 141.1 (splitted, 1C), 133.9 (splitted, 1C), 133.5, 131.5 + 131.4 (1C), 128.6, 128.2 + 128.1 (1C), 127.6, 126.4, 125.8, 125.7, 124.1 + 124.0 (1C), 123.5 (split, 1C), 113.4 + 113.3 (1C), 104.4 + 104.3 (1C), 88.4 (split, 1C), 77.0 (split, 1C), 72.50 + 71.9 (1C), 69.1, 68.3, 62.9 (split, 1C), 35.9, 31.2 (split, 1C); HRMS (ES) calcd [M + Na] for $C_{26}H_{24}N_4NaO_7S$ 559.1263, obsd 559.1250.

4.4.10. Methyl 8-cyclopropyl-2-(1-methyl-1H-1,2,3-triazol-4-yl)-7-(naphthalen-1-ylmethyl)-5-oxo-5H-thiazolo[3,2-a]pyridine-3-carboxylate (10)

NaN$_3$ (0.72 mmol, 47 mg), Iodomethane (0.18 mmol, 11 µl), CuSO$_4$ (0.018 mmol, 3 mg) and Na-ascorbate (0.054 mmol, 11 mg) were dissolved in DMSO:H$_2$O 1:1 (1 ml) and heated to 80 °C with an oil bath for 5 min. 9 (0.12 mmol, 50 mg) dissolved in DMSO (1 ml) was added and the reaction was stirred for 1 h. The reaction mixture was diluted with saturated NaHCO$_3$ (aq) and extracted with DCM, the organic phase was dried (Na$_2$SO$_4$), filtered and concentrated. The crude reaction mixture was purified by column chromatography on silica gel (heptane:EtOAc 50:50 → 20:80). To give 10 (40 mg, 71%) IR λ 1734, 1654, 1560, 1466 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.34 (s, 1H), 8.03–7.94 (m, 1H), 7.94–7.84 (m, 2H), 7.58–7.45 (m, 3H), 7.41–7.34 (m, 1H), 5.55 (s, 1H), 4.58 (s, 2H), 4.14 (s, 3H), 3.85 (s, 3H), 1.99–1.89 (m, 1H), 1.12–0.99 (m, 2H), 0.89–0.78 (m, 2H) ^{13}C NMR (100 MHz, d_6-DMSO) δ 160.7, 157.5, 154.3, 145.3, 135.4, 134.5, 133.5, 131.5, 128.6, 127.5, 127.4, 126.4, 125.8, 125.7, 124.0, 123.9, 123.8, 119.9, 111.9, 109.9, 53.3, 36.8, 35.4, 10.6, 7.5 (2C).

4.4.11. 8-Cyclopropyl-2-(1-methyl-1H-1,2,3-triazol-4-yl)-7-(naphthalen-1-ylmethyl)-5H-thiazolo[3,2-a]pyridin-5-one (11)

IR λ 1637, 1558, 1472 cm^{-1}; ^{1}H NMR (500 MHz, d_4-AcOH) δ 8.73–8.71 (m, 1H), 8.37–8.34 (m, 1H) 7.95–7.89 (m, 2H), 7.85–7.81 (m,1H), 7.52–7.43 (m, 3H), 7.31–7.27 (m, 1H), 6.16 (s, 1H), 4.69 (s, 2H), 4.21 (s, 3H), 2.00–1.92 (m, 1H), 1.16–1.11 (m, 2H), 0.92–0.88 (m, 2H) ^{13}C NMR (125 MHz, d_4-AcOH) δ 160.3, 155.9, 149.2, 139.2, 135.6, 135.2, 133.0, 129.8, 128.6, 128.4, 127.3, 126.8, 126.6, 124.7, 124.3, 122.9, 121.8, 116.5, 110.0, 37.6, 37.0, 11.8, 8.3 (2C).

4.5. Typical procedure for the Huisgen 1,3-dipolar cycloaddition, followed by TMSE deprotection, in the 2-position of the bicyclic 2-pyridones (compounds 13a–f)

4.5.1. 8-Cyclopropyl-2-(1-methyl-1H-1,2,3-triazol-4-yl)-7-(naphthalen-1-ylmethyl)-5-oxo-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (13b)

NaN$_3$ (1.56 mmol, 101 mg), CuSO$_4$ (0.05 mmol, 8 mg), Na-ascorbate (0.12 mmol, 24 mg) and methyliodide (0.39 mmol, 36 µl) were dissolved in DMSO:H$_2$O 9:1 (5 ml) and stirred at rt for 10 min. 12a (0.26 mmol, 130 mg) was added and the reaction was stirred at rt for 18 h. The reaction mixture was diluted with water and pH was set to approx 8 with saturated NaHCO$_3$ (aq) and extracted with EtOAc. The organic phase was dried (Na$_2$SO$_4$), filtered and concentrated. The crude material was dissolved in THF (5 ml) and TBAF·3H$_2$O (0.31 mmol, 98 mg) was added and the reaction was stirred at rt for 3 h. The reaction mixture was diluted with water and pH was set to approx 1 with 1 M HCl (aq), and then extracted with EtOAc. The organic phase was dried (Na$_2$SO$_4$), filtered and concentrated, the crude product was purified by HPLC.

The product was freeze dried, to give 13b (82 mg, 69%) IR λ 1717, 1636, 1558, 1472 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.37 (s, 1H), 7.99–7.93 (m, 1H), 7.93–7.85 (m, 2H), 7.55–7.45 (m, 3H), 7.40–7.35 (m, 1H), 5.53 (s, 1H), 4.57 (s, 2H), 4.14 (s, 3H), 1.95–1.86 (m, 1H), 1.08–1.01 (m, 2H), 0.83–0.76 (m, 2H) ^{13}C NMR (100 MHz, d_6-DMSO) δ 161.4, 157.6, 153.9, 145.6, 136.0, 134.6, 133.5, 131.5, 128.6, 127.6, 127.4, 126.8, 126.4, 125.8, 125.7, 124.0, 123.8, 117.9, 111.5, 110.0, 36.8, 35.4, 10.6, 7.6 (2C) HRMS (ES) calcd [M + Na] for $C_{25}H_{20}N_4NaO_3S$ 479.1154, obsd 479.1156.

4.5.2. 8-Cyclopropyl-7-(naphthalen-1-ylmethyl)-5-oxo-2-(1H-1,2,3-triazol-4-yl)-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (13a)

From 12a (100 mg, 0.2 mmol) was prepared 13a (50 mg, 56% yield) after purification by HPLC; IR λ 1716, 1636, 1464 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.18 (s, 1H), 8.00–7.94 (m, 1H), 7.94–7.86 (m, 2H), 7.56–7.46 (m, 3H), 7.40–7.36 (m, 1H), 5.52 (s, 1H9, 4.58 (s, 2H), 1.96–1.87 (m, 1H), 1.08–0.99 (m, 2H), 0.84–0.76 (m, 2H) ^{13}C NMR (100 MHz, d_6-DMSO) δ 161.6, 157.6, 153.8, 145.8, 136.0 (br), 134.6, 133.5, 131.5, 128.6, 128.3 (br), 127.5, 127.4, 126.4, 126.2 (br), 125.8, 125.7, 124.0, 116.8 (br), 111.4, 110.0, 35.4, 10.6, 7.6 (2C) HRMS (ES) calcd [M + Na] for $C_{24}H_{18}N_4NaO_3S$ 465.0997, obsd 465.0995.

4.5.3. 2-(1-Benzyl-1H-1,2,3-triazol-4-yl)-8-cyclopropyl-7-(naphthalen-1-ylmethyl)-5-oxo-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (13c)

From 12a (100 mg, 0.2 mmol) was prepared 13c (58 mg, 54% yield) after purification by HPLC; IR λ 1716, 1634, 1616, 1551, 1471, 1414 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.53 (s, 1H), 8.00–7.94 (m, 1H), 7.94–7.86 (m, 2H), 7.56–7.46 (m, 3H), 7.41–7.29 (m, 6H), 5.71 (s, 2H), 5.51 (s, 1H), 4.58 (s, 2H), 1.97–1.88 (m, 1H), 1.10–1.02 (m, 2H), 0.85–0.77 (m, 2H) ^{13}C NMR (100 MHz, d_6-DMSO) δ 161.4 (br), 157.6, 153.8, 145.7, 136.3, 135.5, 134.6, 133.5, 131.5, 128.8 (2C), 128.6, 128.3, 128.1 (2C), 127.6, 127.5 (br), 127.3, 126.4, 125.8, 125.7, 124.0, 123.0, 117.4 (br), 111.4, 109.9, 53.2, 35.4, 10.6, 7.6 (2C) HRMS (ES) calcd [M + Na] for $C_{31}H_{24}N_4NaO_3S$ 555.1467, obsd 555.1470.

4.5.4. 7-(naphthalen-1-ylmethyl)-5-oxo-2-(1H-1,2,3-triazol-4-yl)-8-(3-(trifluoromethyl)phenyl)-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (13d)

From 12b (121 mg, 0.2 mmol) was prepared 13d (68 mg, 61% yield) after purification by HPLC; IR λ 1718, 1636, 1472, 1335 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.20 (s, 1H), 7.93–7.87 (m, 1H), 7.86–7.68 (m, 6H), 7.51–7.37 (m, 3H), 7.29–7.24 (m, 1H), 5.87 (s, 1H), 4.16 (s, 2H) ^{13}C NMR (100 MHz, d_6-DMSO) δ 161.4, 157.7, 150.8, 146.2, 136.6, 135.8 (br), 134.3, 134.1, 133.3, 131.2, 130.6, 130.1 (q, J = 31 Hz, 1C), 129.0 (br), 128.5, 127.5, 127.3, 126.8 (br), 126.2, 125.7, 125.6–125.2 (m, 3C), 123.9 (q, J = 271Hz, 1C), 123.7, 116.1 (br), 112.5, 110.4, 35.8; HRMS (ES) calcd [M + Na] for $C_{28}H_{17}F_3N_4NaO_3S$ 569.0871, obsd 569.0873.

4.5.5. 2-(1-Methyl-1H-1,2,3-triazol-4-yl)-7-(naphthalen-1-ylmethyl)-5-oxo-8-(3-(trifluoromethyl)phenyl)-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (13e)

From 12b (121 mg, 0.2 mmol) was prepared 13e (68 mg, 61% yield) after purification by HPLC; IR λ 1748, 1616, 1540, 1466, 1335 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.42 (s, 1H), 7.93–7.88 (m, 1H), 7.86–7.69 (m, 6H), 7.51–7.38 (m, 3H), 7.30–7.25 (m, 1H), 5.88 (s, 1H), 4.17 (s, 2H), 4.09 (s, 3H) ^{13}C NMR (100 MHz, d_6-DMSO) δ 161.3, 157.7, 150.8, 146.1, 136.6, 135.8, 134.3, 134.1, 133.3, 131.2, 130.6, 130.1 (q, J = 31Hz, 1C), 128.5, 127.8 (br), 127.6, 127.3, 126.8 (q, J = 4Hz, 1C), 126.2, 125.7, 125.5, 125.4 (q, J = 4Hz, 1C), 123.9 (q, J = 272Hz, 1C), 123.8, 123.7, 117.0, 112.6, 110.4, 36.8, 35.8 HRMS (ES) calcd [M + Na] for $C_{29}H_{19}F_3N_4NaO_3S$ 583.1028, obsd 583.1036.

4.5.6. 2-(1-Benzyl-1H-1,2,3-triazol-4-yl)-7-(naphthalen-1-ylmethyl)-5-oxo-8-(3-(trifluoromethyl)phenyl)-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (13f)

From **12b** (121 mg, 0.2 mmol) was prepared **13f** (70 mg, 55% yield) after purification by HPLC; IR λ 1718, 1637, 1472, 1430, 1334 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.55 (s, 1H), 7.93–7.87 (m, 1H), 7.86–7.68 (m, 6H), 7.50–7.37 (m, 3H), 7.37–7.24 (m, 6H), 5.88 (s, 1H), 5.68 (s, 2H), 4.17 (s, 2H), ^{13}C NMR (100 MHz, d_6-DMSO) δ 161.2, 157.7, 150.9, 146.0, 136.5, 136.0, 135.4, 134.3, 134.1, 133.3, 131.2, 130.6, 130.1 (q, $J = 32$Hz, 1C), 128.8 (2C), 128.5, 128.3, 128.1 (2C), 127.6, 127.4 (br), 127.3, 126.8 (q, $J = 3$Hz, 1C), 126.2, 125.7, 125.5 (splitted, 2C), 123.9 (q, $J = 272$Hz, 1C), 123.7, 123.1, 117.3, 112.7, 110.4, 53.2, 35.8 HRMS (ES) calcd [M + Na] for $C_{35}H_{23}F_3N_4NaO_3S$ 659.1341, obsd 659.1346.

Acknowledgements

Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.ejmech.2012.06.018.

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