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Microwave-assisted decarboxylation of bicyclic 2-pyridone scaffolds and identification of Aβ-peptide aggregation inhibitors†

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A reagent-free microwave-assisted decarboxylation procedure for carboxylic acid functionalized bicyclic 2-pyridones has been developed. This new method, based on microwave heating at 220 °C for 600 seconds in *N*-methyl pyrrolidone (NMP), proved to be practical and very efficient, resulting in decarboxylated 2-pyridones in near-quantitative yields. The decarboxylated products and the intermediate 2-pyridones in the form of carboxylic acid methyl esters and carboxylic acids were screened for their effect on Aβ-peptide aggregation. Two out of the 21 2-pyridones described in this study inhibited amyloid formation of the Alzheimer Aβ(1–40) peptide. The effect was seen even at a 4 : 1 ratio of 2-pyridone and monomeric Aβ-peptide.

Introduction

Alzheimer's disease (AD) has been correlated to self-assembly of an endogenic 4 kDa peptide (39–43 residues) denoted Aβ-peptide. The pathological hallmark of AD includes formation of extra-cellular plaques (amyloid) constituted by depositions of the Aβ-peptide within the brain of affected individuals. However, the picture is complex and besides the final amyloid, several other assemblies have been isolated and the toxic effect can be correlated to both mature amyloid fibrils as well as soluble diffusible oligomeric assemblies.[1–7] Without question, inhibition of Aβ assembly is a major therapeutical challenge, for which an increased understanding of the mechanism for plaque formation at both the cellular and the molecular level is needed.

Interfering with protein–protein interactions can be a difficult task,[8–10] nevertheless, small molecules containing a 2-pyridone core structure have been reported to have both an enhancing and inhibitory effect on Aβ-peptide aggregation (**1** and **2**, Fig. 1). Their activity was elucidated by screening libraries of non-peptidic synthetic molecules.[11–13]

The earlier reported tricyclic 2-pyridones were synthesized in seven steps with substitution variations in two positions in the 2-pyridone ring (Fig. 1). The 2-pyridone ring formation step gave a poor yield (<40%) which significantly contributed to a low overall yield of ~10%.[11]

We have previously developed several procedures, which provide bicyclic 2-pyridones **3a** and **3b** in high yields.[14–16] These compounds show structural similarity to those reported to affect fibril formation *e.g.* **1** and **2** (Fig. 1), and they also possess a transformable functional group ($R^4 = CO_2Me$ in **3a** and $R^4 = CO_2H$ in **3b**, Fig. 1) in a position that has not previously been studied from a structure–activity relationship (SAR) point of view. A new decarboxylation procedure, described in this article, rendered bicyclic 2-pyridones **3c**, which to a higher extent resembles 2-pyridones **1** and **2** (Fig. 1). Besides the possible biological application of the compounds **3a–c**, we were also encouraged by the novelty of the decarboxylation reaction. Decarboxylations of aromatic and activated carboxylic acids, *e.g.* β-keto acids, are well described in the literature, while only few examples on other systems have been reported.

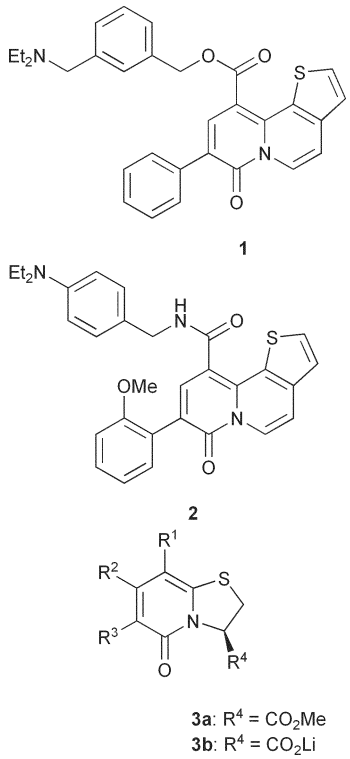

Fig. 1 2-Pyridones with activity as both promoters (**1**: Ro 47–1816/001) and inhibitors (**2**: Ro 65–8815/001) of Aβ-peptide aggregation.[12,13] These molecules show structural resemblance to the substituted 2-pyridones **3a–c** ($R^3 = H$, $R^4 = CO_2Me$, CO_2H, H) described in this paper.

Known methods with limited applicability are, for instance, thermolysis of peresters,[17–19] oxidative decarboxylation with lead tetraacetate[20] and decarboxylation of photolytically induced acyloxy radicals.[21] Two other more general examples that employ preactivated carboxylic acids are the Barton decarboxylation of *N*-carboxythiopyridones[22] and the photolytic cleavage of *N*-acyloxyphthalimides.[23]

Here we describe the development of a new efficient microwave-assisted procedure for the decarboxylation of carboxylic acid functionalized 2-pyridones. In addition, the potential of the generated bicyclic 2-pyridones, which include

† Electronic supplementary information (ESI) available: ^{13}C NMR spectra of **9b–f**, **10b–f**, and **12a–g**. See http://www.rsc.org/suppdata/ob/b5/b503294f/

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carboxylic acid methyl esters, carboxylic acids, and decarboxylated derivatives, to function as inhibitors of Aβ(1–40) self-assembly was evaluated.

Results and discussion

Identification of a new 2-pyridone decarboxylation procedure

Decarboxylation was first observed under modified Rosenmund–von Braun conditions, where refluxing a 6-bromo-2-pyridone carboxylic acid overnight with CuCN in DMF resulted in a mixture of cyanated and decarboxylated products. Repeating the procedure with a non-halogenated starting material **4** gave two decarboxylated products with different oxidation levels (Fig. 2).

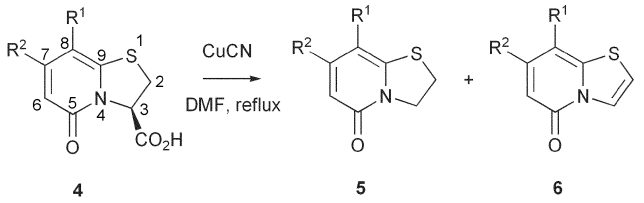


Fig. 2 Schematic picture of the initial decarboxylation reaction, which provides a mixture of saturated and unsaturated products under reflux.

Both the tetrahydro- (**5**) and the dihydro-derivative (**6**) were formed, and the unsaturated 2-pyridone could be isolated as the major product in ~30% yield (Fig. 2).

Improvement of reaction conditions

Decarboxylation was not observed in the absence of CuCN under reflux, and efforts to increase the yield and selectivity by varying the equivalents of CuCN, reaction time, concentrations of reacting species, and solvent (DMF, NMP, DMSO) were not fruitful. The selectivity was at best 1 : 10 (saturated : unsaturated) and even the predominating species could vary between runs. Moreover, the problem with low yields due to poor conversion of the starting material could not be circumvented by a prolonged reaction time, since this led to decomposition.

Microwave-assisted synthesis has previously been successful in both cyanation and aminomethylation reactions of 2-pyridones.[24] Beneficial use of the microwave technique for decarboxylation reactions has also been reported[25–28] and was now applied for the decarboxylations of the 2-pyridones **11a–g** (Scheme 1). Thus, after some adjustment of the reaction conditions, it was found that CuCN (10 eq.) in NMP and microwave heating at 220 °C for 600 seconds solved the selectivity issue and highly favored the saturated 2-pyridones **12a–g** (≥36 : 1, saturated : unsaturated, Scheme 1), as determined by NMR spectroscopy. In addition, full conversion of the starting material could be obtained, and a set of seven decarboxylated products **12a–g** was isolated in high to excellent yields (Method B: 75–98%, Scheme 1 and Table 1). The intermediate carboxylic acid methyl esters **9a–g** and their corresponding lithium carboxylates **10a–g** were synthesized from Δ^2-thiazolines **7a–g** and acyl Meldrum's acid **8** according to published procedures (Scheme 1 and Experimental section).[14–16]

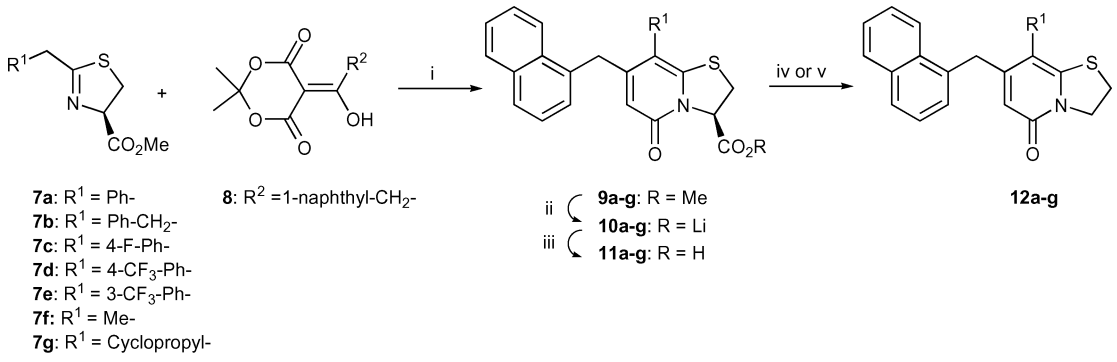
The use of CuCN, however, led to precipitation, and a tedious and time-consuming work-up procedure, including lyophilization, was needed to ensure good overall yields. Therefore, from a practical point of view, the reaction was again tested without the CuCN. Now, in contrast to the results with conventional heating, the reaction proceeded smoothly using the microwave-assisted method. This demonstrated that the reaction was thermally induced when conducted with microwave heating in sealed reaction vessels. Notably, in the absence of the copper reagent, NMR spectroscopy showed an even greater selectivity. Only traces of unsaturated product could be detected and the conversion was so efficient and selective that no additional purification of the decarboxylated products was needed except for a washing step to remove the NMP solvent (Method A, Scheme 1 and Table 1).

By using the microwave technique it was possible to raise the temperature from the solvent boiling point to 220 °C. The choice of solvent was found to be crucial, as was the total volume used

Table 1 Syntheses of decarboxylated 2-pyridones

Entry	Substrate	R^1	Product	Isolated yield (%)[a]	Isolated yield (%)[b]
1	**11a**	Ph–	**12a**	91	97
2	**11b**	Ph–CH_2–	**12b**	94	-[c]
3	**11c**	4-F-Ph–	**12c**	81	99
4	**11d**	4-CF_3-Ph–	**12d**	98	-[c]
5	**11e**	3-CF_3-Ph–	**12e**	87	99
6	**11f**	Me–	**12f**	75	92
7	**11g**	Cyclopropyl–	**12g**	95	99

[a] Method B: CuCN, NMP, MW 220 °C, 600 s, purification by column chromatography. [b] Method A: NMP, MW 220 °C, 600 s, no column chromatography needed. [c] Not included in the study with Method A.



Scheme 1 *Reagents and conditions*: **7a–g**, **8**, and **9a–g** were prepared according to published procedures (see Experimental section) (i) HCl(g), 1,2-dichloroethane, MW 140 °C, 180 s gave **9a–g** (67–99%); (ii) 0.1 M LiOH, THF–MeOH (1 : 4), rt gave **10a–g** (85–98%); (iii) Amberlite IR-120 (H^+), MeOH gave **11a–g** (quant.); (iv) Method A: NMP, MW 220 °C, 600 s for **12a,c,e–g** (92–99%) or (v) Method B: CuCN, NMP, MW 220 °C, 600 s gave **12a–g** (75–98%).

in the reaction vessel (see Experimental section). The reaction could be performed in DMF or DMSO, although these did not lead to full conversion of starting material (220 °C, 600 s). More volatile solvents including toluene, THF, MeOH, MeCN, acetic acid, water, and different solvent mixtures were also tested using the new microwave procedure, but only to find NMP to be the superior solvent. Except for DMF and DMSO, none of the solvents tested reached the target temperature of 220 °C. The decarboxylation could also be carried out with ionic liquid[29] in dioxane (220 °C, 600 s) but in this case unidentified byproducts were formed, which were not observed with NMP as solvent.

Substituent effects

The R^1 substituent has earlier been shown to have an impact on the α-position in the 2-pyridone. For example, a greater loss in enantiomeric excess through racemization of the α-position was observed for 2-pyridone **9g** (R^1 = cyclopropyl) than for 2-pyridone **9a** (R^1 = phenyl) when heated in 1,2-dichloroethane under acidic conditions.[16] We now wanted to study whether the properties of the R^1 substituent affected the decarboxylation, since this reaction also involves the α-position. Thus, both aromatic substituents with different electronic properties (Table 1, Entries 1 and 3–5) and aliphatic substituents (Table 1, Entries 2, 6, and 7) were included in position R^1. The overall high yields indicated that the reaction is more or less independent of the R^1 substituent. It is also worth mentioning that the carboxylic acid **11c** and its corresponding lithium carboxylate **10c** gave comparable yields.

Tentative reaction mechanism

The thermally induced decarboxylation could proceed *via* the formation of an ylide-stabilized anion intermediate. By performing the reaction in DMSO-d_6 it could be concluded from NMR spectroscopy that the solvent acts as a proton donor, resulting in the deuterated decarboxylated product **13** (Fig. 3). This finding opens up possibilities to react the intermediate anion with an electrophile, leading to the formation of new interesting derivatives,[28] currently under investigation in our laboratories.

Method applicability

Decarboxylation was successful for both the carboxylic acids and the lithium carboxylates. In addition, and in agreement with the mechanistic proposal, neither the corresponding aldehyde nor the methyl ester was affected by the decarboxylation procedure.

The use of microwave heating in sealed reaction vessels had an apparent impact on the decarboxylation reaction of the 2-pyridones. Interestingly, CuCN was only important when carrying out the reaction in refluxing DMF, however it was not necessary when using the microwave technique. Altogether, out of the different procedures described herein, the reagent-free microwave-assisted decarboxylation Method A proved to be the most efficient and practical.

The method was also applied to two structurally different carboxylic acids, previously described in the literature. Fluorene 9-carboxylic acid **14** was reported to decarboxylate in MeCN using a Cu(I)-source, while diphenylacetic acid **16** was inert under the same conditions (Fig. 4). The reaction is believed to involve a catalytic cycle with a Cu(I)-stabilized anion intermediate.[30]

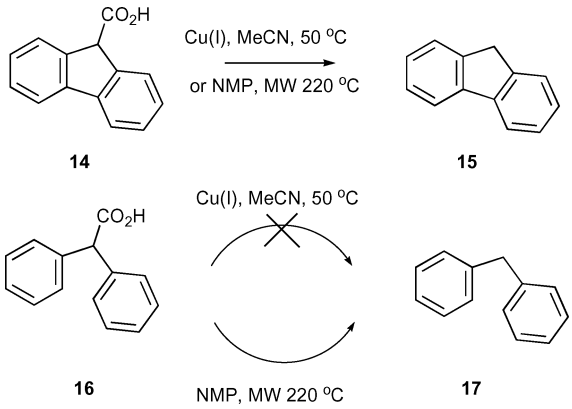


Fig. 4 Fluorene 9-carboxylic acid **14** has previously been decarboxylated using a Cu(I) source in MeCN, whereas diphenylacetic acid **16** was inert. Both of these acids were decarboxylated by using microwave heating in NMP at 220 °C for 600 s.

Both of these acids easily underwent decarboxylation to products **15** and **17**, respectively, in high yields (>90%) using our reagent-free microwave/NMP procedure (Fig. 4). These results suggest that the method may have a broader applicability than investigated in this work.

In total, seven carboxylic acid methyl esters **9a–g** were synthesized, hydrolyzed (**10a–g** and **11a–g**) and subjected to the new decarboxylation method rendering 2-pyridones **12a–g** (Scheme 1).

The derivatives **9a–g** and **11a–g** contain transformable functional groups in R^4 (CO_2Me and CO_2H) which are not present in the corresponding position of the previously reported tricyclic 2-pyridones.[12,13] These substituents are interesting from a SAR point of view and, in addition, enable further derivatization. Thus, the produced compounds **9a–g**, **10a–g** and **12a–g** were evaluated for their ability to obstruct Aβ-peptide aggregation.

Biological significance

Aggregation of the monomeric Aβ(1–40) peptide may readily be observed upon incubation in PBS with slow agitation at 37 °C. After 48 hours of incubation, visualization using atomic force microscopy (AFM) showed that the samples contained fibrillar structures similar to the ones found *in vivo* (see Experimental section and Fig. 5).

The method employed for initiation and following of Aβ-aggregation is highly reproducible and provides a rapid method to study the effects of added substances. In titration series, where only the substance of investigation was varied, a concentration-dependent effect could be monitored. From the initial screening of the 21 synthesized substances neither the decarboxylated

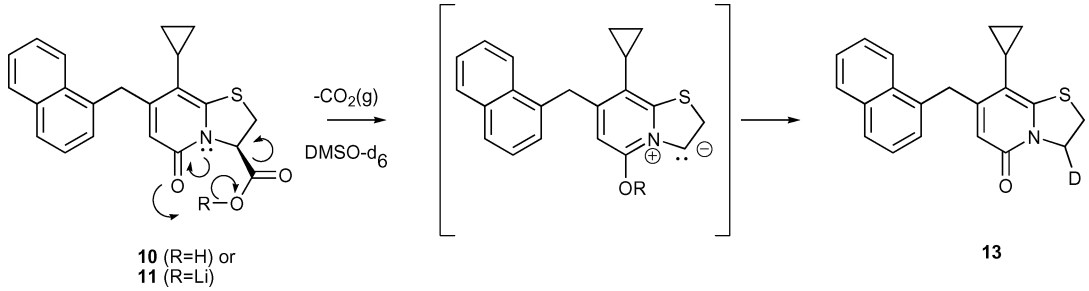


Fig. 3 Thermally induced decarboxylation could proceed *via* an anion/ylide intermediate that is protonated by the solvent.

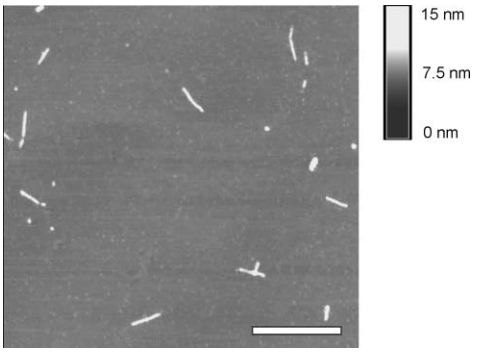


Fig. 5 Atomic force microscopy image of Aβ(1–40) at 50 μM concentration. The sample was incubated in PBS containing 4% DMSO at 37 °C for 48 h with slow agitation (130 rpm). Prior to analysis, an aliquot was withdrawn and diluted 100-fold in double distilled H_2O followed by application to freshly cleaved mica.

derivatives **12a–g** nor the carboxylic acid methyl esters **9a–g** showed any inhibitory effect. Based on earlier results[12,13] we expected primarily the decarboxylated products to exhibit inhibitory activities. It was therefore interesting to find that two lithium carboxylates **10a** and **10e** showed clear inhibitory effects. The corresponding carboxylic acid **11a** was also tested, with comparable results to the lithium carboxylate **10a**.

These findings open up new possibilities for future design and SAR studies. However, at this point we do not know if the bicyclic 2-pyridones tested in this study and the structurally related tricyclic compounds[12,13] have the same mechanism of action.

The level of aggregation of the incubated peptides was judged by polyacrylamide electrophoresis. The results from Aβ(1–40) incubation in the presence of **10a** and **10e**, respectively, are shown in Fig. 6.

The current method is qualitative and therefore inhibition constants cannot be achieved with high accuracy within this study. A rough estimate, however, suggests a 50% inhibitory concentration (IC_{50}) of approximately 200 μM for **10e** and 800 μM for **10a**. Importantly, the estimated IC_{50} value for **10e** was obtained with only a four-fold excess of 2-pyridone over the monomeric peptide.

Conclusion

A practical and efficient microwave-assisted decarboxylation procedure for bicyclic carboxylic acid functionalized 2-pyridones has been described. This reagent-free method is fast and convenient and provides decarboxylated 2-pyridones in near-quantitative yields. It also shows potential use for decarboxylations of other systems.

The method was used to produce a small set of decarboxylated 2-pyridones, which together with the intermediate carboxylic acid methyl esters and lithium carboxylates, were screened for interference of Aβ-peptide aggregation. Two carboxylic acid functionalized 2-pyridones exhibited amyloid inhibitory activities even at a 4 : 1 ratio of 2-pyridone and monomeric Aβ-peptide. These findings encourage further design and SAR studies of ring-fused 2-pyridones as inhibitors of Aβ-peptide fibrilization.

Experimental

General synthesis

All reactions were carried out under an inert atmosphere with dry solvents under anhydrous conditions, unless otherwise stated. CH_2Cl_2 and DMF were passed through a column of Al_2O_3 and DMF was stored over 3 Å molecular sieves. 1,2-Dichloroethane and TEA were freshly distilled before use. EtOH was dried over 3 Å molecular sieves. HCl(g) was passed through concentrated H_2SO_4 prior to use. NMP was not dried before use.

All microwave reactions were carried out in a monomode reactor (Smith Synthesizer, Biotage AB) using Smith Process Vials™ sealed with Teflon septa and an aluminum crimp top. Yield-determining decarboxylation reactions described in the experimental procedure were carried out in process vials with a filling volume of 0.5–2.0 ml and with a solvent volume of 1.5 ml.

TLC was performed on Silica Gel 60 F_{254} (Merck) using UV light detection. Flash column chromatography (eluents given in brackets) employed normal phase silica gel (Matrex, 60 Å, 35–70 μm, Grace Amicon). Ion exchange resin (Amberlite IR-120, H^+-form, 20–50 mesh) was washed with MeOH prior to use. The ^1H and ^{13}C NMR spectra were recorded at 298 K with a Bruker DRX-400 spectrometer in $CDCl_3$ [residual $CHCl_3$ (δ_H 7.26 ppm) or $CDCl_3$ (δ_C 77.0 ppm) as internal standard] or MeOH-d4 [residual CD_2HOD (δ_H 3.30 ppm) or CD_3OD (δ_C 49.0 ppm) as internal standard]. In some cases spectral data of rotameric mixtures are reported and it should also be noted that the presence of fluorine substituents leads to reduced peak intensities. IR spectra were recorded on an ATI Mattson Genesis Series FTIR™ spectrometer. Optical rotations were measured with a Perkin–Elmer 343 polarimeter at 20 °C.

Assay for evaluation of 2-pyridone effects on Aβ(1–40) oligomerization

Aβ(1–40) peptides were obtained from Anaspec (San Jose, California). The lyophilized peptides could be readily dissolved into a monomeric solution using ddH_2O containing 30% dimethylsulfoxide (DMSO). The dissolved peptide was further centrifuged at 20 000*g* for 30 min to remove potentially remaining aggregates, followed by freezing in aliquots at −20 °C at a peptide concentration corresponding to 500 μM. This treatment efficiently conserves the peptide in a monomeric state and from here fibril formation may be induced in a highly reproducible manner *via* a 10× dilution of the stock solution in PBS (20 mM phosphate buffer pH 7.4 containing 150 mM NaCl) followed by incubation at 37 °C with slow

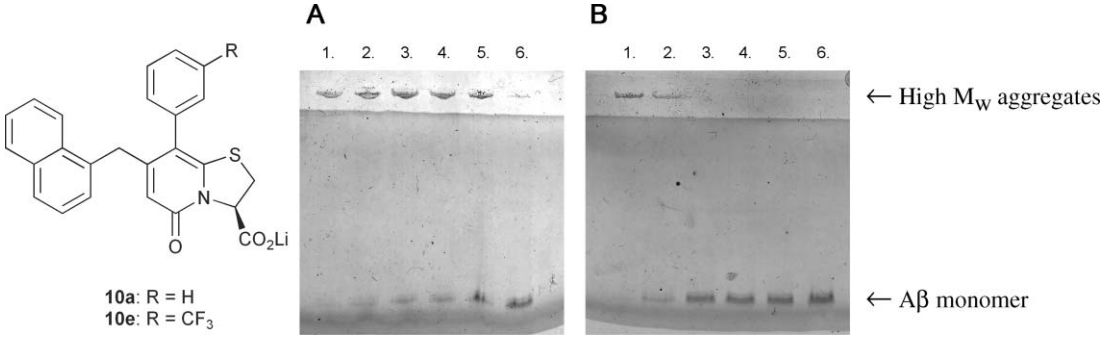


Fig. 6 PAGE analysis of Aβ(1–40) after incubation at 37 °C for 48 h with slow agitation in the presence of various concentrations of 2-pyridone **10a** (A) or **10e** (B): Lane 1, 0 μM; Lane 2, 200 μM; Lane 3, 400 μM; Lane 4, 600 μM; Lane 5, 800 μM; Lane 6, 1 mM.

agitation (130 rpm). Screening for the effects of the substances upon Aβ-oligomerization was performed by addition of the desired compound (dissolved in 100% DMSO) into the PBS solution prior to addition of the monomeric Aβ(1–40) peptide. In this investigation the peptide oligomeric propensities were analyzed at a final DMSO concentration corresponding to 4.0%. Analysis of the aggregation status was performed using 20% tricine polyacrylamide electrophoresis (PAGE) (Amersham Biosciences, Uppsala, Sweden) according to the manufacturer's instructions. Samples were either separated at non-denaturing conditions or in presence of 0.1% sodium dodecyl sulfate (SDS). None of the samples were boiled. All gels were stained using Coomassie brilliant blue staining (Bio-Rad, California).

Atomic force microscopy (AFM)

Prior to analysis, the aggregated Aβ(1–40) was diluted to 5 μM with distilled water and applied onto freshly cleaved ruby red mica (Goodfellow, Cambridge, UK). Samples were allowed to adsorb for 30 s, washed three times with distilled water, and air dried. The bound material was imaged with a Nanoscope IIIa multimode AFM (Digital Instruments Santa Barbara, USA) using Tapping Mode™ in air. A silicon probe was oscillated at 280–300 kHz, and images were collected at an optimized scan rate corresponding to 1 Hz. The image was flattened and presented in height mode using Nanoscope software (Digital Instruments).

Thiazolines 7a–g were prepared according to published procedures

Data in agreement with published data for **7a,f,g**.[14,16]

(4*R*)-2-Phenylethyl-4,5-dihydrothiazole-4-carboxylic acid methyl ester (7b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.24 (m, 2H), 7.23–7.15 (m, 3H), 5.09–5.02 (m, 1H), 3.79 (s, 3H), 3.62–3.45 (m, 2H), 3.02–2.95 (m, 2H), 2.89–2.81 (m, 2H).

(4*R*)-2-(4-Fluorobenzyl)-4,5-dihydrothiazole-4-carboxylic acid methyl ester (7c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.20 (m, 2H), 7.03–6.95 (m, 2H), 5.13–5.05 (m, 1H), 3.88–3.82 (m, 2H), 3.81 (s, 3H), 3.60–3.44 (m, 2H).

(4*R*)-2-(4-(Trifluoromethyl)benzyl)-4,5-dihydrothiazole-4-carboxylic acid methyl ester (7d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.14 Hz, 2H), 7.42 (d, J = 8.14 Hz, 2H), 5.16–5.08 (m, 1H), 3.96–3.91 (m, 2H), 3.82 (s, 3H), 3.64–3.47 (m, 2H).

(4*R*)-2-(3-(Trifluoromethyl)benzyl)-4,5-dihydrothiazole-4-carboxylic acid methyl ester (7e). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.38 (m, 4H), 5.16–5.08 (m, 1H), 3.95–3.89 (m, 2H), 3.80 (s, 3H), 3.63–3.46 (m, 2H).

5-(1-Hydroxy-2-naphthalen-1-ylethylidene)-2,2-dimethyl[1,3]dioxane-4,6-dione (8)

Meldrum's acid derivative **8** was prepared as described below according to a slightly modified published procedure.[31] DCC was dissolved in 100 ml dry CH_2Cl_2 and stirred for 30 min at 0 °C. Then naphthalen-1-yl-acetic acid (11.7 g, 63 mmol), Meldrum's acid (10.0 g, 69 mmol), and DMAP (12.3 g, 101 mmol) was dissolved in 450 ml CH_2Cl_2 and stirred at −10 °C for 45 min. To this solution was added the DCC solution dropwise over 1.5 h. Thereafter, the solution was allowed to reach room temperature overnight. $KHSO_4$ (6% aqueous) was added and the resulting precipitate was filtered off, The filtrate was then washed 4 times with $KHSO_4$ (6% aqueous) and 2 times with brine. The combined aqueous phases were re-extracted with CH_2Cl_2 and the combined organic phases were dried, filtered and concentrated. This gave **8** as a pale yellow solid (19.4 g, 99%). Data in agreement with published data.[14]

Compounds 9a–g

These were prepared from **7a–g** and **8** according to the published procedure. Data in agreement with published data for **9a** and **9g**.[14,16]

(3*R*)-8-Benzyl-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic acid methyl ester (9b). From **7b** (1.1 g, 4.4 mmol) and **8** (4.5 g, 14.4 mmol) was prepared **9b** (1.3 g, 67%): $[\alpha]_D^{20}$ −10.0 (c 1.0, $CHCl_3$); IR λ 3052, 3004, 2954, 1752, 1655, 1580, 1499, 1434, 1213 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.18 Hz, 1H), 7.75 (d, J = 8.22 Hz, 1H), 7.52–7.10 (m, 10H), 6.13 (s, 1H), 5.65 (dd, J = 8.33, 1.83 Hz, 1H), 4.14–3.96 (m, 2H), 3.91–3.69 (m, 6H), 3.57 (dd, J = 11.71, 1.83 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 161, 3, 155.0, 146.1, 138.1, 133.8, 133.1, 131.7, 128.7, 128.6, 127.8, 127.7, 127.4, 126.7, 126.0, 125.6, 125.4, 123.5, 116.1, 111.9, 63.3, 53.2, 36.3, 35.7, 31.7. HRMS (FAB) calcd. for $[M + H]^+$ $C_{27}H_{24}NO_3S$ 442.1477, obsd. 442.1465.

(3*R*)-8-(4-Fluorophenyl)-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic acid methyl ester (9c). From **7c** (1.1 g, 4.4 mmol) and **8** (4.5 g, 14.4 mmol) was prepared **9c** (1.6 g, 83%): $[\alpha]_D^{20}$ −8.8 (c 1.0, $CHCl_3$); IR λ 3044, 3006, 2955, 2850, 1753, 1655, 1602, 1580, 1490, 1435, 1220, 1156 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (m, 1H), 7.73 (d, J = 8.24 Hz, 1H), 7.61 (m, 1H), 7.46–7.23 (m, 5H), 7.19 (d, J = 6.77 Hz, 1H), 7.11–7.03 (m, 2H), 5.86 (s, 1H), 5.59 (dd, J = 8.58, 2.40 Hz, 1H), 4.03–3.85 (m, 2H), 3.78 (s, 3H), 3.61 (dd, J = 11.80, 8.59 Hz, 1H), 3.42 (dd, J = 11.80, 2.41 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2 (broad), 162.4 (d, J = 248.13 Hz), 161.0, 154.1, 146.8, 133.7, 133.4, 132.0 (d, J = 3.40 Hz), 131.9 (d, J = 8.10 Hz), 131.5, 131.4 (d, J = 8.08 Hz), 128.6, 127.6, 127.5, 126.0, 125.5, 125.2, 123.4, 115.9 (d, J = 21.74 Hz), 115.8, 115.1, 114.7, 63.3, 53.1, 36.3, 31.4. HRMS (FAB) calcd. for $[M + H]^+$ $C_{26}H_{21}FNO_3S$ 446.1226, obsd. 446.1225.

(3*R*)-7-Naphthalen-1-ylmethyl-5-oxo-8-(4-(trifluoromethyl)-phenyl)-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic acid methyl ester (9d). From **7d** (303 mg, 3.3 mmol). and **8** (1.0 g, 3.3 mmol) was prepared **9d** (327 mg, 75%): $[\alpha]_D^{20}$ −38.6 (c 0.4, $CHCl_3$); IR λ 3065, 3008, 2957, 1752, 1656, 1583, 1490, 1324, 1214, 1164, 1124 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (m, 1H), 7.74 (d, J = 8.23 Hz, 1H), 7.67–7.55 (m, 3H), 7.47–7.32 (m, 5H), 7.19 (d, J = 6.95 Hz, 1H), 5.91 (s, 1H), 5.63 (dd, J = 8.51, 2.29 Hz, 1H), 4.03–3.88 (m, 2H), 3.82 (s, 3H), 3.68 (dd, J = 11.76, 8.51 Hz, 1H), 3.48 (dd, J = 11.76, 2.29 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 161.1, 153.8, 146.8, 140.0 (broad and split, J = 1.35 Hz, 2C), 133.9, 133.3, 131.6, 130.6, 130.5 (q, J = 32.34 Hz, 2C), 128.8, 127.82, 127.79, 126.2, 125.91 (broad and split, J = 3.71 Hz, 2C), 125.7, 125.4, 123.9 (q, J = 272.16 Hz), 115.8, 114.7, 63.5, 53.3, 36.8, 31.8. HRMS (FAB) calcd. for $[M + H]^+$ $C_{27}H_{21}F_3NO_3S$ 496.1194, obsd. 496.1197.

(3*R*)-7-Naphthalen-1-ylmethyl-5-oxo-8-(3-(trifluoromethyl)-phenyl)-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic acid methyl ester (9e). From **7e** (1.3 g, 4.4 mmol) and **8** (4.5 g, 14.4 mmol) was prepared **9e** (2.1 g, 96%): $[\alpha]_D^{20}$ −26.0 (c 1.0, $CHCl_3$); IR λ 3044, 3007, 2957, 1752, 1657, 1580, 1485, 1438, 1333, 1215, 1165, 1125 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (m, 1H), 7.73 (d, J = 8.22 Hz, 1H), 7.63–7.53 (m, 3H), 7.51–7.32 (m, 5H), 7.18 (m, 1H), 5.94 (bs, 1H), 5.63 (dd, J = 8.53, 2.23 Hz, 1H), 4.05–3.87 (m, 2H), 3.82 (s, 3H), 3.67 (m, 1H), 3.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 161.1, 153.8, 147.0, 137.0, 133.8, 133.7, 133.24, 133.21, 131.5, 129.4, 128.7, 127.8, 127.7, 126.9, 126.1, 125.6, 125.3, 125.1, 123.7 (q, J = 272.84 Hz), 123.4, 115.7, 114.5, 63.5, 53.3, 36.7, 31.7. HRMS (FAB) calcd. for $[M + H]^+$ $C_{27}H_{21}F_3NO_3S$ 496.1194, obsd. 496.1192.

(3*R*)-8-Methyl-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylic acid methyl ester (9f). From **7f** (762 mg, 4.4 mmol) and **8** (4.5 g, 14.4 mmol) was prepared **9f** (1.6 g, 99%): $[\alpha]_D^{20}$ −13.7 (*c* 1.0, $CHCl_3$); IR λ 3004, 2955, 1752, 1655, 1580, 1502, 1436, 1214 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (m, 1H), 7.84 (m, 2H), 7.51–7.43 (m, 2H), 7.40 (m, 1H), 7.21 (d, J = 6.86 Hz, 1H), 5.82 (s, 1H), 5.60 (dd, J = 8.42, 1.92 Hz, 1H), 4.25–4.09 (m, 2H), 3.79 (s, 3H), 3.69 (dd, J = 11.71, 8.42 Hz, 1H), 3.53 (dd, J = 11.71, 1.92 Hz, 1H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 161.2, 154.5, 144.2, 133.8, 133.2, 131.7, 128.8, 127.6, 127.0, 126.2, 125.7, 125.5, 123.5, 115.7, 109.0, 63.2, 53.1, 36.2, 31.8, 15.7. HRMS (FAB) calcd. for $[M + H]^+$ $C_{21}H_{20}NO_3S$ 366.1164, obsd. 366.1159.

General procedure (slightly modified from the published procedure[15]) for the preparation of lithium carboxylates 10a–g from 9a–g

9 (1.6 mmol) was dissolved in THF–MeOH (1 : 4, 56 ml), and 0.1 M aqueous LiOH (1.6 mmol) was added dropwise to the stirred solution at rt. After stirring overnight, the solution was concentrated and lyophilized from acetonitrile–water (2 : 3), giving **10**. Data in agreement with published data for **10a** and **10g**.[15]

Lithium (3*R*)-7-naphthalen-1-ylmethyl-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (10a). Data in agreement with published data.[15]

Lithium (3*R*)-8-benzyl-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (10b). $[\alpha]_D^{20}$ −6.6 (*c* 1.0, MeOH); IR λ 3431, 1640, 1499 cm^{-1}; as a major rotamer; ^1H NMR (400 MHz, MeOH) δ 7.81 (d, J = 8.17 Hz, 1H), 7.74 (d, J = 8.24 Hz, 1H), 7.49–7.10 (m, 10H), 5.56 (s, 1H), 5.42 (dd, J = 8.36, 1.31 Hz, 1H), 4.15–4.02 (m, 2H), 3.97–3.71 (m, 3H), 3.66 (dd, J = 11.33, 1.31 Hz, 1H); ^{13}C NMR (100 MHz, MeOH) δ 173.8, 163.8, 156.8, 150.0, 139.8, 135.3, 134.9, 133.1, 129.7, 129.6, 129.2, 128.7, 128.7, 127.6, 127.1, 126.7, 126.5, 124.9, 115.5, 114.2, 68.0, 37.2, 36.6, 34.1.

Lithium (3*R*)-8-(4-fluorophenyl)-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (10c). $[\alpha]_D^{20}$ −4.3 (*c* 1.0, $CHCl_3$); IR λ 3435, 3154, 3044, 1634, 1489, 1401 cm^{-1}; ^1H NMR (400 MHz, MeOH) δ 7.82 (m, 1H), 7.74 (d, J = 8.19 Hz, 1H), 7.67 (m, 1H), 7.47–7.30 (m, 5H), 7.19 (d, J = 6.95 Hz, 1H), 7.16–7.03 (m, 2H), 5.76 (s, 1H), 5.41 (dd, J = 8.57, 1.37 Hz, 1H), 4.10–3.89 (m, 2H), 3.72 (dd, J = 11.35, 8.57 Hz, 1H), 3.53 (dd, J = 11.40, 1.37 Hz, 1H); ^{13}C NMR (100 MHz, MeOH) δ 173.9 (broad), 164.0 (d, J = 246.45 Hz), 163.8, 155.9, 150.7 (d, J = 1.35 Hz), 135.4, 135.3, 134.1 (d, J = 3.37 Hz), 133.7 (d, J = 8.15 Hz), 133.2 (d, J = 8.23 Hz), 133.1, 129.7, 128.9, 128.6, 127.2, 126.7, 126.5, 124.9, 117.1, 116.74 (d, J = 21.86 Hz), 116.68 (d, J = 21.65 Hz), 114.9, 68.1, 37.5, 34.1.

Lithium (3*R*)-7-naphthalen-1-ylmethyl-5-oxo-8-(4-trifluoromethylphenyl)-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (10d). $[\alpha]_D^{20}$ −22.9 (*c* 0.3, MeOH); IR λ 3394, 1638, 1491, 1401, 1328, 1126 cm^{-1};^1H NMR (400 MHz, MeOH) δ 7.81 (m, 1H), 7.74 (d, J = 8.20 Hz, 1H), 7.70–7.58 (m, 3H), 7.57–7.46 (m, 2H), 7.44–7.33 (m, 3H), 7.25 (d, J = 6.97 Hz, 1H), 5.83 (s, 1H), 5.43 (dd, J = 8.78, 1.19 Hz, 1H), 4.10–3.96 (m, 2H), 3.75 (dd, J = 11.53, 8.70 Hz, 1H), 3.54 (dd, J = 11.53, 1.19 Hz, 1H); ^{13}C NMR (100 MHz, MeOH) δ 173.8, 163.8, 155.4, 150.6, 142.1 (q, J = 1.35 Hz, 2C), 135.31, 135.28, 133.1, 132.5, 132.0, 131.2 (q, J = 32.34 Hz, 2C), 129.7, 128.9, 128.6, 127.2, 126.7 (broad and split, 2C), 126.5, 125.5 (q, J = 271.49 Hz), 124.8, 116.7, 115.3, 68.0, 37.4, 34.3.

Lithium (3*R*)-7-naphthalen-1-ylmethyl-5-oxo-8-(3-(trifluoromethyl)phenyl)-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (10e). $[\alpha]_D^{20}$ −13.1 (*c* 1.0, $CHCl_3$); IR λ 3365, 3083, 2946, 1629, 1560, 1489, 1334, 1125 cm^{-1}; as a mixture of rotamers; ^1H NMR (400 MHz, MeOH) δ 7.80 (m, 1H), 7.72 (d, J = 8.23 Hz, 1H), 7.69–7.62 (m, 2H), 7.61–7.48 (m 3H), 7.44–7.31 (m, 3H), 7.23 (m, 1H), 5.88 (split, 1H), 5.44 (dd, J = 8.69, 1.19 Hz, 1H), 4.09–3.93 (m, 2H), 3.81–3.68 (m, 1H), 3.54 (dd, J = 11.43, 1.46 Hz, 1H); ^{13}C NMR (100 MHz, MeOH) δ 173.9, 163.7, 155.5, 150.9, 138.9, 135.50 (and rotamer at 134.97), 135.3, 135.2, 133.0, 132.1 (q, J = 33.01 Hz), 130.7, 129.7, 128.7 (broad), 128.6, 128.48 (and rotamer at 127.95), 127.1, 126.7, 126.4, 125.9 (q, J = 3.37 Hz), 124.6 (q, J = 3.37 Hz), 125.4 (q, J = 271.8 Hz), 116.6, 115.3 (broad), 68.0, 37.4, 34.2.

Lithium (3*R*)-8-methyl-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (10f). $[\alpha]_D^{20}$ −10.9 (*c* 1.0, MeOH); IR λ 3408, 1640, 1501, 1390 cm^{-1}; ^1H NMR (400 MHz, MeOH) δ 7.88 (m, 2H), 7.79 (d, J = 8.23 Hz, 1H), 7.51–7.38 (m, 3H), 7.28 (d, J = 6.95 Hz, 1H), 5.67 (s, 1H), 5.38 (dd, J = 8.51, 1.37 Hz, 1H), 4.32–4.21 (m, 2H), 3.77 (dd, J = 11.51, 8.51 Hz, 1H), 3.63 (dd, J = 11.51, 1.37 Hz, 1H), 2.07 (s, 2H); ^{13}C NMR (100 MHz, MeOH) δ 173.9, 163.7, 156.5, 148.2, 135.4, 135.2, 133.3, 129.8, 128.6, 128.3, 127.3, 126.8, 126.6, 124.9, 115.2, 111.3, 67.9, 37.0, 34.2, 15.7.

Lithium (3*R*)-8-cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (10g). Data in agreement with published data.[15]

General procedure for the preparation of 11a–g from 10a–g

10 was dissolved in MeOH or in THF–MeOH. Amberlite IR-120 was added with swirling until the solution reached pH ~4; the solid support was then filtered off. The filtrate was concentrated and the residue was lyophilized from acetonitrile–water (2 : 3) giving **11**.

General procedure for the preparation of 12a–g from 11a–g

Method A. 0.36 mmol of **11** was dissolved in 1.5 ml NMP. The reaction vessel was sealed and the reaction mixture was heated by microwave irradiation at 220 °C for 600 s with a fixed hold time. After cooling, EtOAc was added and the solvent was removed by washing with water. The combined organic phases were dried, filtered and concentrated, giving **12**.

Method B. 0.36 mmol of **11** was dissolved in 1.5 ml NMP, and 3.6 mmol CuCN was added to the stirred solution at rt. The reaction vessel was sealed and the reaction mixture was heated by microwave irradiation at 220 °C for 600 s with a fixed hold time. After cooling, the solvent was removed by lyophilization from water and the residue was carefully suspended in CH_2Cl_2 and the product thoroughly extracted. Filtering and concentration was followed by purification by flash column chromatography (heptane–EtOAc–MeOH 1 : 9 : 1) giving **12**.

7-Naphthalen-1-ylmethyl-8-phenyl-2,3-dihydrothiazolo[3,2-*a*]-pyridin-5-one (12a). *Method A*. **11a** (150 mg, 0.36 mmol) gave **12a** as a foam (130 mg, 97%): IR λ 3056, 2990, 2957, 1647, 1575, 1488, 1441 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (m, 1H), 7.73 (d, J = 8.23 Hz, 1H), 7.61 (m, 1H), 7.47–7.30 (m, 8H), 7.20 (d, J = 6.95 Hz, 1H), 5.81 (s, 1H), 4.50 (m, 2H), 3.96 (s, 2H), 3.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 153.5, 147.1, 136.5, 133.8, 133.7, 131.5, 129.8, 128.9, 128.6, 128.2, 127.8, 127.5, 125.9, 125.5, 125.3, 123.7, 115.8, 114.6, 51.2, 36.7, 28.1. HRMS (FAB) calcd. for $[M + H]^+$ $C_{24}H_{20}NOS$ 366.1266, obsd. 366.1261.

8-Benzyl-7-naphthalen-1-ylmethyl-2,3-dihydrothiazolo[3,2-*a*]-pyridin-5-one (12b). *Method B*. **11b** (155 mg, 0.36 mmol) gave **12b** as a foam (130 mg, 94%): IR λ 2926, 2853, 1649, 1572, 1498, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.13 Hz, 1H), 7.75 (d, 8.18 Hz, 1H), 7.51–7.10 (m, 10H), 5.76 (s, 1H), 4.51 (m, 2H), 4.06 (s, 2H), 3.86 (s, 2H), 3.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 154.1, 146.8, 138.4, 133.7, 133.3, 131.6, 128.58, 128.55, 127.8, 127.6, 127.3, 126.6, 126.0, 125.5

125.3, 123.5, 115.7, 111.7, 51.2, 36.3, 35.6, 28.2. HRMS (FAB) calcd. for $[M + H]^+$ $C_{25}H_{22}NOS$ 384.1422, obsd. 384.1419.

8-(4-Fluorophenyl)-7-naphthalen-1-ylmethyl-2,3-dihydrothiazolo[3,2-*a*]pyridin-5-one (12c). *Method A*. **11c** (157 mg, 0.36 mmol) gave **12c** as a foam (140 mg, 99%): IR λ 3046, 2988, 2957, 1648, 1489, 1223 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (m, 1H), 7.73 (d, $J = 8.25$ Hz, 1H), 7.59 (m, 1H), 7.46–7.22 (m, 5H), 7.18 (d, $J = 6.96$ Hz, 1H), 7.13–7.04 (m, 2H), 5.84 (s, 1H), 4.52 (m, 2H), 3.94 (s, 2H), 3.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.50 (d, $J = 123.99$ Hz), 161.4, 153.4, 147.5, 133.8, 133.7, 132.4 (d, $J = 3.42$ Hz), 131.7 (d, $J = 8.08$ Hz, 2C), 131.6, 128.7, 127.64, 127.58, 126.0, 125.5, 125.3, 123.6, 115.9 (d, $J = 21.56$ Hz, 2C), 114.9, 114.7, 51.3, 36.6, 28.1. HRMS (FAB) calcd. for $[M + H]^+$ $C_{24}H_{19}FNOS$ 388.1171, obsd. 388.1173.

7-Naphthalen-1-ylmethyl-8-(4-(trifluoromethyl)phenyl)-2,3-dihydrothiazolo[3,2-*a*]pyridin-5-one (12d). *Method B*. **11d** (175 mg, 0.36 mmol) gave **12d** as a foam (155 mg, 98%): IR λ 3047, 3000, 2929, 1651, 1580, 1491, 1324, 1164, 1123 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (m, 1H), 7.73 (d, $J = 8.23$ Hz, 1H), 7.68 (d, $J = 8.13$ Hz, 2H), 7.56 (d, $J = 8.19$ Hz, 1H), 7.46–7.31 (m, 5H), 7.17 (d, $J = 6.95$ Hz, 1H), 5.90 (s, 1H), 4.53 (m, 2H), 3.94 (s, 2H), 3.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 153.0, 147.4. 140.3 (q, $J = 1.35$ Hz, 2C), 133.8, 133.5, 131.6, 130.5, 130.3 (q, $J = 32.34$ Hz), 128.7, 127.7 (2C), 126.1, 125.9 (q, $J = 3.71$ Hz, 2C), 125.6, 125.3, 123.9 (q, $J = 272.17$ Hz), 123.5, 115.3, 114.4, 51.4, 36.7, 28.3. HRMS (FAB) calcd. for $[M + H]^+$ $C_{25}H_{19}F_3NOS$ 438.1139, obsd. 438.1136.

7-Naphthalen-1-ylmethyl-8-(3-(trifluoromethyl)phenyl)-2,3-dihydrothiazolo[3,2-*a*]pyridin-5-one (12e). *Method A*. **11e** (175 mg, 0.36 mmol) gave **12e** as a foam (158 mg, 99%): IR λ 3061, 3002, 1652, 1578, 1487, 1439, 1334, 1165, 1124 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (m, 1H), 7.72 (d, $J = 8.22$ Hz, 1H), 7.62–7.29 (m, 8H), 7.16 (m, 1H), 5.90 (s, 1H), 4.50 (m, 2H), 4.00–3.85 (m, 2H), 3.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 153.0, 147.7, 137.2, 133.7, 133.4, 133.3 (q, $J = 1.35$ Hz), 131.4, 131.1 (q, $J = 32.42$ Hz), 129.4, 128.6, 127.6 (2C), 126.8 (q, $J = 3.73$ Hz), 126.0, 125.5, 125.2, 124.9 (q, $J = 3.73$ Hz), 123.7 (q, $J = 272.50$ Hz), 123.4, 115.1, 114.2, 51.3, 36.6, 28.2. HRMS (FAB) calcd. for $[M + H]^+$ $C_{25}H_{19}F_3NOS$ 438.1139, obsd. 438.1144.

8-Methyl-7-naphthalen-1-ylmethyl-2,3-dihydrothiazolo[3,2-*a*]-pyridin-5-one (12f). *Method A*. **11f** (128 mg, 0.36 mmol) gave **12f** as a foam (103 mg, 92%): IR λ 3044, 2920, 1649, 1571, 1501 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (m, 1H), 7.84–7.74 (m, 2H), 7.51–7.44 (m, 2H), 7.40 (m, 1H), 7.20 (d, $J = 6.95$ Hz, 1H), 5.81 (s, 1H), 4.52 (m, 2H), 4.17 (s, 2H), 3.38 (m, 2H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 153.7, 145.0, 133.9, 133.4, 131.8, 128.8, 127.7, 127.0, 126.2, 125.7, 125.5, 123.6, 115.5, 108.8, 51.3, 36.2, 28.4, 15.8. HRMS (FAB) calcd. for $[M + H]^+$ $C_{19}H_{18}NOS$ 308.1109, obsd. 308.1107.

8-Cyclopropyl-7-naphthalen-1-ylmethyl-2,3-dihydrothiazolo[-3,2-*a*]pyridin-5-one (12g). *Method A*. **11g** (137 mg, 0.36 mmol) gave **12g** as a foam (120 mg, 99%): IR λ 3061, 2999, 1647, 1571, 1491, 1429 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 1H), 7.82–7.73 (m, 2H), 7.50–7.37 (m, 3H), 7.26 (d, $J = 6.95$ Hz, 1H), 5.72 (s, 1H), 4.42 (m, 2H), 4.40 (s, 2H), 3.32 (m, 2H), 1.64 (m, 1H), 0.98–0.89 (m, 2H), 0.75–0.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 155.9, 147.6, 134.2, 133.9, 131.9, 128.8, 127.6, 127.5, 126.1, 125.6, 125.5, 123.8, 115.1, 113.4, 50.6, 36.1, 28.2, 11.1, 7.67 (2C). HRMS (FAB) calcd. for $[M + H]^+$ $C_{21}H_{20}NOS$ 334.1266, obsd. 334.1272.

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