### Microwave-assisted decarboxylation of bicyclic 2-pyridone scaffolds and identification of Aβ-peptide aggregation inhibitors<sup>†</sup>

Veronica Åberg,<sup>a</sup> Fredrik Norman,<sup>a</sup> Erik Chorell,<sup>a</sup> Andreas Westermark,<sup>a</sup> Anders Olofsson,<sup>b</sup> A. Elisabeth Sauer-Eriksson<sup>b</sup> and Fredrik Almqvist<sup>\*a</sup>

<sup>a</sup> Organic Chemistry, Department of Chemistry, Umeå University, SE-90187, Umeå, Sweden. E-mail: fredrik.almqvist@chem.umu.se

<sup>b</sup> Umeå Centre for Molecular Pathogenesis, Umeå University, SE-90187, Umeå, Sweden

Received 7th March 2005, Accepted 3rd May 2005 First published as an Advance Article on the web 29th June 2005

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 A $\beta$ (1–40) peptide. The effect was seen even at a 4 : 1 ratio of 2-pyridone and monomeric A $\beta$ -peptide.

#### Introduction

Alzheimer's disease (AD) has been correlated to self-assembly of an endogenic 4 kDa peptide (39-43 residues) denoted Aβpeptide. The pathological hallmark of AD includes formation of extra-cellular plaques (amyloid) constituted by depositions of the  $A\beta$ -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.<sup>1-7</sup> Without question, inhibition of A $\beta$  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,<sup>8-10</sup> nevertheless, small molecules containing a 2-pyridone core structure have been reported to have both an enhancing and inhibitory effect on A $\beta$ -peptide aggregation (1 and 2, Fig. 1). Their activity was elucidated by screening libraries of nonpeptidic 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  $\sim 10\%$ .<sup>11</sup>

We have previously developed several procedures, which provide bicyclic 2-pyridones 3a and 3b in high yields.<sup>14-16</sup> 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  $\mathbf{R}^4 = \mathbf{CO}_2 \mathbf{H}$  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.

```
† Electronic supplementary information (ESI) available: <sup>13</sup>C NMR
spectra of 9b-f, 10b-f, and 12a-g. See http://www.rsc.org/suppdata/
ob/b5/b503294f/
```



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.<sup>12,13</sup> These molecules show structural resemblance to the substituted 2-pyridones  $3\mathbf{a}-\mathbf{c}$  (R<sup>3</sup> = H, R<sup>4</sup> = CO<sub>2</sub>Me, CO<sub>2</sub>H, H) described in this paper.

Known methods with limited applicability are, for instance, thermolysis of peresters,17-19 oxidative decarboxylation with lead tetraacetate<sup>20</sup> and decarboxylation of photolytically induced acyloxy radicals.<sup>21</sup> Two other more general examples that employ preactivated carboxylic acids are the Barton decarboxylation of N-carboxythiopyridones<sup>22</sup> and the photolytic cleavage of Nacyloxyphthalimides.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 carboxylic acid methyl esters, carboxylic acids, and decarboxylated derivatives, to function as inhibitors of A $\beta$ (1–40) selfassembly 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  $\sim 30\%$  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 2pyridones.24 Beneficial use of the microwave technique for decarboxylation reactions has also been reported25-28 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  $12a-g (\geq 36: 1,$ 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  $\Delta^2$ -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 microwaveassisted 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	<b>R</b> <sup>1</sup>	Product	Isolated yield (%) <sup>a</sup>	Isolated yield (%) <sup>b</sup>
1	11a	Ph-	12a	91	97
2	11b	Ph-CH <sub>2</sub> -	12b	94	_c
3	11c	4-F-Ph-	12c	81	99
4	11d	4-CF <sub>3</sub> -Ph-	12d	98	_ <sup>c</sup>
5	11e	3-CF <sub>3</sub> -Ph-	12e	87	99
6	11f	Me-	12f	75	92
7	11g	Cyclopropyl-	12g	95	99

<sup>*a*</sup> Method B: CuCN, NMP, MW 220 °C, 600 s, purification by column chromatography. <sup>*b*</sup> Method A: NMP, MW 220 °C, 600 s, no column chromatography needed. <sup>*c*</sup> 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<sup>+</sup>), 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<sup>29</sup> 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<sup>1</sup> substituent has earlier been shown to have an impact on the  $\alpha$ -position in the 2-pyridone. For example, a greater loss in enantiomeric excess through racemization of the  $\alpha$ -position was observed for 2-pyridone **9g** (R<sup>1</sup> = cyclopropyl) than for 2pyridone **9a** (R<sup>1</sup> = phenyl) when heated in 1,2-dichloroethane under acidic conditions.<sup>16</sup> We now wanted to study whether the properties of the R<sup>1</sup> substituent affected the decarboxylation, since this reaction also involves the  $\alpha$ -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<sup>1</sup>. The overall high yields indicated that the reaction is more or less independent of the R<sup>1</sup> 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<sub>6</sub> 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,<sup>28</sup> 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.<sup>30</sup>



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  $^{\circ}$ 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<sup>4</sup> (CO<sub>2</sub>Me and CO<sub>2</sub>H) which are not present in the corresponding position of the previously reported tricyclic 2-pyridones.<sup>12,13</sup> 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 A $\beta$ (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 A $\beta$ 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 concentrationdependent 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  $A\beta(1-40)$  at 50  $\mu$ M 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<sub>2</sub>O 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<sup>12,13</sup> 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<sup>12,13</sup> have the same mechanism of action.

The level of aggregation of the incubated peptides was judged by polyacrylamide electrophoresis. The results from  $A\beta(1-40)$ 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<sub>50</sub>) of approximately 200  $\mu$ M for **10e** and 800  $\mu$ M for **10a**. Importantly, the estimated IC<sub>50</sub> 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 2pyridones 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 A $\beta$ -peptide aggregation. Two carboxylic acid functionalized 2-pyridones exhibited amyloid inhibitory activities even at a 4 : 1 ratio of 2-pyridone and monomeric A $\beta$ -peptide. These findings encourage further design and SAR studies of ring-fused 2-pyridones as inhibitors of A $\beta$ -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<sup>TM</sup> 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<sup>+</sup>-form, 20–50 mesh) was washed with MeOH prior to use. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at 298 K with a Bruker DRX-400 spectrometer in CDCl<sub>3</sub> [residual CHCl<sub>3</sub> ( $\delta_H$ 7.26 ppm) or CDCl<sub>3</sub> ( $\delta_C$  77.0 ppm) as internal standard] or MeOH-d4 [residual CD<sub>2</sub>HOD ( $\delta_H$  3.30 ppm) or CD<sub>3</sub>OD ( $\delta_C$ 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<sup>TM</sup> spectrometer. Optical rotations were measured with a Perkin–Elmer 343 polarimeter at 20 °C.

## Assay for evaluation of 2-pyridone effects on $A\beta(1-40)$ oligomerization

A $\beta$ (1–40) peptides were obtained from Anaspec (San Jose, California). The lyophilized peptides could be readily dissolved into a monomeric solution using ddH<sub>2</sub>O containing 30% dimethylsulfoxide (DMSO). The dissolved peptide was further centrifuged at 20 000g for 30 min to remove potentially remaining aggregates, followed by freezing in aliquots at –20 °C at a peptide concentration corresponding to 500  $\mu$ M. 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 A $\beta$ (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  $\mu$ M; Lane 2, 200  $\mu$ M; Lane 3, 400  $\mu$ M; Lane 4, 600  $\mu$ M; Lane 5, 800  $\mu$ M; 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 A $\beta$ (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  $A\beta(1-40)$  was diluted to  $5 \mu M$  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<sup>TM</sup> 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). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 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-4carboxylic acid methyl ester (7d). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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-4carboxylic acid methyl ester (7e). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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)-2,2dimethyl[1,3]dioxane-4,6-dione (8)

Meldrum's acid derivative **8** was prepared as described below according to a slightly modified published procedure.<sup>31</sup> DCC was dissolved in 100 ml dry CH<sub>2</sub>Cl<sub>2</sub> 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<sub>2</sub>Cl<sub>2</sub> 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<sub>4</sub> (6% aqueous) was added and the resulting precipitate was filtered off, The filtrate was then washed 4 times with KHSO<sub>4</sub> (6% aqueous) and 2 times with brine. The combined aqueous phases were re-extracted with CH<sub>2</sub>Cl<sub>2</sub> 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.<sup>14</sup> These were prepared from 7a-g and 8 according to the published procedure. Data in agreement with published data for 9a and 9g.<sup>14,16</sup>

(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%):  $[a]_D^{20}$  -10.0 (*c* 1.0, CHCl<sub>3</sub>); IR λ 3052, 3004, 2954, 1752, 1655, 1580, 1499, 1434, 1213 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 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]<sup>+</sup> C<sub>27</sub>H<sub>24</sub>NO<sub>3</sub>S 442.1477, obsd. 442.1465.

(3R)-8-(4-Fluorophenyl)-7-naphthalen-1-ylmethyl-5-oxo-2,3dihydro-5H-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%):  $[a]_{D}^{20}$  -8.8 (c 1.0, CHCl<sub>3</sub>); IR  $\lambda$ 3044, 3006, 2955, 2850, 1753, 1655, 1602, 1580, 1490, 1435, 1220, 1156 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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)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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  168.2 (broad), 162.4 (d, J = 248.13Hz), 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.

(3R)-7-Naphthalen-1-ylmethyl-5-oxo-8-(4-(trifluoromethyl)phenyl)-2,3-dihydro-5H-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%):  $[a]_{\rm D}^{20}$  -38.6 (c 0.4, CHCl<sub>3</sub>); IR λ 3065, 3008, 2957, 1752, 1656, 1583, 1490, 1324, 1214, 1164, 1124 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ 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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 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%):  $[a]_D^{20}$  -26.0 (*c* 1.0, CHCl<sub>3</sub>); IR λ 3044, 3007, 2957, 1752, 1657, 1580, 1485, 1438, 1333, 1215, 1165, 1125 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 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]<sup>+</sup> C<sub>27</sub>H<sub>21</sub>F<sub>3</sub>NO<sub>3</sub>S 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%):  $[a]_{20}^{20}$  -13.7 (*c* 1.0, CHCl<sub>3</sub>); IR  $\lambda$ 3004, 2955, 1752, 1655, 1580, 1502, 1436, 1214 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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]<sup>+</sup> C<sub>21</sub>H<sub>20</sub>NO<sub>3</sub>S 366.1164, obsd. 366.1159.

# General procedure (slightly modified from the published procedure<sup>15</sup>) 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**.<sup>15</sup>

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

Lithium (3*R*)-8-benzyl-7-naphthalen-1-ylmethyl-5-oxo-2,3dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (10b).  $[a]_{D}^{20}$ -6.6 (*c* 1.0, MeOH); IR  $\lambda$  3431, 1640, 1499 cm<sup>-1</sup>; as a major rotamer; <sup>1</sup>H NMR (400 MHz, MeOH)  $\delta$  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); <sup>13</sup>C NMR (100 MHz, MeOH)  $\delta$  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-5oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (10c).  $[a]_D^{20}$  -4.3 (*c* 1.0, CHCl<sub>3</sub>); IR  $\lambda$  3435, 3154, 3044, 1634, 1489, 1401 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, MeOH)  $\delta$  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); <sup>13</sup>C NMR (100 MHz, MeOH)  $\delta$  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). [*a*]<sub>20</sub><sup>D</sup> -22.9 (*c* 0.3, MeOH); IR  $\lambda$  3394, 1638, 1491, 1401, 1328, 1126 cm<sup>-1</sup>;<sup>1</sup>H NMR (400 MHz, MeOH)  $\delta$  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); <sup>13</sup>C NMR (100 MHz, MeOH)  $\delta$  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).  $[a]_{D}^{20}$  -13.1 (*c* 1.0, CHCl<sub>3</sub>); IR  $\lambda$  3365, 3083, 2946, 1629, 1560, 1489, 1334, 1125 cm<sup>-1</sup>; as a mixture of rotamers; <sup>1</sup>H NMR (400 MHz, MeOH)  $\delta$  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); <sup>13</sup>C NMR (100 MHz, MeOH)  $\delta$  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-2,3dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (10f).  $[a]_{2^{D}}^{2D}$ -10.9 (*c* 1.0, MeOH); IR  $\lambda$  3408, 1640, 1501, 1390 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, MeOH)  $\delta$  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); <sup>13</sup>C NMR (100 MHz, MeOH)  $\delta$  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 (3R)-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.<sup>15</sup>

#### 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  $\sim$ 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***. <b>11a** (150 mg, 0.36 mmol) gave **12a** as a foam (130 mg, 97%): IR  $\lambda$  3056, 2990, 2957, 1647, 1575, 1488, 1441 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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]<sup>+</sup> C<sub>24</sub>H<sub>20</sub>NOS 366.1266, obsd. 366.1261.

**8-Benzyl-7-naphthalen-1-ylmethyl-2,3-dihydrothiazolo[3,2-***a***]pyridin-5-one (12b).** *Method B.* **<b>11b** (155 mg, 0.36 mmol) gave **12b** as a foam (130 mg, 94%): IR  $\lambda$  2926, 2853, 1649, 1572, 1498, 1453 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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 Downloaded by Duke University on 22 June 2012 Published on 29 June 2005 on http://pubs.rsc.org | doi:10.1039/B503294F 125.3, 123.5, 115.7, 111.7, 51.2, 36.3, 35.6, 28.2. HRMS (FAB) calcd. for  $[M + H]^+$  C<sub>25</sub>H<sub>22</sub>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  $\lambda$  3046, 2988, 2957, 1648, 1489, 1223 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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]<sup>+</sup> C<sub>24</sub>H<sub>19</sub>FNOS 388.1171, obsd. 388.1173.

**7-Naphthalen-1-ylmethyl-8-(4-(trifluoromethyl)phenyl)-2,3dihydrothiazolo[3,2-***a***]pyridin-5-one (12d).** *Method B.* **11d (175 mg, 0.36 mmol) gave 12d as a foam (155 mg, 98%): IR \lambda 3047, 3000, 2929, 1651, 1580, 1491, 1324, 1164, 1123 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) \delta 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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) \delta 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]<sup>+</sup> C<sub>25</sub>H<sub>19</sub>F<sub>3</sub>NOS 438.1139, obsd. 438.1136.** 

**7-Naphthalen-1-ylmethyl-8-(3-(trifluoromethyl)phenyl)-2,3dihydrothiazolo[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<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 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]<sup>+</sup> C<sub>25</sub>H<sub>19</sub>F<sub>3</sub>NOS 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 \lambda 3044, 2920, 1649, 1571, 1501 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) \delta 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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) \delta 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]<sup>+</sup> C<sub>19</sub>H<sub>18</sub>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  $\lambda$  3061, 2999, 1647, 1571, 1491, 1429 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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]<sup>+</sup> C<sub>21</sub>H<sub>20</sub>NOS 334.1266, obsd. 334.1272.

#### Acknowledgements

We thank Dr Anna Linusson at Umeå University for helpful discussions. We are also grateful to the Swedish Natural Science Research Council, the Knut and Alice Wallenberg Foundation, Socialstyrelsen, the Medical faculty of Umeå University, the Magnus Bergvalls Foundation, Hjärnfonden and Insamlingstiftelsen for financial support.

#### References

- 1 W. L. Klein, G. A. Krafft and C. E. Finch, *Trends Neurosci.*, 2001, 24, 219.
- 2 J. P. Cleary, D. M. Walsh, J. J. Hofmeister, G. M. Shankar, M. A. Kuskowski, D. J. Selkoe and K. H. Ashe, *Nat. Neurosci.*, 2005, 8, 79.
- 3 D. M. Walsh, I. Klyubin, J. V. Fadeeva, M. J. Rowan and D. J. Selkoe, Biochem. Soc. Trans., 2002, **30**, 552.
- 4 A. Lorenzo and B. A. Yankner, Proc. Natl. Acad. Sci. USA, 1994, 91, 12243.
- 5 C. J. Pike, A. J. Walencewicz, C. G. Glabe and C. W. Cotman, *Brain Res.*, 1991, **563**, 311.
- 6 A. T. Petkova, R. D. Leapman, Z. H. Guo, W. M. Yau, M. P. Mattson and R. Tycko, *Science*, 2005, **307**, 262.
- 7 R. Kayed, E. Head, J. L. Thompson, T. M. McIntire, S. C. Milton, C. W. Cotman and C. G. Glabe, *Science*, 2003, **300**, 486.
- 8 T. Berg, Angew. Chem., Int. Ed., 2003, 42, 2462.
- 9 P. L. Toogood, J. Med. Chem., 2002, 45, 1543.
- 10 A. G. Cochran, Chem. Biol., 2000, 7, R85.
- 11 G. Huber Trottman, R. Jakob-Roetne, S. Kolczewski, R. D. Norcross and T. J. Woltering, in: Use of Bi- and Tricyclic Pyridone Derivatives Against Alzheimer's Disease, WO 98/25930, 1998.
- 12 P. Kuner, B. Bohrmann, L. O. Tjernberg, J. Naslund, G. Huber, S. Celenk, F. Gruninger-Leitch, J. G. Richards, R. Jakob-Roetne, J. A. Kemp and C. Nordstedt, *J. Biol. Chem.*, 2000, **275**, 1673.
- 13 E. D. Thorsett and L. H. Latimer, Curr. Opin. Chem. Biol., 2000, 4, 377.
- 14 H. Emtenas, L. Alderin and F. Almqvist, J. Org. Chem., 2001, 66, 6756.
- 15 H. Emtenas, K. Ahlin, J. S. Pinkner, S. J. Hultgren and F. Almqvist, J. Comb. Chem., 2002, 4, 630.
- 16 H. Emtenas, C. Taflin and F. Almqvist, Mol. Diversity, 2003, 7, 165.
- 17 J. Meinwald, J. C. Shelton, G. L. Buchanan and A. Courtin, J. Org. Chem., 1968, 33, 99.
- K. B. Wiberg, B. R. Lowry and T. H. Colby, J. Am. Chem. Soc., 1961, 83, 3998.
- 19 P. S. Engel and A. Y. Wu, J. Org. Chem., 1994, 59, 3969.
- 20 W. H. Starnes, J. Am. Chem. Soc., 1964, 86, 5603.
- 21 T. M. Bockman, S. M. Hubig and J. K. Kochi, J. Org. Chem., 1997, 62, 2210.
- 22 D. H. R. Barton, D. Crich and W. B. Motherwell, *Tetrahedron*, 1985, 41, 3901.
- 23 K. Okada, K. Okamoto and M. Oda, J. Am. Chem. Soc., 1988, 110, 8736.
- 24 N. Pemberton, V. Aberg, H. Almstedt, A. Westermark and F. Almqvist, J. Org. Chem., 2004, 69, 7830.
- 25 C. L. Zara, T. Jin and R. J. Giguere, Synth. Commun., 2000, 30, 2099.
- 26 G. B. Jones and B. J. Chapman, J. Org. Chem., 1993, 58, 5558.
- 27 C. X. Kuang, H. Senboku and M. Tokuda, *Tetrahedron Lett.*, 2001, 42, 3893.
- 28 G. Herstad and T. Benneche, J. Heterocycl. Chem., 2003, 40, 219.
- 29 J. G. Huddleston, H. D. Willauer, R. P. Swatloski, A. E. Visser and R. D. Rogers, *Chem. Commun.*, 1998, 1765.
- 30 O. Toussaint, P. Capdevielle and M. Maumy, *Tetrahedron*, 1984, 40, 3229.
- 31 B. Hin, P. Majer and T. Tsukamoto, J. Org. Chem., 2002, 67, 7365.