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$K_2S_2O_8$-mediated coupling of 6-amino-7-amino-methyl-thiazolino-pyridones with aldehydes to construct amyloid affecting pyrimidine-fused thiazolino-2-pyridones†

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We herein present the synthesis of diversely functionalized pyrimidine fused thiazolino-2-pyridones *via* $K_2S_2O_8$-mediated oxidative coupling of 6-amino-7-(aminomethyl)-thiazolino-2-pyridones with aldehydes. The developed protocol is mild, has wide substrate scope, and does not require transition metal catalyst or base. Some of the synthesized compounds have an ability to inhibit the formation of Amyloid-β fibrils associated with Alzheimer's disease, while others bind to mature amyloid-β and α-synuclein fibrils.

Introduction

Nitrogen fused heterocycles have attracted considerable interest among synthetic chemists because of their broad range of pharmacological properties.[1–12] In particular, the pyrimidine is an important heterocyclic motif which is present as a core skeleton in a variety of drugs that possess a wide range of pharmacological activities, including anticancer,[13,14] adrenoreceptor antagonists,[15,16] antitubercular,[17] antimalarial,[18] anxiolytic[19] and Amyloid-β aggregation inhibitory properties[20] *etc.* (Fig. 1). The nucleotide bases and other biomolecules also contain this structural motif. Therefore, the development of different synthetic strategies for the preparation of substituted pyrimidines has received great attention.

The thiazolino fused 2-pyridone central fragment have proven to be a privileged scaffold. By changing the substitution pattern and thus fine-tuning the properties of the compounds, numerous analogues have been made over the years, with varying biological activities.[1,2] Some analogues substituted with smaller alkyl groups at the C-8 position have proven to have interesting antibacterial properties.[21] Rigidification of the central fragment by substituting it with bulkier aryl groups, resulted in analogues which inhibit the formation of amyloids, both bacterial curli as well as human Aβ-peptides (compound **A**, Fig. 2).[8,9] Annulation of bicyclic thiazolino-2-pyridones with different nitrogen heterocycles is another strategy to rigidify the central fragment (compound **B–E**).[21–23] This ring extension approach has resulted in compounds capable of modulating the formation of amyloid fibrils,[21] which is a property of diagnostic and therapeutic value. Recently, through the inter- and intramolecular Povarov reaction, we constructed pyridine/chromeno-fused 2-pyridones where some analogues (*e.g.* com-

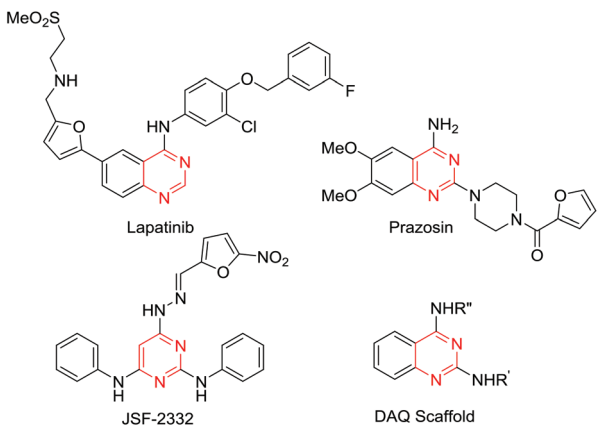

Fig. 1 Structures of the drugs lapatinib (breast cancer and solid tumour inhibitor), adrenoreceptors antagonists, JSF-2332 (antitubercular agent) and DAQ (amyloid aggregation inhibitor). The pyrimidine moiety in their core structures is highlighted in red.

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† Electronic supplementary information (ESI) available: Experimental details. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR for all new compounds and fibril binding assays for carboxylic acids (PDF). See DOI: 10.1039/d1ob01580j

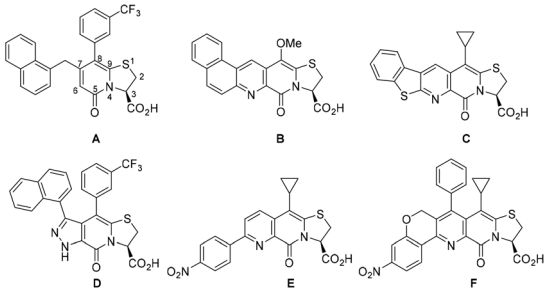


Fig. 2 Thiazolino-2-pyridone based compounds capable of modulating formation (compound **A–D**) and binding to (compound **E** and **F**) α-synuclein and amyloid-β fibrils.

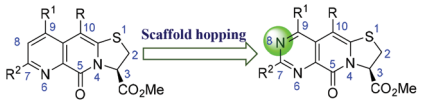


Fig. 3 Scaffold hopping of the tricyclic central fragment.

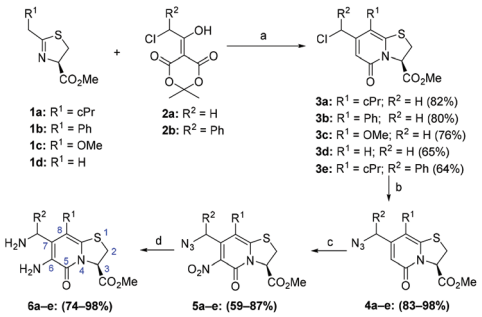
pound **E** and **F**) were shown to bind to Amyloid-β 1–40 (Aβ40) and α-Synuclein (α-Syn) amyloid fibrils.[23,24]

Thus, small changes in the substitution pattern or in the core structure of ring fused 2-pyridones can potentially alter their biological properties significantly. We envisioned that 'Scaffold hopping' by replacing the pyridine ring with a pyrimidine ring in the tricyclic framework (Fig. 3) could change or improve the amyloid affecting properties. The modification would not alter essential features of the central scaffold, but the extra nitrogen could result in additional interactions, such as being an acceptor for hydrogen bonding.

Being equipped with various reactive chemical functionalities, the thiazolino-2-pyridone is potentially a sensitive scaffold to modify, especially under basic and/or oxidative conditions. Hence, a synthetically simple and mild protocol where other reactive functionalities remain untouched is highly desired to install the pyrimidine unit into the thiazolino-2-pyridone scaffold. Oxidative condensation of 2-aminobenzylamines with aldehydes is an attractive strategy to construct the pyrimidine ring.[25] $K_2S_2O_8$ is a mild oxidant, which has been utilized in oxidative coupling reactions to construct nitrogen containing heterocycles.[26–29] Herein, we report $K_2S_2O_8$-mediated aerobic oxidative coupling of 6-amino-7-(aminomethyl)-thiazolino-2-pyridones with aldehydes for the synthesis of a novel tricyclic pyrimidine fused 2-pyridone scaffold. Rewardingly, the scaffold modification resulted in compounds with interesting amyloid modulating properties.

Results and discussion

Our studies began with the synthesis of C-6 and C-7 substituted thiazolino fused 2-pyridones **6a–e** as substrates (Scheme 1). An acyl ketene-imine cyclocondensation between thiazolines **1a–d** and Meldrum's acid derivative **2a–b** afforded

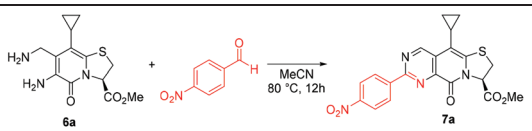


Scheme 1 Synthesis of 6-amino-7-(aminomethyl)-thiazolino-2-pyridones **6a–6e**. Reagents and conditions: (a) TFA (1.0 equiv.), DCE, MWI at 120 °C, 3 min. (b) NaN_3 (1.6 equiv.), DMF, rt, 30 min. (c) $NaNO_2$ (1.02 equiv.), TFA (12 equiv.), DCM, rt, 12 h. (d) Pd/C (0.2 equiv.), MeOH, H_2 (40 bar), rt, 12 h.

thiazolo-2-pyridones **3a–e**. Subsequent azidation gave **4a–e**, which was then nitrated (**5a–e**) and finally reduced to produce 6-amino-7-(aminomethyl)-thiazolino-2-pyridones **6a–e** in good yields.

Heating 6-amino-7-(aminomethyl)-thiazolino-2-pyridone **6a** (1 equiv.) with 4-NO_2-benzaldehyde (1.5 equiv.) in MeCN at 80 °C without oxidant resulted in formation of the tetrahydropyrimidine intermediate but the desired product **7a** was not observed (Table 1, entry 1). The intermediate was found to be unstable as it underwent oxidation spontaneously but very slowly. Encouraged by the formation of this intermediate, we next investigated the reaction in presence of different oxidants. When the reaction was conducted under air and oxygen, only 10% and 15% of **7a** was formed, respectively. Stronger oxidants such as I_2, mCPBA and $(NH_4)_2S_2O_8$ resulted in complex mix-

Table 1 Development of the reaction conditions for synthesis of pyrimidine fused thiazolino-2-pyridones **7a** [a]



Entry	Oxidant (equiv.)	**7a** [b] (% yield)
1	None	0
2	Air	10
3	O_2	15
4	O_2, I_2 (3)	0
5	O_2, mCPBA (3)	0
6	O_2, $(NH_4)_2S_2O_8$ (3)	0
7	O_2, CAN (3)	Trace
8	O_2, IBX (3)	Trace
9	O_2, Oxone (3)	20
10	O_2, Ag_2OAc(3)	28
11	O_2, $K_2S_2O_8$ (1)	67
12	O_2, $K_2S_2O_8$ (2)	75
13	O_2, $K_2S_2O_8$ (3)	79

[a] Reagents and conditions: **6a** (0.34 mmol, 1.0 equiv.), 4-NO_2-benzaldehyde (0.51 mmol, 1.5 equiv.), $K_2S_2O_8$ (1.02 mmol, 3.0 equiv.), O_2, MeCN (3 mL). [b] Isolated yields.

tures as expected, without the formation of **7a**. Only traces of **7a** was formed in the presence of CAN or IBX and although oxone or AgOAc provided the desired product, the yields were still low (entries 9 and 10). To our delight, when the reaction was carried out using $K_2S_2O_8$ under an oxygen atmosphere, 67% of **7a** was isolated (entry 11). The yield could even be improved to 79% by performing the reaction with 3 equiv. of $K_2S_2O_8$ (entry 13).

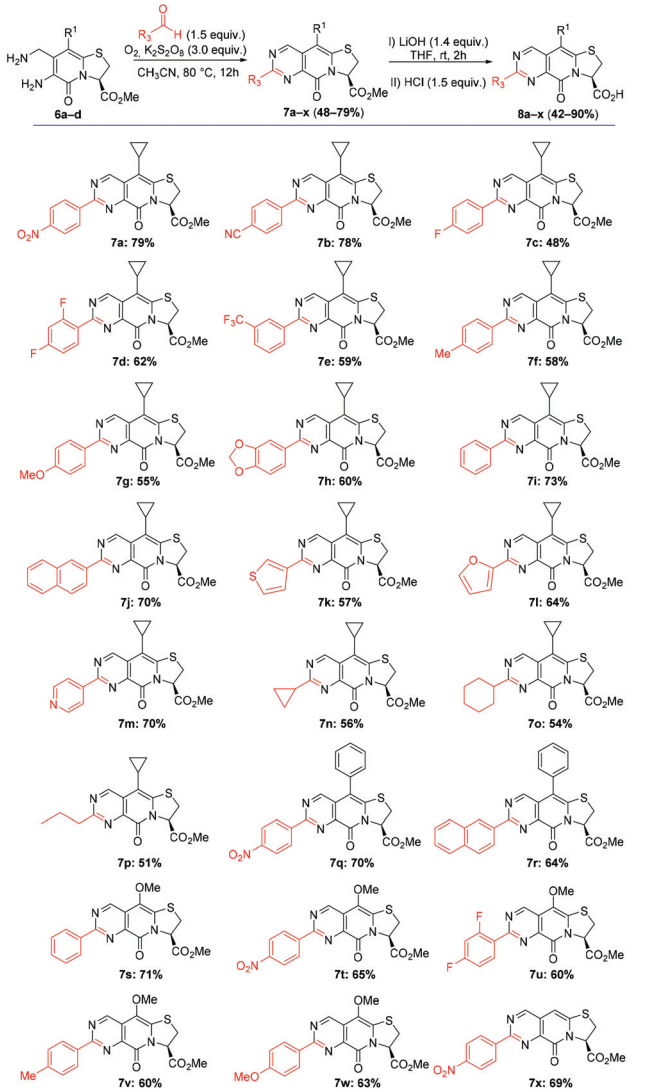
To investigate substrate scope and generate enough diversity for later structure activity relationship studies, different aldehydes and substituted 2-pyridones were used under the established reaction conditions (Scheme 2). Aliphatic aldehydes, benzaldehyde, naphthaldehyde, aryl aldehydes bearing electron-withdrawing/donating groups and heterocyclic aromatic aldehydes were all well tolerated and furnished the desired pyrimidine fused thiazolino-2-pyridones in 48–79% yield. Previous studies have confirmed that the carboxylic acid group is essential for amyloid modulating properties.[23] Thus, all methyl carboxylates were hydrolysed to the corresponding carboxylic acid with LiOH. Saponification resulted in compounds **8a–x** in 42–90% yield.

Further, to construct pyrimidine fused thiazolino-2-pyridone analogues efficiently and to allow late stage fine-tuning of the substitution pattern, C-10 unsubstituted pyrimidine fused thiazolino-2-pyridone **7x** was brominated with NBS in 80% yield. The Suzuki coupling of intermediate **9** with aryl/heteroaryl boronic acids afforded **7y–ad** in good yields (Scheme 3). The corresponding carboxylic acids **8y–ad** were subsequently generated by hydrolysis of the corresponding methyl esters.

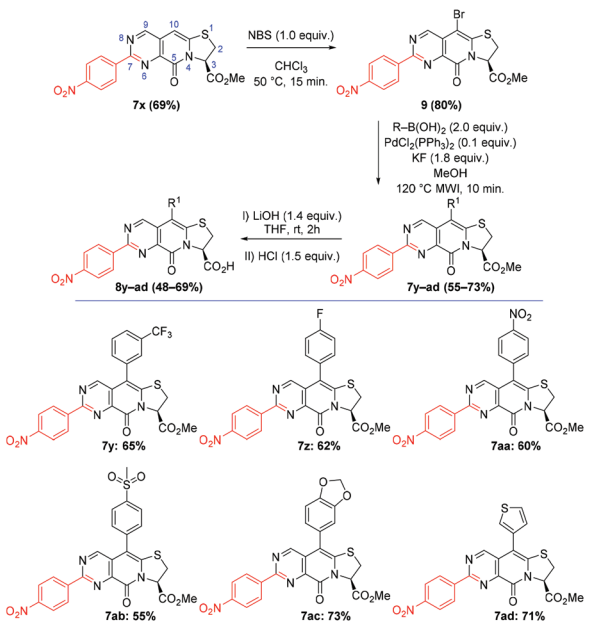
Next, we investigated the suitability of the reaction for preparation of di-aryl substituted pyrimidine fused thiazolino-2-pyridones **10a–i** (Scheme 4). For this, substrate **6e** was used, and it was combined with various substituted aryl aldehydes, as shown in Scheme 4. This reaction also proceeded well with electron withdrawing (**10a**, **10b**, **10c**), electron-donating (**10d**, **10e**), bicyclic (**10e**, **10g**, **10i**), as well as heteroaryl (**10h**) aldehyde substrates. Saponification eventually provided the desired carboxylic acids **11a–i**.

To demonstrate the generality of this mild method, 2-(aminomethyl)-aniline and aryl aldehydes were allowed to react under the established conditions. As expected, these mild reaction conditions proved general and pyrimidines **13a–d** were isolated in 52–85% yields (Scheme 5).

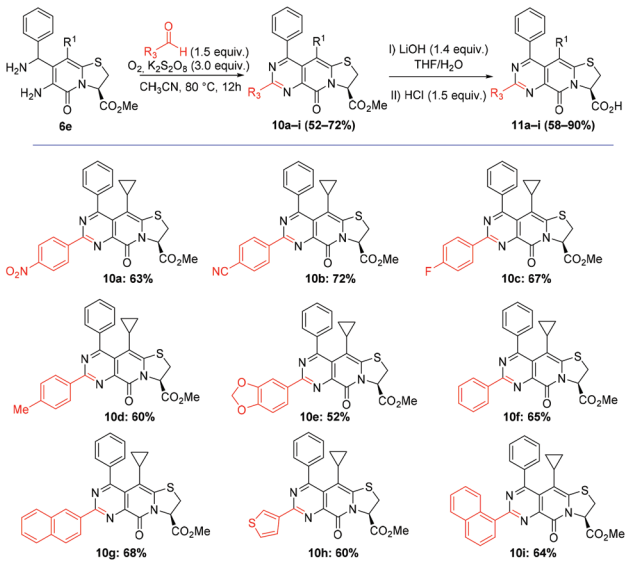
Mechanistically, 6-amino-7-(aminomethyl)-thiazolino-2-pyridone **6a** undergoes condensation reaction with aldehyde to give tetrahydro pyrimidine intermediate **14**. Under heating $K_2S_2O_8$ decomposes to radical anions[30] which oxidize the



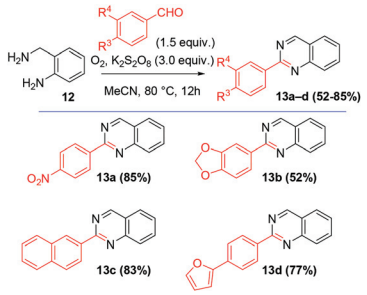
Scheme 2 Substrate scope for the synthesis of pyrimidine fused thiazolino-2-pyridones, **7a–x** under the established reaction conditions.



Scheme 3 Synthesis of C-10 substituted pyrimidine fused thiazolino-2-pyridones *via* bromination and Suzuki coupling.



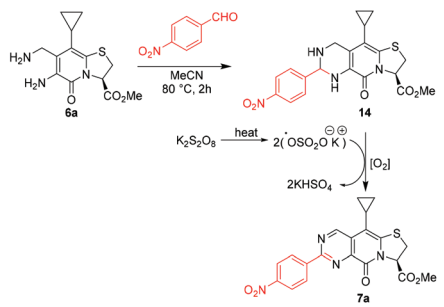
Scheme 4 Substrate scope for the synthesis of disubstituted pyrimidine fused thiazolino-2-pyridones, **10a–i**.



Scheme 5 Substrate scope for the synthesis of 2-substituted quinazolines, **13a–d**.

intermediate **14** to furnish pyrimidine fused thiazolino-2-pyridone **7a** (Scheme 6).

The obtained carboxylic acids **8a–ad** and **11a–i** were first evaluated for their ability to modulate the formation of α-Syn fibrils using a Thioflavin T (ThT) fluorescence assay[31] (Fig. 4



Scheme 6 Possible reaction mechanism for the $K_2S_2O_8$ mediated aerobic oxidative coupling of 6-amino-7-(aminomethyl)-thiazolino-2-pyridones with aldehydes.

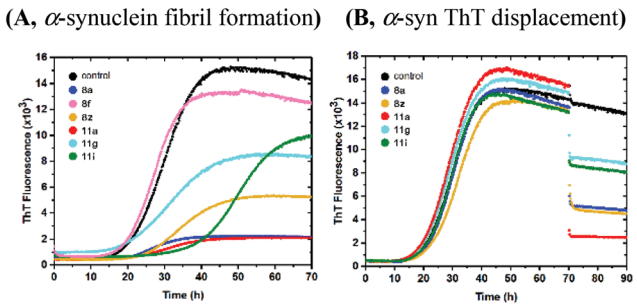


Fig. 4 Evaluation of compounds **8a**, **8f**, **8z**, **11a**, **11g** and **11i** for their effect on α-synuclein fibril formation and mature fibril binding. (A) Compounds were included from the start of the reaction. (B) Compound were added to mature fibrils after 70 hours of incubation.

and S1†). In this assay, the effects on fibril formation is observed as changes of the lag phase duration. Further, the ability to bind α-Syn fibrils and displace fibril bound ThT is indicated by a reduced ThT fluorescence amplitude in comparison to the control experiments, where no peptidomimetic compound was included. Compound **8a**, **8z** and **11a** (Fig. 4A) that were equipped with the 4-nitrophenyl group as R^3-substituent displayed a moderate to strong ability to bind α-Syn fibrils. Conversely, **8f** with a *p*-tolyl group shows no significant ability to bind α-Syn fibrils. Interestingly, compound **11g** with a 2-naphthyl group as R^3-substituent, also displayed moderate fibril binding, while compound **11i** carrying a 1-naphthyl group as R^3-substituent inhibits the amyloid fibril formation to some degree, seen as an extension of the lag time. The R^1 substituent had a minor influence on the binding ability of the compounds to α-Syn fibrils. Of the nine different R^1 substituents investigated in combination with the 4-nitrophenyl group as R^3 substituent, cyclopropyl seems to be superior to the others in terms of amyloid fibril binding (**8a** and **11a**). To verify that the reduced fluorescence indeed is an effect of ThT displacement rather than modulation of amyloid fibril formation, selected compounds were added to already formed α-Syn fibrils (Fig. 4B and S2†). In addition, samples taken after complete fibrilization with compound **8a** was visualized with TEM and found to contain fibrils that were indistinguishable from the control (Fig. S4†).

In similar fibrillation assays, compounds **8a–d** and **11a–i** were evaluated for their ability to affect Aβ40 fibrils, and modulate the fibril formation (Fig. 5 and S4, S5†). Again, an interesting SAR was observed with respect to the R^3-substitutents. Compound **8a** and **8z** were found to bind to Aβ40 fibrils (Fig. 5A). Compound **8f**, which had no effect on α-Syn, inhibited the formation of Aβ40 fibrils. Compound **11g** with a 2-naphthyl group as R^3-substituent was found to be a potent inhibitor of Aβ40 fibril formation, as the lag time was extended beyond the duration of the experiments (70 h), while compound **11i** with a 1-naphthyl group was found to be a very week accelerator of Aβ40 fibril formation (Fig. 5A). Further to confirm the modulating effect of compounds, a ThT displacement assay was performed. To distinguish between modulat-

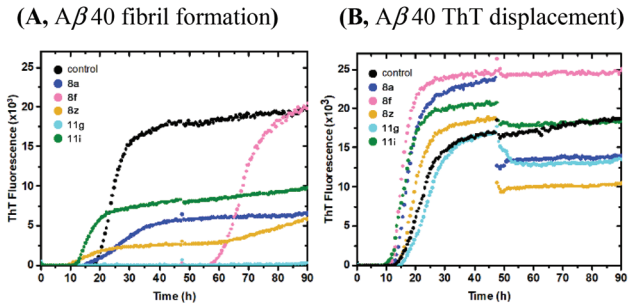
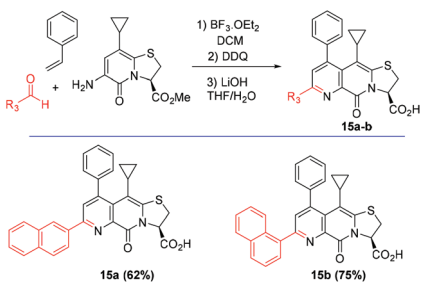


Fig. 5 Evaluation of compounds **8a**, **8f**, **8z**, **11g** and **11i** for their effect on Aβ-fibril formation and fibril binding. (A) Compounds were included from the start of the reaction. (B) Compounds were added to mature fibrils after 47 hours of incubation, and the incubation was continued.

ing and binding activities, compounds were added to mature Aβ40 fibrils (Fig. 5B) using the same approach as for α-synuclein. Indeed, compound **8f** and **11g** were found to be true inhibitors as ThT fluorescence signals were not dropped when the compound was added to mature Aβ fibrils (Fig. 5B). Thus, compound **8f** and **11g** were found to affect Aβ40 fibrils selectively, which previously has been an issue in designing small molecule inhibitors of amyloid fibril formation.[32]

We were delighted by the potent effect of **11g** as an inhibitor of Aβ40 amyloid fibril formation. To explore the structure activity relationship further, the pyridine fused analogues **15a–b** were prepared by employing a three-component procedure published previously (Scheme 7).[23] The pyridine fused thiazolino 2-pyridones **15a–b** display a similar structure activity relationship as their pyrimidine counterparts (compound **11g** and **11i**). While the 2-naphthyl substituted compound **15a** inhibits Aβ40 amyloid formation (Fig. 6B) as effectively as **11g**, the 1-naphthyl substituted **15b** rather accelerate the formation of Aβ40 amyloid fibrils (Fig. 6B). **15b** also accelerates α-synuclein fibril formation slightly, (Fig. 6A), while **15a** instead slightly extend the lag phase of α-synuclein amyloid formation (Fig. 6A).

Next, a set of active compounds were evaluated for their cytotoxicity in HeLa cells using a Neutral Red assay. All the



Scheme 7 Synthesis of the pyridine fused polyheterocycles **15a–b** by three component Povarov reactions, according to established procedure.[23]

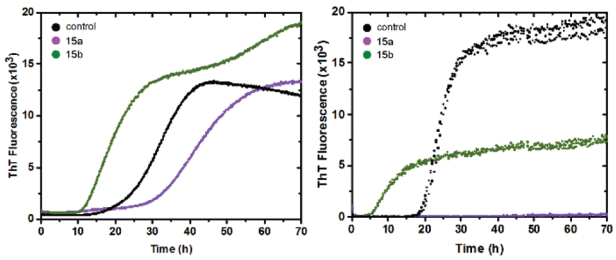


Fig. 6 Evaluation of compounds **15a–b** for their effect against α-synuclein (A) and Aβ40 fibrils *in vitro* (B).

selected compounds were found to have minimal effect on cell viability at the tested concentrations and are less toxic compared to positive control curcumin which is a known amyloid affector (Fig. S7†). The compound **11g** started showing some toxicity when tested at 100 μM, but it is still less toxic compared to curcumin.

While many pharmaceuticals do contain nitroaryl motifs, this functionality is often avoided in drug development due to its genotoxic potential.[33–35]

Since several of the most active amyloid fibril binding 2-pyridones presented above are equipped with the 4-nitrophenyl group, we were prompted to evaluate their mutagenicity by the Ames Salmonella/mammalian-microsome mutagenicity spot test.[36] Compound **8a** and **11a**, which bind to amyloid fibrils, were found to be mutagenic (Fig. S6A†). However, to our delight, none of the active analogues including **11g** that were lacking the *p*-nitro phenyl substituent induced mutations in any of the four *Salmonella typhimurium* strains tested; TA98, TA100, TA1535 and TA1537 (Fig. S6B†).

Conclusion

A series of tricyclic pyrimidine fused thiazolino-2-pyridones were prepared from readily available aldehydes and 6-amino-7-(aminomethyl)-thiazolino-2-pyridones in a single step using inexpensive $K_2S_2O_8$ as oxidant. This is to the best of our knowledge a new heterocyclic scaffold and several of these new pyrimidine fused thiazolino-2-pyridone carboxylic acids display an ability to bind α-synuclein and Aβ40 fibrils. Compound **8f** inhibit and **11g** strongly inhibit Aβ40 fibril formation *in vitro*. Thus, these new compounds have great potential to be developed as tool compounds for further investigations of neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Both nitrophenyl analogues **8a** and **11a**, which were strong binders to α-Syn amyloid fibrils, were mutagenic. Still, the new collection of pyrimidine fused 2-pyridones contained some non-mutagenic analogues where the 2-naphthyl substituted analogue **11g** stood out as very interesting. This analogue displayed weaker binding to α-Syn and Aβ40 amyloid fibrils but in addition had a strong inhibiting effect on Aβ40 amyloid fibril formation. Further studies to develop active compounds as diagnostic/therapeutic agents are currently underway.

Experimental section

General information

Unless stated, all reagents and solvents were used as received from commercial suppliers. All reactions were carried out under an inert atmosphere with dry solvents under anhydrous conditions, unless otherwise indicated. 4 Å molecular sieves (MS) were activated at 300 °C under a vacuum for 4 h. Microwave reactions were performed in sealed vessels using a Biotage Initiator microwave synthesizer; temperatures were monitored by an internal IR probe. TLC was performed on purchased aluminium backed silica gel plates (median pore size 60 Å, fluorescent indicator 254 nm) and detected with UV light at 254 and 366 nm. Flash column chromatography was performed using silica gel (0.063–0.200 mesh). Automated flash column chromatography was performed using a BiotageIsolera One system and purchased prepacked silica gel cartridges (Biotage SNAP Cartridge, KP-Sil). Preparative HPLC was performed with a Gilson instrument using a Phenomenex column (250 × 21.2 mm; Gemini 5 μm NX-C18, 110 Å). The optical rotation was measured with a Rudolph Autopol IV polarimeter 343 at 22 °C and 589 nm. $[\alpha]$ is reported in deg ml g^{-1} dm^{-1}, concentrations (c) are given in g per 100 mL. IR spectra were recorded on a Bruker Alpha-t spectrometer. The samples were prepared as KBr pellets or between NaCl plates; absorbances are given in reciprocal cm. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer with a BBO-F/H Smartprobe, or a Bruker Avance III HD 600 MHz spectrometer with a CP TCI HCN, 5 mm cryoprobe, at 298 K, unless another temperature is given. All spectrometers were operated by Topspin 3.5.7. Resonances are given in ppm relative to TMS and calibrated to solvent residual signals ($CDCl_3$) δ_H = 7.26 ppm; δ_C = 77.16 ppm; $(CD_3)_2SO$ δ_H = 2.50 ppm, δ_C = 39.51 ppm. The following abbreviations are used to indicate splitting patterns: s = singlet; d = doublet; dd = double doublet; t = triplet; m = multiplet; bs = broad singlet. LC-MS was conducted on a Micromass ZQ mass spectrometer using ES^+ ionization unless otherwise stated. HRMS was performed on a mass spectrometer with ESI-TOF (ES^+). Amyloid formation was probed by thioflavin T (ThT) fluorescence, with a FLUOstar Omega instrument (BMG Labtech, Germany), using excitation and emission filters of 440 and 480 nm, respectively.

General procedure for the preparation of Meldrum's acid derivative 2a-b. Chloroacetic acid (26.22 g, 0.27 mol), DMAP (35.60 g, 0.29 mol) and Meldrum's acid (40.0 g, 0.27 mol) were dissolved in DCM (300 mL) at 0 °C. DCC (62.98 g, 0.30 mol) dissolved in DCM (50 mL) was added dropwise to the mixture over 40 min. The reaction mixture was then left stirring at room temperature overnight and subsequently quenched with 6% (aq.) $KHSO_4$(200 mL). The resulting precipitate was filtered off. The filtrate was washed five times with 6% $KHSO_4$, (400 mL) followed by two times with brine (200 mL), then dried over anhydrous Na_2SO_4, filtrated, and concentrated, the crude product was used without further purification. The spectral data of **2a–2b** is provided in ESI.†

General procedure for synthesis of (3a–3e). In a microwave reaction tube equipped with a magnetic stirrer, thiazoline (34.67 mmol, 1.0 equiv.) and Meldrum's acid derivative (19.12 g, 86.69 mmol, 2.5 equiv.) was dissolved in 1,2-dichloroethane (150 mL). TFA (2.70 mL, 35.36 mmol, 1.02 equiv.) was added, the tube was sealed and heated to 120 °C under microwave irradiations for 3 min. The reaction mixture was cooled to room temp.diluted with DCM (100 mL) and washed with saturated aqueous sodium bicarbonate solution (100 mL) followed by brine (100 mL). The aqueous phases were re-extracted with DCM (2 mL each). The organic phases were combined, dried, filtered and evaporated. The compound was purified with flash column chromatography. The spectral data of **3a–3e** is provided in ESI.†

General procedure for synthesis of (4a–4e). To a stirred solution of **3a** (8.84 mmol, 1.0 equiv.) in dry DMF (5 mL) was added sodium azide (14.14 mmol, 1.6 equiv.) The mixture was stirred under an atmosphere of nitrogen at rt for 30 min or until full consumption of starting material was indicated by TLC. The reaction mixture was then diluted with water (100 mL) and extracted with DCM (200 mL) dried over Na_2SO_4, and concentrated. The compound was purified with flash column chromatography. The spectral data of **4a–4e** is provided in ESI.†

General procedure for synthesis of 6-nitro-7-(azidomethyl)-thiazolino-2-pyridones (5a–5c and 5e). The 2-pyridone of general structure **4** (11.75 mmol, 1.0 equiv.) was dissolved in DCM (25 mL) in an open RBF. Air was bubbledthrough the solution for 5–10 minutes. $NaNO_2$ was added to the stirred solution. The reaction mixture was left for another 5–10 min before theair source was removed and TFA was added dropwise over 10–15 min at rt. The reaction mixture was again purged with air bubbleing the solution for 5–10 min. After removal of the air source the reaction was left stirring in the open RBF. The reaction was then quenched with saturated aqueous $NaHCO_3$ (20 mL) and extracted with DCM. The combined organic layers were dried over anhydrous sodium sulphate, filtered and evaporated. The compound was purified with flash column chromatography.

For synthesis of **5d**, the compound **4d** (1.0 mmol, 1.0 equiv.) was dissolved in acetic anhydride (3.4 mL) and cooled to −40 °C. Acetic anhydride (1.7 mL) was cooled on ice, and HNO_3 (65% aq) (0.10 mL, 1.5 mmol, 1.5 equiv.) was added slowly. The diluted acid was transferred to a dropping funnel and added slowly to the stirred solution. The reaction mixture was allowed to warm to 0 °C and stirred until completion was indicated by TLC (EtOAc). The reaction mixture was then quenched with methanol (10 mL) at 0 °C and transferred to a separation funnel with ice-cold $NaHCO_3$ (saturated aqueous) (10 mL) and EtOAc (10 mL). The phases were separated, and the aqueous phase was extracted once more with EtOAc (10 mL). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and evaporated. The crude product was purified with flash column chromatography (100 g SNAP Cartridge; ethyl acetate in heptane, 20–100% in 8 CV): brown solid of **5d**, 2.01 g (48%). The spectral data of **5a–5e** is provided in ESI.†

General procedure for synthesis of 6-amino-7-(aminomethyl)-thiazolino-2-pyridones (6a–6e). The 2-pyridone of

general structure **5** (3.55 mmol, 1.0 equiv.) was dissolved in MeOH (15 mL) in a sealed tube. The solution was purged with nitrogen for 5 min Pd/C (0.71 mmol, 0.2 equiv.) was added to the solution. The reaction mixture was again purged for 5 min. The tube was then inserted in a high pressure reactor. The reaction mixture was then stirred under hydrogen gas (40 bar) at room temp. over night. When TLC (neutral alumina plate, (5% MeOH in DCM) indicated completion. Then solution was filtered through a pad of Celite® and evaporated. The crude product was used for the next step without further purification. The spectral data of **6a–6e** is provided in ESI.†

Synthesis of pyrimidine fused 2-pyridone from aldehydes and 6-amino-7-(aminomethyl)-thiazolino-2-pyridones (7a–x, 10a–i and intermediate 14). A solution of 6-amino-7-(aminomethyl)-2-pyridones (0.34 mmol, 1.0 equiv.), aldehyde (0.51 mmol, 1.5 equiv.) in CH_3CN (2 mL) was stirred at 80 °C until the condensation was found complete by TLC analysis (about 2 h). To the same solution was added $K_2S_2O_8$ (1.02 mmol, 3.0 equiv.), and the mixture was stirred at 80 °C for 12 hours under an O_2 atmosphere (balloon). After completion of the reaction (monitored by TLC), the mixture was diluted with DCM (5 mL), washed with brine (3 mL), dried, over anhydrous sodium sulphate, filtered, and evaporated. The resulting residue was purified by silica gel column chromatography to give the desired product. The identity and purity of the product was confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis. The spectral data of **7a** is shown below, whereas for **7b-x**, **10a-i**, **14**, please see the ESI.† The experimental procedures and spectral data for **9**, **7a–7ad**, **10a-i** are also provided in ESI.†

Methyl (*R*)-5-cyclopropyl-2-(4-nitrophenyl)-10-oxo-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylate (7a). The compound was prepared by following general procedure. The product was purified by automated flash column chromatography (25 g SNAP Cartridge) eluting with 0–80% ethyl acetate in heptane, and 100 mg of **6a** was converted to 114 mg (79%) of **7a**, isolated as a bright yellow solid; $[\alpha]_D^{25}$ −104 (*c* 0.19, $CHCl_3$); IR (KBr): ν 1746, 1672, 1631, 1588, 1502, 1340, 1227, 736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 8.77 (d, *J* = 8.7 Hz, 2H), 8.32 (d, *J* = 8.7 Hz, 2H), 5.79 (d, *J* = 7.5 Hz, 1H), 3.82 (s, 3H), 3.80–3.73 (m, 1H), 3.62 (d, *J* = 11.5 Hz, 1H), 1.87–1.81(m, 1H), 1.15 (dd, *J* = 13.4, 6.2 Hz, 2H), 0.76 (t, *J* = 15.1 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.0, 159.1, 158.9, 156.2, 149.3, 144.5, 144.4, 142.7, 129.9, 129.3, 123.8, 106.7, 63.1, 53.6, 31.7, 9.0, 7.5, 7.4; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{17}N_4O_5S^+$ 425.0920, found 425.0920.

General procedure for preparation of acids (8a–8ad, 11a–11i) and (14a). The ester was dissolved in THF (2 mL) and LiOH (0.1 M aq; 1.4 equiv.) was added while stirring. The reaction mixture was left stirring at r.t. while monitored with TLC (EtOAc). Upon completion, the reaction was quenched with HCl (1 M aq; 1.5 equiv.). The mixture was evaporated and the watery residue was partitioned between chloroform (10 mL) and brine (5 mL). The phases were separated and the aqueous phase was extracted with another portion of $CHCl_3$ (10 mL). The organic phases were combined, dried over anhydrous sodium sulphate, filtered and evaporated. The residue was re-dissolved in DMSO (1 mL) and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min) The fractions containing the desired product were combined and diluted with H_2O (1 : 1) and freeze-dried.

(*R*)-5-Cyclopropyl-2-(4-nitrophenyl)-10-oxo-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8a). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 50 mg of **7a** was converted to 40 mg (83%) of **8a**, isolated as a dark yellow solid; $[\alpha]_D^{25}$ −64 (*c* 0.24, DMSO); IR (KBr): ν 1721, 1649, 1580, 1565, 1521, 1500, 1443, 1337 cm^{-1}; ^{1}H NMR (600 MHz, DMSO) δ 13.75 (s, 1H), 9.75 (s, 1H), 8.68 (d, *J* = 9.0 Hz, 2H), 8.43 (d, *J* = 9.0 Hz, 2H), 5.68 (dd, *J* = 8.7, 1.3 Hz, 1H), 3.89 (dd, *J* = 11.7, 8.7 Hz, 1H), 3.67 (dd, *J* = 11.7, 1.2 Hz, 1H), 1.91–1.86 (m, 1H), 1.14–1.09 (m, 2H), 0.75–0.61 (m, 2H); ^{13}C {^{1}H}NMR (151 MHz, DMSO) δ 169.3, 157.9, 157.2, 156.6, 148.7, 145.7, 143.6, 142.6, 129.8, 128.7, 124.2, 105.3, 63.1, 31.4, 8.7, 7.2, 7.0; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{15}N_4O_5S^+$ 411.0758, found 411.0749.

(*R*)-2-(4-Cyanophenyl)-5-cyclopropyl-10-oxo-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8b). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 50 mg of **7b** was converted to 32 mg (66%) of **8b**, isolated as a bright yellow solid; $[\alpha]_D^{25}$ −28 (*c* 0.23, DMSO); IR (KBr): ν 1722, 1632, 1495, 1444, 1383, 765 cm^{-1}; ^{1}H NMR (600 MHz, DMSO) δ 13.74 (s, 1H), 9.74 (s, 1H), 8.61 (d, *J* = 8.3 Hz, 2H), 8.05 (d, *J* = 8.4 Hz, 2H), 5.66 (d, *J* = 8.6 Hz, 1H), 3.88 (dd, *J* = 11.6, 8.8 Hz, 1H), 3.66 (d, *J* = 11.6 Hz, 1H), 1.91–1.87 (m, 1H), 1.14–1.09 (m, 2H), 0.74–0.62 (m, 2H); ^{13}C{^{1}H} NMR (151 MHz, DMSO) δ 169.2, 157.9, 157.5, 156.6, 145.6, 143.6, 141.0, 132.9, 129.7, 128.2, 118.7, 112.8, 105.2, 63.1, 31.4, 8.7, 7.2, 7.0; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{15}N_4O_3S^+$ 391.0865, found 391.0862.

(*R*)-5-Cyclopropyl-2-(4-fluorophenyl)-10-oxo-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8c). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 50 mg of **7c** was converted to 43 mg (89%) of **8c**, isolated as a light yellow solid; $[\alpha]_D^{25}$ −35 (*c* 0.22, DMSO); IR (KBr): ν 2987, 2911, 1758, 1626, 1599, 1566, 1500, 1445, 1389, 1340, 1223, 856, 817, 767 cm^{-1}; ^{1}H NMR (600 MHz, DMSO) δ 13.68 (s, 1H), 9.69 (s, 1H), 8.52–8.49 (m, 2H), 7.41 (t, *J* = 8.8 Hz, 2H), 5.65 (d, *J* = 8.6 Hz, 1H), 3.87 (dd, *J* = 11.7, 8.7 Hz, 1H), 3.64 (d, *J* = 11.7 Hz, 1H), 1.89–1.87 (m, 1H), 1.13–1.08 (m, 2H), 0.73–0.61 (m, 2H); ^{13}C{^{1}H}NMR (151 MHz, DMSO) δ 169.3, 164.8 (d, *J* = 248.4 Hz), 158.5, 158.1, 156.4, 144.1, 143.7, 133.4 (d, *J* = 2.5 Hz), 130.0 (d, *J* = 8.7 Hz), 129.1, 115.9 (d, *J* = 21.8 Hz), 105.2, 63.0, 31.3, 8.7, 7.2, 7.0; ^{19}F{^{1}H} NMR (376 MHz, DMSO) δ −110.4; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{15}FN_3O_3S^+$ 384.0813, found 384.0810.

(*R*)-5-Cyclopropyl-2-(2,4-difluorophenyl)-10-oxo-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic *A*cid (8d). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 30 mg of **7d** was converted to 20 mg (69%) of **8d**, isolated as a yellow solid; $[\alpha]_D^{25}$ −32 (*c* 0.29, DMSO); IR (KBr): ν 1740, 1680, 1597, 1566, 1445, 1389, 1240, 1223, 856, 767 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 9.71 (s, 1H), 8.23–8.11 (m, 1H), 7.49–7.38 (m, 1H), 7.29 (td, *J* = 8.4, 2.3 Hz, 1H), 5.58 (d, *J* = 8.2 Hz, 1H), 3.83 (dd, *J* = 11.5, 8.6 Hz, 1H), 3.66 (s, 1H), 1.87 (dd, *J* = 9.4, 4.1 Hz, 1H), 1.17–1.01 (m, 2H), 0.67 (dd, *J* = 33.4, 4.9 Hz, 2H); $^{13}C\{^1H\}$NMR (151 MHz, DMSO) δ 169.2, 163.3 (dd, *J* = 250.1, 11.9 Hz), 160.9 (dd, *J* = 257.5, 12.6 Hz), 157.9, 157.2 (d, *J* = 5.1 Hz), 156.1, 145.1, 143.7, 133.3 (d, *J* = 10.2 Hz), 128.9, 123.7 (d, *J* = 13.3 Hz), 112.0 (dd, *J* = 21.4, 3.7 Hz), 105.4, 105.0 (dd, *J* = 61.8, 35.7 Hz), 64.6, 31.7, 8.7, 7.2, 7.0; $^{19}F\{^1H\}$NMR (376 MHz, DMSO) δ −107.2, −108.9; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{14}F_2N_3O_3S^+$ 402.0742, found 402.0745.

(*R*)-5-Cyclopropyl-10-oxo-2-(3-(trifluoromethyl)phenyl)-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8e). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 30 mg of **7e** was converted to 17 mg (59%) of **8e**, isolated as a bright yellow solid; $[\alpha]_D^{25}$ −8 (*c* 0.18, DMSO); IR (KBr): ν 1743, 1642, 1580, 1508, 1437, 1260, 1222, 1123, 763 cm^{-1}; ^1H NMR (600 MHz, DMSO) δ 9.75 (s, 1H), 8.75 (d, *J* = 12.1 Hz, 2H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.85 (t, *J* = 7.8 Hz, 1H), 5.67 (d, *J* = 8.7 Hz, 1H), 3.91–3.87 (m, 1H), 3.66 (d, *J* = 11.7 Hz, 1H), 1.90–1.87 (m, 1H), 1.15–1.10 (m, 2H), 0.74–0.62 (m, 2H); $^{13}C\{^1H\}$NMR (151 MHz, DMSO) δ 169.2, 158.1, 157.7, 156.6, 145.0, 143.6, 137.8, 131.4, 130.3 (q, *J* = 34.7 Hz), 130.0, 129.8, 127.2 (q, *J* = 3.5 Hz), 123.7 (q, *J* = 272.3 Hz), 121.5, 105.3, 63.0, 31.3, 8.7, 7.2, 7.0; $^{19}F\{^1H\}$NMR (376 MHz, $CDCl_3$) δ −62.5; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{15}F_3N_3O_3S^+$ 434.0781, found 434.0776.

(*R*)-5-Cyclopropyl-10-oxo-2-(*p*-tolyl)-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8f). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 30 mg of **7f** was converted to 23 mg (80%) of **8f**, isolated as a yellow solid; $[\alpha]_D^{25}$ −23 (*c* 0.20, DMSO); IR (KBr): ν 1748, 1644, 1580, 1500, 1443, 1409, 1228 cm^{-1}; ^1H NMR (600 MHz, DMSO) δ 13.65 (s, 1H), 9.68 (s, 1H), 8.37 (d, *J* = 7.9 Hz, 2H), 7.38 (d, *J* = 7.9 Hz, 2H), 5.65 (d, *J* = 8.6 Hz, 1H), 3.92–3.83 (m, 1H), 3.64 (d, *J* = 11.7 Hz, 1H), 2.40 (s, 3H), 1.89–1.87 (m, 1H), 1.13–1.08 (m, 2H), 0.73–0.61 (m, 2H); $^{13}C\{^1H\}$NMR (151 MHz, DMSO) δ 169.4, 159.5, 158.2, 156.3, 143.7, 143.6, 140.7, 134.2, 130.0, 129.5, 128.9, 105.3, 62.8, 31.2, 21.0, 8.7, 7.2, 7.0; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{18}N_3O_3S^+$ 380.1063, found 380.1058.

(*R*)-5-Cyclopropyl-2-(4-methoxyphenyl)-10-oxo-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*] pyrimidine-8-carboxylic acid (8g). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 30 mg of **7g** was converted to 18 mg (62%) of **8g**, isolated as a bright yellow solid; $[\alpha]_D^{25}$ −51 (*c* 0.20, DMSO); IR (KBr): ν 1745, 1641, 1581, 1501, 1440, 1385, 1303, 1255, 1183 cm^{-1}; ^1H NMR (600 MHz, DMSO) δ 13.67 (s, 1H), 9.63 (s, 1H), 8.41 (d, *J* = 8.9 Hz, 2H), 7.11 (d, *J* = 8.9 Hz, 2H), 5.63 (dd, *J* = 8.6, 1.1 Hz, 1H), 3.87 (s, 1H), 3.86 (s, 3H), 3.62 (dd, *J* = 11.7, 1.1 Hz, 1H), 1.87–1.84 (m, 1H), 1.10–106 (m, 2H), 0.72–0.59 (m, 2H); $^{13}C\{^1H\}$NMR (151 MHz, DMSO) δ 169.4, 161.6, 159.4, 158.2, 156.2, 143.8, 143.2, 129.4, 128.3, 128.5, 114.2, 105.3, 62.9, 55.4, 31.2, 8.7, 7.2, 7.0; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{18}N_3O_4S^+$ 396.1018, found 396.1013.

(*R*)-2-(Benzo[*d*][1,3]dioxol-5-yl)-5-cyclopropyl-10-oxo-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8h). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 50 mg of **7h** was converted to 32 mg (66%) of **8h**, isolated as a bright yellow solid; $[\alpha]_D^{25}$ −27 (*c* 0.30, DMSO); IR (KBr): ν 2932, 2589, 1742, 1639, 1591, 1560, 1522, 1491, 1467, 1250 cm^{-1}; ^1H NMR (600 MHz, DMSO) δ 9.63 (s, 1H), 8.08 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.90 (d, *J* = 1.5 Hz, 1H), 7.10 (d, *J* = 8.2 Hz, 1H), 6.14 (s, 2H), 5.66–5.58 (m, 1H), 3.85 (dd, *J* = 11.7, 8.7 Hz, 1H), 3.63 (dd, *J* = 11.7, 1.3 Hz, 1H), 1.86 (td, *J* = 8.1, 4.1 Hz, 1H), 1.12–1.06 (m, 2H), 0.72–0.60 (m, 2H); $^{13}C\{^1H\}$NMR (151 MHz, DMSO) δ 169.3, 159.0, 158.2, 156.2, 149.7, 148.0, 143.7, 143.6, 131.2, 128.7, 122.7, 108.6, 107.2, 105.3, 101.7, 63.1, 31.4, 8.7, 7.2, 7.0; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{16}N_3O_5S^+$ 410.0805, found 410.0802.

(*R*)-5-Cyclopropyl-10-oxo-2-phenyl-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8i). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 30 mg of **7i** was converted to 16 mg (55%) of **8i**, isolated as a yellow solid; $[\alpha]_D^{25}$ −39 (*c* 0.21, DMSO); IR (KBr): ν 1737, 1635, 1589, 1559, 1518, 1464, 1442, 1413, 1229 cm^{-1}; ^1H NMR (600 MHz, DMSO) δ 9.67 (s, 1H), 8.46 (d, *J* = 6.5 Hz, 2H), 7.56 (t, *J* = 7.7 Hz, 3H), 5.65 (dd, *J* = 8.6, 1.0 Hz, 1H), 3.88 (dd, *J* = 11.7, 8.7 Hz, 1H), 3.64 (dd, *J* = 11.7, 1.2 Hz, 1H), 1.88–1.84 (m, 1H), 1.12–1.07 (m, 2H), 0.72–0.67 (m, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO) δ 169.4, 159.4, 158.2, 156.3, 144.0, 143.7, 136.8, 130.8, 129.1, 128.8, 127.7, 105.3, 62.9, 31.3, 8.7, 7.2, 7.0; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{16}N_3O_3S^+$ 366.0912, found 366.0902.

(*R*)-5-Cyclopropyl-2-(naphthalen-2-yl)-10-oxo-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8j). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 50 mg of **7j** was converted to 43 mg (90%) of **8j**, isolated as a dark yellow solid; $[\alpha]_D^{25}$ −10 (*c* 0.20, DMSO); IR (KBr): ν 1749, 1644, 1582, 1494, 1437, 1390, 1341, 1221, 772 cm^{-1}; ^1H NMR (600 MHz, DMSO) δ 13.69 (s, 1H), 9.74 (s, 1H), 9.05 (s, 1H), 8.58 (dd, *J* = 8.6, 1.5 Hz, 1H), 8.16–8.13 (m, 1H), 8.09 (d, *J* = 8.7

Hz, 1H), 8.01–7.98 (m, 1H), 7.62–7.57 (m, 2H), 5.67 (d, J = 8.0 Hz, 1H), 3.88 (dd, J = 11.6, 8.7 Hz, 1H), 3.69–3.63 (m, 1H), 1.93–1.85 (m, 1H), 1.14–1.09 (m, 2H), 0.76–0.62 (m, 2H); ^{13}C {^{1}H}NMR (151 MHz, DMSO) δ 169.3, 159.4, 158.2, 156.4, 144.2, 143.8, 134.3, 134.2, 132.8, 129.2, 129.1, 127.8, 127.5, 126.7, 124.6, 105.3, 63.0, 31.3, 8.8, 7.3, 7.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{18}N_3O_3S^+$ 416.1069, found 416.1080.

(*R*)-5-Cyclopropyl-10-oxo-2-(thiophen-3-yl)-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8k). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 50 mg of **7k** was converted to 28 mg (58%) of **8k**, isolated as a light yellow solid; $[\alpha]_D^{25}$ −27 (c 0.17, DMSO); IR (KBr): ν 1756, 1725, 1631, 1582, 1538, 1501, 1451, 1391, 1222, 756 cm^{-1}; ^{1}H NMR (600 MHz, DMSO) δ 13.70 (s, 1H), 9.63 (s, 1H), 8.46–8.36 (m, 1H), 7.91–7.83 (m, 1H), 7.71 (dd, J = 4.9, 3.1 Hz, 1H), 5.63 (d, J = 8.6 Hz, 1H), 3.86 (dd, J = 11.6, 8.8 Hz, 1H), 3.63 (d, J = 11.6 Hz, 1H), 1.86 (dd, J = 9.4, 4.0 Hz, 1H), 1.13–1.07 (m, 2H), 0.73–0.60 (m, 2H); ^{13}C{^{1}H} NMR (151 MHz, DMSO) δ 169.3, 158.1, 157.1, 156.3, 143.7, 143.6, 140.9, 128.7, 128.3, 127.5, 127.0, 105.3, 63.0, 31.3, 8.7, 7.2, 7.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{14}N_3O_3S_2^+$ 372.0477, found 372.0478.

(*R*)-5-Cyclopropyl-2-(furan-2-yl)-10-oxo-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8l). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 35 mg of **7l** was converted to 22 mg (52%) of **8l**, isolated as a yellow solid; $[\alpha]_D^{25}$ −39 (c 0.27, DMSO); IR (KBr): ν 1740, 1678, 1632, 1581, 1502, 1442, 1406, 1278 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 9.59 (s, 1H), 7.98 (s, 1H), 7.35 (d, J = 3.3 Hz, 1H), 6.74 (dd, J = 3.3, 1.7 Hz, 1H), 5.64 (d, J = 8.5 Hz, 1H), 3.87 (dd, J = 11.8, 8.7 Hz, 1H), 3.63 (d, J = 11.8 Hz, 1H), 1.91–1.81 (m, 1H), 1.13–1.01 (m, 2H), 0.65 (dt, J = 10.9, 7.5 Hz, 2H); ^{13}C{^{1}H}NMR (100 MHz, DMSO) δ 169.3, 158.0, 156.8, 153.1, 151.7, 146.0, 144.0, 143.5, 128.7, 113.6, 112.7, 105.4, 63.0, 31.3, 8.7, 7.2, 7.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{14}N_3O_4S^+$ 356.0707, found 356.0707.

(*R*)-5-Cyclopropyl-10-oxo-2-(pyridin-4-yl)-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8m). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 40 mg of **7m** was converted to 25 mg (65%) of **8m**, isolated as a bright yellow solid; $[\alpha]_D^{25}$ −8 (c 0.18, DMSO); IR (KBr): ν 1637, 1556, 1493, 1443, 1383, 761 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 9.74 (s, 1H), 8.79 (s, 2H), 8.31 (d, J = 5.7 Hz, 2H), 5.66 (d, J = 7.5 Hz, 1H), 3.91–3.84 (m, 1H), 3.65 (d, J = 11.7 Hz, 1H), 1.87 (dd, J = 9.3, 4.0 Hz, 1H), 1.17–1.05 (m, 2H), 0.67 (dd, J = 37.1, 4.2 Hz, 2H); ^{13}C{^{1}H}NMR (100 MHz, DMSO) δ 169.3, 157.9, 157.3, 156.6, 150.6, 145.7, 143.9, 143.6, 130.2, 121.4, 105.3, 63.1, 31.4, 8.7, 7.3, 7.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{15}N_4O_3S^+$ 367.0865, found 367.0868.

(*R*)-2,5-Dicyclopropyl-10-oxo-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8n). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 50 mg of **7n** was converted to 36 mg (75%) of **8n**, isolated as a pale yellow solid; $[\alpha]_D^{25}$ −10 (c 0.25, DMSO); IR (KBr): ν 1736, 1663, 1630, 1589, 1509, 1461, 1406, 1227, 1030 cm^{-1}; ^{1}H NMR (600 MHz, DMSO) δ 13.63 (s, 1H), 9.47 (s, 1H), 5.59 (d, J = 8.6 Hz, 1H), 3.83 (dd, J = 11.7, 8.7 Hz, 1H), 3.60 (d, J = 11.7 Hz, 1H), 2.36–2.31 (m, 1H), 1.89–1.75 (m, 1H), 1.13–1.04 (m, 6H), 0.73–0.51 (m, 2H); ^{13}C {^{1}H} NMR (151 MHz, DMSO) δ 169.4, 167.3, 158.1, 156.0, 143.4, 142.3, 128.2, 105.1, 63.8, 31.2, 18.0, 10.5, 8.7, 7.1, 6.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{16}N_3O_3S^+$ 330.0912, found 330.0908.

(*R*)-2-Cyclohexyl-5-cyclopropyl-10-oxo-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8o). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 30 mg of **7o** was converted to 18 mg (62%) of **8o**, isolated as a pale yellow solid; $[\alpha]_D^{25}$ −6 (c 0.18, DMSO); IR (KBr) ν 3429, 2863, 1752, 1616, 1579, 1554, 1521, 1493, 1466, 1411, 1344, 1218 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 9.56 (s, 1H), 5.58 (d, J = 8.2 Hz, 1H), 3.81 (dd, J = 11.7, 8.7 Hz, 1H), 3.60 (d, J = 11.7 Hz, 1H), 2.94 (dd, J = 9.2, 5.8 Hz, 1H), 1.96 (d, J = 11.7 Hz, 2H), 1.82 (dd, J = 7.3, 4.6 Hz, 3H), 1.74–1.54 (m, 3H), 1.47–1.35 (m, 2H), 1.32–1.23 (m, 1H), 1.13–1.02 (m, 2H), 0.69–0.54 (m, 2H); ^{13}C {^{1}H}NMR (100 MHz, DMSO) δ 169.7, 169.4, 158.2, 155.9, 143.4, 143.1, 128.5, 104.9, 63.1, 46.5, 31.6, 31.5, 31.3, 25.7, 8.7, 7.1, 6.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{22}N_3O_3S^+$ 372.1376, found 372.1378.

(*R*)-5-Cyclopropyl-10-oxo-2-propyl-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8p). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 30 mg of **7p** was converted to 12 mg (42%) of **8p**, isolated as a pale yellow solid; $[\alpha]_D^{25}$ −8 (c 0.26, DMSO); IR (KBr) ν 1748, 1665, 1600, 1491, 1219 cm^{-1}; ^{1}H NMR (600 MHz, DMSO) δ 9.54 (s, 1H), 5.57 (d, J = 8.3 Hz, 1H), 3.81 (dd, J = 11.5, 8.8 Hz, 1H), 3.60 (d, J = 11.6 Hz, 1H), 2.96 (t, J = 7.5 Hz, 2H), 1.84–1.80 (m, 3H), 1.09–1.04 (m, 2H), 0.93 (d, J = 7.4 Hz, 3H), 0.63–0.57 (m, 2H); ^{13}C{^{1}H} NMR (151 MHz, DMSO) δ 169.4, 166.4, 163.1, 158.2, 155.8, 143.4, 128.4, 104.9, 63.1, 40.4, 31.4, 21.5, 13.7, 8.7, 7.1, 6.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{18}N_3O_3S^+$ 332.1063, found 332.1054.

(*R*)-2-(4-Nitrophenyl)-10-oxo-5-phenyl-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8q). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 50 mg of **7q** was converted to 34 mg (70%) of **8q**, isolated as a yellow solid; $[\alpha]_D^{25}$ −37 (c 0.24, DMSO); IR (KBr): ν 1646, 1523, 1501, 1438, 1375, 1342, 1222 cm^{-1}; ^{1}H NMR (600 MHz, DMSO) δ 8.94 (s, 1H), 8.67 (dd, J = 8.8, 2.0 Hz, 2H), 8.43–8.41 (m, 2H), 7.58 (t, J = 7.7 Hz, 3H), 7.52 (t, J = 7.4 Hz, 2H), 5.75 (d, J = 8.4 Hz, 1H), 3.90–3.87 (m, 1H), 3.64 (d, J = 11.6 Hz, 1H); ^{13}C {^{1}H}NMR

(151 MHz, DMSO) δ 169.1, 157.7, 157.4, 156.2, 148.8, 145.2, 143.5, 142.5, 133.5, 130.1, 129.3, 128.8, 128.7, 128.6, 124.2, 107.3, 64.0, 31.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{15}N_4O_5S^+$ 447.0758, found 447.0748.

(*R*)-2-(Naphthalen-2-yl)-10-oxo-5-phenyl-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8r). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 50 mg of **7r** was converted to 35 mg (72%) of **8r**, isolated as a bright yellow solid; $[\alpha]_D^{25}$ −11 (*c* 0.22, DMSO); IR (KBr): ν 1736, 1642, 1585, 1512, 1494, 1437, 1383, 1219, 1194 cm^{-1}; ^1H NMR (600 MHz, DMSO) δ 13.84 (s, 1H), 9.02 (s, 1H), 8.92 (s, 1H), 8.56 (dd, J = 8.7, 1.3 Hz, 1H), 8.13 (d, J = 7.5 Hz, 1H), 8.09 (d, J = 8.7 Hz, 1H), 7.98 (d, J = 7.6 Hz, 1H), 7.61–7.58 (m, 5H), 7.52 (t, J = 7.4 Hz, 2H), 5.78 (d, J = 8.5 Hz, 1H), 3.91–3.88 (m, 1H), 3.63 (d, J = 8.0 Hz, 1H); ^{13}C $\{^1H\}$NMR (151 MHz, DMSO) δ 169.3, 159.6, 158.0, 156.0, 143.6, 143.5, 134.2, 133.6, 133.0, 130.1, 129.3, 129.1, 128.7, 128.4, 128.0, 127.7, 126.5, 126.7, 124.6, 107.5, 63.7, 31.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{18}N_3O_3S^+$ 452.1063, found 452.1061.

(*R*)-5-Methoxy-10-oxo-2-phenyl-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8s). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 30 mg of **7s** was converted to 14 mg (49%) of **8s**, isolated as a yellow solid; $[\alpha]_D^{25}$ −253 (*c* 0.15, DMSO); IR (KBr): ν 1745, 1638, 1562, 1509, 1459, 1422, 1308, 1218 cm^{-1}; ^1H NMR (600 MHz, DMSO) δ 9.44 (s, 1H), 8.48 (dd, J = 7.8, 1.6 Hz, 2H), 7.59–7.56 (m, 3H), 5.66 (d, J = 7.9 Hz, 1H), 3.95–3.92 (m, 1H), 3.85 (s, 3H), 3.72 (dd, J = 11.6, 0.9 Hz, 1H); ^{13}C $\{^1H\}$NMR (151 MHz, DMSO) δ 169.2, 160.0, 157.3, 153.5, 143.6, 136.8, 136.6, 131.0, 129.1, 128.9, 127.7, 124.9, 63.4, 61.0, 32.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{14}N_3O_4S^+$ 356.0705, found 356.0702.

(*R*)-5-Methoxy-2-(4-nitrophenyl)-10-oxo-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8t). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 50 mg of **7t** was converted to 28 mg (58%) of **8t**, isolated as a bright yellow solid; $[\alpha]_D^{25}$ −36 (*c* 0.39, DMSO); IR (KBr): ν 1748, 1649, 1631, 1524, 1504, 1339, 1220 cm^{-1}; ^1H NMR (600 MHz, DMSO) δ 9.50 (s, 1H), 8.70 (d, J = 9.0 Hz, 2H), 8.44 (d, J = 9.0 Hz, 2H), 5.56 (d, J = 7.7 Hz, 1H), 3.92–3.87 (m, 1H), 3.85 (s, 3H), 3.74 (d, J = 11.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO) δ 168.6, 157.6, 157.1, 153.7, 153.6, 148.7, 143.4, 142.7, 137.8, 128.8, 125.5, 124.2, 64.5, 61.0, 32.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{13}N_4O_6S^+$ 401.0556, found 401.0549.

(*R*)-2-(2,4-Difluorophenyl)-5-methoxy-10-oxo-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8u). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 40 mg of **7u** was converted to 22 mg (57%) of **8u**, isolated as a light yellow solid; $[\alpha]_D^{25}$ −76 (*c* 0.33, DMSO); IR (KBr): ν 1746, 1636, 1507, 1457, 1422, 1328, 1218 cm^{-1}; ^1H NMR (600 MHz, DMSO) δ 9.46 (s, 1H), 8.18 (dd, J = 8.8, 6.9 Hz, 1H), 7.44 (td, J = 9.3, 4.8 Hz, 1H), 7.30 (td, J = 8.4, 2.3 Hz, 1H), 5.62 (d, J = 7.9 Hz, 1H), 3.92 (dd, J = 11.5, 8.5 Hz, 1H), 3.85 (s, 3H), 3.74–3.72 (m, 1H); $^{13}C\{^1H\}$NMR (151 MHz, DMSO) δ 168.9, 163.1 (dd, J = 250.3, 11.9 Hz), 160.9 (dd, J = 257.7, 12.6 Hz), 157.8, 157.1, 153.4, 143.4, 136.5, 133.3 (d, J = 10.2 Hz), 128.8, 124.8, 122.6 (dd, J = 9.5, 3.6 Hz), 112.0 (dd, J = 21.4, 3.6 Hz), 105.3 (d, J = 26.2 Hz), 63.7, 61.0, 32.2; ^{19}F $\{^1H\}$NMR (356 MHz, DMSO) δ −108.6 to −108.9 (m), −109.2 (dd, J = 19.3, 9.5 Hz); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{12}F_2N_3O_4S^+$ 392.0511, found 392.0506.

(*R*)-5-Methoxy-10-oxo-2-(p-tolyl)-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8v). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 20 mg of **7v** was converted to 10 mg (52%) of **8v**, isolated as a light yellow solid; $[\alpha]_D^{25}$ −33 (*c* 0.42, DMSO); IR (KBr): ν 1744, 1631, 1507, 1458, 1422, 1328, 1219 cm^{-1}; ^1H NMR (600 MHz, DMSO) δ 9.40 (s, 1H), 8.37 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 5.55 (d, J = 7.7 Hz, 1H), 3.87 (d, J = 8.4 Hz, 1H), 3.84 (s, 3H), 3.71 (d, J = 11.3 Hz, 1H), 2.40 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO) δ 168.9, 159.9, 157.3, 153.3, 143.6, 140.8, 135.6, 134.2, 129.5, 128.8, 127.7, 124.6, 64.3, 60.9, 32.5, 21.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{16}N_3O_4S^+$ 370.0856, found 370.0853.

(*R*)-5-Methoxy-2-(4-methoxyphenyl)-10-oxo-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8w). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 30 mg of **7w** was converted to 21 mg (73%) of **8w**, isolated as a yellow solid; $[\alpha]_D^{25}$ −16 (*c* 0.40, DMSO); IR (KBr): ν 1736, 1645, 1505, 1460, 1431, 1373, 1253 cm^{-1}; ^1H NMR (600 MHz, DMSO) δ 9.37 (s, 1H), 8.42 (d, J = 8.9 Hz, 2H), 7.12 (d, J = 9.0 Hz, 2H), 5.57 (d, J = 8.0 Hz, 1H), 3.90–3.87 (m, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.70 (d, J = 11.4 Hz, 1H); ^{13}C $\{^1H\}$NMR (151 MHz, DMSO) δ 168.8, 161.7, 159.8, 157.4, 153.3, 143.6, 135.0, 129.5, 129.4, 129.0, 124.3, 114.3, 63.8, 60.9, 55.4, 32.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{16}N_3O_5S^+$ 386.0805, found 386.0798.

(*R*)-2-(4-Nitrophenyl)-10-oxo-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8x). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 35 mg of **7x** was converted to 21 mg (62%) of **8x**, isolated as a yellow solid; $[\alpha]_D^{25}$ −24 (*c* 0.29, DMSO); IR (KBr): ν 1748, 1671, 1587, 1523, 1436, 1348 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 9.38 (s, 1H), 8.66 (d, J = 8.8 Hz, 2H), 8.41 (d, J = 8.8 Hz, 2H), 6.81 (s, 1H), 5.65 (d, J = 8.0 Hz, 1H), 3.96 (dd, J = 11.7, 8.6 Hz, 1H), 3.71 (d, J = 11.8 Hz, 1H); ^{13}C $\{^1H\}$NMR (100 MHz, DMSO) δ 169.1, 158.4, 158.3, 157.5, 148.7, 145.9, 142.8, 142.7, 130.0, 129.6, 128.7, 124.1, 94.3, 63.1, 32.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{11}N_4O_5S^+$ 371.0445, found 371.0451.

(*R*)-2-(4-Nitrophenyl)-10-oxo-5-(3-(trifluoromethyl)phenyl)-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic

acid (8y). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 30 mg of **7y** was converted to 15 mg (52%) of **8y**, isolated as a bright yellow solid; $[\alpha]_D^{25}$ −213 (*c* 0.15, DMSO); IR (KBr): ν 1753, 1679, 1639, 1524, 1502, 1445, 1341, 1169 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 8.96 (s, 1H), 8.68 (d, *J* = 8.9 Hz, 2H), 8.44 (d, *J* = 8.9 Hz, 2H), 7.88 (dd, *J* = 25.2, 7.3 Hz, 4H), 5.80 (d, *J* = 8.2 Hz, 1H), 3.93 (d, *J* = 2.5 Hz, 1H), 3.68 (d, *J* = 11.3 Hz, 1H); $^{13}C\{^1H\}$NMR (100 MHz, DMSO) δ 169.1, 157.8, 157.6, 156.1, 148.8, 145.7, 143.5, 142.4, 134.7, 134.6, 129.6 (dd, *J* = 52.4, 21.4 Hz), 128.8, 128.5, 126.8, 125.5 (dd, *J* = 18.3, 3.5 Hz), 124.2, 122.7, 106.1, 63.8, 31.7; ^{19}F $\{^1H\}$NMR (376 MHz, DMSO) δ −61.0 to −61.1 (m); HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{14}F_3N_4O_5S^+$ 515.0632, found 515.0634.

(*R*)-5-(4-Fluorophenyl)-2-(4-nitrophenyl)-10-oxo-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8z). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 25 mg of **7z** was converted to 15 mg (62%) of **8z**, isolated as a light yellow solid; $[\alpha]_D^{25}$ −72 (*c* 0.18, DMSO); IR (KBr): ν 1739, 1650, 1605, 1580, 1526, 1509, 1489, 1339, 1221, 734 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 8.94 (s, 1H), 8.67 (d, *J* = 8.8 Hz, 2H), 8.43 (d, *J* = 8.8 Hz, 2H), 7.54 (s, 2H), 7.42 (t, *J* = 8.8 Hz, 2H), 5.78 (d, *J* = 7.9 Hz, 1H), 3.93–3.88 (m, 1H), 3.66 (d, *J* = 11.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO) δ 169.1, 163.4, 160.9, 157.6 (d, *J* = 28.6 Hz), 156.3, 149.8, 145.4, 143.5, 142.5, 132.5 (d, *J* = 8.7 Hz), 129.8 (d, *J* = 9.5 Hz), 128.8, 128.7, 124.2, 116.3 (d, *J* = 21.7 Hz), 106.4, 63.9, 31.6; $^{19}F\{^1H\}$NMR (376 MHz, DMSO) δ −112.6; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{14}FN_4O_5S^+$ 465.0663, found 465.0666.

(*R*)-2,5-Bis(4-nitrophenyl)-10-oxo-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8aa). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 30 mg of **7aa** was converted to 19 mg (65%) of **8aa**, isolated as a dark yellow solid; $[\alpha]_D^{25}$ −23 (*c* 0.22, DMSO); IR (KBr): ν 1752, 1677, 1635, 1601, 1520, 1441, 1345 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 9.03 (s, 1H), 8.69 (d, *J* = 8.9 Hz, 2H), 8.45–8.42 (m, 4H), 7.83 (d, *J* = 6.6 Hz, 2H), 5.79 (d, *J* = 7.9 Hz, 1H), 3.96–3.91 (m, 1H), 3.70 (d, *J* = 11.2 Hz, 1H); $^{13}C\{^1H\}$NMR (100 MHz, DMSO) δ 169.0, 157.7, 156.2, 148.8, 147.3, 145.9, 143.5, 142.4, 140.6, 131.8, 128.8, 128.7, 128.2, 124.4, 124.2, 105.7, 64.0, 31.9; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{14}N_5O_7S^+$ 492.0608, found 492.0604.

(*R*)-5-(4-(Methylsulfonyl)phenyl)-2-(4-nitrophenyl)-10-oxo-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8ab). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 30 mg of **7ab** was converted to 14 mg (48%) of **8ab**, isolated as a yellow solid; $[\alpha]_D^{25}$ −13 (*c* 0.20, DMSO); IR (KBr): ν 1752, 1681, 1634, 1521, 1501, 1440, 1342, 1150 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 9.00 (s, 1H), 8.69 (d, *J* = 8.8 Hz, 2H), 8.44 (d, *J* = 8.9 Hz, 2H), 8.13 (d, *J* = 8.7 Hz, 2H), 7.65–7.60 (m, 2H), 5.81 (d, *J* = 7.9 Hz, 1H), 3.94 (dd, *J* = 11.7, 8.7 Hz, 1H), 3.70 (d, *J* = 11.1 Hz, 1H), 3.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO) δ 169.1, 157.7, 156.2, 148.8, 145.6, 143.5, 142.4, 140.8, 138.7, 132.1, 131.5, 131.3, 128.8, 127.9, 124.2, 106.1, 64.8, 43.4, 31.7; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{17}N_4O_7S_2^+$ 525.0533, found 525.0525.

(*R*)-5-(Benzo[*d*][1,3]dioxol-5-yl)-2-(4-nitrophenyl)-10-oxo-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8ac). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 35 mg of **7ac** was converted to 17 mg (50%) of **8ac**, isolated as a bright yellow solid; $[\alpha]_D^{25}$ −102 (*c* 0.16, DMSO); IR (KBr): ν 1751, 1680, 1649, 1567, 1339, 1230 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 9.00 (s, 1H), 8.68 (d, *J* = 8.9 Hz, 2H), 8.43 (d, *J* = 8.9 Hz, 2H), 7.03 (dd, *J* = 58.6, 25.1 Hz, 3H), 6.15 (s, 2H), 5.77 (d, *J* = 8.3 Hz, 1H), 3.89 (s, 1H), 3.64 (d, *J* = 11.5 Hz, 1H); $^{13}C\{^1H\}$NMR (100 MHz, DMSO) δ 169.2, 157.7, 157.4, 156.5, 148.7, 147.9, 147.6, 145.2, 143.4, 142.5, 142.4, 128.9, 128.7, 124.2, 123.9, 110.4, 109.0, 107.1, 101.5, 63.8, 31.4; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{15}N_4O_7S^+$ 491.0656, found 491.0646.

(*R*)-2-(4-Nitrophenyl)-10-oxo-5-(thiophen-3-yl)-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (8ad). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 30 mg of **7ad** was converted to 20 mg (69%) of (**8ad**), isolated as a bright yellow solid; $[\alpha]_D^{25}$ −16 (*c* 0.33, DMSO); IR (KBr): ν 1752, 1680, 1632, 1529, 1443, 1258 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 9.06 (s, 1H), 8.68 (d, *J* = 8.9 Hz, 2H), 8.42 (d, *J* = 8.9 Hz, 2H), 7.85–7.74 (m, 2H), 7.32 (d, *J* = 4.8 Hz, 1H), 5.68 (d, *J* = 8.3 Hz, 1H), 3.88–3.83 (m, 1H), 3.64 (s, 1H); $^{13}C\{^1H\}$NMR (151 MHz, DMSO) δ 168.9, 157.7, 157.4, 156.4, 148.8, 145.8, 143.4, 142.5, 133.2, 129.0, 128.8, 128.6, 127.6, 126.7, 124.2, 102.5, 64.6, 31.8; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{13}N_4O_5S_2^+$ 453.0322, found 453.0324.

(*R*)-5-Cyclopropyl-2-(4-nitrophenyl)-10-oxo-4-phenyl-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido [3,4-*d*]pyrimidine-8-carboxylic acid (11a). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 25 mg of **10a** was converted to 22 mg (90%) of **11a**, isolated as a dark yellow solid; $[\alpha]_D^{25}$ −128 (*c* 0.28, DMSO); IR (KBr): ν 1746, 1678, 1339, 1565, 1525, 1503, 1431, 1343, 1219 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 8.78–8.63 (m, 2H), 8.50–8.34 (m, 2H), 7.81–7.67 (m, 2H), 7.62–7.45 (m, 3H), 5.71 (dd, *J* = 8.7, 1.8 Hz, 1H), 3.91 (dd, *J* = 11.8, 8.8 Hz, 1H), 3.65 (dd, *J* = 11.8, 1.8 Hz, 1H), 1.24 (dd, *J* = 13.1, 6.9 Hz, 1H), 0.32–0.16 (m, 2H), 0.15–0.03 (m, 2H); $^{13}C\{^1H\}$NMR (100 MHz, DMSO) δ 169.3, 164.8, 157.7, 155.7, 148.6, 148.1, 145.4, 142.5, 140.4, 129.6, 129.5, 128.7, 128.6, 127.8, 124.1, 105.9, 63.6, 31.3, 15.0, 9.9, 9.6; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{19}N_4O_5S^+$ 487.1076, found 487.1084.

(*R*)-2-(4-Cyanophenyl)-5-cyclopropyl-10-oxo-4-phenyl-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-car-

boxylic acid (11b). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 25 mg of **10b** was converted to 21 mg (87%) of (**11b**), isolated as a dark yellow solid; $[\alpha]_D^{25}$ −115 (*c* 0.26, DMSO); IR (KBr): ν 2226, 1752, 1665, 1590, 1553, 1457, 1441, 1216, 1180, 749 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 8.61 (d, *J* = 8.4 Hz, 2H), 8.02 (d, *J* = 8.4 Hz, 2H), 7.73 (dd, *J* = 5.0, 2.2 Hz, 2H), 7.52 (d, *J* = 5.5 Hz, 3H), 5.70 (d, *J* = 8.7 Hz, 1H), 3.91 (dd, *J* = 11.7, 8.9 Hz, 1H), 3.64 (d, *J* = 11.7 Hz, 1H), 1.28–1.18 (m, 1H), 0.32–0.13 (m, 2H), 0.09 (d, *J* = 4.8 Hz, 2H); $^{13}C\{^1H\}$NMR (100 MHz, DMSO) δ 169.3, 164.7, 157.8, 156.0, 147.7, 145.4, 140.8, 140.4, 132.8, 129.6, 129.5, 128.5, 128.2, 127.8, 118.7, 112.7, 105.9, 63.5, 31.2, 15.0, 9.9, 9.6; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{19}N_4O_3S^+$ 467.1172, found 467.1168.

(*R*)-5-Cyclopropyl-2-(4-fluorophenyl)-10-oxo-4-phenyl-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (11c). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 25 mg of **10c** was converted to 14 mg (58%) of **11c**, isolated as a dark yellow solid; $[\alpha]_D^{25}$ −8 (*c* 0.26, DMSO); IR (KBr): ν 1748, 1672, 1638, 1574, 1484, 1428, 1235, 1221, 1151 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 8.53 (dd, *J* = 9.0, 5.7 Hz, 2H), 7.75 (dd, *J* = 6.5, 2.8 Hz, 2H), 7.53 (dd, *J* = 5.1, 1.8 Hz, 3H), 7.40 (t, *J* = 8.9 Hz, 2H), 5.67 (dd, *J* = 8.7, 1.7 Hz, 1H), 3.89 (dd, *J* = 11.8, 8.7 Hz, 1H), 3.63 (dd, *J* = 11.8, 1.8 Hz, 1H), 1.24 (td, *J* = 7.8, 4.0 Hz, 1H), 0.30–0.16 (m, 2H), 0.15–0.10 (m, 2H); $^{13}C\{^1H\}$NMR (100 MHz, DMSO) δ 169.3, 165.1, 164.6, 162.6, 157.9, 156.9, 146.6, 145.5, 140.6, 133.2, (d, *J* = 2.8 Hz), 130.1 (d, *J* = 8.9 Hz), 129.5, 127.8, 127.2, 115.8 (d, *J* = 21.9 Hz), 105.7, 63.6, 31.2, 15.1, 9.9, 9.6; ^{19}F $\{^1H\}$NMR (376 MHz, DMSO) δ −110.4; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{19}FN_3O_3S^+$ 460.1131, found 460.1138.

(*R*)-5-Cyclopropyl-10-oxo-4-phenyl-2-(p-tolyl)-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (11d). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 25 mg of **10d** was converted to 18 mg (74%) of **11d**, isolated as a dark yellow solid; $[\alpha]_D^{25}$ −16 (*c* 0.32, DMSO); IR (KBr): ν 1748, 1674, 1574, 1535, 1499, 1482, 1427, 1217 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 8.39 (d, *J* = 8.2 Hz, 2H), 7.74 (dd, *J* = 6.5, 2.9 Hz, 2H), 7.56–7.51 (m, 3H), 7.38 (d, *J* = 8.1 Hz, 2H), 5.61 (d, *J* = 8.0 Hz, 1H), 3.85 (dd, *J* = 11.4, 8.8 Hz, 1H), 3.62 (dd, *J* = 11.6, 1.5 Hz, 1H), 2.40 (s, 3H), 1.22 (dd, *J* = 12.3, 6.6 Hz, 1H), 0.28–0.15 (m, 2H), 0.12 (dd, *J* = 8.7, 3.4 Hz, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO) δ 169.2, 164.4, 158.0, 157.8, 146.4, 145.6, 140.8, 140.5, 134.0, 129.5, 129.4, 129.3, 127.7, 127.7, 127.6, 105.6, 64.0, 31.5, 21.1, 15.0, 9.9, 9.6; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{22}N_3O_3S^+$ 456.1382, found 456.1387.

(*R*)-2-(Benzo[*d*][1,3]dioxol-5-yl)-5-cyclopropyl-10-oxo-4-phenyl-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (11e). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 25 mg of **10e** was converted to 14 mg (58%) of **11e**, isolated as a dark yellow solid; $[\alpha]_D^{25}$ −13 (*c* 0.30, DMSO); IR (KBr): ν 1752, 1663, 1592, 1459, 1221, 1130 cm^{-1}; ^1H NMR (600 MHz, DMSO) δ 8.09 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.91 (d, *J* = 1.5 Hz, 1H), 7.78–7.62 (m, 2H), 7.52–7.50 (m, 3H), 7.09 (d, *J* = 8.2 Hz, 1H), 6.13 (s, 2H), 5.52 (d, *J* = 7.5 Hz, 1H), 3.80 (d, *J* = 8.8 Hz, 1H), 3.62 (d, *J* = 10.5 Hz, 1H), 1.23–1.19 (m, 1H), 0.22–0.19 (m, 2H), 0.16–0.07 (m, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO) δ 168.9, 164.1, 157.9, 157.1, 149.5, 147.9, 145.6, 140.8, 131.1, 129.5, 129.3, 127.7, 127.4, 124.2, 122.6, 108.5, 107.2, 105.1, 101.7, 63.1, 31.9, 15.0, 9.9, 9.7; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{20}N_3O_5S^+$ 486.1118, found 486.1123.

(*R*)-5-Cyclopropyl-10-oxo-2,4-diphenyl-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (11f). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 25 mg of **10f** was converted to 17 mg (70%) of **11f**, isolated as a dark yellow solid; $[\alpha]_D^{25}$ −15 (*c* 0.19, DMSO); IR (KBr): ν 1751, 1673, 1574, 1534, 1503, 1427, 1215 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 8.49 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.75 (dd, *J* = 6.4, 2.9 Hz, 2H), 7.58–7.51 (m, 6H), 5.68 (dd, *J* = 8.7, 1.8 Hz, 1H), 3.89 (dd, *J* = 11.8, 8.7 Hz, 1H), 3.63 (dd, *J* = 11.8, 1.8 Hz, 1H), 1.27–1.21 (m, 1H), 0.21 (ddd, *J* = 11.3, 10.0, 5.2 Hz, 2H), 0.15–0.08 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO) δ 169.3, 164.6, 158.0, 158.8, 146.8, 145.5, 140.5, 136.6, 130.7, 129.5, 129.4, 128.8, 127.9, 127.8, 127.7, 105.8, 63.4, 31.2, 15.0, 9.9, 9.6; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{20}N_3O_3S^+$ 442.1225, found 442.1234.

(*R*)-5-Cyclopropyl-2-(naphthalen-2-yl)-10-oxo-4-phenyl-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (11g). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 25 mg of **10g** was converted to 16 mg (66%) of **11g**, isolated as a dark yellow solid; $[\alpha]_D^{25}$ −5 (*c* 0.21, DMSO); IR (KBr): ν 1746, 1671, 1631, 1575, 1484, 1426, 1218 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 9.05 (s, 1H), 8.61 (dd, *J* = 8.7, 1.6 Hz, 1H), 8.15 (dd, *J* = 5.7, 3.4 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 1H), 8.02–7.98 (m, 1H), 7.81–7.75 (m, 2H), 7.63–7.59 (m, 2H), 7.55 (dd, *J* = 6.2, 2.7 Hz, 3H), 5.73–5.63 (m, 1H), 3.89 (dd, *J* = 11.6, 8.7 Hz, 1H), 3.64 (dd, *J* = 11.7, 1.6 Hz, 1H), 1.28–1.22(m, 1H), 0.30–0.18 (m, 2H), 0.16–0.11 (m, 2H); $^{13}C\{^1H\}$NMR (151 MHz, DMSO) δ 169.3, 164.6, 158.0, 157.7, 146.7, 145.6, 140.7, 134.2, 134.1, 132.8, 129.6, 129.5, 129.0, 128.3, 127.0, 127.8, 127.7, 126.8, 124.8, 105.8, 63.8, 31.3, 15.1, 9.9, 9.6; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{22}N_3O_3S^+$ 492.1382, found 492.1384.

(*R*)-5-Cyclopropyl-10-oxo-4-phenyl-2-(thiophen-3-yl)-7,8-dihydro-10*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (11h). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 25 mg of **10h** was converted to 15 mg (62%) of **11h**, isolated as

a dark yellow solid; $[\alpha]_D^{25}$ −4 (*c* 0.25, DMSO); IR (KBr): ν 1750, 1670, 1573, 1533, 1481, 1438, 1218 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 8.42 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.88 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.69 (ddd, *J* = 8.1, 5.6, 2.3 Hz, 3H), 7.52 (dd, *J* = 5.1, 1.8 Hz, 3H), 5.66 (dd, *J* = 8.6, 1.7 Hz, 1H), 3.88 (s, 1H), 3.62 (dd, *J* = 11.8, 1.8 Hz, 1H), 1.26–1.19 (m, 1H), 0.25–0.13 (m, 2H), 0.14–0.06 (m, 2H); $^{13}C\{^1H\}$NMR (100 MHz, DMSO) δ 169.4, 164.5, 157.9, 155.7, 146.1, 145.5, 140.7, 140.6, 129.5, 129.4, 128.2, 127.8, 127.5, 127.4, 127.1, 105.8, 63.5, 31.9, 15.0, 9.9, 9.6; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{18}N_3O_3S_2^+$ 448.0784, found 448.0791.

(*R*)-5-Cyclopropyl-2-(naphthalen-1-yl)-10-oxo-4-phenyl-7,8-dihydro-10*H* thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (11i). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 30 mg of **10i** was converted to 20 mg (69%) of **11i**, isolated as a bright yellow solid; $[\alpha]_D^{25}$ −9 (*c* 0.23, DMSO); IR (KBr): ν 1744, 1663, 1642, 1571, 1534, 1499, 1354, 1294, 778 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 9.00–8.89 (m, 1H), 8.28 (dd, *J* = 7.2, 1.1 Hz, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 8.06–8.01 (m, 1H), 7.75 (dd, *J* = 6.6, 2.9 Hz, 2H), 7.70–7.65 (m, 1H), 7.59 (dd, *J* = 6.9, 3.0 Hz, 2H), 7.54–7.48 (m, 3H), 5.64 (d, *J* = 7.4 Hz, 1H), 3.87 (dd, *J* = 11.6, 8.7 Hz, 1H), 3.64 (dd, *J* = 11.6, 1.5 Hz, 1H), 1.25 (dd, *J* = 13.5, 7.0 Hz, 1H), 0.28–0.11 (m, 4H); $^{13}C\{^1H\}$NMR (100 MHz, DMSO) δ 169.2, 164.2, 159.9, 158.0, 147.2, 145.3, 140.7, 134.5, 133.7, 130.6, 130.5, 129.5, 129.4, 128.5, 127.8, 127.3, 126.1, 126.0, 125.3, 105.4, 64.1, 31.6, 15.0, 9.9, 9.7; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{22}N_3O_3S^+$ 492.1376, found 492.1380.

General procedure for synthesis of 2-substituted quinazolines (13a–d). A solution of 2-aminobenzylamines (0.34 mmol, 1.0 equiv.), aldehydes (0.51 mmol, 1.5 equiv.) in CH_3CN (2 mL) was stirred at 80 °C until the condensation was found complete by TLC analysis (about 2 h). To the same solution was then added $K_2S_2O_8$ (1.02 mmol, 3.0 equiv.), and the mixture was stirred at 80 °C for 12 hours more under O_2 atmosphere (balloon). After completion of the reaction (monitored by TLC), the mixture was diluted with DCM (5 mL), washed with brine (3 mL), dried, over anhydrous sodium sulfate, filtered, and evaporated. The resulting residue was purified by silica gel column chromatography to give the desired product. The identity and purity of the product was confirmed by ^1H and ^{13}C NMR spectroscopic analysis.

2-(4-Nitrophenyl)quinazoline (13a).[37] The product was prepared by following the general procedure and purified by automated flash column chromatography (25 g SNAP Cartridge) eluting with 0–30% ethyl acetate in heptane, and 42 mg of **12** was converted to 73 mg (85%) of **13a**, isolated as a brown solid; IR (KBr): ν 1618, 1605, 1584, 1554, 1346 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 8.82 (d, *J* = 8.9 Hz, 2H), 8.37 (d, *J* = 8.9 Hz, 2H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.97 (dd, *J* = 12.6, 4.3 Hz, 2H), 7.73–7.68 (m, 1H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 160.8, 158.9, 150.7, 149.4, 143.8, 134.9, 129.6, 129.0, 128.5, 127.4, 124.0, 123.9; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{10}N_3O_2^+$ 252.0777, found 252.0777.

2-(Benzo[*d*][1,3]dioxol-5-yl)quinazoline (13b).[38] The product was prepared by following the general procedure and purified by automated flash column chromatography (25 g SNAP Cartridge) eluting with 0–30% ethyl acetate in heptane, and 42 mg of **12** was converted to 44 mg (52%) of **13b**, isolated as a yellow solid; IR (KBr): ν 1678, 1617, 1568, 1453, 1277 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.23 (dd, *J* = 8.2, 1.7 Hz, 1H), 8.11 (d, *J* = 1.7 Hz, 1H), 8.05–7.99 (m, 1H), 7.91–7.84 (m, 2H), 7.57 (td, *J* = 7.3, 1.0 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.05 (s, 2H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 160.7, 160.5, 150.9, 150.0, 148.3, 134.2, 132.7, 128.6, 127.2, 127.1, 123.7, 123.5, 108.9, 108.5, 101.6; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{11}N_2O_2^+$ 251.0821, found 251.0821.

2-(Naphthalen-2-yl)quinazoline (13c).[39] The product was prepared by following the general procedure and purified by automated flash column chromatography (25 g SNAP Cartridge) eluting with 0–30% ethyl acetate in heptane, and 42 mg of **12** was converted to 72 mg (83%) of **13c**, isolated as a white solid; IR (KBr): ν 1619, 1598, 1566, 1476, 1409 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.44 (s, 1H), 9.17 (s, 1H), 8.76 (dd, *J* = 8.6, 1.6 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 8.05 (dd, *J* = 7.8, 4.6 Hz, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.92–7.88 (m, 1H), 7.87–7.82 (m, 2H), 7.55–7.50 (m, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 160.9, 160.5, 150.8, 135.4, 134.7, 134.2, 133.5, 129.3, 129.0, 128.6, 128.3, 127.8, 127.3, 126.3, 125.5, 123.6; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{13}N_2^+$ 257.1079, found 257.1081.

2-(Furan-2-yl)quinazoline (13d).[37] The product was prepared by following the general procedure and purified by automated flash column chromatography (25 g SNAP Cartridge) eluting with 0–30% ethyl acetate in heptane, and 42 mg of **12** was converted to 51 mg (77%) of **13d**, isolated as a yellow solid; IR (KBr): ν 1617, 1589, 1582, 1497, 1339 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.01(d, *J* = 9.2 Hz, 1H), 7.80 (ddd, *J* = 12.4, 7.0, 3.5 Hz, 2H), 7.64–7.62 (m, 1H), 7.48 (ddd, *J* = 8.0, 7.0, 0.9 Hz, 1H), 7.39 (dd, *J* = 2.8, 0.8 Hz, 1H), 6.54 (dd, *J* = 3.6, 1.6 Hz, 1H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 160.7, 154.0, 152.5, 150.3, 145.3, 134.5, 128.3, 127.2, 123.3, 114.1, 112.3; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{12}H_9N_2O^+$ 197.0715, found 197.0718.

(*R*)-5-Cyclopropyl-2-(4-nitrophenyl)-10-oxo-2,3,4,7,8,10-hexahydro-1*H*-thiazolo[3′,2′:1,6]pyrido[3,4-*d*]pyrimidine-8-carboxylic acid (14a). The compound was prepared by following general procedure and purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), 25 mg of **14** was converted to 8 mg (33%) of **14a**, isolated as a yellow solid; $[\alpha]_D^{25}$ −81 (*c* 0.21, DMSO); IR (KBr): ν 1722, 1642, 1587, 1509, 1498, 1448, 1422, 1400, 1249 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 8.22 (dd, *J* = 8.7, 6.0 Hz, 2H), 7.69 (dd, *J* = 16.0, 8.7 Hz, 2H), 5.71 (dd, *J* = 52.1, 3.1 Hz, 1H), 5.42 (d, *J* = 8.6 Hz, 1H), 5.30 (dd, *J* = 23.4, 2.9 Hz, 1H), 3.91 (dd, *J* = 17.6, 10.4 Hz, 1H), 3.73–3.67 (m, 1H), 3.52 (d, *J* = 16.5 Hz, 1H), 3.46 (d, *J* = 11.9 Hz, 2H), 1.57–1.41 (m, 1H), 0.77 (dd, *J* = 8.0, 2.0 Hz, 2H), 0.54–0.28 (m, 2H); $^{13}C\{^1H\}$NMR (100 MHz, DMSO) δ 169.8, 155.2, 150.6, 146.8, 130.1, 128.9, 128.4, 124.5, 123.3, 110.6, 65.6, 62.6, 54.1, 31.3, 9.9, 6.8, 6.4; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{19}N_4O_5S^+$ 415.1076, found 415.1077.

(*R*)-10-Cyclopropyl-7-(naphthalen-2-yl)-5-oxo-9-phenyl-2,3-dihydro-5*H*-thiazolo[2,3-*g*][1,7]naphthyridine-3-carboxylic acid (15a). (*R*)-Methyl 6-amino-8-cyclopropyl-5-oxo-3,5-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (100 mg, 0.4 mmol) was used to prepare (*R*)-methyl 10-cyclopropyl-7-(naphthalen-2-yl)-5-oxo-9-phenyl-2,3-dihydro-5*H*-thiazolo[2,3-*g*][1,7]naphthyridine-3-carboxylate (105 mg, 55%) according to the general procedure described earlier.[23] The product was purified by automated flash column chromatography (25 g SNAP Cartridge) eluting with 0–80% ethyl acetate in heptane, isolated as a dark yellow solid. 30 mg of the methyl ester was hydrolysed as described,[23] purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), to give the title compound (18 mg, 62%) isolated as a bright yellow solid; $[\alpha]_D^{25}$ −29 (*c* 0.13, DMSO); IR (KBr): ν 1744, 1670, 1586, 1556, 1511, 1487, 1469, 1440, 1255, 804 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 8.84 (s, 1H), 8.47 (dd, *J* = 8.7, 1.7 Hz, 1H), 8.26 (s, 1H), 8.08–8.05 (m, 2H), 7.99–7.96 (m, 1H), 7.59–7.47 (m, 7H), 5.65 (dd, *J* = 8.7, 1.9 Hz, 1H), 4.00–3.66 (m, 1H), 3.58 (dd, *J* = 11.7, 1.9 Hz, 1H), 1.14 (dd, *J* = 9.4, 4.0 Hz, 1H), 0.21–0.08 (m, 4H); $^{13}C\{^1H\}$NMR (100 MHz, DMSO) δ 169.6, 158.4, 152.4, 147.0, 145.4, 141.2, 140.6, 135.1, 133.4, 133.1, 132.4, 129.3, 128.7, 127.8, 127.6, 126.9, 126.7, 126.6, 126.3, 126.0, 124.5, 63.3, 31.1, 15.7, 10.5, 10.4; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{24}N_3O_3S^+$ 491.1424, found 491.1423.

(*R*)-10-Cyclopropyl-7-(naphthalen-1-yl)-5-oxo-9-phenyl-2,3-dihydro-5*H*-thiazolo[2,3-*g*][1,7]naphthyridine-3-carboxylic acid (15b). (*R*)-Methyl 6-amino-8-cyclopropyl-5-oxo-3,5-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (100 mg, 0.4 mmol) was used to prepare(*R*)-methyl 10-cyclopropyl-7-(naphthalen-1-yl)-5-oxo-9-phenyl-2,3-dihydro-5*H*-thiazolo[2,3-*g*][1,7]naphthyridine-3-carboxylate (108 mg, 57%) according to the general procedure described earlier.[23] The product was purified by automated flash column chromatography (25 g SNAP Cartridge) eluting with 0–80% ethyl acetate in heptane, isolated as a dark yellow solid. 30 mg of the methyl ester was hydrolysed as described,[23] purified with preparative HPLC (30–100% MeCN in water + 0.75% HCOOH; gradient in 40 min, 100% for 10 min), to give the title compound (22 mg, 75%) isolated as a bright yellow solid; $[\alpha]_D^{25}$ −25 (*c* 0.15, DMSO); IR (KBr): ν 1743, 1671, 1649, 1631, 1586, 1555, 1511, 1487, 1453, 804 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 13.58 (s, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 8.03 (t, *J* = 7.2 Hz, 2H), 7.82–7.71 (m, 2H), 7.65–7.60 (m, 1H), 7.59–7.47 (m, 4H), 7.47–7.38 (m, 3H), 5.66 (dd, *J* = 8.5, 1.5 Hz, 1H), 3.88 (dd, *J* = 11.7, 8.7 Hz, 1H), 3.59 (dd, *J* = 11.7, 1.5 Hz, 1H), 1.17 (dd, *J* = 9.4, 3.8 Hz, 1H), 0.23–0.01 (m, 4H); $^{13}C\{^1H\}$NMR (100 MHz, DMSO) δ 170.2, 158.9, 155.4, 147.0, 146.0, 141.5, 141.0, 137.2, 134.4, 132.5, 131.1, 130.1, 129.6, 128.8, 128.4, 127.2, 126.5, 126.0, 125.9, 107.2, 63.8, 31.6, 16.2, 11.0, 10.8; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{24}N_3O_3S^+$ 491.1424, found 491.1423.

Conflicts of interest

F.A. has ownership interests in Quretech Bio AB. Other authors have no competing financial interest.

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