Synthesis of Tricyclic Lactams from Heterocyclic Imines

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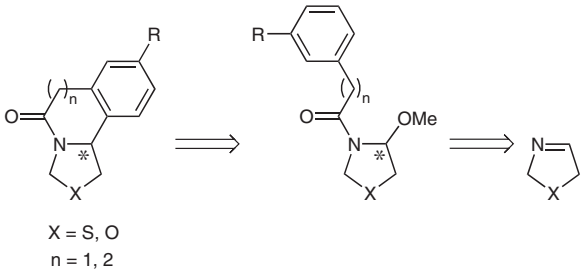
Abstract: Starting from different heterocyclic imines, a large number of annulated tricyclic lactams were prepared in a two-step synthesis. First, methoxyamides with a phenyl ring in α- or β-position were generated. Finally, these substrates were converted to valero- and caprolactams, respectively, via intramolecular Friedel–Crafts cyclization in the presence of a Lewis acid. Additionally, effects of substituent groups at the phenyl ring in the electrophilic aromatic substitution were investigated.

Key words: heterocycles, imines, amides, lactams, cyclization, electrophilic aromatic substitution



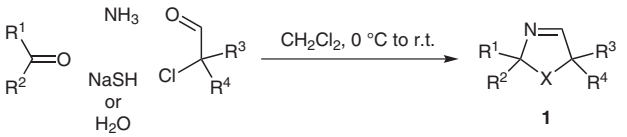
Scheme 1 Retrosynthetic consideration of the target structure

Lactam systems are popular and widely used substructures due to their multifaceted possible uses.[1] In view of their prevalence in biologically active compounds,[2–6] the development of methods to prepare these molecules is still in the focus of many investigations.[7] Based on these facts a range of synthetic routes were published.[8] Apart from that, articles dealing with a general access starting from imines, especially from cyclic imines, are extremely seldom, whereas syntheses of β-lactams are well studied.[9] On the other hand, synthetic routes involving several kinds of reactive *N*-acyliminium ions, which often play a dominant role in the environment of imines, are well known.[10] However, some of these methods feature several disadvantages such as harsh reaction conditions, costly and sensitive reagents, or long reaction times.[10]

Thus, cyclic imines are suitable starting materials for such a targeted synthetic pathway generating different types of new lactam structures due to their reactive C=N bond in the ring. In the recent past, we often took advantage of this property to form lactam structures.[11] In combination with the addition of acyl chlorides, which was previously established in our group,[12] an array of tricyclic lactams with an annulated phenyl ring based on cyclic imines was available in only two steps (Scheme 1). The lactamization was completed by means of a Lewis acid as part of an intramolecular Friedel–Crafts cyclization. Bearing the isoquinoline skeleton, the target structures could attract a great deal of attention in the pharmacological field. Similar isoquinoline derivatives are known as receptor agonist[13] or anticonvulsant agent.[14]

Due to the high pharmacological activity of their corresponding amines, 2,5-dihydrothiazoles and -oxazoles were selected as applicable starting materials.[15] In this context, a large number of different substituents at the five-membered imine were investigated and offer the possibility to examine their effects in consecutive reactions.

The new two-step reaction sequence for preparing different classes of lactams is based on heterocyclic imines. The known precursor compounds **1**, 2,5-dihydrothiazoles and 2,5-dihydrooxazole, were synthesized by a modified Asinger protocol in a multicomponent reaction.[16,17] Choosing an α-chloroaldehyde, a second variable carbonyl compound, ammonia, and sodium hydrosulfide or water in dichloromethane, the monocyclic imines **1** were obtained in a one-pot reaction in good yields (up to 73%) (Scheme 2).



Scheme 2 Synthesis of 2,5-dihydrothiazoles and 2,5-dihydrooxazole **1** (R^1–R^4 = alkyl; X = S, O)[16,17]

In the first step of the described synthesis, the imines **1** were treated with acyl chlorides, which are characterized by a phenyl ring in the α- or β-position (Scheme 3). The substitution pattern at the phenyl ring was selected considering directing effects on the aromatic substitution in the last step. Without isolation of the resulting hydrolysis-sensitive chloroamides, addition of methanol in the presence of triethylamine led to the racemic methoxyamides **2** and **3**.

The described procedure affords the desired methoxyamides **2** and **3** in good to excellent yields of up to 99% after workup by column chromatography (Table 1). It should be noted in particular that the amides **2i** and **3b**, which belong to the class of oxazolidines, resulted in higher yields than the corresponding thiazolidine compounds **2c** and **3a**,

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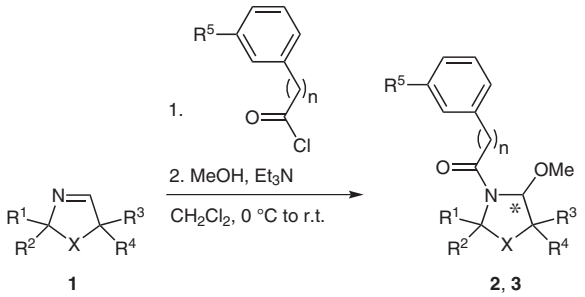
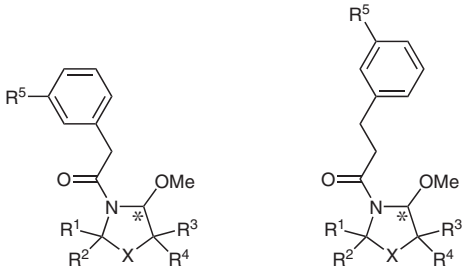


Scheme 3 Synthesis of the methoxyamides **2** and **3** starting from the heterocyclic imines **1** (R^1–R^4 = alkyl; R^5 = H, Me, OMe; n = 1, 2) (yields are given in Table 1)

respectively. Concerning the substituent at the phenyl ring, the best result was achieved with the unsubstituted substrate (i.e., **2a**, 99%). Apart from that, a significant dependence of the yields on the substituents at the phenyl ring, the five-membered imine ring, or on the chain length of the acyl group cannot be noticed.

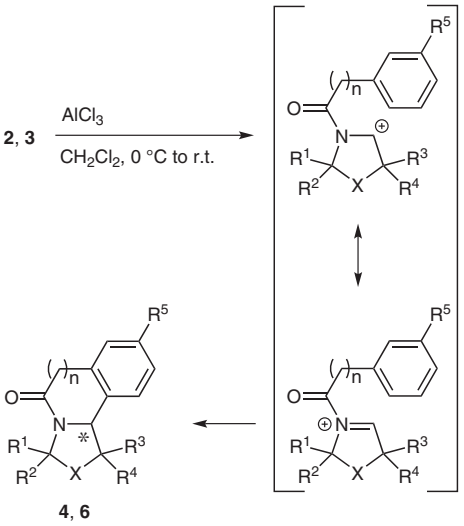
Table 1 Methoxyamides **2** and **3**



Entry	Imine	Amide	X	R^1	R^2	R^3	R^4	R^5	Yield (%)[a]
1	**1a**	**2a**	S	Me	Me	Me	Me	H	99
2	**1a**	**2b**	S	Me	Me	Me	Me	Me	49
3	**1a**	**2c**	S	Me	Me	Me	Me	OMe	61
4	**1b**	**2d**	S	–$(CH_2)_5$–		Me	Me	Me	65
5	**1b**	**2e**	S	–$(CH_2)_5$–		Me	Me	OMe	38
6	**1c**	**2f**	S	Me	Me	–$(CH_2)_5$–		OMe	72
7	**1d**	**2g**	S	–$(CH_2)_5$–		–$(CH_2)_5$–		Me	67
8	**1d**	**2h**	S	–$(CH_2)_5$–		–$(CH_2)_5$–		OMe	24
9	**1e**	**2i**	O	Me	Me	Me	Me	OMe	67
10	**1a**	**3a**	S	Me	Me	Me	Me	OMe	53
11	**1e**	**3b**	O	Me	Me	Me	Me	OMe	88

[a] Isolated yields.

The next step of the synthetic strategy towards tricyclic lactams was initiated by treating the methoxyamides **2** and **3** with the Lewis acid aluminum trichloride (Scheme 4). By elimination of the methoxy group, reactive *N*-acyliminium ions were generated. These intermediates are predestined to react with an aromatic compound.[10] In this manner, the methoxyamides were successfully converted to the six-membered valerolactams **4** in an intramolecular Friedel–Crafts cyclization. To extend the utility and to establish the diversity of this strategy, the procedure was also applied exemplary to the synthesis of the seven-membered caprolactams **6**.

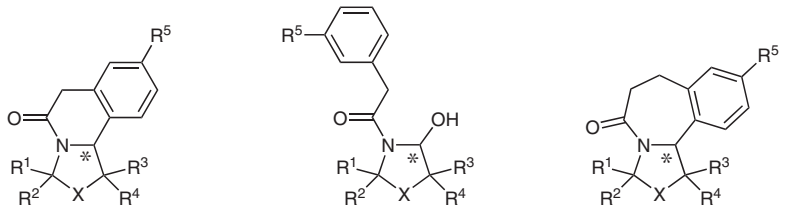


Scheme 4 Synthesis of the lactams **4** and **6** starting from the methoxyamides **2** and **3** (R^1–R^4 = alkyl; R^5 = H, Me, OMe; n = 1, 2) (yields are given in Table 2)

Following this synthetic route, the racemic lactams **4** and **6** resulted predominantly in high yields (up to ~100%) after workup by column chromatography in several cases (Table 2). It is worth mentioning that the lactams **4c**, **4e**, **4i**, and **6a** were obtained in pure form without any further purification. Unlike in the synthesis of all other lactams, we failed to obtain a good yield of the valerolactam **4d** (8%).

Analysis of all the crude products by ^{1}H NMR spectroscopy showed a single regioisomer of valero- and caprolactams **4** and **6**. Due to steric hindrance, the substitution occurs only in the para position of the mentioned groups. These assumptions are based on the interpretation of the NMR data of **4** and **6** and are verified by the X-ray crystal structure determination of **4i** (see below). As known, methyl and methoxy groups increase the rate of reaction due to their donating electron inductive and resonance effect, respectively. The conversion of the substrates **2c**, **2e**, and **2h** with a methoxy group at the phenyl ring provided correspondingly higher yields (up to ~100%) in comparison with the compounds **2b**, **2d**, and **2g** (up to 38%) containing a methyl group at the phenyl ring. Based on this knowledge, an activated aromatic compound (R^5 = OMe) was systematically chosen in the case of the methoxyamides **3** to achieve high yields. This goal was easily accomplished with the excellent yields of 94% (i.e., **6a**) and ~100% (i.e., **6b**).

Table 2 Lactams **4**, **6**, and Hydroxyamides **5**



4 **5** **6**

Entry	Amide	Lactam	X	R^1	R^2	R^3	R^4	R^5	Yield (%)[a]
1	**2a**	**4a**	S	Me	Me	Me	Me	H	25 (31)[b]
2	**2b**	**4b**	S	Me	Me	Me	Me	Me	35 (43)[b]
3	**2c**	**4c**	S	Me	Me	Me	Me	OMe	75
4	**2d**	**4d**	S	$-(CH_2)_5-$		Me	Me	Me	8 (35)[b]
5	**2e**	**4e**	S	$-(CH_2)_5-$		Me	Me	OMe	~100
6	**2f**	**4f**	S	Me	Me	$-(CH_2)_5-$		OMe	69
7	**2g**	**4g**	S	$-(CH_2)_5-$		$-(CH_2)_5-$		Me	38 (27)[b]
8	**2h**	**4h**	S	$-(CH_2)_5-$		$-(CH_2)_5-$		OMe	85
9	**2i**	**4i**	O	Me	Me	Me	Me	OMe	97
10	**3a**	**6a**	S	Me	Me	Me	Me	OMe	94
11	**3b**	**6b**	O	Me	Me	Me	Me	OMe	~100

[a] Isolated yields.
[b] Yield of the respective hydroxyamide **5**, which results as a by-product.

Cyclization of the methoxyamides **2a**, **2b**, **2d**, and **2g** led to the hydroxyamides **5** as the by-product. In regard to the discussion above, this fact documents an insufficient activation of the phenyl rings for further substitution. Instead, the reactive *N*-acyliminium ions are quenched with water in the course of the aqueous purification forming the hydroxyamides **5**. This fact gives an adequate explanation for the unsatisfactory yields in the reaction of the lactams **4a**, **4b**, **4d**, and **4g**.

Supplemental to the methoxy group, the methoxyamides **2** and **3** contain additional Lewis basic functional groups, such as an amide group and a sulfide or an ether group. This fact justifies the use of 2.5 equivalents of aluminum trichloride in order to separate the methoxy group completely.

As mentioned above, only a single regioisomer was found in the ^{1}H NMR spectra of the crude lactams **4** and **6**. In the case of the racemic valerolactam **4i**, single crystals could be obtained and the proposed structural features were established by X-ray analysis (Figure 1).

The X-ray crystal structure determination of **4i** verifies the postulated constitution and moreover proves the expected position of the relatively voluminous substituent at the phenyl ring due to steric hindrance. Consequently, the constitution of all other prepared lactams **4** and **6** was assigned by analogy comparing the NMR data with **4i**.

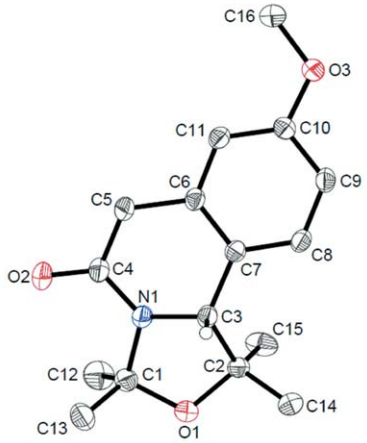


Figure 1 X-ray crystal structure of the racemic valerolactam **4i** (only one enantiomer is shown).[18] The atom-numbering in the X-ray structure does not follow the IUPAC nomenclature.

In conclusion, we have presented a new two-step sequence for the synthesis of different types of lactams starting from the heterocyclic imines **1**. Treating these precursors with an acyl chloride followed by addition of

methanol, the methoxyamides **2** and **3** were obtained in up to quantitative yields. Finally, the desired lactamization was initiated by means of the Lewis acid aluminum trichloride. Via an intramolecular Friedel–Crafts cyclization, the annulated tricyclic valerolactams **4** and caprolactams **6** were obtained in good to excellent yields depending on the influence of the substituent at the phenyl ring. The constitution of the lactams **4** and **6** was clarified by a single-crystal X-ray structure analysis of a selected valerolactam **4**.

Synthetic procedures under argon atmosphere were performed on a vacuum line using standard Schlenk techniques. Preparative column chromatography was carried out using Grace SiO_2 (0.035–0.070 mm, type KG 60). TLC was performed on Merck SiO_2 F254 plates on aluminum sheets. Melting points were obtained on a melting point apparatus of Laboratory Devices and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX R 500 (measuring frequency: ^1H NMR = 500.1 MHz, ^{13}C NMR = 125.8 MHz) or a Bruker Avance III 500 (measuring frequency: ^1H NMR = 499.9 MHz, ^{13}C NMR = 125.7 MHz) spectrometer in $CDCl_3$ solution. As an internal standard, the residual signal was used [7.26 ppm (^1H NMR), 77.16 ppm (^{13}C NMR)].[19] Assignments of the signals were supported by measurements applying DEPT and COSY techniques. The abbreviation n.r. in the ^1H NMR spectral data of **3b** (2 ×) and **4f** (1 ×) denotes not resolved. Mass spectra were obtained on a Finnigan-MAT 95 mass spectrometer with isobutane as the reagent gas. The IR spectra were recorded with a Bruker Tensor 27 spectrometer equipped with a 'Golden Gate' diamond-ATR (attenuated total reflection) unit. 2-Phenylacetyl chloride,[20] 2-(3-methylphenyl)acetyl chloride,[21] 2-(3-methoxyphenyl)acetyl chloride,[22] 2,2,5,5-tetramethyl-2,5-dihydrothiazole (**1a**),[23] 2,2-dimethyl-1-thia-4-azaspiro[4.5]dec-3-ene (**1b**),[24] 2,2-dimethyl-1-thia-3-azaspiro[4.5]dec-3-ene (**1c**),[25] 7-thia-14-azadispiro[5.1.5^8.2^6]pentadec-14-ene (**1d**),[26] and 2,2,5,5-tetramethyl-2,5-dihydro-oxazole (**1e**)[17] were prepared according to published procedures. CH_2Cl_2 was refluxed with CaH_2 and freshly distilled prior to use. MeOH was refluxed with Mg and freshly distilled prior to use. Et_3N was dried over molecular sieves and freshly distilled prior to use.

Methoxyamides 2 and 3; General Procedure A (GP A)

Under argon atmosphere, the respective imine **1** (1 equiv), dissolved in anhyd CH_2Cl_2 (2 mL per mmol imine), was cooled down to 0–5 °C. A solution of the respective acyl chloride (1.1 equiv) in anhyd CH_2Cl_2 (3 mL per mmol imine) was added dropwise. After stirring for 5 h at r.t., a solution of anhyd MeOH (3.7 equiv) and anhyd Et_3N (1.75 equiv) in anhyd CH_2Cl_2 (2 mL per mmol imine) was added dropwise at 0–5 °C. After stirring overnight at r.t., the solution was poured into ice-water (7 mL per mmol imine). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 4 mL per mmol imine). The combined organic phases were washed with sat. aq $NaHCO_3$ (1 × 4 mL per mmol imine), H_2O (1 × 4 mL per mmol imine), and dried ($MgSO_4$). The solvent was removed on a rotary evaporator. The crude product was purified as described below for individual cases.

(*RS*)-1-(4-Methoxy-2,2,5,5-tetramethyl-1,3-thiazolidin-3-yl)-2-phenylethan-1-one (2a)

Following GP A, dihydrothiazole **1a** (320 mg, 2.24 mmol), 2-phenylacetyl chloride (380 mg, 2.46 mmol), anhyd MeOH (261 mg, 330 μL, 8.14 mmol), and anhyd Et_3N (411 mg, 563 μL, 4.07 mmol) were used. The crude product was purified by column chromatography (silica gel; *n*-hexane–MTBE, 4:1); yield: 647 mg (99%); colorless, extremely viscous oil; R_f = 0.24 (*n*-hexane–MTBE, 4:1).

IR (ATR): 2979, 2931, 2827, 1654, 1604, 1584, 1496, 1454, 1387, 1367, 1264, 1210, 1195, 1165, 1140, 1080, 923, 718, 696 cm^{-1}.

^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.04, 1.32, 1.83, 1.91 [4 s, 12 H, 2 × $C(CH_3)_2$], 3.50 (s, 3 H, OCH_3), 3.82 (d, ^2J = 15.8 Hz, 1 H, CH_2), 3.85 (d, ^2J = 15.6 Hz, 1 H, CH_2), 4.87 (s, 1 H, NCH), 7.24–7.26 (m, 3 H, 2 × *o*-CH_{Ar}, *p*-CH_{Ar}), 7.31–7.34 (m, 2 H, *m*-CH_{Ar}).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 23.3, 30.4, 30.9, 31.7 [2 × $C(CH_3)_2$], 44.6 (CH_2), 52.9 [$C(CH_3)_2CH$], 56.1 (OCH_3), 72.6 [$C(CH_3)_2N$], 99.3 (NCH), 127.3 (*p*-CH_{Ar}), 128.9, 128.9 (2 × *o*-CH_{Ar}, 2 × *m*-CH_{Ar}), 134.8 (C_{Ar}), 170.4 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 294.3 (84, $[MH]^+$).

HRMS (CI, isobutane): *m*/*z* calcd for $C_{16}H_{24}NO_2S^+$: 294.1528; found: 294.1526.

(*RS*)-1-(4-Methoxy-2,2,5,5-tetramethyl-1,3-thiazolidin-3-yl)-2-(3-methylphenyl)ethan-1-one (2b)

Following GP A, dihydrothiazole **1a** (286 mg, 2.00 mmol), 2-(3-methylphenyl)acetyl chloride (371 mg, 2.20 mmol), anhyd MeOH (237 mg, 300 μL, 7.40 mmol), and anhyd Et_3N (354 mg, 485 μL, 3.50 mmol) were used. The crude product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 4:1); yield: 300 mg (49%); colorless, extremely viscous oil; R_f = 0.43 (*n*-hexane–EtOAc, 4:1).

IR (ATR): 2981, 2932, 2867, 2828, 1658, 1610, 1592, 1490, 1467, 1449, 1388, 1368, 1270, 1213, 1197, 1167, 1142, 1081, 927, 765, 726, 695 cm^{-1}.

^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.06, 1.33, 1.83, 1.92 [4 s, 12 H, 2 × $C(CH_3)_2$], 2.33 (s, 3 H, $C_{Ar}CH_3$), 3.51 (s, 3 H, OCH_3), 3.78 (d, ^2J = 15.9 Hz, 1 H, CH_2), 3.81 (d, ^2J = 15.7 Hz, 1 H, CH_2), 4.88 (s, 1 H, NCH), 7.03–7.07 (m, 3 H, *p*-CH_{Ar}CH$_2$, *o*-CH_{Ar}CH$_3$, *p*-CH_{Ar}CH$_3$), 7.20–7.23 (m, 1 H, *m*-CH_{Ar}).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 21.5 ($C_{Ar}CH_3$), 23.4, 30.4, 30.9, 31.7, [2 × $C(CH_3)_2$], 44.6 (CH_2), 52.9 [$C(CH_3)_2CH$], 56.1 (OCH_3), 72.6 [$C(CH_3)_2N$], 99.3 (NCH), 126.0, 128.0 (2 × CH_{Ar}), 128.8 (*m*-CH_{Ar}), 129.6 (CH_{Ar}), 134.7 ($C_{Ar}CH_2$), 138.6 ($C_{Ar}CH_3$), 170.6 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 308.3 (100, $[MH]^+$), 276.2 (46, $[MH - CH_4O]^+$).

HRMS (CI, isobutane): *m*/*z* calcd for $C_{17}H_{26}NO_2S^+$: 308.1684; found: 308.1684.

(*RS*)-1-(4-Methoxy-2,2,5,5-tetramethyl-1,3-thiazolidin-3-yl)-2-(3-methoxyphenyl)ethan-1-one (2c)

Following GP A, dihydrothiazole **1a** (280 mg, 1.95 mmol), 2-(3-methoxyphenyl)acetyl chloride (397 mg, 2.15 mmol), anhyd MeOH (231 mg, 292 μL, 7.22 mmol), and anhyd Et_3N (345 mg, 473 μL, 3.41 mmol) were used. The crude product was purified by column chromatography (silica gel; *n*-hexane–MTBE, 7:3); yield: 385 mg (61%); yellow solid; mp 37–38 °C; R_f = 0.32 (*n*-hexane–MTBE, 7:3).

IR (ATR): 3005, 2970, 2932, 2893, 2837, 2820, 1642, 1609, 1584, 1453, 1371, 1252, 1152, 1139, 1085, 925, 765, 720 cm^{-1}.

^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.07, 1.33, 1.84, 1.93 [4 s, 12 H, 2 × $C(CH_3)_2$], 3.51 (s, 3 H, NCHOCH_3), 3.79 (s, 3 H, $C_{Ar}OCH_3$), 3.80, 3.84 (2 d, ^2J = 15.2 Hz, 2 H, CH_2), 4.88 (s, 1 H, NCH), 6.80–6.85 (m, 3 H, *p*-CH_{Ar}CH$_2$, *o*-CH_{Ar}OCH$_3$, *p*-CH_{Ar}OCH$_3$), 7.24–7.28 (m, 1 H, *m*-CH_{Ar}).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 23.3, 30.4, 30.9, 31.6 [2 × $C(CH_3)_2$], 44.7 (CH_2), 52.9 [$C(CH_3)_2CH$], 55.3 ($C_{Ar}OCH_3$), 56.1 (NCHOCH_3), 72.6 [$C(CH_3)_2N$], 99.3 (NCH), 112.7 (*p*-$CH_{Ar}CH_2$), 114.4 (*o*-$CH_{Ar}OCH_3$), 121.2 (*p*-$CH_{Ar}OCH_3$), 129.9 (*m*-CH_{Ar}), 136.3 ($C_{Ar}CH_2$), 160.0 ($C_{Ar}OCH_3$), 170.3 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 324.1 (91, $[MH]^+$), 292.1 (100, $[MH - CH_4O]^+$).

HRMS (CI, isobutane): *m*/*z* calcd for $C_{17}H_{26}NO_3S^+$: 324.1633; found: 324.1640.

(*RS*)-1-(3-Methoxy-2,2-dimethyl-1-thia-4-azaspiro[4.5]decan-4-yl)-2-(3-methylphenyl)ethan-1-one (2d)

Following GP A, dihydrothiazole **1b** (367 mg, 2.00 mmol), 2-(3-methylphenyl)acetyl chloride (371 mg, 2.20 mmol), anhyd MeOH (237 mg, 300 μL, 7.40 mmol), and anhyd Et_3N (354 mg, 485 μL, 3.50 mmol) were used. The crude product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 4:1); yield: 448 mg (65%); colorless solid; mp 100 °C; R_f = 0.49 (*n*-hexane–EtOAc, 4:1).

IR (ATR): 3020, 3007, 2984, 2965, 2926, 2861, 2851, 2821, 1661, 1625, 1609, 1591, 1492, 1464, 1455, 1384, 1366, 1271, 1259, 1244, 1179, 1144, 1086, 920, 778, 758, 720, 695 cm^{-1}.

^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.04 [s, 3 H, $C(CH_3)_2$], 1.12–1.22, 1.27–1.36 (2 m, 2 H, $CH_{2,Cy}$), 1.32 [s, 3 H, $C(CH_3)_2$], 1.51–1.59 (m, 3 H, $CH_{2,Cy}$), 1.67–1.78 (m, 2 H, $CH_{2,Cy}$), 1.87–1.89 (m, 1 H, $CH_{2,Cy}$), 2.32 (s, 3 H, $C_{Ar}CH_3$), 2.75–2.81, 3.17–3.22 (2 m, 2 H, $CH_{2,Cy}$), 3.49 (s, 3 H, OCH_3), 3.78 (d, ^2J = 15.4 Hz, 1 H, CH_2C_{Ar}), 3.81 (d, ^2J = 15.2 Hz, 1 H, CH_2C_{Ar}), 4.91 (s, 1 H, NCH), 7.02–7.06 (m, 3 H, *p*-C$H_{Ar}CH_2$, *o*-C$H_{Ar}CH_2$, *p*-C$H_{Ar}CH_3$), 7.19–7.22 (m, 1 H, *m*-CH_{Ar}).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 21.5 ($C_{Ar}CH_3$), 23.5 [$C(CH_3)_2$], 24.6, 25.1, 25.9 (3 × $CH_{2,Cy}$), 30.4 [$C(CH_3)_2$], 36.7, 38.2 (2 × $CH_{2,Cy}$), 45.2 (CH_2C_{Ar}), 52.0 [$C(CH_3)_2$], 56.1 (OCH_3), 80.2 [$C(CH_{2,Cy})_5$], 99.1 (NCH), 126.0, 127.9 (2 × CH_{Ar}), 128.8 (*m*-CH_{Ar}), 129.7 (CH_{Ar}), 134.8 ($C_{Ar}CH_2$), 138.5 ($C_{Ar}CH_3$), 170.9 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 348.3 (54, $[MH]^+$), 316.3 (100, $[MH - CH_4O]^+$).

HRMS (CI, isobutane): *m*/*z* calcd for $C_{20}H_{30}NO_2S^+$: 348.1997; found: 348.1990.

(*RS*)-1-(3-Methoxy-2,2-dimethyl-1-thia-4-azaspiro[4.5]decan-4-yl)-2-(3-methoxyphenyl)ethan-1-one (2e)

Following GP A, dihydrothiazole **1b** (367 mg, 2.00 mmol), 2-(3-methoxyphenyl)acetyl chloride (406 mg, 2.20 mmol), anhyd MeOH (237 mg, 300 μL, 7.40 mmol), and anhyd Et_3N (354 mg, 485 μL, 3.50 mmol) were used. The crude product was purified by column chromatography (silica gel; *n*-hexane–MTBE, 9:1); yield: 278 mg (38%); colorless, extremely viscous oil; R_f = 0.08 (*n*-hexane–MTBE, 9:1).

IR (ATR): 2930, 2857, 2834, 1654, 1600, 1585, 1491, 1453, 1439, 1386, 1367, 1299, 1254, 1165, 1140, 1083, 1049, 922, 767, 718, 691 cm^{-1}.

^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.03 [s, 3 H, $C(CH_3)_2$], 1.13–1.21, 1.26–1.35 (2 m, 2 H, $CH_{2,Cy}$), 1.31 [s, 3 H, $C(CH_3)_2$], 1.51–1.59 (m, 3 H, $CH_{2,Cy}$), 1.69–1.78 (m, 2 H, $CH_{2,Cy}$), 1.86–1.88, 2.75–2.81, 3.17–3.21 (3 m, 3 H, $CH_{2,Cy}$), 3.49 (s, 3 H, NCHOCH_3), 3.78 (d, ^2J = 15.3 Hz, 1 H, CH_2C_{Ar}), 3.78 (s, 3 H, $C_{Ar}OCH_3$), 3.82 (d, ^2J = 15.3 Hz, 1 H, CH_2C_{Ar}), 4.90 (s, 1 H, NCH), 6.77–6.82 (m, 3 H, *p*-C$H_{Ar}CH_2$, *o*-C$H_{Ar}OCH_3$, *p*-C$H_{Ar}OCH_3$), 7.21–7.24 (m, 1 H, *m*-CH_{Ar}).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 23.5 [$C(CH_3)_2$], 24.6, 25.1, 25.9 (3 × $CH_{2,Cy}$), 30.3 [$C(CH_3)_2$], 36.7, 38.2 (2 × $CH_{2,Cy}$), 45.3 (CH_2C_{Ar}), 52.0 [$C(CH_3)_2$], 55.3 ($C_{Ar}OCH_3$), 56.1 (NCHOCH_3), 80.2 [$C(CH_{2,Cy})_5$], 99.1 (NCH), 112.7 (*p*-$CH_{Ar}CH_2$), 114.5 (*o*-$CH_{Ar}OCH_3$), 121.3 (*p*-$CH_{Ar}OCH_3$), 129.9 (*m*-CH_{Ar}), 136.4 ($C_{Ar}CH_2$), 160.0 ($C_{Ar}OCH_3$), 170.6 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 364.2 (88, $[MH]^+$), 332.2 (100, $[MH - CH_4O]^+$).

HRMS (CI, isobutane): *m*/*z* calcd for $C_{20}H_{30}NO_3S^+$: 364.1946; found: 364.1944.

(*RS*)-1-(4-Methoxy-2,2-dimethyl-1-thia-3-azaspiro[4.5]decan-3-yl)-2-(3-methoxyphenyl)ethan-1-one (2f)

Following GP A, dihydrothiazole **1c** (367 mg, 2.00 mmol), 2-(3-methoxyphenyl)acetyl chloride (406 mg, 2.20 mmol), anhyd MeOH (237 mg, 300 μL, 7.40 mmol), and anhyd Et_3N (354 mg, 485 μL, 3.50 mmol) were used. The crude product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 4:1); yield: 522 mg (72%); colorless solid; mp 45 °C; R_f = 0.33 (*n*-hexane–EtOAc, 4:1).

IR (ATR): 3001, 2971, 2929, 2852, 2834, 1638, 1610, 1583, 1488, 1456, 1435, 1378, 1353, 1282, 1183, 1166, 1148, 1076, 895, 773, 722 cm^{-1}.

^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.07–1.32 (m, 5 H, $CH_{2,Cy}$), 1.41–1.44 (m, 1 H, $CH_{2,Cy}$), 1.51–1.67 (m, 4 H, $CH_{2,Cy}$), 1.84, 1.90 [2 s, 6 H, $C(CH_3)_2$], 3.50 (s, 3 H, NCHOCH_3), 3.80 (d, ^2J = 15.2 Hz, 1 H, CH_2C_{Ar}), 3.80 (s, 3 H, $C_{Ar}OCH_3$), 3.85 (d, ^2J = 15.2 Hz, 1 H, CH_2C_{Ar}), 4.96 (s, 1 H, NCH), 6.81–6.84 (m, 3 H, *p*-C$H_{Ar}CH_2$, *o*-C$H_{Ar}OCH_3$, *p*-C$H_{Ar}OCH_3$), 7.24–7.28 (m, 1 H, *m*-CH_{Ar}).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 22.2, 24.4, 25.6 (3 × $CH_{2,Cy}$), 31.0, 32.1 [$C(CH_3)_2$], 33.2, 37.4 (2 × $CH_{2,Cy}$), 44.5 (CH_2C_{Ar}), 55.3 ($C_{Ar}OCH_3$), 56.0 (NCHOCH_3), 59.1 [$C(CH_{2,Cy})_5$], 71.6 [$C(CH_3)_2$], 98.6 (NCH), 112.7 (*p*-$CH_{Ar}CH_2$), 114.4 (*o*-$CH_{Ar}OCH_3$), 121.2 (*p*-$CH_{Ar}OCH_3$), 129.9 (*m*-CH_{Ar}), 136.3 (C_{Ar} CH_2), 160.0 ($C_{Ar}OCH_3$), 170.5 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 364.4 (99, $[MH]^+$), 332.3 (100, $[MH - CH_4O]^+$).

HRMS (CI, isobutane): *m*/*z* calcd for $C_{20}H_{30}NO_3S^+$: 364.1946; found: 364.1955.

(*RS*)-1-(15-Methoxy-7-thia-14-azadispiro[5.1.5^8.2^6]pentadecan-14-yl)-2-(3-methylphenyl)ethan-1-one (2g)

Following GP A, dihydrothiazole **1d** (447 mg, 2.00 mmol), 2-(3-methylphenyl)acetyl chloride (371 mg, 2.20 mmol), anhyd MeOH (237 mg, 300 μL, 7.40 mmol), and anhyd Et_3N (354 mg, 485 μL, 3.50 mmol) were used. The crude product was purified by column chromatography twice (silica gel; 1. *n*-hexane–EtOAc, 7:3; 2. CH_2Cl_2–*n*-hexane, 4:1); yield: 516 mg (67%); colorless solid; mp 79–82 °C; R_f = 0.73 (*n*-hexane–EtOAc, 7:3).

IR (ATR): 2929, 2856, 1657, 1610, 1591, 1491, 1451, 1372, 1273, 1254, 1179, 1081, 895, 764, 719, 694 cm^{-1}.

^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.04–1.77 (m, 16 H, $CH_{2,Cy}$), 1.87–1.88 (m, 2 H, $CH_{2,Cy}$), 2.32 (s, 3 H, $C_{Ar}CH_3$), 2.74–2.78, 3.16–3.20 (2 m, 2 H, $CH_{2,Cy}$), 3.47 (s, 3 H, OCH_3), 3.79–3.80 (m, 2 H, CH_2C_{Ar}), 4.98 (s, 1 H, NCH), 7.01–7.06 (m, 3 H, *p*-C$H_{Ar}CH_2$, *o*-C$H_{Ar}CH_2$, *p*-C$H_{Ar}CH_3$), 7.19–7.22 (m, 1 H, *m*-CH_{Ar}).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 21.5 ($C_{Ar}CH_3$), 22.2, 24.3, 24.6, 25.0, 25.6, 25.8, 33.3, 37.1, 37.2, 38.2 (10 × $CH_{2,Cy}$), 45.0 (CH_2C_{Ar}), 56.0 (OCH_3), 58.0 [$C(CH_{2,Cy})_5CH$], 79.1 [$C(CH_{2,Cy})_5N$], 98.4 (NCH), 126.0, 127.9 (2 × CH_{Ar}), 128.7 (*m*-CH_{Ar}), 129.7 (CH_{Ar}), 134.8 ($C_{Ar}CH_2$), 138.5 ($C_{Ar}CH_3$), 171.0 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 388.2 (33, $[MH]^+$), 356.2 (100, $[MH - CH_4O]^+$).

HRMS (CI, isobutane): *m*/*z* calcd for $C_{23}H_{34}NO_2S^+$: 388.2310; found: 388.2301.

(*RS*)-1-(15-Methoxy-7-thia-14-azadispiro[5.1.5^8.2^6]pentadecan-14-yl)-2-(3-methoxyphenyl)ethan-1-one (2h)

Following GP A, dihydrothiazole **1d** (447 mg, 2.00 mmol), 2-(3-methoxyphenyl)acetyl chloride (406 mg, 2.20 mmol), anhyd MeOH (237 mg, 300 μL, 7.40 mmol), and anhyd Et_3N (354 mg, 485 μL, 3.50 mmol) were used. The crude product was purified by column chromatography (silica gel; *n*-hexane–MTBE, 9:1); yield: 193 mg (24%); colorless, extremely viscous oil; R_f = 0.08 (*n*-hexane–MTBE, 9:1).

IR (ATR): 2928, 2855, 1653, 1600, 1585, 1491, 1450, 1371, 1300, 1253, 1176, 1149, 1079, 1050, 893, 767, 729, 691 cm^{-1}.

^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.01–1.77 (m, 16 H, $CH_{2,Cy}$), 1.86–1.88 (m, 2 H, $CH_{2,Cy}$), 2.74–2.78, 3.16–3.20 (2 m, 2 H, $CH_{2,Cy}$), 3.47 (s, 3 H, NCHOCH_3), 3.78 (s, 3 H, $C_{Ar}OCH_3$), 3.79 (d, ^2J = 15.2 Hz, 1 H, CH_2C_{Ar}), 3.83 (d, ^2J = 15.3 Hz, 1 H, CH_2C_{Ar}),

4.97 (s, 1 H, NCH), 6.78–6.82 (m, 3 H, *p*-CH_{Ar}CH$_2$, *o*-CH_{Ar}OCH$_3$, *p*-CH_{Ar}OCH$_3$), 7.21–7.24 (m, 1 H, *m*-CH$_{Ar}$).

^{13}C NMR (125.8 MHz, CDCl$_3$): δ = 22.2, 24.4, 24.6, 25.0, 25.6, 25.8, 33.3, 37.1, 37.2, 38.2 (10xCH$_{2,Cy}$), 45.2 (*C*H$_2$C$_{Ar}$), 55.4 (C$_{Ar}$O*C*H$_3$), 56.1 (NCHO*C*H$_3$), 58.0 [*C*(CH$_{2,Cy}$)$_5$CH], 79.2 [*C*(CH$_{2,Cy}$)$_5$N], 98.5 (NCH), 112.7 (*p*-*C*H$_{Ar}$CH$_2$), 114.5 (*o*-*C*H$_{Ar}$OCH$_3$), 121.3 (*p*-*C*H$_{Ar}$OCH$_3$), 129.9 (*m*-CH$_{Ar}$), 136.4 (*C*$_{Ar}$CH$_2$), 160.0 (*C*$_{Ar}$OCH$_3$), 170.6 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 404.5 (24, [MH]$^+$), 372.5 (100, [MH – CH$_4$O]$^+$).

HRMS (CI, isobutane): *m*/*z* calcd for C$_{23}$H$_{34}$NO$_3$S$^+$: 404.2259; found: 404.2263.

(*RS*)-1-(4-Methoxy-2,2,5,5-tetramethyl-1,3-oxazolidin-3-yl)-2-(3-methoxyphenyl)ethan-1-one (2i)

Following GP A, dihydrooxazole **1e** (320 mg, 2.52 mmol), 2-(3-methoxyphenyl)acetyl chloride (511 mg, 2.77 mmol), anhyd MeOH (299 mg, 378 μL, 9.32 mmol), and anhyd Et$_3$N (446 mg, 611 μL, 4.41 mmol) were used. The crude product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 7:3); yield: 518 mg (67%); yellow, extremely viscous oil; R_f = 0.21 (*n*-hexane–EtOAc, 7:3).

IR (ATR): 2982, 2938, 2835, 1660, 1600, 1585, 1491, 1455, 1437, 1392, 1373, 1256, 1196, 1163, 1075, 1049, 1004, 902, 771, 715, 691 cm^{-1}.

^{1}H NMR (500.1 MHz, CDCl$_3$): δ = 1.09, 1.33, 1.59, 1.63 [4 s, 12 H, 2 × C(CH$_3$)$_2$], 3.46 (s, 3 H, NCHOC*H*$_3$), 3.72–3.72 (m, 2 H, CH$_2$), 3.79 (s, 3 H, C$_{Ar}$OCH$_3$), 4.62 (s, 1 H, NCH), 6.79–6.85 (m, 3 H, *p*-C*H*$_{Ar}$CH$_2$, *o*-C*H*$_{Ar}$OCH$_3$, *p*-C*H*$_{Ar}$OCH$_3$), 7.23–7.26 (m, 1 H, *m*-CH$_{Ar}$).

^{13}C NMR (125.8 MHz, CDCl$_3$): δ = 22.9, 27.5, 27.5, 28.0 [2 × C(*C*H$_3$)$_2$], 43.0 (CH$_2$), 55.3 (C$_{Ar}$O*C*H$_3$), 57.0 (NCHO*C*H$_3$), 81.9 [*C*(CH$_3$)$_2$CH], 94.0 (NCH), 95.5 [*C*(CH$_3$)$_2$N], 112.6 (*p*-*C*H$_{Ar}$CH$_2$), 114.6 (*o*-*C*H$_{Ar}$OCH$_3$), 121.3 (*p*-*C*H$_{Ar}$OCH$_3$), 129.8 (*m*-CH$_{Ar}$), 136.3 (CH$_2$*C*$_{Ar}$), 160.0 (*C*$_{Ar}$OCH$_3$), 170.0 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 308.2 (67, [MH]$^+$), 276.2 (100, [MH – CH$_4$O]$^+$).

HRMS (CI, isobutane): *m*/*z* calcd for C$_{17}$H$_{26}$NO$_4^+$: 308.1862; found: 308.1855.

(*RS*)-1-(4-Methoxy-2,2,5,5-tetramethyl-1,3-thiazolidin-3-yl)-3-(3-methoxyphenyl)propan-1-one (3a)

Following GP A, dihydrothiazole **1a** (287 mg, 2.00 mmol), 3-(3-methoxyphenyl)propanoyl chloride (437 mg, 2.20 mmol), anhyd MeOH (237 mg, 300 μL, 7.40 mmol), and anhyd Et$_3$N (354 mg, 485 μL, 3.50 mmol) were used. The crude product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 4:1); yield: 359 mg (53%); colorless, extremely viscous oil; R_f = 0.38 (*n*-hexane–EtOAc, 4:1).

IR (ATR): 2962, 2933, 2865, 2833, 1656, 1601, 1584, 1489, 1465, 1454, 1438, 1388, 1376, 1260, 1165, 1151, 1080, 1051, 919, 779, 697 cm^{-1}.

^{1}H NMR (500.1 MHz, CDCl$_3$): δ = 1.36 [s, 6 H, C(CH$_3$)$_2$], 1.81, 1.91 [2 s, 6 H, C(CH$_3$)$_2$], 2.68–2.79 (m, 2 H, CH$_2$CO), 2.96–2.99 (m, 2 H, CH$_2$C$_{Ar}$), 3.39 (s, 3 H, NCHOC*H*$_3$), 3.78 (s, 3 H, C$_{Ar}$OCH$_3$), 4.82 (s, 1 H, NCH), 6.73–6.76 (m, 2 H, *p*-C*H*$_{Ar}$CH$_2$, *o*-C*H*$_{Ar}$OCH$_3$), 6.79–6.80 (m, 1 H, *p*-C*H*$_{Ar}$OCH$_3$), 7.18–7.21 (m, 1 H, *m*-CH$_{Ar}$).

^{13}C NMR (125.8 MHz, CDCl$_3$): δ = 23.4, 30.8, 30.9 [C(*C*H$_3$)$_2$], 31.7 (*C*H$_2$C$_{Ar}$), 32.1 [C(*C*H$_3$)$_2$], 38.5 (*C*H$_2$CO), 52.7 [*C*(CH$_3$)$_2$CH], 55.3 (C$_{Ar}$O*C*H$_3$), 56.0 (NCHO*C*H$_3$), 72.7 [*C*(CH$_3$)$_2$N], 99.4 (NCH), 111.5 (*p*-*C*H$_{Ar}$CH$_2$), 114.4 (*o*-*C*H$_{Ar}$OCH$_3$), 120.9 (*p*-*C*H$_{Ar}$OCH$_3$), 129.7 (*m*-CH$_{Ar}$), 142.7 (*C*$_{Ar}$CH$_2$), 159.9 (*C*$_{Ar}$OCH$_3$), 171.5 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 338.3 (66, [MH]$^+$), 306.2 (53, [MH – CH$_4$O]$^+$).

HRMS (CI, isobutane): *m*/*z* calcd for C$_{18}$H$_{28}$NO$_3$S$^+$: 338.1790; found: 338.1786.

(*RS*)-1-(4-Methoxy-2,2,5,5-tetramethyl-1,3-oxazolidin-3-yl)-3-(3-methoxyphenyl)propan-1-one (3b)

Following GP A, dihydrooxazole **1e** (254 mg, 2.00 mmol), 3-(3-methoxyphenyl)propanoyl chloride (437 mg, 2.20 mmol), anhyd MeOH (237 mg, 300 μL, 7.40 mmol), and anhyd Et$_3$N (354 mg, 485 μL, 3.50 mmol) were used. The crude product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 7:3); yield: 565 mg (88%); colorless, extremely viscous oil; R_f = 0.32 (*n*-hexane–EtOAc, 7:3).

IR (ATR): 2983, 2937, 2834, 1659, 1602, 1585, 1489, 1454, 1398, 1368, 1259, 1204, 1152, 1076, 1052, 1005, 900, 778, 696 cm^{-1}.

^{1}H NMR (500.1 MHz, CDCl$_3$): δ = 1.16, 1.33, 1.57, 1.61 [4 s, 12 H, 2 × C(CH$_3$)$_2$], 2.66–2.69 (m, 2 H, CH$_2$CO), 2.97–3.02 (m, 2 H, CH$_2$C$_{Ar}$), 3.37 (s, 3 H, NCHOC*H*$_3$), 3.79 (s, 3 H, C$_{Ar}$OCH$_3$), 4.51 (s, 1 H, NCH), 6.75 (dd, ^3J = 8.3 Hz, ^4J = 2.3 Hz, 1 H, *p*-C*H*$_{Ar}$CH$_2$), 6.78 (d, ^4J = n.r., 1 H, *o*-C*H*$_{Ar}$OCH$_3$), 6.82 (d, ^3J = 7.5 Hz, 1 H, *p*-C*H*$_{Ar}$OCH$_3$), 7.21 (dd, ^3J = 7.8 Hz, ^3J = n.r., 1 H, *m*-CH$_{Ar}$).

^{13}C NMR (125.8 MHz, CDCl$_3$): δ = 22.9, 27.7, 27.8, 27.9 [2 × C(*C*H$_3$)$_2$], 31.4 (*C*H$_2$C$_{Ar}$), 37.2 (*C*H$_2$CO), 55.3 (C$_{Ar}$O*C*H$_3$), 56.9 (NCHO*C*H$_3$), 81.8 [*C*(CH$_3$)$_2$CH], 94.2 (NCH), 95.5 [*C*(CH$_3$)$_2$N], 111.6 (*p*-*C*H$_{Ar}$CH$_2$), 114.4 (*o*-*C*H$_{Ar}$OCH$_3$), 120.9 (*p*-*C*H$_{Ar}$OCH$_3$), 129.7 (*m*-CH$_{Ar}$), 142.9 (*C*$_{Ar}$CH$_2$), 159.9 (*C*$_{Ar}$OCH$_3$), 171.0 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 322.4 (66, [MH]$^+$), 290.4 (100, [MH – CH$_4$O]$^+$).

HRMS (CI, isobutane): *m*/*z* calcd for C$_{18}$H$_{28}$NO$_4^+$: 322.2018; found: 322.2010.

Lactams 4 and 6; General Procedure B (GP B)

Under argon atmosphere, the respective methoxyamide (1 equiv), dissolved in anhyd CH$_2$Cl$_2$ (10 mL per mmol amide), was added dropwise to a suspension of AlCl$_3$ (2.5 equiv) in anhyd CH$_2$Cl$_2$ (7 mL per mmol amide) at 0–5 °C. After stirring for 2 h at r.t., the suspension was filtered. The filtrate was stirred overnight and then poured into ice-water (17 mL per mmol imine). The phases were separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 20 mL per mmol imine). The combined organic phases were washed with aq NaOH (2 × 8 mL per mmol amide, 2%), H$_2$O (1 × 8 mL per mmol amide), and dried (MgSO$_4$). The solvent was removed on a rotary evaporator. The crude product was purified as described below for individual cases.

(*RS*)-1,1,3,3-Tetramethyl-6,10b-dihydro-3*H*-[1,3]thiazolo[4,3-*a*]isoquinolin-5-one (4a)

Following GP B, methoxyamide **2a** (94 mg, 0.32 mmol) and AlCl$_3$ (107 mg, 0.80 mmol) were used. The crude product was purified by column chromatography (silica gel; *n*-hexane–MTBE, 7:3); yield: 20 mg (25%); colorless solid; mp 92–94 °C; R_f = 0.28 (*n*-hexane–MTBE, 7:3).

IR (ATR): 3016, 2968, 2927, 2857, 1650, 1590, 1498, 1464, 1421, 1401, 1375, 1362, 1316, 1282, 1190, 1166, 1155, 1127, 760 cm^{-1}.

^{1}H NMR (500.1 MHz, CDCl$_3$): δ = 1.20, 1.65, 1.81, 2.09 [4 s, 12 H, 4 × CH$_3$], 3.56 (dd, ^2J = 20.3 Hz, ^5J = 1.3 Hz, 1 H, CH$_2$), 3.85 (dd, ^2J = 20.3 Hz, ^5J = 2.0 Hz, 1 H, CH$_2$), 4.98–4.99 (m, 1 H, NCH), 7.13–7.15 (m, 1 H, *o*-C*H*$_{Ar}$CH$_2$), 7.23–7.30 (m, 2 H, *p*-C*H*$_{Ar}$CH$_2$, *p*-C*H*$_{Ar}$CH), 7.34–7.36 (m, 1 H, *o*-C*H*$_{Ar}$CH).

^{13}C NMR (125.8 MHz, CDCl$_3$): δ = 25.3, 26.6, 30.4, 32.2 (4 × CH$_3$), 38.7 (CH$_2$), 54.4 [*C*(CH$_3$)$_2$CH], 69.4 [*C*(CH$_3$)$_2$N], 72.7 (NCH), 125.8 (*o*-*C*H$_{Ar}$CH), 126.5 (CH$_{Ar}$), 127.8 (*o*-*C*H$_{Ar}$CH$_2$), 128.1 (CH$_{Ar}$), 130.0 (*C*$_{Ar}$CH), 132.4 (*C*$_{Ar}$CH$_2$), 167.1 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 262.3 (100, [MH]$^+$).

HRMS (CI, isobutane): *m*/*z* calcd for C$_{15}$H$_{20}$NOS$^+$: 262.1266; found: 262.1262.

(*RS*)-1-(4-Hydroxy-2,2,5,5-tetramethyl-1,3-thiazolidin-3-yl)-2-phenylethan-1-one (5a)
By-product of **4a**; yield: 29 mg (31%); colorless solid; mp 127–128 °C; R_f = 0.13 (*n*-hexane–MTBE, 7:3).

IR (ATR): 3394, 2976, 2929, 1640, 1604, 1498, 1467, 1445, 1423, 1376, 1269, 1204, 1162, 1140, 1120, 1063, 745, 714, 697 cm^{-1}.

^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.24, 1.31, 1.87, 1.95 (4 s, 12 H, 4 × CH_3), 2.94 (d, ^3J = 11.7 Hz, 1 H, OH), 3.86, 3.90 (2 d, ^2J = 15.3 Hz, 2 H, CH_2), 5.11 (d, ^3J = 11.5 Hz, 1 H, NCH), 7.28–7.29 (m, 3 H, 2 × *o*-CH_{Ar}, *p*-CH_{Ar}), 7.34–7.37 (m, 2 H, 2 × *m*-CH_{Ar}).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 23.9, 29.5, 31.3, 31.9 (4 × CH_3), 44.3 (CH_2), 53.4 [$C(CH_3)_2CH$], 72.2 [$C(CH_3)_2N$], 92.4 (NCH), 127.1 (*p*-CH_{Ar}), 128.8, 128.9 (2 × *o*-CH_{Ar}, 2 × *m*-CH_{Ar}), 135.0 (C_{Ar}), 170.7 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 280.3 (95, $[MH]^+$), 262.3 (100, $[MH - H_2O]^+$).

HRMS (CI, isobutane): *m*/*z* calcd for $C_{15}H_{22}NO_2S^+$: 280.1371; found: 280.1375.

(*RS*)-1,1,3,3,8-Pentamethyl-6,10b-dihydro-3*H*-[1,3]thiazolo[4,3-*a*]isoquinolin-5-one (4b)
Following GP B, methoxyamide **2b** (80 mg, 0.26 mmol) and $AlCl_3$ (87 mg, 0.65 mmol) were used. Analysis of the crude product by ^1H NMR spectroscopy showed a single regioisomer. The crude product was purified by column chromatography (silica gel; *n*-hexane–MTBE, 7:3); yield: 26 mg (35%); colorless solid; mp 157–160 °C; R_f = 0.30 (*n*-hexane–MTBE, 7:3).

IR (ATR): 2990, 2966, 2945, 2923, 2862, 1639, 1581, 1506, 1461, 1399, 1373, 1357, 1278, 1193, 1162, 1125, 944, 834, 787 cm^{-1}.

^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.19, 1.64, 1.80, 2.08 [4 s, 12 H, 2 × $C(CH_3)_2$], 2.33 (s, 3 H, $C_{Ar}CH_3$), 3.49–3.53 (m, 1 H, CH_2), 3.78–3.82 (m, 1 H, CH_2), 4.95–4.96 (m, 1 H, NCH), 6.94–6.95 (m, 1 H, *o*-$CH_{Ar}CH_2$), 7.04–7.06 (m, 1 H, *p*-$CH_{Ar}CH_2$), 7.23 (d, ^3J = 8.0 Hz, 1 H, *o*-$CH_{Ar}CH$).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 21.1 ($C_{Ar}CH_3$), 25.2, 26.6, 30.4, 32.2 [2 × $C(CH_3)_2$], 38.7 (CH_2), 54.3 [$C(CH_3)_2CH$], 69.4 [$C(CH_3)_2N$], 72.6 (NCH), 125.6 (*o*-$CH_{Ar}CH$), 127.1 ($C_{Ar}CH$), 127.4 (*p*-$CH_{Ar}CH_2$), 128.2 (*o*-$CH_{Ar}CH_2$), 132.3 ($C_{Ar}CH_2$), 137.9 ($C_{Ar}CH_3$), 167.1 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 276.3 (100, $[MH]^+$).

HRMS (CI, isobutane): *m*/*z* calcd for $C_{16}H_{22}NOS^+$: 276.1422; found: 276.1430.

(*RS*)-1-(4-Hydroxy-2,2,5,5-tetramethyl-1,3-thiazolidin-3-yl)-2-(3-methylphenyl)ethan-1-one (5b)
By-product of **4b**; yield: 32 mg (43%); yellow solid; mp 117–119 °C; R_f = 0.15 (*n*-hexane–MTBE, 7:3).

IR (ATR): 3417, 2998, 2980, 2963, 2929, 2868, 1639, 1611, 1593, 1491, 1466, 1445, 1374, 1270, 1246, 1205, 1163, 1141, 1118, 1060, 884, 766, 722 cm^{-1}.

^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.24, 1.30, 1.85, 1.93 [4 s, 12 H, 2 × $C(CH_3)_2$], 2.33 (s, 3 H, $C_{Ar}CH_3$), 2.83 (d, ^3J = 11.8 Hz, 1 H, OH), 3.80, 3.85 (2 d, ^2J = 15.3 Hz, 2 H, CH_2), 5.10 (d, ^3J = 11.7 Hz, 1 H, NCH), 7.05–7.08 (m, 3 H, *p*-$CH_{Ar}CH_2$, *o*-$CH_{Ar}CH_2$, *p*-$CH_{Ar}CH_3$), 7.20–7.23 (m, 1 H, *m*-CH_{Ar}).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 21.5 ($C_{Ar}CH_3$), 23.9, 29.6, 31.3, 31.9 [2 × $C(CH_3)_2$], 44.2 (CH_2), 53.4 [$C(CH_3)_2CH$], 72.2 [$C(CH_3)_2N$], 92.4 (NCH), 125.8, 127.9 (2 × CH_{Ar}), 128.8 (*m*-CH_{Ar}), 129.6 (CH_{Ar}), 134.9 ($C_{Ar}CH_2$), 138.6 ($C_{Ar}CH_3$), 170.8 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 294.3 (22, $[MH]^+$).

HRMS (CI, isobutane): *m*/*z* calcd for $C_{16}H_{24}NO_2S^+$: 294.1528; found: 294.1525.

(*RS*)-8-Methoxy-1,1,3,3-tetramethyl-6,10b-dihydro-3*H*-[1,3]thiazolo[4,3-*a*]isoquinolin-5-one (4c)
Following GP B, methoxyamide **2c** (102 mg, 0.32 mmol) and $AlCl_3$ (107 mg, 0.80 mmol) were used. Analysis of the crude product by ^1H NMR spectroscopy showed a single regioisomer. Purification was not necessary; yield: 70 mg (75%); yellow solid; mp 139–140 °C.

IR (ATR): 3015, 2964, 2917, 2856, 2827, 1652, 1612, 1508, 1464, 1444, 1427, 1401, 1293, 1256, 1247, 1224, 1157, 1031, 833, 793 cm^{-1}.

^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.18, 1.62, 1.80, 2.07 [4 s, 12 H, 2 × $C(CH_3)_2$], 3.52 (dd, ^2J = 20.4 Hz, ^5J = 1.3 Hz, 1 H, CH_2), 3.80 (s, 3 H, OCH_3), 3.80–3.84 (m, 1 H, CH_2), 4.92–4.93 (m, 1 H, NCH), 6.62 (d, ^4J = 2.3 Hz, 1 H, *o*-$CH_{Ar}CH_2$), 6.80 (dd, ^3J = 8.7 Hz, ^4J = 2.5 Hz, 1 H, *p*-$CH_{Ar}CH_2$), 7.25 (d, ^3J = 8.9 Hz, 1 H, *m*-$CH_{Ar}OCH_3$).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 25.1, 26.6, 30.4, 32.2 [2 × $C(CH_3)_2$], 38.9 (CH_2), 54.3 [$C(CH_3)_2CH$], 55.4 (OCH_3), 69.4 [$C(CH_3)_2N$], 72.3 (NCH), 111.6 (*o*-$CH_{Ar}CH_2$), 113.3 (*p*-$CH_{Ar}CH_2$), 122.3 ($C_{Ar}CH$), 127.0 (*m*-$CH_{Ar}OCH_3$), 133.9 ($C_{Ar}CH_2$), 159.2 ($C_{Ar}OCH_3$), 167.0 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 292.2 (100, $[MH]^+$).

HRMS (CI, isobutane): *m*/*z* calcd for $C_{16}H_{22}NO_2S^+$: 292.1371; found: 292.1364.

(*RS*)-1′,1′,8′-Trimethyl-6′,10b′-dihydrospiro[cyclohexane-1,3′-thiazolo[4,3-*a*]isoquinolin]-5′-one (4d)
Following GP B, methoxyamide **2d** (90 mg, 0.26 mmol) and $AlCl_3$ (87 mg, 0.65 mmol) were used. Analysis of the crude product by ^1H NMR spectroscopy showed a single regioisomer. The crude product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 4:1); yield: 5 mg (8%); yellow, extremely viscous oil; R_f = 0.41 (*n*-hexane–EtOAc, 4:1).

IR (ATR): 2925, 2855, 1656, 1510, 1459, 1447, 1428, 1404, 1290, 1128, 904, 823, 784 cm^{-1}.

^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.15 [s, 3 H, $C(CH_3)_2$], 1.24–1.31 (m, 1 H, $CH_{2,Cy}$), 1.38–1.55 (m, 2 H, $CH_{2,Cy}$), 1.60–1.64 (m, 1 H, $CH_{2,Cy}$), 1.63 [s, 3 H, $C(CH_3)_2$], 1.75–1.87 (m, 3 H, $CH_{2,Cy}$), 1.98–2.00 (m, 1 H, $CH_{2,Cy}$), 2.33 (s, 3 H, $C_{Ar}CH_3$), 2.36–2.42, 3.45–3.51 (2 m, 2 H, $CH_{2,Cy}$), 3.50–3.54 (m, 1 H, CH_2C_{Ar}), 3.82 (dd, ^2J = 20.2 Hz, ^5J = 2.2 Hz, 1 H, CH_2C_{Ar}), 4.93–4.94 (m, 1 H, NCH), 6.94–6.95 (m, 1 H, *o*-$CH_{Ar}CH_2$), 7.04–7.05 (m, 1 H, *p*-$CH_{Ar}CH_2$), 7.21 (d, ^3J = 8.0 Hz, 1 H, *o*-$CH_{Ar}CH$).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 21.1 ($C_{Ar}CH_3$), 24.1, 24.8 (2 × $CH_{2,Cy}$), 25.2 [$C(CH_3)_2$], 26.1 ($CH_{2,Cy}$), 26.7 [$C(CH_3)_2$], 37.6, 38.1 (2 × $CH_{2,Cy}$), 39.3 (CH_2C_{Ar}), 53.1 [$C(CH_3)_2$], 72.4 (NCH), 77.0 [$C(CH_{2,Cy})_5$], 125.7 (*o*-$CH_{Ar}CH$), 127.2 ($C_{Ar}CH$), 127.4 (*p*-$CH_{Ar}CH_2$), 128.1 (*o*-$CH_{Ar}CH_2$), 132.1 ($C_{Ar}CH_2$), 137.9 ($C_{Ar}CH_3$), 167.4 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 316.3 (100, $[MH]^+$).

HRMS (CI, isobutane): *m*/*z* calcd for $C_{19}H_{26}NOS^+$: 316.1735; found: 316.1738.

(*RS*)-1-(3-Hydroxy-2,2-dimethyl-1-thia-4-azaspiro[4.5]decan-4-yl)-2-(3-methylphenyl)ethan-1-one (5d)
By-product of **4d**; yield: 31 mg (35%); colorless solid; mp 98–100 °C; R_f = 0.21 (*n*-hexane–EtOAc, 4:1).

IR (ATR): 3269, 3014, 2984, 2926, 2858, 1625, 1607, 1589, 1487, 1448, 1404, 1373, 1180, 1167, 1154, 1134, 1077, 767, 720, 691 cm^{-1}.

^1H NMR (499.9 MHz, $CDCl_3$): δ = 1.20 [s, 3 H, $C(CH_3)_2$], 1.17–1.28 (m, 2 H, $CH_{2,Cy}$), 1.29 [s, 3 H, $C(CH_3)_2$], 1.54–1.78 (m, 6 H, $CH_{2,Cy}$), 2.32 (s, 3 H, $C_{Ar}CH_3$), 2.85 (d, ^3J = 11.7 Hz, 1 H, OH), 3.00–3.12 (m, 2 H, $CH_{2,Cy}$), 3.80 (d, ^2J = 15.4 Hz, 1 H, CH_2C_{Ar}), 3.84 (d, ^2J = 15.3 Hz, 1 H, CH_2C_{Ar}), 5.13 (d, ^3J = 11.7 Hz, 1 H,

NCH), 7.04–7.07 (m, 3 H, *p*-C$H_{Ar}CH_2$, *o*-C$H_{Ar}CH_3$, *p*-C$H_{Ar}CH_3$), 7.19–7.22 (m, 1 H, *m*-CH_{Ar}).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.5 ($C_{Ar}CH_3$), 24.1 [C(CH_3)$_2$], 24.6, 25.4, 25.6 (3 × $CH_{2,Cy}$), 29.8 [C(CH_3)$_2$], 36.7, 39.8 (2 × $CH_{2,Cy}$), 44.9 (CH_2C_{Ar}), 52.5 [C(CH_3)$_2$], 80.1 [C($CH_{2,Cy}$)$_5$], 92.3 (NCH), 125.9, 127.8 (2xCH_{Ar}), 128.8 (*m*-CH_{Ar}), 129.6 (CH_{Ar}), 135.1 ($C_{Ar}CH_2$), 138.5 ($C_{Ar}CH_3$), 171.0 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 334.4 (100, [MH]$^+$), 316.3 (44, [MH – H_2O]$^+$).

HRMS (CI, isobutane): *m*/*z* calcd for $C_{19}H_{28}NO_2S^+$: 334.1841; found: 334.1835.

(*RS*)-8′-Methoxy-1′,1′-Dimethyl-6′,10b′-dihydrospiro[cyclohexane-1,3′-thiazolo[4,3-*a*]isoquinolin]-5′-one (4e)

Following GP B, methoxyamide **2e** (102 mg, 0.28 mmol) and $AlCl_3$ (94 mg, 0.70 mmol) were used. Analysis of the crude product by ^{1}H NMR spectroscopy showed a single regioisomer. Purification was not necessary; yield: 92 mg (100%); yellow solid; mp 121–123 °C.

IR (ATR): 2921, 2855, 1649, 1616, 1561, 1509, 1450, 1419, 1398, 1320, 1288, 1269, 1169, 1124, 1037, 861, 842, 824, 783, 739 cm^{-1}.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.13 [s, 3 H, C(CH_3)$_2$], 1.19–1.28 (m, 1 H, $CH_{2,Cy}$), 1.37–1.53 (m, 2 H, $CH_{2,Cy}$), 1.58–1.60 (m, 1 H, $CH_{2,Cy}$), 1.59 [s, 3 H, C(CH_3)$_2$], 1.73–1.85 (m, 3 H, $CH_{2,Cy}$), 1.96–1.99, 2.35–2.41, 3.43–3.49 (3 m, 3 H, $CH_{2,Cy}$), 3.49–3.53 (m, 1 H, CH_2C_{Ar}), 3.78 (s, 3 H, OCH_3), 3.82 (dd, ^2J = 20.3 Hz, ^5J = 2.3 Hz, 1 H, CH_2C_{Ar}), 4.90–4.91 (m, 1 H, NCH), 6.61 (d, ^4J = 2.5 Hz, 1 H, *o*-C$H_{Ar}CH_2$), 6.78 (dd, ^3J = 8.7 Hz, ^4J = 2.6 Hz, 1 H, *p*-C$H_{Ar}CH_2$), 7.22 (d, ^3J = 8.7 Hz, 1 H, *m*-C$H_{Ar}OCH_3$).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 24.1, 24.8 (2 × $CH_{2,Cy}$), 25.1 [C(CH_3)$_2$], 26.1 ($CH_{2,Cy}$), 26.6 [C(CH_3)$_2$], 37.5, 38.0 (2 × $CH_{2,Cy}$), 39.6 (CH_2C_{Ar}), 53.0 [C(CH_3)$_2$], 55.4 (OCH_3), 72.1 (NCH), 76.9 [C($CH_{2,Cy}$)$_5$], 111.5 (*o*-$CH_{Ar}CH_2$), 113.2 (*p*-$CH_{Ar}CH_2$), 122.3 ($C_{Ar}CH$), 127.1 (*m*-$CH_{Ar}OCH_3$), 133.6 ($C_{Ar}CH_2$), 159.1 ($C_{Ar}OCH_3$), 167.0 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 332.2 (100, [MH]$^+$).

HRMS (CI, isobutane): *m*/*z* calcd for $C_{19}H_{26}NO_2S^+$: 332.1684; found: 332.1675.

(*RS*)-8′-Methoxy-3′,3′-Dimethyl-6′,10b′-dihydro-3′*H*,5′*H*-spiro[cyclohexane-1,1′-thiazolo[4,3-*a*]isoquinolin]-5′-one (4f)

Following GP B, methoxyamide **2f** (94 mg, 0.26 mmol) and $AlCl_3$ (87 mg, 0.65 mmol) were used. Analysis of the crude product by ^{1}H NMR spectroscopy showed a single regioisomer. The crude product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 4:1); yield: 60 mg (69%); yellow solid; mp 126–127 °C; R_f = 0.22 (*n*-hexane–EtOAc, 4:1).

IR (ATR): 3013, 2996, 2971, 2933, 2920, 2859, 2841, 1655, 1613, 1590, 1505, 1464, 1444, 1417, 1290, 1265, 1238, 1227, 1130, 1039, 855, 837, 824 cm^{-1}.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 0.93–1.06 (m, 2 H, $CH_{2,Cy}$), 1.20–1.29 (m, 1 H, $CH_{2,Cy}$), 1.55–1.80 (m, 5 H, $CH_{2,Cy}$), 1.76 [s, 3 H, C(CH_3)$_2$], 1.87–1.93, 1.97–2.00 (2 m, 2 H, $CH_{2,Cy}$), 2.07 [s, 3 H, C(CH_3)$_2$], 3.44–3.48 (m, 1 H, CH_2C_{Ar}), 3.80 (s, 3 H, OCH_3), 3.80–3.85 (dd, ^2J = n.r., ^5J = 0.9 Hz, 1 H, CH_2C_{Ar}), 4.88–4.89 (m, 1 H, NCH), 6.61 (d, ^4J = 1.6 Hz, 1 H, *o*-C$H_{Ar}CH_2$), 6.80 (dd, ^3J = 8.6 Hz, ^4J = 2.3 Hz, 1 H, *p*-C$H_{Ar}CH_2$), 7.18 (d, ^3J = 8.6 Hz, 1 H, *m*-C$H_{Ar}OCH_3$).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 22.2, 25.7, 25.7 (3 × $CH_{2,Cy}$), 31.0 [C(CH_3)$_2$], 31.2 ($CH_{2,Cy}$), 32.4 [C(CH_3)$_2$], 36.8 ($CH_{2,Cy}$), 39.3 (CH_2C_{Ar}), 55.4 (OCH_3), 63.2 [C($CH_{2,Cy}$)$_5$], 69.5 [C(CH_3)$_2$], 72.5 (NCH), 111.6 (*o*-$CH_{Ar}CH_2$), 113.1 (*p*-$CH_{Ar}CH_2$), 121.3 ($C_{Ar}CH$), 128.2 (*m*-$CH_{Ar}OCH_3$), 134.2 ($C_{Ar}CH_2$), 159.2 ($C_{Ar}OCH_3$), 166.9 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 332.4 (100, [MH]$^+$).

HRMS (CI, isobutane): *m*/*z* calcd for $C_{19}H_{26}NO_2S^+$: 332.1684; found: 332.1676.

(*RS*)-8′-Methyl-6′,10b′-dihydro-5′*H*-dispiro[cyclohexane-1,1′-thiazolo[4,3-*a*]isoquinoline-3′,1′′-cyclohexan]-5′-one (4g)

Following GP B, methoxyamide **2g** (101 mg, 0.26 mmol) and $AlCl_3$ (87 mg, 0.65 mmol) were used. Analysis of the crude product by ^{1}H NMR spectroscopy showed a single regioisomer. The crude product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 4:1); yield: 34 mg (38%); colorless solid; mp 141–142 °C; R_f = 0.45 (*n*-hexane–EtOAc, 4:1).

IR (ATR): 2927, 2849, 1656, 1617, 1590, 1509, 1448, 1424, 1402, 1287, 1264, 1246, 1219, 1188, 1172, 1130, 1119, 907, 830, 725 cm^{-1}.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 0.92–1.03 (m, 2 H, $CH_{2,Cy}$), 1.21–1.42 (m, 2 H, $CH_{2,Cy}$), 1.47–2.06 (m, 13 H, $CH_{2,Cy}$), 2.13–2.19 (m, 1 H, $CH_{2,Cy}$), 2.34 (s, 3 H, CH_3), 3.44–3.48 (m, 1 H, CH_2C_{Ar}), 3.45–3.51 (m, 1 H, $CH_{2,Cy}$), 3.80–3.84 (m, 1 H, CH_2C_{Ar}), 4.89–4.90 (m, 1 H, NCH), 6.93–6.94 (m, 1 H, *o*-C$H_{Ar}CH_2$), 7.04–7.06 (m, 1 H, *p*-C$H_{Ar}CH_2$), 7.13 (d, ^3J = 8.0 Hz, 1 H, *o*-CH_{Ar}CH).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 21.2 (CH_3), 22.2, 23.9, 25.0, 25.6, 25.7, 26.2, 31.2, 36.8, 38.2, 38.6 (10x$CH_{2,Cy}$), 39.8 (CH_2C_{Ar}), 61.5 [C($CH_{2,Cy}$)$_5$CH], 72.7 (NCH), 77.0 [C($CH_{2,Cy}$)$_5$N], 126.4 (C_{Ar}CH), 127.0 (*o*-CH_{Ar}CH), 127.1 (*p*-$CH_{Ar}CH_2$), 128.0 (*o*-$CH_{Ar}CH_2$), 132.6 ($C_{Ar}CH_2$), 137.8 ($C_{Ar}CH_3$), 167.3 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 356.4 (100, [MH]$^+$).

HRMS (CI, isobutane): *m*/*z* calcd for $C_{22}H_{30}NOS^+$: 356.2048; found: 356.2039.

(*RS*)-1-(15-Hydroxy-7-thia-14-azadispiro[5.1.5^8.2^6]pentadecan-14-yl)-2-(3-methylphenyl)ethan-1-one (5g)

By-product of **4g**; yield: 25 mg (27%); colorless, extremely viscous oil; R_f = 0.30 (*n*-hexane–EtOAc, 4:1).

IR (ATR): 3379, 2926, 2855, 1628, 1590, 1489, 1448, 1374, 1267, 1252, 1178, 1108, 1072, 1027, 905, 763, 728, 692 cm^{-1}.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.15–1.38 (m, 6 H, $CH_{2,Cy}$), 1.48–1.76 (m, 12 H, $CH_{2,Cy}$), 2.32 (s, 3 H, CH_3), 2.87 (d, ^3J = 11.6 Hz, 1 H, OH), 2.98–3.04, 3.06–3.12 (2 m, 2 H, $CH_{2,Cy}$), 3.80, 3.85 (2 d, ^2J = 15.3 Hz, 2 H, CH_2C_{Ar}), 5.23 (d, ^3J = 11.6 Hz, 1 H, NCH), 7.03–7.06 (m, 3 H, *p*-C$H_{Ar}CH_2$, *o*-C$H_{Ar}CH_2$, *p*-C$H_{Ar}CH_3$), 7.19–7.22 (m, 1 H, *m*-CH_{Ar}).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 21.5 (CH_3), 22.2, 24.1, 24.5, 25.3, 25.5, 25.5, 33.6, 36.9, 37.1, 39.7 (10 × $CH_{2,Cy}$), 44.8 (CH_2C_{Ar}), 58.3 [C($CH_{2,Cy}$)$_5$CH], 78.9 [C($CH_{2,Cy}$)$_5$N], 90.7 (NCH), 125.8, 127.8 (2 × CH_{Ar}), 128.7 (*m*-CH_{Ar}), 129.5 (CH_{Ar}), 135.1 ($C_{Ar}CH_2$), 138.5 ($C_{Ar}CH_3$), 171.2 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 374.5 (100, [MH]$^+$), 356.4 (66, [MH – H_2O]$^+$).

HRMS (CI, isobutane): *m*/*z* calcd for $C_{22}H_{32}NO_2S^+$: 374.2154; found: 374.2148.

(*RS*)-8′-Methoxy-6′,10b′-dihydro-5′*H*-dispiro[cyclohexane-1,1′-thiazolo[4,3-*a*]isoquinoline-3′,1′′-cyclohexan]-5′-one (4h)

Following GP B, methoxyamide **2h** (81 mg, 0.20 mmol) and $AlCl_3$ (67 mg, 0.50 mmol) were used. Analysis of the crude product by ^{1}H NMR spectroscopy showed a single regioisomer. The crude product was purified by column chromatography (silica gel; *n*-hexane–MTBE, 7:3); yield: 63 mg (85%); colorless solid; mp 144–146 °C; R_f = 0.18 (*n*-hexane–MTBE, 7:3).

IR (ATR): 2928, 2852, 1654, 1613, 1508, 1448, 1410, 1341, 1290, 1265, 1243, 1221, 1169, 1134, 1036, 906, 729 cm^{-1}.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 0.92–1.03 (m, 2 H, $CH_{2,Cy}$), 1.20–1.41 (m, 2 H, $CH_{2,Cy}$), 1.47–1.88 (m, 12 H, $CH_{2,Cy}$), 1.94–1.96, 2.02–2.05, 2.13–2.19 (3 m, 3 H, $CH_{2,Cy}$), 3.44–3.48 (m, 1 H, CH_2C_{Ar}), 3.46–3.50 (m, 1 H, $CH_{2,Cy}$), 3.80 (s, 3 H, OCH_3), 3.84 (dd,

^2J = 19.8 Hz, ^5J = 1.0 Hz, 1 H, CH_2C_{Ar}), 4.86–4.87 (m, 1 H, NCH), 6.62 (d, ^4J = 2.3 Hz, 1 H, *o*-$CH_{Ar}CH_2$), 6.80 (dd, ^3J = 8.6 Hz, ^4J = 2.5 Hz, 1 H, *p*-$CH_{Ar}CH_2$), 7.15 (d, ^3J = 8.6 Hz, 1 H, *m*-$CH_{Ar}OCH_3$).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 22.2, 23.9, 24.9, 25.6, 25.8, 26.1, 31.2, 36.7, 38.2, 38.6 (10 × $CH_{2,Cy}$), 40.0 (CH_2C_{Ar}), 55.4 (OCH_3), 61.5 [$C(CH_{2,Cy})_5CH$], 72.4 (NCH), 76.9 [$C(CH_{2,Cy})_5N$], 111.5 (*o*-$CH_{Ar}CH_2$), 113.0 (*p*-$CH_{Ar}CH_2$), 121.5 ($C_{Ar}CH$), 128.3 (*m*-$CH_{Ar}OCH_3$), 134.2 ($C_{Ar}CH_2$), 159.2 ($C_{Ar}OCH_3$), 167.0 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 372.4 (100, $[MH]^+$).

HRMS (CI, isobutane): *m*/*z* calcd for $C_{22}H_{30}NO_2S^+$: 372.1997; found: 372.1999.

(*RS*)-8-Methoxy-1,1,3,3-tetramethyl-6,10b-dihydro-3*H*-[1,3]oxazolo[4,3]isoquinolin-5-one (4i)

Following GP B, methoxyamide **2i** (111 mg, 0.36 mmol) and $AlCl_3$ (120 mg, 0.90 mmol) were used. Analysis of the crude product by ^{1}H NMR spectroscopy showed a single regioisomer. Purification was not necessary; yield: 96 mg (97%); yellow solid; mp 133–134 °C.

IR (ATR): 3077, 2987, 2963, 2938, 2839, 1654, 1612, 1593, 1510, 1463, 1451, 1436, 1401, 1373, 1257, 1245, 1213, 1201, 1169, 1035, 999, 945, 869, 829, 782 cm^{-1}.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.14, 1.61, 1.67, 1.76 [4 s, 12 H, 2 × $C(CH_3)_2$], 3.56–3.66 (m, 2 H, CH_2), 3.80 (s, 3 H, OCH_3), 4.62–4.63 (m, 1 H, NCH), 6.69 (d, ^4J = 2.0 Hz, 1 H, *o*-$CH_{Ar}CH_2$), 6.80 (dd, ^3J = 8.6 Hz, ^4J = 2.4 Hz, 1 H, *p*-$CH_{Ar}CH_2$), 7.17 (d, ^3J = 8.6 Hz, 1 H, *m*-$CH_{Ar}OCH_3$).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 23.5, 26.7, 27.5, 28.2 [2 × $C(CH_3)_2$], 38.8 (CH_2), 55.4 (OCH_3), 65.7 (NCH), 81.0 [$C(CH_3)_2CH$], 92.7 [$C(CH_3)_2N$], 112.2 (*o*-$CH_{Ar}CH_2$), 113.1 (*p*-$CH_{Ar}CH_2$), 122.9 ($C_{Ar}CH$), 125.4 (*m*-$CH_{Ar}OCH_3$), 134.8 ($C_{Ar}CH_2$), 159.2 ($C_{Ar}OCH_3$), 165.7 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 276.2 (100, $[MH]^+$).

HRMS (CI, isobutane): *m*/*z* calcd for $C_{16}H_{22}NO_3^+$: 276.1600; found: 276.1602.

Crystal Data of 4i

Data collection was performed at 153(2) K on a Bruker Kappa Apex II CCD diffractometer, using MoK_α radiation. $C_{16}H_{21}NO_3$, *Mr* = 275.34, λ = 0.71073 Å, orthorhombic, space group Pbcn, unit cell dimensions: *a* = 30.1103(6) Å, *b* = 8.4760(2) Å, *c* = 11.3052(2) Å, α = 90°, β = 90°, γ = 90°, V = 2885.26(10) Å^3, Z = 8, D_C = 1.268 Mg/m^3, absorption coefficient = 0.087 mm^{-1}, F(000) = 1184, reflections collected 57332, independent reflections 4226 (R_{int} = 0.0757). Reflections were collected over the range 3.08° < 2θ < 30.11°, index ranges: –42 < *h* < 42; –11 < *k* < 7; –15 < *l* < 15, completeness to θ = 30.11° is 99.7%. To solve the crystal structure, the SHELXS-97 program was used and for least-squares refinement on F^2 the SHELXL-97 program, respectively. Non-hydrogen atoms were refined with anisotropic displacement parameters. All H atoms were placed in calculated positions and refined using a riding model. 4226 reflections were included in calculation, giving final standard residual R_1 value of 0.0476 (ωR_2 = 0.1154) for observed data [$I > 2\sigma(I)$] and 0.0674 for all data (ωR_2 = 0.1273) (data/restraints/parameters = 4226:0:186). Largest diff. peak hole 0.374 and –0.242 e/Å^3. The goodness-of-fit on F^2 was 1.064.

(*RS*)-9-Methoxy-1,1,3,3-tetramethyl-1,6,7,11b-tetrahydro-3*H*,5*H*-benzo[c]thiazolo[3,4-*a*]azepin-5-one (6a)

Following GP B, methoxyamide **3a** (108 mg, 0.32 mmol) and $AlCl_3$ (107 mg, 0.80 mmol) were used. Analysis of the crude product by ^{1}H NMR spectroscopy showed a single regioisomer. Purification was not necessary; yield: 92 mg (94%); colorless solid; mp 116–118 °C.

IR (ATR): 3067, 2983, 2967, 2928, 1634, 1610, 1506, 1462, 1446, 1404, 1338, 1291, 1253, 1208, 1190, 1174, 1156, 1112, 1038, 852, 833, 772 cm^{-1}.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.37, 1.42, 1.72, 1.89 [4 s, 12 H, 2 × $C(CH_3)_2$], 2.58–3.07 (m, 4 H, 2 × CH_2), 3.78 (s, 3 H, OCH_3), 4.84 (s, 1 H, NCH), 6.68 (d, ^4J = 2.4 Hz, 1 H, *o*-$CH_{Ar}CH_2$), 6.71 (dd, ^3J = 8.5 Hz, ^4J = 2.6 Hz, 1 H, *p*-$CH_{Ar}CH_2$), 7.42–7.46 (m, 1 H, *m*-$CH_{Ar}OCH_3$).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 25.2, 30.1, 30.2, 30.2 [2 × $C(CH_3)_2$], 30.9 (CH_2C_{Ar}), 39.0 (CH_2CO), 51.0 [$C(CH_3)_2CH$], 55.3 (OCH_3), 71.1 [$C(CH_3)_2N$], 73.8 (NCH), 110.8 (*o*-$CH_{Ar}CH_2$), 114.9 (*p*-$CH_{Ar}CH_2$), 125.1 ($C_{Ar}CH$), 130.5 (*m*-$CH_{Ar}OCH_3$), 142.5 ($C_{Ar}CH_2$), 159.1 ($C_{Ar}OCH_3$), 171.6 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 306.3 (100, $[MH]^+$).

HRMS (CI, isobutane): *m*/*z* calcd for $C_{17}H_{24}NO_2S^+$: 306.1528; found: 306.1526.

(*RS*)-9-Methoxy-1,1,3,3-tetramethyl-1,6,7,11b-tetrahydro-3*H*,5*H*-benzo[c]oxazolo[3,4-*a*]azepin-5-one (6b)

Following GP B, methoxyamide **3b** (150 mg, 0.47 mmol) and $AlCl_3$ (156 mg, 1.17 mmol) were used. Analysis of the crude product by ^{1}H NMR spectroscopy showed a single regioisomer. The crude product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 7:3); yield: 136 mg (~100%); colorless, extremely viscous oil; R_f = 0.31 (*n*-hexane–EtOAc, 7:3).

IR (ATR): 2978, 2934, 2862, 2838, 1644, 1612, 1508, 1444, 1414, 1365, 1343, 1278, 1255, 1205, 1171, 1139, 1125, 1103, 1040, 1010, 908, 856, 731 cm^{-1}.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 0.91, 1.39, 1.60, 1.73 [4 s, 12 H, 2 × $C(CH_3)_2$], 2.46–2.51 (m, 1 H, CH_2CO), 2.63–2.68 (m, 1 H, CH_2C_{Ar}), 2.75–2.80 (m, 1 H, CH_2CO), 3.22–3.27 (m, 1 H, CH_2C_{Ar}), 3.80 (s, 3 H, OCH_3), 4.66 (s, 1 H, NCH), 6.66 (d, ^4J = 2.7 Hz, 1 H, *o*-$CH_{Ar}CH_2$), 6.75 (dd, ^3J = 8.6 Hz, ^4J = 2.7 Hz, 1 H, *p*-$CH_{Ar}CH_2$), 7.13 (d, ^3J = 8.6 Hz, 1 H, *m*-$CH_{Ar}OCH_3$).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 22.7, 26.2, 26.9, 27.7 [2 × $C(CH_3)_2$], 31.7 (CH_2C_{Ar}), 39.5 (CH_2CO), 55.4 (OCH_3), 69.9 (NCH), 82.8 [$C(CH_3)_2CH$], 93.7 [$C(CH_3)_2N$], 111.5 (*o*-$CH_{Ar}CH_2$), 114.9 (*p*-$CH_{Ar}CH_2$), 124.3 ($C_{Ar}CH$), 130.0 (*m*-$CH_{Ar}OCH_3$), 142.9 ($C_{Ar}CH_2$), 158.6 ($C_{Ar}OCH_3$), 173.1 (C=O).

MS (CI, isobutane): *m*/*z* (%) = 290.2 (100, $[MH]^+$).

HRMS (CI, isobutane): *m*/*z* calcd for $C_{17}H_{24}NO_3^+$: 290.1756; found: 290.1759.

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