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Spirocyclic Pyridoazepine Analogues of Galanthamine: Synthesis, Modelling Studies and Evaluation as Inhibitors of Acetylcholinesterase

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Spirocyclic pyridoazepines, designed as simplified analogues of the alkaloid galanthamine, were synthesised and evaluated as inhibitors of acetylcholinesterase. The key cyclisation step involved internal displacement of 2-chloro or 2-iodopyridine by either nucleophilic aromatic substitution or a Heck reaction. The target compounds showed significant inhibition of acetylcholinesterase but lower than that of galanthamine. This result could be rationalised by comparative docking simulation studies based on the known crystal structure of the acetylcholinesterase–galanthamine complex; multiple hydrogen bonding of a cocrystallised water molecule to both the receptor and the ligand was found to be of crucial importance for effective binding to the active site of the enzyme.

Introduction

The enzyme acetylcholinesterase (AChE) is currently the most important target for the treatment of Alzheimers' disease (AD). The principal role of this enzyme is the hydrolysis of acetylcholine (ACh). According to the "cholinergic hypothesis", patients suffering from AD have a lack of cholinergic neurotransmission. Treatment for Alzheimers' disease involves restoring the acetylcholine levels in patients by means of inhibitors of acetylcholinesterase (AChE). Tacrine, donepezil,[1] rivastigmine[2] and galanthamine (**1**; GAL) are AChE inhibitors that are able to enhance memory in AD patients (Figure 1). Those four inhibitors have been approved for the symptomatic treatment of AD.

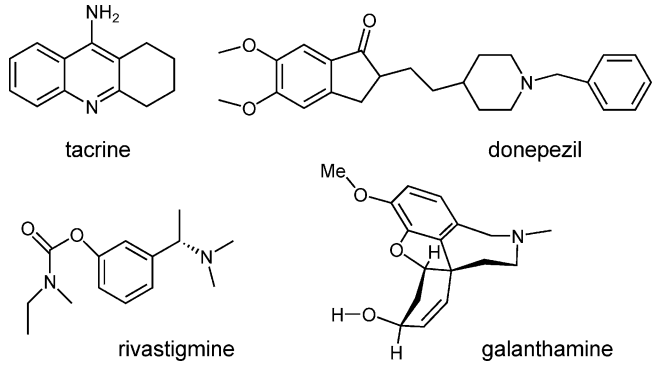

Figure 1. Four inhibitors of AChE that have been approved for the symptomatic treatment of AD.

GAL is an alkaloid isolated from the Amaryllidaceae species and is a centrally acting, selective, competitive and reversible inhibitor of AChE.[3] It significantly enhances cognitive functions in AD patients,[4] and it is the most recently approved AChE inhibitor in Europe and the USA. Galanthamine can be isolated from botanical sources but these are limited and isolation of GAL is difficult. Consequently, a few total syntheses of GAL[5] and the synthesis of various analogues have been reported.[6] Galanthamine is structurally related to morphine (**2**) (Figure 2). Morphine and analogues are used for the treatment of severe pain. Therefore, compounds containing a simplified galanthamine skeleton might be of interest for the development of both new inhibitors of acetylcholinesterase and further analogues of morphine.

Our goal is to make simplified analogues of GAL, in which the benzene ring is replaced with a pyridine moiety. Thus, whereas our pyridine target structures of type **3** and **4** retain the spiroannulation, the ether linkage between the aromatic ring and the spiroring is disconnected (Figure 2).

Compound **5**, a synthetic analogue of GAL that also lacks this heterocyclic connection, was claimed to have the desired, albeit weak, activity.[7]

An overlay of the geometrically optimised model structures of GAL and targets **3c** and **3d** reveals an excellent fit of the superimposed benzo- and pyridoazepine ring moieties and that of the corresponding spiroring moieties as well

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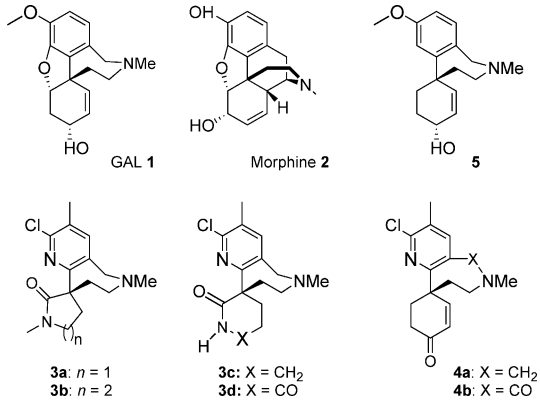


Figure 2. GAL (**1**), morphine (**2**), targets **3a**–**d** and **4a**,**b** and GAL-analogue **5**.

(Figure 3). The chlorine atom on the pyridine nucleus was meant to mimic the methoxy group of GAL. The amide oxygen atoms in the enantiomeric forms of **3a**–**d** shown in Figure 1 could serve as a mimic for the ether bridge of GAL. Alternatively, the planar amide bond present in the image forms of **3a**–**d** can be superimposed on the alkenic linkage of the cyclohexene ring (not shown in Figure 3).

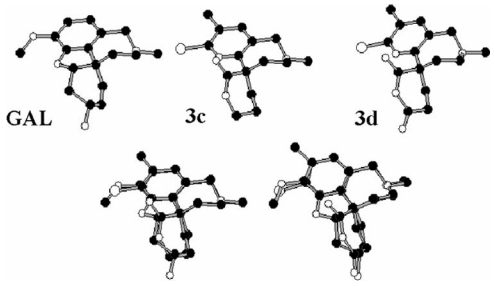
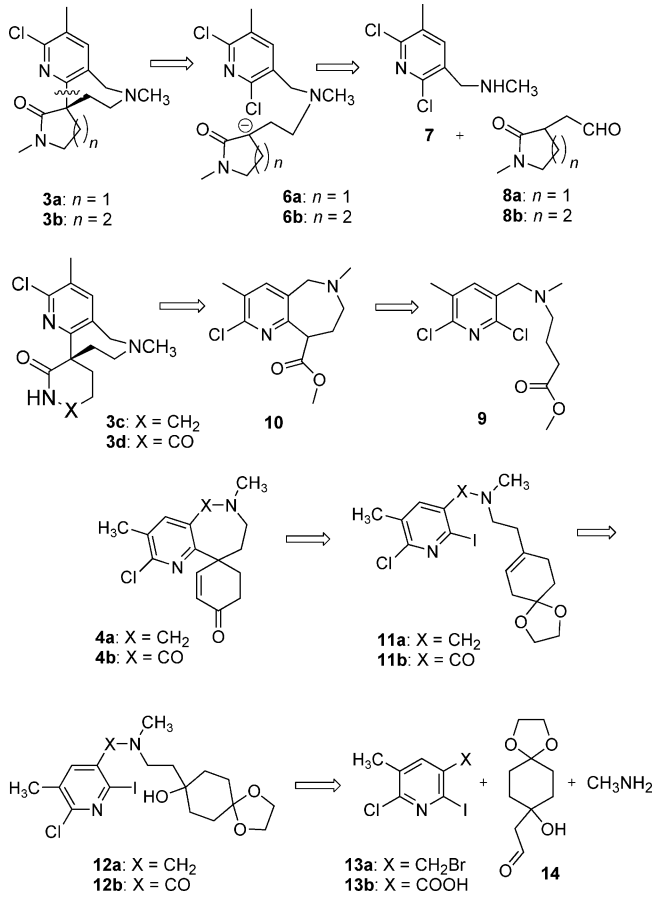


Figure 3. Geometrically optimised structures of Gal, **3c** and **3d**; overlay of GAL and targets **3c** and **3d** by using Hyperchem MM+.

Retrosynthetic Analysis

Our synthetic approach towards spirocyclic pyridoazepines **3a**,**b** was based on intramolecular ring closure of appropriate 3-substituted 2-chloropyridines **6a**,**b** carrying a nucleophilic lactam entity (Scheme 1). The latter pyridine precursors can be constructed by reductive coupling of secondary amine **7** and lactam aldehyde derivatives **8a**,**b**. Alternatively, instead of forming the spirocyclic ring system by nucleophilic aromatic substitution (NAS) in the final ring-closure step, spirocyclic pyridoazepines **3c**,**d** can be constructed by manipulation of appropriate bicyclic pyridoazepine **10**. This key intermediate in turn can form by intramolecular NAS of chloropyridine **9**. Consequently, the critical NAS ring-closure step now involves a less-hindered precursor than lactam precursors **6a**,**b** used for **3a**,**b**.



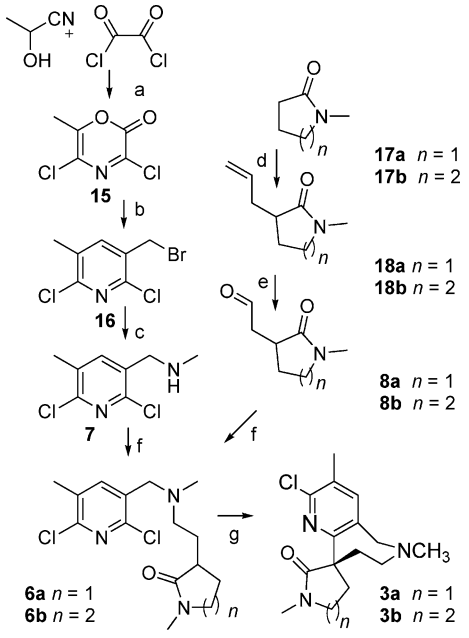
Scheme 1. Retrosynthetic analysis of targets **3a**–**d** and **4**.

The cyclohene-based spirocyclic pyridoazepines **4a**,**b** can be accessed by using an intramolecular Heck reaction of appropriate 2-iodopyridines **11a**,**b** bearing a cyclohexenyl end group in the side chain at the 3-position. A similar approach was used by Liang et al. for the construction of compound **5**.[7] The cyclohexene functionality of compounds **11a**,**b** may form by elimination of tertiary alcohols **12a**,**b**, which in their turn can be assembled from functionalised pyridines **13a**,**b**, aldehyde **14** and methylamine.

Results and Discussion

First Synthetic Approach: Ring Closure by Nucleophilic Aromatic Substitution

The synthesis of the substituted pyridine component started with the cyclocondensation of lactonitrile and oxalyl chloride to form **15**,[8] which was submitted to a Diels–Alder reaction with propargyl bromide (Scheme 2).[9] This cycloaddition was 100% regioselective, and only 3-(bromomethyl)pyridine **16** was formed. Subsequent reaction with methylamine afforded the corresponding 3-(methylaminomethyl)pyridine **7**.



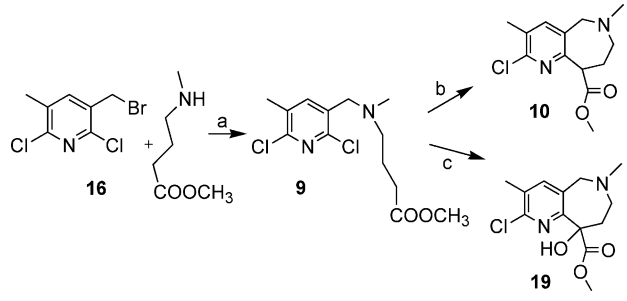
Scheme 2. Reagents and conditions: (a) lactonitrile, oxalyl chloride (3 equiv.), $Et_3N.HCl$ (0.1 equiv.), chlorobenzene, 90 °C, 3 h (90%); (b) propargyl bromide (2 equiv.), toluene, 70 °C, overnight (92%); (c) CH_3NH_2 (5 equiv.), MeOH, room temp., 4 h (85%); (d) (i) LDA (1 equiv.), THF, –78 °C, 10 min (ii) allyl bromide (1 equiv.), –78 °C, 30 min (**18a**: 97%, **18b**: 80%); (e) cat. OsO_4, $NaIO_4$ (2 equiv.), Et_2O, H_2O, room temp., 12 h or (i) O_3, CH_2Cl_2, MeOH, –78 °C, 30 min (ii) NEt_3, –78 °C to room temp., overnight (the crude compound was used immediately in the next step); (f) amine **7** (1 equiv.), MeOH, acetic acid (pH = 6), $NaCNBH_3$ (1 equiv.), aldehyde **8a**,**b** (1 equiv.), room temp., 15 min (**8a**: 85%, **8b**: 60% over 2 steps); (g) $KN(SiMe_3)_2$ (1 equiv.), toluene, MW (**3a**: 85%, **3b**: 5%).

The aldehyde component was prepared by initial α-allylation of commercial lactams **17a**,**b** to give compounds **18a**,**b**. Subsequent oxidative cleavage of the allyl group yielded aldehydes **8a**,**b**; this conversion was effected either by overnight reaction with $NaIO_4$ and catalytic OsO_4 or by ozonolysis (the ozonide intermediate was cleaved by treatment with NEt_3).[10] Final reductive amination with amine **7** by using $NaCNBH_3$ as a reducing agent afforded precursors **6a**,**b** in good yield.

The crucial and most difficult step in the reaction sequence was the final ring closure of precursors **6a**,**b** by NAS to form the spiroannulated seven-membered ring products **3a**,**b**. Indeed, generation of the quaternary carbon centre of the spirocycle requires attack of a sterically encumbered anion at the 2-chloro position. Several methods were tried to generate the lactam anion and effect ring closure under conventional heating conditions by using various strong bases [NaH, KH, $KN(SiMe_3)_2$] in THF or toluene, but desired products **3a**,**b** could not be detected. This conversion could, however, be achieved by applying microwave irradiation by using $KN(SiMe_3)_2$ as a base in toluene. Presumably, the initial failure was due to decomposition of the desired product when applying elevated temperatures or prolonged reaction times. Temperature and reaction time conditions also were of critical importance in the microwave reaction. The best conditions to effect spirocyclisation of **6a** consisted of irradiating the reaction mixture at 100 °C for 15 min, which provided target compound **3a** in 85% yield after flash column chromatography. Under these conditions, no by-products due to either competing side reactions or further decomposition of the initial spirocyclic compound **3a** were detected by MS (CI).

In contrast to the straightforward synthesis of **3a**, the transformation of the six-membered lactam analogue **6b** into the corresponding spirocyclic product **3b** proved to be erratic. The best conditions to perform the spirocyclisation reaction of **6b** were heating at 80 °C for 10 min. Presumably due to further decomposition of the unstable spirocyclic product **3b**, numerous side products were detected and following purification by reverse-phase HPLC, **3b** was isolated in poor yield (ca. 5%).

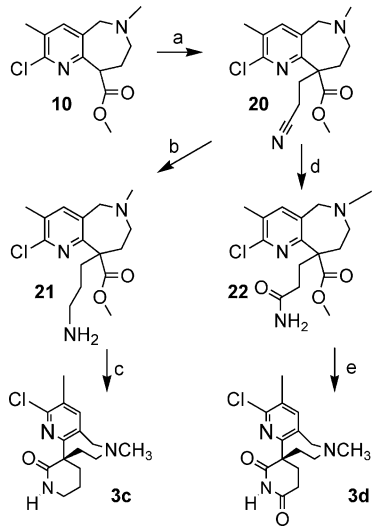
In view of our failure to produce the six-membered lactam target compound **3b** in satisfactory yield, we next applied the alternative route proceeding via the bicyclic pyridoazepine **10** (Scheme 1). Substitution of 3-(bromomethyl)-pyridine **16** with methyl 4-(methylamino)butanoate furnished amine **9**, which smoothly underwent internal NAS to form pyridoazepine **10** under conventional heating conditions (Scheme 3). Two equivalents of base are required to effect complete conversion into compound **10**, which is generated as the corresponding anion. The latter turned out to be very sensitive to oxidation; hence, air must be rigorously excluded. Final workup of the reaction mixture was carried out by cooling down to –78 °C, followed by careful addition of a saturated aqueous solution of NH_4Cl. When the reaction was carried out in the presence of air, oxidation of the anion intermediate resulted in detection of alcohol **19** as a side product. Finally, alcohol **19** could be isolated as the sole product in high yield when oxygen was admitted to the reaction mixture.



Scheme 3. Reagents and conditions: (a) NEt_3 (3 equiv.), MeOH, room temp., 4 h (85%); (b) (i) $KN(SiMe_3)_2$ (2.2 equiv.), toluene, 80 °C, 10 min, (ii) –78 °C, saturated NH_4Cl, 5 min. (90%); (c) $KN(SiMe_3)_2$ (2.2 equiv.) toluene, 10 min, 80 °C, O_2 (85%).

To construct the spirolactam ring of target compounds **3c**,**d**, we envisaged initial Michael reaction of pyridoazepine **10** with either acrylonitrile, methyl acrylate or acrylamide. However, as a result of the unreactive character and steric crowding of the stabilised ester enolate anion of **10**, addition only succeeded with acrylonitrile. Selective reduction of the resulting nitrile adduct **20** by using $NaBH_4$ in the presence of $CoCl_2$ furnished primary amine **21**,[11] which underwent ring closure in refluxing methanol to provide

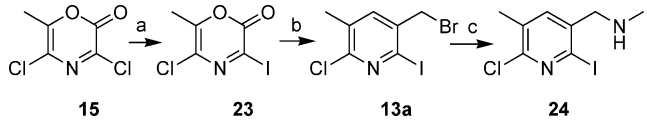
target product **3c**. Nitrile adduct **20** could also be converted into the corresponding amide **22** by heating with methanesulfonic acid in toluene. Final ring closure was effected by reaction with KO*t*Bu in *t*BuOH at room temperature to form the cyclic imide salt; acidic workup furnished target product **3d** (Scheme 4).



Scheme 4. Reagents and conditions: (a) (i) KO*t*Bu (1.2 equiv.), THF, room temp., 10 min (ii) acrylonitrile (1.2 equiv.), *t*BuOH, room temp., 15 min (61%); (b) $CoCl_2$ (2 equiv.), $NaBH_4$ (10 equiv.), MeOH, room temp., overnight; (c) MeOH, reflux, overnight (57% over 2 steps); (d) CH_3SO_3H, toluene, 100 °C, 2 h (83%); (e) KO*t*Bu (1.2 equiv.), *t*BuOH, room temp., 1 h (60%).

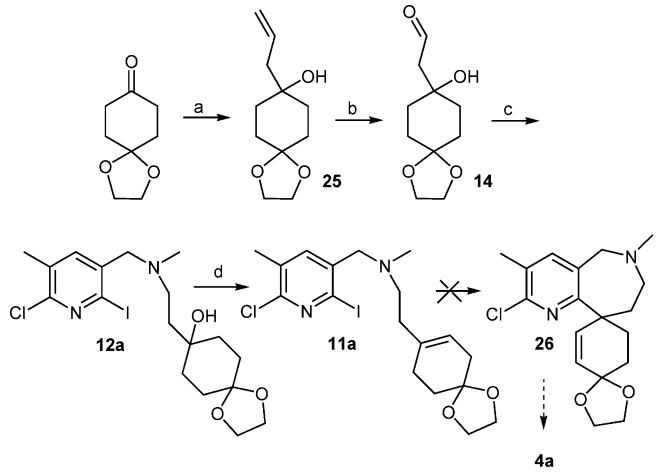
Second Synthetic Approach: Ring Closure by Heck Reaction

To enable an intramolecular Heck cyclisation of 2-iodopyridines **11a**,**b** bearing a cyclohexenyl end group in the side chain at the 3-position, we first envisaged the synthesis of 2-iodopyridine **24** (Scheme 5). To this end, the more reactive imidoyl chloride functionality of **15** was substituted with iodide by using NaI (2 equiv.) and a catalytic amount of camphorsulfonic acid in acetone to give 2-iodooxazinone **23**. Subsequent Diels–Alder reaction with propargyl bromide regioselectively furnished 3-(bromomethyl)pyridine **13a**, which was converted into the required 3-(methylaminomethyl)pyridine **24** by reaction with methylamine.



Scheme 5. Reagents and conditions: (a) NaI (2 equiv.), CSA, acetone, room temp., 2 h (98%); (b) propargyl bromide (3 equiv.), toluene, 70 °C, 2 d (80%); (c) methylamine (5 equiv.), NEt_3, CH_2Cl_2, room temp., 3 h (92%).

Aldehyde **14** was prepared by starting from semi-protected 1,4-cyclohexanedione, which was subjected to Grignard reaction with allylmagnesium chloride to form alcohol **25**, followed by oxidative cleavage of the allyl group by reaction with OsO_4 and $NaIO_4$ (Scheme 6). Reductive amination of aldehyde **14** with amine **24** by using $NaCNBH_3$ as the reducing agent afforded tertiary amine **12a**. Subsequent elimination of the tertiary alcohol group was effected by treatment with methanesulfonyl chloride and triethylamine to provide the required cyclohexene 2-iodopyridine precursor **11a** ready for intramolecular Heck reaction.

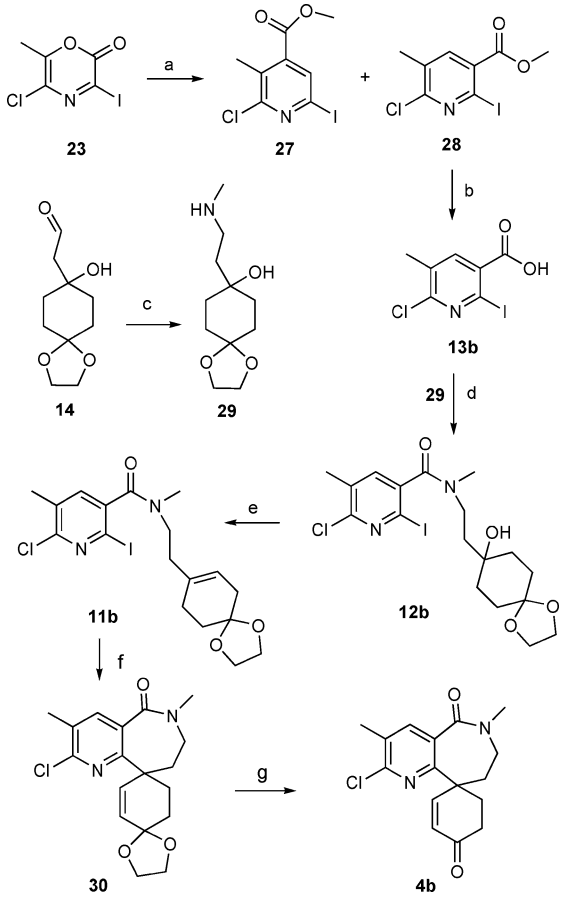


Scheme 6. Reagents and conditions: (a) allylmagnesium chloride (2 equiv.), THF, –78 °C, 30 min. (85%); (b) cat. OsO_4, $NaIO_4$ (3 equiv.), Et_2O, H_2O, room temp., overnight (80%); (c) amine **24** (1 equiv.), $NaCNBH_3$ (1 equiv.) acetic acid (pH = 6), CH_3OH, room temp., 30 min (72%); (d) CH_3SO_2Cl (3 equiv.), NEt_3, CH_2Cl_2, room temp., 30 min. (60%).

Final ring closure of precursor **11a** to form the spiroannulated product **26** is a difficult step because it involves the generation of a seven-membered ring by attack of the trisubstituted end of the alkene on the palladated 2-I position. Various conditions including microwave irradiation were attempted to achieve this conversion, but the desired ring-closed product **26** could not be detected. This lack of success could also be due to complexation of the amine functionality of **11a** with the catalyst. Therefore, we tried to overcome this problem by using amide precursor **11b** instead of amine **11a**.

To synthesise precursor **11b**, we started with the Diels–Alder reaction of methyl propiolate on 2-iodooxazinone **23**, which provided a mixture of regioisomers **27** and **28** (Scheme 7). These were easily separated by column chromatography and characterised by ^1H and ^{13}C NMR spectroscopy, and their data was found to be in accordance with the spectroscopic data for the already known 2-chloropyridine regioisomers.[9] Methyl ester saponification of regioisomer **28** afforded the corresponding 3-substituted acid **13b**.

Amide **12b** was prepared (60%) by coupling acid **13b** with amine **29** by using 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDCI) and 1-hydroxybenzotriazole (HOBt) in dichloromethane. Required amine **29** was generated by treatment of aldehyde **14** with methylamine, followed by addition of sodium borohydride to the preformed imine. Following elimination of the tertiary alcohol functionality in



Scheme 7. Reagents and conditions: (a) methyl propiolate (2 equiv.), toluene, 80 °C, 2 d (**27**: 20%; **28**: 60%); (b) NaOH, H_2O, 100 °C, 1 h (90%); (c) (i) CH_3NH_2 (5 equiv.), MeOH, room temp., 15 min (ii) $NaBH_4$ (1 equiv.) room temp., 15 min (82%); (d) EDCI (1.5 equiv.), HOBt (1.2 equiv.), CH_2Cl_2, room temp., 2 h, (60%); (e) CH_3SO_2Cl (3 equiv.), NEt_3, CH_2Cl_2, room temp., 30 min (60%); (f) $Pd(OAc)_2$ (0.4 equiv.), resin-bound triphenylphosphane (0.5 equiv.), K_2CO_3 (4 equiv.) acetonitrile, microwave, 100 °C, 15 min, 150 W (40%). or $Pd(OAc)_2$ (0.2 equiv.), resin-bound triphenylphosphane (0.5 equiv.), K_2CO_3 (4 equiv.), acetonitrile, 120 °C, 3 h (18%); (g) HCl, H_2O, CH_2Cl_2, room temp., 4 h (60%).

12b, Heck reaction was carried out on the resulting cyclohexene 2-iodopyridine precursor **11b**, which produced spirocyclic compound **30** in 40% (microwave conditions) and 18% (normal heating conditions) yield. To prevent difficult chromatographic separations, resin-bound triphenylphosphane was used as a ligand for the $Pd(OAc)_2$ catalyst. In a last step, the ketone functionality was deprotected by using hydrochloric acid to provide target **4b**.

Enzyme Kinetic Experiments

The ability of new ligands **3a**–**d** and **4b** to inhibit the enzymatic activity of acetylcholinesterase was measured spectrophotometrically and is expressed as inhibition constants K_I. Values for K_I were calculated from the equation for competitive inhibition, which relates the reaction velocity in the presence of inhibitor to the substrate concentration by using the relevant K_M. The assays were carried out according to the colorimetric method of Ellman.[12]

The tested compounds showed significant AChE inhibition activity (K_I = 514 μM for **3a**; K_I = 70 μM for **3b**; K_I = 99 μM for **3c**; K_I = 150 μM for **3d**; K_I = 77 μM for **4b**), but it was lower than that of galanthamine (K_I = 3 μM).[13] From these data, it clearly appears that six-membered lactam compounds **3b**,**c** exhibit superior activity relative to five-membered lactam **3a**.

Modelling

The influence of structural variations on the inhibition activities of galanthamine and target structures **3a**–**d** and **4** was investigated by comparative modelling studies and docking simulations. Molecular modelling was performed by using the Molecular Operating Environment (MOE).[14] Docking experiments were based on the crystal structure of the acetylcholinesterase–galanthamine complex retrieved from the pdb databank (pdb entry 1QTI[15]). In a first step, the binding site was defined by using the site-finder algorithm implemented in MOE.[16] The site was filled with alpha spheres. The centres of these spheres were used for the placement of the ligands by using the Alpha Triangle placement method. The different conformations used for docking were calculated by using a stochastic conformational search, which included a change in chirality at the stereogenic centre. For each compound, a total number of 100 different binding modes were allowed. London ΔG was used as a scoring function to calculate the estimated free energy of binding. In a first approach, the docking protocol was verified by reproducing the binding mode of galanthamine in the crystal structure. Noticeably, docking of galanthamine succeeded only after the addition of cocrystallised water molecule 820 to the receptor structure. Clearly, this water molecule is important, as it interacts with both the receptor and the ligand through two hydrogen bonds involving, respectively, the NH groups of Gly-119 and Ala-201 and the oxygen atoms of the aromatic MeO group and the axial OH group on the cyclohexene ring. The cyclohexene ring in turn interacts with the aromatic residues Trp-84, Phe-330 and Tyr-334 in the hydrophobic pocket. Galanthamine thus acts as a reversible inhibitor that competes with acetylcholine for access to the catalytic triad Ser-203, His-447 and Glu-334 at the bottom of the cleft.

By using similar settings, the target structures discussed in this study were docked in the receptor and their binding modes and estimated binding energy were analysed. The scoring values of these docking simulations (galanthamine: –9.3 kcal/mol, **3a**: –6.1 kcal/mol, **3b**: –7.2 kcal/mol, **3c**: –6.8 kcal/mol, **3d**: –7.0 kcal/mol and **4b**: –8.3 kcal/mol) are in line with the inhibitor activities mentioned before.

In comparison to galanthamine, both hydrogen-accepting properties of the aromatic MeO and axial OH group are absent in the target structures, which explains the overall decrease in the estimated binding energy to the receptor–water complex. Six-membered spiro structures (*R*)-

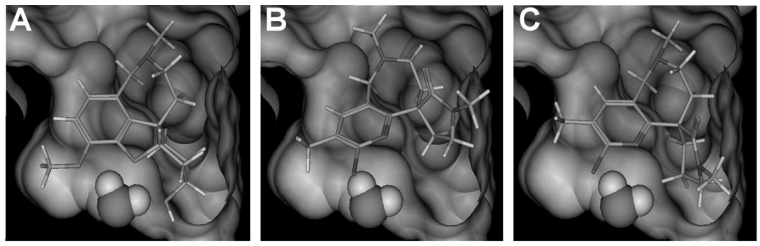


Figure 4. The binding mode of galanthamine in the catalytic cleft of the enzyme clearly reveals the hydrogen bonding interactions with a water molecule (a). The target compounds presented in this study no longer exhibit this interaction, which explains the decrease in activity. The least potent derivative (**3a**) is unable to fill the hydrophobic pocket (b) in comparison to other more potent derivatives such as compound **3b** (c). Graphic representations were rendered by using MOE. The ligands are visualised as sticks inside the receptor cartoon and surface. The water molecule is represented as spheres.

3b–**d** and **4b** retain a favourable interaction with the hydrophobic pocket. In the case of amide compounds (*R*)-**3b**–**d**, it should be noticed that the carbonyl group next to the stereogenic centre points upward into a void volume, which allows solvation by water [see form (*R*)-**3b** in Figure 4]. For enantiomeric amides (*S*)-**3b**–**d**, however, the corresponding carbonyl group is oriented downward, which clashes with the wall of the hydrophobic pocket. Finally, unlike six-membered spirocycles **3b**–**d** and **4b**, five-membered spirocycle **3a** is unable to fill the hydrophobic pocket. This unfavourable unoccupied space causes a significant decrease in binding interactions with the pocket, which results in a further loss in activity.

These insights should permit the design of new derivatives based on the same scaffold, in which the pharmacophoric properties of galanthamine − involving hydrogen bonding with the receptor bound water molecule − are conserved, which thus maintains a similar inhibition potency.

Conclusions

In this work, spirocyclic pyridoazepines designed as simplified analogues of the alkaloid galanthamine were synthesised and evaluated as inhibitors of acetylcholinesterase. The key cyclisation step of our synthesis was accomplished either by nucleophilic aromatic substitution (targets **3**) or by Heck reaction (targets **4**).

Experimental Section

General Remarks: Analytical and preparative thin-layer chromatography were performed on TLC plates coated with Alugram Sil G/UV254. Column chromatography was carried out by using 70–230 mesh silica gel 60 (E.M. Merck) as the stationary phase. ^{1}H and ^{13}C NMR spectra were recorded with Bruker AMX 400 and Bruker Avance 300 spectrometers; chemical shifts (δ) are given in ppm relative to tetramethylsilane as an internal reference. Mass spectra were recorded with a Hewlett Packard MS Engine 5989 apparatus for EI and CI spectra and a Kratos MS 50 TC instrument by using a MASPEC II data system for exact mass measurements performed in the EI mode at a resolution of 10000. Infrared spectra were recorded with a Perkin –Elmer 1720 Fourier transform spectrometer. All melting points are uncorrected and were measured with an Electrothermal IA 9000 digital melting point apparatus. Preparative HPLC separations were performed with an Alltech Prevail C18 column (5 μM) by using a gradient of MeOH and H_2O with 0.5% formic acid.

Enzyme Kinetic Experiments: Following solutions were used: acetylthiocholine iodide (substrate; Sigma): 30 mM (43.3 mg in 5 mL water), 15 mM, 6 mM, 3 mM, 1.5 mM; 5,5′-dithiobis-2-nitrobenzoic acid (reagent; Aldrich): 10 mM (39.6 mg in 10 mL 0.1 M sodium phosphate buffer pH 7.0); AChE from electric eel (enzyme; Sigma, lyophilised powder): 5 units/mL (0.20 mg in 11.4 mL 0.1 M sodium phosphate buffer pH 7.0); 0.1 M sodium phosphate buffer pH 8.0; inhibitors are dissolved in [D_6]DMSO (approximately 2 mg/mL).

Measurements are performed at 25 °C with a Shimadzu UV-1601 spectrophotometer equipped with a temperature-controlled cuvette holder and PC for data storage by using 1-cm polystyrene cuvettes: 0.725 mL buffer solution pH 8, 12.5 μL substrate, 25 μL reagent, 12.5 μL inhibitor (or [D_6]DMSO in tests without inhibitor) were mixed; after autozero, 12.5 μL enzyme is added. The absorbance at 412 nm is measured for 5 min, which allows determination of the initial velocity (ΔA/s). Tests were done without inhibitor, with galanthamine hydrobromide as inhibitor and with compounds **3a**–**d** and **4b** as inhibitor. Inhibitors were tested at 3 to 5 substrate concentrations.

3,5-Dichloro-6-methyl-2*H*-1,4-oxazin-2-one (15): A solution of lactonitrile (10 mL, 0.139 mol) in chlorobenzene (90 mL) was added slowly to a stirred solution of oxalyl chloride (53.08 mL, 0.556 mol) in chlorobenzene (400 mL) under an inert atmosphere at 0 °C. The temperature was raised to 90 °C, and triethylammonium chloride (9.625 g, 70 mmol) was added. After stirring at 90 °C for 3 h, the solvent was evaporated under reduced pressure. The residue was dissolved in Et_2O (400 mL). The precipitated triethylammonium chloride was filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel; heptane/EtOAc, 80:20). Yield: 22.4 g (90%). M.p. 70 °C. IR (KBr): $\tilde{\nu}$ = 2921, 1756 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.7, 150.1, 142.2, 123.8, 17.3 ppm. MS (EI): *m*/*z* (%) = 179 (100), 152 (4). HRMS (EI): calcd. for $C_5H_3Cl_2NO_2$ 178.9541; found 178.9545.

3-Bromomethyl-2,6-dichloro-5-methylpyridine (16): A solution of **15** (1 g, 5.6 mmol) and propargyl bromide (2 g, 16.8 mmol) in toluene was stirred overnight at 80 °C. After completion of the reaction, the solvent was removed under reduced pressure, and the crude compound was purified by column chromatography (silica gel; heptane/EtOAc, 95:5). Yield: 1.30 g (92%). M.p. 56 °C. IR (KBr): $\tilde{\nu}$ = 1590, 1550 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (s, 1 H), 4.53 (s, 2 H), 2.40 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.4, 147.1, 142.7, 132.6, 131.3, 28.5, 19.2 ppm. MS (EI): *m*/*z* (%)

= 253 (5), 174 (100). HRMS (EI): calcd. for $C_7H_6Cl_2BrN$ 252.9061; found 252.9099.

***N*-[(2,6-Dichloro-5-methyl-3-pyridyl)methyl]-*N*-methylamine (7):** A solution of methylamine in ethanol (33%, 7.2 mL, 165 mmol) was added to a solution of **16** (8 g, 33 mmol) in MeOH (100 mL) at 0 °C. The reaction mixture was stirred at room temp. for 4 h. After addition of H_2O (100 mL), the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layer was dried with $MgSO_4$. After evaporation of the solvent under reduced pressure, the product was purified by column chromatography (silica gel; heptane/EtOAc, 30:70). Yield: 5.72 g (85%). Yellow oil. IR (NaCl): $\tilde{\nu}$ = 3390, 2932, 2854, 2796 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.67 (s, 1 H), 3.79 (s, 2 H), 2.48 (s, 3 H), 2.36 (s, 3 H), 1.88 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.5, 146.6, 141.8, 133.3, 131.9, 52.0, 36.4, 19.1 ppm. MS (EI): *m*/*z* (%) = 204 (54), 189 (21), 174 (70), 169 (100). HRMS (EI): calcd. for $C_8H_{10}Cl_2N_2$ 204.0221; found 204.0181.

3-Allyl-1-methylpyrrolidine-2-one (18a) and 3-Allyl-1-methylpiperidine-2-one (18b): Lactam **17a** or **17b**. (10 mmol) was added to a stirred solution of LDA (2 M in heptane/THF, 5 mL, 10 mmol) in dry THF (10 mL) at –78 °C. After stirring for 15 min at –78 °C, allyl bromide (1.2 g, 10 mmol) was added. The mixture was stirred for 30 min at –78 °C. A saturated aqueous solution of NH_4Cl (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by distillation (**18a**) or by column chromatography (**18b**) (silica gel, heptane). Data for **18a**: Yield: 1.35 g (97%). Colourless oil. IR (NaCl): $\tilde{\nu}$ = 2960, 1691 cm^{-1}. ^1H NMR (300Mz, $CDCl_3$): δ = 5.77 (dtd, *J* = 24 Hz, *J* = 9 Hz, *J* = 4 Hz, 1 H), 5.06 (d, *J* = 24 Hz, 1 H), 5.04 (s, 1 H), 3.36 (td, *J* = 8 Hz, *J* = 3 Hz, 1 H), 3.28 (td, *J* = 8 Hz, *J* = 3 Hz, 1 H), 2.83 (s, 3 H), 2.64 (td, *J* = 7.5 Hz, *J* = 2 Hz, 2 H), 2.36 (t, *J* = 7.5 Hz, 1 H), 2.18–2.10 (m, 1 H), 2.00 (td, *J* = 7.3 Hz, *J* = 1.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.4, 136.0, 117.1, 48.0, 41.6, 35.9, 30.1, 24.3 ppm. MS (EI): *m*/*z* (%) = 139 (100), 98 (80). HRMS (EI): calcd. for $C_7H_{13}NO$ 139.0997; found 139.0998. Data for **18b**: Yield: 1.22 g (80%). Yellow oil. IR (NaCl): $\tilde{\nu}$ = 2940, 2866, 1636 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.60 (m, 1 H), 4.88 (d, *J* = 21 Hz, 1 H), 4.87 (d, *J* = 4 Hz, 1 H), 3.16–3.10 (m, 2 H), 2.77 (s, 3 H), 2.54–2.46 (m, 1 H), 2.20–2.14 (m, 2 H), 1.76–1.70 (m, 2 H), 1.64–1.56 (m, 1 H), 1.45–1.38 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.8, 116.9, 50.4, 41.3, 36.6, 35.1, 26.3, 21.8 ppm. MS (EI): *m*/*z* (%) = 153 (100), 112 (67). HRMS (EI): calcd. for $C_9H_{15}NO$ 153.1154; found 153.1162.

Aldehydes 8a and 8b

Procedure A: A solution of **18a** or **18b** (6.5 mmol) in CH_2Cl_2 (20 mL) and MeOH (10 mL) was cooled to –78 °C. Ozone was passed through the reaction mixture for 20 min. The mixture was stirred at –78 °C for 10 min; then, oxygen was passed through the flask to remove the excess amount of ozone. NEt_3 (2 mL) was added, and the reaction mixture was warmed to room temp. After stirring overnight, the mixture was concentrated under reduced pressure.

Procedure B: A catalytic amount of OsO_4 and $NaIO_4$ (4.1 g, 19.5 mmol) was added to a solution of **18a**,**b** (6.5 mmol) in Et_2O (10 mL) and H_2O (10 mL). The heterogeneous mixture was stirred at room temp. overnight. After addition of water, the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was concentrated under reduced pressure. Crude **8a** and **8b** were used immediately in the next step. The aldehydes could be detected by MS (CI; $[M + H]^+$ ions at *m*/*z* = 142 for **8a** and *m*/*z* = 156 for **8b**) and NMR spectroscopy (characteristic peaks for the CHO group: δ = 9.76 ppm in ^1H NMR and 201.0 ppm in ^{13}C NMR for **8a**; δ = 9.79 ppm in ^1H NMR and 201.2 ppm in ^{13}C NMR for **8b**).

3-(2-{[(2,6-Dichloro-5-methyl-3-pyridinyl)methyl](methyl)amino}-ethyl)-1-methyl-2-pyrrolidinone (6a) and 3-(2-{[(2,6-Dichloro-5-methyl-3-pyridinyl)methyl](methyl)amino}ethyl)-1-methyl-2-piperidinone (6b): Acetic acid was added to a solution of amine **7** (1 g, 4.8 mmol) in MeOH (50 mL) until pH 6. $NaCNBH_3$ (0.32 g, 4.8 mmol) was added followed by aldehyde **8a** or **8b** (4.8 mmol). The mixture was stirred at room temp. for 15 min. After addition of a saturated aqueous solution of K_2CO_3 (50 mL), the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel; CH_2Cl_2/MeOH, 98:2). Data for **6a**: Yield: 1.34 g (85%). Yellow oil. IR (NaCl): $\tilde{\nu}$ = 3053, 2985, 2305, 2254 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.69 (s, 1 H), 3.54 (s, 2 H), 3.29 (t, *J* = 6.7 Hz, 2 H), 2.85 (s, 3 H), 2.55 (t, *J* = 7.1 Hz, 2 H), 2.51–2.45 (m, 1 H), 2.36 (s, 3 H), 2.24 (s, 3 H), 2.15–2.12 (m, 2 H), 1.72–1.58 (m, 1 H), 1.57–1.45 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.9, 148.6, 147.0, 142.5, 132.8, 131.8, 57.9, 55.9, 48.0, 42.6, 40.0, 30.1, 29.6, 25.5, 19.3 ppm. MS (EI): *m*/*z* (%) = 329 (20), 217 (55), 174 (100). HRMS (EI): calcd. for $C_{15}H_{21}N_3OCl_2$ 329.1062; found 329.1063. Data for **6b**:Yield: 0.99 g (60%). Yellow oil. IR (NaCl): $\tilde{\nu}$ = 3053, 2950, 1627 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.73 (s, 1 H), 3.46 (s, 2 H), 3.28–3.18 (m, 2 H), 2.92 (s, 3 H), 2.52–2.42 (m, 2 H), 2.35–2.28 (m, 1 H), 2.26 (s, 3 H), 2.25 (s, 3 H), 1.90–1.80 (m, 2 H), 1.76–1.66 (m, 1 H), 1.55–1.40 (m, 3 H) ppm.^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9, 148.4, 146.9, 142.7, 132.8, 131.8, 57.7, 55.8, 50.4, 42.4, 39.6, 35.3, 29.7, 27.1, 22.2, 19.2 ppm. MS (EI): *m*/*z* (%) = 343 (13), 231 (74), 113 (100), 169 (93). HRMS (EI): calcd. for $C_{16}H_{23}N_3OCl_2$ 343.1219; found 343.1210.

Spirocyclic Compound 3a: Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 0.06 mL, 0.03 mmol) was added to a solution of compound **6a** (10 mg, 0.03 mmol) in dry toluene (1 mL). The reaction mixture was flushed with argon, and the reaction vessel was closed. The mixture was irradiated in the microwave apparatus at 100 °C for 15 min (200 W, no simultaneous cooling). After addition of water (5 mL), the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel; heptane/EtOAc, 50:50). Yield: 7 mg (85%). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.24 (s, 1 H), 4.20 (d, *J* = 14.6 Hz, 1 H), 3.62 (d, *J* = 14.6 Hz, 1 H), 3.46 (dd, *J* = 16.3 Hz, *J* = 9 Hz, 1 H), 3.30 (td, *J* = 9 Hz, *J* = 3.4 Hz, 1 H), 3.11–3.05 (m, 1 H), 3.02–2.95 (m, 1 H), 2.92 (s, 3 H), 2.73–2.65 (m, 1 H), 2.47 (s, 3 H), 2.48–2.40 (m, 1 H), 2.29 (s, 3 H), 2.09 (dt, *J* = 13 Hz, *J* = 8 Hz, 1 H), 1.85–1.80 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.6, 158.8, 148.5, 141.9, 130.1, 58.2, 55.1, 54.0, 46.8, 43.9, 32.3, 32.1, 30.1, 18.8 ppm. MS (EI): *m*/*z* (%) = 293 (100), 278 (32), 264 (51), 236 (74), 149 (21), 97 (15), 57 (30). HRMS: calcd. for $C_{15}H_{20}ClN_3O$ 293.1295; found 293.1297.

Spirocyclic Compound 3b: Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 0.06 mL, 0.03 mmol) was added to a solution of compound **6b** (10 mg, 0.03 mmol) in dry toluene (1 mL). The reaction mixture was flushed with argon, and the reaction vessel was closed. The mixture was irradiated in the microwave apparatus at 80 °C for 10 min (200 W, no simultaneous cooling). After addition of water (5 mL), the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by reverse-phase HPLC (MeOH/H_2O with 0.1% formic acid). Yield: 0.4 mg (5%).

Yellow oil. MS (EI): *m/z* (%) = 307 (18), 292 (15), 272 (100), 149 (32), 97 (47), 57 (100). HRMS: calcd. for $C_{16}H_{22}ClN_3O$ 307.1451; found 307.1448.

Methyl 4-{[(2,6-Dichloro-5-methyl-3-pyridyl)methyl](methyl)amino}-butanoate (9): To a solution of bromomethylpyridine **16** (16 g, 63 mmol) in CH_2Cl_2 (400 mL) was added (11 g, 63 mmol) methyl (methylamino)butanoate and NEt_3 (36 mL,189 mmol). After stirring at room temp. for 30 min, H_2O (300 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 300 mL). The combined organic layer was dried with $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel; heptane/EtOAc, 80:20 to 0:1). Yield: 15.5 g (81%). Yellow oil. IR (NaCl): $\tilde{\nu}$ = 2952, 1739 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.71 (s, 1 H), 3.56 (s, 3 H), 3.51 (s, 2 H), 2.44 (t, *J* = 7.2 Hz, 2 H), 2.29 (t, *J* = 7.2 Hz, 2 H), 2.27 (s, 3 H), 2.18 (s, 3 H), 1.79 (q, *J* = 7.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.1, 148.8, 146.9, 142.8, 132.0, 131.9, 57.7, 57.0, 51.9, 42.1, 31.9, 22.6, 19.1 ppm. MS (EI): *m/z* (%) = 305 (5), 203 (6), 174 (100). HRMS (EI): calcd. for $C_{13}H_{18}N_2O_2Cl_2$ 304.0745; found 304.0728.

Methyl 2-Chloro-3,6-dimethyl-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]-azepine-9-carboxylate (10): A solution of $KN(SiMe_3)_2$ in toluene (0.5 M, 14.4 mL, 7.21 mmol) was added to a solution of pyridine **9** (1 g, 3.28 mmol) in dry toluene (50 mL) under argon atmosphere. The reaction mixture was stirred at 80 °C for 10 min and cooled to –78 °C; a saturated aqueous solution NH_4Cl (10 mL) was then added. After 10 min, the mixture was warmed up to room temp. A saturated aqueous solution of K_2CO_3 was added to pH 8. After extraction with CH_2Cl_2 (3 × 50 mL), the organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel; CH_2Cl_2/MeOH, 95:5). Yield: 659 mg (75%). Yellow oil. IR (NaCl): $\tilde{\nu}$ = 2956, 1741 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.32 (s, 1 H), 4.15 (dd, *J* = 6.8 Hz, 2.8 Hz, 1 H), 3.80 (d, *J* = 14.8 Hz, 1 H), 3.75 (s, 3 H), 3.59 (d, *J* = 14.8 Hz, 1 H), 3.08–2.90 (m, 2 H), 2.34 (s, 3 H), 2.33 (s, 3 H), 2.24–2.19 (m, 1 H), 2.12–2.06 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 172.4, 156.5, 148.4, 141.4, 133.5, 130.5, 59.7, 56.8, 53.0, 52.1, 43.7, 26.2, 18.9 ppm. MS (EI): *m/z* (%) = 268 (29), 253 (26), 209 (100). HRMS: calcd. for $C_{13}H_{17}ClN_2O_2$ 268.0978; found 268.0971.

Methyl 2-Chloro-9-(2-cyanoethyl)-3,6-dimethyl-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepine-9-carboxylate (20): Potassium *tert*-butoxide (120 mg, 0.98 mmol) was added to a solution of **10** (222 mg, 0.82 mmol) in dry THF (l0 mL) under a nitrogen atmosphere. After stirring at room temp. for 10 min, acrylonitrile (53 mg, 0.98 mmol) and *tert*-butyl alcohol (5 mL) were added. The reaction mixture was stirred at room temp. for 15 min and a saturated aqueous solution of NH_4Cl (10 mL) was then added. The mixture was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic layer was dried with $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (silica gel; CH_2Cl_2/MeOH, 98:2). Yield: 160 mg (61%). Brown oil. IR (NaCl): $\tilde{\nu}$ = 3054, 2984, 1728 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (s, 1 H), 3.70 (s, 3 H), 3.66 (d, *J* = 7.5 Hz, 1 H), 3.51 (d, *J* = 7.5 Hz, 1 H), 2.87–2.83 (m, 2 H), 2.62–2.59 (m, 3 H), 2.34–2.24 (m, 2 H), 2.30 (s, 3 H), 2.29 (s, 3 H), 1.90–1.80 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 155.8 147.8, 141.3, 133.3, 130.6, 120.2, 59.8, 55.1, 54.6, 52.2, 44.6, 34.5, 33.9, 18.8, 13.5 ppm. MS (EI): *m/z* (%) = 321 (28), 235 (85), 223 (100), 174 (60). HRMS: calcd. for $C_{16}H_{20}ClN_3O_2$ 321.1244; found 321.1249.

Spirocyclic Compound 3c: $CoCl_2$ (400 mg, 3.10 mmol) and $NaBH_4$ (465 mg,15.5 mmol) were added to a solution of nitrile **20** (0.5 g, 1.55 mmol) in MeOH (30 mL). The reaction mixture was stirred at room temp. overnight to form amine **21** and then H_2O (10 mL) was added slowly. Following the addition of saturated K_2CO_3 solution (25 mL), the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was dried with $MgSO_4$, and the solvent was evaporated under reduced pressure. Crude **21** was dissolved in MeOH, and the solution was heated at reflux overnight to effect ring closure. Crude lactam product **3c** was purified by reverse-phase HPLC (MeOH/H_2O with 0.1% formic acid). Yield: 259 mg (57%). Yellow oil. ^1H NMR (300 MHz, CD_3OD): δ = 8.47 (br. s, 1 H), 7.64 (s, 1 H), 4.45 (d, *J* = 12.3 Hz, 1 H), 4.19 (d, *J* = 12.3 Hz, 1 H), 3.65–3.35 (m, 3 H), 3.18–3.10 (m, 1 H), 2.77 (s, 3 H), 2.68–2.50 (m, 2 H), 2.37 (s, 3 H), 2.25–2.19 (m, 1 H), 2.08–1.96 (m, 1 H), 1.94–1.84 (m, 2 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 173.6, 161.4, 146.6, 141.9, 132.7, 128.7, 56.3, 52.7, 52.6, 44.4, 41.5, 32.0, 31.8, 18.2, 18.1 ppm. MS (EI): *m/z* (%) = 293 (100), 278 (22), 264 (44), 207 (33). HRMS: calcd. for $C_{15}H_{20}ClN_3O$ 293.1295; found 293.1293.

Methyl 9-(3-Amino-3-oxopropyl)-2-chloro-3,6-dimethyl-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepine-9-carboxylate (22): A solution of nitrile **20** (0.5 g, 1.55 mmol.) and CH_3SO_3H (3 mL) in toluene (10 mL) was heated at 100 °C for 2 h. After addition of a saturated aqueous solution of K_2CO_3 until basic, the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layer was dried with $MgSO_4$. The residue was purified by reverse-phase HPLC (MeOH/H_2O with 0.1% formic acid) to give product **22**. Yield: 436 mg (83%). Yellow oil. ^1H NMR (400 MHz,$CDCl_3$): δ = 7.38 (s, 1 H), 6.30 (br. s, 1 H), 5.45 (br. s, 1 H), 3.81 (s, 2 H), 3.72 (s, 3 H), 3.11–3.07 (m, 2 H), 2.56–2.47 (m, 3 H), 2.45 (s, 3 H), 2.35 (s, 3 H), 2.31–2.16 (m, 2 H), 2.10–2.01 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.7, 173.7, 157.1, 148.8, 142.6, 131.1, 130.5, 58.5, 55.5, 54.6, 52.4, 43.1, 34.8, 32.6, 32.2, 18.7 ppm. MS (EI): *m/z* (%) = 339 (45), 235 (100). HRMS: calcd. for $C_{16}H_{22}ClN_3O_3$ 339.1350; found 339.1345.

Spirocyclic Compound 3d: A solution of amide **22** (200 mg, 0.58 mmol) and *t*BuOK (80 mg, 0.70 mmol) in *t*BuOH (5 mL) was stirred at room temp. for 1 h. Following addition of a saturated aqueous solution of NH_4Cl (10 mL), the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried with $MgSO_4$. The residue was purified by reverse-phase HPLC (MeOH/H_2O with 0.1% formic acid) to give product **3d**. Yield: 107 mg (60%). Yellow oil. ^1H NMR (400 MHz, CD_3OD): δ = 8.43 (br. s, 1 H), 7.65 (s, 1 H), 4.24 (d, *J* = 14.6 Hz, 1 H), 3.99 (d, *J* = 14.6 Hz, 1 H), 3.36–3.27 (m, 1 H), 3.18–3.12 (m, 1 H), 2.82–2.68 (m, 2 H), 2.61 (s, 3 H), 2.60–2.54 (m, 1 H), 2.39 (s, 3 H), 2.44–2.28 (m, 1 H), 2.24–2.16 (m, 1 H), 2.04–1.96 (m, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 178.7, 176.1, 159.7, 150.6, 145.2, 133.3, 124.7, 58.5, 55.0, 54.8, 44.7, 33.2, 30.1, 29.7, 19.4 ppm. MS (EI): *m/z* (%) = 307 (75), 235 (36), 213 (35), 170 (100). HRMS: calcd. for $C_{15}H_{18}ClN_3O_2$ 307.1088; found 307.1097.

5-Chloro-3-iodo-6-methyl-2*H*-1,4-oxazin-2-one (23): NaI (2 g, 13.36 mmol) and a catalytic amount of camphorsulfonic acid were added to a solution of **15** (1.00 g, 5.56 mmol) in acetone (50 mL). The reaction mixture was stirred at room temp. for 3 h. After addition of H_2O (50 mL), the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with brine and dried with $MgSO_4$. After evaporation of the solvent under reduced pressure, compound **23** was isolated as a solid. Yield: 3.55 g (98%). M.p. 200 °C (decomp.). IR (KBr): $\tilde{\nu}$ = 2912, 1729 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.31 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.0, 150.1, 125.6, 115.0, 17.21 ppm. MS (EI): *m/z* (%) = 272 (100), 244 (11). HRMS (EI): calcd. for $C_5H_3ClINO_2$ 270.8897; found 270.8931.

3-(Bromomethyl)-6-chloro-2-iodo-5-methylpyridine (13a): A solution of **23** (7.00 g, 25.7 mmol) and propargyl bromide (9 mL, 77 mmol) in toluene (30 mL) was heated at 80 °C for 2 d. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (silica gel; heptane/EtOAc, 95:5) to give product **13a**. Yield: 7.16 g (81%). M.p. 69 °C. IR (KBr): $\tilde{\nu}$ = 2955, 2913 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.54 (s, 1 H), 4.47 (s, 2 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.1, 140.1, 137.4, 132.6, 116.9, 34.7, 18.9 ppm. MS (EI): *m*/*z* (%) = 345 (64); 210 (7) 266 (100). HRMS: calcd. for $C_7H_6ClBrIN$ 344.8417; found 344.8428.

***N*-[(6-Chloro-2-iodo-5-methyl-3-pyridinyl)methyl]-*N*-methylamine (24):** Methylamine (40% in ethanol, 2.1 mL, 22.7 mmol) was added to a solution of **13a** (1.58 g, 4.55 mmol) in CH_3OH (30 mL). The reaction mixture was stirred at room temp. for 4 h. A saturated solution of K_2CO_3 (40 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel; heptane/EtOAc, 70:30) to give product **24**. Yield: 1.24 g (92%). M.p. 59 °C. IR (KBr): $\tilde{\nu}$ = 3300, 2931, 2840, 2792 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.46 (s, 1 H), 3.55 (s, 2 H), 2.44 (s, 3 H), 2.16 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.7, 146.7, 141.8, 138.5, 131.9, 52.1, 36.4, 19.2 ppm. MS (EI): *m*/*z* (%) = 339 (45), 235 (100). HRMS: calcd. for $C_8H_{10}ClIN_2$ 295.9577; found 295.9567.

8-Allyl-1,4-dioxaspiro[4.5]decan-8-ol (25): Allylmagnesium chloride (2 M in THF, 15 mL, 25.64 mmol) was added to a cooled (–78 °C) stirred solution of 1,4-cyclohexanedione monoethylene ketal (2 g, 12.82 mmol) in dry THF (20 mL). After reaction at –78 °C for 30 min, a saturated NH_4Cl solution (20 mL) was added. The mixture was warmed to room temp. and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel; heptane/EtOAc, 90:10) to give product **25**. Yield: 2.16 g (85%). Yellow oil. IR (NaCl): $\tilde{\nu}$ = 3473, 3055, 2935 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.91–5.67 (m, 1 H), 5.15–4.85 (m, 2 H), 3.90 (s, 4 H), 2.19 (d, *J* = 7.2 Hz, 2 H), 1.64–1.45 (m, 8 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.9, 119.2, 109.2, 70.3, 64.5, 47.2, 34.9, 30.8 ppm (2D spectra showed coincidence of some signals). MS (EI): *m*/*z* (%) = 198 (6), 180 (24), 257 (100). HRMS (EI): calcd. for $C_{11}H_{18}O_3$ 198.1256; found 198.1253.

8-Hydroxy-1,4-dioxaspiro[4.5]dec-8-ylacetaldehyde (14): $NaIO_4$ (6 g, 28.1 mmol) and a catalytic amount of OsO_4 were added to a solution of compound **25** (2 g, 10.1 mmol) in Et_2O/H_2O (3:4, 50 mL). The mixture was stirred at room temp. overnight. After addition of H_2O (50 mL), the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was dried with $MgSO_4$, and the solvent was evaporated under reduced pressure to give aldehyde **14**, which was used in the next step without further purification. Yield: 1.62 g (80%). Yellow oil. IR (NaCl): $\tilde{\nu}$ = 3473, 3054, 2957, 1710 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.85 (s, 1 H), 3.92 (s, 4 H), 2.61 (s, 2 H), 1.98–1.48 (m, 8 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.6, 110.0, 70.2, 64.7, 54.9, 35.4, 30.5 ppm (2D spectra showed coincidence of some signals). MS (EI): *m*/*z* (%) = 200 (25), 182 (100), 157 (65), 156 (35). HRMS (EI): calcd. for $C_{10}H_{16}O_4$ 200.1045; found 200.1049.

8-(2-{[(6-Chloro-2-iodo-5-methyl-3-pyridinyl)methyl](methyl)-amino}ethyl)-1,4-dioxaspiro[4.5]decan-8-ol (12a): A mixture of **24** (400 mg, 0.83 mmol), aldehyde **14** (166 mg, 0.83 mmol) and $NaCNBH_3$ (46 mg, 0.83 mmol) in CH_3OH (10 mL) was acidified with CH_3COOH until pH 6. The reaction mixture was stirred at room temp. for 30 min. After slow addition of H_2O (10 mL), a saturated aqueous solution of K_2CO_3 (15 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was dried with $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel; CH_2Cl_2/MeOH, 98:2) to give product **12a**. Yield: 287 mg (72%). Yellow oil. IR (NaCl): $\tilde{\nu}$ = 3053, 2986, 2305, 1421, 1101 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43 (s, 1 H), 3.96 (s, 4 H), 3.53 (s, 2 H), 2.69 (t, *J* = 5.8 Hz, 2 H), 2.32 (s, 3 H), 2.31 (s, 3 H), 1.98–1.92 (m, 4 H), 1.68 (t, *J* = 6 Hz, 2 H), 1.57–1.47 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.5, 140.5, 137.0, 132.1, 117.8, 109.1, 70.6, 64.2, 64.1, 53.4, 41.8, 36.2, 35.1, 30.3, 18.9 ppm (2D spectra showed coincidence of some signals). MS (EI): *m*/*z* (%) = 480 (3), 309 (100), 295 (24), 265 (50). HRMS: calcd. for $C_{18}H_{26}ClIN_2O_3$ 480.0677; found 480.0669.

***N*-[(6-Chloro-2-iodo-5-methyl-3-pyridiyl)methyl](1,4-dioxaspiro[4.5]-dec-7-en-8-yl)-*N*-methylethanamine (11a):** Methanesulfonyl chloride (0.3 mL, 3 mmol) and triethylamine (1 mL) were added to a solution of **12a** (475 mg, 1 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temp. for 45 min and then H_2O (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic layer was dried with $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (alumina; CH_2Cl_2/MeOH, 97:3) to give product **11a**. Yield: 277 mg (60%). Yellow oil. IR (NaCl): $\tilde{\nu}$ = 3053, 2986, 1654, 1421, 1265 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.97 (s, 1 H), 5.37 (s, 1 H), 3.95 (s, 4 H), 3.85 (s, 2 H), 2.85 (t, *J* = 7.3 Hz, 2 H), 2.49 (s, 3 H), 2.36 (t, *J* = 7.3 Hz, 2 H), 2.34 (s, 3 H), 2.23 (s, 2 H), 2.17 (t, *J* = 6.2 Hz, 2 H), 1.74 (t, *J* = 6.3 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.3, 141.7, 134.0, 134.0, 132.9, 120.6, 117.9, 107.7, 64.4, 62.2, 55.5, 41.1, 35.7, 31.5, 31.1, 27.7, 18.8 ppm (2D spectra showed coincidence of some signals). MS (EI): *m*/*z* (%) = 462 (25), 217 (100). HRMS (EI): calcd. for $C_{18}H_{24}O_2ClIN_2$ 462.0571; found 462.0565.

Methyl 6-Chloro-2-iodo-5-methylnicotinate (28) and Methyl 2-Chloro-6-iodo-3-methylisonicotinate (27): A solution of oxazinone **23** (3 g, 11 mmol) and methyl propiolate (2.8 mL, 33 mmol) in toluene (10 mL) was stirred at 80 °C for 2 d. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (silica gel; heptane/EtOAc, 97:3) to give products **27** and **28**. Data for **27**: Yield: 684 mg (20%). M.p. 90 °C. IR (KBr): $\tilde{\nu}$ = 2957, 1723 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.90 (s, 1 H), 3.90 (s, 3 H), 2.46 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 153.0, 141.5, 133.7, 132.2, 111.4, 53.5, 17.1 ppm. MS (EI): *m*/*z* (%) = 311 (100), 279 (26), 252 (11), 184 (100). HRMS (EI): calcd. for $C_8H_7ClINO_2$ 310.9210; found 310.9211. Data for **28**: Yield: 2.05 g (60%). M.p. 76 °C. IR (KBr): $\tilde{\nu}$ = 2937, 1731 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.87 (s, 1 H), 3.96 (s, 3 H), 2.37 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 153.3, 141.3, 132.2, 131.9, 112.0, 53.3, 19.3 ppm. MS (EI): *m*/*z* (%) = 311 (87), 279 (30), 252 (10), 184 (100). HRMS (EI): calcd. for $C_8H_7ClINO_2$ 310.9210; found 310.9211.

Acid 13b: Compound **28** (1.00 g, 3.2 mmol) was heated in an aqueous solution of NaOH (0.5 M, 50 mL) at reflux for 30 min. After cooling to room temp., the solution was acidified with aqueous 2 M HCl. After extraction with CH_2Cl_2 (3 × 50 mL), the combined organic layer was dried with $MgSO_4$, filtered and evaporated under reduced pressure. Acid **13b** was isolated as a solid. Yield: 852 mg (90%). M.p. 159 °C. IR (KBr): $\tilde{\nu}$ = 3452, 2927, 1707, 1376, 1150 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 13.76 (br. s, 1 H), 8.02 (s, 1 H), 2.30 (s, 3 H) ppm. MS (EI): *m*/*z* (%) = 297 (100), 170

(38), 135 (19). HRMS (EI): calcd. for $C_7H_5ClINO_2$ 296.9054; found 296.9058.

8-[2-(Methylamino)ethyl]-1,4-dioxaspiro[4.5]decane-8-ol (29): A mixture of aldehyde **14** (700 mg, 3.50 mmol) and methylamine (33% in ethanol, 1 mL) in CH_3OH (10 mL) was stirred at room temp. for 15 min. The solution was cooled to 0 °C and $NaBH_4$ (265 mg, 7.2 mmol) was added slowly. After stirring at 0 °C for 10 min, H_2O (20 mL) was slowly added. The mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel; heptane/EtOAc, 70:30). Yield: 211 mg (28%). Brown oil. IR (NaCl): $\tilde{\nu}$ = 3270, 2955 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.90 (s, 4 H), 2.83 (t, J = 5.4 Hz, 2 H), 2.37 (s, 3 H), 1.95–1.90 (m, 2 H), 1.64–1.57 (m, 2 H), 1.48–1.38 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 109.6, 70.9, 64.6, 48.2, 38.9, 36.4, 35.8, 30.8 ppm (2D spectra showed coincidence of some signals). MS (EI): m/z (%) = 215 (9), 197 (100), 157 (17). HRMS (EI): calcd. for $C_{11}H_{21}NO_3$ 215.1521; found 215.1523.

6-Chloro-*N*-{2-(8-hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)ethyl}-2-iodo-*N*,5-dimethylnicotinamide (12b): A mixture of nicotinic acid **13b** (800 mg, 2.7 mmol) in dry CH_2Cl_2 (10 mL), EDCI (800 mg, 4.2 mmol) and HOBt (480 mg, 3.55 mmol) was stirred at room temp. for 10 min and then amine **29** (480 mg, 2.2 mmol) was added. After reaction at room temp. for 20 min, H_2O (15 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel; CH_2Cl_2/MeOH, 98:2) to give product **12b**. Yield: 652 mg (60%). Yellow oil. IR (NaCl): $\tilde{\nu}$ = 3054, 2985, 1637 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 2 amide rotamers): δ = 7.29 (s, 1 H), 3.98–3.92 (m, 4 H), 3.66 (t, J = 7.4 Hz, 1.4 H), 3.28 (t, J = 7.4 Hz, 0.6 H), 3.07 (s, 0.9 H), 2.88 (s, 2.1 H), 2.34 (s, 3 H), 1.87 (t, J = 7.4 Hz, 2 H), 1.90–1.53 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 2 amide rotamers): δ = 168.1, 150.6, 139.4, 139.1, 137.5, 133.7, 108.7, 69.4, 64.2, 46.4 and 43.3, 38.5, 36.7 and 32.6, 35.1, 30.4, 19.0 ppm (2D spectra showed coincidence of some signals). MS (EI): m/z (%) = 494 (18), 476 (16), 432 (10), 367 (15), 279 (100). HRMS (EI): calcd. for $C_{18}H_{24}O_4ClIN_2$ 494.0469; found 494.0469.

6-Chloro-*N*{2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)ethyl}-2-iodo-*N*,5-dimethylnicotinamide (11b): Methanesulfonyl chloride (0.3 mL, 3 mmol) and triethylamine (1 mL) were added to a solution of amide **12b** (475 mg, 1 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temp for 45 min and then H_2O (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic layer was dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (alumina; CH_2Cl_2/MeOH, 99:1) to give product **11b**. Yield: 286 mg (60%). Yellow oil. IR (NaCl): $\tilde{\nu}$ = 3054, 2985, 1637, 1375 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 2 amide rotamers): δ = 7.25 (s, 1 H), 5.31 (t, J = 6.7 Hz, 0.6 H), 5.11 (t, J = 6.7 Hz, 0.4 H), 3.95 (s, 4 H), 3.63 (t, J = 7.6 Hz, 1.2 H), 3.22 (t, J = 7.6 Hz, 0.8 H), 3.08 (s, 1.2 H), 2.84 (s, 1.8 H), 2.42–2.18 (m, 5 H), 2.32 (s, 3 H), 1.77 (t, J = 6.4 Hz, 1 H), 1.74–1.66 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 2 amide rotamers): δ = 168.0 and 167.6, 150.4, 143.0 and 142.6, 139.6 and 139.2, 137.5 and 137.4, 132.6 and 132.4, 121.6 and 120.6, 116.6 and 116.1, 107.9 and 107.5, 64.4, 49.8 and 45.6, 36.5 and 32.5, 35.9 and 35.8, 34.1 and 33.6, 31.1, 27.8 and 27.4, 19.0 and 18.9 ppm (2D spectra showed coincidence of some signals). MS (EI): m/z (%) = 476 (44), 349 (100). HRMS (EI): calcd. for $C_{18}H_{22}O_3ClIN_2$ 476.0364; found 476.0358.

2′-Chloro-3′,6′-dimethyl-7′,8′-dihydro-4*H*-spiro[cyclohex-2-ene-1,9′-pyrido(3,2-*c*)azepine]-4,5′(6′*H*)-dione Ethanediol Acetal (30)

Procedure A: Amide **11b** (30 mg, 0.06 mmol) was dissolved in CH_3CN (2 mL). Resin-bound PPh_3 (7 mg, 0.03 mmol, crosslinked with 2% DVB 200–400 mesh), $Pd(OAc)_2$ (3 mg, 0.0015 mmol) and K_2CO_3 (20 mg, 0.15 mmol) were then added. The reaction mixture was irradiated in the microwave oven at 100 °C for 15 min (150 W, no simultaneous cooling). After filtration of the catalyst and phosphane resin, H_2O (10 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the organic layers were dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by preparative thin-layer chromatography (silica gel, EtOAc) to give product **30**.

Procedure B: The same reagents as used in procedure A were stirred and heated under an inert atmosphere at 100 °C for 3 h. Work up was the same as that in procedure A.

Yield: procedure A: 12.5 mg (60%), procedure B: 3.1 mg (15%). Yellow oil. IR (NaCl): $\tilde{\nu}$ = 3054, 2985, 1637, 1375 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.84 (s, 1 H), 6.09 (d, J = 10.2 Hz, 1 H), 5.59 (d, J = 10.2 Hz, 1 H), 3.94 (m, 4 H), 3.30 (t, J = 6.3 Hz, 2 H), 3.16 (s, 3 H), 2.48–2.42 (m, 1 H), 2.36 (s, 3 H), 2.25–2.10 (m, 2 H), 1.97–1.85 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 158.0, 151.8, 140.9, 137.8, 130.9, 130.0, 126.8, 104.7, 64.6, 48.6, 44.6, 41.4, 34.4, 33.9, 30.6, 18.9 ppm (2D spectra showed coincidence of some signals). MS (EI): m/z (%) = 348 (19), 205 (69), 248 (100), 177 (22). HRMS (EI): calcd. for $C_{18}H_{21}O_3ClN_2$ 348.1241; found 348.1240.

Spirocyclic Compound 4b: A mixture of acetal **30** (50 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) and aqueous HCl (1 M, 0.2 mL) was stirred at room temp. for 4 h and then a saturated aqueous solution of K_2CO_3 (5 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the organic layer was dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by reverse-phase HPLC (MeOH/H_2O with 0.1% formic acid) to give product **4b**. Yield: 29.3 mg (60%). Yellow oil. ^1H NMR (400 MHz, [D_6]DMSO): δ = 7.96 (s, 1 H), 7.17 (d, J = 10.3 Hz, 1 H), 5.90 (d, J = 10.3 Hz, 1 H), 3.36–3.32 (m, 2 H), 3.08 (s, 3 H) 2.55–2.50 (m, 1 H), 2.42–2.38 (m, 1 H), 2.37 (s, 3 H), 2.35–2.30 (m, 1 H), 2.28–2.21 (m, 1 H), 2.15–2.10 (m, 2 H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 197.9, 166.9, 157.1, 155.0, 150.5, 141.5, 131.3, 131.2, 126.5, 47.6, 44.7, 38.0, 34.6, 33.8, 33.7, 18.3 ppm. MS (EI): m/z (%) = 304 (34), 276 (22), 248 (100), 209 (73), 177 (30). HRMS (EI): calcd. for $C_{16}H_{17}O_2ClN_2$ 304.0979; found 304.0985.

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