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Synthesis of Spirocyclic Pyridoazepines as Analogues of Galanthamine by Nucleophilic Aromatic Substitution of 3-Substituted 2-Chloropyridines

Sofie Vanlaer,[a] Wim M. De Borggraeve,[a] and Frans Compernolle*[a]

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In this report we describe the synthesis of spirocyclic pyridoazepines starting from easily available precursors. The key step of our synthesis is an intramolecular nucleophilic aromatic substitution of the appropriate 3-substituted 2-chloropyridines. The final compounds, designed as simplified analogues of the alkaloid galanthamine, showed significant acetylcholinesterase inhibition activity.

Introduction

Galanthamine (GAL; **1**), an alkaloid isolated from the *Amaryllidaceae* species, is a centrally acting, selective, competitive and reversible inhibitor of the neurotransmitter acetylcholinesterase (AChE).[1] Symptomatic treatment for Alzheimer's disease (AD) involves restoring the acetylcholine levels in patients by means of inhibitors of AChE. In this respect, galanthamine significantly enhances cognitive functions in AD patients,[2] and recently it was approved in Europe and in the USA for treatment of AD. Galanthamine can be isolated from botanical sources but these sources are limited. A few total syntheses of GAL,[3] and the synthesis of various analogues,[4] have been reported. Galanthamine is structurally related to morphine (Figure 1). Morphine and some simplified structural 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 unit. Thus, whereas our pyridine target structures of type **2** retain the spiroannulation, the ether linkage between the aromatic ring and the spiro ring is disconnected (Figure 1a). In this work, we present a synthetic route towards spirocyclic pyridoazepines **2a**–**d** starting from easily available precursors. Pyridoazepines are rather unknown, and to the best of our knowledge, pyridoazepine ring systems encompassing a spiroannulation have not yet been reported. Compound **3**, a synthetic analogue of GAL that also lacks this heterocyclic connection, was claimed to have the desired, albeit weak, activity.[5]

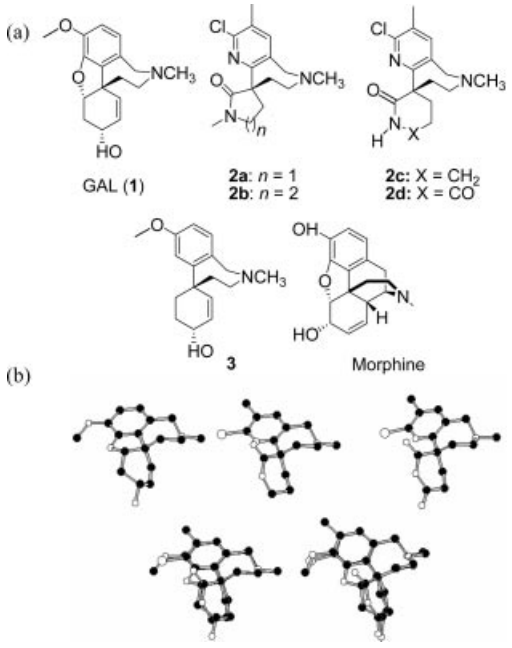


Figure 1. (a) GAL, targets **2a**–**d**, GAL analogue **3** and morphine; (b) Geometrically optimised structures of Gal, **2c** and **2d**, and overlay of GAL and targets **2c** and **2d** by using Hyperchem MM+ molecular mechanics.

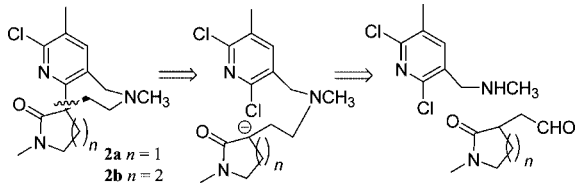
An overlay of the geometrically optimised model structures of GAL and targets **2c** and **2d** reveals an excellent fit of the superimposed benzo- and pyridoazepine ring moieties and of the corresponding spiro ring moieties (Figure 1b). The chlorine in the pyridine nucleus of **2a**–**d** was meant to mimic the methoxy group of GAL and in future work may be substituted by various nucleophiles. The amide oxygen atoms in the enantiomeric forms of **2a**–**c** (Figure 1) could serve as a mimic for the ether bridge of GAL. Alternatively, the planar amide bond present in the

[a] Chemistry Department, K. U. Leuven,
Celestijnenlaan 200F, 3001 Heverlee, Belgium
Fax: +32-16-327990
E-mail: Frans.Compernolle@chem.kuleuven.be

image forms of **2a**–**c** can be superimposed on the alkenic linkage of the cyclohexene ring (not shown in Figure 1b).

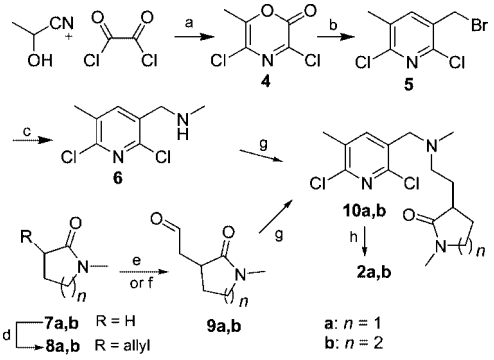
Results and Discussion

Our first synthetic approach to form the desired spirocyclic pyridoazepines was based on intramolecular ring closure of the appropriate 3-substituted 2-chloropyridines carrying a nucleophilic lactam enolate entity (Scheme 1). The latter pyridine precursors in their turn can be constructed by reductive coupling of the corresponding secondary amine and lactam aldehyde derivatives.



Scheme 1. Retrosynthetic approach to target compounds **2a**,**b**.

The synthesis of the substituted pyridine component started with the cyclocondensation of lactonitrile and oxalyl chloride to form 3,5-dichloro-2*H*-1,4-oxazin-2-one (**4**), which was subjected to a Diels–Alder reaction with propargyl bromide (Scheme 2).[6] This cycloaddition (followed by the elimination of CO_2) is 100% regioselective and only 3-(bromomethyl)pyridine **5** is formed. Subsequent amination afforded corresponding 3-(methylaminomethyl)pyridine **6**.

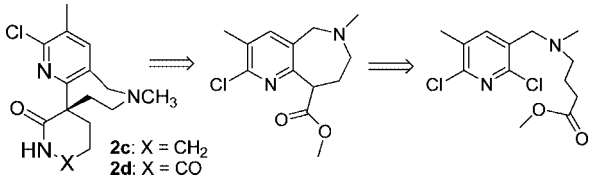


Scheme 2. Reagents and conditions: (a) lactonitrile, oxalyl chloride (3 equiv.), $Et_3N{\cdot}HCl$ (0.1 equiv.), chlorobenzene, 90 °C, 3 h (90%); (b) propargyl bromide (2 equiv.), toluene, 70 °C, overnight (92%); (c) NH_2CH_3 (5 equiv.), MeOH, room temp., 4 h (85%); (d) (i) LDA (1 equiv.), THF, –78 °C, 10 min. (ii) allyl bromide (1 equiv.), –78 °C, 30 min. (97%); (e) cat. OsO_4, $NaIO_4$ (2 equiv.), Et_2O, H_2O, room temp., 12 h (99%); (f) (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); (g) amine **9** (1 equiv.), MeOH, acetic acid (pH = 6), $NaCNBH_3$ (1 equiv.), aldehyde **9a**,**b** (1 equiv.), room temp., 15 min (85% over 2 steps); (h) $KN(SiMe_3)_2$ (1 equiv.), toluene, microwave irradiation (**2a**, 85%).

The aldehyde component was prepared by initial α allylation of commercial lactams **7a**,**b** to give compounds **8a**,**b**. Subsequent oxidative cleavage of the allyl group yielded aldehydes **9a**,**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).[7] Final reductive amination of aldehydes **9a**,**b** with amine **6** by using $NaCNBH_3$ as a reducing agent afforded precursors **10a**,**b** in good yields.[8]

The crucial and most difficult step in this reaction sequence was the final ring closure of precursors **10a**,**b** by nucleophilic aromatic substitution (NAS) to form the spiro-annulated seven-membered ring products **2a**,**b**. Indeed, generation of the quaternary carbon centre of the spirocycle requires attack of a sterically encumbered anion at the 2-chloro position. This conversion could, however, be achieved by applying microwave irradiation with $KN(SiMe_3)_2$ as a base in toluene.[9,10] Desired products **2a**,**b** were not detected with the use of conventional heating conditions. Presumably, this was due to decomposition of the desired product when elevated temperatures or prolonged reaction times were applied. The temperature and reaction time conditions were also of critical importance in the microwave reaction. The best conditions to effect spirocyclisation of **10a** consisted of irradiation of the reaction mixture at 100 °C for 15 min, which provided target compound **2a** in 85% yield after flash column chromatography.[11] In contrast to the straightforward synthesis of **2a**, the transformation of six-membered lactam analogue **10b** into corresponding spirocyclic product **2b** proved to be erratic. Ring closure was best carried out by irradiating the reaction mixture at 80 °C for 10 min.[12] However, numerous side products were formed and following purification by reverse-phase HPLC, **2b** was isolated in poor yield (ca. 5%).[11]

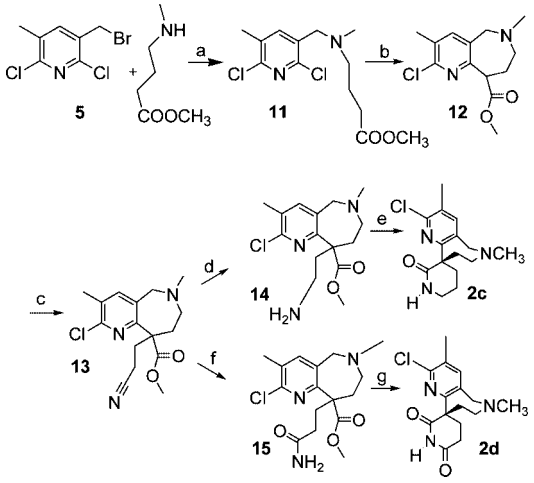
In view of our failure to produce six-membered lactam target compound **2b** in satisfactory yield, we envisaged the alternative approach outlined in Scheme 3. Instead of forming the spirocyclic ring system by NAS in the final ring closure step, spirocyclic pyridoazepines **2c**,**d** were constructed by manipulation of an appropriate bicyclic pyridoazepine. This key intermediate in turn can be formed by intramolecular NAS of the corresponding 3-[(4-methoxy-4-oxobutyl)(methyl)amino]-substituted 2-chloropyridine. Consequently, the critical NAS ring-closure step involved a less-hindered precursor than that used in our first approach.



Scheme 3. Retrosynthetic approach to **2c**,**d**.

Substitution of 3-(bromomethyl)pyridine **5** with methyl 4-(methylamino)butanoate afforded amine **11**, which smoothly underwent internal NAS to form pyridoazepine **12** under conventional heating conditions (Scheme 4).[13] Two equivalents of base were required to effect complete conversion into compound **12**, which was 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 the careful addition of a saturated aqueous solution of NH_4Cl.[14]



Scheme 4. 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) (i) KO*t*Bu (1.2 equiv.), THF, room temp., 10 min (ii) acrylonitrile (1.2 equiv.), *t*BuOH, room temp., 15 min. (61%); (d) $CoCl_2$ (2 equiv.), $NaBH_4$ (10 equiv.), MeOH, room temp., overnight; (e) MeOH, overnight, reflux (57% over 2steps); (f) CH_3SO_3H, toluene, 100 °C, 2 h. (83%); (g) (i) KO*t*Bu (1.2 equiv.), *t*BuOH, room temp., 1 h (ii) NH_4Cl, H_2O (60%).

To construct the spirolactam ring of target compounds **2c**,**d**, we envisaged initial Michael reaction of pyridoazepine **12** with either acrylonitrile, methyl acrylate or acrylamide. However, because of the unreactive character and steric crowding of the stabilised ester enolate anion of **12**, the addition reaction only succeeded with acrylonitrile.[15] Selective reduction of resulting nitrile adduct **13** with $NaBH_4$ in the presence of $CoCl_2$ furnished primary amine **14**, which underwent ring closure in refluxing methanol to provide target product **2c**.[16] Nitrile adduct **13** also could be converted into corresponding amide **15** 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 **2d**.[17]

Compounds **2a**–**d** were tested for their inhibition activity on acetylcholinesterase relative to that of galanthamine. Tests were performed by using Ellman's colorimetric method.[18] The K_M measured was 186 μM. The tested compounds showed significant AChE inhibition activity (K_I = 514 μM for **2a**; K_I = 70 μM for **2b**; K_I = 99 μM for **2c**; K_I = 150 μM for **2d**; K_M = 186 μM), but lower than that of galanthamine (K_I = 3 μM). From these data it clearly appears that six-membered lactam compounds **2b**,**c** exhibit superior activity relative to that of five-membered lactam **2a**.

Conclusions

Two synthetic routes towards spirocyclic pyridoazepines were developed starting from easily available precursors. In each case, the critical reaction step was ring closure of the 3-substituted 2-chloropyridine precursors, which proceeded through intramolecular nucleophilic aromatic substitution. In the first route, this NAS reaction directly afforded the desired spirocyclic lactam compounds. However, this method gave unsatisfactory results for the synthesis of six-membered spirocyclic lactams. In the second route proceeding via an early NAS step, bicyclic pyridoazepine ester **12** was generated as the key intermediate and the spirolactam ring was constructed later on. Our target compounds **2a**–**d** showed significant AChE inhibition activity.

Acknowledgments

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[8] Spectroscopic data for compound **10a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (s, 1 H), 3.54 (s, 2 H), 3.29 (dd, J = 8.4, 5.4 Hz, 2 H), 2.85 (s, 3 H), 2.55 (t, J = 7.5 Hz, 2 H), 2.51–2.45 (m, 1 H), 2.36 (s, 3 H), 2.24 (s, 3 H), 2.18–2.12 (m, 2 H), 1.72–1.58 (m,1 H), 1.57–1.45 (m, 1 H) ppm. ^{13}C NMR (100 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. HRMS: calcd. for $C_{15}H_{21}Cl_2N_3O$ 329.1062; found 329.1063. Spectroscopic data for compound **10b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (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), 2.18 (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 (100 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. HRMS: calcd. for $C_{16}H_{23}Cl_2N_3O$ 343.1218; found 343.1210.

[9] *CEM-Discover*, CEM Corporation P. O. Box 200 Matthews, NC 28106.

[10] Optimised procedure for NAS of **10a**: To a solution of compound **10a** (10 mg, 0.03 mmol) in dry toluene was added potassium bis(trimethylsilyl)amide (0.5 M in toluene, 0.06 mL, 0.03 mmol). 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 the addition of water, the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure.

[11] Spectroscopic data for compound **2a**: ^{1}H 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, 9 Hz, 1 H), 3.30 (td, J = 9, 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, 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. HRMS: calcd. for $C_{15}H_{20}ClN_3O$ 293.1295; found 293.1297. Spectroscopic data for compound **2b**: HRMS: calcd. for $C_{16}H_{22}ClN_3O$ 307.1451; found 307.1448.

[12] This ring closure was carried out at 80 °C for 10 min instead of 100 °C for 15 min. At 100 °C, compound **2b** could not be detected.

[13] Spectroscopic data for compound **12**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (s, 1 H), 4.15 (dd, J = 6.8, 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, $CDCl_3$): δ = 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. HRMS: calcd. for $C_{13}H_{17}ClN_2O_2$ 268.0978; found 268.0971.

[14] Optimised procedure for NAS of **11**: To a solution of pyridine **11** (1 gram, 3.28 mmol) in dry toluene (50 mL) was added $KN(SiMe_3)_2$ (0.5 M in toluene, 14.4 mL, 7.21 mmol) under an atmosphere of argon. The reaction mixture was stirred at 80 °C for 10 min, and then it was cooled to –78 °C and a saturated aqueous solution of NH_4Cl (10 mL) was added. After 10 min, the mixture was warmed to room temp. A saturated aqueous solution of K_2CO_3 was added until pH 8. After extraction with CH_2Cl_2 the organic layer was dried with $MgSO_4$.

[15] Spectroscopic data for compound **13**: ^{1}H 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. HRMS: calcd. for $C_{16}H_{20}ClN_3O_2$ 321.1244; found 321.1249.

[16] Spectroscopic data for compound **2c**: ^{1}H 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, 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. HRMS: calcd. for $C_{15}H_{20}ClN_3O$ 293.1295; found 293.1293.

[17] Spectroscopic data for compound **2d**: ^{1}H 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. HRMS: calcd. for $C_{15}H_{18}ClN_3O_2$ 307.1088; found 307.1097.

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