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SYNTHESIS AND BIOLOGICAL ACTIVITY OF NOVEL HETEROCYCLIC RING SYSTEMS: IMIDAZO[4',5':3,4]PYRIDO-[2,1-*a*]ISOQUINOLINES AND IMIDAZO[4,5-*f*][3]BENZAZECINES

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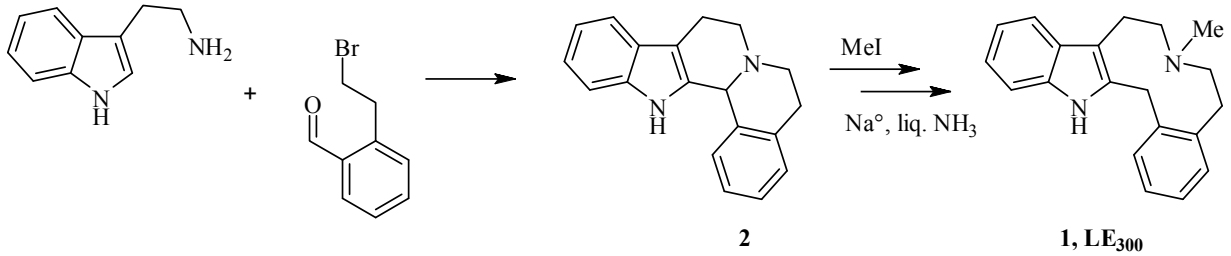
Abstract – Derivatives of two novel heterocyclic ring systems were synthesized and their affinities for dopamine receptors were measured. The compounds were obtained by reacting histamine with 2-(2-bromoethyl)benzaldehyde including an atypical *Pictet-Spengler* condensation, which afforded basic and not the usual neutral or acidic conditions. The resulting imidazo[4',5':3,4]pyrido[2,1-*a*]-isoquinoline derivative **4** was Boc protected at the most basic imidazole nitrogen, the isoquinoline nitrogen then quaternized by using methyl iodide and the tetracyclic isoquinolinium salt was both deprotected and cleaved under *Birch* conditions in one step to give a tricyclic imidazo[4,5-*f*][3]benzazecine derivative (**3**) by opening two 6-membered heterocycles towards one 10-membered. Radioligand binding studies showed a significant affinity of the moderately constrained **3** but not of **4** for dopamine receptors. Similar to the analogous indolo-benzazecine **LE300**, a preference of **3** for the D_1 receptor family was observed, but with some loss of affinity over all.

INTRODUCTION

Dopamine is a key neurotransmitter in the brain with various physiological functions, e.g. regulation of locomotion, cognition, emotion and event prediction, and dopamine receptor antagonists play a crucial role in the treatment of neuropsychiatric diseases. Azecine-type dopamine receptor antagonists, with 7-methyl-6,7,8,9,14,15-hexahydro-5*H*-indolo[3,2-*f*][3]benzazecine (**1**, **LE 300**) as a lead, represent a chemically new class of potential antipsycotics with high affinities for dopamine receptors and a rather unique selectivity profile, showing prevalence for the dopamine D_1 subtype receptor family.[1-3] Both, the

annulated azecine ring itself, but also a moderately rigidized phenylethyl- or heteroarylethyl-amine partial structures are considered to be essential for the biological activity,[4] so further variations of these scaffolds are interesting. The azecine **1** and its precursor quinolizine **2** have been obtained in our group by a *Bischler-Napieralski* cyclization but synthesis has been recently improved by performing a *Pictet-Spengler* condensation of tryptamine and 2-(2-bromoethyl)benzaldehyde (Scheme 1).[5]

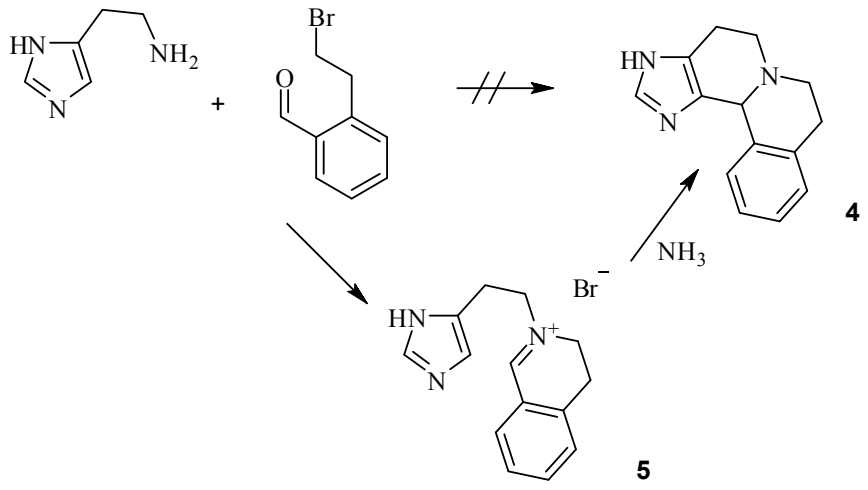


Scheme 1. Synthesis of the lead compound 1 (LE 300)[5]

Changing the biogenic amines from tryptamine to histamine should give the novel heterocycles **4** and **3**.

RESULTS AND DISCUSSION

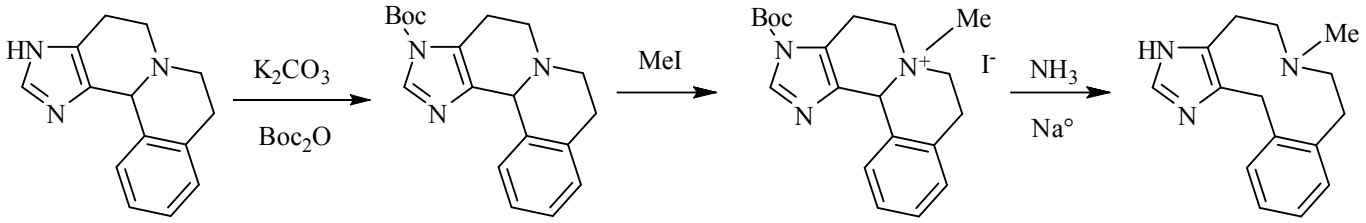
Compound **3** combines structural aspects of both histamine and phenylethylamine in one heterocycle and hence might have interesting biological activities. We refluxed the histamine free base with 2-(2-bromoethyl)benzaldehyde[6] in dichloromethane for 24 h (Scheme 2) which was expected to form the imidazo[4',5':3,4]pyrido[2,1-*a*]isoquinoline **4** by *Pictet-Spengler* cyclization, since many analogous indole- or thiophene-ethylamines have reacted this way.[7] But in this particular case of histamine, the reaction stopped at the intermediate Schiff base **5** which did not undergo any further spontaneous ring closure (Scheme 2).



Scheme 2. Synthesis of **4** stops at the intermediate imminium salt **5** under non-basic conditions

Pictet-Spengler condensations generally undergo various steps and the final cyclization of the intermediate Schiff base occurs either spontaneously or can be promoted by heating under acidic conditions.[7] With histamine and 2-(2-bromoethyl)benzaldehyde these conditions did not lead to the fully cyclized product. We tried various solvents and pH ranges from neutral to acidic. Even with very strong acids like TFA in dichloromethane -these conditions easily induce cyclizations with tryptamine[5]- no reaction of **5** towards **4** was observed. But surprisingly, we detected the desired cyclized isoquinoline **4** by GC/MS analysis after preparing a sample of **5** for GC/MS analysis by adding aqueous ammonia solution and extracting with ethyl acetate. So we found and reconfirmed after repeating and upscaling that in this particular case a *Pictet-Spengler* condensation was achieved not under acidic but rather under basic conditions. Actually, a base-promoted (excess of Et_3N) *Pictet-Spengler* reaction for serotonin has been reported[8] and other authors reacted histamine with carbonyl compounds in ethanolic KOH.[9] So we applied these conditions from the beginning by reacting histamine and 2-(2-bromoethyl)benzaldehyde in ethanol with an excess of Et_3N, or alternatively by using ethanolic KOH. In both cases only traces (~ 0.4%) or no **4** at all were detected (GC/MS). Since the preparation of the intermediate **5** under non-acidic conditions showed to be simple, we just dissolved **5** in water and added aqueous conc. ammonia. Cyclization took place within less than 5 min. and **4** could be extracted with ethyl acetate.

Annulated isoquinolines as precursors for the *N*-methylated azecines were usually quaternized at the quinolizine nitrogen and then the central C-N bond cleaved with sodium in liq. ammonia. To prevent any alkylation of **4** at the imidazole, a Boc group was introduced giving the *tert*-butyl imidazo[4',5':3,4]pyrido[2,1-*a*]isoquinoline-3(5*H*)-carboxylate **6**. It is not obvious at which of the imidazole nitrogens the Boc-group is attached, but only one regioisomer was formed. Comparison with calculated spectra (ACD-Chem-Sketch, ^{1}H-NMR Predictor) suggests that the BOC group is at the more exposed position 3. The chemical shift for the proton attached to carbon 12b was calculated with $\delta = 5.12$ ppm for the 3-Boc isomere and $\delta = 4.72$ ppm for the 1-Boc isomere and it was found at $\delta = 5.04$ ppm. So there is some preference for the 3-Boc compound. This preference is confirmed by the ^{13}C shift for imidazole carbon 3a which was calculated with $\delta = 139.63$ ppm for 1-Boc and $\delta = 124.35$ ppm for 3-Boc and was found to be $\delta = 123.9$ ppm. The position of the Boc group at the intermediates is not relevant in view of the desired target compounds; nevertheless, not only steric considerations but also NMR data strongly suggest the 3-Boc intermediates. The Boc-protected isoquinoline **6** was quaternized with methyl iodide yielding the corresponding isoquinolinium iodide **7** (Scheme 3). When performing the finalizing cleavage of the quinolizine C-N-bond towards the azecine ring under *Birch* conditions the Boc group fortunately was also cleaved off although it is described to be stable against Na in liq. ammonia.[10,11]



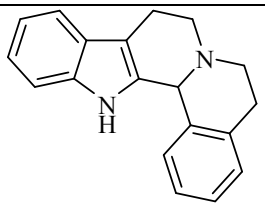
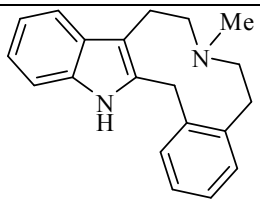
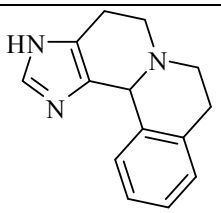
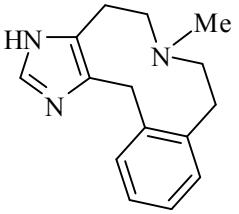
4 **6** **7** **3**

Scheme 3. Synthesis of target azecine

BIOLOGICAL ACTIVITIES

The affinities of the target compounds **3** and **4** for stably cloned human dopamine receptors were evaluated by radioligand binding experiments using a protocol which we have described previously.[12] The Ki values (low value means high affinity) are given in Table 1.

Table 1. Affinities (*Ki* values) for the human cloned dopamine receptors D_1-D_5, measured by radioligand binding experiments

Compounds		*Ki* [nM] (Radioligand binding studies)				
		HEK D_1	HEK D_{2L}	HEK D_3	CHO $D_{4.4}$	HEK D_5
	**2**	> 10 000	> 10 000[a]	> 10 000	> 10 000	> 10 000
	**1, LE300**	1.9±0.5[b]	44.7±15.8[b]	40.35[b]	74.9±50[b]	7.5±0.3[b]
	**4**	> 10 000	> 10 000	> 10 000	> 10 000	> 10 000
	**3**	769.5±36.5[c]	> 10 000	> 10 000	5035± 2577[c]	366±211[d]

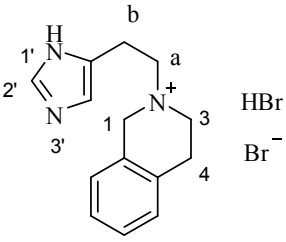
[a]Values from Ref.[3], [b]values from Ref.[2], [c]values are the mean of two experiments, performed in triplicate (± SEM), [d]values are the mean of three experiments, performed in triplicate (± SD)

The azecine **3** is the more active compound compared to its precursor **4,** which is in line to all previous data comparing annulated isoquinoline and azecine derivatives. Target compound **3** is less affine compared to **LE300** but still offers submicromolecular affinities for D_1 and D_5.

EXPERIMENTAL

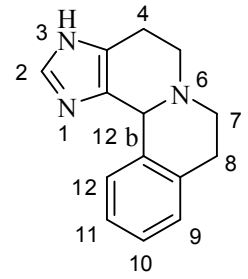
Melting points are uncorrected and were measured in open capillary tubes, using a Gallenkamp melting point apparatus. ^{1}H- and ^{13}C-NMR spectral data were obtained from a Bruker Advance 250 spectrometer (250 MHz) and Advance 400 spectrometer (400 MHz). TLC was performed on silica gel F254 plates (Merck). MS data were determined by GC/MS, using a Hewlett Packard GCD-Plus (G1800C) apparatus (HP-5MS column; J&W Scientific). High resolution mass spectrometry (HRMS) data were determined on a TSQ Quantum Access Mass Spectrometer (Therma Electron Corporation). Purities of the compounds were determined by elemental analysis, performed on a Hereaus Vario EL apparatus. All values for C, H, and N were found to be within ± 0.4. All compounds showed > 95% purity.

2-[2-(1*H*-Imidazol-5-yl)ethyl]-3,4-dihydroisoquinolinium bromide hydrobromide (**5**)



In a 250 mL round bottom flask 610 mg (5 mmol) of histamine free base (purchased from Sigma Aldrich) and 1.4 g (6 mmol) of 2-(2-bromoethyl)-benzaldehyde[6] were dissolved in 130 mL CH_2Cl_2 and refluxed for 24 h. The mixture was cooled to room temperature and the precipitated light yellow solid was filtered off, dried under reduced pressure and recrystallized from isopropanol to give **5** as white crystals. (950 mg, 49%); mp 213 °C; ^{1}H NMR (DMSO-d_6, 250 MHz): δ (ppm) 3.24 (t, J = 8.0 Hz, 2H, Hb), 3.35 (t, J = 6.9 Hz, 2H, H4), 4.12 (t, J = 8.0 Hz, 2H, Ha), 4.31 (t, J = 6.9 Hz, 2H, H3), 7.53 (m, 2H, H5 and H6), 7.63 (s, 1H, H4'), 7.82 (m, 2H, H8 and H7), 9.12 (s, 1H, H2'), 9.36 (s, 1H, H1); ^{13}C NMR (DMSO-d_6): δ (ppm) 22.76, 24.92, 48.35, 58.78, 117.71, 125.07, 128.56, 128.73, 128.82, 134.01, 135.09, 137.23, 138.19, 167.38; Anal. Calcd for $C_{14}H_{17}Br_2N_3$: C, 43.4; H, 4.43; N, 10.9. Found: C, 43.1; H, 4.62; N, 10.8. HRMS calcd for $C_{14}H_{16}N_3$: 226.13442. Found: 226.13426.

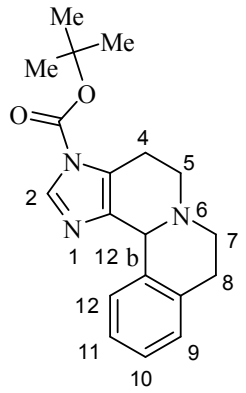
3,4,5,7,8,12b-Hexahydroimidazo[4',5':3,4]pyrido[2,1-*a*]isoquinoline (**4**)



In a 100 mL round bottom flask 810 mg **5** (2.1 mmol) were dissolved in 20 mL water and conc. ammonia solution was added to adjust the pH at 10. After 5 min, the mixture was extracted with EtOAc (3 x 15 mL). The combined organic phases were dried over Na_2SO_4, evaporated and dried under reduced pressure to give **4** as a yellow amorphous solid. (320 mg, 67%) For analytical purpose a dihydrochloric salt was formed by dissolving **4** in isopropanol and adding conc. HCl

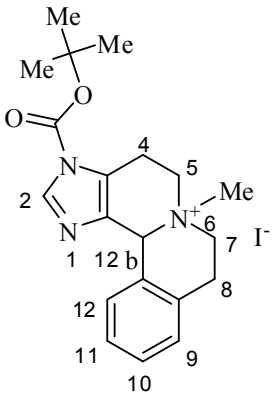
dropwise until the pH reached 5. The formed salt was collected and recrystallized from acetone/water. mp 275 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 3.04 (m, 2H, H8), 3.19 (m, 2H, H4), 3.51 (m, 2H, H5), 3.71 (m, 2H, H7), 6.04 (s, 1H, H12b), 7.32-7.36 (m, 3H, H9-11), 7.50 (d, J = 7.1 Hz, 1H, H12), 9.06 (s, 1H, H2); ^{13}C NMR (DMSO-d_6): δ (ppm) 17.77, 23.68, 46.26, 46.80, 54.40, 123.90, 124.58, 127.65, 128.21, 128.95, 129.09, 129.50, 131.41, 135.81; Anal. Calcd for $C_{14}H_{17}Cl_2N_3$ + 1/3 H_2O: C, 55.3; H, 5.85; N, 13.8. Found: C, 55.1; H, 5.58; N, 13.6. HRMS Calcd for $C_{14}H_{16}N_3$: 226.13442. Found: 226.13519.

Tert-butyl 4,7,8,12b-tetrahydroimidazo[4',5':3,4]pyrido[2,1-*a*]isoquinoline-3(5*H*)-carboxylate (**6**)



To a solution of 330 mg **4** (1.47 mmol) in 50 mL isopropanol:water (5:6) 223 mg K_2CO_3 (1.61 mmol) and 344 μL of di-*tert*-butyl dicarbonate were added. The mixture was stirred at room temperature for 17 h, then concentrated under reduced pressure and extracted with EtOAc (3x 20 mL). Organic layers were combined, dried over Na_2SO_4 and evaporated. The resulting yellow oil was purified by column chromatography (Silicagel, MeOH : CH_2Cl_2 (1:9)) to give 112mg (23%) of **6** as light yellow oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) 1.59 (s, 9H, *tert*-butyl), 2.79-3.23 (m, 8H, H4-8), 5.04 (s, 1H, H12b), 7.07-7.26 (m, 3H, H9-11), 7.92 (d, J = 7.2 Hz, 1H, H12), 8.02 (s, 1H, H2); ^{13}C NMR ($CDCl_3$): δ (ppm) 22.64, 26.54, 27.93, 47.70, 28.28, 57.29, 85.18, 123.92, 125.81, 126.43, 128.70, 128.80, 133.48, 135.18, 136.20, 139.17, 147.81; Anal. Calcd for $C_{19}H_{23}N_3O_2$ * 1.2 MeOH: C, 66.7; H, 7.70; N, 11.5. Found: C, 67.1; H, 7.84; N, 11.1.

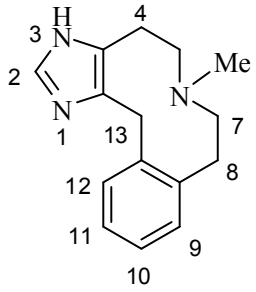
3-(*Tert*-butoxycarbonyl)-6-methyl-3,4,5,7,8,12b-hexahydroimidazo[4',5':3,4]pyrido[2,1-*a*]isoquinolin-6-ium iodide (**7**)



In a 50 mL round bottom flask 64 μL (1 mmol) of methyl iodide was added to 100 mg **6** (0.3 mmol) dissolved in 30 mL acetone and the mixture was stirred at room temperature for 72 h. The resulting solid was filtered off and dried under reduced pressure to give 138 mg (96 %) of **7** as white crystal solid. mp 209 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 1.57 (s, 9H, *tert*-butyl), 3.20-3.26 (m, 4H, H4+H8), 3.32 (s, 3H, N-CH_3), 3.72-3.92 (m, 4H, H5+H7), 5.91 (s, 1H, H12b), 7.25-7.38 (m, 3H, H9-11), 7.60 (d, J = 7.4 Hz, 1H, H12), 8.27 (s, 1H, H2); ^{13}C NMR (DMSO-d_6): δ (ppm) 19.49, 23.25, 27.86, 49.32, 66.05, 86,47, 121.25, 127.26, 128.42, 128.73, 129.24, 133.74, 138.83, 147.27. Anal. Calcd for

$C_{20}H_{26}IN_3O_2$ 129.24, 133.74, 138.83, 147.27. Anal. Calcd for $C_{20}H_{26}IN_3O_2$ + 0.8 H_2O: C, 49.9; H, 5.77; N, 8.7. Found: C, 49.5; H, 5.67; N, 9.1.

6-Methyl-4,5,6,7,8,13-hexahydro-3*H*-imidazo[4,5-*f*][3]benzazecine (**3**)



A mixture of 120 mg (0.25 mmol) **7** and 50 mL of freshly condensed liquid ammonia were stirred at – 40 °C and small pieces of sodium metal were added portionwise until the mixture maintained a deep blue color for 7 min. The reaction was quenched by adding dropwise a saturated solution of NH_4Cl in water until the blue color disappeared. The mixture was stirred at room temperature under nitrogen and all ammonia was allowed to evaporate under a stream of nitrogen. To the remaining solids 30 mL of water were added and the emulsion was extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were evaporated to dryness to yield the crude product. The pale yellow oil upon trituration with a small amount of Et_2O to give 38 mg (63%) of white crystals which were dried under reduced pressure. mp 130 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) 2.21 (s, 3H, N-CH_3), 2.55-2.70 (m, 6H, H5-8), 2.83 (t, J = 6.1 Hz, 2H, H4), 4.07 (s, 2H, H13), 7.03-7.18 (m, 3H, H9-11), 7.33 (d, J = 4.1 Hz, 1H, H12), 7.36 (s, 1H, H2); ^{13}C NMR ($CDCl_3$): δ (ppm) 26.48, 30.83, 34.23, 45.70, 57.12, 58.80, 126.32, 126.47, 130.17, 130.27, 132.76, 138.79, 139.89. Anal. Calcd for $C_{15}H_{19}N_3$ * 0.04 CH_2Cl_2: C, 73.8; H, 7.86; N, 17.2. Found: C, 74.1; H, 7.56; N, 16.9. HRMS calcd for $C_{15}H_{20}N_3$: 242.1657226. Found: 242.16549.

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