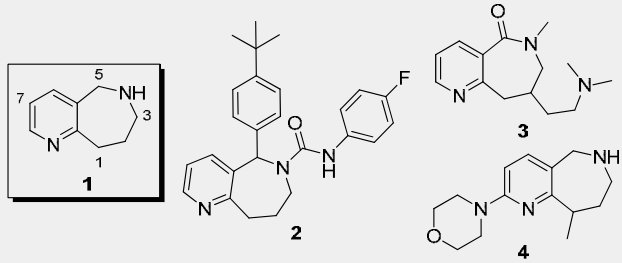
An Efficient Synthesis of Novel Drug-like Tetrahydropyridoazepines.

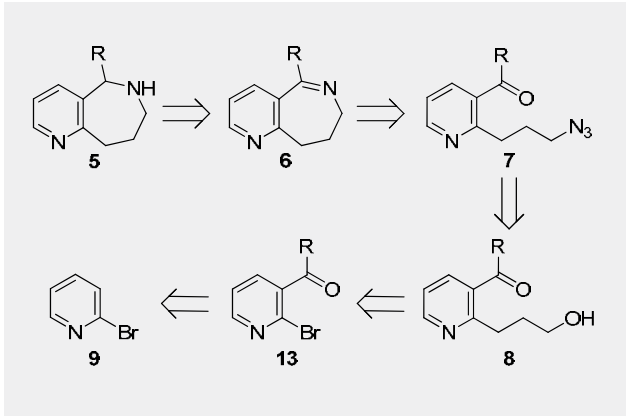
D. Volochnyuk, A. Subota, S. Ryabukhin, O. Grygorenko

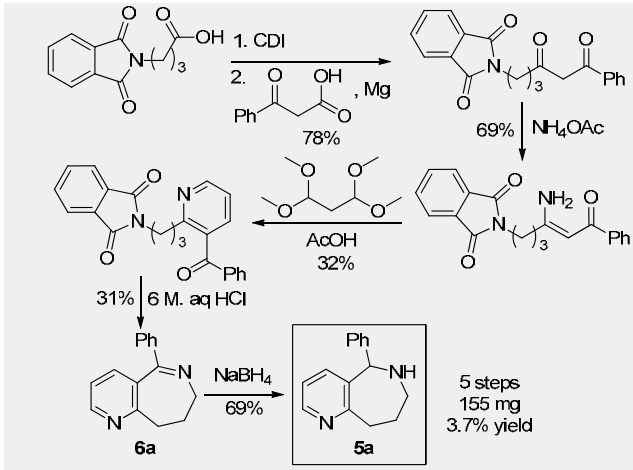
Introduction and Aim

The quest for lead-oriented synthesis proposed by medicinal chemistry in early 2010s have prompted the design and study of low-molecular-weight, hydrophilic, conformationally restricted and sp^3-enriched molecular scaffolds. Fused azepanes are promising chemotypes which comply with these criteria and in most cases possess sufficient novelty; moreover, the azepane motif is in the top 100 most frequently used ring systems for small molecule drugs. 6,7,8,9-Tetrahydro-5*H*-pyrido[3,2-*c*]azepines (**1**), which contain fused azepane and pyridine rings, were evaluated as cannabinoid (CB2) receptor modulators (**2**), H_1-antihistamines (**3**), or serotonin ($5HT_{2c}$) receptor agonists (**4**).[1]



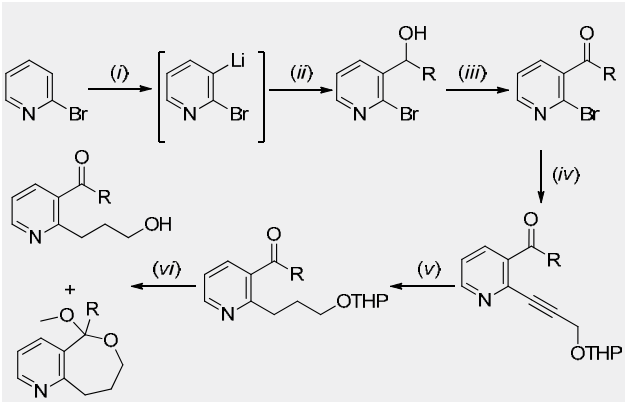
Herein, we report an alternative approach to 5-substituted 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepines, which also relies on the formation of imines as the key step.



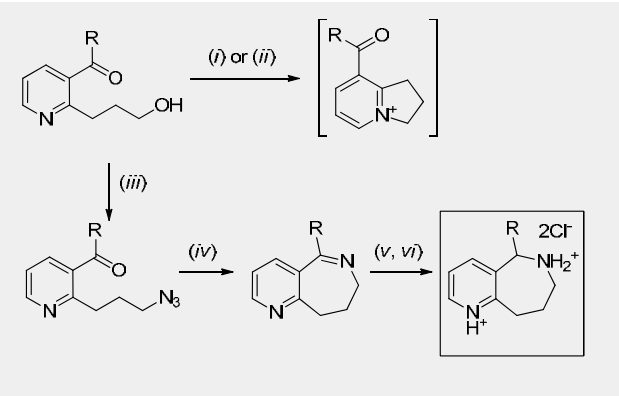


Literature synthesis of 5H-pyrido[3,2-c]azepines[3]

Synthesis

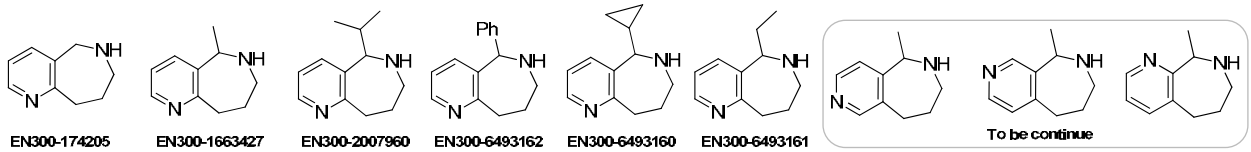


(*i*) LDA (1.2 eq), THF, –78 °C, 90 min; (*ii*) (1.13 eq), THF, –78 °C, 80 min; (*iii*) $CrO_3$2py (3 eq), CH_2Cl_2, rt, 24 h or CrO_3 (3 eq), acetone, rt, 18 h; (*iv*) 2-prop-2-ynyloxytetrahydropyran (1.5 eq), $Pd(OAc)_2$ (1% mol), PPh_3 (2% mol), CuI (0.19% mol), Et_3N, 80 °C, 16 h; (*v*) H_2 (1 atm), 10% Pd-C (4% mol), MeOH, rt, monitored by TLC; (*vi*) TsOH·H_2O (1.05 eq), MeOH, rt, 12 h.



(*i*) MsCl (1.05 eq), Et_3N (1.5 eq), CH_2Cl_2, 0 °C to rt, 24 h; (*ii*) phthalimide (1.5 eq), DIAD (1.5 eq), PPh_3 (1.5 eq), THF, –30 °C to rt, 24 h; (*iii*) DIAD (1.5 eq), PPh_3 (1.5 eq), $NaHCO_3$ (3% mol), THF, $(PhO)_2P(O)N_3$ (1.5 eq), –30 to 20 C, 3 h; (*iv*) PMe_3 (1.4 eq), THF, rt, 6 h; (*v*) $NaBH_4$ (3 eq), MeOH, 0 °C to rt, 8 h; (*vi*) sat. HCl in Et_2O, rt

Results



Contacts

Dmitriy M. Volochnyuk, Prof. Dr. Sci; Sergey V. Ryabukhin, Prof. Dr. Sci.
d,volochnyuk@gmail.com s.v.ryabukhin@gmail.com
Enamine Ltd, www.enamine.net
78 Chervonotkatska St, 02660 Kyiv, Ukraine

References

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