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Pyridine analogs of (−)-cytisine and varenicline: cholinergic receptor probes

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Abstract

A series of bicyclic pyridine containing alkaloids related to (−)-cytisine and varenicline are described. Synthetic access via regioisomeric metalation of alkoxy- and halo-pyridines gains entry to all four isomeric [3.3.1]-bicyclic targets. Regioselective and sequential oxidative cleavage of dicyclopentadiene generates a related [3.2.1]-bicyclic analog.

Of the naturally occurring nicotinic acetylcholine receptor (nAChR) ligands, the most potent and extensively studied include acetylcholine, nicotine, epibatidine and anatoxin *a* (Fig. 1).[1] All possess rotatable bonds that compromise their utility as pharmacophore probes. To better establish receptor–ligand interactions, conformationally restricted analogs of these inherently 'flexible' systems have been prepared and studied.[2,3] These derivatives often exhibit decreased binding affinities due to newly imposed steric restrictions or sub optimal alignment of pharmacophore elements and thus fail to elucidate the 'ideal' orientation of essential functionality. The pyridine analog by Kanne et al. is a rare example that exhibits favored alignment requirements for the anatoxin *a* system.[4]

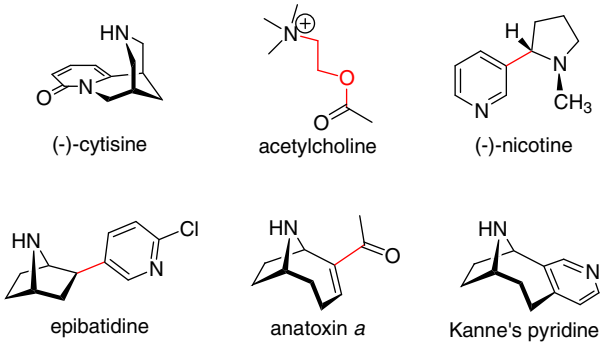

Fig. 1. Prototypical nicotinic receptor ligands (*rotatable bonds, red*).

(−)-Cytisine, a pyridone containing natural product from the lupin alkaloid family,[5] differs from these ligands. Constrained by its bicyclic framework, a lack of rotatable bonds fixes the pyridone carbonyl relative to the 'basic' piperidine nitrogen atom. We report herein the preparation of cytisine mimics that are conformationally constrained tools intended to ascertain specific interactions at nicotinic receptor subtypes.[6] Deviations within this compound-set are restricted only to the position of the pyridine or pyridone heteroatoms, thereby minimizing the ambiguity as to spatial relationships of polar functionality and steric perturbations between derivatives.

In the course of our work leading to the discovery of varenicline,[7] we generated the bicyclic pyridyl piperidine **50** (see Scheme 6), a derivative that exhibited particularly high affinity at the muscle receptor subtype of the nAChR (~47 nM @ $\alpha_1\beta\gamma\delta$). Considerable work has been focused on gaining insights into muscle receptor interactions since the seminal work of Beers and Reich in the 1970s.[8] Recent contributions have markedly improved our understanding of receptor–ligand topology, highlighted by the homology

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models based on the snail derived acetylcholine binding protein (AChBP),[9] which has triggered a surge of research to further elucidate the structure—function relationships.[10] These investigations herald a future with improved predictive tools to impact the design of novel nAChRs ligands. Inspired by the activity of **50** and the importance of this receptor in drug discovery efforts, we have undertaken the synthesis of this set of related analogs to examine the effects of pyridine and piperidine nitrogen atom positional relationships within this skeletal framework.

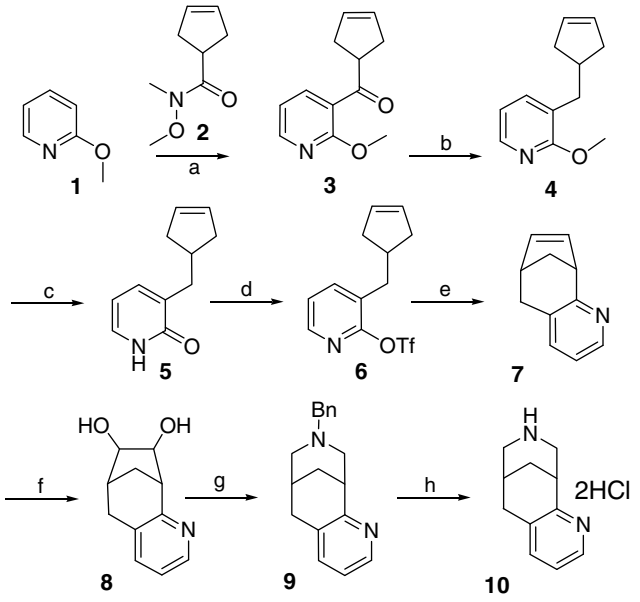
We recently described the syntheses of (−)-cytisine.[11] One approach employed a Heck cyclization to assemble the requisite bicyclic core from the readily available materials.[11a] Herein, we extend the approach to generate hitherto unknown bicyclic [3.3.1]-pyridine and pyridone derivatives. The closely related bicyclic [3.2.1]-bicyclic pyridine **50** was prepared from dicyclopentadiene by a related approach.

Directed orthometalation of alkoxypyridines described by Comins achieves the regioselective introduction of pyridine functionality (Scheme 1).[12] By this approach, the addition of 3-lithio-2-methoxypyridine **1** to 3-cyclopentylcarboxamide **2** gave access to keto-pyridine **3**. Wolff–Kishner reduction generated **4** (51%) and an undesired diazindole derivative (40%), which was readily separated (3-cyclopent-3-enyl-1*H*-pyrazolo[3,4-*b*]pyridine, not shown). Demethylation (TMSCl/NaI)[13] and activation as the trifluoromethanesulfonate ester (triflate)[14] gave **6**, which was cyclized under Heck conditions to the bicyclic olefin **7**.[15]

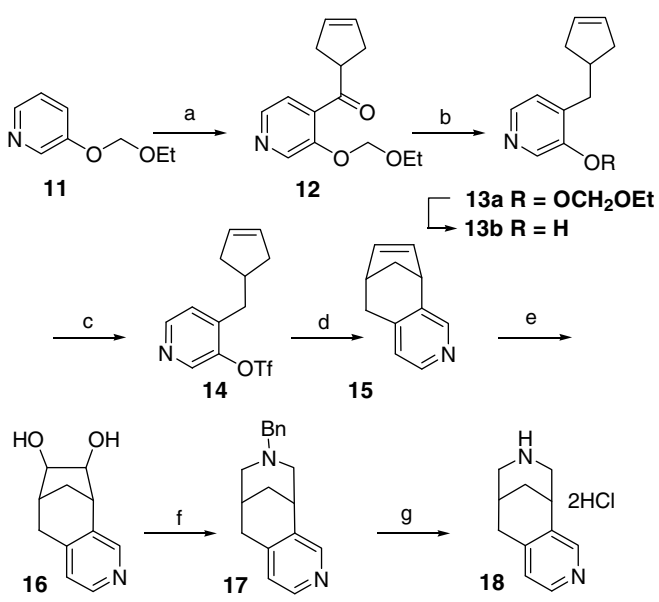
Olefin **7** was converted to its corresponding diol **8** by dihydroxylation.[16] Oxidative cleavage with $NaIO_4$ provided an intermediate dialdehyde (or glycal, not shown) that was condensed with benzylamine and reduced by $NaBH(OAc)_3$ to give **9**.[17] Benzyl group removal by transfer hydrogenolysis and purification as the *t*-Boc derivative followed by HCl mediated deprotection afforded the crystalline 3,11-diaza-pyridine derivative **10** as its bis-HCl salt.

The isomeric 3-alkoxy-4-keto-derivative **12** was accessed using the directing effects described by Ronald (Scheme 2).[18] LDA mediated metalation at the 4-position of 3-alkoxyalkoxypyridine **11** and trapping with **2** proceeded in 75% yield. Wolff–Kishner reduction not only generated the expected reduced product, **13a**, the 3-alkoxyalkyl group was removed under these conditions to give phenol **13b** directly in 51% yield. Mixtures of **13a** and **13b** were initially formed, along with the corresponding hydrazone precursors; these ultimately converged to give **13b** exclusively with prolonged heating in hot KOH/ethylene glycol. Though the displacement of 3-halopyridines by alkoxide is known,[19] the simultaneous reduction and dealkylation/hydroxide displacement under Wolff–Kishner conditions was an unexpected and fortuitous finding, making this approach quite attractive. Activation of **13** as the triflate provided **14**, which was converted to the isomeric bicyclic olefin **15** and ultimately the target 4,11-diazabicyclic pyridine derivative **18** as described for **10**.

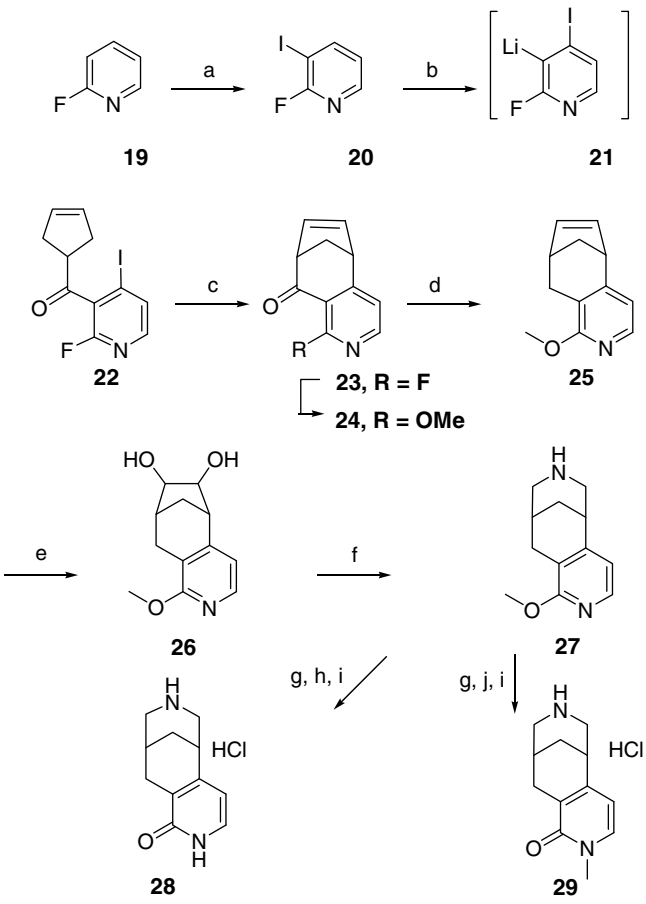
The Heck approach allows for the installation of additional functionality to generate substituted pyridines and pyridone derivatives (Scheme 3).[20] 3-Lithio-2-fluoro-4-



Scheme 1. 3,11-Diaza-tricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene. Reagents and conditions: (a) Mesityl lithium, THF, −78 °C, **2**, 75%; (b) NH_2NH_2, KOH, ethylene glycol, 180 °C, 18 h, 51%; (c) TMSCl, NaI, CH_3CN, 100%; (d) Tf_2O, lutidine, CH_2Cl_2, 93%; (e) $Pd(OAc)_2$, DPPP, TEA, DMF 77%; (f) NMO, OsO_4, acetone/H_2O, 100%; (g) (1) $NaIO_4$, (2) $BnNH_2$, (3) $NaBH(OAc)_3$, 50%; (h) (1) NH_4HCO_2, $Pd(OH)_2$, MeOH, (2) *t*-Boc_2O, 32%; (i) HCl, EtOAc, 43%.



Scheme 2. 4,11-Diaza-tricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene. Reagents and conditions: (a) *t*-BuLi, Et_2O, −78 °C, **2**; (b) NH_2NH_2, KOH, ethylene glycol, 180 °C, 18 h, 51%; (c), Tf_2O, py, CH_2Cl_2, 96%; (d) $Pd(OAc)_2$, DPPP, TEA, DMF, 80%; (e) NMO, OsO_4, acetone/H_2O, 68%; (f) (1) $NaIO_4$, 2-propanol/H_2O, (2) $BnNH_2$; (3) $NaBH(OAc)_3$, 50%; (g) (1) HCl, piperidine, HCOOH, $Pd(OH)_2$, MeOH, (2) *t*-Boc_2O, Na_2CO_3, H_2O, CH_2Cl_2, 32%; (i) HCl, EtOAc 43%.

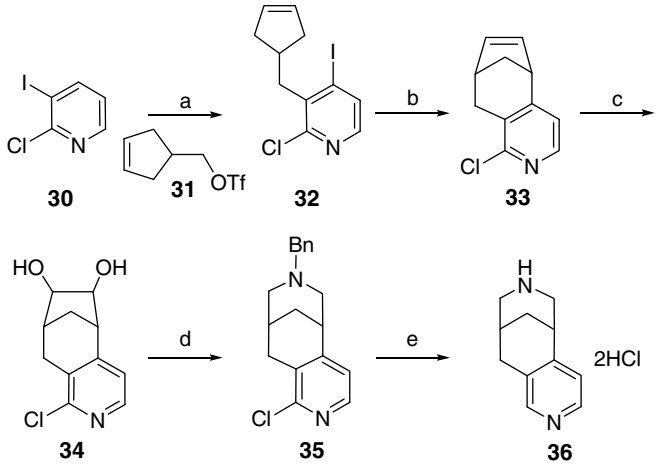


Scheme 3. 5,11-Diaza-pyridines and pyridones. Reagents and conditions: (a) LDA, THF, −78 °C, I_2, 78%; (b) LDA, THF, −78 °C, 2 h, **2**, 48%; (c) $Pd(OAc)_2$, PPh_3, KOAc, *n*-Bu_4NBr, DMF, 0.3 h; MeONa, MeOH, 60%; (d) $TsNHNH_2$, EtOH, 80%; $(PhCOO)_2BH$, $CHCl_3$, 0 °C, 2 h, 48%; (e) $(CH_3)_3NO$, OsO_4, CH_2Cl_2, 96%; (f) $NaIO_4$, EtOH/H_2O; NH_4OH, $Pd(OH)_2$, H_2, 16 h, 54%. (g) *t*-Boc_2O, Na_2CO_3, H_2O, CH_2Cl_2, 95%; (h) TMSCl, NaI, CH_3CN, 50%; (i) HCl, EtOAc, 100%; (j) MeI, 130 °C, 4 h, then HCl, EtOAc, 40%.

iodopyridine **21** was prepared via 'halogen dance' metalation as described by Queguiner[21] and reacted with **2** at low temperature to generate iodo-Heck precursor **22**.

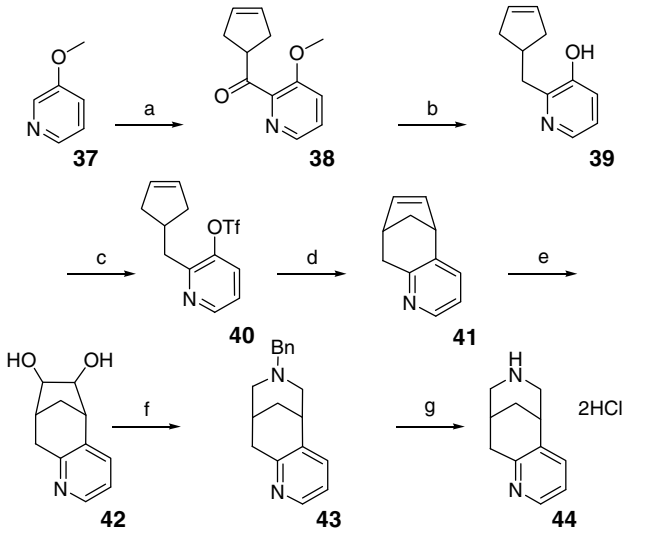
Conversion under the conditions of Jeffery[22] spared the fluoro group and afforded the bicyclic ring system **23**. This reactive material was directly converted to the methoxyl derivative **24** in high overall yield upon exposure to alkoxide. Ketone reduction in this case via the tosylhydrazone avoided both methoxyl group dealkylation and heterocycle formation under reducing conditions.[23] The piperidine was exposed as described before[11a] to give the target methoxy pyridine **27**. The conversion of **27** to the *NH*-pyridone **28** was accomplished on the *t*-Boc derivative with TMSI, while the methylated derivative **29** was accessed from the *t*-Boc derivative via pyridine *N*-methylation (MeI, sealed tube) and subsequent pyridone formation (HCl).

This sequence was further streamlined to afford pyridine **36** in 5 steps from 3-iodo-2-chloropyridine **30** (Scheme 4). Metalation (LDA) and aging provided the thermodynamic lithium species via 'halogen dance' (3-lithio-4-iodo-2-chloropyridine), which was quenched with triflate-activated cyclopentene-3-carbinol **31**.[24] The resulting alkylated product **32** was cyclized in 76% yield to give olefin **33** and converted as before to piperidine **35**. Hydrogenation affords target **36** in 45% yield from **34**.

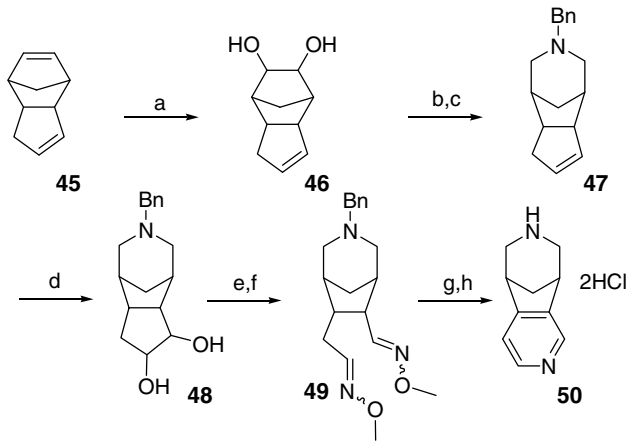


Scheme 4. 5,11-Diaza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene. Reagents and condition: (a) LDA, −78 °C, THF, **31**, 89%; (b) $Pd(OAc)_2$, P(*o*-tolyl)$_3$, TEA, DMF 76%; (c) NMO, OsO_4, acetone/H_2O, 7d, 89%; (d) (1) $NaIO_4$, DCE/H_2O; (2) $BnNH_2$, $NaBH(OAc)_3$, 45%; (e) $Pd(OH)_2$, MeOH, HCl, 100%.

The final [3.3.1]-bicyclic 6,11-diaza-pyridine derivative was prepared from 3-methoxy pyridine **37** by regioselective metalation at 2-position by mesityl lithium[12] and addition to Weinreb amide **2** (Scheme 5). Reduction under Wolff–Kishner conditions again simultaneously demethylated **38** to give phenol **39** directly. The resulting ketone was converted to target **44** as described above.



Scheme 5. 6,11-Diaza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene. Reagents and conditions: (a) Mesityl lithium, −78 °C, THF, **2**; (b) NH_2NH_2, KOH, ethylene glycol, 180 °C, 18 h, 50%; (c) Tf_2O, pyridine, CH_2Cl_2, 86%; (d) $Pd(OAc)_2$, DPPP, TEA, DMF 80%; (e) NMO, OsO_4, acetone/H_2O, 72%; (f) (1) $NaIO_4$, 2-propanol/H_2O; (2) $BnNH_2$; (3) $NaBH(OAc)_3$, 50%; (g) HCl, piperidine, HCOOH, $Pd(OH)_2$, MeOH; (2) *t*-Boc_2O, Na_2CO_3, H_2O, DCM, 32%; (i) HCl, EtOAc 43%.



Scheme 6. 4,10-Diaza-tricyclo[6.3.1.02,7]dodeca-2(7),3,5-triene. (a) NMO, OsO_4, acetone, 20%; (b) $NaIO_4$ dioxane, H_2O; (c) $BnNH_2$, $NaBH(OAc)_3$, DCE, 76%; (d) NMO, OsO_4, acetone, 80%; (e) $NaIO_4$, dioxane, H_2O; (f) $NH_2OCH_3{\cdot}HCl$, NaOAc, MeOH/H_2O; (g) 9/1 DCE/TFA; (h) NH_4HCO_2/$Pd(OH)_2$, MeOH, 35%.

Finally, the [3.2.1]-bicyclic derivative **50** was prepared from dicyclopentadiene diol **46** (Scheme 6). This was converted to the *N*-benzyl piperidine **47** by the oxidative cleavage/reductive amination procedure. Diol **48** was generated (NMO, OsO_4) and cleaved ($NaIO_4$) to provide an intermediate dialdehyde, which was condensed directly with *O*-methyl hydroxylamine to provide the bis-*O*-methyl-oxime **49**. This crude mixture of geometric isomers was warmed in 9/1 DCE/TFA to provide the corresponding pyridine.[4] Debenzylation by methods described above provides target [3.2.1]-bicyclic pyridine **50**.

These syntheses demonstrate additional applications of the Heck strategy and cyclopentene/piperidine synthesis to the preparation of heterocycle containing bicyclic alkaloids. The pyridine derivatives described herein are conformationally constrained tools designed to explore specific interactions at nicotinic receptor subtypes. The results of these interaction studies will be reported separately where this unique set of valuable probes will hopefully contribute to a better of understanding nicotinic receptor–ligand interactions.

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