Synthesis and Pharmacological Evaluation of Novel 9- and 10-Substituted Cytisine Derivatives. Nicotinic Ligands of Enhanced Subtype Selectivity

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Abstract: We report the synthesis and pharmacological properties of several cytisine derivatives. Among them, two 10-substituted derivatives showed much higher selectivities for the α4β2 nAChR subtype in binding assays than cytisine. The 9-vinyl derivative was found to have a very similar agonist activity profile to that of cytisine.

Neuronal nicotinic acetylcholine receptors (nAChRs) belong to a heterogeneous family of pentameric ligand-gated ion channels which are differently expressed in many regions of the central nervous system (CNS) and peripheral nervous system.[1,2] In the CNS, nAChRs regulate transmitter release, cell excitability, and neuronal integration. Neuronal nicotinic receptors constitute therapeutically relevant targets for the treatment of neurodegenerative disorders and other CNS disorders including Alzheimer's and Parkinson's disease, Tourette's syndrome, schizophrenia, attention deficit disorder, anxiety, and pain. Moreover, as the addictive properties of tobacco products are due to the nicotine contained therein, nAChRs also become important targets for the discovery of medications for use in smoking cessation.[3]

The nAChRs are composed of various combinations of different subunits, of which 17 (α1-α10, β1-β4, γ, δ, and ε) are known at present. Different subunit combinations define the various nAChR subtypes, and different receptor subtypes have characteristic pharmacological and biophysical properties, as well as different locations within the nervous system.[4] Therefore, subtype selectivity is an important issue for the effectiveness and safety of nicotinic therapeutics.

While a host of nAChR ligands have been identified, there is still a substantial need to discover subtype-selective ligands that can be used to establish the physiological and pathophysiological significance of each of the receptor subtypes. As is now apparent from clinical results obtained with a variety of drugs, both the safety and efficacy of therapeutic agents often depend on their subtype selectivity. While, as noted, a large number of nicotinic agonists and noncompetitive antagonists exist, very few of these are subtype-selective.[1,6] Exquisite subtype selectivity is difficult to achieve because of the large number of possible subtypes together with their relatively subtle structural differences, but is of great societal value in terms of possible disease treatment.

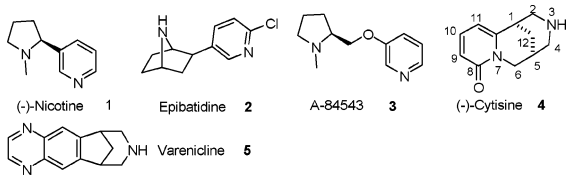

Figure 1.

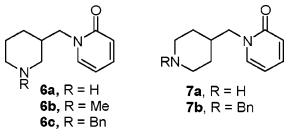

Figure 2.

The α4β2 nAChR is the most abundant subtype in the brain.[7] Several findings suggest that α4β2 receptors are involved in behavioral activity such as nicotine dependence, avoidance learning, and antinociception.[8] Nicotine (**1**) and epibatidine (**2**) are both naturally occurring nAChR agonists that have attracted interest as lead candidates for analogue synthesis aimed at identifying structures with improved pharmacological properties.[1,9,10] For example, we recently reported that introduction of a hydrophobic or hydrogen-bonding alkynyl group into the C-5 position of the pyridine ring of epibatidine and A-84543 (**3**) significantly increased the selectivity for nAChRs containing β2 subunits.[11] As part of our continuing interest in this project, we focused on chemically modifying (−)-cytisine **4**, a natural chiral quinolizidine alkaloid with a unique tricyclic structure (Figure 1).[12]

(−)-Cytisine (**4**) is reported to behave as a partial agonist at the α4β2 nAChR with $EC_{50} \approx 1$ μM and possess a low nanomolar binding affinity ($K_i \approx 1$ nM).[13−16] [^{3}H]Cytisine is frequently used as a radioligand in the study of nAChRs.[13,17] Three total syntheses of cytisine[18] were achieved in the 1950s. Recently, further interest in this alkaloid was stimulated by the two alternative approaches to cytisine reported by Coe[19] and O'Neill et al.[20] Their efforts eventually resulted in the discovery of varenicline (**5**), a substantially re-engineered version of cytisine which has become a clinical candidate for use in smoking cessation.[21] Following these reports, several other reports, including two enantioselective routes to this alkaloid as well the synthesis of other novel cytisine analogues have been published.[22−24]

Our own work in the nicotine area has been ongoing for approximately four years. Herein we report the synthesis and pharmacological evaluation of novel 9- and 10-substituted cytisine derivatives. To the best of our knowledge, the present work provides the first example of cytisine derivatives with 10-substitution. We modified O'Neill's synthetic strategy so as to allow implementation of the desired structural changes.[20]

At the onset of our work in this area, we chose to synthesize some simplified cytisine analogues. Deletion of the C-1/C-13 bond in cytisine yields structure **6** (Figure 2). This compound and its isomers **7a** and **7b** can be prepared from piperidin-3-yl- and −4-ylmethanol by N-protection, iodide installation, and then reaction with α-pyridone, followed by deprotection (for the synthetic scheme, see Supporting Information).

As initial biological assays revealed that the binding affinities of compounds **6a**−**c** and **7a**,**b** at the nAChR subtypes were

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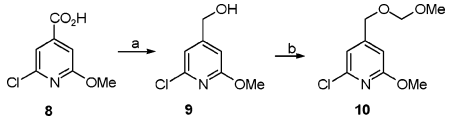
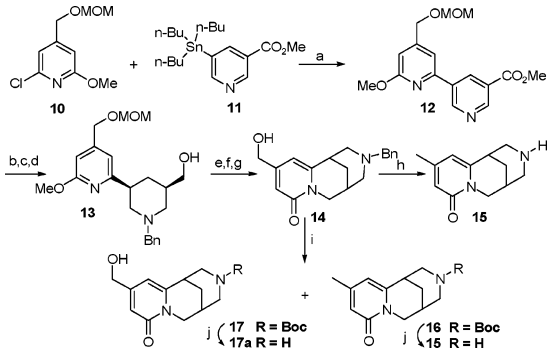
Scheme 1[a]



[a] Reagents and conditions: (a) BH_3-THF, THF, 0 °C, 5 h, 85%; (b) $CH_2(OMe)_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 3 h, 85%.

Scheme 2[a]



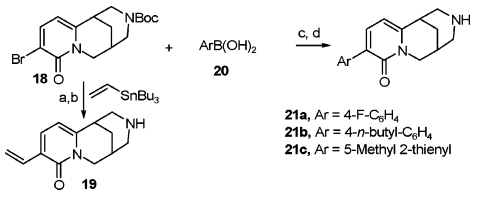
[a] Reagents and conditions: (a) $Pd(PPh_3)_4$, DMF, 130 °C, 15 h, 79%; (b) $LiAlH_4$, THF, −20 °C, 3.5 h, 59%; (c) BnBr, CH_3CN, reflux, 2 h; (d) H_2 (1 atm), PtO_2, Et_3N, MeOH, rt, 15 h, cis:trans = 5:1; cis, 67%; (e) MsCl, Et_3N, DCM, 0 °C, 30 min, 84%; (f) toluene, reflux, 3 h, 83%; (g) TFA, rt, 3 h, 91%; (h) H_2 (1 atm), 10% Pd−C (1 equiv w/w), MeOH, rt, 15 h; (i) H_2 (1 atm), 20% $Pd(OH)_2$−C (0.1 equiv), $(Boc)_2O$, MeOH, reflux, 30 min, 92%; (j) TFA, CH_2Cl_2, rt, 1 h, 87−93%.

much lower (Supporting Information, Table A) than that of cytisine,[16] we subsequently retained the core tricyclic structure while placing substituents on the pyridone ring. Our first objective was to introduce a hydroxymethyl group at the 10-position. The modified starting material required for this purpose, compound **10**, was prepared by borane reduction of commercially available 2-chloro-6-methoxyisonicotinic acid (**8**),[25] followed by hydroxyl protection (Scheme 1).

Pd-catalyzed Stille coupling of the preformed stannane[20] **11** with **10** under the optimized conditions proceeded smoothly to afford compound **12** in 79% isolated yield (Scheme 2). With *trans*-benzyl(chloro)bis(triphenylphosphine)palladium(II) as the catalyst, the reaction proceeded much faster, but gave low yields especially on scale-up. The in situ Stille coupling reaction gave inferior results.[20] Our attempts to repeat O'Neill's ester reduction at room temperature gave only the over-reduced methyl derivative. The required alcohol was obtained when the reduction was carried out using 1 M $LiAlH_4$ solution in THF at −20 °C for 3.5 h. Following the strategy of O'Neill with some modifications, and after deprotection of the methoxymethyl (MOM) group with trifluoroacetic acid (TFA) at room temperature, we obtained *N*-benzyl-10-(hydroxymethyl) cytisine (**14**).

Attempted N-debenzylation of this compound using a variety of methods failed. Several catalytic hydrogenation protocols as well as the use of allyloxycarbonyl chloride[26] resulted in either no reaction or the formation of complex mixtures. Prolonged hydrogenation over 10% Pd−C at room temperature and 1 atm in MeOH gave the over-reduced product **15**. Our difficulty in carrying out this step was finally resolved by hydrogenation over Pd−C in the presence of $(Boc)_2O$.[27] A mixture of two products was formed, separation of which by semipreparative HPLC gave the less polar over-reduced compound **16** and the more polar 10-hydroxymethyl derivative **17**. Final N-Boc deprotection with TFA[28] gave the 10-substituted racemic cytisine derivatives **15** and **17a**. Later we found that, under optimized conditions (20% $Pd(OH)_2$−C, (0.1 eq), H_2 (1 atm), $(Boc)_2O$, MeOH, 5 min, reflux), N-debenzylation proceeded smoothly to afford the 10-hydroxymethyl derivative **17** in 97% yield.

Scheme 3[a]



[a] Reagents and conditions: (a) $PdCl_2(PPh_3)_2$, Dioxane, 120 °C, 1 h, 73%; (b) TFA, CH_2Cl_2, 30 min, 81%. (c) Pd $(PPh_3)_4$, K_2CO_3, DME/H_2O, 85 °C, 15 h, 87%; (d) TFA, CH_2Cl_2, 30 min, 85%.

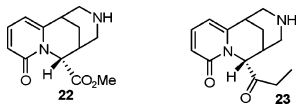


Figure 3.

We further expanded the SAR of cytisine by preparing some additional analogues starting from (−)-cytisine itself. Most of the previously reported SAR of this molecule has focused on modifications at the alicyclic nitrogen (position 3) and also on the 9- and 11- positions of the pyridone ring.[24,29,30] Moreover, a recent report showed that substitution at the 6-position could be brought about via a novel *N*-acyl migration reaction.[31] As the biological activity of some of these known compounds has not been described in full, we selected four of the reported compounds together with new analogues in order to more fully flesh out our SAR studies. Following a literature procedure we synthesized the N-Boc-protected 9-bromocytisine **18** and its Stille coupling product with tri-*n*-butylvinylstannane.[29] Final deprotection with TFA afforded the derivative (−)-**19** (Scheme 3).[29b]

We succeeded in carrying out a Suzuki coupling reaction of **18** with various boronic acids **20** to afford **21a**−**c** (Scheme 3). The synthesis of **21a** using the Stille coupling procedure[29] has already been reported. The 6-substituted derivatives **22** and **23** were also prepared following known procedures (Figure 3).[31]

In vitro binding affinities (K_i values) of the eight cytisine analogues **15**, **17a**, **19**, **21a**, **21b**, **21c**, **22**, and **23** were measured at six defined nAChR subtypes expressed in stably transfected cell lines, using competition binding assays as previously reported (Table 1).[10,16,32] In comparison to cytisine, the 10-methyl derivative **15** showed a similar binding affinity to α4*β*2 nAChRs, the major subtype in brain, but its affinities to the other subtypes were lower than those of cytisine. Thus, the selectivity of **15** for the α4*β*2 subtype over the other subtypes was improved significantly. This is especially true for selectivity between the α4*β*2 subtype and α3*β*4 subtype, the main subtype of ganglionic nAChRs. The affinity ratio of α3*β*4/α4*β*2 is larger than 3000-fold, which puts compound **15** among the most selective cytisine analogues that have been reported to date. The racemic nature of **15** probably will not have a substantial impact on this selectivity ratio. Interestingly, compound **17a** with a 10-hydroxymethyl group showed reduced activity at all subtypes, but again displays a larger α3*β*4/α4*β*2 affinity ratio. The 9-vinyl compound **19** was slightly more potent than cytisine at some of the nAChRs, but overall it behaves much like cytisine. All of the other six cytisine analogues showed considerably reduced binding affinities at all nAChRs. Compound **21a** did, however, retain its selectivity for the α4*β*2 nAChR.

The above eight cytisine analogues were next tested for their agonist activities at the two major neuronal nAChR subtypes,

Table 1. Binding Affinities and Calculated Lipophilicities of (±)-Epibatidine (**2**), (−)-Cytisine (**4**), and Cytisine Analogues at nAChR Subtypes[a]

ligand	K_i (nM)[b] α2β2	α2β4	α3β2	α3β4	α4β2	α4β4	forebrain	affinity ratio (α3β4/α4β2)	calculated ClogP[c]
rac-**15**	7.5	180	540	6700	1.9	38	20	3526	1.15
rac-**17a**	32	300	467	10000	11	68	38	909	-0.32
(−)-**19**	0.7	9.0	28	95	0.73	2.3	5.2	130	1.50
(−)-**21a**	820	8100	12000	66000	420	3300	3100	157	2.56
(−)-**21b**	8000	28000	36000	140000	8200	13000	21000	17	4.38
(−)-**21c**	500	1700	6000	23000	390	590	1200	59	2.73
(−)-**22**	17000	75000	250000	320000	24000	33000	48000	13	0.57
(−)-**23**	14000	50000	300000	280000	16000	20000	23000	18	0.71
(±)-epibatidine (**2**)	0.02	0.09	0.04	0.57	0.06	0.16	0.06	10	1.81
(−)-cytisine (**4**)	1.07	5.41	37.20	217.00	1.51	2.10	1.92	144	0.60

[a] Competition binding assays were carried out in membrane homogenates of stably transfected cells or rat forebrain tissue as described previously.[16] The nAChRs were labeled with [^{3}H]epibatidine. The K_d values for [^{3}H]epibatidine used for calculating K_i values were 0.02 for α2β2, 0.08 for α2β4, 0.03 for α3β2, 0.3 for α3β4, 0.04 for α4β2, 0.09 for α4β4, and 0.05 for rat forebrain. [b] K_i values of the cytisine analogues shown are the mean of three to five independent measurements. For clarity and to save space, the SEM for the K_i values shown are omitted, but in all cases were less than 45% of the mean values. The K_i values of epibatidine (**2**) and cytisine (**4**) were published previously and are shown here for comparison.[16] [c] The ClogP values are calculated using the online version of Syracuse Research Corporation's LogKow/KOWWIN program; *J. Phram. Sci.* **1995**, *84*, 83−92.

Table 2. Comparison of Agonist Activities of (−)-Nicotine and (−)-**19** at Two Major nAChR Subtypes, α3β4 and α4β2

compound	α3β4 nAChRs[b] EC$_{50}$ (μM)	α3β4 nAChRs[b] relative E_{max} (% of nicotine E_{max})	α4β2 nAChRs[c] EC$_{50}$ (μM)	α4β2 nAChRs[c] relative E_{max} (% of nicotine E_{max})
(−)-nicotine	35 ± 8	100	10 ± 1	100
(−)-**19**	30 ± 7	83 ± 3	1.3 ± 0.4	22 ± 2

[a] Agonist activities were measured using $^{86}Rb^+$ efflux assays. Values shown are the mean ± standard error of three independent experiments performed in quadruplicate. [b] KXα3β4R2 cells stably expressing rat α3β4 nAChRs were used as described previously.[16,32,33] [c] A procedure for measuring $^{86}Rb^+$ efflux from SH-EP1-hα4β2 cells was adopted[15] with minor modifications.

α3β4 and α4β2, using $^{86}Rb^+$ efflux assays previously reported.[15,32] They were tested at four concentrations, 0.1, 1, 10, and 100 μM. Compound **19** stimulated $^{86}Rb^+$ efflux from cells expressing either α3β4 or α4β2 nAChR subtypes. The other seven compounds failed to show agonist activity at any of the concentrations used at these two nAChR subtypes. Compound **19** was further evaluated for its agonist potency and efficacy (Table 2). Consistent with its higher binding affinity at α4β2 than at α3β4 nAChRs, the compound was 20-fold more potent at the α4β2 subtype (EC$_{50}$ = 1.3 μM) than at the α3β4 subtype (EC$_{50}$ = 30 μM). Compared to the efficacy of (−)-nicotine, the maximal efficacies of **19** were 83% and 22% of those of nicotine at the α3β4 receptors and α4β2 receptors, respectively. The overall agonist activity profile of **19** is very similar to that of cytisine.[15,33] Compounds **15** and **17a** did not show agonist activity at α4β2 nAChRs despite their high selectivity for this nAChR subtype in the binding assays. We tested these two compounds at concentrations from 0.1 μM to 100 μM for their antagonist activities at the α4β2 and α3β4 receptors. At concentrations up to 10 μM, the compounds did not significantly block nicotine stimulated responses. However, at 100 μM, both compounds inhibited more than 50% of the function of the α4β2 nAChR subtype but only slightly inhibited the function of the α3β4 nAChR subtype. These results indicate that the two 10-substituted cytisine analogues, compound **15** and **17a**, are weak antagonists of the α4β2 nAChR subtype. These two compounds appear to have high affinity for the α4β2 nAChR subtype in its desensitized conformation (i.e., in the receptor binding assays), but low affinity for the receptors in their resting conformation, as shown by their low potency in functional assays. This is typical of most classical nicotinic ligands.[34]

While (−)-cytisine is a potent, partial α4β2 nAChR agonist, it does not show strong efficacy as a smoking cessation aid.[35] This lack of efficacy may result at least in part from its poor penetration of the blood−brain barrier (BBB).[36] Lipophilicity is one of the important indicators for predicting absorption and BBB penetration.[37] Compound **19** has a higher calculated ClogP value than that of cytisine (Table 1). Its ClogP value is between those of nicotine (1.00) and epibatidine (1.80), both of which penetrate the BBB easily. Though far from conclusive, these data indicate that compound **19** may have an improved BBB penetration in comparison to cytisine. In light of the similarity of **19** and cytisine in relation to their binding affinity profiles and agonist activity profiles, if **19** is confirmed to have a better absorption and BBB penetration profile, it may be a better candidate to use in targeting CNS receptors in vivo, in particular for use in smoking cessation.

In conclusion, we have synthesized several new cytisine derivatives. The 10-substituted analogues **15** and **17a** are more than 3000-fold and 900-fold selective for the α4β2 subtype over the α3β4 nAChR subtype in binding assays, respectively, making them among the most discriminating nicotinic ligands that have been derived from cytisine. The 9-vinyl derivative **19** showed very similar functional features to those of cytisine. The fact that compound **19** may have an improved ability to penetrate the BBB adds to the value of this compound as a research tool. Therefore, compared to cytisine, ligand **19** may be a better compound for targeting CNS nicotinic receptors. Further efforts to characterize the pharmacological properties of these three compounds both in vitro as well as in vivo (drug discrimination) are underway.

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Supporting Information Available: Detailed experimental procedures with spectroscopic data for all new compounds are available at http://pubs.acs.org.

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