Varenicline: An α4β2 Nicotinic Receptor Partial Agonist for Smoking Cessation

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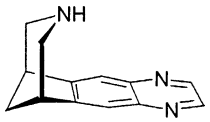
Abstract: Herein we describe a novel series of compounds from which varenicline (**1**, 6,7,8,9-tetrahydro-6,10-methano-6*H*-pyrazino[2,3-*h*][3]benzazepine) has been identified for smoking cessation. Neuronal nicotinic acetylcholine receptors (nAChRs) mediate the dependence-producing effects of nicotine. We have pursued α4β2 nicotinic receptor partial agonists to inhibit dopaminergic activation produced by smoking while simultaneously providing relief from the craving and withdrawal syndrome that accompanies cessation attempts. Varenicline displays high α4β2 nAChR affinity and the desired in vivo dopaminergic profile.



varenicline (1)

Within 20 years of its introduction to Britain in 1584, King James I scorned "tobacco taking" as a "vile and stinking custome" that is "hurtfull to the health of the whole body".[1] In the ensuing 400 years, we have learned that although other tobacco ingredients cause the negative health effects of smoking, it is the nicotine in tobacco that produces dependence and maintains smoking behavior. Ultimately, the toll on human health today is staggering, as half of the world's 1.25 billion smokers will die from smoking-related illnesses, such as chronic obstructive pulmonary disorder, cancer, and cardiovascular disease.[2,3]

Neuronal nicotinic acetylcholine receptors (nAChRs), which mediate fast synaptic transmission via the endogenous ligand acetylcholine (ACh), have become key targets for therapeutic approaches to treat pain, cognition, schizophrenia, and nicotine dependence.[4] Found in the peripheral and central nervous systems, these pentameric ligand-gated ion channels consist of 17 known receptor subunits ($\alpha_{(1-10)}$, $\beta_{(1-4)}$, γ, δ, and ϵ).[5] Although a large number of neuronal subtypes have been identified, α4β2, α3β4, and α7 predominate in the central nervous system.

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The dependence-producing effects of nicotine are believed to be mediated in part through its action as an agonist at α4β2 nAChRs.[6,7] Activation of α4β2 receptors by nicotine increases the release of dopamine in the nucleus accumbens and prefrontal cortex,[8] an effect shared by most substances of abuse, although each through distinct neurochemical pathways.[9]

We sought to develop a nicotinic receptor partial agonist of the α4β2 nAChR for smoking cessation. It was hypothesized that an effective agent would, through its intrinsic partial activation of the α4β2 nAChR, elicit a moderate and sustained increase in mesolimbic dopamine levels, counteracting the low dopamine levels encountered in the absence of nicotine during smoking cessation attempts. Low levels of dopamine have been associated with craving for and withdrawal from nicotine and are the key syndromes that precipitate relapse to smoking behavior.[10] Additionally, by competitively binding to the α4β2 nAChR, a partial agonist will shield the smoker from nicotine-induced dopaminergic activation in the event that they smoke.[11] In theory, without the nicotine-induced elevation in mesolimbic dopamine levels, tobacco will not produce a pharmacologic reward. Thus, we anticipated that a partial agonist would be uniquely suited as a treatment for this condition.[12]

At the outset of our program only two natural compounds were known to have partial agonist activity at the α4β2 nAChR.[13] Of these,[14] we chose (−)-cytisine, a natural product found in numerous plant species, as a starting point for our studies.[15] (−)-Cytisine displays potent α4β2 nAChR affinity and possesses a unique bicyclic structure lacking rotatable bonds. A key 1994 publication showed that (−)-cytisine was a partial agonist of the α4β2 nAChR and antagonized the receptor response to its endogenous neurotransmitter, acetylcholine.[16] This work confirmed earlier reports on (−)-cytisine's pharmacological profile at β2-containing receptors: it elicited a markedly reduced response to that of acetylcholine.[17] In the 1960s an early smoking cessation study with (−)-cytisine failed to exhibit robust efficacy,[18] possibly as a result of poor absorption[19] and limited brain penetration.[20] More recently, efforts to combine nicotine replacement therapy with the nicotinic antagonist mecamylamine were more successful.[21] These latter results of combining an agonist and antagonist—essentially creating a partial agonist—suggested that an agent with an optimal partial agonist profile and physicochemical properties could provide improved relief to patients during smoking cessation attempts.

On the basis of these considerations and the structural starting point provided by (−)-cytisine, we initiated synthetic efforts to generate novel compounds with improved potency and efficacy. Our studies revealed that α4β2 nAChR binding affinity was considerably reduced with alterations at positions N-9 and C-5, but maintained or improved with substitution at C-3 of (−)-cytisine (Chart 1).[22] These results led us to explore pyridone replacements based on **2**. Compounds from this series exhibited reduced affinity and weak partial agonist activity, a result that prompted a search for alternative templates with improved partial agonist

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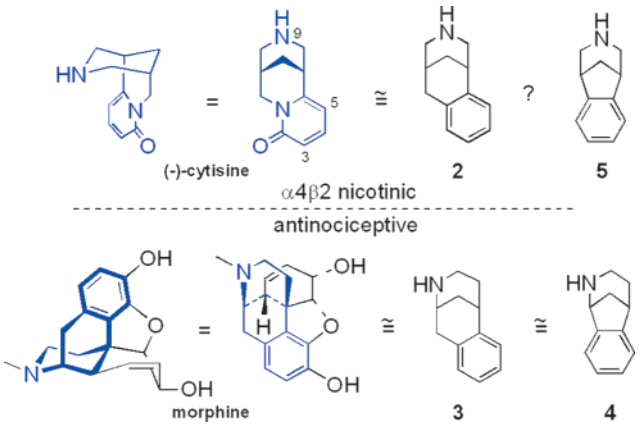
Chart 1. Related Substructures of (−)-Cytisine and Morphine



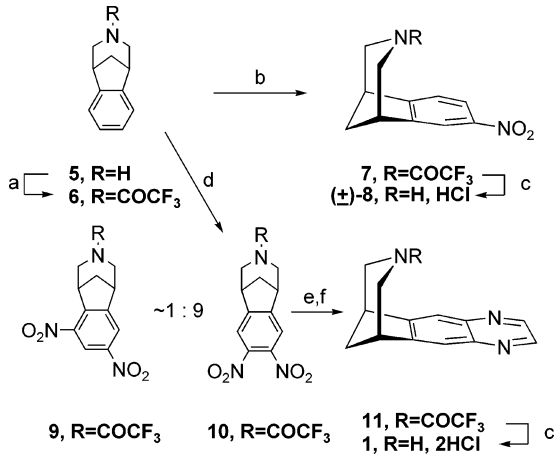
profiles. We also recognized the striking resemblance between substructures of (−)-cytisine and morphine: their [3.3.1]-bicyclic skeletons differ only by nitrogen atom placement (cf. **2** vs **3**, Chart 1). In the 1970s, the [3.3.1]-bicyclic benzomorphan **3** was found to have morphine-like antinociceptive activity, as did the modified [3.2.1]-bicyclic derivative **4**; however, the N-positional [3.2.1]-bicyclic isomer, benzazapine **5**, was devoid of antinociceptive activity.[23] Interestingly, benzazapine **5** displayed in vivo pharmacology reminiscent of natural nicotinic agents. On the basis of the similarity between **3** and **4**, both antinociceptive compounds, we speculated that **2** and **5** might share a similar nicotinic pharmacology. This hypothesis was borne out, as **5**[24] was found to be a nicotinic antagonist with a K_i of 20 nM.

Nicotinic agents share two common structural components: an ammonium headgroup at physiological pH, and a π-system.[25] Potent natural nicotinic agonists, including epibatidine,[26] (−)-nicotine, (+)-anatoxin *a*,[27] and (−)-cytisine ($K_i \sim 0.07$, 0.95, 4.4, 0.17 nM, respectively), possess electron-deficient π-systems. As shown in Scheme 1, we introduced an electron-withdrawing group to benzazapine **5** by conversion to trifluoroacetamide **6**, nitration,[28] and deprotection to afford (±)-**8**, which displayed potent α4β2 nAChR binding affinity (K_i 0.75 nM) and partial agonist activity (vide infra).

Examination of the crude nitrated reaction mixture (**6**→**7**) revealed dinitrated products, separable on crystallization. We attribute their formation to the exceptionally powerful and soluble nitrating agent, nitronium triflate ($CF_3SO_2O^-NO_2^+$). Unexpectedly, the major dinitrated product was **10**, the result of vicinal-dinitration.[29] Exposure to 2.3 equiv of nitronium triflate in CH_2Cl_2 gave complete consumption of **6** in 28 h to provide **10**, isolated in pure form by crystallization in 77% yield from the crude mixture, which contained <10% of meta-isomer **9**.

Isomer **10** has proven to be a very useful intermediate for the preparation of analogues such as achiral quinoxaline **1**, varenicline, which was prepared as follows: Reduction of **10** to the corresponding diaminophenyl derivative and condensation with glyoxal (sodium bisulfite addition adduct) afforded crystalline quinoxaline trifluoroacetamide **11**.[30] Deprotection, salt formation, and crystallization completed the synthesis of **1** in 44% overall yield from **5**.

Scheme 1. Nitration Route to **7** and Varenicline, **1**[a]



[a] Reagents: (a) TFAA, py, CH_2Cl_2 (94%); (b) 1.3 equiv HNO_3, 2.6 equiv CF_3SO_2OH, −78 °C, CH_2Cl_2 (78%); (c) [1] Na_2CO_3, aq. MeOH (95%); [2] HCl, EtOAc; (d) [I] 2.3 equiv HNO_3, 4.6 equiv CF_3SO_2OH, 0−20 °C, 28 h, CH_2Cl_2 (77%); (e) H_2, $Pd(OH)_2$, MeOH (96%); (f) glyoxal, THF, H_2O, 80 °C, (60)%.

Table 1. In Vitro Affinity at nAChR Subtypes and Agonist/Antagonist Activity at the *h*α4β2 Receptor

	affinity (K_i [nM])				% current evoked by 10 μM agent at *h*α4β2 nAChR	
	α4β2[a]	α3β4[b]	α1βγδ[c]	α7[d]	% response of nicotine[e]	% inhibition of nicotine[f]
(−)-cytisine	0.17	840	250	4200	56	30
5	20	2850	370	>5000	0	35
(±)-**8**	0.75	210	690	7340	65	20
varenicline **1**	0.06	240	3540	322	68	34
(−)-nicotine	0.95	530	6270	6290	100	—

[a] [3H]-nicotine; rat cortex. [b] [3H]-epibatidine; IM*R*32 cells. [c] [125I]-α-bungarotoxin; electroplax. [d] [125I]-α-bungarotoxin; GH4C1 cells. (All determinations $N = 3$). [e] Percent agonist activity of 10 μM test compound relative to 10 μM (−)-nicotine (SEM ≤10%). [f] Percent antagonist activity of 10 μM test compound against 10 μM nicotine (SEM ≤ 10%).

Varenicline (**1**) and (±)-**8** display high binding affinity and selectivity for the rat α4β2 over the nAChR subtypes evaluated (Table 1).[31] No appreciable affinity was observed with **1** in an in vitro receptor binding panel of nonnicotinic targets (IC_{50} > 1000 nM).[32] In functional electrophysiological assays in *Xenopus* oocytes expressing the *h*α4β2 nAChR, nicotine had an EC_{50} of 15 μM. Due to concerns about receptor desensitization, benchmark responses to nicotine were routinely determined using a lower test concentration of 10 μM. At this concentration (−)-cytisine, (±)-**8**, and **1** were shown to act as agonists with lower efficacy than 10 μM nicotine (56%, 65%, and 68%, respectively).

Antagonist properties were determined by coapplication with 10 μM nicotine. Evaluating responses in the presence of a single concentration of nicotine (10 μM) allows the assessment of functional potencies and agonist/antagonist properties of compounds relative to nicotine. Potent agonists or low potency partial agonists would not be expected to antagonize the effects of 10 μM nicotine, but agents that act as potent partial agonists alone should functionally antagonize nicotine's effect at 10 μM.[33] The data in Table 1 reveal desirable partial agonist profiles for (−)-cytisine, (±)-**8**, and **1**. The full concentration−response curve of varenicline (**1**)

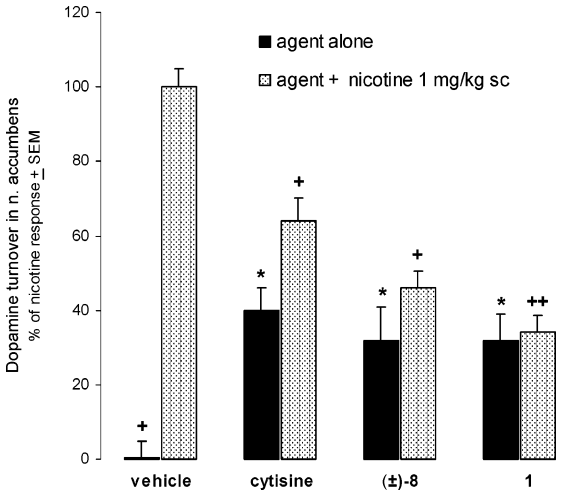


Figure 1. Effects of (−)-nicotine, (−)-cytisine, (±)-**8**, and **1** on dopamine turnover in rat nucleus accumbens 1 h postdose. All values are expressed as percentages of the effect of 1.0 mg/kg sc nicotine (100%) ± SEM ($N = 5-10$). Each compound was administered at 5.6 mg/kg sc alone (filled bars) and with 1 mg/kg sc nicotine (shaded bars). $^{*}p < 0.05$ agent alone vs vehicle; $^{+}p < 0.05$ and $^{++}p < 0.01$: agent with nicotine vs nicotine alone (one-way ANOVA with posthoc Dunnett's test).

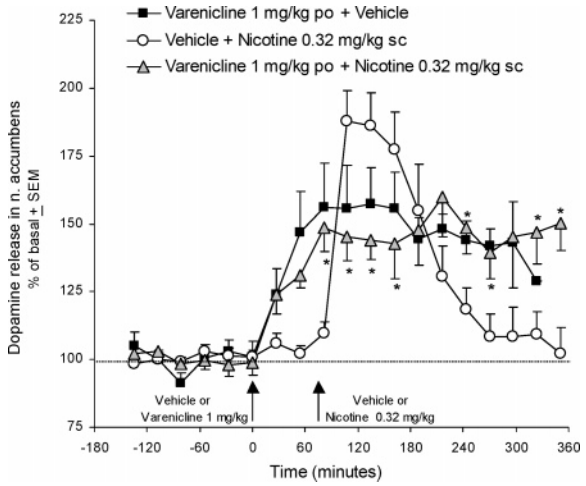


Figure 2. Time courses for the effects of 0.32 mg/kg sc nicotine (open circles) and 1.0 mg/kg po varenicline (**1**, filled squares) alone and in combination (triangles) on extracellular dopamine levels in the nucleus accumbens of conscious Sprague−Dawley rats. Varenicline was administered 1 h before nicotine (arrows), and effects on dopamine release are expressed as a percentage of baseline (mean of last five predrug basal levels) ± SEM ($N = 4-6$). $^{*}p < 0.05$: varenicline with nicotine vs nicotine alone (two-factor analysis, repeated measures, Western-Electric).

revealed an EC_{50} of 2.3 μM with a maximal efficacy of 24% relative to nicotine in this in vitro model.

We assessed the in vivo efficacy of the compounds by their effects on mesolimbic dopamine turnover, a measure of the utilization and biosynthesis of dopamine (Figure 1).[34] Concentrations of dopamine and its metabolites were determined in the nucleus accumbens of male Sprague Dawley rats (200−300 g) 1 h postdose. The results demonstrate that nicotine has a maximal effect on dopamine turnover (177% of controls) at 1 mg/kg sc. The effects of 5.6 mg/kg sc (−)-cytisine, (±)-**8**, and varenicline (**1**) were 40%, 32%, and 32%, respectively, of the maximal nicotine response. These were maximal effects for (−)-cytisine and varenicline (**1**), demonstrating partial agonist behavior.

Partial agonist activity was further demonstrated in vivo by evaluating the antagonist properties of (−)-cytisine, (±)-**8**, and varenicline (**1**). Their ability to attenuate nicotine's effect on the mesolimbic dopamine system was determined in animals concurrently treated with 1 mg/kg sc nicotine. (−)-Cytisine and (±)-**8** reduced the nicotine-induced increase in dopamine turnover in the nucleus accumbens. Unlike (−)-cytisine and (±)-**8**, however, at 5.6 mg/kg sc **1** fully blocked nicotine's effect: increases in dopamine turnover with **1** after 1 h were the same alone and in the presence of nicotine. These data demonstrate that all three are partial agonists and that varenicline is more potent in vivo than (−)-cytisine and (±)-**8**. Figure 1 shows that (−)-cytisine, (±)-**8**, and varenicline (**1**) inhibited the nicotine response by 36%, 54%, and 66% respectively (5.6 mg/kg sc agent with 1 mg/kg s.c nicotine is the maximum tolerated combination dose).

A related measure of partial agonist activity in vivo included the measurement of extracellular dopamine levels over a 6 h time course in conscious rats. Microdialysis studies with nicotine and varenicline (**1**) measuring in vivo dopamine release in rat nucleus accumbens confirmed the partial agonist effect of **1** (Figure 2). At a maximally effective dose of 1 mg/kg po, varenicline produced a sustained increase in dopamine release to ∼60% of the maximal nicotine effect (188% at 0.32 mg/kg sc). In addition, 1 mg/kg po varenicline reduced the dopamine-enhancing effects of a subsequent dose of 0.32 mg/kg sc nicotine to that of varenicline alone.

Our data show that varenicline (**1**) is an orally active α4β2 nAChR partial agonist that displays ∼30−60% of the in vivo efficacy of nicotine. Moreover, varenicline (**1**) effectively blocks the nicotine response both in vivo and in vitro, demonstrating the appropriate antagonist profile. These attributes are desirable from the perspective of controlling nicotine dependence and reducing the potential for side effects mediated via overactivation of nicotinic receptors.[35]

The discovery and identification of a new class of α4β2 nicotinic receptor partial agonists for the treatment of smoking cessation has been described. Our key finding is that benzazapine **5** is a nicotinic ligand that can be structurally modified to afford highly selective and potent α4β2 agents, culminating in the identification of varenicline (**1**). The in vivo properties of varenicline demonstrate its ability to attenuate the central dopaminergic response to nicotine while providing sufficient and sustained dopaminergic tone to limit craving and withdrawal. Varenicline represents a novel treatment for tobacco dependence and has been advanced to human clinical trials for smoking cessation.

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Supporting Information Available: Experimental procedures for all new compounds and methods for in vitro and in vivo experiments are available at: http://pubs.acs.org.

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