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In pursuit of α4β2 nicotinic receptor partial agonists for smoking cessation: Carbon analogs of (−)-cytisine

Jotham W. Coe,* Michael G. Vetelino, Crystal G. Bashore, Michael C. Wirtz, Paige R. Brooks, Eric P. Arnold, Lorraine A. Lebel, Carol B. Fox, Steven B. Sands, Thomas I. Davis, David W. Schulz, Hans Rollema, F. David Tingley, III and Brian T. O'Neill

Pfizer Global Research and Development, Groton Laboratories, Eastern Point Road, Groton, CT 06340, USA

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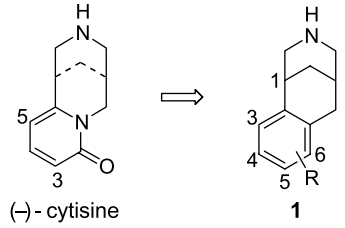
Abstract—The preparation and biological activity of analogs of (−)-cytisine, an α4β2 nicotinic receptor partial agonist, are discussed. All-carbon-containing phenyl ring replacements of the pyridone ring system, generated via Heck cyclization protocols, exhibited weaker affinity and lower efficacy partial agonist profiles relative to (−)-cytisine. In vivo, selected compounds exhibit lower efficacy partial agonist profiles than that of (−)-cytisine.

Since its introduction to Britain from Virginia in 1584,[1] tobacco has profoundly impacted humankind. Today tobacco smoking is the leading cause of preventable death worldwide.[2] Approximately five million people died in 2000 from tobacco-related illnesses, including chronic obstructive pulmonary disease, numerous cancers, and cardiovascular disease.[3] Approved therapies to treat tobacco dependence, including nicotine replacement therapy[4] and the antidepressant bupropion,[5] demonstrate that pharmacotherapy can improve initial quit rates above those seen with placebo. However, long-term relapse rates are as high as 80%, suggesting the need for therapies with improved long-term efficacy.[6] Improved treatments promise additional benefits to public health because smoking cessation before middle age reduces more than 90% of the health risk attributable to smoking.[7]

We recently described our pharmacological approach to the treatment of tobacco dependence, which has culminated in the discovery of varenicline, a clinical candidate for smoking cessation.[8] The key feature of our strategy has been to identify partial agonists of the α4β2 neuronal nicotinic acetylcholine receptor (nAChR). The α4β2 nAChR subtype has been implicated in regulating the mesolimbic dopaminergic pathway, which is thought to mediate many aspects of tobacco dependence; therefore, it is a key component to consider when pursuing novel pharmacotherapies for smoking cessation.[9] Herein, we elaborate on the synthesis and preliminary pharmacological evaluation of derivatives of (−)-cytisine based on all-carbon analogs **1** (Eq. 1). Results from these studies were pivotal to our decision to pursue structures that diverge from direct (−)-cytisine mimics and in the eventual discovery of varenicline. As detailed herein, these agents exhibited lower affinity and decreased agonist efficacy relative to (−)-cytisine.



(1)

From the beginning of our program we targeted the α4β2 nAChR, the most abundant high-affinity nicotinic subtype in the brain, one believed to be important for nicotine's reinforcing effects. The nAChRs are

Keywords: α4β2 Nicotinic receptor; nAChR; Partial agonist; Smoking cessation; Alkaloid.
* Corresponding author. Tel.: +1 860 441 3271; fax: +1 860 686 0013; e-mail: jwcoe@pfizer.com

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pentameric ligand-gated ion channels that mediate fast synaptic neurotransmission in the central nervous system and autonomic ganglia.[10] The acute psychoactive effects and dependence-producing properties of tobacco are in part due to nicotine's activation of α4β2 nAChRs in the ventral tegmental area of the mesolimbic dopamine system, which results in downstream dopamine release in the nucleus accumbens and prefrontal cortex.[11] The α4β2 receptor is considered to be particularly relevant because data from experiments performed with both knock-out and knock-in mice suggest a central role for these two nAChR subunits.[12,13] Other subtypes, including multimeric combinations containing α4 and β2 subunits, have been recently identified and are additional subtypes for future study.[14] Nicotine, a powerful agonist at the α4β2 nAChR, is more potent than the endogenous ligand ACh (EC_{50} is 3.5 vs 100 μM) but is less efficacious (~67% maximal efficacy vs ACh).[15] Activation of nAChRs by nicotine induces a complex array of downstream events, including receptor desensitization and upregulation, that contribute to the behavioral dependence experienced by smokers.[16]

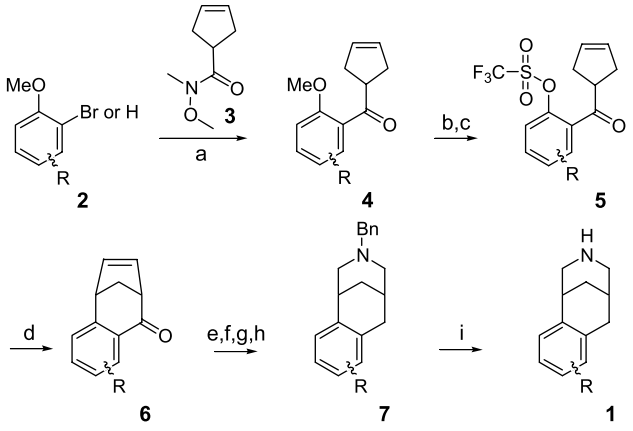
Theoretically, an α4β2 nicotinic receptor partial agonist will elicit a dopamine response itself, in the absence of nicotine.[17] Low dopaminergic tone from acute smoking cessation has been associated with craving for and withdrawal from nicotine, the key components of the tobacco dependence syndrome that precipitates relapse to smoking behavior.[18] To address this syndrome, we sought partial agonists relative to nicotine. However, the key benefit of a partial agonist may be that it limits any further mesolimbic system activation or psychogenic reward from nicotine obtained through smoking. Thus, a partial agonist should address withdrawal, craving and nicotine-induced reward simultaneously. For these reasons, we believed that an α4β2 nicotinic receptor partial agonist would be uniquely suited for treating this relapsing condition.[19]

In 1994, (−)-cytisine, a natural product from numerous plant species,[20] was shown to be a partial agonist of the α4β2 nAChR.[21] A human smoking cessation study with (−)-cytisine performed in the 1960s, before a modern understanding of its pharmacology, failed to exhibit robust efficacy.[22] We presume that poor bioavailability[23] and poor brain penetration[24] limited its effectiveness. Efforts to combine nicotine replacement therapy with the nicotinic antagonist mecamylamine have been shown to be more successful than either treatment alone.[25] These positive results are consistent with the theory that a partial agonist would provide better relief than would current treatments for smokers attempting to quit. With these insights, we initiated a synthetic effort to generate effective partial agonists using (−)-cytisine as a starting point.

Our initial studies of (−)-cytisine derivatives[26] revealed that substitutions at the piperidine nitrogen and the C-5 position reduced α4β2 receptor binding affinity, a result subsequently duplicated by others.[27] Potent affinity was retained or improved with C-3 substitution (Eq. 1). These results prompted our exploration of pyridone ring replacements (e.g., **1**). Although a number of synthetic approaches to cytisine have recently appeared, all rely on closures of the central ring in the penultimate steps,[28] making the generation of non-pyridone-containing analogs particularly challenging. Herein, we report the synthesis and biological evaluation of a number of substituted aromatic ring analogs.[29] We have readily prepared these[30] following the synthetic strategy revealed in our recent total synthesis of cytisine[31] as shown in Scheme 1.

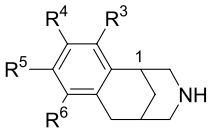
Substituted lithiated anisole derivatives served as starting points, accessed from precursors **2** via halogen–metal exchange or directed metalation (Scheme 1).[32] Treatment with Weinreb amide **3** of cyclopentene-4-carboxylic acid provided ketones **4**, which were routinely demethylated and converted to the corresponding triflate intermediates **5**.[33] Cyclization of derivatives **5** under standard Heck conditions[34] was slow and low yielding (4 days, 15–25% yield); these results were attributed to the instability of aryl palladium triflate intermediates.[35] After considerable experimentation, we found that the addition of catalytic KOAc (20 mol %) improved the reaction rates (1–4 h) and elevated the yields of bicyclic adducts **6** to 57–85%. We suspect that KOAc intercepts unstable ArPdOTf species, converting them to ArPdOAc intermediates that more effectively participate in the Heck addition to the cyclopentene olefin.[35] Excess KOAc and other bases induce enolization followed by a non-palladium-mediated process that competes with the Heck reaction and gives spiro benzofuran-3-ones.[33] The conversion of **6** to target analogs **1** (Table 1) involved Wolff–Kishner reduction, oxidative cleavage, reductive amination, and debenzylation using previously described methods.[36]

These analogs also served as intermediates to other derivatives (Scheme 2). For example, bromination of anisole **7g** selectively gave **8**, which was converted to phenol **7d** via halogen–metal exchange,[32] treatment with



Scheme 1. Reagents and conditions: (a) [1] *n*-BuLi, THF −78 to 20 °C [2] HCl (>90%); (b) BCl_3, CH_2Cl_2; (c) $(CF_3SO_2)_2O$, pyr, CH_2Cl_2 (55–85%); (d) 4 mol % $Pd(OAc)_2$, 10 mol % $Ph_3P(CH_2)_3PPh_3$, 20 mol % KOAc, 1.5 equiv Et_3N, DMF, 1–3 h, 110 °C (57–85%); (e) NH_2NH_2, KOH, $(HOCH_2)_2$, Δ (93%); (f) OsO_4, $(CH_2)_5NCH_3O{\cdot}H_2O$ acetone, H_2O; (g) $NaIO_4$, $ClCH_2CH_2Cl/H_2O$; (h) $BnNH_2$, $ClCH_2CH_2Cl$, $NaBH(OAc)_3$ (30–78%); (i) NH_4HCO_2, $Pd(OH)_2$, MeOH, Δ (30–90%).

Table 1. α4β2 nAChR K_i values for analogs of (±)-**1**



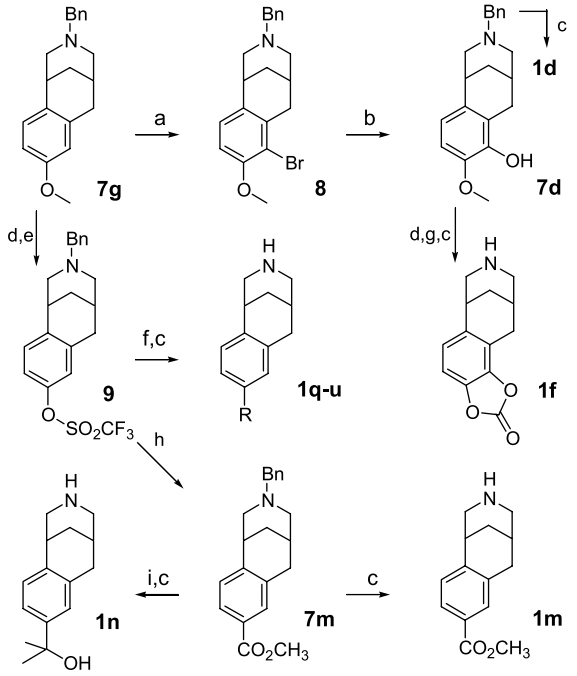
Compound	R^6	R^5	R^4	R^3	α4β2 (K_i [nM])[a]
1a	H	H	H	H	34/65*
1b	OMe	H	H	H	>500
1c	OH	H	H	H	2.9
1d	OH	OMe	H	H	13
1e	F	H	H	H	6.5
1f	OCO–	–O	H	H	>500
1g	H	OMe	H	H	1.4/3.2*
1h	H	OH	H	H	90
1i	H	$OCHF_2$	H	H	7.0
1j	H	OEt	H	H	13
1k	H	O*i*-Pr	H	H	72
1l	H	F	H	H	2.0
1m	H	CO_2Me	H	H	34
1n	H	CMe_2OH	H	H	264
1o	H	OCH_2CONH_2	H	H	>500
1p	H	NO_2	H	H	4.9
1q	H	Ph	H	H	>500
1r	H	4-PhOMe	H	H	370
1s	H	4-PhCF_3	H	H	200
1t	H	3-PhNH_2	H	H	>500
1u	H	3-py	H	H	>500
1v	H	H	OMe	H	90*
1w	H	H	OH	H	75*
1x	H	OCH_2^-	O	H	5.7
1y	H	H	NO_2	H	6.5
1z	H	H	H	NO_2	14
1za	F	F	H	H	0.44
(−)-Cytisine	—	—	—	—	0.23/0.17*
(−)-Nicotine[b]	—	—	—	—	1.6/0.95*

(—) = not applicable. Results suggests that the R^6 position is important for overall binding affinity and that small polar groups are preferred.

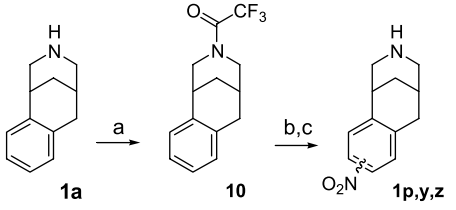
* [^{3}H] Nicotine; rat cortex (N = 2–4).

[a] [^{3}H] Nicotine; *h*α4β2 nAChR in HEK293 cells.

[b] For additional values for (−)-nicotine, see *J. Med. Chem.* **1997**, *40*, 4169.



Scheme 2. Reagents and conditions: (a) Br_2, AcOH, CH_2Cl_2, 0–20 °C (28%); (b) [1] *n*-BuLi, THF −78 °C $B(O\text{-}i\text{-}Pr)_3$, −78 to 20 °C (67%); [2] H_2O_2, H_2O/THF (64%); (c) NH_4HCO_2, $Pd(OH)_2$, MeOH, Δ (30–90%); (d) 48% HBr Δ (90%); (e) $(CF_3SO_2)_2O$, pyr, CH_2Cl_2 (94%); (f) 1.5 equiv $ArB(OH)_2$, 5 mol %, $Pd(PPh_3)_4$, 8 equiv KOAc, EtOH/H_2O 18 h, 90 °C (23%); (g) carbonyl diimidazole, Et_3N, CH_2Cl_2 (94%); (h) 10 mol % KOAc, 2 equiv TEA, 10 mol % $Pd(OAc)_2$, 10 mol % $Ph_3P(CH_2)_3PPh_3$, CO, MeOH/DMSO (38%); (i) MeMgBr, THF (50%).



Scheme 3. Reagents and conditions: (a) TFAA, py, CH_2Cl_2, 0–20 °C (99%); (b) HNO_3, CF_3SO_2OH, CH_2Cl_2, −78 °C; (c) Na_2CO_3, H_2O (23%).

triisopropyl borate,[30] and peroxide-mediated oxidation. Benzyl group deprotection gave **1d** (see Table 1). Demethylation of **7d**, carbonate formation, and deprotection gave **1f**. Conversion of **7g** to its corresponding phenol (from which debenzylation gave **1h**) and triflate **9** ultimately gave access to aryl-substituted derivatives **1q**–**u** via Suzuki couplings and methyl ester **7m** via Heck carbonylation.[37] This intermediate (**7m**) was further converted to an isopropoxy derivative (**1n**) after treatment with excess methylmagnesium bromide.

Parent derivative **1a** was converted to trifluoroacetamide **10** (Scheme 3). Nitration gave a mixture of three mononitrated derivatives, which were purified by chromatography in 2%, 50%, and 2% yield and deprotected to give **1p**, **1y**, and **1z**, respectively.

The in vitro K_i values of compounds **1a**–**1za** were measured using inhibition of radioligand binding to the α4β2 nAChR.[38] An affinity range of 0.44 nM to >500 nM (inactive) was observed and appears in Table 1. The most potent of the R^6-substituted compounds was phenol analog **1c**, followed by fluoro-derivative **1e** and parent **1a**. Anisole **1b** was inactive, suggesting unfavorable contacts in this region of the receptor–ligand interaction. The introduction of a methoxyl group neighboring the R^6 phenol was tolerated, but it decreased activity to 13 nM (i.e., **1d**). Bridging the corresponding catechol as a carbonate (**1f**) eliminates activity altogether. These results suggest that the R^6 position is important for overall binding affinity and that small polar groups are preferred.

Substitution at R^5 was extensively studied in part because this position parallels the C-3 position of derivatives of (−)-cytisine itself (e.g., Br, Cl, Ac, Ar).[26,27] In

contrast to substituent effects at the R^6 position, R^5 phenol **1h** is considerably less potent than the corresponding anisole, fluoro, and nitro compounds (**1g**, **1i**, **1l**, **1p**). Increasing the size of the alkyl group diminishes activity, and substitution by methyl ester, carbinol, and aryl groups is poorly tolerated. Phenol and anisole derivatives in the R^4 position (**1v**,**w**) exhibit diminished activity relative to the parent compound (≧150 nM). The R^4 nitro and R^4/R^5 methylene-dioxy derivative retained reasonable potency (10–13 nM). Only the R^3 nitro derivative (**1z**) was explored, and it is less potent (28 nM) than the R^4 and R^5 nitro derivatives.

High-affinity compounds share a common structure–activity relationship/substitution pattern of possessing small electron-withdrawing groups (OH, OMe, F, and NO_2). These groups are either poor H-bond acceptors—each presents distinct H-bond orientations and directional vectors—or devoid of H-bond acceptor capability altogether. This set of examples, while limited, is inconsistent with existing pharmacophore models of the α4β2 nAChR that purport to include important H-bond contributions in receptor binding.[39] The most potent compound combines two adjacent fluorine atoms (**1za**, 0.44 nM) and has affinity comparable to (−)-cytisine itself. These results suggest the interesting possibility that π-system dipole alignment may be involved in favorable ligand–receptor interactions in this series of compounds. Other known nicotinic agents, including the 2-pyridone in (−)-cytisine derivatives, also may be consistent with dipole-mediated ligand–receptor interactions.

Several of the high-affinity compounds were further evaluated in vitro. All were >100-fold selective in binding models for the α4β2 nAChR over the α3β4, α7, and α1βγδ nAChR subtypes (Table 2).[38] The functional agonist, partial agonist, or antagonist properties of the compounds were characterized in a two-step process using established electrophysiological techniques in *Xenopus* oocytes expressing the *h*α4β2 nAChR.[40] First, the presence of agonist or partial agonist activity was detected by comparing the effect of compounds at 10 μM to the response elicited by 10 μM nicotine (EC_{50} = 15 μM). Second, antagonist effects were assessed in a similar paradigm that measured the compounds' (10 μM) ability to inhibit the current evoked by 10 μM nicotine. These values are expressed as the percentage of the response evoked by 10 μM nicotine. A model potent partial agonist would theoretically antagonize nicotine's effect to the level achieved by the compound alone (i.e., the agonist and antagonist activities [reversal of nicotine response] ideally sum to 100%), whereas an agonist could increase the response relative to nicotine, and a low-potency partial agonist would have no effect. Compounds **1g**, **1i**, and **1p** appear to be weak partial agonists compared to (−)-cytisine (all compounds have a response that alone is less than (−)-cytisine's response of 56% of nicotine's effect at 10 μM).

In vivo, a two-step assessment of agonist activity paralleled the in vitro measurements. First, the agonist activity of agents was determined by measuring effects on dopamine turnover in the nucleus accumbens relative to the maximum agonist effects of nicotine.[41] The levels of dopamine and its metabolites were determined in the nucleus accumbens of male Sprague Dawley rats (200–300 g) 1 h post-dose. The results demonstrate that nicotine has a maximal effect at 1 mg/kg s.c. (177% of controls, normalized to 100% in Fig. 1). Maximum well-tolerated doses of each agent were determined, and dopamine turnover was measured at that dose. The data appear in Fig. 1 (filled bars). Second, concurrent treatment of agents (s.c.) with 1 mg/kg s.c. nicotine, again at maximum well-tolerated doses, produced dopamine turnover levels as shown (open bars). (−)-Cytisine and **1g** produce similar effects in both measures. Compounds **1i** and **1za** appear to exhibit antagonist profiles consistent with the in vitro results (Table 2). Compared with compound **1g**, carbon analogs **1i** and **1za** are less efficacious agonists than (−)-cytisine and behave as weak antagonists in vivo.

Table 2. In vitro affinity for agents at nAChR subtypes and 10 μM functional activity at the α4β2 nAChR subtype

	Affinity (K_i [nM])				Functional activity at *h*α4β2 nAChR	
	α4β2[a]	α3β4[b]	α1βγδ[c]	α7[d]	% Response relative to nicotine[e]	% Inhibition of nicotine[f]
cyt	0.23	840	250	4200	56	30
1e	6.5	—	—	830	0	61
1g	1.4	810	—	2400	30	51
1i	7.0	—	—	1700	27	83
1l	2.0	710	—	350	4	68
1p	4.9	340	—	—	20	40
1x	5.7	1900	4500	5100	0	68
1y	6.5	980	—	—	2	50
1za	0.44	810	3000	520	3	85
nic	1.6	530	6300	6300	100	—

(—) = Not determined.

[a] [^{3}H] Nicotine; *h*α4β2 nAChR in HEK293 cells.

[b] [^{3}H] epibatidine; IMR32 cells.

[c] [^{125}I]-α-Bungarotoxin; cells electroplax.

[d] [^{125}I]-α-Bungarotoxin; IMR32.

[e] Percent response of 10 μM test compound relative to 10 μM (−)-nicotine (SEM ⩽ 10%).

[f] Percent response of 10 μM test compound against 10 μM nicotine (SEM ⩽ 10%).

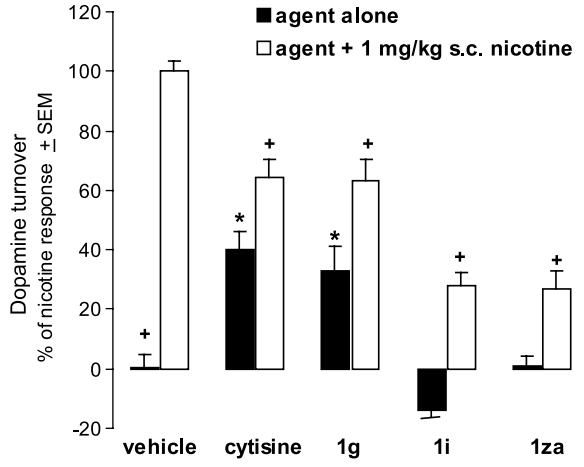


Figure 1. Effects of nicotine, (−)-cytisine, **1g**, **1i**, and **1za** on dopamine turnover in rat nucleus accumbens 1 h post-dose. All values are normalized to the effect of 1.0 mg/kg s.c. nicotine (=100%). Compounds were administered alone (at maximum tolerated doses [filled bars] of (−)-(−)-cytisine, 5.6 mg/kg; **1g**, 8 mg/kg; **1i**, 10 mg/kg; and **1za**, 5 mg/kg) and concurrently with 1 mg/kg s.c. nicotine (open bars). Mean nicotine increase alone = 177% control; $N = 5$–10 (all agents alone: $^{*}p < .05$ compared to vehicle; all agents with nicotine: $^{+}p < .05$ compared to nicotine, One-Way ANOVA, post hoc, Dunnett's). Doses were selected through experimental determination of behavioral limited ceilings for each agent alone and in combination.

Partial agonists of the α4β2 nAChR hold promise as novel therapeutic aids for smoking cessation. This work explores carbon analogs of (−)-cytisine for their potential as partial agonists of the α4β2 nAChR. Although some of the derivatives exhibit hints of desirable in vitro activity, insufficient in vivo efficacy limits their potential as therapeutic agents. These results encouraged us to explore modifications to this chemical series that have yielded compounds with promising in vitro and in vivo profiles, culminating in the identification of varenicline, a partial agonist that has been advanced to clinical trials.[42]

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42. See Refs. 8, 30, and 36 for all experimental details.