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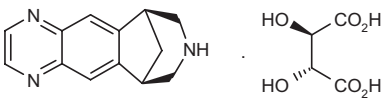
Varenicline Tartrate

Prop INNM; USAN

Aid to Smoking Cessation
Nicotinic $\alpha_4\beta_2$ Partial Agonist

CP-526555-18
Champix®

7,8,9,10-Tetrahydro-6*H*-6,10-methanopyrazino[2,3-*h*][3]benzazepine L-tartrate
7,8,9,10-Tetrahydro-6*H*-6,10-methanoazepino[4,5-*g*]quinoxaline L-tartrate



$C_{17}H_{19}N_3O_6$
Mol wt: 361.3494
CAS: 375815-87-5
CAS: 249296-44-4 (as free base)
EN: 330290

Abstract

Nicotine addiction is one of the most prevalent addictive behaviors worldwide and more than half of the estimated 1.25 billion smokers will die from tobacco-related illness. Tobacco smoking induces and sustains a series of neurochemical events that are mediated via nicotine's agonist activity at neuronal nicotinic acetylcholine receptors (nAChRs). Current options for smoking cessation include nicotine replacement therapy, which can be effective but does not prevent nAChR activation, nicotine vaccines, which can block nicotine activation but may not improve craving and withdrawal, behavioral treatment and acupuncture, which are not always effective, and pharmacotherapy comprised of substances selectively targeting the action of nicotine. Researchers continue to investigate possible targets for the development of more effective agents to aid in smoking cessation. One promising agent to emerge is the partial $\alpha_4\beta_2$ nAChR agonist varenicline tartrate. This 3,5-bicyclic arylpiperidine selectively binds to the $\alpha_4\beta_2$ nAChR and exhibits both potent preclinical partial agonist efficacy and safe and effective clinical activity. Varenicline has been submitted for regulatory approval in the U.S. and Europe for smoking cessation.

Synthesis

Reaction of 2-fluorobromobenzene (I) with cyclopentadiene (II) by means of ethylmagnesium bromide in THF gives 1,4-dihydro-1,4-methanonaphthalene (III), which is oxidized with OsO_4 and NMMO in acetone to yield 1,2,3,4-tetrahydro-1,4-methanonaphthalene-2,3-diol (IV). Further oxidation of bicyclic diol (IV) with $NaIO_4$ in CH_2Cl_2 affords the dialdehyde derivative (V), which after reductive amination with benzylamine (VI) by means of $NaBH(OAc)_3$ in CH_2Cl_2 provides 10-benzyl-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (VII).

Debenzylation of compound (VII) with H_2 over Pd/C in MeOH gives the bicyclic benzazepine (VIII) (1, 2), which is treated with trifluoroacetic anhydride and pyridine in CH_2Cl_2 to yield the trifluoroacetamide (IX). Nitration of (IX) by means of HNO_3/CF_3SO_3H in CH_2Cl_2 affords the 4,5-dinitro derivative (X), which is reduced with H_2 over $Pd(OH)_2$ in MeOH to provide the corresponding diamino derivative (XI). Condensation of compound (XI) with glyoxal (XII) in refluxing THF/water gives the tetracyclic quinoxaline derivative (XIII), which is finally deprotected with Na_2CO_3 in aqueous MeOH (1-3) and treated with L-tartaric acid (4). Scheme 1.

Bicyclic benzazepine (VIII) can also be prepared by condensation of 2-(2-bromophenyl)acetonitrile (XIV) with methyl 3-methoxyacrylate (XV) by means of *t*-BuONa in THF at 0 °C to give 4-(2-bromophenyl)-4-cyanobutenoic acid methyl ester (XVI), which is cyclized by means of tris(cyclohexyl)phosphine, $Pd(OAc)_2$ and *t*-BuONa in ethyleneglycol dimethyl ether to afford the 3-cyanoindene derivative (XVII). Hydrogenation of compound (XVII) with H_2 over Pd/C in MeOH provides the aminomethyl derivative (XVIII), which is cyclized by means of *t*-BuONa in MeOH to give 10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-9-one (XIX). Finally, the ketone group of (XIX) is reduced with $NaBH_4$ and BF_3/Et_2O in THF (5). Scheme 2.

Alternatively, one-pot reaction of 2-(2-bromophenyl)acetonitrile (XIV) with ethyl 3-methoxyacrylate (XX) by means of tris(cyclohexyl)phosphine, $Pd(OAc)_2$ and *t*-BuONa in THF followed by treatment with ethylene glycol and H_2SO_4 provides 1-(1,3-dioxolan-2-ylidene)-1*H*-indene-3-carbonitrile (XXI), which is reduced with H_2 over

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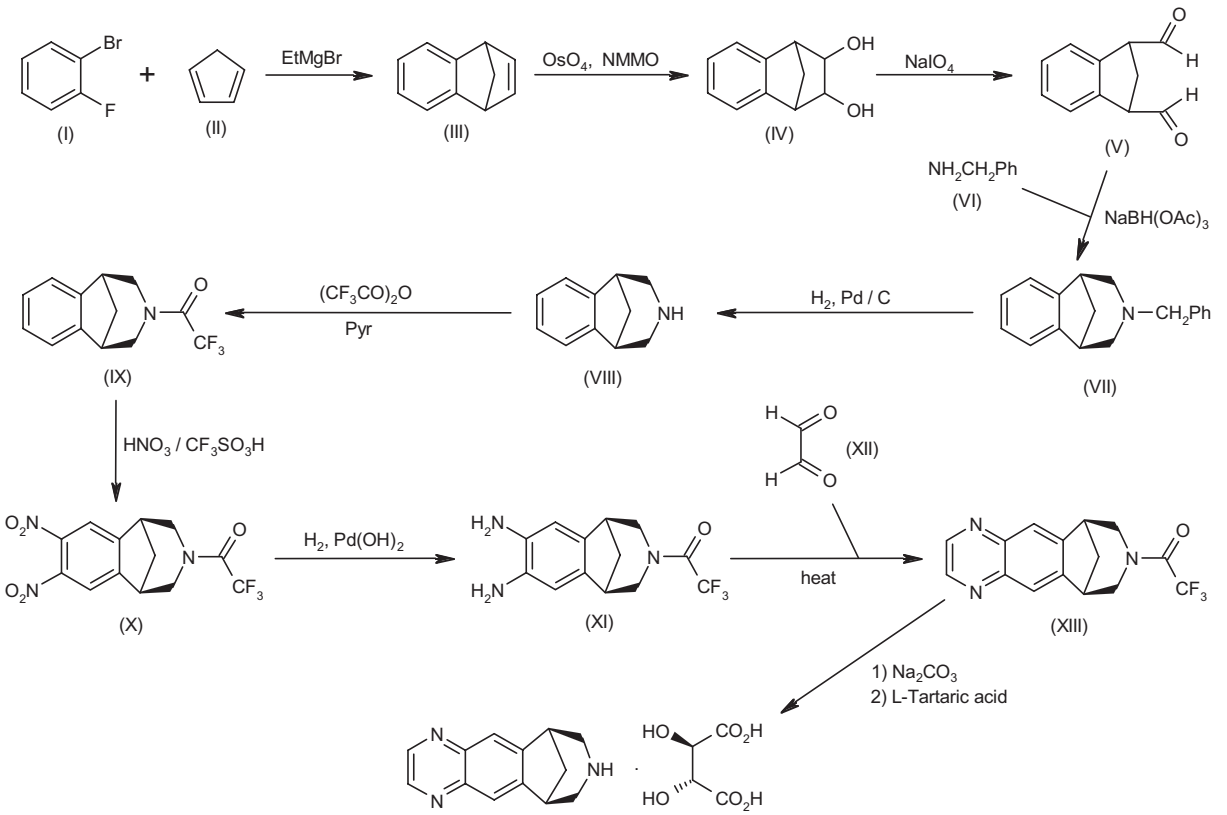
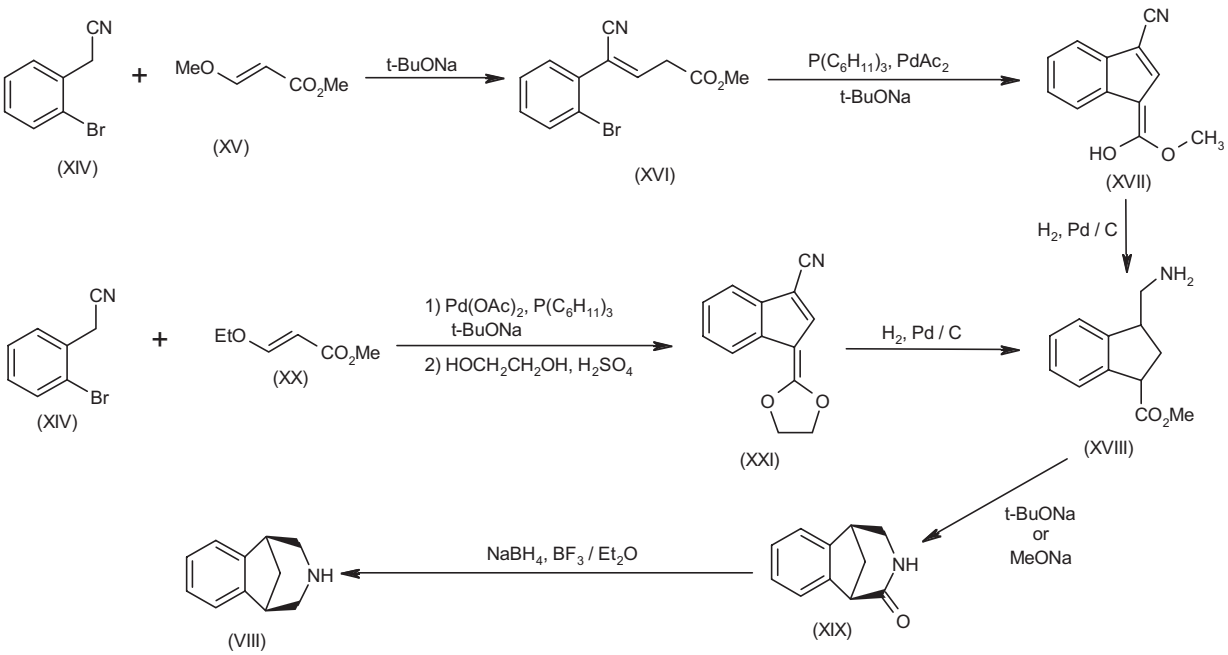
Scheme 1: Synthesis of Varenicline Tartrate



Scheme 2: Synthesis of Intermediate VIII



Pd/C in methanol to yield the aminomethyl derivative (XVIII). Finally, compound (XVIII) is cyclized by means of MeONa/MeOH to afford the cyclic lactam (XIX) (5, 6). Scheme 2.

Background

According to the Global Tobacco Research Network, almost 1 billion men and 250 million women worldwide smoke daily. This represents 35% of men and 22% of women in developed countries and 50% of men and 9% of women in developing countries. Nicotine addiction is one of the most prevalent addictive behaviors worldwide and more than half of the estimated 1.25 billion smokers will die from tobacco-related illnesses, including cancer, cardiovascular disease and lung disease, among others. A 50-year observational study has demonstrated that cigarette smokers die an average of 10 years sooner than nonsmokers. Despite increased awareness, tobacco continues to be the leading cause of preventable death in the U.S. and other countries, and global smoking rates continue to rise (7-11).

Tobacco smoke is composed of over 4,000 chemicals, and most illnesses derived from tobacco use are caused by substances other than nicotine, such as tar, carbon monoxide and other gases. However, nicotine is the predominant psychoactive and addictive component present in tobacco. According to the Massachusetts Department of Health, most marketed cigarettes deliver 1.2-2.9 mg of nicotine, so that an individual who smokes 1 pack/day absorbs 20-40 mg/day of nicotine, resulting in plasma nicotine concentrations of 23-35 ng/ml by the afternoon. These levels are sufficient to induce a cascade of physiological and behavioral events that ultimately result in powerful dependence. Unfortunately, although smoking cessation significantly improves the risk of smoking-related disease and death, the majority of smokers are unable to overcome this dependence (7, 12, 13).

Tobacco smoking induces and maintains a series of neurochemical events that are mediated by nicotine's agonist activity at neuronal nicotinic acetylcholine receptors (nAChRs). Nicotine modulates nAChR desensitization and upregulation, regional glucose metabolism, electroencephalographic parameters and the release of catecholamines, and induces tolerance and physiological dependence. The dependence effects of nicotine are suspected to occur via its action on the $\alpha_4\beta_2$ nAChR subtype. Studies have shown that transgenic mice bearing certain α_4 subtype mutants are hypersensitive to nicotine, and restoration of ventral tegmental β_2 expression in the mesolimbic dopamine system of nicotine-insensitive β_2-deletion mutants results in wild-type responses to nicotine. Nicotine causes the release of dopamine from the mesolimbic dopamine system, and as nicotine levels decrease, dopamine levels decline, stimulating the urge to smoke. Moreover, a reduced dopaminergic tone due to abstinence from smoking stimulates craving and the withdrawal syndrome (7, 14-21).

Tobacco addiction or dependence is comprised of two recognized clinical disorders which comprise the FDA-approved medical indication for treatment: nicotine dependence due to maladaptive and chronic tobacco use, and nicotine withdrawal characterized by the presence of withdrawal symptoms (*e.g.*, increased anger, hostility and/or aggression, loss of social cooperation, impairment in psychomotor and cognitive function) during abstinence from tobacco. Investigators are searching for agents to aid in smoking cessation to relieve nicotine withdrawal symptoms. Treatment options to date include substitution of other forms of nicotine delivery, behavioral treatment and acupuncture, and pharmacotherapy involving the administration of substances that selectively target neuropharmacological and endocrine effects related to nicotine action (7, 22).

There have been several promising advances in the area of smoking cessation. However, long-term cessation rates continue to be low. Nicotine replacement therapy provides controlled release of nicotine, suppressing craving and withdrawal symptoms. However, it does not prevent nAChR activation. In contrast, nicotine vaccines, which sequester nicotine to block nicotine activation, may not improve craving and withdrawal. Bupropion (Zyban®), a dopamine transporter (DAT) inhibitor launched in 1997 by GlaxoSmithKline for smoking cessation, reduces the urge to smoke, although it does not prevent the response to smoking (23-26). Researchers are currently investigating other possible targets for the development of more effective agents to aid in smoking cessation. Those agents currently under development for smoking cessation are shown in Table I.

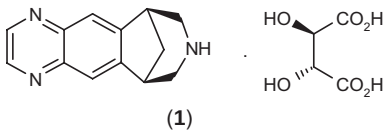
Researchers have speculated that an effective agent for aiding in smoking cessation would target the craving and withdrawal symptoms while also attenuating the nicotine-induced effects of smoking. A partial agonist could inhibit nicotine-induced dopaminergic activation via competitive $\alpha_4\beta_2$ nAChR suppression, and also slightly elevate dopaminergic tone to relieve craving and withdrawal symptoms. One promising partial $\alpha_4\beta_2$ nAChR agonist to emerge is the 3,5-bicyclic arylpiperidine varenicline tartrate (Champix®). The agent selectively binds to the $\alpha_4\beta_2$ nAChR and has demonstrated a potent partial agonist effect, and was chosen for further development as an aid for smoking cessation (2, 3).

Preclinical Pharmacology

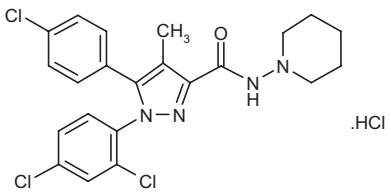
Two studies reported the *in vitro* affinity and functional agonist/antagonist activity of varenicline, with results indicating an excellent partial agonist profile for the agent. In experiments using [^{3}H]-nicotine, varenicline displayed high affinity for the human $\alpha_4\beta_2$ nAChR expressed in HEK-293 cells and from rat cortex (K_i = 0.11 and 0.06 nM, respectively). K_i values obtained for the $\alpha_3\beta_4$ subtype expressed in IMR32 cells ([^{3}H]-epibatidine), the α_7 subtype expressed in IMR32 and GH4C1 cells ([^{125}I]-α-bungarotoxin) and the $\alpha_1\beta\gamma\delta$ subtype in an electroplax system ([^{125}I]-α-bungarotoxin) were 240, 322-617 and 3540 nM,

Table I: Agents under active clinical development for smoking cessation (from Prous Science Integrity®).

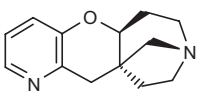
Drug	Mechanism of action	Source	Phase
1. Varenicline tartrate (Champix®)	Nicotinic $\alpha_4\beta_2$ partial agonist	Pfizer	Prereg.
2. Rimonabant hydrochloride (Acomplia®)	Cannabinoid CB_1 antagonist	Sanofi-Aventis	Prereg.
3. 468816*	Glycine receptor antagonist	GlaxoSmithKline	II
4. CYT002-NicQb*		Cytos Biotechnology	II
5. Dianicline	Nicotinic $\alpha_4\beta_2$ partial agonist	Sanofi-Aventis	II
6. Nicotine conjugate vaccine (NicVAX™)*		Nabi Biopharmaceuticals	II
7. ADX-10061 (formely CEE-03-310)*	Dopamine D1 antagonist	Addex Pharmaceuticlas; CeNeS	I
8. Nicotine conjugate vaccine (TA-NIC)*		Xenova (Celtic Pharma)	I



(**1**)



(**2**)



(**5**)

* Structure not available.

respectively. The functional activity of the agent was examined *in vitro* using nicotine (10 μM)-induced currents in *Xenopus* oocytes expressing human $\alpha_4\beta_2$ nAChRs. Varenicline (10 μM) inhibited nicotine-induced current by 32-34% and the percent response of varenicline relative to nicotine was 68%. Examination of the full concentration-response curve for the agent indicated an EC_{50} value of 2.3 μM, with a maximal efficacy of 24% relative to nicotine (2, 3).

The effects of varenicline were also examined *in vivo*. When administered alone to rats, varenicline (5.6 mg/kg s.c.) increased dopamine turnover in the nucleus accumbens to levels that were 32% of the maximal nicotine (1 mg/kg s.c.) response at 1 h postdosing. When given in combination with nicotine, varenicline completely blocked nicotine's effects on dopamine turnover. Microdialysis studies measuring extracellular dopamine levels over a 6-h period in conscious rats confirmed the partial agonist activity of varenicline. The agent administered at the maximally effective dose (1 mg/kg p.o.) caused a sustained increase in dopamine release that was about 60% of the maximal nicotine effect (188% at 0.32 mg/kg s.c.) and also reduced the dopamine-enhancing effects of a subsequent nicotine dose (0.32 mg/kg s.c.) (2, 3).

Pharmacokinetics and Metabolism

The pharmacokinetics, metabolism and disposition of varenicline were examined in rats, mice, cynomolgus monkeys and healthy human volunteers following oral administration of the [^{14}C]-labeled compound (3 mg/kg, 25 μCi/250 g in rats; 3 mg/kg, 20 μCi/20 g in mice; 0.08 mg/kg, 200 μCi/4 kg in monkeys; and 1 mg/100 μCi in humans). The half-lives for the parent drug and total radioactivity were longer in monkeys ($t_{1/2}$ = 24 ± 6 and 30 ± 3 h, respectively) and humans ($t_{1/2}$ = 17 ± 3 and 17 ± 2 h, respectively) than in rats ($t_{1/2}$ = 4.0 ± 0.9 and 5.1 ± 0.6 h, respectively) and mice ($t_{1/2}$ = 1.4 and 1.8 h, respectively). First-order decreases in circulating concentrations were observed for both the parent compound and radioactivity. Because half-lives were comparable for total radioactivity and parent drug, it is possible that the metabolites of varenicline have slightly longer half-lives. Comparison of AUC values for total radioactivity and varenicline revealed that the parent compound comprises 70%, 55%, 63% and 79% of the total drug-related material in mice, rats, monkeys and humans, respectively; similar relationships were obtained for C_{max} values. Unchanged varenicline was the main product found in the circulation. The majority of drug-related material was secreted in urine and consisted predominantly of the unchanged parent compound (90%, 84%, 75% and 81%, respectively). Metabolites detected in excreta and the circulation were derived from *N*-carbamoyl glucuronidation and oxidation; additional metabolites were also detected in the circulation and were the products of *N*-formylation and the formation of a novel hexose conjugate. Further *in vitro* experiments using human liver microsomes subjected to a CO_2 atmosphere showed that UGT2B7 catalyzed *N*-carbamoyl glucuronidation of varenicline (27).

Clinical Studies

The safety and efficacy of varenicline were examined in two randomized, double-blind, placebo-controlled phase II studies conducted in healthy cigarette smokers (18-65 years). Varenicline was safe and well tolerated in both trials. In the first study, 638 subjects were random-

ized to varenicline 0.3 or 1 mg once daily or 1 mg b.i.d. for 6 weeks plus placebo for 1 week or to 7 weeks of 150-mg sustained-release bupropion b.i.d. (titrated over week 1) or placebo. Treatment with varenicline dose-dependently increased carbon monoxide-confirmed continuous quit rates (CQRs; 28.6%, 37.3% and 48% for the respective varenicline regimens *vs.* 33.3% and 17.1% for the bupropion and placebo groups, respectively); significant increases as compared to placebo were observed with all varenicline regimens except the lowest dose, and with bupropion. In the second trial, 647 subjects were randomized to receive varenicline (0.5 or 1 mg b.i.d. with or without titration) or placebo for 12 weeks. Titration in this study was found to attenuate the mild to moderate self-limiting nausea reported. CQRs at 9-12 weeks of treatment were significantly greater for both doses of varenicline as compared to placebo (45.1% and 50.6%, respectively, *vs.* 12.4%). It was concluded that 1-2 mg/day varenicline promoted smoking cessation and that a dose of 1 mg b.i.d. resulted in higher quit rates as compared to bupropion or placebo (28, 29).

In two double-blind, placebo-controlled studies involving about 2,000 smokers, subjects received either varenicline (1 mg b.i.d.), sustained-release bupropion (150 mg b.i.d.) or placebo for 12 weeks. Subjects were followed for an additional 40 weeks without treatment. In both studies, 44% of varenicline-treated subjects quit by the end of the 12-week treatment period, which was significantly greater than the rate of 30% observed with bupropion. Among patients who received placebo, 18% had quit by the end of the 12-week treatment period. The odds of quitting smoking for subjects taking varenicline were approximately twice as high as those for bupropion and 4 times higher than those for placebo. After 1 year, patients who received varenicline were significantly more likely to remain smoke-free as compared to patients who received bupropion or placebo. A third study randomized smokers who successfully quit smoking after 12 weeks of varenicline to 12 weeks of either placebo or an additional 12 weeks of varenicline. These patients were followed for 28 weeks after the treatment period. A total of 71% of patients who received the additional course of varenicline remained abstinent after 6 months compared to 50% of those who received placebo as the second course (30).

A randomized, double-blind, placebo-controlled, parallel phase III trial is currently recruiting cigarette smokers (n=250; 18-75 years) in Taiwan and South Korea. Subjects will receive varenicline titrated up to 1 mg b.i.d. over 1 week for a total of 3 months. The study includes a follow-up period of 3 months posttreatment (31).

The FDA granted a 6-month priority review to the NDA submitted for varenicline in November 2005. Pfizer also submitted regulatory applications in Europe in November 2005 seeking approval of varenicline for smoking cessation (32).

Source

Pfizer, Inc. (US).

References

1. Brooks, P.R.P., Coe, J.W. (Pfizer Products Inc.). *Aryl fused azapolycyclic compounds*. EP 1259489, JP 2003524002, US 6605610, WO 2001062736.

2. Coe, J.W., Brooks, P.R., Wirtz, M.C. et al. *3,5-Bicyclic aryl piperidines: A novel class of $\alpha_4\beta_2$ neuronal nicotinic receptor partial agonists for smoking cessation*. Bioorg Med Chem Lett 2005, 15: 4889-97.

3. Coe, J.W., Brooks, P.R., Vetelino, M.G. et al. *Varenicline: An $\alpha_4\beta_2$ nicotinic receptor partial agonist for smoking cessation*. J Med Chem 2005, 48: 3474-7.

4. Bogle, D.E., Rose, P.R., Williams, G.R. (Pfizer Products Inc.). *Tartrate salts of 5,8,14-triazatetracyclo[10.3.1.0(2,11).0(4,9)]-hexadeca-2(11),3,5,7,9-pentaene and pharmaceutical compositions thereof*. EP 1392307, JP 2004533446, US 2003166701, US 6890927, WO 2002092089.

5. Singer, R.A., McKinley, J.D. (Pfizer Products Inc.). *Process for the preparation of 1,3-substituted indenes and aryl-fused azapolycyclic compounds*. EP 1383733, JP 2004527545, US 2003060624, WO 2002085843.

6. Handfield, R.E. Jr., Watson, T.J.N. (Pfizer Products Inc.). *Process for the preparation of aryl fused polycyclic lactams*. CA 513293, EP 1587794, WO 2004063164.

7. Prous Science R&D Drug Backgrounders: *Nicotine addiction (online publication)*. Updated February 13, 2006.

8. World Health Organization. Geneva, 1997.

9. Doll, R., Peto, R., Boreham, J.K., Sutherland, I. *Mortality in relation to smoking. 50 Years' observations on male British doctors*. BMJ 2004, 328: 1519-33.

10. Center for Disease Control and Prevention. *Cigarette smoking among adults - United States, 2002*. Morb Mort Wkly Rep 2004, 53: 427-31.

11. Centers for Disease Control and Prevention. *Annual smoking-attributable mortality, years of potential life lost, and economic costs - United States, 1995-1999*. Morb Mort Wkly Rep 2002, 51: 300-3.

12. Benowitz, N.L., Porchet, H., Sheiner, L., Jacob, P. III. *Nicotine absorption and cardiovascular effects with smokeless tobacco use: Comparison with cigarettes and nicotine gum*. Clin Pharmacol Ther 1988, 44: 23-8.

13. Benowitz, N.L., Henningfield, J.E. *Establishing a nicotine threshold for addiction. The implications for tobacco regulation*. New Engl J Med 1994, 331: 123-5.

14. Hogg, R.C., Bertrand, D. *Nicotinic acetylcholine receptors as drug targets*. Curr Drugs Targets CNS Neurol Disord 2004, 3: 123-30.

15. Cohen, C., Bergis, O.E., Galli, F. et al. *SSR591813, a novel selective and partial $\alpha_4\beta_2$ nicotinic receptor agonist with potential as an aid to smoking cessation*. J Pharmacol Exp Ther 2003, 306: 407-20.

16. Tapper, A.R., McKinney, S.L., Nashmi, R. et al. *Nicotine activation of α_4 receptors: Sufficient for reward, tolerance, and sensitization*. Science 2004, 306: 1029-32.

17. Maskos, U., Molles, B.E., Pons, S. et al. *Nicotine reinforcement and cognition restored by targeted expression of nicotine receptors*. Nature 2005, 436: 103-7.

18. Mansbach, R.S., Chambers, L.K., Rovetti, C.C. *Effects of the competitive nicotine antagonist erysodine on behavior occasioned or maintained by nicotine: Comparison with mecamylamine*. Psychopharmacology (Berlin) 2000, 148: 234-42.

19. Dani, J.A., De Biasi, M. *Cellular mechanisms of nicotine addiction*. Pharmacol Biochem Behav 2001, 70: 439-46.

20. Malin, D.H. *Nicotine dependence: Studies with a laboratory model*. Pharmacol Biochem Behav 2001, 70: 551-9.

21. US Department of Health and Human Services. *The health consequences of smoking: Nicotine addiction, a report of the Surgeon General*. US Government Printing Office: Washington, DC, 1988.

22. Henningfield, J.E., Fant, R.V., Buchhlalter, R., Stitzer, M.L. *Pharmacotherapy for nicotine dependence*. CA - Cancer J Clin 2005, 55: 281-99.

23. Fiore, M.C., Bailey, W.C., Cohen, S.J. et al. *Treating tobacco use and dependence: Clinical practice guideline*. Department of Health and Human Services, Washington, DC, 2000.

24. Hays, J.T., Ebbert, J.O. *Bupropion sustained release for treatment of tobacco dependence*. Mayo Clin Proc 2003, 78: 1020-4.

25. Rose, J.E. *Nicotine addiction and treatment*. Annu Rev Med 1996, 47: 493-507.

26. Lindblom, N., de Villiers, S.H., Kalayanov, G., Gordon, S., Johansson, A.M., Svensson, T.H. *Active immunization against nicotine prevents reinstatement of nicotine-seeking behavior in rats*. Respiration 2002, 69: 254-60.

27. Obach, R.S., Reed-Hagen, A.E., Krueger, S.S., Obach, B.J., O'Connell, T.N., Zandi, K.S., Miller, S., Coe, J.W. *Metabolism and disposition of varenicline, a selective $\alpha_4\beta_2$ acetylcholine receptor partial agonist, in vivo and in vitro*. Drug Metab Disp 2006, 34: 121-30.

28. Oncken, C., Watsky, E., Reeves, K., Anziano, R., The Varenicline Study Group. *Efficacy and safety of the novel selective nicotinic receptor partial agonist varenicline for smoking cessation*. 54th Annu Sci Sess Am Coll Cardiol (ACC) (March 6-9, Orlando) 2005, Abst 1043-121.

29. Oncken, C.A., Reeves, K., Watsky, E., Anziano, R. *Efficacy and safety of varenicline for smoking cessation*. Nat Conf Tobacco Health (May 4-6, Chicago) 2005, Abst.

30. *Varenicline, an effective and safe treatment for smoking cessation*. DailyDrugNews.com (Daily Essentials) November 29, 2005.

31. *A 12-week double-blind, placebo-controlled, multicenter study with varenicline tartrate 1 mg bid for smoking cessation (NCT00155298)*. ClinicalTrials.gov Website 2005, December 8.

32. *Priority review for varenicline tartrate in smoking cessation*. DailyDrugNews.com (Daily Essentials) December 23, 2005.