

# [Manuscript introduction and methods sections](https://assignbuster.com/manuscript-introduction-and-methods-sections/)

nAChRs are members of the Cys-loop ligand-gated ion channel superfamily (Gay, and Yakel, 2007). Neuronal nAChRs are pentamers formed by just one subunit (homomeric) (e. g., 7, 8, and 9) or assembled by the combination of and subunits (heteromeric) (e. g., 34 and 42). nAChRs have essential physiological roles in the central and peripheral nervous systems that depend on the subunit composition and are considered to be primary mediators of nicotine addiction (Walsh, H. et al., 2008). An acceptable strategy for pharmacological intervention in nicotine dependence would be the use of a drug with partial agonist properties at nicotinic receptors (Clementi et al., 2000). Indeed, such a compound might prevent the occurrence of the withdrawal phase and dysregulation of the reinforcement mechanism that is known to be involved in compulsive smoking.   
Tobacco smoke contians several substances. Of them, nicotine appears to be the critical reinforcing component of tobacco smoke. A large body of evidence implicates a4b2 nAChrs in the reinforcing effects of nicotine. The initial effect of nicotine is probably to activate 42-nicotinic acetylcholine receptors located on dopamine neurons in the ventral tegmental area; however, it is likely that these receptors are rapidly desensitized, whereas nicotine produces a sustained effect on dopamine release in the nucleus accumbens (Foll and George, 2007). Bupropion and varenicline are accepted as therapy for niocotine addiction. Bupropion can block nicotinic receptor function. varenicline however is a partial agonist or an antagonist depending on the state of activation of the a4b2 receptors. Through its intrinsic partial activation of the 42-nicotinic acetylcholine receptors, varenicline may elicit a moderate and sustained increase in mesolimbic dopamine levels, which would counteract the low dopamine levels encountered in the absence of nicotine during smoking cessation attempts. In addition, by competitively binding to the 42-nicotinic acetylcholine receptors, the drug, as a partial agonist, protects against nicotine-induced dopaminergic activation in the event that the patient smokes (Tonstad S et al., 2006). Thus, 42-nicotinic receptor partial agonists may disrupt the reinforcing effects of nicotine and compensate for withdrawal symptoms.   
The main brain target for the pharmacological intervention of drug addiction has been the " brain reward circuitry." However, new evidence indicates that a secondary brain pathway, the hebenulo-interpeduncular pathway, is also important in the mechanism of drug addiction. Interestingly, this pathway is mainly cholinergic, and the most important nAChR expressed is the 34 subtype (Besson, M et al., 2007). Therefore, drawing upon this, a selective nAChR antagonist interacting with the 34 nAChR subtype is expected to induce less drug abuse and could be of therapeutic significance in the treatment of drug addiction (Glick et al., 2002). In this regard, we like to test the hypothesis that novel ibogaine analogues interact with the human 34 nAChR ion channel in a specific manner. Thus, the aim of this Thesis is to characterize the ibogaine binding site within the human (h)34 nAChR ion channel by determining: (1) the interaction of [3H]ibogaine to the h34 nAChR by [3H]ibogaine equilibrium binding and Scatchard-plot analysis using h34 membranes prepared from HEK293-h34 cells; (2) the affinity of natural and synthetic ibogaine analogs (see Fig. ) for the human 34 nAChR by [3H]ibogaine competition experiments; and (3) the affinity of a series of noncompetitive antagonists (see Fig. ) for the ibogaine locus by [3H]ibogaine competition experiments.   
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