Imotine™: A Novel Non-nicotine Compound with CNS Activity

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Poster #6

Abstract

Imotine™ ((S)-3-(N-Methylpyrollidino)-6-methyl-pyridine Benzoate; CAS 2861225-70-7) is a new non-nicotine compound that is reported to have Central Nervous System activity similar to nicotine. Imotine exists as the s-isomer. The compound is not manufactured from nicotine and does not contain any nicotine nor tobacco specific nitrosamine impurities. Analysis of the pure material did not reveal any chemicals of toxicologic concern. The pKa1 and pKa2 are reported to be 8.26 and 3.75 (respectively) as compared to 8.04 and 2.91 for nicotine. The compound is reported to be about 2.6 times more potent than s-nicotine on a molar basis in a mouse LD50 study. The compound is reported to have a similar affinity (K_i= 1.8 nM) for rat brain nicotinic acetylcholinergic receptors (nAChRs) as nicotine (K_i= 1.26 nM). Specific receptor binding data using [^{3}H](-)-nicotine in rat brain (minus cerebellum) preparations containing nAchR alpha4-beta2 subunits showed a K_i of 1.8 nM compared to a K_i= of 2nM for nicotine. It has been concluded that the activity of Imotine is related to its structure and lipophilicity.

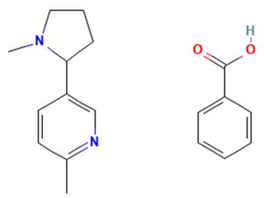
History

Starting in the late 60's and early 70's Philip Morris was interested in developing nicotine analogues that would possibly separate the effects of nicotine on blood pressure (Jeffery I. Seeman 1965). At lower doses, nicotine has a pressor effect and at high doses it has a depressor effect. The program came to be known as "The Nicotine Analogue Program." It evolved over decades and generally focused on synthesis or isolation of compounds that equal or surpass nicotine in activity. Researchers tried to ascertain the structural features of the nicotine molecule which were responsible for its various pharmacological properties. The purpose of this nicotine analog program evolved to develop an analog that would retain the physiological effects of nicotine in the brain, as well as the behavioral effects, but not have adverse effects on the cardiovascular system. When the program started, the nicotinic acetylcholine receptor had not been identified (Changeux 2020).

Assays were known that selectively seemed to respond to nicotine. Scientist synthesized and tested over 65 analogues (INBIFO 1982). Four different pharmacologic test models and determination of the LD50 were used to draw conclusions on the chemical's nicotine like properties. The models included the guinea pig ileum, rat phrenic nerve in the diaphragm, guinea pig auricle and the rat aortic strip. Binding affinity to Torpedo and rat brain membranes were measured on select chemicals. One chemical, CR-1542, appeared to have increased activity when compared to s-nicotine. This chemical was identified as (S)6-Methyl Nicotine (6-MN). Reynolds appeared to have a similar program (Patrick Lippiello et al. 1988). The Reynolds program ultimately resulted in the formation of Targacept, an independent pharmaceutical company dedicated to the discovery of nicotinic compounds for therapeutic uses. Philip Morris attempted to publish the results in a paper entitled "Steric and Conformational Effects in Nicotine Pharmacology" in Science and Nature but the paper was rejected. The authors did not choose to submit it for publication elsewhere. There is no indication that Philip Morris attempted to commercialize CR-1542. The program did not identify any compounds that had increased (relative to nicotine) CNS properties and decreased peripheral nervous system properties. A summary of the industry interest in nicotine analogues may be found in a review by Vagg and Chapman (2005).

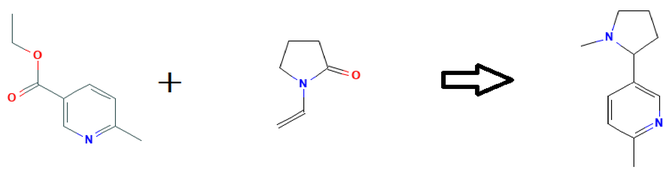
Chemical Information

(S)-3-(N-Methylpyrollidino)-6-methyl-pyridine Benzoate Structure



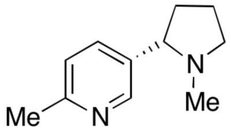
Synthetic Route

Imotine is synthesized using a trade secret process. The starting material is not nicotine and the finished product does not contain nicotine.

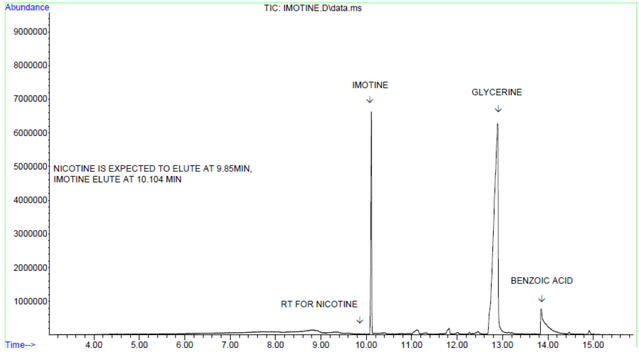


Analysis

Similar to tobacco derived nicotine, the 6-methyl nicotine (6-MN) in Imotine exists as the s-isomer (>98.5%).



Imotine does not contain nicotine



Imotine does not contain TSNAs

Nitrosamines	Imotine™ (µg/g)
N-Nitrosonornicotine (NNN)	<LOQ (0.041)
Nitrosamine Ketone (NNK)	<LOD

pKa (INBIFO 1982)

Chemical	pKa1	pKa2
(S) Nicotine	8.03	2.85
(S) 6-MN	8.26	3.75

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Pharmacology

Binding to Nicotine Receptors

David Wang, Nicole Marmarosh, and Leo Abood (1998) evaluated the binding of many of the nicotine analogues developed by Philip Morris. The analogs were compared for their ability to compete with [^{3}H]nicotine for binding to membranes isolated from rat brain and the electric organ of Torpedo *Californica*. The authors concluded that **methyl substitution in the 6-position resulted in over a 3-fold greater potency when compared to nicotine.**

Chemical	Rat Brain Ki	Torpedo Ki
(S) Nicotine	6.0 x 10^{-9}	3.1 x 10^{-7}
(S) 6-MN	2.0 x 10^{-9}	8.0 x 10^{-7}

Dukat et al. (1999) also evaluated the binding of 6-methyl nicotine and nicotine to rat brain nicotinic acetylcholinergic receptors (nAChRs). It was not clear from the publication if S or RS isomers were synthesized and tested. Hansch analysis of various structural analogs suggests that lipophilic substituents at the pyridine 6-position contribute to nAChR affinity of nicotine analogs, but that affinity is further modulated by the steric size of this substituent in that increased size results in decreased affinity.

Chemical	*Ki* (nM)
(S) Nicotine	1.26
(S) 6-MN	1.8

Toxicity

The mouse oral LD_{50} of 6-MN was 1.10 µmol/kg body weight compared to 1.96 for (S) nicotine (INBIFO 1982).

The chemical was not a skin or eye irritant in rabbits (CAS Testing Technical Services Report GXX22090172B).

The chemical was not genotoxic (did not cause an increase in micronuclei in polychromatic erythrocytes in mice (CAS Testing Technical Services Report GXX22090172B)).

In human bronchial epithelial cells 6-MN was about twice as toxic as nicotine (Qi et al. 2023).

Nicotine and 6-MN did not produce DNA damage in human bronchial epithelial cells Transcriptome analysis indicated nicotine and 6-MN appeared to work through the same pathways (Qi et al. 2023).

6-MN exhibited a more significant effect than nicotine on the expression of most cancer-related genes (CRGs), in terms of both the upregulation and downregulation. 6-MN exhibited a more significant inhibitory effect than nicotine on the expression of most CRGs (Qi et al. 2023).

Summary

Imotine is the benzoic acid salt of 6-methyl nicotine. Analysis of the product indicates that it is the S isomer and devoid of nicotine and TSNAs. The pure chemical has nicotine like pharmacologic activity and appears to have a higher binding efficiency to rat brain nicotinic acetylcholinergic receptors than nicotine. The chemical does not appear to be mutagenic. It is not listed as a carcinogen by IARC, NTP, NIOSH, or FDA

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