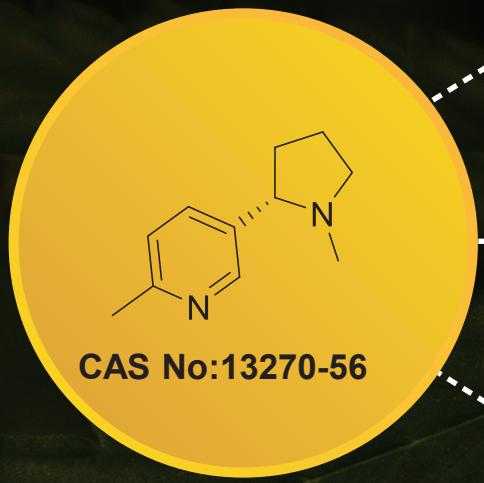
META KING

A SUBSTITUTE FOR NICOTINE

Introduction of (S)-6-methyl nicotine

Presented by: GM2 Manufacturing

WHAT IS (S)-6-METHYL NICOTINE ?



Appearance

It is a colorless and transparent liquid which has similar physical and chemical properties to nicotine

Source

It is an unnatural product produced by che mical and biological synthesis, Tobacco free

Features

It is a Nicotine structural analogues that have better pharmacological action and lower toxicity.

WHY DO WE CHOOSE
[S]-6-METHYL NICOTINE AS A SUBSTITUTE?

Compare to nicotine

01、Better pharmacological activity ensures a better product experience at lower doses

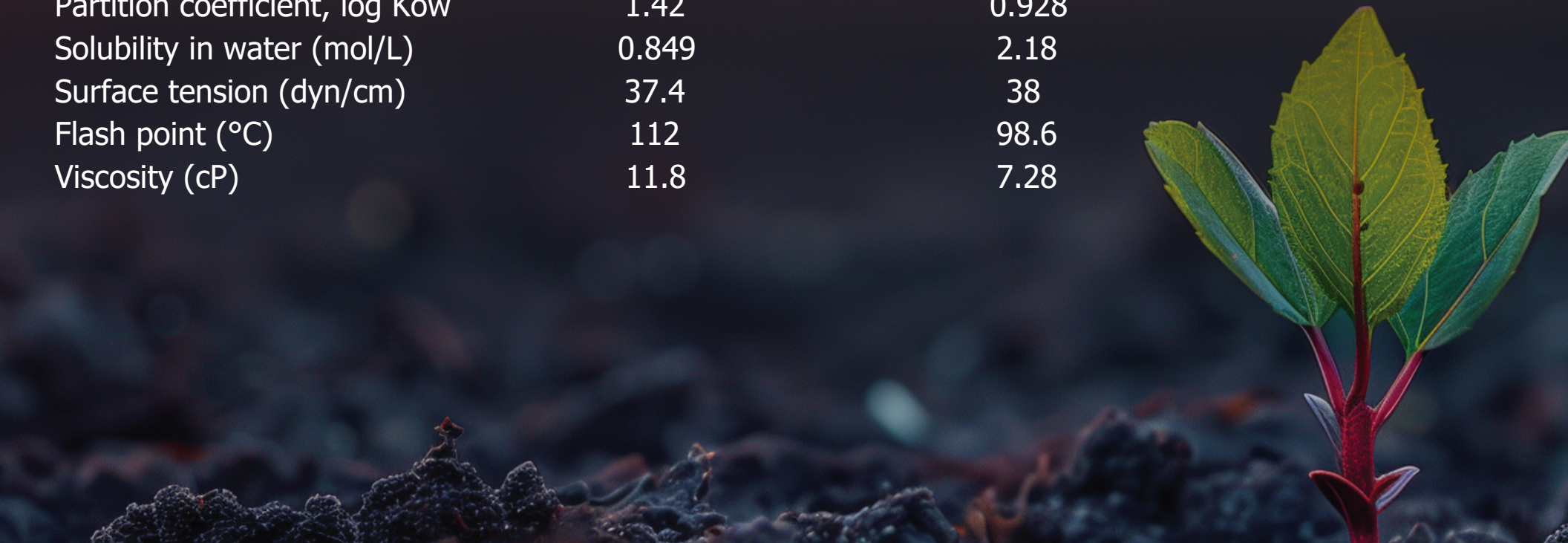
02、Low toxicity ensures the safety of customers' products using

03、Its similar physicochemical properties to nicotine ensures its application without any limitation as nicotine substitute

PREDICTED PHYSICOCHEMICAL PROPERTIES COMPARISON

PREDICTED AVERAGE VALUES

Physicochemical Property	(S)-6-Methyl Nicotine	(S)-Nicotine
Physical State	Liquid	Liquid
Melting Point (°C)	20.9	18.1
Boiling Point (°C)	259	246
Density (g/cm^3)	1.01	1.03
Vapor pressure (mm Hg)	7.30×10^{-3}	2.39×10^{-2}
Partition coefficient, log Kow	1.42	0.928
Solubility in water (mol/L)	0.849	2.18
Surface tension (dyn/cm)	37.4	38
Flash point (°C)	112	98.6
Viscosity (cP)	11.8	7.28



AEROSOL TRANSFER

EFFICIENCY COMPARISON

"NICOTINE" CONC. (MG/G)

Form	Active Agent	E-Liquid	Aerosol	Transfer Efficiency (%)
Freebase	(S)-Nicotine	43.0±0.0	36.8±1.2	85.6±2.9
	(S)-6-Methyl-Nicotine	41.5±0.1	34.2±0.2	82.5±0.6
Benzoate	(S)-Nicotine	40.4±0.1	36.4±0.8	90.2±2.1
	(S)-6-Methyl-Nicotine	42.3±0.1	37.4±2.0	88.3±4.6

Aerosol transfer efficiency comparison between (S)-6-Methyl Nicotine and(S)-Nicotine. Values are average ± standard deviation(n=3).

RELATIVE AFFINITY AND POTENCY OF (S)-6-METHYLNICOTINE COMPARED TO (S)-NICOTINE

Affinity Experiments (Rat Model)	Relative Affinity (Higher = stronger)	Ref.
Brain	8.33	1
Nic	0.38	1
ACh - Ki(relative)	0.08	1
nAChRradioligand binding (rat brain)	0.70	2

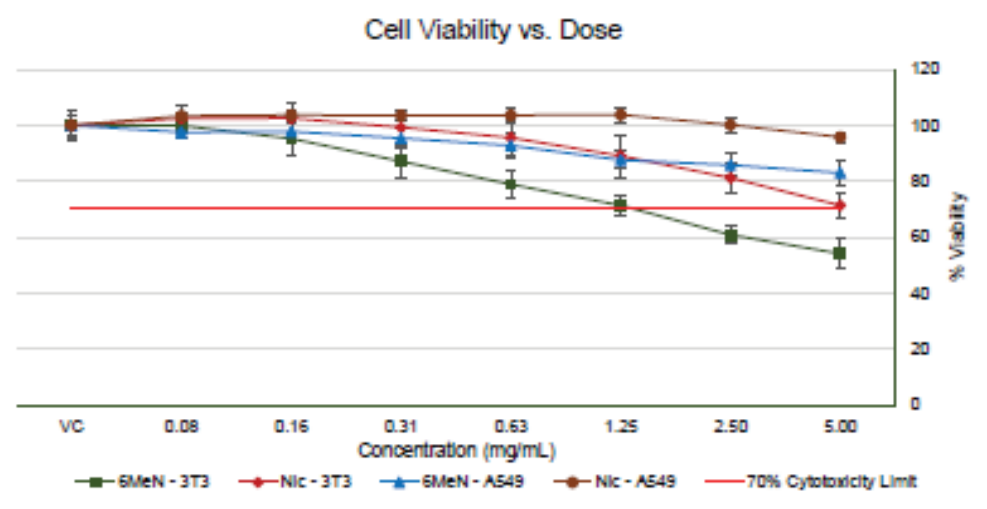
Functional Experiments	Relative Potency (Higher = more potent)	Ref.
LD50 (mice)	2.61	1
ED50 (mice; effect: convulsions)	2.62	1
Model 03 Guinea Pig Ilieum	1.96	3
Model 05 Rat Phrenic Nerve-Diaphragm	0.46	3
Model 06 Guinea Pig Auricle	1.47	3
Model 09 Rabbit Aortic Strip	1.10	4
Blood Pressure (Increase by 25%)	0.42	1
Drug Discrimination	1.09-2.19	1
Prostration	1.08	

However, caution should be taken since these studies are not pe-reviewed and used potentially outdated methodologies

Reference:

1. INBIFO, https://www.industrydocuments.ucsf.edu/docs/gscv0119
2. Dukat, M., et al., Bioorg. Med. Chem. Lett, 2002, 12(20), 3005-3007
3. INBIFO, https://www.industrydocuments.ucsf.edu/docs/prjb0115
4. INBIFO, https://www.industrydocuments.ucsf.edu/docs/mnjw0118

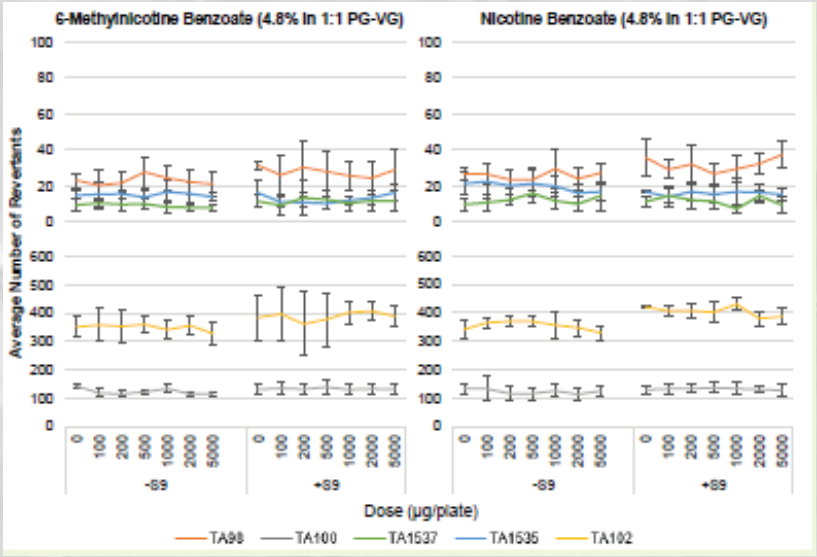
CYTOTOXICITY-NEUTRAL RED UPTAKE (NRU) RESULTS



Dosing 0.08 to 5mg.mL and cell incubated for 48hrs, No substantial cytotoxicity observed and IC50 values could not be determined for either formulation.

Neutral Red Uptake (NRU) Results for 6-MeN and Nic e-liquid formulations (n=9)

MUTAGENICITY-AMES
TEST RESULTS



Dosing 0 5000µg/plate; ncubated for 48-72h.

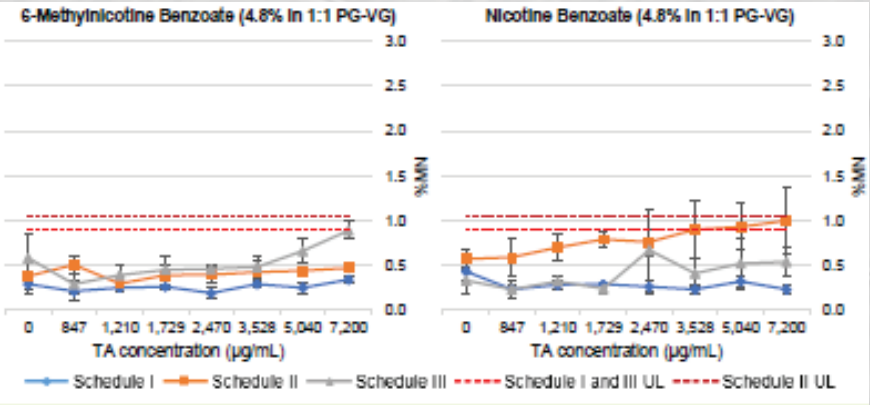
No dose-response behavior observed in any test strain for both agents.

Revertant formation is comparable to the vehicle control (0µg/mL dosage) at all doses.

Both6MeNandNicshownomutagenicactivity.

Ames test results for 6MeN (left) and Nic (right) e-iquid formulations (n=6).

GENOTOXICITY-IN VITRO
MICRO NUCLEUS (MN) TEST RESULTS



In vitro Micro nucleus (MN) test results for 6MeN (left) and Nic (right) e-liquid formulations(n=4)

Identifies agents that induce cytogenetic damage via the observation of micro nuclei in daughter cells.

TK6 cells treated with serial dilutions (7200 to 847 µg/mL e-liquid) under three conditions:

Revertant formation is comparable to the vehicle control (0µg/mL dosage) at all doses

- **Schedule (i): short term (4h) with no metabolic activation.**
- **Schedule (ii): short term (4h) with metabolic activation.**
- **Schedule (iii): long-term (22h) with no metabolic activation**

- **Both formulations were determined to be negative for genotoxicity under all conditions.**

SUMMARY

- (S)-6-methyl nicotine has similar chemical characteristics to (S)-nicotine and behaves similarly under different testing conditions.
- In silico toxicological and historical pharmacological studies suggest some what comparable activity.
- 6-methyl nicotine exhibits comparable toxicological behaviour to (S)-nicotine with no mutagenicor genotoxicactivity and limited cytotoxicity.
- Initial experiments suggest(S)-6-methyl nicotine could be a suitable replacement for (S)-Nocotine.

BUT WHY CHOOSE OUR (S)-6-METHYL NICOTINE?

Stable and repeatable process

Different forms of product

High Quality

Global service support

DIFFERENCE OF OUR PROCESS

Long-term stability study

Product quality, packaging and storage conditions have been verified by long term studies.

Process validation

Based on QbD, risk assesments were conductedfor all of process parameter, and commercial process verification was carried ot to prove that its good process repeatability and stability.

Product quality inspection

All analytical methods were validated based on ICH guidelines, the validation of analytical methods and the batch release carried out in the GLP lab.

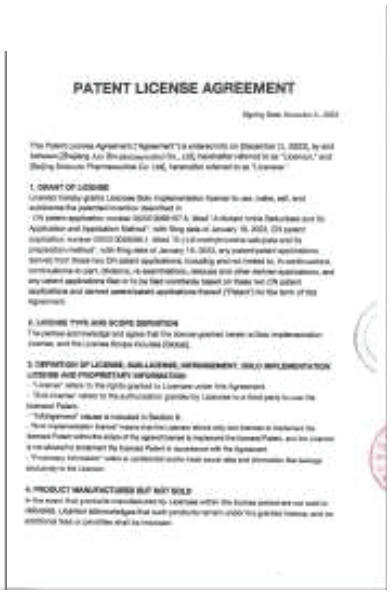
Construction of chiral center

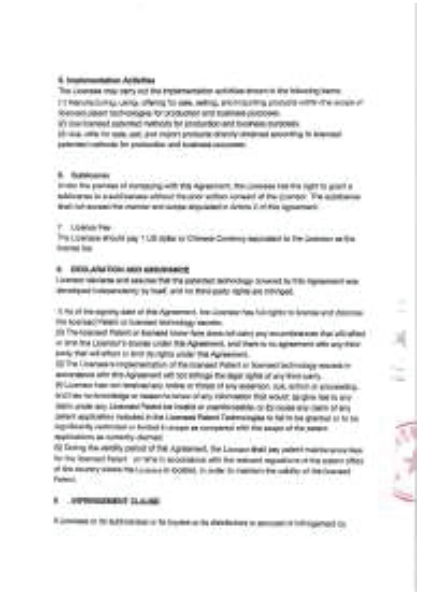
Apply the green synthetic biology techniques, Construct the chiral center by enzyme to control the level of enantiomer less than 0.15%

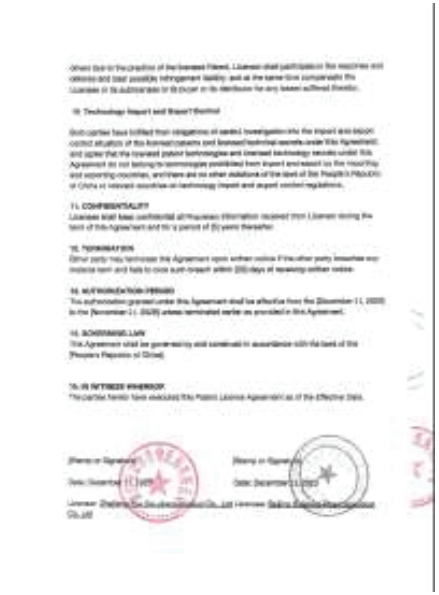
Quality assurance

The whole quality management is implemented under GMP conditions.

CERTIFICATES AND PATENTS


PATENT LICENSE AGREEMENT





The two patents respectively protect the method of constructing the chiral center and the crystal form of the product's unique solid salt

OUR QUALITY SYSTEM

NMPA, FDA and EP audience certification


CELTIC
GOLD
TOBACCO-FREE POUCHES
BLUEBERRY
GOLD
CELTIC
GOLD
TOBACCO-FREE POUCHES
SPEARMINT
CELTIC
GOLD
TOBACCO-FREE POUCHES
STRAWBERRY
CELTIC
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