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INNOVATIVE COMPUTATIONAL STRATEGIES FOR TROPANE ALKALOID DESIGN: A HOLISTIC PERSPECTIVE

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ABSTRACT

This study explores natural products, focusing on alkaloids—especially tropane alkaloids like atropine. It details their classification, biosynthesis, pharmacological significance, isolation, identification, and structural elucidation. Atropine's chemistry, therapeutic uses, and potential enhancements via complexation and computational tools highlight its importance in drug development and natural product research. The present study focuses on the in silico design and evaluation of ten novel analogues of Atropine to enhance its pharmacological potential. Various computational tools were utilized for analogue generation, structure drawing, and comprehensive profiling. QSAR Toolbox was used to identify structurally similar analogues, while ChemSketch aided in drawing their 2D structures. Molinspiration assessed drug-likeness via Lipinski's Rule of Five, indicating all analogues had favorable properties. PASS predicted strong spasmolytic and antiparkinsonian activities. ADMETlab 3.0 evaluated absorption, distribution, metabolism, and excretion profiles, showing optimal permeability, volume of distribution, and moderate plasma clearance. None of the analogues inhibited CYP1A2, suggesting low drug-drug interaction risk. Toxicity profiles predicted via ProTox 3.0 showed all compounds to be non-hepatotoxic, non-mutagenic, and non-carcinogenic, with good blood-brain barrier permeability. Overall, the designed analogues exhibited promising pharmacokinetic and safety profiles, supporting their potential as viable therapeutic candidates for further experimental validation.

KEYWORDS: Natural products, Tropane alkaloid, Atropine, Analogues.

INTRODUCTION

Natural products

Natural products are the chemical ingredients synthesized by living organisms via semisynthetic or synthetic methods. Since ancient times natural sources are being utilized by human beings as a primary source for food, shelter, and curative remedies and since the last few decades tremendous research has been carried out on natural herbs for the search and development of novel therapeutic agents beneficial for human health without or with least side effects. Commonly, the term natural product is considered the other name for secondary metabolites. These secondary metabolites are the organic ingredients that exert various pharmacological effects on human health, but do not contribute directly in various process like reproduction, growth, development, etc. Nutraceuticals, cosmetics, and pharmaceuticals are the main industries in which natural ingredients are purposely used as the main constituents. These are basically small molecules with some structural changes and are less than 3000 Da in molecular weight.

The relative study of natural products inspires scientists to isolate, identify, and characterize active compounds from natural plants and further use them to develop pharmacologically active molecules. However, natural ingredients are extremely cumbersome to isolate and very challenging to synthesize. Natural products are frequently regarded as an initial point for drug discovery in chemical synthesis, from which synthetic derivatives can be synthesized with upgraded efficiency, safety, and purity. Natural products include alkaloids, steroids, terpenoids, amino acids, proteins, carbohydrates, lipids, nucleic acids, vitamins, hormones, insect and plant growth regulators, natural pigments and dyes etc.[1]

Problems with synthetic drugs: Potency, Cost, Side effects, Requires close supervision of clinician, Resistance, Unavailability, Stability.[16]

Classification of natural products

Natural products chemistry has originated from mankind’s curiosity about colour, taste odour, and cures for human, animal and plant diseases.

Primary and Secondary Metabolites

Plants produce an enormous variety of natural products with highly diverse structures. These products are commonly termed “secondary metabolites” in contrast to the “primary metabolites” which are essential for plant growth and development. The term natural product

is applied to materials derived from plants, microorganisms, invertebrates and vertebrates, which are fine biochemical factories for the biosynthesis of both primary and secondary metabolites.

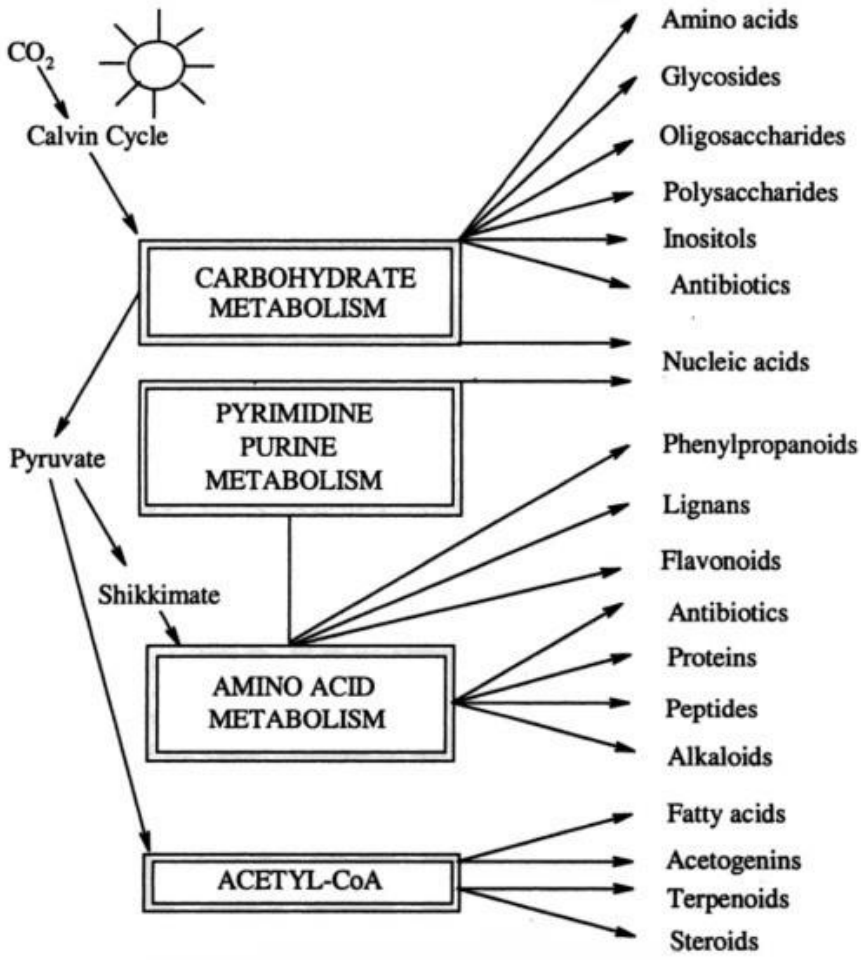


Fig. 1

Secondary metabolites play ecologically significant roles in how the living organisms deal with their surroundings and therefore are important for their ultimate survival. They were formerly regarded as "waste products" without physiological function for the plant. With the emergence of the field of chemical ecology about 30 years ago, it became evident, however, that these natural products fulfil important functions in the interaction between plants and their biotic and abiotic environment. They can serve, for example, as defence compounds against herbivores and pathogens, as flower pigments that attract pollinators, or as hormones or signal molecules. In addition to their physiological function in plants, natural products also

have a strong impact on human culture and have been used throughout human history as condiments, pigments, and pharmaceuticals.

The secondary metabolite compounds are classified into four different groups according to their biosynthetic origin: alkaloids, phenylpropanoids, polyketides, and terpenoids.[1]

Alkaloids

Alkaloids are classically defined as being plant derived, pharmacologically active, basic compounds derived from amino acids that contain one or more heterocyclic nitrogen atoms.[2] Alkaloids are mainly biosynthetically derived from amino acids resulting in variety of chemical structures, mostly isolated from plants. Alkaloids can be found in about 20% of plant species in small qualities and their production (including in biotechnology), extraction and processing remain major areas of research and development. Alkaloid biosynthetic pathways can be manipulated genetically for example in order to achieve higher production levels of alkaloids.

There is a need for drug discoveries from natural sources to result in a more diversified medicine portfolio for human use. Furthermore, natural products are more likely to resemble endogenous metabolites and biosynthetic intermediates compared to synthetic compounds which can be recognized as substrate by active transporters. Despite the changes in discovery strategies and most notably the emergence of medicines derived from molecular biology, there remains a need to develop natural product-based medicines which has shown great success as a strategy.

Alkaloids play an essential role in both human medicine and in an organism’s natural defence. Alkaloids make up approximately 20% of the known secondary metabolites founds in plants. In plants, alkaloids protect plants from predators and regulate their growth. Therapeutically, alkaloids are particularly well known as anaesthetics, cardioprotective, and anti-inflammatory agents. Well-known alkaloids used in clinical settings include morphine, strychnine, quinine, ephedrine, and nicotine. As of 25 October 2020, 27,683 alkaloids were included in the Dictionary of Natural Products (DNP) with 990 hits of newly reported or reinvestigated alkaloids from nature between 2014 to 2020.[3]

Classification of Alkaloids

1. Classification established upon the biogenesis

From a structural perception, alkaloids can be classified, based on their molecular precursor, structures, and origins or on the biological pathways used to obtain the molecule. There are three central types of alkaloids: (1) true alkaloids, (2) protoalkaloids, and (3) pseudoalkaloids. True alkaloids and protoalkaloids are produced from amino acids, whereas pseudoalkaloids are not derived from these compounds.

True alkaloids

This type of alkaloids are obtained from amino acids and they share a nitrogen-containing heterocyclic ring. They are highly reactive in nature and have potent biological activity. They form water-soluble salts, and many of them are crystalline in nature, which conjugates with acid and forms a salt. Almost all true alkaloids are bitter in taste and solid, except nicotine, which is a brown liquid. Various amino acids like L-phenylalanine/L-tyrosine, L-ornithine, L-histidine, L-lysine are the main sources of true alkaloids. Cocaine, morphine, quinine are the common true alkaloids found in nature.

Protoalkaloids

This type of alkaloids contains a nitrogen atom, which is derived from an amino acid but is not part of the heterocyclic ring system. L-Tryptophan and L-tyrosine are the main precursors of this type of alkaloids. Yohimbine, mescaline, and hordenine are the main alkaloids of this type. They are used in various health disorders, including mental illness, pain, and neuralgia.

Pseudoalkaloids

The basic carbon skeleton of pseudoalkaloids is not directly derived from amino acids; instead, they are connected with amino acid pathways where they are derived from by amination or transamination reaction from forerunners or post cursors of amino acid. Nonamino-acid precursors can also produce pseudoalkaloids. They can be phenylalanine or acetate derived. Capsaicin, caffeine, ephedrine are very common examples of pseudoalkaloids.

2. Classification established upon the ring structure

This is the most comprehensively established classification, based on the presence of a basic heterocyclic nucleus in their structure.

Tropane alkaloid

This category of alkaloids has tropane (C4N skeleton) nucleus. They are abundantly found in the Solanaceae family. They are derived from ornithine and acetoacetate. Structurally, pyrrolines are the precursor of these type of alkaloids Cocaine, atropine, scopolamine, and their derivatives are widely studied since the 19th century because of their enormous pharmacological actions.

Pyrrolizidine alkaloids

The pyrrolizidine nucleus is distinctive of this group of alkaloids. They occur in the plants from Asteraceae and Fabaceae family. These alkaloids enter into the food chain and become antifeedants for the animals who eat them. Senecionine is the popular alkaloid of this type.

Piperidine alkaloids

Piperidine nucleus is the basic ring system of this group of alkaloids. Monocycle compounds with the C5N nucleus is the important feature of true piperidine alkaloids. Presence of odour is the common feature of piperidine alkaloids. They exert chronic neurotoxicity. Many of them are originated from plants. Although piperidine itself is a lysine-derived alkaloid, some of the piperidine alkaloids also derived from acetate, acetoacetate, in an analogous fashion to the simple pyrrolidine alkaloids. Lobeline is one of the important alkaloids in this group.

Quinolines alkaloid

This type of quinolone-nucleus-containing alkaloid is achieved exclusively from the bark of the Cinchona plant. But a variety of simple heteroaromatic quinolines are also isolated from various marine sources (4,8-quinolinediol from cephalopod ink and 2-heptyl-4 hydroxyquinoline from a marine pseudomonad). The major alkaloid of this specific group is cinchonine, cinchonidine, quinine, and quinidine.

Isoquinoline alkaloids

Isoquinoline alkaloids are an extremely large group of alkaloids mostly occurring in higher plants, but few groups are also isoquinolinoid marine alkaloids. Isoquinoline nucleus is the basic structural feature. These groups of alkaloids have huge types of medicinal properties like antiviral, antifungal, anticancer, antioxidant, antispasmodic, and an enzyme inhibitor.

Morphine and codeine are the major and widely studied isoquinoline alkaloids. They are derived from tyrosine or phenylalanine.

Indole alkaloids

This is the largest and most interesting alkaloid group derived from tryptophan. Although structural diversity varies according to the terrestrial and marine source, classical research studies have been carried out on alkaloids from both origins and the fungal source. Polyhalogenation is a common feature of these alkaloids.

Steroidal alkaloids

1,2-Cyclopentane phenanthrene ring system is the characteristic of this type of alkaloids. They are typically originated from higher plants, which belong to Liliaceae, Solanaceae, Apocynaceae, Buxaceae families, but some are also isolated from amphibians too.

Imidazole alkaloid

The imidazole ring structure is the characteristic of this type of alkaloid. The imidazole ring of these alkaloids is previously made at the stage of the precursor, so they are an exemption in the transformation procedure of structures. This type of alkaloids contains numerous structurally different examples, particularly among marine and microbial alkaloids. They display a wide array of biological activities and significant pharmaceutical potential. Pilocarpine is the most pharmaceutically significant imidazole alkaloid.

Purine alkaloids

Purine is the nitrogenous base of nucleotide (building block of DNA and RNA), which consist of purine ring and pentose sugar along with another base pyrimidine. Caffeine, Theophylline and Theobromine are typical examples of purine alkaloids. They are popular as plant alkaloids, but they can be also originated in marine organisms with substituted purines (e.g., Phidolopin) and a variety of terpenoid-purine alkaloids, such as the age lines and others.

Pyrrolidine alkaloids

Pyrrolidine (C4N skeleton) nucleus constitutes the basic nucleus of pyrrolidine alkaloids. Many pyrrolidine alkaloids are known from plants. Hygrine(biosynthesized from ornithine), ficine (where the pyrrolidine ring is involved to a flavone nucleus), and brevicolline (wherein it is attached to a β-carboline unit) are some examples of this type of alkaloids.[4]

Tropane Alkaloids

Tropane alkaloids (TA) are valuable secondary plant metabolites which are mostly found in high concentrations in the Solanaceae and Erythroxylaceae families. The TAs, which are

characterized by their unique bicyclic tropane ring system, can be divided into three major groups: hyoscyamine and scopolamine, cocaine and calystegines. Although all TAs have the same basic structure, they differ immensely in their biological, chemical and pharmacological properties. Scopolamine, also known as hyoscine, has the largest legitimate market as a pharmacological agent due to its treatment of nausea, vomiting, motion sickness, as well as smooth muscle spasms while cocaine is the 2nd most frequently consumed illicit drug globally.

Tropane alkaloids (TAs) are a specific class of alkaloid and can be more specifically defined as all molecules that possess a tropane ring system.

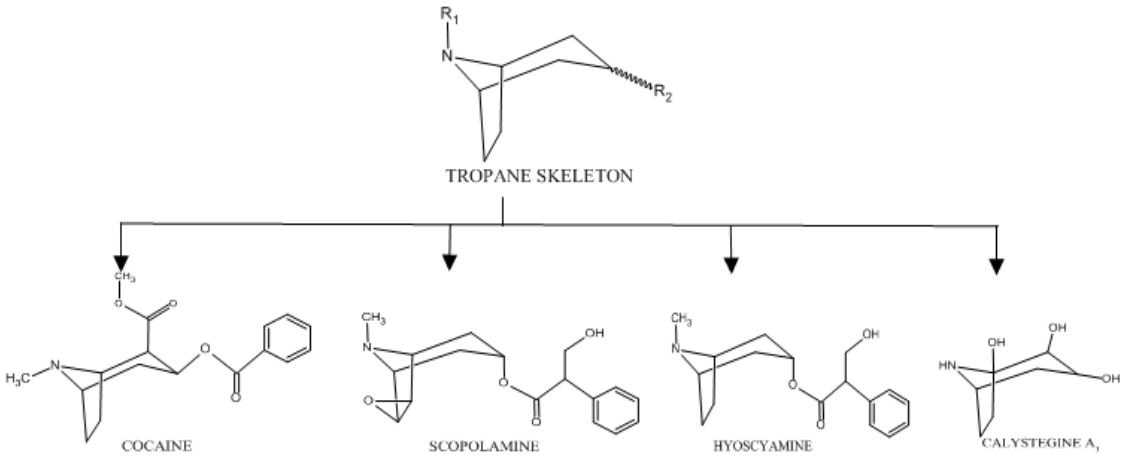


Fig. 2

Although all TAs have a high degree of structural similarity due to their tropane ring, the pharmacological effects of these compounds differ significantly. Cocaine and hyoscyamine/scopolamine are able to pass the blood-brain barrier and commit dose-dependent hallucination and psychoactive effects. Calystegines do not cause these effects due to their polarity as well as hydrophilicity and consequent inability to pass this barrier.[5]

Chemistry

Tropane alkaloids are a class of organic compounds found naturally in plants, particularly within the Solanaceae family. They are characterized by the presence of a tropane ring system within their molecular structure. This bicyclic ring system consists of a piperidine ring fused to a pyrrolidine ring, with a nitrogen atom bridging the two rings. The nitrogen atom is also typically attached to a methyl group.

Here's a more detailed look at their chemistry:

Key Features

Tropane Ring: The defining structural feature is the tropane ring, a bicyclic system with a nitrogen bridge.

Nitrogen Atom: The nitrogen atom in the tropane ring is usually tertiary (containing a methyl group).

Alkaloids: They are classified as alkaloids because they contain nitrogen and are derived from amino acids.

Solanaceae Family: Many tropane alkaloids are found in plants of the Solanaceae family, which includes familiar plants like tomatoes, potatoes, and tobacco.

Stereochemistry: Tropane itself is a symmetrical molecule, but many tropane alkaloids have chiral centers (asymmetric carbons) leading to different stereoisomers.

Biological Activity: Some tropane alkaloids have pharmacological properties, acting as anticholinergics or stimulants.

Examples

Atropine: A well-known tropane alkaloid found in plants like deadly nightshade (Atropa belladonna). Scopolamine: Another tropane alkaloid with anticholinergic and sedative effects. Cocaine: A tropane alkaloid known for its stimulant properties.[7]

Atropine

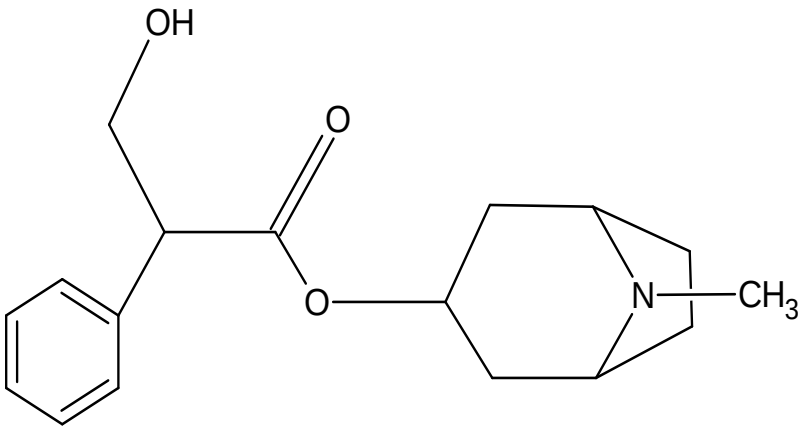


Fig. 3

Table 1: Properties of Atropine.

Molecular Formula	$C_{17}H_{23}NO_3$
Molecular Weight	289.4 g/mol
SMILES	CN1[C@@H]2CC[C@H]1CC(C2)OC(=O)C(CO)C3=CC=CC=C3
IUPAC Name	[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl] 3-hydroxy-2-phenylpropanoate
Melting Point	91.791
Boiling Point	269.853

Isolation Of Atropine

Atropine occurs in several solanaceous plants these include species of Atropa, Datura, Hyoscyamus, Duboisia, Mandragora and Scopolia. It is claimed that atropine does not occur as such in the plants, but 2-hyoscyamine present in plants, and during extraction process, 2-hyoscyamine undergoes racemization to give atropine.

One of the best methods for the isolation of atropine is as follows. The powdered drug is thoroughly moistened with an aqueous solution of sodium carbonate and extracted with ether or benzene. The alkaloidal bases are extracted from the solvent with water acidified with acetic acid. The acid solution is then shaken with ether as long as the latter takes up colouring matters. The alkaloids are precipitated with sodium carbonate, filtered off, washed and dried. The dried precipitate is dissolved in ether or acetone, dehydrated with anhydrous sodium sulphate and filtered. The filtrate is concentrated, cooled, when crude hyoscyamine and atropine crystallize from the solution. The crude crystalline mass resulted is filtered off and dissolved in alcohol, sodium hydroxide solution is added and the mixture is allowed to stand until racemization of hyoscyamine to atropine is completed (as indicated by the absence of optical activity). The crude atropine is purified by crystallisation from acetone.

Identification Tests of Atropine

The following identification tests are mentioned in the British Pharmacopoeia of 1963(70)–
1 mg of atropine is added to 4 drops of fuming nitric acid and the mixture is evaporated to dryness on a water bath; a yellow residue is obtained. 2 ml of acetone and 4 drops of a 3% w/v solution of potassium hydroxide in methyl alcohol are added to the cooled residue; a deep violet colour is produced.

Other identification tests are as follows:

The Gerrard Reaction

To about 6 mg of atropine, 1 ml of 2% solution of mercuric chloride in 50% aqueous methanol is added; a deep red colour is produced.

To a trace of atropine in an evaporating dish, drops of the p-dimethylaminobenzaldehyde reagent are added as well as 0.4 ml of water. The resulting mixture is heated on a boiling water bath; an intense red colour is produced which changing to Permanent cherry red on cooling.

Physiological Test

Induction of mydriasis

An aqueous, alcohol free solution of atropine or its sulphate is dropped into the conjunctival sac of the eye and held so that non is lost by overflow of tears. It will cause dilation of pupil of eye in 1 hour.[6]

Biosynthesis Of Atropine

The initial stages of Atropine biosynthesis is identical to that that of all tropane alkaloids. Arginine and Ornithine metabolism leads to the formation of Putrescine, Putrescine is methylated to form N-Methyl putrescine by the enzyme N putrescine Methyltransferase. N-Methyl putrescine is converted to N-methylpyrrolinium by spontaneous cyclization. N-methylpyrrolinium serves as the branch point for tropane synthesis. The biosynthesis of Atropine starting from L-Phenylalanine first undergoes a transamination forming Phenyl pyruvic acid which is then reduced to Phenyl lactic Acid. Coenzyme A then couples Phenyl-lactic acid with Tropine forming Littorine, which then undergoes a radical rearrangement initiated with a P450 enzyme forming hyoscyamine aldehyde. A dehydrogenase then reduces the aldehyde to a primary alcohol making Hyoscyamine, which upon racemization forms atropine.[8]

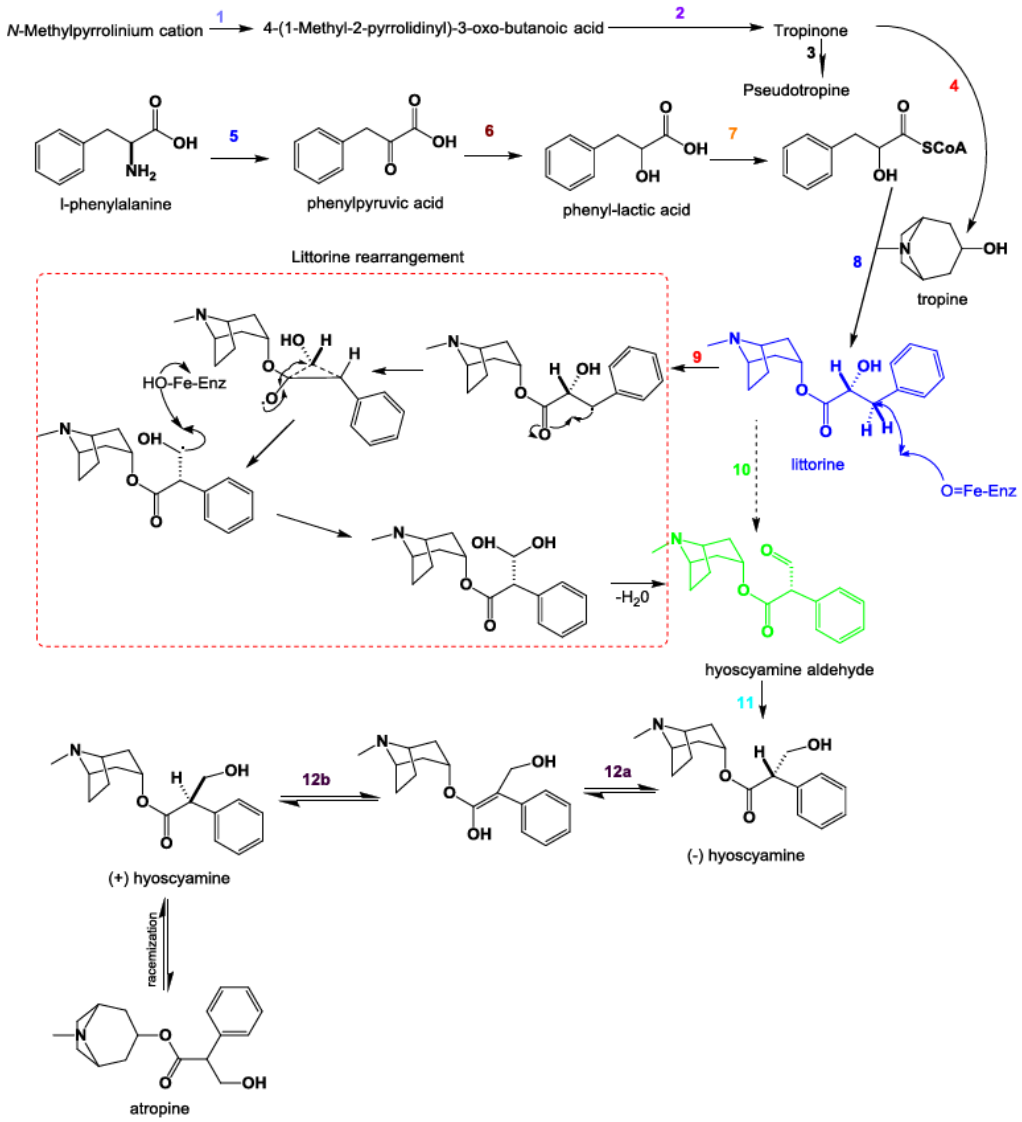


Fig. 4: Atropine biosynthesis, starting with the L-phenylalanine; 1 = polyketide synthase; 2 = cytochrome P450 enzyme; 3,4 = tropinone reductase I/II; 5 = L-phenylalanine deaminase; 6 = D-phenyl lactate dehydrogenase; 7 = phenyl lactate CoA-transferase 8 = littorine synthase; 9 and 10 = cytochrome P450 littorine mutase/monooxygenase; 11 = unidentified alcohol dehydrogenase; 12a and 12b = hyoscyamine 6β hydroxylase.

LITERATURE REVIEW

- The Oral carcinoma drug targets were identified by literature search and its 3D structure was downloaded from RCSB PDB. The indole alkaloids with anticancer property were identified by literature search and their 3D structure was retrieved from Pubchem. The docking was carried out using iGEMDOCKv2.1. Ajmalicine shows good interaction with both drug targets and possesses the best fitness energy of all 5 tropane alkaloids.[9]

- a study on the use of intravenous atropine in patients suffering from acute myocardial infarction (heart attack) complicated by sinus bradycardia (slow heart rate) showed that atropine is effective in treating patients with sinus bradycardia and hypotension following a heart attack. It is also useful in managing ventricular arrhythmias and conduction disturbances. However, due to its potential for serious side effects, it should only be used under careful medical supervision to avoid complications.[10]

- Atropine was administered to clinically normal ponies at two different dosages (high and low) Atropine can cause or mimic signs of gastrointestinal dysfunction, such as colic, and can mask or confuse the diagnosis of Gl disorders. Because of this atropine is not recommended for treating intestinal spasms in horses.[11]

- Myopia is rapidly increasing worldwide, especially among children in East Asia. This review highlights low-dose atropine (particularly 0.01%) as an effective and safe treatment to slow myopia progression. It discusses recent clinical trials, potential rebound effects, treatment strategies, and the need for broader research, especially in non-Asian populations.[12]

- This study critically evaluates the OECD QSAR Toolbox profilers for their utility in identifying suitable chemical analogues for read-across in toxicity assessment. Using extensive datasets across mutagenicity, carcinogenicity, and skin sensitisation endpoints, it highlights inconsistencies in profiler performance—where some structural alerts effectively identify meaningful analogues, while others contribute to over-prediction or poor specificity. The results underscore the need for refining these profilers to ensure accurate analogue selection, ultimately improving the reliability of in silico chemical categorization and regulatory read-across.[13]

- ADMETlab 3.0 is an enhanced web-based platform that predicts the pharmacokinetic (ADME) and toxicity (T) properties of drug-like molecules. It features expanded data coverage (119 endpoints), improved prediction accuracy using a deep learning model (DMPNN-Des), uncertainty scoring for confidence in results, and an API for automated, large-scale compound evaluation—making it a powerful tool for early drug development and virtual screening.[14]

- PROTOX 3.0 is a publicly accessible web platform for predicting the toxicity of chemical compounds using machine learning, molecular similarity, and pharmacophore modelling. It evaluates 61 toxicity endpoints—including acute and organ toxicity, toxicological pathways, metabolism, and more—based on a compound's 2D structure. The tool enhances early-stage drug safety assessment, supports green toxicology by reducing animal testing, and offers easy-to-interpret visual outputs like radar and network plots.[15]

- This study shows that when atropine is combined with β-cyclodextrin—a ring-shaped molecule—it forms a stable inclusion complex. That structure tucks atropine inside the cyclodextrin's cavity, dramatically boosting its water solubility. This makes atropine more viable as a biodegradable, eco-friendly agent in agricultural formulations like natural pesticides.[17]

STRUCTURAL ELUCIDATION OF ATROPINE

I. Molecular Formula: $C_{17}H_{23}NO_3$

II. Presence of a primary alcoholic group

Atropine undergo acetylation or benzoylation to give the corresponding monoacetyl or monobenzyl derivatives indicating the presence of an alcoholic group.

The nature of alcoholic group is determined by oxidation. On oxidation, it gives an aldehyde proving the presence of primary alcoholic group.

III. Hydrolysis

When warmed with Barium hydroxide solution atropine is hydrolysed to tropic acid and tropine. Thus, atropine is the tropine ester of tropic acid.

$$C_{17}H_{23}NO_3 \xrightarrow[H_2O]{Ba(OH)_2} \underset{\text{Tropic acid}}{C_9H_{10}O_3} + \underset{\text{Tropine (Tropanol)}}{C_4H_{15}NO}$$

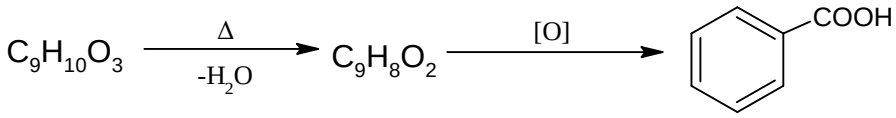
Since atropine on hydrolysis gives tropic acid and tropanol, Atropine is an ester.

Tropic Acid

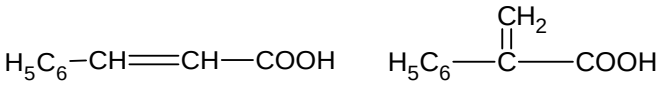
Molecular Formula: $C_9H_{10}O_3$

Possess one alcoholic and one carboxylic group by usual test.

Tropic acid on heating strongly loses a molecule of water to form atropic acid with molecular formula $C_9H_8O_2$ which on oxidation gives benzoic acid.



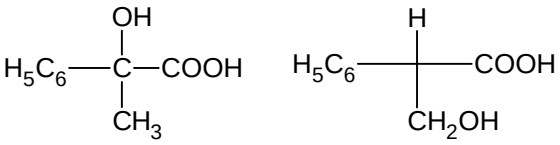
The formation of benzene suggests that atropic acid and hence tropic acid both contain a benzene ring with a side chain.



I II

Since structure I is cinnamic acid, structure of atropic acid should be II.

Addition of a molecule of water to II gives tropic acid, which may be III or IV

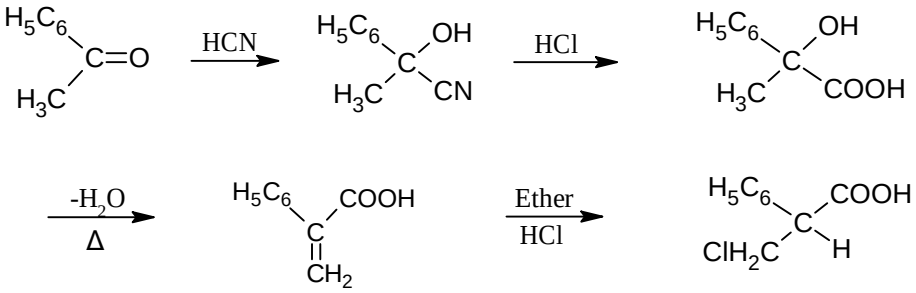


III IV

Tropic acid has structure IV which is confirmed by its synthesis.

Synthesis Of Tropic Acid:

From acetophenone



Tropic acid

Tropine

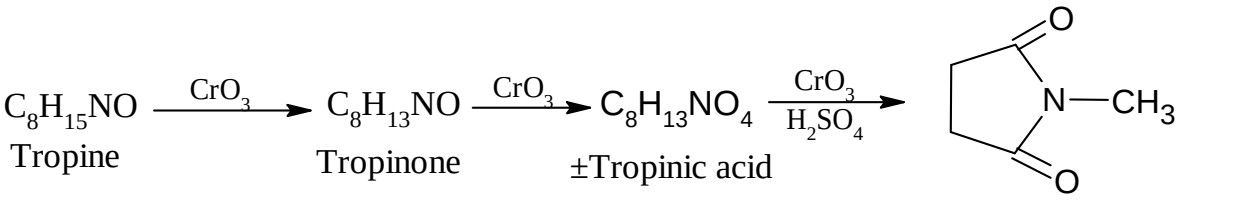
Molecular Formula: $C_8H_{15}NO$

Tropine is a saturated compound. On hydrogenating tropine gives hydrogenated product. So, it is a saturated compound.

It contains an alcoholic group i.e. a secondary alcoholic group. It is confirmed by its oxidation to ketone.

It contains a tertiary nitrogen which is identified by treating tropine with methyl iodide to get a quaternary salt.

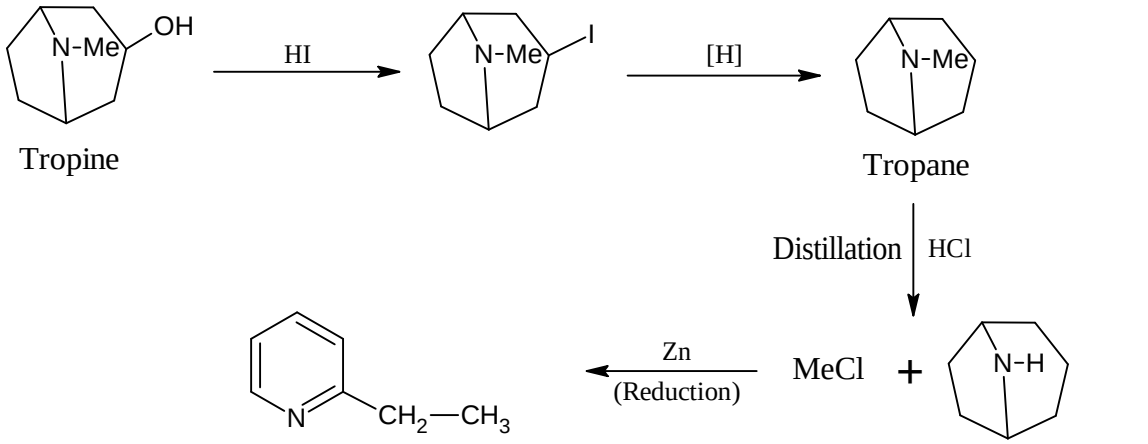
Willstatter examined the oxidation product of tropine as follows



Tropine — Tropinone — ±Tropinic acid — N-methyl succinimide

Tropinone is a ketone, thus tropine is a secondary alcohol. Tropinone on oxidation with CrO_3. H_2SO_4 gives N-methyl succinimide. It indicates the presence of pyrrolidine ring in tropinone. The structure of tropine is confirmed by its degradation reaction.

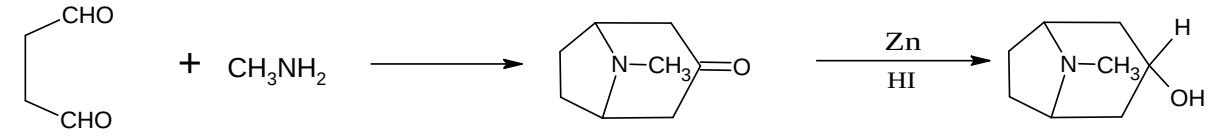
Formation of 2-ethyl pyridine from tropine indicate the presence of pyridine ring in tropine.



Tropine — Tropane — 2 - Ethyl pyridine — Nordihydrotropidine

Structure of tropine has been confirmed by synthesis.

Robinson synthesis



Succinaldehyde — Methyl amine — Tropinone — Tropine

By knowing the structure of tropic acid and tropine, atropine can be written as:[18]

IN SILICO DESIGN OF ANALOGUES

MATERIALS AND METHODS

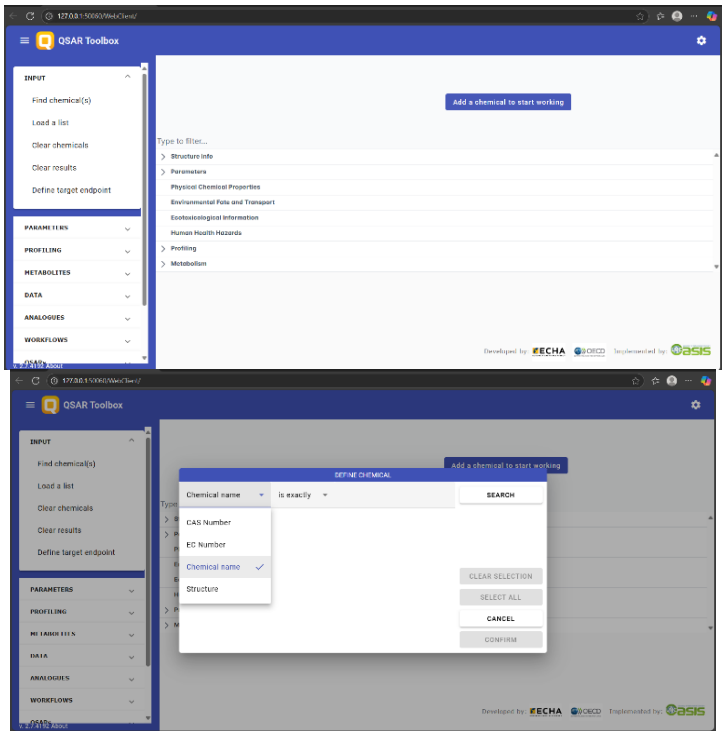
Table 2

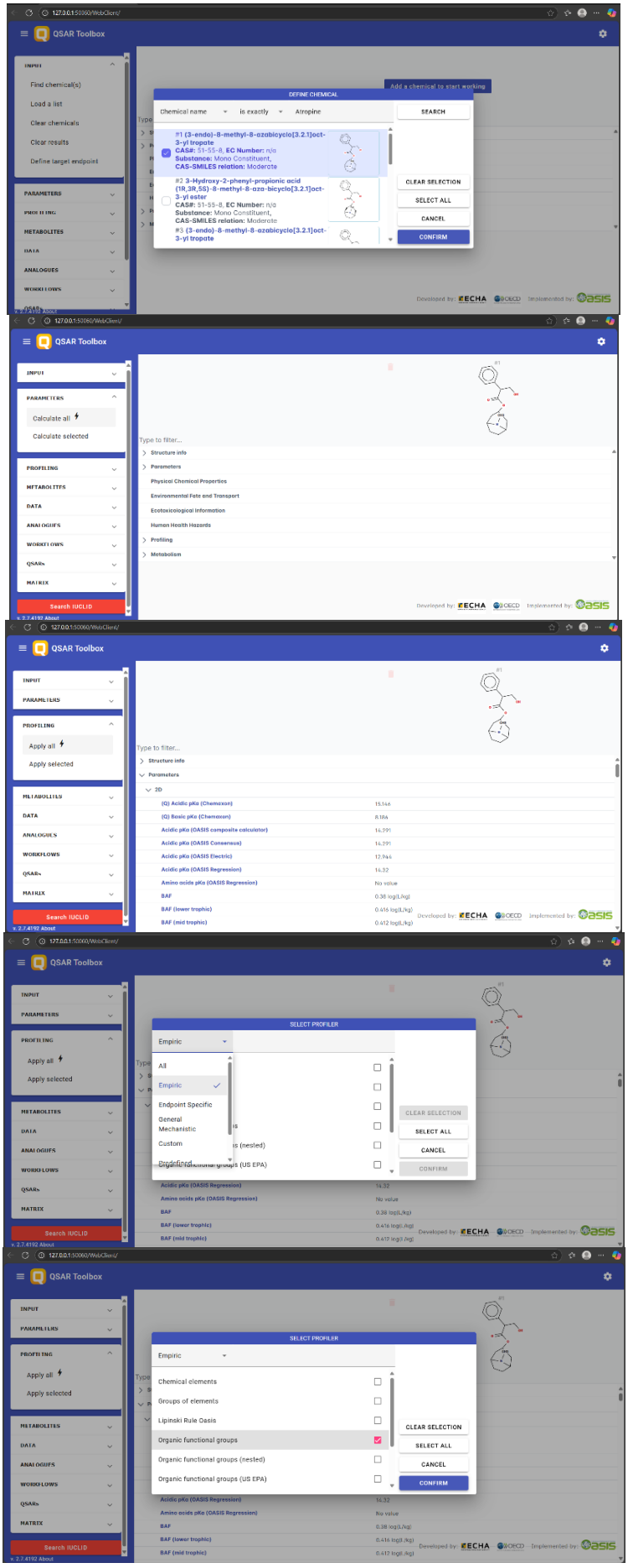
SI No.	SOFTWARE USED	USAGE
1	QSAR TOOLBOX	It is used for finding the analogues
2	CHEMSKETCH	It is used to draw 2D structures.
3	MOLINSPIRATION	It is used to calculate drug likeliness property
4	PASS	To predicts biological activity
5	ADMET lab 3.0	Used to predict the ADME parameters of synthesized compounds.
6	PROTOX 3.0	Used to predict the toxicity of chemical compounds.

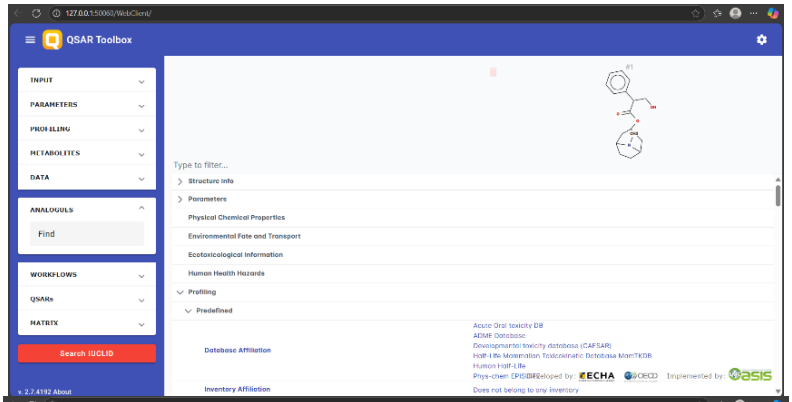
Introduction to various software's

QSAR TOOLBOX

QSAR Toolbox is a software designed to support hazard assessment of chemicals as well as to increase mechanistic and other knowledge on chemical substances in a cost-efficient way. As a freely available computational tool, it promotes the use of assessment methods alternative to animals and minimizes unnecessary animal testing without reducing the safety of human health and environment.




QSAR Toolbox
DEFINE CHEMICAL
SEARCH
CLEAR SELECTION
SELECT ALL
CANCEL
CONFIRM
SELECT PROFILER
Empiric
Chemical elements
Groups of elements
Lipinski Rule Oasis
Organic functional groups
Organic functional groups (nested)
Organic functional groups (US EPA)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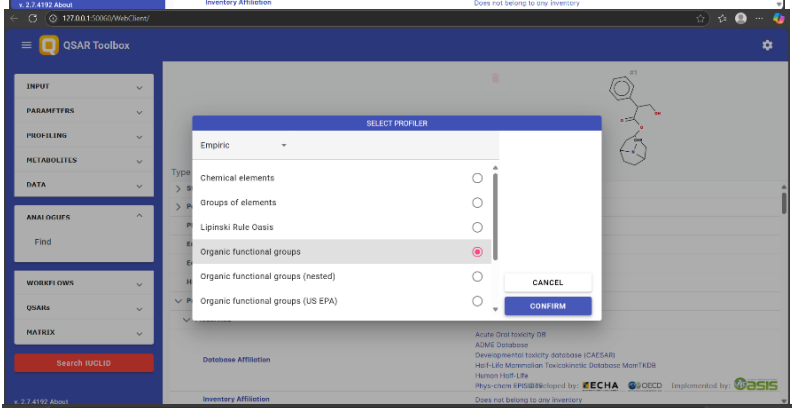
PARAMETERS
PROFILING
METABOLITES
DATA
ANALOGUES
Find
WORKFLOWS
QSARs
MATRIX
Search IUCLID
Type to filter...
Structure info
Parameters
Physical Chemical Properties
Environmental Fate and Transport
Ecotoxicological Information
Human Health Hazards
Profiling
Predefined
Database Affiliation
Inventory Affiliation


QSAR Toolbox
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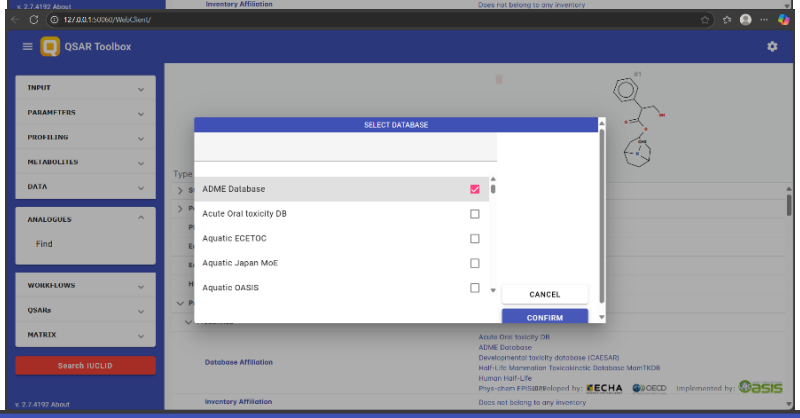
Empiric
Chemical elements
Groups of elements
Lipinski Rule Oasis
Organic functional groups
Organic functional groups (nested)
Organic functional groups (US EPA)
CANCEL
CONFIRM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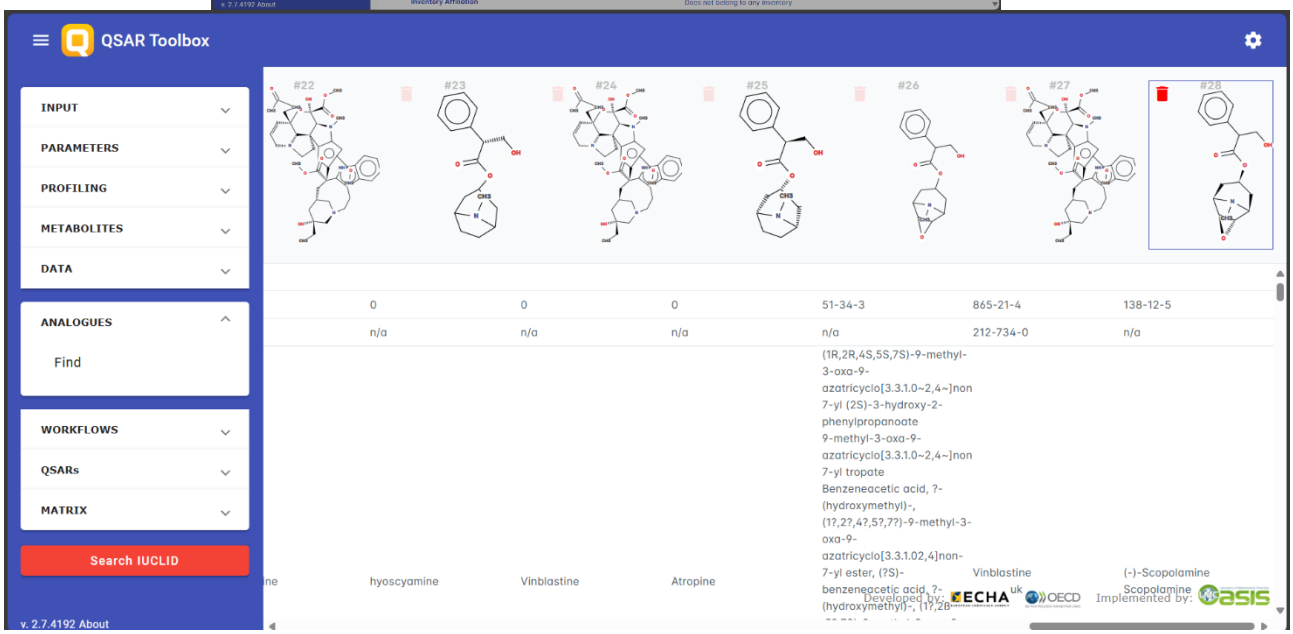
ADME Database
Acute Oral toxicity DB
Aquatic ECETOC
Aquatic Japan MoE
Aquatic OASIS
CANCEL
CONFIRM


QSAR Toolbox
INPUT
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138-12-5
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n/a
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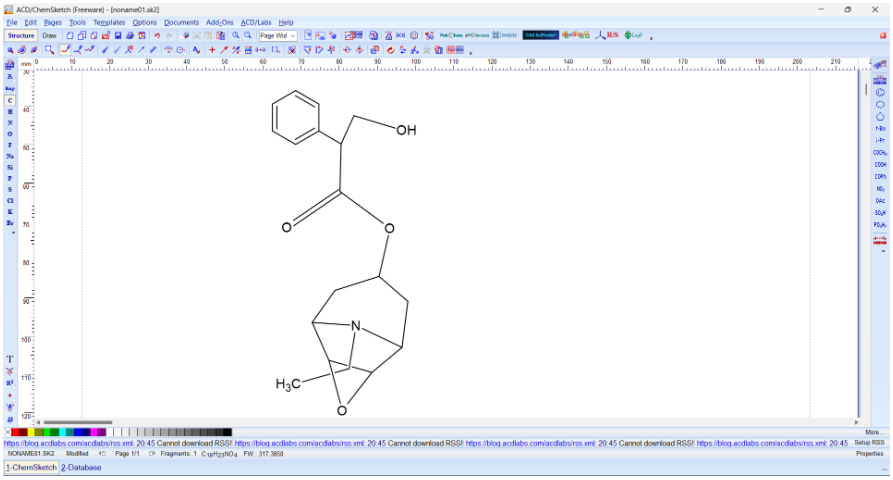
n/a
(1R,2R,4S,5S,7S)-9-methyl-3-oxa-9-azatricyclo[3.3.1.0~2,4~]non-7-yl (2S)-3-hydroxy-2-phenylpropanoate
9-methyl-3-oxa-9-azatricyclo[3.3.1.0~2,4~]non-7-yl tropate
Benzeneacetic acid, ?-(hydroxymethyl)-, (1?,2?,4?,5?,7?)-9-methyl-3-oxa-9-azatricyclo[3.3.1.02,4]non-7-yl ester, (?S)-
hyoscyamine
Vinblastine
Atropine
Vinblastine
(-)-Scopolamine
Scopolamine
Developed by:
Implemented by:

CHEMSKETCH

Chem Sketch is a molecular modelling program used to create and modify images of chemical structures. The software allows for the importation and display of molecules and molecular models displayed in two and three dimensions.



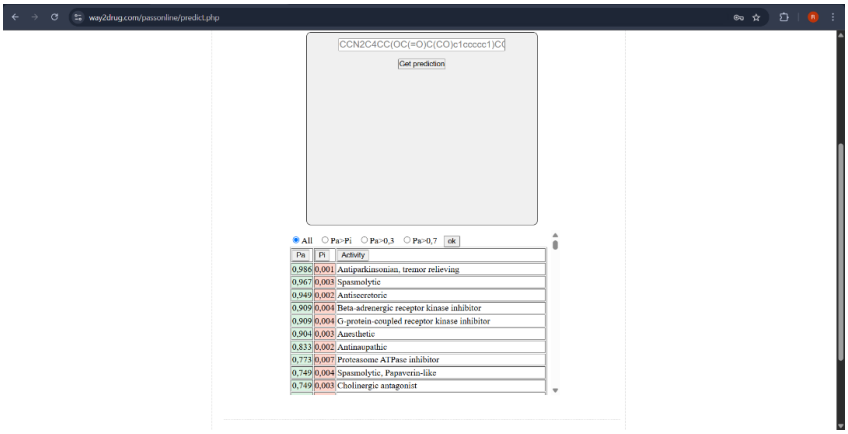
All of the 10 analogues of Atropine were drawn using Chem sketch.

MOLINSPIRATION

Molinspiration is a widely utilized cheminformatics platform designed to assist in the prediction of molecular properties and biological activities of chemical compounds.

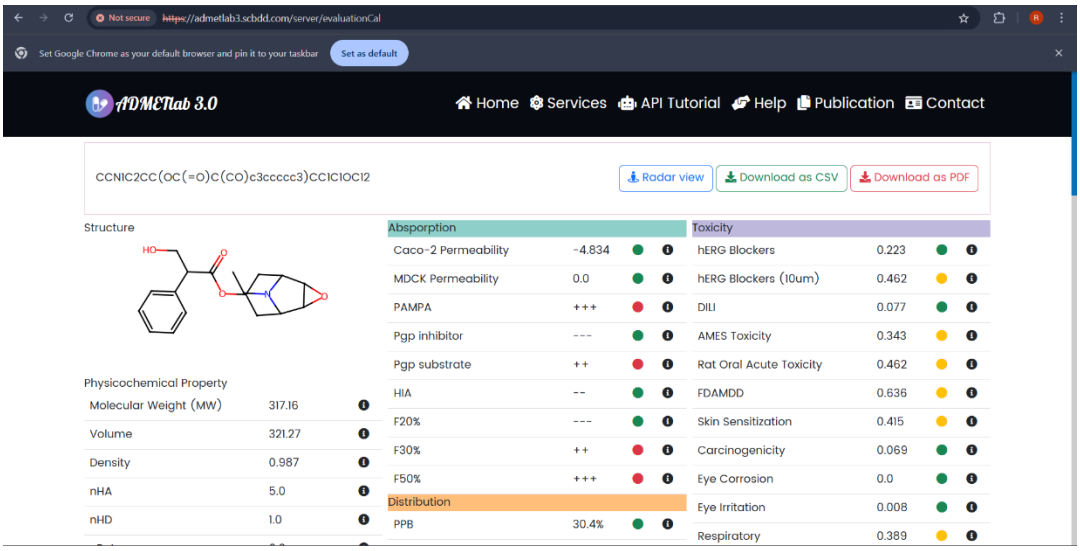
PASS (Prediction of Activity Spectra for Substances):

PASS is a software product designed as a tool for evaluating the general biological potential of an organic drug-like molecule. PASS provides simultaneous predictions of many types of biological activity based on the structure of organic compounds.



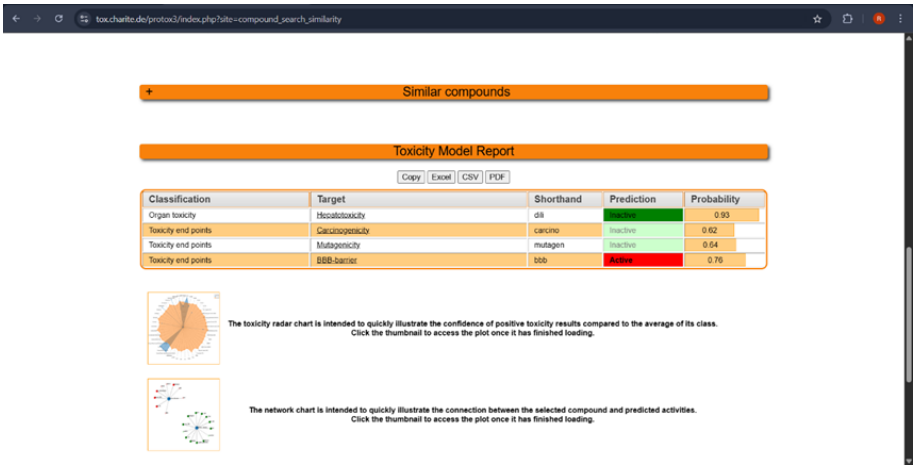
ADMET lab 3.0

It provides a comprehensive and efficient platform for evaluating ADMET-related parameters as well as physicochemical properties and medicinal chemistry characteristics involved in the drug discovery process.



PROTOX 3.0

ProTox 3.0 incorporates molecular similarity, most frequent features and machine-learning, based a total of 61 models for the prediction of toxicity endpoints such as acute toxicity, organ toxicity, toxicological endpoints, molecular initiating events, metabolism, adverse outcomes pathways and toxicity targets.

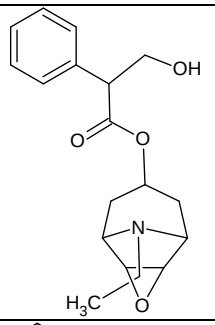
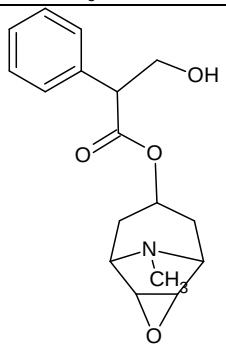
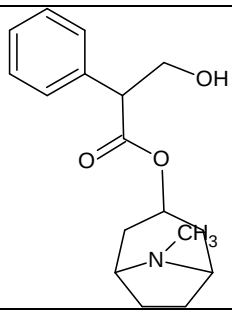


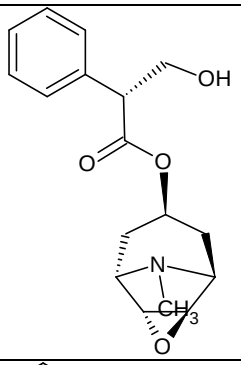
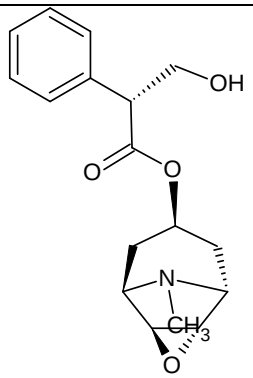
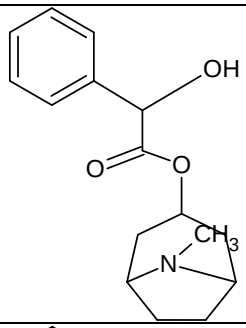
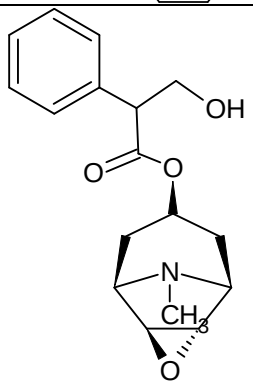
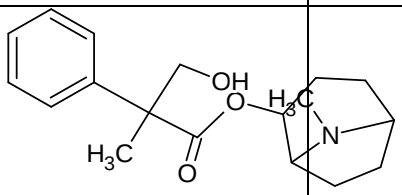
RESULTS AND DISCUSSION

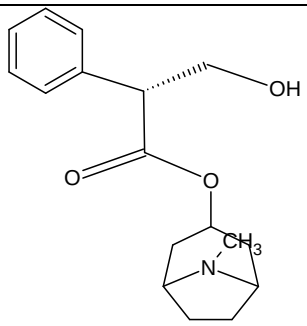
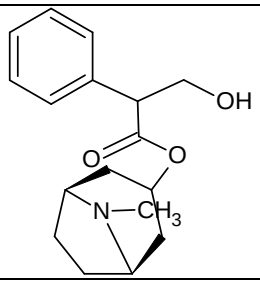
QSAR Toolbox

The QSAR Toolbox is a free software application developed by the OECD to support chemical hazard assessment using non-testing methods.

Table 3

SL. NO.	STRUCTURE	COMPOUND CODE NO.	SMILES NOTATION	IUPAC NAME
1		TA 1	CCN2C4CC(OC(=O)C(CO)c1ccccc1)CC2C3OC34	(9-Ethyl-3-oxa-9-azatricyclo[3.3.1.02,4]nonan-7-yl) 3-hydroxy-2-phenylpropanoate
2		TA 2	CN2C4CC(OC(=O)C(CO)c1ccccc1)CC2C3OC34	(9-methyl-3-oxa-9-azatricyclo[3.3.1.02,4]nonan-7-yl) 3-hydroxy-2-phenylpropanoate
3		TA 3	CN1C3CCC1CC(OC(=O)C(CO)c2ccccc2)C3	(8-methyl-8-azabicyclo[3.2.1]octan-3-yl) 3-hydroxy-2-phenylpropanoate

4		TA 4	CN2[C@H]4C[C@H](OC(=O)[C@@H](CO)c1ccccc1)C[C@H]2[C@H]3O[C@@H]34	[(1S,2R,4R,5S)-9-methyl-3-oxa-9-azatricyclo[3.3.1.02,4]nonan-7-yl] (2R)-3-hydroxy-2-phenylpropanoate
5		TA 5	CN2[C@@H]4C[C@@H](OC(=O)[C@@H](CO)c1ccccc1)C[C@@H]2[C@@H]3O[C@H]34	[(1R,2S,4S,5R)-9-methyl-3-oxa-9-azatricyclo[3.3.1.02,4]nonan-7-yl] (2R)-3-hydroxy-2-phenylpropanoate
6		TA 6	O=C(OC1CC2CCC(C1)N2C)C(O)c1ccccc1	(8-methyl-8-azabicyclo[3.2.1]octan-3-yl) 2-hydroxy-2-phenylacetate
7		TA 7	O=C(OC1C[C@H]2N(C)[C@@H](C1)[C@@H]1O[C@H]12)C(CO)c1ccccc1	[(1R,2S,4S,5S)-9-methyl-3-oxa-9-azatricyclo[3.3.1.02,4]nonan-7-yl] 3-hydroxy-2-phenylpropanoate
8		TA 8	O=C(OC1CCC2CCC1N2C)C©(CO)c1ccccc1	(8-methyl-8-azabicyclo[3.2.1]octan-3-yl) (2R)-3-hydroxy-2-phenylpropanoate

9		TA 9	O=C(OC1CC2CCC(C1)N2C)[C@@H](CO)c1ccccc1	(8-methyl-8-azabicyclo[3.2.1]octan-3-yl) (2R)-3-hydroxy-2-phenylpropanoate
10		TA 10	O=C(OC1C[C@@H]2CC[C@H](C1)N2C)C(CO)c1ccccc1	[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl] 3-hydroxy-2-phenylpropanoate

All of the 10 analogues of Atropine were selected using QSAR Toolbox.

Chemsketch

ChemSketch is a program created by ACD/Labs that helps users draw and view molecules, chemical reactions, and lab-related diagrams on a computer.

All of the 10 analogues of Atropine were drawn using Chem sketch.

Molinspiration

Molinspiration is used to evaluating drug-likeness using Lipinski's Rule of Five.

Table 4

Sl No.	COMPOUND CODE	MOLECULAR WEIGHT	No. of H BOND ACCEPTORS	No. of H BOND DONORS	LOG P VALUE	No of VIOLATIONS
1.	TA 1	317.38	5	1	1.42	0
2.	TA 2	303.36	5	1	1.05	0
3.	TA 3	289.38	4	1	1.77	0
4.	TA 4	303.36	5	1	1.05	0
5.	TA 5	303.36	5	1	1.05	0
6.	TA 6	275.35	4	1	1.78	0
7.	TA 7	303.36	5	1	1.05	0
8.	TA 8	303.40	4	1	2.56	0
9.	TA 9	289.38	4	1	1.77	0
10.	TA 10	289.38	4	1	1.77	0

The drug likeness properties of proposed derivatives were determined by Molinspiration.

Pass (Prediction of Activity Spectra for Substances)

PASS Online is a **web-based tool** that predicts the **biological activity spectrum** of chemical compounds based on their structural formula where Pa indicates probability to be active and Pi indicate probability to be inactive.

Table 5

COMPOUND CODE	PASS VALUE			
	SPASMOLYTIC		ANTIPARKINSONISM	
	Pa	Pi	Pa	Pi
TA 1	0,967	0,003	0,986	0,001
TA 2	0,970	0,003	0,933	0,001
TA 3	0,959	0,003	0,964	0,001
TA 4	0,970	0,003	0,933	0,001
TA 5	0,970	0,003	0,933	0,001
TA 6	0,949	0,003	0,707	0,003
TA 7	0,970	0,003	0,933	0,001
TA 8	0,846	0,004	0,733	0,003
TA 9	0,959	0,003	0,964	0,001
TA 10	0,959	0,003	0,964	0,001

Pass (Prediction of Activity Spectra for Substances) values for the above compounds showed that they possess spasmolytic and antiparkinsonism activity.

ADMETlab 3.0

ADMETlab 3.0 is used for predicting absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of chemical compounds.

1) ABSORPTION

Table 6

Compound Code	PROPERTY	VALUE	DECISION	COMMENT
TA 1	Caco-2 Permeability	-4.834	🟢	Optimal: higher than -5.15 Log unit
	MDCK Permeability	-4.858	🔴	low permeability: < 2 × 10-6 cm/s medium permeability: 2-20 × 10-6 cm/s high passive permeability: > 20 × 10-6 cm/s
TA 2	Caco-2 Permeability	-4.853	🟢	Optimal: higher than -5.15 Log unit
	MDCK	-4.864		low permeability: < 2 × 10-6

🔴

	Permeability			cm/s medium permeability: 2-20 × 10-6 cm/s high passive permeability: > 20 × 10-6 cm/s
TA 3	Caco-2 Permeability	-4.707		Optimal: higher than -5.15 Log unit
	MDCK Permeability	-4.776		low permeability: < 2 × 10-6 cm/s medium permeability: 2-20 × 10-6 cm/s high passive permeability: > 20 × 10-6 cm/s
TA 4	Caco-2 Permeability	-4.925		Optimal: higher than -5.15 Log unit
	MDCK Permeability	-5.108		low permeability: < 2 × 10-6 cm/s medium permeability: 2-20 × 10-6 cm/s high passive permeability: > 20 × 10-6 cm/s
TA 5	Caco-2 Permeability	-4.925		Optimal: higher than -5.15 Log unit
	MDCK Permeability	-5.108		low permeability: < 2 × 10-6 cm/s medium permeability: 2-20 × 10-6 cm/s high passive permeability: > 20 × 10-6 cm/s
TA 6	Caco-2 Permeability	-4.8		Optimal: higher than -5.15 Log unit
	MDCK Permeability	-4.799		low permeability: < 2 × 10-6 cm/s medium permeability: 2-20 × 10-6 cm/s high passive permeability: > 20 × 10-6 cm/s
TA 7	Caco-2 Permeability	-4.83		Optimal: higher than -5.15 Log unit
	MDCK Permeability	-4.846		low permeability: < 2 × 10-6 cm/s medium permeability: 2-20 × 10-6 cm/s high passive permeability: > 20 × 10-6 cm/s
TA 8	Caco-2 Permeability	-4.915		Optimal: higher than -5.15 Log unit
	MDCK Permeability	-4.889		low permeability: < 2 × 10-6 cm/s medium permeability: 2-20 ×

				10-6 cm/s high passive permeability: > 20 × 10-6 cm/s
TA 9	Caco-2 Permeability	-4.828		Optimal: higher than -5.15 Log unit
	MDCK Permeability	-5.003		low permeability: < 2 × 10-6 cm/s medium permeability: 2-20 × 10-6 cm/s high passive permeability: > 20 × 10-6 cm/s
TA 10	Caco-2 Permeability	-4.707		Optimal: higher than -5.15 Log unit
	MDCK Permeability	-4.776		low permeability: < 2 × 10-6 cm/s medium permeability: 2-20 × 10-6 cm/s high passive permeability: > 20 × 10-6 cm/s

Caco-2 Permeability and MDCK Permeability of all the 10 analogues were determined.

2) DISTRIBUTION

Table 7

COMPOUND CODE	PROPERTY	VALUE	DECISION	COMMENT
TA 1	VDss	0.539		Volume Distribution Optimal: 0.04-20L/kg
	BBB	0.007		Blood-Brain Barrier Penetration Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
TA 2	VDss	0.564		Volume Distribution Optimal: 0.04-20L/kg
	BBB	0.005		Blood-Brain Barrier Penetration Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
TA 3	VDss	0.591		Volume Distribution Optimal: 0.04-20L/kg
	BBB	0.047		Blood-Brain Barrier Penetration Category 1: BBB+; Category 0: BBB-;

				The output value is the probability of being BBB+
TA 4	VDss	0.426		Volume Distribution Optimal: 0.04-20L/kg
	BBB	0.0		Blood-Brain Barrier Penetration Category 1: BBB+; Category 0: BBB-; The output value is the probability of being BBB+
TA 5	VDss	0.481		Volume Distribution Optimal: 0.04-20L/kg
	BBB	0.002		Barrier Penetration Category 1: Blood-Brain BBB+; Category 0: BBB-; The output value is the probability of being BBB+
TA 6	VDss	0.666		Volume Distribution Optimal: 0.04-20L/kg
	BBB	0.157		Barrier Penetration Category 1: Blood-Brain BBB+; Category 0: BBB-; The output value is the probability of being BBB+
TA 7	VDss	0.524		Volume Distribution Optimal: 0.04-20L/kg
	BBB	0.003		Barrier Penetration Category 1: Blood-Brain BBB+; Category 0: BBB-; The output value is the probability of being BBB+
TA 8	VDss	0.587		Volume Distribution Optimal: 0.04-20L/kg
	BBB	0.961		Barrier Penetration Category 1: Blood-Brain BBB+; Category 0: BBB-; The output value is the probability of being BBB+
TA 9	VDss	0.554		Volume Distribution Optimal: 0.04-20L/kg

	BBB	0.023		Barrier Penetration Category 1: Blood-Brain BBB+; Category 0: BBB-; The output value is the probability of being BBB+
TA 10	VDss	0.591		Volume Distribution Optimal: 0.04-20L/kg
	BBB	0.047		Barrier Penetration Category 1: Blood-Brain BBB+; Category 0: BBB-; The output value is the probability of being BBB+

Volume of Distribution at Steady State (VDss) and blood brain barrier (BBB) of all the 10 analogues were determined.

3) METABOLISM

Table 8

COMPOUND CODE	PROPERTY	VALUE	DECISION	COMMENT
TA 1	CYP1A2 inhibitor	0.0		Category 1: Inhibitor; Category 0: Non-inhibitor The output value is the probability of being inhibitor
TA 2	CYP1A2 inhibitor	0.0		Category 1: Inhibitor; Category 0: Non-inhibitor The output value is the probability of being inhibitor
TA 3	CYP1A2 inhibitor	0.0		Category 1: Inhibitor; Category 0: Non-inhibitor The output value is the probability of being inhibitor
TA 4	CYP1A2 inhibitor	0.0		Category 1: Inhibitor; Category 0: Non-inhibitor The output value is the probability of being inhibitor
TA 5	CYP1A2 inhibitor	0.0		Category 1: Inhibitor; Category 0: Non-inhibitor. The output value is the probability of being inhibitor
TA 6	CYP1A2 inhibitor	0.0		Category 1: Inhibitor; Category 0: Non-inhibitor The output value is the probability of being inhibitor
TA 7	CYP1A2	0.0		Category 1: Inhibitor;

	inhibitor			Category 0: Non-inhibitor The output value is the probability of being inhibitor
TA 8	CYP1A2 inhibitor	0.0		Category 1: Inhibitor; Category 0: Non-inhibitor The output value is the probability of being inhibitor
TA 9	CYP1A2 inhibitor	0.0		Category 1: Inhibitor; Category 0: Non-inhibitor The output value is the probability of being inhibitor
TA 10	CYP1A2 inhibitor	0.0		Category 1: Inhibitor; Category 0: Non-inhibitor The output value is the probability of being inhibitor

CYP1A2 inhibiting activity of all the 10 analogues were determined.

4) EXCRETION

Table 9

COMPOUND CODE	PROPERTY	VALUE	DECISION	COMMENT
TA 1	CL_{plasma}	10.122		**.** The unit of predicted CLplasma penetration is ml/min/kg. >15 ml/min/kg: high clearance;5-15 ml/min/kg: moderate clearance; < 5 ml/min/kg: low clearance
TA 2	CL_{plasma}	12.329		**.** The unit of predicted CLplasma penetration is ml/min/kg. >15 ml/min/kg: high clearance;5-15 ml/min/kg: moderate clearance; < 5 ml/min/kg: low clearance
TA 3	CL_{plasma}	10.678		**.** The unit of predicted CLplasma penetration is ml/min/kg. >15 ml/min/kg: high clearance;5-15 ml/min/kg: moderate clearance; < 5 ml/min/kg: low clearance
TA 4	CL_{plasma}	15.054		**.** The unit of predicted CLplasma penetration is ml/min/kg. >15 ml/min/kg: high clearance;5-15 ml/min/kg: moderate clearance; < 5 ml/min/kg: low clearance
TA 5	CL_{plasma}	9.439		**.** The unit of predicted CLplasma penetration is ml/min/kg. >15 ml/min/kg: high clearance;5-15 ml/min/kg: moderate clearance; < 5 ml/min/kg: low clearance
TA 6	CL_{plasma}	8.776		**.** The unit of predicted CLplasma penetration is ml/min/kg. >15 ml/min/kg: high clearance;5-15

				ml/min/kg: moderate clearance; < 5 ml/min/kg: low clearance
TA 7	CL_{plasma}	9.641		**.** The unit of predicted CLplasma penetration is ml/min/kg. >15 ml/min/kg: high clearance;5-15 ml/min/kg: moderate clearance; < 5 ml/min/kg: low clearance
TA 8	CL_{plasma}	11.082		**.** The unit of predicted CLplasma penetration is ml/min/kg. >15 ml/min/kg: high clearance;5-15 ml/min/kg: moderate clearance; < 5 ml/min/kg: low clearance
TA 9	CL_{plasma}	10.627		**.** The unit of predicted CLplasma penetration is ml/min/kg. >15 ml/min/kg: high clearance;5-15 ml/min/kg: moderate clearance; < 5 ml/min/kg: low clearance
TA 10	CL_{plasma}	10.678		**.** The unit of predicted CLplasma penetration is ml/min/kg. >15 ml/min/kg: high clearance;5-15 ml/min/kg: moderate clearance; < 5 ml/min/kg: low clearance

Plasma clearance (CL_{plasma}) of all the 10 analogues were determined.

PROTOX 3.0

PROTOX 3.0 is used to predict the toxicological profile of molecules using advanced computational models.

Table 10

COMPOUND CODE	TARGET	PREDICTION	PROBABILITY
TA 1	Hepatotoxicity	Inactive	0.93
	Carcinogenicity	Inactive	0.62
	Mutagenicity	Inactive	0.64
	BBB-barrier	Active	0.76
TA 2	Hepatotoxicity	Inactive	0.97
	Carcinogenicity	Inactive	0.75
	Mutagenicity	Inactive	0.88
	BBB-barrier	Active	0.77
TA 3	Hepatotoxicity	Inactive	0.98
	Carcinogenicity	Inactive	0.86
	Mutagenicity	Inactive	0.76
	BBB-barrier	Active	0.99
TA 4	Hepatotoxicity	Inactive	0.98
	Carcinogenicity	Inactive	0.86
	Mutagenicity	Inactive	0.76
	BBB-barrier	Active	0.99
TA 5	Hepatotoxicity	Inactive	0.97

	Carcinogenicity	Inactive	0.75
	Mutagenicity	Inactive	0.88
	BBB-barrier	Active	0.77
TA 6	Hepatotoxicity	Inactive	0.96
	Carcinogenicity	Inactive	0.73
	Mutagenicity	Inactive	0.73
	BBB-barrier	Active	0.99
TA 7	Hepatotoxicity	Inactive	0.96
	Carcinogenicity	Inactive	0.81
	Mutagenicity	Inactive	0.71
	BBB-barrier	Active	0.94
TA 8	Hepatotoxicity	Inactive	0.96
	Carcinogenicity	Inactive	0.81
	Mutagenicity	Inactive	0.77
	BBB-barrier	Active	0.99
TA 9	Hepatotoxicity	Inactive	0.98
	Carcinogenicity	Inactive	0.86
	Mutagenicity	Inactive	0.76
	BBB-barrier	Active	0.99
TA 10	Hepatotoxicity	Inactive	0.98
	Carcinogenicity	Inactive	0.86
	Mutagenicity	Inactive	0.76
	BBB-barrier	Active	0.99

Hepatotoxicity, Carcinogenicity, Mutagenicity and the ability to cross the BBB-barrier of all the 10 analogues were determined.

CONCLUSION

This study successfully explored the potential of computational tools in the design and evaluation of novel tropane alkaloid analogues particularly focusing on atropine and its derivations. Through an in-depth study of the structural chemistry, biosynthesis and pharmacological relevance of tropane alkaloids, atropine was identified as a valuable template for analogue development due to its diverse therapeutic applications.

The application of various in silico tools such as QSAR Toolbox, Chem Sketch, Mol inspiration, PASS, ADMET Lab 3.0 and PROTOX 3.0 enabled a comprehensive assessment of the analogues drug likeness, biological activity, ADMET properties and toxicity profiles.

All 10 designed analogues adhered to Lipinski's rule of five, showed promising biological activities including spasmolytic and antiparkinsonism effects and demonstrated favourable absorption, distribution, metabolism and excretion characteristics. Importantly none of the analogues were predicted to exhibit mutagenic, carcinogenic or hepatotoxic effects, indicating a strong safety profile.

The integration of computational methods in this study highlights their value in streamlining drug discovery by predicting pharmacokinetics and toxicological profiles early in the design phase. This not only reduces the need of animal testing but also accelerates the identification of promising therapeutic candidates. The findings affirm the significant potential of tropane-based molecules and support further experimental validation to confirm their efficacy and safety for clinical applications.

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