IJMPR 2025, 9(9), 22-43

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article

SJIF Impact Factor: 6.669

INTEGRATING STRUCTURAL ANALYSIS COMPUTATIONAL DESIGN AND AI ASSISTED SYNTHESIS OF CARDIAC GLYCOSIDE ANALOGUES

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Article Received on: 13/07/2025

Article Revised on: 02/08/2025

Article Accepted on: 21/08/2025

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ABSTRACT

Cardiac glycosides are a class of naturally derived compounds with potent therapeutic effects, particularly in the treatment of heart failure and arrhythmias. However, their narrow therapeutic index and potential toxicity necessitate the development of safer, more effective analogues. This study presents an integrated approach combining structural analysis, computational design, and AI-assisted synthesis to innovate and optimize cardiac glycoside analogues. Detailed structural elucidation through techniques such as X-ray crystallography, NMR spectroscopy, and molecular docking provides insights into key pharmacophores and structure–activity relationships. Computational modeling and in silico screening, including molecular dynamics simulations and QSAR analyses, guide the rational design of analogues with improved binding affinity and reduced off-target effects. Artificial intelligence tools are employed to predict synthetic pathways, optimize reaction conditions, and accelerate lead compound generation. This multidisciplinary strategy enhances the efficiency of drug discovery, reduces development time, and increases the likelihood of identifying novel analogues with better therapeutic profiles. The integrated platform outlined in this work holds promise for advancing cardiac glycoside research and developing next-generation cardiovascular therapeutics.

KEYWORDS: Anti arrhythmic, Artificial Intelligence, Cardiac Glycoside, Digoxin.

1.INTRODUCTION

History and background of Natural products

The earliest records of natural products were depicted on clay tablets in cuneiform fromMesopotamia (2600 B.C.) which documented oils from Cupressus sempervirens (Cypress) and Commiphora species (myrrh) which are still used today to treat coughs, colds and inflammation. Myrrh can be defined as an oleo-gum resin produced by different *Commiphora* species. It is constituted by 3–4% impurities, 7–17% volatile oils, 25–40% alcohol soluble resins, and 57– 61% water soluble gum. Myrrh resin constituents soluble in alcohol are commiphorinic acids, commiphoric acids, commiferin, heerabomyrrhols, and heeraboresene.Natural products chemistry has originated from mankind's curiosity about colour, taste, odour,and cures for human, animal and plant diseases. The term natural product is applied to materials derived from plants, microorganisms, invertebrates and vertebrates. Natural products include alkaloid, steroids, terpenoids, amino acids, proteins, carbohydrates, lipids nucleic acids, vitamins, hormones, insect and plant growth regulators, natural pigments and dyes etc. For centuries people have revered the extraordinary medicinal properties of garlic (Allium sativum, Linn). The Babylonian used to treat disease as early as 3000 BC. In Egypt, garlic was supposed to be powerful restorative. A decoction of garlic in milk was given in hysteria, sciatica and heart disease. However, during the last few decades the hypocholesterolaemia properties of garlic have been widely reported. sulfur containing compounds Alliin and Allicin have been shown to lower cholesterol levels in cholesterol fed as well as normal rats and other species. Plants have been used for centuries for the treatment of heart problems, the most important being the foxgloves Digitalis purpurea and the latest species and Strophanthus gratus containing active principles digitalin and ouabain respectively. The latex of the upas tree Antiaris toxic (cardiac glycoside) was used in Java, cardiotonic properties.[1]

problem with synthetic products

1. Environmental Impact:The production and disposal of synthetic materials can have significant environmental consequences, including pollution and contribution to plastic waste. Many polymers are nonbiodegradable.

2. Health Concerns: Some synthetic materials can release harmful chemicals during production or degradation.

3. Limited Thermal Stability: Certain synthetic materials may degrade at high temperatures, limiting their use in applications where heat resistance is required.

4. Aesthetic Limitations: While many synthetic materials can mimic natural materials, they may lack the aesthetic qualities, texture, or feel that some consumers prefer in products like clothing or furniture.

5. Dependency on Fossil Fuels: Many synthetic polymers are derived from petrochemicals, leading to concerns about sustainability and reliance on fossil fuels.

6. Recycling Challenges:While some synthetic materials can be recycled, the recycling processes can be complex and not all types of synthetic materials are accepted in recycling programs.[2]

Classification of natural products

1. Primary metabolites- Primary metabolites are the compounds that are directly involved in the metabolic pathways of an organism necessary for its growth, development, and reproduction. Example: Carbohydrates, amino acids, nucleic acids, lipids, peptides etc.

2. Secondary metabolites - Secondary metabolites are the organic compounds that are produced by various organisms that are not directly involved in the growth, development, or reproduction of the organism.example: terpenoids and steroids, fatty acids, alkaloids, no ribosomal, enzyme cofactor[1]

Among natural product Glycosides is one of the several components found in these plants, have distinguished themselves as an intriguing class of substances with tremendous potential as therapeutic intervention. Glycosides have unique physicochemical features due to the complex interaction between glycone and aglycone, which makes it easier for them to interact with biological systems. The intricate connectedness between the glycone and aglycone is further highlighted by the glycosidic linkages, which include S-, N-, C-, and O-glycosidic bonds. This connectivity affects the biological activity and stability of the molecules. The therapeutic potential of glycosides derived from medicinal plants has been the focus of research in recent years. These substances have shown amazing health benefits for a variety of ailments, including antibacterial and anticancer effects as well as anti-inflammatory, cardiovascular, and neurological capabilities. Additionally, the structural variety of glycosides and their capacity for synergistic interactions with other bioactive components found in medicinal plants make their therapeutic uses more complex[3]

Glycoside

Glycosides are the molecules in which a sugar part glycoside is bound to some other nonsugar part Glycosides play numerous important roles in living organisms. Plants store important chemicals in the form of inactive glycosides; if these chemicals are needed, the glycosides are brought in contact with water and an enzyme and the sugar part is broken off, making the chemical available for use. Many such plant glycosides are used as medications. Formally, a glycoside is any molecule in which a sugar group is bonded through its anomeric carbon to another group via a glycosidic bond. A glycosidic bond is a certain type of a functional group that joins alcoholic group of a Carbohydrate molecule to a glycone molecule. A substance containing a glycosidic bond is a Glycoside. The sugar group is known as the glycone and the non-sugar group as the Aglycone or Genin part of the glycoside. The glycone can consist of Single sugar group (Monosaccharide) or Several sugar groups (oligosaccharide).[4]

History of glycoside

The study of glycosides, particularly plant C-glycosides, dates back to the 19th century, with early isolations like aloin and scoparin in 1851. The first glycoside identified; amygdalin isolated from almonds in 1830 by French Chemist Pierre Robiquet and Antonie Boutron and Charlard. Structural determination of these early compounds was achieved later, through techniques like NMR spectroscopy in the 1950s. The number of identified plant C-glycosides has grown significantly with advancement in analytical technique over the past four decades[4]

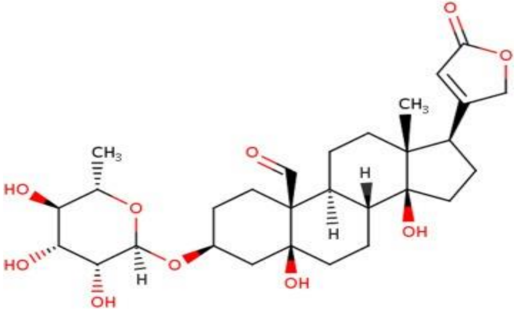
Classification

1. Based on nature of sugar moiety

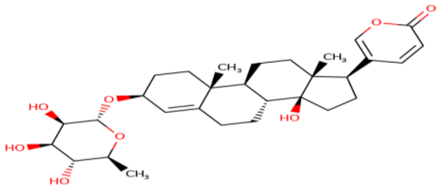
- Glucoside
- Rhamnoside
- Pentoside
- Fructoside
- Arabinoside

Based on nature of lactone ring

1. Cardenolides- these are characterized by butanolides (five membered lactone ring) and are derived from plants. Example-Digoxin .

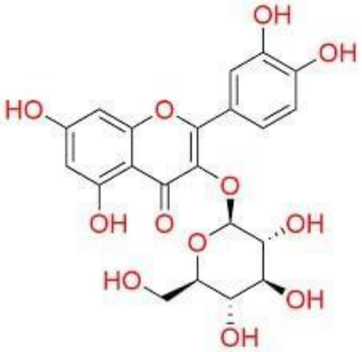


2. Bufadienolides -these are a pyrone ring (six membered) lactone ring and are often found in toad venom and some plant. Example-Bufalin

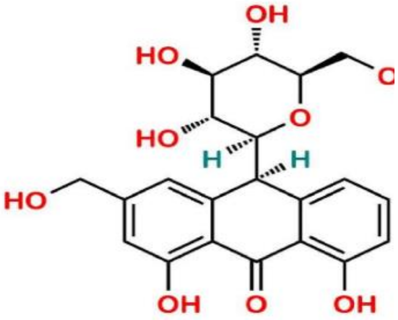


Based on linkage

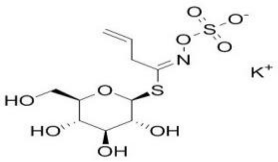
1. O-glycoside -molecule where sugar is linked to a non-sugar compound through a glycosidic bond involving an oxygen atom. Example-Isoquercetin



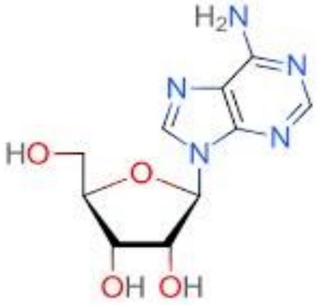
2. C glycoside – where sugar moiety is linked to a non sugar moiety through a carbon carbon bond (C-C).Example Aloin



3. S glycoside – type of glycoside where a sugar molecule is linked to a sulphur atom of the aglycone (non sugar compound) through a glycosidic bond. Example Singrin



4. N-Glycoside- a type of glycoside where sugar molecule (glycone) is linked to a non-sugar (aglycone) with nitrogen bonds especially C-N-C bond.Example Adenosine



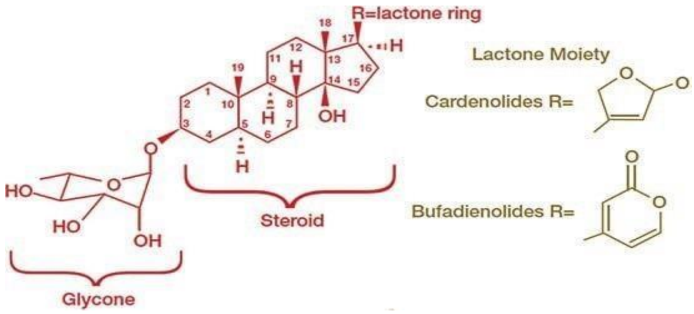
Based on nature of non-sugar moiety

- Anthraquinone glycoside: Senna
- Sterol or cardiac glycoside: digitalis
- Saponin glycoside: liquorice
- Cyanogenic glycoside: Amygdalin
- Isothiocyanate glycoside: sinigrin
- Flavonoid glycoside: citrous bio flavonoid
- Coumarin glycoside: celery fruit
- Phenol glycoside: Arbutin
- Steroidal glycoside
- Lactone glycoside: cantharide[4]

Cardiac glycoside

Cardiac glycosides are widely distributed substances found in nature, produced by different species of plants and amphibians. The leading Cardiac Glycosides in the present review are digoxin. Their chemical structure is very similar, consisting of a steroid ring, a lactone ring with five or six carbons, and a sugar moiety. Cardiac Glycoside known toxicity may restrict its clinical use.[5]

Chemistry



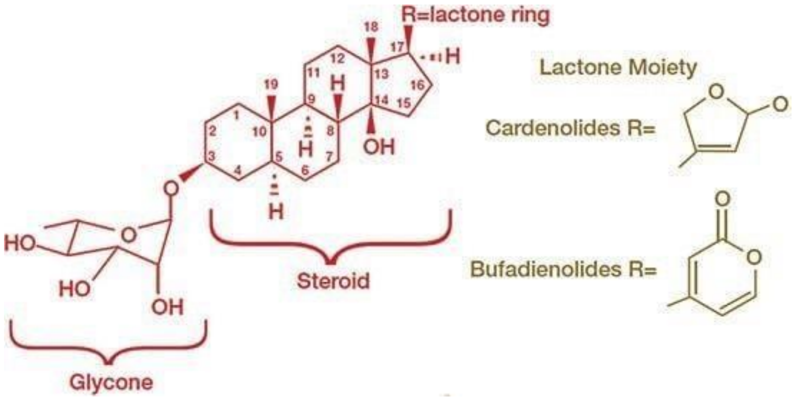
Cardiac glycosides are a large group of secondary compounds widely distributed in nature from different sources with varying applications, yet similar chemical structure. All Cardiac Glycosides have a steroid ring attached to an unsaturated lactone ring in position 17, and most of them are also connected to a sugar moiety in position 3.

These have a pyrone (six-membered lactone) ring at the C-17 position and are often found in toad venoms and some plants. Bufalin is a well-known example of a bufadienolide. These are a subgroup of cardenolides where the double bond in the butanolide ring is at position 21 or 22 instead of 20. Structural features.cardiac glycosides are molecules with a basic structure consisting of a steroid nucleus, a lactone ring, and a sugar moiety. The steroid nucleus is a fused ring system, with a lactone ring attached at position 17, and a sugar group (glycone) linked through a hydroxyl group at position 3. This structure is classified into two main types: cardenolides and bufadienolides, differentiated by the size of the lactone ring.

Cardenolides: Have a five-membered butyrolactone ring.

Bufadienolides: Have a six-membered α-pyrone ring.[5]

SAR of cardenolide



1. Sugar Moiety (Glycone)

- One or more sugar units attached to the steroid nucleus through a glycosidic bond.
- It appears to be important only for partitioning and kinetics of action.
- It possesses no biologic activity.
- Deoxy sugars are more potent than those with fully oxygenated sugars.
- The sugar moieties as such have no digitalis like activity but when attached to the 3OH of the steroid, can modify greatly activity of the parent.
- The sugar such as rhamnose can increase the potency but mannose had no effect on potency and certain substituted sugar decrease the activity.

2. Steroid Nucleus: A cyclopentanoperhydrophenanthrene nucleus, a four-ring system.

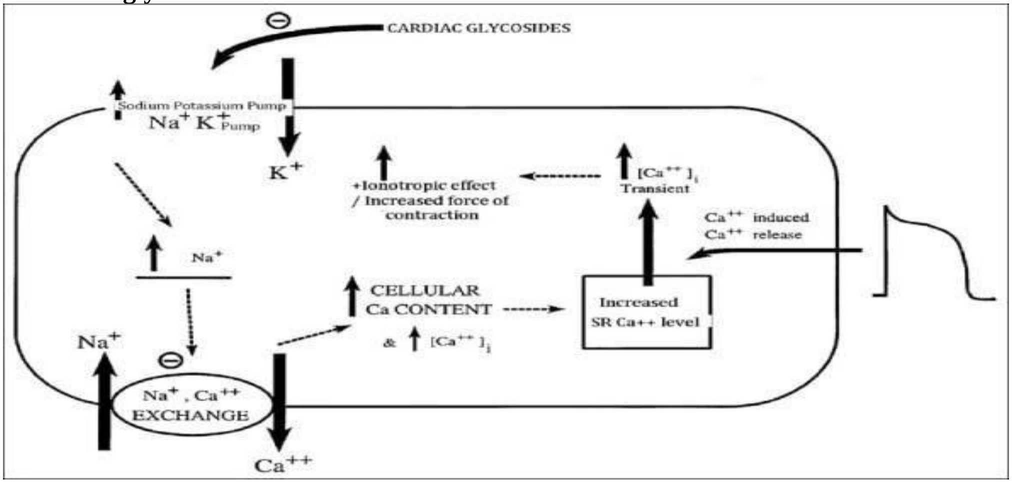
- It has a unique set fused ring system that makes the aglycone moiety structurally distinct from the other common

3. Steroid ring system

- The ring junctions are cis trans cis fusion and give a “U” shaped skeleton which give more binding.
- The steroid nucleus has hydroxyl group at third and fourteenth position of which the sugar attachment uses the 3-OH group. The 14th OH group is unsubstituted.
- The additional hydroxyl group influences the partitioning of cardiac glycosides into the aqueous media affect the duration of action a quick onset of action.
- Conversion to A/B trans system leads to marked drop-in activity.
- The C/D cis ring seems essential.

- A skeleton without OH group but retaining the CD cis fusion was found to retain activity.
- The longer duration and increased half-life are due to lack of C-12 hydroxy that is present in digoxin. In digoxin the OH serves as a site for metabolism, which reduces the compounds half-life. It gives more hydrophilic character, which results a greater water solubility and ease in renal elimination of systolic contraction. An increase in contractility in the failing heart results in a more complete emptying of a ventricle.[6]

Mechanism of cardiac glycoside

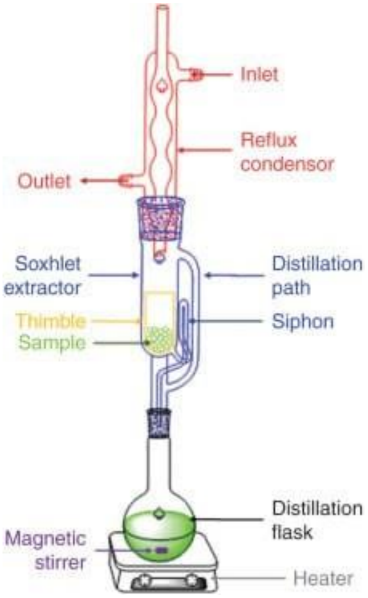


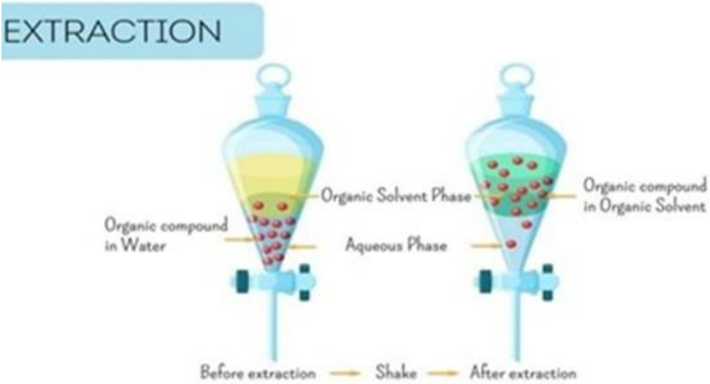
Cardiac glycosides affect the sodium-potassium ATPase pump in cardiac muscle cells to alter their function. Firstly, cardiac glycosides bind to Na+/K+ATPase pump. cardiac glycosides prevent sodium from being pumped out of the cell, leading to a buildup of sodium inside the cardiac cell. The increased sodium inside the cell indirectly affects.

calcium levels. The sodium-calcium exchanger (Na/Ca exchanger) is responsible for transporting calcium out of the cell in exchange for sodium. With increased sodium, the Na/Ca exchanger's ability to remove calcium is reduced, resulting in an increase in intracellular calcium. The increased calcium within the cell triggers the muscle contraction process, leading to stronger and more forceful heart muscle contractions. This results in a higher stroke volume (amount of blood pumped with each beat) and increased cardiac output (total amount of blood pumped per minute). Cardiac glycosides also indirectly affect heart rate. They stimulate the vagus nerve, which slows down conduction through the SA and AV nodes, resulting in a decreased heart rate.[7]

Isolation

Statts otto method:





The Stas-Otto method is a process used for isolating glycosides from plant materials. It involves extracting the plant material with alcohol in a Soxhlet apparatus, then purifying the extract through various steps like lead acetate precipitation, distillation, and chromatography. The method is particularly useful for isolating glycosides that are sensitive to heat or other harsh extraction conditions.

1. Extraction: The plant material, finely powdered, is extracted using a Soxhlet apparatus with alcohol or a suitable solvent. During this process, various enzymes present in plant parts are also deactivated due to heating. The thermolabile glycosides should be extracted at temperature below 45°C.

2. Purification:The extract is then purified through various steps, including:Chromatography: Techniques like chromatography are employed to separate and isolate the pure glycoside.

3. Characterization:The isolated glycoside is then characterized using various spectroscopic methods like UV, IR, NMR, and mass spectroscopy to determine its molecular structure.

Thin-Layer Chromatography (TLC): TLC can be used to confirm the purity and identity of the glycosides.

the following stages:
(1) the solvent penetrates into the solid matrix.
(2) the solute dissolves in the solvents.
(3) the solute is diffused out of the solid matrix.
(4) the extracted solutes are collected.[8]

Identification test for cardiac glycoside[8]

Experiment	Observations	Inference
1. Raymonds test To the drug add a few ml of 50% ethanol and 0.1 ml of 1% of dinitrobenzene in	violet colours appear	This is due to presence of active methylene group
ethanol. To this solution, add 2-3 drops of sodium hydroxide solution		
2. To the drug add few ml of pyridine and 2 drops of nitroprusside and a drop of 20% sodium hydroxide solution	A deep red colour is produced	
3. Xanthydrol test The crude is heated with 0.1-5% of xanthydrol in glacial acetic acid containing 1% hydrochloric acid	A red colour is produced	Presence of deoxy sugar
4. Baljet test Take piece of lamina or thick section of leaf. Add sodium picrate reagent	Yellow to orange colour	Presence of glycoside
5. kedde test A solution of glycoside is treated with kedde's reagent (mix equal volume of 2% solution of 3,5 dinitro benzoic acid in methanol and 7.5% aqueous solution of KOH)	Development of blue or violet colour that faded away in 1 to 2 hr	Presence of cardenolide
5. Antimony	Appearance of blue or violet	Presence of cardenolides and

trichloride test To a solution of glycoside add a solution of Antimony trichloride and trichloro acetic acid and then heat the mixture	colour	bufadienolides
6. Keller killiani test Glycoside is dissolved in a mixture of 1% ferric sulphate in 5% glacial acetic acid. Add one to two drops of concentrated sulphuric acid.	A blue colour develops	Presence of deoxy sugar

USES: Cardiac glycosides constitute a diverse family of naturally derived compounds widely known for their ability to bind to and inhibit the sodium pump.

- Members of this family have been used in the clinic for many years for the treatment of heart failure and atrial arrhythmia.
- Recent findings report additional signalling modes of action of the sodium pump and implicate cardiac glycosides in the regulation of several important cellular processes, including gene expression profiling, apoptosis, proliferation and cell–cell interactions.
- Cancer cells are more vulnerable to the effects of these compounds compared with normal cells. The increased susceptibility of cancer cells to these compounds supports their potential use as novel antineoplastic agents.
- Early epidemiological studies in patients with heart failure under cardiac glycoside treatment revealed the potential use of these drugs as novel antineoplastic agents.
- Accumulating studies from the past decade verify the anticancer effects of these drugs both *in vitro* and *in vivo*. The first generation of cardiac-glycoside-based anticancer drugs is currently in clinical trials (for example, Anvirzel and UNBS1450).
- Novel insights into the mode of action of these drugs reveal potential therapeutic uses of these drugs for the treatment of several diseases, including cystic fibrosis,[9]

INSILICO DESIGN: Commonly known as Computer aided drug design, involves using computational techniques and models to identify drug likeness property of the molecule. ACD/Chemsketch, SMILES, Molinspiration, PASS is used. Chemsketch is used for drawing chemical structures and calculating molecular properties. Simplified Molecular Input Line Entry Sytem (SMILES) are a combination of text symbols that represent atoms, bonds and ring closure. Molinspiration is a cheminformatics software that offers a range of tools for molecule manipulation and processing. PASS ONLINE predicts over the 4000 kinds of biologic activity, including pharmacological effects, mechanism of action.

AI ASSISTED SYNTHESIS:AI has emerged as a transformative technology in the field of drug discovery and pharmaceutical research. It is aid to design and optimization of chemical synthesis. We used IBM ROBO RXN for the AI assisted synthesis.

Structural elucidation

- Empirical formula: C, H, O, N, S, P
- Molecular formula:$C_{41}H_{64}O_{14}$
- acetylated product is obtained by acetylation of OH group at C3 position
- Glycoside on degradation by hydrolysis with dilute acid, sugar and aglycone parts are separated

1) Elucidation of sugar part-size of the sugar bond is elucidated by
   a) Methylation method
   b) Periodate method

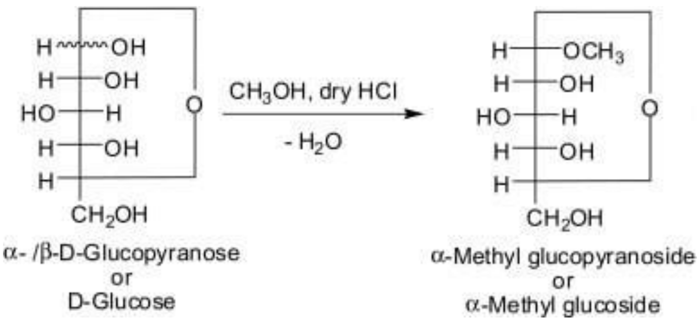
Methylation Method

Sugar part is first methylated, then it is subjected to hydrolysis by dilute HCL, When only the glycosidic methyl group is hydrolysed and the product is oxidised. If the oxidation product is identified, the ring size can be determined.

1. Purdie’s Method
2. Haworth’s Method
3. Diazomethane Method
4. P-Toluene Method
5. Sodium Methyl Iodide Method

1. Purdie’s Method

When the sugar is heated with methanol in the presence of HCL gas, methyl glycoside is obtained, which is then heated with methyl iodide and dry silver oxide in methanol solution.



Disadvantage: this applied only to glycosides without a reducing group, as methylation of a free reducing sugar leads to its oxidation by silver oxide.

It can be used for such sugars for which suitable solvents are known.

2. Haworth’s Method

Dimethyl sulphate and aqueous NAOH are added to a solution, the resulting solution remains neutral

$CHOH+(CH_3)_2SO_4+NAOH \rightarrow CHOCH_3+CH_3NaSO_4+H_2O$

Disadvantage: dimethyl sulphate is poisonous

3. Diazomethane Method

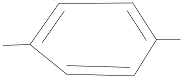
It is used for the methylation of hydroxy compound in alcohol ethereal solution

$R\text{-}OH+CH_2N_2 \rightarrow R\text{-}O\text{-}CH_3+N_2$

It is mainly used for the methylation of acidic OH group.

4. P-Toluene Method

Also known as tosylation

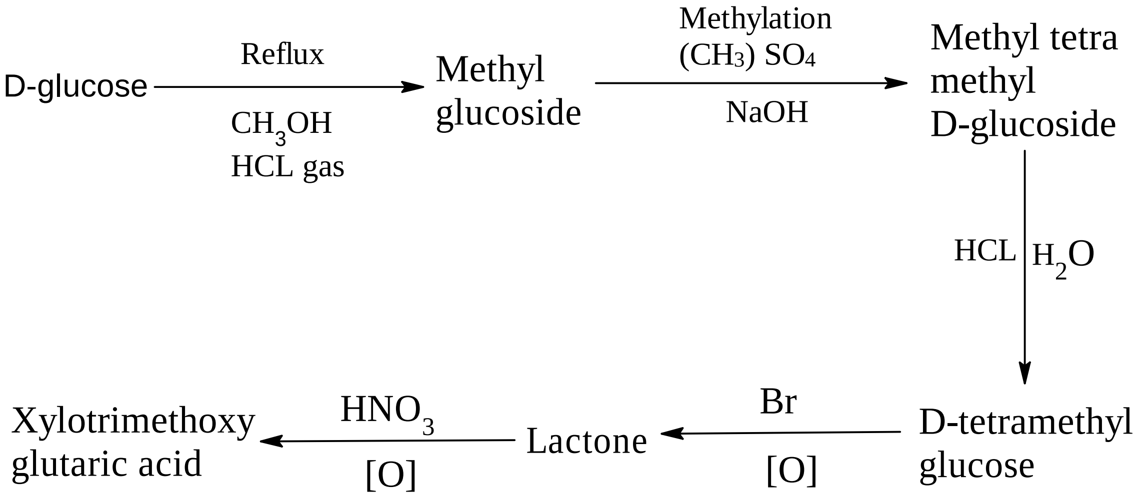
R-OH + H3C  SO3CH3 +NaOH ⟶ R-OCH3 +H2O+ CH3-C6H4-SO3Na

5. Sodium Methyl Iodine Method

Compound is treated with Na and CH3I in liquor ammonia.

After methylation the ring size is determined. It can be determined by Haworth’s method for pyranose (6membere ring) and Hirst method for furanose (five membered ring)

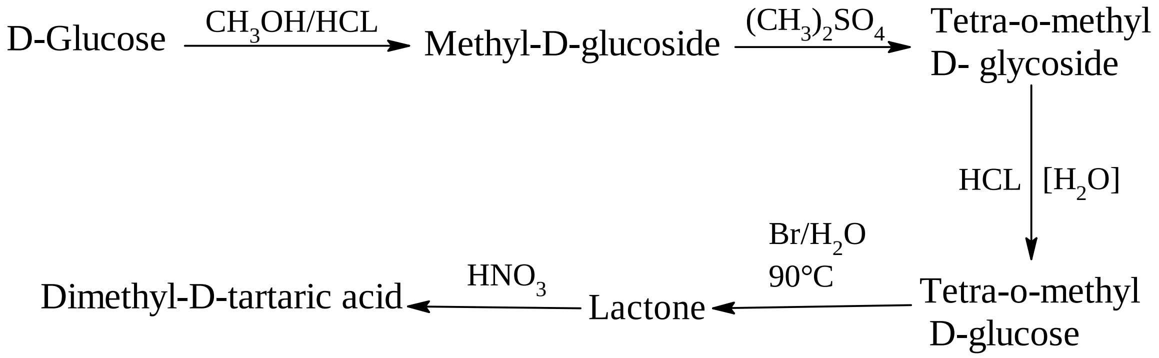
Pyranose Ring Structure Determination:



The compound D-tetramethyl is debaric acid. In compound lactone, one COOH group forms a lactone ring, while the other comes from a non-methylated CHOH group.

The lactone ring has 3-methoxyl groups, indicating that C5 is involved in the ring formation. This confirms that glucose, as well as other hexoses and pentoses have a pyranose structure.

Furanose Ring Structure Determination:



Fisher prepared Methyl D- Glucoside by dissolving glucose in CH_3OH followed by addition of 1% HCL at 0°C to produce Methyl γ glucoside, which contain a mixture of Methyl α and ß glucofuranoside.

From the backward reaction, we conclude that 1 is methyl D glucoside and A is D-glucofuranose.

Therefore, the glucose itself existing in pyranose (1,5) or furanose (1,4).so it has been confirmed that hexoses and pentoses gives methyl glycoside possessing a furanose structure when prepared at 0°C.

Periodate Method
Used to determine both the ring size and configuration at positions of glycosidic linkage.

Methyl D-glucoside was oxidised with periodic acid, two moles of periodic acid were consumed and one mole of formic acid was produced.

Periodic acid has ability to degrade free sugar, but it is unable to open the oxide ring in glycosides.
Eg: hexofuranoside oxidised with periodic acid, it consumes two moles of periodic acid and gives one mole of formaldehyde so it contains 5 membered rings.

If the compound is pentopyranose, it oxidised with periodic acid, it consumes one mole of periodic acid without liberation of formaldehyde, suggesting the ring is 5 membered.

- Furanose ring have more vicinal diols than pyranose ring.
- 5 membered furanose ring have 3 vicinal diols
- 6 membered pyranose rings have 2 vicinal diols
- Glycosidic linkage configuration is determined by enzyme hydrolysis
- ß-glycoside is hydrolysed by emulsin and α-glycoside is hydrolysed by maltase

ELUCIDATION OF STEROID RING

1. Presence of double bond: -Saturated product is formed by the hydrogenation of a compound. It gives an idea about the presence of double bond.
2. Presence of ring structure: -Compound on distillation with selenium at 360° gives Diel’s hydrocarbon.it indicate the presence of phenanthrene nucleus
3. Presence of OH: - compound on acetylation gives acetylated product.it indicates that the presence of OH group.
4. Nature of OH group: -with neutral $FeCl_3$,it gives characteristic colour reaction reveals that the hydroxyl group in phenolic in nature.

Elucidation of lactone ring

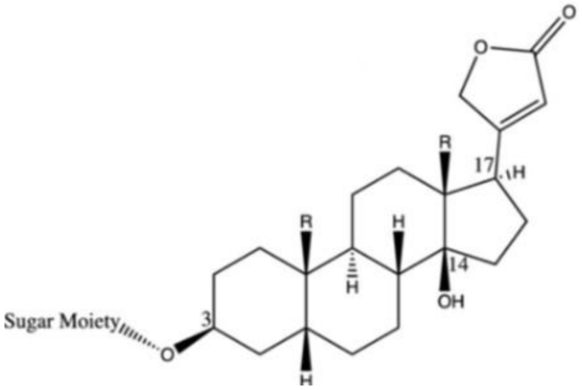
1. Chemical Method

a. Hydrolysis :Lactone ring will be opened on hydrolysis and gives a hydroxy acid.
b. Reduction: Lactone ring of cardiac glycoside undergo reduction to give a saturated product which gives an idea about the unsaturation present in the lactone.

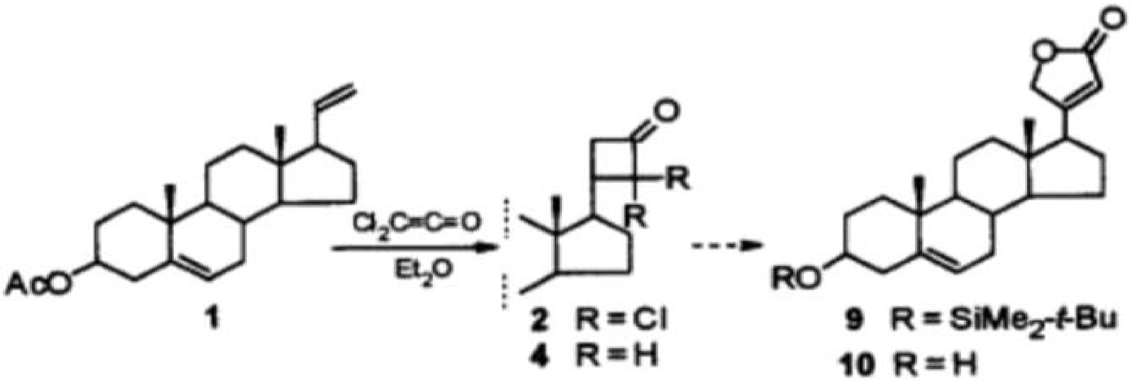
2. Spectroscopic Method

a. UV spectroscopy :The alpha, beta unsaturated lactone shows a characteristic absorption in 220-240 nm.
b. IR spectroscopy :The carboxyl group in the lactone ring shows a strong peak at 1740-1750 cm-1.
c. NMR spectroscopy :HNMR gives the signals for olefinic protons at 6.0-7.0 ppm.

CNMR shows carbonyl carbon lactone at 170-175 ppm.[10]



Synthesis of cardiac glycoside



Step 1: Building the steroid core

Starting materials-Cradenolides synthesis often utilizes readily available steroid precursor like Sandaracopimaric acid or Wieland-Miez. Functionalization is done byspecific functional groups need to be introduced at C14 and C16.This might involve hydroboration-oxidation or other reactions. Butenolides Ring Formation- The characteristic five membered lactone ring at C17 is crucial.it can be formed through a Reformatsky reaction or [2+2] cycloaddition with dichloroketone.

Step 2: Glycosilation

Attaching Sugars: Cardenolides are often glycosylated meaning a sugar molecule is attached. Common sugar include glucose,digitoxose.Modified Koenigs-Knorr procedure:A modified Koenigs-Knorr procedure is often used for glycosylation, where peracetylated glycosyl bromides react with Cardenolides in the presence of a base.Deprotection: After glycosylation, the protecting groups (example acetyl groups) are removed to yield the final Cardenolides glycoside.

STEP 3: Examples of synthetic approaches

Total Synthesis : Research have achieved total synthesis of specific synthesis of specific Cardenolides like Acospectoside A and Acovenoside B,demonstrating the complexity of the synthesis..Diterpene Analogues: synthesis of diterpene analogues of Cardenolides from Sandaracopimaric acid has also been reported 17 beta[11] Butenolide Fragment : Efficient synthesis of the beta butenolides fragments.a key component of cardenolides, has been achieved through [2+2] cycloaddition. Sequential Micheal /Aldol Reactions: A new stratergy

MATERIAL AND METHODS

SOFTWARE USED	USAGE
ACD/Chemsketch	To draw 2-d structure
SMILES (Simplified Molecular Input Line Entry System)	To translate a chemical’s 3-D structure into a string of symbols that is easily understood by computer software
Molinspiration	To calculate drug likeliness property
PASS (Prediction of activity spectra for substance)	To predict the activity
IBM ROBO RXN	To predict retro synthetic pathway

ACD/Chemsketch Is a molecular modelling programme used to create and modify images of chemical structure. Also, there is a software (chem 3-D) that allows molecules and molecular models displayed in two or three dimensions, to understand the structure of chemical bonds and nature of functional groups. It is the product of advanced chemistry development laboratories. This program offers some advanced features that allows the molecules rotate and apply colour to improve visualization. It has several templates with ions and functional groups with the possibility to add text and use other tools to optimize productions created by the software names of organic molecules as well as Lewis Structure, 3D Structure, Space Filling Models, or Ball and Stick Models.[12]

Molinspiration offers broad range of cheminformatics software tools supporting molecule manipulation and processing including SMILES and SD file conversion, normalization of molecules, generation of tautomer's, molecule fragmentation, calculation of various molecular properties needed in QSAR, molecular modelling and drug design, high-quality molecule depiction, molecular database tools supporting substructure and similarity searches. Our products support also fragmented-based virtual screening, bioactivity prediction, and data visualization.[13]

SMILES Notation is a chemical notation that allows a user to represent a chemical structure in a way that can be used by the computer. SMILES is an easily learned and flexible notation. The SMILES notation requires that you learn a handful of rules. You do not need to worry about ambiguous representations because the software will automatically reorder your entry into a unique SMILES string when necessary. SMILES have five basic syntax rules which must be observed. If basic rules of chemistry are not allowed in SMILES entry, the system will warn the user and ask that the structure be edited or re-entered.[14]

PASS is a computer-aided software tool that predicts the biological activity spectrum of different compounds based on their structure. PASS works on the principle that the biological activity of a compound equates its structure. To obtain the expected biological activity profile of the compound solely structural / molecular formula is necessary, so prediction is possible even for those virtual structures designed in the computer but not synthesized yet. PASS Online has the ability to predict over 4000 different kinds of biological activities that include therapeutic effects, toxic effects, adverse effects, enzyme interaction, mechanism of action, etc. PASS Online allows its users to identify and denote the potential lead structure out of millions of chemical substances, therefore effortlessly shortening development times for specific drugs or molecular probes for research and analysis. Pa (probability "to be active") evaluates the possibility that the predicted compound belongs to the category of active compounds. Pi (probability "to be inactive") evaluates the possibility that the predicted compound belongs to the category of inactive compounds. Use PASS program before initializing research and synthesis phases[14]

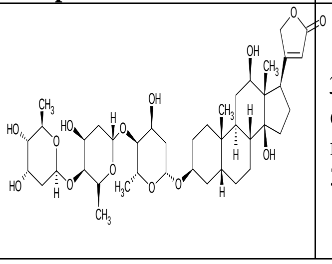
IBM ROBO RXN for chemistry is a pioneer project combining AI, Automation and Cloud to accelerate material discovery. State of the art artificial intelligence architectures are the brain of RoboRXN.Trained to learn the art of synthetic organic chemistry, it automates synthesis procedures by converting chemical recipes to machine-readable instructions.Robotic Chemical Hardware is hardware agnostic. It combines artificial intelligence with a commercially available automation hardware to execute complex sequences of chemical procedures.Cloud Technology is cloud-native by design, making your chemical laboratory accessible from anywhere in the world. RXN is revolutionizing industrial chemistry, by transforming it into a high tech business. The combination of AI, Automation and Cloud relieves the chemist from tedious repetitive tasks, allowing more time and space for what really matters - design and innovation[16,17,18]

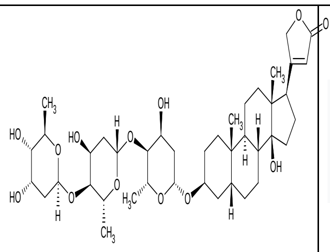
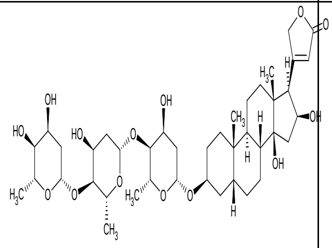
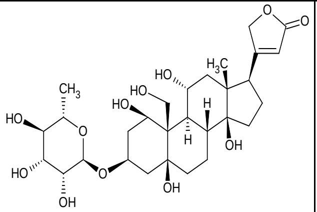
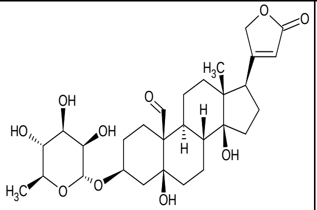
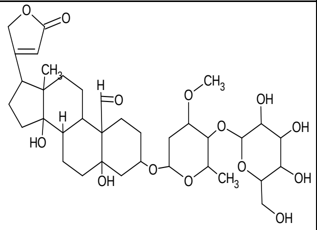
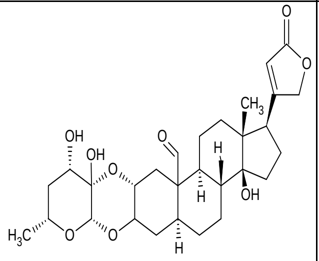
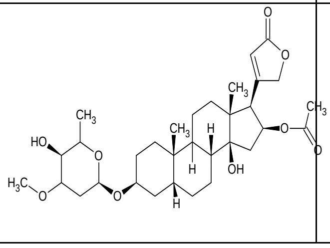
5. RESULTS AND DISCUSSION

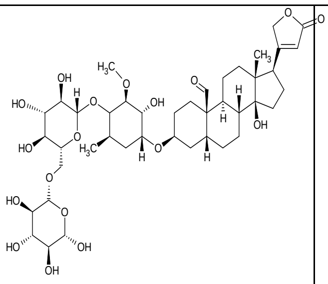
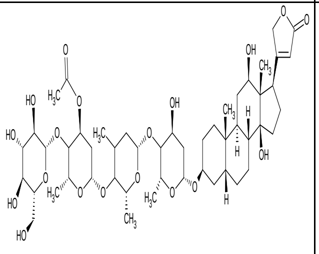
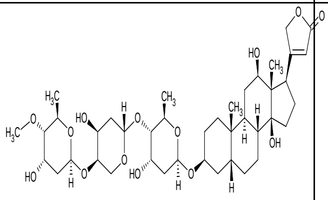
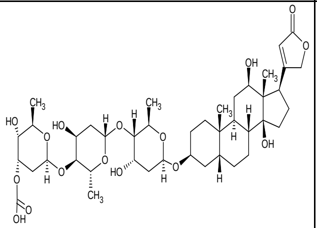
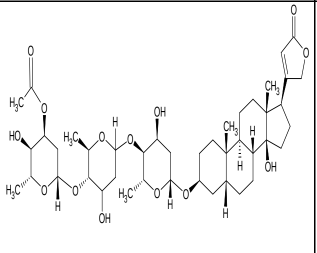
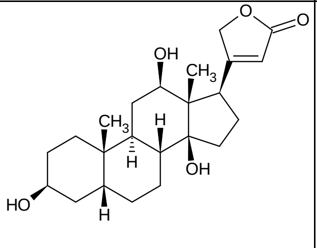
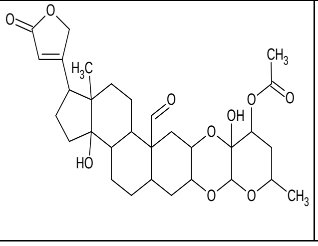
ACD/CHEMSKETCH

The analogues are drawn by ACD/chemsketch

Table no :1 The structure, SMILES and IUPAC names of Cardiac Glycoside analogues

Sl.no.	Name of the compound	Structure of the compound	IUPAC NAME
1.	DIGOXIN		3β-[(O-2,6-dideoxy-β-D-ribo-hexopyranosyl-(1→4)-O-2,6-dideoxy-β-D-ribo-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-ribo-hexopyranosyl) oxy]-12β,14-dihydroxy-5β-card-20(22)-enol ide

2	DIGITOXIN		(3β,5β)-3-[(O-2,6-dideoxy-β-D-ribo-hexapyranosyl-(1->4)-2,6-dideoxy-β-D-ribo-hexopyranosyl) oxy]-14-hydroxycard-20(22)-enol ide
3	GITOXIN		(3β,5β,16β)-3-{[2,6-Dideoxy-β-D-ribo-hexopyranosyl-(1->4)-2,6-dideoxy-β-D-ribo-hexopyranosyl-(1->4)-2,6-dideoxy-β-D-ribo-hexopyranosyl] oxy}-14,16-dihydroxycard-20(22)-enol ide
4	OUBAIN		1β,3β,5β,11α,14,19-Hexahydroxycard-20(22)-enol ide 3-(6-deoxy-α-L-mannopyranoside)
5	CONVALLOTOXIN		(3β,5β)-3-[(6-Deoxy-α-L-mannopyranosyl) oxy]-5,14-dihydroxy-19-oxocard-20(22)-enol ide
6	STROPHANTHIN		(3β,5β)-3-{[2,6-Dideoxy-4-O-(β-D-glucopyranosyl)-3-O-methyl-β-D-ribo-hexopyranosyl] oxy}-5,14-dihydroxy-19-oxocard-20(22)-enol ide
7	CALOTROPIN		Card-20(22)-enol ide, 14-hydroxy-19-oxo-3,2-((tetrahydro-3,4-dihydroxy-6-methyl-2H-pyran-2,3-diyl) bis(oxy))-, (2alpha(2S,4S,6R),3beta,5alpha)-
8	OLEANDRIN		(3β,5β,16β)-16-(acetyloxy)-3-[(2,6-dideoxy-3-O-methyl-α-L-arabino-hexopyranosyl) oxy]-14-hydroxycard-20(22)-enol ide

9	THEVETIN		(3β,5β)-3-{[β-D-Glucopyranosyl-(1->6)-β-D-glucopyranosyl-(1->4)-6-desoxy-3-O-methyl-α-L-glucopyranosyl] oxy}-14-hydroxycard-20(22)-enol ide
10	LANATOSIDE C		3β,5β,12β)- 3- {[β-D- glucopyranosyl- (1→4)- 3-O-acetyl-2,6-dideoxy- β-D-ribo- hexopyranosyl- (1→4)- 2,6-dideoxy- β-D- ribo- hexopyranosyl- (1→4)- 2,6-dideoxy-β-D- ribo- hexopyranosyl] oxy}- 12,14-dihydroxycard-20(22)- enol ide
11	METILDIGOXIN		(3β,5β,12β)-3-{[2,6-dideoxy-4-O-methyl-β-D-ribo-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-ribo-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-ribo-hexopyranosyl] oxy}-12,14-dihydroxycard-20(22)-enol ide
12	ACETYL DIGOXIN		[6- [6- [[6- [[12,14-dihydroxy-10,13-dimethyl-17
13	ACETYL DIGITOXIN		[(2R,3R,4S,6S)-3-Hydroxy-6-[(2R,4S,6S)-4-hydroxy-6-[(2R,3S,4S,6R)-4-hydroxy-6-[[(5R,8R,9S,10S,13R,14S,17R')-14-hydroxy-10,13-dimethyl-17-(5-oxo-2H-furan-3-yl)-1,2,3,4,5,6,7,8,9,11,12,15,16,17-tetradecahydrocyclopenta[a]phenanthren-3-yl]oxy]-2-methyloxan-3-yl]oxy-2-methyloxan-3-yl]oxy-2-methyloxan-4-yl] acetate
14	DIGOXIGENIN		3β,12β,14-Trihydroxy-5β-card-20(22)-enol ide
15	ASCLEPIN		(1R,3aS,3bR,5aS,6aR,7aS,9R,11S,11aS,12aR,13aR,13bS,15aR)-13a-Formyl-3a,11a-dihydroxy-9,15a-dimethyl-1-(5-oxo-2,5-dihydro-3-furanyl) icosahydro-1H,7aH-cyclopenta [7,8] phenanthrol[2,3-b] pyrano[3,2-e] [1,4] d ioxin-11-yl acetate

This table gives an idea about the Compound structure, SMILES, and IUPAC name.

MOLINSPIRATION
EG:ASCLEPIN

SMILES
CC(=O)OC6CC(C)OC7OC5CC4CCC2C(CCC3(C)C(C1=CC(=O)OC1)CCC23O)C4(C=O)CC5OC67O [14-formyl-10,22-dihydroxy-7,18-dimethyl-19-(5-oxo-2H-furan-3-yl) 4,6,11trioxahexacyclo[12.11.0.03,12.05,10.015,23.018,22]pentacosan-9-yl] acetate
Molinspiration property engine v2022.08

The drug likeness properties of analogues were analysed by the Molinspiration and parameters are depicted in the table no :2

Lipinski's Rule of cardiac glycoside anlogues

Sl.no	**Compound name**	**Molecular weight > 500**	**No. of hydrogen bond donors >10**	**No. of hydrogen bond acceptors >5**	**Log p value >5**	**No. of rotatable bond >10**	**No. of violations**
1.	Acetyl digitoxin	806.99	14	4	2.74	9	2
2.	Acetyl digoxin	822.99	15	5	1.82	9	2
3.	Digitoxin	778.98	13	5	2.51	7	2
4.	Digoxigenin	390.52	5	3	1.56	1	0
5.	Gitoxin	790.95	14	6	1.12	7	3
6.	Metildigoxin	794.98	14	5	3.17	8	2
7.	Lanatoside c	999.15	20	9	0.44	12	3
8.	Oleandrin	576.73	9	2	2.88	6	1
9.	Ouabain	570.63	12	8	-2.42	4	3
10.	Calotropin	502.65	7	2	3.24	2	1
11.	convallotoxin	550.64	10	5	0.11	4	1
12.	Digoxin	780.95	14	6	1.12	7	3
13.	Strophanthin	710.81	14	6	-0.51	8	3
14.	Thevetin	872.96	19	9	-2.18	11	3
15.	asclepin	574.67	10	2	1.85	4	1

It gives molecular weight, no. of hydrogen bond acceptors, no. of hydrogen bond donors, Log p value, no. of rotatable bonds and no. of violations.Among 15 compounds Digoxigenin only shows zero number of violation.All the other shows violation against Lipinski rule

PASS
The biologic activity is predicted by PASS online.The probability to be active or inactive was predicted and shows in table no:3

Table no :3 The PASS value of Cradiac Glycoside analogues.

SERIAL NUMBER	**COMPOUND**	**PASS Activity**	
		Pa	**Pi**
1.	Digoxin	0.925	0.004
2.	Digitoxin	0.894	0.004
3.	Gitoxin	0.956	0.003
4.	Ouabain	0.911	0.004
5.	Convallotoxin	0.911	0.004
6.	Strophanthin	0.929	0.003
7.	Calotropin	0.833	0.004
8.	Oleandrin	0.929	0.003
9.	Thevetin	0.833	0.004
10.	Lanatoside	0.925	0.004
11.	Metidigoxin	0.930	0.003
12.	Acetyl Digoxin	0.919	0.004

13.	Acetyl Digitoxin	0.935	0.002
14	Digoxigenin	0.946	0.003
15	Asclepin	0.929	0.003

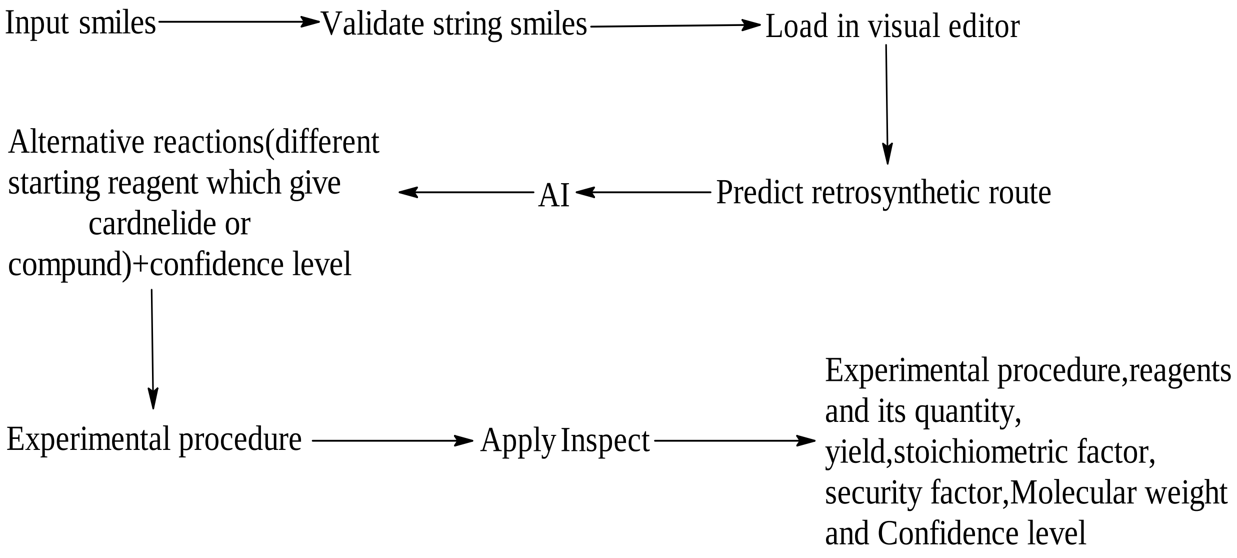
15 analogues shows cardiotonic activity above 0.07 It gives Pa (Probability to be active) value and Pi (Probability to be inactive) value of the compound.

AI assisted synthesis

IBM ROBO RXN: New drugs and materials traditionally require an average of 10 years and $10 million to discover and bring to market. Much of that time is taken up by the laborious repetition of experiments to synthesize new compounds and learn from trial and error. IBM hopes that a platform like RoboRXN could dramatically speed up that process by predicting the recipes for compounds and automating experiments. In theory, it would lower the costs of drug development and allow scientists to react faster to health crises like the current pandemic, in which social distancing requirements have caused slowdowns in lab work.

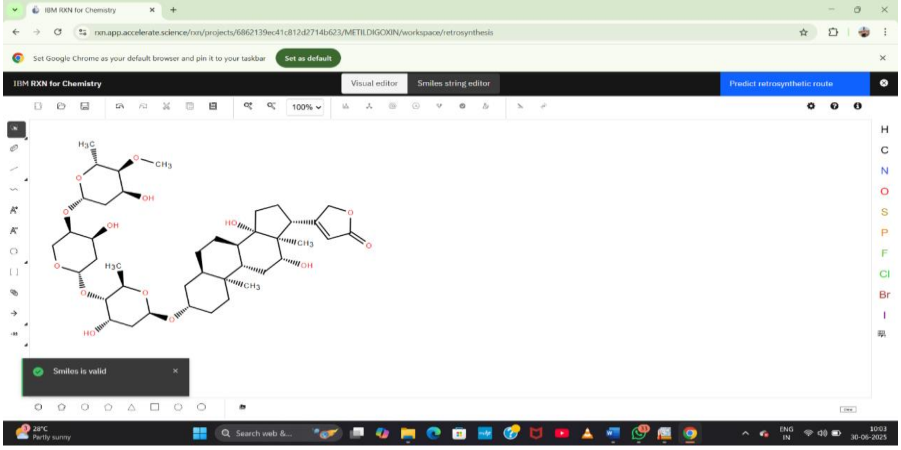
It is an online lab platform allows scientists to log on through a web browser. On a blank canvas, they draw the skeletal structure of the molecular compounds they want to make the molecules are encoded as sequences of characters called Simplified Molecular Input Line Entry System (SMILES) notations and the platform uses machine learning to predict the ingredients required and the order in which they should be mixed. It then sends the instructions to a robot in a remote lab to execute. Once the experiment is done, the platform sends a report to the scientists with the results.

PROCEDURE



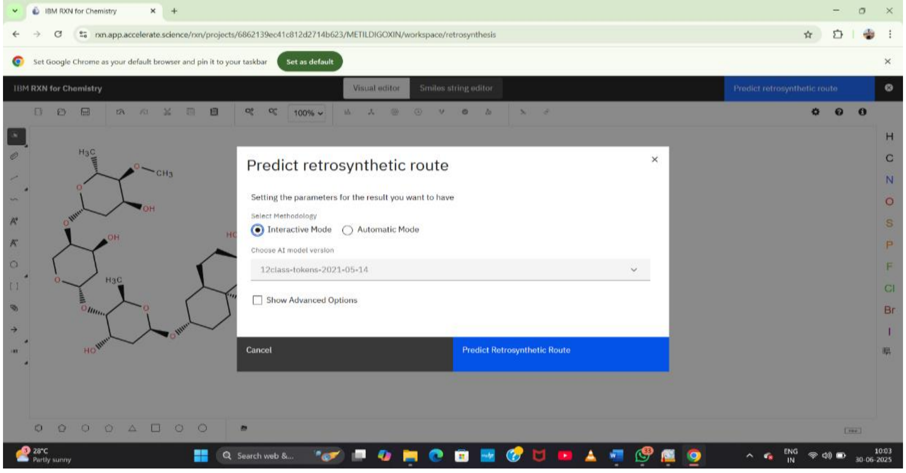
EG: METILDIGOXIN

PROCEDURE


rxn.app.accelerate.science/rxn/projects/6862139ec41c812d2714b623/METILDIGOXIN/workspace/retrosynthesis

Smiles is valid

↓


rxn.app.accelerate.science/rxn/projects/6862139ec41c812d2714b623/METILDIGOXIN/workspace/retrosynthesis

Predict retrosynthetic route

Setting the parameters for the result you want to have

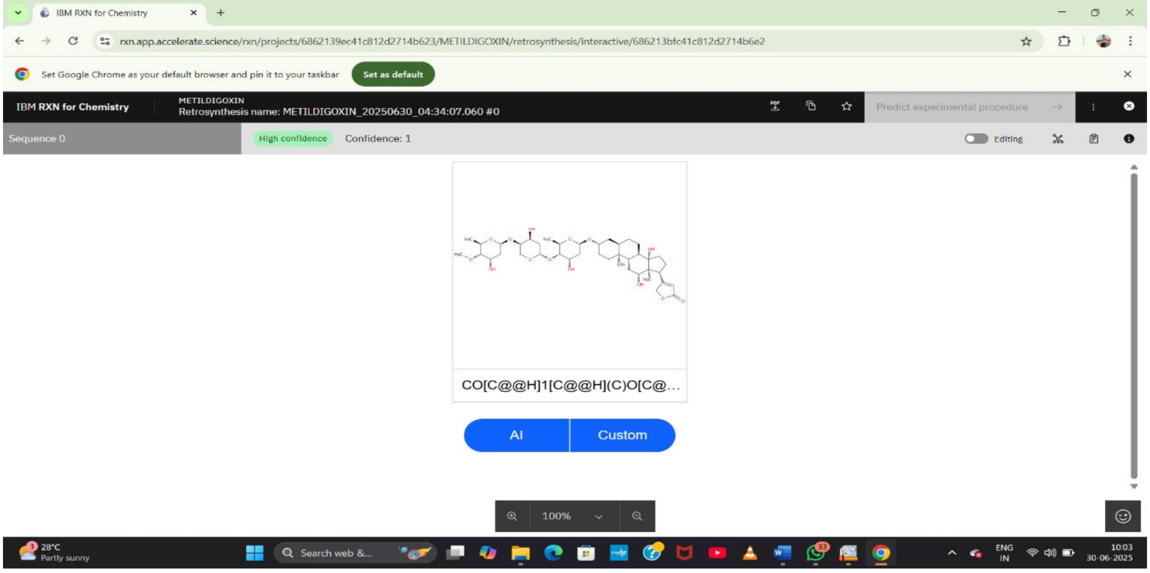
Select Methodology

● Interactive Mode ○ Automatic Mode

Choose AI model version: 12class-tokens-2021-05-14

☐ Show Advanced Options

↓


rxn.app.accelerate.science/rxn/projects/6862139ec41c812d2714b623/METILDIGOXIN/retrosynthesis/interactive/686213bfc41c812d2714b6e2

METILDIGOXIN

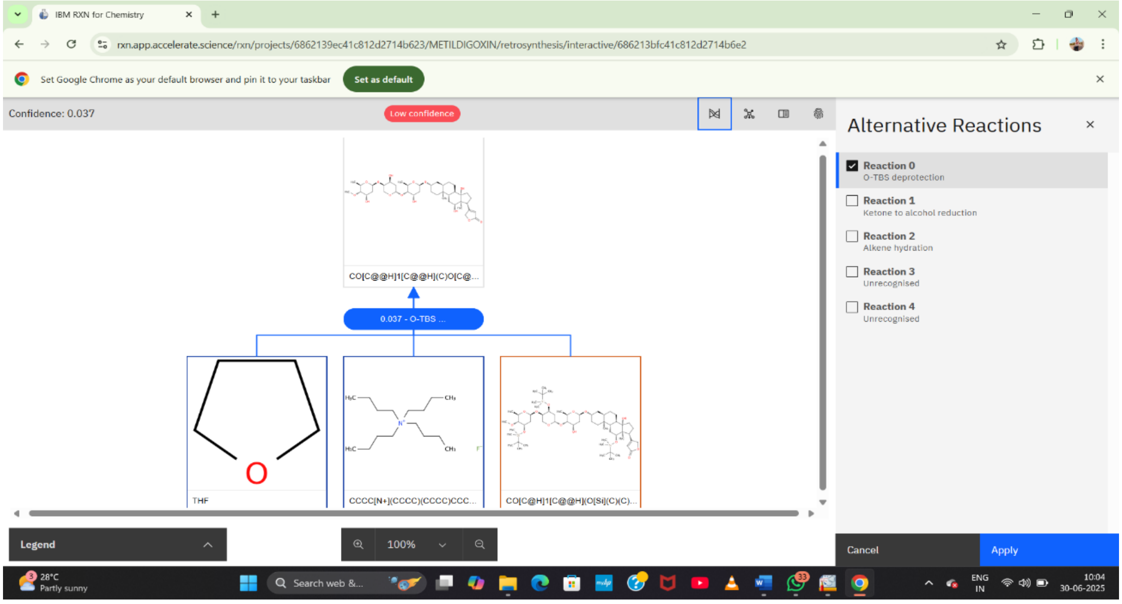
Retrosynthesis name: METILDIGOXIN_20250630_04:34:07.060 #0

Sequence 0

High confidence Confidence: 1

CO[C@@H]1[C@@H](C)O[C@...

↓


IBM RXN for Chemistry
rxn.app.accelerate.science/rxn/projects/6862139ec41c812d2714b623/METILDIGOXIN/retrosynthesis/interactive/686213bfc41c812d2714b6e2
Set Google Chrome as your default browser and pin it to your taskbar
Set as default
Confidence: 0.037
Low confidence
Alternative Reactions
☑ Reaction 0
O-TBS deprotection
☐ Reaction 1
Ketone to alcohol reduction
☐ Reaction 2
Alkene hydration
☐ Reaction 3
Unrecognised
☐ Reaction 4
Unrecognised
CO[C@@H]1[C@@H](C)O[C@...
0.037 - O-TBS ...
THF
O
CCCC[N+](CCCC)(CCCC)CCC...
CO[C@H]1[C@@H](O[Si](C)(C)...
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Cancel
Apply
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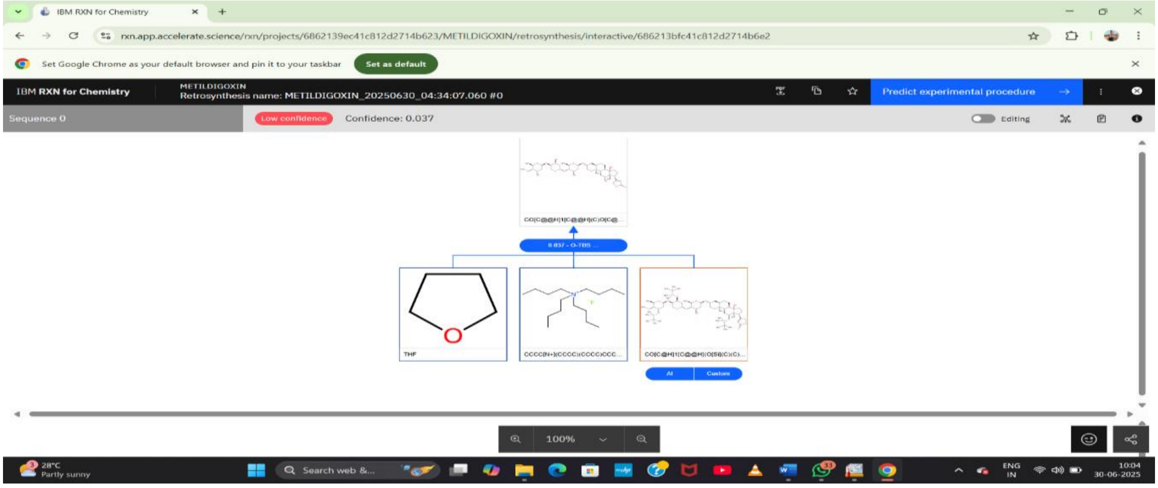
ENG
IN
10:04
30-06-2025


IBM RXN for Chemistry
rxn.app.accelerate.science/rxn/projects/6862139ec41c812d2714b623/METILDIGOXIN/retrosynthesis/interactive/686213bfc41c812d2714b6e2
Set Google Chrome as your default browser and pin it to your taskbar
Set as default
IBM RXN for Chemistry
METILDIGOXIN
Retrosynthesis name: METILDIGOXIN_20250630_04:34:07.060 #0
Predict experimental procedure
Sequence 0
Low confidence
Confidence: 0.037
Editing
CO[C@@H]1[C@@H](C)O[C@...
0.037 - O-TBS ...
THF
O
CCCC[N+](CCCC)(CCCC)CCC...
CO[C@H]1[C@@H](O[Si](C)(C)...
AI
Custom
100%
28°C
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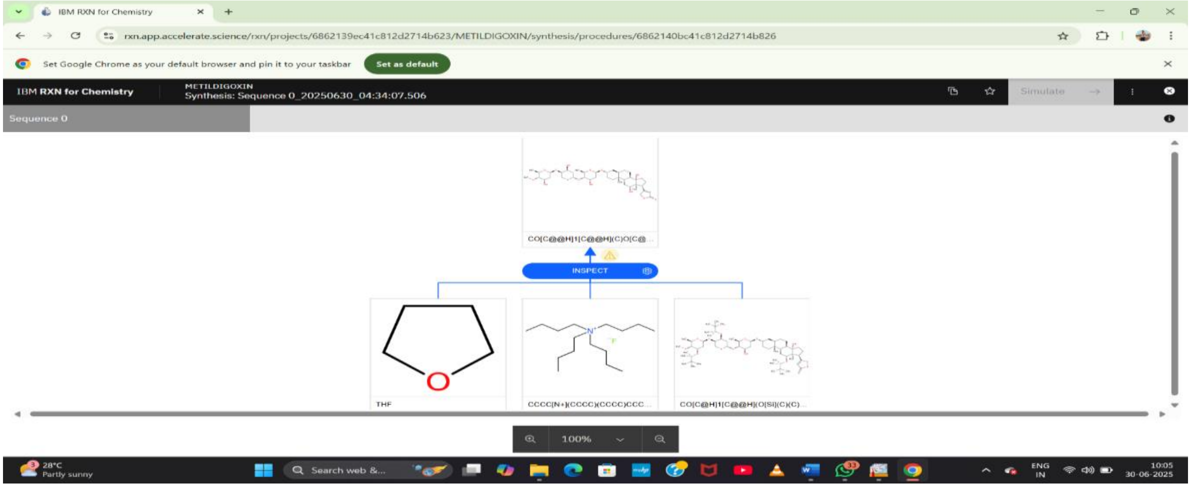
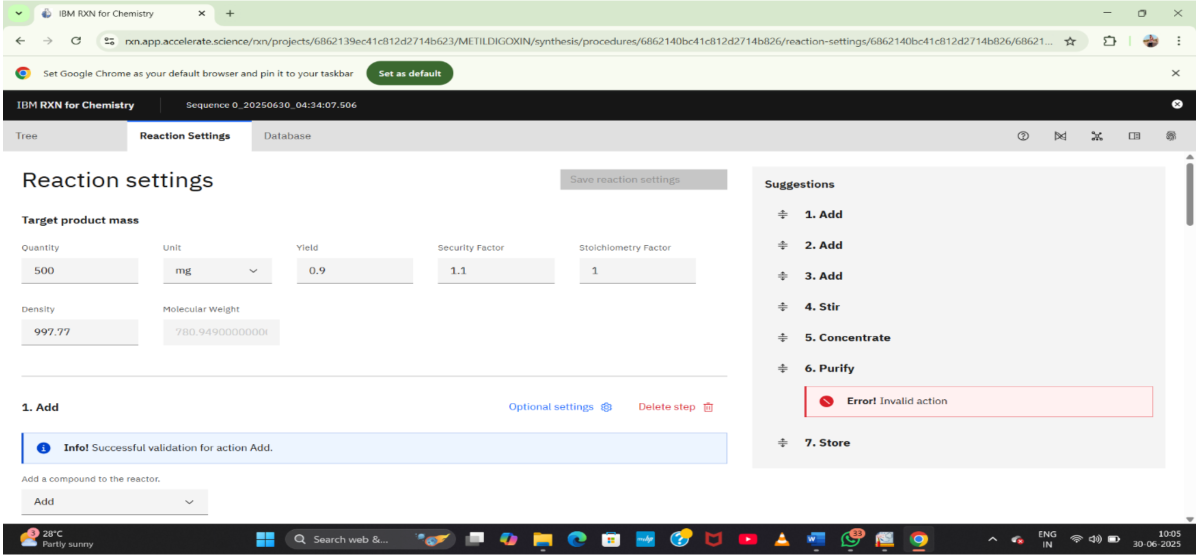
ENG
IN
10:04
30-06-2025


IBM RXN for Chemistry
rxn.app.accelerate.science/rxn/projects/6862139ec41c812d2714b623/METILDIGOXIN/synthesis/procedures/6862140bc41c812d2714b826
Set Google Chrome as your default browser and pin it to your taskbar
Set as default
IBM RXN for Chemistry
METILDIGOXIN
Synthesis: Sequence 0_20250630_04:34:07.506
Simulate
Sequence 0
CO[C@@H]1[C@@H](C)O[C@...
INSPECT
THF
O
CCCC[N+](CCCC)(CCCC)CCC...
CO[C@H]1[C@@H](O[Si](C)(C)...
100%
28°C
Partly sunny
Search web &...
ENG
IN
10:05
30-06-2025



Reaction settings

Target product mass

Quantity: 500
Unit: mg
Yield: 0.9
Security Factor: 1.1
Stoichiometry Factor: 1
Density: 997.77
Molecular Weight: 780.9490000000(

1. Add

Info! Successful validation for action Add.

Add a compound to the reactor.

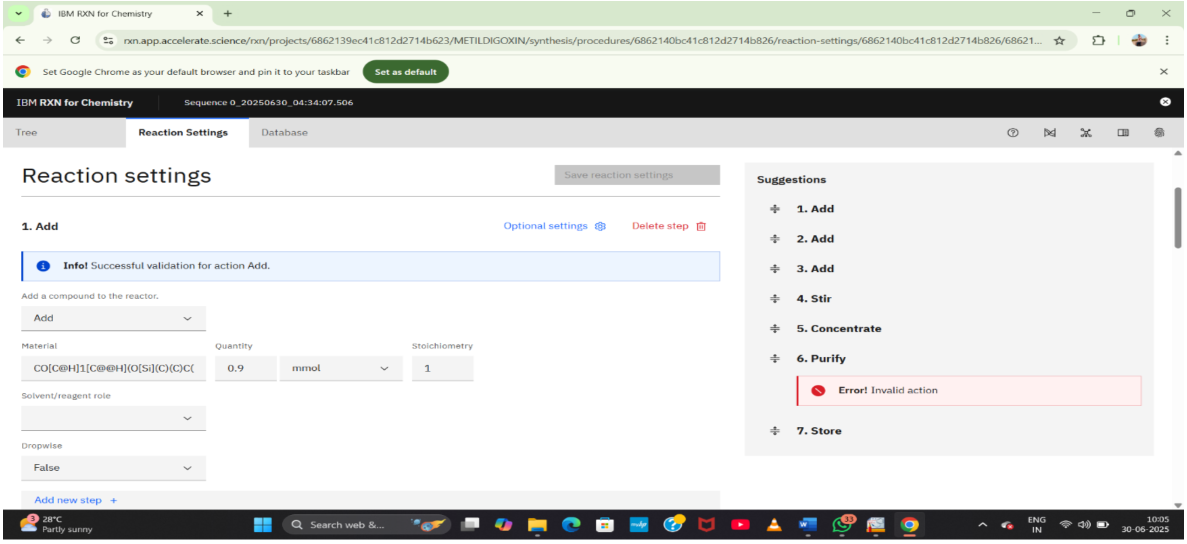
Add

Suggestions

1. Add
2. Add
3. Add
4. Stir
5. Concentrate
6. Purify

Error! Invalid action

7. Store



Reaction settings

1. Add

Info! Successful validation for action Add.

Add a compound to the reactor.

Add

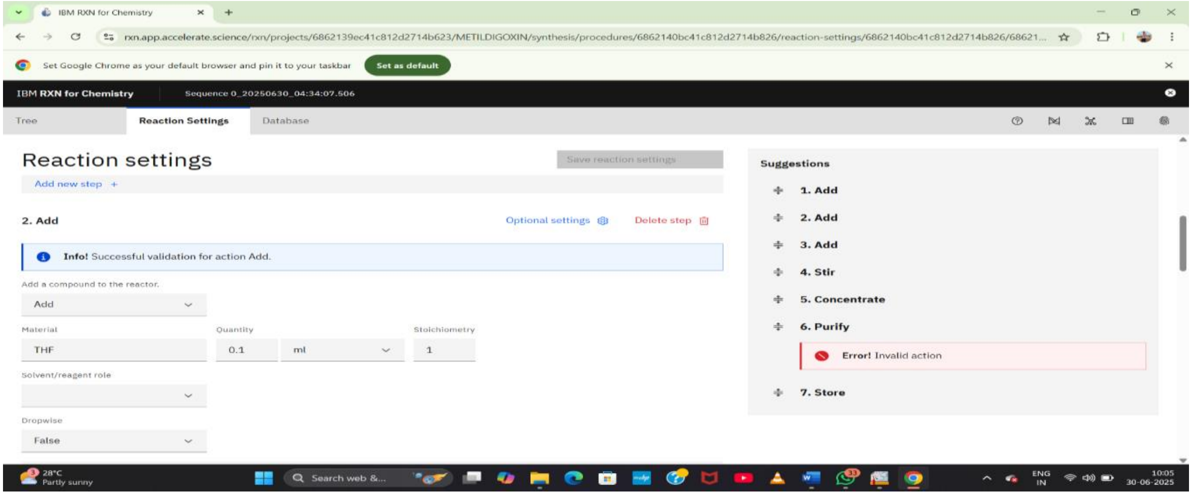
Material: CO[C@H]1[C@@H](O[Si](C)(C)C(
Quantity: 0.9 mmol
Stoichiometry: 1
Solvent/reagent role:
Dropwise: False

Suggestions

1. Add
2. Add
3. Add
4. Stir
5. Concentrate
6. Purify

Error! Invalid action

7. Store



Reaction settings

2. Add

Info! Successful validation for action Add.

Add a compound to the reactor.

Add

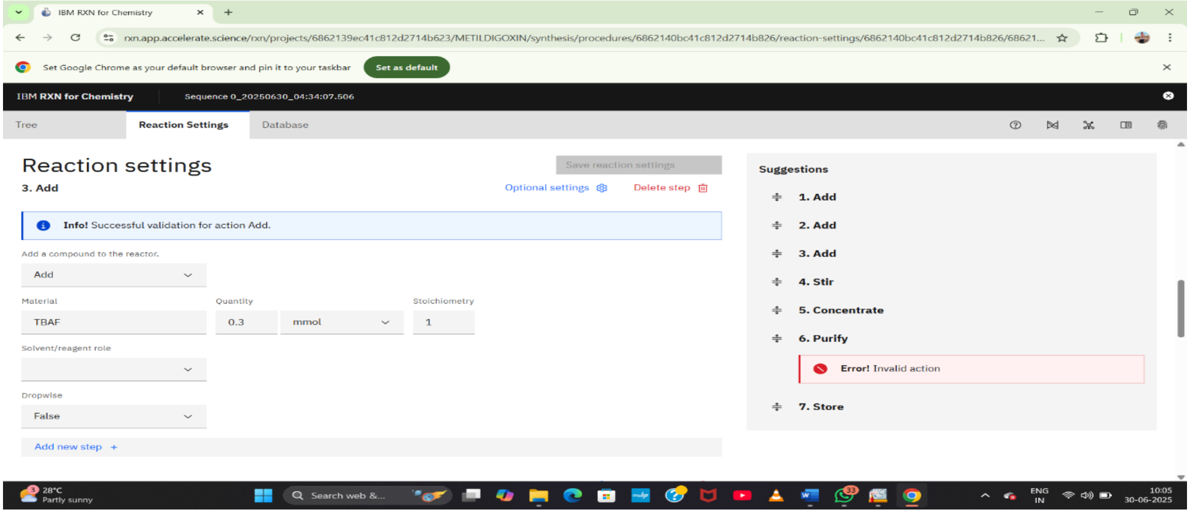
Material: THF
Quantity: 0.1 ml
Stoichiometry: 1
Solvent/reagent role:
Dropwise: False

Suggestions

1. Add
2. Add
3. Add
4. Stir
5. Concentrate
6. Purify

Error! Invalid action

7. Store



Reaction settings

3. Add

Info! Successful validation for action Add.

Add a compound to the reactor.

Add

Material: TBAF

Quantity: 0.3 mmol

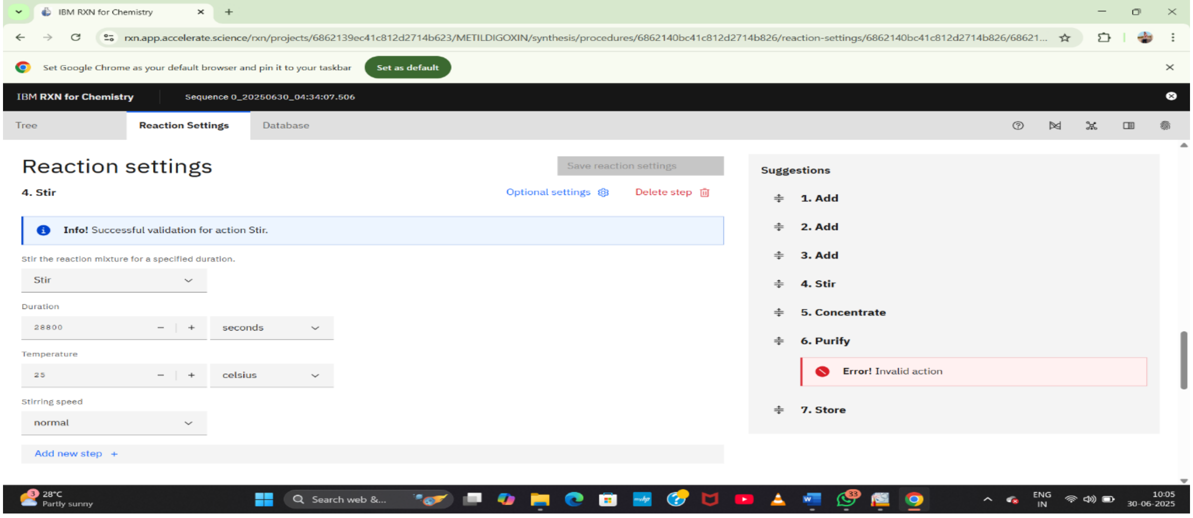
Stoichiometry: 1

Solvent/reagent role:

Dropwise: False

Suggestions

1. Add
2. Add
3. Add
4. Stir
5. Concentrate
6. Purify
   - Error! Invalid action
7. Store



Reaction settings

4. Stir

Info! Successful validation for action Stir.

Stir the reaction mixture for a specified duration.

Stir

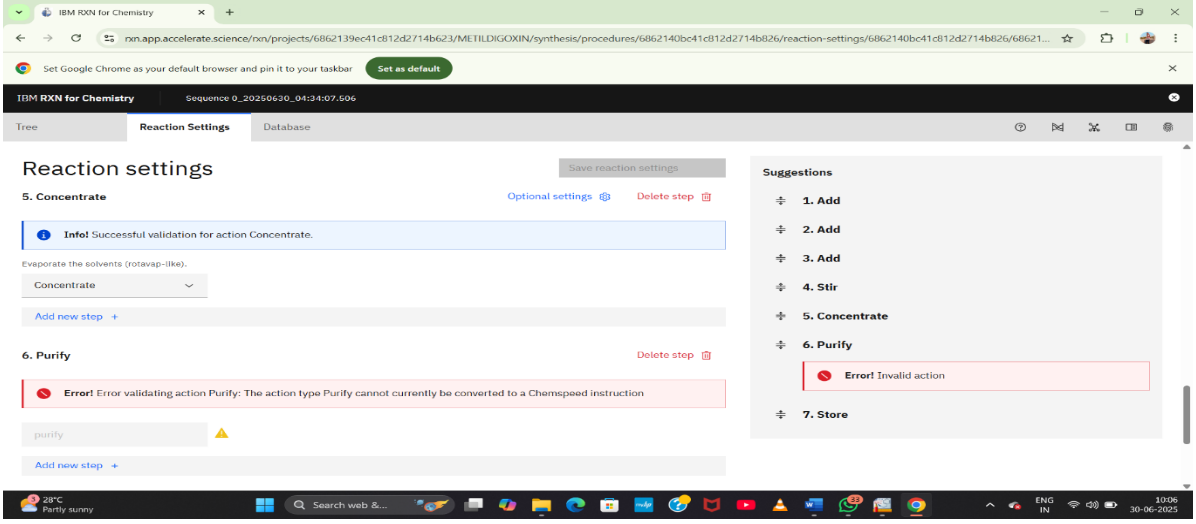
Duration: 28800 seconds

Temperature: 25 celsius

Stirring speed: normal

Suggestions

1. Add
2. Add
3. Add
4. Stir
5. Concentrate
6. Purify
   - Error! Invalid action
7. Store



Reaction settings

5. Concentrate

Info! Successful validation for action Concentrate.

Evaporate the solvents (rotavap-like).

Concentrate

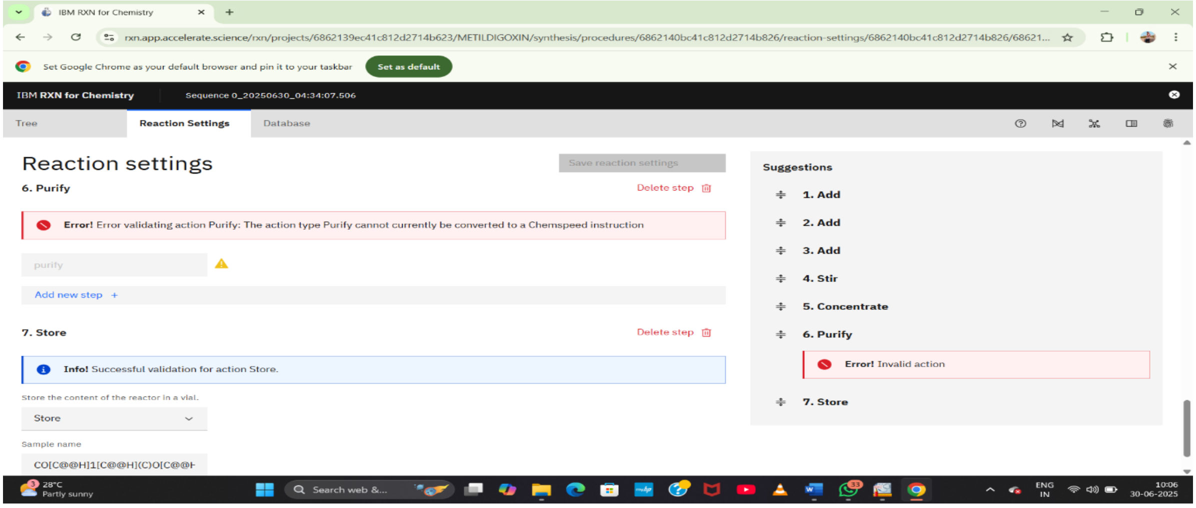
6. Purify

Error! Error validating action Purify: The action type Purify cannot currently be converted to a Chemspeed instruction

purify

Suggestions

1. Add
2. Add
3. Add
4. Stir
5. Concentrate
6. Purify
   - Error! Invalid action
7. Store



Reaction settings

6. Purify

Error! Error validating action Purify: The action type Purify cannot currently be converted to a Chemspeed instruction

purify

7. Store

Info! Successful validation for action Store.

Store the content of the reactor in a vial.

Store

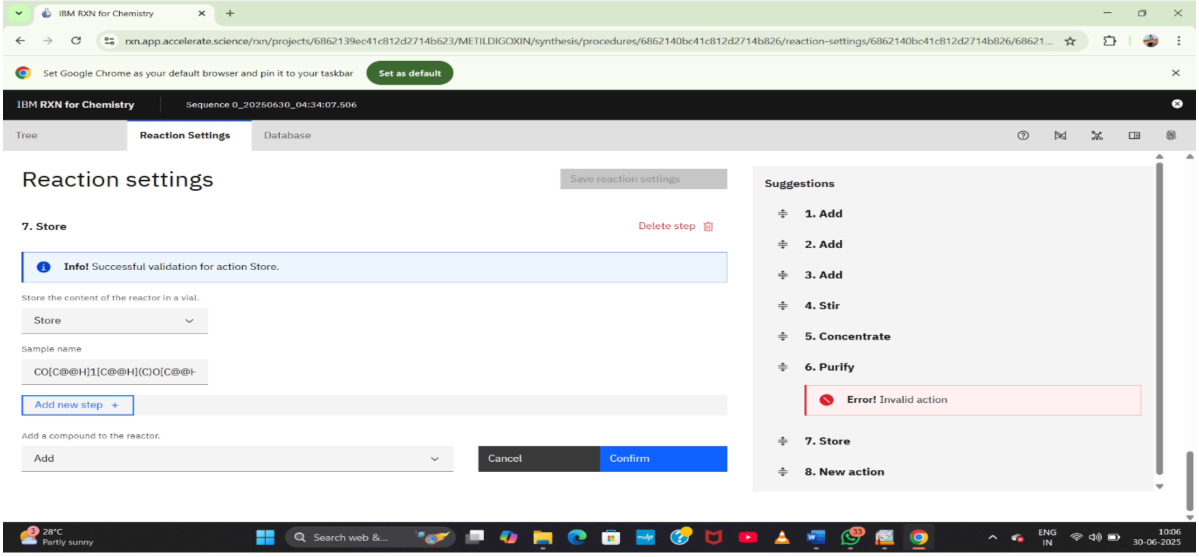
Sample name

CO[C@@H]1[C@@H](C)O[C@@H

1. Add
2. Add
3. Add
4. Stir
5. Concentrate
6. Purify

Error! Invalid action

7. Store



Reaction settings

7. Store

Info! Successful validation for action Store.

Store the content of the reactor in a vial.

Store

Sample name

CO[C@@H]1[C@@H](C)O[C@@H

Add a compound to the reactor.

Add

1. Add
2. Add
3. Add
4. Stir
5. Concentrate
6. Purify

Error! Invalid action

7. Store
8. New action

The analogues were synthesised by means of AI wing IBM ROBO and the reagents used,yield,stochiometric factor, molecular weight,confidence level were displayed in the table : 4

SL. no.	Compound name	Reagents used	Quantity of reagents	yield	Stoichiometric factor	Molecular weight	Confidence level
1	Acetyl Digoxin	1.Chloroform 2.Methanol 3.Sodium borohydride 4.water	20 ml 0.1 ml 0.1 mol 10 ml	0.9	1	824.95	low
2	Acetyl Digitoxin	1.tert-Butyldiphenyl silyl chloride (TBDPS-Cl) 2.THF 3.TBAF	20 ml 0.1 ml 0.2 mol	0.9	1	806.95	low
3	Metildigoxin	1.Butyldimethylsilyl chloride 2.THF 3.TBAF	0.9 mol 0.1 ml 0.3 mol	0.9	1	780.94	low
4	Digoxigenin	1.HCL	0.1ml	0.9	1	390.520	high

5	Oleandrin	1.Paclitaxel 2.Dichloromethane 3.TFA	0.7 mol 0.1 ml 0.2 mol	0.9	1	576.72	medium
6	Gitoxin	1.complex glycosylated bromosteroid 2.Dioxane 3.Pd(pph3)4 4.2-Acetoxyphen ylboronic acid pinacol ester 5.k3po4 6.Water 7.Ethyl Acetate 8.Brine 9.Na2SO4	0.7 mol 0.3 ml 1 mol 20 ml 0.3 ml 0.2 ml 10 ml 10 ml	0.9	1	780.94	low

It gives reagent used and their quantity, yield, quantity, stochiometric and security factor, density, molecular weight and confidence level of the compound.

6. CONCLUSION

The present study successfully integrated traditional phytochemical analysis with modern computational and AI-assisted methodologies to explore and optimize cardiac glycoside analogues. Through extensive structural elucidation using chemical and spectroscopic techniques, the core glycosidic and aglycone components of cardiac glycosides were characterized. The project demonstrated the rational design of analogues using computer-aided drug design tools such as ACD/Chemsketch, Molinspiration, SMILES, PASS, and IBM Robo RXN.

Among the 15 designed analogues, **Digoxigenin** stood out with no violations of Lipinski’s Rule of Five, indicating high potential for oral bioavailability. PASS prediction further confirmed that all analogues had significant cardiotonic activity (Pa > 0.7), validating their relevance for therapeutic development. The AI-assisted synthesis using IBM Robo RXN illustrated a futuristic and scalable method for compound synthesis, reducing manual labor, optimizing reaction conditions, and accelerating the discovery process.

Overall, this interdisciplinary project bridges natural product chemistry, computational modeling, and artificial intelligence to enhance the efficiency of cardiovascular drug discovery. The findings open new avenues for developing safer and more efficacious cardiac glycoside analogues with improved pharmacokinetic and pharmacodynamic profiles. Further in vitro and in vivo studies are warranted to translate these analogues into clinically viable candidates.

ACKNOWLEDGEMENT

We want to offer this endeavour to GOD ALMIGHTY for all the blessings showered on us during the course of this research. We express deep sense of gratitude to the Department of Pharmaceutical Chemistry of Mar Dioscorus College of Pharmacy, for helping in the completion of the review. We are extremely grateful to our principal, for her guidance and we are deeply obliged to Dr Sreeja S, our guide as well as mentor, for her guidance, constant support and encouragement which completing our work within time schedule. We express our sincere gratitude to Mrs Anjana V S, our co guide for sharing her expertise and suggestions upon our work

REFERENCE

1. Dias DA, Urban S, Roessner U. A historical overview of natural products in drug discovery. Metabolites, 2012; 2(2): 303–36. SCIRP.
2. Kowsalya K, Vidya N, Halka J, Yazhini Preetha S, Saradhadevi M, Sahayarayan JJ, et al. Plant glycosides and glycosidases: classification, sources, and therapeutic insights in current medicine. Glycoconj J., 2025 Apr; 42(2): 107–24.
3. Newman DJ, Cragg GM. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. J Nat Prod., 2020 Mar 27; 83(3): 770-803. doi:10.1021/acs.jnatprod.9b01285.
4. Bhatt SV, Nagasampagi BA, Sivakumar M. Chemistry of natural products. Berlin: Springer; p. 105–106.
5. Botelho AFM, Pierezan F, Soto-Blanco B, Melo MM. A review of cardiac glycosides: structure, toxicokinetics, clinical signs, diagnosis and antineoplastic potential. Toxicon, 2019 Mar; 158: 63–70.
6. Triana-Martínez F, Picallos-Rabina P, Da Silva-Álvarez S, Pietrocola F, Llanos S, Rodilla V, et al. Identification and characterization of cardiac glycosides as senolytic compounds. Nat Commun., 2019 Oct 24; 10(1): 4731.
7. Calderón-Montaño JM, Burgos-Morón E, Orta ML, Maldonado-Navas D, García-Domínguez I, López-Lázaro M. Evaluating the cancer therapeutic potential of cardiac glycosides. Biomed Res Int., 2014; 2014: 794930. doi: 10.1155/2014/794930.

Epub 2014 May 8. PMID: 24895612; PMCID: PMC4033509.

8. Patel S. Cardiac glycosides in therapeutics. J Med Genet Clin Biol., 2024; 1(7).
9. Prassas I, Diamandis EP. Novel therapeutic applications of cardiac glycosides. *Nat Rev Drug Discov*., 2008; 7(11): 926–35. doi:10.1038/nrd2682.
10. Dev SM, Bhattacharya SC. The structure of glycosides. Part II. Periodate oxidation of sarmentogenin glycosides. *J Chem Soc*., 1954; 1954: 3860–3. doi:10.1039/JR9540003860.
11. Kovac P, Moller G, Schmid H. Synthesis of cardiac glycosides. *Pure Appl Chem*., 1972; 31(4): 495–526. doi:10.1351/pac197231040495.
12. ACD/ChemSketch, version 2021.1.1 [Internet]. Toronto (ON): Advanced Chemistry Development, Inc.; 2021 [cited 2025 Aug 2]. Available from: https://www.acdlabs.com
13. Bai SB, Geethavani M, Ramakrishna C. Synthesis, characterization and Molinspiration analysis, anti-bacterial activity of novel 2,4,6-tri substituted pyrimidines. Int J Pharm Sci Rev Res., 2022; 75(1): 58–63.
14. Weininger D. SMILES, a chemical language and information system. 1. Introduction to methodology and encoding rules. *J Chem Inf Comput Sci*., 1988; 28(1): 31–6. doi:10.1021/ci00057a00.
15. Abrams MP, Carleton RN, Asmundson GJG. An exploration of the psychometric properties of the PASS-20 with a nonclinical sample. J Anxiety Disord., 2007; 21(4): 522–36
16. Laino T, Vaucher A, Manica M. IBM RoboRXN: a cloud-accessible, AI-driven autonomous chemical laboratory. AI Journal. 2022 Jan 24.
17. Hao K. IBM has built a new drug-making lab entirely in the cloud. MIT Technology Review. 2020 Sep 1.
18. Laino T, Vaucher A, Manica M. IBM RoboRXN: a cloud-based AI-driven platform for chemical synthesis planning. ChemRxiv [Preprint]. 2020; https://doi.org/10.26434/chemrxiv.11474586.v3.