MALAYSIAN JOURNAL OF ANALYTICAL SCIENCES

Journal homepage: https://mjas.analis.com.my/

Review Article

Exploring synthesis of pyrrolidine-based iminosugars for antihypertensive therapy: A mini-review

Nur Khairunsyahida Nazri[1,2], Noor Hidayah Pungot[1,2*], Agustono Wibowo[1,3], and Mohd Fazli Mohammat[1,2]

[1]Organic Synthesis Laboratory, Institute of Science, Universiti Teknologi Mara (UiTM), Puncak Alam Campus, 42300 Bandar Puncak Alam, Selangor.
[2]School of Chemistry and Environment, Faculty of Applied Sciences, Universiti Teknologi Mara (UiTM), 40450 Shah Alam, Selangor, Malaysia
[3]Faculty of Applied Sciences, Universiti Teknologi Mara (UiTM), Pahang Branch, Jengka Campus, Pahang, Malaysia

[*]Corresponding author: noorhidayah977@uitm.edu.my

Received: 9 January 2025; Revised: 8 October 2025; Accepted: 10 October 2025; Published: 31 October 2025

Abstract
Hypertension remains one of the most prevalent and challenging cardiovascular disorders, necessitating innovative therapeutic strategies beyond conventional drug classes. Pyrrolidine-based iminosugars have gained increasing attention as promising candidates for antihypertensive therapy owing to their close structural resemblance to carbohydrates. Their potent glycosidase inhibitory activity enables modulation of key enzymatic pathways associated with vascular function and blood pressure regulation. This mini-review explores recent advances in the synthesis of pyrrolidine-based iminosugars, with particular emphasis on methodologies such as D-glycal derivatization, nucleophilic substitution, and targeted functional group transformations. Furthermore, the review highlights emerging preclinical findings that underscore their therapeutic potential in hypertension management. By bridging synthetic innovations with biological insights, this work provides a critical perspective on the translational potential of pyrrolidine-based iminosugars and outlines opportunities for their integration into future antihypertensive drug discovery pipelines.

Keywords: Pyrrolidine-based iminosugar, carbohydrate, glycosidase inhibitory, antihypertensive drug

Introduction

Hypertension remains a leading modifiable risk factor for cardiovascular morbidity and premature mortality, affecting an estimated 1.28 billion adults aged 30-79 years, with the majority residing in low- and middle-income countries. Despite widespread awareness campaigns, approximately 46% of individuals remain undiagnosed, and only 42% of patients receive treatment, with fewer than one in four women and one in five men achieving effective blood pressure control. These statistics underscore the urgent need for improved therapeutic interventions and global treatment equity [1,2], specifically innovative agents that extend beyond existing drug classes.

The International Society of Hypertension (ISH) has outlined practical categories of blood pressure namely normal (<130/85 mmHg), high-normal (130-139/85-89 mmHg), grade 1 hypertension (140-159/90-99 mmHg), and grade 2 hypertension (≥160/100 mmHg), emphasizing the importance of early detection and guideline-directed therapy. However, real-world adherence and control rates remain suboptimal, motivating the search for novel chemotypes with unique mechanisms of action [3,4].

Despite the availability of various antihypertensive drugs, many patients fail to achieve adequate blood pressure regulation, necessitating the development of novel therapeutic agents. Iminosugars are a class of carbohydrate mimetics characterized by the substitution of a nitrogen atom for the ring oxygen found in natural sugars. This structural modification gives iminosugars unique chemical and biological properties compared to their natural counterparts [5]. Iminosugars can vary widely in structure, including saturated and unsaturated forms with different substituents attached to the ring nitrogen. These variations allow iminosugars to mimic the three-dimensional shape and functional groups of sugars, enabling interactions with enzymes and receptors involved in carbohydrate metabolism and cellular signaling [6]. Within this family, pyrrolidine-based iminosugars are gaining attention due to their synthetic.

Recent advances in synthetic chemistry, ranging from stereocontrolled derivatization of glycals, nucleophilic substitution, amination-cyclization cascades, C-glycoside construction, and targeted functional group transformations, have significantly expanded the accessible chemical space of pyrrolidine iminosugars [7,8,9, 10]. These developments not only enhance structural diversity, but also improve prospects for medicinal chemistry optimization. Clinically, the potential of iminosugars is supported by approved agents such as miglustat (Zavesca®) which inhibits glucosylceramide synthase in lysosomal storage disorders. Although not an antihypertensive, it exemplifies the translatability of iminosugar scaffolds into viable therapeutics [11,12]. Meanwhile, α-glucosidase inhibitors such as deoxynojirimycin derivatives have demonstrated ancillary effects on vascular function and blood pressure control, providing a rationale for further exploration in cardiovascular contexts [13].

It is also being explored for other therapeutic applications, including Fabry disease and Niemann-Pick disease type C, due to its ability to modulate glycosphingolipid metabolism [14]. Another drug, DNJ, is known for its inhibition of α-glucosidases and has been investigated for its potential therapeutic applications, including as an antiviral agent against HIV and potential treatment for diabetes [15]. While not primarily used as an antihypertensive medication, NB-DNJ (N-butyl-deoxynojirimycin) or miglitol is an α-glucosidase inhibitor that has been investigated for its effects on blood pressure regulation, among its other metabolic effects [16]. These examples illustrate the diverse applications and therapeutic potentials of iminosugars in medicine and biotechnology.

By focusing on pyrrolidine-based iminosugar derivatives, this review aims to advance the field of pharmaceutical science by exploring compounds that could potentially offer enhanced efficacy and safety profiles in treating hypertension. Furthermore, advancements in synthetic chemistry have enabled the development of diverse pyrrolidine iminosugar derivatives, providing opportunities to optimize their therapeutic properties.

Heterocyclic containing nitrogen: Pyrrolidine

Pyrrolidine is a saturated five-membered heterocyclic compound containing a single nitrogen atom. Unlike its aromatic analogue, pyrrole, pyrrolidine is non-aromatic and exhibits distinct chemical reactivity, which makes it an important scaffold in synthetic and medicinal chemistry. Its molecular formula is C_4H_9N, and the core structure is presented in **Figure 1**. Other five-membered nitrogen heterocycles, such as pyrrole, have also been extensively studied due to their biological activities; however, the saturated nature of pyrrolidine imparts unique stereo-electronic features that broaden its synthetic utility [17].

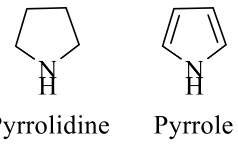


Figure 1. Pyrrolidine and Pyrrole

In nature, pyrrolidine is a structural motif found in various alkaloids, including nicotine and hygrine, contributing to their neurological activity [18], widely recognized for their biological significance. Nicotine, extracted from Nicotiana tabacum, exemplifies a natural compound containing a pyrrolidine ring and remains one of the most studied alkaloids due to its central nervous system effects [19,20]. Other notable pyrrolidine alkaloids include ruspolinone and norruspoline, isolated from Ruspolia species, which have sparked interest due to their pharmacological potential [21]. Additionally, pyrrolidine is present in the amino acid proline, a key residue that confers rigidity in protein secondary structures and contributes to enzyme catalysis and stability [22]. Other naturally occurring derivatives, such as hydroxyproline and prolinol, also play vital biochemical roles and are presented in **Figure 2**. These natural sources highlight the broad biological and synthetic utility of the pyrrolidine scaffold

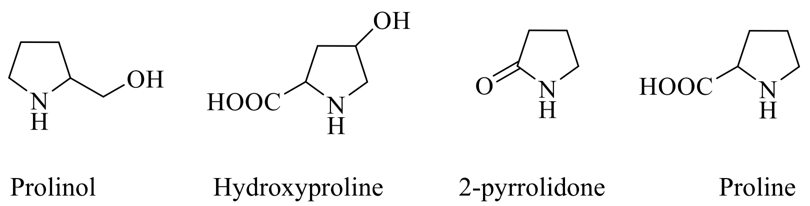


Figure 2. Pyrrolidine derivatives

Table 1. Synthetic approaches to pyrrolidine derivatives

Synthetic Approaches	Description	References
Catalytic hydrogenation of pyrrole	Reduces the aromatic double bonds in pyrrole to form pyrrolidine.	[23,24]
Intramolecular cyclization of amino alcohols or amino acids	Enables efficient ring closure under mild conditions	[25,26]
Mannich reaction	Condensation of formaldehyde, amines, and ketones or aldehydes to yield substituted pyrrolidines.	[27,28]
Multicomponent reactions (MCRs)	Including synthesis of 2,3-dioxopyrrolidine derivatives for pharmaceutical and materials applications.	[7,29]
[3+2] Cycloaddition of azomethine ylides	A powerful method to construct highly substituted pyrrolidines with stereo control.	[30,31]
Reductive amination followed by cyclization	Sequential approach using carbonyl compounds and amines, followed by intramolecular closure.	[32]
Radical cyclization strategies	Employing radical precursors under photo-redox or metal catalysis to access complex pyrrolidines.	[33,34]
Asymmetric organocatalysis	Chiral secondary amines (e.g., proline-derived catalysts) promote enantioselective pyrrolidine formation.	[35,36]
Metal-catalyzed C–H functionalization	Transition-metal catalysis enables late-stage diversification of pyrrolidine scaffolds.	[37,38]
Biocatalytic/enzymatic synthesis	Enzyme-mediated ring formation provides sustainable and regioselective access to derivatives.	[39,40]

Several strategies have been developed for the laboratory synthesis of pyrrolidine and its derivatives. Classical and modern methods include those presented in **Table 1**. In addition to these methods, the synthesis of 2,3-dioxopyrrolidine via a multicomponent reaction has gained attention due to its efficiency and versatility in creating complex structures with potential applications in pharmaceuticals and materials science.

Iminosugars

Iminosugars, also referred to as polyhydroxylated alkaloids, are a unique class of carbohydrate mimetics in which a cyclic-bound nitrogen atom replaces the ring oxygen of monosaccharides. This subtle yet crucial modification confers the ability to imitate natural sugars while altering their biochemical reactivity. Iminosugars typically inhibit glycosidases by mimicking unstable transition states in glycosidic bond hydrolysis, thereby competing for the enzyme's active site with high affinity [5]. Several examples of pyrrolidine-based iminosugars are shown in **Figure 3**. The broad therapeutic potential of iminosugars arises from their glycosidase inhibitory activity, which disrupts enzymatic pathways central to numerous diseases. These include antiviral, anticancer, antidiabetic, anti-inflammatory, and antihypertensive effects [6,41]

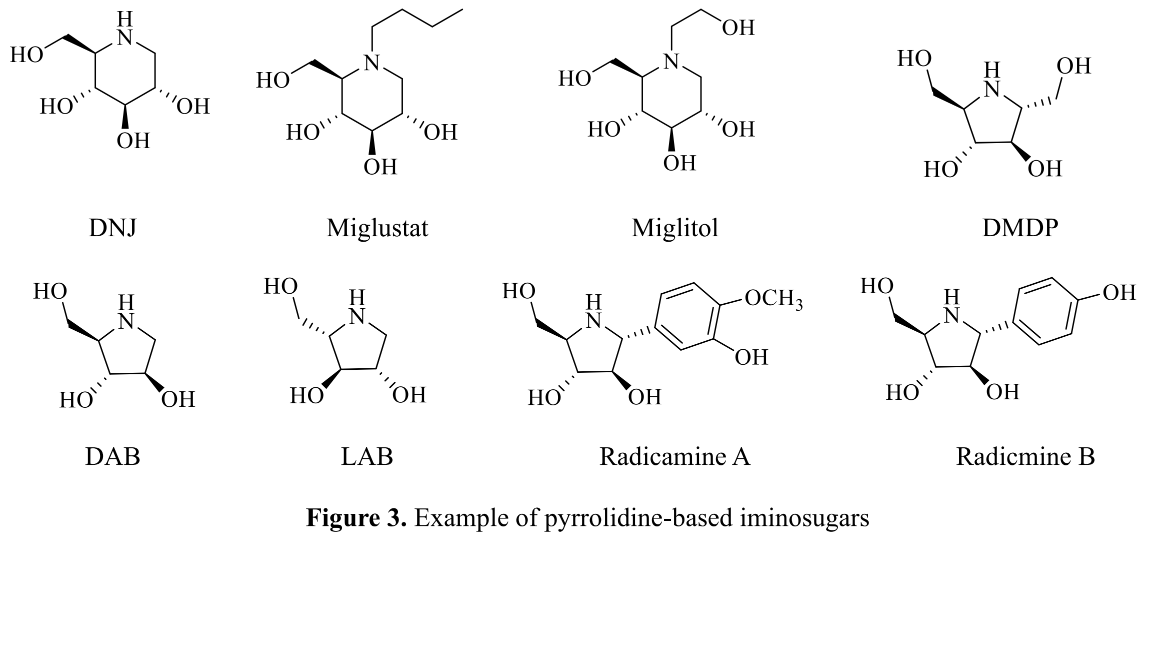


Figure 3. Example of pyrrolidine-based iminosugars

Iminosugars are classified into monocyclic (piperidine, pyrrolidine) and bicyclic (pyrrolizidine, indolizidine, nortropane) derivatives. Representative examples and their therapeutic relevance are summarized in **Table 2**.

Iminosugars exert their biological effects by mimicking the unstable transition state of glycosidase-catalyzed reactions, thereby stabilizing enzyme-substrate intermediates and competitively inhibiting glycosidase activity [7]. This transition-state mimicry forms the foundation of their pharmacological potential across multiple therapeutic areas. For instance, α-glucosidase inhibitors such as miglitol and voglibose can delay the digestion of carbohydrates, effectively lowering postprandial glucose levels and offering a valuable approach to diabetes management [13]. Similarly, β-glucosidase inhibitors like miglustat disrupt glucosylceramide degradation, an essential pathway in lysosomal function, making them highly effective in the treatment of lysosomal storage disorders such as Gaucher's disease and Niemann-Pick disease type C [50]. In addition, α-mannosidase inhibitors derived from nojirimycin interfere with viral glycoprotein maturation, thereby reducing viral infectivity and highlighting their potential as antiviral agents [51]. Together, these mechanisms underscore the versatility of iminosugars as glycosidase inhibitors and their relevance in the development of novel therapeutic interventions [52].

Iminosugars exhibit remarkable specificity in their ability to selectively inhibit distinct glycosidases, a property that hinges on their unique structural features. For instance, α-glucosidases, enzymes critical to carbohydrate digestion, are targeted by iminosugars like miglitol and voglibose. These inhibitors mimic the natural substrates of α-glucosidases, thereby preventing the breakdown of carbohydrates into absorbable monosaccharides, which can help manage control blood glucose levels [52]. Similarly, β-glucosidases, which play a pivotal role in lysosomal function by catalyzing the hydrolysis of glucosylceramide, are inhibited by iminosugars such as miglustat. This inhibition has therapeutic significance, particularly in the management of lysosomal storage disorders like Gaucher's disease where substrate accumulation is pathologic [53]. Another notable example involves α-mannosidases, which are essential for the maturation of glycoproteins. Iminosugar derivatives like nojirimycin disrupt the processing of viral glycoproteins, thereby reducing viral infectivity, a mechanism that holds potential in antiviral therapies [54]. This selective inhibition of glycosidases by iminosugars underscores their versatility and therapeutic potential in diverse biological contexts.

Recent research extends iminosugar relevance to oncology (targeting glycosidases in tumor progression), neurodegeneration (modulation of glycosphingolipids in Alzheimer's and Parkinson's), and cardiovascular disorders (linking glycosidase inhibition to improved vascular tone and antihypertensive outcomes) [29,55]. Advances in synthetic methodologies such as multicomponent reactions, stereoselective glycal derivatization, and late-stage functionalization continue to expand the accessible diversity of iminosugar derivatives [9,43].

Pyrrolidine-based iminosugar: Synthesis, biological assay and mechanism of action

Recent advances in synthetic methodologies, such as transition-metal catalysis, multicomponent reactions, and chemo-enzymatic transformations, have enabled access to structurally diverse pyrrolidine-based iminosugars with improved pharmacological profiles. The following subsections highlight representative strategies including Negishi coupling, amide coupling, and chemo-enzymatic synthesis and demonstrate how synthetic design impacts biological potency. The Negishi cross-coupling reaction has become a cornerstone methodology for introducing alkyl substituents onto heterocyclic scaffolds, and its application to pyrrolidine-based iminosugars is particularly noteworthy. Pyrrolidine-based pharmacological chaperones have been designed through the synthesis of α-1-C-alkyl-1,4-dideoxy-1,4-imino-D-arabinitol (α-1-C-alkyl-DAB) derivatives (**Scheme 1**) [56]. In this approach, a $Ni(cod)_2$ catalyst complexed with a chiral bis(oxazoline) ligand mediated the coupling between intermediate **1** and a series of alkylzinc bromides, affording products **2a-j** in moderate to excellent yields (57-89%).

Table 2. Classification of iminosugars and its examples

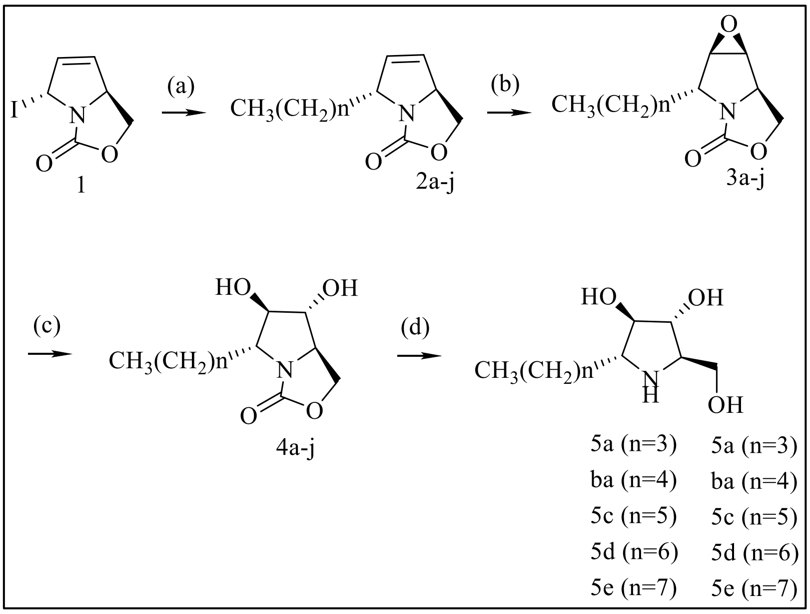
Classification	Therapeutic Applications	Compounds example	References
Piperidine	Antiviral, antidiabetic	DNJ, Fagomine	[9,42,43]
Pyrrolidine	Anticancer, antidiabetic	DAB	[26,44,45]
Pyrrolizidine	Antiviral, anti-HIV	Australine	[19,46]
Indolizidine	Anti-inflammatory, antiviral	Castanospermine, Swainsonine	[21,47,48]
Nor-tropane	Anticancer, antiviral	Calistegine B2	[18,49]

The synthetic sequence included diastereoselective epoxidation of the dihydropyrrole intermediates (**2a-j**) using trifluorodimethyldioxirane, generated in situ from trifluoroacetone and Oxone™. This step provided single diastereomers (**3a-j**) due to steric hindrance from the bulky C-1 substituents, which directed the approach of the oxidant to the less hindered α-face of the dihydropyrrole ring [10]. Subsequent acid-mediated oxirane cleavage yielded trans-diols (4a–j), which upon base treatment in aqueous ethanol produced α-1-C-alkyl-DAB derivatives (**5a-j**) in 46-90% yields. In this study, the iminosugars precursor is synthesized with different lengths of alkyl chain [20]. This may affect its stability under the extreme condition of treatment if used in pharmacological.

The α-1-C-alkyl-DABs were evaluated for their inhibitory activity against β-glucocerebrosidase (GCase), a lysosomal enzyme responsible for hydrolyzing glucosylceramide into ceramide and glucose. Dysfunction of GCase is the molecular hallmark of Gaucher's disease, and pharmacological chaperones that stabilize the enzyme under lysosomal conditions are highly sought after [57]. Biochemical assays demonstrated that α-1-C-octyl-DAB was the most potent inhibitor, with an IC_{50} of 6.2 μM, outperforming shorter-chain analogues [56]. The enhanced potency was attributed to hydrophobic interactions between the alkyl chain and the lipid-binding pocket of GCase, in addition to the canonical transition-state mimicry conferred by the iminosugar ring [58]. Mechanistically, the pyrrolidine ring nitrogen engages in protonation/deprotonation dynamics that mimic the oxocarbenium ion transition state of glycosidase catalysis, thereby stabilizing the enzyme-inhibitor complex [51]. Molecular docking and dynamics simulations have further confirmed that the alkyl chain extension allows deeper insertion into hydrophobic sub-pockets adjacent to the active site, which improves binding affinity and selectivity [13].

These findings highlight the dual contribution of the pyrrolidine scaffold: (i) as a transition-state mimic that competitively inhibits glycosidases, and (ii) as a hydrophobic substituent carrier that modulates interactions with the enzyme's lipid-binding region. Thus, Negishi coupling offers a robust platform for tailoring iminosugar derivatives with optimized enzyme affinity and therapeutic potential for lysosomal storage disorders and beyond.

Following the successful application of Negishi coupling in the synthesis of α-1-C-alkyl-DAB derivatives, researchers have also explored amide bond formation as a complementary route to generate structurally diverse iminosugar inhibitors. Amide bond formation remains one of the most reliable and widely applied reactions in medicinal chemistry, and its utility extends to the synthesis of iminosugar-based glycosidase inhibitors. A streamlined synthesis of monovalent α-L-fucosidase inhibitors (**Scheme 2**) using a classical amide coupling approach has been



Scheme 1. Synthesis of α-1-C-alkyl-DAB [56]. Reagents: (a) alkylzinc bromide (3.2 eq.), $Ni(cod)_2$ (16 mol%), (*R,R*)-2,6-bis(4-isopropyl-2-oxazolin-2-yl)pyridine (32 mol%), *N,N*-dimethylacetamide, rt, 20 h (b) Oxone™ (5.0 eq.), CF_3COCH_3 (10.0 eq.), $NaHCO_3$ (7.5 eq.), 0 °C, 2 h (c) CF_3CO_2H (12.0 eq.), THF/H_2O (3 : 2), reflux, 72 h (d) NaOH (10 eq.), EtOH/H_2O (2 :1), reflux, 1 h.

reported [59]. Starting from commercially available benzylamine **7** and an O- and N-protected carboxylic acid precursor, PyBOP **6** was employed as an efficient coupling agent in the presence of DIPEA as base. This reaction furnished amide-linked intermediates in high yield with excellent chemoselectivity. The simplicity of purification achieved by removing excess benzylamine through column chromatography underscored the practical nature and scalability of this approach [59].

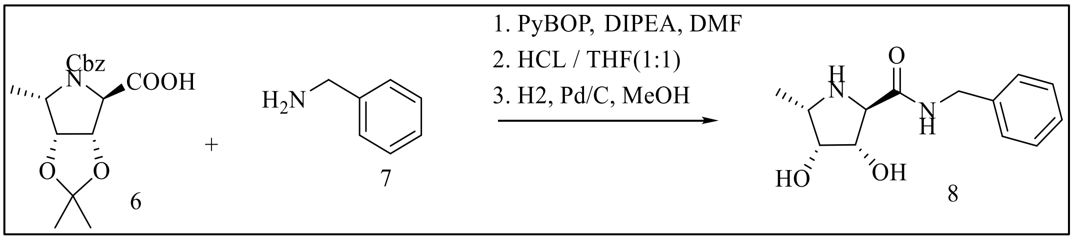
Subsequent acid-mediated deprotection followed by catalytic hydrogenation (H_2/Pd-C) afforded the final α-L-fucosidase **8** inhibitors in yields up to 84%. This methodology demonstrates the advantage of minimal protecting group manipulation, a significant factor in reducing synthetic complexity and improving overall efficiency [42]. Compared to multistep protecting-deprotecting sequences often required for iminosugar synthesis, this direct amide coupling route represents a more sustainable and scalable approach.

α-L-Fucosidase is a lysosomal exoglycosidase responsible for cleaving terminal L-fucose residues from glycoproteins and glycolipids. Deficiency in this enzyme leads to fucosidosis, a rare lysosomal storage disorder, while dysregulated α-L-fucosidase activity has been implicated in cancer progression and inflammatory processes [60]. Monovalent α-L-fucosidase inhibitors derived from pyrrolidine-based iminosugars act by transition-state mimicry, competitively occupying the enzyme's active site and blocking glycosidic bond hydrolysis. Cell-based assays have shown that such inhibitors can reduce fucose-dependent glycoprotein processing, potentially impacting cell adhesion and tumor metastasis [61]. Furthermore, molecular docking and dynamics simulations suggest that the amide linkage provides an additional hydrogen-bonding anchor within the enzyme's active site, improving binding affinity compared to unmodified iminosugars [41].

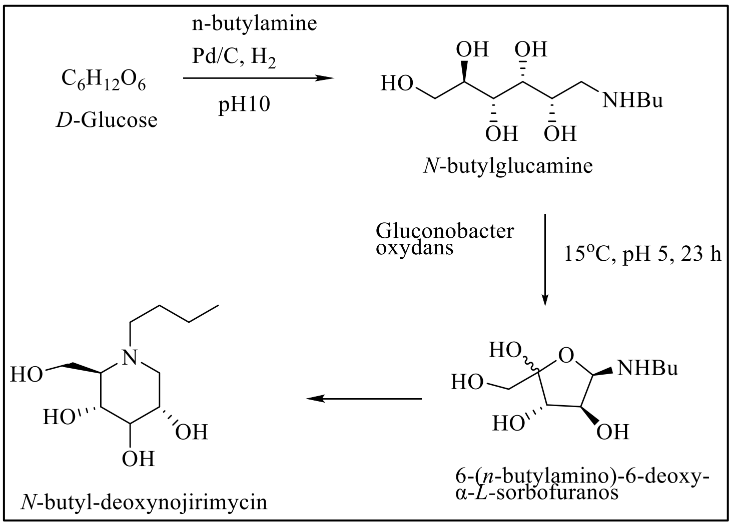
Recent studies also emphasize the potential of amide-modified iminosugars as multi-target inhibitors. By fine-tuning amide substituents, researchers have created derivatives capable of dual inhibition of α-L-fucosidase and α-glucosidase, highlighting opportunities in designing broad-spectrum glycosidase modulators for metabolic and oncological applications [21,29]. Thus, while Negishi coupling provides a powerful route to α-1-C-alkylated iminosugars with hydrophobic tuning for β-glucocerebrosidase inhibition, amide coupling strategies expand the chemical space toward α-L-fucosidase inhibitors, offering a complementary path for designing pharmacologically relevant iminosugars with therapeutic promise across metabolic, oncological, and lysosomal diseases.

In continuation of the synthetic strategies afforded by Negishi and amide coupling, the chemo-enzymatic route to Miglustat (NBDNJ) underscores the versatility of combining biocatalysis with classical organic transformations to generate pharmaceutically relevant iminosugars. This hybrid approach not only enhances stereoselectivity, but also improves atom economy, offering a sustainable platform for the large-scale production of iminosugar derivatives. Miglustat (NBDNJ), the first clinically approved iminosugar, provides proof of concept that glycomimetic compounds can achieve therapeutic relevance. Originally developed by Searle/Monsanto, its chemo-enzymatic synthesis (**Scheme 3**) exemplifies the synergy between biocatalysis and traditional organic chemistry in iminosugar production. The process begins with the selective oxidation of the C-2 hydroxyl group of glucose by Gluconobacter oxydans, which introduces the required carbonyl functionality with excellent regioselectivity, a transformation difficult to achieve using purely chemical routes [51]. The subsequent ring expansion under reductive conditions with butylamine provides access to NBDNJ in a streamlined, scalable, and one-pot process [41].

This hybrid chemo-enzymatic approach is advantageous for several reasons. First, it avoids protecting group manipulation, thereby improving step economy and atom efficiency compared to multistep purely chemical syntheses [62].Second, the microbial oxidation step is highly selective, reducing by-product formation and enabling industrial-scale synthesis under relatively mild conditions [63]. Importantly, this route was developed not only for commercial-scale manufacturing of miglustat but also



Scheme 2. Monovalent α-L-fucosidase inhibitors **8** [59]



Scheme 3. Chemo-enzymatic synthesis of NBDNJ [62]

as a platform for generating diverse N-alkyl DNJ derivatives, many of which were subsequently evaluated in anti-HIV and cystic fibrosis clinical studies [64,65].

Mechanistically, miglustat functions as a competitive inhibitor of β-glucosidase and glucosylceramide synthase, reducing the accumulation of glycosphingolipids in lysosomal storage disorders such as Gaucher's disease and Niemann-Pick disease type C [66]. More recent investigations have expanded its therapeutic relevance to oncology and virology, where N-alkyl DNJ derivatives interfere with viral glycoprotein maturation and modulate glycosphingolipid-mediated tumor signaling pathways [29,67]. Additionally, new synthetic refinements using engineered oxidoreductases and tailored fermentation conditions have improved yields, offering a sustainable route to structurally modified analogues with enhanced pharmacological properties [68].

Thus, the chemo-enzymatic synthesis of miglustat not only demonstrates the feasibility of large-scale iminosugar production but also highlights the broader utility of biocatalysis-driven synthetic platforms in developing next-generation iminosugar therapeutics across metabolic, viral, and oncological diseases.

ACE inhibitors as anti-hypertensive agents

Following the synthetic advancements in pyrrolidine-containing iminosugars, another important therapeutic strategy for hypertension involves the modulation of the renin-angiotensin system (RAS). At the center of this system lies the angiotensin-converting enzyme (ACE), a zinc metallopeptidase that plays a dual role: it catalyzes the conversion of angiotensin I (Ang I) into the potent vasoconstrictor angiotensin II (Ang II) and simultaneously degrades bradykinin (BK) into inactive metabolites [69,70]. The combined effect of increased Ang II and reduced BK leads to enhanced vasoconstriction, sodium retention, and elevated blood pressure, making ACE a prime pharmacological target in the management of cardiovascular disorders [71,72,73].

ACE inhibitors act by competitively blocking the active site of ACE, preventing the conversion of Ang I to Ang II and preserving bradykinin activity, thereby reducing vascular resistance and blood pressure [74]. Among the earliest examples, captopril was introduced as a first-generation ACE inhibitor derived from structural modification of proline, a pyrrolidine-containing amino acid, which was chemically optimized to bind the zinc ion in ACE's active site [75]. This structural connection highlights how heterocyclic scaffolds such as pyrrolidine central to iminosugar synthesis also underpin the rational design of antihypertensive drugs.

Over time, second- and third-generation ACE inhibitors such as enalapril, lisinopril, ramipril, and benazepril were developed to improve potency, bioavailability, and safety profiles. For instance, enalapril and lisinopril remain widely prescribed due to their efficacy in controlling hypertension and reducing cardiovascular morbidity, while ramipril is frequently used post-myocardial infarction due to its cardioprotective benefits [76]. More importantly, ACE inhibitors are not only beneficial in blood pressure control but also play critical roles in renal protection, endothelial function, and immune regulation [77].

Structurally, ACE inhibitors are classified into three groups based on modifications of the tetrahydropyrrole (pyrrolidine/proline) ring scaffold: (i) five-membered monocyclic inhibitors, (ii) bicyclic derivatives with two fused medium rings, and (iii) bicyclic derivatives with one medium ring and one large ring (**Figure 4**). These structural variations demonstrate the power of synthetic chemistry in tailoring heterocyclic frameworks for optimized enzyme binding and therapeutic performance [78].

Table 3 summarizes key examples of clinically used ACE inhibitors, highlighting their trade names, therapeutic applications, and notable side effects. While older ACE inhibitors such as captopril are associated with adverse events including rash and taste disturbances, newer derivatives exhibit improved safety and tolerability. The continued exploration of heterocyclic scaffolds such as pyrrolidines whether in iminosugar synthesis or ACE inhibitor development emphasizes the broad potential of nitrogen-containing five-membered rings as versatile pharmacophores in antihypertensive drug discovery.

Research gaps and future perspectives for improvement

Although notable progress has been made in the synthesis and evaluation of pyrrolidine-based iminosugars, several gaps remain that hinder their full translation into clinical applications. Current literature still lacks comprehensive structure–activity relationship (SAR) studies that systematically link structural modifications, such as alkyl chain length, stereochemistry, and ring substitutions, to antihypertensive potency and selectivity [26,29]. In addition, most investigations have emphasized glycosidase inhibition in metabolic and lysosomal storage disorders, with limited insight into the direct molecular mechanisms of these compounds in vascular regulation, endothelial signaling, and blood pressure control [51,66]. Biological assessments are also largely confined to in vitro or computational models, and robust in vivo pharmacological validation or clinical trials are still scarce, presenting a major barrier to translational development [13,84].

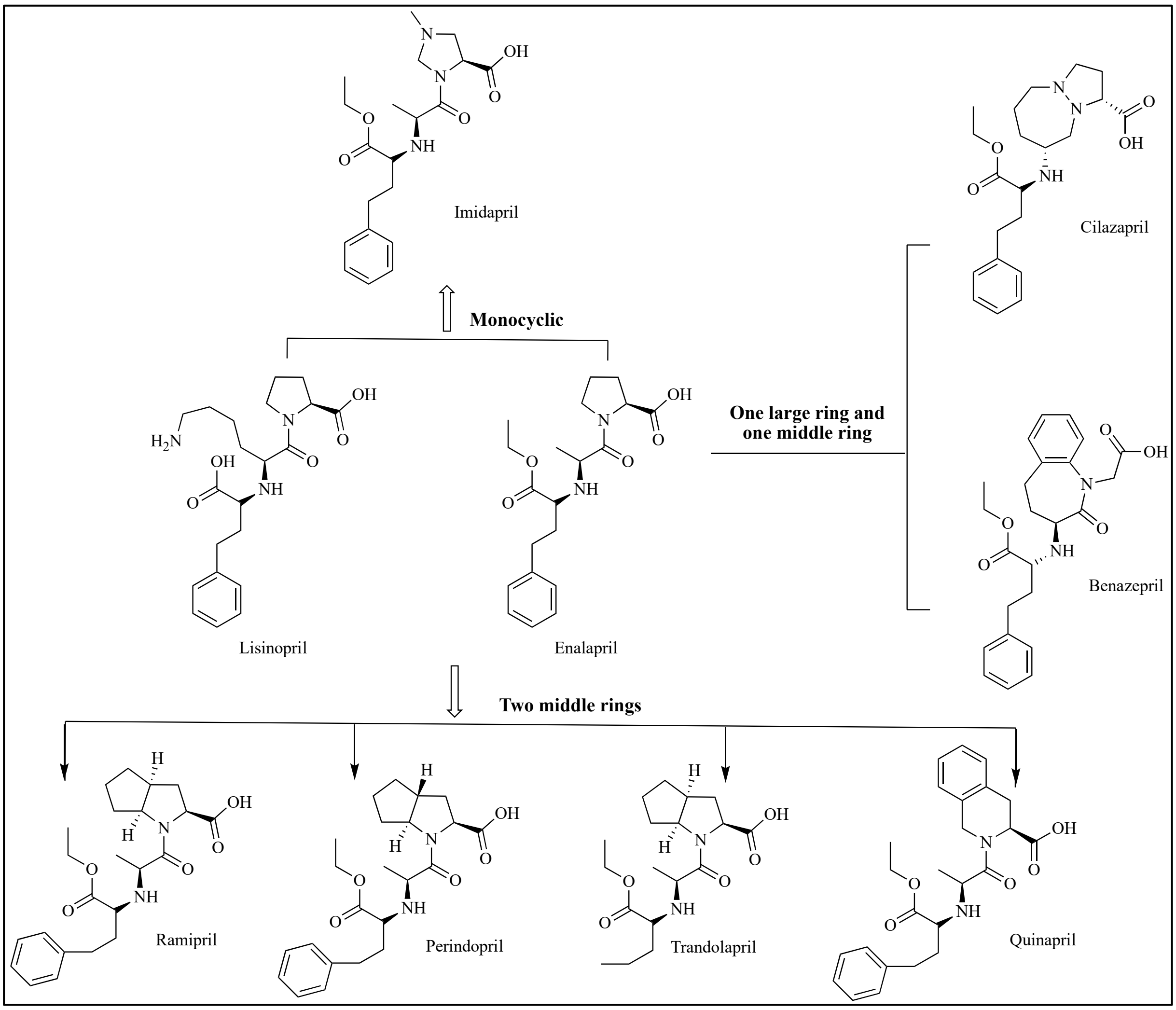


Figure 4. Classification of ACE inhibitors

Table 3. Examples of ACE Inhibitors

ACE Inhibitors	Example	Prescription/Clinical Use	References
Captopril	Capoten	• First ACE inhibitor approved • Associated with adverse effects such as rash and taste disturbances • Short half-life	[75,79]
Enalapril	Vasotec	• Widely prescribed due to effectiveness and favorable safety profile • Prodrug converted to enalaprilat in vivo	[74,80]
Lisinopril	Prinivil, Zestril	• Long-acting inhibitor used for hypertension and heart failure • Does not require metabolic activation	[69,81]
Ramipril	Altace	• Prodrug hydrolyzed to ramiprilat • Commonly prescribed post-myocardial infarction for cardioprotection	[76,82]
Benazepril	Lotensin	• Long-acting ACE inhibitor often used in combination with diuretics or calcium-channel blockers for resistant hypertension.	[77,83]

From a synthetic perspective, while strategies such as Negishi coupling, amide coupling, and chemo-enzymatic methods have expanded accessibility, many existing approaches remain constrained by multi-step protection-deprotection sequences, low yields, or reliance on non-sustainable reagents, thus limiting scalability [56,62,68]. Furthermore, the potential of pyrrolidine-based iminosugars to act synergistically with established antihypertensive therapies, such as ACE inhibitors or angiotensin receptor blockers, has not been systematically investigated [69,74].

Looking forward, future research should prioritize the development of comprehensive SAR and QSAR analyses to optimize scaffold design, supported by molecular docking, dynamics simulations, and omics-based studies to better elucidate mechanisms of action in hypertension models [7,13]. Expanding in vivo investigations and progressing to early-phase clinical evaluations will be crucial in validating therapeutic potential. On the synthetic front, the adoption of green and scalable approaches including biocatalytic, continuous-flow, and one-pot methodologies will be essential for industrial application [41,63]. Finally, exploring the role of iminosugars in combination therapy with conventional antihypertensives may open new avenues for multi-targeted strategies in blood pressure management [77,78]. By addressing these gaps, pyrrolidine-based iminosugars can be advanced as next-generation candidates in antihypertensive therapy, bridging innovative synthetic chemistry with clinical pharmacology.

Conclusion

In conclusion, pyrrolidine-based iminosugars represent a promising and versatile class of compounds at the intersection of synthetic chemistry and cardiovascular pharmacology. Recent advances in transition-metal catalysis, amide coupling strategies, and chemo-enzymatic methodologies have greatly expanded the diversity and accessibility of these molecules, allowing fine-tuning of their structural and functional properties. Their ability to act as potent glycosidase inhibitors provides a mechanistic foundation for therapeutic intervention in hypertension, with emerging evidence suggesting beneficial effects on vascular function, endothelial signaling, and metabolic regulation.

Moreover, the structural parallels between pyrrolidine scaffolds in iminosugars and proline-derived ACE inhibitors underscore the broader role of five-membered nitrogen heterocycles in antihypertensive drug discovery. While current findings highlight strong potential, the translation of these compounds into clinical applications remains at an early stage. Future work should prioritize structure-activity relationship studies, molecular docking and dynamic simulations, in vivo pharmacological validation, and clinical investigations to fully establish their therapeutic utility.

In summary, pyrrolidine-based iminosugars offer innovative opportunities for next-generation antihypertensive therapy, bridging synthetic innovation with biomedical application. Continued interdisciplinary research integrating organic synthesis, computational modeling, and pharmacological testing will be essential to unlock their clinical relevance and to expand the arsenal of agents available for combating hypertension a persistent global health challenge.

Acknowledgement
This work was financially supported under the Fundamental Research Grant Scheme 2021 (FRGS/1/2021/WAB04/UITM/02/3) funded by the Ministry of Higher Education (MOHE), Malaysia. The authors acknowledge the generous support of Organic Synthesis Laboratory, Institute of Science, Universiti Teknologi MARA (UiTM) for the facilities provided.

References

1. World Health Organization: WHO. (2021, August 25). More than 700 million people with untreated hypertension. *World Health Organization and Imperial College London Joint Press Release*. Access from https://www.who.int/news/ item/25-08-2021-more-than-700-million-people-with-untreated-hypertension
2. Singh, S. D. (2024). Treating hypertension: Important for heart and kidney health. *Journal of Family Medicine and Primary Care*, 13(2): 101-105.
3. Nugroho, P., Andrew, H., Kohar, K., Noor, C. A., and Sutranto, A. L. (2022). Comparison between the world health organization (WHO) and international society of hypertension (ISH) guidelines for hypertension. *Annals of Medicine,* 54(1): 837-845.
4. Unger, T., Borghi, C., Charchar, F., Khan, N. A., Poulter, N. R., Prabhakaran, D., Ramirez, A., Schlaich, M., Stergiou, G. S., Tomaszewski, M., Wainford, R. D., Williams, B., Schutte, A. E., and on behalf of the International Society of Hypertension. (2020). 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension*, 75(6): 1334-1357.
5. Conforti, I., Ramos-Soriano, J., and Bernardes, G. J. L. (2021). Iminosugars as glycosyltransferase inhibitors: Recent advances and future perspectives. *Organic & Biomolecular Chemistry*, 19(36): 7939-7956.
6. Ferjančič, Ž., Ilić, J., and Svete, J. (2023). Development of iminosugar-based glycosidase inhibitors: Current status and future directions. *Drug Discovery Today*, 28(7): 103536.
7. Hunt-Painter, A. A., Chapman, M. S., and Fleet, G. W. J. (2022). An amination–cyclization cascade for the stereoselective synthesis of iminosugars. *ACS Omega*, 7(12): 10125-10136.
8. Liotta, L. J., Jackson, D., and Chen, M. (2024). Efficient synthesis for each of the eight stereoisomers of pyrrolidine-containing iminosugars. *Carbohydrate Research*, 532: 108885.
9. Wang, H., Zhou, J., and Zhang, Y. (2022). Design and synthesis of N-substituted iminosugar C-glycosides as potent α-glucosidase inhibitors. *Molecules*, 27(15): 4901.
10. Lu, T. T., Yang, X., and Li, H. (2021). Synthesis and glycosidase inhibition of 5-C-alkyl and 6-C-alkyl deoxynojirimycin derivatives. *European Journal of Medicinal Chemistry*, 221: 113559.
11. U.S. Food and Drug Administration. (2020). Zavesca (miglustat) prescribing information. FDA. Access from https://www.access data.fda.gov.
12. European Medicines Agency. (2022). Zavesca: Summary of product characteristics. EMA. Access from https://www.ema.europa.eu.
13. Mhaldar, S. N., Chavan, S. S., and More, S. N. (2022). Computational and experimental studies of pyrrolidine-based iminosugars as α-glucosidase inhibitors. *Chemical Physics Letters*, 799: 139638.
14. Compain, P., Chagnault, V., and Martin, O. R. (2009). Tactics and strategies for the synthesis of iminosugar C-glycosides: A review. *Tetrahedron: Asymmetry*, 20(6-8): 672-711.
15. Slivnick, J., and Lampert, B. C. (2019). Hypertension and Heart Failure. *Heart Failure Clinics,* 15(4): 531-541.
16. Borges de Melo, E., da Silveira Gomes, A., & Carvalho, I. (2006). α- and β-Glucosidase inhibitors: chemical structure and biological activity. *Tetrahedron*, 62(44): 10277-10302.
17. Smolobochkin, A. N. (2024). Structural and stereoelectronic properties of pyrrolidine: A five-membered saturated nitrogen heterocycle. *Journal of Heterocyclic Chemistry*, 61(4): 345-356.
18. Sahu, R. (2024). Recent advancement in pyrrolidine moiety: Natural occurrence and medicinal importance. *Journal of Natural Products Research*, 8(3): 201-213.
19. Jessen, S., Rauhut, T., and Bräse, S. (2020). Alkaloids containing pyrrolidine and piperidine frameworks: Natural products and synthetic advances. *Chemical Reviews*, 120(12): 10175-10221.
20. Massiot, G., and Delaude, C. (1986). Pyrrolidine alkaloids. *The Alkaloids: Chemistry and Pharmacology*, 28: 151-238.
21. Bailly, C., and Vergoten, G. (2025). Overview of the Ruspolia genus: Chemical diversity and bioactive potentials of isolated pyrrolidine alkaloids. *Phytochemistry Reviews*, 24(2): 233249.
22. Barth, M., Seebeck, F. P., and Süssmuth, R. D. (2022). Proline and hydroxyproline derivatives

in peptide natural products. *Natural Product Reports*, 39(8): 1445-1468.

23. Kuwano, R., Kashiwabara, M., Ohsumi, M., and Kusano, H. (2008). Catalytic asymmetric hydrogenation of 2,3,5-trisubstituted pyrroles. *Journal of the American Chemical Society*, *130*(3): 808-809.
24. Greene, M. J., Patel, S., and Kappe, C. O. (2019). Continuous-flow hydrogenation of pyrroles to pyrrolidines: Advances and applications. *Organic Process Research & Development,* 23(11): 2401-2409.
25. Back, T. G., Parvez, M., and Zhai, H. (2003). Stereospecific rearrangements during the synthesis of pyrrolidines and related heterocycles from cyclizations of amino alcohols with vinyl sulfones. *Journal of Organic Chemistry*, 68(24): 9389-9393.
26. Liotta, L. J., Jackson, D., and Chen, M. (2024). Efficient synthesis for each of the eight stereoisomers of pyrrolidine-containing iminosugars. *Carbohydrate Research*, 532: 108885.
27. Hayashi, Y. (2014). The asymmetric catalytic mannich reaction catalyzed by organocatalyst. *Journal of Synthetic Organic Chemistry, Japan,* 72(11): 1228-1238.
28. Zhang, X., Chen, P., and Zhang, L. (2025). Recent synthetic methodologies for pyrrolidine derivatives via multicomponent reactions. *Synthetic Communications,* 55(4): 523-534.
29. Rahman, A. (2025). A review on recent progress in synthesis and biological significance of pyrrolidine derivatives via multicomponent reactions. *Journal of Heterocyclic Chemistry*, 62(3): 455-472.
30. Coldham, I., and Hufton, R. (2005). Intramolecular dipolar cycloaddition reactions of azomethineylides. *Chemical Reviews*, 105(7): 2765-2809.
31. Najera, C., and Sansano, J. M. (2007). 1,3-Dipolar cycloaddition of azomethine ylides: An entry to enantiopure pyrrolidines. *Angewandte Chemie International Edition*, 46(32): 6276-6287.
32. Cozzi, P. G. (2006). Metal–Salen Schiff base complexes in catalysis: Practical aspects. *Chemical Society Reviews*, 33(7): 410-421.
33. Prier, C. K., Rankic, D. A., and MacMillan, D. W. C. (2013). Visible light photo-redox catalysis with transition metal complexes: Applications in organic synthesis. *Chemical Reviews*, 113(7): 5322-5363.
34. Choi, G. J., Knowles, R. R. (2015). Catalytic alkylation of remote C-H bonds enabled by proton-coupled electron transfer. *Journal of the American Chemical Society*, 137(29): 9226-9229.
35. List, B. (2002). Proline-catalyzed asymmetric reactions. *Tetrahedron*, 58(28): 5573-5590.
36. Melchiorre, P., Marigo, M., Carlone, A., and Bartoli, G. (2008). Asymmetric aminocatalysis-gold rush in organic chemistry. *Angewandte Chemie International Edition*, 47(33): 6138-6171.
37. Labinger, J. A., and Bercaw, J. E. (2002). Understanding and exploiting C–H bond activation. *Nature*, 417(6888): 507-514.
38. Chen, X., Engle, K. M., Wang, D. H., and Yu, J. Q. (2009). Palladium(II)-catalyzed C–H activation/C–C cross-coupling reactions: Versatility and practicality. *Angewandte Chemie International Edition*, 48(28): 5094-5115.
39. Bornscheuer, U. T., and Kazlauskas, R. J. (2006). Catalytic promiscuity in biocatalysis: Using old enzymes to form new bonds and follow new pathways. *Angewandte Chemie International Edition*, 45(41): 6156-6165.
40. Schrittwieser, J. H., Velikogne, S., Hall, M., and Kroutil, W. (2018). Artificial biocatalytic linear cascades for preparation of organic molecules. *Chemical Reviews*, 118(1): 270-348.
41. Smiljanic, K., van der Walt, J., and van Zyl, R. L. (2022). Polyhydroxylated alkaloids: Novel scaffolds for drug discovery. *Molecules*, 27(18): 5903.
42. Muraoka, T., Kameda, Y., & Nishimura, S. (2020). Fagomine: Biosynthesis and therapeutic applications of a piperidine alkaloid. *Phytochemistry*, 170: 112215.
43. Wang, G., Chen, M., Wang, J., Peng, Y., Li, L, Xie, Z. Z., et al. (2017). Synthesis, biological evaluation and molecular docking studies of chromone hydrazone derivatives as a-glucosidase inhibitors. *Bioorganic and Medicinal Chemistry Letters*, 27(13): 2957-2961.
44. Song, Y. Y, Kinami, K, Kato, A., Jia, Y. M., Li, Y. X., Fleet, G. W.J., and Yu, C.Y.(2016). First total synthesis of *(+)*-broussonetine W: Glycosidase inhibition of natural product & analogs. *Organic and Biomolecular Chemistry*, 14(22), 5157-5174.
45. Gavale, K. S., Chavan, S. R., Kumbhar, N., Kawade, S., Doshi, P., Khan, A., and Dhavale, D. D. (2017). α-Geminal disubstituted pyrrolidine iminosugars and their C-4-fluoro analogues: Synthesis, glycosidase inhibition and molecular docking studies. *Bioorganic and Medicinal Chemistry*, 25(19): 5148-5159.
46. Li, Y.X, Shimada, Y., Sato, K., Kato, A., Zhang, W., Jia, Y.M., et al. (2015). Synthesis and glycosidase inhibition of Australine and its fluorinated derivatives. *Organic Letters*, 17(3): 716-719.
47. Poyraz, S. (2023). Recent insights about

pyrrolidine core skeletons in pharmacology. *Frontiers in Pharmacology*, 14: 1239658.
48. Machan, T., Davis, A. S., Liawruangrath, B, and Pyne, S. G. (2008). Synthesis of castanospermine. *Tetrahedron*, 64(12): 2725-2732.
49. Garcia-Moreno, M. I., Benito, J. M., Ortiz Mellet, C., and García Fernández, J. M. (2001). Synthesis and evaluation of calystegine B2 analogues as glycosidase inhibitors. *Journal of Organic Chemistry*, 66(23): 7604-14.
50. EMA. (2022). Zavesca (miglustat): Summary of product characteristics. European Medicines Agency. Access https://www.ema.europa.eu
51. Alonzi, D. S., Scott, K. A., Dwek, R. A., and Zitzmann, N. (2018). Iminosugar antivirals: The therapeutic potential of glycosidase inhibitors for hepatitis and other viruses. *Antiviral Research*, 158: 79-94.
52. Nash, R.J., Kato, A., Yu, C.Y., and Fleet, G. W. (2011). Iminosugars as therapeutic agents: recent advances and promising trends. *Future Medicine Chemistry*, 3(12): 1513-21.
53. Terry D. Butters, Raymond A. Dwek, Frances M. Platt (2005). Iminosugar inhibitors for treating the lysosomal glycosphingolipido ses, *Glycobiology*, 15(10): 43R-52R.
54. Alonzi DS, Scott KA, Dwek RA, Zitzmann N (2017). Iminosugar antivirals: the therapeutic sweet spot. *Biochemistry Society Trans*, 45(2): 571-582.
55. Singh, S. D. (2024). Treating hypertension: Important for heart and kidney health. *Journal of Family Medicine and Primary Care*, 13(2): 101-105.
56. Kato, A., Nakagome, I., Sato, K., Yamamoto, A., Adachi, I., Nash, R. J., and Hirono, S. (2016). Docking study and biological evaluation of pyrrolidine-based iminosugars as pharmacological chaperones for Gaucher disease. *Organic & Biomolecular Chemistry*, 14(3): 1039-1048.
57. Pastores, G. M., Hughes, D. A., and Grabowski, G. A. (2020). Gaucher disease: Pathophysiology, clinical presentation, and therapy. *American Journal of Hematology*, 95(1): 43-45.
58. Nair, A. K. N., Rankin, C., and Butters, T. D. (2019). Structural insights into iminosugar interactions with glycosidases. *Glycobiology*, 29(11): 785-797.
59. Wang, H., Zhou, J., and Zhang, Y. (2021). Design and synthesis of monovalent α-L-fucosidase inhibitors via amide coupling. *Molecules*, 26(22): 6945.
60. Bekri, S., Ouzzine, M., and Netter, P. (2022). α-L-Fucosidase: Biochemical function and therapeutic potential. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, 1868(12): 166543.
61. Wu, L., Pan, Q., and Li, X. (2021). Targeting α-L-fucosidase in cancer progression: Emerging strategies. *Frontiers in Oncology*, 11: 789654.
62. Durantie, E., Werz, D. B., and Seeberger, P. H. (2019). Chemoenzymatic synthesis of carbohydrates and glycomimetics. *Chemical Reviews*, 119(7): 3883-3962.
63. McEachern, K. A., Fung, J., and Valenzano, K. J. (2020). Industrial development of iminosugar therapeutics: Miglustat as a case study. Trends in Biotechnology, 38(12): 1357-1369.
64. Butters, T. D., and Dwek, R. A. (2021). Glycomimetics in clinical use: The story of miglustat. *Drug Discovery Today*, 26(9): 2115-2124.
65. Esposito, A., D'Alonzo, D., De Fenza, M., De Gregorio, E., Tamanini, A., Lippi, G., ... and Guaragna, A. (2020). Synthesis and therapeutic applications of iminosugars in cystic fibrosis. *International Journal of Molecular Sciences*, 21(9): 3353.
66. Platt, F. M., d'Azzo, A., Davidson, B. L., Neufeld, E. F., and Tifft, C. J. (2019). Lysosomal storage diseases. *Nature Reviews Disease Primers*, 5(1): 1-21.
67. Mikhailov, A., Jensen, K., and Platt, F. M. (2021). Expanding therapeutic applications of iminosugars: From lysosomal storage disorders to oncology. *Nature Reviews Drug Discovery*, 20(11): 841-860.
68. Gutiérrez, M. C., and Fernández, M. J. (2023). Biocatalysis in iminosugar synthesis: Advances in enzymatic oxidation and reductive transformations. *ACS Catalysis*, 13(5): 3221-3235.
69. Dzau, V. J., and Antman, E. M. (2021). The cardiovascular continuum and renin-angiotensin–aldosterone system blockade. *Journal of the American College of Cardiology,* 78(9): 941-954.
70. Fyhrquist, F., and Saijonmaa, O. (2020). Renin–angiotensin system revisited. *Journal of Internal Medicine*, 288(2): 161-175.
71. Cao, D. Y., Spivia, W. R., Veiras, L. C., Khan, Z., Peng, Z., Jones, A. E., Bernstein, E. A., Saito, S., Okwan-Duodu, D., Parker, S. J., Giani, J. F., Divakaruni, A. S., Van Eyk, J. E., and Bernstein, K. E. (2020). ACE overexpression in myeloid cells increases oxidative metabolism and cellular ATP. *Journal of Biological Chemistry,* 295(5): 1369-1384.
72. Shirbhate, E., Pandey, J., Patel, V. K., Kamal, M., Jawaid, T., Gorain, B., Kesharwani, P., and Rajak, H. (2021). Understanding the role of ACE-2 receptor in pathogenesis of COVID-19 disease: a potential approach for therapeutic intervention. *Pharmacology Reports,* 73(6):

1539-1550.

73. Bernstein, K. E., Ong, F. S., Blackwell, W.-L. B., Shah, K. H., Giani, J. F., Gonzalez-Villalobos, R. A., Shen, X. Z., and Fuchs, S. (2013). A modern understanding of the traditional and nontraditional biological functions of angiotensin-converting enzyme. *Pharmacological Reviews,* 65(1): 1-46.
74. Brown, N. J., and Vaughan, D. E. (2020). Angiotensin-converting enzyme inhibitors. *Circulation Research*, 126(12): 1682-1700.
75. Patel, R., Shahane, S., and Singh, R. (2019). Rational design of ACE inhibitors: Role of proline and its analogs. *Bioorganic & Medicinal Chemistry Letters,* 29(14): 1711-1719.
76. Ferrario, C. M., and Strawn, W. B. (2019). Role of the renin-angiotensin-aldosterone system and proline-derived drugs in cardiovascular disease. *American Journal of Medicine*, 132(2): 123-134.
77. Kokkinos, P., Faselis, C., and Myers, J. (2022). ACE inhibitors and their pleiotropic effects in hypertension and beyond. *Current Hypertension Reports*, 24(5): 145-156.
78. He, Y., Zhao, J., Xu, X., and Ma, Y. (2021). Structural diversity of ACE inhibitors: Advances in design and therapeutic perspectives. *European Journal of Medicinal Chemistry*, 225: 113803.
79. Watanabe, Y., and Yasuda, S. (2020). Captopril: Revisiting the first ACE inhibitor in cardiovascular therapy. *Hypertension Research*, 43(6): 563-573.
80. Messerli, F. H., Bangalore, S., & Bavishi, C. (2018). Angiotensin-converting enzyme inhibitors in hypertension: To use or not to use? *Journal of the American College of Cardiology*, 71(13): 1474-1482.
81. Mahmood, S. S., and Levy, D. (2020). Lisinopril in heart failure management: Past, present, and future. *European Heart Journal Supplements*, 22: 112-118.
82. Yusuf, S., Sleight, P., Pogue, J., Bosch, J., Davies, R., and Dagenais, G. (2000). Effects of an angiotensin-converting–enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *The New England Journal of Medicine,* 342(3): 145-153.
83. Bakris, G. L., Sica, D., Weber, M., White, W. B., Roberts, A., Perez, A., Cao, C., Kupfer, S., and Cao, C. (2019). The comparative effects of benazepril and amlodipine in hypertensive patients: Long-term outcomes. *Journal of Clinical Hypertension*, 21(9): 1342-1350.
84. Nair, A. K. N., Rankin, C., and Butters, T. D. (2019). Structural insights into iminosugar interactions with glycosidases. *Glycobiology*, 29(11): 785-797.