A Review on Calcium Channel Blockers as an Effective Treatment Strategy for Hypertension

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

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Brac University
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled "A Review on Calcium Channel Blockers as an Effective Treatment Strategy for Hypertension." submitted by Partho Saha Shuvo (ID: 19346003) of Summer, 2023 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This study involves no animal and human trial.

Abstract

A higher force that blood applies to artery walls is characteristic of hypertension, known as high blood pressure. Calcium channel blockers (CCBs) treat hypertension via specifically blocking voltage-gated calcium channels found in the smooth muscle cells of the arterial walls. CCBs prevent calcium ions from entering these cells which relaxes the arterial smooth muscle cells and widens the blood vessels. DHP-CCBs e.g. amlodipine and nifedipine are the most frequently suggested CCBs because they are well-tolerated, have few adverse effects, and effectively control blood pressure. Diltiazem and verapamil, two non-DHP-CCBs are alternative therapies used to treat hypertension, angina and arrhythmias and block calcium channels in the heart, causing a heart rate and contractility drop. This review article covers mechanism of action, synthesis and SARs of CCBs. It aims to assist medicinal chemists in the field of developing new antihypertensive agents through presenting recent information on producing CCBs and their synthetic techniques in the literature.

Keywords: Anti-hypertensive drugs; Calcium channel; CCBs; DHP; Non-DHP; Benzodiazepines.

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List of Acronyms

CCBs	Calcium Channel Blockers
DHP	Dihydropyridine
Non-DHP	Non-Dihydropyridine
CYP	Cytochrome P450
DCM	Dichloromethane
MAA	Methylacetoacetate
NH_4SCN	Ammonium Thiocyanate
ACE	Angiotensin-converting enzyme
LTCCs	L-Type Calcium Channels
CaV2.2	N-Type Calcium Channels
ARBs	Angiotensin Receptor Blockers
CVD	Cardiovascular Disease
SA	Sinoatrial
AV	Atrioventricular
SAH	Subarachnoid Hemorrhage

Chapter 1

Introduction

1.1 Hypertension and Anti-Hypertensive Drugs

A chronic medical disease called hypertension sometimes referred to as high blood pressure, is defined by an increased force that the blood exerts opposing the inner linings of the arterial walls. Over one billion people are affected globally, and it is the primary cause of cardiovascular disease (CVD), stroke, and kidney failure (Kearney et al., 2005)

Calcium channel blockers (CCBs) is frequently prescribed to treat cardiovascular diseases such as hypertension. The ability of CCBs to selectively block voltage-gated calcium channels, which are located in the smooth muscle cells of the artery walls, is the primary mechanism by which they work to treat hypertension.(Godfraind, 2017)
By obstructing calcium channels, CCBs stop calcium ions from entering these cells, which causes the arterial smooth muscle cells to relax and the blood arteries to dilate. Because of this, CCBs help treat hypertension by lowering blood pressure and reducing peripheral resistance (Morales-Suárez-Varela et al., 2010)

Other problems like angina, arrhythmias, and migraines are also managed with CCBs. Dihydropyridine (DHP) and non-dihydropyridine (non-DHP) CCBs are the two primary categories of CCBs. (McKeever & Hamilton, 2023)
Amlodipine and nifedipine are two examples of the DHP-CCBs most frequently recommended for hypertension. According to (Brugts et al., 2010), they selectively block calcium channels in vascular smooth muscle cells, which causes vasodilation and a reduction in peripheral resistance, which lower blood pressure. (Dariush Mozaffarian,

n.d.) state that DHP-CCBs are well-tolerated, seldom cause adverse effects, and successfully lower blood pressure.

Diltiazem and verapamil are examples of non-DHP-CCBs that block calcium channels in the heart, causing a reduction in heart rate and contractility. Non-DHP-CCBs provide treatment for hypertension, angina, and arrhythmias. Compared to DHP-CCBs, they are fewer effective vasodilators and may have more significant adverse effects, including constipation, vertigo, and headaches (Brugts et al., 2010)

In hypertensive individuals, CCBs have been demonstrated to help lower blood pressure and cardiovascular disease risk. CCBs were discovered to be equally beneficial as other antihypertensive medications in lowering blood pressure and preventing cardiovascular events in a meta-analysis of randomized controlled trials. (Haller, 2008a)

A common and deadly medical disease called hypertension can cause a lot of morbidity and mortality. A group of antihypertensive medications known as CCBs are efficient at lowering blood pressure and reducing the risk of cardiovascular disease. The most frequently recommended CCBs for hypertension are DHP-CCBs, which are well-tolerated and have few adverse effects. Non-DHP-CCBs treat arrhythmias, hypertension, and anginal pain but may have more side effects than DHP-CCBs. (Basile, 2004a)

1.2: Calcium Channel Blockers & Classification of Calcium Channel Blockers

By obstructing the L-type calcium channel (LTCCs), calcium channel blocking agents (CCBs) prevent the flow of calcium ions across the cell membrane. This blockage inhibits the contraction of cells in the sinoatrial (SA) and atrioventricular (AV) nodes and smooth and cardiac muscle. The principal effects of CCBs include decreasing AV conduction, lowering heart rate, dilatation of the coronary and peripheral artery vasculature, and negative inotropic action. However, the degree of selectivity at various tissue sites and the responses of baroreceptors to the vasodilation brought on by the CCB make each drug's effects unique. (Zamponi et al., 2015) Calcium channel blockers fall into one of two categories based on their chemical makeup:

Amlodipine, benidipine, clinidine, felodipine, nisoldipine, nicardipine, nifedipine, and nimodipine are examples of dihydropyridines. Phenylalkylamines (verapamil) and benzothiazepines (diltiazem) are examples of non-dihydropyridines. There is the worry that the efficacy and safety may differ between the dihydropyridine and non-dihydropyridine groupings because they belong to the same pharmacological class but have some variances in their modes of action and adverse effects. (Handler, 2005)

Dihydropyridines exhibit a higher degree of specificity towards vascular smooth muscle compared to myocardium. This is due to their ability to inhibit calcium channels in smooth muscle at concentrations that do not elicit significant cardiac effects. Consequently, dihydropyridines demonstrate less negative inotropic activity when compared to verapamil or diltiazem. (Cataldi & Bruno, 2012)

Benzothiazepines and phenylalkylamines exhibit lower levels of selectivity in their vasodilator activity compared to dihydropyridines. Additionally, they directly affect the myocardium, leading to a decrease in SA and AV nodal conduction. (Mcdonagh et al., 2005)

Peripheral edema, flushing, tachycardia, and dizziness are frequently observed as adverse effects of dihydropyridine calcium channel blockers (CCBs). Non-dihydropyridine calcium channel blockers (CCBs) exert inhibitory effects on cardiac tissue, resulting in cardiac depression and atrioventricular block. It has been established that verapamil is associated with the occurrence of constipation. (Laurent, 2017)

On occasion, both dihydropyridine calcium channel blockers (CCBs) and non-dihydropyridine CCBs have been associated with the occurrence of gingival hyperplasia, esophageal dysfunction, and a slight increase in hepatic transaminase levels. (Dougall & Mclay, n.d.)

Patients who have exhibited allergies to any component of the medication should refrain from using calcium channel blockers (CCBs). Moreover, it is not recommended for individuals with high blood pressure, sick sinus syndrome, second or third-degree heart blocks, auxiliary bypass tract patients, acute myocardial infarction (MI), or pulmonary congestion to utilize calcium channel blockers (CCBs). (Ojha et al., 2022a)

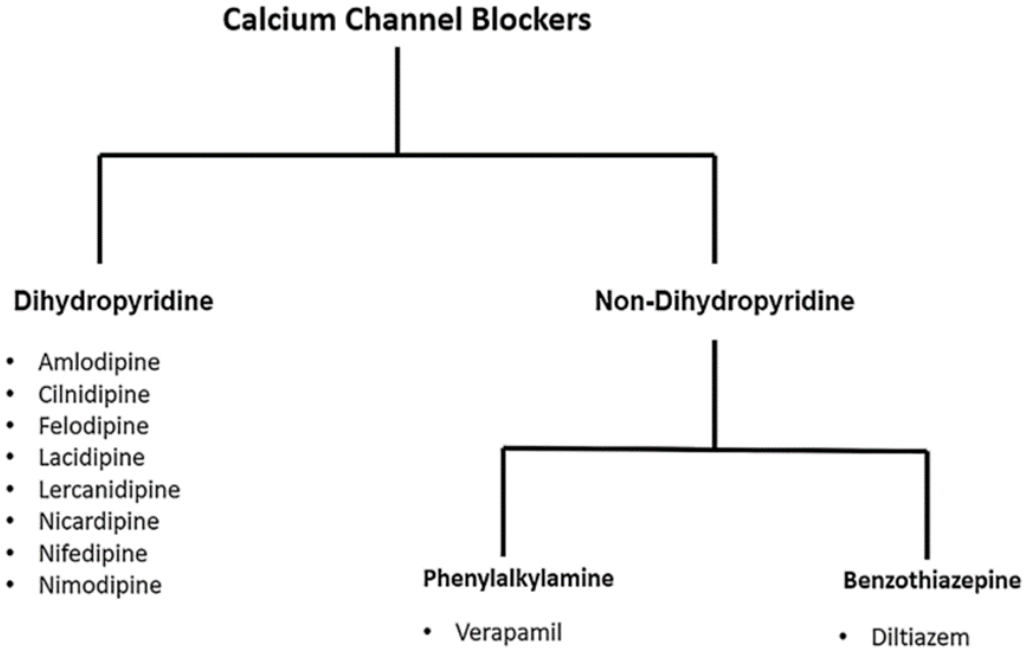

Figure 1: Classification of Calcium Channel Blockers (Ojha et al., 2022a)

1.3: Methodology

This review paper has been combined by incorporating the latest and pertinent research papers and articles obtained from journals with significant impact factors. A thorough investigation has been conducted by carefully examining reputable academic publications, articles, and official reports. To augment the comprehensiveness of the review paper, primary and secondary data were collected from diverse scholarly sources. The data for this study was obtained from a variety of search engines, including ResearchGate, PubMed, Google Scholar, Science Direct, Elsevier, and additional sources. The main sources consulted for this study encompassed a range of academic publications, such as Frontiers in Neurology, the American Chemistry Society (ACS), LiverTox, the Journal of Clinical Hypertension, the Journal of Pharmacological Sciences, and The American Journal of Cardiology, among others. In order to develop a comprehensive review on the synthesis of calcium channel blockers for the management of hypertension, a thorough examination of scholarly literature was conducted. This involved conducting an extensive search across various academic journals, followed by a meticulous selection process to identify the most recent publications within the past fifteen years that were pertinent to the topic.

Chapter 2

Dihydropyridines

2.1: Amlodipine

A common antihypertensive drug, amlodipine, is among the group of calcium channel blockers (CCBs) known as dihydropyridine. Amlodipine is classified as a calcium channel blocker within the subclass of calcium channel blockers known as the 1,4-dihydropyridine ring structure. It selectively prevents calcium ions from entering L-type calcium channels, which dilates the arteries (vasodilation) and lowers blood pressure. Angina and heart failure are two more cardiovascular diseases treated with amlodipine. Since it has a long half-life, once-daily dosing is possible, and patients typically tolerate it well.

In accordance with the guidelines established by the American College of Cardiology/American Heart Association, Amlodipine is considered a recommended pharmaceutical intervention for the management of hypertension. This recommendation is based on the drug's demonstrated efficacy and favorable tolerability profile. (*4. Whelton2018*, n.d.) According to research by (Thomopoulos et al., 2015) , amlodipine has also been proven to improve cardiovascular outcomes, such as lowering the risk of heart attacks, strokes, myocardial infarctions (MI), and heart failure.

2.1.1: Synthesis of Amlodipine

Amlodipine is synthesized via several steps. Which are:

1. The reaction between ethyl-4-chloroacetoacetate and 2-azidoethanol in the presence of sodium hydride results in the formation of ethyl-4-(2-azidoethoxy)-acetoacetate.

2. The final compound undergoes a reaction with 2-chlorobenzaldehyde and methyl. The conversion of -3-aminocrotonate to yield 3-ethyl is the desired outcome -5-methyl-2-[(-azidoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinecarboxylate.

3. Upon reduction of the aforementioned compound, the formation of amlodipine occurs.

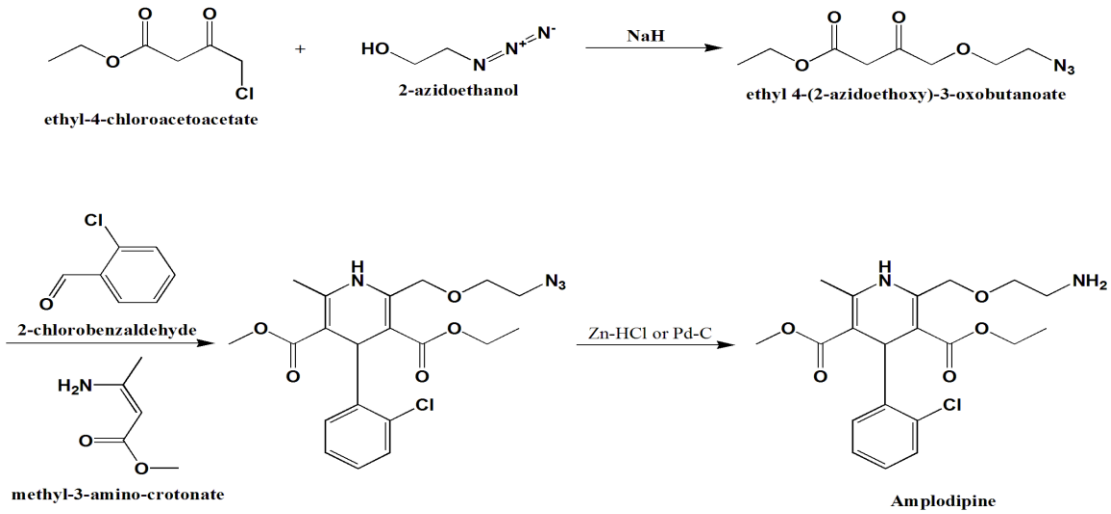

Figure 2: Synthesis of Amlodipine *(Vardanyan & Hruby, 2006a)*

2.2: Benidipine

The compound Benidipine has been identified as a dihydropyridine calcium channel blocker that exhibits selective inhibition of L-type calcium channels in smooth muscle

cells. This unique mechanism of action leads to the relaxation and dilation of blood vessels, ultimately reducing blood pressure. The pharmacological activity of the compound under investigation is attributed to its chemical structure, which comprises a substituted pyridine ring and a dihydropyridine ring. These structural features are crucial for the observed pharmacological effects. (Yao et al., 2006)

The significance of the pyridine ring in the binding of Benidipine to the calcium channel receptor site was emphasized in a review conducted by (Ding et al., 2019). This study provides a comprehensive review of the impact of substituents on the pyridine ring on the affinity and selectivity of drugs for various types of calcium channels.

The findings suggest that these substituents' hydrophobic and steric properties play a crucial role in determining the drug's binding affinity and selectivity towards specific calcium channels. These results have significant implications for designing and developing novel calcium channel modulators with improved therapeutic efficacy and reduced side effects. (Catterall, 1993)

Pharmacokinetic analysis of Benidipine reveals that it undergoes rapid absorption after oral administration, leading to peak plasma concentrations within 1 to 2 hours.

The bioavailability of the substance under investigation is approximately 80%. Furthermore, it undergoes significant hepatic metabolism via hydrolysis and oxidation reactions. The pharmacological activity of the parent drug is similar to that of its active metabolite, benidipine acid. (Yao et al., 2006)

In this study, (Yamamoto et al., 2010) investigated the pharmacological properties of Benidipine enantiomers. The study aimed to determine the potency of the (S)-enantiomer compared to the (R)-enantiomer in inhibiting L-type calcium channels. The study's results revealed that the (S)-enantiomer exhibited greater potency in inhibiting

L-type calcium channels than the (R)-enantiomer. These findings provide important insights into the pharmacological properties of Benidipine enantiomers and their potential applications in treating conditions related to L-type calcium channels. The present investigation has demonstrated that the (S)-enantiomer exhibits a prolonged duration of action and reduced toxicity compared to the (R)-enantiomer.

The present study investigates the impact of chemical structure and metabolism on the pharmacokinetics and pharmacodynamics of Benidipine. Findings suggest that the pharmacokinetics and pharmacodynamics of Benidipine are significantly influenced by its chemical structure and metabolism. These results provide valuable insights into the mechanisms underlying the therapeutic effects of Benidipine and may have implications for developing novel therapeutic agents.

Cytochrome P450 (CYP) enzymes facilitate the metabolic process of the subject under study, and the possibility of drug interactions cannot be ruled out with inhibitors of these enzymes. The pharmacological properties of Benidipine's enantiomers have been found to differ significantly. The (S)-enantiomer has been observed to exhibit greater potency and lesser toxicity than the (R)-enantiomer. (Yun et al., 2005)

2.2.1: Synthesis of Benidipine

An Analysis of Chemical Properties and Reactions: The synthesis of Benidipine, a highly efficacious calcium channel blocker, was accomplished via a sequential progression of chemical transformations.

1. The chemical compound referred to as 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-p The 3-methyl ester is suspended in a mixture of dichloromethane (DCM) and dimethyl formamide. It is necessary to cool the suspension to a temperature range of 0–

5 °C.

2. The mixture was subjected to the addition of thionyl chloride and subsequently stirred for a duration of one hour.

3. Subsequently, the compound 1-benzyl-3-piperidinol was introduced into the reaction mixture and subjected to stirring for a duration of 2 hours at a temperature range of 0-5 °C, followed by an additional hour of stirring at 25 °C.

4. The reaction was halted by the introduction of water. The organic phase was isolated, subjected to brine washing, dehydrated using anhydrous sodium sulphate, and subsequently filtered.

5. The filtrate underwent vacuum evaporation to remove solvent, resulting in a concentrated residue. This residue was subsequently subjected to crystallisation using a mixture of ethanol and acetone. The raw material underwent filtration and vacuum drying.

6. Pharmaceutical grade α-benidipine hydrochloride was effectively produced as the produced powder was crystalline and yellowish. Through the implementation of multiple recrystallization procedures involving ethanol and acetone.

The overall yield achieved was 45%.

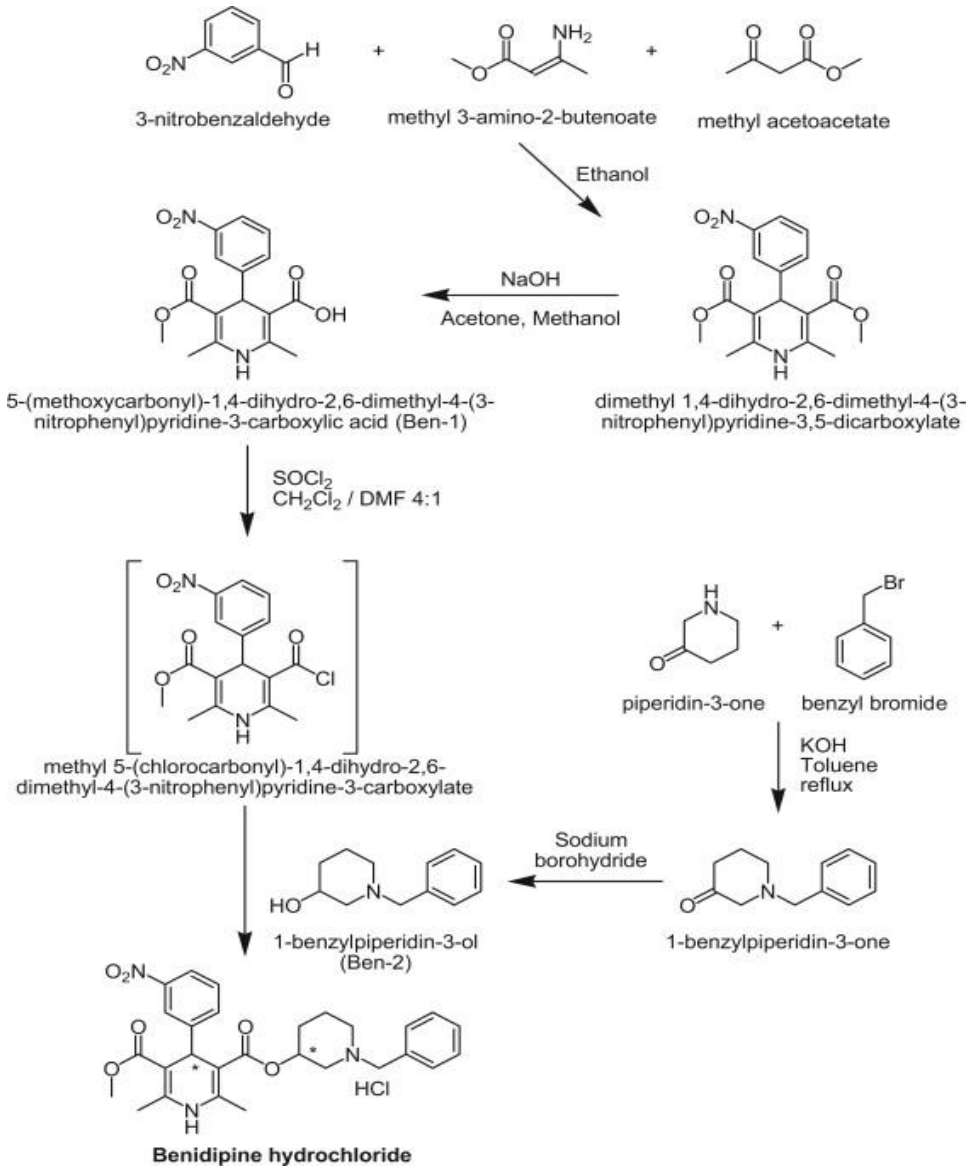

Figure 3: Synthesis of Benidipine *(Bellur Atici & Karliıa, 2015)*

2.3: Clonidine

Clonidine is a medication primarily used as an antihypertensive agent, meaning it is prescribed to manage hypertension. This medication is classified as a calcium channel blocker, specifically a unique subclass known as dual alpha and calcium channel blockers. (Stähle, 2000)

Clonidine works by targeting two key mechanisms involved in blood pressure regulation. Firstly, it acts as an alpha-adrenergic antagonist, which means it blocks certain receptors in the sympathetic nervous system that are responsible for regulating blood vessel constriction. By blocking these receptors, clonidine causes blood vessels to dilate, resulting in decreased peripheral vascular resistance and subsequently lowering blood pressure. Secondly, clonidine acts as a calcium channel blocker, selectively blocking the influx of calcium ions into smooth muscle cells lining the blood vessels. This action inhibits the muscle's ability to contract, leading to relaxation and further dilation of blood vessels. As a result, blood flow improves, and blood pressure is further reduced. (Isaac, 1980)

Clonidine has been found to be particularly effective in treating hypertension, as it not only lowers blood pressure but also provides some additional benefits. It has been shown to have a relatively long duration of action, allowing for once-daily dosing, which enhances patient compliance. Additionally, clonidine has demonstrated a favorable side effect profile, with a lower prevalence of negative outcomes incidence of adverse effects such as ankle swelling compared to other calcium channel blockers. It is important to note that clonidine should be taken under the supervision of a healthcare professional and in accordance with their instructions. The dosage and treatment duration may vary depending on the individual's condition and response to the medication. As with any medication, there may be potential side effects or interactions with other drugs, so it is crucial to consult with a healthcare provider for personalized advice. (Sica & Grubbs, 2005)

In summary, clonidine is an antihypertensive medication belonging to the calcium channel blocker class. Its unique dual action as an alpha-adrenergic antagonist and calcium channel blocker helps in the potential approach to lowering blood pressure

involves the dilation of blood vessels and enhancement of blood circulation. One of the benefits it provides is the convenience of administering the medication once per day, along with a favorable profile of side effects. If you have hypertension or any concerns about your blood pressure, it is essential to seek medical advice and follow the guidance of a healthcare professional. (Stähle, 2000)

2.3.1: Synthesis of Clonidine

Several steps are involved in the synthesis of clonidine, as detailed below:

1. The compound 2,3-dichloroanilline undergoes a reaction with ammonium thiocyanate (NH4SCN), resulting in the formation of thiourea.

2. Thiourea undergoes a reaction with methyl iodide, resulting in the formation of S-methylthiouronium salt.

3. The second compound is subjected to a reaction with ethylenediamine, resulting in the formation of clonidine.

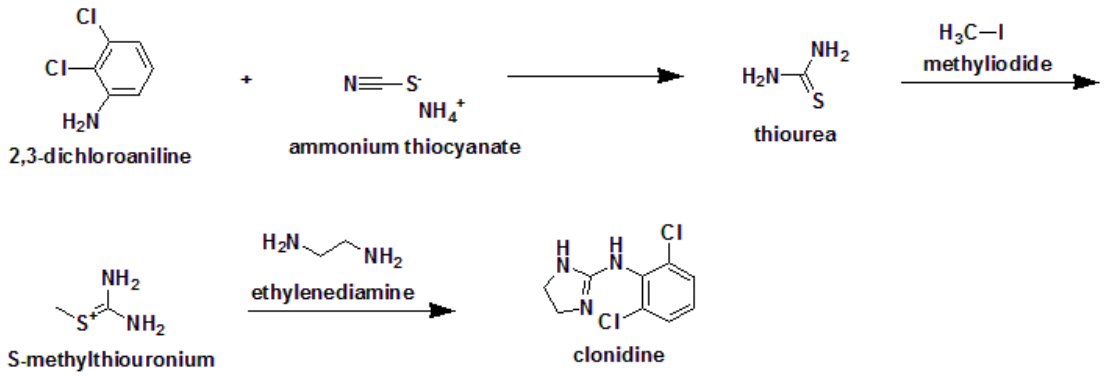

Figure 4: Synthesis of Clonidine (*Thomas Lemke_ David A. Williams - Foye's Principles of Medicinal Chemistry-Lippincott Williams & Wilkins (2012)*, n.d.)

2.4: Felodipine

Felodipine, a pharmacological agent belonging to the subclass of calcium channel blockers (CCBs), is commonly prescribed for the treatment and control of hypertension. The mechanism of action of the drug involves the inhibition of calcium ion influx into cells of vascular smooth muscle, leading to the dilation of blood vessels and subsequent reduction in blood pressure. The compound being examined is a derivative of dihydropyridine. The mechanism of action of this substance entails the inhibition of the influx of calcium ions across the cell membrane. Consequently, the relaxation of smooth muscles occurs, leading to the subsequent dilation of blood vessels, ultimately resulting in a reduction in blood pressure. (Mace et al., 1985)

Felodipine is a medication widely accepted by patients due to its high tolerability. This drug's most frequently reported adverse effects include flushing, headache, and peripheral edema. The administration of medications, despite their therapeutic benefits, may result in severe adverse effects. One such medication is known to cause hypotension, myocardial infarction, and ventricular arrhythmia, especially in patients with preexisting cardiovascular disease. (Schaefer et al., 1998)

Felodipine, a dihydropyridine calcium channel blocker, exhibits a prolonged half-life of approximately 11-16 hours, enabling convenient once-daily administration. The administration of the substance is commonly done through the oral route and can be consumed with or without food intake. (Saltiel et al., 1988)

Felodipine has been extensively studied in various clinical trials to evaluate its efficacy in reducing blood pressure and improving cardiovascular outcomes. The results of these trials have consistently demonstrated the effectiveness of felodipine in achieving these goals. The drug is a potent antihypertensive agent, significantly reducing systolic and

diastolic blood pressure observed in patients treated with felodipine. Moreover, felodipine has been shown to improve cardiovascular outcomes, including reducing the risk of stroke, myocardial infarction, and heart failure. These findings suggest that felodipine is a promising therapeutic option for hypertension and cardiovascular disease patients. (Todd & Faulds, 1992)

Felodipine, a calcium channel blocker, has been extensively employed to manage hypertension. The present study concludes that felodipine is an effective therapeutic agent for the treatment of hypertension. The safety and efficacy of the medication have been widely established; however, as with any pharmacological intervention, it may elicit unfavorable reactions. Felodipine's efficacy in reducing blood pressure and enhancing cardiovascular outcomes has been demonstrated through clinical trials. (Tocci et al., 2018)

2.4.1: Synthesis of Felodipine

i. Methylacetoacetate (MAA) reacts with 2,3-dichlorobenzaldehyde to give methyl-2-(2,3-dichlorobenzyidene)-acetoacetate.

ii. The last is reacted with ethyl acetoacetate in presence of ammonia to give felodipine.

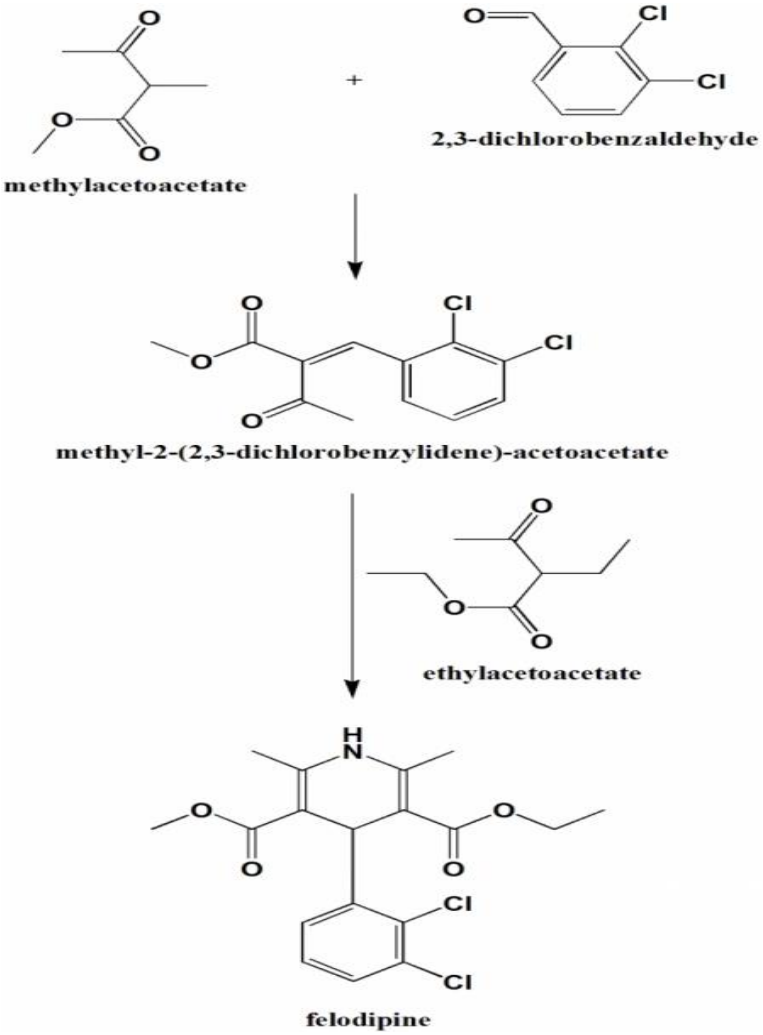

Figure 5: Synthesis of Felodipine *(Yiu & Knaus, 1996)*

2.5: Nisoldipine

Nisoldipine is a pharmaceutical agent employed in the management of hypertension. It belongs to the group of calcium channel blockers called dihydropyridine. Nisoldipine is a 1,4-dihydropyridine calcium-channel blocker that has FDA approval for the treatment of hypertension. (Sidhu & Hashmi, 2023a)

The medication can be taken either on its own or in combination with other antihypertensive medications (such as beta-blockers, diuretics, or ACE inhibitors). Also safe and efficient for usage in the elderly population is the medicine. (Guerrero-García & Rubio-Guerra, 2018)

Nisoldipine is sometimes used off-label to treat ischemic heart diseases such stable angina or prinzmetal angina. Dihydropyridine calcium channel blockers include nisoldipine in its class. By preventing calcium from entering the cells and by blocking voltage-gated calcium channels, the medication reduces the size of the systemic smooth muscle cells. Due to its capacity to lower systemic blood pressure and the myocardial oxygen demand (thereby boosting myocardial oxygen delivery to cells), nisoldipine demonstrates both antihypertensive and anti-anginal effect. The ultimate outcomes of this action include vasodilation and a decrease in peripheral vascular resistance. (Friedel & Sorkin, 1988)

The CYP3A4 pathway is used by the liver to break down nisoldipine, and the renal pathway is used for excretion. It has a bioavailability of about 5% and a half-life of between 9 and 18 hours. The medication is insoluble in water and exhibits no changes in serum calcium levels. (Sidhu & Hashmi, 2023b)

It is unknown why some calcium channel blockers, such nisoldipine, do not produce idiosyncratic liver harm whereas others, like amlodipine, diltiazem, and nifedipine, do. Because calcium channel blockers seldom induce liver damage, there may not have been enough exposure to the rarely used substances to create cases that were clinically evident. Like many calcium channel blockers, nisoldipine is metabolized by CYP 3A4 in the liver and is therefore sensitive to pharmacological interactions with CYP 3A4 substrates, inhibitors, and inducers. (“Metabolism of Nisoldipine,” 2012)

2.5.1: Synthesis of Nisoldipine

1. The Knovenagel condensation of 2-nitrobenzaldehyde with isobutyl acetoacetate, which results in a highly reactive a,8-unsaturated ketone, is the first step in the production of nisoldipine.

2. This intermediate acts as a substrate for the cyclizing Michael addition of methyl 3-aminocrotonate, which can be obtained from methyl acetoacetate and ammonia and produces nisoldipine in generally good yields.

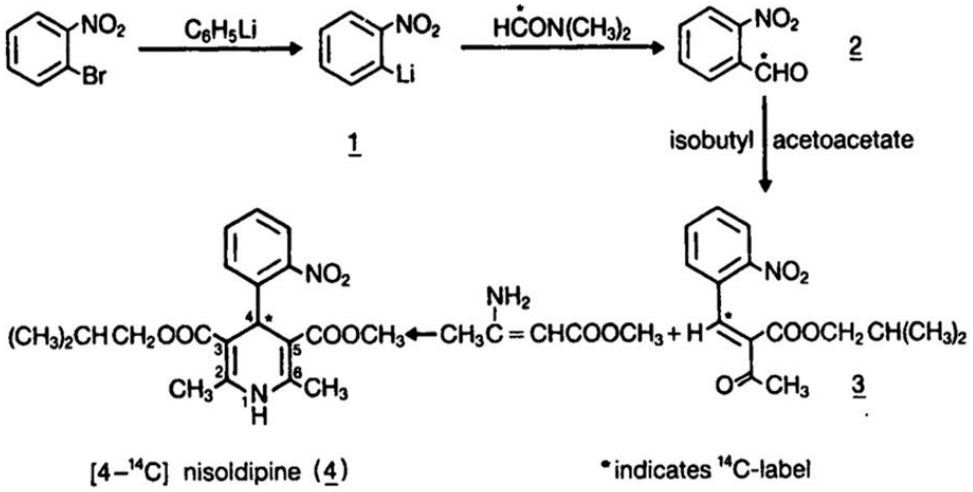

Figure 6: Synthesis of Nisoldipine (Scherling & Plei8, n.d.)

2.6: Nicardipine

Nicardipine, a pharmaceutical compound classified as a calcium channel blocker, is a commonly employed medication for the treatment of hypertension. The mechanism of action entails the suppression of calcium ion influx into smooth muscle cells, leading

to the relaxation of arterial walls and subsequent decrease in blood pressure. (Scherling & Plei8, n.d.)

Nicardipine is a pharmacological compound that falls under the category of calcium channel blockers. It is commonly employed in the medical field to manage and regulate conditions such as hypertension, angina, and subarachnoid hemorrhage. The compound's mechanism of action involves the inhibition of calcium ion influx into vascular smooth muscle cells, leading to vasodilation and subsequent reduction in blood pressure. Nicardipine has demonstrated efficacy in the treatment of subarachnoid hemorrhage and angina, in addition to its antihypertensive properties. Its use in these conditions is thought to be due to its ability to improve cerebral blood flow and reduce myocardial oxygen demand, respectively. Overall, nicardipine is a versatile medication that has demonstrated efficacy in the management of a variety of cardiovascular and cerebrovascular conditions. The medication is offered in two forms: oral and intravenous formulations. The intravenous formulation is typically administered in acute scenarios, such as hypertensive emergencies and postoperative hypertension. (Fujii et al., 1995)

Extensive research has been conducted on Nicardipine to evaluate its efficacy in the management of hypertension. Multiple research studies have provided evidence of the effectiveness of nicardipine in lowering blood pressure levels among individuals diagnosed with hypertension. In a scientific investigation conducted by (Kim et al., 2012), it was discovered that nicardipine exhibited efficacy in the context of patients exhibiting mild to moderate hypertension, the objective was to investigate the efficacy of interventions aimed at reducing blood pressure levels. In a previous investigation conducted by (Badillo-Alonso et al., 2023), it was demonstrated that nicardipine

exhibited superior efficacy compared to enalapril in the management of severe hypertension by reducing blood pressure levels in affected patients.

Nicardipine is a calcium channel blocker that exhibits a relatively short half-life and undergoes hepatic metabolism. The primary objective of this study is to examine the potential negative consequences associated with the administration of nicardipine, a widely utilized calcium channel blocker in the treatment of hypertension and angina. The study involved a comprehensive analysis of the available literature on the subject, including clinical trials, case reports, and observational studies. The results of the analysis revealed that the most commonly reported adverse effects of nicardipine were hypotension, headache, dizziness, and flushing. These effects were found to be dose-dependent and generally mild to moderate in severity. However, in rare cases, severe hypotension and cardiovascular collapse have been reported. The findings of this study highlight the importance of careful monitoring of patients receiving nicardipine therapy, particularly those with pre-existing cardiovascular disease or other risk factors for adverse effects. Further research is needed to better understand the mechanisms underlying the adverse effects of nicardipine and to develop strategies for minimizing their occurrence. (Sorkin &)

The primary objective of this study was to assess the effectiveness of nicardipine, a calcium channel blocker, in the reduction of blood pressure in individuals diagnosed with hypertension. The research investigation was carried out on a cohort of individuals diagnosed with hypertension, and the findings demonstrated that the administration of nicardipine yielded significant reductions in blood pressure levels. The results of this study indicate that nicardipine may be a viable therapeutic choice for the treatment of hypertension. Additional research is necessary to investigate the potential long-term effects and safety characteristics of nicardipine in individuals with hypertension. This

specific treatment modality finds application in the management of subarachnoid hemorrhage and angina. Despite the potential adverse effects, the compound has exhibited effectiveness in numerous studies and is generally well-tolerated. (Armstrong et al., 1987)

2.6.1: Synthesis of Nicardipine

The reaction involves the combination of the methyl ester of ß-aminocrotonic acid with the 2-methyl-2-benzylaminoethyl ester of acetoacetic acid, resulting in the formation of nicardipine.

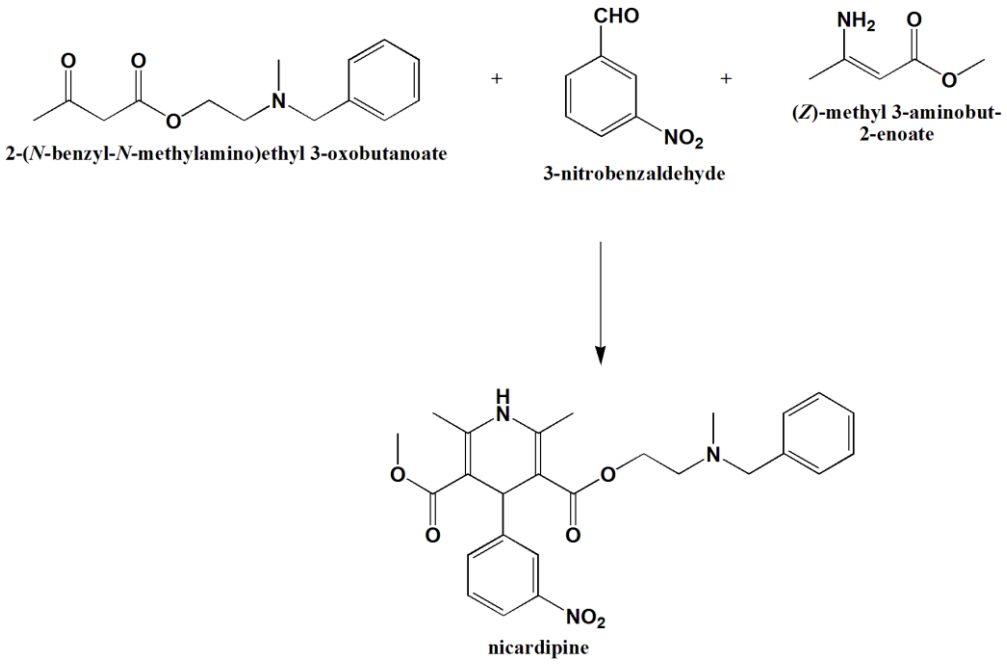

Figure 7: Synthesis of Nicardipine *(Vardanyan & Hruby, 2006b)*

2.7: Nifedipine

Nifedipine, a calcium channel blocker, is a pharmacological agent commonly prescribed for managing hypertension and angina pectoris. The mechanism of action involves vasodilation and decreased cardiac workload. The pharmacological effects of Nifedipine have been studied extensively in the context of its ability to block the entry of calcium ions into smooth muscle cells. This mechanism of action results in a reduction in contractility of the smooth muscle cells and subsequent dilation of blood vessels. Nifedipine's vasodilatory effects are effective in treating hypertension, angina pectoris, and other cardiovascular disorders. The precise molecular interactions between Nifedipine and the calcium channels responsible for its pharmacological effects are still under investigation, but the clinical utility of this drug is well-established. (Murphy et al., 1983)

The pharmacokinetics of Nifedipine, a calcium channel blocker, were investigated in this study. The drug was found to undergo hepatic metabolism and renal excretion as the primary elimination pathways. The bioavailability of the substance under investigation is subject to the influence of food and maybe diminished in individuals with hepatic impairment. The medication is currently accessible in immediate and extended-release formulations, allowing various dosing options. (Kleinbloesem et al., 1987)

Nifedipine effectively reduced blood pressure in patients with hypertension—the present investigation aimed to evaluate the safety and tolerability of Nifedipine. The study results indicated that Nifedipine exhibited a favorable safety profile and was well-tolerated by the participants. The incidence of adverse events was minimal, suggesting

that Nifedipine is a safe therapeutic option for managing the condition under investigation. (Hermida et al., 2008)

A recent publication in the Journal of Cardiovascular Pharmacology reported that Nifedipine demonstrated efficacy in enhancing exercise tolerance and mitigating angina attacks among patients diagnosed with stable angina pectoris. The present research article reveals that Nifedipine exhibited favorable tolerability and a minimal occurrence of unfavorable events. (Mueller et al., 1981)

Numerous clinical studies have documented its effectiveness in reducing blood pressure and relieving chest pain. Therefore, Nifedipine is a valuable therapeutic option for patients with these conditions. The mechanism of action involves vasodilation and decreased cardiac workload. The safety and tolerability of Nifedipine have been extensively studied, and it is generally safe and well-tolerated with minimal adverse effects. (Clark et al., 1981)

2.7.1: Synthesis of Nifedipine

Nifedipine is synthesized through a multistep procedure. The methods required to synthesize Nifedipine are as follows:

Two molecules of methylacetoacetate (MAA), one molecule of 2-benzaldehyde, and ammonia undergo a chemical reaction to yield the pharmaceutical compound known as nifedipine.

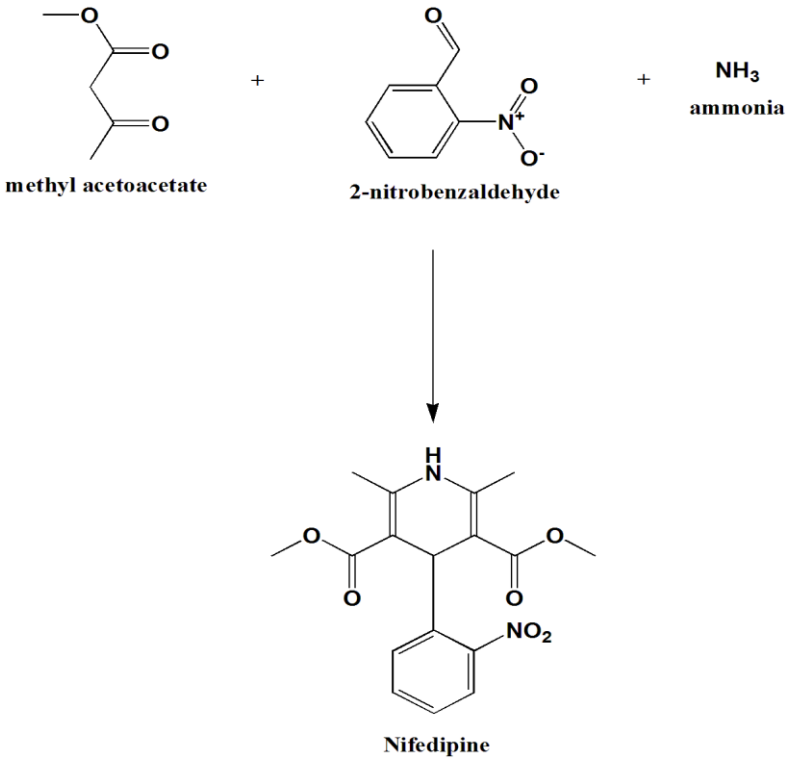

Figure 8: Synthesis of Nifedipine *(Vardanyan & Hruby, 2006b)*

2.8: Nimodipine

Nimodipine is a pharmacological compound classified as a 1,4-dihydropyridine calcium channel antagonist. Its primary impact is on the cells of vascular smooth muscle by stabilizing the inactive state of voltage-gated L-type calcium channels. Nimodipine exerts its inhibitory effects by blocking the entry of calcium ions into smooth muscle cells. This action effectively hinders the process of smooth muscle contraction, which is dependent on calcium levels, ultimately leading to the prevention of vasoconstriction. In comparison to other calcium channel blockers, nimodipine exerts a notably greater influence on cerebral circulation as opposed to peripheral circulation. Nimodipine is administered as an adjunctive therapy to improve the neurological outcome after the occurrence of subarachnoid haemorrhage resulting from the rupture of an intracranial aneurysm. (SCRIABINE & KERCKHOFF, 1988)

Nimodipine is predominantly used to prevent and treat cerebral vasospasm following subarachnoid hemorrhage (SAH) (Zhang et al., 2018). It increases blood flow to the brain by relaxing the smooth muscle in the walls of blood vessels (Littlejohn et al., 2013). Nimodipine has been demonstrated to reduce the incidence of delayed cerebral ischemia and enhance neurological outcomes in SAH patients (Tong et al., 2016).

Common adverse effects of nimodipine include hypotension, headache, and gastrointestinal disturbances (Zhang et al., 2018). Blood pressure must be carefully monitored during treatment to prevent hypotension, which can cause cerebral ischemia (Fischer et al., 2019).

2.8.1: Synthesis of Nimodipine

The synthesis of Nimodipine involves a multi-step process:

Step 1: Synthesis of (E)-isopropyl 3-aminobut-2-enoate:

1. The compound 4-methyleneoxetan-2-one undergoes a reaction with propan-2-ol in the presence of triethylamine, resulting in the formation of isopropyl-3-oxoutanoate.

2. The compound mentioned above undergoes a reaction with 4-methylbenzenesulfonic acid in the presence of ammonia, resulting in the formation of (E)-isopropyl 3-aminobut-2-enoate.

Step 2: Synthesis of 2-methoxyethyl 2-(3-nitrobenzyl)-3-oxobutanoate:

1. The compound 4-methyleneoxetan-2-on undergoes a reaction with 2-methoxyethanol in the presence of triethylamine, resulting in the formation of 2-methoxyethyl 3-oxobutanoate.

2. Above formed compound is subjected to a reaction with 3-nitrobenzaldehyde, resulting in the formation of 2-methoxyethyl 2-(3-nitrobenzyl)-3-oxobutanoate

Step 3: Synthesis of Nimodipine:

The ultimate compound resulting from the sequential reactions in steps 1 and 2 is subjected to a reaction in the presence of ethanol, resulting in the formation of

nimodipine.

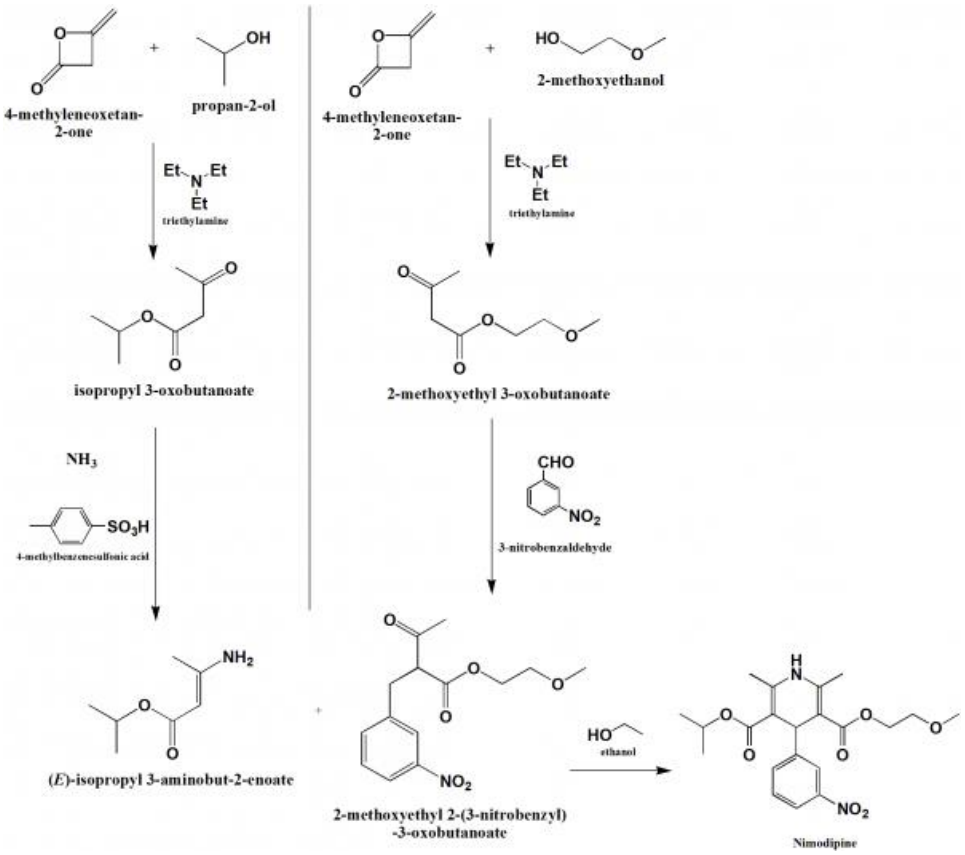

Figure 9: Synthesis of Nimodipine *(*Meyer1983*, n.d.)*

Chapter 3

Non-dihydropyridines

3.1: Phenylalkylamine

3.1.1: Verapamil

Verapamil is a pharmaceutical compound classified as a calcium channel blocker, primarily used for the treatment of hypertension, angina, and specific cardiac arrhythmias. The mechanism of action involves the suppression of calcium ion entry into cells of both cardiac and smooth muscle, leading to vasodilation and decreased contractility of the myocardium. Verapamil is available in both immediate-release and sustained-release formulations. (Lewis et al., 1978)

Verapamil is primarily metabolized by the CYP3A4 enzyme of the cytochrome P450 system in the liver. Its half-life is approximately 4 to 6 hours, whereas its metabolites have half-lives of up to 14 hours. Verapamil is predominantly eliminated in the feces, with only a tiny amount eliminated in the urine. (Kroemer et al., 1993)

Verapamil has demonstrated efficacy in treating hypertension alone and in combination with other antihypertensive drugs. In addition, it has been used to treat angina and certain cardiac arrhythmias, including supraventricular tachycardia and atrial fibrillation. (McTavish & Sorkin, 1989) Verapamil is an effective and well-tolerated medication for treating hypertension, angina, and certain cardiac arrhythmias. It has also been studied with promising results in treating other conditions, such as migraine attacks.

3.1.1.1: Synthesis of Verapamil

The synthesis process of verapamil is given below:

1.1,5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4 dimethoxyphenyl)isopropylvaleronitrile is produced through a synthetic process involving the use of 3,4-dimethoxyphenylacetonitrile as the starting material.

2. The final product is synthesized through the process of alkylating 2-(3.4-dimethoxyphenyl)-3-methylbutyronitrile with N-[2-(3,4-dimethoxyphenyl)-ethyl]-N-3-(chloropropyl)-N-methylamine.

3. The compound 2-(3,4-dimethoxyphenyl)-3-methylbutyronitrile is formed through a chemical reaction known as alkylation. In this process, 3,4-dimethoxyphenylacetonitrile is reacted with isopropyl chloride in the presence of sodium amide.

4. The alkylating agent, N-[2-(3,4-dimethoxyphenyl)-ethyl]-N-3-(chloropropyl)-N-methylamine, is produced through a synthetic process starting with 3,4-dimethoxyphenylacetonitrile. This compound is then reduced to form 3,4-dimethoxyphenylethylamine, which is subsequently methylated to yield N-methyl-N-3,4-dimethoxyphenylethylamine.

5. Subsequently, the resultant N-[2-(3,4-dimethoxyphenyl)-ethyl] compound was obtained. The process of alkylation involves the reaction between N-methylamine and 1-chloro-3-bromopropane, resulting in the formation of the desired N-[2-(3,4-dimethoxyphenyl)-ethyl] compound. The compound N-methylamine undergoes alkylation with 2-(3,4-dimethoxyphenyl)-3-methylbutyronitrile to produce the ultimate compound known as verapamil.

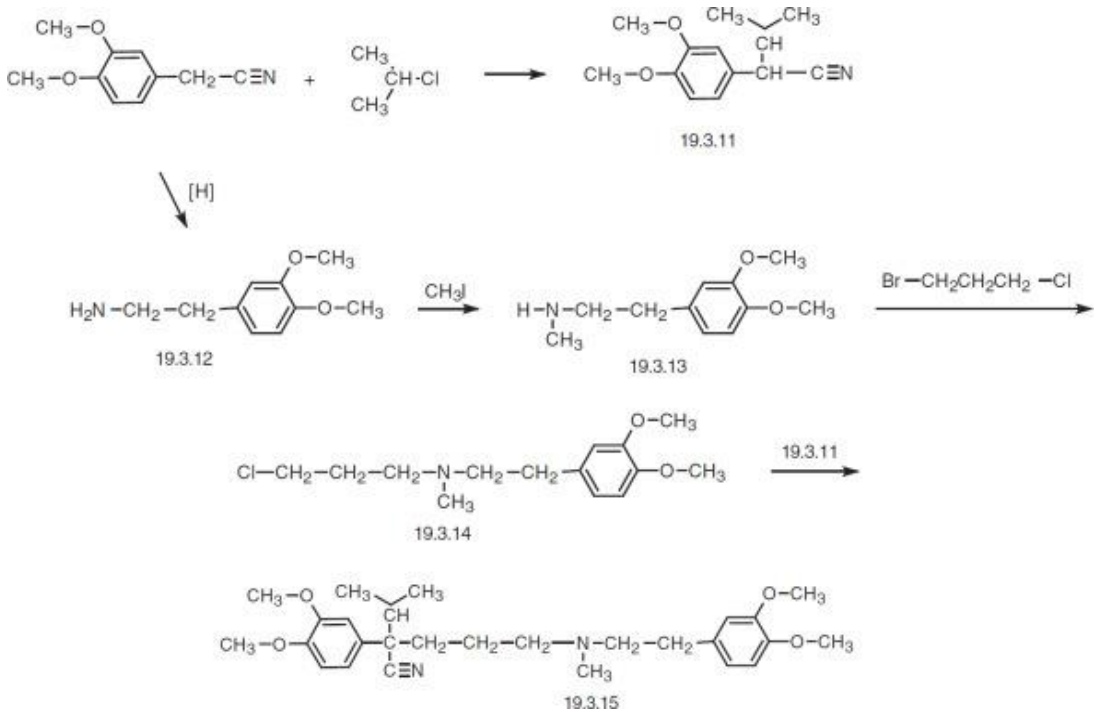

Figure 10: Synthesis of Verapamil *(Vardanyan & Hruby, 2006b)*

3.2: Benzothiazepine

3.2.1: Diltiazem

Diltiazem is a pharmacological agent utilized for the treatment of hypertension and angina pectoris, as it exerts its therapeutic effects by inducing vasodilation and enhancing systemic blood circulation. The medication is categorized as a calcium channel blocker (CCB) and operates by impeding the influx of calcium ions into the smooth muscle cells present in both the cardiovascular system's blood vessels and the heart. Consequently, this leads to reduced contraction of these muscles and the dilation of blood vessels, a process known as vasodilation. (Matlib & Schwartz, 1983)

Diltiazem is available in various forms, such as immediate-release tablets, extended-

release capsules, and injectable formulations. It is typically administered orally and has a relatively short half-life of 3-4 hours, although the extended-release formulation has a longer duration of action. (Smith et al., 1983)

Based on a study conducted, it has been determined that diltiazem exhibits efficacy as a therapeutic intervention for angina, resulting in a reduction in both the frequency and severity of episodes experienced by individuals diagnosed with stable angina. A separate investigation revealed that the administration of diltiazem has the potential to enhance the capacity for physical exertion and mitigate the likelihood of coronary incidents among individuals diagnosed with chronic stable angina. (Rodríguez Padial et al., 2016) Diltiazem is generally well-tolerated, but like all medications, it may cause side effects such as dizziness, headache, flushing, nausea, and constipation.

In rare cases, more severe side effects such as low blood pressure, heart rhythm disturbances, or liver damage may occur. Diltiazem is a valuable medication in treating hypertension and angina, but it should be used under the guidance of a healthcare provider. (Smith et al., 1983)

3.2.1.1: Synthesis of Diltiazem

The synthesis process of diltiazem is given below:

1. The reaction between 4-methoxybenzaldehyde and methylchloroacetate, catalyzed by sodium methoxide under Darzens reaction conditions, results in the formation of the methyl ester of 3-(4-methoxyphenyl)-glycidylic acid.

2. The compound is subjected to a reaction with 2-aminothiophenol, resulting in the opening of the epoxide ring. This reaction produces the methyl ester of 2-hydroxy-3-(2-aminophenylthio)-3-(4-methoxyphenyl) propionic acid.

3. The resulting compound undergoes hydrolysis with alkali, resulting in the formation of the corresponding acid as a racemic mixture. Upon interaction with (+)-α-phenyl ethylaminethreo-(+)-2-hydroxy-3-(2'-aminophenylthio)-3-(4'' methoxyphenylpropionic acid is produced.

4. In order to induce cyclization of the thiazepine ring and simultaneously acrylate the hydroxyl group, the substance should be subjected to boiling in a mixture of acetic anhydride, dimethylformamide, and pyridine. This process results in the formation of the compound (+) -cis-2-(4-methoxyphenyl). The compound mentioned is known as -3-acetoxy-2,3-dihydro-1,5-benzothiaz

5. The diltiazem compound is synthesized through the alkylation of the resultant product with 2,2-dimethylaminoethylchloride.

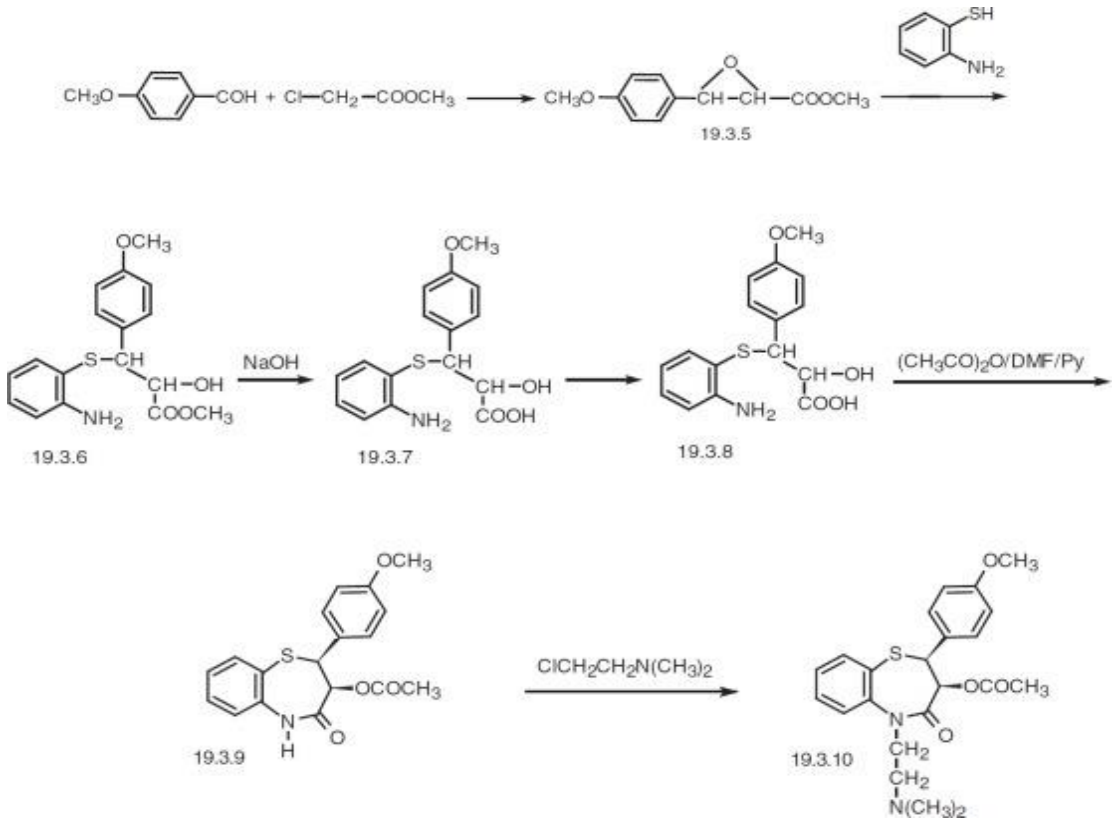

Figure 11: Synthesis of Diltiazem *(Vardanyan & Hruby, 2006b)*

Chapter 4

Discussion

Tolerated agents are used for the treatment of hypertension. The extended duration of their therapeutic effects and their favorable profile of adverse effects render them advantageous, leading to their widespread prescription. In the context of observational studies, it has been observed that a range of 30% to 40% of individuals diagnosed with hypertension are prescribed a calcium channel blocker (CCB). Furthermore, there is evidence to suggest that the prevalence of CCB usage among these patients is on the rise. (*Sica2006*, n.d.)

When employed as a standalone treatment, calcium channel blockers (CCBs) appear to exhibit comparable or enhanced efficacy compared to medications from alternative therapeutic categories in reducing blood pressure. While the available data may not exhibit complete consistency, it suggests that when utilized as monotherapy, the efficacy of certain agents in reducing cardiovascular morbidity and mortality is not superior, and may even be inferior, to alternative options such as β-blockers, ACE inhibitors, and diuretics. However, it is worth noting that dihydropyridine agents may have a favorable impact on reducing the risk of stroke. Nevertheless, when utilized alongside other medications like ACE inhibitors, they effectively reduce the incidence of cardiovascular morbidity, particularly when aiming for ambitious blood pressure targets. (Messerli et al., 2018)

The use of calcium channel blockers as a single form of treatment is unlikely to raise the likelihood of renal disease in individuals with hypertension who do not have diabetes. However, these blockers may not be as effective as medications that target the

renin-angiotensin-aldosterone system, particularly ACE inhibitors, in preventing the onset of renal disease in individuals with diabetes. When employed as an initial therapeutic approach or as a standalone treatment, dihydropyridine calcium channel blockers (CCBs) appear to exhibit inferior efficacy compared to angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in terms of mitigating the advancement of renal disease, particularly in individuals with diabetes. The majority of research investigations have been conducted utilizing dihydropyridine calcium channel blockers (CCBs). The available data on non-dihydropyridine calcium channel blockers (CCBs) is limited, and there is a potential for non-dihydropyridine agents to exhibit a similar level of protective effects as renin-angiotensin-aldosterone blockers. When administered concurrently with ACE inhibitors or angiotensin receptor blockers, calcium channel blockers (CCBs) do not compromise the renal protective effects of these medications. In fact, CCBs may have an additional positive impact on slowing down the progression of kidney disease if they further reduce blood pressure. There exists evidence suggesting a potential association between the utilization of ACE inhibitors or angiotensin receptor blockers and a survival advantage. However, it is important to note that the majority of available data originates from studies characterized by limited rates of utilization of these medications. Calcium channel blockers (CCBs) have demonstrated efficacy as antihypertensive agents in individuals who have undergone renal transplantation, particularly when used concurrently with cyclosporine. There appears to be no discernible independent impact of these factors on renal transplant function. (Haider et al., 2015)

In brief, calcium channel blockers (CCBs) can be employed as a primary treatment or as a standalone therapy for individuals with uncomplicated hypertension. Alternatively, they can be utilized as adjunctive therapy to attain a blood pressure goal below 140/90 mm Hg. Initial therapy or monotherapy with these medications is contraindicated in patients who have an elevated risk of cardiovascular disease, renal disease, diabetes, or renal disease progression. Second-line, third-line or fourth-line agents may be chosen in order to attain a blood pressure target of less than 130/80 mm Hg. The continued prevalence of their utilization persists due to the inherent challenge of attaining a low blood pressure threshold without their assistance. (Shemin & Dworkin, n.d.)

Chapter 5

Conclusion

Calcium channel blockers encompass a diverse array of medications that exhibit both structural and functional variations. These pharmaceutical agents are commonly employed in the treatment of individuals suffering from hypertension or angina. As a collective group, they are generally well tolerated and demonstrate a minimal incidence of side effects. In spite of apprehensions regarding their safety, recent extensive clinical trials have yielded no evidence of a correlation between long-acting calcium channel blockers and detrimental cardiovascular outcomes. Nevertheless, there is a correlation between the utilization of calcium channel blockers and a heightened susceptibility to heart failure. Based on the findings presented, it can be inferred that the utilization of long-acting calcium channel blockers is a viable and secure approach in the treatment of hypertension and angina. Nevertheless, when considered collectively, they do not exhibit the same level of efficacy in preventing heart failure as other antihypertensive medications. (Eisenberg et al., 2004)

In contemporary times, notable progress has been made in the field of antihypertensive and antianginal medications, with the objective of leveraging the variations in blood pressure and heart rate that occur throughout the day. Calcium channel blockers exhibit a wide range of pharmacological, pharmacodynamic, and pharmacokinetic characteristics. The consistent efficacy of Amlodipine and other recently developed medications in reducing blood pressure has been observed. Nevertheless, the novel calcium channel blockers (CCBs) possess unique attributes, such as variations in lipophilicity, cardiovascular selectivity, pharmacodynamics characteristics, anti-ischemic effects, anti-atherosclerotic properties, reno-protective effects, and

neuroprotective effects. Therefore, it is possible that these newly developed calcium channel blockers (CCBs) could emerge as the preferred treatment option for hypertension accompanied by angina, atherosclerosis, renal failure, cerebral ischemia, nephropathy, and coronary artery disease in the future. (Kishor, 2019)

The initial perception of long-acting calcium channel blockers (CCBs) as substances that induce cardiovascular events has been reevaluated. Subsequent investigations have provided evidence of the advantageous effects of these agents in the realm of cardiovascular and renal disorders. An increasing amount of research indicates that several newly-developed calcium channel blockers (CCBs) have the ability to inhibit multiple subtypes of calcium channels, such as L-, T-, and N-type channels ($Ca_V2.2$). Given the wide distribution and significant impact of these channels on cardiovascular and neurohumoral systems, the implementation of dual or triple blockade of calcium channels could potentially provide supplementary advantages as a therapeutic approach for hypertension. (Ozawa et al., 2006)

The significance of the thesis project carries significant weight in the realm of pharmacology and cardiovascular medicine. Due to its asymptomatic nature, hypertension is frequently referred to as the "silent killer" and is a common and dangerous health problem around the world. Calcium influx into vascular smooth muscle cells is prevented by calcium channel blockers, providing a novel mode of action that lowers blood pressure and causes vasodilation. Calcium channel blockers have long been acknowledged as an essential class of medications in the treatment of hypertension. This initiative provides a thorough resource for pharmaceutical scientists and healthcare experts by delving into the complex production mechanisms of numerous calcium channel blockers. (Basile, 2004b)

The review article contributes to a better understanding of the rational design of novel CCBs and optimizes their therapeutic efficacy while minimizing adverse effects by revealing how these medicines function at a cellular level. Additionally, a thorough investigation of the clinical use and effectiveness of calcium channel blockers as antihypertensive medications offers insightful information about their role in the management of hypertension and directs healthcare professionals toward more evidence-based treatment choices. The results of this initiative may help hypertension patients receive better care and stimulate the creation of new drugs. It might open the door to the development of more effective and selective calcium channel blockers in the future, as well as their use in the treatment of other cardiovascular and non-cardiovascular disorders. (Haller, 2008b)

In conclusion, this thesis project, "A Review on Calcium Channel Blockers as an Effective Treatment Strategy for Hypertension," provides an extensive and in-depth analysis of the synthesis mechanisms and therapeutic value of calcium channel blockers in the context of managing hypertension. This review article advances the comprehension of these essential drugs by illuminating the complex procedures involved in the manufacture of these substances and revealing their molecular mechanisms of action. The review article presented here offers pharmaceutical researchers and medical experts a useful resource that will aid in the creation of more potent hypertension treatment plans. This thesis article serves as a basic reference that not only helps the optimization of current medicines but also shows the way to prospective advances in the treatment of hypertension as we traverse the always changing landscape of cardiovascular medicine.

In the end, we can aim that our effort will improve patient outcomes and advance the science of pharmacology, opening the door to safer, more effective methods of treating one of the most widespread health problems in the world. (Ojha et al., 2022b)

References:

Armstrong, C., Garnham, J., & Blackwood, R. (1987). Comparison of the efficacy of nicardipine, a new calcium channel blocker, with nifedipine in the treatment of mild to moderate essential hypertension. *Postgraduate Medical Journal*, *63*(740), 463–466. https://doi.org/10.1136/pgmj.63.740.463

Badillo-Alonso, H., Martínez-Alanis, M., Sánchez-Huesca, R., Lerma, A., & Lerma, C. (2023). Effectiveness of the Combination of Enalapril and Nifedipine for the Treatment of Hypertension versus Empirical Treatment in Primary Care Patients. *Journal of Cardiovascular Development and Disease*, *10*(6), 243. https://doi.org/10.3390/jcdd10060243

Basile, J. (2004a). The role of existing and newer calcium channel blockers in the treatment of hypertension. *Journal of Clinical Hypertension (Greenwich, Conn.)*, *6*(11), 621–629; quiz 630–631. https://doi.org/10.1111/j.1524-6175.2004.03683.x

Bellur Atici, E., & Karliłа, B. (2015). Identification, synthesis and characterization of process related impurities of benidipine hydrochloride, stress-testing/stability studies and HPLC/UPLC method validations. *Journal of Pharmaceutical Analysis*, *5*(4), 256–268. https://doi.org/10.1016/j.jpha.2015.02.001

Brugts, J. J., Isaacs, A., Boersma, E., Van Duijn, C. M., Uitterlinden, A. G., Remme, W., Bertrand, M., Ninomiya, T., Ceconi, C., Chalmers, J., MacMahon, S., Fox, K., Ferrari, R., Witteman, J. C. M., Danser, A. H. J., Simoons, M. L., & De Maat, M. P. M. (2010). Genetic determinants of treatment benefit of the angiotensin-converting enzyme-inhibitor perindopril in patients with stable coronary artery disease. *European Heart Journal*, *31*(15), 1854–1864. https://doi.org/10.1093/eurheartj/ehq169

Cataldi, M., & Bruno, F. (2012). 1,4-dihydropyridines: the multiple personalities of a blockbuster drug family. *Translational Medicine @ UniSa*, *4*, 12–26.

Catterall, W. A. (1993). Structure and function of voltage-gated ion channels. *Trends in Neurosciences*, *16*(12), 500–506. https://doi.org/10.1016/0166-2236(93)90193-P

Clark, R. E., Christlieb, I. Y., Ferguson, T. B., Weldon, C. S., Marbarger, J. P., Sobel, B. E., Roberts, R., Henry, P. D., Ludbrook, P. A., Biello, D., & Clark, B. K. (1981). Laboratory and initial clinical studies of nifedipine, a calcium antagonist for improved myocardial preservation. *Annals of Surgery*, *193*(6), 719–732. https://doi.org/10.1097/00000658-198106000-00007

Dariush Mozaffarian, M. D. F. E. J. B. (n.d.). *Heart Disease and Stroke Statistics*.

Ding, W. G., Tano, A., Mi, X., Kojima, A., Seto, T., & Matsuura, H. (2019). Identification of verapamil binding sites within human Kv1.5 channel using mutagenesis and docking simulation. *Cellular Physiology and Biochemistry*, *52*(2), 302–314. https://doi.org/10.33594/000000022

Dougall, H. T., & Mclay, J. (n.d.). *A Comparative Review of the Adverse Effects of Calcium Antagonists* (Vol. 9, Issue 2).

Eisenberg, M. J., Brox, A., & Bestawros, A. N. (2004). Calcium channel blockers: An update. In *American Journal of Medicine* (Vol. 116, Issue 1, pp. 35–43). Elsevier Inc. https://doi.org/10.1016/j.amjmed.2003.08.027

Fischer, C., Goldberg, J., Vulcu, S., Wagner, F., Schöni, D., Söll, N., Hänggi, M., Schefold, J., Fung, C., Beck, J., Raabe, A., & Z'Graggen, W. J. (2019). Nimodipine-Induced Blood Pressure Changes Can Predict Delayed Cerebral Ischemia. *Frontiers in Neurology*, *10*, 1161. https://doi.org/10.3389/fneur.2019.01161

Friedel, H. A., & Sorkin, E. M. (1988). Nisoldipine. *Drugs*, *36*(6), 682–731. https://doi.org/10.2165/00003495-198836060-00003

Fujii, Y., Tanaka, H., Saitoh, Y., & Toyooka, H. (1995). Effects of calcium channel blockers on circulatory response to tracheal intubation in hypertensive patients: nicardipine versus diltiazem. *Canadian Journal of Anaesthesia*, *42*(9), 785–788. https://doi.org/10.1007/BF03011177

Godfraind, T. (2017). Discovery and development of calcium channel blockers. In *Frontiers in Pharmacology* (Vol. 8, Issue MAY). Frontiers Media S.A. https://doi.org/10.3389/fphar.2017.00286

Guerrero-García, C., & Rubio-Guerra, A. F. (2018). Combination therapy in the treatment of hypertension. *Drugs in Context*, *7*, 212531. https://doi.org/10.7573/dic.212531

Haider, D. G., Sauter, T., Lindner, G., Masghati, S., Peric, S., Friedl, A., Wolzt, M., Hörl, W. H., Soleiman, A., Exadaktylos, A., & Fuhrmann, V. (2015). Use of Calcium Channel Blockers is Associated with Mortality in Patients with Chronic Kidney Disease. *Kidney and Blood Pressure Research*, *40*(6), 630–637. https://doi.org/10.1159/000368539

Haller, H. (2008a). Effective management of hypertension with dihydropyridine calcium channel blocker-based combination therapy in patients at high cardiovascular risk. *International Journal of Clinical Practice*, *62*(5), 781–790. https://doi.org/10.1111/j.1742-1241.2008.01713.x

Handler, J. (2005). Case studies in hypertension. Dihydropyridine/nondihydropyridine calcium channel blocker combination therapy. *Journal of Clinical Hypertension (Greenwich,Conn.)*,*7*(1),50–53.https://doi.org/10.1111/j.15246175.2005.04091.x

Hermida, R. C., Ayala, D. E., Mojon, A., & Fernandez, J. R. (2008). Chronotherapy With Nifedipine GITS in Hypertensive Patients: Improved Efficacy and Safety With Bedtime Dosing. *American Journal of Hypertension*, *21*(8), 948–954. https://doi.org/10.1038/ajh.2008.216

Isaac, L. (1980). Clonidine in the central nervous system: site and mechanism of hypotensive action. *Journal of Cardiovascular Pharmacology*, *2 Suppl 1*, S5-19.

Kearney, P. M., Whelton, M. B., Reynolds, K., Muntner, P., Whelton, P. K., He, J., Muntner, M. P., He, J., Kearney, P. M., Whelton, M., Reynolds, K., Muntner, P., & Whelton, P. K. (2005). Articles Introduction Global burden of hypertension: analysis of worldwide data. In *www.thelancet.com* (Vol. 365). www.thelancet.com

Kim, S. Y., Kim, S. M., Park, M. S., Kim, H. K., Park, K. S., & Chung, S. Y. (2012). Effectiveness of nicardipine for blood pressure control in patients with subarachnoid hemorrhage. *Journal of Cerebrovascular and Endovascular Neurosurgery*, *14*(2), 84–89. https://doi.org/10.7461/jcen.2012.14.2.84

Kishor, S. (2019). A COMPLETE GUIDE ON THE PHARMACOLOGIC AND PHARMACOTHERAPEUTIC ASPECTS OF CALCIUM CHANNEL BLOCKERS: AN EXTENSIVE REVIEW. *International Journal of Pharmaceutical Sciences and Research*, *10*(11), 4830. https://doi.org/10.13040/IJPSR.0975-8232.10(11).4830-43

Kleinbloesem, C. H., van Brummelen, P., & Breimer, D. D. (1987). Nifedipine. *Clinical Pharmacokinetics*, *12*(1), 12–29. https://doi.org/10.2165/00003088-198712010-00002

Kroemer, HeyoK., Gautier, J.-C., Beaune, P., Henderson, C., Roland Wolf, C., & Eichelbaum, M. (1993). Identification of P450 enzymes involved in metabolism of verapamil in humans. *Naunyn-Schmiedeberg's Archives of Pharmacology*, *348*(3). https://doi.org/10.1007/BF00169164

Laurent, S. (2017). Antihypertensive drugs. In *Pharmacological Research* (Vol. 124, pp. 116–125). Academic Press. https://doi.org/10.1016/j.phrs.2017.07.026

Lewis, G. R., Morley, K. D., Lewis, B. M., & Bones, P. J. (1978). The treatment of hypertension with verapamil. *The New Zealand Medical Journal*, *87*(612), 351–354.

Littlejohn, N. K., Siel, R. B., Ketsawatsomkron, P., Pelham, C. J., Pearson, N. A., Hilzendeger, A. M., Buehrer, B. A., Weidemann, B. J., Li, H., Davis, D. R., Thompson, A. P., Liu, X., Cassell, M. D., Sigmund, C. D., & Grobe, J. L. (2013). Hypertension in mice with transgenic activation of the brain renin-angiotensin system is vasopressin dependent. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *304*(10), R818–R828. https://doi.org/10.1152/ajpregu.00082.2013

Mace, P. J. E., Stallard, T. J., & Littler, W. A. (1985). Felodipine in hypertension. *European Journal of Clinical Pharmacology*, *29*(4), 383–389. https://doi.org/10.1007/BF00613449

Matlib, M. A., & Schwartz, A. (1983). Selective effects of diltiazem, a benzothiazepine calcium channel blocker, and diazepam, and other benzodiazepines on the Na+/Ca2+ exchange carrier system of heart and brain mitochondria. *Life Sciences*, *32*(25), 2837–2842. https://doi.org/10.1016/0024-3205(83)90319-3

Mcdonagh, M. S., Eden, K. B., Peterson, K., & Helfand, M. (2005). *Drug-Class-Review on-Calcium-Channel-Blockers*. http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm

McKeever, R. G., & Hamilton, R. J. (2023). *Calcium Channel Blockers*.

McTavish, D., & Sorkin, E. M. (1989). Verapamil. *Drugs*, *38*(1), 19–76. https://doi.org/10.2165/00003495-198938010-00003

Messerli, F. H., Bangalore, S., Bavishi, C., & Rimoldi, S. F. (2018). Angiotensin-Converting Enzyme Inhibitors in Hypertension: To Use or Not to Use? In *Journal of the American College of Cardiology* (Vol. 71, Issue 13, pp. 1474–1482). Elsevier USA. https://doi.org/10.1016/j.jacc.2018.01.058

Metabolism of Nisoldipine. (2012). *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*.

meyer1983. (n.d.).

Morales-Suárez-Varela, M. M., Mansego, M. L., Martín-Escudero, J. C., Llopis-González, A., Chaves, F. J., López-Izquierdo, R., Frutos-Llanes, R., & Vicedo-Cabrera, A. M. (2010). How ineffective hypertension control in subjects treated with angiotensin-converting enzyme inhibitors is related to polymorphisms in the renin-angiotensin-aldosterone system. *European Journal of Pharmaceutical Sciences*, *39*(5), 380–386. https://doi.org/10.1016/j.ejps.2010.01.007

Mueller, H. S., Antman, E. M., Ferst, J. A., & Muller, J. E. (1981). Nifedipine in the Treatment of Cardiovascular Disease. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *1*(2), 78–90. https://doi.org/10.1002/j.1875-9114.1981.tb03555.x

Murphy, M. B., Scriven, A. J., & Dollery, C. T. (1983). Role of nifedipine in treatment of hypertension. *BMJ*, *287*(6387), 257–259. https://doi.org/10.1136/bmj.287.6387.257

Ojha, U., Ruddaraju, S., Sabapathy, N., Ravindran, V., Worapongsatitaya, P., Haq, J., Mohammed, R., & Patel, V. (2022a). Current and Emerging Classes of Pharmacological Agents for the Management of Hypertension. In *American Journal of Cardiovascular Drugs* (Vol. 22, Issue 3, pp. 271–285). Adis. https://doi.org/10.1007/s40256-021-00510-9

Ozawa, Y., Hayashi, K., & Kobori, H. (2006). New Generation Calcium Channel Blockers in Hypertensive Treatment. In *Current Hypertension Reviews* (Vol. 2).

Reynolds, N. A., Wagstaff, A. J., & Keam, S. J. (2005). Trandolapril/Verapamil Sustained Release. *Drugs*, *65*(13), 1893–1914. https://doi.org/10.2165/00003495-200565130-00011

Rodríguez Padial, L., Barón-Esquivias, G., Hernández Madrid, A., Marzal Martín, D., Pallarés-Carratalá, V., & de la Sierra, A. (2016). Clinical Experience with Diltiazem in the Treatment of Cardiovascular Diseases. *Cardiology and Therapy*, *5*(1), 75–82. https://doi.org/10.1007/s40119-016-0059-1

Saltiel, E., Ellrodt, A. G., Monk, J. P., & Langley, M. S. (1988). Felodipine. *Drugs*, *36*(4), 387–428. https://doi.org/10.2165/00003495-198836040-00002

Schaefer, R., Aldons, P., Burgess, E., Tilvis, R., Girerd, X., Singh, G., Rehn, L., & Morgan, T. (1998). IMPROVED TOLERABILITY OF FELODIPINE COMPARED WITH AMLODIPINE IN ELDERLY HYPERTENSIVES: A RANDOMISED, DOUBLE-BLIND STUDY IN 535 PATIENTS, FOCUSING ON VASODILATORY ADVERSE EVENTS. *International Journal of Clinical Practice*, *52*(6), 381–386. https://doi.org/10.1111/j.1742-1241.1998.tb08887.x

Scherling, D., & Plei8, U. (n.d.). Syntheses of [4-14C] and [6-14C]Nisoldipine. In *Journal of Lnbelkd Compounds and Radiophamaceuticals: Vol. XXV* (Issue 12).

SCRIABINE, A., & KERCKHOFF, W. (1988). Pharmacology of Nimodipine. *Annals of the New York Academy of Sciences*, *522*(1 Calcium Antag), 698–706. https://doi.org/10.1111/j.1749-6632.1988.tb33415.x

Shemin, D. G., & Dworkin, L. D. (n.d.). *Calcium Channel Blockers*. https://doi.org/10.1016/B978-1-4160-5484-9.50055-1

Sica, D. A., & Grubbs, R. (2005). Transdermal clonidine: therapeutic considerations. *Journal of Clinical Hypertension (Greenwich, Conn.)*, *7*(9), 558–562. https://doi.org/10.1111/j.1524-6175.2005.04133.x

sica2006. (n.d.).

Sidhu, G., & Hashmi, M. F. (2023a). *Nisoldipine*.

Smith, M. S., Verghese, C. P., Shand, D. G., & Pritchett, E. L. C. (1983). Pharmacokinetic and pharmacodynamic effects of diltiazem. *The American Journal of Cardiology*, *51*(8), 1369–1374. https://doi.org/10.1016/0002-9149(83)90314-4

Sorkin, E. M., & Clissold, S. P. (1987). Nicardipine. *Drugs*, *33*(4), 296–345. https://doi.org/10.2165/00003495-198733040-00002

Stähle, H. (2000). A historical perspective: development of clonidine. *Best Practice & Research Clinical Anaesthesiology*, *14*(2), 237–246. https://doi.org/10.1053/bean.2000.0079

Thomas Lemke_ David A. Williams - Foye's Principles of Medicinal Chemistry-Lippincott Williams & Wilkins (2012). (n.d.).

Thomopoulos, C., Parati, G., & Zanchetti, A. (2015). Effects of blood pressure lowering on outcome incidence in hypertension: 4. effects of various classes of antihypertensive drugs - Overview and meta-analyses. *Journal of Hypertension*, *33*(2), 195–211. https://doi.org/10.1097/HJH.0000000000000447

Tocci, G., Desideri, G., Roca, E., Calcullo, C., Crippa, M., De Luca, N., Gaudio, G. V., Lonati, L. M., Orselli, L., Scuteri, A., Vulpis, V., Acone, B., & Zaninelli, A. (2018). How to Improve Effectiveness and Adherence to Antihypertensive Drug Therapy: Central Role of Dihydropyridinic Calcium Channel Blockers in Hypertension. *High Blood Pressure & Cardiovascular Prevention*, *25*(1), 25–34. https://doi.org/10.1007/s40292-017-0242-z

Todd, P. A., & Faulds, D. (1992). Felodipine. *Drugs*, *44*(2), 251–277. https://doi.org/10.2165/00003495-199244020-00008

Vardanyan, R. S. (Ruben S.), & Hruby, V. J. (2006a). *Synthesis of essential drugs*. Elsevier.

Yamamoto, E., Kataoka, K., Dong, Y. F., Nakamura, T., Fukuda, M., Nako, H., Ogawa, H., & Kim-Mitsuyama, S. (2010). Benidipine, a dihydropyridine L-type/T-type calcium channel blocker, affords additive benefits for prevention of cardiorenal injury in hypertensive rats. *Journal of Hypertension*, *28*(6), 1321–1329. https://doi.org/10.1097/HJH.0b013e3283388045

Yao, K., Nagashima, K., & Miki, H. (2006). Pharmacological, pharmacokinetic, and clinical properties of benidipine hydrochloride, a novel, long-acting calcium channel blocker. *Journal of Pharmacological Sciences*, *100*(4), 243–261. https://doi.org/10.1254/jphs.dtj05001x

Yiu, S.-H., & Knaus, E. E. (1996). *Synthesis, Biological Evaluation, Calcium Channel Antagonist Activity, and Anticonvulsant Activity of Felodipine Coupled to a Dihydropyridine-Pyridinium Salt Redox Chemical Delivery System*.

Yun, H.-Y., Yun, M.-H., Kang, W., & Kwon, K.-I. (2005). Pharmacokinetics and pharmacodynamics of benidipine using a slow receptor-binding model. *Journal of Clinical Pharmacy and Therapeutics*, *30*(6), 541–547. https://doi.org/10.1111/j.1365-2710.2005.00682.x

Zamponi, G. W., Striessnig, J., Koschak, A., & Dolphin, A. C. (2015). The Physiology, Pathology, and Pharmacology of Voltage-Gated Calcium Channels and Their Future Therapeutic Potential. *Pharmacological Reviews*, *67*(4), 821–870. https://doi.org/10.1124/pr.114.009654

Zhang, C., Zhao, S., Zang, Y., Zhao, W., Song, Q., Feng, S., Hu, L., & Gu, F. (2018). Magnesium sulfate in combination with nimodipine for the treatment of subarachnoid hemorrhage: a randomized controlled clinical study. *Neurological Research*, *40*(4), 283–291. https://doi.org/10.1080/01616412.2018.1426207