CHAPTER – 1

Introduction
1.1 Introduction

Today, approximately 1 billion people worldwide have high blood pressure (BP), and this number is expected to increase to 1.56 billion people by the year 2025. That translates to about 1 out of every 4 adults being afflicted with hypertension.¹

Human immunodeficiency virus (HIV) is still the biggest challenge. The global statistics of people infected with HIV around the world so far is ~34 millions, while another 25 millions have lost their lives due to HIV. In 2008 itself, about 33.4 million people were diagnosed living with HIV, with a new addition of 2.7 million. The total number of deaths due to acquired immunodeficiency syndrome (AIDS) was 2 million. 40% of all HIV patients around the world are youth. 2.9 million HIV patients are ever younger in age.² Because of emerging trend, there is a necessity to work more in this area to get better hypertensive drugs as well as antiviral drugs.

Hypertension is one of the most common medical conditions. In most cases, it is a silent risk factor for other health conditions, such as a heart attack. The medical society greatly emphasizes the importance of controlling BP. Numerous drugs are available in market to treat the same and work in many pathways.³ The major classes of antihypertensive medications are angiotensin II receptor blockers, diuretics, β-adrenoreceptor blockers, angiotensin converting
enzyme inhibitors, and calcium channel blockers. Among all the antihypertensive drugs, angiotensin II receptor blockers and β-adrenoreceptor blockers have special focus to develop new derivatives as well as process improvement in existing drugs. Typically, Valsartan blocks angiotensin II receptor while carvedilol acts on the β-adrenoreceptor.

One of the common methodologies in drug design and developing new biologically active compounds involves modification of existing active molecules by changing of functional groups/substituents with basic nucleus unchanged.

AIDS is a disease of the human immune system caused by the human immunodeficiency virus (HIV). The pandemic spread of AIDS has promoted an unprecedented scientific and clinical effort to understand and combat this lethal disease. Many research laboratories have developed HIV-1 protease inhibitors that have become lead compounds for antiviral drugs, and some of these compounds have been approved for therapeutic use. Still one of the pervading problems found in these therapies is the development of drug resistance. However, the capacity of HIV-1 protease inhibitor to develop resistance to previously effective drugs has necessitated the application of multi-drug therapy and medicinal chemists presented with an ongoing challenge to develop new inhibitors.
With the available infrastructure for chemical and analytical research, and in the absence of biological evaluation, the present work has followed semi-rational approach to synthesize and characterize new molecules that are included in various chapters.

### 1.2. Antihypertensive

Antihypertensive drug therapy has been remarkably improved in the last 40 years. The antihypertensive of the 1960-70s were methyldopa, β blockers, thiazide and high ceiling diuretics and clonidine. The status of β blockers and diuretics was consolidated in the 1970s and selective α₁ blocker prazosin broke new grounds. The antihypertensive of the 1980-90s are angiotensin II converting enzyme (ACE) inhibitors (captopril), angiotensin II receptor antagonist (losartan, valsartan) and calcium channel blockers (nifedipine). Typical classifications of antihypertensive agents are as follows:

#### 1.2.1. Calcium channel blockers: Calcium channel blockers are now front line antihypertensive drugs. They lower BP by decreasing peripheral resistance without compromising cardiac output. Calcium channel blockers are clean drugs suitable for majority of hypertensive patients with various grades of the disease.

**Nifedipine:** It is a derivative of 2-nitrophenyl-1,4-dihydropyridine. Bossert et al., reported⁵ the synthesis of nifedipine (III) by Hantzsch reaction of 2-nitrobenzaldehyde (I) with methyl acetoacetate (II) and ammonia.
**Nicardipine:** It is a derivative of 3-nitophenyl-1,4-dihydropyridine. Murakami et al., reported the synthesis of nicardipine (VII) by Hantzsch reaction of 3-nitrobenzaldehyde (IV) with methyl 3-aminocrotonate (VI) and 2-(N-benzyl-N-methyl)ethyl acetoacetate (V) in isopropyl alcohol at 80°C.

**Barnidipine:** Kojima and Takenaka synthesized barnidipine (IX) by Hantzch reaction of [(3S)-(1-benzylpyrrolidin-3-yl)]-3-oxobutanoate (VIII) with 3-nitrobenzaldehyde (IV) and methyl 3-aminocrotonate (VI) in isopropyl alcohol at reflux temperature.
**Amlodipine**: Campbell et al., reported the synthesis of amlodipine (XV) starting from commercially available N-(2-hydroxyethyl)phthalimide (X). O-alkylation of compound X with ethyl 4-chloroacetoacetate (XI) in the presence of sodium hydride at room temperature gave compound XII. The resulting compound (XII) undergoes Hantzsch reaction with 2-chlorobenzaldehyde (XIII) and methyl 3-aminocrotonate in isopropanol at reflux temperature gave compound XIV. Finally, phthalolyl amlodipine (XIV) upon deprotection with ethanolic methylamine at room temperature produce amlodipine (XV).
**Isradipine:** Hantzsch reaction of 2,1,3-benzoxadiazole-4-carbaldehyde (XVI) with isopropyl acetoacetate (XVII) and methyl 3-aminocrotonate (VI) in ethanol at reflux temperature gave isradipine\(^9\) (XVIII).
Manidipine: Meguro and Nagaoka reported\textsuperscript{10} the synthesis of manidipine (XX) by the following reaction sequence.
**Nisoldipine:** Wehinger et al., reported\(^{11}\) the synthesis of nisoldipine (XXII) by cyclization of 2-nitrobenzylideneisobutyl acetoacetate (XXI) with methyl 3-aminocrotonate (VI) in ethanol at reflux temperature.

![Diagram of nisoldipine synthesis](image)

**Felodipine:** It is a derivative of 2,3-dichloro-1,4-dihydropyridine. Cyclization of 3-aminocrotonate (VI) with methyl 2,3-dichlorobenzylideneacetylacetate (XXIII) in t-butanol gave felodipine\(^{12}\) (XXIV).

![Diagram of felodipine synthesis](image)
The following are some of the famous calcium channel blockers:

(XXV) (Nimodipine)

(XXVI) (Nilvadipine)

(XXVII) (Lercanidipine)

(XXVIII) (Pranidipine)

(XXIX) (Cilnidipine)

(XXX) (Lacidipine)
1.2.2. Angiotensin converting enzyme (ACE) inhibitors:

Angiotensin II (A-II) is formed from angiotensin I (A-I) in a reaction catalyzed by ACE. A-II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, cardiac stimulation and renal absorption of sodium, stimulation of synthesis and release of aldosterone.

**Captopril**: Ondetti et al., reported the synthesis of captopril (XXXV) starting from L-proline t-butyl ester by reacting with compound XXXII and then hydrolysed with trifluoroacetic acid and treated with methanolic ammonia.

![Chemical Structures](https://example.com)

**Ramipril**: Condensation of substituted proline (XXXVII) with substituted (S)-alanine (XXXVI), followed by catalytic hydrogenation gave ramipril (XXXIX).
**Lisinopril**: Condensation of compound XL with compound XLI followed by reduction with sodium cyanoborohydride gave lisinopril\(^{20}\) (XLII).

**Trandolapril**: It is a derivative of (2S,3aR,7aS)-octahydroindole derivative. Urbach et al., reported\(^{21}\) the synthesis of trandolapril (XLV) by condensation of (2S,3aR,7aS)-octahydroindole (XLIII) with (S)-alanine derivative (XXXVI) followed by catalytic hydrogenation.
Perindopril: It is a derivative of (2S,3aS,7aS)-octahydroindole. Vincent et al., reported the synthesis of perindopril (XLIX) by the condensation of (2S,3aS,7aS)-octahydroindole (XLVI) with substituted (S)-alanine (XLVII) followed by catalytic hydrogenation.
Spirapril: Gold et al., reported the synthesis of spirapril (LIX) starting from 1-benzoxycarbonyl-4-keto-(S)-proline methyl ester (L).

\[
\begin{align*}
&\text{Ph} = O\text{C}\text{OCH}_3 + \text{HS-SSH} \xrightarrow{\text{Glacial acetic acid PTSA}} \text{Ph-O\text{C}\text{OCH}_3} \\
&\text{(L)} & \text{(LI)} & \text{(LII)} \\
&\text{Glacial acetic acid} HBr / RT \xrightarrow{} \text{HN-O\text{C}\text{OCH}_3} & \text{(LIII)} & \text{(LV)} \\
&\text{NaOH / methanol RT} \xrightarrow{} \text{Ph-O\text{C}\text{NCH}_3\text{NCH}_3\text{NCH}_3\text{NCH}_3\text{OCH}_3} & \text{(LVI)} & \text{Glacial acetic acid HBr} \xrightarrow{} \text{H_2N-O\text{C}\text{OCH}_3} & \text{(LVII)} \\
&\text{H}_3\text{C-O\text{COO}} \xrightarrow{\text{Methanol sodium cyanoborohydride}} \text{H}_3\text{C-O\text{COO}} & \text{Ph-O\text{C}\text{NCH}_3\text{NCH}_3\text{NCH}_3\text{NCH}_3\text{OCH}_3} & \text{(LIX)} \\
\end{align*}
\]
**Imidapril:** It is a derivative of imidazole. Yoneda et al., reported the synthesis of imidapril (LXV) by following reaction sequence.

\[
\text{(LX)} \xrightarrow{\text{DCC} / \text{THF}} \text{(LXII)}
\]

**Enalapril:** Condensation of compound LXVI with compound LXVII followed by reduction with sodium cyanoborohydride gave enalapril (LXVIII).
Here some of the known angiotensin converting enzyme inhibitors whose structures are:
1.2.3. **Diuretics**: They have been the standard antihypertensive drugs used over the past 3 decades, at present those are the first choice agents in selected fewer patients. The major drawback of diuretics, for example, hydrochlorothiazide (LXXIV), is carbohydrate intolerance and precipitation of diabetes due to inhibition of insulin release.

![Image](LXXIV)

*(Hydrochlorothiazide)*

1.2.4. **β Adrenergic blockers**: They are mild antihypertensives and do not significantly lower blood pressure in normotensives. All β blockers, irrespective of associated properties, exert similar antihypertensive effect.

**Propranolol**: Condensation of compound LXXVI with compound LXXV at moderate temperature/pressure gave propranolol\(^30\) (LXXVII).

![Image](LXXV) + ![Image](LXXVI) \(\xrightarrow{70-80^\circ\text{C}}\) ![Image](LXXVII)

*(LXXV) *(LXXVI) *(LXXVII)*

**Metoprolol**: Ring opening of oxirane (LXXVIII) with isopropylamine in isopropyl alcohol at reflux temperature gave metoprolol\(^31\) (LXXIX).

![Image](LXXVIII) + ![Image](LXXIX) \(\xrightarrow{\text{reflux}}\) ![Image](LXXIX)

*(LXXVIII) *(LXXIX)*
The following are some of famous β-blockers:

1.2.5. α-adrenergic blockers:
1.2.6. Central sympatholytics:

\[
\text{Clonidine} \quad (\text{LXXXIV})
\]

\[
\text{Methyldopa} \quad (\text{LXXXV})
\]

1.2.7. Adrenergic neurone blockers:

\[
\text{Bethanidine} \quad (\text{LXXXVI})
\]

\[
\text{Guanethidine} \quad (\text{LXXXVII})
\]

\[
\text{Reserpine} \quad (\text{LXXXVIII})
\]

1.2.8. Ganglion blocker: They are potent hypotensives, extensively used in the 1950s, but have gone into disuse because of marked
postural and exercise hypotension and other side effects. They are not commercially available now.

\[ \text{(LXXXIX)} \quad \text{(Pentolinium Tartrate)} \]

\[ \text{(XC)} \quad \text{(Trimethaphan Camsylate)} \]

1.3. Antiviral

The rapid spread of the AIDS epidemic has stimulated the discovery of therapeutic agents for arresting the replication of the causative HIV, there has been an intense worldwide search to find useful chemotherapeutic agents. Here, classification of a few typical antiviral agents is described.

**Abacavir:** It is a derivative of adenine. N-alkylation of compound \( \text{XCII} \) with compound \( \text{XCI} \) produced compound \( \text{XCIII} \). The resulting compound \( \text{XCIII} \) was treated with sodium hydroxide to obtained abacavir\(^{37} \) \( \text{XCIV} \).

\[ \text{(XCI)} + \text{(XClII)} \xrightarrow{\text{Pd(PPh)\text{4} / NaH, THF}} \text{(XCIII)} \]
**Tenofovir:** It is an acyclic nucleotide analog of adenosine monophosphate. Arimilli et al., reported the synthesis of tenofovir (C) and its prodrug tenofovir-dipivoxil as its (1:1) fumarate salt (CI) starting from (S)-glycidol (XCV).

![Chemical diagrams showing the synthesis of Tenofovir and its prodrug.](image-url)
**Zidovudine:** It is a derivative of thymine. Chu et al., reported the synthesis of zidovudine (CIV) by the following reaction sequence.

Here, some of the antiviral drugs that presently in clinical use are given below:
**Saquinavir:** It is a peptidomimetic hydroxyethylamine. Decahydroisoquinoline (DIQ) group is one of the most significant in saquinavir. Parkes et al., reported\(^{43}\) the synthesis of saquinavir (Ro 31-8959) *(CXVI)* by the following reaction sequence.
Nelfinavir: It contains a novel 2-methyl-3-hydroxybenzamide group, whereas its carboxyl terminal contains the same decahydroisoquinoline (DIQ) group as saquinavir. Condensation of compound CXVII with compound CXVIII in ethanol at reflux temperature produced compound CXIX. The resulting compound CXIX was treated with concentrated hydrochloric acid followed by condensation with compound CXXI gave nelfinavir⁴⁴ (CXXII).
Lopinavir: It is a peptidomimetic HIV protease inhibitor, which contains phenoxyacetyl group in one end and six-membered cyclic urea in other end of hydroxyl ethylene dipeptide moiety. Stoner et al., described\textsuperscript{45} the synthesis of lopinavir (CXXVIII), starting from
compound (CXXIII) by the following reaction sequence.

\[
\begin{align*}
\text{(CXXIII)} & \xrightarrow{\text{SOCl}_2, \text{THF},} \text{(CXXIV)} \\
\text{(CXXVI)} & \xrightarrow{i) \text{Pd/C, HCO}_2\text{NH}_4, \text{Methanol} \quad \text{ii) L-Pyroglutamic acid, Dioxane}} \text{(CXXVII)} \\
\text{(CX)} & \xrightarrow{\text{Aq. NaHCO}_3, \text{ethyl acetate}} \text{(CXXVIII)}
\end{align*}
\]
1.4. References


44. Dressman, B. A., Fritz, J. E., Hammond, M., Hornback, W. J., Kaldor, S. W., Kalish, V. J., Munroe, J. E., Reich, S. H.,