Medicinal Chemistry of Drugs Affecting Cardiovascular and Endocrine Systems

Editor:
M. O. Faruk Khan

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(Volume 3)

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FOREWORD

For a pharmacist, medicinal chemistry education is critical to developing an adequate knowledge base and critical thinking skills. In this *eBook,* the fundamental principles of medicinal chemistry including the functional groups occurring in medicinal agents, the acidity and basicity of drugs, and their water and lipid solubility as well as drug-receptor interactions are described. The physicochemical principles, isosterism, and spatial characteristics of drugs are prerequisites to understanding drug pharmacodynamics. Another important aspect that is crucial to comprehending the mechanism of drug action is the knowledge of important biosynthetic pathways that are frequently encountered in pharmaceutical interventions; a chapter has been devoted to this important aspect in this first volume. In this book, a comprehensive approach has been taken to explain the phases of drug metabolism, modifications of drug chemical structures, and their effects on drug pharmacokinetics, safety, and efficacy.

It is apparent that the authors have taken into consideration the integrated aspect of PharmD curricula while developing the contents. The standout feature of this *eBook* series is its layout, which includes 4 volumes in three distinct areas - the fundamental concepts, detailed structure-activity relationships of different drug classes, and recent developments in the area of medicinal chemistry and drug discovery. It offers students the opportunity to learn the principles of drug action in a stepwise manner. The case studies, student's self-study guide, and self-assessment at the end of each chapter are unique features of this book that would be beneficial to both students and instructors. Although there are several medicinal chemistry textbooks available on the market, to my understanding this is the first textbook of its kind focusing on the integrated aspects of PharmD curricula.

As a pharmacy educator, leader, journal editor, and an expert in pharmacy curriculum, I am pleased to testify and endorse this *eBook* to pharmacy educators, and learners as one of the most useful resources in medicinal chemistry. Based on my pedagogical research and assessment of student learning, it is my understanding that this book takes a student-friendly approach that incorporates appropriat Reillustrative diagrams and study guides as well as self-assessments. In my early years as a student in the pharmacy, I found medicinal chemistry as a challenging subject area. The inclusion of clinical and management focuses in the modern PharmD curriculum left the students with limited time available to grasp all the basic concepts which made it more challenging for them to manage the old hard-core science-driven medicinal chemistry courses. This *eBook* series brings those memories of my early years as a pharmacy student and the evolution of pharmacy education, and gives me the confidence that it will pave the way for future medicinal chemistry education for pharmacists and other health professionals.

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PREFACE

This is the third volume of the 4-volume eBook series, "*Medicinal Chemistry for Pharmacy Students*". The primary objective of this e-Book series is to educate PharmD students in the area of medicinal chemistry and serve as a reference guide to pharmacists on aspects of the chemical basis of drug action. A thorough discussion of key physicochemical parameters of therapeutic agents and how they affect the biochemical, pharmacological, pharmacokinetic processes and clinical use of these agents is the primary focus of the whole book. The rationale for putting together an e-Book of this nature is to equip PharmD students with the scientific basis to competently evaluate, recommend and counsel patients and healthcare professionals regarding the safe, appropriate, and cost-effective use of medications.

This third volume of the series is comprised of 8 chapters focusing on a comprehensive account of medicinal chemistry of drugs affecting the cardiovascular and endocrine systems. It provides the mechanism of drug action, detailed structure-activity relationships and metabolism as well as the clinical significance of drugs affecting the cardiovascular and endocrine system to give the knowledge base for pharmacists.

Chapter 1 provides a comprehensive account of the medicinal chemistry of drugs affecting the renin-angiotensin system (RAS). This chapter includes pathophysiologic principles, mechanism of action, structure-activity relationships (SAR) and metabolism of drugs affecting RAS including enzymes and hormones and their roles in blood pressure, structures, binding, and chemistry and SAR of the antagonists involved in RAS such as the angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and renin inhibitors. It also discusses the clinical significance and therapeutic evaluations of these classes of drugs by solving case studies as well as the discovery process of ACEIs and ARBs.

Chapter 2 is a comprehensive account of the medicinal chemistry of antihypertensive drugs, Ca^{2+}-channel blockers (CCBs). It details the pathophysiologic principles, mechanism of drug action, SAR, classifications, and their clinical significance.

Chapter 3 focuses on the medicinal chemistry of the diuretic agents. It provides a detailed account of the pathophysiologic principles of diuretics, the mechanism of drug action and the SAR of these drugs. The chemical principles and classification of diuretics, their metabolism and pharmacokinetic parameters, and the clinical significance as well as safety parameters of these drugs have been clearly delineated.

Chapter 4 is a comprehensive account of the medicinal chemistry of the anticoagulants, antiplatelets and thrombolytic agents and their relatives – their pathophysiologic principles, mechanism of action, SAR and metabolism. Topics include the physiology and pathophysiology of clotting, major classes of anticoagulant drugs and their structures and binding, distinctions among drugs used as antiplatelets, anticoagulants, and fibrinolytic agents and delineation of the clinical significance, therapeutic evaluations and discovery story of these classes of drugs.

Chapter 5 is a comprehensive account of the medicinal chemistry of antihistamines, H2 receptor (H2R) blockers, H3 receptor (H3R) blockers, and proton pump inhibitors (PPIs). It provides the pathophysiologic principles, mechanism of drug action, and detailed SAR of the drugs in these classes Topics include a concise account of the physiochemical properties of histamine and histamine receptors, chemical classes of antihistamines, H2R and H3R antagonists, the distinction between sedating and non-sedating antihistamines, as well as the

first generation, second generation, and third generation antihistamines. It also discusses the structural features of cromolyn and related mast cell stabilizers as well as the proton pump inhibitors including their development, mechanism of action, and structural and physicochemical features.

Chapter 6 is a comprehensive account of diabetes and the medicinal chemistry of antidiabetic drugs. It discusses the physicochemical principles, mechanism of action, SAR, and metabolism of the antidiabetic drugs. The clinical features of diabetes and differentiation between type I and type II diabetes, various risk factors and corresponding mechanisms responsible for the development of diabetes and pathophysiologic mechanisms responsible for the clinical features of diabetes have also been discussed. A review of biosynthesis of insulin, its metabolic outcomes, regulation of insulin secretion, and insulin signaling have been explained. This chapter has classified all the injectable and oral antidiabetic drugs and provided their clinical significance as well.

Chapter 7 is a comprehensive account of the medicinal chemistry of hormonal therapy. It provides the physicochemical principles, mechanism of drug action, SAR, and drug metabolism of the hormonal agents. This chapter discusses in detail hormone replacement therapy (HRT), androgen replacement therapy (ART), oral contraceptive pills and gender-affirming hormone therapy. It also provides a detailed understanding of thyroid hormones and their clinical significance.

Chapter 8 provides a comprehensive account of the medicinal chemistry of drugs arising from structural modifications of prostanoids, which are naturally occurring eicosanoids. These drugs are used for a variety of disease states including but not limited to glaucoma, pulmonary arterial hypertension, and peptic ulcers. This chapter provides the pathophysiologic principles, mechanism of drug action, and SAR of these agents with their clinical significance.

The chapters in this volume are designed to guide the reader to review, integrate, and apply principles of medicinal chemistry to drug action of therapeutic agents. All concepts are illustrated with diagrams or figures, with the keywords highlighted, bulleted or numbered. Wherever needed, special boxes and case studies are included. In addition, each chapter is reinforced with student's self-study guides and self-assessment questions. Special notations are highlighted using call-out boxes for visual effect. Tables and figures are used to augment the text as needed.

We would like to express our sincere gratitude to the contributing authors for their time and effort in completing this volume. We would also like to thank Bentham Science Publishers, particularly Ms. Asma Ahmed (Manager Publications) and Mr. Mahmood Alam (Director Publications) for their support. We are confident that this volume of the eBook series will guide students and educators of pharmacy and related health professions worldwide.

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CHAPTER 1

Drugs Affecting Renin-Angiotensin System

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Abstract: This chapter presents a comprehensive account of the medicinal chemistry of drugs affecting the renin-angiotensin system (RAS). It provides the mechanism of drug action and details structure-activity relationships (SAR) of the drugs affecting RAS to give the knowledge base for pharmacists. After studying this chapter, students will be able to:

• Describe the historical background the RAS and drugs acting on this system.

• Explain RAS enzymes and hormones and their roles in blood pressure.

• Classify drugs acting on the RAS and their structures and binding.

• Discuss in detail the chemistry and SAR of the antagonists involved in RAS including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and renin inhibitors.

• Delineate the clinical significance and therapeutic evaluations of these classes of drugs by solving case studies.

• Explain the discovery process of ACEIs and ARBs.

Keywords: ACE, ACEIs, ARBs, Drug receptor interaction, Renin inhibitor, RAS, Structure-activity relationship.

HISTORICAL BACKGROUND

As early as 1898, renin's role in increasing blood pressure was suggested based on the observation that the injection of kidney extracts dramatically increased rabbit's blood pressure [1]. In the 1930s, a pathologist named Harry Goldblatt discovered a vasoconstricting agent (which later appeared to be renin) secreted by the kidneys responsible for increasing blood pressure [2]. In 1939, it was concluded that renin is an enzyme which catalyzes the formation of angiotensin (Ang) [3]. Decades later, two forms of Ang, Ang I and Ang II, were identified.

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A zinc metallopeptidase, angiotensin converting enzyme (ACE), was discovered in 1954 from equine plasma and purified in 1956 [4, 5]. It is now known that renin first converts angiotensinogen (a 14-amino acid peptide) into Ang I (a decapeptide), which is then converted by ACE into Angiotensin II (Ang II, an octapeptide; Asp-Arg-Val-Tyr-Ile-His-Pro-Phe) that causes vasoconstriction and hypertension [6].

In 1965, a Brazilian scientist, Sérgio Henrique Ferreira, reported the presence of a bradykinin potentiating factor (BPF) in the venom of a South American pit viper *Bothrops jararaca* [7], then he moved to the laboratory of Sir John Vane in London, UK for further research. Ng and Vane in 1967 showed that Ang I is quickly converted into Ang II by ACE in the pulmonary circulation and lung. The finding that BPF inhibits the conversion of Ang I into Ang II led to believe that bradykinin also disappears in the lung by the action of ACE [8 - 10].

Vane convinced Bristol Myers Squibb Pharmaceutical Company to work on the project of snake venom and started fractional analysis of the BPF. They isolated a nonapeptide, teprotide (SQ 20,881), to be the most potent ACE inhibitor (ACEI) and antihypertensive agent *in vivo* (see later in drug discovery case studies) [11]. They purified a few more peptides: all of which were found to be ACEIs Table (**1**) [12]. As a peptide, teprotide is orally ineffective. In search of an orally effective drug, they investigated about 2000 non-peptides without any success. In the early 1970s, they started using the other mechanistically similar, but widely studied enzyme carboxypeptidase A and its 3D-structure of the active site to design ACEI and successfully launched captopril as the first orally active ACEI in 1975, which was approved by US Food and Drug Administration (FDA) in 1981 (see later in drug discovery case studies) [13].

Table 1. The peptide inhibitors of ace isolated from snake venom.

Peptide Structure	IC_{50} (µg/mol)[a]
Glu–Trp–Pro–Arg–Pro–Lys–Phe–Ala–Pro–OH	0.05
Glu–Lys–Trp–Ala–Pro–OH	0.05
Glu–Phe–Ala–Pro–OH	2.7
Phe–Ala–Pro–OH	1.4
Ala–Pro–OH	50

[a]IC_{50} is the concentration of peptide needed to inhibit the activity of ACE by 50%.

The first Ang II receptor type 1 (AT_1R) was identified during the 1970s and was cloned in the 1990s. The AT_2R was identified during the early 1980s and cloned in the early 1990s [14] although the existence of different forms of ATRs was suggested in 1974 [15] by Papadimitriou and Worcel. Other ATRs including AT_3R and AT_4R have also been recognized to date, all of which are G-protein

coupled 7-transmembrane (7-TM) containing receptors. Only AT_1R and AT_2R are clinically significant [16]. AT_1R mediates most of the functions of Ang II while AT_2R contributes to the regulation of blood pressure and renal functions. This discovery triggered the development of AT_1R blockers (ARBs). Saralasin, a peptide analog of Ang II, was found to be a potent ARB but lacked oral bioavailability [17]. Takeda, a Japanese company, in the early 1980s, tested a series of compounds to find a lead and developed losartan as the first clinically useful, orally active, potent and selective nonpeptide ARB by DuPont chemists [18].

Another drug acting on the renin-angiotensin system (RAS) is aliskiren, an orally effective, nonpeptide, low-molecular-weight renin inhibitor. It was co-developed by the Swiss pharmaceutical companies Novartis and Speedel through a combination of molecular modeling techniques and crystal structure elucidation of renin and the renin-drug complex [19, 20]. Aliskiren was approved for clinical use in the USA in 2007 for the treatment of primary hypertension.

Angiotensin inhibition has also been combined with neprilysin inhibition for the treatment of chronic heart failure. This angiotensin receptor neprilysin inhibitor (ARNI) is a combination of valsartan (an ARB) and sacubitril, a neprilysin inhibitor approved in July 2015 by the FDA [21, 22]. The development of this drug was prompted by the need to inhibit neprilysin and RAS concurrently. Neprilysin inhibition alone can enhance the beneficial response of natriuretic peptides released in heart failure but can result in in the counteractive activation of the RAS by increasing angiotensin II. Although both ACEIs and ARBs inhibit RAS, only ARBs are recommended to be utilized with neprilysin inhibitors. Prior to valsartan/sacubitril approval, a drug containing an ACEI and a neprilysin inhibitor called omapatrilat was developed. This drug was never marketed due to the increased incidences of angioedema observed in clinical trials [23].

Today, drugs affecting the RAS comprise a large class of clinical agents and many of these frequently are among the top 200 medications dispensed. Those included in the last few years are shown in Fig. (**1**).

INTRODUCTORY CONCEPTS

The Renin-Angiotensin System (RAS)

The RAS regulates blood pressure and fluid balance. Renin, secreted by kidneys when blood volume or blood pressure is low, stimulates the biosynthesis of Ang I from angiotensinogen. ACE in the lung and pulmonary circulations then converts Ang I to Ang II, which causes vasoconstriction resulting in increased blood pressure. Ang II also stimulates the secretion of aldosterone which causes

CHAPTER 2

Ca^{+2} Channel Blockers

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Abstract: This chapter is a comprehensive account of the medicinal chemistry of antihypertensive drugs, Ca^{2+}-channel blockers (CCBs). It provides the mechanism of drug action and detailed structure-activity relationships (SAR) of the CCBs to give the knowledge base for pharmacists. After studying this chapter, students will be able to:

• Comprehend the historical background of the CCBs.

• Classify different types of voltage-gated Ca^{2+} channels (VGCCs) and their clinical significance.

• Explain CCBs and their clinical significance.

• Describe the mechanisms of action of CCBs at the molecular level including their binding modes against the VGCCs.

• Describe the SAR of the different classes of CCBs.

• Delineate clinical significance and therapeutic evaluations of these classes of drugs by solving case studies.

• Articulate the discovery process of a few CCBs.

Keywords: Benzothiazepines (BTZs), Ca^{2+}-channels, CCBs, Drug-receptor interaction, Dihydropyridines (DHPs), Dihydropyridine receptors (DHPR), Diaminopropanol ethers, Phenylalkylamines (PAAs), Structure-activity relationship (SAR), VGCC.

HISTORICAL BACKGROUND OF CA^{2+}-CHANNEL BLOCKERS

Voltage-gated Ca^{2+}-channels (VGCCs) are crucial for the normal as well as abnormal physiological scenarios associated with neuronal, neurosecretory and muscle cells. The latter express VGCCs in their plasma membrane – a feature that

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can be used to categorize these cells as 'excitable' [1]. These channels were first identified in crustacean muscle by Paul Fatt and Bernard Katz who observed that these muscles retained the ability of generating action potential even in the absence of any Na^+ in their bathing medium [2]. Fatt and colleagues further investigated the significance of this observation [3]. Later, Hagiwara and Byerly pursued an in-depth characterization of the currents in various invertebrate tissues [4]. Work on mammalian VGCCs began later and progressed in parallel with the invertebrate VGCCs [5]. By now, it is well established that VGCCs are present in the plasma membrane of all excitable cells including muscle, neurons and exocrine glands where they play a critical role in generating action potential and thereby excitation-contraction as well as excitation-secretion coupling [1]. However, they can also be expressed in low levels in non-excitable cells such as immune cells, but their role associated with such non-canonical distribution is yet to be known [5].

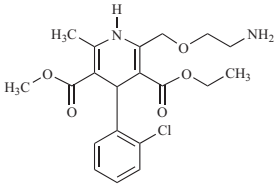
The voltage-gated Ca^{2+}-channel blockers (CCBs) were originally synthesized with the intention of developing some selective inhibitors of the voltage-gated potassium channels. Albrecht Fleckenstein and his colleagues at the University of Freiburg (Germany) first showed that prenylamine and verapamil resulted in electromechanical uncoupling in the heart in a way that mimicked the consequences of removing Ca^{2+} from extracellular solution and such effect could be reversed by increasing intracellular Ca^{2+} concentration [6]. Some diphenylpiperazine derivatives such as cinnarizine and flunarizine were reported by Theophile Godfraind and his colleagues to exhibit similar uncoupling of excitation-contraction in vascular smooth muscle [7, 8]. These initial observations prompted further research into the field and eventually led to the development of structurally diverse, second-generation drugs, including diltiazem and nifedipine (and various other 'dipines'), capable of inhibiting these channels. Up until now, all the official drugs that are known to be inhibitors of VGCCs primarily target the **L-type channels** (see later in next section). Although a growing number of studies indicate that VGCCs other than the L-type channels may also be implicated in some pathophysiological conditions, the development of selective antagonists or blockers of these channels remains investigational. Today, a large number of CCBs frequently occur in the top 200 drugs' list Fig. (**1**).

INTRODUCTORY CONCEPTS

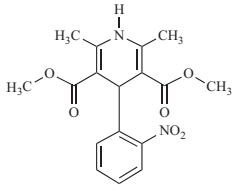
The Voltage Gated Ca^{2+}-Channels (VGCCs) and their Clinical Significance

Calcium is a universal and versatile second messenger, regulating almost every aspect of cellular life [9]. One of the most common ways cells respond to various extracellular stimuli from hormones, growth factors and neurotransmitters is by

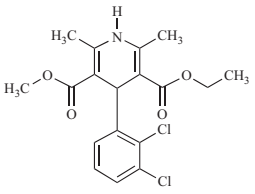
transiently increasing the cytosolic free Ca^{2+} concentration from a basal, resting level (~100-300nM to ~1μM). This elevated cytosolic free Ca^{2+} is then sensed by numerous cellular targets and effector proteins to regulate a diverse array of processes such as fertilization, cell growth and differentiation, muscle contraction, exocytosis, synaptic plasticity, transcriptional regulation and apoptosis [9]. Cells derive the 'extra' Ca^{2+} for signaling purposes both from the internal stores (*e.g.*, endoplasmic and sarcoplasmic reticulum, mitochondria, lysosome, nucleoplasm *etc*.) as well as extracellular space. In both cases, Ca^{2+} flows into cytosol down its concentration gradient through Ca^{2+} permeable pores of various ion channels expressed in the plasma membrane as well as the membranes of intracellular organelles that store Ca^{2+}. Opening of these channels is precisely regulated and triggered either by ligand binding or changes in membrane potential (typically depolarization). Members of the latter group, widely known as the VGCC family and often represented as Ca_V channels [10], have been the major therapeutic targets against diseases involving primarily the cardiovascular and to a lesser extent, the nervous system. Therefore, the present chapter will focus on inhibitors of VGCCs as an important therapeutic class.



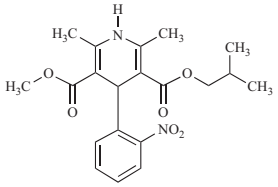
Amlodipine (Norvasc®)



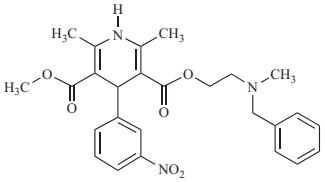
Nifedipine (Adalat®; Afeditab®; Procardia®)



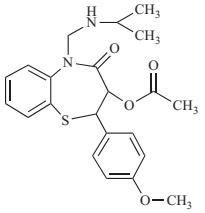
Felodipine (Plendil®)



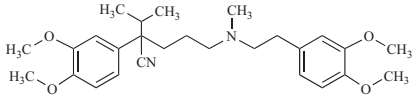
Nisoldipine (Sular®)



Nicardipine (Cardene®; Cardene®)



Diltiazem (Cardizem®; Cartia®; Dilacor®; Diltzac®; Taztia®; Tiazac®)



Verapamil (Calan®; Covera®; Isoptin®; Isoptin®; Verelan®)

Fig. (1). Ca^{2+}-channel blockers frequently occurring in top 200 drug list.

CHAPTER 3

Diuretics

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Abstract: This chapter is a comprehensive account of the medicinal chemistry of diuretic agents. It provides the mechanism of drug action and details the structure-activity relationships (SAR) of these drugs to provide a knowledge base for pharmacists. After studying this chapter, students will be able to:

• Identify the chemical classification to which a diuretic agent or therapeutic belongs based on drug structure.

• Evaluate the chemical principles of different classes of diuretics.

• Compare and contrast the potency, onset, and duration of action of the diuretic agents.

• Identify chemical metabolites of the diuretics that increase the risk of nephron and hepatotoxicity.

• Select an appropriate diuretic agent based on patient-specific symptoms of hypertension or other problems.

• Rationalize the clinical application of all diuretic drug classes.

• Communicate the chemical rationale for a diuretic to health professionals.

• Delineate the clinical significance and therapeutic evaluations of these classes of drugs by solving case studies.

• Identify the discovery process of selected diuretic agents.

Keywords: Carbonic anhydrase inhibitor (CAI), Drug receptor interaction, Loop diuretics, Nephron, Osmotic diuretics, Potassium sparing diuretics, Sulfonamides, Structure activity relationship, Thiazide diuretics.

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HISTORICAL PERSPECTIVES

The sufferings and agonies from excess body fluid have been a matter of medical concern since the earliest days of recorded history. Egyptian concoctions for "causing urination" or "expelling excess fluid from the body and heart" were recorded in the Hearst Medical Papyrus in 1550 BC. Pharaonic medicine for these purposes was guided by religious bindings and was composed of complex mixtures of plants and minerals incorporated into beer and honey. The Greek medicines took a rational and secular approach that was laborious in the sense that patients had to consume dry and acrid substances to increase excretion. Hippocrates' (460-377 B.C.E.) recommendations for the treatment of dropsy (edema) were sweating, catharsis, and bleeding, which remained a mainstay until the 20th century when clinically effective diuretics were developed [1].

The manuscript, Dioscorides' De Materia Medica (40-90 C.E.), recognized as the supreme authority on medicinal substances for over 1500 years, codified the diuretic properties of several plants including juniper, radishes, cassia, cinnamon, dill, wormwood, periwinkle and squill. The boiled bulb of squill (*Scilla siberica*), a coastal Mediterranean plant, flavored with vinegar or honey, was recommended by Romans, Celsus, and Pliny as a diuretic, and remained the mainstay in diuretic treatment until the 16th century [1 - 3]. In the next century, an extract of the broom plant became a favorite diuretic treatment and remained in use until the 1920s [4, 5].

In the 16th century, Paracelsus began to march away from herbals and became a key figure in the history of diuretics. He refined the concept of the body as a chemical process and pioneered the use of calomel (mercurous chloride) as a diuretic [6]. Later in the 20th century, organic mercurials, as well as other salts including potassium nitrate, potassium acetate, and potassium citrate, were introduced in widespread use as diuretics [5, 7]. An expert botanist, William Withering, introduced digitalis (*Digitalis purpurea*) as a diuretic agent in 1785 to relieve dropsy. Digitalis was among the first class of diuretics during that time [8].

With the exception of digitalis and caffeine, most of the diuretics used today were developed after World War I. By the time World War II started, only four drugs were accepted as effective agents to increase urine flow: caffeine, digitalis, mercury, and acidifying agents. Caffeine was considered a mild diuretic, digitalis was effective only in heart failure, mercury was potentially a toxic choice, and the acidifying agents' efficacies were questionable [1].

In the early to mid 1900s, John Peters, Alfred N. Richards, Homer Smith, and their associates provided insight into renal physiology and the role of the kidney in the production of urine. This advancement in knowledge led to the subsequent

understanding of the mechanisms underlying diuretic therapy. In 1940, Thaddeus Mann and David Keillin of the University of Cambridge discovered that sulfonamides inhibit carbonic anhydrase (CA), and two years later, Rudolf Hober suggested that this effect accounted for the increased excretion of sodium bicarbonate and more production of urine. In 1949, Boston physician William Schwartz introduced sulfanilamide as an oral diuretic agent but patients required a large dose for an appreciable diuretic effect, which was toxic [1, 9].

These discoveries, together with the understanding of the role of the kidney in diuresis and the increased understanding of organic and molecular chemistry, launched the modern era of diuretics. The pharmaceutical industry became involved directly in the development of new and more potent agents. In 1952, Richard Roblin (Lederle Division of the American Cyanamid Company) and James Clapp developed acetazolamide as a potent CAI and clinically effective diuretic agent. Chlorothiazide, the first thiazide diuretic developed by Merck, was reported in 1957. It was introduced in Australia around 1958 as an injectable and soon after as a tablet. In 1962, Hoechst introduced the modern loop diuretic, furosemide, which could be taken orally or injected, and did not seriously affect blood pressure. Ten years later, Researchers of Burinex Leo Pharma introduced a more potent loop diuretic, bumetanide, and once the patent of furosemide expired, Hoechst Pharma introduced its analog piretanide [1, 9]. Today, a large number of diuretics are in the top 200 drug list Fig. (**1**).

INTRODUCTORY CONCEPTS

Diuresis is the excretion of water from the body in the form of urine. Diuretics are compounds that enhance diuresis due to increased urine flow rate. The net result is lower fluid volume in the circulatory system making diuretics useful in a number of medical conditions including hypertension and primary or secondary edema (from cirrhosis, congestive heart failure, *etc*.). Many diuretics are designed to work in the nephron of the kidney and prevent reabsorption of sodium from the nephron tubule into the circulatory system. The theory is that if more sodium stays in the urine as it is forming in the nephron, then natural osmotic control will also sequester more water in the urine leading to more urine and less water reabsorption. Diuretic drugs not only affect sodium reabsorption, but also the reabsorption and excretion of many electrolytes, such as potassium and calcium. The complicated nature of urine formation in the nephron leads to increases in some electrolytes and decreases in others and is responsible for most of the side effects associated with diuretics shown in Table (**1**).

CHAPTER 4

Anticoagulants, Antiplatelets and Thrombolytic Agents

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Abstract: This chapter is a comprehensive account of the medicinal chemistry of anticoagulants, antiplatelets and thrombolytic agents and related drugs. It provides the mechanism of drug action and detailed structure-activity relationship (SAR) of the drugs affecting in these clinical areas to give the knowledge base for pharmacists. After studying this chapter, students will be able to:

• Describe the historical background of the anticoagulants, antiplatelets and thrombolytic agents and and related drugs.

• Describe the mechanism of action, pharmacokinetics (PK), and adverse drug reaction (ADR) of the anticoagulants, antiplatelets and thrombolytic agents.

• Explain the physiology and pathophysiology of clotting cascades and identify the components of a blood clot.

• Classify major anticoagulant drugs and their structures and binding.

• Discuss in detail the chemistry and SAR of these drugs.

• Distinguish among drugs used as antiplatelets, anticoagulants and fibrinolytic agents.

• Delineate the clinical significance and therapeutic evaluations of these classes of drugs by solving case studies.

• Explain the discovery process of a few specific drugs in these classes.

Keywords: Anticoagulant, Antiplatelet, Antithrombin, Direct thrombin inhibitor (DTI), Fibrinolytic, Glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, Heparin, Low molecular weight heparin (LMWH), Non-vitamin K antagonist oral anticoagulants (NOACs), $P2Y_{12}$ receptor antagonists, Pulmonary embolism (PE),

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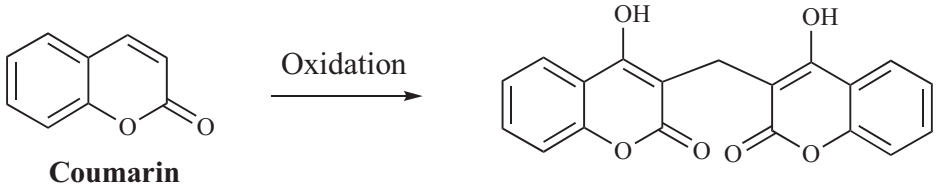
Phosphodiesterase (PDE) inhibitors, PAR-1 antagonists, Thrombolytic, Unfractionated heparin (UFH), Venous thromboembolism (VTE), Vitamin K reductase (VKOR), Xa inhibitors.

HISTORICAL BACKGROUND

The discovery and clinical application of heparin and warfarin for the prophylaxis and treatment of VTE 100 years ago set the milestone for anticoagulant therapy. In 1916, a medical student Jay McLean working under the mentorship of William Henry Howell at Johns Hopkins Medical School in Baltimore, Maryland, USA, extracted fat-soluble compounds with anticoagulant properties *in vitro* from dog liver. After McLean left Howell's lab, Howell continued the work on anticoagulants with another medical student L. Emmett Holt Jr., and in 1918, they isolated another fat-soluble anticoagulant. Since isolated from the liver, Howell coined the name 'heparin' for all these anticoagulants (Greek for 'liver'). Between 1922 and 1926, Howell developed and refined protocols for extracting water-soluble polysaccharide anticoagulant, which was also called heparin. This water-soluble heparin was clinically used and commercially produced. However, due to impurities, its medical use was limited for its adverse reactions, including headaches, fever, and nausea [1, 2].

In 1929, Charles Best, with a graduate student Arthur Charles purified heparin. In 1937, the saline solution of purified heparin was used for the first time in humans, which showed no toxicity while significantly increasing the clotting time. Arthur Charles continued the research and in 1933, along with his colleague David Scott developed a protocol for isolating and purifying heparin from the bovine liver. In 1935, Swedish physiologist J. Erik Jorpes resolved the structure of heparin to allow its commercial production for intravenous use. By 1949, Peter Moloney and Edith Taylor established the low-cost, high-yield method to produce heparin and thus contributed to its widespread availability and use [2]. Between the late 1970s and early 1980s, the LMWHs (MW 4 to 5 kDa) were developed by depolymerization of UFH (MW 12–16 kDa), which opened a new door to the prevention and treatment of VTE [3].

The discovery of warfarin was based on a natural compound from sweet clover (*Melilotus alba* and *Melilotus officinalis*) in the 1920s, when cattle and sheep glazed on its moldy hays in the damp climate on the prairies of Canada and North America showed fetal hemorrhagic disorders. Karl Link, a biochemist, and his colleagues analyzed the unclotted blood of the dead animals. After 6 years of research, they identified and isolated the active compound to be coumarin's oxidation product, dicoumarol (3′-methylene-bis(4-hydroxycoumarin).



Coumarin **Dicoumarol**

Due to the slow action of dicoumarol, Link expanded the research on coumarin derivatives funded by the Wisconsin Alumni Research Foundation (WARF), and discovered a potent compound in 1945, which he named 'warfarin' after the funding agency and marketed it in 1948 as a rodenticide. Warfarin was marketed as an oral anticoagulant under the trade name Coumadin® in 1954 and its mechanism of action was revealed in 1978 to be a disruptor of vitamin K metabolism by inhibiting VKOR [4]. In 1960, a combination of heparin and vitamin K antagonist (dicoumarol) was found to be effective in the treatment and prophylaxis of VTE, which markedly reduced the risk of death and recurrence of PE [5].

The 1960s marked the era of the discovery of antiplatelet properties of aspirin. In 1975, the mechanism of action of aspirin was determined by scientists from Washington University at St. Louis. Later in the 1980s and 1990s, the anti-adenosine diphosphate (ADP) agents (*e.g.*, ticlopidine and clopidogrel) as well as GPIIb/IIIa receptor antagonists (*e.g.*, abciximab) were developed as clinically effective antiplatelet agents. The search for more selective and convenient anticoagulants continued by specifically targeting factor Xa and thrombin. Fondaparinux, a parental pentasaccharide anticoagulant targeting factor Xa (approved by the U.S. Food and Drug Administration (FDA) in 2001), and ximelagatran, an oral direct thrombin inhibitor (never received FDA approval for use due to hepatotoxicity) provided great advantage to both the patients and prescribers in that it could be used in fixed doses without the need for routine monitoring. These agents paved the way for new NOACs class of the latest generation anticoagulants. Dabigatran (Pradaxa®) was the first NOAC, a DTI, to get approval from the European Medicines Agency in March 2008, and by the FDA in October 2010 for the prevention of thromboembolic diseases following hip or knee replacement surgery and for non-valvular atrial fibrillation (AF). Later apixaban, edoxaban, and rivaroxaban (factor Xa inhibitors) also got approval for use in the prevention of stroke in patients with AF and the prevention and treatment of VTE [6 - 8]. Today many anticoagulants are frequently appearing in the top 200 most prescribed drug list. Those that occurred in 2019 and 2020 are shown in Fig. (**1**).

CHAPTER 5

Antihistamines, Proton Pump Inhibitors and Related Drugs

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Abstract: This chapter is a comprehensive account of the medicinal chemistry of antihistamines, H_2 receptor (H_2R) blockers, H_3 receptor (H_3R) blockers, and proton pump inhibitors (PPIs). It provides the mechanism of drug action and detailed structure-activity relationship (SAR) of the drugs in these classes to give the knowledge base for pharmacists. After studying this chapter, students will be able to:

• Describe the physiochemical properties of histamine and histamine receptors.

• Identify chemical classifications and describe the SAR of antihistamines, H_2R and H_3R antagonists.

• Differentiate receptor binding patterns and structural features between histamine receptor agonists and antagonists.

• Distinguish between sedating and non-sedating antihistamines, as well as the first-, second- and third-generation antihistamines.

• Describe the structural features of cromolyn and related mast cell stabilizers and their therapeutic applications.

• Discuss the proton pump inhibitors, including their development, mechanism of action, and structural and physicochemical features.

• Apply the medicinal chemistry principles to the clinically relevant case studies.

• Explain the drug discovery story of representative drugs of different classes.

Keywords: Antihistamine, H_2R inhibitors, H_3R inhibitors, Histamine, Mast cell stabilizers, Proton pump inhibitors, Structure-activity relationship, SAR.

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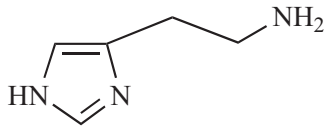
M. O. Faruk Khan (Ed.)

HISTORICAL BACKGROUND

An excellent account of the history of anaphylaxis, histamine, and antihistamine has been published by Emanuel [1]. Numerous studies have been conducted to understand the physiological and cellular mechanisms of the anaphylaxis and allergic reactions, a concept first described as altered reactivity in 1902 [2]. Histamine, a β-imidazolyl ethylamine, was the first biogenic amine in the group of small molecules with potent biological action to be characterized (in 1907) and synthesized by decarboxylation of histidine (in 1910) [3, 4]. During the same time period, Wellcome Pharmaceutical's Dale and Barger isolated ergotoxin from ergot and its decomposition products histamine and acetylcholine. Immediately afterwards they showed that histamine caused constriction of isolated guinea-pig ileum and induced a shock-like syndrome when injected into mammals. Later in 1927, histamine was identified in normal tissues especially in lungs [5 - 7]. Based on these observations, Dale in 1929 postulated that histamine played a major role in anaphylaxis reactions, which was supported by several subsequent observations [8 - 11]. Sir Henry Dale was awarded the Nobel Prize in Physiology or Medicine in 1936 on account of his discoveries relating to chemical transmission of nerve impulses, much of which involved histamine and the histamine receptors.



Histamin

In the 1930s the Pasteur Institute began the search for antihistamines after histamine's role in allergy and anaphylaxis was established [1]. Fourneau and Bovet first reported the antihistaminic properties of certain phenolic ethers in 1933. During the Second World War in the early 1940s, both France and North America separately continued the search for an antihistaminic agent for clinical use. Fig. (**1**) illustrates the structures of a few antihistamines developed during the 1940s [1]. 2-Isopropyl-5-methyl phenoxyethyl diethylamine (**1**) was the most effective of these compounds but was not used clinically due to toxicity [12]. Changing the substitution in the benzene ring furnished a new compound (**2**) with potent antihistaminic potency but had toxicity [13]. Antergan (**3**, phenbenzamine) was patented by Rhone Poulenc in 1941, and was the first antihistamine used clinically in men [14]. By 1950, about 20 antihistamines were available for clinical use including diphenhydramine and promethazine (Phenergan®) [1].

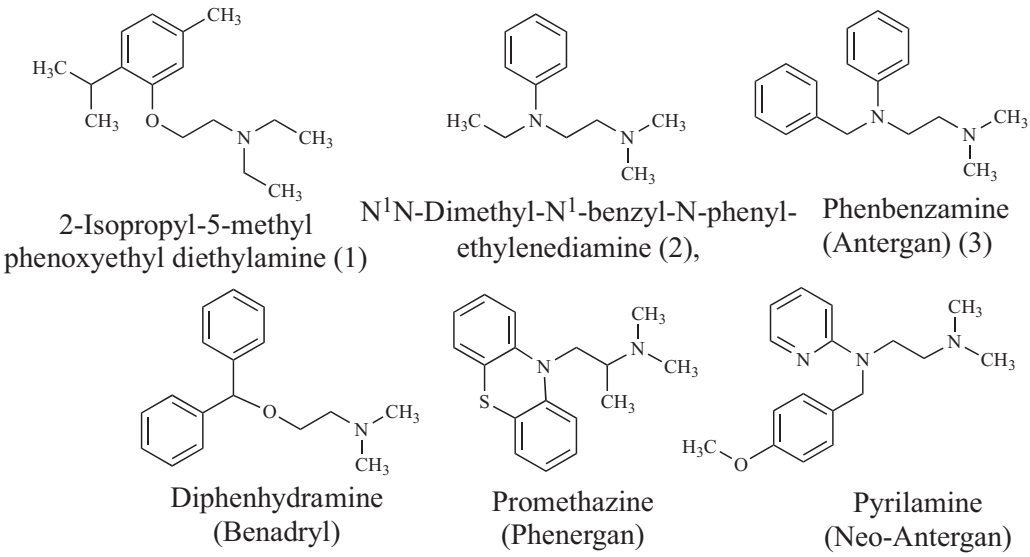


Fig. (1). A few historic antihistamines developed during the 1940s.

Antihistamines rapidly entered into clinical practice and became the drugs of choice for the treatment of various allergic disorders, particularly rhinitis, conjunctivitis, and urticaria. However, a major drawback was sedation and the search for nonsedating antihistamines became a major goal of the pharmaceutical industries. After about four decades of research, the nonsedating antihistamines astemizole and terfenadine were introduced in the 1980s [1].

Because the antihistamines available in 1962 inhibited some but not all the actions of histamine, working on histamine agonists, it was suggested that there had to be more than one histamine receptor. The term H_1 receptor was proposed by Ash and Schild in 1966 to understand the mechanism of action of antihistamines. Some activity of histamines including stimulation of isolated gastric secretion, inhibition of rat uterine contraction, and stimulation of isolated atria were not blocked by these antihistamines, which were proposed to be mediated through H_2 receptors (H_2R) [15]. The existence of H_2R were confirmed by Black *et al*. in 1972 with the synthesis of burimamide as a selective H_2 blocker [16]. Over the last three decades, two additional histamine receptors, H_3 and H_4, have been characterized. The human H_1 receptor was cloned in 1993 and its polymorphism described in 1998. The cloning of the human H_2, H_3 and H_4 receptors were completed in 1991, 1999, and 2000, respectively [17, 18].

During 1960s, a subdivision of AstraZeneca R&D™ started a research project to find drugs capable of inhibiting gastric acid secretion for use in patients with

CHAPTER 6

Diabetes and Antidiabetic Drugs

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Abstract: This chapter is a comprehensive account of diabetes and the medicinal chemistry of antidiabetic drugs. It provides the mechanism of disease progression and drug action and detailed structure-activity relationships (SAR) of antidiabetic drugs to give the knowledge base for pharmacists. After studying this chapter, students will be able to:

• Discuss the epidemiology and etiology of diabetes.

• Describe the clinical features of diabetes and differentiate between type I and type II diabetes.

• Discuss various risk factors and corresponding mechanisms responsible for the development of diabetes.

• Review biosynthesis of insulin, its metabolic outcomes, regulation of insulin secretion, and insulin signaling.

• Explain in detail the pathophysiologic mechanisms responsible for the clinical features of diabetes.

• Evaluate the clinical role of natural human insulin and commercially available other insulin products and discuss its mechanism of action, pharmacokinetics, adverse effects, motor complications, drug interactions, contraindications, and precautions.

• Discuss the mechanism of action, pharmacokinetics, adverse effects, motor complications, drug interactions, contraindications, and precautions for each class of antidiabetic drugs listed below.

o Sulfonylureas: tolbutamide (Orinase®), tolazamide (Tolinase®), chlorpropamide (Diabinese®), and acetohexamide (Dymelor®), glyburide (Diabeta®), glipizide (Glucotrol®), and glimepiride (Amaryl®).

o Meglitinides: repaglinide (Prandin®), nateglinide (Starlix®).

o Biguanides: metformin (Glucophage®, Glucophage XR).

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o Peroxisome proliferator activated receptor (PPAR) agonists/Thiazolidinediones: pioglitazone (Actos®), rosiglitazone (Avandia®).

o Alpha glucosidase inhibitors: acarbose (Precose®).

o Glucagon-like peptide-1 (*GLP*-1) agonists: dulaglutide (Trulicity®), exenatide (Bydureon®, Byetta®), liraglutide (Victoza®), lixisenatide (Adlyxin®), semalgutide (Ozempic®, Rybelsus®).

o Dipeptidyl peptidase-4 (*DPP-4*) inhibitors: alogliptin (Nesina®), linagliptin (Tradjenta®), saxagliptin (Onglyza®), sitagliptin (Januvia®).

o Amylin agonist: pramlintide (Symlin®).

o Sodium-glucose cotransporter-2 (*SGLT2)* inhibitors: empagliflozin (Jardiance®), canagliflozin (Invokana®), dapagliflozin (Farxiga®), ertugliflozin (Steglatro®).

o Miscellaneous agents.

Keywords: Diabetes mellitus (DM), Antidiabetic drugs, Insulin, Biguanide, Insulin receptor (IR), Metformin, Sulfonylureas, Structure-activity relationship, SAE and drug-receptor.

HISTORICAL BACKGROUND

Although anti-diabetic medication has been known since the prehistoric era, the real breakthrough came in the early twentieth century with the discovery of insulin and biguanides. Table **1** shows the milestones of the discovery of anti-diabetic drugs since the early twentieth century [1]. Dr. Frederick Banting, a surgeon and World War I veteran, became interested in diabetes and was able to extract a substance from canine pancreatic glands. By December 1921, Banting and his student, Charles Best, extracted insulin by combining equal parts of the ground beef pancreas and slightly acidic alcohol. The extracted solution (insulin) was filtered, washed with toluene, sterilized, and given to dogs. Leonard Thompson, a 14-year-old concentration camp victim with diabetic ketoacidosis, was the first patient to receive this insulin solution. On 11 January 1922, a young house officer, Ed Jeffery, injected 7.5 ml of this extract into his buttock which dropped his blood glucose. Banting's team signed an agreement with Eli Lilly Pharmaceuticals and by July 1922, Banting received the first bottle of Lilly's Iletin (insulin). Insulin was commercially available in the United States by 1923. In 1926, the technique for crystallization of insulin was discovered that led to the purer soluble (regular) insulin and opened the door to modified insulin formulations with different time-action profiles. The first commercially available PZI (protamine zinc insulin) with an extended duration of action was released in 1936. Within 10 years, Nordisk Insulin Laboratory in Denmark released NPH

(Neutral Protamine Hagedorn), which has a shorter duration than PZI, but can be combined with regular insulin. The lente insulin series was introduced in 1956. The first recombinant insulin was approved in 1983 (before that all insulins were derived primarily from beef and pork). Insulin lispro, the first rapid-acting human insulin analog, was approved in 1996. The next 15 years added quick and long-acting analogs, including insulins aspart, glulisine, glargine and detemir. The ultra-long-acting insulin degludec (duration of 42 hours) was approved in Europe in 2013 when the U.S. Food and Drug Administration (FDA) declined to approve it; however, it was approved by FDA in 2015 after resubmission. Better formulations as well as techniques for the delivery of insulin have been developed over the years [1].

Table (1). Milestones in antidiabetic medications.

Year	Milestone
1915 early 1920s	Discovery of guanidine from *Galega officinalis* and synthesis of Synthalin
1922	First insulin administered to a human
1923	Insulin (Iletin) commercially available in the US
1936	PZI Insulin
1946	NPH Insulin
1956	First commercially available sulfonylurea in the US; Lente insulins introduced
1959	Metformin introduced in Europe (1990s in the US)
1983	Recombinant human insulin
1984	Second generation sulfonylureas
1995	First AGI (acarbose)
1996	First TZD (troglitazone)
1997	First meglitinide (repaglinide)
2005	First amylin agonist (pramlintide) First GLP-1 receptor agonist (exenatide)
2006	First DPP-4 inhibitor (sitagliptin)
2008	Colesevelam
2009	Bromocriptine
2013	First SGLT2 inhibitor (canagliflozin)

The identification of antihyperglycemic guanidine moiety from the medieval folk remedy of diabetes in Southern and Eastern Europe, *Galega officinalis* (French lilac, or goat's rue), led Frank *et al*. to synthesize Synthalin in Germany in the 1920s. It was in the market to treat diabetes for a short period due to

CHAPTER 7

Hormoneal Therapy

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Abstract: Treatments that involve the use of hormones or their antagonists are commonly referred to as hormone therapy or hormonal therapy. Oncologic hormone therapy, hormone replacement therapy (HRT), androgen replacement therapy (ART), oral contraceptive pills and gender-affirming hormone therapy are the major classes of hormonal therapy in addition to a few others. Some hormonal therapies will be discussed in detail under different chapters including oncologic hormone therapy, glucocorticoids and mineralocorticoids and insulin under antineoplastic agents, anti-inflammatory steroids and antidiabetic agents, respectively. After studying this chapter, students will be able to:

• Define and classify hormonal therapy and differentiate between hormonal therapy and treatment.

• Explain all types of hormone replacement therapy including menopausal, androgens, and oral contraceptives.

• Discuss the use of androgen replacement therapy (ART) in males with low levels of testosterone due to disease or aging.

• Describe gender-affirming hormone therapy such as feminizing hormone therapy and masculinizing hormone therapy.

• Identify appropriate growth hormone therapy for growth hormone deficiency.

• Demonstrate understanding of thyroid hormone replacement in hypothyroidism and antithyroid therapy in hyperthyroidism.

• Demonstrate clear guidance to the use of oral contraceptive pills for various purposes including birth control.

Keywords: Breast cancer, Cardiovascular disease, Contraceptives, Hormone replacement therapy, Osteoporosis, Thyroid hormone (TH), Thyroid receptor (TR).

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HISTORICAL PERSPECTIVE

Hormone Replacement Therapy

Hormone Replacement Therapy (HRT) began with the isolation of estrogen hormone in the early 20th century by Edward Adelbert Doisy and his colleagues at the St. Louis University Medical School in the urine and follicular fluids of pigs. The first commercial preparation of estrogen called Emmenin, an oral solution for treating dysmenorrhea, was described in 1935 in the *Canadian Medical Association Journal*. Its commercial preparation began as an estrogen complex extracted from placentas. Within a few years, Premarin® was commercially manufactured from the urine of pregnant mares, and was approved by the U.S. Food and Drug Administration (FDA) for the treatment of menopausal hot flashes. Premarin® is a combination of at least ten estrogens, with estrone being the dominant one [1].

The real significance of HRT started in the 1960s with the feminist movement. In 1966, Wilson published the bestseller book "Feminine Forever" claiming that menopause is a hormone deficiency disease that is curable and preventable by estrogen. However, it was found in the 1970s that conjugated estrogen therapy may lead to the development of endometrial cancer, a risk that can be lowered by reducing the dose of estrogen and combining it with progesterone. By 1988, HRT comprising estrogen and progesterone received an FDA approval for the treatment of both hot flashes and osteoporosis. It was later found to be beneficial for many other chronic diseases including cardiovascular conditions of postmenopausal women. This greatly increased the popularity of HRT in the 1990s. Their marketing efforts brought Premarin® as the No. 1 prescribed drug in the United States (U.S.) by 1992. By 1997, its sales exceeded $1 billion [1, 2]. In 1998, the Women's Health Initiative (WHI) started the largest clinical trial on HRT and chronic postmenopausal conditions in the U.S. using the combination drug PremPro. The first negative results were announced in 2002 receiving wide publicity and showing that the risks outweighed the benefits of HRT leading to a drop in HRT use. However, no distinction was made between the synthetic and natural hormones which was considered to be a major flaw of the study [2]. Nevertheless, HRT remained an effective treatment for menopausal hot flashes and vaginal dryness with individualized treatment plans from their doctors to minimize the risk. It is thought that relatively younger women (<60 years old) whose menopausal transition took place in less than 10 years may benefit the most from HRT [1].

Another study on the use of testosterone in menopausal women was conducted in 2004 by researchers in Australia administering testosterone pellets underneath the

skin. When testosterone was taken in combination with traditional HRT, it remarkably reduced the incidence of breast cancer in addition to improving the common symptoms of menopause. In 2013, after a 10-year study conducted in the U.S., it was found that testosterone alone improved all symptoms of menopause, including hot flashes, sleep disorder, depression, irritability, anxiety, physical or mental exhaustion, sexual and bladder problems, vaginal dryness, and joint and muscular discomfort, and also substantially (50-70%) reduced breast cancer incidences. No major adverse effects were noticed. A study carried out in 2017 also showed remarkable results in treating stage II breast cancer in combination with chemotherapy and follow-up surgery [3]. However, testosterone is not FDA-approved for widespread use in women. Studies of longer durations are needed to establish the safety and effectiveness for women before its use will become popular.

Oral Contraceptives

Margaret Sanger, who opened the first birth control clinic in America in 1916, pioneered the age-old quest for safe and effective oral contraception in the middle of the 20th century. Sanger, along with her strong collaborator and donor Katharine Dexter McCormick, were the advocates and financial supporters in the efforts to develop an oral contraceptive. In 1953, they financed the contraceptive research of Gregory Pincus and Min Chueh Chang of the Worcester Foundation for Experimental Biology in Massachusetts, who were trying to produce an oral contraceptive based on synthetic progesterone. Sanger and McCormick established Planned Parenthood's research grant program based mostly on donations from McCormick. The basic research of contraceptive development was also largely supported by Russell Marker's discovery of progestin in Barbasco root that had been eaten by generations of Mexican women for contraception. Gregory Pincus combined progestin with estrogen to formulate the first birth control pill. The first clinical trials of the pill were conducted by Dr. John Rock and funded by McCormick. They were conducted in Puerto Rico due to challenges including issues from the Catholic church, Massachusetts law (it was illegal to conduct a contraceptive trial), and the mobility of post-World War II American women of reproductive age. The trials began in April 1956 and the FDA approved the use of the pill to regulate menstruation in 1957. It had a package insert with a warning about its contraceptive activity. After facing critiques and inherent drawbacks of the trials at that time, it was finally successful in receiving FDA approval as an oral contraceptive on June 23, 1960, with the brand name Enovid. The pill was manufactured by G.D. Searle and Company which also supported its basic research for many years. The 1960s also observed sexual revolution and established family planning as the cultural norm. Modern oral contraceptives contain dramatically lower concentrations of both progestin

CHAPTER 8

The Prostanoids

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Abstract: This chapter is a comprehensive account of the medicinal chemistry of drugs arising from structural modifications of prostanoids, which are naturally occurring eicosanoids. These drugs are used for a variety of diseases including but not limited to glaucoma, pulmonary arterial hypertension, and peptic ulcers. This chapter provides the mechanism of drug action and structure-activity relationships (SAR) of these drugs. After studying this chapter, students will be able to:

• Describe the historical background of prostanoids as clinical agents.

• Explain the structure, functions, classifications and biosynthesis of eicosanoids.

• Discuss in detail the chemistry and SAR of the prostanoids involved in the treatment of glaucoma, pulmonary arterial hypertension, peptic ulcer, and other diseases.

• Delineate the clinical significance and therapeutic evaluations of these classes of drugs by solving case studies.

• Explain the discovery process of latanoprost and zafirlukast.

Keywords: Prostaglandins, Prostacyclin, Pulmonary arterial hypertension (PAF), Glaucoma, Structure-activity relationship (SAR), Drug receptor interaction, Intraocular pressure.

HISTORICAL BACKGROUND

In the 1930s, gynecologists at Columbia University in New York published their finding of uteri undergoing artificial insemination and occasional contraction and relaxation. This observation led Ulf von Euler at the Karolinska Institute in Stockholm to discover an acid from extracts of monkey, sheep, and goat seminal vesicles. He named the acid prostaglandin (PG), which lowered blood pressure and caused contraction of smooth muscles. Later along with his student, Sune Bergström, he established PG to be free of nitrogen. In the 1950s, Bergström's

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team isolated and elucidated the structures of several highly potent PGs through grant support from the Upjohn Company. Based on the pattern of the cyclopentane ring in those PGs, he classified those as types A to F with a subscripted number to indicate the number of unsaturated centers in the side chains. He also used suffix α or β to indicate the stereochemical configuration of ring substituents. He isolated crystals of alprostadil (also known as PGE_1) from sheep prostate glands in 1957. Within five years he also isolated dinoprost (or $PGF_{2\alpha}$) and dinoprostone (or PGE_2) as highly potent mammalian PGs.

Phillip Beal and his colleagues first synthesized the natural PG in the Upjohn laboratories in 1965. Within the next five years PGE_1, PGE_2 and $PGF_{2\alpha}$ were also synthesized by different scientists and laboratories. These three PGs were proven to be clinically significant among sixteen naturally occurring PGs. However, the PGEs bearing a β-hydroxy carbonyl in the cyclopentane ring readily undergo an acid or base-catalyzed elimination reaction [1]. Collectively, all these bioactive natural compounds arising from 20-carbon fatty acids are known as *eicosanoids*.

The report in 1967 that a few PGEs inhibited gastric acid secretion was intriguing in the treatment of peptic ulcer but was found inactive by mouth due to oxidative metabolism of the 15-hydroxyl group present in the side chain. The vasodilating properties of PGE_1 have been exploited in neonatal congenital heart diseases. PGE_2 has been exploited for its ability to contract the uterus for inducing abortion. Epoprostenol has been found beneficial in kidney transplantation surgery as an alternative to heparin in patients at high risk of bleeding. They act *via* receptor-mediated G-protein linked signaling pathways [1]. Today, numerous prostanoids and their derivatives are employed in clinical practices for a variety of diseases including glaucoma, pulmonary arterial hypertension (PAH) and peptic ulcers. In modern clinical practice, the commonly used prostanoids are either the analogs of PGs, prostacyclin (PGI_2), or leukotrienes (LT) and a number of these frequently appear in the top 200 drug list, which are shown in Fig. (**1**).

INTRODUCTORY CONCEPTS

Eicosanoids: Structure and Function

Fig. (**2**) shows the structures of all types of prostanoids and prostanoic acids. Prostanoids are eicosanoids derived from 20-carbon fatty acids especially arachidonic acid by oxygenation. These are messenger lipids, produced in almost all cells except red blood cells. *Four principal types* of eicosanoids are: prostaglandins (PGs), thromboxanes (TXs), leukotrienes (LTs) and lipoxins (LXs). The PGs and TXs are collectively known as prostanoids which are commonly used in clinical practice. PGs have a characteristic oxygenated cyclopentane ring formed by a connection between the C_8 and C_{12} of an

arachidonic acid precursor and commonly possess a trans double bond between C_{13} and C_{14}. Usually, C_9 and/or C_{11} is/are oxygenated *via* a keto or hydroxyl function and C_{15} is hydroxylated in different PGs. The PG analogs containing additional endocyclic oxygenated ring system are known as prostacyclin (or PGI_2). In TXs, the cyclopentane ring has been replaced with a six-membered oxygen-containing ring (termed an *oxane*). The LTs contain a conjugated triene system.

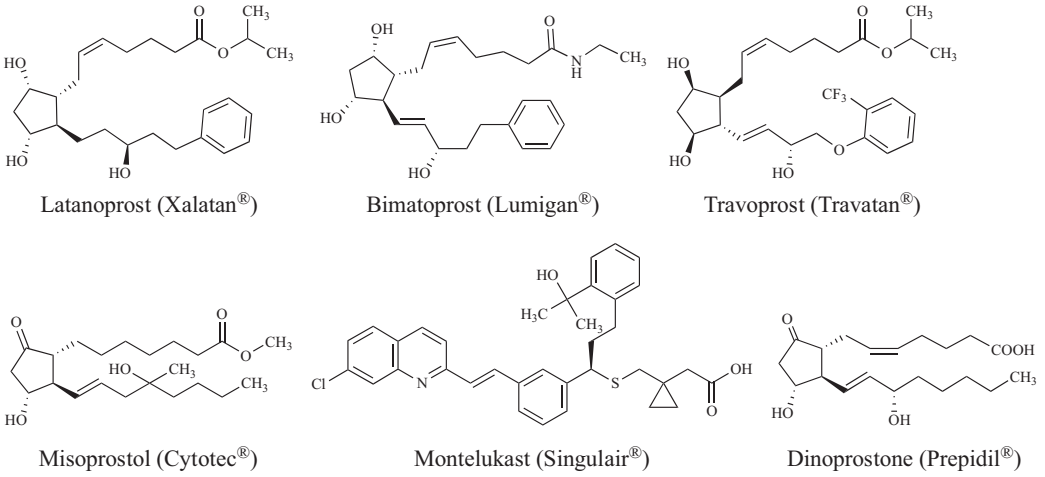

Fig. (1). Frequently prescribed prostanoid analogs.

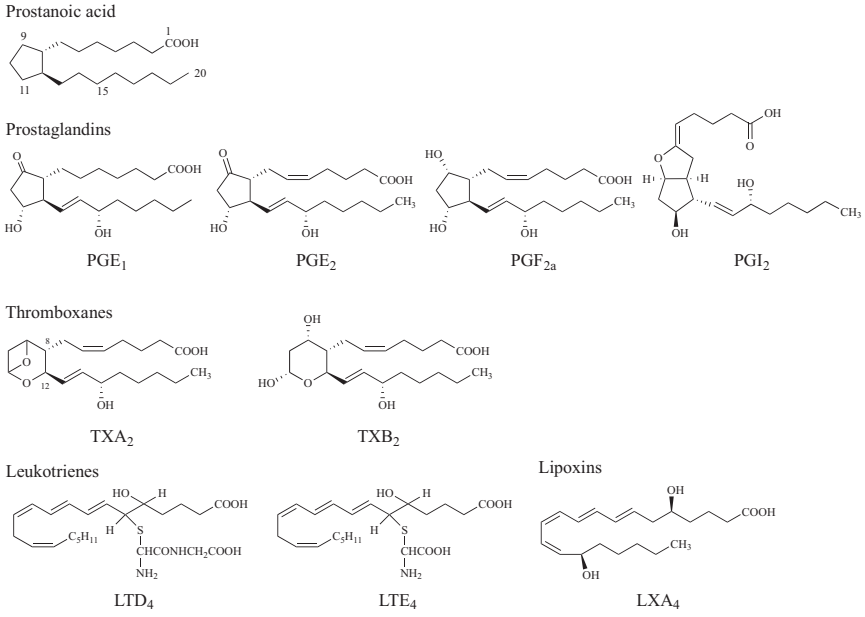

Fig. (2). Structures of all prostanoids and prostanoic acid.

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> Understanding medicinal chemistry is essential for understanding how new drugs are developed and how drugs work in the body. This book is an important contribution to helping students and practitioners deepen their understanding of medicinal chemistry. Of particular note is the integration of clinical content and learning aids for students.
>
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