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G. Patrick

Medicinal Chemistry

医药化学

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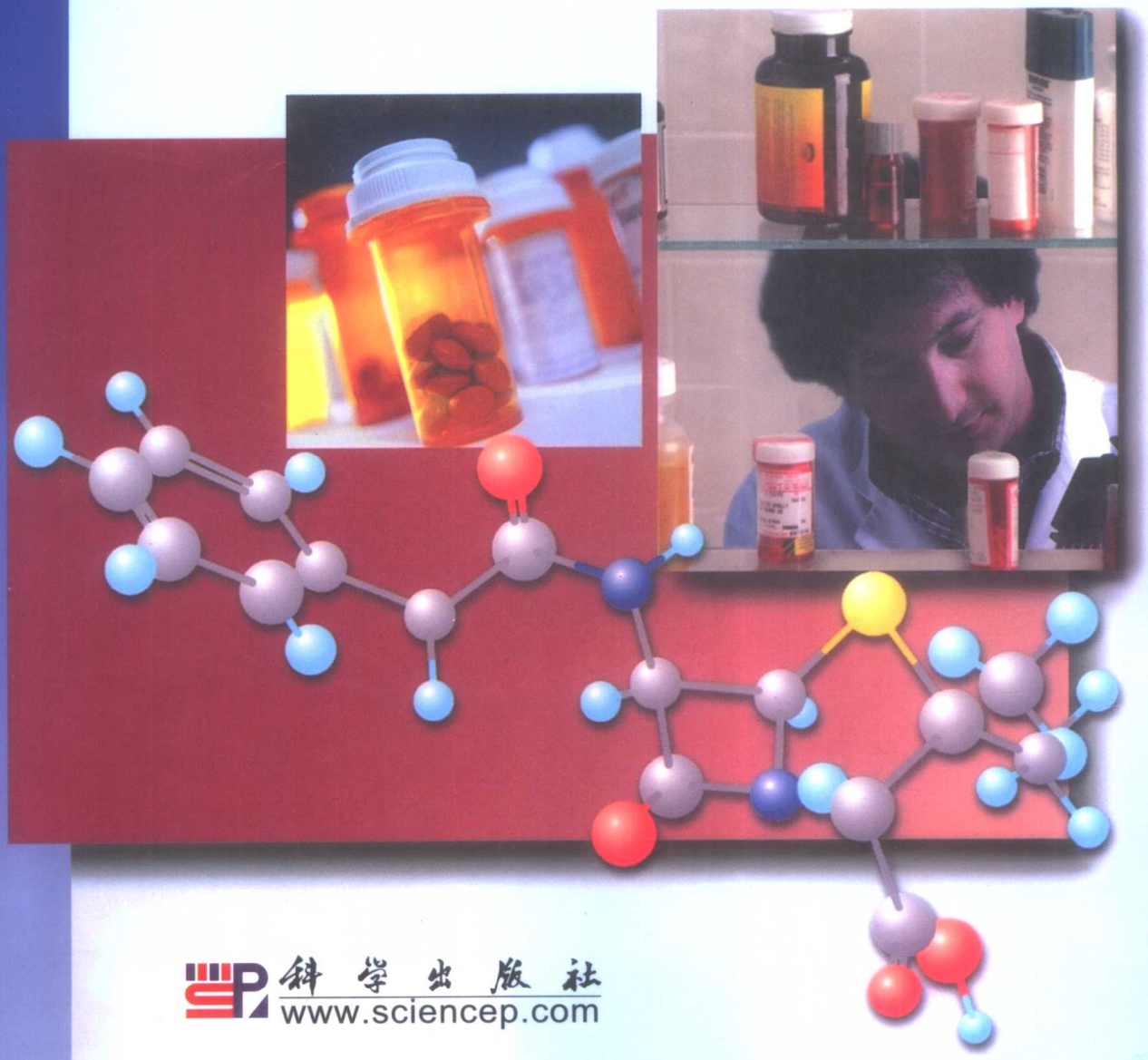

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Instant Notes in

Medicinal Chemistry

医药化学

（影印版）

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北京

图字:01-2002-5306

内 容 简 介

"精要速览系列(*Instant Notes Series*)"丛书是国外教材"Best Seller"榜的上榜教材。该系列结构新颖,视角独特;重点明确,脉络分明;图表简明清晰;英文自然易懂,被国内多所重点院校选用作为双语教材。先锋版是继"现代生物学精要速览"之后推出的跨学科的升级版本。

本书是该系列中的《医药化学》分册,全书共13章,综合了化学、生物学和计算机科学的内容,扼要介绍了药物设计与发现、新药开发与应用、临床试验及专利申请等。

本书是指导大学生快速掌握医药化学基础知识的优秀教材,也是辅助教师授课的极佳教学参考书,同时可供相关专业的研究生参考。

G. Patrick

Instant Notes in Medicinal Chemistry

Original edition published in the United Kingdom under the title of Instant Notes in Medicinal Chemistry

图书在版编目(CIP)数据

医药化学/(英)帕特里克(Patrick,G.)著.—影印本.—北京:科学出版社,2003.4

(精要速览系列——先锋版)

ISBN 7-03-010962-7

Ⅰ.医… Ⅱ.帕… Ⅲ.医用化学-英文 Ⅳ.R313

中国版本图书馆CIP数据核字(2002)第093750号

责任编辑:周 辉 黄 方

责任印制:刘士平/封面设计:王 浩

科学出版社 出版

北京东黄城根北街16号

邮政编码:100717

http://www.sciencep.com

双青印刷厂 印刷

科学出版社发行 各地新华书店经销

*

2003年4月第 一 版 开本:B5(720×1000)

2003年4月第一次印刷 印张:18

印数:1—3 000 字数:350 280

定价:32.00元

(如有印装质量问题,我社负责调换〈环伟〉)

ABBREVIATIONS

AMP	adenosine monophosphate
6-APA	6-aminopenicillanic acid
ATP	adenosine triphosphate
CNS	central nervous system
DAG	diacylglycerol
DNA	deoxyribonucleic acid
DMSO	dimethylsulfoxide
EGF	epidermal growth factor
EGF-R	epidermal growth factor receptor
EP	enzyme-bound product
ES	enzyme–substrate (complex)
FDA	Food and Drugs Agency
GABA	γ-aminobutyric acid
GCP	good clinical practice
GDP	guanosine diphosphate
GLP	good laboratory practice
GMP	good manufacturing practice
GTP	guanosine triphosphate
HBA	hydrogen bond acceptor
HBD	hydrogen bond donor
HPLC	high performance liquid chromatography
IND	Investigational Exemption to a New Drug Application
IP_3	inositol trisphosphate
i.v.	intravenous
MAOI	monoamine oxidase inhibitor
mRNA	messenger RNA
NDA	New Drug Application
NMR	nuclear magnetic resonance
PIP_2	phosphatidylinositol diphosphate
PLC	phospholipase C
QSAR	quantitative structure–activity relationship
RNA	ribonucleic acid
rRNA	ribosomal RNA
SAR	structure–activity relationship
tRNA	transport RNA

PREFACE

This textbook provides a comprehensive set of basic notes in medicinal chemistry, which will be suitable for undergraduate students studying a module in medicinal chemistry as part of a science, pharmacy or medical course. The book concentrates on the fundamental principles of medicinal chemistry and assumes no more than an elementary background of chemistry or biology. It also serves as a useful 'first dip' into the subject for those students wishing to study medicinal chemistry itself.

Medicinal chemistry is an exciting new science, which has only come of age in the last 10–20 years. It is a truly multidisciplinary subject involving such subject specialties as organic chemistry, pharmacology, biochemistry, physiology, microbiology, toxicology, genetics and computer modeling. Indeed, most pharmaceutical companies organize research teams in such a way that scientists of different disciplines interact with each other on a daily basis in order to fight the battle against disease. The very breadth of knowledge required by a medicinal chemist is both a challenge and a reward. Mastering an understanding of such a breadth of subject areas is no straightforward task, but by the same token there is ample intellectual stimulation in understanding the battle against disease at the molecular level and in designing molecular 'soldiers' to win that battle.

This book attempts to condense the essentials of medicinal chemistry into a manageable text, which is student friendly and does not cost an arm and a leg. It does this by concentrating purely on the basics of the subject without going into exhaustive detail or repetitive examples. Furthermore, keynotes at the start of each topic summarize the essential facts covered and help focus the mind on the essentials.

Medicinal chemistry is a peculiar subject in that it feeds off so many other subjects. Understanding disease at the physiological, cellular and molecular levels is crucial if one is to design a suitable drug, and therefore knowledge of the relevant physiology, biochemistry, and pharmacology is of immense aid. However, the rapid advances made in two particular scientific areas are worth emphasizing. Molecular biology and genetic engineering have produced a deluge of potential new targets for drug design and have unraveled the structures and mechanisms of traditional targets, while advances in computers and computer aided design have allowed medicinal chemists to take full advantage of this newly earned knowledge.

The first four sections of this book serve as an introduction to the science of medicinal chemistry. Subsequent sections then follow the identifiable stages that have to be negotiated by any drug candidate on its journey from initial 'brainstorm' to the market place – a journey which takes many years and will see you graduated before it is! There are many difficult hurdles for the novice drug to overcome. The drug has to be 'tuned' so that it recognizes a specific target in the body and does not go flying off 'attacking' all and sundry. It has to gain access to the target by being absorbed into the blood supply, and in doing so it must be sturdy enough to ward off the many attacks that will be made on it by the body's defenses. It must also be controlled in its 'aggression', being a mild and harmless visitor during most of its body tour, but ruthless and efficient when it reaches its target. Designing such characteristics is not straightforward and a drug's behavior involves many tests and trials, both in the lab and in the clinic before it 'comes of age'.

It is hoped that students will find this textbook useful in their studies and that once they have grasped what medicinal chemistry is all about, they will read more widely and enter this truly exciting world of molecular medicine.

ABOUT THE AUTHOR

Graham Patrick studied chemistry at Glasgow University where he gained a BSc Honours (1st) and won the Mackay Smith prize. He was awarded a Carnegie scholarship and successfully completed a PhD degree on the biosynthesis of gliotoxin. Since then he has held postdoctoral research posts at Strathclyde University and the Australian National University, and has had industrial experience working with pharmaceutical firms such as Glaxo, Beechams, and Organon Pharmaceuticals. He lectured at the Department of Chemistry at Leeds University and is currently lecturing in chemistry and medicinal chemistry at Paisley University, where he is also the course leader for medicinal chemistry.

Dr Patrick has written several undergraduate textbooks including *An Introduction to Medicinal Chemistry* (2nd edition, 2001, Oxford University Press), two self-learning texts on basic organic chemistry, and *Instant Notes in Organic Chemistry* (BIOS Scientific Publishers Ltd., 2000). He has several research publications in the area of organic synthesis, medicinal chemistry and bio-organic chemistry, and has also written several reviews. His current research interests are the design and synthesis of novel antifungal and antimalarial agents.

Recently, he has collaborated with the Borders Educational Council of Scotland in the production of video and CD lectures covering aspects of medicinal chemistry for school courses.

CONTENTS

A1 INTRODUCTION

Key Notes

Medicinal chemistry — Medicinal chemistry is the design and synthesis of novel drugs, based on an understanding of how they work at the molecular level. A useful drug must interact with a molecular target in the body (pharmacodynamics) and also be capable of reaching that target (pharmacokinetics).

The medicinal chemist — A medicinal chemist is skilled in the fields of organic synthesis, molecular modeling and drug design, and should have a basic knowledge of relevant subjects such as biochemistry and pharmacology.

Drugs — Drugs are normally low molecular weight chemicals that interact with macromolecular targets in the body to produce a pharmacological effect. That effect may be beneficial or harmful depending on the drug used and the dose administered.

Classifications of drugs — Drugs can be classified according to their pharmacological effect, the particular biochemical process they affect, the type of structures they are, or the molecular target with which they interact. The last classification is the most useful one in medicinal chemistry.

Related topic — From concept to market (A2)

Medicinal chemistry

The science of medicinal chemistry involves the design and synthesis of novel drugs based on an understanding of how drugs work in the body at the molecular level. There are two major considerations that have to be considered in any drug design project. First of all, drugs interact with molecular targets in the body, and so it is important to choose the correct target for the desired pharmaceutical effect. It is then a case of designing a drug that will interact as powerfully and selectively as possible for that target – an area of medicinal chemistry known as **pharmacodynamics**. (Drug targets will be discussed in more detail in Section B.) Secondly, a drug has to travel through the body in order to reach its target, so it is important to design the drug so that it is able to carry out that journey. This is an area known as **pharmacokinetics** and is discussed in Section C.

Medicinal chemistry has come of age in the last 20 years. Before that, advances were often made as a result of trial and error, intuition or pure luck. Large numbers of analogs were synthesized based on the structure of a known active compound (defined as the **lead compound**), but little was known about the detailed mechanism of drug action or the structures of the targets with which they interacted. Advances in the biological sciences have now resulted in a much better understanding of drug targets and the mechanisms of drug action. As a result, drug design is as much 'target oriented' as 'lead compound oriented'.

The medicinal chemist

Medicinal chemistry is an interdisciplinary science that, by its very nature, encompasses the sciences of chemistry, biochemistry, physiology, pharmacology, and molecular modeling, to name but a few. A good understanding of these subject areas is useful, but it is unlikely that any one person could be master of all. Thus, the pharmaceutical industry relies on multidisciplinary teams of scientists who are specialists in their own fields and can work together on a particular project.

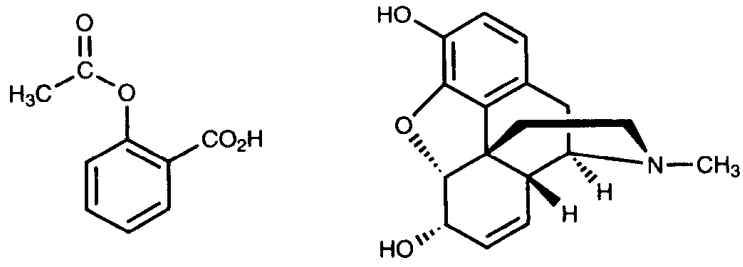
The chief role of the medicinal chemist is to design and synthesize the target structures required. Therefore, the medicinal chemist is an essential member of any drug design team since he or she has to identify whether proposed target structures are likely to be stable and whether they can be synthesized or not. Traditionally, the pharmaceutical industry has recruited graduates with a chemistry degree since this is the best method of acquiring the synthetic organic chemistry skills required for medicinal chemistry. However, it is often the case that graduates with a conventional chemistry degree have little background in the biological sciences and have had to acquire that background 'on the job'. In recent years, many universities have started to offer medicinal chemistry degrees that are specifically designed to prepare chemistry graduates for the pharmaceutical industry. Such degrees contain the important core topics required for a conventional chemistry degree (i.e. physical, inorganic and organic chemistry), but also include topics such as drug design, pharmacology, molecular modeling, combinatorial synthesis, bio-organic and bio-inorganic chemistry.

Drugs

Drugs are chemicals that are normally of low molecular weight (~100–500) and which interact with macromolecular targets to produce a biological response. That biological response may be therapeutically useful in the case of medicines, or harmful in the case of poisons. Most drugs used in medicine are potential poisons if taken in doses higher than those recommended.

Classifications of drugs

There are several ways in which drugs can be classified. First, drugs can be classified according to their pharmacological effect – for example, analgesics are drugs which have a pain-killing effect. This classification is useful for doctors wishing to know the arsenal of drugs available to tackle a particular problem, but it is not satisfactory for a medicinal chemist as there are many different targets and mechanisms by which drugs can have an analgesic effect. Therefore, it is not possible to identify a common feature which is shared by all analgesics. For example, **aspirin** and **morphine** act on different targets and have no structural relationship (*Fig. 1*). Other examples of drugs that are classified in this way



Aspirin **Morphine**

Fig. 1 Analgesics.

are antidepressants, cardiovascular drugs, anti-asthmatics, and anti-ulcer agents.

Second, drugs can be classified depending on whether they act on a particular biochemical process. For example, antihistamines act by inhibiting the action of the inflammatory agent **histamine** in the body. Although this classification is more specific than the above, it is still not possible to identify a common feature relating all antihistamines. This is because there are various ways in which the action of histamine can be inhibited. Other examples of this kind of classification are cholinergic or adrenergic drugs.

A third method of classifying drugs is by their chemical structure (*Fig.* 2). Drugs classified in this way share a common structural feature and often share a similar pharmacological activity. For example, **penicillins** all contain a β-lactam ring and kill bacteria by the same mechanism. As a result, this classification can sometimes be useful in medicinal chemistry. However, it is not foolproof. **Sulfonamides** have a similar structure and are mostly antibacterial. However, some sulfonamides are used for the treatment of diabetes. Similarly, **steroids** all have a tetracyclic structure, but the pharmacological effect of different steroids can be quite different.

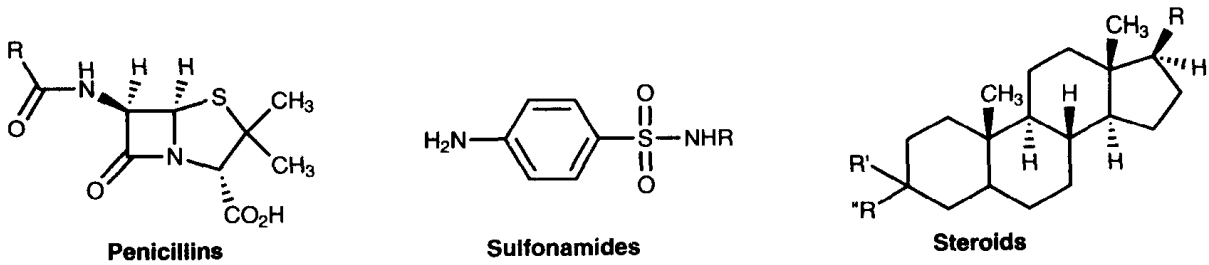


Fig. 2. Drugs classified by structure.

Finally, classifying drugs according to their molecular target is the most useful classification as far as the medicinal chemist is concerned, since it allows a rational comparison of the structures involved. For example, anticholinesterases are compounds that inhibit an enzyme called **acetylcholinesterase**. They have the same mechanism of action and so it is valid to compare the various structures and identify common features.

A2 FROM CONCEPT TO MARKET

Key Notes

Overview

In general, there are three main phases in getting a drug to the market – drug discovery, drug design and drug testing/development.

Phase 1 – drug discovery

Most medicinal chemistry projects start by identifying a drug target. A testing procedure is then developed and a search is made for a compound having the desired activity – a lead compound.

Phase 2 – drug design

Analogs of the lead compound are synthesized and tested, allowing identification of structural features which are important for activity. These features are retained during the design of analogs with improved pharmacodynamic and pharmacokinetic properties.

Phase 3 – drug testing and development

Drugs are patented as quickly as possible. Pre-clinical trials are carried out to assess the properties and safety of the new drug. If these prove satisfactory, clinical trials are carried out. The development of a large-scale synthesis proceeds in parallel to the biological testing. Regulatory authorities are responsible for approving drugs for clinical trials and the market place.

The chemist's contribution

A graduate with a chemistry or medicinal chemistry degree has skills which are applicable to various fields within the pharmaceutical industry, such as drug discovery, drug design, quality control, radiosynthesis and manufacture.

Related topic

Introduction (A1)

Overview

In general, there are three phases involved in discovering a new drug and getting it to market. Phase 1 is drug discovery, which involves finding an active compound for a particular target. Phase 2 is drug design, where the properties of that active compound are improved such that it is potent and selective for its target and can also reach that target. Phase 3 involves all the testing procedures and development work that have to be carried out on the drug in order to get it to the market.

Phase 1 – drug discovery

Nowadays, most medicinal chemistry projects start by identifying a suitable drug target (Section B). Knowledge of the physiological role played by that target allows the researcher to propose what effect a drug would have if it interacted with the target. Drug targets are usually biological macromolecules such as carbohydrates, lipids, proteins and nucleic acids. The most common targets are proteins followed by nucleic acids. Once a target has been chosen, suitable testing methods have to be developed (Section D) which will demonstrate whether potential drugs have the desired activity. It is then a case of finding a

structure that will interact with that target. Such a structure is known as a lead compound (Section E) and is the starting point for drug design.

Phase 2 – drug design

Once a lead compound has been identified, the medicinal chemist will devise synthetic routes that will allow the synthesis of various analogs (Section F). Having produced a series of analogs, the activities of these compounds are compared and certain structural features that are more important to activity than others are identified (structure activity relationships – Section G). These features are retained in the design of further analogs, which will interact more effectively or more selectively with their target (Section H). As well as this, it is necessary to design analogs that have the correct pharmacokinetic properties to reach their target (Section I).

Phase 3 – drug testing and development

As soon as a potentially useful drug is discovered, it is patented (Section J). The potential drug must then be thoroughly tested for any side effects or toxicity (Section K). Drug metabolism studies are also carried out to identify what metabolites are formed. These metabolites are then tested for activity and side effects. If the drug passes these tests, it is put forward for clinical trials (Section K). Finally, the drug can be marketed. At the same time as the pre-clinical and clinical trials are taking place, work is carried out to develop a large-scale synthesis of the compound (section J). The various tests and development work carried out on a new drug must be properly controlled and documented such that they adhere to the requirements laid down by the various regulatory authorities (Section K). Otherwise, the drug may not be allowed to enter clinical trials or the market.

The chemist's contribution

Chemists and medicinal chemists make important contributions at various stages of the drug research program. The medicinal chemist is most involved with drug discovery and drug design. Development chemists are involved in designing a large-scale synthesis for a drug. Organic synthetic chemists are involved in synthesizing radiolabeled drugs for drug metabolism studies, while analytical chemists are involved in quality control, ensuring that the drug satisfies purity specifications. Many of the practical skills acquired in a chemistry or medicinal chemistry degree are invaluable to the pharmaceutical industry. Practical techniques such as extraction, chromatography, distillation and crystallization are vital if a lead compound is to be isolated and purified from a natural extract or a synthetic mixture. Synthetic skills are required in order to synthesize analogs of a lead compound in order to carry out structure activity relationships. Analytical skills, such as the ability to interpret nuclear magnetic resonance (NMR) spectra, are important in determining the structure of a lead compound or a synthetic analog. These skills are just as relevant to the development chemist devising a large-scale synthesis.

B1 ENZYMES

Key Notes

Enzymes

Enzymes are proteins that catalyze the body's chemical reactions. The starting material for an enzyme-catalyzed reaction is known as a substrate.

Active site

The active site is a hollow or cleft on the enzyme surface where the substrate binds and the reaction takes place. The substrate is bound to the active site by intermolecular interactions. The active site contains amino acid residues, which act as nucleophiles or acid/base catalysts in the reaction mechanism

Mechanisms of catalysis

Serine and cysteine can act as nucleophiles in a reaction mechanism, while histidine can act as an acid/base catalyst. Substrate binding weakens important bonds and constrains the substrate in a specific conformation such that it will undergo reaction.

Enzyme inhibitors

Competitive inhibitors compete with the natural substrate for the active site. Noncompetitive inhibitors bind to allosteric binding sites and distort the active site so that it can no longer bind the natural substrate. Reversible inhibitors bind by noncovalent interactions, whereas irreversible inhibitors are linked to the enzyme through covalent bonds.

Enzyme selectivity

Drugs should be as selective as possible for the target enzyme or isozyme.

Related topics

Binding interactions (G2)
Functional groups as binding groups (G3)
Epidermal growth factor receptor (L1)
Modeling studies (L4)
The dawn of the antibacterial age (1930–1945) (M4)

Enzymes

Enzymes are protein structures that act as the body's catalysts. A **catalyst** aids a chemical reaction by lowering the activation energy of the reaction. This speeds up the rate at which the reaction reaches equilibrium but does not affect the equilibrium itself. Therefore, an enzyme can catalyze a reaction in either direction depending on the relative ratio of compounds present. The chemical that undergoes an enzyme-catalyzed reaction is known as a **substrate**. The substrate is bound to the enzyme to form an enzyme–substrate complex (ES), which then undergoes reaction to form the enzyme-bound product (EP) (*Fig. 1*). The product is then released and the enzyme is free to bind another substrate molecule.

Since enzymes are proteins, they are made up of amino acid subunits linked together by peptide bonds. There are 20 essential amino acids in human biochemistry, five of which are shown in *Fig. 2*.

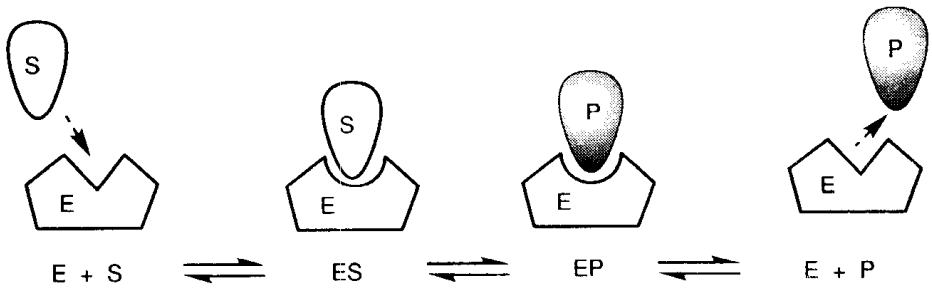


Fig. 1. Enzyme catalyzed reactions.

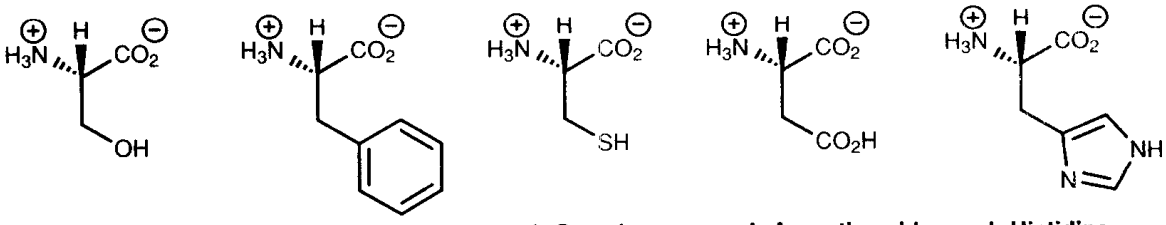


Fig. 2. Amino acids.

Active site

The **active site** of an enzyme is usually a hollow or cleft on the protein surface into which the substrate can fit and bind (*Fig. 3*). The substrate is usually bound to amino acids present in the binding site by a variety of interactions, such as hydrogen bonding, ionic bonding, van der Waals interactions or dipole–dipole interactions. For example, a substrate might bind to a serine residue by H-bonding, to an aspartate residue by ionic binding and to a phenylalanine residue by van der Waals interactions. These binding interactions must be strong enough to hold the substrate long enough for the enzyme-catalyzed reaction to take place, but weak enough to allow the product to depart once it is formed. This is important when it comes to designing inhibitors since one could introduce extra binding interactions such that the inhibitor 'sticks' to the binding site and blocks it.

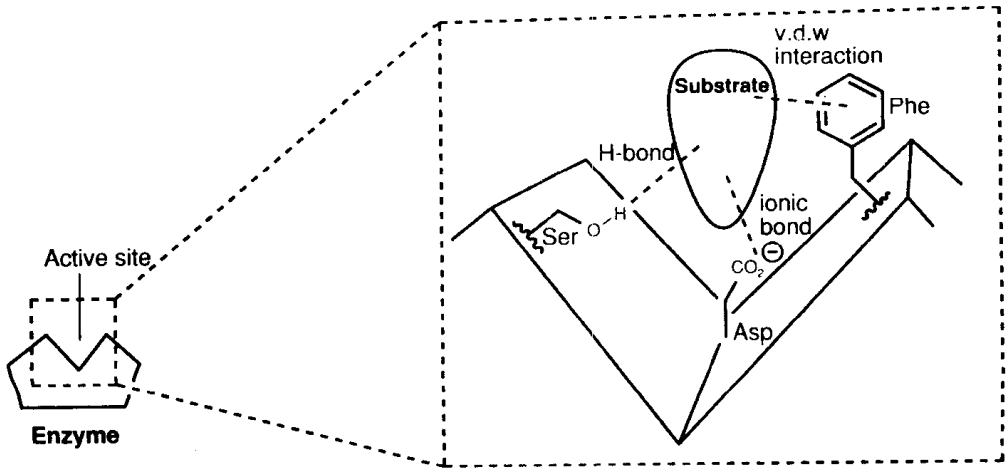


Fig. 3. The active site.

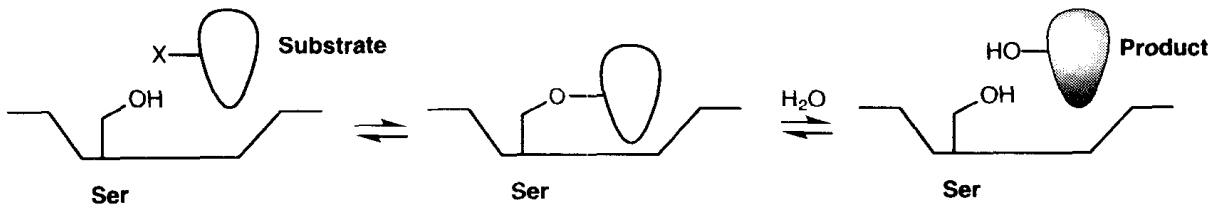


Fig. 4. Serine acting as a nucleophile.

The active site also contains amino acids, which assist in the reaction mechanism. Nucleophilic amino acids, such as serine or cysteine are commonly involved in enzyme-catalyzed mechanisms and will form a temporary covalent bond with the substrate as part of the reaction mechanism (*Fig. 4*).

The amino acid histidine is commonly involved as an acid/base catalyst. This is because the imidazole ring of the histidine residue can easily equilibrate between the ionized and nonionized forms, allowing the amino acid to act both as a source and as a 'sink' for protons (*Fig. 5*).

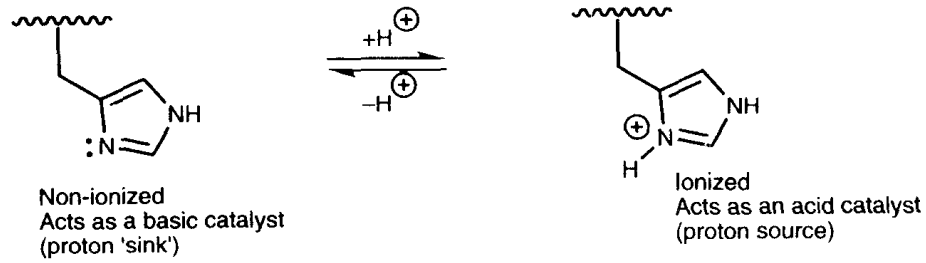


Fig. 5. Histidine as an acid/base catalyst.

Mechanisms of catalysis

There are several reasons why enzymes catalyze reactions. We have already mentioned that amino acids in the active site can aid the enzyme mechanism by acting as nucleophiles or acid/base catalysts. Another reason why enzymes act as catalysts is the binding process itself. The active site is not the ideal shape for the substrate, and when binding takes place it changes shape in order to accommodate the substrate and to maximize the bonding forces between the substrate and the active site. This is known as an **induced fit** (*Fig. 6*).

However, these binding processes also mean that the substrate is forced to adopt a specific conformation (not necessarily the most stable conformation) in

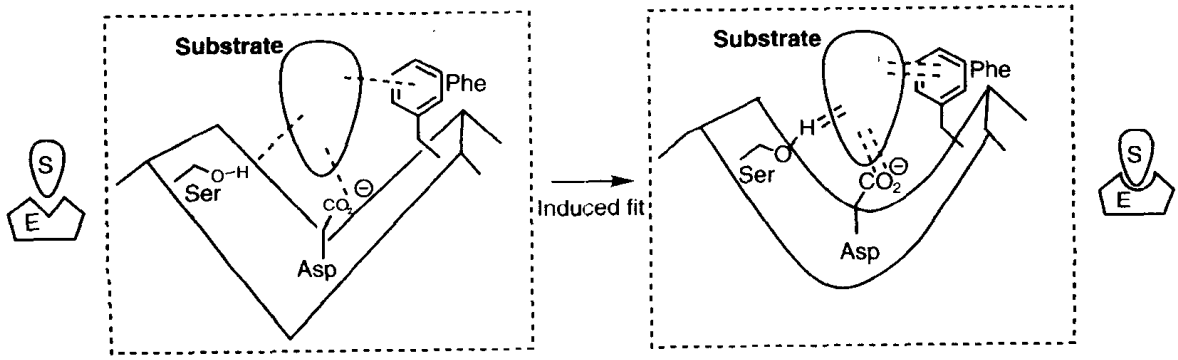


Fig. 6. Induced fit.