
Contents

| | |
|--|----|
| Preface | ix |
| Introduction | xi |
| Chapter 1. Enzyme Kinetics, Inhibition and Activation | 1 |
| 1.1. Michaelis and Menten theory | 2 |
| 1.2. Irreversible inhibitors | 3 |
| 1.3. Reversible inhibitors in a Michaelian system | 4 |
| 1.3.1. Reversible competitive inhibitors | 4 |
| 1.3.2. Reversible non-competitive inhibitors | 7 |
| 1.3.3. Reversible uncompetitive inhibitors. | 11 |
| 1.4. Allostery: inhibitors and activators. | 13 |
| 1.4.1. Allosteric enzyme kinetics | 14 |
| 1.4.2. Mechanism of allosteric enzyme regulation | 16 |
| 1.5. References | 17 |
| Chapter 2. Targeted Viral and Microbial Enzymes | 19 |
| 2.1. Viral targets | 20 |
| 2.1.1. Herpes group viruses: DNA-dependent DNA polymerases (EC 2). | 20 |
| 2.1.2. Influenza virus: exo-alpha-sialidase or neuraminidase (EC 3) | 21 |
| 2.1.3. HIV protease (EC 3) | 22 |
| 2.1.4. HIV reverse transcriptase (RNA/DNA-dependent DNA polymerase – EC 2) | 26 |
| 2.1.5. HIV integrase (EC 2). | 29 |
| 2.1.6. Hepatitis C virus (HCV): RNA-dependent RNA polymerase (NS5B – EC 2) and viral protease (NS3-4A – EC 3) | 30 |

| | |
|--|------------|
| 2.2. Bacterial targets | 31 |
| 2.2.1. Specific target (action mainly focused on the <i>Mycobacterium tuberculosis</i> species) | 31 |
| 2.2.2. General actions | 33 |
| 2.3. Fungal targets | 64 |
| 2.3.1. 1,3-beta-glucan synthase (EC 2) | 64 |
| 2.3.2. Squalene mono-oxygenase (EC 1) | 65 |
| 2.3.3. 14-sterol demethylase (EC 1) | 65 |
| 2.3.4. Thymidylate synthase (EC 2) | 66 |
| 2.4. Parasite targets | 66 |
| 2.4.1. Ornithine decarboxylase (EC 4) | 66 |
| 2.4.2. Heme polymerase (EC 2) | 67 |
| 2.5. References | 67 |
| Chapter 3. Targeted Human Enzymes | 71 |
| 3.1. Treatment via effectors | 71 |
| 3.1.1. Ophthalmology | 71 |
| 3.1.2. Neurology | 73 |
| 3.1.3. Metabolism and endocrinology | 79 |
| 3.1.4. Cardiovascular and immunology | 94 |
| 3.1.5. Oncology | 115 |
| 3.1.6. Phosphatome and Kinome | 131 |
| 3.2. Enzyme replacement therapy | 143 |
| 3.2.1. Gout | 143 |
| 3.2.2. Acute leukemia and non-Hodgkin's lymphoma | 144 |
| 3.2.3. Hypophosphatasia | 144 |
| 3.2.4. Chronic obstructive pulmonary disease | 144 |
| 3.3. References | 144 |
| Chapter 4. What are the New Targets? | 151 |
| 4.1. Inhibition and activation strategies: advantages, disadvantages and current status | 151 |
| 4.1.1. Irreversible inhibitors | 152 |
| 4.1.2. Competitive inhibitors | 153 |
| 4.1.3. Non-competitive inhibitors | 155 |
| 4.1.4. Uncompetitive inhibitors | 156 |
| 4.1.5. Allosteric effectors | 156 |
| 4.1.6. Other strategies | 157 |
| 4.2. Exogenous and endogenous targets | 157 |
| 4.2.1. Exogenous targets | 158 |
| 4.2.2. Endogenous targets | 162 |

| | |
|--|------------|
| 4.3. Rare diseases and enzymes | 166 |
| 4.3.1. Lysosomal storage diseases | 167 |
| 4.3.2. Other rare genetic diseases linked to one or more enzymes | 176 |
| 4.4. References | 176 |
| Chapter 5. Which “New” Drugs are We Moving Towards Now? | 181 |
| 5.1. Chemistry | 181 |
| 5.1.1. Combinatorial chemistry | 181 |
| 5.1.2. Vectorization | 182 |
| 5.2. Biology | 183 |
| 5.2.1. Inducers and repressors | 184 |
| 5.2.2. Antibodies | 184 |
| 5.3. Genetics | 186 |
| 5.3.1. Gene therapy | 186 |
| 5.3.2. Antisense strategies | 193 |
| 5.4. References | 194 |
| Conclusion | 197 |
| Index | 201 |