

Review



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Structure, mechanism and inhibition of
anthranilate phosphoribosyltransferase

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Anthranilate phosphoribosyltransferase catalyses the second reaction in the biosynthesis of tryptophan from chorismate in microorganisms and plants. The enzyme is homodimeric with the active site located in the hinge region between two domains. A range of structures in complex with the substrates, substrate analogues and inhibitors have been determined, and these have provided insights into the catalytic mechanism of this enzyme. Substrate 5-phospho- α -ribose 1-diphosphate (PRPP) binds to the C-terminal domain and coordinates to Mg^{2+} , in a site completed by two flexible loops. Binding of the second substrate anthranilate is more complex, featuring multiple binding sites along an anthranilate channel. This multi-modal binding is consistent with the substrate inhibition observed at high concentrations of anthranilate. A series of structures predict a dissociative mechanism for the reaction, similar to the reaction mechanisms elucidated for other phosphoribosyltransferases. As this enzyme is essential for some pathogens, efforts have been made to develop inhibitors for this enzyme. To date, the best inhibitors exploit the multiple binding sites for anthranilate.

This article is part of the theme issue 'Reactivity and mechanism in chemical and synthetic biology'.

1. Introduction

Anthranilate phosphoribosyltransferase (AnPRT) catalyses the second committed step in tryptophan biosynthesis, in which a phosphoribosyl group is transferred from 5-phospho- α -ribose 1-diphosphate (PRPP) to anthranilate, forming *N*-(5-phosphoribosyl)-anthranilate (PRA) [1,2]. Tryptophan biosynthesis operates in plants and microorganisms [3–5]. Its absence in humans means that the enzymes of tryptophan biosynthesis are an attractive target for developing new therapeutics to combat infectious diseases [6]. AnPRT from *Mycobacterium tuberculosis* (MtuAnPRT) has been validated as an antimicrobial drug target against *M. tuberculosis*, the pathogen responsible for tuberculosis [7–12]. Tuberculosis continues to cause several million deaths annually and the demand for new treatments for this disease will only increase as drug-resistant strains emerge [11–14].

The enzyme AnPRT belongs to a wider group of phosphoribosyltransferases (PRTs) that all catalyse the transfer of a phosphoribosyl moiety from PRPP to a nitrogen-based nucleophile, including purines, pyrimidines and their biosynthetic precursors [15]. PRTs have been divided into four types with characteristic structural properties shared among members in each type (figure 1).

Type I PRT is the largest group and comprises mainly enzymes involved in the nucleotide salvage pathways [4,20–25]. This type includes the enzymes glutamine PRPP amidotransferase, PRPP synthase, uracil PRT, xanthine/hypoxanthine PRT, orotate PRT, guanine PRT and adenine PRT. Type I PRTs share a common α/β fold decorated by a highly flexible and multifunctional loop ($\beta 2$ - $\beta 3$ loop) and a variable hood domain that play essential roles in catalysis and regulation of the corresponding PRT [15]. Type II PRTs include quinolinate and nicotinic acid PRTs of the nicotinamide pathway, and consist of an unusual open seven-stranded α/β

Structure Mechanism In Organo Phosphor

Julia Schneider



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A Guide to Organophosphorus Chemistry Louis D. Quin, 2000-02-04 An authoritative and comprehensive introduction to organophosphorus chemistry The broad exciting field of organophosphorus chemistry has grown tremendously over the last few decades with a wealth of opportunities for research and applications development A Guide to Organophosphorus Chemistry offers chemists in academia and industry complete up to date coverage of the fundamentals with an eye on future developments in this area Internationally recognized authority Louis D Quin extends his experienced perspective and insight on the topic by Surveying the most important phosphorus containing functional groups Including representative methods of synthesis plus references to detailed synthetic procedures Outlining advances in stereochemical aspects of phosphorus chemistry Covering areas of current research such as unusual coordination states heterocycles applications of ^{31}P NMR and other spectroscopic methods Providing numerous references to important review articles and recent literature Presenting electronic mechanisms and reactive intermediates where established Discussing the importance of phosphorus compounds in living systems and in agricultural applications Liberally illustrated with equations and structural formulas A Guide to Organophosphorus Chemistry presents a virtually unparalleled introduction to the subject matter making it an indispensable instructional tool for aspiring chemists and practicing chemists alike

Structure and Mechanism in Organophosphorus Chemistry R. F. Hudson, 1965

The Chemistry of Phosphorus Arthur D. F. Toy, 2016-06-07 Pergamon Texts in Inorganic Chemistry Volume 3 The Chemistry of Phosphorus focuses on the physical and chemical properties of phosphorus This book discusses phosphorus compounds such as phosphorus hydrides and phosphonium compounds phosphorus halides and phosphorus pseudohalides thiophosphoryl halides and thiophosphoryl pseudohalides phosphorus oxides and phosphorus nitrogen compounds The pyrophosphates triphosphates polyphosphates cyclic metaphosphates and ultraphosphates are also covered in this text This publication is intended for chemical engineering students and chemists researching on the characteristics of phosphorus

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however one examines the historical development of these compounds it is apparent that this was preceded by a hundred years of pure chemistry of phosphorus

Best Synthetic Methods Chris Timperley, 2014-12-01 Best Synthetic Methods Organophosphorus V Chemistry provides systematic coverage of the most common classes of pentavalent organophosphorus compounds and reagents including phosphonyl phosphoryl and organophosphates and allows researchers an easy point of entry into this complex and economically important field The book follows the Best Synthetic Methods format containing practical methods synthetic tips and shortcuts Where relevant articles include toxicity data and historical context for the reactions Typical analytical and spectroscopic data are also presented to enable scientists to identify key compound characteristics The book is a valuable companion to research chemists in both academia and industry summarizing the best practical methods often originating in difficult to access foreign language primary literature in one place It is ideally suited for those working on industrial applications of these compounds including insecticides herbicides flame retardants and plasticizers Includes a mixture of tried and tested historical methods that are proven to work alongside new methods to provide scientists with a quick time saving resource of reliable methods Includes tips and tricks to get reactions to work important information often missing from other sources Includes key analytical data for compounds so scientists have one handy resource to select perform and analyze the best reaction

Organophosphorus Pesticides Morifusa Eto, 2018-01-18 In order to get a general concept of organophosphorus pesticides with such a variety in structure and biological activities consideration of each aspect of chemistry biochemistry and the applied sciences is necessary This book consists of these three main parts After the presentation of the background of phosphorus chemistry in Chapter 1 stress was put on the chemical and biochemical reactions of organophosphorus pesticides including synthesis analysis metabolism mode of action and other interesting aspects in Chapter 2 to 4 and on the structure pesticidal activity relationship in Chapter 5

Research Grants Index National Institutes of Health (U.S.). Division of Research Grants, 1966

Aliphatic Compounds M. F. Ansell, 1975-01-01 Aliphatic Compounds *Advanced Organic Chemistry of Nucleic Acids* Zoe A. Shabarova, Alexey A. Bogdanov, 2008-07-11 Sequencing cloning transcription these are but a few key techniques behind the current breathtaking advances in molecular biology and biochemistry As these methods continuously diversify biochemists need a sound chemical understanding to keep the pace Chemists beginning working in the molecular biology lab need an introduction to this field from their point of view This book serves both it describes most of the known chemical reactions of nucleosides nucleotides and nucleic acids in sufficient detail to provide the desired background and additionally the fundamental relations between sequence structure and functionality of nucleic acids are presented The first edition of this book which was published in Russian has immediately become a recognized standard reference This second thoroughly revised and updated edition now published in English is likely to achieve a similar position in the international scientific community

Analysis of Pesticides in Water Alfred S.Y. Chau, 2018-01-18 This book collected by Mr Chau and Dr Afghan is

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Table of Contents Structure Mechanism In Organo Phosphor

1. Understanding the eBook Structure Mechanism In Organo Phosphor
 - The Rise of Digital Reading Structure Mechanism In Organo Phosphor
 - Advantages of eBooks Over Traditional Books
2. Identifying Structure Mechanism In Organo Phosphor
 - Exploring Different Genres
 - Considering Fiction vs. Non-Fiction
 - Determining Your Reading Goals
3. Choosing the Right eBook Platform
 - Popular eBook Platforms
 - Features to Look for in an Structure Mechanism In Organo Phosphor
 - User-Friendly Interface
4. Exploring eBook Recommendations from Structure Mechanism In Organo Phosphor

- Personalized Recommendations
- Structure Mechanism In Organo Phosphor User Reviews and Ratings
- Structure Mechanism In Organo Phosphor and Bestseller Lists
- 5. Accessing Structure Mechanism In Organo Phosphor Free and Paid eBooks
 - Structure Mechanism In Organo Phosphor Public Domain eBooks
 - Structure Mechanism In Organo Phosphor eBook Subscription Services
 - Structure Mechanism In Organo Phosphor Budget-Friendly Options
- 6. Navigating Structure Mechanism In Organo Phosphor eBook Formats
 - ePub, PDF, MOBI, and More
 - Structure Mechanism In Organo Phosphor Compatibility with Devices
 - Structure Mechanism In Organo Phosphor Enhanced eBook Features
- 7. Enhancing Your Reading Experience
 - Adjustable Fonts and Text Sizes of Structure Mechanism In Organo Phosphor
 - Highlighting and Note-Taking Structure Mechanism In Organo Phosphor
 - Interactive Elements Structure Mechanism In Organo Phosphor
- 8. Staying Engaged with Structure Mechanism In Organo Phosphor
 - Joining Online Reading Communities
 - Participating in Virtual Book Clubs
 - Following Authors and Publishers Structure Mechanism In Organo Phosphor
- 9. Balancing eBooks and Physical Books Structure Mechanism In Organo Phosphor
 - Benefits of a Digital Library
 - Creating a Diverse Reading Collection Structure Mechanism In Organo Phosphor
- 10. Overcoming Reading Challenges
 - Dealing with Digital Eye Strain
 - Minimizing Distractions
 - Managing Screen Time
- 11. Cultivating a Reading Routine Structure Mechanism In Organo Phosphor
 - Setting Reading Goals Structure Mechanism In Organo Phosphor
 - Carving Out Dedicated Reading Time
- 12. Sourcing Reliable Information of Structure Mechanism In Organo Phosphor

- Fact-Checking eBook Content of Structure Mechanism In Organo Phosphor
 - Distinguishing Credible Sources
13. Promoting Lifelong Learning
- Utilizing eBooks for Skill Development
 - Exploring Educational eBooks
14. Embracing eBook Trends
- Integration of Multimedia Elements
 - Interactive and Gamified eBooks

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