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Discovery and characterization of verinurad, a potent and specific inhibitor of URAT1 for the treatment of hyperuricemia and gout

Philip K. Tan¹, Sha Liu¹, Esmir Gunic² & Jeffrey N. Miner¹

Gout is caused by elevated serum urate levels, which can be treated using inhibitors of the uric acid transporter, URAT1. Here, we characterize verinurad (RDEA3170), which is currently under evaluation for gout therapy. Verinurad specifically inhibits URAT1 with a potency of 25 nM. High affinity inhibition of uric acid transport requires URAT1 residues Cys-32, Ser-35, Phe-365 and Ile-481. Unlike other available uricosuric agents, the requirement for Cys-32 is unique to verinurad. Two of these residues, Ser-35 and Phe-365, are also important for urate transport kinetics. A URAT1 binding assay using radiolabeled verinurad revealed that distinct URAT1 inhibitors benzbromarone, sulfapyrazone and probenecid all inhibit verinurad binding via a competitive mechanism. However, mutations made within the predicted transporter substrate channel differentially altered the potency for individual URAT1 inhibitors. Overall, our results suggest that URAT1 inhibitors bind to a common site in the core of the transporter and sterically hinder the transit of uric acid through the substrate channel, albeit with vastly different potencies and with differential interactions with specific URAT1 amino acids.

Gout is a metabolic disease caused by chronically elevated serum uric acid (sUA) levels (hyperuricemia), leading to deposition of urate in the joints and acute bouts of painful inflammatory arthritis^{1–3}. Urate homeostasis is balanced by urate production and elimination, and homoinds and certain monkeys have relatively high sUA levels due to the presence of multiple inactivating mutations in the uric acid degrading enzyme uricase and mutations in URAT1 that increase affinity for uric acid^{4–6}. Elimination of urate occurs primarily in the urine; however, in the kidneys approximately 90% of the urate filtered by the glomerulus is reabsorbed back into the bloodstream so that just 10% of the filtered urate is renally excreted^{4–6}. Compared to individuals with normal sUA levels, most patients with gout exhibit reduced fractional excretion of uric acid (FEUA), leading to hyperuricemia⁷. URAT1 is a transporter critical for renal reabsorption of urate. Inactivating mutations of URAT1 lead to high FEUA and hypouricemia (abnormally low sUA levels)⁷. In patients with gout, we previously hypothesized that reduced FEUA could be due to altered URAT1 transport kinetics that increase renal urate reabsorption⁷. However, the reduced FEUA in gout patients could also be due to reduced renal urate secretion^{8–9}.

Benzbromarone, sulfapyrazone, probenecid and lesinurad (Figure S1) are among a class of gout therapeutics that lower sUA levels by inhibiting URAT1 and enhancing FEUA. However, the first three are not widely used due to various safety and availability issues¹⁰. Lesinurad was recently approved for the treatment of hyperuricemia associated with gout, in combination with a xanthine oxidase inhibitor^{11–14}. In this report, we describe the molecular pharmacology of a novel, highly potent and specific URAT1 inhibitor, verinurad (also known as RDEA3170; Figure S1), that is currently under evaluation for the treatment of gout and asymptomatic hyperuricemia. Verinurad-mediated inhibition of URAT1 is highly dependent on human URAT1 Phe-365 and Ser-35, both of which are located in the substrate channel. The high affinity of verinurad allowed development of a novel URAT1 binding assay, and results from this assay showed that all the inhibitors bind to the same site within

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The Top Books of the Year Discovery And Characterization Of Verinurad A Potent And The year 2023 has witnessed a noteworthy surge in literary brilliance, with numerous captivating novels enthralling the hearts of readers worldwide. Lets delve into the realm of popular books, exploring the captivating narratives that have captivated audiences this year. The Must-Read : Colleen Hoover's "It Ends with Us" This heartfelt tale of love, loss, and resilience has captivated readers with its raw and emotional exploration of domestic abuse. Hoover skillfully weaves a story of hope and healing, reminding us that even in the darkest of times, the human spirit can prevail. Discovery And Characterization Of Verinurad A Potent And : Taylor Jenkins Reid's "The Seven Husbands of Evelyn Hugo" This intriguing historical fiction novel unravels the life of Evelyn Hugo, a Hollywood icon who defies expectations and societal norms to pursue her dreams. Reid's compelling storytelling and compelling characters transport readers to a bygone era, immersing them in a world of glamour, ambition, and self-discovery. Discover the Magic : Delia Owens' "Where the Crawdads Sing" This captivating coming-of-age story follows Kya Clark, a young woman who grows up alone in the marshes of North Carolina. Owens weaves a tale of resilience, survival, and the transformative power of nature, captivating readers with its evocative prose and mesmerizing setting. These popular novels represent just a fraction of the literary treasures that have emerged in 2023. Whether you seek tales of romance, adventure, or personal growth, the world of literature offers an abundance of compelling stories waiting to be discovered. The novel begins with Richard Papen, a bright but troubled young man, arriving at Hampden College. Richard is immediately drawn to the group of students who call themselves the Classics Club. The club is led by Henry Winter, a brilliant and charismatic young man. Henry is obsessed with Greek mythology and philosophy, and he quickly draws Richard into his world. The other members of the Classics Club are equally as fascinating. Bunny Corcoran is a wealthy and spoiled young man who is always looking for a good time. Charles Tavis is a quiet and reserved young man who is deeply in love with Henry. Camilla Macaulay is a beautiful and intelligent young woman who is drawn to the power and danger of the Classics Club. The students are all deeply in love with Morrow, and they are willing to do anything to please him. Morrow is a complex and mysterious figure, and he seems to be manipulating the students for his own purposes. As the students become more involved with Morrow, they begin to commit increasingly dangerous acts. The Secret History is a brilliant and suspenseful novel that will keep you guessing until the very end. The novel is a warning tale about the dangers of obsession and the power of evil.

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Table of Contents Discovery And Characterization Of Verinurad A Potent And

1. Understanding the eBook Discovery And Characterization Of Verinurad A Potent And
 - The Rise of Digital Reading Discovery And Characterization Of Verinurad A Potent And
 - Advantages of eBooks Over Traditional Books
2. Identifying Discovery And Characterization Of Verinurad A Potent And
 - 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 eBook Platform
 - User-Friendly Interface
4. Exploring eBook Recommendations from Discovery And Characterization Of Verinurad A Potent And
 - Personalized Recommendations
 - eBook Reviews and Ratings
 - Bestseller Lists
5. Accessing eBook Discovery And Characterization Of Verinurad A Potent And Free and Paid eBooks
 - eBook Discovery And Characterization Of Verinurad A Potent And Public Domain eBooks
 - eBook Subscription Services
 - Budget-Friendly Options
6. Navigating eBook Discovery And Characterization Of Verinurad A Potent And eBook Formats
 - ePub, PDF, MOBI, and More
 - eBook Compatibility with Devices
 - Enhanced eBook Features
7. Enhancing Your Reading Experience
 - Adjustable Fonts and Text Sizes
 - Highlighting and Note-Taking
 - Interactive Elements

8. Staying Engaged with Discovery And Characterization Of Verinurad A Potent And
 - Joining Online Reading Communities
 - Participating in Virtual Book Clubs
 - Following Authors and Publishers Discovery And Characterization Of Verinurad A Potent And
9. Balancing eBooks and Physical Books Discovery And Characterization Of Verinurad A Potent And
 - Benefits of a Digital Library
 - Creating a Diverse Reading Collection Discovery And Characterization Of Verinurad A Potent And
10. Overcoming Reading Challenges
 - Dealing with Digital Eye Strain
 - Minimizing Distractions
 - Managing Screen Time
11. Cultivating a Reading Routine Discovery And Characterization Of Verinurad A Potent And
 - Setting Reading Goals Discovery And Characterization Of Verinurad A Potent And
 - Carving Out Dedicated Reading Time
12. Sourcing Reliable Information of Discovery And Characterization Of Verinurad A Potent And
 - Fact-Checking eBook Content of Discovery And Characterization Of Verinurad A Potent And
 - 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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