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MEDCHEMMEET2022

INTERNATIONAL MEET ON MEDICINAL CHEMISTRY, DRUG DISCOVERY & DRUG DELIVERY

JUNE 23, 2022 | COPENHAGEN, DENMARK

ALBEDO MEETINGS
Floor# 3, Advant Building, 99B, Kakatiya Hills, Kavuri Hills, Madhapur Hyderabad, TS 500033
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FOREWORD

Dear Colleagues,

I am looking forward to meet you in Copenhagen next year. After almost 2 years of mostly staying at home because of the COVID-19, I hope that we shall be able to discuss problems in drug discovery, medicinal chemistry and drug delivery face-to- face, rather than by ZOOM or other modern techniques. For me the old fashioned way of meeting is still the best way.

A lot is happening in our fields of research. Novel methods and novel ideas are being published all the time. But we are still far away from having outstanding drugs for all diseases and for all patients. Indeed the present viral worldwide attack found us without satisfactory drugs. We need additional approaches and additional breakthroughs.

I hope to hear presentations on novel drugs in many disease areas. Hopefully we may learn of new anti-viral drugs, of new antibiotics, which may replace those we already have, but are losing their activity due to bacterial tolerance, of new drugs in neurology and psychiatry etc.

Welcome to wonderful Copenhagen

Raphael Mechoulam
Hebrew University
Israel

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Revisiting γ-Secretase as a Target for Alzheimer's disease

Michael S. Wolfe
Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas, USA

Abstract
Cerebral plaques composed of the 42-residue amyloid β-peptide (Aβ42) are a defining pathological feature of Alzheimer's disease, and targeting Aβ42 to develop disease-modifying therapeutics has been a goal for over 25 years. However, no effective medications have yet emerged, with only one highly controversial recent approval by the United States Food and Drug Administration. Despite the many clinical trial failures and major gaps in understanding of disease etiology, investigations into the details of how dominantly inherited mutations alter Aβ production is providing insight into the nature of the pathogenic trigger. These mutations are associated with familial Alzheimer's disease (FAD) and are found in the substrate (amyloid precursor protein, APP) and the enzyme (γ-secretase) that produce Aβ. These mutations are linked to elevations in the ratio of Aβ42 to Aβ40, which can lead to assembly and aggregation of Aβ42. However, recent studieshave identified a number of outlier mutations. γ-Secretase carries out processiveintramembrane proteolysis of APP substrate to produce Aβ peptides of variable C-termini along two pathways: Aβ49→Aβ46→Aβ43→Aβ40 and Aβ48→Aβ45→Aβ42→Aβ38. Comprehensive biochemical analysis of the effects of FAD mutations on all these proteolytic steps reveal deficiencies in early proteolytic steps as the common feature. Structural and computational analyses support conformational dynamics during γ-secretase intramembrane proteolysis and how FAD mutations alter these dynamics. Moreover, cell and animal models suggest that FAD mutations can lead to neurotoxic effects that are independent of Aβ42 production. Implications for pathogenic mechanisms and drug discovery for FAD and Alzheimer's disease in general will be discussed.

Keywords
Amyloid; Protease; Mechanism; Pathogenesis

Biography
Michael S. Wolfe received his B.S. in chemistry in 1984 from the Philadelphia College of Pharmacy and Science and Ph.D. in medicinal chemistry in 1990 from the University of Kansas. After postdoctoral stints at the University of Kansas (medicinal chemistry) and the NIH (cell biology), he joined the faculty of the University of Tennessee in Memphis in 1994. In 1999, he moved to Harvard Medical School and Brigham and Women's Hospital, where his work focused on understanding the molecular basis of Alzheimer's and related disorders and identifying effective approaches for pharmacological intervention, becoming Professor of Neurology in 2008. He joined the University of Kansas faculty in 2016 as the Mathias P. Mertes Professor of Medicinal Chemistry. Awards for his work include the Sato Memorial International Award in bioorganic and medicinal chemistry from the Pharmaceutical Society of Japan (2003), the MetLife Award for Biomedical Research (2008), a Zenith Fellows Award from the Alzheimer's Association (2008), and the Potamkin Prize from the American Academy of Neurology (2009).

Natural Products as Warheads for Antibody-Drug Conjugates: Challenges and Opportunities

Julia Gavrilyuk
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Abstract
Antibody−drug conjugates (ADCs) have evolved into powerful targeted cancer therapies and are a living example of the “magic bullet” concept of Paul Ehrlich. ADCs consist of three components, the antibody serving as the targeted delivery system, the payload drug that kills the cancer cell, and the chemical linker through which the payload is attached to the antibody. Naturally occurring molecules and their derivatives endowed with high cytotoxic properties have proven to be useful payloads for the first approved ADCs (i.e., Mylotarg, Adcetris, Kadcyla, and Besponsa). Notably, very few classes of payloads dominate the field of ADCs, both approved and in different stages of clinical development: maytansinoids, auristatins, camptothecins and calicheamicins. Synthetic complexity of the natural products that limits access to the property tuneable analogues is only one of the long list of challenges in ADC development. Another challenge is often non-obvious translatability of the free payload activity in vitro and in vivo vs the corresponding ADC properties. We will focus our attention on the enediyne payloads recently reported in the collaborative effort between industry and academia: uncialamycin, shsishjimicin and namenamicin payloads in comparison to the clinically validated calicheamcin gamma.

Keywords
Antibody-Drug Conjugate; Natural Products; Uncialamycin A; Calicheamicin Gamma

Biography
Julia Gavrilyuk was born and raised in Ukraine. She received B.Sc. in polymer science from the National Taras Shevchenko University of Kyiv, Ukraine. She then completed her Ph.D. in organic chemistry at the University of Toronto in 2007 with prof. Robert A. Batey. Julia continued her post-doctoral training at the Scripps Research Institute, La Jolla, California with prof. Carlos F. Barbas, III. There she worked on the development of novel bioconjugation reactions and chemically programmable immunity. Julia has over 15 years of experience in the therapeutic development of antibody-drug conjugates focusing on the novel linker-payloads. She has led discovery chemistry team at Stemcentrx, acquired by AbbVie in 2016. Recently she has joined life science division of the Deep Valley Labs venture capital incubator in San Jose, California. Deep Valley Labs is focusing its attention on significant unsolved problems agnostic of the field. It enables inventors to test and validate ideas at the early stage to translate them into the life changing solutions.

L-Dopa Diketopiperazines: Pharmacological Tools against Parkinson's Disease

Ivana Cacciatore
Department of Pharmacy, University "G. D'Annunzio" of Chieti-Pescara, Italy

Abstract
Parkinson's Disease (PD) is a neurodegenerative disorder of the central nervous system characterized by motor dysfunctions, such as bradykinesia, rigidity, neuropsychiatric symptoms, and others. The pharmacological treatment of the disease is only symptomatic since, to date, there is no treatment to stop or slow PD. Currently, L-Dopa (LD) remains the gold standard therapy even though it undergoes peripheral metabolism causing several side effects, such as nausea, vomiting, and orthostatic hypotension. The main factors responsible for the LD's poor bioavailability are due to its physical-chemical properties: low water and lipid solubility, resulting in unfavorable partition, and the high susceptibility to chemical and enzymatic degradation.

During the last decades, different medicinal chemistry-based approaches were developed to improve the pharmaceutical, pharmacokinetic, and pharmacodynamic properties of hydrophilic compounds, such as LD. The diketopiperazine (DKP) scaffold was recently considered a potential blood-brain barrier shuttle (BBB-shuttle) for the delivery of drugs with limited ability to cross the BBB. The DKP scaffold confers high stability against proteolysis and constitutes a structural requirement for increased cell permeability. Starting from this consideration, a DKP-based motif was introduced into the linear sequence of LD-dipeptides. These novel drugs – beyond their pharmacological activities – can cross the blood-brain barrier via a passive diffusion process representing an exciting challenge for medicinal chemists to improve their pharmacological efficacy.

Keywords
BBB-shuttle; Diketopiperazine; Parkinson's disease.

Biography
Prof. Ivana Cacciatore received her master's degree in Pharmaceutical Chemistry and Technology cum laude from the University of Chieti-Pescara (Italy) in 1999 and she earned her Ph.D. in Pharmaceutical Science (University of Chieti-Pescara, Italy) in 2002. She became an Associate Professor at the Department of Pharmacy, University of Chieti-Pescara (Italy) in 2016. In November 2020 she was elected President of the Degree Course in Eco-Sustainable Technologies and Environmental Toxicology of the Department of Pharmacy of the University "G. D'Annunzio "of Chieti-Pescara (Italy). In May 2020 she became co-founder and member of the Board of Directors of the SPIN-OFF Company "ALGO BIOTECHNOLOGIES s.r.l."

covering the role of Chief Innovation Officer (CIO). Notably, she is responsible for oversight and drive of R&D and innovation of Company strategy.

Her scientific studies are mainly focused on the design and development of new molecular entities for the treatment of neurodegenerative diseases, such as Parkinson's and Alzheimer's diseases. She is co-author of the European Patent EP 3 495 372 A1 "Boronated derivatives for the treatment of diseases and conditions associated with oxidative stress" (2019). She is Editor-in-Chief for Letters in Drug Design & Discovery (Bentham Publisher), Section Editor, and Editorial Board member of several journals.

Her research activity is well documented in more than 100 papers published in peer-reviewed international scientific journals, participation in international and national congresses, and interdisciplinary collaborations with academic institutions and pharmaceutical industries.

New Azaheterocycles Derivatives: Design, Synthesis and Applications

Ionel I. Mangalagiu[1,2*], Violeta Mangalagiu[2], Dorina Amariucai Mantu[1], Vasilichia Antoci[1], Dumitrela Diaconu[2]
Alexandru Ioan Cuza University of Iasi, Faculty of Chemistry[1]; Institute of Interdisciplinary Research- CERNESIM Centre[2]; 11 Carol 1st Bvd, Iasi -700506, Romania;

Abstract
Azaheterocyclic derivatives has been reported as highly valuable scaffolds in medicine and pharmacy, being the core components of a large variety of drugs which posses a large variety of biological activity such as antiplasmodial and antimalarial, antitubercular, antibacterial, antifungal, anti-inflammatory, anti-HIV, anticancer, analgesic, antidepressant, anxiolytics, anti-Alzheimer's, antihypertensive, anticoagulants, diuretics, etc. As a result, obtaining of new azaheterocycles entities with a certain biological activity continues to arouse a strong interest from academia and industry.

As part of our ongoing research in the field of biologically active azaheterocyclic derivatives, we present herein some core results obtained by our group in this field (in the last 10 years), focused on the design, synthesis and molecular docking of some hybrid compounds having in the same molecules a p–reach five member ring azaheterocyclic and a p–deficient six member ring azaheterocyclic, particularly imidazole, azine and diazine heterocycles. The methods of synthesis are straight and efficient, involving typical organic chemistry stuff: alkylation, acylation, estherification, etherification, Huisgen 3+n cycloadditions. Some of the new setup procedures were performed using environmentally friendly methods, by using microwave and ultrasounds technology. The anticancer, antibacterial, antifungal, antituberculosis and antileishmanial activity of compounds was determined, some of the compounds having an excellent biological activity. For the most active compounds, a complete ADMET studies have been performed with very good results. The molecular docking experiments suggest important clues concerning the mechanism of actions of our nitrogen heterocyclic systems. Some of the obtained compounds are promising leading drug candidates.

Keywords
Antimicrobials; Anticancer; Azaheterocycles; Hybrid

Acknowledgements
This work was supported by a grant of the Romanian Ministry of Education and Research, CNCS—UEFISCDI, project number PN-III-P4-ID-PCE-2020-0371, within PNCDI III.

Nanotechnology based-approaches to manage dermatological microbial infections

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Abstract
Microbial diseases represent a worldwide problem responsible for a high rate of morbidity and mortality. Furthermore, damaged tissues are more susceptible to microbial infections, which induce alterations and may delay the wound healing process. Although there are widely available options for antimicrobial therapy and wound healing, in many cases these conventional treatments result unsatisfactory because of the emergence of drug-resistant bacteria. In this context, novel antibacterial strategies are urgently needed. During the last decades, different drug delivery systems were developed to overcome, in clinical application, some limitations of existing antibacterial agents, such as their bioavailability and in vivo bioactivity, thus improving their effectiveness.
Starting from this consideration, in our study, we take advantage of technological-based approaches to develop novel drug delivery systems as therapeutical tools for managing microbial infections and wounds. The developed formulations revealed improved therapeutic outcomes such as good antimicrobial activity and wound healing properties suggesting their suitability for future clinical applications. Further details about their features will be presented during the oral communication.

Keywords
Antimicrobials; Drug delivery systems; Therapeutic strategies; Wound healing.

Biography
Dr. Lisa Marinelli received her master's degree in Pharmacy cum laude from the "G. d'Annunzio" University of Chieti-Pescara (Italy) in 2011 and she earned her Ph.D. in "Drug Science" with an additional title of Doctor Europaeus in 2015 (University of Chieti-Pescara, Italy). After the post-doctoral position (2015-2020), she became Assistant Professor (RTD-A, S.S.D. CHIM/09, S.C. 03/D2) at the Department of Pharmacy "G. d'Annunzio" University of Chieti-Pescara (Italy) in 2020. In May 2020 she was co-founder and member of the board of Directors of the Spin-Off Company "Algo Biotechnologies s.r.l." having the role and responsibilities of CQO: "Oversight and drive the Quality and RA Company Strategy". In the call 2018/2020 (Ministerial Decree n. 2175/2018), for the disciplinary field of 03/D2 Drug technology, socioeconomics, and regulations, she obtained the National Scientific qualification as associate in the Italian higher education system. The research interest of Dr. Lisa Marinelli is focused on Pharmaceutical Technology including the preparation and characterization of drug delivery systems useful for the treatment of neurodegenerative and microbial diseases. Her research activity is documented by 47 papers published in peer-reviewed international scientific journals.

Revealing the Influence of Molecular Dynamics on Inhibitor-Protein Binding: Towards Novel Antimicrobial Agents

Simona Golič Grdadolnik*, Iza Ogris
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Abstract

The importance of identifying and characterising dynamic processes in ligand-protein binding for effective structure-based design of new drug leads will be discussed. The results of our recent studies on ligand binding to the protein targets muramyl ligase D (MurD) and sterol 14-a demethylases (CYP51) will be presented. The Mur enzymes are attractive targets for antibacterial drug development, while the human and fungal CYP51 orthologs enable the development of selective antifungal drugs.

A combination of spectroscopic methods in liquids, including ligand-based NMR, proved to be the only suitable approach to determine the binding mode of pyridylethanol(phenylethyl) amines to CYP51 at the atomic level. Previous attempts to determine the crystal structure of these compounds in complex with CYP51 were unsuccessful, probably because of their dynamic nature. By comparatively studying their binding to C. albicans and human CYP51, we were able to reveal the moieties critical for selectivity and potency and develop highly selective derivatives for C. albicans CYP51 with significantly enhanced inhibitory activity. NMR and molecular modelling methods were used to reveal the unique binding mode of this new chemical class of fungal CYP51 inhibitors. The low molecular weight of the lead derivatives and in-depth studies of their binding provide directions for focused lead optimization that could eventually furnish structurally novel antifungals with clinical candidate potential.

A combination of NMR studies and atomistic molecular dynamics simulations (MD) performed in physiological environments was also crucial for the discovery of the conformational dynamics of MurD inhibitors in their bound state. Our results explain the differences in the inhibitory activities of inhibitors designed as transition-state analogues that could not be understood by comparing their static X-ray crystal structures in complex with MurD. We used advanced isotopic labelling of MurD for protein-based NMR studies. The selectively 13CH3-labelled MurD has provided a solid basis for effective NMR characterization of site-specific MurD ligand binding, as demonstrated for the various types of novel MurD inhibitors. We discovered the rapid (ps-ns) movements of the MurD domains that affect the conformation and flexibility of the bound ligands, the stability of the binding interactions, and the adaptability of the MurD binding site. We investigated these dynamic processes using 15N NMR spin relaxation experiments on perdeuterated MurD in the context of ligand binding.

This work was supported by the Slovenian Research Agency (grant numbers J1-8145 and P1-0010). We recorded NMR spectra using 600- and 800-MHz NMR spectrometers at the Slovenian NMR Centre at the National Institute of Chemistry.

Keywords
NMR In Aqueous Environment; Inhibitor - Protein Complexes; Dynamic Processes; Molecular Dynamics Simulations

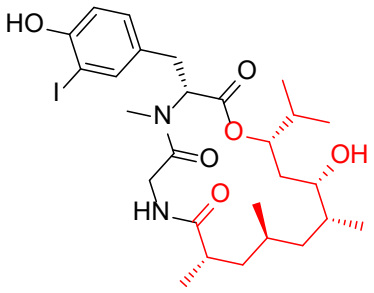
Biography
Simona Golič Grdadolnik is a senior researcher at the National Institute of Chemistry in Ljubljana and a professor at the University of Nova Gorica, Slovenia. She received her PhD in chemistry from the University of Ljubljana in 1994. She performed her doctoral research at the Technical University of Munich under the supervision of Professor Horst Kessler. In 1996 she was a fellow in the group of Professor Dale Mierke at Clark University, USA. She is co-author of 106 publications (https://orcid.org/0000-0002-0873-9593) and has been principal investigator of twenty national and international basic research projects as well as development and industrial projects for the pharmaceutical industry. She is currently investigating the formation of ligand-protein complexes from a structural and dynamic perspective in the context of rational design of new biologically active compounds.

Applications of Matteson Homologations in Natural Product Syntheses

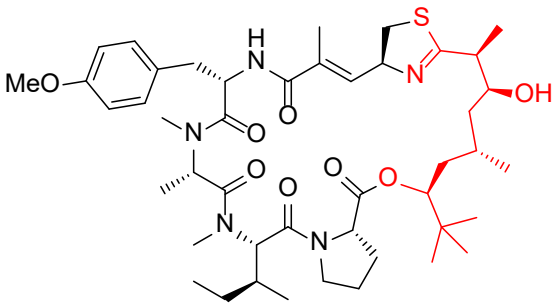
Uli Kazmaier,* Oliver Andler and Markus Tost
Organic Chemistry, Saarland University, Saarbrücken, Germany

Abstract
Cyanobacteria are outstanding producers of highly biological active natural products. Many of them belong to the large group of cyclodepsipeptides, containing a small peptide subunit and a polyketide fragment. Typical examples are doliculide and apratoxin, both showing anticancer activity in the low nanomolar range. Doliculide stabilizes the actin skeleton, altering e.g. anaphase chromosome movement, which finally leads to apoptosis. Apratoxin is acting as a broad-spectrum Sec61 inhibitor targeting HERErbB family proteins. Therefore, these compounds are good candidates for the development of anti cancer drugs.

Since a couple of years our group is involved in the synthesis of natural products, and recently, we have become interested in the synthesis of such peptide/polyketide hybrids, with a focus on aldol-free polyketide synthesis. We developed a protocol based on the Matteson homologation, which allows the incorporation of all substituents in a highly stereoselective fashion by a single reaction. Newest results will be presented on the conference.



Doliculide



Apratoxin A

Keywords
Anti cancer drugs; Matteson Homologation; Natural Products; Polyketides;

Biography
Uli Kazmaier, born in 1960, studied chemistry at the University of Stuttgart where he obtained his diploma (1985) and his PhD (1989). Afterwards he joined as a postdoc the research groups of M.T. Reetz (Marburg) and B.M. Trost (Stanford). In 1992, he moved to Heidelberg starting his own scientific work as a habilitand at the Institute of Organic Chemistry. After his habilitation in 1997 he was privatdozent at the same University, and from 1999-2001 a substitute of a chair in Karlsruhe. In 2000 he received a Novartis Chemistry Lectureship and an offer of a full professorship at the University Bayreuth. In 2001 he also obtained an offer of a full professorship at the University des Saarlandes, which he accepted in 2001. In 2006 he

received a call for a chair at University of Heidelberg, which he declined. His current research interest extends to new organometallic reagents and reactions especially for amino acid and peptide synthesis. Besides the development of new synthetic protocols, the application of these new reactions towards the synthesis of natural products and other pharmaceutical relevant structures plays a central role. He published more than 250 research papers.

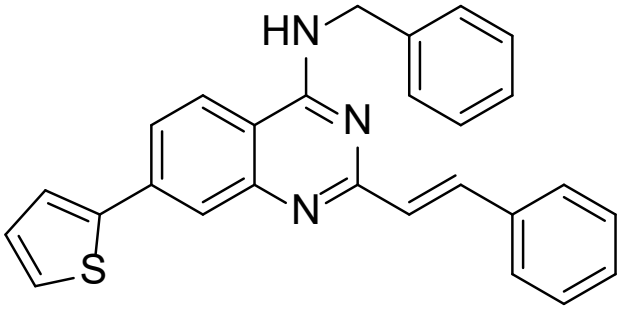
Selective COX-1 Inhibitors Based on Quinazoline Core

Dvorakova M.*, Langhansova L., Landa P.

Institute of experimental botany of the Czech Academy of Sciences, Rozvojova 263, Prague, Czech Republi

Abstract

Cyclooxygenase-1 (COX-1) has long been believed to be a constituonaly expressed COX isoform that protects gastric mucosa from demage. However, with the discovery of its upregulation in various cancers and its cardioprotective role in thrombocyte aggregation it got into a spotlight as a novel therapeutic target. Still, COX-1 selective inhibitors are poorly explored. Therefore, we have designed a series of potential COX-1 inhibitors with quinazoline core. Of the prepared compounds, several exhibited interesting COX-1 selectivity and submicromolar activity in vitro using ELISA kits. The IC50 value of the best inhibitor was 64 nM.



Keywords

Cyclooxygenase; Inhibition; Quinazoline; Selectivity.

Biography

Marcela Dvorakova, received both her MSc. as well as Ph.D. degrees in Organic Chemistry from Charles University in Prague, Czech Republic. In 2007, she was awarded with EST Marie Curie Fellowship for early-stage researchers at School of Chemistry and Chemical Engineering, Queen's University Belfast, United Kingdom, where she worked on the synthesis of sirtuin inhibitors. Currently, she is a senior researcher at the Institute of Experimental Botany of the Czech Academy of Sciences, where she focuses on the synthesis of natural product derivatives and inhibitors of inflammatory processes. She is the main investigator of several research projects, author or co-author of about 30 scientific papers and co-author of 5 patent applications.

Binding and Displacement of Ligands- Small Molecules at Chemerin Receptors

Tina Weiß[1,*], Jan Stichel[1], Annette G. Beck-Sickinger[1]
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Abstract
The chemerin family contains three different receptor subtypes: the chemokine-like receptor (CMKLR) 1, the G protein-coupled receptor 1 (GPR1) and the C-C chemokine receptor-like 2 (CCRL2). Thereby, the CMKLR1 represents the main receptor, which is increasingly expressed on adipocytes and macrophages. The CMKLR1 signals by an inhibitory Gαi protein and can recruit arrestin to the membrane for receptor internalization. The receptors are activated by chemerin, a 137-residue protein, which was characterized as an adipokine in 2007. Furthermore, chemerin-9, a nonapeptide derived from the C-terminal part of the full-length chemerin, displays high affinity. The concentration of chemerin in blood serum is strongly associated with symptoms of obesity and diabetes. Latest data show a correlation of increased inflammation, recruitment of immune cells and chemerin expression in inflamed adipose tissue. Negative small molecules or antagonists of CMKLR1 thus could reduce the inflammation in adipose tissue. Therefore, we performed a high-throughput screening. One promising compound was identified that resulted in a 4-fold higher EC50 value after the stimulation of chemerin-9 at CMKLR1. To study whether this small molecule is an antagonist that binds at the orthosteric binding site or whether the compound acts as a negative allosteric modulator that binds at an allosteric binding site we expressed both chemerin receptors with a Nluc-tag at the receptor N-terminus. By using this receptor construct in a NanoBRET-based approach, we can characterize the binding of peptides and proteins in the binding pocket and the displacement of different TAMRA-labeled ligands with an unlabeled ligand or with a compound. Our hit compound has displaced a TAMRA-labeled ligand at the chemerin receptor GPR1, which characterize it as an antagonistic small molecule.

Our results may lead to a better understanding of the interaction in the binding pockets of chemerin receptors. Accordingly, antagonists at CMKLR1 will maybe lead to a therapeutic approach for inflamed adipose tissue.

Keywords
Chemokine-Like Receptor 1 (CMKLR1);Nanobret; Chemerin; Small Molecule.

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Enhanced Oral Bioavailabilityof 2-(Phosphonomethyl)-Pentanedioic Acid (2-PMPA) Fromits (5-Methyl-2-Oxo-1,3-Dioxol-4-Yl)Methylbasedprodrugs

Tomáš Tichý[1*], Ranjeet P. Dash[2a], Vijayabhaskar Veeravalli[2a], Jenny Lam[2], Jesse Alt[2], Ying Wu[2], Lukáš Tenora[1], Pavel Majer[1], Barbara S. Slusher[2abcde], Rana Rais[2a]

[1]Institute of Organic Chemistry and Biochemistry v.v.i , Czech Academy of Sciences, Prague 166 10, Czech Republic
[2]Johns Hopkins Drug Discovery and Departments of aNeurology, bPsychiatry and Behavioral Sciences, cNeuroscience, dMedicine,eOncology, and fNeurosurgery, Johns Hopkins School of Medicine, Baltimore, Maryland 21205, United States

Abstract
2-(Phosphonomethyl)-pentanedioic acid (2-PMPA) is a potent (IC50 = 300 pM) and selective inhibitor of glutamate carboxypeptidase II (GCPII) with efficacy in multiple neurological and psychiatric disease preclinical models and more recently in models of inflammatory bowel disease (IBD) and cancer. 2-PMPA, however, has not been clinically developed due to its poor oral bioavailability (<1%) imparted by its four acidic functionalities that are ionized at physiological pH. In an attempt to improve the oral bioavailability of 2-PMPA, we explored a prodrug approach using (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl, a cyclic carbonate FDA-approved promoiety, and systematically masked two, three, or all four of its acidic groups. The prodrugs were evaluated for in vitro stability and in vivo pharmacokinetics in mice and dog. All of them were found to be moderately stable at pH 7.4 in phosphate-buffered saline, but rapidly hydrolyzed in plasma and liver microsomes, across species. In vivo, in a single time-point screening study in mice, 10 mg/kg 2-PMPA equivalent doses of respective prodrug delivered significantly higher 2-PMPA plasma concentrations versus 2-PMPA. Given that prodrug consisting of four promoieties delivered the highest 2-PMPA levels, we next evaluated it in an extended time-course pharmacokinetic study in mice. The prodrug demonstrated an 80-fold enhancement in exposure versus oral 2-PMPA with a calculated absolute oral bioavailability of 50%. In mouse brain, the prodrug showed similar exposures to that achieved with the intravenous route. Further, in dogs, relative to orally administered 2-PMPA, the prodrug delivered a 44-fold enhanced 2-PMPA plasma exposure These results suggest that introduction of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl promoieties can serve as a promising strategy for enhancing the oral bioavailability of multiply charged compounds, such as 2-PMPA, and enable its clinical translation.

Keywords
Prodrug; 2-PMPA; Bioavailability; Promoiety.

Biography

Tomáš Tichý is a scientific assistant in a research group of Pavel Majer at the Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences, Prague. He received his doctorate in Organic chemistry from Charles University, Prague. His current research includes medicinal chemistry and synthesis of prodrugs.

Stabilization of Adrenomedullin for Therapeutic Application

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Abstract

Peptide hormones are becoming more and more important for therapeutic application. In contrast to many small molecules, peptides can combine high receptor activity with good target selectivity. Furthermore, the modular structure of peptides allows easy chemical modification. Typically peptides are less prone to induce allergic reactions than antibodies. Adrenomedullin (ADM) is a peptide hormone, that gained high interest.1 It is part of the calcitonin-gene related peptide family and promotes vasodilatory, anti-inflammatory and cardioprotective effects by activation of adrenomedullin receptor 1. However, the natural peptide displays a low in vivo stability, and consequently minor clinical effects.

By using solid phase peptide synthesis, different modifications were introduced in ADM, such as lipidation, lactamization, and amino acid replacement by linker structures. Variation of these motives was studied for receptor activation and selectivity by cell-based reporter gene assay. Additionally, peptide stability was analyzed in human plasma and porcine liver homogenates. Favorable modifications were combined to access multiply modified adrenomedullin analogs with nanomolar receptor activation, high selectivity within the receptor family and strongly increased stability. These optimized compounds have a high potential for future therapeutic application.

[1] Schönauer et al. 2017. J Pept Sci. 23:472.

Keywords

Adrenomedullin; Peptide Therapeutics; Stabilization; Receptor Selectivity

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Hybrid Five and Six Member Ring Azaheterocycles Derivatives with Antimicrobial Activity

Violeta Mangalagiu[2*], Dumitrela Diaconu[2], Dorina Amariucai Mantu[1], Vasilichia Antoci[1], Ionel I. Mangalagiu[1,2]

Alexandru Ioan Cuza University of Iasi, Faculty of Chemistry1; Institute of Interdisciplinary Research- CERNESIM Centre2; 11 Carol 1st Bvd, Iasi -700506, Romania

Abstract

Five and six member ring azaheterocyclic derivatives has been reported as structural scaffolds of huge importance from pharmacological, industrial, and synthetic points of view. Among these, imidazole and quinoline compounds gained the status of a "privileged scaffolds" owing to its significant pharmaceutical profile including antimicrobial (including antituberculosis), antimalarial, antifungal, anti-HIV, anticancer, anti-inflammatory, antidepressant, analgesic, anti- Alzheimer's, antihypertensive, etc

As part of our ongoing research in the field of biologically active heterocyclic derivatives, we present herein the obtained results by our us in the field of hybrid quinoline/imidazole derivatives with antimicrobial activity. The methods of synthesis involve the direct acylation of quinoline derivatives, followed by acylation of imidazole compounds and, finally, a Huisgen 3+2 cycloadditions with variously dipolarophiles with double and triple bonds (activated alkene and alkynes). The setup procedures were performed using both conventional methods (thermal heating) and environmentally friendly methods (using microwave and ultrasounds technology). The antibacterial, antifungal and antituberculosis activity of compounds was determined, some of the compounds having an excellent biological activity. For the most active compounds, a complete ADMET studies have been performed with very good results. The molecular docking experiments suggest important clues concerning the mechanism of actions of our nitrogen heterocyclic systems. Some of the obtained compounds are promising leading drug candidates.

Keywords

Azaheterocycles; Hybrid; Antimicrobials

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N-Substituted Prodrugs of Mebendazole Provide Improved Aqueous Solubility and Oral Bioavailability in Mice and Dogs

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Abstract
Mebendazole (MBZ) was developed as a broad-spectrum anthelmintic but has recently shown efficacy as an anticancer agent. The use of MBZ for cancer, however, is challenging due to its poor solubility leading to poor bioavailability. Herein, we developed a prodrug approach with various N-linked promoieties including acyloxymethyl, aminoacyloxymethyl, and substituted phosphonooxymethyl in attempt to improve these characteristics. The best MBZ derivative containing an (((((isopropoxycarbonyl)oxy)methoxy)phosphoryl)oxy)methyl promoiety, -CH2OP(O)(OH)OCH2OCOOiPr, showed a >10 000-fold improvement in aqueous solubility. When evaluated in mice, this prodrug displayed a 2.2-fold higher plasma AUC0–t and a 1.7-fold improvement in brain AUC0–t with a calculated oral bioavailability of 52%, as compared to 24% for MBZ-polymorph C (MBZ-C), the most bioavailable polymorph. In dogs, the compound showed 3.8-fold higher plasma AUC0–t with oral bioavailability of 41% compared to 11% for MBZ-C. In summary, we have identified a prodrug of MBZ with better physicochemical properties and enhanced bioavailability in both mice and dog.

Keywords
Prodrug; Mebendazole; Bioavailability; Promoiety.

Biography
Tomáš Tichý is a scientific assistant in a research group of Pavel Majer at the Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences, Prague.He received his doctorate in Organic chemistry from Charles University, Prague. His current research includes medicinal chemistryand synthesis of prodrugs.

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