EuroSciCon

DAY 1

Keynote Forum

Annual Congress on

Medicinal Chemistry, Pharmacology & toxicology

July 30-31, 2018 Amsterdam, Netherlands

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CYCLIC SYNTHETIC PEROXIDES AS A BASE FOR ANTIPARASITIC AND ANTICANCER DRUGS

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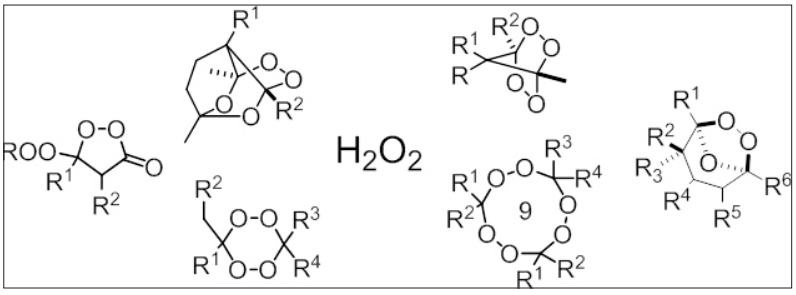
In the last decades, organic peroxides have received considerable attention from chemists and drug design experts, which is associated with a need in the search for drugs for the treatment of parasitic diseases, such as malaria and helminth infections. Peroxides having antitumor or growth-regulatory activity were also documented. Traditionally organic peroxides are applied in industry as initiators of free radical polymerization and oxidants. In our work, we developed new and green methods for synthesis of various types of peroxides using hydrogen peroxide and carbonyl compounds.

Image



Some of prepared cyclic peroxides demonstrate good anticancer and antiparasitic activities

Biography

Alexander O Terent'ev has completed his MS in Chemistry of Biologically Active Compounds from D Mendeleev University of Chemical Technology of Russia, Moscow, PhD degree in 2000 and DSc degree in Organic Chemistry in N D Zelinsky Institute of Organic Chemistry RAS 2009. He worked as Professor in D Mendeleev University of Chemical Technology of Russia 2011. From 2016, he is working as Professor and Head of laboratory in N D Zelinsky Institute of Organic Chemistry RAS, Head of laboratory in All-Russian Research Institute of Phytopathology. His interests are Organic Chemistry, Medical and Agricultural Chemistry, Chemical Technology. He has published three chapters in books, 100 research papers, and 25 patents.

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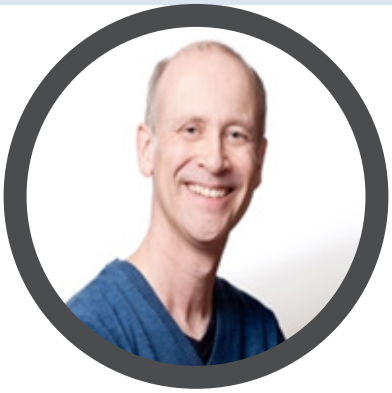
DEVELOPMENT AND APPLICATION OF PHYSIOLOGICALLY RELEVANT IN VITRO MODELS OF HUMAN STEROIDOGENESIS IN TOXICOLOGY: THE ENDOCRINE DISRUPTING POTENTIAL OF NEONICOTINOID PESTICIDES IN HUMANS



J Thomas Sanderson, Elyse Caron-Beaudoin, Rachel Viau

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Humans are exposed to thousands of environmental chemicals with poorly understood toxicological properties. In vivo toxicity testing is time-consuming, costly and ethically questionable because of the large numbers of laboratory animal required. Although current in vitro models have considerably improved our understanding of chemical mechanisms of toxicity, these systems mostly determine single endpoints in single cell types, which poorly reflect the intact organism. The goal of my laboratory is to better reproduce in vivo interactions by developing co-culture models that incorporate physiologically relevant intercellular communications. Our focus is on steroidogenesis, an important but poorly studied target for endocrine disrupting chemicals. In humans, sex steroid hormones are essential for healthy reproduction and pregnancy, but are also involved in diseases such as hormone-dependent breast cancer. Aromatase (*CYP19*) converts androgens to estrogens and, unlike in non-primates (e.g. rodents), where it is expressed only in gonads and brain, human aromatase is expressed in numerous tissues including mammary gland (where it is overexpressed in hormone-dependent breast cancer) and placenta using tissue-specific promoters. As rodent models are inadequate, we developed several physiologically relevant human in vitro models to evaluate the effects of neonicotinoid insecticides, a poorly studied class of emerging pesticides, on sex hormone biosynthesis. Cellular co-culture models of the feto-placental unit and human breast tumor microenvironment were used to determine effects of neonicotinoids on steroid production and promoter-specific regulation of *CYP19*. Neonicotinoids increased *CYP19* gene expression promoter-specifically in our human co-culture models. In the feto-placental co-culture model, neonicotinoids increased estradiol and estrone, but strongly inhibited estriol production. In our breast cancer model, neonicotinoids induced a promoter-switch in *CYP19* expression, with silencing of normal mammary promoter 1.4 and activation of pro-cancerous promoters PII, 1.3 and 1.7, resulting in aromatase overexpression, similar to that observed clinically in patients. These are the first studies to document in vitro, disruptive effects of neonicotinoids on human steroidogenesis in physiologically relevant multi-cell systems.

Biography

Thomas Sanderson has obtained his PhD from the University of British Columbia, Vancouver, Canada and did Postdoctoral studies at Michigan State University, USA. He is an Associate Professor at the INRS-Institut Armand-Frappier, Laval (Québec), Canada and has published more than 70 papers in reputed journals. His toxicology laboratory is focused on studying interactions of chemicals with steroidogenic enzymes in humans and wildlife and is currently funded by the Natural Sciences and Engineering Council (NSERC) of Canada and the Alternatives Research and Development Foundation (USA). He is Editorial Board Member of *Toxicological Sciences and Peer J.*

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Konstantin Volcho, J Org Inorg Chem 2018, Volume 4
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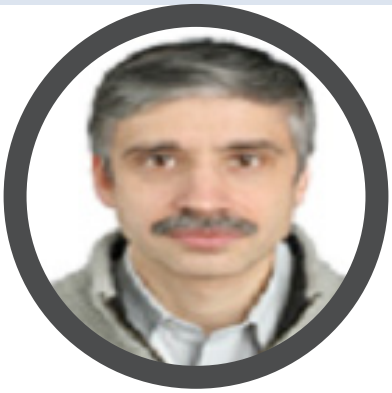
DNA REPAIR ENZYMES INHIBITION AS A PROMISING APPROACH TO NEW ANTI-CANCER DRUGS



Konstantin Volcho
Novosibirsk Institute of Organic Chemistry, Novosibirsk, Russia

The cytotoxic effects of chemotherapy and radiation that are clinically used to treat malignances are directly related to their propensity to generate DNA damage. The capacity of cancer cells to recognize DNA damage and initiate DNA repair is a key mechanism for therapeutic resistance to chemotherapy. Therefore, the targeting of DNA repair enzymes can be used as a strategy to potentiate the cytotoxicity of the currently available DNA damaging agents toward cancer cells. PARP1 (poly ADP ribose polymerase 1, the enzyme involved in DNA repair) inhibitors such as Olaparib, Rucaparib and Niraparib are in clinical use already. New and very promising target for antitumor therapy is tyrosyl-DNA phosphodiesterase 1 (Tdp1). It plays a key role in the removal of DNA damage resulting from inhibition of topoisomerase 1 (Topo1) with camptothecin and its clinical derivatives irinotecan and topotecan. Furthermore, Tdp1 is known to be capable of removing the DNA damage induced by other anticancer drugs commonly used in clinical practice. To date, a number of Tdp1 inhibitors of various types including dual Tdp1/Topo1 inhibitors are known. A set of very potent Tdp1 inhibitors was found by us among natural products derivatives. We designed new inhibitors using targeted modifications of terpenoids, coumarins, usnic acid and other types of natural products. Moreover, we found that benzopentathiepine derivatives are very effective inhibitors of Tdp1. Important that the ability of the inhibitors used in non-toxic concentration to enhance the cytotoxicity of camptothecin and topotecan, the established topoisomerase 1 poison, was demonstrated. Thus, we discovered of new original Tdp1 inhibitors, effectively inhibiting DNA repair in tumour cells for use as the components of complex anticancer drugs.

Biography

Konstantin Volcho received his PhD in 1997 from Novosibirsk State University, Russia. Since that he has been working at Novosibirsk Institute of Organic Chemistry (Russia) in the Department of Medicinal Chemistry. He is a Professor of Russian Academy of Science. His research interests include Development of Novel Treatments against Nervous System Disorders, Antivirals and Anticancer Agents, Usually Based on Natural Products Derivatization. He has published about 150 papers in reputed journals. He is an Inventor in more than 35 issued patents. Three compounds found with his participation are currently in preclinical studies as anti-Parkinsonian, analgesic and antidepressant agents.

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Yue-Wei Guo, J Org Inorg Chem 2018, Volume 4
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CHEMOECOLOGY GUIDED DISCOVERY OF DRUG LEADS FROM SOUTH CHINA SEA MARINE INVERTEBRATES

Yue-Wei Guo
Shanghai Institute of Materia Medica, Chinese Academ of Sciences, Shanghai, China

Natural products have played a significant role in the drug discovery process throughout the last hundreds years. What is the best strategy to investigate the biological potentialities of secondary metabolites? It is generally accepted that there are two ways to explore the pharmaceutical potentialities of natural products. The first way is so called bioassay guided isolation of bioactive natural products; the second one is so called random screening methodology. In fact, every procedure could be only partially satisfactory. Apart the above mentioned two solutions, an alternative way could be a good choice through studying the compounds that really play a biological role in the organism where they are present. This could be the starting point to discover other biological potentialities. Of course, to perform studies like these one needs a careful selection of promising biological systems and, also, the close collaboration among chemists, biologists and pharmacologists. Trying to follow this bio-chemical approach some years ago we started to investigate marine nudibranchs that are extremely interesting from an ecological point of view. In fact, these molluscs are completely devoid of the mechanical protection of the shell. But, in spite of this apparent vulnerability, they are rarely victims of predators. This is due to a series of defensive strategies that include the use of chemicals that either derive from their food habits or are biosynthesized de *novo* by themselves. In this lecture we will report the recent chemical studies on opisthobranch molluscs collected from South China Sea. All work has been performed in close collaboration with marine biologists who have correctly submitted the biological problems to the chemical analysis, and with pharmacologists who have carried out bioassay based on the clue provided through chemoecology studies.

Biography

He received his Ph.D. degree in Natural Product Chemistry in 1997 from Institute of Chemistry of Bio-molecule-CNR & Naples University of Italy. From 1997 to 1999, He spent two postdoctoral years at the Institute of Chemistry of Bio-molecule-CNR in Naples, with Prof. Guido Cimino, working in the field of Marine Natural Products. From 1999 to 2000 he was a TBRS postdoctoral fellow in Hokkaido University, Japan, working with Prof. Jun'ichi Kobayashi. In year 2000, he moved, as a Professor of Chemistry, to the Shanghai Institute of Material Medica, Chinese Academy of Sciences. In these years his main research interests have been in the field of the chemistry of natural products from marine organisms, such as algae, mangrove, porifera, gorgonians, molluscs, in particular focused to the isolation, purification, and structural elucidation of chemical mediators and to biological studies. The more recent interests are directed to the chemical ecology of unprotected marine molluscs from South China Sea and Chinese mangrove plants.

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RESPONSES TO WELL-KNOWN GENOTOXIC AGENTS IN GERM STEM CELLS *IN VITRO*

D.Anderson, K. Habas, M. Najafzadeh, A. Baumgartner and M.H.Brinkworth

School of Medical Sciences, University of Bradford, Bradford, U.K

Germline stem cells are extremely sensitive to genotoxic chemotherapeutic agents which induce DNA damage, and even low doses to the testis may pose reproductive risks with potential treatment-related infertility. Strand breaks represent a great threat to the genomic integrity of spermatogonial stem cells, which are essential to maintain spermatogenesis and prevent reproduction failure. The single-cell gel electrophoresis (Comet) assay has been used to measure DNA damage in male germ cells. We investigated the effects in vitro, of six well-known genotoxins on rat germ stem cells separated using STA-PUT unit-gravity velocity sedimentation. N-ethyl-N-nitrosourea (ENU), N-methyl-N-nitrosourea (MNU), 6-mercaptopurine and 5-bromodeoxyuridine, methyl methanesulfonate (MMS) and ethyl methanesulfonate (EMS) are potent male rodent germ cell mutagens. All compounds were significantly genotoxic in cultured germ cells. Treatment of the isolated germ cells with ENU and MNU produced a concentration-related increase in DNA damage in spermatogonia; spermatocytes were most sensitive to 6-MP and 5-brdU with MMS and EMS most damaging in spermatids. Immunocytochemistry and western blot analysis revealed that the purities of the isolated germ cells were 90% with viability over 95%. These results indicate that STA-PUT isolated rat testicular germ cells are a suitable model to study the genotoxicity of individual chemicals in germ stem cells and could be used as a surrogate system for humans. Only sperm can be examined in this way in humans.

Biography

Professor Anderson completed her PhD at the University of Manchester, UK in the Faculty of Medicine. She is the Established Chair in Biomedical Sciences at the University of Bradford. She has published more than 450 papers, 9 books, successfully supervised 32 PhD students, has a Hirsch index of 59. She is Editor –in- Chief of a Book Series for the Royal Society of Chemistry and is a Consultant to many International Organisations, such as the World Health Organisation/ International Programme of Chemical Safety.

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DAY 2

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Young-Jin Kim et al., J Org Inorg Chem 2018, Volume 4
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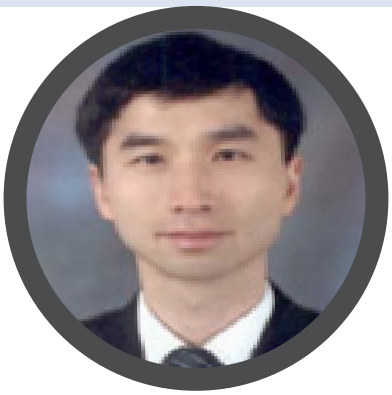
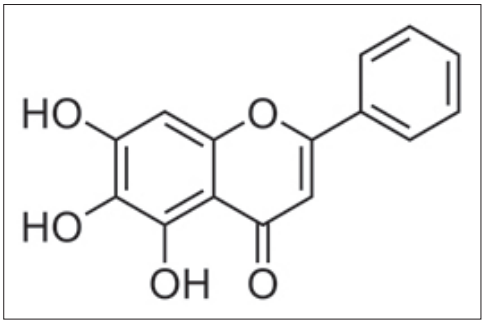
ANTI-INFLAMMATORY EFFECTS OF BAICALEIN ON RAW 264.7 MOUSE MACROPHAGES INDUCED WITH POLYINOSINIC-POLYCYTIDYLIC ACID



Young-Jin Kim, Hyun-Ju Kim, Ji Young Lee, Do-Hoon Kim and Mi Suk Kang

College of Korean Medicine, Gachon University, Republic of Korea

Baicalein (5, 6, 7-trihydroxyflavone) is a flavone, originally isolated from the roots of *Scutellaria baicalensis* and *Scutellaria lateriflora*. It is also reported in *Oroxylum indicum* or Indian trumpet flower. It is the aglycone of baicalin. The roots of *Scutellaria baicalensis* have been used to treat pulmonary infection traditionally in Asia. The water extract of Scutellaria radix is known to have anti-inflammatory effects. However, the effect of baicalein on virus-induced macrophages has not been fully elucidated. In the present study, the anti-inflammatory effects of baicalein on double-stranded RNA (dsRNA)-induced macrophages were examined. Polyinosinic-polycytidylic acid (poly I: C), a synthetic analog of dsRNA, was used to induce RAW 264.7 cells in this study. Baicalein significantly inhibited the production of interleukin (IL)-1α, IL-6, IL-10, interferon gamma-induced protein 10, granulocyte macrophage-colony stimulating factor, leukemia inhibitory factor (IL-6 class cytokine), lipopolysaccharide-induced CXC chemokine (LIX), monocyte chemoattractant protein-1, macrophage inflammatory protein-1α, and vascular endothelial growth factor as well as calcium release and the mRNA expression of signal transducer and activator of transcription 1 (STAT1), STAT3, CHOP (GADD153), and FAS (CD95) in poly I:C-induced RAW 264.7 cells ($P<0.05$). Thus, the present results suggest that baicalein has anti-inflammatory properties, associated with its inhibition of cytokines, chemokines and growth factors in poly I: C-induced macrophages via the calcium-CHOP/STAT pathway.



Structural formula of flavonoid baicalein

Biography

Wansu Park has completed his PhD from Kyung Hee University and Postdoctoral studies from Kyung Hee University College of Korean Medicine. He is the Chief Professor of Pathology in College Of Korean Medicine, Gachon University. He has published more than 25 papers in reputed journals. He has served as the Chief Vice President of The Association of Korean Medicine in Republic of Korea from 2013 to 2017.

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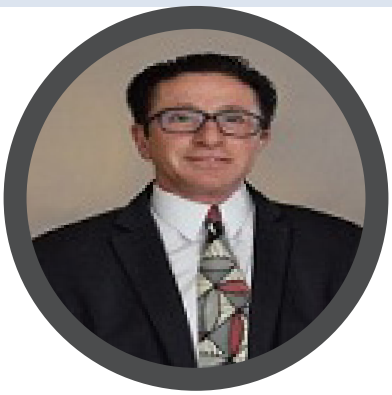
UTILIZING THE SPINNING TUBE IN A TUBE (STT®) REACTOR IN FLOW CHEMISTRY

Rocky Costello[1], Michael Gonzalez[2] and David E Meyer[2]

[1]R C Costello & Assoc., Inc, Redondo Beach, California, USA
[2]NRMRL, US EPA Office of Research and Development, MS Cincinnati, Ohio, USA



A review of the design process used to incorporate a patented spinning tube in a tube (STT®) reactor into a continuous pharmaceutical process for the manufacture of multi-component, single-pass, 2-aminothiophene derivatives is presented. Also the role and utilization of ChemCad® process simulation software and its integration with Comsol® computational fluid dynamics (CFD) modelling will be discussed. These results will demonstrate the advantages of using the STT® reactor in a continuous flow application in pharma applications. In addition to the benefits gained in discovering new approaches to chemical reaction synthesis, this continuous flow reactor can accelerate reaction rates by up to 5,000 times in some cases and can handle slurries, gas-liquid reactions, and liquid-liquid reactions. Applications to optimizing continuous pharmaceutical applications in the real world will also be discussed.

Biography

Rocky C. Costello, P.E. is the president of R.C. Costello & Assoc., Inc. an engineering firm specializing in chemical process engineering. They provide engineering design services to the specialty chemical, chemical and pharmaceutical industries. He obtained his Bachelor's degree from Youngstown State University in 1974 and did further graduate work in Chemical Engineering at Manhattan College in the Bronx. He worked in private industry prior to starting the engineering firm. At Owens-Corning he worked in polymers and plastics, at Rhodia (Now Solvay) he worked in specialty chemicals and pharmaceutical intermediates. At Southdown environmental he was in charge of the Mexican and Californian operations for the recycling of waste solvents into pure solvents for reuse by fractional distillation and thinfilm evaporation. He holds numerous patents and has been published in a number of chemical engineering publications. He is a licensed professional Chemical Engineer in a number of states. His major interests include the design of continuous pharmaceutical plants (Flow Chemistry) utilizing unique unit operations such as the Spinning Tube in a Tube (STT) reactor and the Fluxxion separator. A second interest is the computer modeling and simulation of Flow Chemistry processes utilizing ChemCad simulation software.

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