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N Nadaraia et al., Med Chem (Los Angeles) 2017, 7:4 (Suppl)
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5α-steroidal amines: Synthesis and biological activity

N Nadaraia, M Merlani, N Barbakadze, N Amiranashvili and **M Kakhabrishvili**
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Steroidal amines are characterized with wide spectrum of pharmacological activities such as antitumor, anti-inflammatory, antibacterial and anti-arrhythmic activity. On the basis of epiandrosterone acetate, product of transformation of tigogenin (isolated from plant *Yucca gloriosa*), eight possible epimer of 3-amino-17-hydoxy- and 17-amino-3-hydroxy-5α-androstane have been synthesized and their radioprotective and antiarrhythmic activities have been investigated. Among epimeric aminoalcohols the highest radioprotective activity showed 3β-amino-5α-androstan-3β-ole, while with the highest antiarrhythmic activity is characterized 17β-amino-5α-androstan-3β-ole. Based on these results some conclusion about structure- activity relationship of synthesized compounds could be made. For radioprotective activity more profitable is diaxial orientation of amino- and hydroxy groups; whereas, diequatorial orientation is favorable for the antiarrhythmic activity. Some synthesized of N-alkyl- and N-dialkylamino acetyl derivatives of 17β-amino-5α-androstan-3β-ole and 17β-amino-5α-androst-2-ene exhibit antiviral, antitubercular and antitumor activities.

Biography

N Nadaraia has completed her PhD from Mendeleev Moscow Chemical-Technological Institute. She is a lead research scientist at Tbilisi State Medical University. Her field of interest is a Chemistry and synthesis of biologically active compounds. She is the author of more than 40 papers in reputed journals and has presented at 50 international scientific conferences.

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Jane Otado, Med Chem (Los Angeles) 2017, 7:4 (Suppl)
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Successful strategies for recruitment of african americans into clinical studies

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Objectives: Barriers to participation of African Americans (AA) in clinical trials include lack of awareness about trials, economic factors, mistrust and communication issues. Objectives are: to examine recruitment challenges and experiences; and to determine best practices for researchers to engage AA communities in clinical studies.

Methods & Study Population: We reviewed 50 studies conducted at a historically black institution to determine the type, duration and enrollments. A survey was sent to study coordinators to obtain data on recruitment and retention strategies, challenges and dropout rates. We also interviewed 25 study coordinators on challenges and recruitment strategies.

Results: Studies range from cross-sectional to prospective. The prospective studies have follow-up periods from 3 to over 24 months. The 22 completed studies achieved recruitment rates of over 50%; 12 had over 100% recruitment rates. For 8 studies with dropouts, the average rate was 23.3%. Barriers: lack of trust, life circumstances, low education, lack of interest; the inability to have study partner. Recruitment strategies include field-based, special advertisements and snowballing. Strategies to barriers are informational sessions, rapport, phone calls and caring attitudes.

Discussion: AA seems to be more trusting to participate in a study if their PCP is involved and through community outreach strategies. This is especially true in studies involving medication usage. Minimum risk studies were very successful in recruiting AA<30 years old. Ongoing rapport, caring attitude improves retention rates. Successful recruitment strategies of AA is paramount to better understand how researchers can improve current strategies, thus to increase minority participation in clinical trials.

Biography

Jane Otado has a doctorate degree from Howard University and post-doctoral studies from the Center of Disease Control and Prevention (CDC). She is an associate director of Regulatory, Ethics, Knowledge and Support (REKS), Georgetown-Howard Universities Center for Clinical and Translational Science (GHUCCTS), a NIH, Clinical and Translational Science Awards (CTSAs). Her research areas include: Understanding informed consent, recruitment/retention, perspectives on genetic testing and research relative African American population and ethnic diverse populations. She is a Member of IRB; and Scientific Review Committee (GHUCCTS). She has extensive experience involving community-based outreach and has worked in clinical trials setting for 13 years.

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Notes:

Szu-Han Chen, Med Chem (Los Angeles) 2017, 7:4 (Suppl)
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Synthesis of oseltamivir using Diels–Alder reaction of 1, 3-butadiene bearing 2-carboxy and 4-alkoxy substituents

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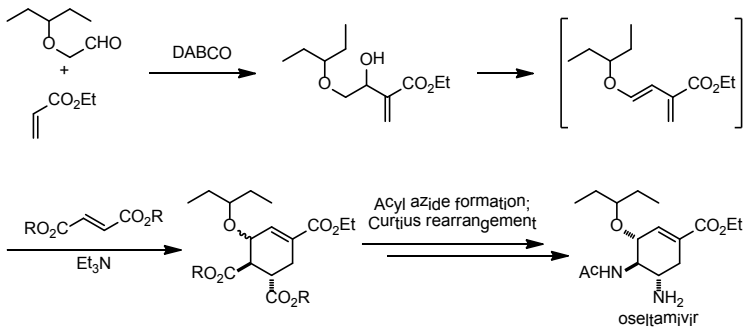
Diels–Alder reactions are particularly useful for the total synthesis of pharmacologically active compounds and natural products. Not only does this strategy construct two new C–C σ-bonds in one step, but it also forms a cyclohexene system with good regio- and stereo-selectivity up to four contiguous stereocenters. Using heteroatom-substituted electron-rich dienes, such as Danishefsky's diene, usually promotes the normal electron-demand Diels–Alder reactions in highly regioselective fashion. Tamiflu, the phosphate salt of oseltamivir, is a popular anti-influenza drug in clinical use. Diels–Alder reactions using 1,3-butadiene, 1-timethylsilyoxy-1,3-butadiene, furan, N-Boc-pyrrole and 1-Cbz-1,2-dihydropyridine have been successfully applied to react with appropriate dienophiles for construction of the cyclohexene core structure of oseltamivir. We synthesized a novel diene precursor bearing both 3-pentoxy and ester groups. Dimerization of this diene was overcome by trapping it *in situ* using activated alkenes as the dienophiles. Inspired by Shibasaki's work, we successfully synthesized a racemic mixture of oseltamivir via a sequence of reactions that comprise acyl azide formation and Curtius rearrangement. The synthesis of optically active oseltamivir via asymmetric Diels–Alder reaction is currently under investigation.



Biography

Szu-Han Chen received her BS in Chemistry from Fu Jen Catholic University in 2008 and her MS degree in Chemistry from National Taiwan Normal University in 2010. She is a PhD student in the Department of Chemistry, National Taiwan University. Her research interests are in total synthesis of drug molecules as well as medicinal and biological chemistry.

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Wei-Hsin Hsu, Med Chem (Los Angeles) 2017, 7:4 (Suppl)
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Design and synthesis of sugar phosphates for inhibition of tuberculosis maltosyl transferase

Wei-Hsin Hsu
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Tuberculosis, a disease caused by bacterial pathogens *Mycobacterium tuberculosis*, was regarded as under control in the past decades. However, the multi-drug-resistant tuberculosis (MDR-TB) and extensively-drug-resistant tuberculosis (XDR-TB) have emerged to become a serious global health crisis. In 2015, there were an estimated 10.4 million new TB cases worldwide, including nearly a half million cases of MDR-TB. 1 Bedaquiline and Delamanid are the effective drugs for treatment of MDR-TB. However, development of new drugs by targeting different TB proteins is still needed for treatment of the MDR-TB and XDR-TB patients. GlgE is a maltosyl transferase that uses maltose-1-phosphate as the substrate. GlgE involves in a four-step pathway for the production of α-glucan from trehalose, an essential process for mycobacterial survival. Inhibition of GlgE will cause accumulation of maltose 1-phosphate, and trigger the self-poisoning of *M. tuberculosis*. GlgE becomes an appealing drug target according to the toxic effect and synthetic lethal pathway. As no effective GlgE inhibitor has been discovered, we thus designed and synthesized some potential GlgE inhibitors by mimicking the structure maltose1-phosphate, the GlgE substrate.

Biography

Wei-Hsin Hsu received her BS from the department of applied chemistry, National Chiao Tung University in Taiwan. Currently, she is a MS student in the department of chemistry, National Taiwan University.

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Yun Lu, Med Chem (Los Angeles) 2017, 7:4 (Suppl)
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Mapping the vibrational transition-state conformational change in enzymes for drug design

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About a quarter of the current registered pharmaceutical drugs are enzyme inhibitors. Many of them are the enzyme transition-state (TS) analogues that are designed largely on the basis of the crystal structure of the stable "frozen" TS analogues or the "still" TS structures from the kinetic studies. Recent decade has, however, witnessed much of the role of the enzyme dynamics in catalysis. Protein vibrations with different time scales have been proposed to assist various processes of the complex enzymatic reactions, including the bond-formation and - cleavage in the active site. The latter suggests a vibrational TS structure on the reaction coordinate, coupled with the local fast motions of enzyme. While study of the vibrational TS that involves the fast fluctuations of the reaction distance is still in its infancy, it would be worthy to consider the concept in design of what may come to be more effective inhibitors and more successful drugs. E.g., a successful inhibitor may be that can also interrupt the TS/enzyme coupled vibrations. In this paper, we present a method to gain the different TS structures at different donor-acceptor distance (DAD) in both solution and enzymatic H-transfer reactions. We use secondary (2°) kinetic isotope effect (KIE) as a structural descriptor. We determine the 2° KIEs and thus TS structures for hydride- and deuteride-tunneling processes that have different DADs. Information about the DAD-dependent TS structures in enzymes would help track the path of the vibrational TS conformational changes. This information would be useful for drug design.

Biography

Yun Lu received his PhD degree in Organic Chemistry from Nankai University, China in 1996. He did his post-doctoral work in Utah State University with professor Vernon D Parker and Wayne State University with professor Martin Newcomb. His research focuses in the field of physical organic chemistry studying the mechanism of organic reactions and the transition state structures. He is now a professor in the department of chemistry at Southern Illinois University Edwardsville, USA. He has published nearly 50 papers in reputed journals.

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Morphological and structural features of adenovirus particles by reacting with bacterial cell

Anna Golovan, S I Voychuk, I L Garmasheva, O Yu Povnitsa, L B Bilyavska, O N Vasilyuk, K S Naumenko and **Yu B Pankivska**
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Antiviral drugs mainly targeted onto prevention of viral synthesis within the host cells or elimination of it enters into the cell through induction of natural defense mechanisms, among which are immune response and interferon synthesis. Recently, it was suggested that human microbiota may play a role in virus infection. Human viruses did not infect bacteria cells, but this does not exclude a possibility of bacteria participation in the virus propagation into the host cells. An interaction of lactic acid bacteria with human adenovirus serotype 5 (HAdV-C5) was studied. We used strains of bacteria some of which are normally can be found in human intestine, while others are supplied with various milk products: *Lactobacillus plantarum* (56 strains), *Enterococcus* spp. (23 strains), *Leuconostoc* spp. (14 strains), *Lactococcus lactis* (3 strains) and *Pediococcus* spp. (1 strain). After 1 h of interaction of viruses (VPs) with bacteria the samples were examined with electron microscopy. In 17% of cases there were no VPs found that can suggest their total destruction, but in other cases the VPs were clearly seen performing well preserved viruses and viral proteins. The direct viral adhesion to the surface of bacteria was noticed for 23% of the strains, while in other cases the VPs were associated with extracellular matrix structures or as the free particles. The current research is one of the first steps in understanding the role of microbiota in the virus infections development. It showed that various strains of the same bacterial species can cause opposite effects and lead both to the virus degradation or preservation and, therefore, can prevent or help virus to enter the human cells.

Biography

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Daniel Ehrsam et al., Med Chem (Los Angeles) 2017, 7:4 (Suppl)
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Early findings in the development of an enzymatically triggered nanoformulation

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In order to spare healthy cells and decrease adverse effects, innovative concepts of tumor targeting aim at bringing the cytotoxic payload most selectively to tumor cells is needed. One concept is to use enzymes overexpressed in the surrounding of proliferating cells, like the gelatinase matrix-metalloproteinase 9 (MMP-9), as a trigger for drug release. Our aim is to synthesize and characterize self-assembling nano-formulations consisting of an MMP9-labile peptide coupled to an anti-cancer drug. By use of bio-conjugate chemistry an amphiphilic molecule containing paclitaxel and an MMP9-labile peptide was synthesized to form nanoparticles. To identify a tumor entity as a target for our novel nano-formulation we quantified expression of MMP-9 in a commercially available tissue collection by multiplex real-time PCR. Several tumor entities showed significantly increased expression comparing normal to malignant tissue. Immunohistochemistry and database analysis suggested brain tumors, particularly glioblastoma multiforme, as a tumor entity where MMP-9 could be used to trigger drug release. Established brain cancer cell lines were characterized for MMP-9 expression and activity. LN-18 and U87-MG cells were selected for *in vitro* characterization of the synthesized nano-formulation. In preparation of *in vivo* xenograft studies LN-18 and U87-MG cells were stably transfected with mKate2 and characterized for expression. Taken together, we verified overexpression of MMP9 in glioblastoma multiforme. Commonly used brain cancer cell lines were characterized prior to *in vitro* studies on MMP9 triggered drug release, and preparations for *in vivo* xenograft studies have been finished. Further studies are needed to fully characterize the nano-formulation and understand its effects *in vivo*.

Biography

Daniel Ehrsam has done his graduation in Pharmaceutical Sciences from the University of Basel in 2014. He did his master's research work on brain ischemia pathways under supervision of Dr. Margaret Weiss at Texas Tech Health Science Center. He has worked at the Swiss Tropical and Public Health Institute on helminth drug development. In 2015, he joined the research group of professor Dr. Henriette E Meyer zu Schwabedissen for his PhD studies. His research is focused on the development of an enzyme based targeted drug delivery system.

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Mohamed A El-Atawy et al., Med Chem (Los Angeles) 2017, 7:4 (Suppl)
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Pyrroles - A novel synthetic method for pyrrole derivatives from nitrodienes

Mohamed A El-Atawy, F Ferretti and **F Ragaini**
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Pyrrole nucleus is one of the most important heterocycles abundantly found in bioactive natural molecules, forming the characteristic subunit of heme, chlorophyll vitamin B12 as well as in melanin pigments. 1,2,5-Trisubstituted pyrroles display interesting biological properties, such as anti-inflammatory, antipsychotic, spasmolytic and radioprotective. Two clinical examples of pyrroles displaying this pattern of substitution are amtolmetin and tolmetin (non-steroidal anti-inflammatory agents). Generally, pharmaceuticals containing pyrroles are of high value as biological agents such as sunitinib (anti-tumor), ketorolac (analgesic) and the highly successful cholesterol-lowering drug atorvastatin calcium (Lipitor), which is notable as the first drug to earn in excess of $1 billion of sales in its first year. The electronic properties of pyrrole are important in the context of conducting polymers, where poly-pyrroles have found many useful applications. Herein, we report a new and facile method for the synthesis of 2,5-di and 2,3,5-trisubstituted pyrrole using intramolecular reductive cyclization of the easily accessible nitrodienes as starting material catalyzed by palladium complex and with carbon monoxide as a reductant.

Biography

Mohamed A El-Atawy has completed his PhD in organic chemistry, department of chemistry, University of Milan, Italy. Currently, he is working as an Assistant Professor in Alexandria University, Egypt.

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Q B C Francisco Humberto González Gutiérrez, Med Chem (Los Angeles) 2017, 7:4 (Suppl)
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Apoptotic mechanism of compounds with antiproliferative activity from *Bursera microphylla* resin

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Studies on resin of *Bursera microphylla* showed that it consist mainly of terpenes; these compounds have been proved to be active against cancer cell lines. Cancer is a public health problem worldwide. Compounds of *Bursera microphylla* showed antiproliferative activity in cancer cell lines. Therefore, knowledge of the action mechanism for future drugs against cancer is required. The aim of this study was to determine the molecular mechanisms of the compounds that displayed antiproliferative activity on human cancer cell line A549 derived from *B. microphylla* resin. The apoptotic activity was measured through annexin V staining and propidium iodide (PI). The breakdown of the mitochondrial membrane potential was measured using the cationic lipophilic fluorochrome JC-1. Determination of cell arrest will be quantified by measuring the amount of genetic material (DNA) using PI. To evaluate the apoptotic induced pathway, caspase activity will be measured using fluorescein staining of active caspase. An apoptotic activity of the dihydroclusin diacetate, betulonic acid, microphyllanin, malabaricatrienol, ariensin and β-caryophyllene molecules of 22.64%, 4.02%, 1.45%, 25.6%, 13.02% and 10.45%, respectively was obtained and a percentage loss of mitochondrial membrane potential of up to 97% and a caspase activity of up to 3.5 fold. Beta caryophyllene, ariensin and betulonic acid induce arrest in G2/M phase; dihydroclusine acetate in S phase and microphyllanin in G0/G1. The ability to induce the apoptosis of the compounds through the caspase pathway, cell cycle arrest and activated by the intrinsic pathway was demonstrated.

Biography

Q B C Francisco Humberto González Gutiérrez has completed his licentiate from Universidad de Sonora. He has done his Master's in faculty of biological sciences and health from Universidad de Sonora. He has two articles published as co-author, participated in multiple school events where he obtained recognition for obtaining first places and in addition to having the participation in a congress at state level.

Notes:

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New 1, 2, 5-oxadiazole Pt(II)complex endowed with STAT3 inhibitory properties as promising anticancer agent

Arianna Gelain[1], Stefania Villa[1], Fiorella Meneghetti[1], Federica Porta[1], Giorgio Facchetti[1], Nicola Ferri[2], Akira Asai[3], Valentina Gandin[2], Cristina Marzano[2] and **Isabella Rimoldi[1]**

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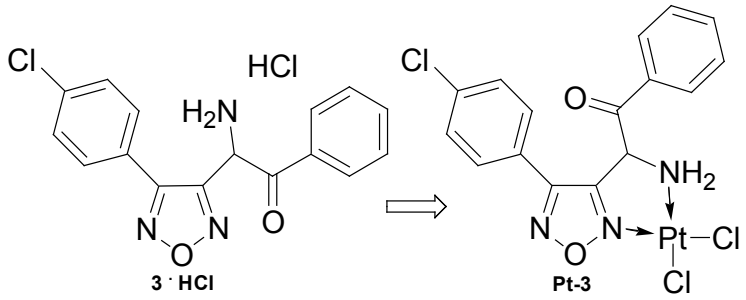
During our ongoing studies, focused on the identification of novel potential anticancer agents inhibiting STAT3 (Signal Transducer and Activator of Transcription 3)1, we synthesized some new 1,2,5-oxadiazole ligands for Pt (II) complexes formation2. In particular ligand 3·HCl exhibited cytotoxicity on HCT116 cells (IC50 = 95.2 μM) and a selective interaction with STAT3 (IC50 = 8.2 μM) respect to STAT1 (IC50> 30 μM). The related platinum complex Pt-3 showed an increased cytotoxic effect (IC50 = 18.4 μM) and a higher interaction with STAT3 (IC50 = 1.4 μM). Noteworthy Pt-3, tested on syngeneic murine Lewis lung carcinoma (LLC) implanted in C57BL/6 mice, exhibited an interesting antitumor activity with fewer side effects than cisplatin.



Biography

Arianna Gelain graduated in Medicinal Chemistry and Technology and achieved her PhD degree in Medicinal Chemistry at University of Milan. She is researcher at Departement of Pharmaceutical Science and assistant professor at faculty of pharmacy. She is co-author of 31 papers, 6 reviews, published in peer reviewed journals and 1 book chapter.

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Synthesis of novel furan-based antituberculars potentially targeting the methionine aminopeptidases (*Mt*MetAP1a)

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Methionine aminopeptidase (MetAP) carries out an essential function of protein N-terminal processing in many bacteria and is a promising target to develop novel antitubercular agents. MetAP is divided into two subtypes, namely type 1 and type 2. Eukaryotic cells have both subtypes, and prokaryotic cells have only one, which codes for a type 1 MetAP. *Mycobacterium tuberculosis* has two MetAP genes and both belong to type 1 MetAP: *Mt*MetAP1a and *Mt*MetAP1c, which are essential for its *in vivo* survival and pathogenicity1.

As furan-based compounds have shown to be promising antitubercular agents as MetAPs inhibitors2, we planned the design and synthesis of new derivatives functionalizing 2 and 5 positions of the furane ring (Figure 1), starting from our hit compound, MM40. This latter is the most potent competitive MbtI inhibitor to date identified and exhibited a promising antibiotic activity. MbtI is the salicylate synthase from *Mycobacterium tuberculosis* which catalyzes the first step in mycobactins biosynthesis, that is a validated target for fighting tuberculosis3. These compounds could be synergically able to act on MetAPs and MbtI, leading to new antituberculars.

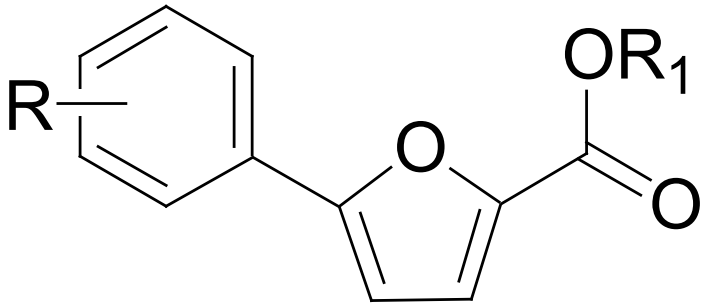

Figure 1. General structure of the new derivatives

Biography

Arianna Gelain graduated in Medicinal Chemistry and Technology and achieved her PhD degree in Medicinal Chemistry at University of Milan. She is researcher at Departement of Pharmaceutical Science and assistant professor at faculty of pharmacy. She is co-author of 31 papers, 6 reviews, published in peer reviewed journals and 1 book chapter.

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Study of protector effect of chemlal olive leaves extract on nephropathy induced by mercury in mouse

Dekdouk Nadia[1], Ameddah Souad[1], Menad Ahmed[1], De Tommasi Nunziatina[2], Malafronte Nicola[2] and **Mekkio Ratiba[1]**
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Olea europaea L. is a typical fruit-tree widely cultivated in the Mediterranean area, belonging to Oleaceae family. The olive leaves contain high concentrations of phenolic compounds. The objective of this study was to evaluate the protector effect of chemlal olive leaves extract on nephropathy induced by mercury in mouse. To evaluate this, five experimental groups (n=6) are used. Group 1 (n=6) only vehicle (0.9% NaCl) in equal volume to mercury treated animals, was given to serve as control, Group 2 (n=6), the animals were treated with HgCl2 5 mg/k.bw in 0.9% NaCl (i.p.). Group 3 (n=6), the animals were administrated with olive leaves extract (OLE) (200 mg/kg b.w.) orally for 10 days. Group 4 (n=6), the animals were administrated sodium selenite (0.1 mg/kg) orally for 10 day before mercuric chloride (5 mg/kg b.w.), in Group 5, the animals were treated with (OLE) (200 mg/kg b.w.) orally for 10 days before mercuric chloride (5 mg/kg b.w.). In this study, treatment with Hg significantly increased serum urea and creatinine levels, myeloperoxidase (MPO) activity, NO and the malondialdehyde (MDA) level, as indicator of lipid peroxidation. The content of LDH, GSH and the activities of kidney antioxidant enzymes: Superoxide dismutase (SOD), catalase (CAT), GSH reductase and transferase were decreased. Selenium or oral administration of (OLE) before mercury treatment significantly lowered the serum levels of urea and creatinine. Furthermore, the content of MDA in kidneys decreased significantly. In addition, this extract increased LDH, the content of GSH, the antioxidant activities and decreased MPO activity and NO production. These results show that leaf extract possessed a protector effects, antioxidant and anti-inflammatory actions and would seem to be applicable in both the health and medical food.

Biography

Dekdouk Nadia has completed her PhD in 2016 from animal biology department, faculty of science, Constantine 1 University and Post-doctoral studies from Constantine 1 University. In collaboration with an Italian research group from University of Salerno, department of pharmaceutical and biomedical sciences, she has published a paper in *Evidence-Based Complementary and Alternative Medicine* titled Phenolic compounds from *Olea europaea* L. possess antioxidant activity and inhibit carbohydrate metabolizing enzymes *in vitro*. The focus of her researches is the investigation of the hepatotoxic, nephrotoxic of some anticancer drugs and the interaction with *Olea europaea* phenolic compounds on rat.

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Kasatkin A et al., Med Chem (Los Angeles) 2017, 7:4 (Suppl)
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Why the drug solutions may cause inflammation at the injection site

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The injections of drug solutions with a high and low concentration (less than 10%) of active drug substance can be followed by the development of local inflammation and complications: cellulitis, phlegmon and necrosis. There are cases of local inflammation after injection solutions of antibacterial, steroidal and non-steroidal anti-inflammatory drugs. We suggested that irritant action of the latter could be caused by high osmolality. The aim of this study is to investigate the local safety drug solutions with different osmolality *in vivo* using infrared thermography. It is found that Ketorolac tromethamine osmolality index was 2971 mmol/kg, metamizole sodium was 4520 mmol/kg and prednisolone was 4205 mmol/kg. Osmolality of sodium chloride 9 mg/ml (control solution) equaled 305 mmol/kg. High osmolality of 50% metamizole sodium solutions was caused primarily by high concentration of active drug substance metamizole sodium (500 mg/ml) in the solution, but high osmolality of ketorolac tromethamine and prednisolone was due to high total concentration of an adjuvants. Thirty minutes after injection local skin hyperthermia at the site of intramuscular injections of ketorolac tromethamine, metamizole sodium and prednisolone solutions were detected. Skin temperature at the site of injecting these solutions was 0.6-1.4°C higher compared with the initial values. Injections of the solutions diluted with sterile water for injections to osmolality index less than 900-1000 mmol/kg did not result in local skin hyperthermia. For safe injecting drug solutions measure their osmolality should be monitored. Infrared thermography can be useful in the local drug safety assessment *in vivo*.

Biography

Kasatkin Anton, PhD, assistant of department of General and Clinical Pharmacologi Izhevsk State Medical Academy. He has published more than 65 papers in journals and received 20 patents for invention. Urakov Aleksandr, MD, Prof. Head of Department of General and Clinical Pharmacologi Izhevsk State Medical Academy. He has published more than 250 papers in journals and received 100 patents for invention.

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Marina V Zueva, Med Chem (Los Angeles) 2017, 7:4 (Suppl)
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The role of technologies of nonlinear stimulation in the treatment of brain diseases and potential of their applications in healthy individuals

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In 2015, the theory was proposed that links the development and maintenance of the typical in norm complex structure of neural networks and the activity of the brain with the complexity of visual and other sensory environmental signals that affect the person during the life. The theory of 'Fractality of sensations' implies that the simplification of the temporal structure of environment cues is associated with abnormal development and aging of the central nervous system. As well, the use of fractal photic stimulation and nonlinear stimuli of other modalities may enhance the effectiveness of strategies for a recovery in the structure and function of the retina and brain, including neurodegenerative pathology, by reactivation of neuroplasticity. Application of nonlinear brain stimulation technology is promising in the treatment of neurological disorders and injuries to increase the effectiveness of restoration of the anatomic and functional structure of the brain, cognitive functions and behavior. In the spectrum of nonlinear stimulating therapy techniques different variants of mono- and multimodal fractal stimulation should be used, as well as its combinations with white noise, music therapy, cognitive, and physical training. We substantiate the potential use of non-linear stimulation technologies in a healthy person in a variety of situations that can lead to a simplification of the neural circuits and pattern of brain activity. Application of physiologically adequate nonlinear stimuli is promising to slow and prevent age-related cognitive impairment in the elderly, in rehabilitation and recovery programs for healthy individuals of certain professions associated with severe physical or psychological stress, and athletes. One can expect that the use of nonlinear techniques to restore physical and mental performance after heavy load and effects of stress factors will help to restore the complex nonlinear dynamics of functional activity, maintaining a high level of criticality and improving the adaptive brain reserve.

Biography

Marina V Zueva has graduated from the Lomonosov Moscow State University (physiology of higher nervous activity), received her PhD and doctor of science from Moscow Helmholtz Research Institute of Eye Diseases. Currently, she is the head of the division of Clinical Physiology of vision at the Moscow Helmholtz Research Institute of Eye Diseases. She is a member of International Society of Clinical Electrophysiology of Vision (ISCEV), European Association on Vision and Eye Research (EVER) and European Society of Retina Specialists (EURETINA). She has published over ten peer-reviewed papers in English (over 86 in Russian) and has presented over 65 topics at international conferences.

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Notes:

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The study *in vitro* of the effects of the inhalant corticosteroids on oral and laryngeal mucosa

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Background: The pharmacology activity of corticosteroids ,is due to the formation in the blood of the complex corticosteroid-protein glycosylated, that, in this form, after the binding to the cytoplasmic receptor ,penetrates in the target cells. This interaction process, also happens with salivary proteins The aim of this study is, to study this process, that precipitate the salivary proteins, and with them, the salivary secreted mucin.

Materials Methods: In two samples of whole saliva provided by volunteers ,are added different concentrations of three corticosteroids , beclometasone, budesonide, fluticasone.The samples are centrifuged, and in surnatant, dosed, the amounts of total salivary proteins and mucins.The results are statistically analyzed with Mann Whitney U Test ,Test T, pearson correlation coefficient

Results –Discussion: With all dosage ,the difference of the proteins and mucins precipitated by the budesonide, and beclometasone vs fluticasone, are statistically different., $p \leq 0.05$. For all three corticosteroids, there is a saturation value, with a good correlation between corticosteroids's dosage and the amount of the protein-mucins precipitation, (Pearson coefficient of 0.91).The little difference in the precipitation of the mucins,and the proteins ,p=0.0334, obtained with the budesonide versus beclometasone, can find an explanation, for the presence in the first, of two hydroxyl groups, (one in beclometasone). The difference of beclometasone and Budesonide, versus Fluticasone, is due assuming that the parameters, that stabilize the (CCP), type hydrogen bonds and Van der Waals forces, are more influenced by solubility in water, there is nothing for the fluticasone, rather than by the chemical conformation of drugs

Biography

Alexandre Henri Didier is a post graduate student in Hospital Pharmacy since 2015. Actually he has a scholarship sponsored by his hospital and he is doing his job into the Nutrition service (Enteral and Parenteral). He has published 4 papers in reputed journals and he has taken part to more than 20 conferences during 2016-2017. He has also a lot of masters in science.

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Drug hunting vs. drug fishing

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The presentation will cover the difference between drug hunting and drug fishing. This will be illustrated by two drug discovery efforts aimed at identifying antiviral and antibiotic clinical agents. Namely, we have discovered azaindole-based molecule acting through a novel mechanism targeting the influenza virus, which led to a clinically effective agent VX-787. The second part will cover efforts aimed at solving medicinally relevant bio-transformations, which can limit progress of clinical molecules, as we discovered a new and pharmacologically effective class of antibiotics, VX-100.

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Adapting DNA-encoded library technology for fragment-based drug discovery

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DNA-encoded library (DEL) technology is a powerful method for rapid drug discovery. Combinatorial synthesis is used to generate large (up to billions of members) libraries of compounds, with each one tagged by a unique barcode made from DNA. A target protein is then screened with a small amount of the library. After non-binding members are washed off, hit compounds are identified by amplifying and sequencing their DNA tags. This method is becoming increasingly popular, but the core workflow has remained largely unchanged in many years. DyNAbind has developed key technologies to overhaul and modernize the DEL discovery process, while also adapting it for a fragment-based discovery approach. Our dynamic fragment libraries allow random pairing and reshuffling of library members in solution, until stabilized by protein binding, resulting in fewer but more reliable hits. Furthermore, our binding profiler technology allows validation and quantification of binding kinetics from fragment-based hits without the need for linker optimization. As a case study, these technologies were deployed to find and characterize new synergistic binders for human carbonic anhydrase 2.

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Phenotypes of a novel series of 3-phosphoglycerate dehydrogenase inhibitors

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PHGDH (3-phosphoglycerate dehydrogenase) is the first enzyme branching from glycolysis into the serine synthetic pathway and it oxidizes 3-phosphoglycerate into phospho-hydroxypyruvate using nicotinamide adenine dinucleotide (NAD) as cofactor. Increase in PHGDH expression at both mRNA and protein levels have been observed in nearly 70% of estrogen receptor-negative breast cancers; in addition a fraction of malignant breast and melanoma cells are dependent on elevated expression of 3-phosphoglycerate dehydrogenase (PHGDH). Furthermore, serine starvation has been shown to have a dramatic effect on tumor growth during *in vivo* mouse xenograft experiments. PHGDH has been a target of interest in the pharma/biotech industry for several years since the initial reports in early 2012 of its relevance in cancer where PHGDH amplified and overexpressing cancer cell lines have been shown to possess unique sensitivity to PHGDH knockdown that cannot be rescued by nutritional serine. The mechanisms underlying these studies have been subjected to intense investigation but remain unclear. We have been able to successfully identify first in class small molecule inhibitors of this target with nanomolar cellular potency, high degree of selectivity and oral bioavailability. In several cancer cell lines, these compounds inhibited glucose derived serine flux with nanomolar median inhibitory concentrations without significantly affecting glucose derived lactate. These compounds also inhibited glucose derived serine in animal studies and have the potential to be highly useful tools for understanding the role of PHGDH in tumor progression. The data presented here will provide unexpected insights on the role of PHGDH in serine biosynthesis and the dependency of cancer cells on PHGDH catalytic function.

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Synthesis and anticancer activity of 6-aryl-2-naphthyl-imidazo[2,1 b][1,3,4]thiadiazole

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A number of imidazo[2,1-b][1,3,4]thiadiazole derivatives having aralkyl and aryl moieties attached to positions 2 and 6 of imidazo[2,1-b][1,3,4]thiadiazole nucleus, respectively, were prepared and characterized by IR, NMR and mass spectrometry. The cytotoxic activity of a new series of 2-naphthyl-imidazo[2,1-b][1,3,4]thiadiazoles against different human and murine cancer cell lines is reported. Among the tested compounds, five derivatives namely CH17, 24, 34, 37 and 39 emerged as the most potent against all the cell lines. To investigate the mechanism of action, we selected compounds CH34, 37 and 39. These compounds induced PARP and caspase-3 cleavages in HSC-2 cells, suggesting the apoptosis induction.

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Comparison of heavy metal levels in the fish oil obtained from the janitor fish (*Pterygoplichthys disjunctivus*) from Marikina River and Laguna de Bay using atomic absorption spectrometry

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The study aimed to compare the heavy metal levels in the fish oil obtained from *Pterygoplichthys disjunctivus* of Marikina River and Laguna de Bay. The oil was extracted using wet reduction method yielding 200 ml of the sample and underwent digestion process prior to heavy metal analysis using aqua regia and perchloric acid. The diluted sample was heated in a water bath at 60°C for three hours until a light-colored or clear solution was obtained. The result of the heavy metal analysis using atomic absorption spectrometry proved that the fish oil from Laguna de Bay contains less heavy metals concentration than of Marikina River. Three heavy metals namely cadmium, copper, and lead were below the detection limit which means that their concentrations in the fish oil were too low to cause toxicity if ingested. Lead has a concentration of -0.61333 ppm (Marikina) and -0.55111 ppm (Laguna), implies that its amount passed the standard limit established by the DENR and US EPA. Nevertheless, chromium with a concentration of 7.22569 ppm (Marikina) and 2.28298 ppm (Laguna) was the only metal that exceeded the maximum value of heavy metals that could produce a toxic effect. Findings and results of test analysis of this study conducted in the fish oil of *P. disjunctivus* could provide information as to which source of fish oil has a low concentration of heavy metals. Thus, it was proved that *P. disjunctivus* oil from Laguna de Bay could be an alternative source of fish oil.

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Investigation of effect of medium on volumetric and ultrasonic studies of pharmaceutical excipients

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In designing and development of drug products from active drugs, some of the important non-therapeutic substances, termed as excipients, are essentially included. The most important part of a medicine is constituted by its excipients, which have the important functions of guaranteeing the dosage, stability and bioavailability of the active principle. Various excipient interactions e.g. with active drug component and packing material, etc., may render the excipient harmful for use in formulation. In order to avoid the use of incompatible excipients and to assure that the excipients are safe and stable for use in the designing of the formulation, various stability testing procedures are carried out. Studies of drug-excipient compatibility represent an important phase in the pre-formulation stage for the development of all dosage forms. Sugars such as xylitol, sorbitol, etc., are being used as an alternative low calorie sweetener and well accepted in formulations of various confectioneries and healthcare products. In the present work, intermolecular interactions of pharmaceutical excipients (D-sorbitol and xylitol) in water and binary solvent mixture of water and organic solvent (DMSO) have been investigated using an easy approaching volumetric and acoustic method. Binary solvent mixtures of different molar ratios help to explore the effect of different mediums on various volumetric and acoustical parameters like apparent and partial molar volume, thermal expansion coefficient, partial molar expansibility, Hepler's constant, compressibility factor, intermolecular free length, relative association and hydration number have been calculated using density and sound velocity data of pharmaceutical excipients in binary solvent mixture at different temperatures (293.15 K-313.15 K). Results give an insight about various physical and chemical interactions that an excipient molecule can undergo in biological system along with an active drug product. Presently, positive apparent molar volume and decrease in intermolecular free length with increasing excipient concentration is an indicative of strong intermolecular interactions.

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The great potential of phenolic compounds isolated from *Limonium* densiflorum to quench and protect human cell against free radicals

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The diversity of plant-based systems has provided an enormous number of lead compounds in healthcare. The crucial factor for the ultimate success of an investigation on bioactive plant constituents is thus the selection of plant materials and the appropriate extraction and purification process of the active compounds. Halophytes plants, living in extreme environments dealing with frequent changes in the salinity level, are used to treat various diseases and aging processes. Among of them, the genus *Limonium* is known in the traditional medicine. The chemical composition of the ethanolic shoot extract of *L. densiflorum* showed excellent radical with scavenging and antioxidant properties. Furthermore, it represents a rich and growing source of natural target molecules, such as phenolic compounds. In order to isolate the active compounds, an *in vitro* fractionation was undertaken by preparative chromatographic techniques. On the basis of nuclear magnetic resonance techniques, the structure of the isolated compounds was determined as gallic acid, epigallocatechin gallate, quercitrin, dihydrokaempferol, pinoresinol, N-*trans*-ferulolyltyramine and (myricetin 3-O-a-rhamnopyranoside and myricetin 3-O-L-arabinofuranoside). All isolated molecules were evaluated for their capacities to inhibit ROS formation on fibroblast cell line (WS-1) by the 2′,7′-dichlorofluorescein assay. Results showed that all compounds tested were found to reduce ROS formation at various doses unless the phenol amide *trans*-N-ferulolyl tyramine (IC_{50}>50 µg/ml). Epigallocatechin gallate followed by gallic acid and the mixture of myricetin 3-O-α-rhamnopyranoside+myricetin 3-O-L-arabinofuranoside, showed the highest antioxidant activity with IC_{50} values of 0.92, 1.22 and 1.5 µg/ml, respectively.

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Cyclopentenes for anti-tuberculosis and antibiotics

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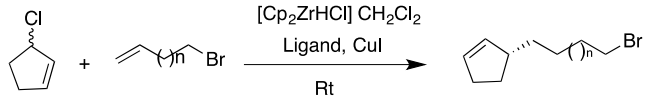
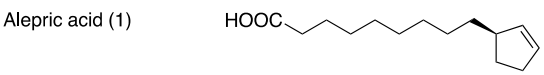
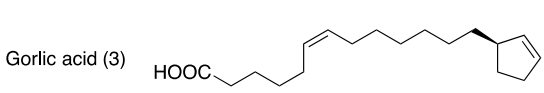
In this presentation the author will describe the asymmetric additions of alkyl nucleophiles to racemic allylic chlorides, to access important cyclopentene containing natural products. These natural products have timely biological activity and the eventual synthesis of derivatives will help develop structure-activity relationships. Cyclopentene natural products Alepric acid (1), aleprestic acid (2), and gorlic acid (3) have not previously had their synthesis reported. The asymmetric addition reaction is a dynamic kinetic asymmetric transformation (DYKAT) to a racemic allylic chloride to give cyclopentenes with high level of ee.







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Synthesis and neuroprotective activity of novel 5,6-diaryl-1,2,4-triazine derivatives with ethyl acetate moiety against H_2O_2 and Aβ-induced neurotoxicity

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Alzheimer's disease (AD) is a neuropathological disorder characterized by intracellular neurofibrillary tangles and amyloid aggregates in the CNS. In recent years, numerous approaches have been used to combat AD like small molecule inhibitors of Aβ aggregation, anti-inflammatory agents, cholinesterase, and β- and γ-secretase. Herein, we report synthesis of some 5,6-diaryl-1,2,4-triazines 3a-f and 8a-e as potential agents for treatment of AD. We evaluated them against both H_2O_2 and β-amyloid induced toxicity in PC-12 and SH-SY5Y cells and the extent of cell viability and apoptosis were assessed. The synthesis of compounds (3a-f) was started by 1,2-diketones, in which triazine ring closure was performed by thiosemicarbazide and alkylation by ethyl chloroacetate to afford compounds 3a-f. Synthetic route for compounds 8a-e was started by an acylation reaction of anisole with phenyl acetic acid derivatives. The oximation in the alpha position of carbonyl group was performed by use of sodium methoxide and butylnitrite. The next two steps were performed similarly to afford final compounds 8a-e. All compounds showed significant neuroprotective activity with EC_{50} values ranging from 14-30 μM. Most compounds could increase cell viability compared to amyloid treated group. Surprisingly, 3-thioxo-1,2,4-triazin-2(3H)-yl)acetate derivative 8e was the most potent compound in both tests with EC_{50} of 14 μM and could increase 40% of cell viability revealed by cytometric analysis with Annexin V/PI staining. It was also shown that 8e has more neuroprotective activity than quercetin. Morphologic evaluation of cells by DAPI staining and TUNEL assay showed the effectiveness of this compound to improve neurite outgrowth in neuronal cells.

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Anticancer activity of some [1,2,4]triazepino[2,3-a] quinazoline derivatives: Monolayer and multicellular spheroids *in vitro* models

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In this study, five derivatives of triazepino[2,3-a] quinazoline-2,7(1H)-dione were synthesized and their anticancer activities were investigated both in two-dimensional-monolayer and three-dimensional-multicellular spheroids cancer models. All the five compounds showed very high anticancer activities against the 11 cancer cell types that have been investigated in the monolayer model. Comparing the results of both monolayer and multicellular spheroids models of the anticancer activity of these five compounds, we can conclude that the meta-methyl derivative induced its anticancer activity through apoptosis to give the best results in the monolayer model. However, in the multicellular spheroids model its apoptotic activity induced moderate anticancer activity (64% cytotoxicity). On the other hand, both two nitro-derivatives either in meta-position or para-position, did not show potent pro-apoptotic activities toward the monolayer model but showed very high cytotoxic activity toward the multicellular spheroids model (100%). These results reveal that the cell death mechanism induced by both nitro-compounds is exerted via other path than the apoptosis. Interestingly, all the tested compounds were generally safe to normal cells spheroids when tested at the same concentration.

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In the pursuit of ideal hits for antifungal research

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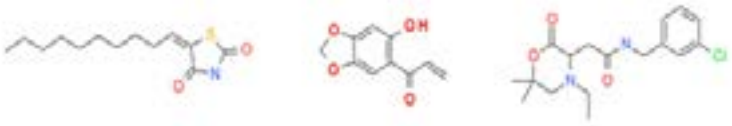
Worldwide, fungal infections take more than 1.3 million lives each year. In addition, over 300 million people are affected by a serious fungal infection. Three classes of antifungals are mainly used to manage these types of invasive fungal infection. The over-reliance on the same medicines acting on a limited number of modes of action has induced a selection pressure amongst the originally susceptible pathogens. As a consequence, drug resistance has become increasingly common and has diminished the arsenal of effective antifungal drugs. Furthermore, some drugs have additional significant limitations. For example, echinocandins need to be administrated intravenously due to their poor oral bioavailability, and amphotericin B has been known to induce adverse nephrotoxicity. This clearly shows the strong need for new molecules which are able to control pathogens showing resistance to our current antifungal products. To bring new antifungals into development, researchers first need to identify new lead molecules. In order to achieve this, they often rely on screening techniques, with phenotypic screening of new compounds being the most preferred. In this presentation, learning's from several years of research and surveys of the antifungal literature will be shared: unwanted compounds not only adversely affect enzyme assays (figure 1) but also phenotypic screens and hits, as a consequence needs to be selected very carefully. In addition, we would like to share examples of what we believe are good hits for antifungal research but that we were not able to pursue further due to resource limitations. We hope that this will encourage scientists to take some of them forward and help to tackle the global challenge of antifungal research.



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Structure-based design of subtype selective antagonists for the ionotropic glutamate receptors: Successes and failures

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Ionotropic glutamate receptor antagonists are highly valuable tool compounds for studies of neurological pathways in the central nervous system. On the basis of rational ligand design, a new class of selective antagonists, represented by (2S,4R)-4-(2-carboxyphenoxy)pyrrolidine-2-carboxylic acid (1b), for cloned homomeric kainic acid receptors subtype 1 (GluK1) was attained (Ki=4 μM). In a functional assay 1b displayed full antagonist activity with IC50=6±2 μM. A crystal structure was obtained of 1b when bound in the ligand binding domain of GluK1. A domain opening of 13-14°C was seen compared to the structure with glutamate, consistent with 1b being an antagonist. A structure-activity-relationship study showed that the chemical nature of the tethering atom (C, O or S) linking the pyrrolidine ring and the phenyl ring plays a key role in the receptor selectivity profile and that substituents on the phenyl ring are well accommodated by the GluK1 receptor. The talk will also cover results from other design studies which have led to successes as well as failures in this field.

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Protective effect of the standardized extract of *Holmskioldia sanguinea* on tumor bearing mice

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Cancer has been considered to be very dreadful disease. *Holmskioldia sanguinea* is a large climbing shrub found in the Himalayas at an altitude of 5,000 feet and preliminary investigation showed the excellent yield of andrographolide and subjected for the anticancer activity. Protective effect of *Holmskioldia sanguinea* leaf ethanolic extract has been investigated against Ehrlich ascites carcinoma (EAC) and Dalton's ascites lymphoma (DAL) in Swiss albino mice and to evaluate the possible mechanism of action. The enzymatic antioxidant status was studied on tumor bearing mice, which shows the potential of the compound to possess significant free radical scavenging property and revealed significant tumor regression and prolonged survival time. The isolated bioactive molecule andrographolide from *Holmskioldia sanguinea* yields 2.5% in subject to HPTLC/HPLC analysis. The cellular defense system constituting the superoxide dismutase, catalysis was enhanced whereby the lipid peroxidation content was restricted to a larger extent. The *Holmskioldia sanguinea* is a new source of andrographolide and demonstrated the potency in treatment of cancer.

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Novel 5-susituated analogues of 4H-3-(2-phenoxy)phenyl–1,2,4-triazole derivatives as agonists of benzodiazepine receptors with anxiolytic effect

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Benzodiazepines are important medicine for treatment and control of a series of disorders including anxiety, insomnia, muscular spasm, and epilepsy. However, they have some unwanted effects such as negative effects on memory and drug dependence. In a search for new active compounds a series of novel non-rigid benzodiazepine ligands, 5-substituted analogues of 4H-3-(2-phenoxy) phenyl-1,2,4-triazole and its chlorinated derivatives were synthesized. The goal is having new ligands with a potential clinical use and less unwanted effects. The novel compounds had several substituents including NH2, SH, S-Methyl groups on position 5 of the 1,2,4-triazole ring. The anxiolytic effects of the novel compounds and diazepam were assessed by elevated plus maze in male NMRI mice. The ED50 was defined as the dose of drug leading to a 100% prolongation in mean duration of staying on open arm of the maze when compared to the control group. Compound with amino substituent at position 5 of the 1,2,4-triazole ring and chloro substituents on position 2 of phenoxy group and position 4 of phenyl ring were the most potent compound in the novel compounds (ED_{50} of 7.6 mg/kg with 95% confidence interval of 5.5-10.3 mg/kg). These findings are in agreement with structure-activity relationship studies of ligands of benzodiazepine receptors. Flumazenil, a selective antagonist of benzodiazepine receptors, was able to reduce the anxiolytic effect of the compounds, which confirms that the anxiolytic effects were seen are results of the interaction of the novel compounds and benzodiazepine receptors.

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Quadruplex DNA stabilizing agents as potential anti-cancer therapeutics

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Over 100 cancers affect human, as per the World Cancer Report, ~14 million new cases of cancer occurred globally resulting ~15% of deaths in 2012. Towards our goal in improving the quality of life for the people suffering from cancer, we are investigating on the identification of small drug-like compounds as potential G-quadruplex (G4s) binders to treat this disease. DNA integrity is critical for proper cellular function and proliferation and has played a key role as successful molecular target for many of the drugs that have been used for decades. Compounds that target DNA are some of the most effective agents in clinical use and produced increase in cancer patients' survival but, they are extremely toxic. Consequently, much effort has been put into finding agents that are more selective and thus presumably will have lesser side effects. Targeting non-canonical DNA secondary structures such as G4s is now considered as an attractive approach toward drug intervention in anti-cancer therapy and thus, significant research is in progress targeting G4 DNAs with small molecules hoping to inhibit cancer growth. We report the design, synthesis of novel small molecules and their evaluation as G4s stabilizing agents. Efficiency of these synthetic compounds was performed to assess the quadruplex binding affinity by using various biophysical and biochemical studies. For the lead compound/s, the binding mode was explained by modeling studies and their *in-vitro* cell growth inhibition was also tested. Finally, drug-likeness of the selected compounds was evaluated for liver microsomal stability, aqueous solubility, CYP inhibition studies.

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Isoconversional approach for non-isothermal decomposition of un-irradiated and photon-irradiated 5-fluorouracil

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Kinetic analysis for the non-isothermal decomposition of un-irradiated and photon-beam-irradiated 5-fluorouracil (5-FU) as anti-cancer drug, was carried out in static air and nitrogen atmospheres. Thermal decomposition of 5-FU, proceeds in two steps. One minor step in the range of (270-280^{o}C) followed by the major step in the temperature range of (285-360^{o}C). The non-isothermal data for un-irradiated and photon-irradiated 5-FU, were analyzed using linear and non-linear Vyazovkin (VYZ) isoconversional methods. The results of the application of these free models on the present kinetic data showed quite dependency of the activation energy on the extent of conversion. The results confirm the complexity of the decomposition of 5-FU and more than one reaction mechanism are involved in the process. In the low conversion range of fraction decomposed , the decomposition is best described by diffusion model, D3. At higher values of decomposition, the nucleation mechanism, A4, gave the best fits to the experimental data. The decomposition path was investigated by intrinsic reaction coordinate (IRC) at the B3LYP/6-311++G(d, p) level of DFT. Two transition states were involved in the process by hemolytic rupture of N−H bond and ring secession, respectively.

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Passiflora incarnata L. of endophytic fungi rooted flavone chrysin (5,7-dihydroxy flavone) and gold nanoparticles towards anticancer activity

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Chrysin (5,7-Dihydroxy flavone ChR) a natural anticancer bioflavonoid, emerged as a potential drug therapy for almost all types of cancer. Since, ChR was produced from endophytic fungal *A. alternate* KT380662, isolated from the leaves of *Passiflora incarnata* L. The ChR production measuring approximately 846 mg L-1 and was confirmed through UV-Vis spectroscopy, FT-IR, LC-ESI-MS, and $_1H^1$ NMR analysis. Further, ChR was used as reduction source and capping agent for gold nanoparticles to improve the bioavailability. Nanomaterials are unique size, shape and composition receives much attention on biomedical applications. Herein, a new approach to formulate biofunctionalized metallic gold (ChR-AuNPs) nanoparticles using ChR as a direct bioreductant and capping agent has been used. Particle size and dispersity were controlled through fixing different reaction conditions such as the temperature, pH, concentration of metal ion, stoichiometric proportion of the reaction mixture and incubation time based on their optical properties and SPR effect in UV-visible spectroscopy. The role of hydroxyl and carbonyl groups in functionalizing the metal ions with ChR was confirmed with Fourier transform infrared spectroscopy (FTIR) and X-ray photoelectron spectroscopy (XPS) analysis. It was also substantiated that the oxygen group from ChR donates electrons to metal ion and results in complexation; ionic Au(3+) was reduced to Au(0) nano-forms. The physiochemical state of obtained NPs was characterized through different exclusive instrumentation, which shows the presence of highly-stable, spherical, crystalline ChR–AuNPs with an average size of 6-2 nm, respectively. *In vitro* anticancer results revealed that the formulated ChR–AuNPs exhibit enhanced cytotoxicity over ChR in the treated two different breast carcinoma cell lines (MDA-MB-231 and MDA-MB-468). Further, it was evident that the cell death via the induction of apoptosis. A hemolysis assay with human erythrocytes demonstrates good blood biocompatibility of ChR–AuNPs. Therefore, ChR functionalized metal can be employed as a nano-drug formulation for cancer therapy.

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The study on serum protein spectrum expression changes for patients with gastrointestinal disease before and after acupuncture

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Objective: To investigate serum protein spectrum expression changes for patients with gastrointestinal disease before and after acupuncture.

Methods: Blood biochemical indexes and serum protein spectrum for 7 patients with gastrointestinal diseases before and after acupuncture were detected by 7600DDP and MALDI-TOF mass spectrometer.

Results: Compared with patients with gastrointestinal disease before acupuncture treatment, the triglyceride (TG) level of patients with gastrointestinal diseases after acupuncture treatment decreased. There were 2 differential protein peaks {2625 (m/z), 2742 (m/z)} between patients with gastrointestinal disease before acupuncture treatment group and after acupuncture treatment group. There were 4 differential protein peaks {2767 (m/z), 2742 (m/z), 2754 (m/z) and 2568 (m/z)} between patients with gastrointestinal disease before acupuncture treatment group and the control group; we establish two-dimensional analysis with 2767 (m/z) (x axis) and 2742 (m/z) (Y axis) and found that acupuncture treatment has obvious effect on patients with gastrointestinal disease , it is close to the normal.

Conclusion: 2742 (m/z) and 2767 (m/z) play an important role in acupuncture treatment mechanism of patients with gastrointestinal disease.

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Design and development of ureas and amides as p38 kinase inhibitors

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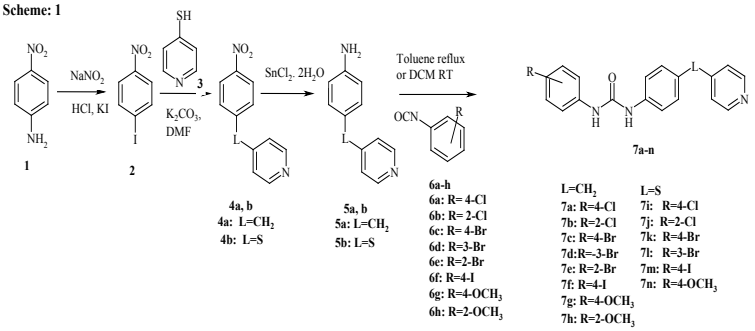
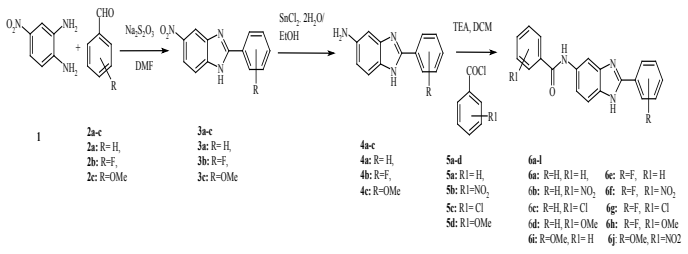
Inflammation is a complex pathological condition associated with exaggerated human immune system involving various activated immune cells and bio-molecules. Current therapeutic approaches to the treatment of inflammatory diseases are centered on inhibition of cyclooxygenases and are associated with undesirable gastrointestinal and cardiovascular side effects. The p38 protein kinase is a serine-threonine mitogen activated protein kinase, which plays an important role in inflammation and arthritis. Inhibition of p38 kinase is highly desired in inflammatory diseases and low molecular weight p38 kinase inhibitors show same therapeutic benefits like biological anti-cytokines but offer advantages in terms of oral dosage and affordable cost. A series of diaryl urea compounds have been synthesized based on the 3D QSAR model and structure based docking studies. The intermediates amines were treated with substituted aromatic isocyanates which afforded the diaryl urea compounds (Scheme 1). All the purified compounds were characterized and subjected for p38 kinase inhibitory and anti-inflammatory activities. Compound 7f demonstrated IC50 value of 1.09 µM in p38 kinase assay and 79.41% inhibition of rat paw edema at the 2nd hour of carrageenan challenge. The molecular docking studies of synthesized compounds indicated some of the important hydrogen bonding interactions and also revealed the minor change in the binding pose when compared to BIRB796. A series of benzimidazoles were designed from our in house urea derivatives and designed molecules have been synthesized from 4-nitro-1, 2-diaminobenzene (Scheme 2). The final compounds were screened for *in vitro* p38 kinase inhibitory and *in vivo* anti-inflammatory activity. Three compounds from the series demonstrated nearly 50% inhibition of p38 kinase in the *in vitro* screening method at 10 µM concentration and two molecules exhibited greater than 75% inhibition of paw oedema volume during the first hour. The docking study of synthesized molecules revealed a new binding pose in ATP binding pocket.

Scheme: 1



Scheme: 2



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