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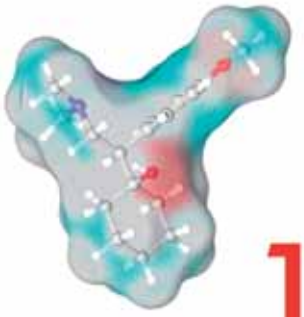

15th HELLENIC SYMPOSIUM ON MEDICINAL CHEMISTRY

ATHENS, May 25•27 2012

Auditorium "Leonidas Zervas"
National Hellenic Research Foundation (NHRF)

Sponsored by EFMC

www.helmedchem2012.gr

ΕΠΕΝΔΥΟΥΜΕ ΣΤΗ

Ο ορισμός της ζωής αποτελεί ακόμη και σήμερα μια πρόκληση για επιστήμονες και φιλοσόφους. Εμείς στην **ELPEN** ορίζουμε τη ζωή σα μια διαρκή διαδικασία εξέλιξης που ανυψώνει τον άνθρωπο σε υπέρτατη αξία.

Γι' αυτό εργαζόμαστε διαρκώς στηρίζοντας αυτή τη διαδικασία με τον άριστο τρόπο:

- Σε επιστημονικό επίπεδο επενδύουμε στην έρευνα και στην τεχνολογία για την ανάπτυξη καινοτόμων φαρμάκων που βελτιώνουν τη ζωή όλων μας.
- Σε οικονομικό επίπεδο, δημιουργούμε προστιθέμενη αξία με την απασχόληση και την οικονομική ευρωστία που μας διακρίνει στην πρώτη θέση της Ελληνικής Φαρμακοβιομηχανίας, στη δύσκολη οικονομική συγκυρία του σήμερα.
- Και σε κοινωνικό επίπεδο, μοιραζόμαστε το όραμα μιας καλύτερης ζωής με ευθύνη και αξιοπρέπεια.

Μεγαλώνουμε διαρκώς με γνώμονα την ανθρώπινη αξία

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Welcome Message

The Organizing and the Scientific Committee cordially welcomes you to the **15th Hellenic Symposium on Medicinal Chemistry (HSMC-15).**

The Symposium is organized by the **Hellenic Society of Medicinal Chemistry (HSMC)** and the **Division of Organic and Medicinal Chemistry of the Association of Greek Chemists (DOMC/AGC)**. HSMC-15 is an event sponsored by the **European Federation of Medicinal Chemistry, EFMC.**

HSMC-15 continues the tradition of biannual meetings established since more than 25 years in Greece, as a forum for the discussion of recent advances in the field of Medicinal Chemistry. The topics of the Symposium cover all therapeutic areas and include: drug design, lead identification and optimization, the impact of ADME/Tox properties and QSAR on drug discovery and development, Organic Synthesis, Natural Products, Biochemistry and Chemical Biology, Pharmacology and Chemoinformatics.

Invited lectures and selected oral communications and poster presentations will provide an insight of the latest achievements in the multidisciplinary field of Medicinal Chemistry and stimulate fruitful interchange of ideas.

Moreover, we do hope that in the frame of the Symposium friendships will be refreshed, new friendships will be forged and collaborations will be reinforced.

Finally, we would like to thank our sponsors who supported our efforts through their generous financial contribution.

We hope that you will enjoy the Symposium and we wish you a nice stay in Athens!

Anna Tsantili-Kakoulidou
President of HSMC

Maria Koufaki
Vice-President of DOPC/AGC

Symposium Co-ordinators

Organizing Committee

Co-ordinators:

- **Mikros E.**
  School of Pharmacy, University of Athens
- **Gimisis A.**
  Department of Chemistry, University of Athens

Members:

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  Institute of Organic & Pharmaceutical Chemistry, National Hellenic Research Foundation
- **Detsi A.**
  School of Chemical Engineering, National Technical University of Athens
- **Kostakis I.**
  School of Pharmacy, University of Athens
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  School of Pharmacy, University of Athens
- **Pirmettis I.**
  Institute of Radioisotopes & Radiodiagnostic Products, NCSR Demokritos
- **Vassiliou S.**
  Department of Chemistry, University of Athens

Scientific Committee

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  HSMC- School of Pharmacy, University of Athens
- **Koufaki M.**
  DOPC/AGC – Institute of Organic & Pharmaceutical Chemistry, National Hellenic Research Foundation

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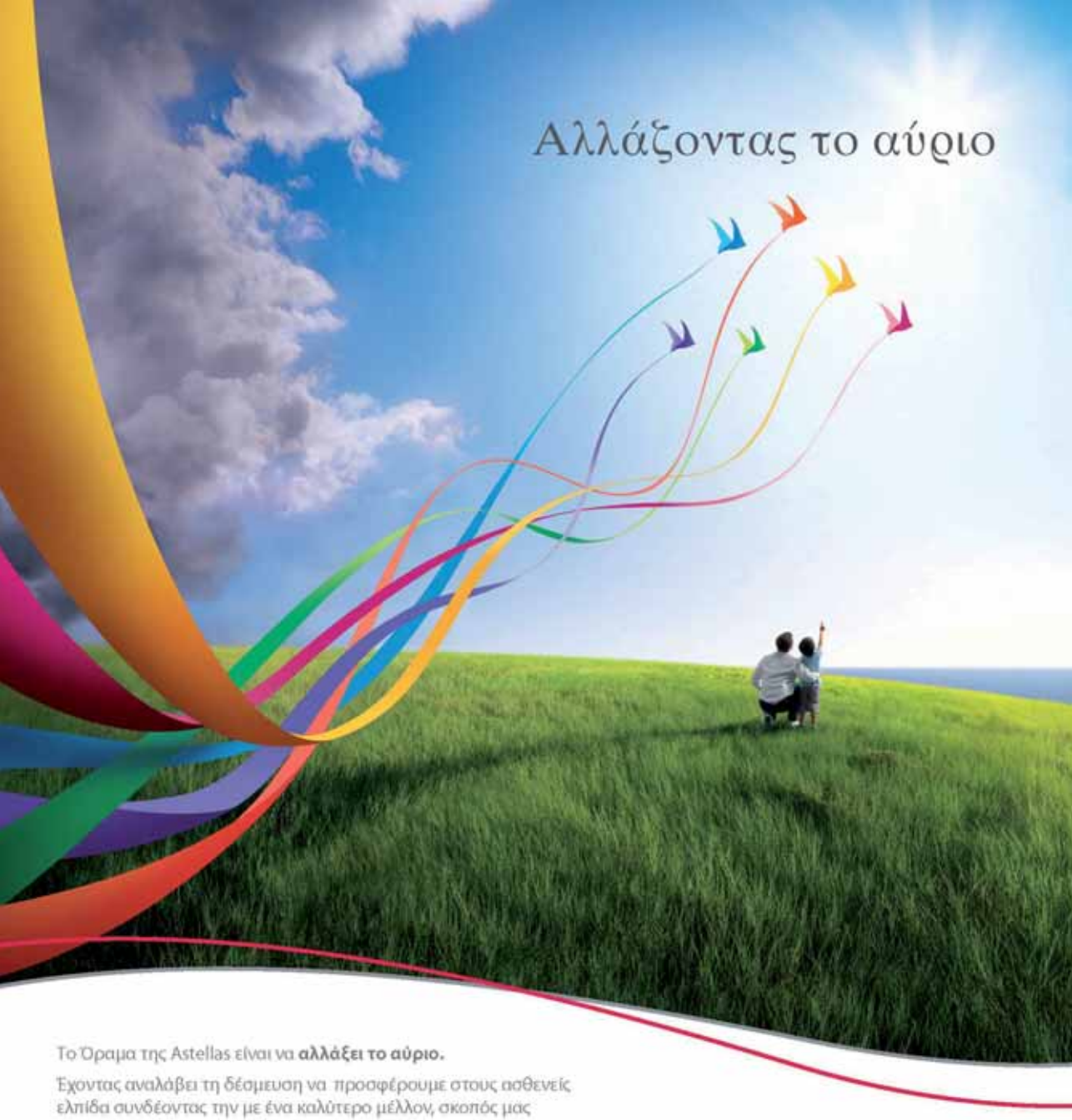

Το Όραμα της Astellas είναι να **αλλάξει το αύριο.**

Έχοντας αναλάβει τη δέσμευση να προσφέρουμε στους ασθενείς ελπίδα συνδέοντας την με ένα καλύτερο μέλλον, σκοπός μας είναι να ηγηθούμε στους θεραπευτικούς τομείς στους οποίους εξειδικευόμαστε, εστιάζοντας ταυτόχρονα εκεί όπου οι ιατρικές ανάγκες εξακολουθούν να παραμένουν ανεκπλήρωτες.

Η Astellas θα συνεχίσει μέσω της έρευνας και της καινοτομίας να αναπτύσσει νέους τρόπους θεραπείας έτσι ώστε να συνεισφέρει στη βελτίωση της υγείας των ασθενών. Στόχος μας είναι να ανακαλύψουμε τις ιατρικές λύσεις του αύριο, στα προβλήματα υγείας του σήμερα.

Η Astellas δεσμεύεται, με οτιδήποτε αναλαμβάνει, να επιτύχει αυτόν το σκοπό **ΑΛΛΑΖΟΝΤΑΣ ΤΟ ΑΥΡΙΟ.**

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FRIDAY 25/5/2012
15:00-16:30 Registration
16:30-17:00 Opening of the Symposium
PROGRESS IN THE DESIGN AND DEVELOPMENT OF DRUGS-STRATEGIES FOR LEAD GENERATION
17:00-17:40 Hubbard R.
17:40-18:20 Supuran C.
18:20-18:45 Bhachoo J.
19:00-21:00 Welcome Reception

SATURDAY 26/5/2012
BIOCHEMICAL PHARMACOLOGY/ CHEMICAL BIOLOGY
09:00-09:30 Martinet N.
09:30-10:05 Filippakopoulos P
10:05-10:30 Fousteris E.
10:30-10:45 Pedersen E.B.
10:45-11:00 Arvaniti Aik.
11:00-11:30 Coffee
NATURAL PRODUCTS AS LEAD COMPOUNDS / CHEMICAL BIOLOGY
11:30-12:10 Theodorakis M.
12:10-12:35 Magiatis P.
12:35-13:00 Koumbis A.E
13:00-13:15 Efstathiou A.
13:15-13:30 Spyroulias G.
13:30-14:30 Lunch
14:10-14:30 Savaidis A
SYNTHETIC APPROACHES IN DRUG DISCOVERY
14:30-15:30 Poster Session
15:30-15:55 Calogeropoulou Th.
15:55-16:20 Georgiadis D.
16:20-16:35 Roussaki M.
16:35-16:50 Mamais M.
16:50-17:15 Coffee
SYNTHETIC APPROACHES IN DRUG DISCOVERY
17:15-17:40 Hadjipavlou-Litina D.
17:40-17:55 Zoidis G.
17:55-18:10 Pontiki E.
18:10- 18:25 Djeddi S.
18:30-19:45 Round Table
DISCIPLINES INVOLVED IN MEDICINAL CHEMISTRY EDUCATION
21:00 Dinner

SUNDAY 27/5/2012
PHARMACOPHORE SEARCHING AND VIRTUAL SCREENING
09:15-9:55 Kontoyianni M.
09:55-10:20 Leonis G.
10:20-10:45 Melagraki G.
10:45-11:00 Cournia Z.
11:00-11:15 Perez – Nueno V.
11:15-11:30 Drakulic B.J.
11:30-12:00 Coffee
MEDICAL APPLICATIONS AND EMERGING TECHNOLOGIES
12:00-12:25 Lianidou E.
12:25-12:50 Gikas V.
12:50-13:05 Kontogiorgis Ch.
13:05-13:20 Sagnou M.
13:20-13:35 Pispas S.
13:35-13:55 3 Poster Presentations
13:55-14:15 Closing of the Symposium

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General Information

Symposium Venue
The Symposium takes place in Athens, at the National Hellenic Research Foundation on 25-27 May 2012.

Language
The official language of the Symposium is English.

Poster Presentations Instructions
1. The poster should be within 80 cm x 120 cm and be written in English.
2. The poster should be displayed on the allocated panel in the venue (National Hellenic Research Foundation) by Friday afternoon, 25th May, till the end of the Symposium, Sunday noon, 27th May.

Audiovisual Equipment
Audiovisual Equipment of the latest technology is used.

Internet Site
All useful information about the Symposium are available on line at www.helmedchem2012.gr

Speakers' Pre View Area
Speakers' Pre View Area will be located close to the Symposium Secretariat. All Power Point files must be delivered to the Speakers' Pre View Area at least one hour before the session starts. Data files must be on CDROM or USB stick and cannot be delivered in the session rooms in order to avoid delay and projection problems. Opening hours of the Speakers' Pre View Area are the same as Secretariat's.

Symposium Badge
The badge will be delivered by the ZITA Congress Secretariat and it is necessary to be worn at all times during the Symposium.

Liability & Insurance
The Secretariat of the Symposium and the organizers accept no responsibility whatsoever for injury or damage involving persons and property during the Symposium.

Certificates of attendance
Certificates of attendance will be delivered only to those who actually attend the Symposium.

Secretariat
The ZITA Congress Secretariat will operate in a central point of the Venue.

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Με εκτίμηση,

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MSc in Molecular Biology

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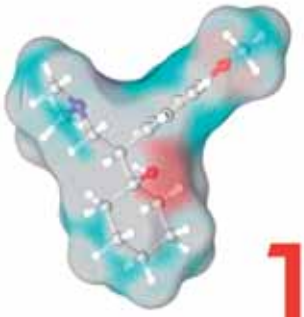

15th HELLENIC SYMPOSIUM ON MEDICINAL CHEMISTRY

FINAL PROGRAM

FRIDAY May 25, 2012

15:00-16:30 Registration

16:30-17:00 Opening of the Symposium

PROGRESS IN THE DESIGN AND DEVELOPMENT OF DRUGS - STRATEGIES FOR LEAD GENERATION

Chairs: Koufaki M., Pouli N.

17:00-17:40 Plenary Lecture - 1

CURRENT PERSPECTIVES IN FRAGMENT AND STRUCTURE-BASED DRUG DISCOVERY

Hubbard R.

University of York, UK

17:40-18:20 Plenary Lecture - 2

CARBONIC ANHYDRASES AS DRUG TARGETS

Supuran C.

University of Florence, Italy

18:20-18:45 Main Lecture - 1

HOLE FILLING AND LIBRARY OPTIMIZATION: APPLICATION TO COMMERCIALLY AVAILABLE FRAGMENT LIBRARIES

Bhachoo J.

Schrödinger

19:00-21:00 **Welcome Reception**

SATURDAY May 26, 2012

BIOCHEMICAL PHARMACOLOGY/ CHEMICAL BIOLOGY

Chairs: Mikros E., Rekka E.

09:00-09:30 Plenary Lecture - 3
EPIGENETIC OVERVIEW: DNA METHYLATION
Martinet N.
Laboratoire de Chimie des Molécules Bioactives, Université de NICE, France

09:30-10:05 Plenary Lecture - 4
INHIBITION OF EPIGENETIC READOUT
Filippakopoulos P.
University of Oxford, UK

10:05-10:30 Main Lecture - 2
PROBING THE BIOACTIVITY OF PYRROLO[2,3-a]CARBAZOLES
Fousteris E.
Department of Pharmacy, University of Patras, Greece

10:30-10:45 Oral Presentation - 1
IMPROVED DRUG POTENTIAL OF DNA G-QUADRUPLEXES BY MODULATION WITH TWISTED INTERCALATING NUCLEIC ACIDS (TINA)
Pedersen E. B.
University of Southern Denmark, Odense, Denmark

10:45-11:00 Oral Presentation - 2
GLOBAL PROTEOME QUANTIFICATION OF NOVEL IMATINIB DERIVATIVES IN K562 HUMAN CHRONIC MYELOID LEYKEMIA CELLS
Arvaniti Aik.
Department of Chemistry, University of Crete, Greece

11:00-11:30 **Coffee**

NATURAL PRODUCTS AS LEAD COMPOUNDS/ CHEMICAL BIOLOGY

Chairs: Detsi A., Nikolaropoulos S.

11:30-12:10 Plenary Lecture - 5
CHEMISTRY AND BIOLOGY OF NATURAL PRODUCTS
Theodorakis M.
University of California, USA

SATURDAY May 26, 2012

12:10-12:35 Main Lecture - 3

ISOLATION, SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF MALASSEZIA METABOLITES WITH POWERFUL AHR ACTIVITY AND IMPLICATION IN SKIN CANCER DEVELOPMENT

Magiatis P.

School of Pharmacy, University of Athens, Greece

12:35-13:00 Main Lecture - 4

POLYPHOSPHORYLATED MYO-INOSITOL AND CARBOHYDRATE DERIVATIVES: SYNTHESIS AND STUDY OF THEIR ALLOSTERIC EFFECT ON HUMAN HEMOGLOBIN

Koumbis A.E.

Department of Chemistry, Aristotle University of Thessaloniki, Greece

13:00-13:15 Oral Presentation - 3

EXPLOITATION OF THE ANTIPARASITIC EFFECT OF INDIRUBIN ANALOGUES ON L. DONOVANI AND T. BRUCEI PARASITES FOR TARGETED DRUG DESIGN

Efstathiou A.

Hellenic Pasteur Institute, Athens, Greece

13:15-13:30 Oral Presentation - 4

IDENTIFYING FUNCTIONAL IMPORTANT OF ARKADIA E3 UBIQUITIN LIGASE RING DOMAIN IN E2 RECRUITEMENT AND E3-E2 INTERACTION

Spyroulias G.

Department of Pharmacy, University of Patras, Greece

13:30-14:30 **Lunch**

14:10-14:30 MCFA Presentation

RESEARCHERS' MOBILITY - THE EXPERIENCE AND ACTIONS OF MARIE CURIE FELLOWS ASSOCIATION-HELLAS

Savaidis A.

14:30-15:30 **Poster Session**

SATURDAY May 26, 2012

SYNTHETIC APPROACHES IN DRUG DISCOVERY

Chairs: Foscolos G. B., Gimisis A.

15:30-15:55 Main Lecture - 5

17-SPIRO-SUBSTITUTED NEUROSTEROID DERIVATIVES: DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION

Calogeropoulou Th.

National Hellenic Research Foundation, Athens, Greece

15:55-16:20 Main Lecture - 6

PHOSPHINIC INHIBITORS OF Zn-METALLOPROTEASES: RECENT ADVANCES AND APPLICATIONS

Georgiadis D.

Department of Chemistry, University of Athens, Greece

16:20-16:35 Oral Presentation - 5

HYBRID QUINOLINYL CHALCONES AS POTENT ANTITRYPANOSOMAL AND ANTILEISHMANIAL AGENTS

Roussaki M.

National Technical University of Athens, Athens, Greece

16:35-16:50 Oral Presentation - 6

4-ARYLAMINO-β-D-GLUCOPYRANOSYL-PYRIMIDINES: EXPLORING THE CATALYTIC SITE OF GLYCOGEN PHOSPHORYLASE

Mamais M.

Department of Chemistry, University of Athens

16:50-17:15 **Coffee**

SATURDAY May 26, 2012

SYNTHETIC APPROACHES IN DRUG DISCOVERY

Chairs: Papahatjis D., Chrysina E.

17:15-17:40 Main Lecture - 7

USING THE ENONE GROUP AS STRUCTURAL TOOL FOR BIOACTIVE COMPOUNDS: STRUCTURAL MODIFICATIONS

Hadjipavlou-Litina D.

School of Pharmacy, University of Thessaloniki, Greece

17:40-17:55 Oral Presentation - 7

NOVEL LIPOPHILIC ACETOHYDROXAMIC ACID DERIVATIVES BASED ON CONFORMATIONALLY CONSTRAINED SPIRO CARBOCYCLIC 2,6-DIKETOPIPERAZINE SCAFFOLDS WITH POTENT TRYPANOCIDAL ACTIVITY

Zoidis G.

School of Pharmacy, University of Athens, Athens, Greece

17:55-18:10 Oral Presentation - 8

DESIGN, SYNTHESIS AND EVALUATION OF NOVEL AGENTS THAT TARGET THE HISTAMINE H4 RECEPTOR

Pontiki E.

Department of Chemistry, University College London, London, UK

18:10- 18:25 Oral Presentation - 9

IN VITRO ANTI-CANCER CELL KILLING EFFICACY OF AQUEOUS ALLIUM SATIVUM L. EXTRACT

Djeddi S.

Faculty of Science, University of Badji Mokhtar, Annaba, Algeria

18:30-19:45 **Round Table**

DISCIPLINES INVOLVED IN MEDICINAL CHEMISTRY EDUCATION

Co-ordinator: Marakos P.

21:00 **Dinner**

SUNDAY May 27, 2012

PHARMACOPHORE SEARCHING AND VIRTUAL SCREENING

Chairs: Mavromoustakos Th., Vasileiou S.

09:15-09:55 Plenary Lecture - 6

A COMPUTATIONAL STRATEGY TO INVESTIGATE SUBSTRATE PROMISCUITY IN THE HUMAN CYTOCHROME P450 SYSTEM

Kontoyianni M.

School of Pharmacy, Southern Illinois University, USA

09:55-10:20 Main lecture - 8

EFFECTIVE INHIBITORS FOR ASPARTIC PROTEASES

Leonis G.

National Hellenic Research Foundation, Athens, Greece

10:20-10:45 Main Lecture - 9

TARGETING PROMISING INHIBITORS FOR RHEUMATOID ARTHRITIS: A MULTI STEP CHEMOINFORMATICS APPROACH

Melagraki G.

National Technical University of Athens, Greece

10:45-11:00 Oral Presentation - 10

FREE ENERGY PERTURBATION CALCULATIONS AS A PREDICTIVE TOOL IN STRUCTURE – BASED DRUG DESIGN

Cournia Z.

Biomedical Research Foundation of the Academy of Athens, Athens, Greece

11:00-11:15 Oral Presentation - 11

GAUSSIAN ENSEMBLE SCREENING: A NOVEL WAY TO ANALYSE VIRTUAL SCREENING IN A SYSTEMS PHARMACOLOGY CONTEXT

Perez – Nueno V.

INRIA Nancy – Grand Est, Loria, Vandoeuvre-les Nancy, France

11:15-11:30 Oral Presentation - 12

THE MEDICINAL CHEMISTRY – RELATED APPLICATIONS IN HP-SEE PROJECT. AN END – USER VIEW

Drakulic B. J.

University of Belgrade, Belgrade, Serbia

11:30-12:00 **Coffee**

SUNDAY May 27, 2012

MEDICAL APPLICATIONS AND EMERGING TECHNOLOGIES

Chairs: Pirmettis I., Kostakis I.

12:00-12:25 Main Lecture - 10

CIRCULATING TUMOR CELLS (CTCS) AS NOVEL TUMOR BIOMARKERS

Lianidou E.

Department of Chemistry, University of Athens, Greece

12:25-12:50 Main Lecture - 11

COMBINATION OF DATA FROM DIFFERENT INSTRUMENTS IN METABONOMIC STUDIES

Gikas V.

School of Pharmacy, University of Athens, Greece

12:50-13:05 Oral Presentation - 13

NANOTECHNOLOGY IN MEDICINAL CHEMISTRY: ENZYME – TRIGGERABLE STEALTH RELEASE (ETSR) OF NANOPARTICLES FOR siRNA DELIVERY

Kontogiorgis Ch.

School of Pharmacy, King's College, University of London, London, UK

13:05-13:20 Oral Presentation - 14

IN VIVO EVALUATION OF A NOVEL IODINATED ELACRIDAR – BASED P-GLYCOPROTEN INHIBITOR AS A POTENTIAL SPECT MDR PROBE

Sagnou M.

National Centre for Scientific Research "Democritos", Athens, Greece

13:20-13:35 Oral Presentation - 15

HIGH CHARGE DENSITY CATIONIC POLYMERS FOR NUCLEIC ACID DELIVERY

Pispas S.

National Hellenic Research Foundation, Athens, Greece

13:35-13:55 **3 Selected Poster Presentations**

13:55-14:15 **Closing of the Symposium**

ABSTRACTS

FRIDAY May 25, 2012

Plenary Lecture - 1

CURRENT PERSPECTIVES IN FRAGMENT AND STRUCTURE BASED DRUG DISCOVERY

Roderick E. Hubbard
Professor, University of York and Senior Fellow, Vernalis (R&D) Ltd

The past ten years has seen continued growth in the use of structure-guided methods to aid the drug discovery process. A particularly exciting development has been the experimental methods based on the use of fragments, with many compounds now in clinical trials and the first compound now on the market. The central feature is that the drug discovery process begins with identification of small (<250 MW), weakly binding (affinity of 100s of μM) compounds which are then optimised to drug candidates by structure-guided design. The advantages are that a small library can sample a potentially large chemical diversity to generate novel lead compounds and that hits can be identified for new classes of target for which existing compound collections cannot provide a hit. One consequence of the work on fragments is the increased reliance on biophysical methods to detect binding which coincides with careful thinking about compound properties.

I will review the current status of the methods and their application and survey the current issues:

- deciding which fragments to progress - between 10-200 chemically diverse fragments can be found as hits from screening 1200 fragments - which fragments should be progressed?
- how to work with non-conventional targets, such as protein-protein interactions, and the critical importance of biophysical methods to characterise binding
- how important is the fragment library?

FRIDAY May 25, 2012

Plenary Lecture - 2

CARBONIC ANHYDRASES AS DRUG TARGETS

Claudiu T. Supuran
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claudiu.supuran@unifi.it

Carbonic anhydrases (CAs, EC 4.2.1.1), a group of ubiquitously expressed metalloenzymes, are involved in numerous physiological and pathological processes, including gluconeogenesis, lipogenesis, ureagenesis, tumorigenicity and the growth and virulence of various pathogens [1,2]. In addition to the established role of CA inhibitors (CAIs) as diuretics and antiglaucoma drugs, it has recently emerged that CAIs could have potential as novel anti-obesity, anticancer and anti-infective drugs. This presentation will discuss the biological rationale for the novel uses of inhibitors or activators of CA activity in multiple diseases, and highlights progress in the development of specific modulators of the relevant CA isoforms, some of which are now being evaluated in clinical trials. For example, CA IX, a membrane-bound, hypoxia-inducible enzyme is highly expressed in many types of solid tumors, showing restricted expression in normal tissues [1,2]. CA IX plays an important functional role in processes critical for tumor cell growth and metastasis, including pH regulation, survival, adhesion and migration [1,2]. The tumor-specific expression of CA IX and its association with cancer progression and poor treatment outcome has led to interest in targeting it for cancer therapy. The development of pharmacologic inhibitors that selectively target tumor-associated, extracellular CAs without "off-target" inhibition of cytosolic isoforms is critical for their use as cancer therapeutics [1,2]. We have recently described novel ureido-substituted benzenesulfonamides and glycosyl coumarins that selectively and potently inhibit CA IX activity *in vitro*, and reduce breast tumor growth and metastasis *in vivo* [3-5]. Treatment of animals harboring highly CA IX positive MDA-MB-231 LM2-4 orthotopic breast tumors resulted in significant inhibition of tumor growth and increased survival times. Furthermore, treatment of mice harboring human orthotopic breast tumors with an ureido-sulfonamide in combination with paclitaxel resulted in significantly reduced tumor growth compared to either treatment administered alone. Bioluminescence imaging of lungs resected from treated mice revealed that lung metastases were virtually absent from animals treated with the combination therapy. Collectively, these studies provide strong "proof of principle" data for the therapeutic inhibition of CA IX activity for breast tumor growth and metastasis formation, especially when used in combination with conventional chemotherapy. Many pathogenic bacteria also encode CAs belonging to the α-, β-, and/or γ-CA families. The α-CAs from *Neisseria spp*. and *Helicobacter pylori* as well as the β-class enzymes from *Escherichia coli*, *H. pylori, Mycobacterium tuberculosis*, *Brucella spp., Streptococcus pneumoniae, Salmonella enterica* and *Haemophilus influenzae* have been cloned and characterized in detail, with various classes of inhibitors (anions, sulfonamides and sulfamates) being reported. However, only for *Nessseria spp.*, *H. pylori, B. suis* and *S. pneumoniae* enzymes it has been possible to evidence inhibition of bacterial growth *in vivo*. Thus, bacterial CAs represent promising targets for obtaining antibacterials devoid of the resistance problems of the clinically used such agents but further studies are needed to validate these and other less investigated enzymes as novel drug targets [6]

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FRIDAY May 25, 2012

Main Lecture - 1

HOLE FILLING AND LIBRARY OPTIMIZATION: APPLICATION TO COMMERCIALLY AVAILABLE FRAGMENT LIBRARIES

Bhachoo J.
Schrödinger

We present an automated method to fill holes in a library using compounds from an external source and apply it to commercially available fragment libraries. The method, called Canvas HF, uses distances computed from 2D chemical fingerprints and selects compounds that fill vacuous regions while not suffering from the problem of selecting only compounds at the edge of the chemical space. Overall, the method presented here offers an efficient and effective hole-filling strategy to augment compound libraries with compounds from external sources.

SATURDAY May 26, 2012

Plenary Lecture - 3

EPIGENETIC OVERVIEW: DNA METHYLATION

Nadine Martinet
Institute of Chemistry, CNRS UMR 7272, University of Nice Sophia Antipolis, NICE, France

The word epigenetic was first coined to describe all those phenomena which are not explained by the basic genetic information encoded into the DNA sequence. This corresponds also to our understanding why identical genotypes can lead to different phenotypes as seen in twins when they age. DNA methylation is the first epigenetic modification described. Produced by DNA methyltransferases (DNMTs). It occurs mainly on cytosine residues contained in CpG islands. DNA methylation prevents binding of the transcriptional machinery by changing the charge of DNA to induce gene silencing. It is physiologically imprinted during the embryo maturation to allow cell lineage differentiation. Pathological DNA methylation patterns are seen in a wide range of cancers. DNA methylation is reversible and could go through Cytosine hydoxymethylation with the TET enzymes. DNMT inhibitors are used to treat patients with preleukemic disorders. However, less toxic molecules are needed. The possibility to reprogram cell epigenome opens the doors to tissues engineering and stem cells programming. DNA methylation cross talk with several histones modifications: acetylation, methylation, ubiquitination and phosphorylation.

SATURDAY May 26, 2012

Plenary Lecture - 4

INHIBITION OF EPIGENETIC READOUT

Panagis Filippakopoulos
Department of Clinical Medicine, Structural Genomics Consortium, University of Oxford, Old Road Campus, Roosevelt Drive, Oxford OX3 7DQ, UK

Lysine acetylation has emerged as a signalling modification of broad relevance to cellular and disease biology. Targeting the enzymes which reversibly mediate side-chain acetylation has been an active area of drug discovery research for many years. To date, successful efforts have been limited to the "erasers" (histone deacetylases) of covalent modifications arising in the context of nuclear chromatin. Bromodomains (BRDs) are evolutionary conserved protein interaction modules that specifically recognize ε-N-lysine acetylation (K_{ac}) motifs ("readers"), a key event in the reading process of epigenetic marks. They are of substantial biological interest, as components of transcription factor complexes and determinants of epigenetic memory. We identified 61 BRDs in the human genome that cluster into 8 families based on sequence similarity. Crystallization trials led to 29 high-resolution crystal structures, covering all BRD families. Comprehensive cross-family structural analysis identified conserved and family specific structural features necessary for specific acetylation-dependent substrate recognition and systematic screening against peptide arrays covering all possible histone acetylation sites, as well as combinations with other histone modifications, resulted in the identification of novel BRD substrates. This structural and substrate specificity data allowed for the development of biophysical and biochemical assay platforms that we now use to identify and characterize small molecule binding to BRDs and to drive target specific lead development. Employing Virtual Ligand Screening, fragment- and diversity- library screening, published known K_{ac}-mimetic information as well as available patent information, we have established proof of concept for targeting this class of reader domains. We initially reported a cell-permeable, potent small-molecule inhibitor (JQ1) with biochemical selectivity for the bromo and extra terminal (BET) sub-family of bromodomains. High-resolution co-crystal structures with BET bromodomains revealed excellent shape complementarity with the acetyl-lysine binding cavity. Binding of JQ1 to the tandem bromodomains of BRD4 was shown to be acetyl-lysine competitive and displaced BRD4 from chromatin in human cells. Competitive binding of JQ1 to the BRD4-NUT fusion oncoprotein in NMC carcinomas results in squamous differentiation and specific anti-proliferative effects both in BRD4-dependent cell lines as well as in patient-derived xenograft models. We have now expanded our efforts to target other sub-families of this class of proteins seeking to generate well characterized, highly specific, potent and cell permeable chemical tools. These reagents are essential for the early stages of drug discovery by allowing preclinical target validation in both academic and industrial laboratories and we seek to distribute them without restrictions in order to promote both fundamental and applied biological research.

SATURDAY May 26, 2012

Main Lecture - 2

PROBING THE BIOACTIVITY OF PYRROLO[2,3-a]CARBAZOLES

Fousteris Manolis*, Spyropoulos Efstathios*, Koutsourea Anna*, Nikolaropoulos Sotiris*, Chatzianastasiou Athanasia, Papapetropoulos Andreas**, Manioudaki Maria**, Lampropoulou Evgenia**, Papadimitriou Evangelia****

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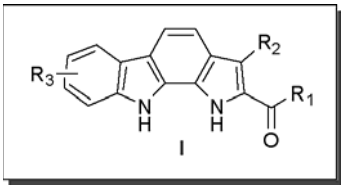
Protein kinases are implicated in many signaling cascades related with vital biological processes. Deregulation of their activity has been correlated with pathological disorders such as cancer, inflammation, neurodegenerative and metabolic disorders. Over the past few years, there has been an intense interest in the discovery of novel small molecules as selective protein kinase inhibitors for the targeted and personalized treatment of these diseases [2,3]. Among other kinases, cyclin dependent kinases (CDKs) play pivotal role in the cell cycle and transcription regulation [4], while they are involved in various tumor types [5]. Consequently, they have been identified as potential therapeutic targets. Small heterocycles of diverse chemical origin have been proved either broad range or selective ATP competitive CDK inhibitors [6].



I

Recently, we have reported on the CDK1 inhibitory activity of the pyrrolo[2,3-a]carbazole core I [7]. In continuation of our efforts in the field, a focused library of modified pyrrolo[2,3-a]carbazoles has been synthesized and their *in vitro* CDK1 inhibitory activity has been determined. Subsequently, the profile of the most potent CDK1 inhibitor was evaluated against a panel of protein kinase targets. Moreover, the effects of this derivative on the proliferation and the apoptosis of various cancer cell lines were studied. In an attempt to further explore the bioactivity of the pyrrolo[2,3-a]carbazole core, selected derivatives were tested as potential topoisomerase I inhibitors, as well as for their activity on the viability of glioma and endothial cells *in vitro* and on angiogenesis *in vivo*, providing new insights on the biological effects of these heterocyclic compounds [8].

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SATURDAY May 26, 2012

Oral Presentation - 1

IMPROVED DRUG POTENTIAL OF DNA G-QUADRUPLEXES BY MODULATION WITH TWISTED INTERCALATING NUCLEIC ACIDS (TINA)

Erik B. Pedersen, Imrich Géci, Maha I. I. Fatthalla and Amro M. El-Madani
Department of Physics and Chemistry, University of Southern Denmark, Campusvej 55, 5230 Odense C, Denmark (erik@sdu.dk)

AS1411 is a prominent example of a DNA quadruplex anticancer agent and although a high concentration of the drug was needed to achieve a therapeutic effect, it was brought to phase 2 clinical trials. However, G-Rich oligonucleotides often form complex mixtures of quadruplexes. When such an oligonucleotide is influencing the transcription process as a decoy quadruplex, the biological activity can be ascribed to only one or a few of the possible quadruplexes in the mixture. It is therefore tempting to modulate the equilibrium mixture of quadruplexes into the highest possible concentration of the bioactive quadruplex structure and we think this possible by inserting a **t**wisted **i**ntercalating **n**ucleic **a**cid monomer (TINA) into the quadruplex structure.
On the other hand, improper insertions of conjugated intercalators into G-rich oligonucleotidesare are found to diminish quadruplex structures and in this way breaking down the self-association of G-rich oligonucleotides under physiologically potassium ion conditions.
Pancreatic cancer can be affected both by treatment with triplex forming oligonucleotides and with aptameric G-quadruplexes with a decoy effect. The trick is to use proper insertion of TINA to modulate the G-rich oligonucleotide. To modulate polymorphic quadruplexes, an intercalator was covalently inserted in the sugar-phosphate backbone in a position adjacent to the runs of guanines, so that the intercalator moiety could stack to the ends of the quadruplex structure. A strong antiproliferative effect was then observed. Also quadruplex drugs against bladder cancer, human acute myeloid leukemia and Hela cells showed improved activities upon insertion of TINA. Quadruplex aptamers with TINA insertions also showed promising results against HIV and in blood clotting experiments. Indeed, a TINA modified quadruplex HD1-22 r8P was found to be a candidate for the development of a potent and safe anticoagulant for use in patients at increased risk of bleeding complications and it seems to be one of the most potent aptamer-based thrombin inhibitors reported to date.

SATURDAY May 26, 2012

Oral Presentation - 2

GLOBAL PROTEOME QUANTIFICATION OF NOVEL IMATINIB DERIVATIVES IN K562 HUMAN CHRONIC MYELOID LEYKEMIA CELLS

Arvaniti Aikaterini*, De Bock Pieter-Jan,,***, Papadioti Anastasia*, Kinigopoulou Maria****, Skobridis Kostas****, Gevaert Kris**,***, Tsiotis Georgios***

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Inhibition of deregulated protein kinases by small molecule drugs has evolved into a major therapeutic strategy for the treatment of human malignancies. Imatinib mesylate has emerged as the leading compound to treat the chronic phase of chronic myeloid leukemia (CML), through its inhibition of Bcr- Abl tyrosine kinases, and other cancers. However, resistance to imatinib develops frequently, particularly in late-stage disease and has necessitated the development of new Bcr-Abl inhibitors. The synthesis of a new series of phenylaminopyrimidines, structurally related to imatinib showed greater activity against the PDGFR family and poorer activity against Abl. To identify the cellular pathways affected by the new compounds, we applied mass spectrometry together with stable isotope labeling by amino acids in cell culture (SILAC) for the comparative study of protein expression in K562 cells that were untreated or treated with imatinib and the imatinib derivates. Further, the global proteome of the K 562 cells treated with imatinib were quantitative compare with the K 562 cells treated with the new compounds. This study enrich our knowledge about direct cellular targets of kinase selective drugs and the identification of druggable downstream mediators of oncogenic signaling.

SATURDAY May 26, 2012

Plenary Lecture - 5

CHEMISTRY AND BIOLOGY OF NATURAL PRODUCTS

Jing Xu, Michelle H. Lacoske, J. E. Caro-Diaz, Emmanuel A. Theodorakis
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Research in the Theodorakis laboratory focuses around natural products and has two major goals: (a) to develop efficient methods and strategies that are applicable to the synthesis of the target molecules; and (b) to apply the synthetic expertise toward the investigation of the biological mode of action of the target molecules. Such efforts to translate chemical structure and reactivity to biological properties yield important insights regarding natural products-based cellular biology and guide the search for new small molecules as leads for drug discovery. Accomplishing these goals requires an interdisciplinary approach to science that combines expertise from synthetic chemistry, biochemistry, pharmacology and cell biology. The seminar will focus mainly on the development of unified enantioselective strategies toward the synthesis of jiadifenolide and fusarisetin A and will briefly present ongoing structure-activity relationship studies.

SATURDAY May 26, 2012

Main Lecture - 3

ISOLATION, SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF MALASSEZIA METABOLITES WITH POWERFUL AHR ACTIVITY AND IMPLICATION IN SKIN CANCER DEVELOPMENT

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[2]Department of Environmental Toxicology, University of California, Davis

Malassezia is a genus of human symbiotic yeasts that can become pathogenic under currently insufficiently understood conditions and have been correlated with a number of skin diseases, like seborrheic dermatitis, pityriasis versicolor, dandruff etc affecting a major part of the global population. Malassezia has also been proposed to be a factor that promotes basal cell cancer especially due to the production of Aryl hydrocarbon Receptor (AhR) inducers that can locally modify the immune system response and hyperactivate the CYP enzymes leading to local free radical leak.

When we investigated skin extracts from patients they showed 100-1000 times stronger AhR inducing activity than the skin extracts of healthy volunteers. Chemical analysis of the patients' extracts by LC/MS/MS revealed for the first time significant amounts of compounds like 6-formylindolo[3,2-b]carbazole (FICZ), indolo[3,2-b]carbazole (ICZ), malassezin, indirubin and pityriacitrin in human skin. The same compounds in addition to tryptanthrin were also identified and isolated from *Malassezia furfur* extracts revealing the unequivocal origin of them. FICZ, indirubin identified herein as Malassezia metabolites are the two most active known AhR ligands even stronger than dioxin. Evaluation of their AhR inducing activity in human HepG2 cells transfected with a luciferase reporter gene at 6 h showed EC50s $3,85*10^{-11}$ and $9,93*10^{-11}$ M respectively (In comparison with $5.23*10^{-10}$ M for dioxin).

Trying to identify the biosynthetic pathway from tryptophan to indirubin, we investigated the oxidation of indole-3-carboxaldehyde (which is the main catabolic product of tryptophan in Malassezia cultures) using hydrogen peroxide and selenium based catalysts. Interestingly, this biomimetic reaction led simultaneously to indirubin and tryptanthrin showing their possible common biosynthesis. Application of this reaction to substituted indoles and indole-3-carboxaldehydes led to a series of new symmetrically (or not) indirubins and tryptanthrins bearing a variety of substituents. In parallel, a number of indolo[3,2-b]carbazole derivatives were also synthesized to investigate the role of the formyl group in AhR activation. All the new compounds as well as a number of previously synthesized indirubins (in total >50 compounds) were evaluated as AhR inducers in 4 different species cell lines and several structure-activity/selectivity relationships were observed for each class of compounds.

SATURDAY May 26, 2012

Main Lecture - 4

POLYPHOSPHORYLATED MYO-INOSITOL AND CARBOHYDRATE DERIVATIVES: SYNTHESIS AND STUDY OF THEIR ALLOSTERIC EFFECT ON HUMAN HEMOGLOBIN

Koumbis A. E.,* Fylaktakidou K. C., Duarte C. D.,*** R. Jogireddy,*** Nicolau C.,**** Lehn J.-M. *****

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**** NormOxys, Inc., Medford, MA, USA

Oxygen delivery is regulated by allosteric effectors (AEs) that bind to hemoglobin (Hb) and decrease its oxygen binding affinity. As numerous diseases, such as cardiovascular ones as well as cancer, involve hypoxia, achieving increased oxygen release may be expected to restore normoxia, and to possess major therapeutical potential. *myo*-Inositol Hexakis Phosphate and its tris pyrophosphate are the most potent AEs of Hb [1], with the latter displaying remarkable cardiovascular [2], and anti-oncological effects [3].

Libraries of 1,4- and 2,5-disubstituted *myo*-Inositol Tetrakis Phosphates (ITPs) and differentially phosphorylated hexopyranoses (D-glucose, D-mannose and D-galactose derivatives) as well as pentopyranoses and pentofuranoses (D- and L-arabinose, D-rhamnose and D-ribose derivatives) were prepared in very good yields upon direct phosphorylation, hydrogenation and counter cation exchange of the appropriately protected myo-inositol derivatives or parent carbohydrates [4]. ITPs were also used to prepare the corresponding bispyrophosphates (IBPPs) upon reaction with dicyclohexyl carbodiimide.

All compounds were tested for their effect on the partial pressure of oxygen for half-saturation (P50) of Hb. Both ITPs and carbohydrate polyphosphates were able to shift the Hb oxygenation curves to remarkably high values (113-550%) whereas IBPPs were less potent (11-96%). Structure-activity relationships studies revealed that the observed efficacy increases with the strength of Hb binding and corresponds primarily to electrostatic interactions. Stereochemical and steric factors also play a significant but secondary role in molecular recognition.

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SATURDAY May 26, 2012

Oral Presentation - 3

EXPLOITATION OF THE ANTIPARASITIC EFFECT OF INDIRUBIN ANALOGUES ON L. DONOVANI AND T. BRUCEI PARASITES FOR TARGETED DRUG DESIGN

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Leishmania and Trypanosomes are the etiological agents of parasitic diseases such as leishmaniasis and human African trypanosomiasis (HAT), affecting more than 27 million people worldwide. There is an urgent need for new targeted drugs against these diseases as the current treatment is unsatisfactory due to the toxicity and the resistance of the parasites to currently used drugs. Indirubins, a bis-indole family known as a minor constituent of plant, animal and microorganism-derived indigo, are known mammalian Glycogen-synthase kinase-3 (GSK-3) and the cyclin-dependent kinases (CDKs). In trypanosomatid parasites, CDK1 and GSK-3 homologues were shown to be essential genes required for parasite cell-cycle progression. Previous studies from our lab demonstrated that the indirubin analogues 5-Me-6-BIO and 6-BIO had potent antileishmanial activity (<1μM) and induced cell-cycle deregulation and apoptosis by inhibiting the parasitic GSK-3 and CRK-3 (CDK1 homologue) kinases. The above observation suggests that indirubins could be exploited as potential lead drug candidates for the treatment of parasitic diseases. To this end we screened 70 indirubins with different 1, 5, 5′, 3′, 6, 6′and 7 substitutions on the indirubin backbone for antiparasitic activity against L. donovani promastigotes and amastigotes and T. brucei bloodstream parasites. 29 indirubins displayed potent antitrypanosomal activity, whereas only 6 displayed antileishmanial activity against L. donovani parasites (<1.5 μM). Interestingly, they showed high (>10) cytotoxic index (ratio of macrophage J774 cytotoxicity to antiparasitic activity). Diffrerent indirubin analogues promoted apoptosis with completely different ratios of necrotic/apoptotic cells and different cell-cycle defects in T. brucei parasites. This implies that indirubins may target different parasitic kinases. We are currently evaluating the inhibitory activity of these agents against selected parasitic kinases (GSK-3, CDK1/CRK3) with the hope to identify the proteins they target and to design better antiparasitic drugs.

SATURDAY May 26, 2012

Oral Presentation - 4

IDENTIFYING FUNCTIONALLY IMPORTANT RESIDUES OF ARKADIA E3 UBIQUITIN LIGASE RING DOMAIN IN E2 RECRUITEMENT AND E3-E2 INTERACTION

Georgios A. Spyroulias*, Christos T Chasapis*, Nikos Kandias*, Maria-Polytimi Vlachou*, Ariadni Loutsidou*, Danai Giannari*, Detlef Bentrop#, Vasso Episkopou+

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E3 ubiquitin ligases play a key role in the proteolytic degradation of proteins through the Ubiquitin-Proteasome pathway [Hershko A & Ciechanover A, Annu Rev Biochem 1998, 67, 425]. ARKADIA is the first example of an E3 ligase that positively regulates TGF–β family signaling through its C-terminal RING finger domain [Episkopou V et al. PLoS Biol 2007, 5, e67].

The ARKADIA RING finger, was cloned and expressed in its zinc-loaded form and studied through multi-nuclear and multi-dimensional NMR Spectroscopy [Kandias NG et al. BBRC 2009, 378, 498]. The 3D NMR solution structure of ARKADIA RING finger was determined and deposited in PDB (2KIZ). NMR-driven titration studies were also performed to probe the interaction interface of ARKADIA RING and the partner E2 (UbcH5B) enzyme and the RING-E2 complex was constructed through an NMR-driven docking protocol (Chasapis CT et al. Proteins 2012).

Additionally, this study resulted to the identification of ARKADIA RING functionally important residues, such as the conserved, in many RING domains, Trp972. Trp972 is considered as one of the key residues for E2 recognition and binding [Huang A, et al. J Mol Biol 2009, 385, 507]. According to recent experimental evidence, the mutation of the Trp972 to Arg abolishes the ability of Arkadia to amplify TGF-b-Smad2/3 signaling responses in tissue culture transcription assays [Episkopou V, et al. Cancer Res. 2011, 71, 6438] suggesting that this residue is essential in the ubiquitin ligase enzymatic activity, consistent with the E2 recruitment. Various ARKADIA Trp mutants were prepared and are studied through NMR spectroscopy in order to obtain an atomic-level insight about the structural base of ARKADIA RING capability to select and bind the appropriate E2 in order to exhibit its ubiquitin ligase activity.

SATURDAY May 26, 2012

Main Lecture - 5

17-SPIRO-SUBSTITUTED NEUROSTEROID DERIVATIVES: DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION

Calogeropoulou Theodora
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Neuronal cell death by apoptosis is the 'end-point' of many human neurological disorders (e.g. Alzheimer's, Parkinson's diseases, stroke/trauma, multiple sclerosis). Currently, there is little or no treatment for most neurodegenerative diseases. At best, available treatments are symptomatic in nature and do not prevent or slow the progression of disease.

A fundamental approach for reducing the burden of neurodegenerative diseases is to slow or halt progression, and ultimately, to prevent the onset of the disease process. Thus, strategies for neuroprotection, preventing apoptotic neuronal cell loss may offer new therapeutic interventions. Neurosteroids are synthesized in the central and peripheral nervous system, affect neuronal function and differentiation and provide for neuroprotection against ischemia and stroke. Dehydroepiandrosterone (DHEA) is one of the most potent neuroactive neurosteroids, and the precipitous decline of both brain and circulating DHEA with advancing age has been associated to neuronal dysfunction and degeneration. However, naturally occurring neurosteroids are metabolized in humans into estrogens, androgens, or progestins which are known to exert important generalized endocrine side effects, including hormone-dependent neoplasias, thus limiting their clinical use.

As a continuation of our studies on probing the stereoelectronic requirements of steroids for optimum meuroprotective activity, we designed and synthesized several novel C17-spiro DHEA derivatives. A number of the new analogues exhibit strong neuroprotective activity against the neural-crest derived PC12 cell model of serum deprivation-induced apoptosis. Moreover, the new analogues are devoid of androgenic and estrogenic effects, they bind with high affinity to membrane DHEA binding sites and mimic endogenous neurosteroids in inducing prosurvival anti-apoptotic Bcl-2 proteins. Preliminary findings show that the 17-spiro DHEA derivatives bind with high affinity to NGF receptors. The *in vivo* activity of the new analogues was investigated in several animal models.

Acknowledgement: This work was supported in part by the European Union's Seventh Framework Programme (FP7-REGPOT-2009-1) under grant agreement no. 245866, "ARCADE".

SATURDAY May 26, 2012

Main Lecture - 6

PHOSPHINIC INHIBITORS OF Zn-METALLOPROTEASES: RECENT ADVANCES AND APPLICATIONS

Georgiadis Dimitris
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Enzyme inhibitors that act as transition state analogues comprise an important class of bioactive compounds with numerous applications in medicinal chemistry and chemical biology. In the field of Zn-metalloproteases, the replacement of the scissile bond of a peptidic enzymatic substrate by a phosphinic acid moiety leads to chemically stable pseudopeptidic scaffolds which are able to reversibly inhibit the enzymatic action of proteases. This property combined with the weak zinc-binding ability of the phosphinic group enables the rational design of extremely potent inhibitors able to target specific Zn-metalloproteases with a high degree of selectivity. The research interests of our group are mainly focused on a) the development of novel synthetic technologies towards phosphinic building blocks, b) the application of combinatorial techniques for the assembly of phosphinic peptide chemical libraries, c) the identification of selective Zn-metalloproteases inhibitors (i.e. MMPs, ACE, ER aminopeptidases) via iterative lead optimization and high throughput screening (HTS) and d) the evaluation of phosphinic peptides as chemical probes for proteomic analysis. The most recent synthetic and biological results obtained in our laboratory will be presented.

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2) Dive, V.; Georgiadis, D. et al. J.*Biol.Chem.* **2010**, *285*, 35900-35909
3) Stratikos, E.; Georgiadis, D. et al. *EMBO J.* **2012**, submitted

SATURDAY May 26, 2012

Oral Presentation - 5

HYBRID QUINOLINYL CHALCONES AS POTENT ANTITRYPANOSOMAL AND ANTILEISHMANIAL AGENTS

Marina Roussaki*, Belinda Hall, Shane Wilkinson**,**
Sofia Costa Lima*, Anabela Cordeiro da Silva***, Anastasia Detsi***
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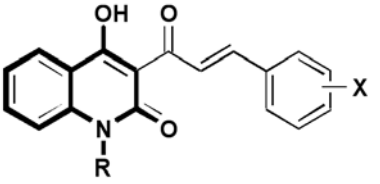
***Instituto de Biologia Molecular e Celular and Faculdade de Farmácia da Universidade do Porto, Porto, Portugal

Owning to the lack of effective and affordable treatments, as well as of vaccines, there is an urgent need to reinforce the existing therapeutic arsenal against parasitic diseases which are responsible for an extensive amount of human infections worldwide.
In the present study, the novel 'bioinspired' hybrid compounds, encompassing the quinolinone and the chalcone moiety in one molecular scaffold, were evaluated for their *in vitro* antiparasitic activity against *Leishmania Infantum* and *Trypanosoma brucei*. The powerful and diverse biological properties of quinolinones and chalcones, in the field of the antioxidant, anti – parasitic, anticancer and antivirus activities, were combined to a novel hybrid skeleton of Quinolinyl – Chalcone.



R=H, C_2H_5, $CH_2C_6H_5$
X=CH_3, OCH_3, OH, NO_2, CF_3, COOH

Quinolinyl - Chalcone

The new series of these heterocyclic, α,β-unsaturated carbonyl compounds, were prepared via a crossed aldol coupling reaction between 3-acetyl-4-hydroxy-quinolinone and various aromatic aldehydes using piperidine as a basic catalyst. The starting 3-acetyl 4-hydroxyquinolin-2(1H)-one was synthesized through a C- acylation reaction of ethyl acetoacetate by 2-methyl-3,1-benzoxazin-4-one and further cyclization of the C-acylated intermediates under basic conditions.
In order to investigate further the structure - activity relationship of the new series of quinolinyl chalcones, we proceeded to the modification of the two more important structural characteristics of these molecules, i.e. the amide hydrogen of the heterocyclic ring of the quinolinone and the α,β-unsaturated system of the chalcone.
The study has identified potential lead compounds that inhibit parasite growth in the low micromolar range, encouraging us for further investigation of the structure - activity relationship.

Acknowledgements: This collaboration was promoted by COST Action CM0801 'New Drugs for Neglected Diseases'

4-ARYLAMINO-β-D-GLUCOPYRANOSYL-PYRIMIDINES: EXPLORING THE CATALYTIC SITE OF GLYCOGEN PHOSPHORYLASE

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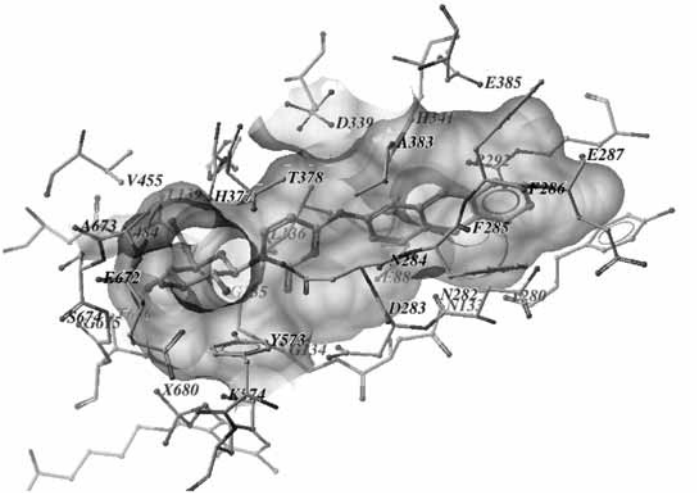
Glycogen Phosphorylase (GP) is a key enzyme involved in the regulation of blood glucose levels and as such, represents a molecular target for fighting Type II diabetes. Various derivatives of β-D-glucose exhibit strong inhibition of GP.[1] In our laboratory we have synthesized a number of β-D-glucopyranosyl pyrimidines which have appeared to be strong inhibitors of GP, with binding constants K_i up to 5,5 μM.[2] A number of molecular modeling techniques have been utilized to calculate the theoretical binding energies at the catalytic centre of GP and have been correlated with the experimental values in order to build a trustworthy correlation model, which was used to predict new, more potent inhibitors.[3] Through this process, one of the best so far inhibitor of the catalytic site of GP was found, with a K_i equal to 0,35 μM.
In this poster, a number of 3rd generation inhibitors is presented, which aim at optimizing the ligand-receptor interactions at the β-channel of the catalytic site, by introducing aromatic moieties of different geometry, including or not some polar heteroatom groups. The synthetic methodology is presented, together with the experimental binding constants and some preliminary crystallographic data, which provide information regarding the favorable enzyme-inhibitor interactions.



Scheme 1. Surface representation of g2anthra at the catalytic site of RMGPb

1 Chrysina, E.D. *Mini Rev. Med. Chem.* **2010**, *10*, 1093-1101.
2 Gimisis, T. *Mini Rev. Med. Chem.* **2010**, *10*, 1127-1138.
3 Socaci, C. *et al. Proteins, submitted.*

This research has been co-financed by the European Union (European Social Fund – ESF) and Greek national funds through the Operational Program "Education and Lifelong Learning" of the National Strategic Reference Framework (NSRF) - Research Funding Program: Heracleitus II. Investing in knowledge society through the European Social Fund.

SATURDAY May 26, 2012

Main Lecture - 7

USING THE ENONE GROUP AS STRUCTURAL TOOL FOR BIOACTIVE COMPOUNDS: STRUCTURAL MODIFICATIONS

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In nature, the presence of an enone group is correlated with bioactivity as well as a synthetic pathway for structurally modified new bioactive molecules. Chalcone is the simplest naturally/synthetically occurred enone derivative. It presents biosynthetic interest for the synthesis of flavonoids and flavones as phytochemicals and phytonutrients.[1] Chalcone is an aromatic ketone with several substituents leading to several derivatives with important biological activities eg. pyrazolines, pyrroles, Mannich bases etc.[2] Several synthetic approaches for this group of compounds have been published. Many papers have been presented in the literature with references to structural modifications of the enone template.[3]
In this presentation we will present a number of chalcones and enone derivatives targeting inflammation and cancer. Quantitative Structure activity relationships have been performed and their results have been used for the synthesis of enone derivatives which have been biologically evaluated.[4,5] They have been shown to possess antioxidant, oxygen scavenging and anti-inflammatory properties in a variety of experimental systems and can trigger the intracellular cascade of protective pathways offering a promising strategy for therapeutic applications.

Acknowledgements: *Biobyte Corp., 201 West 4th St, Suite 204, Claremont CA 91711, USA*

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SATURDAY May 26, 2012

Oral Presentation - 7

NOVEL LIPOPHILIC ACETOHYDROXAMIC ACID DERIVATIVES BASED ON CONFORMATIONALLY CONSTRAINED SPIRO CARBOCYCLIC 2,6-DIKETOPIPERAZINE SCAFFOLDS WITH POTENT TRYPANOCIDAL ACTIVITY

Zoidis Grigoris*, Fytas Christos*, Tzoutzas Nikolaos*, Taylor Martin C., Fytas George*, Kelly John M.****

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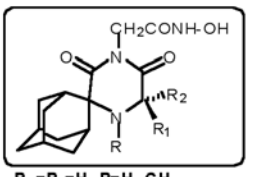
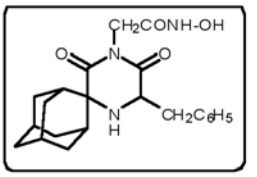
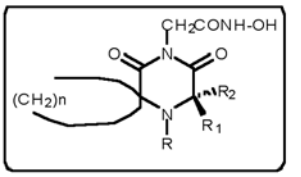
Novel acetohydroxamic acid derivatives have been developed as potent trypanocidal agents (2a-e, 3, 4a-d, 5a, and 5b). These analogues were derived from conformationally constrained, lipophilic, spiro carbocyclic 2,6-diketopiperazine (2,6-DKP) scaffolds (ie a spiro adamantane 2,6-DKP scaffold) by attaching on their imidic nitrogen acetohydroxamic acid moiety as a strong metal-chelating functional group. Their in vitro trypanocidal activity data revealed that these hydroxamic acid analogues are potently active toward Trypanosoma brucei with IC50 values in the range of 6.8-1870 nM. Compounds 2a, 2b, and 2d were also found to be significantly active against Trypanosoma cruzi (IC_{50}=0.21-5.51 μM). SAR studies showed a substantial optimization in activity of the parent compounds 2a and 4a against T. brucei by placing a benzyl group at the position adjacent to basic nitrogen of the spiro carbocyclic 2,6-DKP core (2d, 2e, 3, and 4d). In particular, the benzyl substituted S-enantiomer 2d was the most active against both parasites (T. brucei and T. cruzi) with IC50 values 6.8 nM and 0.21 μM, respectively. On the other hand, modifications including the replacement of the hydroxamic acid functionality with amide (6), hydrazide (7), O-methyl hydroxamate (8), and carboxylic acid (25-29, 39, 51, 54, and 66) ones resulted to a substantially loss of activity. These results demonstrate that the hydroxamic acid unit is indispensable for the trypanocidal activity. This in turn might imply that our acetohydroxamate derivatives were toxic to the parasite due to inhibition of a vital metalloenzyme, through metal ion binding mechanism of action.



R_1=R_2=H, R=H, CH_3
R=R_1=H, R_2=CH_3, $CH_2C_6H_5$
R=R_2=H, R_1=$CH_2C_6H_5$





n=6 or 7, R_1=R_2=H, R=H, CH_3
n=7, R=R_1=H, R_2=CH_3, $CH_2C_6H_5$

SATURDAY May 26, 2012

Oral Presentation - 8

DESIGN, SYNTHESIS AND EVALUATION OF NOVEL AGENTS THAT TARGET THE HISTAMINE H_4 RECEPTOR

Pontiki Eleni, Marson Charles
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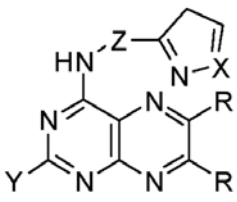
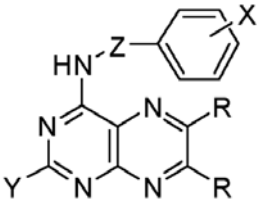
Histamine is an important chemical mediator in physiological and pathological responses. The biological functions of histamine are mediated through 4 histamine receptors (H_1R, H_2R, H_3R and H_4R), which vary in expression, signaling, function and histamine binding ability, and therefore, have different potential therapeutic applications. Of the four identified histamine receptors, H_1R, H_2R and H_4R have been shown to affect inflammation and other immune responses and have been used or have been proposed to be useful for treating immune and inflammatory disorders. The H_4R is expressed primarily in cells involved in inflammation and immune response.

H_4R antagonists, JNJ7777120 and JNJ10191584 (also known as VUF 6002) have been developed with excellent affinity and selectivity towards human and rodent H_4R. These antagonists also demonstrate efficacy as anti-inflammatory agents in vivo. Due to its distribution to immune cells and its proven role in inflammatory functions, the H_4R receptor appears to be a therapeutic target for the treatment of a variety of immune disorders. The benchmark antagonist of the H_4 receptor, JNJ7777120, has an indole ring as its bicyclic core but a short half-life that prevents its use as a drug. While a pyrimidine ring alone shows weak H_4 antagonism, selectivity is poor and potency is reduced. Since the bicylic system indole and quinazoline (benzo-pyrazine) shows efficacy (but not optimal drug-like properties) against the H_4 receptor, we propose to combine the efficacy of the pyrazine ring with that of a pyrimidine ring (known to confer effective H_4 antagonism on its own), by studying pteridines (a formal fusion of a pyrimidine and a pyrazine ring) to give more potent, selective and drug-like agents than those currently known.

Based on docking studies a series of suitable substituted pteridines were designed and synthesized:





The novel pteridines will be evaluated for their activity on the histamine H4 receptor.

Acknowledgments: Eleni Pontiki is grateful to the Onassis Public Benefit Foundation for Postdoctoral fellowship at UCL.

SATURDAY May 26, 2012

Oral Presentation - 9

IN VITRO ANTI-CANCER CELL KILLING EFFICACY OF AQUEOUS ALLIUM SATIVUM L. EXTRACT

Samah Djeddi*, Ouahiba Meziou, Abdelaziz Lankar**, Fatiha Yassi** and Bochra Tiffouti***
*Laboratory of of Ecobiology of Marine and Littoral Environment, Department of Biology, Faculty of Science, University of Badji Mokhtar BP 12, Annaba 23000, Algeria
**Laboratory of Anatomic Pathology, Ibn Rochd University Hospital Center. Annaba 23000, Algeria

Garlic (*Allium sativum L.*) belongs to *Allium* genus and Alliaceae family, this herb has been used for thousand of years to treat various diseases. Hippocrates was the first to recommend its use for cancer. Many studies showed that organosulfur compounds originating from garlic inhibit carcinogen activation. In this study we tested aqueous garlic extract (AGE) against fresh cancer breast cell lines in order to observe the cancer cell killing efficacy. The cancer cell lines were provided immediately after mastectomy from Ibn Rochd (UHC). Different concentrations of AGE like 100, 200 and 300 µg/mL were tested. The data represent the mean of three experiments in triplicate. The results revealed that about 75.2% breast cancer cells were destructed in a dose of 300 µL, whereas about 29.4 and 60.5% cancer cells were destructed in a dose of 100 and 200 µL of AGE, respectively.

Key words:Aqueous garlic extract; Breast cancer cells; Anti-cancer activity.

SUNDAY May 27, 2012

Plenary Lecture - 6

A COMPUTATIONAL STRATEGY TO INVESTIGATE SUBSTRATE PROMISCUITY IN THE HUMAN CYTOCHROME 3A4

Maria Kontoyianni
Department of Pharmaceutical Sciences, Southern Illinois University Edwardsville, Edwardsville, Illinois 62026, United States

Drug attrition due to bioavailability and toxicity continue to present problems in the development of new drugs. The cytochrome P450 enzymes (CYPs) are heme-protein mono-oxygenases, which catalyze oxidative and reductive reactions of a broad spectrum of substrates, thus influencing drug-drug interactions and subsequent unwanted effects due to co-administration. The isoform which metabolizes over one third of drugs, CYP 3A4, was investigated via cross-docking experiments of a 200-substrate library using the three currently available crystal 3A4 structures. All calculations were performed in duplicates, with and without inclusion of crystallographic waters, employing the Glide and GOLD docking algorithms and a number of scoring functions. Resultant poses were assessed based on accuracy of site of metabolism prediction, with Glide performing the best. Analyses of the docked solutions pertaining to ranking efficacy, ligand molecular properties, types of metabolic reactions, and stabilizing residues in the ligand-protein complexes will also be presented.

SUNDAY May 27, 2012

Main Lecture - 8

EFFECTIVE INHIBITORS FOR ASPARTIC PROTEASES

Leonis G.
National Hellenic Research Foundation, Athens, Greece

Human immunodeficiency virus type 1 protease (HIV-1 PR) and renin are primary targets toward AIDS and hypertension therapies, respectively. Although HIV-1 PR and renin share the same active site sequence among other structural features, extensive comparisons regarding their action are lacking. Molecular dynamics (MD), molecular mechanics Poisson-Boltzmann surface area (MM–PBSA) free energy calculations and inhibition assays for canagliflozin, an anti-diabetic agent, verified its effective binding to both proteins ($\Delta G_{bind} \approx -9.5$ kcal mol^{-1}). Moreover, drugs aliskiren (a renin inhibitor) and darunavir (an HIV-1 PR inhibitor) showed high affinity for HIV-1 PR ($K_{i,exp} = 76.5$ nM) and renin ($K_{i,pred} = 261$ nM), respectively. This study suggests that canagliflozin, aliskiren and darunavir may induce profound effects toward dual HIV-1 PR and renin inhibition. Importantly, since it is known that AIDS patients on highly-active antiretroviral therapy (HAART) have a high risk of developing hypertension and diabetes, aliskiren-based or canagliflozin-based drug design against HIV-1 PR may eliminate these side-effects and at the same time facilitate AIDS therapy.

SUNDAY May 27, 2012

Main Lecture - 9

TARGETING PROMISING INHIBITORS FOR RHEUMATOID ARTHRITIS: A MULTI STEP CHEMOINFORMATICS APPROACH

Georgia Melagraki[a,b], Antreas Afantitis[bc], Evangelos Ntougkos[c], Olga Igglessi- Markopoulou[a], George Kollias[c]

[a]School of Chemical Engineering, National Technical University of Athens, Athens, Greece
[b]Department of ChemoInformatics, NovaMechanics Ltd, Nicosia, Cyprus
[c]Biomedical Sciences Research Center "Alexander Fleming", Athens, Greece

Rheumatoid Arthritis (RA) is a devastating, chronic inflammatory disorder that affects approximately 1% of the worldwide population, and is characterized by persistent active inflammation with concurrent tissue destruction. Recent reports from several major pharmaceutical companies indicate that there is a significant interest for the identification of small-molecule antagonists of RA. Small-molecule inhibitors could provide a less-expensive, orally administered alternative to parenteral biologic agents.

In this work we have developed in silico workflows for exploring the relationship between the structural characteristics of small molecules and their RA inhibition activity. Among a pool of molecular, topological, structural and electronic descriptors the most important features responsible for the inhibition activity were identified. Different machine learning and variable selection methodologies have been explored individually and in combination. One of the common core structures identified in the study has been used for data mining databases of commercially available chemicals to identify more similar molecules in terms of structural, pharmacophore, shape similarity and scaffold relatedness. Several promising synthetically accessible small molecules have been identified with based on principles of chemical similarity to a probe (lead compound) and/or predictions from in silico models and/or chemical space. In addition solubility and toxicity prediction studies have been performed by applying in house models. The proposed methodology utilizes multiple sources of information rather than just activity assay data. The series of compounds identified in silico by the proposed workflow have been evaluated and validated *in vitro*.

SUNDAY May 27, 2012

Oral Presentation - 10

FREE ENERGY PERTURBATION CALCULATIONS AS A PREDICTIVE TOOL IN STRUCTURE-BASED DRUG DESIGN

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Structure-based drug discovery is central to the efficient development of therapeutic agents and to the understanding of metabolic processes. In recent years, advances in computer simulations have facilitated the calculation of changes in free energies of binding and the description of detailed underlying molecular and atomic interactions involved in ligand-protein interactions, which help guide molecular design. State of the art structure-based drug design methods include virtual screening and de *novo* drug design; these serve as an efficient, alternative approach to experimental high-throughput screening. However, these methods have inherent limitations such as the absence of solvent and protein flexibility as well as the limited accuracy of scoring functions implemented in them [1]. Thus, these methods are rarely used for the ranking of congeneric series or for the optimization of lead compounds. In contrast, free energy perturbation calculations are currently considered state of the art method to estimate relative free energies of binding, ΔΔG, between similar ligands [2].

In this talk, a series of docking and free energy perturbation calculations coupled with Molecular Dynamics or Monte Carlo calculations targeting the M2TM channel and the Arp2/3 complex, are presented [3]. Low correlation between docking scores and the experimentally measured binding affinities of congeneric compound sets was obtained for both proteins. Our analysis suggests that the weak correlation between the binding affinities predicted from docking calculations and the measured inhibition constants is at least partly due to the fact that protein and water molecules are kept rigid in the docking process. FEP calculations in contrast, allow the system to evolve dynamically and provide a more realistic representation of protein-ligand interactions. A high correlation (>0.65) between the FEP-calculated and experimental results was found. In several instances, when comparing the FEP calculations of the parent compound with respect to the analogs, we noted changes in the positions of water molecules, side chains and even of the protein backbone. These movements appeared to be critical contributors to the ΔΔG of binding. It is also demonstrated in which cases one can perform FEP calculations keeping a rigid backbone and when the protein should be left fully flexible. The correlation between the FEP calculations and the measured inhibition constants, manifest the value of the FEP calculations in predicting the difference in binding affinity of close analogs without the immediate need for synthesis. Moreover, they allow us to construct structure-activity relationships and streamline the development of improved inhibitors of the M2TM channel and the Arp2/3 complex.

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SUNDAY May 27, 2012

Oral Presentation - 11

GAUSSIAN ENSEMBLE SCREENING: A NOVEL WAY TO ANALYSE VIRTUAL SCREENING IN A SYSTEMS PHARMACOLOGY CONTEXT

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In recent years, polypharmacology has increasingly gained attention. Highthroughput screening (HTS) and computational screening have greatly aided in the identification of early lead compounds for drug discovery. However, the large numbers of assays required to identify drugs that interact with multiple proteins make HTS a very slow and costly way to detect promiscuity. Therefore, in silico strategies able to both identify novel scaffold-hopping compounds and assess their polypharmacology are needed.

We previously introduced a spherical harmonic (SH) based approach called Gaussian Ensemble Screening (GES) to predict quantitatively the relationships between drug classes [1][2][3][4]. Using GES, we treat a cluster of similar molecules as a Gaussian distribution with respect to a calculated centre molecule. By calculating the Gaussian overlap between pairs of such clusters, we can calculate the similarity between drug classes rapidly and reliably.

Here, we present a novel extension of the GES approach to allow classical virtual screening (VS) to be applied in the context of systems pharmacology. In the classic view of drug action, a drug interacts with a therapeutic target and modifies its effector pathway in order to achieve a therapeutic effect. However, additional off-target interactions can modify other pathways, thus leading to other adverse or undesired side effects. Our approach aims to improve the efficacy of selecting compounds in VS by taking into account polypharmacology relationships, specific drug information, biological target data, or other specific disease information. This will provide a more rational way to select compounds for testing in a systems-level context than simply selecting a given percentage of hits.

In this contribution, we present results obtained when using the GES/VS approach to analyse polypharmacology relationships amongst the ligands in the DUD dataset [5].

Our results indicate that GES is a useful way to study polypharmacology relationships and provides a novel way to analyse large scale VS with the aim to both identify unknown targets and propose new targets for drug repositioning.

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SUNDAY May 27, 2012

Oral Presentation - 12

THE MEDICINAL CHEMISTRY-RELATED APPLICATIONS IN HP-SEE PROJECT. AN END-USER VIEW

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100 years after Alan Turing was born [1], this communication deals with the high-performance computing (HPC) applied to medicinal chemistry in South East Europe. HP-SEE project (the High-Performance Computing Infrastructure for South East Europe's Research Communities) links existing and upcoming HPC facilities in South East Europe in a common infrastructure, and provides operational solutions for it. Partners span area from Hungary to Azerbaijan. The project includes virtual research communities (VRC): Computational Physics, Computational Chemistry, and Computational Life Sciences. The computational chemistry (including material science) is one of the highlighted research areas in computational science, and a typical heavy user of HPC resources. Considering the size of the problems to be studied, the required calculations are often extremely computationally intensive. Ported software in production phase covers the methods spanning from quantum-mechanics to molecular mechanics level of theory (including hybrid methods, molecular dynamics and molecular docking), as well as cheminformatics applications, and are available mainly from HPC centers in Bulgaria, Romania, and Serbia. In the frame of VRC Computational chemistry, following applications are related to medicinal chemistry: a) CompChem (RS) - QM calculations and molecular dynamics (MD) simulation, for the examination of ligands interaction with proteins, as well as for conformational sampling of small drug-like molecules in explicit solvents; b) IsyMAB (RO) - Provide an efficient, interactive tool for the input preparation and data analysis, obtained by MD simulation in NAMD on large biomolecular systems. The main focus is in the modeling of the G Protein-coupled receptors; c) MD Cisplatin (BG) - QM calculations of Pt(II) type complexes with sulfur-containing ligands, as well as organic molecules of biological interest - peptides, comprising non-natural amino acids; d) PCACIC (BG) - MD of the conformational interconversions in large-ring cyclodextrins, typically during 100 ns, in explicit solvent. Trajectories are analyzed by principal component analysis. Usage examples are given, emphasizing need for the HPC resources to cover size of systems under simulation, and/or the complexity of problem solved.

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SUNDAY May 27, 2012

Main Lecture - 10

CIRCULATING TUMOR CELLS (CTCS) AS NOVEL TUMOR BIOMARKERS

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Blood testing using Circulating Tumor Cells (CTCs) has emerged as one of the hottest fields in cancer diagnosis. Research on CTCs present nowadays a challenge, as these cells are well defined targets for understanding tumour biology and improving cancer treatment. The presence of tumor cells in patient's bone marrow or peripheral blood is an early indicator of metastasis and may signal tumor spread sooner than clinical symptoms appear and imaging results confirm a poor prognosis. CTC enumeration can serve as a "liquid biopsy" and an early marker to assess response to systemic therapy. The detection and analysis of biomarkers characterizing CTCs should allow a greater level of personalized treatment than was previously possible. This lecture will highlight important steps in this field, related to technical advancements in the isolation, detection and molecular characterization of CTCs, and their present use in cancer staging and real time monitoring of systemic anticancer therapies.

SUNDAY May 27, 2012

Main Lecture - 11

COMBINATION OF DATA FROM DIFFERENT INSTRUMENTS IN METABONOMIC STUDIES

Evagelos Gikas[1], Maria Halabalaki[2], Nikolaos Lemonakis[2], Anna Stefanou[2], Samuel Bertrand[3], Julien Boccard[3], Jean-Luc Wolfender[3], Gindro Kati[4], Alexios-Leandros Skaltsounis[2]

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The metabonomics approach is the "systematic study of the unique chemical fingerprints that specific cellular processes leave behind". Many analytical methodologies have been used for the completion of the metabonomics experiments, the main percentage belonging to NMR and MS based techniques. In the current study two high resolution MS instruments (an Orbitrap and a ToF) have been used for the analysis of three variants of the genus *Vitis* one control and two resistant strains to either *Votrytis cinerea or Plasmopara viticola* and the results obtained were initially treated using routine multivariate analysis techniques such as PCA. As the two data sets code for same samples using similar spectrometric techniques, their common informational content has been examined employing various multivariate approaches such as sPCA, sIPCA, sPLS-DA and rCCA.

SUNDAY May 27, 2012

Oral Presentation - 13

NANOTECHNOLOGY IN MEDICINAL CHEMSITRY: ENZYME-TRIGGERABLE STEALTH RELEASE (ETSR) OF NANOPARTICLES FOR siRNA DELIVERY

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Molecular targeted cancer therapy mediated by nanoparticles (NPs) is a promising strategy to overcome the lack of specificity of conventional chemotherapeutic agents. Nanoparticles for drug delivery to tumours are coated with a stealth layer composed of polyethylenglycol (PEG) tethered onto the surface of nanoparticles. [1] The stealth layer provides stability against reticuloendothelial nanoparticle clearance. However it has been found that PEG inhibits cell uptake and escape from endosome. To attain the benefit of stealth property, a site-specific triggerable release mechanism for PEG detachment will be needed. [2]

In our group we have designed enzyme triggerable stealth release nanoparticles. These nanoparticles are removed from the tethered PEG via an enzyme specific cleavage. We have prepared PEG-peptide-lipid conjugates in which the peptide is substrate of matrix- metalloproteinase 2 that is secreted in tumours. In the presence of MMP-2 the peptide is cleaved removing the PEG from the surface of the nanoparticles thereby, facilitating cellular uptake. [3] The newly synthesised PEG-peptide-lipid was used in liposome formulation for siRNA delivery. siRNA (small interfering ribonucleic acid) is a RNA interference (RNAi) technology product, used for silence gene knockdown, which leads to the possibility of its use as a cancer therapy. [4]

siRNA encapsulation in the new nanoparticles was monitored and siRNA transfection was performed in cell studies. The new formulated nanoparticles presented high encapsulation and siRNA transfection efficiency and were compared with the previous studied liposome formulations. It was observed that the enzyme triggered release nanoparticles showed improved uptake and gene silencing effect compared to the stealth nanoparticles.

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SUNDAY May 27, 2012

Oral Presentation - 14

IN VIVO EVALUATION OF A NOVEL IODINATED ELACRIDAR-BASED P-GLYCOPROTEIN INHIBITOR AS A POTENTIAL SPECT MDR PROBE

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Epilepsy affects approximately 3% of the population. The majority of epileptic patients succeed to control epileptic crisis with anticonvulsant drugs, however, 30%-40% became refractory to pharmacological therapies. Multidrug-resistance (MDR) mechanisms observed in cancer, primarily related with the over-expression of P-glycoprotein (P-gp, MDR1, ABCB1), could be also present in Refractory Epilepsy (RE), preventing anti-epileptic drugs (AEDs) to reach their parenchyma brain targets. To study the P-gp function in vivo, high-affinity P-gp substrate, such as racemic [11C]-verapamil and [11C]-loperamide, which are efficiently kept out of the brain by P-gp-transport, have been used as potential PET tracers. On the other hand, in order to map regional differences in cerebral P-gp activity, it would be more advantageous to use a probe based on known and clinically used P-gp inhibitors, such as elacridar or tariquidar. In the present study the main pharmacophoric moiety of elacridar was converted into an iodo-bearing urea derivative. The novel compound exhibited comparable to elacridar in vitro P-gp inhibitory activity. The appropriate stannyl- precursor was radioiododestannylated with ^{125}INa under various oxidizing conditions. In vivo biodistribution and imaging studies in normal mice, with and without tariquidar pretreatment, *in vitro* and *in vivo* stability evaluation and metabolite analysis are strongly encouraging for further evaluation of this potential SPECT tracer of P-gp function in epilepsy and in other MDR phenotypes.

SUNDAY May 27, 2012

Oral Presentation - 15

HIGH CHARGE DENSITY CATIONIC POLYMERS FOR NUCLEIC ACID DELIVERY

Pispas Stergios*, Mountrichas Grigoris*, Varkouhi Amir K., Schiffelers Raymond** M., Lammers Twan**, Storm Gert**, Hennink Wim. E.****

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Cationic polymers have been studied for nucleic acid delivery both in vitro and in vivo.[1] However, many polymer based formulations suffer lack of stability in biological fluids due to interactions with anionic biomacromolecules such as proteins and polysaccharides.[2] It is expected that the stronger electrostatic interactions between a cationic polymer and nucleic acids, the higher the stability of the polyplexes. In trying to alleviate some of the problems we synthesized quaternized poly[3,5-bis(dimethylaminomethylene)-p-hydroxyl styrene] (QNPHOS) with two permanently charged cationic sites per monomer unit, as well as its block copolymer with poly(ethylene oxide), also known as PEG, (QNPHOS-b-PEO), utilizing anionic polymerization and post-polymerization functionalization techniques.[3] The polymers were evaluated in terms of nucleic acid binding strength and gene silencing and transfection activities of the complexes which these polymers form with siRNA and plasmid DNA, respectively. It was found that siRNA complexes based on QNPHOS and QNPHOS-b-PEO dissociated in the presence of a four fold higher heparin concentration than necessary to destabilize pDMAEMA complexes, a reference cationic homopolymer. Under the same conditions, complexes of DNA and QNPHOS or QNPHOS-PEO did not show any dissociation, in contrast to pDMAEMA polyplexes. The DNA polyplexes based on QNPHOS or QNPHOS-PEO did not show transfection activity, which might be ascribed to their high physicochemical/colloidal stability. On the other hand, siRNA complexes based on QNPHOS and QNPHOS-PEO showed a high gene silencing activity, even better than those based on pDMAEMA. This might be due to the excellent binding characteristics of QNPHOS and QNPHOS-PEO to siRNA, which in turn is ascribed to the presence of two permanently charged cationic sites per monomer unit of these polymers.[4]

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POSTER PRESENTATIONS

Poster - 1

NOVEL 2-ARYL-3-BENZOTHIAZOLE-1,3-THIAZOLIDIN-4-ONES AS POTENT ANTIFUNGAL AGENTS

Pitta Eleni P*., Tsingour Etze T*., Tsolaki Evangelia P*., Geronikaki Athina A*., Ćirić Ana, Soković Marina**, Glamočlija Jasmina****

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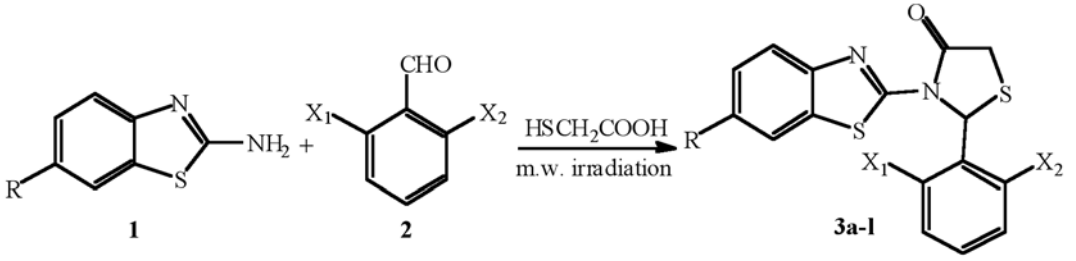
Infectious diseases represent a critical health problem, being one of the main causes of morbidity and mortality worldwide. During the past several years, there has been an increasing incidence of fungal infections due to a growth in immunocompromised population such as organ transplant recipients, cancer and HIV/AIDS patients. A potential approach to overcome the urgent need for antimicrobials and antifungals is to design innovative agents with original modes of action that could target both sensitive and resistant strains. Heterocycles represent "privileged structures" capable of binding to receptors with high affinity. Considering the biological significance of thiazolidinone and benzothiazole and in continuation of our outgoing project on synthesis of pharmacologically significant heterocycles, a novel series of 2-aryl-3-(6-substituted benzo[d]thiazol-2-yl) thiazolidin-4-ones has been synthesized according to Scheme 1.



3a R=-F, X_1, X_2 = -F, **3b** R=-F, X_1=-F, X_2 = -Cl, **3c** R=-F, X_1, X_2 = -Cl, **3d** R=-Cl, X_1, X_2 = -F, **3e** R=-Cl, X_1=-F, X_2 = -Cl, **3f** R=-Cl, X_1, X_2 = -Cl, **3g** R=-OMe, X_1, X_2 = -F, **3h** R=-OMe, X_1=-F, X_2 = -Cl, **3i** R=-OMe, X_1, X_2 = -Cl, **3j** R=-OEt, X_1, X_2 = -F, **3k** R=-OEt, X_1=-F, X_2 = -Cl, **3l** R=-OEt, X_1, X_2 = -Cl

Scheme 1

In order to investigate their antifungal activity they were tested against human pathogenic fungi by using the microdilution method. The following fungi: Aspergillus ochraceus, Aspergillus fumigatus, Aspergillus niger, Aspergillus versicolor, Penicillium funiculosum, Penicillium ochrochloron and Trichoderma viride were used. All the compounds showed very good antifungal activity against all the tested fungi, with MICs in range of 11.75-50.00 μmol/ml x 10^{-2} and MFCs in range of 23.50-104.48 μmol/ml x 10-2, in some cases even excellent, compared to commercial antimycotics, bifonazole and ketoconazole. Thus, they are considered as promising lead compounds in the search for antifungal agents.

Poster - 2

SYNTHESIS OF GLUCOSYL DONORS FROM N-PROTECTED GLUCOSAMINE

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We report efficient and scalable synthetic protocols for preparation of some glucosyl donors that can be used as monosaccharide precursors in the synthesis of more complex oligosaccharide structures. The starting compound glucosamine hydrochloride was converted into the protected intermediates phthalamate (Phth) and tetrachlorophthalamate (TCP) and further acetylated. Recrystalization yielded the N-phthaloyl and N-TCP glucosamine tetraacetate as predominant β-isomer. The obtained products were further used for the preparation of glycosyl donors such as glycosyl bromide, 1-thioglycoside and glycoside azide. To introduce an azide at C-1, the N-phthalimido peracetylated glycosamine was treated with HBr/AcOH. This reaction resulted in formation of corresponding glycosyl bromide as predominantly β-anomer ($J_{H1,H2}$ 9.4 Hz). The second step involved nucelophilic substitution of the bromide by sodium azide in DMF. This reaction gave glycosyl azide as α-anomer ($J_{H1,H2}$ 4.2 Hz).

Acetylated products of N-phthaloyl /N-TCP glucosamine were efficiently converted into the corresponding β-thioetyl glycosides. Acetylated phtaloyl / tetrachlorophtaloyl glucosamine reacted with thioethanol in the presence of boron trifluoride diethyl etherate $BF_3 \cdot Et_2O$ and gave the 1,2-trans product in a high yield.

Poster - 3

PERI -TRIGGERED ANIONIC ORTHO-FRIES REARRANGEMENT: A RECLUSIVE REACTION OF SYNTHETIC POTENTIAL

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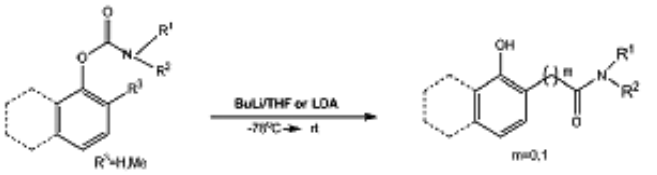
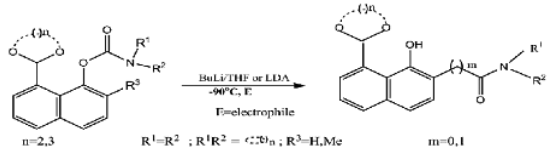
The anionic ortho-Fries rearrangement, also known as Snieckus rearrangement[1], is a 1,3-acyl migration, taking place on an aryl O-carbamate, a synthetically useful entity in its own right[2]. Its homologous version is also known[3] and involves side chain deprotonation of ortho-alkyl substituted congeners followed by intramolecular rearrangement (Scheme 1). The resulting amides are potential precursors to diverse structures.



Scheme 1.

The rearrangement normally occurs at room temperature. However,when intercepted by an electrophile, the carbamate, acting as a Directed Metallation Group (DMG), directs an ortho-aromatic functionalization. Interestingly, substitution at C-8 (*peri-*) position by a bulky group (Scheme 2) triggers the anionic rearrangement (its homologous variant, R^3=Me, too) to proceed rapidly and exclusively in ca. 90% yield at a temperature as low as -90° C. Furthermore, it predominates over any competing ortho-derivatization by a variety of electrophiles (e.g. PhCHO, TMS, MeI, PhCOCl) present , during the reaction.



Scheme 2.

Its facile formation and dominance are attributed to a peri-interaction while the relief of peri-strain[4] provides the driving force.

A theoretical insight as well as its synthetic potential are currently under scrutiny.

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Poster - 4

SYNTHESIS OF 4-SUBSTITUTED 6-METHYLENE-7,8-DIHYDRO-6*H*-PYRROLO[1,2-e]PURINES WITH BIOLOGICAL INTEREST

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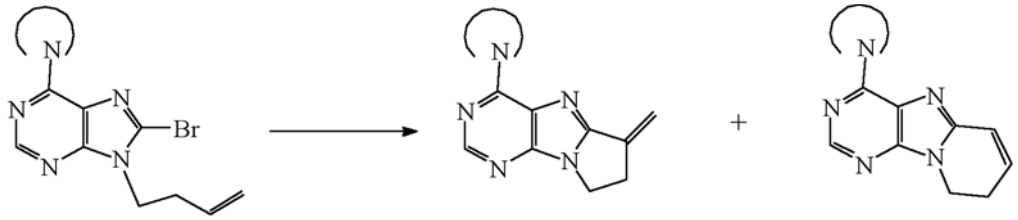
Nucleosides, modified nucleosides [1] and cyclonucleosides [2] represent classes of compounds that possess very interesting biological activities, especially antiviral and anticancer. We have reported recently the synthesis [3] of fused dihydropyrido[e]purines via ring closing metathesis reactions and the study [4] of the reactions of 9-allylpurines with mesityl nitriloxide followed by the evaluation of their products as lipid peroxidation and thrombin inhibitors. In continuation to these studies we like to present here the intramolecular Heck coupling of 6-substituted 8-bromo-9-butenylpurines **1a-c** mainly to the exo products **2a-c** in very good yields (70-90%), while the endo products **3a-c** [3] are formed in traces. The reactions were performed in $MeCN/Et_3N/N_2$ in the presence of $Pd(PPh_3)_4$ as a catalyst under reflux. Different reaction conditions by using of $Pd(OAc)_2$ were tried also for those reactions. These compounds were tested for their biological activity.



1a-c **2a-c** **3a-c**

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Poster - 5

ORGANOCATALYTIC ACTIVITY OF NOVEL PROLINE-BASED DERIVATIVES IN ASYMMETRIC MICHAEL AND DIRECT ALDOL REACTIONS

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Asymmetric organocatalysis has emerged as a rapidly growing and important field in organic chemistry.
The Michael and direct aldol reactions have attracted a great deal of attention because of the important role these reactions play in carbon–carbon bond formation in synthetic organic chemistry. In particular, cross aldol condensation between ketones and aldehydes yields β-hydroxy ketones, which are structural units found in many naturally occurring molecules and pharmaceuticals. On the other hand the asymmetric Michael addition of carbonyl compounds to nitroalkenes remains a great challenge for organic chemists, because it leads to the construction of C-C bond with simultaneous generation of up to three stereogenic centers and because of the pivotal role of the nitro group as a precursor to many functionalities.
The enantioselective Michael and aldol reactions catalyzed by small molecule organocatalysts are important C-C bond forming reactions for which excellent enantioselectivities have been achieved in organic solvents. It would be promising from a green chemistry perspective if high enantiocontrol is achieved using small organic molecule organocatalysts on water. Water is a green, safe, nontoxic, nonflammable and also inexpensive solvent for organic reactions.
In the present communication, we present efficient enamine based organocatalytic direct asymmetric aldol and Michael reactions on water without any organic cosolvent. Reactions afforded the desired products in high yields with high diastereoselectivities and excellent enantioselectivities using novel proline-based organocatalysts.

Acknowledgements: The research leading to these results has received funding from the European Union's Seventh Framework Programme (FP7-REGPOT-2009-1) under grant agreement no. 245866.

Poster - 6

NOVEL 3′-AZIDO AND 3′-AMINO PYRANONUCLEOSIDES: SYNTHESIS AND EVALUATION OF THEIR ANTITUMOR ACTIVITIES

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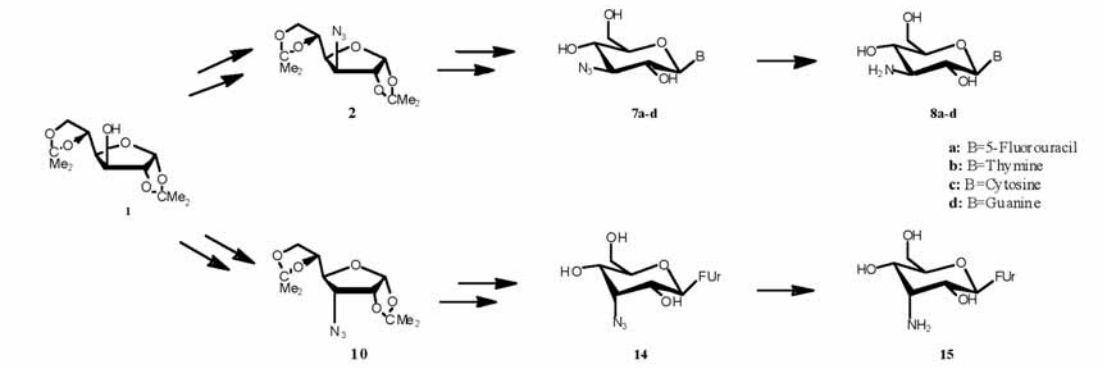
A series of novel 3′-azido-3′-deoxy and 3′-amino-3′-deoxy pyranonucleoside analogues has been designed and synthesized. Two different synthetic routes were investigated for the conversion of diacetone-D-glucose (1) to the desired compounds 8a-d and 15. In the first approach, 3′-azido-3′-deoxy-α-D-glucopyranonucleosides 7a-d were readily prepared from furanose 1, *via* a protection/deprotection sequence. Finally, catalytic hydrogenation of 7a-d afforded the desired 3′-amino-3′-deoxy-glucopyranonucleosides 8a-d. In the second approach, diacetone-D-glucose (1) was easily converted into the β-nucleoside 14 *via* a series of transformations of functional groups involved. Finally, conversion of azido group to amino group afforded the desired 3′-amino-3′-deoxy-allpyranonucleoside 15. The novel 5-fluorouracil pyranonucleosides 7a, 8a and 15 proved to be cytostatic against a variety of tumor cell lines. The compounds should be regarded as potential new lead compounds to be further investigated for anticancer therapy.



Poster - 7

NEW METHODS OF SYNTHESIS OF 1,3,5-TRIAZINE-2,4(1*H*,3*H*)-DIONES, 4-METHOXY-1,3,5-TRIAZIN-2(1*H*)-ONES AND 1,3-DIMETHYL-1,3,5-TRIAZINE-2,4-DIONES

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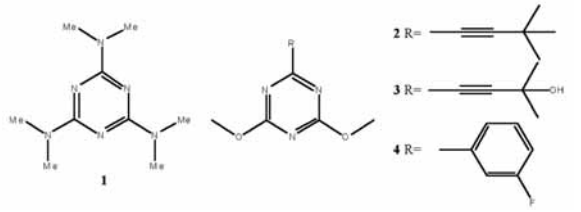
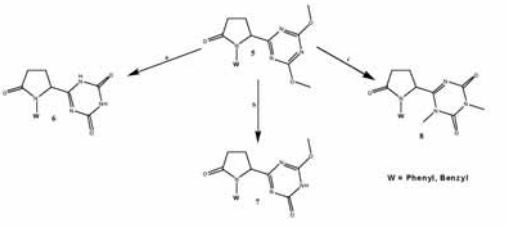
A series of 2,4,6-tris(*N*,*N*-dialkylamino)-1,3,5-triazines has been studied for their antitumoral activity[1-3]. Among these derivates, hexamethylmelamine (1), an alkylating agent, is very efficient against ovarian, breast, and lung cancers but it generates side effects limiting its use in clinic. Thereafter, similar compounds such as 2-alkyl-4,6-diheteroalkyl-1,3,5-triazines demonstrated a significant cytotoxicity towards various tumor cell lines *in vitro*.



It was suggested that the antitumoral activity of some triazinic derivates is related to the fact that these compunds represented antimetabolites wich are able to accumulate in tumor cells. Currently, the chemical reactivity of these triazines attached in position 5 to *N*-benzylpyroglutamic or *N*-phenylpyroglutamic derivatives **5** has been explored under different conditions in order to access to new aza-analogs with potential bioactivity.



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Poster - 8

A CASE OF KETONE HOMOLOGATION VIA WITTIG REACTION

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It has been recently described that a new family of substituted 1,1-diarylethylenes, called isocombretastatins, displays a biological activity similar to the one of their combretastatin or phenstatin homologues [1] (Figure 1).

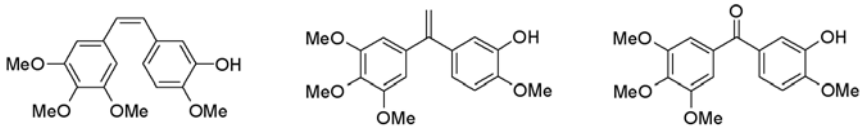

Figure 1: Structure of combretastatin A-4 (1) and corresponding isocombretastatin A-4 (2) and phenstatin (3).

In order to synthesize novel isocombretastatins, numerous benzophenones were engaged into a Wittig reaction. We observed, in the case of ketone 4, that the corresponding 1,1-diarylethylene was not formed, instead ketone 5 was isolated (Figure 2).

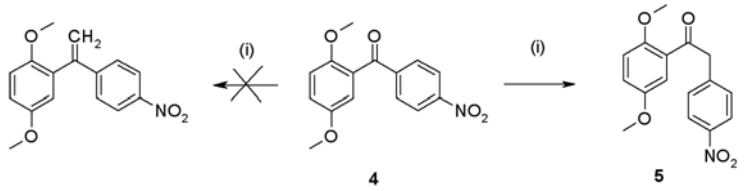

Figure 2: (i) CH_3PPh_3Br (2 equiv.), tBuOK (5 equiv.), THF, rt, 18h.

A study of the influence of the aryl substituants on this ketone homologation was carried out, and a mechanism was proposed to explain the methylene insertion.

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Poster - 9

SYNTHESIS OF NEW PHENOTHIAZINE AND CARBAZOLE DERIVATIVES AS POTENTIAL INHIBITORS OF HUMAN FARNESYLTRANSFERASE

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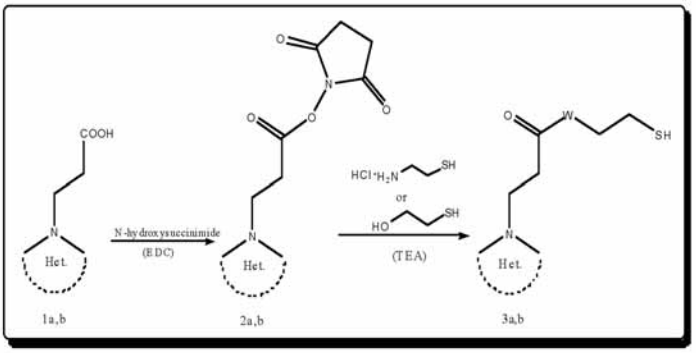
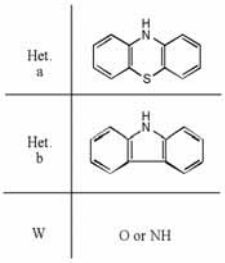
Many biological properties have already been described for phenothiazine and carbazole derivatives,[1] some of phenothiazine derivatives display anthelmintic activities,[2] and others are (reversible) inhibitors of trypanothione reductase,[3] inhibit lipid peroxidation[4] or tubulin polymerization[5], and some carbazole derivatives are inhibitors of human adipocyte fatty acid-binding protein.[6]
To the best of our knowledge, the carbazole and the phenothiazine scaffolds were not encountered in the field of inhibitors of human farnesyltransferase. We report here the synthesis of such derivatives (Scheme 1).



Scheme 1. Synthesis of new phenothiazine and carbazole derivatives, potential inhibitors of farnesyltransferase



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Poster - 10

ECO-FRIENDLY METHOD FOR THE SYNTHESIS OF CHERYLLINE DERIVATIVES

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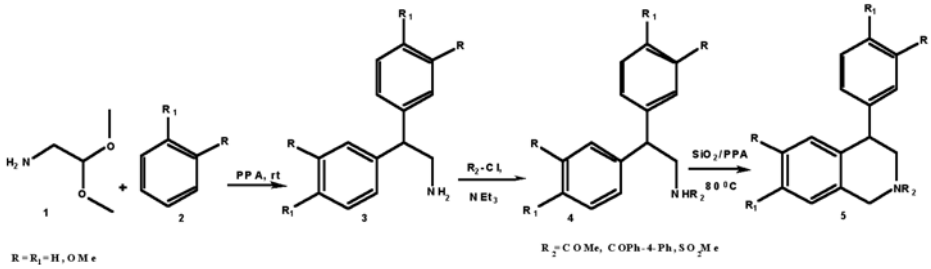
Amaryllidaceae is one of the most studied families of plants because of its alkaloid composition. Rare natural 4-aryl-1,2,3,4-tetrahydroisoquinoline alkaloids have been isolated from *Crinum powellii* var. *alba* and other *Crinum* species. Due to the uniqueness of the structure and the potential medicinal properties of the 4-arylisoquinoline derivatives, many synthetic routes for these compounds and especially cherylline have been reported. Most of the reported methods for the synthesis of these compounds are either multistep or low yielding.



Scheme 1

We synthesized cherylline analogues **5** from amides **4** through α-amidoalkylation reaction. The required amides **4** we prepared from amines **3** via acylation with different acid chlorides. The amines **3** were obtained from aminoacetaldehyd-dimethylacetal **1** and benzene or different substituted benzenes **2**. For the synthesis of **5** we have developed a highly efficient SiO_2/PPA catalyzed method for construction of 4-aryl-1,2,3,4-tetrahydroisoquinoline ring system. We found that in comparison to conventional methods, the yields of the reaction are greater and the reaction time is shorter. The catalyst is completely recoverable and the efficiency of the catalyst remains unaltered even after three to four cycles. The structure of the obtained compounds was determined using spectral methods (IR, ^{1}H-, ^{13}C-NMR).

Poster - 11

ENANTIOSELECTIVE TOTAL SYNTHESIS OF LAURENDITERPENOL, A POTENT AND SELECTIVE INHIBITOR OF HIF-1

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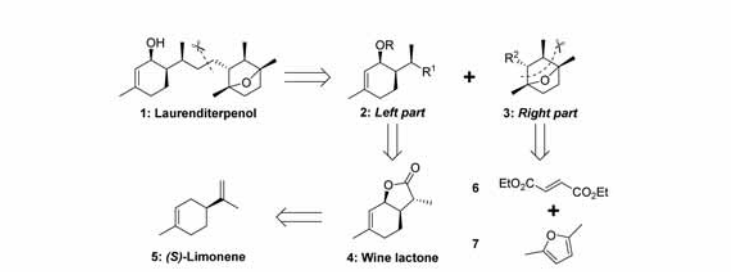
Inhibitors of Hypoxia Inducible Factor-1 (HIF-1) activation represent potential novel anticancer drug leads.[1] In this context, Laurenditerpenol (**1**) was isolated by bioassay-guided fractionation of the lipid extract of the red alga *Laurencia intricata* as a potent and selective inhibitor of HIF-1 hypoxia triggered activation (IC_{50}: 0.4 μM) and hypoxia-induced VEGF (a potent angiogenic factor) in T47D cells.[2] It features an unprecedented 7-oxabicyclo[2.2.1]-heptane ring system and several contiguous stereogenic centers.



The combination of structural novelty and complexity along with its important biological properties have attracted the attention of synthetic organic and medicinal chemists.[3] According to our strategy towards this natural product, **2** and **3** have been targeted as advanced key intermediates. Various methods, such as olefin cross-metathesis[4](R^1, R^2 = CH=CH_2) or metal-catalyzed alkyl–alkyl cross-coupling reaction[5](R^1 = CH_2Br; R^2 = CH_2BR_2), could in principle be exploited to establish the complete carbon framework. The enantioselective preparation of the prerequisite key building blocks **2** and **3** exploiting the chirality of (*S*)-limonene (**5**) and a catalytic enantioselective Diels-Alder addition of **6** to furan **7**, construction of the complete carbon framework and progress towards completion of the total synthesis will be presented.

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Poster - 12

SYNTHESIS, STRUCTURE ELUCIDATION AND CONFORMATIONAL ANALYSIS OF NOVEL QUINOLINYL-CHALCONES WITH ANTIOXIDANT AND ANTI-INFLAMMATORY ACTIVITY

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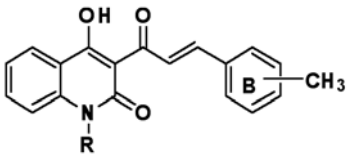
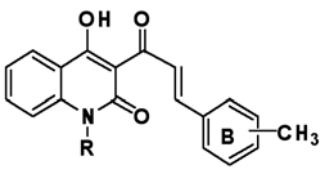
The fused heterocyclic system of quinolinones is present in numerous natural products, especially alkaloids and exhibit a wide range of biological activities. Chalcones are flavonoid precursors encountered in edible plants, which possess important bioactive properties. The aim of this work is the synthesis of novel quinolinyl-chalcones, which combine the heterocyclic system of quinolinones and the α,β-unsaturated carbonyl system of chalcones in the same molecular scaffold in order to investigate their antioxidant and anti-inflammatory properties.

The desired compounds were synthesized via aldol condensation between N-substituted-3-acetyl-4-hydroxy-2-quinolinone with appropriately substituted aromatic aldehydes. The antioxidant activity of the new analogues was evaluated using two different assays, namely interaction with the stable free radical DPPH and ability to inhibit lipid peroxidation. In addition, the molecules were tested for their ability to inhibit soybean lipoxygenase *in vitro* as an indication of their anti-inflammatory activity. The best combined activity was exhibited by the chalcone possessing a benzyl group on the heterocyclic nitrogen.



s-cis



s-trans

The structure of all the novel quinolinyl-chalcones was elucidated using one and two-dimensional NMR spectroscopy. The position of the methyl substituent on ring B of the chalcone moiety was found to affect the conformation (*s-cis* or *s-trans*) adopted by the molecule in DMSO solution. In order to further explore this finding, conformational analysis techniques were implemented in order to correlate different substitutions with low energy conformers, bearing physicochemical properties possibly related to increased activities.

Poster - 13

SYNTHESIS AND STRUCTURAL CHARACTERIZATION OF NOVEL FLAVANONE AND ARYLIDENE-FLAVANONE DERIVATIVES WITH ANTIOXIDANT ACTIVITY

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Flavanones and arylideneflavanones are important natural products and represent a significant intermediate in many pharmaceutical syntheses. Being members of the flavonoid family, they are attracting increased attention due to results of studies documenting their anticancer, antiinflammatory, antibacterial and anti-HIV pharmacological activity.

Our goal was to synthesize flavanones and arylideneflavanones via a condensation reaction between appropriately substituted 2′-hydroxy-acetophenones and 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde in saturated hydrogen chloride methanol solution. The antioxidant activity of the new compounds was evaluated using the luminol chemiluminescence assay which measures the ability of a compound to scavenge H_2O_2.

The isomerization-tautomerization of the new compounds in solution was extensively studied using NMR and UV-Vis spectrocopy in different solvents. The studies reveal the tendency of halogen-substituted flavanones to exist in equilibrium with the corresponding chalcones in DMSO solution.

Poster - 14

MICROWAVE ASSISTED SYNTHESIS OF HYDROXYTYROSOL

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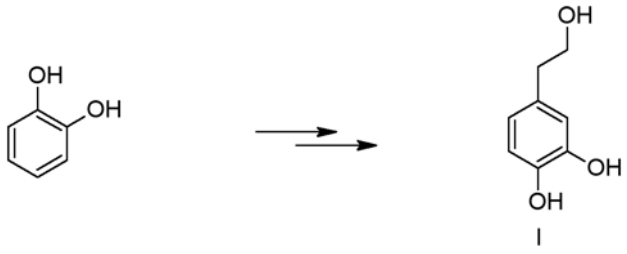
Hydroxytyrosol I is the main phenolic compound of olive oil. This o-diphenol has strong antioxidant and antimicrobial properties, as well as beneficial effects on the cardio-vascular system and in several human diseases. Clear epidemiological and biochemical evidence indicates that hydroxytyrosol is endowed with significant antithrombotic, antiatherogenic, and anti-inflammatory activities.
Prompted by the above mentioned biological properties of hydroxytyrosol, we decided to investigate the large scale synthesis of this bioactive compound using reactants and techniques offering operational, economic and environmental benefits, over conventional methods. Consequently, we present here the microwave assisted preparation of hydroxytyrosol I, in three steps, starting from catechol.



I

Poster - 15

DESIGN AND SYNTHESIS OF A SERIES OF A NOVEL THIAZOLO FUSED XANTHONES

Iliopoulos-Tsoutsouvas Christos, Paraskevas Konstantinos, Kostakis K. Ioannis, Marakos Panagiotis, Pouli Nicole
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Many compounds based on tricyclic planar chromophore framework, fully or partially consisting of anthraquinone, anthrapyrazole, or acridine, show interesting cytostatic and antitumor properties. We have been involved in the design, synthesis and cytotoxic activity evaluation of a series of amino substituted xanthones with a fused imidazolo moiety. These compounds have shown promising antiproliferative activity against human breast cancer cells. During the exploration of the structure activity relationship of this class of compounds we have found that imidazole tautomerism is crucial for the improvement of the antiproliferative activity. Prompted by the above mentioned considerations we describe here the design and synthesis of some novel thiazolo-fused xanthones, in order to evaluate the effect of this structural modification on the tumor cell growth inhibition. The compounds were prepared using ethyl salicylate as starting material, which after a series of reactions led to 4-amino-3-bromo-1-chloro-9*H*-xanthen-9-one. This compound was used as an intermediate for the synthesis of the aminosubstituted target derivatives.

Poster - 16

DESIGN AND SYNTHESIS OF SOME NEW AMINOSUBSTITUTED XANTHONES

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9-Methoxypyrazoloacridine (PZA) combines the DNA complexing activity of the acridine chromophore with the potential hypoxic cell-selectivity deriving from a reducible nitro group substitution, which is present on this scaffold. This compound retains full activity against resistant cell lines that exhibit the MDR phenotype, probably targeting both topoisomerases simultaneously without stabilization of the topoisomerase-DNA cleavable complexes.

We have previously been involved in the synthesis and antiproliferative activity study of a number of cytotoxic xanthone aminoderivatives, which showed interesting cytotoxic activity against leukemia as well as against human solid tumor cell lines. As a continuation of this study we present here the synthesis of a series of novel aminosubstituted xanthones, possessing structural analogy to PZA. The preparation of the title compounds proceeds through coupling of ethyl 2-iodobenzoate with m-cresol, followed by nitration, saponification and cyclization to the corresponding 1-methyl-2-nitro-9*H*-xanthen-9-one. This was brominated, hydrolyzed and oxidized to afford the corresponding acid, which was reacted with suitable amines to provide the target compounds. The antiproliferative activity of the new molecules will be evaluated against wild type and resistant tumor cell lines.

Poster - 17

NEW AMINOSUBSTITUTED PYRAZOLOPYRIDINE DERIVATIVES AS POTENTIAL KINASE INHIBITORS

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During the last years, due to the need for improvement of cancer cure, the scientific research has focused on the estimation of molecular targets and on the prediction of the structure of potential drugs. Numerous investigations have led to substantial knowledge of the mechanisms of carcinogenesis and this has resulted, among others, to the development of kinase inhibitors as very promising pharmacological targets. These enzymes control cell cycle via protein biophosphorylation, an important reaction in the post translational regulation of enzymes and structural proteins. Abnormal activation of kinases or absence of their naturally occurring inhibitors results in many human disorders and even to the loss of control of cell proliferation. A number of diverse classes of kinase inhibitors have been reported at the present and many of them have derived from the purine scaffold, like the established inhibitors of cyclin depended kinases olomoucine, roscovitine and purvalanol A and B. Based on the above mentioned considerations we describe here the design and synthesis of some new substituted pyrazolo[3,4-*c*]pyridines, a scaffold that can be regarded as the 8-aza-3,9-deazapurine condensed heterocyclic system. The compounds were prepared using 2-amino-4-picoline as starting material, which after a series of reactions led to 3-acetamido-2-chloro-4-picoline which through diazotation, ring closure and nitration provided the corresponding 7-chloro-3-nitro-1*H*-pyrazolo[3,4-*c*]pyridine. This analogue was used as a common intermediate which upon substitution, reduction and chloroacetylation provided the route for the synthesis of the aminosubstituted target derivatives. The aim of the project is to study the new derivatives against a panel of kinases and extract structure activity relationships concerning this scaffold.

Poster - 18

TAUTOMERIC EQUILIBRIA OF SUBSTITUTED PYRAZOLO[4,3-*c*] PYRAZOLES: SYNTHESIS OF THEIR POSSIBLE N-METHYL ISOMERS

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Substituted purines and purine analogues consist a biologically important group of heterocyclic compounds. Among them a number of variously substituted pyrazolopyridines have been shown to be potent inhibitors of phosphodiesterases, matrix metalloproteinases, glycogen synthase kinase-3, and cyclin-dependent kinases. Generally, these compounds could exist in a number of tautomeric forms. The tautomerism of isolated nucleic acid bases and several purine derivatives have been investigated extensively, since tautomeric equilibria should be considered in any study of their binding modes with biological targets. We have been previously involved in the systematic study of various pyrazolopyridines, focusing in their possible tautomeric species. As a continuation of our investigation we have also prepared a series of derivatives belonging to the closely related scaffold pyrazolo[4,3-c]pyrazole. We have thus decided to study the tautomeric equilibria of this scaffold by means of NMR experiments and theoretical calculations and for this purpose we have synthesized a number of substituted pyrazolo[4,3-c]pyrazoles along with their N-methylated isomers. For the preparation of the compounds we have used suitably substituted pyrazoles as starting materials, which underwent nitration, reduction and thermal cyclization to provide the pyrazolopyrazole ring system. The compounds were fully N-methylated and the resulting isomers were separated and studied.

Poster - 19

THE DESIGN AND SYNTHESIS OF NOVEL TRICYCLIC NUCLEOSIDES AS POTENTIAL ANTIPROLIFERATIVE AGENTS

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The nucleotides are the structural units of nucleic acids and play a crucial role in many metabolic processes. The study of their structural analogues is an important area of research within biological sciences, and numerous derivatives possess therapeutic interest, mainly as antiviral and anticancer drugs. The plant hormones cytokinins, which chemically are adenine analogues, promote cell division and differentiation. Their physiological role has prompted the development of compounds that might repair dysfunctions of cell division and differentiation in animal cells, as in the case of cancer cells. Furthermore their ribonucleotide derivatives, natural and synthetic, inhibit proliferation of cancer cells through selective activation of apoptosis and simultaneous blockade of the transition of G1 / S cell cycle. Based on the above mentioned considerations, a number of non-classical adenosine derivatives have been prepared in order to study their potential antiproliferative activity. The new molecules bear a tricyclic structure mimicking the purine system and possess alkylamino substituents which are present into active cytokinins. The derivatives were synthesized using as starting material 2,6-diaminopyridine which upon acetylation, nitration, selective deacetylation and reduction of the nitro group revealed an intermediate o-diamine. This compound was converted to the corresponding imidazolpyridine which was then subjected to nitration, reduction of the nitro group and reaction with glyoxal to provide imidazo[4′,5′:5.6]pyrido[2,3-*b*]pyrazine. Glycosylation of this molecule gave the two possible regio-isomers. The major isomer was converted to the 9-chloro derivative which was used for the preparation of the 9-aminosubstituted analogues.

Poster - 20

STUDIES TOWARD A NOVEL TOTAL SYNTHESIS OF ECTEINASCIDIN-743: DISCOVERY OF A NEW SYNTHESIS OF B-LACTAMS

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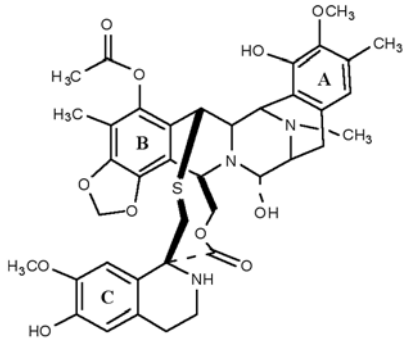
Ecteinascidin-743 **(1)** isolated from the Caribbean tunicate Ecteinascidia turbinate, [1] is arguably the most potent cytotoxin known as indicated by its evaluation against the National Cancer Institute's human *in vitro* cell line panel including melanoma, non-small-cell lung, ovarian, renal, prostate, and breast cancer, demonstrating **potencies** ranging from ***1 pM to 10 nM.***[2] In fact, the antiproliferative activity of Et-743 is greater than that of Taxol, camptothecin, adriamycin, mitomycin C, cisplatin, bleomycin, and etoposide by 1-3 orders of magnitude, propelling trabectidin **(1)** to become the first marine anticancer drug to be approved (October 2007) in the European Union (EU),[3] as a first-line treatment for soft tissue sarcomas. The complexity of molecular architecture, the remarkable biological activities, and the restricted natural availability (1.0 g from about 1.0 ton of tunicate) have made **1** an exceedingly attractive synthetic target for total synthesis. [4] Our studies toward the validation of key elements of our retrosynthetic analysis will be presented including the general and useful synthesis of the title.



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Poster - 21

SOLID PHASE PEPTIDE SYNTHESIS OF THE TRANSMEMBRANE DOMAIN OF TETRAMERIC INFLUENZA A M2 PROTEIN (M2TM) AND MEASUREMENTS OF BINDING AFFINITIES OF SOME AMINOADAMANTANE LIGANDS AGAINST THE A/M2TM TETRAMERS USING ISOTHERMAL TITRATION CALORIMETRY

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The biological activity of aminoadamantane ligands against influenza A virus is due to inhibition of membrane M2 protein. The ligands block the ion channel pore formed by the transmembrane domain of M2 protein (M2TM) consisting by residues 22-46. The detailed molecular basis of the activity of these compounds provides an essential prerequisite in order to develop refined ligands structures against mutant and amantadine resistant viruses.

To explore this host – guest problem, we undertook first the synthesis of some 25-residues M2TM peptides using solid phase peptide synthesis. Some peptides have been already synthesized including the wild type Udorn sequence (SSDPLVVAASIIGILHLILWILDRL(amide)), other mutant peptides, fluorine labeled sequence with F-Trp-41 for SAR by ^{19}F NMR etc.[1] The purification of these highly lipophilic peptides is a laborious procedure.

When the peptides were inserted in a suitable DPC environment at alkaline pH M2TM tetramers are formed spontaneously; these architectures represent suitable models of the full M2 protein as regards the interaction with aminoadamantane ligands. The binding affinities of some aminoadamantane ligands ligands were measured using Isothermal Titration Calorimetry (ITC) against the M2TM receptor formed by a mutant Weybridge sequence (SSDPLIVAASIIGILHFILWILDRL(amide)). The measured binding constants provide the necessary experimental probes for understanding the ligand – receptor interaction using structure calculations (docking methods, simulations etc).

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Acknowledgements: We thank Chiesi Hellas for the financial support.

Poster - 22

ISOLATION AND CHARACTERIZATION OF THE OZONOLYSIS INTERMEDIATES AND PRODUCTS OF PROTECTED THYMIDINES

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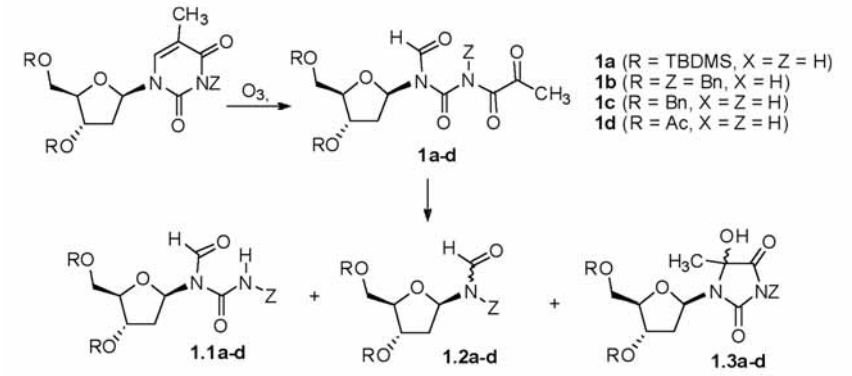
A number of environmental pollutants and endogenous oxidation agents may generate 1-(2-Deoxy-β-D-ribofuranosyl)-5-hydroxy-5-methylhydantoin (**1.3**, 5-OH-5-Me-dHyd), a known DNA lesion, after hydroxyl radical addition, electron abstraction by Type I photosensitizer or ozone oxidation of thymidine. The lesion is repaired by enzymes, which exhibit both on *N*-glycosylase and AP-lyase activity such as Endo III (*E.coli*) or Fpg but not by human or yeast Ogg1. It exists in equilibrium with *N*-(2-deoxy-β-D-ribofuranosyl)-*N'*-(pyruvoyl)-urea, an open chain form, which has been speculated to play an important role in the lesion recognition mechanism.[1] In this work, the products of the ozonolysis reaction of protected thymidines have been characterized. Specifically, the precursor compounds *N*[1]-formyl-*N*[1]-pyruvoylurea intermediates **1a-d** were characterized for the first time. These structures have been postulated in the literature[2] but have not been characterized to date. The decomposition products were also isolated and characterized and more specifically, the *N*-formylurea **1.1a-c**, the N-formamide **1.2a-c** and the hydantoin **1.3a-c**. In the case of the tribenzylated thymidine, the hydantoin **1.3c** was isolated directly from the ozonolysis reaction, which led to a proposed mechanism. The open-chain pyruvoyl-urea isomer of **1.3a-d**, although not observed under ozonolysis, was successfully synthesized in preliminary *de novo* synthetic studies providing further insights in the reaction mechanism.



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Poster - 23

SYNTHESIS OF SOME AMIDE DERIVATIVES AS NEW ANTIMICROBIAL AGENTS

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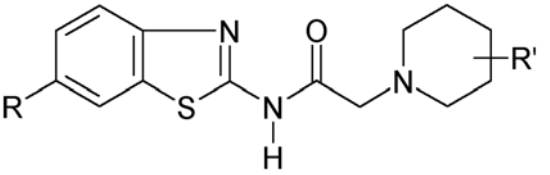
Medicinal chemists have carried out considerable research for novel antimicrobial agents bearing amide moiety. Penicillins and cephalosporins, which possess cyclic amide as the main scaffold and acetamide moiety as the side chain, are widely used antibiotics for the treatment of systemic infections. In this study, N-(benzo[d]thiazol-2-yl)-2-(piperidin-1-yl)acetamide derivatives were obtained by the reaction of 2-chloro-N-(benzothiazole-2-yl)acetamides with piperidine derivatives. The compounds were investigated for their antimicrobial effects and compared with ketoconazole and chloramphenicol. The microbiological results revealed that some derivatives showed good activity.



Poster - 24

ANTIPROLIFERATIVE EFFECTS OF SOME BISTHIAZOLES

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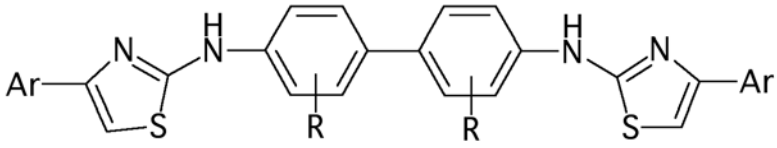
Cancer, which is characterized by the uncontrolled growth of abnormal cells in the body, has emerged as the second leading cause of death throughout the world after cardiovascular disorders. The incidence of cancer has increased dramatically in the last decades. As a consequence of this situation, the treatment of cancer has gained great importance [1-3].
From the above, it is clear that the search for new effective compounds which can selectively inhibit the proliferation of abnormal cells only with least or no affect on normal cells has gained great importance [4].
Prompted by these observations, we prepared some bisthiazole derivatives and investigated their antiproliferative effects.



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Poster - 25

SYNTHESIS OF NOVEL IMIDAZOLE DERIVATIVES AS ANTIFUNGAL AGENTS

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Imidazoles constitute a class of antifungal agents. Treatment of fungal diseases with imidazoles has started with miconazole and ketoconazole and then fluconazole and itraconazole have been developed. Thus, imidazoles have become the most attractive group in the last two decades because they have been the most successful agents among the antifungal drugs. They act by competitive inhibition of the lanosterol 14α-demethylase (CYP51), [25] which is a key enzyme in sterol biosynthesis of fungi. Selective inhibition of CYP51 would cause depletion of ergosterol and accumulation of lanosterol and other 14-methyl sterols resulting in the growth inhibition of fungal cells. Unfortunately, imidazoles are fungistatic against yeasts and their broad use leads to development of resistance showing the urgent need for new and effective antifungal agents. Depending on this requirement, in the present study new imidazole derivatives, which display structural similarity to existing antifungal drugs, were synthesized. Chemical structures of the obtained compounds were confirmed by spectral data. Antifungal activity measurements were performed on four different *Candida* strains and MIC values were determined. The compounds 4, 8, 12, and 16, which bear 2,4-dichlorobenzyloxy structural fragment, were the most active compounds in the series. MIC values of such compounds were lower than that of reference drug ketoconazole against some of the strains.

Poster - 26

SYNTHESIS OF NEW HYDRAZONE DERIVATIVES AND EVALUATION OF THEIR ANTIMICROBIAL ACTIVITY

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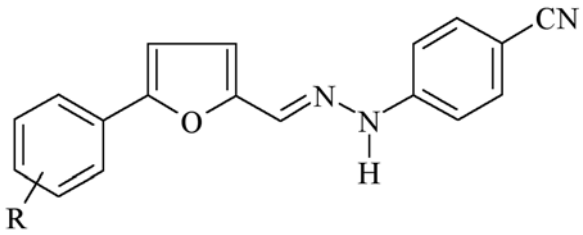
Hydrazones have received considerable attention due to their biological importance in medicinal chemistry. Many studies have confirmed that hydrazone derivatives exhibit a wide spectrum of biological effects including antimicrobial activity. In the present study, some hydrazone derivatives were synthesized via the reaction of 4-cyanophenylhydrazine hydrochloride with 5-substituted furfural derivatives. The compounds were evaluated for their antimicrobial effects. The biological results indicated that the compounds showed different levels of antimicrobial activity.



Poster - 27

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF CHALCONE DERIVATIVES BEARING INDOLE MOIETY

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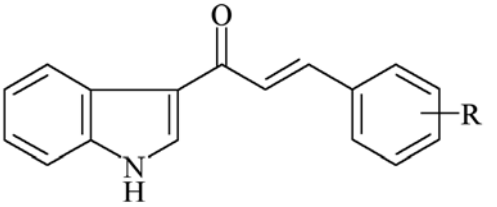
Chalcones have attracted a great deal of interest owing to their biological importance in organic and medicinal chemistry. Many studies have confirmed that chalcone derivatives exhibit a wide spectrum of biological effects including antimicrobial activity. In the present work, 1-(1H-indol-3-yl)-3-phenylprop-2-en-1-ones were obtained by the reaction of 3-acetylindole with various benzaldehyde derivatives in the presence of potassium hydroxide. The synthesized compounds were evaluated for their antimicrobial activity. The compounds showed different levels of antimicrobial activity.



Poster - 28

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEW HYDRAZONE-BRIDGED PYRROLE-THIAZOLE DERIVATIVES

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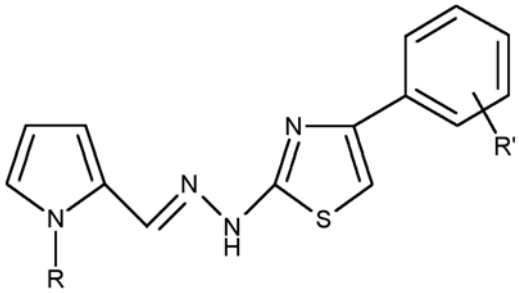
In this work, we synthesized fourteen different compounds which are containing hydrazone bridged thiazole and pyrrole rings. For this purpose pyrrole-2-carboxaldehyde was reacted directly with thiosemicarbazide in ethanol by refluxing and then obtained thiosemicarbazone was condensed with α-bromo-4-substituted acetophenone derivatives (Hantzsch reaction) to give 2-[4-(substituted phenyl)-2-thiazolyl]hydrazone pyrrole-2-carboxaldehydes. The structures of the obtained compounds were elucidated by using IR, ^{1}H-NMR and FAB$^+$-MS spectral data and elemental analyses results.
All of the the compounds were screened for their antibacterial and antifungal activities against twelve different microorganisms by using microbroth dilution method. Ketoconazole and chloramphenicol were used as standard drugs. All of the compounds showed good activity against *S. aureus and E. faecalis*.



Keywords: Antimicrobial activity, Hydrazone, Thiazole, Pyrrole

Poster - 29

STRUCTURAL MODIFICATION OF VIRTUAL LEAD ACTIVE ON ALPHA 7 NICOTINIC ACETYLCHOLINE AS ANTICANCER AGENTS

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Alpha 7 nicotinic acetylcholine receptors (α7-nAChRs) are the homopentameric ligand-gated ion channel. According to the high permeability to calcium ion, α7-nAChRs have been intensively studied on their relevance to various pharmacological processes, especially neurological disorders and malignancies. The aim of this study was to modify the core structure of virtual lead as active ligands on α7-nAChR. The method of the study began with the structure-based drug design and modification using a validated acetylcholine binding protein from PDB coded 1UW6. The optimization of virtual lead gave a 90-ligand library that was further brought to the molecular docking (AutoDock) and ranking. The 20-top ranked compounds were filtered by three parameters: free binding energy (ΔG) less than -8.0 kcal/mol, ligand efficiency less than -0.3 kcal/mol/non-hydrogen atom, and member in the highest cluster more than 50%, yielding 6 optimized compounds. Six compounds were synthesized by the nucleophillic substitution reaction between monocyclic and bicyclic system linked with amine linkage. The newly synthesized compounds were tested for the cytotoxicities against lung cancer cell lines (H187, H460). The cytotoxicity against cancer cell lines revealed that QN1 and BZ1 are active against human small cell lung carcinoma (H187) with the IC_{50} of 27.02 and 66.43 μM, respectively. Not only H187, QN1 was also found to be active against human non small cell lung carcinoma (H460). In conclusion, two potential compounds (QN1 and BZ1) were identified as anticancer agents by in silico experiment. The molecular mechanisms of action of active compounds are currently investigated in order to evidence α7-nAChR as new therapeutic target for cancer.

Poster - 30

DIRECT ANTIPROLIFERATIVE EFFECT ON BREAST CANCER CELLS OF [Mpa¹, D-(Et)Tyr²] OR [Mpa¹, D-1-Nal²] OXYTOCIN ANALOGUES CONTAINING β-(2-THIENYL)-ALANINE IN POSITION 3 OR 7

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Oxytocin (OT) is a hypothalamic cyclic nanopeptide that is secreted in the blood from the posterior lobe of the pituitary gland, inducing uterine contractions during parturition and milk ejection during suckling. The widespread allocation of OT receptors (OTR) in the central nervous system has firmly established OT as a central neurotransmitter with roles in reproductive and social behaviors. The role of oxytocin in provocation of premature birth led to the design of synthetic peptide and non-peptide OT antagonists as potential tocolytic agents for the prevention of premature birth. The last years, a new role of OT in the pathology of cancer is promoted. Several tumor types have been reported to express OT receptors (OTRs) including primary breast cancers, endometrial carcinomas, neuroblastomas, glioblastomas. Current data suggest that in breast-cancer cells OT inhibits cell proliferation both *in vitro* and *in vivo*. Based on these findings, we herein report the synthesis of analogues of OT: [Mpa¹, D-Tyr(Et)2] or [Mpa¹, D-1-Nal²]OT containing L or D-β-(2-thienyl)-alanine [Thi] in position 3 or 7. The analogues were tested for the inhibition of proliferation on human hormone-dependent and -independent breast cancer cells MCF-7 and MDA-MB468, respectively. The analogues were synthesized by the Fmoc/But solid phase methodology utilizing a 2-chlorotrityl chloride resin as solid support bearing a Rink-Bernatowitz linker to provide the peptidic amide and diisopropylcarbodiimide/1-hydroxy-benzotriazole (DIC/HOBt) as coupling agent. Furthermore the analogues were tested for uterotonic activity in the rat uterus in vitro test, for pressor activity in the rat pressor assay and for the affinity to human OT receptor using [³H]OT. Cell proliferation was estimated using the colorimetric methyl triazolium (MTT) assay. Replacement of Ile³ by L- or D-Thi³ decreased biological activities significantly. With regard to antitumor effect, we found that the analogues with D-Tyr(Et) in position 2 have in MDA-MB-468 cells a dual effect on proliferation 48 and 72h after cell treatment. These analogues inhibited cell proliferation when cells were treated with serum supplemented medium but increased cell proliferation when cells were treated with medium without serum. None of the analogues showed any antitumor effect in MCF-7 cell line.

Acknowledgments: The authors thank the University of Patras for the K. Karatheodoris Research Grant (to V. Magafa_2010_D.156)

Poster - 31

DESIGN, SYNTHESIS AND PHARMACOCHEMICAL EVALUATION OF NEW THIAZOLE DERIVATIVES AS POSSIBLE METALLOENZYME INHIBITORS

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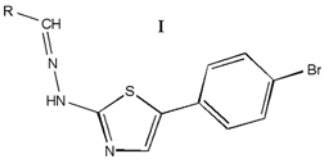
The general family of functional proteins containing metal ions is the metalloproteins, of which one important branch is the metalloenzymes. The active site of a metalloenzyme, features one or more metal ion(s) in a defined coordination environment that exists within a wider environment defined by the shape of the surrounding biopolymer. Metalloenzymes such as COX, LOX, Xanthinoxidase etc. involve to inflammatory responses appearing in tissues due to several inflammatory diseases.
Thiazoles and their derivatives are found to be associated with various biological activities such as antibacterial, antifungal and anti-inflammatory activities. Similarly, compounds containing an azomethine group (-C=N-) in their structure, known as Schiff bases, present important biological activities. Compounds in which a thiazolyl nucleus is coupled with an azomethine group have also been synthesized in order to furnish better therapeutic results.[1]
According to the literature and from our QSAR study some new 2,4-disubstituted thiazole derivatives have been designed and synthesized in order to improve their biological activity.
The final product was obtained in two steps. The synthesis of the Schiff bases is taken place by the condensation of the appropriate substituted aldehyde with thiosemicarbazide, following in the second step with the synthesis of the final product (**I**) by the reflux of thiosemicarbazone and 4-Br-phenacyl bromide.



I

The chemical structures of the synthesized compounds were established by spectroscopic and elemental analyses. Lipophilicity values of derivatives were calculated theoretically and experimentally, because lipophilicity is an important physicochemical parameter for biologically active compounds.
The compounds are tested in vitro for their ability to inhibit metalloenzymes and in vivo for the inhibition of carrageenin induced rat paw edema. The results are evaluated as a result of their structural and physicochemical features.

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Acknowledgements: Biobyte Corp., 201 West 4th St, Suite 204, Claremont CA 91711, USA

Poster - 32

DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF ENONIC COMPOUNDS

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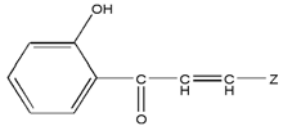
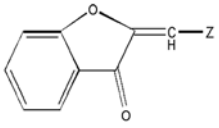
Chalcones are enone derivatives, which are abundant in edible plants. They are precursors of flavonoids and many other biologically active molecules, such as aurones. Chalcones display a wide variety of biological activities including anti-inflammatory, antioxidant, antibacterial, anticancer, antiangiogenic and antileishmanial activities. [1]

Aurones are rarely occuring in nature and they are biosynthesized from chalcones by the enzyme auresidin synthetase. The existing data on the bioactivity of natural and synthetic aurones is very promising, thus these heterocyclic compounds can be considered as an attractive scaffold for drug design and development. Aurones have been reported to possess insect antifeedant activities, anticancer, antileishmanial, anti-inflammatory and antibacterial properties. In the nature they are found in the flowering parts of many plants, and they are named after their bright yellow color.

Using computer aided drug design and previous biological data from known chalcones and aurones we designed a series of chalcones and aurones with possible inhibition on lipoxygenase, anticancer and anti-inflammatory activities in vivo. [2, 3]



(I)



(II)

2′-Hydroxy-chalcones (I) were synthesized via the Claisen–Schmidt condensation reaction between 2′-hydroxy-acetophenones and appropriately substituted aromatic aldehydes in basic conditions. The synthesis of the desired aurones (II) includes the oxidative cyclization methodology using mercury(II) acetate in pyridine. [1, 3] The structures of the synthesized compounds were confirmed by spectroscopy and elemental analysis.

The compounds were tested in vitro for their ability to: a) scavenge the 1, 1-diphenyl-2-picryl-hydrazyl (DPPH) free radical in different concentrations, b) inhibit lipid peroxidation of linoleic acid, c) inhibit in vitro soybean lipoxygenase, d) interact with glutathione and e) inhibit in vivo carrageenin-induced rat's paw edema. The results were characterized based on the structural characteristics and physicochemical properties of the molecules.

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Acknowledgements: Biobyte Corp., 201 West 4th St, Suite 204, Claremont CA 91711, USA

Poster - 33

SYNTHESIS OF POLYFLUOROKETONES CONTAINING AN INDOLE RING AS INHIBITORS OF HUMAN Ca^{2+}- INDEPENDENT PHOSPHOLIPASE A_2

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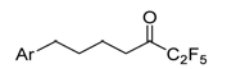
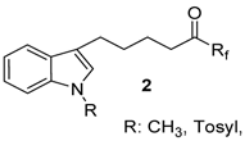
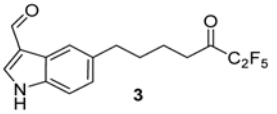
Phospholipase A_2 (PLA_2) enzymes catalyze the hydrolysis of the sn-2 ester bond of glycerophospholipids producing free fatty acids, including arachidonic acid, and lysophospholipids.
Both products are precursor signaling molecules that are involved in inflammation. We have recently demonstrated that Ca^{2+}-independent phospholipase A_2 (GVIA $iPLA_2$) plays a key-role in experimental autoimmune encephalomyelitis and that GVIA $iPLA_2$ is a novel target for the development of new therapies for multiple sclerosis.[1]
Polyfluoroketones of the general structure 1 are potent and selective inhibitors of GVIA $iPLA_2$. [2] To extend our studies, we have synthesized a variety of polyfluoroketones containing an indole ring.
For the synthesis of the desired fluoroketones, commercially available indole-5-carboxaldehyde and indole-3-carboxaldehyde, easily obtained from indole, were used as starting materials. Indole-3- carboxaldehyde was then protected with a tosyl or a methyl group. Each aldehyde underwent a Wadsworth-Horner-Emmons reaction with triethyl 4-phosphonocrotonate to yield the corresponding unsaturated ester. After catalytic hydrogenation and saponification, the carboxylic acids were converted to acyl chlorides and treated with pyridine and polyfluoroalkyl anhydrides to provide various polyfluoroketones (2, 3). The evaluation of the inhibitory activity is in progress.



1
Ar: benzene (FKGK11)
Ar: naphthalene (FKGK18)



2
R: CH_3, Tosyl, H
R_f: CF_3, C_2F_5



3

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This research has been co-financed by the European Union (European Social Fund – ESF) and Greek national funds through the Operational Program "Education and Lifelong Learning" of the National Strategic Reference Framework (NSRF) - Research Funding Program: Heracleitus II. Investing in knowledge society through the European Social Fund.

Poster - 34

DEVELOPMENT OF SYNTHETIC 2-ARYLBENZOFURANS AND CHALCONOIDS AS POTENTIAL ANGIOGENETIC MODULATORS

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The aim of this work was the development of synthetic analogues of 2-arylbenzofurans and chalconoids and investigation of their ability to induce or inhibit angiogenesis.

Twenty 2-arylobenzofuran analogues have been synthesized by the following three synthetic pathways; Sonogashira coupling, as the main method of synthesis, and as alternative methods, Castro reaction, a condensation reaction of copper aketylides with aryl-halogens, and Suzuki reaction, a catalytic method utilizing boronic acid derivatives with vinylethers. Furthermore, eleven substituted and non-substituted chalcones, ten diarylopropanes and one dihydrochalcone were designed and synthesized. The synthesis started from acetophenones and benzaldehydes via Claisen-Schmidt reaction, giving excellent yields of chalcones. The latter compounds, upon catalytic hydrogenation in the presence of Pd/C 10% in ethanol/ethyl acetate (1/1) at 55 psi, are converted to the corresponding diarylopropanes. In the case of dihydrochalcone the corresponding chalcone was submitted to catalytic hydrogenation in the presence of Pd/C 5%. All new compounds were fully characterized by spectroscopic methods and high resolution mass spectrometry. The coumpounds were studied as angiogenesis inhibitors/inducers on endothelial cells.

The results obtained indicated that 2-arylbenzofurans, diarylopropanes and the dihydrochalcone were able to inhibit angiogenesis. Chalcones did not demonstrate inhibition properties. Interestingly, a prenyl diarylopropane in low concentration induced angiogenesis.

A number of substituted and non-substituted 2-arylbenzofurans, chalcones, diarylopropanes and one dihydrochalcone were designed, synthesized and examined for their ability to modulate angiogenesis. The results obtained were very important to determine the structural and stereoelectronic requirements in the research of an optimal angiogenetic inhibitor.

Poster - 35

DEVELOPMENT OF SYNTHETIC DEOXYBENZOINS AND DIHYDROSTILBENES AS POTENTIAL TYROSINASE INHIBITORS

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The aim of this work was to develop a lead compound by investigating the structural requirements for optimal tyrosinase inhibition using molecular simulation studies.
Five substituted and non-substituted deoxybenzoins and five dihydrostilbenes were designed and synthesized. Resorcinols and substituted resorcinols reacted with variously substituted phenylacetic acids, giving excellent to moderate yields of deoxybenzoins catalyzed by $BF_3 \bullet OEt_2$. The latter compounds, upon catalytic hydrogenation in the presence of Pd/C 10% in ethanol/ethyl acetate (1/1) at 55 psi, are converted to the corresponding dihydrostilbenes. All new compounds were fully characterized by spectroscopic methods and high resolution mass spectrometry. The tyrosinase inhibitory activity was evaluated by using L-DOPA as a substrate. The produced amount of dopachrome was measured at 475 nm. Gallic acid and kojic acid were used as positive controls. Recent crystallographic structures of tyrosinase in complex with known inhibitors were utilized in order to perform flexible docking simulations for in silico evaluation of the binding mode of all new synthesized molecules.
The results obtained indicated that all samples were able to inhibit tyrosinase activity in comparison to the positive control gallic acid. Deoxybenzoins demonstrated moderate inhibition properties. All dihydrostilbenes showed a strong tyrosinase inhibitory activity in comparison to gallic acid and were further examined and compared to a more potent inhibitor, kojic acid. Dihydrostilbene 4-(4-hydroxyphenethyl)benzene-1,3-diol exhibited high inhibition of mushroom tyrosinase (IC_{50}=8.44 μM), higher than kojic acid (IC_{50}=9.96 μM). Dose-activity relation was also determined. Molecular simulations suggest that the formation of intramolecular hydrogen bond in deoxybenzoins prevents the optimum interaction with the receptor, explaining their lower inhibition.
A number of substituted and non-substituted deoxybenzoins and dihydrostilbenes were designed, synthesized and examined for their potent tyrosinase inhibitory activity in vitro and in silico. The results obtained were very important to determine the structural requirements in the research of an optimal tyrosinase inhibitor.

Poster - 36

BARBITURIC /THIOBARBITURIC ACID DERIVATIVES WITH POSSIBLE ANTI-INFLAMATORY-ANTICANCER ACTIVITY

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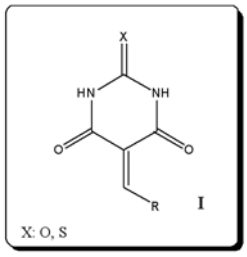
It is believed that cancer arises, or a pre-existing cancer is encouraged, during the process of repairing a trauma. However, repeated injuries to the same tissue might promote excessive cell proliferation, which could then increase the odds of a cancerous mutation[1]. Inflammation orchestrates the microenvironment around tumors, contributing to proliferation, survival and migration. Cancer and atherosclerosis, two major causes of death, are due to the salient "free radical" impact. It is possible that endogenous free radical reactions may result in tumors formation. Today, it is evident that the use of multitarget-directed ligands, that combine anti-inflammatory and anticancer activities interacting with multiple targets, could be valuable for the treatment of the above mentioned pathophysiological conditions.

According to the literature and from our modeling studies on soybean Lipoxygenase new barbituric and thiobarbituric acid derivatives with the general structure **I**, have been designed and synthesized in order to improve their biological activity. Inhibitors of LOX have attracted attention initially as potential agents for the treatment of inflammatory and allergic diseases and certain types of cancer.



I

For the synthesis of barbituric acid derivatives several substituted aromatic aldehydes undergo Knoevenagel condensation with barbiturates. To a solution of the desired aldehydes (1 equivalent) in 6-7 mL acetic acid, barbiturates (1.1 equivalents) were added. The reaction mixture was then refluxed for 6-7 h. After completion (TLC) the reaction mixture was poured into crushed ice with constant stirring. Crude product was isolated and recrystallized from suitable solvents to yield target compounds[2]. A microwave assisted reaction was also established. Structures of the products thus obtained were confirmed by their m.p., elemental analysis, IR, ^{1}H NMR and ^{13}C NMR.

The compounds are tested *in vitro* for their antioxidant and anti-lipoxygenase and in vivo for the inhibition of carrageenin induced rat paw edema. The results are discussed in terms of the physicochemical characteristics of the compounds.

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Poster - 37

HYPERFORIN AND DEOXYCOHUMULONE AS POTENTIAL LARVICIDAL MOSQUITO AGENTS

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Hyperforin **(1), (Figure 1)** a polycyclic polyprenylated acylphloroglucinol, is the most popular bioactive compound found in *Hypericum perforatum*, with fascinating chemical structure and intriguing biological activities[1]. Hyperforin, biosynthetically derives from deoxycohumulone (**2**). *Hypericum perforatum* has antidepressan, anticarcinogenic, angiogenesis inhibition and antibacterial[2,3]. Although it shows antimalarial activities[4], there is no report for bioactivity against mosquito.Main objectives of this study were to evaluate the larvicidal activity of hyperforin (**1**), its bioprecursor, deoxycohumulone (**2**) against *Cx. pipiens* (Diptera: Culicidae) and to examine any relation between chemical structure and effectiveness of three new acetylated deoxycohumulone derivatives. Therefore, mono-acetyl deoxycohumulone (**3**), di-acetyl deoxycohumulone (**4**) and tri-acetyl deoxycohumulone (**5**), which are synthesized for the first time (**Figure 1**). The larval mortality bioassays revealed that hyperforin (**1**) and deoxycohumulone (**2**) were very effective (LD_{50} = 43.87 and 51.03 mg/L, respectively) while the presence of one or more acetates decreases molecule's activity. As a result the mono acetyl deoxycohumulone analogue (**3**) was less effective (LD_{50} = 135.92mg/L) and the other two acetylated analogues (**4**) and (**5**) were inactive (LD_{50} >300mg/L).

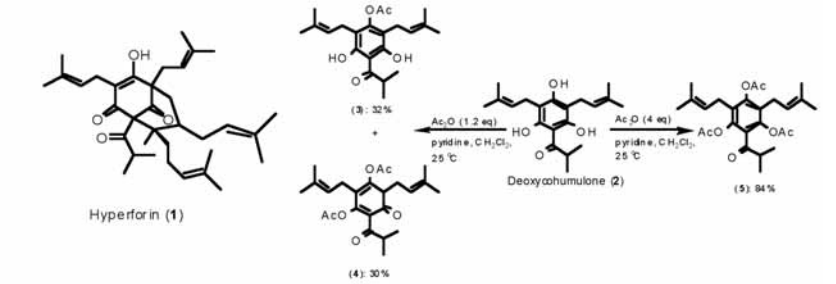

Figure 1. Structures of Hyperforin (**1**) and Deoxycohumulone (**2**). Synthesis of Mono-acetyl deoxycohumulone (**3**), Di-acetyl deoxycohumulone (**4**) and Tri-acetyl deoxycohumulone (**5**).

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Poster - 38

STRUCTURE-BASED DESIGN, SYNTHESIS AND IN VIVO ANTIDIABETIC ACTIVITIES OF NOVEL NON-ELECTROPHILIC ANALOGUES OF VILDAGLIPTIN

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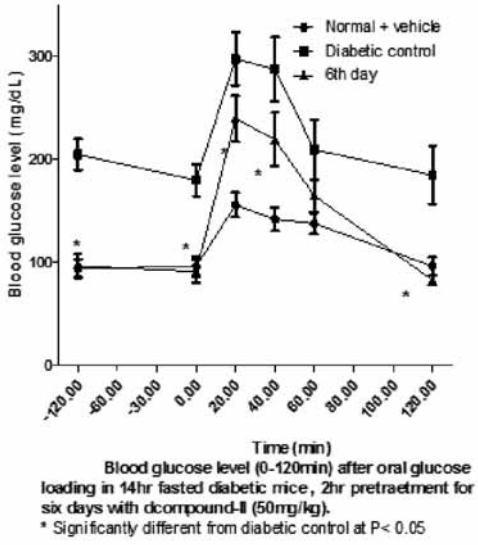
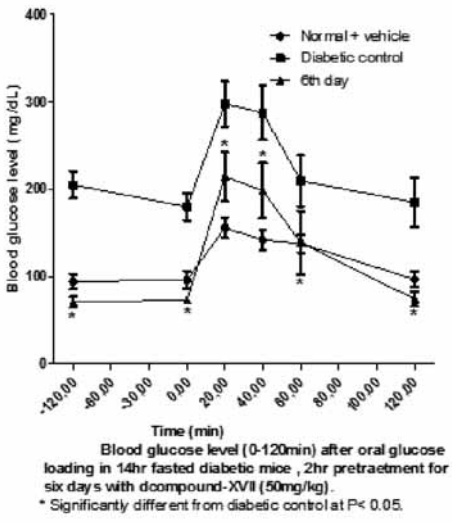
After five years of entering clinical practice, gliptins (antidiabetic drugs acting by inhibition of dipeptidyl peptidase, DPP-IV) have been established as leading approach of the 21st century's therapies of type-II diabetes mellitus. This is evidenced by recent approvals of new molecular Entities (NMEs) belonging to gliptins. For instance, Linaglitin (Tradjenta™) have been approved by FDA in May 2011 for treatment of Type-II diabetes. The common pharmacological profile of gliptins reveals that they improve glycaemic control in diabetes that has not been adequately controlled with metformin or sulfonylurea. Gliptins do not affect weight and there is no significant increase in the rate of hypoglycaemic events when combined with metformin.
In this work, we have utilized structure-based computational tools to design novel compounds directed to inhibit dipeptidyl peptidase-4 (DPP-4) without forming covalent bonds with the enzyme. Some of these analogues showed in vivo potency that exceeded vildagliptin at the same doses.



Blood glucose level (0-120min) after oral glucose loading in 14hr fasted diabetic mice , 2hr pretraetment for six days with dcompound-II (50mg/kg).
* Significantly different from diabetic control at P< 0.05



Blood glucose level (0-120min) after oral glucose loading in 14hr fasted diabetic mice , 2hr pretraetment for six days with dcompound-XVII (50mg/kg).
* Significantly different from diabetic control at P< 0.05.

Aknowledgment: I'd like to thank King Abdul Aziz City for Science and Technology for funding and supporting this research work.

Poster - 39

TRIPEPTIDE-LIKE PROLINAMIDE CATALYSTS FOR THE ALDOL REACTION

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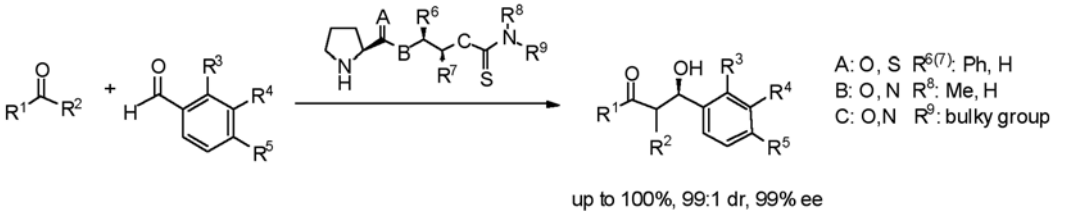
Organocatalysis is a powerful methodology for the synthesis of chiral bioactive compounds. Proline and its derivatives containing bio-isosteric groups as replacements of the carboxylic group constitute a good example of catalysts that bring out asymmetric transformations as the aldol and Michael reaction successfully, via bifunctional catalysis.[1] Important improvement has been the development of catalysts combining a proline or proline derivative unit with additional functionalities able to act as hydrogen bond donors. Amide catalysts based on (S)-proline and (1S,2S)-1,2-diphenylethylenediamine or (1S,2S)-1,2-diphenyl-2-aminoethanol are representative examples featuring amine or hydroxyl group respectively, as the terminal donor group.[2] These analogues provide the opportunity of introducing chiral substituents between donor groups and/or to the terminal heteroatom, thus enhancing the efficacy of the resulting catalyst. Furthermore, combination of additional chiral units, together with even more hydrogen bond donors, would mimic much better a "miniature active site", providing therefore multifunctional organocatalysts. We have shown that a prolinamide catalyst based on (1S,2S)-1,2-diphenylethylenediamine bearing a double hydrogen bond donor thiourea group linked to a substituted aromatic ring, efficiently catalyzes the aldol reaction between ketones and aromatic aldehydes in high to quantitative yields and with high stereoselectivities.3 Herein, we report a structure activity relationship study undertaken to identify the structural elements of the catalyst responsible for the activity. A tripeptide-like prolinamide-thiourea catalyst having as building blocks (S)-proline (1S,2S)-1,2-diphenylenediamine and (S)-di-tert-butyl aspartate has been proven an excellent catalyst for the aldol reaction providing the products in high to quantitative yields and in high stereoselectivities (up to 99:1 dr and 99% ee).



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Poster - 40

SYNTHESIS OF FUSED [5,6], [7,8] DIPYRIDOCOUMARIN DERIVATIVES

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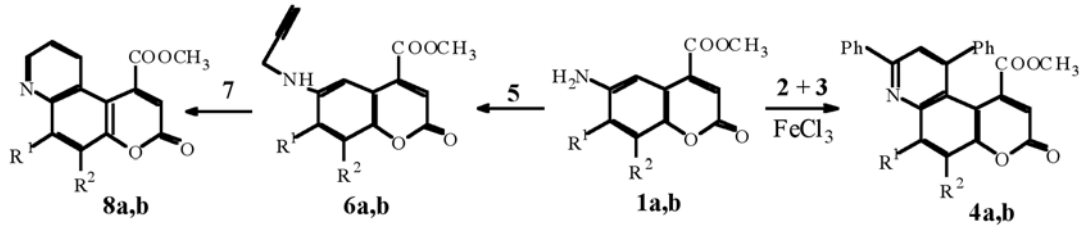
Fused pyridocoumarins present interesting biological activities.[1] We have prepared recently pyridocoumarins by the reaction[2] of quinolinols with DMAD/PPh_3 or through the aza-Claisen rearrangement of 6-propargylaminocoumarins[3] under MW with $BF_3.Et_2O$. The three component reactions have been used for the synthesis of quinoline derivatives under the catalytic action[4,5] of $AuCl_3$ or $FeCl_3$. The transformation of propargyloxycoumarins to pyranocoumarins has been achieved by using catalysis with Gold nanoparticles.[6] In continuation of our interest in the synthesis of pyridocoumarin derivatives we like to present here the synthesis of fused [5,6], [7,8] dipyridocoumarin derivatives in three different ways. Reactions of aminocoumarins **1a,b** with PhCHO (**2**) and phenylacetylene (**3**) in the presence of catalytic amount of $FeCl_3$ in toluene under reflux resulted to the diphenyl-substituted fused [5,6], [7,8] dipyridocoumarin derivatives **4a,b.** The heating of propargylaminocoumarin derivative **6b** [prepared from **1b** by treatment with propargyl bromide (**5**) in the presence of Cs_2CO_3] in 1,2-dichloroethane in the presence of Au supported in TiO_2 (**7**) gave the dipyridocoumarin derivative **8b**. We studied also the reactions of propargylaminocoumarin derivatives **6a,b** with $BF_3.Et_2O$ under MW irradiation.



1,4,6,8 a: R^1-R^2=N=CH-CH=CH
b: R^1-R^2=CH=CH-CH=N

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Ευρωπαϊκό Κοινωνικό Ταμείο

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Poster - 41

SYNTHESIS AND STRUCTURE IDENTIFICATION OF BIOISOSTERIC 3-CARBOXAMIDE-2-QUINOLINONE ANALOGUES AND STUDY OF THEIR ANTI-INFLAMMATORY, ANTIOXIDANT AND NEUROPROTECTIVE ACTIVITY

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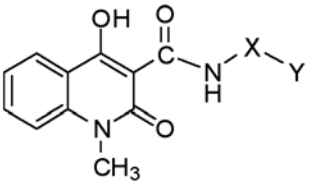
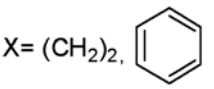
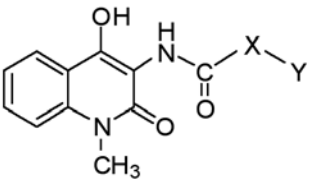
The aim of the present research is the design and synthesis of new quinolinone analogues based on the concept of bioisosterism and the study of their biological properties, including their ability to inhibit soybean lipoxygenase, their antioxidant activity and their ability to protect HT22 neuronal cells from oxidative stress.
Quinolinones are nitrogen containing heterocyclic compounds mainly found in nature as alkaloids, as chemical intermediates in the biosynthesis of other compounds or as components produced during the metabolism of microorganisms and display a wide range of biological activity.



Series A



Y= CH_3 , OH



Series B

In this work, two series of N-methyl-quinolinone carboxamide analogues have been designed and synthesized: series A is based on the classic bioisosteric replacement, which includes the substitution of the amine group of the carboxamide with a hydroxyl and a methyl group, whereas series B is based on the non-classic bioisosteric replacement of the amide group with the reverse amide.
The anti-inflammatory activity of the new analogues was evaluated using the soybean lipoxygenase assay, whereas the antioxidant activity was estimated using the methods of DPPH and the inhibition of lipid peroxidation (AAPH). The ability of the compounds to protect HT22 cells from oxidative stress was also determined. Two of the compounds exhibit important combined ability to inhibit lipid peroxidation, soybean lipoxygenase and to protect HT22 cells from oxidative stress.

Poster - 42

ANTIDEPRESSANT-LIKE ACTIVITY OF SOME 2-PYRAZOLINE DERIVATES

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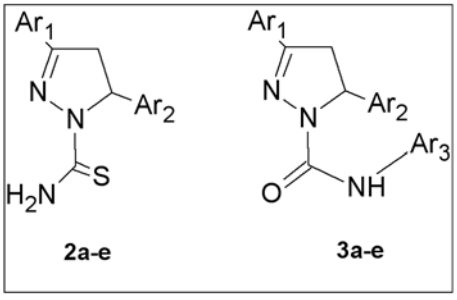
Mood disorders such as major depressive disorder are common, chronic, and recurrent conditions affecting individuals worldwide and existing antidepressants are insufficient. 2-Pyrazolines represent an important class of heterocycles due to their highly pronounced biological and pharmacological activities. It has been reported that, 3,5-diaryl-1-thiocarbamoyl-2-pyrazoline derivatives possess considerable antidepresant-like activity. Furthermore, many analogues were found to be highly active inhibitory agents against both monoamine oxidase A and B (MAO-A and MAO-B) isoforms. In the present study, some pyrazoline derivatives were synthesized to investigate their potential antidepressant-like activities. As starting compounds, a series of chalcones were prepared by Claisen Schmidt condensation and 2-pyrazoline derivatives have been synthesized by the reaction of chalcones with thiosemicarbazide and substituted semicarbazides. Antidepressant-like activities of 2-pyrazoline analogues have been evaluated by tail suspension test (TST) and forced swim test (FST).



A mild antidepressant-like activity of **3a** (Ar_1: phenyl, Ar_2: 2,6-dichlorophenyl Ar3:4-chlorophenyl) and **3b** (Ar_1: 4-methylsulphonylphenyl, Ar_2: 2,6-dichlorophenyl, Ar_3: 4-chlorophenyl) may be reached after evaluating results of the TST, as providing a marked decrease in immobility time of mice. This effect of two compounds had not been encouraged by FST, in which decrease in immobility time reflects the antidepressant activity, too.

Poster - 43

DESIGN AND SYNTHESIS OF 5,7,8-TRIMETHYL-1,4-BENZOXAZINE DERIVATIVES ACTIVE AGAINST *TOXOPLASMA GONDII*

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Toxoplasma gondii, the causative agent of toxoplasmosis, is a ubiquitous opportunistic pathogen that infects individuals worldwide and a wide range of animals including those of the *Felidae* family. It is a leading cause of severe congenital, neurologic and ocular disease in humans. In developing tropical countries, the problems for persons with AIDS can be exacerbated due to lack of both anti-retroviral treatment and anti-*Toxoplasma gondii* treatment. Throughout the world, new *T. gondii* infection during pregnancy can lead to devastating disease for the fetus and newborn infant, later impacting on the child's health and development and potentially on his/her later productivity. The treatment of choice for toxoplasmosis is the combined administration of pyrimethamine with either sulfadiazine or clindamycin. Since no vaccine for humans is available, and hypersensitivity and toxicity limit the use of the few available drugs safer and more effective medicines to treat toxoplasmosis are urgently needed.

The 2H-1,4-benzoxazine-3-(4H)-one and 3,4-dihydro-2H-1,4-benzoxazine systems can be considered as privileged scaffolds for the development of potential new drugs since they have been studied extensively for building natural and designed biologically active compounds, which span from herbicides, fungicides, cardiovascular agents, compounds against diabetes and neuroprotectants. As part of our investigations on biologically active 5,7,8-trimethyl-1,4-benzoxazines, series of novel derivatives modified at positions C2, C3, N4, C6 or C2 and C6 were synthesized and evaluated against *T. gondii* infected LLC-MK_2 cells in vitro. The majority of the compounds exhibited excellent activity with IC_{50} values < 1 μM. The most active compound was the 2-phenyl-6-(3-hydroxyphenyl)-5,7,8-trimethyl-1,4-benzoxazine (**1**), with an IC_{50} value 0.8 nM after 48h. The ultrastructural analysis by transmission electron microscopy of infected cells treated with compound **1**, demonstrated several cellular damages, with the mitochondrion and the apicoplast being the principal organelles affected.

Acknowledgement: The research leading to these results has received funding from the European Union's Seventh Framework Programme (FP7-REGPOT-2009-1) under
grant agreement no. 245866, "ARCADE".

Poster - 44

DESIGN AND SYNTHESIS OF NEW BENZOTHIAZINE DERIVATIVES AS MULTI-TARGETED ANTI-ATHEROSCLEROTIC AGENTS

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Simultaneously addressing a multiplicity of targets is considered to be beneficial in the treatment of a wide range of multi-factorial disorders. This approach seems to provide superior therapeutic effects and side-effect profile compared to the action of a selective, single targeted, ligand as a therapeutic agent.[1] Atherosclerosis is a multi-factorial disease that eventually leads to coronary heart disease. A correlation exists between hyperlipidemia, oxidative stress, inflammation and atherosclerosis.[2] We have previously applied a multi-targeted drug design strategy, by developing molecules that incorporate antihyperlipidemic (squalene synthase inhibitory activity), antioxidant and anti-inflammatory activity in one structure to address the multi-faceted nature of atherosclerosis. Thus, we have synthesized and evaluated morpholine and benzothiazine derivatives with increased antidyslipidemic and antioxidant properties.[3,4] We hereby designed two novel benzothiazine derivatives by incorporating further antioxidant moieties. The new molecules were prepared via a facile 5-step synthetic procedure that included a Suzuki-Miyaura cross coupling reaction of 4-acetylphenylboronic acid with the appropriately substituted bromophenol. The product from coupling was then selectively brominated at the α-position of the acetyl group and reacted with benzothiazole to give the respective N-substituted benzothiazole bromibe salt which then rearranged to N-carbaldehyde benzothiazine via a cycloaddition reaction. Finally, the aldehyde group was reduced to the desired N-methyl 2-substituted benzothiazine derivatives. The new molecules were evaluated for their activity *in vitro*. They exhibited potent antioxidant activity (IC_{50} values for protection against lipid peroxidation were 6-40 μM) and cycloxygenase inhibition comparable to reference NSAIDs such as nimesulide. The evaluation and activity of these new antioxidant benzothiazine derivatives on multiple targets supports their potential as anti-atherosclerotic agents.

[1]Morphy et al., Curr. Pharm. Des., 2009, 15, 587
[2]Libby et al., Circulation, 2002, 105, 1135
[3]Kourounakis, A.P. et al., Bioorg. Med. Chem., 2010, 51, 7402.
[3]Matralis et al., J. Med. Chem., 2011, 54, 5583

Poster - 45

SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL ISOCA-4 DERIVATIVES

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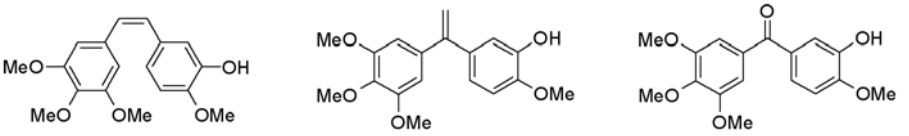
Among the large class of products known as tubulin inhibitors, the combretastatin family, and notably the combretastatin A-4 (Figure 1), exhibits a strong cytotoxicity and an antitubulin activity. But, despite their therapeutic interests, these compounds are prone to double-bond isomerization leading to E-isomer which decreases dramatically the activities.[1]

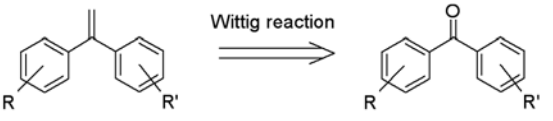
It has been recently described a new family of substituted 1,1-diarylethylenes called isocombretastatins.[2] These compounds display an activity similar to the one of their combretastatin homologues as inhibitors of tubulin polymerization and cytotoxic compounds.[2, 3,4] Moreover, these products does not suffer any isomerization of the double bond.



1 Combretastatin A-4 **2a** /socombretastatin A-4 **3a** Phenstatin

Figure 1: Structure of combretastatin A-4 (1) and corresponding isocombretastatin A-4 (2a) and phenstatin (3a).

These derivatives were easily prepared from phenstatin analogues by Wittig reaction (Figure 2).[4]



2 **3**

Figure 2: Synthesis of isocombretastatins derivatives by Wittig reaction.

We have synthesized a wide family of diversely substituted isocombretastatins by this method. Their cytotoxic activities were evaluated by the National Cancer Institute, and the results are presented here.

1 Pettit, G. R. and al. J. *Med. Chem.* **1999**, *42*, 1459.
2 Messaoudi, S. and al. J. *Med. Chem.* **2009**, *52*, 4538.
3 Alvarez, R. and al. Bioorg. *Med. Chem.* **2009**, *17*, 6422.
4 Hamze, A. and al. *ChemMedChem.* **2009**, *4*, 1912

Poster - 46

NEW PURINE ANALOGUES AS PHARMACOLOGICAL PRECONDITIONING AND POSTCONDITIONING AGENTS *IN VIVO*

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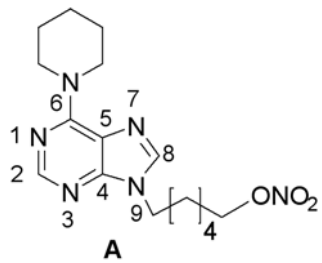
Ischemic preconditioning (IPC) constitutes an endogenous protective mechanism in which one or more brief periods of myocardial ischemia and reperfusion render the myocardium resistant to a subsequent more-sustained ischemic insult. Postconditioning (PostC) is similar to IPC but applicable at the time of reperfusion, involving short series of repetitive cycles of brief reperfusion and re-occlusion of the coronary artery applied at the onset of reperfusion, that reduce the infarct size and coronary artery endothelial dysfunction. Pharmacological IPC and PostC represent ideal alternatives that may substitute the short ischemic insults. Adenosine, nicorandil and other agents have been already used as pharmacological mimetics of IPC in multicenter trials[1].

Our group has been involved in the design and synthesis of novel molecules, which may confer their protection by using intracellular pathways involved in IPC. Our preliminary *in vivo* data in rabbits, showed that the presence of a purine moiety and of a nitrate ester (NO donor) is necessary for cardioprotection by means of infarct size reduction[2]. 6-Piperidinyl purine derivative (**A**) bearing a nitroxyhexyl chain at position 9 was the basic molecule for the design and synthesis of the new analogues.



A

The aim of the present study was to synthesize analogues of this lead compound and evaluate them as pharmacological IPC or postC agents. Thus we synthesized the 6-piperidinyl purine analogues in which the nitroxyhexyl chain has been replaced by the nitroxyethyl carboxamide group or a 5-nitroxy-ribosyl moiety, as well as 6-piperidinyl purine bearing the nitrate ester at position 8. In addition the purine analogues substituted at position 6 by moieties containing nitrate esters have also been synthesized.

All the compounds were administered in anesthetized male rabbits before ischemia or before reperfusion, at the same dose as the lead compound **A** in our previous study (3.8 μmol/kg). The effect of the tested compounds on infarct size reduction is compared with the control group as well as to the IPC or postC group.

References

1. Andreadou I., Iliodromitis E. K., Koufaki M., Farmakis D., Tsotinis A., Kremastinos D. Th. *Cur. Med. Chem.,* **2008***, 15*, 3204
2. Fotopoulou T., Iliodromitis E. K., Koufaki M., Tsotinis A., Zoga A., Gizas V., Pyriochou A., Papapetropoulos A., Andreadou I., Kremastinos D. Th. *Bioorg. Med. Chem.,* **2008***, 16*, 4523

Acknowledgments: This work was supported by Novartis Hellas, by Hellenic Cardiological Society and by the European Union's Seventh Framework Programme (FP7-REGPOT-2009-1) under grant agreement no. 245866

Poster - 47

SYNTHESIS OF NOVEL COUMARIN DERIVATIVES AND EVALUATION OF THEIR ANTIOXIDANT AND LOX INHIBITORY ACTIVITY

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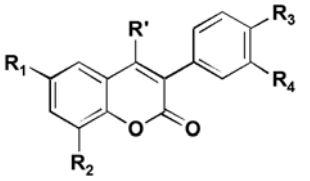
Coumarins constitute an important class of naturally occurring compounds many of which exhibit interesting pharmacological activity including antioxidant, anticancer, vasorelaxant, and anti-inflammatory.[1]
Our research aims at the synthesis of novel bioactive compounds via an efficient one-step novel synthetic approach towards 3-aryl-coumarin derivatives and the evaluation of their antioxidant and lipoxygenase inhibitory activity. [2] In order to further investigate the structural requirements that enhance dual antioxidant and anti-inflammatory activity, a series of novel coumarin analogues, bearing a substituted phenyl ring on position 3 was prepared. Demethylation of the 3,4-dimethoxy substituents as well as prenylation of the corresponding 3,4-dihydroxyl groups and Suzuki coupling reactions were investigated, in order to examine the influence of these structural features on the biological activity.



The in vitro antioxidant activity of the synthesized compounds was evaluated using two different antioxidant assays (radical scavenging ability of the DPPH stable free radical and inhibition of lipid peroxidation induced by the thermal free radical AAPH). Moreover, the ability of the compounds to inhibit soybean lipoxygenase was determined as an indication of potential anti-inflammatory activity.

1. Kontogiorgis, C. A.; Savvoglou, K.; Hadjipavlou-Litina, D. J. *J. Enzyme Inhib. Med.Chem.,* (2006) 21, 21.
2. M.Roussaki, C. A. Kontogiorgis, D. Hadjipavlou-Litina, S.Hamilakis, A.Detsi, *Bioorganic & Medicinal Chemistry Letters, 20* (2010) 3889–3892.

Acknowledgements: Financial support by the Basic Research Committee Programme 'PEBE 2009, 65/1796' is gratefully acknowledged (M. Roussaki).

Poster - 48

ONE-STEP MICROWAVE SYNTHESIS OF NOVEL QUINAZOLINONE-QUINOLINONE HYBRIDS AND EVALUATION OF ENZYME INHIBITORY ACTIVITY

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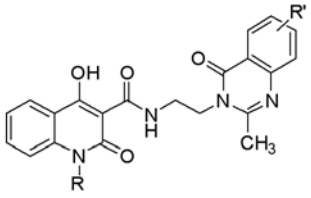
Quinazolinones and quinolinones constitute classes of fused heterocycles that are of considerable interest because of the diverse range of their biological and pharmacological activity. These molecular scaffolds are found in natural products whereas numerous analogues have been synthetically produced and were found to display interesting insecticidal, analgesic, antifungal, antibacterial, antiallergic, anticancer and anti-inflammatory properties.

In this work we present the microwave assisted synthesis of novel quinazolinone-quinolinone hybrids which combine the two heterocyclic moieties in one molecular scaffold. The synthesis is effected via a one-step reaction between N-substituted-4-hydroxy-2-quinolinone-3-aminoamides and appropriately substituted 2-methyl-benzo[1,3]oxazin-4-ones, under carefully selected microwave irradiation conditions.



Quinazolinone-quinolinone hybrids

The new compounds were evaluated for their ability to inhibit soybean lipoxygenase and mushroom tyrosinase activity *in vitro*. The structure-activity relationships concerning the influence of the substituents of each heterocyclic moiety on bioactivity will be discussed.

Poster - 49

SYNTHESIS OF SUBSTITUTED 2′-HYDROXY-CHALCONE ANALOGUES AND EVALUATION OF THEIR ANTIOXIDANT ACTIVITY

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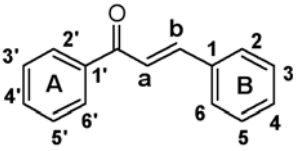
Chalcones are natural products widely distributed in edible plants. They mainly act as the precursors of flavonoids and exhibit important bioactivity such as antioxidant, anti-inflammatory, antimicrobial and anticancer. The key structural feature of chalcones is the α,β-unsaturated carbonyl system which connects two aryl groups.



In the present work the synthesis of a series of chalcone analogues, possessing various substituents on rings A and B and the evaluation of their antioxidant activity will be described. The synthesis involves a Claisen-Schmidt condensation reaction between appropriately substituted 2′-hydroxy-acetophenones and benzaldehydes in basic environment. Moreover, in order to investigate the effect of the presence of the α, β-unsaturated carbonyl system on the antioxidant activity, two types of structural modifications were performed: a) the synthesis of pyrazoline analogues, in which the α, β-unsaturated carbonyl system was replaced by a five-membered heterocyclic ring and b) the synthesis of the corresponding dihydrochalcones via selective hydrogenation of the carbon-carbon double bond using biomimetic catalytic transfer hydrogenation.
The antioxidant activity of the compounds was evaluated with two different assays: determination of their ability to scavenge H_2O_2 (luminol chemiluminescence method), and of their ability to reduce Fe^{3+} to Fe^{2+} (FRAP method). The antioxidant activity of the compounds was found to be dependent on the position and electronic characteristics of the substituents as well as the presence of the pyrazoline moiety.

Poster - 50

SYNTHESIS AND BIOLOGICAL EVALUATION OF SULPHONYL AMIDOXIMES

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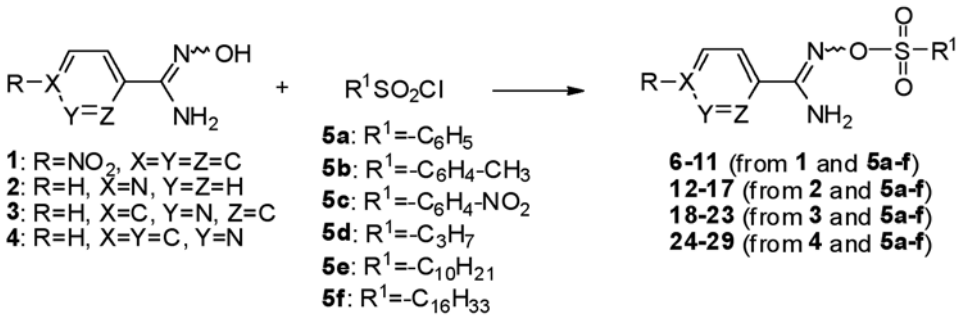
Sulphonyl amidoximes (SAs) are well known intermediates for the synthesis of cyanamides, 2-amino-1-azirines, 5-amino-1,2,4-thiadiazoles and ureas due to their instability and tendency to eliminate the sulphonic group with or without rearrangement. However, among the various isolated SAs only one has been biologically evaluated as antimalarial agent and, interestingly, exhibited the best activity among all other commonly substituted amidoximes. In a recent course related to SA we have realized that some are relatively stable to chemical transformations, to chromatographic and recrystallization processes and long-term storage. Therefore, we have synthesized a series of them having a variety of aromatic rings (either electron poor or rich) and aliphatic chains (from short to long length) on the sulphonyl group, in order to establish a structure-activity relationship. All compounds prepared are new and were fully characterized with spectroscopic methods. Our preliminary studies on their antioxidant activity, using the stable radical DPPH, showed a moderate antioxidant activity for compounds 8, 18, 19, 21 and 22, comparing to the reference compound, nordihydroguaiaretic acid. Nevertheless, the fact that nearly all nicotine amidoxime derivatives showed antioxidant activity may lead to the discovery of novel scaffolds of this pharmacophore with improved activities in the field of inflammation and cancer. Other biological experiments, like NO release are in due course.



Poster - 51

AMELIORATIVE EFFECTS OF MELATONIN AND DERIVATIVE ON LEARNING AND MEMORY DEFICITS IN OLFACTORY BULBECTOMIZED MICE

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Alzheimer disease (AD) is a progressive degenerative disorder characterized by the presence of amyloid deposits, neurofibrillary tangles and neuronal loss. Emerging evidence indicates that antioxidants could be useful either for the prevention or treatment of AD. Several studies showed that melatonin may play an important role in AD as an antioxidant and neuroprotector. Recently, our group developed a new melatonin derivative, naphthoyl melatonin with potent antioxidant activity. Therefore, the present study was conducted to investigate the effect of naphthoyl melatonin on improvement of learning and memory in olfactory bulbectomized (OBX) mice. The OBX ddY mice were treated with melatonin or its derivative, naphthoyl melatonin (10 μmole/kg) for 14 consecutive days and their cognitive performances were evaluated by the modified Y-maze test, novel object recognition test, and fear conditioning test. In addition, locomotor function test was also performed via the open field model. The results showed that OBX animal demonstrate a characteristic syndrome consisting increased activity in the open field test, disrupted responding in the modified Y-maze, ORT and fear conditioning test. Chronic treatment with naphthoyl melatonin at a dose 10 μmole/kg showed improvement of the spatial working memory, non-spatial short term memory, and long-term memory deficits induced by OBX in the modified Y-maze, ORT and fear conditioning test, respectively. All results demonstrate that naphthoyl melatonin improves both short term and long term memory deficits caused by OBX. This finding suggests that naphthoyl melatonin may hold alternative in alleviating certain memory impairments observed in Alzheimer's disease in the future.

Poster - 52

HIT-TO-LEAD (H2L) OPTIMIZATION OF PYRROLYL-DIFLUOROPHENOL ALDOSE REDUCTASE INHIBITORS

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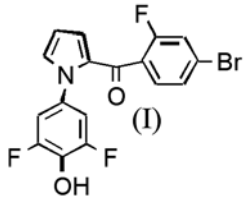
In recent years it has been observed worldwide a striking increase of cases of diabetes mellitus, which tend to attain an epidemic prevalence. Aldose reductase (ALR2, AR, AKR1B1, EC 1.1.1.21) belongs to the aldo-keto reductase super-family. It is the first enzyme of the polyol pathway, which converts glucose to sorbitol, using NADPH as a cofactor. The second (and last) enzyme of the pathway is sorbitol dehydrogenase (SDH), which converts sorbitol to fructose, using NAD^+ as a cofactor. The physiological role of ALR2 is detoxifying and regulating, but in cases of diabetes and/or hyperglycemia, glucose is converted rapidly to sorbitol, which tends to concentrate into the cells, damaging them in many tissues. Therefore, initially ALR2 was found responsible for the long term complications of diabetes, such as neuropathy, nephropathy, retinopathy and cataract.
However, a number of reports have suggested that under normal glucose concentrations, ALR2 could be up-regulated due to factors other than hyperglycemia. This implies that the enzyme is additionally responsible for pathological states, such as cardiovascular disorders, mood disorders, inflammation, renal insufficiency and ovarian abnormalities. Furthermore, ALR2 is found to be over-expressed in some particular types of human cancers. These new findings have drawn even more the attention of the scientific community towards finding new, efficient and, at the same time, safer aldose reductase inhibitors, since currently only one is on the market.
In our lab, and searching for novel ARI chemotypes[1], we have prepared and in-vitro tested a number of aroyl-pyrrolyl-difluorophenol derivatives. The synthetic strategy involved an efficient pyrrole ring formation under Clauson-Kaas cyclization conditions, catalyzed with nicotinamide, as well as a regioselective Friedel-Crafts aroylation in the presence of a defined ratio of $AlCl_3$/aroyl-chloride. We found that the most active derivative was the (4-bromo-2-fluorophenyl)(1-(3,5-difluoro-4-hydroxyphenyl)-1H-pyrrol-2-yl)methanone (I) with an ALR2 inhibitory IC_{50} of 190nM. We consider this compound a promising lead, derived from the hit scaffold of pyrrolyl-difluorophenol ARIs.



(I)

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Poster - 53

SCAFFOLD MORPHING OF THE AROYLPYRROLE ARI CHEMOTYPE: TOWARDS NON-ANIONIC ALDOSE REDUCTASE INHIBITORS

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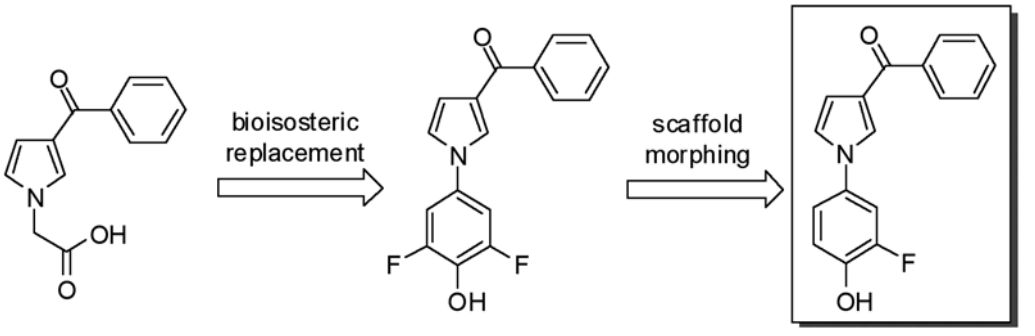
Aldose reductase (ALR2) comprises an elusive yet very significant target for drug design. During the past decades, focus was on the involvement of ALR2 in the polyol pathway, linking the enzyme to the long-term complications of diabetes mellitus. Many inhibitors reached clinical trials, mainly for their potential use in the therapeutics of diabetic neuropathy and retinopathy. However, only one is marketed in Japan (epalrestat, ONO Pharmaceuticals). Recent studies suggest that inhibition of ALR2 is also a promising strategy for the treatment of endotoxin-related inflammatory diseases and the interest in aldose reductase inhibitors (ARIs) has been renewed, aiming for novel structures with improved PKPD properties.

The first generation of ARIs included two main categories of inhibitors, namely hydantoin and carboxylic acid derivatives. Hydantoins were quickly withdrawn from clinical trials due to acute adverse effects. On the other hand, carboxylic acid derivatives, although less toxic, presented overall low penetration of biological membranes, thus arriving to the target tissue in an insufficient quantity and exhibiting problematic efficacy. As the need for novel chemotypes is growing, it should be emphasized, that ALR2 exhibits induced fit conformational adaptations with inhibitors, rendering the de novo design of inhibitors a challenging effort.

In our previous work, we have presented a successful bioisosteric replacement of a carboxylic acid moiety with that of a 2,6-difluorophenol. 2,6-Difluorophenol has a pKa value of 7.12, therefore its derivatives could diffuse through membranes more adequately than their carboxylate counterparts. In the present work, we investigated the synthetic feasibility and ARI activity of aroylpyrroles bearing the 2-fluorophenol moiety. 2-Fluorophenol has a pKa of 8.48, therefore the synthesized pyrrolyl derivatives would not be anionic at physiological pH. However, and in contrast to the prevalent notion that anionic species inhibit ALR2, we found that a number of the prepared 2-fluorophenol derivatives are active inhibitors of ALR2 with an IC_{50} in the low micromolar range. The structure-activity relationship of these novel hit compounds is discussed in terms of calculated physicochemical and structural properties.



Poster - 54

DESIGN AND SYNTHESIS OF NOVEL ALDOSE REDUCTASE INHIBITORS: 1-HYDROXYPYRAZOLE AS A BIOISOSTERE OF THE CARBOXYLIC ACID MOIETY

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Aldose reductase (ALR2), the first and rate-limiting enzyme of the polyol pathway, has long been associated with diabetes mellitus, as the cause of its long-term complications, which include retinopathy, neuropathy, nephropathy and various vascular diseases. Recently emerged data, however, concerning high levels of ALR2 under normal glucose concentration suggest its implication in other pathological conditions too. Specifically, ALR2 is reported to play a pivotal role in cardiac disorders, such as myocardial ischemic injury, as well as inflammatory signal regulation, leading to sepsis, asthma and uveitis, through increased oxygen species generation and lipid peroxidation. In addition, increased polyol pathway flux is observed in patients with bipolar and unipolar mood disorders and is also the cause of renal hemodynamic abnormalities in the diabetic kidney. More interesting though, is the connection of ALR2 with a number of human cancers, including liver, breast, lung, prostate, ovarian, cervical and rectal cancers.

Consequently, ALR2 has emerged as a major therapeutic target over the last years and the development of aldose reductase inhibitors (ARIs) has been gaining growing attention by the pharmaceutical community ever since. As a result, structurally diverse ARIs have progressed to clinical trials, with carboxyl acids and cyclic imides being the main classes. However, poor tissue penetration was observed in carboxylic acid inhibitors due to their low pK_a values, whereas adverse side effects, such as hypersensitivity and liver toxicity were the main drawbacks in cyclic imides. In an effort to develop ARIs of a novel scaffold, with improved calculated tissue penetration, 1-hydroxypyrazole was introduced as a potential bioisostere of the carboxylic acid moiety, based on a previous study that examined the same group as a bioisostere of (S)-Glu for AMPA receptors. The 1-hydropyrazole moiety can be regarded a bioisostere to carboxylic acids since the pka is 6.3.

The synthesized compound is assayed in an in vitro protocol for rat lens ALR2 as well as rat kidney aldehyde reductase (ALR1) inhibition. ALR1 is a homologous aldoketoreductase and is used as a measure for inhibitor's selectivity. Furthermore, certain calculated physicochemical properties are reported in aim to approximate the ability of the synthesized 1-hydroxypyrazole derivative to penetrate biological barriers.

Poster - 55

BENZENESULFONAMIDES AS ALDOSE REDUCTASE INHIBITORS (ARIs): DESIGN, SYNTHESIS, IN VITRO ACTIVITY AND MOLECULAR MODELING

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The successful replacement of a carboxylic acid functionality with that of a difluorophenolic group on the known aldose reductase inhibitors (ARIs) of 2-(phenylsulfonamido)acetic acid chemotype has been reported [1]. In the present work, based on biosteric principles, additional 2,6-difluorophenol, as well as tetrazole, methylsulfonylamide and isoxazolidin-3-one phenylsulfonamide derivatives were synthesized and tested in vitro in protocols primarly related to the long-term diabetic complications [2]. Most of the compounds were found as ARIs at an IC_{50} range of <100 μM, while the introduction of the 4-bromo-2-fluoromethylbenzene in a phenylsulfonamidodiflurophenol structure resulted in a compound (4c) presenting submicromolar inhibitory profile. Molecular modeling and docking simulations were used to support the structure-activity relationship (SAR) points. The human aldose reductase holoenzyme complexed with the inhibitor IDD 594 (PDB entry 1US0) was chosen [3], since it was determined at the highest resolution (0.66 Å) among all the available structures. Docking was carried out using the automated docking program Autodock Vina [4].

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Poster - 56

DESIGN AND STUDY OF NEW NSAID - CONJUGATES WITH ANTIOXIDANT MOLECULES

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Inflammation is implicated in several pathologic conditions. During the inflammation process, active oxygen species are generated at inflammatory sites and aggravate tissue damage. Thus, oxidative stress is considered to be one of the pathogenic factors in acute and chronic inflammation, while the discovery of molecules, which combine anti-inflammatory and antioxidant activities, may lead to the development of drugs with an improved therapeutic index. In this respect, the chemical derivatization of known NSAIDs to incorporate antioxidant properties may be a useful approach. The carboxylic moiety of the NSAIDs, not being mandatory for anti-inflammatory activity, comprises a convenient group for this derivatization. In addition, oxidative stress is a possible link between inflammation and atherosclerosis.

Herein, we report the design, synthesis and pharmacological evaluation of new NSAID derivatives conjugated with moieties expected to possess antioxidant properties. The compounds were synthesized by conventional methods, isolated by flash chromatography and identified. COX (1 and 2) activities were measured via enzyme immunoassay. The effect of the compounds on rat hepatic microsomal membrane lipid peroxidation was determined spectrophotometrically. Anti-inflammatory activity was assessed as reduction of rat paw oedema, produced by carrageenan injection. Finally, compounds were administered i.p. to hyperlipidemic rats and plasma total cholesterol, HDL-cholesterol and triglyceride levels were determined.

From the positive results can be concluded that these structural modifications may offer a viable route to anti-inflammatory agents which, having additional beneficial properties such as antioxidant and hypolipidemic activities, may offer a hopeful route to multi-targeted molecules for chronic inflammatory conditions like atherosclerosis.

Poster - 57

SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL 4-HYDROXYCOUMARIN HYBRID DERIVATIVES

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Coumarins and chalcones are naturally occurring derivatives, found in a variety of plant sources. Chalcones are α,β-unsaturated ketones and in nature are biosynthesized through the polyketide pathway. The last decades much attention has been paid on the synthesis of chalcones mainly from acetophenones and aromatic aldehydes. Coumarin derivatives, as well as chalcones, were found to possess antioxidant, anticancer, antibacterial, antiviral and antifungal activities.

Taking under consideration the wide range of biological properties of these compounds, we designed a series of hybrid molecules. Chalcones were developed through a base-catalysed Claisen-Schmidt condensation reaction between the appropriate substituted acetophenone and aldehyde. The corresponding chalcones are conjugated with 4-hydroxy-coumarin, following a Michael phase transfer catalyzed reaction, giving the desired hybrid products. The compounds have been identified using IR, ^{1}H-NMR, ^{13}C-NMR, elemental analyses and mass spectroscopy. Compounds have been tested for their antioxidant and anti-inflammatory activity in vitro and in vivo. Docking simulations studies with Lipoxygenase Soybean enzyme were performed. The results are discussed in terms of structural characteristics and physicochemical properties.

Acknowledgements: Katsori A-M is thankful to "Bodossakis foundation" for PhD scholarship.

Poster - 58

SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY OF 5-NONSUBSTITUTED/ SUBSTITUTED 2-[(4-ADAMANTINE THIAZOL-2-YL) IMINO] – 4 THIAZOLIDINONES

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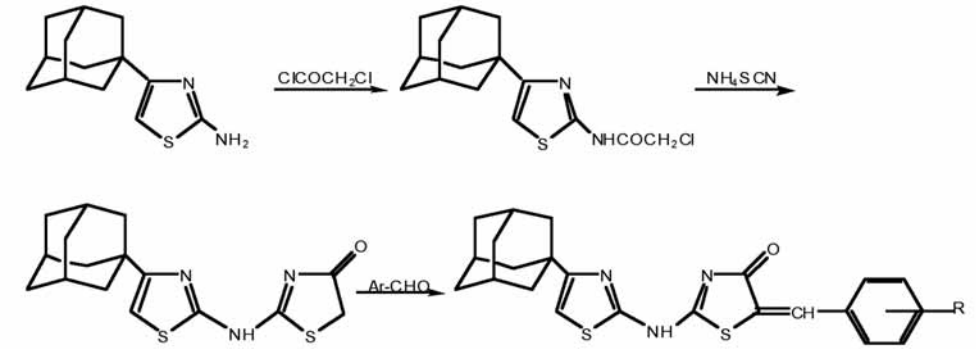
Inflammatory processes contribute to a number of serious and chronic disorders ranging from asthma, atherosclerosis, osteoarthritis and diabetes to neurodegenerative diseases such as Alzheimer and Parkinson's diseases. Inflammation is a natural protective reaction of human organism to tissue damage which is induced by physical injuries, chemical substances, pathogenic microorganisms and other factors and involves several mediators, among them over-expressed enzymes such as cyclooxygenases COXs, lipoxygenases LOXs. The main characteristics of inflammation are redness, warmth, swelling and pain.

Various thiazolidinone derivatives, synthesised by us, have been found to have interesting *in vitro* and *in vivo* antinflammatory activity and their structure-activity has been studied.

Giving the promising results obtained with benzothiazole and benzisothiazole azomethine derivatives with antinflammatory and antioxidant activity we have recently moved forward to their structural diversification namely by linking the thiazole and adamantane to a thiazolidinone ring, whose potential as biologically active nucleus is well known, as well.

New compounds were synthesized according to Scheme 1. and evaluated for their anti-inflammatory activity.



Scheme1.

R	R	R
1. 2,6-dichloro	5. 4-Br	9. 4-Fluoro
2. 2-chloro-6-Fluoro	6. 4-N(CH_3)$_2$	
3. 2,3-dichloro	7. 3-Br	
4. 2,4-dichloro	8. 3-Fluoro	

Poster - 59

STRUCTURE AND BIOLOGICAL EVALUATION OF ZINC COMPLEXES WITH FLUFENAMIC ACID

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The interaction between drugs and transition metals is an important and active research area in bioinorganic chemistry [1]. Zinc, an element of great biological interest, is the second most prominent trace metal in the human body. Diverse structurally characterized zinc complexes with antidiabetic, antifungal, anti–inflammatory, antimicrobial, antitumor and antiulcer activity have been reported [2,3].

Flufenamic acid (=Hfluf) is a non-steroidal anti-inflammatory drug (NSAID) that belongs to the derivatives of the N-phenyl-anthranilic acid exhibiting analgesic, anti-inflammatory and antipyretic properties. It resembles mefenamic and tolfenamic acids [4,5] and is used in musculoskeletal and joint disorders and administered by mouth or topically [6].

We have synthesized and characterised zinc complexes with flufenamic acid in the absence or presence of nitrogen donor ligands 1,10-phenanthroline (=phen), 2,2′-bipyridine (=bipy). Competitive studies with ethidium bromide and binding studies with CT DNA as well as human and bovine serum albumins have been employed in order to evaluate the biological behavior of the resultant complexes. The crystal structure of complex $[Zn(fluf)(phen)_2(H_2O)](fluf)$ has been determined by X-ray crystallography.

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Acknowledgment

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Poster - 60

ZINC(II) COMPLEXES WITH MEFENAMIC ACID: STRUCTURE AND BIOLOGICAL ACTIVITY

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Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently medicinal drugs used as analgesic, anti-inflammatory and antipyretic agents. NSAIDs have also exhibited chemo preventive and anti-tumorigenic activity by reducing the number and size of carcinogen-induced colon tumors and exhibiting a synergistic role on the activity of certain antitumor drugs [1]. The NSAID mefenamic acid (=Hmef) belongs to the derivatives of N-phenylanthranilic acid and resembles chemically tolfenamic and flufenamic acids and other fenamates in clinical use [2,3].
Zinc has an important role in various biological systems since it is critical for numerous cell processes and is a major regulatory ion in metabolism of cells. Diverse zinc complexes with biological activity are reported in the literature [4,5].
In this context, the synthesis, the characterization and the DNA or serum albumin binding properties of the zinc complexes with mefenamic acid in the absence or presence of the N,N′-donor heterocyclic ligand 1,10-phenanthroline (=phen) are presented. The crystal structure of $[Zn(mef)_2(phen)(H_2O)]$ has been determined by X-ray crystallography.

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Poster - 61

INTERACTION OF MANGANESE(II) WITH ANTIMICROBIAL DRUG OXOLINIC ACID

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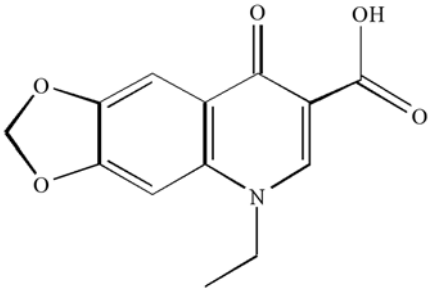
Quinolones are synthetic antibacterial agents containing a 4-oxo-1,4- dihydroquinoline skeleton and are commonly used as treatment for many infections. The target of quinolones are both gyrases (type II topoisomerases) and topoisomerase IV and they inhibit effectively DNA replication by interrupting the reunion of genomic DNA at the end of the cleavage ligation cycle in the active site of the gyrases [1].

Oxolinic acid (=Hoxo, figure) is a first-generation quinolone antimicrobial drug and is known for its antibacterial activity, which is the treatment of urinary tract infections. Although the pharmaceutical role of oxolinic acid is known for the last four decades [2], only four complexes of oxolinic acid as ligand with Cu(II) [3], Zn(II) [4] and Ni(II) [5] have been structurally characterized and recently reported by our lab.



Given the importance and the role of manganese [6] in the biological systems, we have initiated the interaction of manganese with drugs. In this context herein, we present the synthesis, structural characterization, electrochemical and biological properties (interaction with DNA, competitive studies with ethidium bromide and binding to bovine and human serum albumin) of Mn(II) complexes with oxolinic acid. The crystal structure of $\{K[Mn(oxo)_3](MeOH)_3\}n$ has been determined by X-ray crystallography.

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Poster - 62

MECHLORETHAMINE PLATINUM(II) COMPLEX AS AN ARTIFICIAL METALLOPEPTIDASE

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The reaction of K_2PtCl_4 with the alkylating agent mechlorethamine hydrochloride, at a molar ratio of 1:2, results in the formation of 2-chloro-*N*-(2-chloroethyl)-*N*-methylethylammoniumtetrachloridoplatinate(II) complex, whose optimized structure is given in Fig. 1. It was shown that this complex can successfully to terminate peptide bond of the *N*-acetylated *L*-histidylglycine dipeptide.[1] We have now tested the hydrolytic ability of the complex in the reaction with *N*-acetylated L-methyonylglycine dipeptide. It was shown that the hydrolytic reaction (molar ratio 1:1), performed at 60 °C in acidic medium (pH=2), leads to the regioselective cleavage of the amide bond involving the carboxylic group of methyionine. This confirms that this compound can be artificial metallopeptidase. The hydrolyitic reaction can be followed successfully using ^{1}H NMR spectroscopy, Graphic 1. Mixing of the Pt(II) complex with an equimolar amount of AcMet-Gly

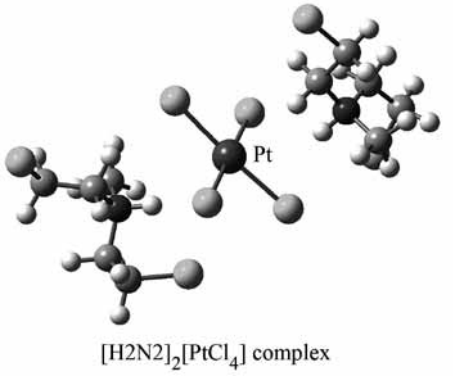
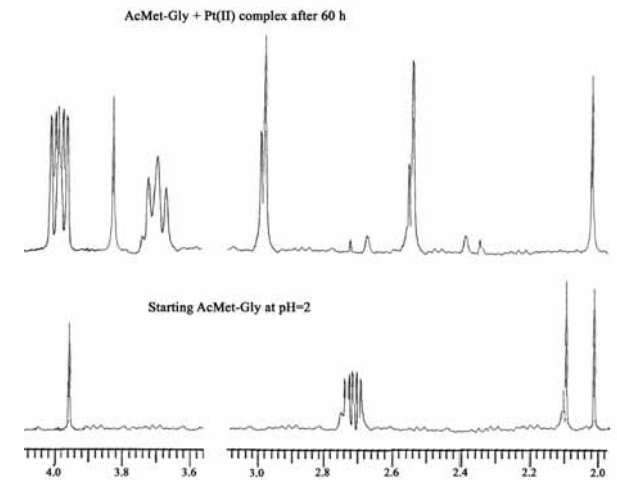


Fig. 1.



Graphic 1.

resulted in the spontaneous coordination of the Pt(II) complex to the sulfur atom of methionine residue. The signals which refer to the non-hydrolyzed and free glycine are detected. The resonance at 3.96 ppm corresponds to the glycine protons of the non-hydrolyzed AcMet-Gly, while that at 3.82 ppm for the released free glycine, Graphic 1. The hydrolytic reaction was finished after 60 hours.

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Poster - 63

STRUCTURE AND BIOLOGICAL EVALUATION OF Ni(II)-DICLOFENAC COMPLEXES

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Nickel is an element of expanding biological interest due to its presence in the active centre of enzymes such as urease and in diverse metal complexes of biological activity [1]. Regarding the interaction of Ni(II) complexes with DNA, it is mainly dependent on the structure of the ligand exhibiting intercalative behaviour and/or DNA cleavage ability [1-3].
Sodium diclofenac (=Nadicl) is a non-steroidal anti-inflammatory drug (=NSAID) belonging to the NSAID group of phenylalkanoic acids and exhibits noticeable anti-inflammatory, analgesic and antipyretic properties [4-6].
In the present contribution, we report the synthesis, spectroscopic and electrochemical characterization of Ni(II) complexes with diclofenac in the absence or presence of nitrogen-donor heterocyclic ligand such as 2,2′-bipyridine (=bipy), 1,10-phenanthroline (=phen) and 2,2′-dipyridylketonoxime (=Hpko). The crystal structure of $[Ni(dicl)(Hdicl)(Hpko)_2](dicl)$ has been determined by X-ray crystallography.
The binding properties of the complexes with calf-thymus DNA have been investigated by spectroscopic, electrochemical and physicochemical techniques. Competitive binding studies with ethidium bromide have been studied by fluorescence spectroscopy in order to investigate the existence of a potential intercalation of the complexes to DNA. The affinity of the complexes for bovine and human serum albumin proteins has been investigated by fluorescence spectroscopy.

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Poster - 64

COBALT(II) COMPLEXES WITH NON-STEROIDAL ANTI-INFLAMMATORY DRUGS: STRUCTURE AND BIOLOGICAL PROPERTIES

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Cobalt is a transition metal with structural and functional in vivo properties. Its biological role is mainly focused on its presence in the active center of cobalamine, which regulates indirectly the synthesis of DNA and blood cells, and the involvement in the co-enzyme of vitamin B12 used as a supplement of the vitamin and in other cobalt-dependent proteins [1]. So far, many cobalt complexes have been structurally characterized, showing antitumor, antiproliferative, antimicrobial, antifungal, antiviral and antioxidant activity [2-4].
Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used medicinal agents with analgesic, anti-inflammatory and antipyretic action [5]. Additionally, NSAIDs have exhibited a synergistic role on the activity of certain antitumor drugs. The metal complexes of NSAIDs have also exhibited more pronounced biological activity in comparison to free NSAIDs [6-8].
In this context, we present the synthesis, the structural characterization and biological behaviour of Co(II) complexes with the NSAIDs flufenamic acid (=Hfluf) and diflunisal (=Hdifl) in the presence of N- or O-donor ligands such as 2,2′-bipyridylamine (=bipyam) and methanol, respectively. The crystal structures of the complexes $[Co(difl)_2(MeOH)_4]$ and $[Co(fluf)_2(bipyam)]$ have been determined by X-ray crystallography. Additionally, the interaction of the complexes with calf-thymus DNA and human and bovine serum albumin proteins have been studied with diverse spectroscopic and physicochemical techniques.

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Poster - 65

MANGANESE(II) COMPLEXES WITH NON-STEROIDAL ANTI-INFLAMMATORY DRUG TOLFENAMIC ACID: STRUCTURE AND BIOACTIVITY

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Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently medicinal agents used as analgesics, anti-inflammatories and antipyretics. NSAIDs have also exhibited chemopreventive and anti-tumorigenic activity and a synergistic role on the activity of certain antitumor drugs. Their main known mode of action is through inhibition of the cyclooxygenase-mediated production of prostaglandins [1]. The interaction of NSAIDs directly at the DNA level is of great interest in order to explain the tentative anticancer as well as the anti-inflammatory activity. Additionally, metal complexes of NSAIDs have also exhibited synergistic activity [2-4]. Tolfenamic acid (=Htolf) belongs to the NSAID group of N-phenylanthranilic acid, is found in analgesic, antiinflammatory, antipyretic and antirheumatoid drugs and is also used for veterinary purposes [5,6].
Given the importance and role of manganese [7] in the biological systems, we have initiated the interaction of manganese with diverse drugs. In this context, we present herein the structural characterization, the electrochemical properties as well as the biological evaluation (binding to calf-thymus DNA, competitive studies with ethidium bromide and interaction with bovine and human serum albumina) of the Mn(II) complexes with the tolfenamic acid in the absence or presence of the N-donor heterocyclic 2,2′-bipyridylamine (=bipyam). The crystal structure of $[Mn_2(tolf)_4(bipyam)_2]$ has been determined by X-ray crystallography.

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Poster - 66

BIOLOGICAL ACTIVITY OF THE DIETHANOLAMINE AND TRIETHANOLAMINE IONIC LIQUIDS AND ITS CORRESPONDING PALLADIUM(II) COMPLEXES

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trans-dichlorobis(triethanolamine-N)palladium(II) complex (*trans*-$[PdCl_2(TEA)_2]$) was obtained in the reaction of $PdCl_2$ with triethanolamine acetate [TEA][HOAc] in molar ratio of 1:2 at 90 °C (TEA = triethanolamine),[1] while $[HDEA]_2[PdCl_4]$ complex was obtained in the reaction of $PdCl_2$ with diethanolamine chloride.[2] The optimized structures of the ionic liquids and their corresponding complexes are presented in Figure 1. The antimicrobial activity of the ionic liquids triethanolamine acetate [TEA][HOAc] and diethanolamine chloride [HDEA][Cl], as well as of their Pd(II) complexes is investigated using microdilution method. The investigated compounds showed low antibacterial activity. Better results were for antifungal activity. [TEA][HOAc] exhibited better activity than corresponding complex (MIC values were between 15.6 – 1000 μg/ml for [TEA][HOAc], and MIC values for corresponding complex from 250 μg/ml to 1000 μg/ml). *Aspergillus* species were especially sensitive to $[HDEA]_2[PdCl_4]$. The activity of this complex against *A. restrictus, A. fumigatus* was up to ten times higher than the activity of positive control, fluconazole.

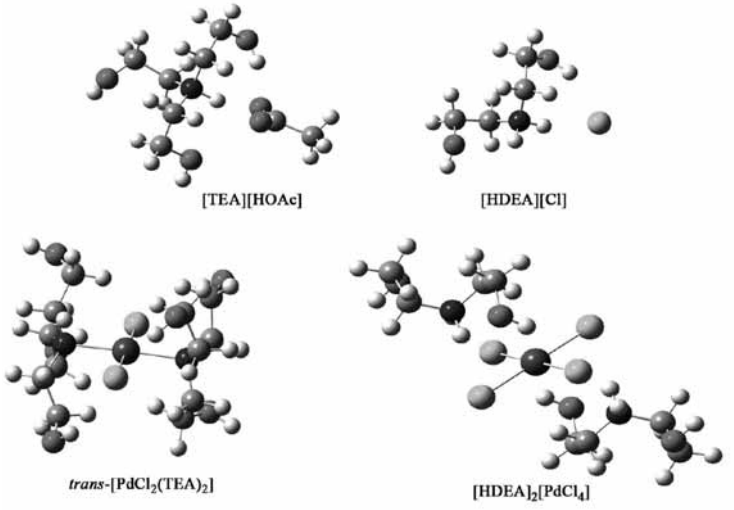

Figure 1.

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Poster - 67

SYNTHESIS AND BIOLOGICAL STUDY OF 2-(PYRROLESULFONYLMETHYL)-*N*-ARYLIMINES: NEW INHIBITORS FOR HUMAN GLUTATHIONE S-TRANSFERASE A1-1 (hGSTA1-1)

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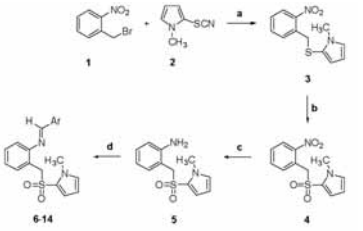
Glutathione transferases (GSTs) are a family of enzymes involved in cellular detoxification from several xenobiotics and drugs [1]. They do so by catalysing the nucleophilic attack of glutathione (GSH) to the electrophilic centre of a number of hydrophobic compounds, including certain chemotherapeutic drugs, thus promoting the transport and degradation of the respective conjugates. Earlier observations suggested that chemotherapeutic resistance of tumour cells is associated with elevated GST expression. Therefore, the development of new GST inhibitors and respective pro-drugs [2] could lead to new pharmaceutical tools useful in cancer combat. This is the first report on pyrrole derivatives as GST inhibitors. We synthesised 11 new pyrrole derivatives 4-14 and studied them against the medically most important human GST isoenzyme, hGSTA1-1. The study of the pyrrole analogue library, combined enzyme inhibition screening with *in silico* molecular docking analysis followed by enzyme inhibition kinetics. Pyrrole analogue 9 bearing a p-nitroarylimino moiety showed the highest GST inhibitory potency (90%). We propose the 2-(pyrrolesulfonylmethyl)-*N*-arylimine structure as a pharmacophore (GST inhibiting scaffold) for designing more potent GST inhibitors and pro-drugs combating MDR.



6 Ar = Ph, 7 Ar = 4-$F_3CC_6H_4$, 8 Ar = 4-$(CH_3)2NC_6H_4$, 9 Ar = 4-$NO_2C_6H_4$, 10 Ar = 5-Br, 2-$CH_3OC_6H_3$, 11 Ar = 4-FC_6H_4, 12 Ar = 2-ClC_6H_4, 13 Ar = 4-ClC_6H_4, 14 Ar = 2-pyrrolyl

Scheme. Synthetic route leading to tested pyrrole derivatives **4-14**. Reactions and conditions: (a) (1) $NaBH_4$, dry *i*-PrOH, 0 oC, 1.5 h; (2) 1M NaOH in H_2O, 0 oC to room temp, 2 h; (b) $2KHSO_5.KHSO_4.K_2SO_4$, H_2O, MeOH, room temp, 14 h; (c) $FeSO_4{\cdot}7H_2O$, 25% NH_4OH, EtOH, 2 h; (d) ArCHO, dry *i*-PrOH, glacial CH_3CO_2H, Na_2SO4, argon, under reflux, 10 h.

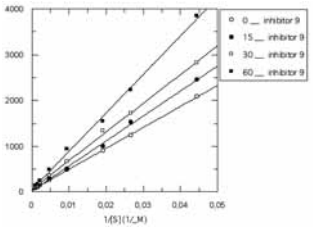


Figure. Double reciprocal graph of GST velocity vs. substrate (CDNB) concentration at three constant concentrations (15, 30, 60 μM) of inhibitor (derivative 9), showing the competitive nature of inhibition of derivative 9 vs. CDNB for hGSTA1-1.

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Poster - 68

NOVEL CYSTEINE-BASED α4β1 INTEGRIN LIGANDS: CORRELATION OF *in silico* PHARMACEUTICALLY RELEVANT PROPERTIES WITH THEIR *in vivo* PROFILE

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The antigen α4β1 (VLA-4, very late activating antigen-4), a member of the integrin family, is involved in the migration of lymphocytes through endothelium to the site of inflammation [1]. For this reason α4β1 antagonists may be useful tools for the treatment of various inflammation disorders such as asthma, inflammatory arthritis and inflammatory bowel disease. In addition, recent studies indicate that α4β1 integrin is implicated in angiogenesis. Specifically, α4β1 promotes angiogenesis by allowing the invasion of myeloid cells into tumors, and α4β1 antagonists prevent monocyte-induced angiogenesis, macrophage colonization of tumors and tumor angiogenesis [2].

Aiming to the discovery of novel α4β1 antagonists, a series of new peptide analogues cyclized through cysteine disulphide bonds were synthesized and tested *in vivo* against angiogenesis in chicken embryo chorioallantoic membrane (CAM model) [3].

Peptide	Activity
Tyr-Arg-c(Cys-Asp-Pro-Cys)-$CONH_2$	• promotes angiogenesis at the higher concentration • shows slight inhibition at the lower concentration
Sal-Arg-c(Cys-Asp-Pro-Cys)-OH	• shows important inhibition of angiogenesis at dose-dependent manner
Tyr-Arg-c(Cys-Asp-Pro-Cys)-OH **Sal-Tyr-Arg-c(Cys-Asp-Pro-Cys)-OH**	• show no activity in angiogenesis

QikProp module of Schrödinger Suite 2011 was applied as it enables the prediction of physically significant descriptors and pharmaceutically relevant properties of the synthesized peptides. For the appropriate calculation of the conformation-dependent properties, low energy peptide conformers were initially determined using Molecular Dynamics simulations under constrains from 2D NOESY NMR experiments.

Multivariate data analysis based on the calculated physicochemical properties probed to the different biological profile of the studied peptides clearly differentiating inhibition versus promotion. Crucial descriptors for this differentiation were identified to be the number of H-bond donors and acceptors, the aqueous solubility (QPlogS), the octanol/water partition coefficient (QPlogPo/w) and the hydrophilic component of the solvent accessible surface area (FISA). This study aspires to guide the design of novel peptide α4β1 Integrin inhibitors.

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Poster - 69

RATIONAL DESIGN AND BIOLOGICAL EVALUATION OF NOVEL RESVERATROL AND GLYOXYLATO-AROYLHYDRAZONE ANALOGS AGAINST ALZHEIMER DISEASE

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β-Secretase (BACE-1) is a membrane-bound aspartyl protease that proteolyses the amyloid precursor protein (APP) resulting in the generation of peptide fragments. These fragments are found to aggregate in the brain of Alzheimer's patients. For this reason, inhibition of this enzyme has been regarded as a key target for the therapeutic intervention in Alzheimer's disease. Recent findings have shed light on the potential role of resveratrol and its analogs as inhibitors of BACE-1. Furthermore, metal complexes have shown to be directly implicated in mechanisms leading to oxidative stress, which is a key factor involved in the development of age-related disorders such as Alzheimer's disease.

The above findings are further rationalized by preliminary docking studies. Therefore, a series of resveratrol derivatives and glyoxylato-aroylhydrazones designed as chelators against BACE-1 were biologically evaluated using a homogeneous time resolved fluorescence (TRF) assay. Four resveratrol analogs demonstrated higher activity than resveratrol, whereas glyoxylato-aroylhydrazones showed almost no inhibitory activity. The discovery of some "hits" led us to initiate in detail docking studies. Both chemical classes of molecules were subjected to Glide docking algorithm of SchrÖdinger software in an attempt to explain their biological activity using scoring functions and considering specific key interactions with the aminoacids of the active site of BACE-1.

Poster - 70

DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW COUMARIN DERIVATIVES WITH A POTENTIALLY ANTITHROMBOTIC ROLE

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Inflammation and blood's coagulation are two physiologic mechanisms, with strong interaction.[1] Problems with coagulation may dispose to hemorrhage, thrombosis, and occasionally both, depending on the nature of the pathology[2,3]. Coumarin-derivatives consist a particular category of chemical compounds, presenting an increased biological interest.[4] Coumarin-derivatives present a potent anti-inflammatory activity combined with free radical scavenging activity.[5]

In this study, a series of 3-, 4- and 7- substituted coumarin derivatives is presented. All coumarin derivatives were synthesized according to Mannich Reaction. They have been previously evaluated for their antioxidant and free radical scavenging activity. The compounds were also found to inhibit enzymes implicated in inflammation, like soybean lipoxygenase and bovine trypsin for their role antithrombotic activity. They have been evaluated for their possible role as NO donors. They were studied as NO donors in the presence of thiol cofactors such as L-Cystein and thiophenol.

In parallel they were evaluated for their ability to inhibit the formulation of thrombus in vitro using the clot retraction assay. Blood from rats was used and Platelet Rich Plasma (PRP) was separated. The thrombus formulation was induced by the presence of thrombin.

Molecular Modeling and docking studies were performed to analyze the above results. The results are discussed in terms of structural characteristics considering further design of new potent coumarin derivatives with both antioxidant and antithrombotic activity.

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Poster - 71

BINDING OF NOVEL FULLERENE INHIBITORS TO HIV-1 PROTEASE: INSIGHT THROUGH MOLECULAR DYNAMICS AND MOLECULAR MECHANICS POISSON–BOLTZMANN SURFACE AREA CALCULATIONS

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The objectives of this study include the design of a series of novel fullerene-based inhibitors for HIV-1 protease (HIV-1 PR), by employing two strategies that can also be applied to the design of inhibitors for any other target. Additionally, the interactions which contribute to the observed exceptionally high binding free energies were analyzed. In particular, we investigated: (i) hydrogen bonding (H-bond) interactions between specific fullerene derivatives and the protease, (ii) the regions of HIV-1 PR that play a significant role in binding, (iii) protease changes upon binding and (iv) various contributions to the binding free energy, in order to identify the most significant of them. This study has been performed by employing a docking technique, two 3D-QSAR models, molecular dynamics (MD) simulations and the molecular mechanics Poisson–Boltzmann surface area (MM–PBSA) method. Our computed binding free energies are in satisfactory agreement with the experimental results. The suitability of specific fullerene derivatives as drug candidates was further enhanced, after ADMET (absorption, distribution, metabolism, excretion and toxicity) properties have been estimated to be promising. The outcomes of this study revealed important protein-ligand interaction patterns that may lead towards the development of novel, potent HIV-1 PR inhibitors.

Poster - 72

QSAR STUDIES ON 2-(5H-[1,2,4]TRIAZINO[5,6-B]INDOL-3-YLTHIO)-N-(R-PHENYL)ACETAMIDE DERIVATIVES WITH ANTIDEPRESSANT ACTIVITY

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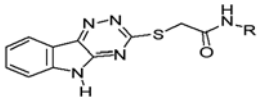
Derivatives of 1,2,4-triazino[5,6-b]indole are known to possess diverse biological activities like actoprotector[1], antiviral [2], anti-inflammatory [3], anti-microbial [4], antitumor [5] and hepatoprotective [6]. Importantly, this tricyclic structure is comparable to β-carboline (9H-pyrido[3,4-b]indole), an endogenous monoamine oxidase (MAO) inhibitor [7]. In search for novel antidepressants,a series of 2-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio-N-(R-phenyl) acetamides was synthesized and screened for potential antidepressant activity [8]. While designing present series, cognizance was taken of central nervous system activity of various heterocyclic phenylacetamides [9].
Using the above results, we performed a QSAR analysis using the C-QSAR program (BioByte), to identify which physicochemical parameters affect the biological activity of 17 indolyl derivatives of the below given structure.



This study revealed that inductive electronic effect (F) is one of the most important determinants of activity. Additionally, sterimole parameters of Verloop(B1, B5) are also important, highlighting the role of the steric effect. Lipophilicity was not found to play any role.

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Acknowledgments:To Biobyte Corp. 201 West 4th St. Suite 204, Claremont CA 91711, USA for free access to C-QSAR program.

Poster - 73

QSAR OF INTERLEUKIN INHIBITORS: A TOOL FOR ANTI-INFLAMMATORY DRUG DESIGN

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Interleukins are a family of cytokines involved in the multi-step biological reaction of inflammation. Inteleukin-5 acts selectively on eosinophil cells [1] and its inhibition represents a new therapeutic target for treating allergic diseases. Interleukin-6 is a pleiotropic cytokine produced by a variety of cells and seems to be the main mediator in various inflammatory diseases. Interleukin-8 is a pro-inflammatory CXC chemokine binding to two known receptors and participates in a series of inflammatory conditions. Designing small molecules as interleukin inhibitors is a target of anti-inflammatory drug development.
In the present study we performed QSAR analysis to identify the physicochemical parameters implicated in interleukin inhibition using the C-QSAR program. In our study we analysed: 1) a group of 17 chalcones as potent IL-5 inhibitors [2], 2) 15 4-styrylcoumarins as potent IL-6 inhibitors [3] and 3) 39 2-amino-3-heteroaryl quinoxalines as potent IL-8 inhibitors [4].The data were examined separately and the final equations were compared. Molar volume and the sterimol parameters of Verloop are significant for the biological response whereas lipophilicity (ClogP) seems to be important in one case only. Electronic properties as Hammett's σ constant contribute significantly.

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Acknowledgments: To Biobyte Corp.201 West 4th St. Suite 204, Claremont CA 91711, USA for free access to C-QSAR program.

Poster - 74

PROBING FOR NOVEL AND SELECTIVE MONOGLYCERIDE LIPASE INHIBITORS

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2-Arachidonoylglycerol (2-AG) possesses a wide range of pharmacological properties. These include the modulation of neurotransmitter release, control of neuro-inflammation and regulation of cancer cell growth to stress-induced analgesia. The enzyme monoacylglycerol lipase (MAGL) plays an important role in its metabolism by in vivo hydrolyzing it. To restore its pharmacological properties, MAGL inhibition is considered a putative therapeutic target.

One significant problem we faced exploring the literature data is that the inhibition of MAGL enzyme has been determined by various biological assays which in some cases lead to controversial results. To overcome this difficulty, we have applied and compared docking results at the molecules subjected to identical biological assays. Another problem encountered in the application of docking studies is the presence of only two x-ray crystallographic results in which MAGL is co-crystallized with an inhibitor. Such a short number of crystallographic data makes difficult the decision of the exact mode of action for novel compounds as they are found to approach in different ways the active or allosteric sites. Except that, there is a difference between the open and the close form of the tunnel containing the catalytic triad, so we had to test the results in both forms of the enzyme.

After we have validated the data with known experimental biological values, we applied molecular docking using a data base of novel compounds that have not been evaluated biologically. Those compounds that showed the highest score were also docked at the enzyme FAAH to test their selectivity between the two enzymes. The pyrrolydinone analogues that were initially synthesized as renin inhibitors showed the highest potency towards MAGL and adequate selectivity to FAAH, indicating that they constitute a promising class of molecules to further explore.

Poster - 75

NATURAL PRODUCTS WITH INHIBITORY ACTIVITY TOWARDS GLYCOGEN PHOSPHORYLASE IDENTIFIED BY VIRTUAL SCREENING CALCULATIONS

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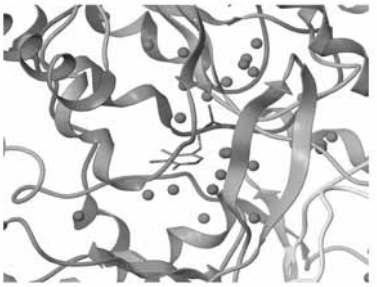

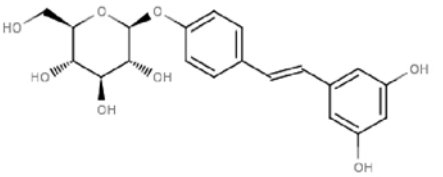

Glycogen phosphorylase (GP) is an important allosteric enzyme involved in the regulation of the glucose blood levels. As such, it is considered as a valid therapeutic target for the discovery and development of new antidiabetic drugs. Several binding sites on the enzyme such as the catalytic, allosteric, inhibitor, and the new allosteric site have been identified as specific targets for inhibitor binding.

In this study, we present a combined implementation of computational and physical screening approaches targeting at the discovery of compounds that might constitute new leads for the development of potent and selective GP inhibitors. As a first step, a highly specific Virtual Screening protocol was developed for GP by using a set of known active compounds along with a set of inactive decoys. The protocol optimization was performed by considering the effect of several critical factors of the theoretical calculations on the resulting enrichment. Among the factors influencing the protocol performance, the most important was the presence of a wide set of structural water molecules that have been determined by crystallography studies as a functional part of the binding cavity of the enzyme. The scaling of the Van der Waals radii of the protein and ligand atoms and the resulting simulated induced fit effects was a second factor improving the enrichment of the protocol.

The optimized VS protocol was utilized for the evaluation of two compound libraries comprising a total of ~2000 molecules and the 18 top-ranked compounds were assayed *in vitro* with respect to their GP-inhibitory activity. Ten compounds were found active and for two of them the IC_{50} value was determined in the mid-micromolar range. Interestingly, both of them are natural products with a well described antioxidant activity, namely 4-O-β-D-glycoside of resveratrol and the phenolic glycoside tachioside. The abundant presence of similar compounds in foods like wine can be of high interest since their moderate activity as GP inhibitors can confer them a role as mild modulators of blood glucose level.

Poster - 76

COMBINING LIGAND- AND STRUCTURE-BASED METHODS OF VIRTUAL SCREENING IN SEARCH OF NOVEL BROMODOMAIN PROTEIN LIGANDS

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Bromodomains are a recently discovered group of proteins belonging to the field of study of epigenetics. Their physiological role is in post-translational regulation of gene expression via the recognition and binding of acetylated lysines belonging to DNA histones and the consecutive silencing of the genes by preventing the unraveling of chromatin. Their involvement in pathological conditions such as cancer or viral replication has been recently documented thus leading to their establishment as novel and emerging drug targets. Potent inhibition of bromodomains of the BET family was achieved only recently. In this study the effort of identifying drug like compounds with binding properties towards members of the bromodomain group based on the combination of two different approaches in the field of molecular simulations is described.

The implementation of two complementary methods of Virtual screening, namely ligand-based similarity and fingerprint searches as well as structure-based docking screening was performed in a consensus fashion. The aforementioned approach was undertaken in order to achieve better enrichment and complement the weaknesses of each methodology with the strengths of the other. In practice software Glide, Openeye and Canvas were utilized to screen the database of the National Cancer Institute comprising approximately 260K compounds for molecules that can bind to bromodomain proteins. The combined results from these approaches were used to select about 40 molecules from the compound collection as possibly having activity on the target. Those molecules were tested *in vitro* for their bromodomain binding properties using a Differential Scanning Fluorimetry assay and results returned one active molecule with satisfactory binding affinity towards the fifth bromodomain of PB1.

Poster - 77

UNCONSTRAINED, UNBIASED, MD SIMULATION OF THE LOW NANOMOLAR DUAL AChE INHIBITOR INTERACTION WITH THE ENZYME

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Acethylcholinesterase (AChE) is well-known target for the treatment of Alzheimer's disease. Number of articles deal with the small-molecules that act as AChE reversible inhibitors, but there is a limited number of FDA approved drugs. We report molecular dynamics simulation of the entrance of low nanomolar AChE inhibitor (1, Figure 1) to the enzyme active site.

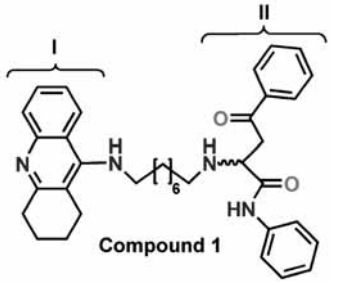

Figure 1

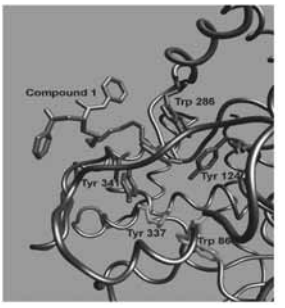

Figure 2

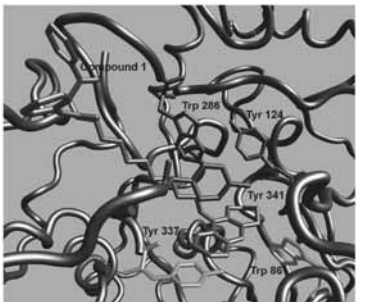

Figure 3

Simulation was performed to gain deeper insight in enzyme-ligand interactions, and to guide us to design more potent inhibitors. Set of congeners, including compound 1, is prepared, purified and characterized in our laboratories. Anticholinesterase activity was obtained by Ellman spectrophotometric method. For the modelling, mouse AChE structure was used (PDB code 2HA2). After protein structure preparation and the 2 ns molecular dynamics equilibration, compound 1 was docked to the enzyme active site using AutoDock 4.0. For the further MD simulations we chose the pose having tacrine moiety bounded to peripheral active site (PAS), and the rest of the ligand pointing toward surroundings (Figure 2). System was neutralized, and the 45 Å water sphere was added. Unconstrained, unbiased MD simulation in NAMD 2.8 was performed, using CHARMm22 force field, periodic boundary conditions, PME for electrostatics, and 12 Å cutoff. During the first 15 ns of the simulation ligand entered deep into the enzyme active site, interacting with the Tyr337, but does not produce stacking with the Trp86 (Figure 3). We continued simulation during additional 25 ns. Interactions of the tacrine moiety (I, Figure 1) with the residues of the active site gorge, and the 4-phenyl-4-oxobutanoic phenylamide moiety (II, Figure 1) with the PAS of the enzyme is described. Buried surface area of the ligand, strength of interaction of ligand-enzyme complex, and hydrophobic interactions of the ligand bound to enzyme, as obtained by GRID programme, during different phases of simulation is commented.

Acknowledgement This communication is supported by the European Commission under EU FP7 project HP-SEE, http://www.hp-see.eu/. Contract number 261499. The Ministry of Education and Science of Serbia support this work in part, under Grant 172035.

Poster - 78

QSAR ANALYSIS OF PPAR-α/γ ACTIVITY USING MULTIVARIATE STATISTICS AND MOLECULAR SIMULATION

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Peroxisome proliferator-activated receptors alpha and gamma (PPAR-α, PPAR-γ) play a crucial role in the regulation of lipid and glucose metabolism. PPAR-γ has been extensively investigated as a target of a large number of anti-diabetic agents. However, as the simultaneous activation of PPAR-α is postulated to alleviate the side effects, related with PPAR-γ activation, research interest has recently been shifted towards dual PPAR-α/γ agonists. In the present study, Multivariate Data Analysis (MVDA) was combined with information on crystallographic data and molecular modeling, in order to investigate dual PPAR-α/γ activity (pEC_{50}-α and pEC_{50}-γ) using a data set of 71 carboxylic acid derivatives collected from ref.[1-5]. The pool of descriptors comprised physicochemical/molecular properties, constitutional and 3-D descriptors, as well as connectivity and electrotopological state indices, the latter calculated by MOLCONN-Z. Satisfactory PLS models were generated for each receptor subtype separately (R^2 =0.791, Q^2 =0.754 and R^2=0.782, Q^2=0.742 for PPAR-α and PPAR-γ activity respectively). The models were based on simple and easily interpretable druglike and constitutional descriptors, while the inclusion of MOLCONN-Z descriptors in the initial pool of variables had no considerable impact in model predictivity. By simultaneous analysis of both types of activity a consensus PLS model for dual PPAR-α/γ activity could be derived (R^2=0.755and Q^2=0.713), displaying the molecular features, which may lead to a balanced activity. All models were validated by permutation tests and by external validation, dividing the data set into training and test sets. Multiple Linear Regression Analysis was applied in order to establish inter-relation activity equations, which were found to be consistent with the separate PLS models. The differentiation of most important descriptors in the separate models, e.g. the higher impact of lipophilicity and bulk descriptors in PPAR-α and PPAR-γ activity respectively, as well as the effect of specific structural descriptors, were further validated by detailed inspection of the relevant crystal structures and molecular simulation.

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Poster - 79

MODELLING AND PREDICTING OXIDATIVE STRESS-INDUCED NEURONAL DAMAGE BY CHROMAN ANALOGUES

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Novel chroman analogues have been recently synthesized and their neuroprotective activity was evaluated against oxidative stress-induced cell death of glutamate-challenged HT22 hippocampal neurons [1-3]. These analogues were compiled in a single database and a workflow for the *in silico* exploration of the relationship between the structural characteristics of the new chroman derivatives and their neuroprotective activity has been developed. Among a pool of 800 molecular descriptors the most important features responsible for the oxidative stress were identified. Different machine learning and variable selection methodologies have been explored individually and in combination. A robust and validated *in silico* model including physicochemical and structural descriptors that are able to predict successfully oxidative stress-induced neuronal damage is reported. The accuracy of the proposed *in silico* model is illustrated using various evaluation techniques such as: cross-validation, validation through an external test set and Y-randomization [4]. Furthermore, the domain of applicability which indicates the area of reliable predictions is defined. The propose workflow can serve as a first guideline for the design of novel and potent chroman analogues.

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Poster - 80

DOCKING CALCULATIONS AND BINDING AFFINITIES OF AMINOADAMANTANE LIGANDS TO THE HYDRATED INFLUENZA A/M2TM

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The Udorn A/H3N2 M2TM peptide (SSDPLVVAASIIGILHLILWILDRL(amide)) was synthesized using solid phase peptide synthesis and was purified using a carefully chosen solvent gradient due to the highly lipophilic nature of the peptide. The binding affinity of previously synthesized aminoadamantane derivatives 1-31 was measured against: a) The full M2 protein using an assay based on the inhibition of quenching of Trp41 fluorescence at acidic pH induced by the aminoadamantane ligand binding in the M2 channel pore b) The Udorn M2TM tetramer at alkaline pH in DPC using Isothermal Titration Calorimetry (ITC). Although a series of highly hydrophobic ligands, which seem to have little capacity for different specific interactions with their receptor, the measured binding affinity varied with small changes in the ligand's structure.

Three series of docking calculations were preformed using Gold software and the implemented scoring functions (GoldScore, Chemscore, ASP) to test: a) The pore blocking model; in the last case the docking calculations were tested by including water molecules inside the pore or without water molecules. b) The peripheral allosteric binding site of M2TM which is outside the pore in the region of Asp44.

It was shown that water molecules must be included inside the pore during the calculations in order to predict the experimentally observed orientation of amino group towards the His37 of C-end. This orientation is stabilized through a water wire hydrogen bonding between ammonium group of the ligand and His37 (lig-N-H$\cdots$(water)$_n\cdots$nitrogen-His). The docking calculations predicted poses in which the adamantane ring is surrounded mainly by the alkyl side chains of Val27 and Ala30. In the case of an empty pore the molecules turn so that the amino group of the ligands points to the N-end forming H-bonds with hydroxyl groups of Ser31.

Surprisingly, a high correlation between docking scores calculated with conventional scoring functions, reflecting free energy of binding, and binding affinities was predicted ($R^2 = 0.40$ using GoldScore scoring function, acidic pH system, and $R^2 = 0.74$ using GoldScore scoring function, basic pH system) using the pore blocking model and water molecules ($\sim$ 10 water molecules) inside the pore with the GoldScore function.

Poster - 81

A STUDY OF HISTONE DEACETYLASE INHIBITORS AS POTENTIAL HBF INDUCERS

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The pharmacological reactivation of HbF is a promising strategy for the treatment of sickle-cell disease and β-thalassemia. Although, many agents have HbF-inducing activity their use is problematic, therefore the need to identify good drug candidates still remains high.

Histone deacetylase inhibitors (HDACi) are compounds that can suppress the activity of histone deacetylase enzymes and can play an important role in the regulation of gene transcription. Recently HDACi have been shown to induce γ-globin gene expression. The aim of this study was to identify new HDACi with HbF-inducing activity as potential drugs for β-thalassaemia, as well as starting points for drug design.

The effect of 15 HDACi on γ- and β-globin-gene promoter activity was examined using a dual luciferase assay in GM-979 cells and erythroid liquid cultures (BFUe) derived from healthy and thalassaemic individuals. The effect on the acetylation status of the γ-promoter and Locus Control Region (LCR) after administration of the most active of the 15 compounds was studied in K562 cells using Chromatin Immunoprecipitation assays (ChIP).

Three compounds, MS275, oxamflatin and apicidin, increased γ-globin promoter activity significantly and were subsequently tested further. Oxamflatin was shown by ChIP studies to increase acetylation levels of histones H3 and H4 in the γ-globin promoter as well as in DNAseI Hypersensitive Sites 1, 2, 3 and 4 in the LCR.

The effect of the studied HDACi on the β- and γ-globin promoters is not directly related to their inhibitory strength. Apicidin, Oxamflantin and MS-275 caused increased HbF production in BFUe cultures derived from both healthy and thalassaemic donors although not all patient samples responded to all three chemicals. It is unlikely that the HbF induction effects observed are caused solely through the histone deacetylase inhibitory activity of the chemicals tested.

Poster - 82

P2X$_7$: A POTENT NEW TARGET IN INFLAMMATION AND CANCER

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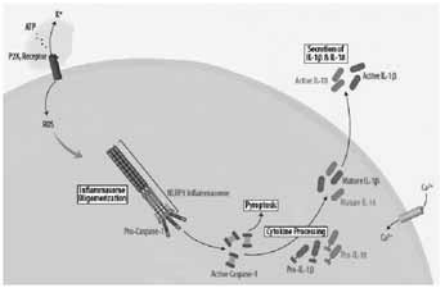
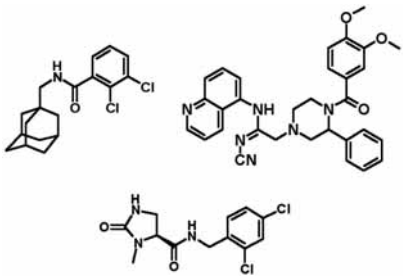
The purinergic P2X$_7$ receptor (P2X$_7$R) is a ligand-gated ion channel which belongs to the family of ATP-sensitive receptors. P2X$_7$R is present in a variety of cells types, like haematopoietic cells, immune cells, microglia and astrocytes.[1] This receptor is implicated in numerous diseases including pain, neurodegeneration, inflammation and cancer.[2] Thus, this ionotropic receptor makes a new interest target to a novel therapeutic approach to the treatment of these diseases.

In lymphocytes and macrophages, P2X$_7$R activation results in the activation of phospholipase D and, in human macrophages, it elicits the release of the inflammatory cytokine IL-1β via activation of caspase-1 (Scheme 1).[1] This pro-inflammatory activity can be decreased by using P2X$_7$R selective antagonists (Scheme 2). [3,4,5]



Scheme 1 : Release of pro-inflammatory cytokines by P2X$_7$R activation



Scheme 2 : Examples of selective P2X$_7$R antagonists[3,4,5]

- It has been reported that the activation of P2X$_7$R by using agonists, can lead to an anti-tumoral activity.
- However, in some different types of cancer, the opposite situation occurs, and the P2X$_7$ antagonists have benefic effects,[7] due to their capacity to inhibit multiple pro-tumoral cell signaling pathways.

Thus, taking these facts in consideration, we decided to study new selective P2X$_7$ antagonists in order to increase their anti-inflammatory and anti-tumoral activities.

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Poster - 83

LABORATORY METHODS USED TO MEASURE GLYCATED HEMOGLOBIN: COMPARISON STUDY

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Introduction: Glycated hemoglobin (HbA1c) is an important parameter in monitoring diabetic patients. Using adequate methods is essential to obtain reliable results.
The aim of the study is to compare four methods used to measure HbA1c.
Material and methods: The majority of the sam1ples were analyzed using the Variant Hemoglobin Testing System (Bio-Rad). Several results were obtained working on the new generation of this analyzer called Variant II. We also used the Biomidi reagent kit working with a manual chromatographic method, and some samples were analyzed with Micromat II (Bio-Rad).
Results: The Variant I method has the advantage over the manual processes that simultaneously up to 100 determinations can be performed. The newer, computerized generation of Variant II can handle an unlimited number of tubes and its not necessary the dilution of the probes.The exact value of glycated hemoglobin can be read from the cromatograms.
In the majority of the diabetic patients the values of the manual method and Variant I device Using the manual chromatographic method falsely high glycated hemoglobin values were calculated from the probes containing high fetal hemoglobin because the HbF is coeluted with the HbA1c on the column.
The pathological hemoglobin derivatives also affect the result becauses the glycosylated form of HbS, E, D, C may appear in a different fraction from the HbA1c.
The reproducibility test of the manual method using chromatographic columns showed the following values: coefficient of variation 1,45% (formula SD/M × 100) and relative error 1,02% (formula IXi-MI /M × 100).
The reproducibility test of Variant I showed the following values: coefficient of variation 0,9%, relative error 0,77%.
The advantage of the portable Micromat II is the small size, we can work on it using capillary blood.
The obtained values showed good correlation with the results obtained from Variant I ($r = 0,9742$, $p < 0,05$) but we observed that the values obtained from the automatic device were higher. This is probably a systemic failure of the device from the production of the device because we observed this at several Micromat II (based on the external control). For the tests, which were not always stored in a refrigerator, the value is 1.5 to 2% less compared to the value shown in the Variant I. The Variant I device is less sensitive to storage tests, the probes keeped a few hours at room temperature had only decimal differences compared to the original values.

Poster - 84

COGNITIVE FUNCTION IN PATIENTS WITH TYPE 1 DIABETES

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Most of the data suggest that the patient with diabetes have reduced performance on numerous domain of cognitive function. In patients with type 1 diabetes(T1DM), specific and global deficits evolving speed of psychomotor efficiency, information processing, mental flexibility, attention, and visual perception seem to be present. Complex pathophysiology of changes in central nervous system in T1DM has not yet been fully elucidated.

Aims: Our aims were to compare executive function in patient with T1DM to healthy controls (C), and evaluate the association between executive dysfunction and the diabetes specific parameters.

Methods: One domain of the cognitive function, the executive function was studied in 64 patients with T1DM (age: 35,63±11,45, 35 men and 29 women), and 64 control participants (age: 32,63±11,45, 35 men and 29 women), who were matched for sex and age. Two computerized neuropsychological test was used as a tool in the evaluation of executive functions. The Stroop test is considered to measure selective attention and the Wisconsin Card Sorting Test (WCST) to examine the integrity of frontal lobe functions.

Results: In Stroop-test significantly larger (p=0,005) Stroop-test interference score (106,97±73,16 msec) were found in patients with type 1 diabetes than individuals without diabetes (72,27±64,44 msec). The performance showed association with HbA1C and the duration of diabetes (p=0,026).

The performance measured with WCST was worse in diabetic patients (ratio of correct answer: 78±8,56%, ratio of perseverative errors: 39,5±11,7%) compared with individuals without diabetes (ratio of correct answer: 80,39±8,23%, ratio of perseverative errors: 36,92±9,43%), however this differences weren't statistically significant (p>0,05).

Conclusions: Our results suggest that the patients with diabetes have reduced executive function compared with individuals without diabetes. The poor carbohydrate metabolism may induce attention dysfunction in patients with T1DM. Stroop test performance and the responsible regions of the brain may be more sensitive to chronic hyperglycaemia than other areas.

Poster - 85

STUDY OF THE PHOTOREACTIVITY OF A MIXED LIGAND SILVER(I) COMPLEX WITH ASPIRIN AND TRIPHENYLPHOSPHINE; ITS APPLICATION IN PHOTOACTIVATED CHEMOTHERAPY

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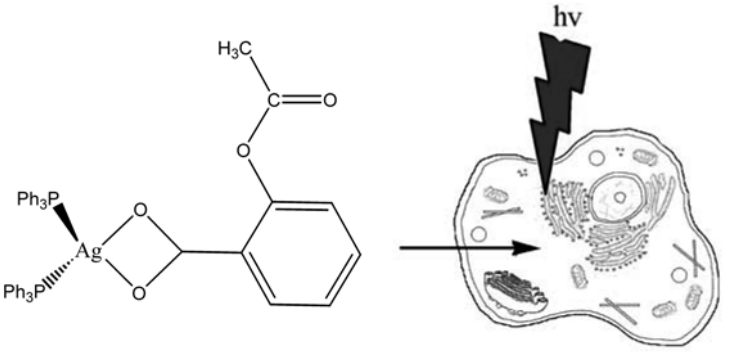
Cancer is one of the most fatal diseases on the 21st century [1]. Platinum complexes are used in about 50% of all tumour therapies and display a remarkable therapeutic activity in a series of solid tumours [2]. However, the use of these type of chemotherapeutics for the treatment of cancer is often limited due to severe side effects [3]. Thus, the development of stimuli-responsive drug delivery systems that allow selective activation of the drugs at the target site is an attractive strategy for the establishment of new successful therapies [3]. In this direction the use of light allows the control of the location, timing, and dosage of the therapeutic agent generated [3]. Metal complexes with a d^{10} electronic configuration such as silver(I), are also known to exhibit interesting photophysical and photochemical properties [3]. The photochemical properties of silver complexes is well known and silver - based photographic processes eventually prevailed [4].

The biomedical application of silver(I) compounds, on the other hand, are related with their antimicrobial properties which appears to involve interaction with DNA [5]. Recently, silver(I) complexes of anti-inflammatory drugs such as aspirin or salicylic acid have also been studied for their antitumor activity [5]. Their high antitumor activity is attributed to the high binding ability of these compounds towards DNA and to their inhibitory activity of lipoxygenase (LOX), an enzyme distributed to mitochondrion, which catalyzes the oxidation of arachidonic acid to leukotrienes, in an essential mechanism for the cell life involving in inflammation mechanism [5].

In the course of our studies in the field of the design and development of new metallotherapeutics, we studied the photo-reactivity of the {[$Ag(tpp)_3$(asp)](dmf)} (**1**) (aspH= aspirin, tpp= triphenylphosphine and dmf= dimethyformamide) complex. The photo-activated properties of **1** against MCF-7 cells are also study under uvc light. The influence of **1** towards CTDNA and LOX under uvc radiation is also evaluated and the results are presented here.



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Poster - 86

INHIBITION OF TNF-a AND RANKL CYTOKINES; AN APPROACH TO RA TREATMENT

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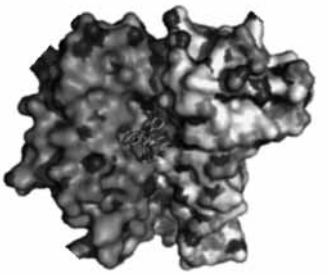
Tumor Necrosis Factor, is a trimeric cytokine which has been associated with the inflammatory response to tissue injury and various viral - bacterial infections. It is found to possess a key role in Rheumatoid Arthritis pathogenesis. TNF has two specific receptors that transmit its signal and binds to; TNF-a receptor 1 (TNFR1) and TNF-a receptor 2 (TNFR2). In this way, receptor trimerization is induced, which in turn triggers the biological responses. According to the traditional anti-TNF treatment of RA, we aim at extracellular inhibition of this pro inflammatory cytokine as an effective therapy. The first step of this process is the design of molecules with inhibitor activity (ligands). These small molecules interact with protein trimers, promote trimer dissociation and therefore, an inactivated dimer arises. The purpose of this project is not only to design but also evaluate potential inhibitors *in vitro* as well as *in vivo*. According to an in *silico* optimization of candidate hits approach, an extended virtual library of SPD304 analogues based on the proposed modifications, has been created. The project plan comprises synthesis and validation of the most promising compounds with biophysical methods such as fluorescence spectrometry and isothermal titration calorimetry following the initial solubility assays, an important parameter for ligands' evaluation.



TNF-a dimer /SPD304 complex

Poster - 87

CALCIUM INDUCED BIOENERGETICAL CHANGES IN ISOLATED MYOCARDIAL MITOCHONDRIA

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The increase of intracellular Ca^{2+} level is a necessary accompany of myocardial ischemia-reperfusion process. Mitochondrial dysfunction contributes to the increased intracellular Ca^{2+} concentration, but mitochondrial functions are also influenced by the rise of Ca^{2+} level. In the present study the effects of high concentration of Ca^{2+} on the bioenergetic functions of isolated guinea pig myocardial mitochondria were investigated. Similar conditions could occur under pathological conditions. The mitochondrial membrane potential was measured with safranine-fluorescence, ATP production was assessed online using a combined enzyme reaction. Mitochondria were supported by glutamate plus malate respiratory substrates. Under pathological Ca^{2+} concentration (10μM Ca^{2+}) membrane hyperpolarization was observed. Further increase of Ca^{2+} concentration (to 50 μM) would evoke a long-lasting and irreversible decrease of membrane potential. Under physiological Ca^{2+} level (hundred nanomolar range) increased rate of ATP synthesis was detected, however at 10μM [Ca^{2+}] a significant decline of ATP production was observed. Further increase of [Ca^{2+}] (50μM) resulted in a cessation of ATP synthesis. In case of 10μM Ca^{2+}, the reduction of extracellular Ca^{2+} concentration and the stimulation of Na^{+}/Ca^{2+} exchange induced a partial recovery of ATP output.

Summary: On the effect of 10μM Ca^{2+} load myocardial mitochondria undergo persistent membrane hyperpolarization and a fall of ATP production, which decline seems to be partially reversible by the elimination of Ca^{2+}.

Poster - 88

THE EFFECT OF Ca^{2+}-LOAD ON RESPIRATORY PARAMETERS IN CARDIOMYOCYTE MITOCHONDRIA

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Mitochondria play a key role in the energy production of most cells, particularly in the cardiomyocytes because their energy production is predominantly aerobic. The mitochondrial functions can be sensitively followed measuring the O_2 consumption. Mitochondrial energy production is regulated by cytosolic signals, one of the most important of these is the change of $[Ca^{2+}]$. The aim of our study was to describe and interpret Ca^{2+}-induced changes of mitochondrial respiration. O_2 consumption in isolated guinea pig heart mitochondria was measured with Clark-type O_2 electrode, mitochondrial Ca^{2+}-uptake was followed with Ca-green fluorescent dye. Using respiratory substrates glutamate plus malate increased rate of ADP-induced respiration was detected at nanomolar $[Ca^{2+}]$, however with low micromolar $[Ca^{2+}]$ a large decrease of the rate of respiration followed by a partial recovery was observed. The Ca^{2+}-uptake with Ca^{2+}-green was measured and a high speed Ca^{2+}-uptake from the medium without Ca^{2+}-induced Ca^{2+} release was observed. Similar phenomena were detected using succinate as a respiratory substrate. The decrease of respiratory rate with oligomycin (ATP synthase inhibitor) or with carboxyatractyloside (adenine nucleotide translocase inhibitor) indicates the proportion of O_2 used for ATP synthesis from the total of O_2 consumption. Using 10 micromolar $[Ca^{2+}]$ the O_2 consumption is only slightly reduced by oligomycin or carboxyatractyloside indicating a decrease in mitochondrial ATP synthesis. We conclude that pathological (micromolar) Ca^{2+}-load significantly reduced the mitochondrial respiration rate using both complex I and complex II substrates. As a reason for this effect the direct inhibition of the respiratory chain, and the opening of mitochondrial permeability transition pore can be excluded.

Poster - 89

FOLLOWING THE LEVEL OF CALCIUM AND PHOSPHATE AT PATIENTS UNDER TREATMENT OF HAEMODYALISIS, SAINT GEORGE CITY, B.BRAUN CENTRE OF HAEMODYALISIS

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Introduction: With the destruction of the kidney substance the level of phosphate excretion is decreasing and evolving into hyperphosphataemia, the synthesis of vitamin D3 is decreasing too which takes to hypocalcaemia and by this to secondary hyperparathyroidism.
Intention (setting the objectives): Following the level of serum calcium and phosphate pre- respectively, postdialytic.
Material and method (manner): Between July 4th and the 1st of October 2010, we followed the variation of the level of serum calcium and phosphate at 54 patients at the B.Braun dialysis centre.
Outcome (results): We haven't found significant differences, at any laboratory parameters, between ages and sexes ($p=0.7539>0.05$), but between quarterly analysis, higher values (phosphate: 6.3→3.8 mg/dl, calcium: 11.019→10.007 mg/dl) and respectively lower values (phosphate: 2.14→2.24 mg/dl, calcium: 8.63→9.2 mg/dl) will become normal from one quarter to another. The values of predialytic phosphate are higher, but at the end of the treatment gets back to normal (5.48→2.7 mg/dl). The level of calcium at the end of the treatment is increasing saltatory. There are no significant differences between the underlying disease ($p=0.7539>0.05$). The result of calcium x phosphate remained within normal limits: <4.44 $mmol^2/l^2$.
Conclusion: The balance of calcium and phosphate is not disintegrated, we suggest to measure bone density pre- respectively postdialytic, because of the higher values of postdialytic calcium.

Poster - 90

A_1 AND A_{2B} BUT NOT A_{2A} AND A_3 ADENOSINE RECEPTOR AGONISTS ARE ESSENTIAL PHARMACOLOGICAL TRIGGERS OF POSTCONDITIONING IN ANESTHETIZED RABBITS

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Background: Adenosine A_1, A_2 and A_3 receptor agonists given prior to myocardial ischemia limit ischemic injury in several species. However receptor subtypes which are involved in the reduction of the infarct size when their agonists are given at reperfusion have not been fully elucidated. We designed an experimental study to test the hypothesis that adenosine A_1, A_{2A}, A_{2B} and A_3 receptor activation during early reperfusion can limit the infarct size. We used four human adenosine receptor agonists: compound AR 230, 2-cloro-N6-cyclopentiladenosine, an A1 selective agonist, two adenosine derivatives substituted in 2- and 4'-position, namely compounds SP 35 and VT 7, an A_{2B} and an A_{2A} agonist respectively, as well as an A_3 selective agonist, compound AR 170.

Methods: Anesthetized open-chest male rabbits were subjected to 30-min regional myocardial ischemia and 3-hour reperfusion and randomized into 5 groups as follows: 1) Control group no intervention, 2) group A, administration of AR 230, 3) group B, administration of SP 37, 4) group C, administration of VT 7 5) group D, administration of AR 170. Compounds were administered bolus in a total dose of 3.8 μmol kg-1, at the 20th min of ischemia and at the 1st min of reperfusion. After the end of the experiments the infarct size (I) and the area at risk (R) were estimated in percent as % I/R with the aid of triphenyl tetrazolium chloride (TTC) staining and fluorescent particles. In a second series of experiments, 20 additional rabbits were subjected to 30 min ischemia/10min reperfusion and were randomly divided into 4 groups (n=5/group): 1) Control, 2) administration of AR 230, 3) administration of SP 35 and 4) administration of AR170. Heart tissue samples were quickly excised for immunoblotting of Akt kinase, eNOs, GSK3 β and STAT3.

Results: The administration of the selective A_1 adenosine receptor agonist as well as of A_{2B} adenosine receptor agonist reduced the infarct size (17.9±2.0% and 17.2±2.9%, respectively) compared to Control group (48.05 ± 1.9%, $P<0.05$). The selective A_{2A} adenosine receptor agonist as well as the A_3 adenosine receptor agonist did not reduce the infarct size (39.5±0.8%, and 38.7± 3.5%, respectively, vs Control, P=NS). Activation of eNOs, Akt and STAT3 and inhibition of GSK3β was observed in heart tissues treated with AR 230 and SP 35 in comparison to A3AR and the control group.

Conclusion: A_{2B} receptor subtype is involved in the protection at reperfusion as has been supported by experimental studies. However, the ability of A_{2A} receptor agonist to limit infarct size when given before reperfusion has proved controversial. Furthermore, the A_3 agonist AR170 given at the time of ischemia and at the beginning of reperfusion does not reduce the infarct size. This is possibly related to its inability to activate RISK and JAK/STAT3 pathways. A_1 and A_{2B} but not A_{2A} and A_3 adenosine receptor agonists activate eNOs, Akt and STAT3 and inhibit GSK3β. We conclude that the administration of A_1 and A_{2B} but not A_{2A} and A_3 adenosine receptor agonists is essential of triggering cardioprotection at the time of reperfusion.

Poster - 91

STUDY OF THE INFLUNCE OF SWEETENERS ON BLOOD GLUCOSE LEVEL

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The aim of the study is monitoring the blood glucose level at the consumption of different sweeteners. Material and method: the effect of different sweeteners was measured on healthy volunteers, between the ages of 22 and 76. The method used was the glucose tolerance test which consists in taking an amount of 1g/kg sweetener dissolved in 300 ml water, and then drinking within 5-10 minutes. The time intervals in which the blood glucose level was measured were 0, 5, 10, 15, 30 and 60 minutes with the glucometer using peripheral blood. The standard sweetener was the crystalline sugar. Further sweeteners were the following: fructose, saccharin and xylitol.

Results. Our research studies show the blood glucose peak 30 minutes after eating sweeteners. The glycemic index comes in increasing order: saccharine = 0 < xylitol = 7 < fructose = 20 < sugar = 100. The maximum blood glucose levels reached in increasing order: saccharine < fructose < xylitol < sugar. According to glycemic index the blood glucose level should be higher with fructose than with xylitol. However, as can be seen, in the case of the above presented study, the blood glucose levels reached with xylitol are higher than the levels reached with fructose. This can be explained by the fact that xylitol is metabolises slowly. Xylitol is a natural insulin stabilizer, therefore it causes none of the abrupt rises and falls that occur with sugar. Foods sweetened with xylitol will not raise insulin levels. This makes it a perfect sweetener for people with diabetes.

Conclusion. Consequently, this simple method can be used at any medical clinic for examining the different types of recommended sweeteners on both healthy and ill patients who wish to know which of the many sweeteners is most tolerated by their bodies.

Poster - 92

INHIBITION OF COX-1 / COX-2 BY ANTIOXIDANT AND ANTIHYPERLIPIDEMIC COMPOUNDS

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Inflammation, via different pathways, is the link between risk factors of atherosclerosis and the pathological arterial endothelium.[1] An excessive accumulation of modified, mainly oxidized lipids within the arterial wall leads to an innate immune response involving several types of immune cells (e.g. macrophages), cytokines, inflammatory enzymes such as lipoxygenases (LOX) and cycloxygenases (COX-1,2), as well as other elements such as metalloproteinases and adhesion molecules. In this ongoing inflammatory response, these factors influence formation and stability of atherosclerotic lesions.

Selective COX-2 inhibitors were developed to provide anti-inflammatory effects without inhibiting physiological COX-1-mediated functions such as protection of gastric mucosa.[2] Recently, they have been shown to prevent or reduce atherosclerotic lesions in Apo E-/- or LDL receptor-deficient mice.[3,4] Thus, consideration of atherosclerosis as an inflammatory disease provides the basis for developing novel therapeutic strategies targeting the inflammatory component of this disorder.

We have previously developed antihyperlipidemic morpholine derivatives, designed to act as antioxidants and squalene synthase inhibitors, that where shown to posses anti-inflammatory activity.[5,6] In order to elucidate the mechanism of this activity, we evaluated the activity of several derivatives in vitro for their inhibition of LOX as well as of COX-1 and COX-2. The activity of these compounds was hereby assessed using 1) a soybean lipoxygenase inhibitor screening assay[7] and b) a COX inhibitor screening assay based on quantification, via an Enzyme Immunoassay, of $PGF_{2\alpha}$ formed by COX-derived PGH_2. Cycloxygenase enzymes used were ovine, for COX-1, and human recombinant, for COX-2.[8]

Most compounds that were evaluated were shown to significantly inhibit cycloxygenase activity. Several exhibited selectivity towards the COX-2 isoenzyme while a small number inhibited lipoxygenase. Activities where compared to those of know NSAIDs such as indomethacin or nimesulide. The COX-inhibitory effects reported here, add to the multiple activities that have been previously shown for these compounds (e.g. SQS inhibition, antioxidant) and enhance their potential as antiatherosclerotic agents.

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Poster - 93

COMPARATIVE ANALYSIS OF GLYCOPROTEINS ISOLATED FROM HUMAN PERIPHERAL NERVE AND *CAMPYLOBACTER JEJUNI* O:19 USING TWO DIMENSIONAL GEL ELECTROPHORESIS

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Antibodies to peripheral nerve myelin proteins were detected in sera from patients with Guillain–Barré Syndrome (GBS), but their role in the development of GBS was not sufficiently investigated. Sera from patients with GBS following infection with *C.jejuni*, also show cross-reactivity to several Gal-GalNAc–bearing glycoproteins from human peripheral nerve and C. jejuni (O:19). These data indicate on possible molecular mimicry of glycoproteins present in *C.jejuni* and GalGalNAc - bearing glycoproteins present in human peripheral nerve and its potential role in the development of neuropathies. The aim of this study was to isolate and analyze glycoproteins from human peripheral nerve and from *C.jejuni* (O:19) using two dimensional electrophoresis. For that purpose we have isolated total glycoproteins from human peripheral nerve, from *C.jejuni* (O:19) obtained from patient with uncomplicated enteritis and *C.jejuni* (O:19) obtained from patient with enteritis followed by GBS. Isolated glycoproteins were separated using two-dimensional gel electrophoresis, visualized with Silver stain and analysed using PD Quest 2D analysis software. Isolated proteins, separated by 2D electrophoresis, were analysed on western blot by incubating with peanut agglutinin (PNA) as a marker for the GalGalNAc determinant and sera from patients with GBS. Results have shown presence of several GalGalNAc bearing proteins with same electrophoretic mobility and same isoelectric points in all of the three isolates. More cross-reactive bands with human peripheral nerve proteins were detected in isolate from *C.jejuni* (O:19) GBS associated, compared to isolate from *C.jejuni* (O:19) enteritis associated. These data indicated the possible role of some protein antigens from *C. jejuni* in the pathogenesis of GBS. Further studies are needed for determination of the molecular structure of glycoproteins present in the human peripheral nerves and in the bacteria *C. jejuni* which is necessary for elucidation of their antigenicity and their potentional role in the development of GBS.

Poster - 94

DETERMINATION OF ANTIOXIDANT PROPERTIES OF ESSENTIAL OIL AND VARIOUS EXTRACTS OF THYMUS NUMIDICUS POIRET

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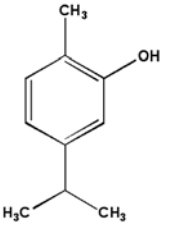
In this work we present the total antioxidant activities of essential oils and those of various organic and aqueous extracts (dichloromethane, methanol, methanol-water 5:1, and water) of Thymus numidicus an endemic plant from Algeria. The antioxidant activities have been estimated by a spectrophotometric method (DPPH-method) and a spectrofluorimetric one using lucigenin (bis-N-methyl-acridinium nitrate) and hydrogen peroxide as an oxidizing reagent. The assessed antioxidant activity of each extract was correlated to the corresponding total phenolic content measured by the Follin-Ciocalteu assay. It was found that methanolic or aqueous methanolic extracts exerted the highest free radical scavenging activity (> 92 %) as well as very high hydrogen peroxide blocking activity (> 93 %) at concentration level of 1000 μg. mL-1 extract). These results correlate well to the high content of phenolic compounds found in the corresponding essential oils or aqueous methanolic extracts (965.60 and 513.41 mg GAEs/gram extract, respectively). The high antioxidant activity of the essential oil of T. numidicus or aqueous methanolic extracts has been attributed to the phenols contained in them and more specifically to the phenol carvacrol which constitutes the major component in them (about 34 %) and is similar to the well-known antioxidant compound butylated hydroxytoluene (BHT).



Molecular structure of carvacrol

Key words: Thymus numidicus; free radical scavenging activity; DPPH; hydrogen peroxide; lucigenin; total phenolic contents.

Poster - 95

SPECTROSCOPIC CHARACTERISATION OF NATURAL PRODUCTS EXTRACTED FROM BETULA PENDULA ROTH BIRCH TREE

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Natural products, which are known and used with great results since ancient times, have contributed and still contributes to the development of the modern drugs.
Pentacyclic triterpenes with lupan skeleton such as betulinic acid, betulin and lupeol are important antitumor agents with a very low solubility. The substances isolated from plants have to be investigated using modern analitycal methods and subjected to in vitro and in vivo biological assays. Among the modern analitycal techniques Solid-State Nuclear Magnetic Resonance Spectroscopy and Raman Spectroscopy are the most useful for characterising especially the insoluble forms of the systems.
The Betula Pendula Roth birch tree, a wide spread plant especially in Northern temperate climates, has proved since ancient times to have a broad range of beneficial medicinal properties. The outer bark of this tree is rich in pentacyclic triterpenes such as betulin, betulinic acid, lupeol, oleanolic acid and others. Different extraction products from birch bark have been obtained using various protocols and solvents. The products with the highest content of betulin (97%) were determined by HPLC methods [1].
Using Raman Spectroscopy based on accurate vibrational characterization of betuluin [2] we were able to discuss and quantitatively asses different extracts obtained with different protocols and solvents. Using small extract amount we were able to detect betulin species with high reproductibility.
Betulin (lup-20(29)-ene-3β,28-diol) is found mainly as crystalline deposits in the outer layers of the bark, consisting of large cells with thin walls and can be easily obtained by sublimation or by extraction with organic solvents. Betulin was used in skin treatment as anti-inflammatory for a long time and it was recently found to be active on some types of cancer cells or even to induce apoptosis, therefore, a special attention was paid to the possibility of creating pharmaceutical formulations based on betulin and its metabolic successor betulinic acid, to be tested on skin malignancies, including melanoma and skin cancer. Betulin can be easily converted to BA, which possesses a varied spectrum of biological and pharmacological activities, too. The extraction products have been accurately characterized using sensitive ^{13}C solid-state NMR, FT-Raman and surface-enhanced Raman Scattering (SERS).
Keywords: natural products; solid-state NMR; FT-Raman and SERS

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Poster - 96

FERMENTED WHEAT GERM EXTRACT (AVEMAR) AS A NATURAL IMMUNOMODULATOR IN CANCER

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Objective: To summarize the anti-cancer effects of Avemar from fermented wheat germ.
Material and method: Electronic database were searched. I included randomized and non-randomized human clinical trials, animal studies and in vitro cell studies.
Results: Avemar significantly reduces the immune deficiency caused by thymectomy, and provides stimulatory effect on cellular immune response. The effect of Avemar on autoantibody levels was also measured in mice with experimentally induced SLE (systemic lupus erythematosus). The results demonstrated the inhibitory effect of Avemar on autoantibody production. Avemar caused a reduction in Th2 cytokine production while simultaneously increasing the production of Th1 cytokines. While Th1 cytokines help to regulate and 'execute' cellular immune response, Th2 cytokines are parts of humoral response, which may very well account for the efficiency of Avemar in combatting both autoimmune diseases and human cancers. The inhibition of humoral immune response is beneficial in the treatment of autoimmune diseases, while the enhancement of the cellular immune response helps in defeating malignant tumors.
Conclusions: Avemar has multiple immunological effects and is approved as a dietary food for cancer patients.

Keywords: Fermented wheat germ, cancer, medical nutriment.

Poster - 97

EVALUATION SOME CATIONIC SURFACTANTS PREPARED FROM OLIVE OIL HAVING ANTIBACTERIAL ACTIVITY

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The present work is concerned with the preparation, characterization, and evaluation of some cationic surfactants having surface and biological activities. The starting materials used were the fatty acids differing in alkyl chains lengths were procured from two different sources; the first one was the commercially available fatty acids (Aldrich), the second source was the fatty acids obtained from hydrolysis of locally available olive oil.
The cationic surfactant compounds with different head groups such as, pyridiunium chloride, trimethyammoniumm chloride, and triethanolammonium chloride were prepared. The surfactants were characterized by spectral (FT-IR and ^{1}H NMR) and physicochemical properties (surface tension, critical micelles concentration, Kraft point, cloud point, foaming height, wetting power, and emulsification power). Biodegradability and antimicrobial activity were studied for the synthesized cationic surfactants.
The biodegradability study of synthesized surfactants showed that they are acceptable cationic surfactants for the environment. All of the synthesized surfactants inhibited the growth of gram negative and gram positive bacteria as well as fungi.

Poster - 98

PHYTOCHEMICAL INVESTIGATION OF THE STEM BARK OF *STRYCHNOS AFF. DARIENENSIS*

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The stem bark of *Strychnos aff. darienensis* has been used for centuries for the preparation of curare from the South American Indian hunters [1] and from the tribe Yanesha as a medicine [2], but although its pharmacological interest, this plant has never been investigated phytochemically. In continuation of our interest for the plants of Amazonia [3] we report herein the investigation of the stem bark of *Strychnos aff. Darienensis*. The genus *Strychnos* is rich in alkaloids, whereas the content of other secondary metabolites is in many cases neglected. The evaluation of the best extraction procedure in order to recover a vast range of metabolites was of great importance. Plant material was collected from Peru and profiling of the extracts with TLC revealed that the best approach was the maceration of the stem bark with EtOAc-EtOH-NH_3 (96:3:1) and extraction with EtOAc and then with MeOH. The methanolic extract was basified with NH_3 and the alkaloids were extracted in the organic phase. The isolation procedure was performed using chromatography techniques and structure determination was based on 1D, 2D NMR experiments and ESI-HRMS techniques. The phytochemical investigation of this plant led to the isolation and structure elucidation of 14 compounds that belong to the categories of phenolic acids, flavonoids, lignans and alkaloids. In species of *Strychnos* with a relatively low percentage of alkaloids, it has been reported that 11-methoxy-diaboline constitutes the main component, whereas in others with a high percentage of alkaloids, it is present only as a minor component [4]. This observation was confirmed also in *Strychnos aff. darienensis*, where 11-methoxy-diaboline was the major constituent and only very few other alkaloids were isolated from the plant. Interestingly, 11-methoxy-diaboline was isolated as two confomomers, probably due to the limited rotation of the N-acetyl group. Overall this is the first report for isolation of 3 methyl quercetin, minaxin, balanophonin and ficusal from the genus *Strychnos* whereas strychnobiflavone and minaxin are reported for the second time to be isolated from the plant kingdom.

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Poster - 99

THE USE OF DIETARY SUPPLEMENTS BY PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Although diabetic patients in Romania get an efficient treatment for free, media and surroundings suggest the use of supplementary, which cannot be controlled by doctors.
Purpose: to study the frequency of use of dietary supplements by patients with diabetes mellitus type 2.
Materials and methods: We have interrogated 200 patients with DM2 (average age: 60.07). We divided their supplements in 4 groups: dietary supplements for diabetes, tea, vitamins and other dietary supplements without effect on diabetes. We made a survey about their price, mechanism of action, frequency of use, effect using a questionnaire (13 questions). Data was analyzed with GraphPad InStat and IBM SPSS statistical programs. We gave a mark for each supplement.
Results: 54.5% of 200 diabetic patients use some kind of dietary supplement; 22.94% use more than 1 type; 12.84% use dietary supplements for diabetes, 63.3% use tea, 31.19% some kind of vitamins and 17.43% dietary supplements without effect on diabetes. 36.7% of the patients used supplements suggested by their doctor. 38.5% doesn't know the mechanism of action of dietary supplements they take. 41.3% couldn't detect any kind of effect after taking them but the others (positive effect) informed their doctor significantly more frequently ($p=0.0005$) about the supplement. Young patients take them more frequently than elders ($p=0.01$). We didn't find significant correlation between gender, diabetic antecedents, the adjusted treatment and the frequency of use of dietary supplements. The dietary supplements suggested by doctors or books were cheaper, than those suggested by pharmacists or media ($p=0.03$). Only 50% of the leaflets were adequate. 100% of vitamins can cause side effects. Dietary supplements for diabetes got higher mark than vitamins.
Conclusion: Diabetic patients use very frequently dietary supplements. In half of the cases, particularly the supplements suggested by media, were expensive, ineffective and 8.3% toxic.

Poster - 100

THE MARKET OF DIETARY SUPPLEMENTS RECOMMENDED FOR PATIENTS WITH DIABETES IN TIRGU MURES: SURVEY

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Although the type II diabetics' medical attendance is free and adequate in Tirgu Mures, more than 50% of these patients use dietary supplements.
Purpose: the scientific revision of supplements that can be found in the pharmacies and herb stores of Tirgu Mures.
Material and methods: we analyzed all the supplements from 16 pharmacies and herb stores by the following aspects: role played in reducing blood-sugar levels, effect on cardio-vascular risk and on polyneuropathy, evidence in the scientific literature, proven side effects, quality of leaflet and price. We made a ranking of the products and the manufacturers according to the final marks.
Results: Altogether, we found 69 products with 311 components. The worst mark (0 points) was received by Konjac, the best (11 points) by "Extract hidroalcoolic de afin". The supplement manufacturers' ranking is the following: Hofigal (8.17 points), Walmark (7.42 points) and Wave pharma (7.23 points). 72.46% of the products reduces blood-sugar levels, 63.76% influences the cardio-vascular risk and 15.94% helps avoiding polyneuropathy. We also found that Commiphora wightii is toxic. 27.7% of the components' claimed effects cannot be found in the scientific literature and 56% of the products have side effects. The given drug information wasn't satisfactory in 42% of the cases. The two most frequent components were the common Vaccinium extractum (bilberry extract) and Gymnema sylvestre. The cheaper products than 50 RON received higher marks than the more expensive ones ($p=0.01$). Those that were cheaper than 10 RON, had more scientific data behind them than those, that were more expensive ($p=0.03$).
Conclusion: The expensive drugs are not proven to be as effective as the cheap bilberry extract. Because side effects can be found in the majority of the cases, it is advisable to take these supplements with precaution. There should be more information provided for the patients.

Poster - 101

CHARTING POLYPHENOL INTERACTIONS WITH BCL-2 AND BCL-XL VIA NMR, CALORIMETRY, DOCKING CALCULATIONS AND IN VITRO STUDIES

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Protein-protein interactions (PPIs) play a central role in various cell functions and disruptions of such processes are involved in pathogenesis of several diseases, as is cancer, making them significant targets for therapeutic intervention [1, 2]. Several studies currently focus on the regulation of PPIs, by designing or discovering small molecules that can interact with flat and extended surfaces of proteins of therapeutic interest [2, 3]. The Bcl-2 family is of major importance since its network regulates the mitochondrial pathway of apoptosis [4]. The Bcl-2 family is composed of anti-apoptotic members including Bcl-2, Bcl-x_L, Mcl-1 and A1 proteins and their up-regulation has been detected in many cancer types [5].

We screened plant derived polyphenols as potential inhibitors of PPIs by using an array of *in silico* and experimental approaches. We performed calorimetry and 2D ^{1}H-^{15}N HSQC NMR experiments to map the ligand-protein interfaces implicated in binding and docking calculations to determine the 3D structures of the relevant complexes. *In vitro* studies were performed to evaluate the mechanism of cytotoxicity expressed by the relevant molecules in three human lymphoma cell lines, Jurkat T lymphoma cells and their derivatives Jurkat Puro and Jurkat overexpressing Bcl-2 protein [6].

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Poster - 102

THE EFFECT OF ALCOHOLIC COCKTAILS ON CARBOHYDRATE METABOLISM

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Metabolic X syndrome (MXS) is a cluster of conditions — increased blood pressure, a high blood sugar level, excess body fat around the waist or abnormal cholesterol levels — that occur together, increasing the risk of heart disease, stroke and diabetes. MXS is also known as insulin resistance syndrome.
The aim of our research is to show the influence of alcohol consumption on the development of MXS.
Material and method: Alcohol consumption which leads to one of the most frequent diseases of our century is widespread among young people. In our study we included healthy students in their 20's. We measured blood glucose, blood pressure and saliva pH levels before and after drinking wine, cocktails, coffee and energy drinks. These drinks are vital for students that are why we thought we would do research work in the field among students from Targu -Mures.
Results: Before consuming coffee the blood glucose of students was 101.6 mg/dL. 30 minutes after consuming coffee the blood glucose reached maximum level 118.2 mg/dL. This is more than 16% increase ($p<0.001$). Two hours later the blood glucose decreased to normal. In the case of wine the blood glucose before drinking was 100.4mg/dL. 30 minutes later 106.6mg/dL, and 2 hours later 115 mg/dL, this is more than 15% of the origin level ($p<0.001$). In the case of cocktails the level increases 12% after 30 minutes, after 2 hours we can notice 10% decrease of the blood glucose level compared to the original value ($p<0.001$).
Conclusion: You should pay attention to the influences of cocktails because 30 minutes after consuming them you become hyperglycemic and 2 hours later hypoglycemic. The increase of blood glucose after alcohol consumtion is statistically significant, it is a cause of MXS.

Keywords: Metabolic X syndrome, alcoholic cocktails, blood glucose.

Poster - 103

ARYLSULPHATASE A ACTIVITY RELATED TO DIABETES TYPE 2

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Sulfatide is a glycosphingolipid found in the islets of Langerhans. Sulfatide preserves the insulin crystals, it facilitates the instant monomerisation, and it acts as a molecular chaperon for insulin. It also facilitates insulin secretion, and sulfatide treatment of experimental diabetic mice has positive effects. Sulfatide is primarily produced by a recycling pathway in beta cells. Arylsulphatase A (ASA) catalyzes the hydrolisis of sulfatide in lysosomes. Studies revealed that a decay of lysosomal enzyme activity appears during Diabetes Type 2 (DM2). It is known that ASA deficiency leads to accumulation of sulfatide. Interestingly, lack of sulfatide was found in experimental diabetic mice and insulin resistance is associated with low serum levels of sulfatide in DM2.
Objectives: Evaluation of arylsulphatase A serous activity in patients suffering of Diabetes Type 2.
Material and method: The study includes 36 patients examined at the Mures County Clinical Hospital's Diabetology Department. Blood serum samples were collected. We determined the ASA activity through spectrophotometer. The method of enzyme dosage is based on a 4 hour long hydrolysis of the ASA enzyme on 4-nitrocatechol sulfate (p-NCS) substrate. The unit of measurement used for the ASA substrate concentration p-NCS is nmol/ml/4h.
Results: The minimum value of the ASA substrate concentration p-NCS is 0.47($\times 10^2$nmol/ml/4h), the maximum 5.45($\times 10^2$nmol/ml/4h). Statistical analysis: mean value of p-NCS is 3.02 ± 1.17. Grubbs test for outliers was performed. Normality test P value >0.1.
Conclusion: In case of Diabetes Type 2 patients, arylsulphatase A shows wide enzyme activity range which follows Gaussian distribution.
Discussion: The scientific literature describes a wide normal ASA activity range, similar to our findings. It was shown that these variations are caused by allelic mutations, but have no consequences on human health. We call pseudodeficiency the case when clinically healthy individuals have reduced enzyme activity. It was suggested that even the low activity (<10% of the mean normal), it is sufficient in vivo for hydrolisis and disease prevention. However, since we know the importance of sulfatide related to DM2 and the great ASA enzyme activity variation in these patients, it is most probably the arylsulphatase A activity plays important role in Diabetes Type 2.

Keywords: arylsulphatase A, Diabetes Type 2, sulfatide

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STRUCTURAL AND BIOLOGICAL EVALUATION STUDIES OF COLIVELIN THROUGH THE USE OF LABELED DERIVATIVES

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Colivelin (CL) is the most potent (femtoM) member of the humanin (HN) family of neuroprotective peptides with *in vitro* and *in vivo* rescuing action against insults associated with Alzheimer's disease (AD). CL, which is a hybrid 26-peptide (SALLRSIPAPAGASRLLLLTGEIDLP), is composed of the neuroprotective factor ADNF-9 (the nonapeptide SALLRSIPA) C-terminally attached to the bioactive modified core of the HN sequence (PAGASRLLLLTGEIDLP).

Aiming at the investigation of the mode of action of CL, three CL derivatives bearing suitable labeling moieties, i.e the fluorescent molecule FITC, the streptavidin-counterpart biotinyl-group and the ^{99m}Tc-radiometal chelating unit dimethylGly-Ser-Cys, were designed synthesized, purified, and characterized. These derivatives will be applied, along with the parent CL, to *in vitro* cell survival assays and to cellular component-binding studies as well as to *in vivo* biodistribution experiments in suitable mouse-models.

The structure of the CL derivatives in aqueous solutions was studied with Nuclear Magnetic Resonance (NMR) in parallel and in comparison with the parent molecule CL, in order to examine whether the presence of the labeling moieties has induced changes to the structure of the biologically active part of CL. In addition, Circular Dichroism studies were carried out at various experimental conditions, in order to investigate the potential interaction of CL with the β-amyloid peptide, the hallmark of AD pathogenesis.

Furthermore, the CL derivative bearing the dimethylGly-Ser-Cys moiety was successfully radiolabeled with ^{99m}Tc and its stability was assessed over time in its synthesis reaction mixture and in plasma. The ^{99m}Tc-radiolabeled derivative was subsequently administered to Swiss albino mice in order to determine the biodistribution of CL in the living organism and its route of excretion, a study that has not been carried out so far for any peptide of the neuroprotective HN family.

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EVALUATING PERMEABILITY CHARACTERISTICS USING PAMPA: THE IMPORTANCE OF COMPOSITION OF DONOR COMPARTMENT

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Introduction: PAMPA (parallel artificial membrane permeability assay) is a high throughput screening technique that is used for the assessment of the permeability characteristics of new molecules with potential pharmacological activity. Relevant experiments are typically performed using simple aqueous media and data are interpreted on a comparative basis.
Purpose: To evaluate the importance of composition of donor compartment on the value of permeability coefficient estimated by using double sink PAMPA.
Methods: Assays were performed using a conventional buffer system, a medium simulating the conditions in the fasted upper small intestine (FaSSIF-V2) and a medium simulating the conditions in the fed upper small intestine (FeSSIF-V2) in the donor compartment. Double sink was ensured by using different pH in donor and acceptor compartment and by using pION's acceptor sink buffer (Prisma™ HT). All assays were performed by using pION's Gut-Box®. Danazol (clogP 4.2) and two Roche model compounds, Compound A (clogP 9.0) and Compound B (clogP 2.07), were used as model compounds. Permeability coefficients were estimated by assuming non-reversible transport of danazol from the donor to the acceptor compartment.
Results. Based on preliminary experiments with standard compounds of known permeability, danazol and compound B are highly permeable compounds. Micelles decrease significantly the apparent permeability coefficient of danazol and of compound B but not of compound A.
Conclusions: Present study only partially confirms previous data (Lu et al. AAPS annual meeting, San Diego, 2007) on the effect of micelles on permeability coefficients estimated using PAMPA. The effect of micelles on the permeability coefficient of very lipophilic compounds seems to be less apparent.

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SYNTHESIS OF 1,2,3-TRIAZOLE FURANONUCLEOSIDES AS NOVEL INHIBITORS OF RIBONUCLEASE A

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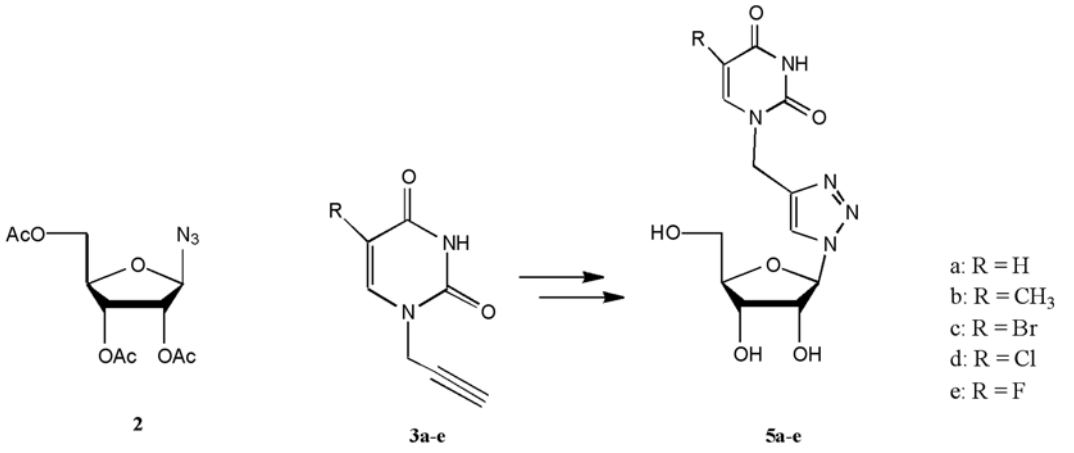
A series of novel 1,2,3-triazole furanonucleosides has been designed and synthesized. Azidation of commercially available 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose with trimethylsilyl azide led to ribofuranosyl azide 2. Uracil, thymine, 5-bromouracil, 5-chlorouracil and 5-fluorouracil were treated with propargyl bromide to afford *N*-1-isomers 3a-e. Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC) reaction was utilized to couple the 1-azido-2,3,5-tri-O-acetyl-β-D-ribofuranose 2 with *N*-1 propargylpyrimidines, respectively and subsequent treatment with saturated methanolic ammonia afforded the novel 1,2,3-triazole furanonucleosides 5a-e. To evaluate the biological significance of the compounds, they were tested for their effect on the activity of enzymes with biomedical significance and known preference for nucleoside binding, including members of the pancreatic ribonuclease A (RNase A) family. Detailed kinetic analysis revealed that the nucleosides behave as competitive inhibitors of the enzyme, with K_i values in the low μM range.



Poster - 107

POLYSACCHARIDES AS SOURCE OF ADVANCED MATERIALS: CELLULOSE HOLLOW MICROSPHERES FOR DRUG DELIVERY IN CANCER THERAPY

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Nanostructures made of biodegradable polysaccharides could prolong the residence time and therefore increase the absorbance of loaded drugs. As natural materials, polysaccharides present important advantages such as high stability, safety, improving the traditional drugs toxicity, hydrophilicity and biodegradability. [1-2]

In this work we have synthesized and characterized pH, thermo and ionic strength sensitive and biocompatible cellulose succinate spheres. Hollow P(MAA-*co*-NIPAAM-*co*-EGDMA)@CS microspheres have been synthesized by employing uniform silica nanospheres as templates. Distillation precipitation polymerization method was carried out with 2,2-azobis (2-methylpropionitrile) as initiator in acetonitrile aiming at coating the inorganic microspheres' surface with organic shell of poly(methyl methacrylic acid-*co*-N-isopropyl acrylamide-*co*-ethyleneglycol dimethacrylate). In continuation, cellulose succinate and cellulose powder was absorbed through intra- molecular interactions onto microspheres' surface and the isolated product was cross linked through esteric bonds formation. The cellulose succinate (CS) hollow microspheres were obtained after the silica core removal.

The resulting microspheres were characterized by Fourier transform infrared spectroscopy (FT-IR) and observed by scanning electron microscopy (SEM) and transmission electron microscopy (TEM). Dynamic light scattering was used to study the hydrodynamic diameter in different conditions. Loading and release behavior of the anthracycline drug Daunorubicin (DNR) was evaluated by UV-vis spectroscopy.

According to the literature, it is well known that tumor tissues show a slight acidic environment in contrast with the healthy cells. Taking into consideration the better releasing behavior of the drug at acidic conditions than the neutral, our system is promising drug-carrier for cancer treatment.

Keywords: cellulose, hollow microspheres, drug release

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Poster - 108

PEO-b-PCL GRAFTED DPPC LIPOSOMES: SELF-ASSEMBLY, STABILITY AND FRACTAL ANALYSIS OF THE NANOSTRUCTURES

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Amphiphilic block copolymers and vesicle forming surfactants have attracted major scientific interest in recent years due to their intriguing self-assembly behavior in aqueous media, which results in a plethora of nanoassemblies [1,2] and their potential applications in Pharmaceutical Nanotechnology. By combing liposomes with amphiphilic copolymers, more stable systems could be obtained, usually known as Stealth or Sterically Stabilized liposomes [3]. In this work, we report on the self assembly behavior and on stability studies of mixed systems consisted of DPPC (dipalmitoylphosphatidylcholine) and poly(ethylene oxide)-block-poly(ε-caprolactone) (PEO-b-PCL) block copolymer in aqueous media. These chimeric nanosystems can be utilized as Advanced Drug Delivery nano Systems. Static, dynamic and electrophoretic light scattering were used in order to extract information on the structure, morphology, size and effective charge of the nanostructures formed, as a function of block copolymer concentration, as well as temperature. The different mixed liposomal formulations have been prepared using the thin-film hydration method and their physicochemical characteristics are presented in Table 1. The incorporation of PEO-b-PCL leads to liposomes of smaller size [4]. All the mixed formulations were found to retain their original physicochemical characteristics at least for the time period that they were studied [4]. The temperature dependence of the physicochemical parameters of mixed liposomes in the process of heating is shown in Figure 1. The hydrodynamic radii (R_h) of mixed systems decreased in the process of heating up to 50°C [1,2]. The fractal dimension (d_f) values also decreased during heating. These lower values are in agreement with the concept of a rough surface [5] and the larger curvature [6] of the mixed liposome membrane. Therefore, the composition of the mixed systems play a key role on their self-assembly properties and their morphological characteristics.

Composition	R_h (nm)	PD.I.	d_f	ζ- potential (mV)
DPPC	62.5±2.5	0.605±0.016	2.51	1±0.4
DPPC:PEO PCL 1mol%	44.75±2.0	0.352±0.070	2.42	-0.9±1
DPPC:PEO PCL 5mol%	40.65±1.4	0.248±0.012	2.56	-8.6±4.7
DPPC:PEO PCL 10mol%	41.25±1.8	0.274±0.006	1.83	-5.6±1.9

Table 1. The physicochemical characteristics of mixed liposomes in HPLC water.

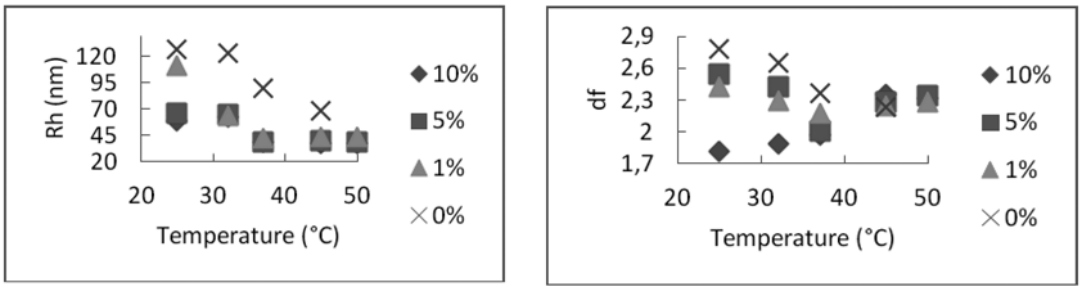

Figure 1. (a) R_h (b) d_f vs. temperature for DPPC:PEO-b-PCL mixed liposomes with 0,1,5 and 10mol% of incorporated block copolymer.

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Poster - 109

ZINC(II) METALLACROWNS HOSTING NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

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Zinc is the second most prominent trace metal in human body and plays an important role in various biological systems. It is critical for numerous cells processes and is a major regulatory ion in the metabolism of cells [1]. In the literature, diverse zinc complexes with biological activity are reported, but only a few zinc complexes with anti-inflammatory drugs are structurally characterized [2,3].
The chemical classes of non-steroidal anti-inflammatory drugs (NSAIDs) comprise salicylate derivatives, phenylalkanoic acids, oxicams, anthranilic acids, sulfonamides and furanones. NSAIDs exhibit favourable anti-inflammatory, analgesic and antipyretic properties and are used in painful and inflammation conditions like rheumatoid arthritis, spondilytis and osteoarthritis [4,5].
Our recent studies have been focused on the synthesis, characterization and biological evaluation (binding to calf-thymus DNA and to bovine or human serum albumin proteins) of zinc metallacrowns hosting NSAIDs. In this context, we present herein the study of the inverse Zn(II) metallacrowns hosting the NSAIDs naproxen (=Hnap) and tolfenamic acid (=Htolf) that belong to the phenylalkanoic acids and anthranilic acids, respectively. The crystal structure of the inverse Zn(II) metallacrown $[Zn_4(OH)_2(pko)_4(nap)_2]\cdot Et_2O$ where Hpko = di-2-pyridyl-ketoxime has been determined by X-ray crystallography.

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Acknowledgemen

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European Union
European Social Fund

Poster - 110

NEW $^{99m}Tc(CO)_3$ MANNOSYLATED DEXTRAN FOR SENTINEL LYMPH NODE DETECTION

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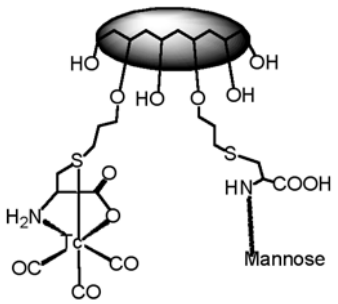
The aim of the present study is to synthesize new mannosylated dextran derivatives that can be labelled with Tc-99m for potential use in sentinel lymph node detection (SLND). The compounds were designed to have a dextran with molecular weight of 10 KD as a backbone, mannose for binding to mannose receptors of the lymph node and S-derivatized cysteine as a suitable chelator for labelling with $[^{99m}Tc(H_2O)_3(CO)_3]^+$ precursor. Reaction of allyl bromide with dextran (MW 11800) yielded the intermediate allyl-dextran (**1**) with about 40% coupling. Addition of cysteine to allyl-dextran resulted in the S-derivatized cysteine, compound DC15 (**2**). The final product DCM20 (**3**) was obtained in good yield after in situ hydrolysis and activation of cyanomethyl tetraacetyl-1-thio-D-mannopyranoside and coupling to DC15. All derivatives were purified by ultrafiltration and characterized by NMR. DC15 and DCM20 were quantitatively labelled with ^{99m}Tc (>95% radiochemical purity) using the fac-$[^{99m}Tc(OH_2)_3(CO)_3]^+$ precursor and ligand concentration of 1.5 x 10^{-6} M at neutral pH. Both ^{99m}Tc-labeled compounds $^{99m}Tc(CO)_3$-DC15 (**6**) and $^{99m}Tc(CO)_3$-DCM20 (**7**) remained stable after 6 h incubation at 37 °C in the presence of excess histidine or cysteine, as well as even after 20-fold dilution and incubation for 24 h at room temperature. The characterization of the compounds 6 and 7 was performed by comparing their HPLC radiochromatograms with those of their rhenium surrogates $Re(CO)_3$-DC15 (**4**) and $Re(CO)_3$-DCM20 (**5**) respectively that were prepared using the precursor $[NEt_4]_2$*fac*-$[ReBr_3(CO)_3]$ and characterized by IR and NMR spectroscopy. When injected subcutaneously from the foot pad of mice, ^{99m}Tc-labeled mannosylated dextran (**7**), showed accumulation in the popliteal lymph node (SLN in this model) higher than that of non-mannosylated analogue (6) and the ^{99m}Tc-phytate serving as standard. Compound 7 also exhibited lower radioactivity levels at the injection site compared to ^{99m}Tc-phytate. The SPECT/CT studies in mice confirmed that 7 accumulated in the popliteal lymph node allowing its clear visualization. The present findings demonstrate that compound 7 (^{99m}Tc-DCM20) is promising and merits further evaluation as a radiopharmaceutical for sentinel lymph node detection.



Poster - 111

TECHNETIUM-LABELED FATTY ACIDS FOR MYOCARDIAL METABOLISM IMAGING

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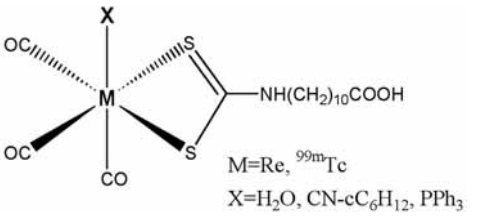
In the framework of our study for the development of new technetium-99m labelled fatty acids for potential use in imaging heart metabolism, we report herein the synthesis and characterization of novel ^{99m}Tc tricarbonyl complexes based on the "2+1" mixed ligand approach (scheme 1). The synthesis and characterization of the analogous rhenium complexes is also reported. Reaction of equimolar amounts of ω-[(dithiocarbamato)amino]undecanoic acid with the $[NEt_4]_2[Re(CO)_3Br_3]$ precursor resulted in the formation of the hexacordinated neutral complex in which the ligand coordinates to the metal through the SS system of dithiocarbamate. The sixth position is occupied by a labile molecule of water that is replaced by cyclohexyl-isonitrile or triphenylphosphine. The rhenium complexes have been characterized by elemental analysis, IR and NMR spectroscopies. The analogous technetium-99m complexes were prepared by incubation of 175 μg of the ligand with 500 μL of the precursor $[^{99m}Tc(CO)_3(H_2O)_3]^+$ (radiochemical yield ≥98%), followed by the addition of 500 μL of methanolic solutions ($2x10^{-3}$M) of cyclohexyl-isonitrile and triphenylphosphine respectively. Their structure was established by comparative HPLC techniques. In vitro studies established the stability of the complexes towards transchelation, in plasma and in liver and kidney homogenates. In vivo studies in mice showed high initial heart uptake for all complexes (up to 14 %ID/g at 1 min p.i.) and sufficient retention for all complexes (up to 5.47 %ID/g at 15 min p.i.). However the heart to blood ratio was low (up to 0.77).



Poster - 112

INVESTIGATION OF THIALYSINE AS BIFUNCTIONAL CHELATOR FOR THE DEVELOPMENT OF RE/TC TRICARBONYL BASED RADIOPHARMACEUTICALS AND ITS UNEXPECTED METAL-ASSISTED CLEAVAGE PRODUCTS

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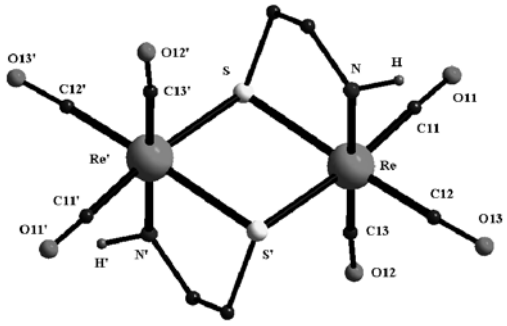
Lanthionine is a dimeric cysteine aminoacid that has been used for the development of *fac*-$[^{99m}Tc(CO)_3]^+$ renal imaging radiopharmaceuticals. In this work, we are focused on the investigation of the analogous thialysine aminoacid as bifunctional chelator for the development of novel *fac*-$[^{99m}Tc(CO)_3]^+$ radiopharmaceuticals. Herein we synthesized and characterized the rhenium complex of thialysine *fac*-[Re(thialysine-N,S,N)$(CO)_3$] after reaction of the ligand with *fac*-$[Re(OH_2)_3(CO)_3]^+$. HPLC analysis of the reaction mixture showed quantitative formation of the complex that appears as two isomers (at 10.3 and 10.9 min). Successive re-crystallization efforts in order to obtain single crystals for X ray analysis of the complex led to the unexpected isolation of a new species that after X-ray characterization, was proven to belong to the dimeric complex with formula *fac*-$[Re(cysteamine\text{-}S,N)(CO)_3]_2$. Apparently, this complex was formed by metal-assisted cleavage of thialysine to cysteamine, which has been observed elsewhere too. Furthermore, the analogous technetium complex *fac*-$[^{99m}Tc$(thialysine-N,S,N)$(CO)_3]^+$ was synthesized in high yield by reacting thialysine with the *fac*-$[^{99m}Tc(OH_2)_3(CO)_3]^+$ precursor in high radiochemical yield. The purified mixture of isomers was evaluated for its radiochemical stability over 24 h in histidine and >95% stability was observed. In order to study thialysine as bifunctional chelator, the benzylamide of thialysine was synthesized as a model compound, by BOC protection and CDI amidation. Reaction of this ligand with both *fac*-$[Re/^{99m}Tc(OH_2)_3(CO)_3]^+$ precursors as well as the investigation of the cysteamine dimeric species for the development of 2+1 mixed ligand complexes, are part of our currently ongoing research.



Poster - 113

^{99m}TC(I)$(CO)_3$-LABELED BIOTIN CONJUGATE IN A TUMOR "PRETARGETING" APPROACH WITH MONOCLONAL ANTIBODY BEVACIZUMAB

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Vascular endothelial growth factor (VEGF), released by tumor cells, is an important growth factor in tumor angiogenesis. Bevacizumab is designed to directly bind to VEGF extracellulary to prevent interaction with VEGF receptors.

^{99m}Tc is the most popular radionuclide for clinical imaging because it has ideal nuclear properties (a single photon energy of 140 keV, a half-life of 6 h, and it is readily available from a ^{99}Mo-^{99m}Tc generator).

Given the drawbacks of radiolabeled humanized monoclonal antibody (mAbs) such as slow blood clearance and unspecific binding to normal tissues, antibody pretargeting is an approach which combines the desirable properties of high tumor uptake of antibodies with rapid pharmacokinetics and fast whole-body clearance of radioactivity. According to this method streptavidin/avidin is covalently attached to a tumor-specific antibody at a site that does not interfere with the biological activity of the antibody. The conjugate is first administered and allowed to accumulate in tumors, and then a radiolabelled-biotin derivative is given in the form of a small molecule that binds rapidly with high affinity to the mAb-streptavidin/avidin.

In this study, we synthesized and characterized a biotin derivative, that contains a NSO donor atom system which can act as a tridentate chelator for the ^{99m}Tc(I)-tricarbonyl core. ^{99m}Tc$(CO)_3$(NSO)-biotin derivative was then prepared and quality control of this complex was performed with HPLC. A streptavidin conjugate of the bevacizumab, which binds 4 molecules of radiolabeled biotin, has also been prepared. HPLC studies has been performed in order to determined the binding of the ^{99m}Tc$(CO)_3$(NSO)-biotin derivative and streptavidin-bevacizumab conjugate. In vivo biodistribution studies were performed on mice bearing M165 carcinoma cell lines.

Poster - 114

COMPARATIVE BINDING EFFECTS OF ASPIRIN AT LOX WITH ITS METAL COMPLEX

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An anti-inflammatory complex of Ag(I) namely $Ag(tpp)_3(asp)$ [tpp=triphenylphosphine and asp=aspirin] was synthesized in an attempt to develop novel metallotherapeutic molecules. We have initiated studies using STD (Saturation Transfer Difference) ^1H NMR experiments in an attempt to examine if this complex is binding to LOX-1. For this study, experiments without or with sonication were performed in order to increase the low soluble complex in the enzyme environment. The complex in DMSO and TRIS/D_2O environments shows two distinct conformers. Signals attributed to tpp were eminent only when sonication was applied. Both sonicated and not sonicated samples showed that aromatic ring of aspirin adopts a specific conformation when the complex is docked to the LOX-1. Docking experiments of the complex with LOX-1 were conducted using Surflex-dock and Glide algorithms. Molecular docking using Glide algorithm confirmed the STD ^1H-NMR experiments. STD ^1H NMR experiments and *in silico* molecular docking experiments of aspirin showed no binding with LOX-1. When in the solution containing LOX and the complex $[Cu(tpp)(pmt)]_2$ [pmt =2-mercaptopyrimidine) was added aspirin the former was shown to hinder the binding of the latter significantly. This is interpreted that copper complex aids the transfer of aspirin through acid-base reaction at LOX enzyme.

Poster - 115

ITC STUDY OF LECTIN BINDING TO NOVEL MULTIFUNCTIONAL CARBOHYDRATE HYPERBRANCHED POLYMERS

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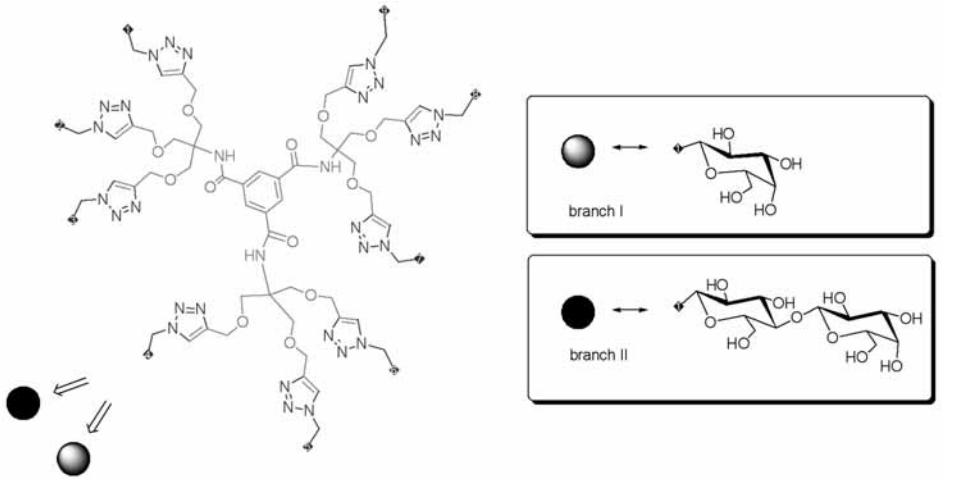
Lectins are proteins which have a distinct role in molecular recognition since they are able to identify saccharides by their structures and reversibly bind them. A wide variety of living organisms use these proteins for different purposes. For example, it is believed that plants lectins have defensive purposes during germination while bacteria use lectins for cell surface binding that enables them to enter the cells.

Isothermal titration calorimetry (ITC) is very useful tool for the quantification of protein binding capacity. The thermodynamic data (K, ΔH, ΔS, ΔG) and the stoichiometry of binding (n) obtained can provide an excellent description of the interaction. We have applied ITC to the study of a new series of glycodendrimeric compounds which were prepared by the incorporation of "click chemistry" synthetic routes involving divergent and convergent strategies. Three classes of compounds were synthesised containing 1-β-azido-D-galactose and 1-β-azido-lactose units resulting in molecules with up to 63 hydroxyl groups on the periphery.

Increasing the number of potential recognition points for lectins in order to achieve multivalent binding is one possible approach towards effective lectin inhibitors. Our glycodendrimers showed affinity in the $K \approx 10^3\ M^{-1}$ region comparable with similar structures known from the literature.



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Poster - 116

CHROMATOGRAPHIC BEHAVIOR OF PROLINE DERIVATIVES ON PARTICULATE, MONOLITHIC AND FUSED CORE NARROW BORE COLUMNS: DETERMINATION OF CAPTOPRIL IN DISSOLUTION SAMPLES

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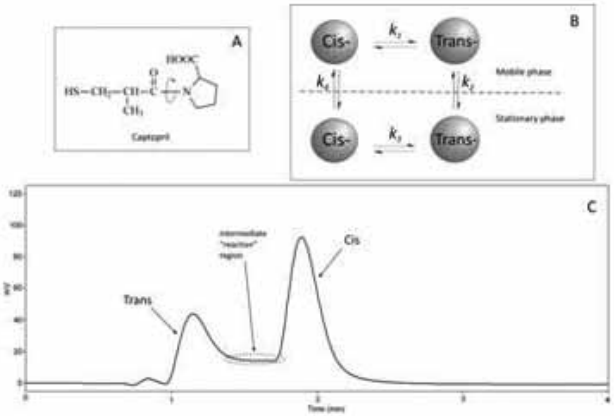
Proline drug derivatives such as captopril exists in two conformational isomers of cis-trans isomers due to its reversible equilibrium between its two forms (Fig. A). This phenomenon occurs even during chromatographic analysis of this compound producing a "split" peak or abnormal peak shapes since its isomeric form has different mass transfer on the stationary phase. Basically, there are two main processes which take place on the stationary phase when a molecule of captopril is chromatographed: i) equilibrium process between the cis & trans isomeric forms of captopril (isomerization) and ii) the equilibrium/partition process (mass transfer) of each of these forms between the mobile phase and the stationary phase (Fig. B). Single captopril peak is achieved when the rates of both processes are become comparable while the discrimination of the conformational isomers is taken place as the isomerization is slower than partitioning rate (Fig. C).

The scope of this investigation was to study the chromatographic behavior of captopril in four modern commercially available narrow-bore (50 × 2.1 mm i.d.) columns (two based on core-shell particles, a monolithic column and a typical particulate one–fully porous). An LC method has been developed and validated for the determination of captopril in dissolution samples from commercially available formulations.



Poster - 117

PHYSICOCHEMICAL BASIS FOR MICROBICIDAL ACTION OF DISINFECTANT AQUEOUS SOLUTIONS

Biljana Gjorgjeska
Faculty of medical science, University "Goce Delcev"-Stip

Knowing antiseptic activity of chemical disinfectant substances has great practical value. It is evidential that there is the need for defining standard technique for quantitative determination of bactericidal activity of chemical disinfectant substances, as well as the need for defining parameter for comparing various chemical disinfectants. Solution of phenol (5%) was considered as referent standard for evaluation of efficacy of disinfectant aqueous solutions. Phenol coefficient shows how many times bactericidal activity of examined disinfectant is greater or lower than bactericidal activity of standard phenol solution (5%). However, phenol coefficient gives only limited information. Suitability of phenol coefficient for evaluation of nonphenolic disinfectants is still opened question. On the other side the methods for evaluation of antiseptic activity of disinfectant aqueous solutions are microbiological methods.

The aim of this study is to develop a new empirical coefficient which is capable to express the various physic-chemical properties of disinfectant solutions on bactericidal activity. The basic duty of this parameter (Disinfection Activity Coefficient of Solution - DACS) is to express capability for comparison and prediction of disinfectant activity. The DACS index, which is the sum of four terms (fluidity, surface tension, redox potential and osmolality), results in good correlation with the activity at different disinfectant aqueous solutions. The DACS index can be calculated using additive and statistical models. Statistical model is adequate for evaluation of different disinfectant solutions because of better expressing the bactericidal activity then additive model. For analyze of various dilutions of one disinfectant there is no significant difference between this two models. The usefulness of DACS is demonstrated for analyze of bactericidal activities on different disinfectant solutions containing boric acid, chlorhexidne, chlorhexidine with cetrimide, chloroxylenol, chlorophen, eosin, hydrogen peroxide, phenyl mercury borate, povidon-iodine, thiomersal, tosilchloramide and phenol. Results for bactericidal activities obtained from microbiological tests on Staphylococcus aureus was compared with activities predicted with DACS. As the conclusion, it is considered good correlation between experimental and calculated values for bactericidal activity.

Poster - 118

INVESTIGATION OF PERMEABILITY THROUGH CELL MEMBRANES AND PROTEIN BINDING OF BIOLOGICALLY ACTIVE SELENIUM SPECIES USING BIOMIMETIC CHROMATROGRAPHY

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Selenium is an essential micronutrient for human life. It exhibits considerable antioxidant properties and it is considered to contribute to prevention of heart diseases and possibly cancer. In any case, in order to reach a chemical its target site, the key-step is the absorption, which is governed to a great extent by lipophilicity and ionization. Octanol-water partition/ distribution coefficient, as a measure of lipophilicity, has been widely applied to simulate this process. Biomimetic chromatography is a popular alternative, offering a rapid and user's friendly technique to model biological processes contributing to bioavailability, such as permeability through membranes and protein binding. Biomimetic chromatography uses silica based stationary phases containing immobilized artificial membranes (IAM) or proteins such as human serum albumin (HSA) or 1-acid glycoprotein (AGP).

The present work is a continuation of our previous investigation on the lipophilicity profile and the retention behavior on IAM and protein containing stationary phases of selenium species by enriching the data set with three more derivatives, namely Dimethyl-2-selenourea (DMe-SeU), Se-Methyl-Selenocysteine (Me-SeC) and Methaneseleninic acid (MeSeA). Chromatographic indices on four biomimetic columns (IAM-MG, IAM-DD2, HSA, AGP) as well as octanol-water partitioning data were inter-related and submitted to principal component analysis to reveal similaritites/ dissimilirities in the elution mechanism. Retention factors on IAM stationary phases were further compared with literature permeability data through human colon adenocarcinoma cell line (Caco-2 cell model). The effect of the presence of reduced glutathione (GSH) to the retention on biomimetic stationary phases was studied and chromatographic indices were used to evaluate the permeability and protein binding of investigated Se species.

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Poster - 119

ZWITTERIONIC CHARACTERISTICS OF LOSARTAN AND A NOVEL CARBOXY METHYLATED PYRIDOINDOLE DERIVATIVE INVESTIGATED BY THEIR IAM RETENTION AND OCTANOL-WATER PARTITIONING AS A FUNCTION OF PH

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Ampholytes, forming zwitterions, represent a particular type of solutes with intra- and inter-molecular interactions, which influence their physicochemical characteristics, among them lipophilicity, a property with vital biochemical and pharmacological significance. In fact, their partitioning behavior changes as a function of pH resulting in most cases in a bell shaped profile, which may favor membrane permeation and tissue distribution at pH conditions around the isoelectric point. A U- shaped profile may also be obtained for ampholytes with large tautomeric constant Kz. Immobilized Artificial Membrane Chromatography (IAM) offers a promising perspective to investigate cell membrane partitioning, which, in contrast to octanol-water, allows the expression of electrostatic interactions with the charged centers of the phospholipids. In the case of zwitterionic compounds such interactions may affect the retention /pH profile, although no systematic studies have been reported in literature.

In the present study the IAM retention behavior as a function of pH has been investigated for the zwitterionic drug losartan and a novel carboxy methylated pyridoindole derivative. Isocratic retention factors (logk) were measured in a pH range 3.0-7.4 using different mixtures of phosphate buffered saline and acetonitrile and were linearly extrapolated to $\log k_w$ values, corresponding to pure aqueous mobile phase. Isocratic and extrapolated retention factors were plotted versus pH. In the case of losartan a bell shaped profile was obtained, in accordance with its logD/pH profile, established by direct octanol-water partitioning experiments. A different behavior was observed for the carboxy methylated pyridoindole derivative, which produced a U-shaped profile in IAM Chromatography, in contrast to its bell shaped logD/pH profile. These findings indicate stronger intramolecular interactions in the molecules of losartan, which are not affected by the presence of charged centers on IAM surface. However in the case of the carboxy methylated pyridoindole derivative the zwitterionic structure is disrupted upon contact with the IAM stationary phase, indicating weaker charge compensation within the molecules.

Poster - 120

DEVELOPMENT AND VALIDATION OF A GENERIC SCREENING METHOD IN HORSE DOPING CONTROL BY LC-QTOF-MS, GC-HRMS AND GC-MS

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In the present study a general screening protocol was developed to detect pharmaceutical substances and metabolites like anabolic steroids, analgesics, antihistamines, antipsychotics, beta-agonists, beta-blockers, bronchodilators, corticosteroids, diuretics, non steroidal antiinflammatory drugs, opioid analgesics and stimulants for doping control purposes. The proposed method aims at the determination of prohibited compounds in equine urine using a unified sample preparation procedure. The analysis of doping agents is accomplished by LCQTOF-MS, GC-HRMS and GC-MS techniques that act complementarily. The majority of the prohibited substances are identified through a high mass accuracy technique, such as LCQTOF-MS, without prior derivatization. The sample preparation procedure begins with two parallel stages. The first one includes the hydrolysis of sulphate and glucuronide conjugates, except for the 17β-sulphate steroid conjugates, that are deconjugated through the second step. In the first stage, enzymatic hydrolysis of 5 mL urine is accomplished with β-glucuronidase/arylsulfatase, followed by basic liquid-liquid extraction with ethyl acetate and separation of the organic phase into three fractions evaporated to dryness. The first reconstituted fraction is appropriate for LC-QTOF-MS analysis in positive electrospray mode, whereas the second methyl-derivatized fraction is submitted to GC-MS analysis. The remaining third fraction is mixed with the extract of the second stage and their per-TMS derivatives undergo GC-HRMS analysis. The second stage involves the isolation of the sulphate and glucuronide conjugates contained in 2.5 mL urine using a C18 solid-phase extraction (SPE) cartridge followed by hydrolysis with anhydrous methanolic hydrogen chloride. The extraction is carried out at pH 9.5-10 with diethylether. Each compound of interest is identified by means of the technique in which the lower detection limit is achieved.

Validation was performed for 56 selected compounds according to the Eurachem guidelines for qualitative validation. Validation parameters included detection limit, identification capability, specificity, extraction recovery, matrix effect, matrix interferences, repeatability, reproducibility, mass accuracy and carry over contamination. The preliminary results fulfill the requirements regarding the horse doping control criteria.

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QUALITY METHODOLOGY IN FORMULATION AND DEVELOPMENT

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In the past ten years, FDA, followed by other regional and national Regulatory Authorities, has initiated a number of Quality approaches, such as Quality-by-Design (QbD) and Process Analytical Technology (PAT), with the intent to enable flexibility in designing robust manufacturing processes capable of producing quality products. The latest of these initiative is the Design Space (DS) approach, according to which no additional inspections or testing are required when changes to raw material attributes and process parameters stay within the DS.
Quality of tablets, in terms of composition consistency, powder flowability, tablet friability and dissolution is studied using various multivariate methods, such as Principal Component Analysis (PCA) and Partial Least Squares Regression (PLS), in combination with Design-of-Experiments (DOE) and Optimization techniques. The results of this analysis are used to define DS, the part of the domain of definition of the raw Material Attributes (MA) and Critical Process Parameters (CPP) that ensures the Critical Quality Attributes (CQA) to stay within specifications.

Keywords: Design Space; Critical Quality Attribute (CQA); Critical Process Parameter (CPP)

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