Innovations in sequence selection methods, modification strategies and coupling siRNA knockdown with sophisticated profiling technologies will be discussed. The development of predictive methods for creating high potency gene silencing reagents and the ability to modify them to enhance their biological properties should greatly facilitate high throughput, genome-wide gene functional analyses.

Oral Presentations

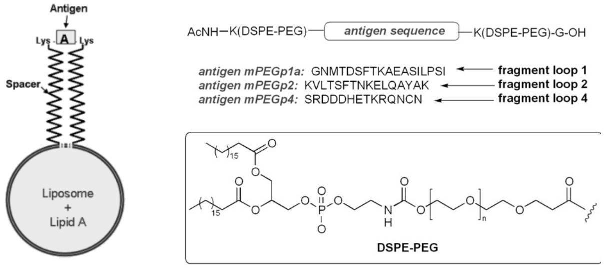
O1

Pegylated lipopeptides in liposomes as MDR therapeutic vaccine

P. Lopez[1], Claudie Madoulet[2], David Hickman[1], Pierre-François Tosi[2], Andrea Pfeifer[1], Andreas Muhs[1] & Claude Nicolau[3]

[1]ACImmune S.A., EPFL-PSE B, 1015 Lausanne, Suisse. [2]IFR53, UFR Pharmacie, 3 avenue du Maréchal Juin, 51096 Reims Cedex, France. [3]Tufts University, Friedman School of Nutrition Science and Policy, Boston, MA 02115, USA

Active immunisation of mice with P-glycoprotein-derived peptides in liposomes has shown to produce a strong immune response specific for the Pgp170 efflux pump[1]. The antibodies raised against these tetrapalmitoylated peptides were capable of reverting the MDR phenotype *in vitro* and increasing the efficiency of chemotherapy *in vivo*. With the aim to improve antigen presentation, we have introduced a polyethylene glycol linker between the peptide and the lipid anchor to mimic the loop conformation adopted by the membrane protein. In contrast to the tetrapalmitoylated antigen resting flat on the surface, in this new construct the peptide is sufficiently far located from the liposome bilayer to be independently paralleled by an enhanced and linker-lasting immune response.



Peptides bearing the extracellular sequences of the murine *mdr1* protein, with two Lys(ivDde) residues at each N- and C-terminal end, were synthesized on the 2-chloro-trityl resin using standard peptide chemistry. After chemoselective deprotection and mild cleavage from the resin, the internally protected peptides underwent site-specific conjugation to the DSPE-PEG group on the terminal free lysines. Antigen constructs obtained after side-chain deprotection and HPLC purification were characterized by MALDI-TOF mass spectrometry. Intraperitoneal inoculation to mice of these lipopegylated peptides reconstituted in liposomes containing Lipid A, elicited significant and long-lasting titers of anti-Pgp170 antibodies.

[1] Pawlak-Roblin C, Tosi PF, Perrin L, Devy J, Venteo L, Albert P, Nicolau C, Madoulet C. Inhibition of multidrug resistance by immunisation with synthetic P-glycoprotein-derived peptides . Eur J Cancer 2004;40:606-613.

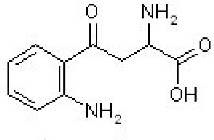
O2

Kynurenic acid and Schizophrenia: Design and Synthesis of potential Kynurenine Aminotransferase Inhibitors

U. Dijkman*, C. Grol*, T. Cremers**, H. Wikström*, S. Erhardt***, G. Engberg***, D. Dijkstra*

*Dept. of Medicinal Chemistry, Groningen University, A. Deusinglaan 1, 9713 AV Groningen, The Netherlands. **Dept. of Biomonitoring and Sensoring / Brains-on-Line, Groningen University, A. Deusinglaan 1, 9713AV Groningen. ***Dept. of Physiology and Pharmacology, Karolinska Institutet, Nanna Swartz väg 2, SE 17177 Stockholm, Sweden

Kynurenic acid (KYNA) is a metabolite of the kynurenine pathway, originating from tryptophan. The compound is biosynthesized by kynurenine aminotransferases (KAT) from the key intermediate kynurenine. It is the only known endogenous antagonist of ionotropic glutamate receptors. In particular, it blocks the glycine coagonist site of the NMDA receptor. In addition, KYNA inhibits the α7* nicotinic acid receptor in a noncompetitive way. Elevated levels of kynurenic acid have been found in patients suffering from schizophrenia. To study the importance of this observation, a selective KAT inhibitor is needed to decrease KYNA levels in the brain. To study spatial requirements in the binding pocket of the enzyme, an additional aim is to rigidify the chemical structures. Mono- and bicyclic analogs of the endogenous KAT substrate kynurenine were synthesized. The compounds were tested in vitro for KAT inhibitory activity. Since kynurenine is a substrate for two additional enzymes, kynurenine 3-hydroxylase and kynureninase, selectivity of the synthesized compounds for KAT over those two enzymes was addressed. Selected compounds were tested in vivo, using microdialysis.Structure activity relationships of the synthesized KAT inhibitors will be discussed in detail.



kynurenine

O3

Transcriptomic and quantitative proteomic analyses of a series of anticancer sulfonamides

T. Owa

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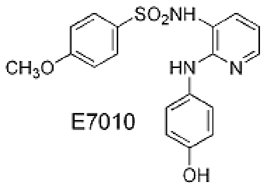
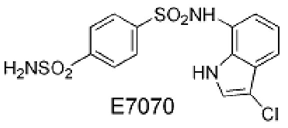
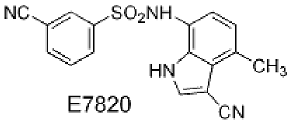
In the long history of drug discovery, sulfonamide therapeutics have been sequentially developed as possessing a variety of pharmacological effects such as antibacterial, hypoglycemic, diuretic, and antihypertensive activities. These serendipitous findings indicate that the sulfonamide moiety is a kind of “privileged structure” capable of interacting with multiple cellular targets. On the basis of this consideration, we have prepared a sulfonamide-focused compound library for biological evaluation to discover a novel class of cancer chemotherapeutics. E7010, E7070 and E7820, all of which were selected from the library via cell-based phenotypic screens, are currently under clinical trials as novel anticancer agents to demonstrate some objective responses in patients with refractory solid tumors. In my talk, our research programs utilizing DNA microarray gene expression analysis and quantitative proteomic analysis will be presented with particular focus on the application of these new technologies to profiling our anticancer sulfonamides.



E7010



E7070



E7820

1. Owa T, Yokoi A, Yamazaki K, Yoshimatsu K, Yamori T, Nagasu T. Array-Based Structure and Gene Expression Relationship Study of Antitumor Sulfonamides Including *N*-[2-[(4-Hydroxyphenyl)amino]-3-pyridinyl]-4-methoxybenzenesulfonamide and *N*-(3-Chloro-7-indolyl)-1,4-benzenedisulfonamide. J Med Chem 2002, 45, 4913-4922.
2. Oda Y, Owa T, Sato T, Boucher B, Daniels S, Yamanaka H, Shinohara Y, Yokoi A, Kuromitsu J, Nagasu T. Quantitative Chemical Proteomics for Identifying Candidate Drug Targets. Anal Chem 2003, 75, 2159-2165.
3. Banerjee M, Poddar A, Mitra G, Surolia A, Owa T, Bhattacharyya B. Sulfonamide Drugs Binding to the Colchicine Site of Tubulin: Thermodynamic Analysis of the Drug-Tubulin Interactions by Isothermal Titration Calorimetry. J Med Chem 2005, 48, 547-555.

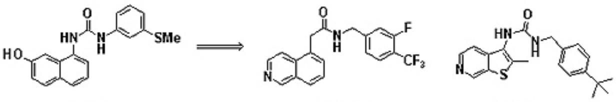
O4

The Discovery of A-548192 and A-780150: Novel TRPV1 Antagonists Active in Models of Inflammatory and Neuropathic Pain

S. Turner*, T. Jinkerson**, A. Gomtsyan**, E. Bayburt**, R. Perner**, J. Koenig**, H. Mcdonald**, P. Honore**, C. Wismer**, K. Marsh**, J. Wetter**, M. Jarvis**, C. Lee**, C. Faltynek**, J. Sullivan**

*Neuroscience Discovery Research, Abbott GmbH, Knollstrasse 50, Ludwigshafen, Germany. **Neuroscience Research, GPRD, Abbott Laboratories, Abbott Park, IL, USA

The capsaicin sensitive TRPV1 receptor is a member of the mammalian transient receptor potential (TRP) channel family and is highly expressed on small diameter (C-fiber) nociceptive sensory neurons and at lower levels in other non-neuronal tissues such as skin and bladder. This receptor has been called a polymodal detector of noxious stimuli since it can be activated by low pH, heat and naturally occurring ligands such as capsaicin, causing burning pain sensation. There has been widespread interest in exploring TRPV1 antagonists as therapeutic agents in the treatment of chronic pain, which is supported by the finding that TRPV1 receptor knock-out mice do not develop thermal hyperalgesia following acute inflammation.


HTS hit A-548192 A-780150

Following optimization of an HTS hit, we discovered a novel series of 2-(isoquinolin-5-yl)acetamides that were potent TRPV1 antagonists. The SAR investigations around the key amide and benzyl groups are described. A-548192, a prototype compound of this series, was found to have potent in vitro activity in blocking capsaicin activation of TRPV1 and also to be orally efficacious in both inflammatory (Complete Freund´s Adjuvant) and neuropathic (Chung and Bennett) in vivo pain models. Further exploration of new heterocyclic cores led to the discovery of 1-(2-methylthieno[2,3-c]pyridin-3-yl)ureas such as A-780150 which, in addition to activity in the models already mentioned, was also orally active in the abdominal constriction model of visceral pain.

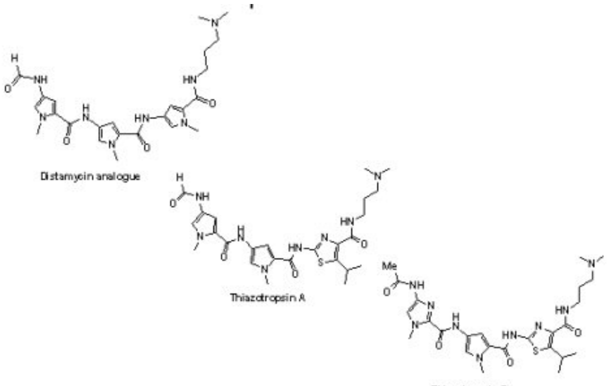
O5

Antibacterial and antifungal compounds that bind to the minor groove of DNA

C. Suckling*, E. Ellis***, G. Ford***, I. Hunter***, A. Khalaf*, S. Mackay***, R. Waigh**, C. Gemmell****, K. Fox*****

* WestCHEM Research School, Department of Pure & Applied Chemistry, University of Strathclyde, Glasgow, Scotland. **Department of Pharmaceutical Sciences, University of Strathclyde, Glasgow, Scotland. *** Department of Bioscience, University of Strathclyde, Glasgow, Scotland. ****Department of Clinincal Microbiology, Glasgow Royal Infirmary, University of Glasgow, Glasgow, Scotland. ***** School of Biological Sciences, University of Southampton, Southampton, UK

At Strathclyde, we have developed design strategies and novel synthetic methodologies for polyamide MGBs suitable for the production of drugs specifically targeted to DNA [1,2]. More than 100 Strathclyde MGBs (sMGBs) have been synthesised to include a number of novel structural features that promote high affinity binding to DNA with exceptional selectivity for small, non-covalently binding compounds. The key structural features include hydrophobic alkyl side chains, especially branched alkyl groups, substituted thiazoles, and planar, aromatic head groups.The properties of a series of antibacterial and antifungal polyamide minor groove binders (MGBs) for DNA will be presented. New evidence for exceptionally high sequence selectivity in small, non-covalently binding MGBs has been obtained from footprinting and NMR studies. Several MGBs in the series show significant bacteriocidal and fungicidal activity with selectivity compared with mammalian cell lines. Rapid cell Hill and synergism with respect to established antiinfective drugs has also been established. *In vivo* activity has been demonstrated for antibacterial compounds in mice.


Distamycin analogue

Thiazotropsin A

Thiazotropsin B

[1] Anthony NG, Fox KR, Johnston BF, Khalaf AI, Mackay SP, McGroarty IS, Parkinson JA, Skellern GG, Suckling CJ, Waigh RD, DNA binding of a short lexitropsin. Bioorg. Med. Chem. Letters, 2004;14; 1353-1356.

[2] Khalaf AI, Suckling CJ, Waigh RD, PCT WO 03059881

O6

Rapid array informed fragment to lead evolution

H.D. Junker, T. Neumann, I. Ott, S. Maier, K. Burkert, O. Keil, K. Schmidt and R. Sekul

Graffinity GmbH, Im Neuenheimer Feld 518-519, D-69120 Heidelberg, Germany

Low affinity fragment based screening is an excellent complement to traditional HTS approaches. Fragments are compounds with lower molecular complexity and molecular weight (100-300 Da) than traditional screening library members (1). A powerful, fast and reliable method for the detection of fragment-protein interactions is the simultaneous surface plasmon imaging of 9216 member compound libraries immobilized on a chemical microarray (2). This function blind detection method needs only µg protein amounts for each array and allows the direct analysis of binding events without the need of further reporter systems (3). Additional information on the fragment binding mode can be obtained by on array competition studies using compounds with an established interaction mode (4). This technology was applied to proteases, kinases and several other protein families by screening a collection of 110.000 different lead-like compounds with a subset of >10.000 structurally diverse fragments. Several case studies show how the in-depth analysis of the array data in combination with high throughput chemistry can efficiently accelerate the transformation of fragments into compounds with µM to nM potency.

1) R.A.E. Carr., M Congreve, Ch. W. Murray et al, Drug Discov. Today 10, 987-992 (2005)

2) G. Metz, H. Ottleben, D. Vetter, Meth. Princ. Med. Chem. 19, 213-236 (2003)

3) S. Dickopf, Frank M, H.-D. Junker et al., Anal Biochem. 335(1), 50-7 (2004)

4) T. Neumann, H.-D. Junker, O. Keil et al. Letters in Drug Des.& Disc. 2, 590-594 (2005)

O7

Random chemistry, a new strategy to create a library: Development of new acetylcholinesterase inhibitors

P. Kapková[*], E. Heller[*], M. Unger[*], E. Kugelmann[*],G. Folkers[**], U. Holzgrabe[*]

[*] Institute of Pharmacy, University of Wuerzburg, Germany
[**]Institute of Pharmaceutical Sciences, ETH Zurich, Switzerland

Acetylcholinesterase inhibitors represent the most widely used class of drugs for the therapy of Alzheimer´s disease. For 20 years, many drugs have been developed for clinical use. Even though their activity was promising, many of them showed only limited clinical success beside side effects, e.g. observed for tacrine.

Our research objective was to enrich this therapy class by new lead structures which perform better. Random chemistry represents a new methodology providing compounds of resembling molecular structure and also rearranged structures not previously known. The original idea of this technology relies on using the g-irradiation as an initiator of random free radical recombinations in aqueous or alcohol solution of starting compound(s) [1]. The method showed reproducible results. Recently we could demonstrate that the application of Fenton´s reagent is able to produce a similar compound library.

Via random chemistry we generated a small mixture-based compound library. Bioassay-guided HPLC-fractionation as a deconvolution strategy was employed to search for potent hits. Additionally, the fractions obtained from HPLC were structurally on-line characterized by means of MS^n.

A new potent acetylcholinesterase inhibitor (ATAM) of the acridine-type resulted from this study. The structure of the compound was elucidated by ^1H and ^{13}C NMR spectroscopy, ESI-(tandem)-mass spectrometry and FTIR-spectroscopy. The biological potency of the new anti-Alzheimer candidate was examined by Ellman's test (AChE; E.C.3.1.1.7 from Electric Eel; 0.1 M phosphate buffer, pH 8.0; 20°C) and found to be as active as the potent AChE inhibitor tacrine.

[1] Kapkova, P., Heller, E., Unger, M., Folkers, G., **Holzgrabe, U**. 2005. **J. Med. Chem**. 48: 7496-7499.

O8

Solid-Phase Chemoenzymatic Synthesis of Neuraminic Acid C-Glycosides as Neuraminidase inhibitors

S. Baytas*, Q. Wang**, R. Linhardt*/**

*Department of Chemistry and Chemical Biology,Rensselaer Polytechnic Institute, Troy, NY, USA. **Division of Medicinal and Natural Product Chemistry, The University of Iowa, Iowa City, IA, USA

Infectious diseases caused by bacterial and viral pathogens pose important challenges in prevention, protection and therapy. Approaches most often rely on targeting the proteins of pathogens. Carbohydrates often provide camouflage to pathogens, a means of interacting with their hosts and less frequently change their structure. Microbial carbohydrates are believed to have co-evolved with the carbohydrates of their mammalian hosts. The static structure and surface localization of microbial carbohydrates offer a potential target and their similarity to our own carbohydrates require innovative methods for their selective targeting. Catabolically stable carbohydrates are important yet underexploited targets in controlling infectious disease. Both microbial and mammalian carbohydrates are often linked through their reducing ends to glycoproteins and glycolipids carriers for appropriate display on the surface of cells. The non-reducing ends of these carbohydrates are displayed to their protein receptors. Ulosonic acids are often found at the non-reducing terminus of glycoconjugates. Sialic acid is a common ulosonic acid found in the glycocalyx and in mucins. Since glycoconjugates are both remodeled and catabolized from the non-reducing terminus by stepwise enzymatic removal of their monosaccharide units, the modification of their ulosonic acid component represents an intriguing target for blocking such transformation. Glycoconjugates, containing a modified ulosonic acids resistant to *in vivo* modification and catabolism, may have significant potential in infectious disease prevention, protection and therapy. The possible applications of such derivatives would include inhibitors of enzymes, such as neuraminidases, and as inhibitors of sialic acid-binding proteins, such as hemagglutinins.

Based on diastereocontrolled synthesis of sialic acid based a-*C*-glycosides, using SmI_2 mediated coupling reaction, we have set out to synthesize *C*-glycoside analogs. This chemistry has been successfully performed on solid support, which should facilitate the construction of a combinatorial library for screening as inhibitors of sialidase activity and hemagglutinin interaction.

O9

Insight into the Binding Mode for Cyclopentapeptide Antagonists of the CXCR4 Receptor

J. VåBenø, G. Nikiforovich, G. Marshall

Center for Computational Biology, Department of Biochemistry and Molecular Biophysics, Washington University School of Medicine, St. Louis, MO, USA

Due to its involvement in T-cell HIV entry, the G-protein coupled chemokine receptor CXCR4 represents an attractive target for anti-retroviral drugs; however, the 3D pharmacophore for binding of CXCR4 antagonists remains elusive. We have performed an exhaustive systematic exploration of the conformational space for 11 cyclopentapeptide CXCR4 antagonists of the type *c*(Gly^1-D-Tyr^2-L/D-Xaa^3-L-Arg^4-L/D-Nal^5), where Xaa^3 = Ala, D-Ala, NMe-Ala, D-NMe-Ala, Pro, D-Pro, Arg, and *cis*/*trans*-4-guanidino-Pro, as well as for four retro-inverso cyclopentapeptide analogs. By comparing the resulting low-energy conformations using different sets of atoms, we identified specific conformational features common only to the compounds with high/medium affinity. These features included the spatial arrangement of the three most important pharmacophoric side chains Tyr^2, Arg^4, and Nal^5 as well as the orientation of the Xaa^3-Arg^4 amide bond, which together represent a “minimalistic” 3D pharmacophore model for binding of cyclopentapeptide antagonists to CXCR4 [1]. The model enables rationalization of biological data for cyclopentapeptides as well as for the peptidomimetic CXCR4 antagonist KRH-1636.

The high/medium affinity cyclopentapeptides in conformations corresponding to the deduced 3D model were subsequently docked to a model of the CXCR4 transmembrane helix bundle obtained by homology modeling. Only two binding modes common for all ligands were identified in the docking procedure. Interestingly, a salt bridge between the crucial Arg^4 of the ligand and Glu288, an important residue for the HIV co-receptor function of CXCR4, was seen in both of these modes. The other pharmacophoric groups of the ligand were also involved in favorable interactions with their counterparts in CXCR4. These findings give additional support for the suggested 3D pharmacophore model, and also provide a guide for rational design of CXCR4 mutants to map potential contacts with small peptide ligands.

[1] Våbenø J, Nikiforovich GV, Marshall GR. A minimalistic 3D pharmacophore model for cyclopentapeptide CXCR4 antagonists. Biopolymers (Pept Sci) 2006; in press.

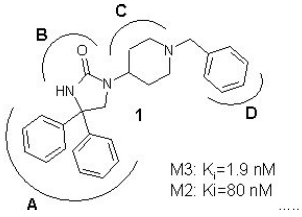
O10

Diarylimidazolidin-2-one derivatives: a novel class of selective muscarinic M3 receptor antagonists

I. Peretto*, C. Fossati*, G. Giardina*, A. Giardini*, E. La Porta*, P. Petrillo*, S. Radaelli*, L. Radice*, L. Raveglia*, E. Santoro*, F. Scarpitta*, A. Rizzi**, E. Armani**, G. Amari**, B. Imbimbo**

*NiKem Research Srl. via Zambeletti 25, 20021 Baranzate (Milan), Italy. **Chiesi Farmaceutici S. p. A. Via Palermo 26/A, 43100 Parma, Italy

Muscarinic receptors belong to the GPCR superfamily and are activated by acetylcholine. Five different muscarinic receptor subtypes have been cloned. The M_3 Receptor (M3R) subtype is mainly expressed in smooth muscle, salivary glands and blood vessels. M3R is involved in many pathological states such as urinary incontinence, irritable bowel syndrome, asthma and chronic obstructive pulmonary disease. Notwithstanding the high potential of M3R antagonists, relatively few drugs with this mechanism of action have been developed, mainly due to the significant side effects associated to the lack of selectivity *versus* other muscarinic receptor subtypes (particularly M2R involved in vagal control of heart rate and contraction). Aim of our study was the identification of novel M3R antagonists, selective towards M2R, showing optimized developability profile.



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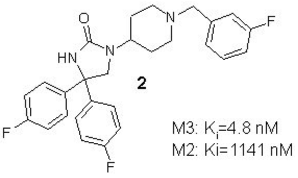

2

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After developing a pharmacophore model based on known M3R antagonists, a number of novel chemical scaffolds were selected and small arrays were synthesized around each scaffold. Biological evaluation of these compounds allowed identifying compound **1** that showed high M3R affinity (K_i = 1.9 nM) and a 40 fold selectivity towards the M2R (K_i = 80 nM). A multiparametric (potency, selectivity, early ADMET) lead optimisation program was started around compound **1**, the four regions A-D being investigated. This investigation culminated with the discovery of compound **2** (M3R K_i = 4.8 nM, M2R K_i = 1141 nM, low intrinsic clearance in rat and human microsomes, high Caco-2 membrane permeability). The versatility of the discovered scaffold allowed several structural modifications that resulted in modulation of the selectivity profile as well as optimization of developability parameters and of chemical-physical properties suitable for different routes of administration.

O11

TAC-Scaffolded Peptides for Mimicry of Antibodies

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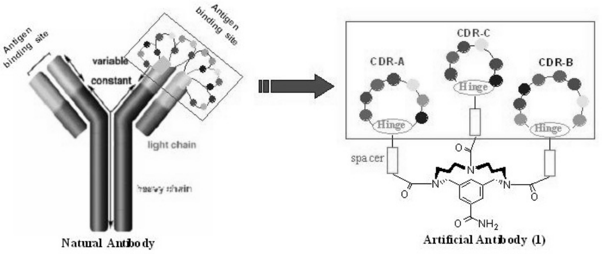
Department of Medicinal Chemistry, Utrecht Institute for Pharmaceutical Sciences, Utrecht University; The Netherlands

Protein-protein interactions play an essential role in many biological processes. One interesting example of these interactions is the antibody-antigen interaction. The antigen binding site of an antibody contains six hipervariable peptide loops so-called Complementary Determining Regions (CDR's), responsible of the recognition of the antigen. The generation of synthetic molecules capable of mimicking the CDR's of an antibody represents a promising strategy to understand and even further modulate the interaction with the antigen. However, mimicry of an antibody is still a big challenge. For this goal, promising scaffolded peptides can be used. They present different protein fragments in a discontinuous way. Among the few suitable scaffolds, the TriAzaCyclophane (TAC), developed in our group, contains three semi-orthogonal protecting groups which allow the site-selective attachment of peptide fragments to the scaffold molecule. Thus, cyclic peptide fragments can be presented by TAC.

Convergent solid phase synthesis for the preparation of TAC-scaffolded cyclic CDR's is herein described.



[1] Opatz, T.; Liskamp, R. M. J. *Org. Lett.* **2001**, *3*, 3499-3502.

[2] Monnee, M.C.F.; Brouwer, A.J.; Verbeek, L.M.; van Wageningen, A.M.A.; Liskamp, R.M.J. *Bioorganic & Med. Chem. Lett.*, **2001**, *11,* 1521-1525.

[3] Opatz, T.; Liskamp, R. M. J. *J. Comb. Chem.* **2002**, *4*, 275-284.

[4] Chamorro, C.; Hofman, J.-W.; Liskamp, R. M. J. *Tetrahedron.* **2004**, *60*, 8691-8697

[5] Monnee, M.C.F.; Brouwer, A.J.; Liskamp, R.M.J. *QSAR*, **2004**, *23,* 546-559

O12

Heterobiaryl hydroxamic acids as potent inhibitors of histone deacetylase (HDAC) possessing significant anti-proliferative cellular activity.

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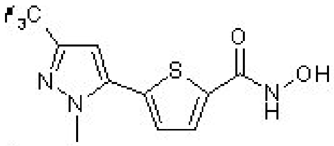
Argenta Discovery, 8/9 Spire Green Centre, Flex Meadow, Harlow, Essex, CM19 5TR, UK

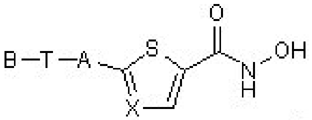
Over recent years a number of small molecule HDAC inhibitors have been progressed into the clinic as potential anti-cancer agents [1]. The majority of these compounds contain a hydroxamic acid zinc binding group which has resulted in an extremely crowded intellectual property (IP) arena around such HDAC inhibitors. A virtual screening exercise conducted at Argenta identified the heterobiaryl hydroxamic acid ADS100380 as a novel weak HDAC inhibitor [2]. The subsequent design and synthesis of several novel heterobiaryl hydroxamic acid series (**1**) [2-4] has identified compounds that possess improved HDAC inhibitory activity. In addition, these compounds are able to inhibit the proliferation of a range of tumour cell lines, and provide a range of physicochemical, eADME and pharmacokinetic properties.



ADS100380

HDAC IC_{50}= 0.75 µM

MCF-7 IC_{50}= 11.4 µM



(**1**)

A = Heteroaromatic

B = Aromatic

T = tether (1-5 atoms)

X = N or CH

[1] Marks, P. A.; Dokmanovic, M. Histone deacetylase inhibitors: discovery and development as anticancer agents. Expert Opinion on Investigational Drugs 2005, 14(12), 1497-1511.

[2] Substituted thienyl-hydroxamic acids as histone deacetylase inhibitors. Price, S.; Bordogna, W.; Clark, D. E.; Dyke, H. J.; *et al.* WO 2004013130.

[3] Substituted thienyl-hydroxamic acids having histone deacetylase activity. Price, S.; Bordogna, Dyke, H. J.; *et al.* WO2005014588.

[4] Thiazolyl-hydroxamic acids and thiadiazolyl-hydroxamic acids, and use thereof for treating diseases associated with histone deacetylase enzymatic activity. Price, S.; Bordogna, W.; Dyke, H. J.; *et al.* WO2005075469.

O13

Laying the Loops: Automated GPCR Loop Modeling and Its Implications on Structure-Based Virtual Screening

C. De Graaf, D. Rognan

Bioinformatics of the Drug, Laboratoire de Pharmacochimie et de la Communication Cellulaire, CNRS UMR 7175-LC1 - Université

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G protein-coupled receptors (GPCRs) constitute a superfamily of transmembrane proteins of outmost pharmaceutical importance. Knowledge of the three-dimensional structure of GPCRs can provide important insights into receptor function and receptor-ligand interactions, and can be used for the discovery and development of new drugs.

GPCRs share a common membrane topology, with an extracellular N terminus, a cytoplasmic C terminus, and 7 transmembrane helices (TMs) connected by 3 intracellular (ICLs) and 3 extracellular loops (ECLs). In most of the cases, the ligand binding cavity is delimited by the 7 TM domains. Our original in-house database of high-throughput human GPCR models only include the 7 TMs. These models have already been shown to be suitable for in silico inverse screening purposes [1], and for detecting key residues that drive ligand selectivity [2]. In many GPCRs however, also extracellular residues, especially those in ECL2, may participate in ligand binding.

We have set up a high-throughput modeling procedure for the construction of the second extracellular loop of most human GPCRs. Our loop modeling flowchart is based on the alignment of essential residues determining the particular ECL2 fold observed in the bovine rhodopsin crystal structure. For a set of GPCR targets, the implications of including ECL2 is evaluated in terms of structure-based virtual screening accuracy: the suitability of the 3D-models to distinguish between known antagonists and randomly chosen drug-like compounds using automated docking approaches.

[1] Bissantz C, Logean A, Rognan D. High-throughput modeling of human G-Protein Coupled Receptors: Amino acid sequence alignment, three-dimensional model building, and receptor library screening. J Chem Inf Comput Sci 2004;44:1162-1176.

[2] Surgand J-S, Rodrigo J, Kellenberger E, Rognan D. A chemogenomic analysis of the transmembrane binding cavity of human G-Protein-Coupled Receptors. Proteins 2006;62:509-538.

O14

Investigation of the lipophilic behavior of the PPAR-γ ligands Thiazolidinediones as an important issue for their action

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Thiazolidinediones (TZDs) represent a new class of oral anti-diabetic agents approved for the treatment of type 2 diabetes mellitus, mediating their action via the nuclear receptor and transcription factor peroxisome proliferator-activated receptor gamma (PPAR-γ) [1]. The understanding of TZDs mechanism of action and its bioavailability is essential for the development of next generation analogous drugs. Physicochemical properties and especially lipophilicity constitute a useful tool in Drug Design, playing an important role in the pharmacokinetic, pharmacodynamic and toxicological profile of drugs. The aim of the present study was to investigate the lipophilicity profile of five TZDs: Troglitazone, Ciglitazone, Pioglitazone, Rosiglitazone and Netoglitazone. For this purpose direct octanol-water partitioning experiments were performed to determine distribution coefficients logD. For Pioglitazone and Rosiglitazone, which are ampholytes forming zwitterionic species, the logD /pH profile was monitored in a broad pH range and a bell shaped curve was obtained for both compounds, showing a fairly stable lipophilicity in the pH range 6-7.4. Extrapolated retention factors were determined by reverse-phase HPLC using a BDS column ($\log k_{wBDS}$) and by Immobilized Artificial Membrane Chromatography (IAM) using an IAM.PC.DD2 column ($\log k_{wIAM}$). Differences in the lipophilicity of the TZD analogues were observed for octanol-water and reverse-phase HPLC systems, while a lower degree of differentiation was obtained by IAM Chromatography.The differences in logD and $\log k_{wBDS}$ values of TZDs were found to reflect differences in their biological activity as well. In particular, comparison with literature EC_{50} transactivation data revealed a decrease in activity with increase in lipophilicity.

[1] Willson TM., Brown PJ, Sternbach DD, Henke BR, The PPARs: From Orphan Receptors to Drug Discovery, J Med Chem 2000; 43: 527-550.

O15

Molecular Dynamics Simulation and Essential Dynamics Analysis of the Farnesoid X Receptor (FXR). Differential Response upon Binding of Agonists, Partial Agonists and Antagonists

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Farnesoid X Receptor (FXR), a nuclear receptor activated by bile acids, is emerging as a central player in an intricate regulatory network controlling lipid, glucose and energy metabolism. The deeper understanding of the physiological role of FXR, as well as the potential for its therapeutic exploitation requires the availability of ligands able to selectively activate individual gene(s) among the wide variety which are targets for FXR activation. As a part of a wider project aiming at the identification of potent and selective modulators of FXR, we report here molecular dynamics simulations of the interaction between the FXR ligand binding domain and three potent modulators endowed with the profile of full agonist, partial agonist, and antagonist, respectively. Principal component analysis (PCA) of the covariance matrix constructed from individual trajectories (> 5 ns each) permitted the isolation of a few low-frequency essential motions in the protein structure in response to ligand binding. A significant yet quite unexpected feature that emerged from the essential dynamics calculation is that the concerted internal motions of the LBD of ligand-bound FXR is basically limited to fluctuation in the region comprising the loop H1-H2, the bottom of H3, and the top of H5 (the receptor's 'backdoor'). Interestingly, the crucial H12 showed limited movements in all the three simulations, thus pointing forward that, at least under the simulation's condition, is not the H12 displacement that determines the change in profile from agonism to antagonism. This appears even clearer when the trajectories were concatenated and analysed by PCA. Finally, the analysis of the r.m.s.d of individual residues allowed to unravel the differential motion of distinct micro-domains in response to agonist, partial agonist, and antagonist binding. These information are consistent with the known S.A.R of FXR modulators and can be translated into the design of novel selective modulators

O16

In Silico ADME Modelling : Computational Models to Predict Human Serum Albumin Binding Affinity Using Ant Colony Systems

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The binding affinity of new chemical entities (NCE's) to Human Serum Albumin (HSA) is one of the important ADMET properties considered in drug discovery and development. Modelling of in vitro HSA binding data of 94 diverse drugs and drug-like compounds is performed to develop global predictive models that are applicable to the whole medicinal chemistry space. For this aim, ant colony systems, a stochastic method along with multiple linear regression (MLR) is employed to exhaustively search and select multivariate linear equations, from a pool of 327 molecular descriptors. This methodology helped us to derive optimal quantitative structure-property relationship (QSPR) models based on five and six descriptors with excellent predictive power. The performance of our models is compared with other reported models in literature. From the analysis of the physical meaning of the selected descriptors, it is inferred that the binding affinity of small organic compounds to human serum albumin is principally dependent on the following fundamental properties: 1) hydrophobic interactions 2) solubility 3) size and 4) shape. Finally, as the models reported herein, are based on computed properties, they appear a valuable tool in virtual screening, where selection and prioritisation of candidates is required. The presentation will discuss the predictive approaches employed by us and the scope and limitations of our models for virtual screening studies.

O17

Speeding up chiral purification in support of medicinal chemistry

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To assert that 40% of compounds under development in the pharmaceutical industry today are chiral is a conservative estimate. Oftentimes, these compounds are purified rather than being produced by chiral-specific synthesis. However, the volume of samples for purification can create a bottleneck in the discovery process. The first step in the chiral purification process is to screen numerous separation methods for selectivity at the analytical scale, followed by scale-up to preparative or semi-preprep. scale. In this paper we describe how an analytical laboratory can speed up chiral method development using specialized software. The software accumulates, evaluates, and links chemical structures to chromatographic methods. This database of information can be accessed and searched to prioritize purification methods for subsequent samples thus reducing the amount of time required to collect and review data, and allowing timely delivery of results to chemists.

O18

Carbamates derivatives as in vivo active 5-HT4 receptor antagonists

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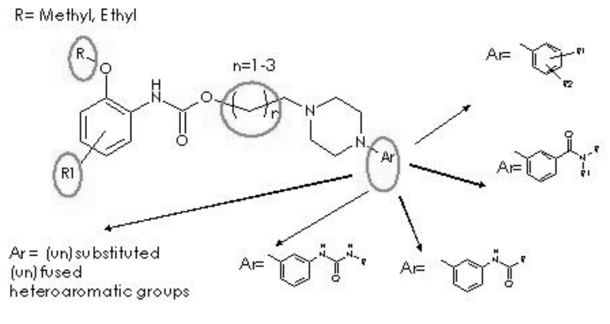
The pattern of expression of human 5-HT4 receptors (members of the G protein coupled receptor family (GPCRs)), as well as their functional activity, support the use of 5HT4 ligands in multiple therapeutic indications.

5-HT4 receptor antagonists have been proposed as potential therapeutic agents for the treatment of urinary incontinence associated with detrusor muscle hyper contractility, atrial fibrillation, visceral pain and gastrointestinal disorders.

Using the Cerep technology platform, we have identified a series of antagonists, showing high affinity for the 5-HT4 receptor. Selectivity and ADME properties were optimized. This poster will highlight the strategic approaches of the project, combining parallel synthesis and medicinal chemistry. *In vitro* binding, pharmacological profiles and *in vivo* data will be shown.



O19

2-{6-Chloro-5-[4-(4-Fluoro-benzyl)-2R,5S-dimethyl-piperazine-1-carbonyl]-1H-indol-3-yl}-2-oxo-acetamides as Potent Inhibitors of p38 α- MAP Kinase

J. Perumattam, B. Mavunkel, S. Chakravarty, Q. Lu, G. Luedtke, A. Protter, L. Higgins, M. Laney, D. Liu, G. Schreiner, S. Dugar

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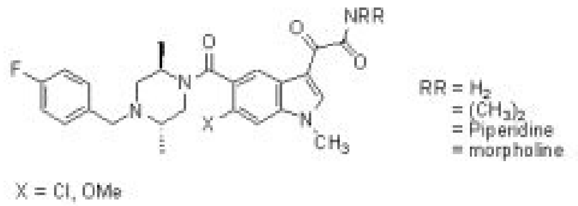
Inhibition of p38α kinase is evolving as an approach to the discovery of new anti-inflammatory agents. Inhibitors of this enzyme modulate cytokine production, especially proinflammatory TNF-α and IL-1. These cytokines and others mediate a wide spectrum of diseases, notably rheumatoid arthritis. While chronic inflammation was the early focus

for the development of p38α kinase inhibitors, there are several new reports and efforts that speak of the potential utility of such inhibitors in more acute inflammatory states. There is a growing body of evidence that elucidiates the benefits of inhibiting p38α kinase in the treatment of diseases such as diabetes, cancer and acute myocardial infarctions. In this presentation we discuss the discovery and development of a new class of orally active p38α MAP kinase inhibitors.



1. Babu J. Mavunkel, Sarvajit Chakravarty, John J. Perumattam, Gregory R. Luedtke, Xi Liang, Don Lim, Yong-jin Xu, Maureen Laney, David Y. Liu, George F. Schreiner, John A. Lewicki and Sundeep Dugar, Indole-based Heterocyclic Inhibitors of MAPa Kinase: Designing a Confirmationally Restricted Analogue, Bioorganic & Medicinal Chemistry Letters, 13 (2003) 3087-3090.

O20

A New Drug Delivery System Consisting of Caged Compounds and Sugars Attached at the Peripheries of Dendrimers

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Whereas “caged compounds” are usually used for the study of the mechanism of biological processes, we have tried to use them as a new type of prodrugs that recover their pharmaceutical activity upon irradiation. To upgrade the caged compounds to more sophisticated drug delivery systems that can deliver drugs to target cells efficiently, we modified them by attaching with particular sugars that can be recognized by the lectins. For determination of the inter-sugar distance suitable for the most efficient multipoint binding of the sugars to the lectins, we used the peripheries of dendrimers of various generations modified with sugars and caged compounds. In this paper, we will report the design and synthesis of the sugarball-type dendritic compounds prepared from DAB dendrimers and newly designed polyester dendrimers. Throughout our study, we used Leu-Leu-OMe as a drug and mannose as a sugar. The former is known to induce apoptosis to macrophages that have lectin receptors for mannose.

β-Carboxy-(2-nitro-5-mannopyranosyl)benzyl-caged Leu-Leu-OMe was incorporated into the peripheries of DAB dendrimers (G-0 to G-4), and their photochemical properties were examined. All of them released Leu-Leu-OMe upon irradiation at 350 nm. Using a series of our dendritic compounds, the multivalent binding to multiple binding sites of *Concanavalin A* was found to be most efficient in G3 dendrimer, less efficient in G1, G2 and G4, and negligible in G0. Uptake of these dendrimers into mouse peritoneal macrophages was confirmed by using fluorescent-labeled analogues.

O21

FORSKOLINS - Enhancement of Activation of Tumor Suppressor Protein Phosphatase 2A to Prevent Leukemogenesis

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Forskolin, a unique adenylate cyclase activator, was clinically considered in the 1980s for the treatment of congestive cardiomyopathy, glaucoma and bronchoconstriction [1]. In the 2000s, it is, however, its activation of protein phosphatase 2A (PP2A) that has been invoked for the inhibition of the oncogenic BCR-ABL kinase, thereby impairing leukemogenesis in blast crisis chronic myeloid leukemia (BC-CML) [2]. Additionally, 1,9-dideoxyforskolin, which lacks adenylate cyclase activating properties, also displayed similar antileukemic effects as forskolin [2].

Over a 30-year period, structure-function studies of several hundreds of analogs of forskolin have resulted in compounds with specificity of action against different membrane proteins, including the glucose transporter, the multidrug transporter, and ion channel proteins through mechanisms that do not involve the production of cAMP [1,3].

This report critically analyses and reviews the different structural variants of described forskolin analogs and the multiple sites of protein action affected by them. It arrives at optimal structural designs with potential selectivity to be specific for pharmacologic enhancement of PP2A activation in the Yin-Yang role played by BCR-ABL and PP2A in BC-CML, conducive to the potential prevention of leukemogenesis.

[1] N. J. de Souza, Forskolin – An Example of Innovative Drug Research on Natural Products in Innovative Approaches in Drug Research, A.F.Harms(Editor), Elsevier Science Publishers B.V., Amsterdam, 1986, pp. 191–207and references therein.

[2] P. Neviani, R. Santhanam, R. Trotta, M. Notari, B.W.Blaser, S. Liu, H. Mao, J.S. Chang, A.Galietta, A. Uttam, D. Roy, M. Valtieri, R. Bruner-Klisovic, M.A.Caliguri, C.D. Bloomfield, G. Marcucci and D. Perrotti, The tumor suppressor PP2A is functionally inactivated in blast crisis CM L through the inhibitory activity of the BCR/ABL regulated SET protein. Cancer Cell 2005;8:355-368 and references therein.

[3] Diane I. Morris, Joan Robbins, Arnold E. Ruoho, Elizabeth McHugh Sutkowski and Kenneth B. Seamon. Forskolin Photoaffinity Labels With Specificity for Adenylyl Cyclase and the Glucose Transporter. J. Biol.Chem. 1991;266:13377-13384

O22

Combining label free techniques and virtual screening for identification of hits and leads

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Following the success of the genomics era, proteomics is now opening up new possibilities for identifying novel target proteins. Virtual screening can be performed using binding site information from the 3D-structure, or if a natural binder and/or known drugs can be used to construct a pharmacophore model. If the 3D-structure of the target is unknown, or if the natural binder is unstable or difficult to label, screening methods based on labeling are not possible. Label free screening (LFS) methods are therefore an interesting alternative also for such difficult targets. The throughput of LFS is currently around 10 000 compounds/week, making it suitable for selected diversities, target-focused and fragment libraries. For orphan receptors, a strategy is proposed where LFS and virtual screening are used iteratively. A set of target proteins (n = 2-16) are first screened against an appropriate library to generate selectivity data. The number of unique binding sites on each target is then identified using competition experiments. The target-selective and binding site-specific compounds provide the basis for construction of pharmacophore models. Virtual screening is performed using the pharmacophores and new, structurally similar compounds are identified from the in-house library or available chemical directory. The LFS steps are repeated and the pharmacophore model(s) is validated and improved, enabling a new virtual screen. When a significant number of compounds are identified, they are further characterized by measuring on/off-rates and affinity. Target and binding site selectivity (on/off/K_D) is used as driving force for SAR and QSAR studies. Data will be presented to show that compounds selected using such a strategy express strong potency in a cell-based activity assay.

O23

A novel approach to treating dyslipidemia: development of PGD2 receptor 1 antagonists to suppress niacin-induced flushing

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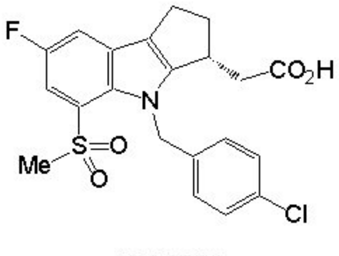
Niacin is commonly used to effectively treat dyslipidemia, but its widespread use has been limited by symptoms of flushing, which consist of cutaneous vasodilation with associated discomfort. It has been shown that niacin greatly increases the plasma levels of prostaglandin D2 (PGD2), and that the skin is the major source of this vasodilatory prostanoid after niacin treatment. These results led to the hypothesis that PGD2 generation in the skin drives niacin-induced flushing through activation of PGD2 receptors (DP1 and/or DP2). We will describe the development of a DP1 selective antagonist (MK-0524) and demonstrate that MK-0524 can significantly suppress niacin-induced vasodilation in a mouse model. Some preliminary clinical results of treatment with MK-0524 to suppress symptoms of niacin-induced flushing will also be presented.



MK-0524

O24

Plants Proteins/Peptides as Natural Antibiotics to Combat the Infectious and other Diseases

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Microbial infections and other diseases emerged as a growing threat to human health and agricultural domain. Bioactive compounds hold promise in combating microbial infections.The increasing recognition of microbial infections, difficulties encountered in their treatment and the toxicity associated with synthetic drugs, has stimulated the search for therapeutic alternatives. In the present study some traditionally used indigenous medicinal plants viz *Hygrophila auriculata*, *Abrus precatorius*, *Moringa oleifera*, *Croton tiglium, Withania somnifera*, *Solanum nigrum*, *Psoralae corylifolia* and *Ocimum basilicum* were evaluated for bioactivities petides/proteins as antifungal against *Aspergillus niger, Mucor mucedo, Fusarium solani, Ganoderma lucidum* and antibacterial against *Bacillus subtilus*, *Pasturella multocida, Escherichia coli*. A number of crude extract as well as purified peptide exihibited significantly high antifunfal and antibacterial activities. The carcinogenicity by Ames test and antioxidant enzymes like peroxidases (POD), catalases (CAT), superoxide dismutase (SOD) and the proteases were also quantified in the leaves and seeds of the plants under investigation. Moreover organic antioxidants, total phenolics content, inorganic antioxidant elements were also evaluated in the leaves, seeds, roots and stems of the plants. The antimicrobial, antioxidant, carcenogenicity studies of these medicinal plants demonstrated their potent therapeutic ability which might be explored for the treatment of different human and plant diseases

O25

Conformational plasticity of kinases: molecular dynamics simulation of the conformational changes in the activation loop and the PSSARLE helix of Cdk5

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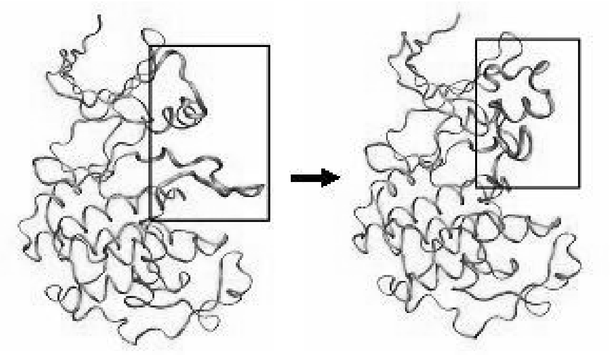
Cyclin-dependent kinases (CDKs) are mostly known for their role in the cell cycle regulation. The activation mechanism of all CDKs involves the association with a regulatory protein, generally a cyclin, that binds to the kinase unit and stabilizes a catalytically active conformation. Active and inactive conformations of CDKs are characterized by the different spatial localization of two typical elements, namely the activation loop and an a-helix, whose amino-acid composition varies throughout the family.

Extensive X-ray crystallographic studies carried out in recent years allowed to elucidate the 3D structure of both the active and inactive CDK conformations, but the details of the conformational change remained elusive. Yet, it is generally accepted that specific CDK inhibitors will be obtained only exploiting the subtle structural differences existing among the protein family members [1].



Considering Cdk5, a neuronal CDK whose deregulation has been associated with the neurofibrillary tangles formation in Alzheimer's disease, we aimed at modeling the conformational transition with a particular attention at finding possible stable intermediate states. To pursue this goal, different molecular dynamics-based tools were employed, like classical molecular dynamics, essential dynamics, and the recently developed metadynamics [2].

[1] Noble M, Barrett P, Endicott J, Johnson L, Bruned C, McDonnell J, Robertson G, Zawaira A. Exploiting structural principles to design cyclin-dependent kinase inhibitors. Biochim Biophys Acta 2005;1754:58-64.

[2] Laio A, Parrinello M. Escaping free-energy minima. Proc Nat Acad Sci USA 2002;99:12562-12566.

O26

Solid Phase Synthesis of Polyamine Spider Toxins JSTX-3 and ArgTX-636 and Their Analogues

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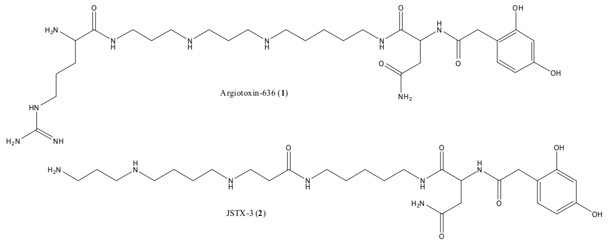
Polyamine spider toxins represent a diverse class of neuroactive compounds, including Argiotoxin-636 (**1**), and Joro spider toxin JSTX-3 (**2**). These compounds non-competitively antagonize Ca2+-permeable ionotropic Glutamate receptors (iGluRs)[1]. Their high specificity and potency lend them to be excellent lead compounds for the design of neuroprotective agents. To this end, we developed the first synthesis of polyamine spider toxins ArgTX-636 and JSTX-3 and their analogues on solid phase. The synthesis incorporated a variety of solid- and solution-phase techniques including reverse peptide couplings (NàC direction) and selective amine alkylation strategies. We were thus able to examine the role of the individual functionality within the polyamine and peptide portions of these compounds.



Argiotoxin-636 (**1**)

JSTX-3 (**2**)

This allowed us to build a small library of functionalized polyamines, enabling the elucidation of the structure-activity relationship for this ever-important class of substances. Reactions were optimized to develop a robust, routine synthesis of these compounds and to exploit them for their full potential in the synthesis of a diverse class of potential iGluR antagonists.

[1] Strømgaard, K. and I. Mellor, AMPA Receptor Ligands: Synthetic and Pharmacological Studies of Polyamines and PolyamineToxins. Medicinal Research Reviews, 2004. 24(5): p. 589-620.

O27

Potent Selective GABAC Receptor Antagonists

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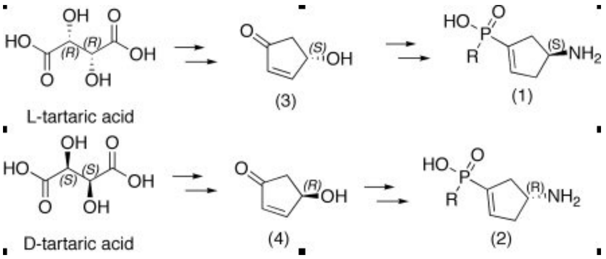
The amino acid γ-amino butyric acid (GABA) is the major inhibitory mammalian neurotransmitter and mediates both ionotropic and metabotropic transmission via three subclasses of neuroreceptors. Ionotropic transmission is mediated by ligand gated ion channels (LGICs). GABA$_A$ receptors are heterooligomeric LGICs whereas GABA$_C$ are homooligomeric LGICs.

GABA$_C$ receptors are possible therapeutic targets in the areas of myopia and cognition enhancement^1. In order to maximise beneficial therapeutic effects, subtype selective compounds have become desirable targets. TPMPA^2 was the first GABA$_C$ selective compound and is a conformationally restricted, phosphinic acid analogue of GABA.

Here, the synthesis of enantiomerically pure S and R-4-aminocyclopent-1-ene (alkyl)phosphinic acids is presented (1 and 2 respectively). L and D-tartaric acid were used to produce S and R-hydroxycylopent-2-en-1-one (3 and 4 respectivley), which was reacted as previously reported to give the title compounds.



Pharmacological evalution of these compounds was carried out via functional assays using 2-electrode voltage clamp methods on recombinant GABA$_C$, GABA$_A$ and GABA$_B$ receptors (coexpressed with Kir 3.1 and Kir 3.4 K$^+$ channels) in *Xenopus laevis* oocytes. These assays indicate that the S-isomer is signifigantly more potent than the R-isomer at GABA$_C$ ρ_1 receptors (R=Me, Ki = 0.78 μM vs 18.8 μM), and that these compounds are the most potent and selective GABA$_C$ antagonists currently known.

[1] Johnston GAR, Chebib M, Hanrahan JR, Mewett.KN, *Current Drug Targets: CNS & Neurological Disorders,* **2**, 265 (2003).

[2] Murata Y, Woodward RM, Miledi R, Overman LE, *Bioorg. Med. Chem.Lett.,* **6**, 2073 (1996).

O28

Synthesis and evaluation of a library of small molecules as inhibitors of DNA methyltransferases or thymidilate synthases

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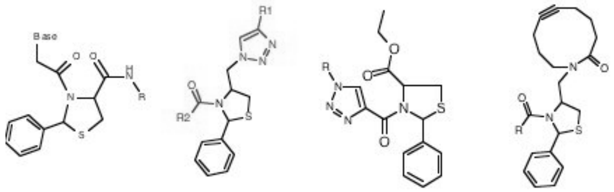
*Unité de Pharmacologie Chimique et Génétique U 640 INSERM UMR 8151. École Nationale Supérieure de Chimie de Paris, 11 rue Pierre et Marie Curie, 75231 Paris, France. Faculté de Sciences Pharmaceutiques et Biologiques, 4 avenue de l'Observatoire 75270 Paris, France. **Laboratoire de Génomique et de Physiologie Microbienne

Université Paris Sud XI Faculté des Sciences d'Orsay-Bâtiment 409 - 91405 Orsay, FranceChemical genetics is an emerging method positioned at the interface between chemistry and genetics and consists on the use of small molecule libraries in order to study biological systems. As in classical genetics, we can distinguish two different approaches in chemical genetics : forward and reverse chemical genetics. Forward chemical genetics involves the use of small molecules to screen for a desired phenotypic effect on the biological system under investigation, whereas reverse chemical genetics uses the library against a specific protein in order to determine the phenotypic effect of a disruption caused by a ligand/protein interaction[1],[2],[3].

We sought to develop a strategy that uses the reverse approach where targeted proteins are DNA methyltransferases and thymidylate synthases as their inhibition can lead to an anticancer therapy.

The library that we have synthesized can be organized around four scaffolds :



We will present the synthetic pathways that lead to these structures. Data on screening will also be provided as classical enzymatic tests were used for thymidilate synthases and high throughput screening methods have been settled for the evaluation of the inhibition of DNA methyltransferases.

[1] Spring D., *Chem. Soc. Rev.*, **2005**, *34*, 472-482

[2] Smukste I., Stockwell B.R.*, Annu. Rev. Genemics Hum. Gen.*, **2005**, *6*, 261-286

[3] Stockwell B.R., *Nature Reviews*, **2000**, *1*, 116-125

O29

Novel sulfonyl-phenyl-ureido benzamidines as potent antimalarial agents

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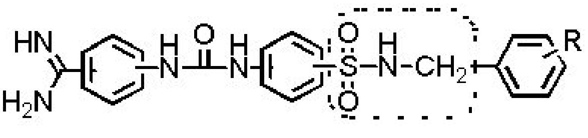
We were able to develop a new class of compounds which posses high activity vs. multidrug-resistant P. falciparum strains with IC50 as low as 7 nm [1].The compounds showed no cytotoxicity in an assay with a liver cell line and no mutagenicity in the AMES assay, but displayed poor pharmacokinetic properties when tested in vivo. In particular, in vitro metabolic studies showed an early cleavage by hepatic enzymes at the level of the sulfonylaminomethylene moiety.



To improve the poor PK properties of these substances, structural modifications were introduced to the lead structure, mostly focusing on and "around" the metabolic labile bond. These new compounds, with their antimalaria activities and metabolic properties will be presented.

[1] Leban J, Pegoraro S, Dormeyer M, Lanzer M, Aschenbrenner A, Kramer B. Sulfonyl-phenyl-ureido benzamidines: a novel structural class of potent antimalarial agents. Bioorg. Med. Chem. Lett. 2004;14:1979-1982.

O30

Rapid drug discovery by systematically scanning diversity space: Identification of preclinical candidates targeting SSTR's

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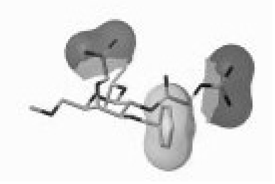
Monosaccharides are excellent scaffolds for creating peptide mimetic bioactive small molecules. Since the early pioneering work from Hirshmann et al [1], many such examples have been published utilising various monosaccharide building blocks and associated chemistries.

Alchemia has developed a drug discovery approach based on carbohydrate scaffolds [2], that has facilitated the identification of preclinical candidates for its anti-cancer and AMD drug discovery programmes. The approach involves the production of systematic scanning libraries, where each compound in the library carries the required binding elements in a different topology and where the library as a whole systematically 'covers' the full structural diversity space. Controlled variation in topology is enabled by the presence of five functionalised stereo-centres, providing a versatile 3D-platform for appending a selection of binding elements in a great variety of ways.

The strategy will be exemplified using the development of somatostatin agonists, including *in vitro* receptor affinity and ADME data , and *in vivo* PK and efficacy results.



[1] Hirschmann, R.; Nicalou, K. C.; Pietranico, S.; Salvino, J.; Leahy, E. M. et al. Nonpeptidal Peptidomimetics with a b-D-Glucose Scaffolding. A Partial Somatostatin Agonist Bearing a Close Structural Relationship to a Potent, Selective Substance P Antagonist. J. Am. Chem. Soc. 1992; 114: 9217-9218.

[2] Le Thanh, G. A., G.; Becker,B.; Grathwohl,M.; Halliday,J.; Tometzki,G.; Zuegg,J. and Meutermans,W. Molecular diversity through sugar scaffolds. Drug Discovery Today 2003; 8: 701-709.