

Biographies & Abstracts

UK-Singapore Symposium on Contemporary Strategies and Practices in Medicinal Chemistry
8 September 2011, Biopolis, Singapore



Prof. Adam Nelson
University of Leeds, UK

Adam Nelson is Professor of Chemical Biology at the University of Leeds, UK. He obtained a BA in Natural Sciences from Churchill College, University of Cambridge in 1993, and his PhD (under the supervisor of Dr Stuart Warren) in Synthetic Organic Chemistry, also from Cambridge, in 1996. He undertook postdoctoral research with Prof. E. J. Thomas at the University of Manchester before joining the academic staff at the University of Leeds in 1998. He is currently the Director of the Astbury Centre for Structural Molecular Biology, an interdisciplinary research centre that brings together >250 researchers at the life/physical science interface at the University of Leeds. Professor Nelson has broad research interests at the interface between chemistry and biology. Current projects focus on the development of synthetic methods for the systematic exploration of chemical space; the directed evolution of enzymes with synthetically-useful properties; and the discovery of small molecule probes of biological systems. He has been distinguished through the award of the RSC Meldola medal (2001), a Pfizer academic award (2002), an EPSRC Advanced Research fellowship (2004-2009), an AstraZeneca research award in organic chemistry (2005) and the RSC Corday-Morgan medal (2007).

The Development of Synthetic Methods that Allow the Systematic Exploration of Chemical Space

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Our knowledge of the biological relevance of chemical space is based, to a large extent, on its historical exploration by synthesis (and biosynthesis). However, chemists' exploration of chemical space has been uneven and unsystematic: the known organic chemistry 'universe' is dominated by a small number of scaffolds that are found in a large number of small molecules. Developing synthetic approaches that allow broad tracts of chemical space to be explored has proved extremely challenging.

This presentation will describe synthetic approaches that enable the preparation of libraries of diverse small molecules.^[1] Methods which allow the systematic variation of ligand scaffold are particularly rare, and the scaffold diversity of chemical libraries does not approach that of natural products. One of the synthetic approaches that will be described has yielded a small molecule library of unprecedented skeletal diversity. In addition, synthetic approaches that yield compounds based on diverse lead-like scaffolds will also be described.^[2]

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Prof. Martin J Drysdale

The Beatson Institute for Cancer Research, UK

Martin Drysdale received his B.Sc. (1986) and Ph.D. (1990) in chemistry from St. Andrews University in Scotland. From the end of 1989 to 1991 he was a Parke-Davis Neuroscience Post-Doctoral Research Fellow at the PD site in Cambridge, UK and then spent 6 years at Wellcome and GlaxoWellcome in the UK working on projects in the CNS and inflammatory therapeutic areas. In 1997 he joined RiboTargets back in Cambridge UK, then a Biotech start-up company, to head up and develop the chemistry group there working on anti-infective targets. After surviving several rounds of mergers, acquisitions and company name changes he became Director of Chemistry & Structural Science and finally Deputy Director of Research at Vernalis working in the oncology and CNS areas, with a particular interest in Structure Based Drug Design and Fragment Based Methods of hit

identification. In January 2009 he moved to his current position as Head of Drug Discovery at the Beatson Institute for Cancer Research in Glasgow, Scotland.

Fragment Based Hit Identification and Structure Based Approaches to Cancer Drug Discovery

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The use of weak binding "fragments" of molecules is now recognised as an efficient and robust method of hit identification in the drug discovery process. The use and integration of fragment hits into successful lead optimisation is the critical determinant of whether this technology will become accepted as a significant tool in drug discovery. A number of compounds which have evolved using fragment based hit identification are now in phase I-III clinical trials suggesting that this is a technology which will find a permanent place in the armory of the Drug Discovery Scientist.

At the newly established Drug Discovery Programme at the Beatson Institute for Cancer Research we are exploiting the basic biology strengths within the Beatson Institute and wider Cancer Research UK network, to investigate some of the most exciting and challenging cancer targets. Central to our strategy is Fragment-Based Drug Discovery methods and we will use NMR and Surface Plasmon Resonance as primary tools for fragment-based hit identification. I will discuss some results around our initial forays into some of these areas.

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Assoc. Prof. Young-Tae Chang
National University of Singapore, Singapore

Young-Tae Chang was born in Busan, Korea, in 1968. He studied chemistry in Pohang University of Science and Technology (POSTECH, Korea) and received his B.S. in 1991. After one and half years of army service in Korea, he started his graduate study at POSTECH and received a Ph.D. in 1997 under the supervision of Prof. Sung-Kee Chung, working on the divergent synthesis of all possible regioisomers of myo-inositol phosphates. He did his postdoctoral work with Prof. Peter Schultz at UC Berkeley and The Scripps Research Institute. In

2000, he was appointed assistant professor at New York University and promoted to associated professor in 2005. He received the NSF Career award in 2005 and his research interests have been chemical genetics, molecular evolution, and artificial tongues. In September, 2007, he moved to National University of Singapore and Singapore Bioimaging Consortium. He is running Medicinal Chemistry Programme of NUS as the leader, and Lab of bioimaging Probe Development at SBIC, Biopolis. His current research interest is Diversity Oriented Fluorescence Library Approach (DOFLA) for bioimaging probe development. He published more than 185 scientific papers / 3 books and filed 30 patents so far.

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Make invisible visible: a Diversity Oriented Fluorescence Library Approach (DOFLA)

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With the successful result of Human Genome Project, we are facing the problem of handling numerous target genes whose functions remain to be studied. In chemical genetics, instead of using gene knock-out or overexpression as in conventional genetics, a small molecule library is used to disclose a novel phenotype, eventually for the study of gene function. While a successful chemical genetics work will identify a novel gene product (target protein) and its on /off switch, the small molecule complement, and thus chemical genetics promises an efficient "two birds with one stone" approach, the most serious bottleneck of modern chemical genetics is the step of target identification. The currently popular affinity matrix technique is challenging because the transformation of the lead compound into an efficient affinity molecule without losing the biological activity is not easy, requiring intensive SAR studies. To surrogate the well known problem, our group has

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developed a linker tagged library and has successfully identified multiple target proteins so far. While successful, the affinity matrix technique requires a breakdown of the biological system to pool the proteins into one extract, which inherently introduce a lot of artifacts, such as dilution and abolishing the biological environment, etc.

As the next generation of tagged library, we are currently developing fluorescence tagged libraries for in situ target identification and a visualisation of the biological events using Diversity Oriented Fluorescence Library Approach (DOFLA). The basic hypothesis is DOFLA of the same fluorescence scaffold, but with various diversity elements directly attached around the core, may selectively respond to a broader range of target proteins in intact biological system and facilitate the mechanism elucidation and target identification. The high throughput strategy using colourful chemical genetics for stem cell study will be discussed.

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Dr. John E Moses

University of Nottingham, UK

John Moses graduated from the University of Bath in 2001 with a 1st class MChem degree in Chemistry. He next moved to the University of Oxford to pursue a DPhil in synthetic organic chemistry, under the supervision of Sir Professor Sir Jack Baldwin, FRS. In 2004, he undertook postdoctoral studies at The Scripps Research Institute, La Jolla, working with Professor K. B. Sharpless.

His independent research career began in 2005 at The University of London, School of Pharmacy, where he was appointed an RCUK-EPSRC academic fellow in chemical biology/cancer medicinal chemistry. In September 2007, John was appointed to his present position as an Associate Professor in Organic Chemistry at The University of Nottingham. His research interests include biomimetic synthesis; click chemistry; anti-cancer drug discovery and chemical biology. He has co-authored over 45 publications including research articles, reviews, book chapters and patents.

Applications of Click Chemistry in Drug Discovery

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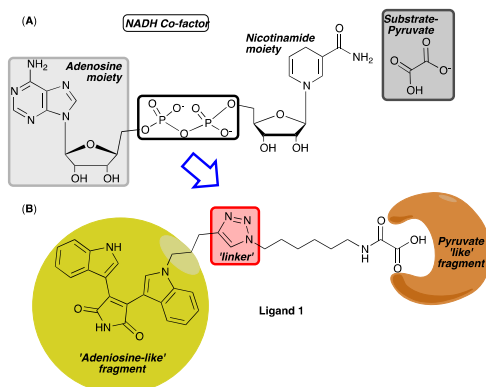


Figure 1: Fragment based approach to LDH-A

Click chemistry is a sensible approach towards chemical synthesis, which relies upon a selection of robust and 'simple' reactions. It enables the rapid and modular synthesis of complex structures in a convenient and 'user friendly' way. In our own studies, we have applied the principles of click chemistry in the design and syntheses of a number of potent and selective ligands against (i) telomerase¹⁻⁵ and (ii) lactate dehydrogenase⁶ A (*h*LDH-A) (Figure 1), both of which have implications in cancer chemotherapy. We will discuss key aspects of these projects and provide a general overview of the principles behind our approach. In particular, we will demonstrate that the 1,4-triazole functional group synonymous with click chemistry is not just a simple linker, but also a useful structural motif for ligand-target interaction.

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Dr. Sebastian Sonntag

Novartis Institute for Tropical Diseases, Singapore

Sebastian Sonntag spent a large proportion of his twenties in various laboratories, mixing chemicals, inhaling toxic fumes and trying to understand quantum mechanics. These pursuits earned him first a diploma in chemistry from the university of Frankfurt in 2001, then a Ph.D. in organic chemistry from the university of Basel in 2005 (with the help of Prof. Helma Wennemers), and finally allowed him to begin his thirties as a post-doctoral researcher at Harvard University (in the lab of Prof. David A. Evans). Thus armed with scholarly knowledge in the fields of conformational analysis and natural product total synthesis, he took a position in the medicinal chemistry group at the Novartis Institute for Tropical Diseases in 2007, where he has been ever since.

Lessons Learned from Dengue Cellular Screening

Cellular screening is a popular approach to finding new starting points in anti-infective research. In antiviral research, cellular screening allows to test compounds for their activity against the virus in the context of the host organism's cells. While less artificial than enzymatic screens, cellular assays are fraught with their own limitations and pitfalls.

The talk will cover examples from our recent hit to lead campaigns based in hits from dengue cellular screening, highlighting the process from the initiation of optimisation to the identification of the target or mode of action.

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Dr. Ed Griffen
AstraZeneca, UK

Ed Griffen received his bachelors degree in 1988 from Imperial College London and studied for his PhD in marine alkaloid synthesis with Professors Charles Rees and Christopher Moody. He joined the research group of Professor Victor Snieckus in 1992 at the University of Waterloo, Ontario as a postdoctoral fellow developing methods in indole metallation and radiometal chelation chemistries. In 1994 he joined Zeneca Pharmaceuticals as a team leader and in 2003 was promoted to the role of Principal Scientist. He has worked in antiinfectives and in the last decade on kinase inhibitors as potential oncology medicines. He is a named inventor on 16 patents, an author on 14 journal publications and is a co-author of a textbook "On Medicinal Chemistry". Ed is a visiting lecturer at the University of Manchester in the medicinal chemistry programme. Recent research work has been in the application of data mining methods to accelerate drug discovery.

Accelerating Drug Discovery by Knowledge based Design

Dr Ed Griffen

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All drug discovery organisations wish to optimise the pharmacokinetic (PK) and toxicological properties of lead compounds rapidly. The optimisation phase of drug discovery is the most chemically resource intensive phase in drug discovery and methods to decide which compounds are to be synthesised are paramount. Broad testing of in vitro and in vivo PK and toxicological endpoints has given large companies massive datasets to analyse. Knowledge based design is the mining and aggregation of this data to produce evidence based "rules" to highlight which structural changes in a molecule are most likely to solve PK and toxicological issues. This lecture will review how we, and others, have developed methods for knowledge extraction and show cases where highly predictive and non intuitive rules have been found in areas such as hERG and Cytochrome P450 inhibition and in vitro metabolic clearance. A view of how these methods could be applied to further accelerate drug discovery will be shared.

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Dr. Anthony William
S*BIO Pte Ltd, Singapore

- **2002:** PhD in Organic Chemistry as a Japanese govt. Fellow (Monbusho) from Tokyo Institute of Technology, Japan. *Prof. Kobayashi Yuichi*
- **2003:** Post Doc. from University of Geneva, Switzerland. *Prof. Peter E Kundig*
- **2004:** Group Leader: Merck & Co., Inc. (formerly Schering-Plough-Singapore)
- **2005:** Team Leader/Project Leader: S*BIO Pte Ltd.

Drove the Kinase chemistry programme at S*BIO and successfully put 3 compounds into clinic

- 1) **SB1518:** *A selective JAK2/FLT3 inhibitor for treatment of Lymphoma and Myelofibrosis in phase 3 clinical trials*
- 2) **SB1317 also known as TG02:** *A novel oral multi-kinase inhibitor of CDKs, JAK2, ERK5 and FLT3 with potent anti-leukemic properties in Phase 1 clinical trials*
- 3) **SB1578:** *A Potent Inhibitor of Janus Kinase 2 (JAK2) for the treatment of Rheumatoid arthritis (RA) in Phase 1 clinical trials*

From bench to clinic: Small molecule Macrocycle SB1518, the first Phase 3-ready clinical candidate from Singapore for the treatment of cancer

Inhibitors of Janus Kinase 2 (JAK2) is an area of very great current interest for the treatment of myelofibrosis, lymphoma and AML as well as other cancer and non-cancer indications (such as rheumatoid arthritis and psoriasis). Much work was initiated in 2005 following the discovery of an activating mutation, V617F, in JAK2 which has resulted in several JAK2 kinase inhibitors entering the clinic. Fms-like tyrosine kinase 3 (FLT3) is the most frequently mutated gene in acute myeloid leukemia (AML) and we saw an opportunity to broaden the appeal of a JAK2 inhibitor in hematological malignancies by adding on FLT3 inhibitory activity. We employed a macrocyclic structure due to its limited available conformational options allowing the binding moieties to be constrained at specific points in space. This strategy led to a novel series of JAK2/FLT3 selective inhibitors able to achieve interactions in the active sites of the target enzymes we believe are not easily accomplished with an acyclic structure. We describe SAR against multiple enzymes leading to the selection of SB1518 as the preferred compound, which was then taken forward for extensive preclinical evaluation. We also describe the in vivo efficacy of SB1518 in a mouse model of JAK2^{V617F}-driven disease demonstrating dose-dependent tumor growth inhibition and normalization of splenomegaly and hepatomegaly at well-tolerated doses. In a second study in a model of FLT3-ITD driven leukemia SB1518 demonstrated significant survival benefits at very well tolerated doses. In the clinic SB1518 has shown benefit in myelofibrosis and lymphoma patients in Phase 1 and 2 trials.

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Dr Simon J. Teague

Novartis Institute for Tropical Diseases (Singapore)

Simon J. Teague is currently a Senior Investigator at the Novartis Institute for Tropical Diseases (Singapore). Formerly he was a Principal Scientist in Medicinal Chemistry at AstraZeneca (UK). He has specialised for a number of years in lead discovery through the assessment of HTS hit sets. Other responsibilities have included in-licensing, designing leads from competitor's patents and lead design using biophysical methods. His work in lead discovery has resulted in AZD1981, currently a phase III candidate for asthma treatment. He first established the concept of lead-like chemical starting points. He has been involved in a large number of projects in the cardiovascular, immunosuppressant and respiratory therapeutic areas. He has first-hand experience of the processes resulting in the

discovery of the drugs; Nedocromil Sodium (Tilade (r)), Dopexamine Hydrochloride, Cangrelor and Ticagrelor (Brilinta (r)).

Lessons from Recent Market Entrants

Which projects are most likely to lead to a launched drug?

Those drugs which have entered the market in recent years are studied and the lessons which can be learned from them are highlighted. Recent entrants are disproportionately aimed at therapeutic objectives that have short trial durations and where the clinical effects are simple to measure. Animal models still play an important role, since both disease and toxicity are expressed at the level of the whole organism rather than the cell. Only a small number of new disease targets are demonstrated to be clinically exploitable in any one year. Both macromolecular and small molecule drugs cluster into treatments aimed at these same few targets. Solutions to low productivity in drug discovery are suggested. These include; managing expectations, improving research organisations, accommodating drug-hunters within large organisations better, abandoning the blockbuster model and improving translational science and trials. It is suggested that these changes will allow companies to serve both patients and their investors better.

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POSTER PRESENTATIONS

Natural product synthesis: inciting the development of expeditive methodologies to complex core frameworks

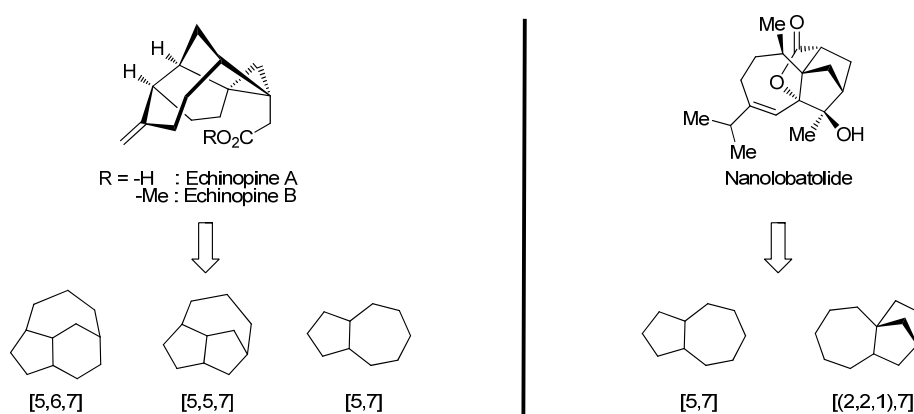
Peixoto, P., A.; Cheng, H., M.; Richard, J., A.; Tian, W.; Severin, R.; Chen, D., Y.-K.

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Even though natural products may not have all co-evolved with human proteins, they have emerged to interact with biomolecules. As reactions in Nature are biased towards function, it follows that every natural product must have a biological receptor to justify the enormous required biochemical expense to produce them.

When compared to classical synthetic compounds, natural products, on average, have higher molecular weights, incorporate fewer nitrogen, halogen or sulfur atoms, but more oxygen atoms. They are sterically more complex, with more bridgehead atoms, rings, and stereogenic centers. At the same time, it is known and well accepted that the architectural complexity is closely linked to the specificity of a drug. The most important challenges remain then to be able to identify and synthesize molecules with more and more complexity. Natural products being a good handle towards complexity, a straightforward access to such structures becomes a real requisite.

In this line of thoughts, the development of expeditive access to complex core frameworks was achieved towards the formal and total synthesis of the two recently isolated natural products, Nanolobatolide^{1,2} and the Echinopines A & B³⁻⁷. Their synthesis as well as the access to unique structures isolated along the way will be presented.



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Automated Targeted Laser-Based Delivery of Proteins and Chemical Compounds into Living Cells for Drug Development

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We utilised the precision of laser transfection, also known as optoporation, to deliver the cell-impermeable histone demethylase inhibitor, 8-hydroxyquinoline (8HQ), of the JmjC-domain protein JMJD3 into living cells. The enzyme, JMJD3, demethylates histone H3 lysine K27 and has been shown in previous studies to play a key role in the formation of tumours, stem cell pluripotency and inflammation^{1,2,3}. We show proof of principle that optoporation can be employed to quickly screen and test the efficacy of novel drugs by delivering them into cells at significantly lower concentrations while still maintaining inhibition activity. We also used optoporation to deliver relatively large proteins and novel synthetic antibodies into living cells without fixatives. This offers the possibility of using reporter systems to monitor living cells over time. Because optoporation is a manual and time consuming procedure, an algorithm to automate optoporation by using image processing to locate the position of cells was developed. To our knowledge, this is the first publication of a system which automates optoporation of human fibroblasts in this way.

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Investigation of Molecular Behaviour of the A2a Adenosine Receptors using Molecular Dynamics Simulations

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The G-protein coupled receptors (GPCRs) belong to the family of 7 transmembrane (TM) α -helices protein and are a versatile group of receptors. They respond to a vast array of neurotransmitters, hormones and metabolites involved in cellular signalling and are also the target of numerous biological and small molecule drugs. Of late, the emergence of new crystal structures and the wealth of structural knowledge that accompanies it have catapulted the field of GPCR computational modelling to a new height. Listed in chronological order are the seven members of the GPCR family whose crystal structure have successfully been elucidated : bovine rhodopsin (2000)[1], human β 2 adrenergic receptor (2007)[2], turkey β 1 adrenergic receptor (2008)[3], human A2a adenosine receptor, A2a AR (2008)[4], human CXCR4 chemokine (2010)[5], human dopamine D3 receptor (2010), human histamine H1 receptor (2011)[6]. The multi-states GPCRs that exist in a spectrum ranging from an inactive R state to the fully active R* state are especially popular targets in molecular dynamics (MD) simulations. Various molecular mechanics forcefields are used to simulate the behaviour of these receptors *in vivo* which are usually directly associated with their functions. Using techniques such as MD and principal component analysis (PCA), we have explored the molecular behaviour of the A2a AR models embedded in palmitoyl-oleoyl-phosphatidylcholine (POPC) bilayer in the absence and presence of a ligand (ZM241385). Focusing on the transmembrane region, we have noticed in the two different systems, interesting dynamics that were associated with the protein as a whole as well as the individual helices. In particular, significant reduction in randomness of motions was observed when the ligand was added; certain helices (e.g. helix IV) were found more stable than others; the two systems occupy significantly different space in the eigenvector1 vs eigenvector2 plot.

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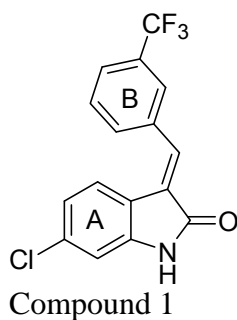
UK-Singapore Symposium on Contemporary Strategies and Practices in Medicinal Chemistry
8 September 2011, Biopolis, Singapore

Antiproliferative activity of functionalised benzylidene indolinones on human cancer cells

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6-Chloro-3-(3-trifluoromethyl-benzylidene)-1,3-dihydroindol-2-one (**1**) has been identified in our laboratory to have potent and selective effects on the viability of hepatocellular carcinoma (HCC) cells. In an attempt to further improve the activity profile of **1** and specifically to address its physicochemical limitations, an exploratory series of functionalized analogs were synthesized and evaluated for effects on the viability of HCC cells using the MTT assay. Preliminary results showed that introducing hydrophilic sulfonylamino or cyano substituents on the benzylidene ring B resulted in analogs that were as active as **1** but with lower lipophilicities (ClogP) and more favorable estimated solubilities. Other promising modifications include di-substitution of the indolinone scaffold (ring A) with fluorine atoms, substitution of a methyl group on the nitrogen of the oxindole ring (ring A), and removing any substitution on either ring. Investigations are ongoing to determine other structural approaches that would result in a further improvement of activity) without adversely affecting the lipophilicity-solubility balance of the final molecules.



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EVALUATION OF CURCUMIN ANALOGS TARGETING NUCLEAR RECEPTOR CO-REPRESSOR PROTEIN IN ACUTE PROMYELOCYTIC LEUKEMIA

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Acute promyelocytic leukemia (APL), resulting from the fusion of promyelocytic leukemia (PML) protein and retinoic acid receptor (RAR), is a subtype of acute myelocytic leukemia. APL displays resistance to programme cell death and is characterized by an accumulation of blast cells in the bone marrow and peripheral blood. Previous reports by Ng *et al* proposed a significant role for Nuclear receptor Co-Repressor (N-CoR) protein in the resistance to apoptosis in APL cells. Accumulation of misfolded N-CoR protein as insoluble aggregates in APL cells was shown to induce endoplasmic reticulum (ER) stress and to activate unfolded protein response (UPR) –induced apoptosis, ultimately contributing to differentiation arrest of APL cells. This establishes the misfolded N-CoR protein as an attractive molecular target in APL. Curcumin, an active component in turmeric has been shown to selectively promote apoptosis in APL cells containing elevated levels of misfolded N-CoR protein over non-APL cells. While curcumin is known to rescue the native conformation of misfolded proteins such as the amyloid β , it appears to inhibit proteasome-mediated degradation of misfolded N-CoR protein in APL cells. Accumulation of misfolded N-CoR therefore aggravates ER stress and results in the selective sensitization of APL cells to UPR-induced apoptosis. This finding illustrates the potential of curcumin in targeting misfolded N-CoR and thus APL. We aim to develop more potent curcumin analogues with high fidelity for N-CoR protein in APL cells. A series of 46 analogs of curcumin have been designed and synthesized with the objective of interrogating structure-activity relationships and providing greater insight into the role of misfolded N-CoR as a drug target in APL. Activity and selectivity profiles have been established on four human leukemic cell lines; NB4 and NB4-R1 (APL), HL60 (AML) and K562 (CML). Herein we report several scaffolds with up to 100-fold improved potency over curcumin on NB4 while maintaining selectivity between APL and non-APL cell lines. Western blotting assay coupled with immunofluorescence bioimaging showed that analogs possessing high APL selectivity increased the accumulation of misfolded N-CoR protein, therefore suggesting involvement of the misfolding process in their anti-proliferative effects on APL. The manipulation of protein conformation in disease states and intervention by chemical entities is an area of growing interest and this study provides an example of how it is used as a platform for the rational design of potent and selective drugs for APL.

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Small Molecule Modulators for Epigenetic Therapy

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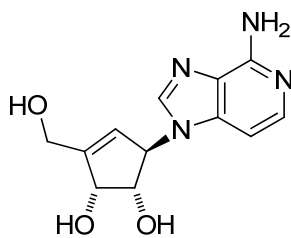
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Cancer epigenesis involves complex biological processes including DNA methylation and chromatin modifications, such as histone deacetylation (HDAC) and methylation. Many tumor suppressor genes have been found to be inactivated by epigenetic silencing, providing cancer cells with selective advantages for clonal expansion and growth.

Epigenetic therapy, which can re-activate the tumor suppressor genes and hence cause cell-death in cancer cells, is a rapidly developing field in medicine. For example a histone deacetylase inhibitor, Vorinostat (also called SAHA), was approved for treatment of cutaneous T cell lymphoma in 2006. In addition to histone deacetylation, histone methylations also play an important role in cancer epigenetics. In particular, histone methylation induced by Polycomb group (Pcg) proteins such as EZH2, which is overexpressed in multiple human cancers, is believed to be part of the mechanisms causing oncogenesis and is thus an attractive target for anti-cancer drug development.

3-Deazaneplanocin A (DZNep), a S-adenosylhomocysteine hydrolase (SAHH) inhibitor, was discovered to inhibit EZH2 complex and the associated H3K27 trimethylation, leading to strong apoptosis in cancer cells but not in normal cells. This discovery establishes the proof of concept that chemical inhibition of EZH2 and the associated histone methylations may represent a promising novel approach for cancer treatment.¹

In this presentation, the anti-cancer activities of DZNep and its derivatives will be discussed.²



DZNep

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UK-Singapore Symposium on Contemporary Strategies and Practices in Medicinal Chemistry
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Exploring Aigialomycin D and Its Analogues as Protein Kinase Inhibitors for Cancer Targets

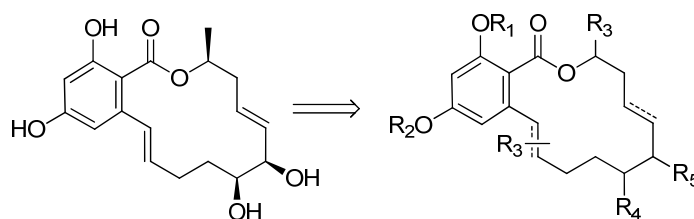
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The natural product aigialomycin D is a member of the resorcylic acid lactone (RAL) family possessing protein kinase inhibitory activities. This work describes the synthesis of aigialomycin D and a series of its analogues and their activity for the inhibition of protein kinases related to cancer pathways. A preliminary study of these compounds in the inhibition of CDK2/cyclin A kinase has found that aigialomycin D and some of its analogues are moderate CDK2/cyclin A inhibitors. Subsequent kinase profiling of aigialomycin D against a panel of 96 kinases has led to the identification of MNK2 as a promising target ($K_d = 0.16 \mu\text{M}$), and preliminary structure-activity relationship studies have been carried out to identify the essential functional groups for activity.



Aigialomycin D
 $K_d = 0.16 \mu\text{M}$ (MNK2)

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SYNTHESIS OF 5-HT₆ ANTAGONISTS WITH POTENTIAL FOR TREATMENT OF OBESITY: AN EFFICIENT CHIRAL RESOLUTION OF EPIMINOCYCLOHEPTA[*b*]INDOLES

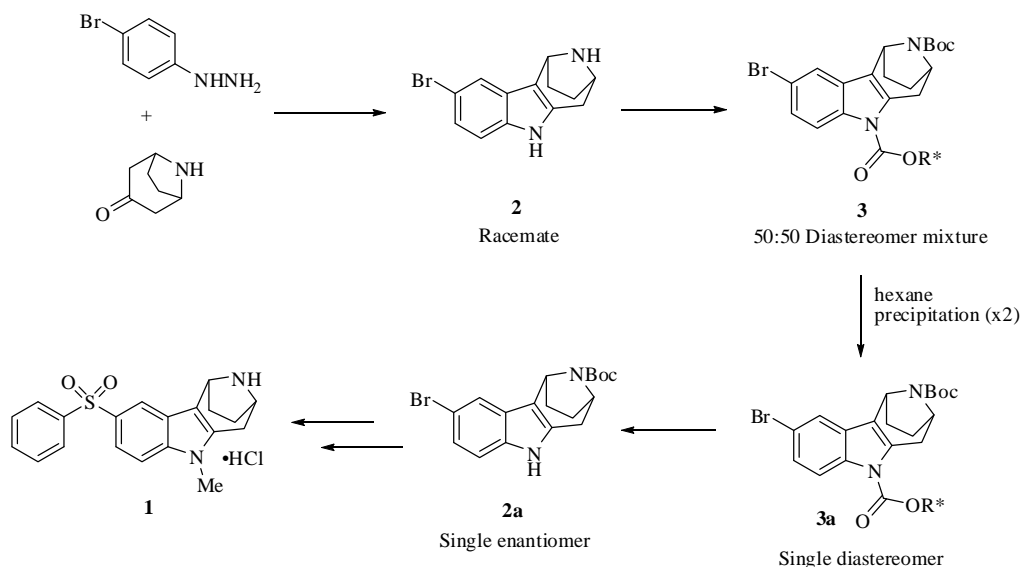
Ghosh Animesh¹, Peter R. Guzzo,² Alan J. Henderson,² Ming Min Hsai,² Jagjit Kaur,¹ Jia Man (Carmen) Koo,¹ Shailaja Panduga,¹ Rashmi Pathak,¹ Bharat Shimpukade,¹ Valentina Tan,¹ Kai Xiang,¹ Matthew Isherwood¹

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Obesity is a major global health concern which has been implicated in numerous life threatening diseases including type-II diabetes, hypertension, cancer, and musculoskeletal problems [1,2]. With the rate of obesity rising steadily every year new safe and effective treatments are urgently needed. 5-HT₆ antagonists have been shown to reduce [appetite](#) and produce [weight loss](#) in animal models indicating the 5-HT₆ receptor as a viable target for anti-obesity drugs [3].

In the course of our research to develop new 5-HT₆ antagonists, we identified a potent lead series derived from an epiminocyclohept[*b*]indole core (**Scheme 1**). Lead compound **1** displayed low nano-molar affinity for the 5-HT₆ receptor (h5-HT₆ K_i = 8.2 nM). Subsequent lead series optimization required a practical route to homochiral analogs for in vitro profiling. Work focussed on chiral resolution of Fisher indole product **2**. Treatment of **2** with chiral acids (e.g. L-tartaric acid) failed to yield diastomeric salts which could be crystallized to diastomeric purity with reasonable yield. We turned our attention to a chiral auxiliary based approach and discovered that derivatization of the indole nitrogen to form a diastomeric carbamate derivative **3** (R* = (+) or (-) menthol) allowed for an efficient chiral resolution. Upon dissolving the diastomeric mixture **3** in hexane a single diastereomer was observed to precipitate preferentially in a 90:10 ratio. A second precipitation of this material from hexane produced diastereomerically pure compound **3a**. Hydrolysis of diastereomer **3a** under basic conditions afforded **2a** in >99% enantiomeric excess with 85% yield based on enantiomer recovery from the *N*-Boc-derivative of **2**. Access to both enantiomers was possible by selecting (+) or (-) menthol chloroformate as the chiral derivatizing agent. In summary a new facile method has been developed for multigram scale chiral resolution of epiminocyclohept[*b*]indoles.



Scheme 1. Synthesis of Homochiral Epiminocyclohepta[*b*]indoles as 5-HT₆ Antagonists

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A Novel Synthesis of a Triazolesulfonyl Chloride as a Precursor for GlyT-1 Inhibitors

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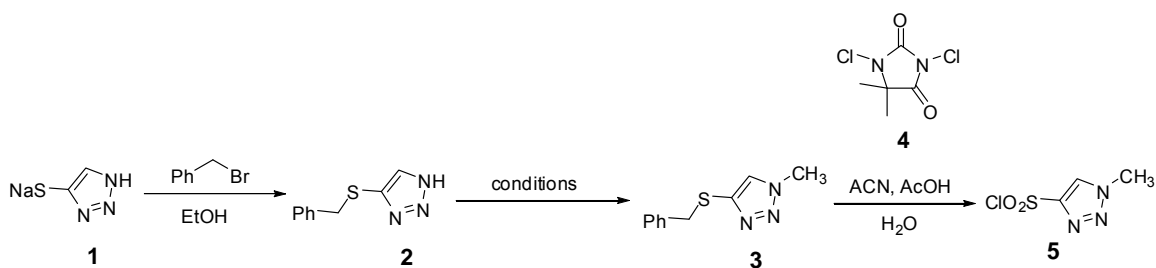
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Emerging evidence has pointed to glycine transporter-1 (GlyT-1) as a promising target for the treatment of schizophrenia based on the *N*-methyl-D-aspartate (NMDA) receptor hypofunction hypothesis.¹ GlyT-1 inhibitors have been reported to be efficacious in animal models predictive of antipsychotic and pro-cognitive activity and in recent human clinical trials, providing compelling evidence that such inhibitors show promise as a novel class of antipsychotics that are effective at treating negative symptoms and cognitive dysfunction associated with schizophrenia.

AMRI has developed a novel series of proprietary GlyT-1 inhibitors. A key structural motif for analogues within the series is a 1-methyl-1*H*-1,2,3-triazole-4-sulfonamide. Previous attempts at synthesizing the sulfonyl chloride precursor **5** involved hazardous reagents and conditions not conducive for scale-up. We have developed an alternative three step route to **5**, starting from commercially available sodium salt **1**. A key reaction of this process utilizes commercially available, safe and inexpensive 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (**4**) for the conversion of mercapto intermediate **3** to desired sulfonyl chloride **5**. Hydantoin **4** has been previously reported as an effective reagent for the oxidative chlorination of aryl sulfides to arenesulfonyl chlorides, however this is the first report of a mercapto triazole to be used for this transformation.^{2,3} The reaction provides a safer and more efficient alternative to previously used conditions to generate **5** and is amenable to scale-up. A detailed description of the procedure and discussion of its benefits relative to existing methods will be provided.



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NITD609: A New Chemotype for the Treatment of Malaria

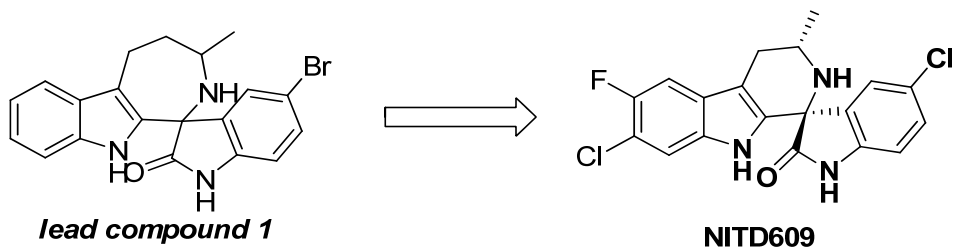
Leong Seh Yong

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Malaria remains a persistent public health problem for about 40 percent of the global population mainly in sub-Saharan Africa. *Plasmodium falciparum*, the most relevant malaria parasite, is estimated to infect 300–500 million people per year and results in over one million deaths of which approximately 90% are children. In an effort to discover new antimalarial leads, a high throughput, whole cell screen based on the proliferation of *P. falciparum* of the Novartis Natural Product library was performed and led to the identification of racemic spiroazepineindole 1. By improving in vitro potency and metabolic stability of the lead compound, we identified NITD609 as preclinical candidate with following properties:

- Sub-nanomolar in vitro activity
- Is fast acting, has a high C_{max} , with long exposure in mice, rats, and dogs
- Oral efficacy (>99% parasitemia reduction) and display mouse survival prolongation even at low doses
- Consistent with requirements for a single or low dose cure
- Active on multiple drug resistant strains as well as *P. falciparum* and *P. vivax* clinical isolates
- Low cytotoxicity and cardiotoxicity potential, and no genotoxicity flags

New and highly specific chemotype for malaria



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Design and Synthesis of Tri-substituted Imidazoles as p38 Mitogen-Activated Protein Kinase Inhibitors for Cardiomyogenesis of Human Embryonic Stem Cells

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p38 Mitogen-activated protein (MAP) kinases are a class of Ser/Thr protein kinases that play key roles in the regulation of inflammatory cytokines like TNF- α and IL-1 β . The anti-inflammatory effects of inhibitors of p38 MAP kinase in clinical trials have led to intense interest in the development of inhibitors as drugs for the treatment of inflammatory diseases like rheumatoid arthritis, inflammatory bowel disease and psoriasis.

One of the first few inhibitors developed against p38 MAP kinase is SB203580, a tri-aryl imidazole compound. This prototypical p38 MAP kinase inhibitor has been applied to various areas of pharmaceutical research including, the area of stem cell differentiation. In particular, two recent reports by Graichen *et al.*ⁱ and by Gaur *et al.*ⁱⁱ suggested that p38 MAP kinase inhibition by SB203580 enhances and speeds up differentiation of human embryonic stem cells (hESC) into cardiomyocytes (cells found in the heart). These findings inspired us to develop better p38 MAP kinase inhibitors with the aim of developing them as small molecules for cardiomyogenesis of hESC.

We have thus developed a series of novel tri-substituted imidazoles as potent p38 MAP kinase inhibitors and selected inhibitors were applied to induce cardiomyogenesis of hESC. Our approach involves docking studies in the design of tri-substituted imidazole compounds followed by their synthesis. The compounds were then assayed for their p38 MAP kinase inhibitory activities and the more potent compounds were used for cell-based cardiomyogenesis experiments. Two of the compounds demonstrated the ability to generate robust beating cardiomyocytes which expressed myosin heavy chain and alpha actinin.

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