

Biographies & Abstracts

UK-Singapore Symposium on Medicinal Chemistry
25– 26 January 2010, Biopolis, Singapore



Paul Wyatt

Paul is currently Director of Drug Discovery for the Wellcome Trust funded Drug Discovery for Tropical Diseases initiative. His current role is to help develop translational research at Dundee, by bringing together his and other's experience of Drug Discovery in the Pharma/Biotech sector with basic academic research to identify new treatments for diseases such as African sleeping sickness and Cancer.

Previously Paul worked within the BioPharma industry for 23 years, gaining experience across a range of therapeutic areas, e.g. oncology, oxytocin antagonists; antiviral agents; TB; and antiobesity agents. He played a significant part in seven compounds entering pre-clinical development, three of which are now in Phase II clinical trials. He gained a rare breadth of knowledge and experience of drug discovery by designing the first analogues of a fragment screening hit, and by leading the resulting Drug Discovery Project through to pre-clinical development, culminating in one of the first compounds from fragment based drug discovery reaching clinical trials. Paul obtained his BSc and PhD in Chemistry from the University of Birmingham. Paul has published over 30 papers and he is an inventor on 34 patents.

Repositioning Enzyme Targets for Neglected Diseases Drug Discovery

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The traditional approach of using genetic manipulation to validate drug targets for neglected diseases is not matching the attrition rate of the drug discovery process. In addition, this approach has afforded mixed results, where potent inhibition of some targets has failed to translate into significant antiparasitic effects. Therefore we are repositioning targets with a history of drug discovery in other therapeutic areas, which have homologues in the parasites. Our efforts are focussing on; i) genetically validated targets which on inhibition would cause pleiotropic effects; and ii) selective polypharmacology through inhibition of targets within gene families.

The talk describes our studies in each of these areas and how we have taken hits into lead optimisation.

A medium throughput screen against N-myristoyl transferase (NMT), shown to be essential in *T. brucei* using genetic manipulation, identified a key hit series. Optimisation of the series gave potent and selective antiparasitic activity; good pharmaceutical properties and cures of the acute stage of African sleeping sickness (HAT) in mice. Substantial evidence links inhibition of NMT and the observed antiparasitic activity.

The gene family approach is illustrated by our investigation of parasite kinases, where we have taken both an individual genetically validated target and a gene family phenotypic screening approach. The compound series from this area currently in lead optimisation initially originated as inhibitors of *T. brucei* GSK3, but optimisation of parasite activity resulted in a reduction of GSK3 activity. This series has potent and selective antiparasitic activity; and cures the acute stage of HAT in mice.

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Brian W Dymock

After completing a BSc (Chemistry, Strathclyde, 1994) and PhD (Organic Chemistry, Southampton & Glasgow, 1997) Brian went straight into an industrial position at Roche as a MedChem Team Leader in Viral Diseases projects. Four years later following the closure of Roche in the UK Brian moved on to a small Biotech environment joining RiboTargets (now Vernalis) targeting Heat Shock Protein (HSP90) for cancer in collaboration with the Institute of Cancer Research (London). A potent new drug, NVP-AUY922, which was out-licensed to Novartis, is now in Phase 1 clinical trials for cancer. Brian then moved to a new challenge at a Contract Research Organization (CRO), Evotec, where he was a Department Manager leading a team of 27 working as the 'medchem' arm of client companies. During this time a rare opportunity arose in Singapore to lead a Chemistry group in an Asian environment. Over 3 years after starting work in Singapore at S*BIO Pte Ltd, this oncology-focused company has become a Research and Development organization with 2 new drugs being tested in cancer patients in clinical trials in Singapore, Australia and North America. Helping to enhance drug discovery in Singapore and bring new drugs to cancer patients is the aim of S*BIO and Brian hopes to continue to add value as part of this team into the future.

How to Make Real Drugs the Singapore Way: Fast, Furious and Fun

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With a plethora of new biological targets and a dearth of good drugs to match them, there are many opportunities in modern Oncology research. At first glance the area appears to be teeming with huge competition and lots of highly potent compounds being reported on a regular basis. However, Oncology drug development has one of the highest failure rates in clinical development. Undoubtedly the sheer challenge of fighting rapidly mutating and proliferating cells that have gone out of control generating resistance to existing therapies is a significant one and the lack of correlation with preclinical biological models is, at best, poor. The medicinal chemist can at least try to ensure that the drugs they design and synthesise do not fail for reasons of poor solubility, high molecular weight, poor selectivity and many other potentially avoidable criteria. Using data from 2 clinical stage programs and other preclinical medicinal chemistry projects this talk will discuss highlights from recent work at S*BIO in Singapore focusing on what are in our view the important aspects for success in the clinic. Topics to be discussed include lead generation using our own brand of fragment methods to lead optimisation within a highly integrated multidisciplinary team.

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Kurt G. Pike

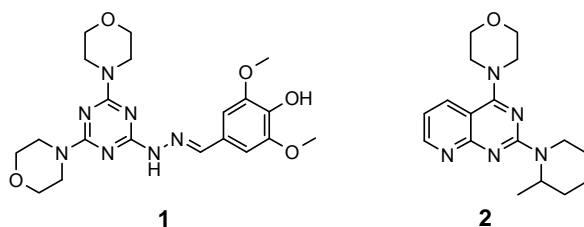
Kurt Pike joined Zeneca Pharmaceuticals, now AstraZeneca, at Alderley Park in 1997 following the completion of a PhD in Organic Chemistry, under the supervision of Professor Jeremy Kilburn at Southampton University. In his time at AstraZeneca, he has worked in a number of different therapeutic areas and been involved in the discovery of a number of clinical candidates in the Diabetes area. He is currently working as a Medicinal Chemistry Team Leader in the Oncology Research Area where he has been involved with the joint KuDOS / AstraZeneca mTOR project.

The Identification and Optimisation of Selective Small Molecule Inhibitors of mTOR Kinase

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The mammalian target of rapamycin (mTOR) is a key target in the development of antitumour therapies.¹ Activated by growth factor/mitogenic stimulation activation of the phosphatidylinositol 3-kinase (PI3K)/Akt signalling pathway mTOR is a central regulator of cell growth and proliferation. This PI3K-Akt-mTOR pathway is one of the most frequently dysregulated pathways in cancer.² The known mTOR inhibitor Rapamycin and its analogues (RAD001, CCI-779, AP23573) bind to the FKBP12/rapamycin complex binding domain (FRB), resulting in suppression of signalling to the downstream targets p70S6K and 4E-BP1.³ However, it has recently been shown that mTOR can exist in an alternative, rapamycin insensitive, complex that signals to Akt.⁴ Therefore, it is proposed that a compound directly targeting the kinase domain of mTOR would inhibit signalling through both the rapamycin sensitive complex (TORC1) and the rapamycin insensitive complex (TORC2) and as such the compound would exhibit a different spectrum of pharmacology compared with rapamycin.



Two alternative approaches to identify selective inhibitors of the mTOR kinase domain resulted in the identification of two distinct lead series, (1) and (2). Further studies were undertaken to investigate the SAR of each series and resulted in the identification of KU-0063794 which has been shown to inhibit both complexes of mTOR (TORC1 and TORC2) and demonstrates dose dependant tumour growth inhibition in xenograft studies. The identification and optimisation of these series will be described.

References

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Matthew D. Surman

Dr. Surman received his Ph.D. in synthetic organic chemistry from the University of Notre Dame under the direction of Prof. Marvin J. Miller. He joined the AMRI Medicinal Chemistry department in 2002 and worked on contract research projects spanning a variety of therapeutic areas including oncology and anti-infectives. In 2005, he joined the newly formed AMRI internal Discovery Research and Development department, focusing his efforts in the area of obesity. Dr. Surman currently is the project leader for the AMRI MCH-1 antagonist programme.

Melanin Concentrating Hormone Receptor-1 (MCH-1) Antagonists for the Treatment of Obesity

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Melanin-concentrating hormone (MCH) is a cyclic 19 amino acid neuropeptide expressed in the zona incerta and lateral hypothalamus, a region of the brain known to play a key role in appetite regulation and energy homeostasis. Antagonists of the MCH-1 receptor have been shown to be a promising new approach for the treatment of obesity.

AMRI has discovered several novel series of melanin-concentrating hormone receptor-1 (MCH-1) antagonists. An overview of the design, synthesis, SAR and pharmacology of representative compounds will be provided. In addition, the design of an ex-vivo receptor occupancy assay using [³H]AMR-MCH-1 and its utilization as a drug discovery tool will be described. Representative AMRI compounds are high affinity functional antagonists of the human MCH-1 receptor, and demonstrate significant and sustained reductions in food intake and body weight in a chronic, 28-day feeding study in male dietary-induced obese (DIO) C57BL/6J mice. Analysis of ex-vivo MCH₁ receptor occupancy demonstrates a correlation with weight loss. Body composition analysis indicates the weight loss caused by AMRI MCH-1 antagonists were associated with selective reductions in fat mass.

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Paul M. O' Neill

Paul M. O' Neill, born in 1969 in Liverpool, graduated with a first class Honours degree in Chemistry and Pharmacology at the University of Liverpool in 1990 and subsequently carried out a Wellcome Trust funded Ph.D degree under the guidance of Dr. Richard C. Storr and Professor B. Kevin Park. Following graduation, he was appointed Roche Lecturer in Medicinal Chemistry in the Department of Pharmacology at Liverpool from 1995-96. In 1997 he carried out postdoctoral research with Professor Gary H. Posner at the Johns Hopkins University, USA before returning to Liverpool in 1998 where he was appointed to a joint lectureship between the Departments of Chemistry and Pharmacology. He was promoted to Senior Lecturer in 2003, Reader in 2005 and Professor of Medicinal Chemistry in 2006. His main research interests include synthetic methodology including catalytic oxidation processes, fluorine substitution in bioorganic chemistry, drug metabolism and the medicinal chemistry of quinoline, quinolone, peptidomimetic and endoperoxide antimalarials. Professor O'Neill has published over 80 papers and five patents. His research has led to a drug candidate (Isoquine) entering clinical trials in 2008 and his group has also recently candidate selected two additional antimalarials for full preclinical testing on route to Phase 1 clinical trials in humans.

Candidate Selection of a 1,2,4,5-Tetraoxane Drug-Development Candidate (RKA 182) with Superior Properties to the Semi-Synthetic Artemisinin Based Antimalarials

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Reliance on semi-synthetic artemisinins limits the ability of the community to respond to the malaria elimination challenge in the face of emerging resistance, highlighting the urgent need for alternatives. From a library of over 150 1,2,4,5-tetraoxanes we have candidate selected a molecule, RKA182, for full formal preclinical development. RKA182 has outstanding *in vitro* activity against sensitive and resistant strains of *P.falciparum* (IC_{50} =2.4nM (K1), 4.7nM (3D7) and $TI > 14000$) and retains this level of activity against South East Asian isolates that failed ACT combination chemotherapy. The drug candidate has a fast rate of parasite kill, superior *in vivo* activity to artesunate (ED_{50} =1.33 mg/kg and ED_{90} =4.18 mg/kg) in rodent models of malaria and improved DMPK characteristics and stability in the presence of infected red blood cells when compared to synthetic ozonides or semi-synthetic artemisinins.

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Chen, David Y.-K.

David Chen received his Bachelor of Science degree (Honors) from the University of Auckland in 1997. In 1998, he was admitted to the Ph.D. programme at Cambridge University where he studied under the supervision of Professor Ian Paterson on the synthesis of macrolide natural products, most notably the total synthesis of spongistatin 1. After graduating in 2001, he worked under the direction of Professor K.C. Nicolaou as a postdoctoral researcher at The Scripps Research Institute on the total synthesis of bioactive natural products diazonamide A and azaspiracid 1. He joined the medicinal chemistry department of the Merck Research Laboratory at Rahway-New Jersey in 2003 as a senior research chemist, and shortly after in 2005, he was appointed as the first Principal Investigator of the Chemical Synthesis Laboratory (CSL) @ Biopolis under the Agency for Science, Technology and Research (A*STAR), Singapore. In the same year, he was also appointed as an Adjunct Assistant Professor, division of Chemistry and Biological Chemistry (CBC) at the Nanyang Technological University, Singapore. Dr. Chen's research interests focus on the total synthesis of bioactive natural products, chemical biology and medicinal chemistry. Dr Chen most recently received the Singapore National Academy of Science Young Scientist Award in 2008.

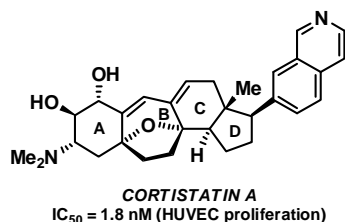
Chemistry and Chemical Biology of Cortistatin A, A Potent and Selective Anti-Proliferative Agent Against HUVEC

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The cortistatins are steroidal alkaloids isolated from the marine sponge *Corticium simplex*.¹ Selected cortistatins demonstrated their potential as promising anti-angiogenic agents, displaying potent growth inhibition of human umbilical vein endothelial cells (HUVECs; e.g. IC₅₀ 1.8 nM for cortistatin A) with remarkable selectivity over normal human dermal fibroblasts (NHDFs) and several other tumor cells (KB3-1, K562, and Neuro2A). The novel molecular architecture and intriguing biological profile of the cortistatins has generated much excitement in the scientific community. While a number of elegant synthetic approaches toward cortistatin A and its corresponding core structure have been reported, however, its precise mode of biological action remained elusive.

Very recently, cortistatin A was reported to be a highly selective inhibitor of a small subset protein kinases, notably ROCK, CDK8, and CDK11.² It was also shown that the AB ring system of cortistatin A is not essential for activity, and unmodified steroidal frameworks may be substituted for the main ring system of the cortistatins without significant loss of potency. These results pave the way to simplified analogs formed by attaching the isoquinoline domain to either the CD ring system or readily available steroids. This significant structural simplification renders the resulting analogs readily accessible synthetically, enabling further mechanistic and pharmacological studies of this exciting class of novel anti-proliferative agents.³



TREEspot™ interaction map for synthetic cortistatin A tested at 10 μM with kinases. (Ambit Biosciences, San Diego, California).

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Martin E Swarbrick

Dr Martin E Swarbrick is a Group Leader in Medicinal Chemistry and Research Project Leader at Cancer Research Technology Ltd., where he moved in 2008 during the expansion of the Discovery Laboratories to their Cambridge site. Before joining CRT, he spent nine years at GlaxoSmithKline where he led medicinal chemistry teams and lead optimisation programmes, contributing to the identification of eight development candidate compounds. Prior to his career in drug discovery, Martin obtained a BSc and PhD in chemistry from the University of Sheffield, and carried out post-doctoral research at the University of Montreal.

Identification of 3-amino-6-arylpyridazines as Selective CB₂ Agonists for the Treatment of Inflammatory Pain

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The discovery and investigation of a series of a series of amino-substituted biaryl compounds, which led to the identification of 3-amino-6-arylpyridazines as CB₂ agonists with high efficacy and selectivity against the CB₁ receptor for the treatment of inflammatory pain, will be presented.

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Mark Bunnage

Mark was born and educated in England and read chemistry at the University of Durham, graduating in 1990. Mark then moved to the University of Oxford to conduct his postgraduate studies with Professor S G Davies. Following completion of his D.Phil., Mark moved to The Scripps Research Institute, La Jolla, California to work with Professor K C Nicolaou as a NATO postdoctoral research fellow.

In February of 1996, Mark returned to the UK to join Pfizer as a medicinal chemist in their research laboratories in Sandwich, Kent. In 2002, Mark was appointed Head of Chemistry for the Allergy & Respiratory Therapeutic Area.

In 2006, Mark became Head of Lead Discovery in Sandwich, with responsibility for Hit-to-Lead chemistry, structural biology & chemical technology. During this period, Mark also helped establish the start-up technology company Cyclofluidic, which aims to develop an integrated microfluidic synthesis and screening platform. From April 2007 to December 2008, Mark returned to a therapeutic area role as Head of Chemistry for Genitourinary research. In January 2009, Mark then took on responsibility for Antivirals Chemistry, Regenerative Medicine chemistry & Lead Discovery Technologies. In November 2009, Mark moved to his current role as Executive Director, Worldwide Medicinal Chemistry with responsibility for Regenerative Medicine chemistry, OBBTU chemistry (Pfizer's new Opportunities-Based Biotechnology Unit), and Lead Discovery Technologies in Sandwich.

Over the past 13 years at Pfizer, Mark has been involved in the discovery of 18 development candidates spanning the Genitourinary, Cardiovascular and Allergy & Respiratory disease areas, of which a number are now in development – including the inhaled once-daily beta-2 agonist PF-610,355 which is currently in advanced Phase II studies. Mark has an active interest in many areas of medicinal chemistry and is an author or inventor on more than 50 scientific publications and patents. He is a member of the strategic advisory teams for the EPSRC physical sciences and healthcare programmes, is a Fellow of the Royal Society of Chemistry, a member of the Executive Committee of the European Federation of Medicinal Chemistry, and will be on the Editorial Board of the RSC's new journal 'Medicinal Chemistry Communications'.

Biophysics in Medicinal Chemistry

Medicinal Chemistry

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Biophysical techniques such as Surface Plasmon Resonance, Isothermal Titration Calorimetry, NMR, & X-ray crystallography can provide unique insights into the nature of the interactions between small molecule ligands and their biological targets. Optimisation of primary biochemical activity is a common goal in hit-to-lead programmes, however biophysical techniques can provide insight that goes well 'beyond the IC₅₀' and has potential to significantly influence series selection and medicinal chemistry design direction. In this presentation, the application of biophysics to establish key characteristics such as the kinetics, thermodynamics and modality of binding will be described and Pfizer project examples will be disclosed to illustrate how these data can have a major influence on project medicinal chemistry strategy.

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Christopher N. Johnson

After graduating in Natural Sciences from the University of Cambridge, UK, Chris joined Beecham Pharmaceuticals (a GSK legacy company) as a medicinal chemist. At GSK and legacy companies, he worked on a wide range of projects, primarily in the Neurosciences field, and contributed as co-inventor and/or project leader to the delivery of multiple clinical candidates. During this time, Chris gained a Ph.D. degree from the University of Bristol by part-time study and developed an interest in strategies for reducing attrition in drug discovery, in particular the use of clinical imaging modalities such as positron emission tomography. In 2008, Chris was appointed Director of Medicinal Chemistry Astex Therapeutics where he is currently applying fragment- and structure-based design techniques to a number of oncology targets.

Case Histories in Fragment Based Drug Discovery

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Five years ago most scientists did not consider low molecular weight fragments (MW = 120-250) with corresponding binding affinities of only mM to μ M to be attractive starting points for drug discovery programs. However, today there is widespread acceptance that these fragments can be progressed into nM lead series and on into clinical trials. Reported examples include candidates that target different protein families such as kinases (CDK, Aurora, Akt, raf), protein-protein interactions (Bcl-X_L), ATPases (HSP-90) and proteases (MMP 2&9).

Fragment based drug discovery uses biophysical screening to identify the initial fragments. Subsequently, in the fragments-to-leads stage, a detailed structural understanding of the binding interactions between the fragment and its target protein utilising X-ray crystallography or NMR is critical. Starting with different fragments allows several lead series to be identified, often by synthesizing only small numbers of compounds.

This presentation has two parts. Firstly, a general overview of the techniques associated with fragment based drug discovery and, secondly, some specific examples from Astex's laboratories of fragments that have been progressed into candidates for clinical trials.

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Young-Tae Chang

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 Program of NUS as the leader, and Lab of bioimaging Probe Development at SBIC, Biopolis. He published more 130 scientific papers / 3 books and filed 20 patents so far.

Colourful Chemical Genetics

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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 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 colorful chemical genetics for stem cell study will be discussed.

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Dominic Reynolds

Born in England, Dominic Reynolds completed first his undergraduate and then his PhD studies in 2000 at the University of Cambridge, under the supervision of Professor Steve Ley. From there he joined Glaxo Wellcome in Stevenage, UK as a process chemist, before moving to the United States to undertake Post-Doctoral studies with Professor Dave Evans at Harvard University. Opting to stay in the US he took a position as a Medicinal Chemist at Millennium Pharmaceuticals working there for 6 years doing drug discovery first in Inflammation and then Oncology disease areas. Following the acquisition of Millennium by Takeda in May 2008, Dominic joined Forma Therapeutics Inc. initially working as a medicinal chemist in

Cambridge, MA before transferring to their site Singapore in August, 2009. Here in Singapore Dominic is focused on the application of DOS in the area of Oncology.

Diversity Oriented Synthesis (DOS) in Drug Discovery

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Natural products have played a critical role in the identification of numerous medicines. Historically the pharmaceutical industry has been challenged with providing compounds synthesised *de novo* that rival the diversity and novelty represented in nature. Combined with the recent lackluster performance of in-house pharmaceutical compound collections we are failing to capitalise on the novel biological targets that the genomic era has unveiled. The talk will focus on Diversity Oriented Synthesis and other technologies that Forma Therapeutics is leveraging to identifying unique chemical matter relevant to drug discovery.

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Bryan K.S. Yeung

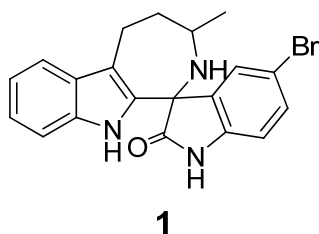
Bryan obtained his B.Sc. in chemistry from the University of Hawaii at Manoa with a focus on marine natural products chemistry. Shortly after he moved to the University of Illinois at Urbana-Champaign and obtained a Ph.D. under Professor Peter Petillo. Following his graduate work, he moved to the Scripps Research Institute in La Jolla to the lab of Professor Dale Boger. Upon completing his postdoc, he worked as a Research Scientist at Exelixis Inc. in South San Francisco for four years on kinase inhibitors. Most recently, he relocated to Singapore to join the newly formed Malaria Unit at NITD in 2007.

Spirotetrahydro β -carbolines (spiroindolones): A New Class of Potent and Orally Efficacious Compounds for the Treatment of Malaria

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The antiplasmodial activity of a series of spirotetrahydro β -carbolines is described. Racemic spiroazepineindole (1) was identified from a phenotypic screen on wild type *Plasmodium falciparum* with an in vitro IC₅₀ of 90 nM. Structure activity relationships for the optimisation of 1 including the identification of the active 1R,3S enantiomer and elimination of metabolic liabilities is described. Improvement of the pharmacokinetic profile of this series translated to exceptional oral efficacy in the *P. berghei* infected malaria mouse model where full cure was achieved in four of five mice with a three daily doses of 30 mg/kg.



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Vincenzo Garzya

Vincenzo Garzya worked within the BioPharma industry for 9 years, gaining experience across a range of therapeutic areas, e.g. Cardiovascular, dopamine antagonists, 5-HT antagonists, Muscarinic agonists, Glutamate receptor antagonists. He played a significant part in the identification of candidate molecules in different areas, two of which went through Phase I & II clinical trials. He gained a breadth of knowledge and experience of drug discovery by contributing to the design of the first selective muscarinic M₁ agonist for cognitive impairments. Vincenzo graduated in Italy where he also obtained his master degrees in Organic chemistry and medicinal chemistry. Vincenzo has contributed to few scientific papers and is an inventor on 20 patents.

Selective Muscarinic M₁ Receptor Agonists for the Treatment of Cognitive Impairment

Neuroscience Centre of Excellence for Drug Discovery, SCD-DPU, GlaxoSmithKline, UK

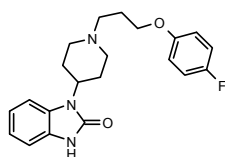
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Alzheimer disease (AD) is a debilitating illness characterised by cognitive decline. Gold standard treatment for AD is Aricept, a cholinesterase inhibitor that addresses AD symptoms by boosting levels of acetylcholine in the brain. Current treatment for AD does not show sustained effects as disease progresses.

Schizophrenia (SZ) is also a chronic and debilitating disease characterised by cognitive impairment. Current treatments for schizophrenia are based upon antipsychotic agents modulating dopamine dysfunction in the brain by primarily acting at dopamine D₂/D₃ receptors. Current drugs for SZ do not fully address cognitive and negative symptoms of the disease.¹

Several approaches are under investigation at GlaxoSmithKline to effectively treat both AD and SZ. Recently, selective muscarinic M₁ receptor agonism has been suggested as a therapeutic approach in both dementia and cognitive impairment associated with AD and SZ respectively.²

In response to the current unmet clinical needs we embarked on a programme targeting selective muscarinic M₁ receptor agonists in the central nervous system.³ Unprecedented selectivity over receptor subtypes (M₂-M₅) was achieved *via* allosteric agonism⁴ at the muscarinic M₁ receptor thus providing a target molecule with good efficacy and minimal side effects. The programme started investigating two diverse chemical series and finally focussed on benzimidazolone SB-328882, a molecule with the most promising developability features. SAR studies around SB-328882 will be presented to illustrate the optimisation of target and DMPK profiles leading to a molecule active in animal models of cognition.



SB-328882

Issues and challenges associated with the identification of an allosteric agonist will be discussed in order to finally focus on the programme's achievements.

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POSTER PRESENTATIONS

1. Total Synthesis of (±)-Cordypyridone A and B and Related Structures

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Abstract

An efficient racemic synthesis of two antibacterial and antimalarial natural products, cordypyridones A and B was achieved from inexpensive, commercially available starting materials in an overall yield of 15% (8% and 7%, respectively). This convergent synthesis utilises a key coupling step of two fragments and the subsequent functional group transformations lead to the target compounds and their 8-*epi*-analogues.

2. Towards a Cyclic Tetrapeptide Library for Biological Activity Screening

Annie Lim, Ariel Ong, Brian Chia
*Experimental Therapeutics Centre, Agency for Science, Technology and Research (A*STAR)*

Abstract

Beta-turns are common structural recognition motifs adopted by many natural peptides and proteins when bound to their corresponding biological receptors, including G protein-coupled receptors (GPCRs). GPCRs are membrane proteins involved in many biological functions including vasodilation/constriction, secretion, cell signaling, cell growth and pain perception. Indeed, approximately 30% of commercial drugs are known to target GPCRs¹. In a survey of 120 GPCRs, it was reported that their corresponding peptide ligands adopt either alpha-turns or beta-turns². This prompted us to build a proprietary cyclic tetrapeptide library for biological activity screening. By cyclising linear tetrapeptides into their head-to-tail cyclic forms, we postulate that they will retain their biological activities. Preliminary studies revealed that cyclic tetrapeptides are stable in acidic conditions and are resistant to trypsin digestion. Hence, they can potentially be developed into drugs. Currently, the peptide group at the Experimental Therapeutics Centre is actively building a cyclic tetrapeptide library and are looking for potential collaborators to screen these peptides for biological activity.

¹ Hopkins *et al.* "The druggable genome." *Nature Reviews Drug Discovery*. 2002, 1, 727-730.

² Tyndall *et al.* "Over 100 peptide-activated GPCRS recognize turn motifs in ligands." *Chemical Reviews*. 2005, 105, 793-826.

Biographies & Abstracts

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3. Investigation of antiprion activity of acridine derivatives

Nguyen Thi Hanh Thuy, GO Mei Lin

Department of Pharmacy, National University of Singapore, Medicinal Chemistry Programme

Abstract

A library of acridine derivatives were synthesised and evaluated in vitro for their antiprion activity. Among compounds tested, compound 6-chloro-2-methoxy-N-(4-(4-methylpiperazin-1-yl)phenyl)acridin-9-amine (compound 17) was able to clear scrapie prion proteins in three different prion strains including two mouse strains (RML and 22L) and one human strain (Fukuoka-1) in N2a, a mouse neuroblastoma cell line and N2a#58 which overexpressed prion proteins. The effects on cellular prion proteins were investigated for these compounds but additional studies are required to confirm.

4. Synthesis of Resorcylic Acid Lactones as Protein Kinase Inhibitors for the Development of Cancer Chemotherapeutics”.

Anqi Chen, Jin Xu, Wendy Goh, Nguyen Quang Vu and Christina L. L. Chai

Institute of Chemical and Engineering Sciences (ICES)

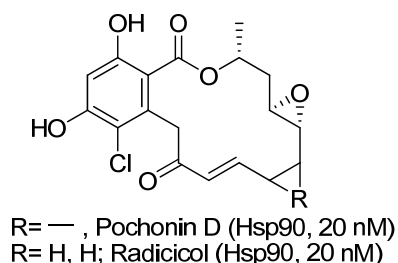
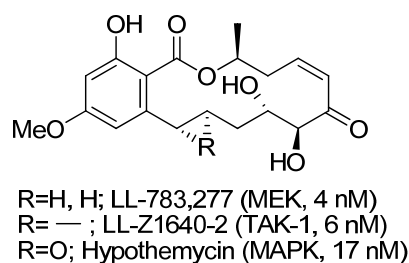
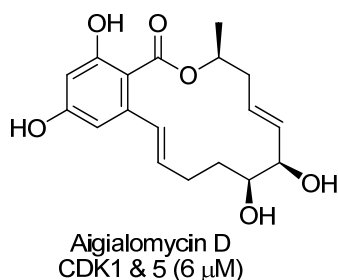
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Abstract

Resorcylic acid lactones (RALs) are a group of polyketide natural products produced by a variety of fungal strains. These natural products display potent yet diverse biological activities, especially as inhibitors of protein kinases and heat shock protein 90 (Hsp90).¹ Amongst the biological targets of these compounds, cyclin-dependent kinases (CDK), mitogen-activated protein kinases (MAPK), TGF β -activated kinase-1 (TAK-1) and Hsp90 are validated targets for anticancer drug development. In this regard, we have been interested in the synthesis of these compounds and their analogues for the understanding of the structure-activity relationship and the exploration of their potential as cancer chemotherapeutics.^{2, 3} We will present our work on the synthesis of selected RALs and their analogues for biological evaluation.



References:

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2. N. Q. Vu, C. L. L. Chai, K. P. Lim, S. C. Chia, A. Chen, *Tetrahedron*, **2007**, 63, 7053.
3. A. Chen, N. Q. Vu, WO/2008/010776, 24 Jan 2008.

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5. Purine derivatives as inhibitors of PDK-1

Stéphanie Blanchard

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<http://www.sbio.com>

Abstract

As part of our program toward the development of kinase inhibitors as potential anti-cancer therapeutics, we have designed a new series of molecules based on an aryl-purine scaffold.

A series of substituted purines were prepared and showed good potency in inhibiting PDK-1, a key enzyme in the PI3K/AKT signaling pathway which plays a key role in cancer cell growth, survival and tumor angiogenesis.

The synthesis and SAR of this series of compounds are presented as well as PK and drug-like properties.

6. Total synthesis of laetirobin: a late-stage mitotic blocker that induces cell death

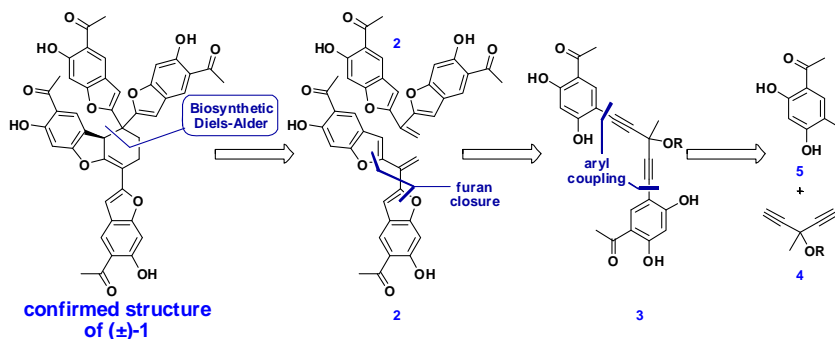
Bastien Reux¹, Oliver Simon¹, James J. La Clair² and Martin J. LEAR¹

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²Xenobe Research Institute, 3371 Adams Avenue, San Diego, California 92116, USA

Abstract

During 2006, a selection of fungal specimens, found growing parasitically on *Robina pseudoacacia*, were collected and analysed for active principals. Unique to this parasitic fungus, identified as *Laetiporus sulphureus*, was a natural product that we coined laetirobin (**1**).^[1] Subsequent studies showed **1** to be a potent cytostatic agent that is derived biosynthetically via a homodimeric Diels-Alder cycloaddition of a natural precursor. The structure of laetiporina (**1**) was determined by a combination of spectroscopic methods and small molecule X-ray crystallography. Our biomimetic total synthesis now provides gram quantities of (\pm)-**1** for mode of action and preclinical studies. The detailed pharmacophoric profiling of laetirobin-scaffolds and the biomolecular targeting of the natural product (\pm -**1**) are ongoing. Currently, laetirobin (\pm -**1**) stands as the first in its structural class. It is a new, potent antimitotic agent (IC₅₀ 0.1-0.5 nM) with moderate cytotoxicity (GI₅₀ 0.16 \pm 0.03 μ M) that displays the ability to invoke programmed cell death, all desirable attributes in the development of a potential anticancer agent.^[2]



[1] Lear, M. J.; Simon, O.; Foley, T. L.; Burkart, M. D.; Baiga, T. J.; Noel, J. P.; DiPasquale, A. G.; Rheingold, A. L.; La Clair, J. J. *J. Nat. Prod.* **2009**, *72*, 1980-87.

[2] Simon, O.; Reux, B.; La Clair, J. J.; Lear, M. J. *Chem-Asian J.* **2010**, *5*, in press (featured as cover page of issue 2).

Biographies & Abstracts

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7. Analogue Total Synthesis and Biological Study of Tetrahydrolipstatin-based Probes

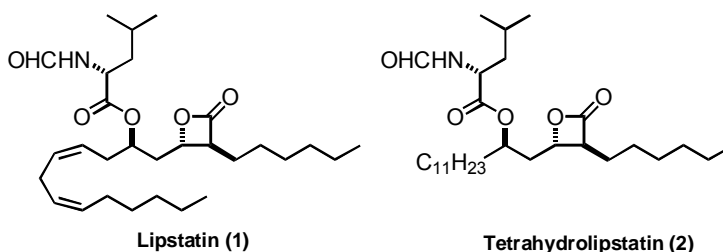
Mun Hong Ngai¹, Pengyu Yang², Kai Liu², Shao Qin Yao² and Martin J. LEAR¹

¹Department of Chemistry, Faculty of Science, and Medicinal Chemistry Programme, Life Sciences Institute, National University of Singapore, Science Drive 3, Singapore 117543

²Departments of Chemistry and Biological Sciences, Faculty of Science, and Medicinal Chemistry Programme, Life Sciences Institute, National University of Singapore, Science Drive 3, Singapore 117543

Abstract

Tetrahydrolipstatin (THL) is an inhibitor of the thioesterase domain of fatty acid synthase (FAS), an enzyme required for tumor cell survival. Herein, we report the analogue total syntheses of THL-alkyne analogues via a tandem Mukaiyama aldol-lactonization (TMAL) as the key step to directly incorporate the β -lactone functionality.^[1] Click-chemistry based inhibitory studies within several cancer cell lines were also performed and will be discussed.



[1] Yang, P.-Y.; Liu, K.; Ngai, M.H.; Lear, M.J.; Wenk, M.; Yao, S.Q. "Activity-Based Proteome Profiling of Potential Cellular Targets of Orlistat – An. FDA-Approved Drug with Anti-Tumor Activities", *J. Am. Chem. Soc.* **2010**, 132, *in press*.

8. Novel inhibitors of PDK1 identified through NMR fragment based screening

P.M.Ramanujulu, Brian Dymock

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Abstract

The PI3K/AKT signaling pathway plays a key role in cancer cell growth, survival and tumor angiogenesis. A number of key enzymes on this pathway represent promising targets for anti cancer drug development. Herein we describe the discovery of weak-binding fragment inhibitors of PDK1 using a NMR Spectroscopy fragment based screening approach. Hits were evolved by focused medicinal chemistry using computational fragment modelling followed by biochemical testing of synthesised novel analogues resulting in novel low micromolar leads with high ligand efficiency.

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9. Lead Optimisation of Meisoindigo as Anti-proliferative Agent

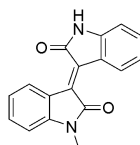
Xi-Kai Wee, Mei-Lin Go

Department of Pharmacy, Faculty of Science, National University of Singapore, 18 Science Drive 4, Singapore 117543.

Abstract

Meisoindigo (甲异靛, 1-methyl-isoindigo) has been utilised as a Chinese medication for chronic myelogenous leukemia (CML) for many years. The development of meisoindigo derived from a structurally similar compound named indirubin- the active entity of the traditional chinese herbal prescription “Danggui-Longhui Wan” for the treatment of chronic myelogenous leukemia. Despite numerous studies were carried out on the indirubin scaffold, further reports of the investigations of the isoindigo scaffold beyond meisoindigo as anti-cancer agents has been limited.

Chemical synthesis of a series of substituted isoindigos and their investigations as anti-proliferative agents were carried out. In particular, several 1-substituted isoindigos with reference to meisoindigo as the lead compound was studied. The isoindigos were synthesised via a modified acid-catalysed aldol condensation assisted by microwave irradiation. The anti-proliferative activities of the compounds were evaluated on a series of cancer cell lines namely HL60 acute promyelocytic leukemic myeloblast cells, K562 chronic myelogenous leukemic lymphoblast cells and HCT116 colorectal carcinoma cells. Selectivity for cancer cell lines were assessed by evaluating their effects on normal lung fibroblast cells. We found that several N-alkylated isoindigos showed more promising anti-proliferative activities than meisoindigo. Such findings led to other functionalised meisoindigo analogues for further optimisation studies.



Meisoindigo

10. Virtual screening of small-molecule libraries against dengue RNA-dependent RNA polymerase

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Abstract

Dengue fever and dengue hemorrhagic fever are mosquito-borne infections caused by the dengue virus, a member of the Genus Flavivirus. The disease occurs in over 100 countries, with more than 2.5 billion people at risk. There are currently no approved antiviral drugs or vaccines to combat dengue infections. The dengue viral RNA-dependent RNA polymerase (RdRp) plays an important role in viral replication and is therefore a potential target for the development of dengue RdRp inhibitors. Ligand candidates were identified from several libraries (total of 2 million compounds) by two virtual screening approaches. In the first approach, a conserved catalytic domain of the dengue RdRp was used as the site for high-throughput docking of small molecules. Hit molecules that interacted with important amino acid residues in the binding pocket were retained and experimentally verified in a dengue polymerase assay. In the second approach, an in-house crystal structure of a compound bound to an allosteric binding pocket ($IC_{50} = 0.35\mu M$) of RdRp was used for mining several small-molecule libraries based on shape and electrostatics matching methods. Further, a pharmacophore was generated from the analogues of the parent compound and their respective IC_{50} activity values. The pharmacophore was then used to sieve through the hit lists in order to identify compounds that possess the key features important for the allosteric binding. The results and performance of the virtual screening approaches in identifying hit compounds against RdRp will be presented.

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11. Small Molecule Inhibitors of Bcl-X_L and Mcl-1 Based on Pyridine Analogues of BH3I-1

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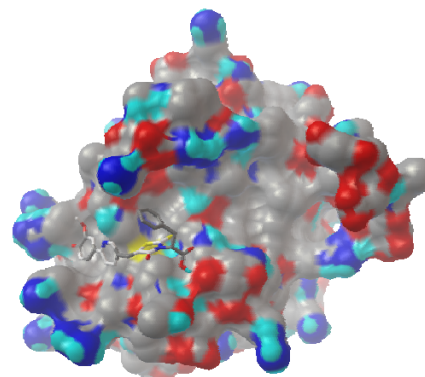
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Abstract

The Bcl family of proteins regulates the apoptotic pathway in cells, a process by which unwanted or damaged cells are removed. The over-expression of anti-apoptosis Bcl-2 proteins such as Bcl-X_L and Mcl-1 have been linked to resilience of cancer cells towards chemotherapy by preventing programmed cell death. The inhibition of these anti-apoptosis proteins can restore the propensity of cancer cells to undergo cell death, which makes these proteins an attractive target for drug discovery.¹

Several small molecule inhibitors of Bcl-X_L and Mcl-1 have been reported in the literature including the rhodanine-based BH3I-1. This has been shown to bind to a hydrophobic cleft which is highly conserved across anti-apoptosis Bcl proteins.^{2,3} Our work has focused on the synthesis of a small library of BH3I-1 derivatives using docking studies to guide the design and selection of the target molecules. We have identified several potent mixed inhibitors of Bcl-X_L and Mcl-1 as well as selective inhibitors of Mcl-1 using a fluorescence-based polarization assay.



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3. C. Day, L. Chen, S. Richardson, J. Harrison, D. Huang, M. Hinds, *J. Biol. Chem.* **2005**, *280*, 4738

Biographies & Abstracts

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12. Effect of Lovastatin on RSV Infection—a possible link to lipid rafts and a potential treatment

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1. Singapore-MIT Alliance for Research & Technology (SMART) ID IRG
2. School of Biological Sciences, Nanyang Technological University

Abstract

Lovastatin is a drug approved by FDA for treatment of hypercholesterolemia. It can be used to suppress cholesterol synthesis in cells by inhibiting hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase. In epithelial cells, RSV infection was shown to be associated with lipid rafts. During RSV replication, there was an increase in the HMG-CoA reductase expression.

To study the effect of Lovastatin on RSV infection and to examine whether it can be a potential treatment for RSV infection, we chose two types of cells to study, HEp-2 cells and mouse lung macrophages.

Epithelial cells in the respiratory system are a major site for RSV infection and replication. HEp-2 cells were chosen to represent them. In HEp-2 cells, Lovastatin-treated cells showed a marked reduction in cholesterol level. Less virus filaments were found on the surface of the treated cells, and cell-to-cell transmission of RSV was also inhibited.

The immune cells in the respiratory system can have strong inflammation response and cause serious consequences in the host in response to RSV infection. Mouse lung macrophages were chosen to investigate this response. RSV infected macrophages secreted a panel of pro-inflammatory cytokines, and Lovastatin treatment decreased this inflammation response.

Based on these results, Lovastatin was shown to have an effect of inhibiting RSV infection and reducing the inflammation response in the respiratory system. A possible link to lipid rafts involvement in the inflammation response of RSV infection on macrophages was speculated, and Lovastatin showed some potential to be used to reduce the destructive response in RSV infection. Further investigation will be conducted to confirm these findings in the *in vivo* context.

13. Chemistry and Chemical-Biology Inspired by Natural Products

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Abstract

Over the course of history, natural products have served admirably as the cradle for the evolution of chemical sciences, and nurtured the discovery of novel synthetic technologies and strategies. In conjunction with the biological activities harnessed by the natural substances, accessing natural and designed compounds by chemical means also has a cemented position in bridging biology and medicine. Chemical Synthesis Laboratory @ Biopolis has been actively pursuing number of architecturally complex natural products exhibiting promising therapeutic potentials, thereby advancing our understanding in chemistry and chemical biology.

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14. An experimental and molecular docking study to identify the antifolate activity of phytochemicals in *Pseudomonas aeruginosa*

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Abstract

Pseudomonas aeruginosa is a major nosocomial and opportunistic pathogen, vulnerable mostly to patients suffering from cystic fibrosis and people with weak immune system. Moreover, this organism has the ability to develop resistance which significantly reduces the efficacy of many commercially available antifolate drugs such as sulfonamides and trimethoprim. Efflux pumps and permeability barrier are considered as the main reason for the drug resistance mechanism to the antifolates. In order to eradicate the resistance development, we approached an analogous strategy of combining phytochemicals along with the classical antifolates. Phytochemicals are natural products which have always been used for the development of novel drugs for the treatment of various organisms. The phytochemicals (Protocatechuic acid, Gallic acid, Quercetin and Myricetin) chosen for this study are structural analogues of trimethoprim. Combination therapy by susceptibility testing was done using broth microdilution assay. The studied organism was susceptible to both Trimethoprim and Sulfamethoxazole. Drug interaction studies for the phytochemicals in combination with antifolates, sulfamethoxazole resulted in synergism and additivity in combination with trimethoprim.

P. aeruginosa dihydrofolate reductase enzyme is an important target for antimicrobial chemotherapy. To validate the hypothesis of these phytochemicals could act as an antifolate drug, we proceeded with computational analysis using molecular docking study to investigate the binding modes of these phytochemicals in the DHFR active site using molegro virtual docker (MVD). Homology modelling was used to generate 3D structure of *P. aeruginosa* DHFR for the first time using *E. coli* DHFR (PDB code: 1RA2) as the template structure. Structural validation of the 3D protein was carried out using SWISS-MODEL structure assessment tool. The phytochemicals, quercetin and myricetin docks in the active site of *P. aeruginosa* with promoted binding at the NADP site wherein protocatechuic acid and gallic acid docks in the active site of *P. aeruginosa* with promoted binding at the folate site. Key active site residues are found interacting with the functional groups of the phytochemicals forming strong hydrogen and hydrophobic interactions. The reason for the additivity is trimethoprim and these active inhibitors act at independent sites in the active site cavity interacting with common target residues which implies that, each drug has no affect on the binding of the other.

There is good correlation with the experimental inhibitory activities and the computationally predicted binding energies of the inhibitors to *P. aeruginosa* DHFR suggesting possible mode of action of these polyphenols as antiDHFR compounds in bacteria. The above findings from this study provide novel insights to prevent the emergence of drug resistance and can serve as a prospective lead in the development of antipseudomonal drug developments.

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15. Phenylpropanoid Esters of Sucrose: First Total Synthesis of Lapathoside D and Helonioside A and their Antioxidant Activities

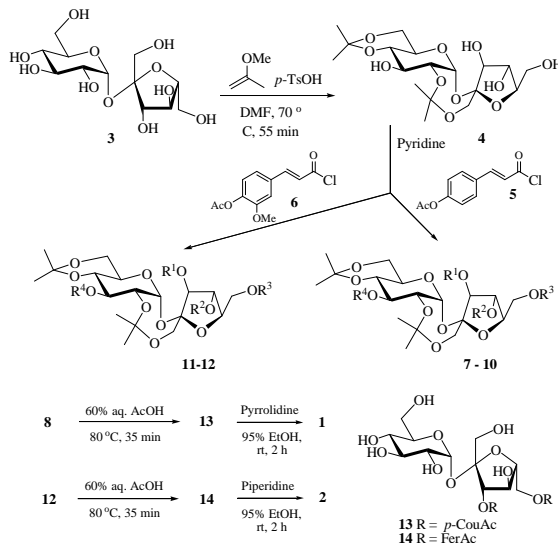
Parthasarathi Panda, Manjuvani A and Zaher M. A. Judeh

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Abstract

The first total synthesis of Lapathoside D **1** and Helonioside A **2** has been achieved successfully in four synthetic steps *via* regio- and chemoselective acylation of 2,1':4,6-O-di-isopropylidene sucrose **4** (obtained from sucrose **3**) with *p*-acetylcoumaroyl chloride **5** and *p*-O-acetylferuloyl chloride **6**, respectively (Scheme below). The antioxidant activities of Lapathoside D **1**, Helonioside A **2** and their analogues were evaluated by the DPPH free radical scavenging assay method. Helonioside A **2** proved to be a potent antioxidant compound. Structural features that contribute to the antioxidant activity were examined.

Pharmacologically active phenylpropanoid esters of sucrose such as Lapathosides, Heloniosides, Vanicosides etc were isolated from various plant species. The extracts from these plants have been used for many years as folk medicines for treatment of various diseases like cancer, haemostatics, inflammation, tumors, nephritis etc. Detailed study and investigation of these natural products having a promising biological activities as a lead compounds that have been successfully developed into drugs is limited because of more reasonable amounts of materials are required for investigation. Moreover, laborious and expensive methods are required to extract and purify of these compounds from their natural resources since there are no routes to describe their laboratory synthesis. We envision that the present approach will form a model synthesis for various natural and unnatural sucrose phenylpropanoid esters.



| Compound | R ¹ | R ² | R ³ | R ⁴ |
|----------|-----------------|-----------------|-----------------|-----------------|
| 7 | H | H | <i>p</i> -CouAc | H |
| 8 | <i>p</i> -CouAc | H | <i>p</i> -CouAc | H |
| 9 | <i>p</i> -CouAc | <i>p</i> -CouAc | <i>p</i> -CouAc | H |
| 10 | <i>p</i> -CouAc | <i>p</i> -CouAc | <i>p</i> -CouAc | <i>p</i> -CouAc |
| 11 | H | H | FerAc | H |
| 12 | FerAc | H | FerAc | H |

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