Friday 28th September 2012
Cavanagh Pharmacy Building, LG51, UCC

1.00pm  Opening of meeting:  Professor Anita R Maguire, Vice President for Research & Innovation, UCC  
Chair: TBC

1.05  Seamus Malone, Eli Lilly, Cork
Pharmaceutical Overview

1.30  Donal Harrold
Synthesis of Furanolipids as Antitumor Agents

1.50  Lorna Lennon
Crystallisation and Crystal forms of Carbohydrate Derivatives

2.10  Leslie Ann Clarke
Copper Catalysed Asymmetric C-H Insertion Reactions of α-Diazo-β-Oxo Sulfones

2.30  Jonathan Quille
Forensic Impurity Profiling and Synthesis of Precursors to the Hallucinogenic Amphetamine DOB

2.50  Tea/Coffee

3.15  Roisin O’Keeffe
The Synthesis and Biological Evaluation of Lanostane type Natural Products

3.35  Christina McSweeney
New Methods for the Asymmetric α-Alkylation of Ketones

3.55  Harold Moloney

4.15  Kate O’Reilly
Towards an enantioselective synthesis of Plakortide P and its application to the development of drugs for the treatment of Chagas Disease

4.35  Eli Lilly Presentations / Close of Meeting Reception

Speakers:
- Donal Harrold
- Lorna Lennon
- Leslie Ann Clarke
- Jonathan Quille
- Roisin O’Keeffe
- Christina McSweeney
- Harold Moloney
- Kate O’Reilly

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SYNTHESIS OF FURANOLIPIDS AS ANTITUMOR AGENTS

Donal P Harrold & S.G. Collins

Dept of Chemistry & Analytical & Biological Chemistry Research Facility, University College, Cork.

The transcription factor hypoxia-inducible factor-1 (HIF-1) has recently become a major antitumor molecular target and inhibition of HIF-1 activation has been shown to suppress the growth and spread of hypoxic tumors. The effect of hypoxia on tumor cells is twofold: reduction of cellular metabolism and cell proliferation that leads to cell death and promotion of aggressive tumor growth by selecting highly malignant tumor cells. At the present moment, despite extensive drug discovery research there is no approved drug that specifically targets tumor hypoxia. Preclinical studies have shown that inhibition of HIF-1 retards tumor growth and improves treatment outcome when combined with radiation and chemotherapeutic agents.

The challenge is to discover some potent HIF-1 inhibitors with a high therapeutic index toward tumor cells without targeting normal cells. Recently the novel terpene-derived Furospongolide 1 below has been isolated from the marine sponge Lendenfeldia sp. The structurally unique compound 1 was found to inhibit hypoxia induced HIF-1 activation (IC$_{50}$ 2.9μM) in T47D human breast tumor cells. Limited quantities of 1 after isolation from Lendenfeldia sp. have prohibited studies for its mode of action and further investigation as an antitumor agent. Therefore this project will focus primarily on the total synthesis of compound 1 and also on producing synthetic analogues and investigating their biological activity and toxicity effects.

![Structural formula of Furospongolide 1](image)

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(2) Vaupel, P.; Mayer, A. Cancer and Metastasis Rev 2007, 26, 225-239.
Carbohydrates are used extensively in the pharmaceutical sector as excipients to facilitate packaging and delivery of drugs. Apart from being very diverse in structure and properties, carbohydrates benefit from a safe history of usage with a positive health profile. Additives, or excipients, are included in the formulation to stabilize and improve the final drug product. Degradation not only results in product loss, but also can lead to issues in regulatory approval.

Although glycosides play a vital role in the metabolic process, in new drug discovery and API development, there are limited crystal structures of such compounds present in the crystal structure database. The difficulty in solving crystal structures for glycosides is the lack of a strong functional group for hydrogen bonding. Therefore the O-glycosylation with various phenols adds improved functionality for crystalline material formation and packing.

O-Glycosylation to form these novel crystal structures showed clearly the partition of the crystal structure into hydrophilic regions containing the sugar moieties and hydrophobic regions containing the aromatic groups. This leads to the formation of common bonding motifs for glycoside derivatives. Research was also carried out on the presence of polymorphs of the synthesised compounds.

Various functional groups were added to the sugar moiety in an attempt to obtain crystalline material and to assess the difference a bulky organic group can have on the crystal packing. Amides, aromatics and pyranose rings were all studied.

The methodology that was studied in glucose and cellobiose was extended to further cellodextrin derivatives. Removal of the 1-hydroxy group of the pyranose ring was carried out in order to get a clearer understanding of the cellulose bonding motif.

Cocrystallisation was carried out on the glycoside derivatives with API compounds. Grinds, crystallisations and melts were all carried out and analysed.

COPPER CATALYSED ASYMMETRIC C-H INSERTION REACTIONS OF ALPHA-DIAZO- BETA-OXO SULFONES

Leslie Ann Clarke & Anita R Maguire
Analytical and Biological Chemistry Research Facility & Chemistry Department, University College, Cork.

The stereoselective synthesis of organic compounds has a central role in organic synthesis. A recent report by this research group has shown that enantioselectivities of up to 98% can be achieved in the copper catalysed C-H insertion reactions of a wide range of α-diazo- β-oxo sulfones to yield cis thiopyrans.1 Further developing on this work, a number of the original catalytic components were systematically changed, including the bis-oxazoline ligand, the copper source and the counterion.

Additionally, a range of novel α-diazo-β-oxo sulfone substrates have been synthesised and cyclised using the aforementioned catalytic system. The efficiency, regio- chemo- and enantioselectivity of the reactions of these α-diazo-β-oxo sulfone substrates were investigated. One substrate modification was the inclusion of a non-flexible benzene ring into the linker chain. The C-H insertion reactions of these substrates produced trans sulfolanes attaining ee’s of up to 70-80%, the highest to date for this series. In addition, a vinyl group was placed adjacent to the C-H insertion site, opening up the possibility of cyclopropanation. The nature of the carbonyl group was also varied, to include an amide group allowing the possibility of lactam synthesis.

Impurity profiling is a method of characterisation of illicit drug samples. Each illegal drug will contain its own set of impurities, which allows the chemist to ascertain its unique “chemical fingerprint”. The impurity profile of an illicit drug sample may then be used as an intelligence gathering tool to link related samples, identify a possible manufacturing source and to gather information on trafficking routes.

DOB (4-bromo-2,5-dimethoxyamphetamine) is a newly emerging hallucinogenic amphetamine that sparked serious health warnings in Ireland following its first seizure back in 2003. Known more commonly as “snowball”, this drug is highly potent and may be used as a substitute to ecstasy (MDMA) and lysergic acid diethylamide (LSD). Its hallucinogenic response can be attributed to the molecules’ interaction with the 5HT2A and 5HT2C (serotonin) receptors. To date, the work carried out on the impurity profiling of DOB is limited in comparison to MDMA and methamphetamine.

This project will focus on the isolation and characterisation of impurities from the synthesis of DOB and its precursors. Following this, independent synthesis of some of these impurities will be carried out for use as reference standards. It is hoped also that street samples of DOB will be acquired so that authentic impurity profiles can be established.

In order to build an impurity profile, DOB and its precursors are synthesised using both literature and novel routes. Extensive chromatographic and spectroscopic analysis is performed on the newly prepared compounds, to determine their purity and chromatographic profile. This would allow for the conformation of previously proposed impurity structures, preparation of standard reference samples for use by forensic laboratories and evaluation of possible pharmacological properties.

In this work, the phenylacetic acid synthetic route to 2,5-dimethoxypropan-2-one (a precursor to DOB) is under investigation. The most common impurity of this step is based on a dibenzylketone core structure. For use as reference standards, a number of isomeric brominated dibenzylketones were independently synthesised as potential impurities of the phenylacetic acid route to DOB. These various brominated analogues may arise due to a non-regiospecific bromination step in the synthesis of DOB.
This project focuses on the synthesis of various derivatives of lanostane type natural products. In view of its similar structure, lanosterol was chosen as a starting material in the semi-synthesis of these natural products. The purification of commercial lanosterol, which is highly contaminated with the impurity dihydrolanosterol, into two viable starting materials has been explored. The main avenues being investigated are the modification of the skeletal framework of the lanostane steroid by allylic oxidation and side chain functionalisation to encompass various oxidation products and tertiary nitrogen moieties. These novel target molecules will be tested for their inhibitory or cytotoxicity effects against various cancer cell lines. The precedent for the synthesis of these compounds as viable target molecules comes from recent reports on the biological activities of the extracts from the Antrodia camphorata fungus including anticancer activity for urinary bladder cancer1 and breast cancer cells2. An initial collaboration with Professor John Luong of the Biotechnology Research Institute, Montreal, directed our interest towards the mimicking of the structural features of the Antrodia camphorata isolates as one of the aims of the project3. This project is also linked with ongoing work within our research group involving the synthetic modification of the aglycone solanidine, which contains a tertiary amine moiety in its skeletal framework. Therefore another aim of the project is to synthesise a variety of tertiary nitrogen containing lanosterol moieties.

Therefore, the overall aim of the project is to produce a library of compounds using efficient and high yielding synthetic methodology. Once this library is established, a further aim of this work is to examine these novel compounds for their cytotoxicity in cancer cell lines.

Figure 1:
1 Antcin B. A potent isolate from Antrodia camphorata.
2 Lanosterol oxidation product currently in biological testing.
3 Various tertiary amine moieties currently being synthesised.

Despite its abundance, targeting the α-position of ketones in an asymmetric fashion represents a significant challenge for organic chemists. In fact the only method to synthesize these compounds involves chiral auxiliaries. The SAMP/RAMP methodology is by far the most popular, it is over 30 years old and has been used in the synthesis of many natural products.

This project details the successful application of non-chiral auxiliary methodology in asymmetric α-alkylations, using (-)-sparteine as a chiral ligand. (-)-Sparteine is a widely used chiral diamine for asymmetric synthesis however, there is no reported route to α-alkylated ketones using this, or any other organic ligand system.

The hydrazone function was chosen as a ketone surrogate to facilitate smoother alkylation; also the dimethyl-amino group of the hydrazone could co-ordinate to the lithium in a highly structured azaenolate intermediate. It is this rigid system which likely promotes addition, of the alkylating agent, from one side preferentially.

The ketone surrogate chosen, was prepared in 81% yield from 3-pentanone. Subjecting this to secBuLi/(-)-sparteine, followed by addition of benzyl bromide and hydrolytic cleavage afforded benzylated pentanone in 60% ee.

References
3-(2H)-Furanones are novel heterocycles incorporating a β-hydroxyenone moiety enclosed by a five-membered ring. In the course of synthetic chemistry studies on these compounds, we noted that certain 3-(2H)-furanones exhibited interesting optical properties. This effect is unprecedented for furanone structures and is significant for their potential applications in the areas of photonics, organic light emitting diodes (OLEDs) and in development of materials for non-linear optical (NLO) applications. Structures 1 and 2 are representative of the compounds under investigation.

These and related substances were prepared using Pd(0)-mediated C-C bond forming reactions on halogenated furanone substrates as key reactions. Choice of catalyst and ligands is critical since heterocycles of this type undergo competing catalyst induced reductive dehalogenations under typical Sonogashira reaction conditions.

“Push-pull” conjugated frameworks are becoming an increasingly common feature of materials under investigation for NLO applications. We are currently incorporating this feature into a number of 3-(2H)-furanones, e.g. 3.
Between 8-11 million people in Mexico, Central America and South America are estimated to have Chagas disease[1]. Chagas disease is a tropical vector-borne disease caused by the parasite Trypanosoma cruzi and transmitted by the triatomine insect. The Plakortide series of molecules show potent anti-Chagasic effects antileishmanial, antitrypanosomal, antineuroinflammatory and cytotoxic activity when assayed[2]. The crucial aspect of their structure is that they contain an \( \alpha,\beta \)–unsaturated carbonyl moiety and a cycloperoxide, which has been postulated is responsible for its selectivity and apparent activity against \( P.falciparum \) and \( T.cruzi \). It was found that Plakortide \( P \) is highly selective for \( T.cruzi \) and was reported to be 15 times more potent than the conventionally used drug, Benznidazole[2].

To date, no stereoselective synthesis has been published for the 6-membered, 1,2-dioxane cycloperoxides in the Plakortide series. While some work has been published on the 5-membered 1,2-dioxalane cycloperoxides, the methodology utilized has little application for the 1,2-dioxanes[3]. Synthetic methods for the preparation of chiral peroxides remain limited. Utilising the recent work on the catalytic, enantioselective peroxidation of \( \alpha,\beta \)-unsaturated ketones[4], we aim to develop this methodology further such that bioactive, chiral 1,2-dioxanes can be readily synthesized in the laboratory on a large scale, allowing for further biological studies.

With thanks to:

Lilly

Answers That Matter.