MHRD Scheme onGlobal Initiative on Academic Network (GIAN)

MODERN ASPECTS OF ORGANIC SYNTHESIS

1.0 Overview

Organic molecules (i.e. those made up principally of carbonatoms) are key to the functional molecules of society; they form our pharmaceuticals, our agrochemicals, and our new materials (plastics, etc.), as well as being the molecules of life. We need such molecules for current and new applications. A key part of organic chemistry is the ability to synthesize new and novel molecules and structural types for those applications. In addition, we need organic molecules to improve our understanding of our life processes, in order to make advances in healthcare.

Despite a good portfolio of synthetic methods developed over the last century, there remained some molecular transformations that were difficult, even impossible to achieve. Furthermore, there is a need to find shorter routes to known transformations, with the target of more sustainable methodology. All of these factors make the development of new synthetic methods an ongoing goal for organic chemists. Most organic synthesis relies on reactions of conventional electron-rich species (nucleophiles) with electron-deficient counterparts (electrophiles) to form new carbon-carbon bonds. There are, however, bond-forming processes that do not fall into this category. They may depend simply on electron rearrangements and FMO control (*pericyclic reactions*); on *reactive intermediates* (benzyne, carbenes, radicals); or on catalytic cycles where conventional nucleophile/electrophile interactions are less relevant (*organometallic reagents*). The course proposed herein will examine recent advances in these areas.

2.0 Objectives

The primary objectives of the course are as follows:

i) To expose participants to modern synthetic methodologies that do not depend on conventional nucleophile/electrophile interactions, highlighting the below modern areas, and their applications;
ii) to explore the Frontier Molecular Orbital (FMO) concept and *pericyclic reactions*, focusing on cycloaddition reactions, sigmatropic rearrangements;
iii) to introduce *reactive intermediates*, focusing on carbenes, benzynes and free radicals;
iv) and to highlight the rapidly-growing area of *d*-block *organometallic reagents* and their uses in catalytic processes.

3.0 Teaching Faculty with allotment of Lectures and Tutorials

1. **Prof Raymond C F Jones(RCFJ) : 13 hrs lectures and 3 hrs tutorials**

4.0 Course details

4.1 Tentative Duration: November 19-23, 2018 (5 days): 13 hrs lectures and 3 hrs workshops

4.2 Tentative Lecture Schedule

Day 1

Lecture 1:1 hrs: RCFJ

Introduction to pericyclic reactions; pericyclic reactiont ypes; molecular orbitals and the FMO concept

Lecture 2: 1 hrs: RCFJ

4+2 cycloadditions: the Diels-Alder reaction, reactivity, regiochemistry, stereochemistry

Lecture 3: 1 hrs: RCFJ

4+2 cycloadditions: the 1,3-dipolar cycloaddition; dipoles and dipolarophiles; examples in target synthesis

Lecture 4: 1 hrs

2+2 photocycloadditions; Electrocyclic reactions, 4p and 6p cases

Day 2

Lecture 5: 1 hrs; RCFJ

3,3-sigmatropic rearrangements: Cope and Claisen rearrangements plus variants

Tutorial 1: 1 hrs: RCFJ

Problem session: pericyclic reactions in target synthesis, e.g endiandricacids, etc.

Lecture 6: 1 hrs: RCFJ

Introduction to reactive intermediates; carbene generation and reactivity; N-heterocycliccarbenes (NHCs) in organocatalysis

Day 3

Lecture 7: 1 hrs: RCFJ

Benzynes: history, evidence for existence, structure; modern methods for generation, reactivity

Lecture 8: 1hrs: RCFJ

Radicals, structure, stereochemistry; chain reactions, cyclisations, cascade reactions

Tutorial 2: 1 hrs; RCFJ

Problem session: radical reactions in target synthesis, e.g., hirsutene, etc.

Day 4

Lecture 9: 1 hrs: RCFJ

Introduction to *d*-block transitionmetals and metal-ligand bonding; Palladium-catalysed coupling reactions, Heck, Stille, Negishi, Kumadareactions

Lecture 10:1 hrs: RCFJ

Palladium continued: Suzuki-Miyaura, Sonogashira reactions; Buchwald-Hartwig reaction; C-H activation

Lecture 11:1 hrs: RCFJ

Ruthenium-catalysed reactions (1): metathesis, including ring-closing metathesis (RCM), cross-metathesis (CM), ene-ynemetathesis (EYM)

Day 5

Lecture 12: 1 hrs: RCFJ

Ruthenium-catalysed reactions (2): ring-opening metathesis (ROM), ring-opening metathesis polymerization (ROMP), alkyne metathesis

Lecture 13 : 1 hrs: RCFJ

Gold-mediated homogeneous processes: alkyne activation; examples of metal-mediated reactions in synthesis

Tutorial 3: 1 hrs; RCFJ

Problem session: metal-mediated reactions in complex molecule synthesis

Date of Examination: November 23, 2018

5.0 Who can attend

Students at BSc/MSc, PhD students and from reputed academic & technical institutions

Researchers upto PhD levels at R & D laboratories

6.0 Detailed CV of Experts

6.1 CV of Prof Raymond C F Jones

Professor Raymond C F Jones is presently Emeritus Professor of Organic & Biological Chemistry, Loughborough University, UK. He has been teaching organic chemistry to students at all levels (foundation year, BSc/MChem years 1-4, MSc and PhD; approx. 50 lecture hours per annum plus tutorials/workshops and lab classes) for 42 years, covering all topics within organic chemistry, including synthetic methods, heterocyclic chemistry and biological chemistry. He has also been active in research for over 40 years, publishing to date 133 papers in international high-impact journals, plus 14 review articles and 3 book chapters or edited volumes. He has given 68 invited and plenary conference lectures, and delivered 99 invited research seminars at universities and 35 such seminars at industry locations. His research can be described as *Organic Synthesis in Heterocyclic & Heteroatom Chemistry*: Principal research themes are: (i) total synthesis & methodology aimed at key structural units of naturally occurring molecules; (ii) synthetic molecules designed to have, biological properties. Current research emphases are: asymmetric synthesis (heterocyclic templates as control elements); dipolar cycloadditions; modified bi-

omolecules (peptide mimetics; unusual amino acids, e.g. amidine amino acids in siderophores; heterocyclic amino acids as peptide-nucleic acid building blocks). This research and teaching equips him perfectly for teaching the course proposed herein.

Positions and Employment

• I.C.I. Postdoctoral Fellowship: EidgenössischeTechnischeHochschule, Zürich, Switzerland (1973–74).

• University of Nottingham: Lecturer in Chemistry (1974–92); Senior Lecturer (1992–95)

• Open University (OU) Professor of Organic Chemistry, Head of Chemistry (1995-99).

• Visiting Research Professor, Open University (2000-2004).

• Loughborough University, Professor of Organic and Biological Chemistry (2000-2016); Director of Studies for Chemistry (2013-2016).

• *Current post*: Loughborough University, Emeritus Professor of Organic and Biological Chemistry

Other Experience and Professional Memberships (selected)

• Fellow of Royal Society of Chemistry (F.R.S.C., C.Chem.), elected 1980; member of RSC since 1970.

• Chartered Scientist (C.Sci.) elected 2004.

• Sir William Evans Fellow, University of Otago, Dunedin New Zealand, 2000.

• External Examiner for BSc/MChem degrees at 17 universities in UK and West Indies.

• External Examiner for approx. 115 PhD/MSc/MPhil theses at 45-plus institutions in UK, Ireland and internationally

• External Assessor for internal reviews of Chemistry at 8 institutions in UK and West Indies

• Member of 1st Quality Assurance Agency (QAA) Benchmarking Group for Chemistry (1998-1999).

• Chair of Heads of Chemistry UK (2001-2003).

• Member of Engineering & Science Research Council Peer Review College (1997-2015).

• Member of Editorial Board of *Tetrahedron Letters* and*ARKIVOC*, and of referee panels for *Chem. Commun.*;*J. Am. Chem. Soc.*; *J. Chem. Soc., Perkin Trans. 1*; *J. Heterocycl. Chem*; *J. Org. Chem.*; *Org. Biol. Chem.*; *Tetrahedron*; *Tetrahedron Lett.*;*Synlett*; *Synthesis*; *Synth. Commun.*;*Eur. J. Org. Chem.*; *ARKIVOC*.

Royal Society of Chemistry service (selected)

• Elected President, RSC Organic Division, 2013-16; President-elect 2012-13, Immediate Past-President 2016-17

• President, RSC Organic Division 2004-07; Vice-President from 2000; President-elect from 2003; Council/Executive Member from 1997-present; International Activities Coordinator (Organic

Division was formerly Perkin Division); Chair, Organic Division Awards Committee and Travel Grants Committee 2013-16

• Elected Member & Trustee RSC Council 2007-2011

• RSC Audit Committee 2009-11; Disciplinary Audit Committee 2008-09

• Member, High Level Steering Group for Chemistry Centre Project

• Member, RSC Science and Technology Board (to 2007); Awards, Conferences & Travel Grants Committee, also sub-committees: Travel Grants; Awards; Organic Division Awards (to 2010).

• Member, RSC Science, Education & Industry Board, Awards Working Group (both 2013-16)

• Chair, Heterocyclic & Synthesis Group of Perkin Division, RSC (2002-04), Secretary/Treasurer (1992-96), Committee member (1989-96)

• Member of organizing committee of approx. 35 national and international conferences (in addition, 35 with Society for Chemical Industry).

Contribution to Science

1. **Synthetic studies towards the cyclic tricarbonyl metabolites and analogues**. The 3-acyltetramic acid, 3-acyl-4-hydroxy-2-pyridone and coleophomone families of natural; products have a 2-acyl-substituted cyclic1,3-dicarbonyl ('cyclic tricarbonyl') sub-structure whose synthesis the Jones group has been investigating for many years. These natural products have a range of biological activities including antibiotic, antiviral, antitumour, antiulcerative, fungicidal, cytotoxic and mycotoxic properties, and as enzyme inhibitors (e.g. of protein tyrosine kinase bacterial cell-wall transglycosylase & human heart chymase). The Jones group has reported a range of novel synthetic approaches to the natural products and their analogues, most recently using 4-acylisoxazoles as masked cyclic tricarbonyl moieties. Recent publications (which also reference earlier contributions) include:

   1.'New Methodologies for Synthesis of 3-Acylpyridone Metabolites', **R.C.F. Jones**, A.K. Choudhury, J.N. Iley, G. Loizou, C. Lumley and V. McKee, *Synlett*, 2010, 654-658.

   2.'A New 3-Ethoxycarbonylmethylisoxazolopyridone as a Precursor to Acylpyridones', **R.C.F. Jones**, J.N. Iley and G. Loizou, *Heterocycles* 2012, **84**, 1235-1244.

   3. 'Aldol elaboration of 4,5,6,7-tetrahydroisoxazolo[4,3-*c*]pyridin-4-ones, masked precursors to acylpyridones', **R.C.F. Jones**, A.K. Choudhury, J.N. Iley, M.E. Light, G. Loizou and T.A. Pillainayagam, *Beilstein J. Org. Chem.*, 2012, **8**, 308-312.

   4. 'New routes towards reutericyclin analogues', **R.C.F. Jones**, J.P. Bullous, C.C.M. Law and M.R.J. Elsegood, *Chem. Commun.*, 2014, **50**, 1588-1590.

   5. 'Isoxazole to oxazole: a mild and unexpected transformation', **R.C.F. Jones**, A. Chatterley, R. Marty, W.M. Owton and M.R.J. Elsegood,*Chem. Commun.*, 2015, **51**, 1112-1115.

2. **2-Imidazolinesas building blocks for N-heterocyclic molecules**. The majority of pharmaceutically useful molecules contain an N-heterocyclic ring, and the Jones group has developed the use of the 2-imidazoline (4,5-dihydroimidazole) unit as a template for building N-heterocycles, including with a defined and predictable stereochemistry; shape is key to biological activity. The biological targets were initially adrenergic receptors but could range across a much broader spectrum. Jones's synthetic contributions include anion formation and elaboration, dipolar cycloadditions and enzyme mimicry. Representative recent publications include:

   1. 'The Annulation of 2-Imidazolines',**R.C.F. Jones**, *Adv. Heterocycl. Chem.*, 2010, **101**, 125-160.

   2. 'Cycloaddition of HomochiralDihydroimidazoles: A 1,3-Dipolar Cycloaddition Route to Optically Active Pyrrolo[1,2-*a*]imidazoles', **R.C.F. Jones**, K.J. Howard, J.S. Snaith, [A.J. Blake], W.-S. Li and P.J. Steel, *Org. Biomol. Chem*., 2011, **9**, 297-306.

   3. 'ImidazoliumYlides from a Conjugate Addition–Proton Transfer Route and their Cycloaddition Reactions', **R.C.F. Jones**, J.N. Iley, M. Sanchis-Amat, X. Zhang, V. McKee, S.J. Coles and T. Gelbrich, *Chem. Commun.*, 2011, **47**, 7965-7967.

   4. 'An Enantioselective Route to Pyrrolidines: Removal of the Chiral Template from HomochiralPyrroloimidazoles', **R.C.F. Jones**, K.J. Howard, J.S. Snaith, [A.J. Blake], W.-S. Li and P.J. Steel, *Tetrahedron*, 2011, **67**, 8925-8936.

   5. 'Coenzyme-inspired chemistry 1: the C-2 alkylation of 4,5-dihydroimidazoles', **R.C.F. Jones** and J.R. Nichols, *Tetrahedron*, 2013, **69**, 4114-4119.

   6. 'Coenzyme-inspired chemistry 2: 4,5-dihydroimidazolium 2-(1-hydroxyalkyl)-4,5-dihydroimidazoles ylides (NHCs) and the reactions of 2-(1-hydroxyalkyl)-4,5-dihydroimidazoles', **R.C.F. Jones** and J.R. Nichols, *Org. Biomol. Chem*., 2013, **11**, 5926-5935.

3. **Modified biomolecules: peptide mimetics and unusual amino acids**. The Jones group has investigated new non-proteinogenic amino acids, peptide mimetics and amino acid-derived natural products. These include heterocycles as peptide bond replacements, residues with non-natural heterocyclic side chains, and the pyoverdinsiderophore natural products that contain oxidized tyrosine moieties. Representative recent publications include:

   1. 'Synthesis of the PyoverdinChromophore by a Biomimetic Oxidative Cyclisation', **R.C.F Jones**, S.C Yau, J.N. Iley, J.E. Smith, J. Dickson, M.R.J. Elsegood, V. McKee and S.J. Coles, *Org. Lett.*,2009, **11**, 1519-1522.

   2. '3-(1-Aminoalkyl)pyrazole- and 4,5-dihydropyrazole-5-carboxylic Acids as Peptide Bond Replacements', **R.C.F. Jones**, L.E. Seager and M.R.J. Elsegood, *Synlett*, 2011, 211-214.

3. ‘Novel heterocyclic α-amino acids with sulfur-containing side-chains’, **R.C.F. Jones**, L.J. Crumpling and J.N. Iley, *ARKIVOC*, 2011, (iv), 82-103.

4. **Novel methods in heterocyclic chemistry**. This strand of the Jones group work has been ongoing over many years, with diverse contributions made to synthetic heterocyclic methodology. Recent examples are exemplified by collaborations with Prof SM Allin (Nottingham Trent University) on a Fries-Claisen dual rearrangements sequence, and with Professor M S Singh at Banaras Hindu University to explore multi-component reactions (MCR) in various heterocyclic systems. The resulting publications are:

   1. ‘Development of a Dual Fries-Claisen Rearrangement Strategy’, L.J. Duffy, J. Garcia-Torres, **R.C.F. Jones** and S.M. Allin, *Synlett*, 2012, **23**, 1821-1823.

   2. ‘Application of a Dual Fries-Claisen Protocol to Access Pyranonaphthoquinone Natural Products’, L.J. Duffy, J. Garcia-Torres, **R.C.F. Jones**, M.R.J. Elsegood and S.M. Allin, *Synlett*, 2013, **24**, 185-188.

   3. ‘Palladium Catalyzed Oxidative Coupling of α-enolic dithioesters: a new entry to 3,4,5-trisubstituted 1,2-dithioles via a double activation strategy’, S. Chowdhury, T. Chanda, S. Koley, B.J. Ramulu, **R.C.F. Jones** and M.S. Singh, *Org. Lett.*, 2013, **15**, 5386-5389.

   4. ‘Regioselective quadruple domino aldolization/aldol condensation/Michael/S_NAr cyclization: Construction of hexacyclic indeno-fused C-nor-D-homo-steroid frameworks’, T. Chanda, S. Chowdhury, B.J. Ramulu, S. Koley, **R.C.F. Jones** and M.S. Singh, *Tetrahedron*, 2014, **70**, 2190-2194.

   5. ‘Indium(0)-Mediated Csp^3–S/O Cross-Coupling Approach Towards the Regioselective Alkylation of α-Enolic Esters/Dithioesters: A Mechanistic Insight’, S. Chowdhury, T. Chanda, A. Gupta, S. Koley, B.J. Ramulu, **R.C.F. Jones** and M.S. Singh, *Eur. J. Org. Chem.*, 2014, 2964-2971.

   6. ‘$In(OTf)_3$-Catalysed One-pot Versatile Pyrrole Synthesis through Domino Annulation of α-Oxoketene-N,S-acetals with Nitroolefins’, M.S. Singh, A. Srivastava, G. Shukla, A. Nagaraju, G.K. Verma, **R.C.F. Jones** and K. Raghuvanshi, *Org. Biomol. Chem.*, 2014, **12**, 5484-5491.

   7. ‘Organoindium mediated Csp^3-S cross-coupling/migratory allenylation/thioannulation cascade: Expedient synthesis of highly substituted thiophene frameworks’, S. Chowdhury, T. Chanda, S. Koley, B.J. Ramulu, **R.C.F. Jones** and M.S. Singh, *Tetrahedron*, 2015, **71**, 1844-1850.

A list of research publications (total of 133 research papers as of Dec 2016) is available on request from Professor Jones.

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6.2 CV of Prof Palwinder Singh

Prof. Palwinder Singh is the faculty of Organic Chemistry in the Department of Chemistry, Guru Nanak Dev University. His research interest is in the area of medicinal and bioorganic chemistry. Rational design of the molecules on the basis of the results of molecular modeling studies, synthesis of the compounds and enzyme/cell based evaluation of the compounds for: (i) anti-inflammatory activities, (ii) anti-cancer activities, (iii) anti-fungal activities, (iv) mechanistic studies underlying the mode of action of the compounds, (v) removal of cyanide from Cyt c oxidase, (vi) modeling to thymidylate synthase, retroaldolase, dihydrofolate reductase and (vii) development of new synthetic protocols are the recent research activities being undertaken by the host faculty. Making extensive use of various spectroscopic techniques, the host faculty is well equipped with 300 MHz, 400 MHz and 500 MHz NMR spectrometers, high resolution mass spectrometer (LC-MS), UV-Vis and fluorescence spectrophotometer, Scanning Electron Microscope, Transmission Electron Microscope and other characterization techniques. The host faculty will be responsible for coordinating the interactive sessions as well as extend practical training to the participants.

Selected publications of the Host Faculty

P. Singh, A. Kumar, S. Kaur, J. Kaur, H. Singh. The bioinspired design of a reagent allows the functionalization of C_{α}–H of α, β-unsaturated carbonyl compounds via the Baylis–Hillman chemistry under ambient conditions. **Chem. Commun. 2016**, *52*, 2936 – 2939

P. Singh, J. Kaur, G. Singh, R. Bhatti. Tri-block Conjugates: Identification of a Highly Potent Anti-inflammatory Agent. **J. Med. Chem. 2015, 58 *(15),* 5989–6001.**

P. Singh, A. Kumar, A. Sharma, G. Kaur. Identification of Amino Acid Appended Acridines as Potential Leads to Anti-cancer Drugs. **Bioorg. Med. Chem. Lett. 2015, 25, 3854–3858**.

K. Pawar, A. Yadav, P. Prasher, S. Mishra, B. Singh, Palwinder Singh and Sneha Sudha Komath. Identification of an indole–triazole–amino acid conjugate as a highly effective antifungal agent. **Med. Chem. Comm. 2015, 6, 1352 – 1359**.

Palwinder Singh, Arun Kumar, Sukhmeet Kaur, Amrinder Singh. Thymidylate Synthase Inspired Biomodel Reagent for the Conversion of Uracil to Thymine. **Chem. Commun. 2015, 51, 9961-9964.**

P. Singh, A. Kumar, S. Kaur, A. Singh. Strategically Designed Biomodel: Engineering C3-C4 cleavage of D-Fructose. **Org. Biomol. Chem. 2015, 13, 4210-4220.**

S. Kaur, A. Singh, V. Singh, P. Singh. A rationally designed molecule for removal of cyanide from human blood serum and cytochrome c oxidase. **RSC Adv., 2014, 4, 61884**.

Shaveta, A. Singh, R. Bhatti, P. Singh. Rational design, synthesis and evaluation of chromone-indole and chromone-pyrazole based conjugates: Identification of a lead for anti-inflammatory drug.

Eur. J. Med. Chem., 2014, 77, 185-192.

A. Kumar, P. Prasher, P. Singh. A Fluorescent Probe for Estimation of Adenosine Diphosphate and Monitoring of Glucose Metabolism. **Org. Biomol. Chem., 2014, 12 (19), 3071 – 3079.**

Palwinder Singh, Pooja. N-1, C-3 Substituted Indoles as 5-LOX Inhibitors- In Vitro Enzyme Immunoaasay, Mass spectral and Molecular Docking Investigations. **Bioorg. Med. Chem. Lett. 2013, 23, 1433-1437.**

Palwinder Singh, Matinder Kaur, Shaveta. Mechanism inspired development of rationally designed dihydrofolate reductase inhibitors as anti-cancer agents. **J. Med. Chem. 2012, 55, 6381-6390.**

Jatinder Kaur, Palwinder Singh. ATP selective acridone based fluorescent probes for monitoring of metabolic events. **Chem. Commun**., **2011**, **47, 4472**.

Palwinder Singh, Matinder Kaur. CN^- scavenger: A leap towards development of CN^- antidote. **Chem. Commun**., **2011**, **47, 9122.**

Course Coordinator

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7.0 Regd fee

The participation fees for taking the course is as follows:

Participants from abroad : US $200

Industry/ Research Organizations: Rs. 5000/-

Academic Institutions:

BSc Students: Rs. 500/-

MSc Students: Rs. 1000/-

PhD Students: Rs. 1500/-

Faculty members: Rs. 2000/-

REGISTRATION CUM ACCOMODATION REQUEST FORM

(To reach electronically by Oct. 15, 2018 and hard copy by Oct. 31, 2018)

MODERN ASPECTS OF ORGANIC SYNTHESIS

Nov 19-23, 2018

Department of Chemistry, Guru Nanak Dev University

Amritsar, Punjab

Name (Block Letters): …… M/F: ……

Designation/ Professional Title: ….……..

Organization: ……

Address: ……

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Tel.: …….. . Mobile: ……....

E- mail: …….

Accommodation Required (Yes/ No): ……..……...

The Registration fee of Rupees ……has been paid via Demand Draft No……..in favour of The Registrar, Guru Nanak Dev University, Amritsar Through online/offline banking bearing Transaction No. ……..... to Punjab & Sind Bank, Guru Nanak Dev University Campus (RTGS/IFSC code: PSIB0000288) A/Ct No. 02881000007953 of Guru Nanak Dev University. Demand Draft/ Fee Receipt have been enclosed herewith.

Date: Signature