



**Shri Narendrabhai Modi**

Chief Minister  
Gujarat State



सत्यमेव जयते

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20<sup>th</sup> January 2003

## Message from Chief Guest

It gives me pleasure to know that Zydus Research Centre is organising Ramanbhai Foundation 1<sup>st</sup> International Symposium on "Recent Trends in Pharmaceutical Sciences" in Ahmedabad on 23<sup>rd</sup> and 24<sup>th</sup> January, 2003.

I am sure that the interaction of scientists of India with various internationally renowned counterparts will go a long way in knowledge sharing to help our pharmaceutical industry to grow and to compete globally.

Gujarat is the pioneer state in pharma industry. It has to face challenges with the rapidly changing scenario in drug research and development in the fields of Bio-Technology and Genetic Science.

The symposium will provide a platform for exchanging scientific ideas on these latest developments.

I wish all success to the occasion.

Narendra Modi



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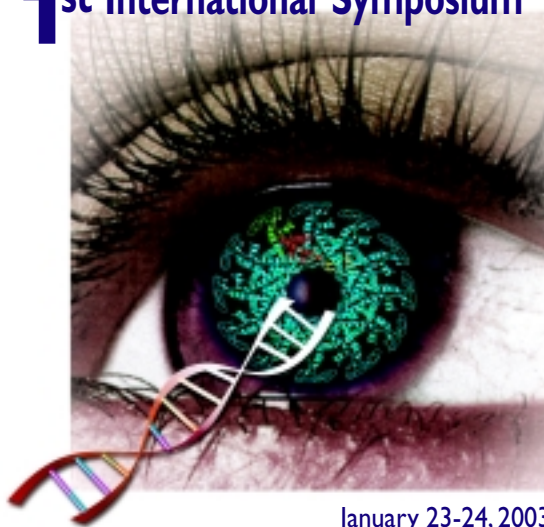
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# Symposium Companion



## Recent Trends in Pharmaceutical Sciences

The Ramanbhai Foundation  
1<sup>st</sup> International Symposium



January 23-24, 2003  
Ahmedabad



**Late Shri Ramanbhai B. Patel**

Founder, Zydus Cadila

August 19, 1925 - September 19, 2001

પેગામ છે અમ તણો અમ જિંદગાની...

Our life itself should convey our message finally.

રહે મધુરતા બની જીવનમાં સખી જો અહો

મને ન પરવા કશી, મુજ પથે ગમે તે બને.

If our life together is ever overflowing with sweetness,  
Oh Sakhi, then, little do I care for whatever comes to pass in traversing the path.

From 'Pratiti' (Conviction-Realisation), A collection of Poems by Ramanbhai B. Patel

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**Dr. B. B. Lohray**  
President, Zydus Research Centre  
Ahmedabad, India.

## Welcome Note



*I*t gives me immense pleasure to welcome all the delegates and invitees to the Ramanbhai foundation 1<sup>st</sup> International Symposium hosted by Zydus Research Centre. This Symposium will provide us an opportunity to interact with scientists from various Indian academic institutions and industries. At the same time, Indian pharma industries will also have opportunities to share their knowledge and strength with some of the renowned scientists from abroad.

Zydus Research Centre invites you all to take the maximum advantage of this meeting for mutual benefit. I am sure you are going to meet some of your earlier colleagues and make new friends which will build a lasting relationship in the years to come. I also hope that during several scientific sessions, new ideas may take birth, seeds of future collaboration may be sowed and better professional relationship may be created. Zydus Research Centre will keep its door open and welcome one and all for such an interaction and to have a mutually rewarding experience.

I wish all of you a very fruitful and enjoyable stay at Ahmedabad.

Ahmedabad  
Date : 23 January, 2003

Dr. B. B. Lohray





## Message from Chairman and Managing Director



**Mr. Pankaj R. Patel**

Chairman and Managing Director  
Zydus Cadila Healthcare Ltd.  
Ahmedabad, India.

It is a matter of immense pleasure to welcome you to the first International Symposium being held under the aegis of Ramanbhai Foundation and hosted by the Zydus Research Centre, the research and development wing of Zydus Cadila.

The Founder Chairman of Zydus Cadila, my father Mr. Ramanbhai Patel realised quite early in his life that research and development would play a critical role in the growth of pharmaceutical industry. He was the driving force behind the research initiatives in Zydus Cadila. The state-of-the-art Zydus research Centre is an expression of his vision. He believed that new avenues would surely emerge if one has the will to discover it. He dedicated his entire lifetime to the quest for knowledge, as an academician, entrepreneur and a researcher.

The Zydus Research Centre supports this quest for innovations and excellence in the field of research and spearheads the research initiatives of the group.

My father strongly believed that research must be the fountainhead of any pharmaceutical enterprise. "Never before has the Pharma industry faced such a challenge, never before has its commitment been so severely tested and never before has there been a more exciting time. One thing that will not be different in the year 2005 is the fact that the research based pharmaceutical industry would be driving force behind innovations in modern healthcare. Our discoveries will continue to improve lives." His prophetic words have now found a new meaning.

In such an era of rapid change it becomes highly critical to be at par with scientific knowledge across the globe. We need to keep pace with latest trends in research and development and extend our learning curve. Knowledge without innovation is of no value and the need of the hour is to harmonise short term and long term goals and encourage innovation and creativity.

The Ramanabhai Foundation First International Symposium is the first in the series of events devoted to the discussion on the 'Recent Trends in Pharmaceutical Sciences'. Through this symposium, the foundation aims to bridge the research endeavours taking place across the world and create a platform for knowledge sharing, tracing the development of new molecules from the laboratory to the market.

Ahmedabad

Pankaj R. Patel

Date : 23 January, 2003



## About Ramanbhai Foundation



The Ramanbhai Foundation is dedicated to encourage learning and knowledge-sharing in the field of pharmaceutical research, education and healthcare. This mission is based on the philosophy of our late Founder Chairman, Mr. Ramanbhai B. Patel, who believed in the importance of research and enriching oneself through an ongoing quest for learning.

A first-generation entrepreneur, Mr. Ramanbhai Patel was one of the stalwarts of the Indian Pharmaceutical Industry. At a time when the newly independent nation was heavily dependent on imports of drugs and pharmaceuticals, he had set out to prove that an indigenous company could provide innovative, research-based quality medicines.

Born at Kathor in South Gujarat on the 19th of August 1925, he began his career as an academician at the L. M. College of Pharmacy, one of the oldest pharmacy institutes in India. This short stint in academics formed a lasting imprint on his mind and the resolve to contribute to the cause of research and education grew stronger over the years.

In 1952, Mr. Ramanbhai Patel turned a pharma entrepreneur. Armed with a sound business acumen, he laid a strong foundation for Cadila and contributed to the growth of the Indian Pharmaceutical Industry. Zydus Cadila today enjoys the coveted distinction of being one of the largest pharma groups in the country.

Mr. Ramanbhai Patel had published several outstanding research papers and took a keen interest in research and was actively involved in the research activities of the group. Today, Zydus Cadila is amongst the top investors in research.

Mr. Ramanbhai Patel's contributions in the field of pharmaceutical education were equally noteworthy. Gujarat which earlier had only one pharmacy college now has ten reputed pharmacy colleges. More importantly, Ramanbhai was instrumental in taking pharmaceutical education to the rural heartland of Gujarat, making professional courses more accessible to students in smaller townships.

In recognition of his services, Mr. Ramanbhai Patel had been bestowed with several prestigious awards : President of India's Import Substitution Award in 1973, Prof. M.L. Shroff Memorial National Award in 1987, The Glory of India Award in 1991 at Washington, Grahak Suraksha Award in 1992, Acharya Prafulla Chandra Ray Memorial Gold Medal in 1993 and the Eminent Pharmacist Award in 1994, to name a few.

In a fitting tribute to his outstanding contributions to the growth of the pharma industry in India, he was conferred the Gujarat Businessman of the Year Award in the year 2000. He was also honoured by Express Pharma Pulse with the 'Lifetime Contribution Award' for his lasting contributions to the Indian pharma industry.

With a firm belief that new avenues would surely emerge if one has the will to discover it, he dedicated his life to the quest for knowledge, as an academician, entrepreneur and a researcher.

The Zydus Research Centre, a state-of-the-art facility which was set up during his lifetime, spearheads the research initiatives of the Zydus group and supports the quest for innovations and excellence in the field of research.

The Ramanbhai Foundation is also committed to a number of special initiatives in the field of education. The Zydus School for Excellence which was a dream nurtured by Mr. Ramanbhai B. Patel has been set up to provide a rich academic environment where children can seek creative expressions for their endeavours.

The Ramanbhai Patel - AMA Centre for Excellence in Education has also been set up to raise the bars of excellence in the field of education through progressive learning programmes for academicians, knowledge sharing forums and by studying successful models of education and creating a platform for sharing these experiences.

The Ramanbhai Foundation First International Symposium is the first in the series of events devoted to the discussion on the 'Recent Trends in Pharmaceutical Sciences'. Through the symposium, the Foundation aims to bridge the research endeavours taking place across the world and create a platform for knowledge sharing, tracing the development of new molecules from the laboratory to the market.

## About Zydus Cadila

Zydus Cadila, one of India's leading healthcare groups provides total healthcare solutions in the field of healthcare ranging from formulations, active pharmaceutical ingredients, biologicals, diagnostics, herbals, animal healthcare to cosmetics. Headquartered in Ahmedabad, the group is spearheaded by Chairman and Managing Director, Mr. Pankaj R. Patel.

Established in 1952, as Cadila Laboratories, the group's association with the industry spans five decades. The company, founded by the Late Mr. Ramanbhai B. Patel, grew to become the third largest Indian pharmaceutical company in the early 1990s. In 1995, the group restructured its operations and emerged with a new identity under the aegis of the Zydus group.

The key to the group's success has been in its commitment to accelerate growth, globalise business operations and lead in a highly competitive environment. The new product launches coupled with therapy management and brand management skills have helped sharpen Zydus Cadila's competitive edge in the domestic formulation market. The group's strategic focus has been on fast growing therapeutic segments such as cardiovasculars, gastrointestinals, pain management, preventives, anti-infectives, neuropsychiatry, respiratory and women's healthcare. Zydus Cadila also has an extensive marketing network with one of the strongest distribution networks in the industry.

To further consolidate its operations, the group has been looking at strategic acquisitions. Adding value to the group's operations are the Bangalore-based Recon Healthcare Ltd., Mumbai-based German Remedies which is one of the leading players in the respiratory, women's healthcare and oncology segments and Banyan Chemicals Ltd., a company with a USFDA approved plant manufacturing high value Active Pharmaceutical Ingredients (API).

With a thrust on international operations, Zydus Cadila has been firming up plans to enter the high value markets of U.K., Europe and the U.S. The group is one of the major players in the Asian markets, ranking eighth amongst the top ten branded formulation exporters from India.

Successful operations in the domestic and international market and strengths in research are backed by a strong infrastructure network. The group has eight state-of-the-art vertically integrated manufacturing facilities spread across 3 states.



The formulation facilities at Ahmedabad are spread over 1,40,000 square metres and is perhaps one of the largest of its kind at a single location in Asia. The plant has received approvals from some of the world's leading regulatory authorities such as the MCA of U.K., MCC of South Africa, ANVISA of Brazil, BFAD of Philippines, NMA of Romania, NDA of Uganda and MoH of Latvia and Namibia.

To successfully address the challenges of the post 2005 era, Zydus Cadila has a team of 150 research scientists at the Zydus Research Centre working in the frontier areas of New Chemical Entities, New Drug Delivery Systems and Biotechnology. One of the leading investors in research, Zydus Cadila invests more than 7% of its turnover on research.

By leveraging existing strengths and building on new competencies, the group aims to be one of the leading Asian players by 2010 and a global player by 2020.

In its pursuit of these goals the group is supported by a team of 6000 people, comprising professionals, research scientists, medical advisors and workers. Poised for a higher growth and more success in the coming years, Zydus Cadila draws confidence from its proven track record which both prescribes and projects a vibrant and soundly based future.



## About Zydus Research Centre (ZRC)

The Zydus Research Centre (ZRC) is the research arm of Zydus Cadila, one of the leading healthcare groups in India. The centre is located at Moraiya, around 20 kms from Ahmedabad.

The state-of-the-art research centre has a built up area of about 1,80,000 square feet, spread over an area of 80,000 square meters. It is recognized by the Department of Science and Industrial Research (DSIR), Government of India and has a team of 150 research scientists actively engaged in research, in various disciplines of Medicinal Chemistry, Pharmacology, Biotechnology, Cell Biology, Molecular Biology, Analytical Research, Clinical Research, Process Research and Drug Delivery. The centre is equipped with sophisticated equipment and infrastructure, necessary to carry out research in modern drug discovery and development.

The focus of the drug discovery programme at ZRC is to design New Molecular Entities (NMEs) based on a defined target for therapeutic uses. The major therapeutic interests are in the area of metabolic disorders, inflammation and pain management. The discovery programme also focuses on cloning receptors and target validation for screening NMEs. Departments of Pharmacology, Toxicology and Cell Biology are integral parts of this discovery effort.

The drug research programme is fully supported by excellent Process Research, DM-PK, Product Formulation & Analytical Departments. At ZRC several biologicals including therapeutic proteins are being synthesized using r-DNA technology. ZRC also has an excellent facility to carry out clinical evaluation of drug in healthy human volunteers, under GCP conditions.

A number of patents have been filed from ZRC and several NMEs are in pre-clinical evaluation stages.

At ZRC research is being initiated towards unraveling new frontiers in the relationship that exists between human genes, chromosomes and diseases. Future research efforts in this area will probe the cause of several diseases based on genetic disorders or defects.

As a part of a learning organisation which continuously seeks to attain and maintain the competitive edge through innovation, Zydus Research Centre accords a high value to diversity of thought. ZRC believes that this is critical for arriving at the most innovative, customer-focussed solutions to many issues, problems and challenges confronting the healthcare business.



# Ramanbhai Foundation 1<sup>st</sup> International Symposium

## Programme Schedule

### Day I : Thursday : 23<sup>rd</sup> January, 2003

8.00 – 9.00 hr		Registration
9.00 – 9.15 hr		Inauguration
9.20 – 10.20 hr		Introductory remarks - : Dr. B. B. Lohray, President, An overview to the Symposium Zydus Research Centre Welcome address - : Mr. Pankaj R. Patel, Towards new research initiatives Chairman & Managing Director, in an evolving landscape Zydus Cadila Inaugural address : Chief-Guest
10.20 hr.		TEA BREAK
<b>Session I : Medicinal Chemistry</b>		
		Chairpersons : Prof. R. K. Goyal and Dr. Rashmi Barbhuiya
10.40 hr.		Key-Note Address : Role of PPAR's in Metabolism and Cell Physiology Prof Walter Wahli, Institut de Biologie Animale, Université de Lausanne, Switzerland.
11.30 hr.		RXR's, PPAR's and Metabolic Diseases Dr. Ranjan Mukherjee, Senior Research Investigator, Bristol-Myers Squibb Co., Wilmington, USA
12.15 hr.		Development of Medicines Controlling Renin-Angiotensin System at Sankyo Dr. Hiroaki Yanagisawa, Director, Medicinal Chemistry Research Laboratories, Sankyo Co., Ltd., Japan
13.00 – 14.00 hr		LUNCH BREAK
		Chairpersons : Prof. S. Chandrasekran and Dr. Bansi Lal
14.00 hr		A New Paradigm of Drug Discovery in the Twenty-First Century Dr. Peter Lawrence Bullock, Purdue Pharma LP, Ardsley, New York, USA
14.45 hr		The Control of Acid Secretion by Proton Pump Inhibitors – An Ongoing Success Story of Tailored Molecules Dr. Volker Figala, Vice President, Preclinical Development, Altana Pharma AG Byk-Gulden, Germany
15.30 hr		Novel Synthetic Methods for Fluorine-Containing Molecules Prof. Tamejiro Hiyama, Department of Chemistry, Kyoto University, Japan
16.15 – 17.15 hr		TEA BREAK and POSTER SESSION
		Chairpersons : Prof. Bharath Chatto and Dr. Ranjan Mukherjee
17.15 hr		Microcalorimetry and Spectroscopy : Drug-DNA interactions and Drug-Protein interactions Prof. C. Vijaya Kumar, Professor of Chemistry, Physical and Biological Chemistry, University of Connecticut, USA
18.00 hr		Human Genome and DNA Technology Dr. Pradeep Kumar Srivastava, CDRI, Lucknow, India
19.00 -21.00 hr		Cultural Programme
20.00 hr onwards		DINNER

## Day II : Friday : 24<sup>th</sup> January, 2003

### Session II : Separation Technology

Chairpersons : Dr. J. S. Yadav and Dr. J. M. Khanna

08.30 hr Immobilized Drug Receptors & Transporters in Drug Discovery and Drug Development  
Professor Irving W. Wainer, Director, Drug Discovery and Bioanalytical Chemistry Laboratory,  
Laboratory of Clinical Investigation, National Institute on Aging / National Institutes of Health, USA

09.15 hr Chiral Resolution: Past, Present & Future  
Dr William John Lough, Reader in Pharmaceutical Analysis, Institute of Pharmacy, Chemistry &  
Biomedical Sciences, University of Sunderland, UK.

10.00 hr Capillary Electrophoresis, Chiral Separation in Pharmaceutical Analysis  
Dr. David Llyod, Principal Scientist, Analytical R&D, Bristol Myers Squibb, Wilmington, USA

10.45 – 11.00 hr  TEA BREAK


11.00 hr Preparative Chromatographic Separation of Enantiomers  
Dr. Eric R. Francotte, Head Separation & Cold Metabolism, Novartis Pharma AG, Research  
Department, Central Technologies, Basel, Switzerland.

### Session III : Pre-clinical / Clinical Development of NCE's

Chairpersons : Prof. H. L. Bhalla and Prof. Y. K. Gupta

11.45 hr Trends in New Medicine Development  
Dr. J Angus Bell, General Manager, Quintiles Limited, Early Development & Laboratory Services,  
Edinburgh, Scotland

12.30 hr Evolving Paradigms of Preclinical Drug Development Processes : Bridging the Gap Between Discovery  
and Clinical Development  
Dr Subrahmanyam Vangala, Site Head, Preclinical Pharmacokinetics,  
Johnson and Johnson Pharmaceutical Research and Development, USA


13.15 – 14.15 hr  LUNCH

Chairpersons : Prof. Mukesh Gohel and Prof. Y. K. Gupta

14.15 hr Optimising Drug Development in Phase I/IIa  
Prof. Dr. Monika Seibert-Grafe, Board Certified Anaesthesiologist and Clinical Pharmacologist,  
Head of Coordination Centre for Clinical Trials, University Hospital Heidelberg, Germany

15.00 hr Project Management in Clinical Drug Development  
Dr. Heinz W. Radtke, Executive Vice-President, Research and Development, Byk-Gulden, Altana Pharma, Germany

15.45 hr International Harmonisation – Impact of ICH on Impurity testing  
Dr. Fritz Erni, Head Novartis Pharamanalytica SA, Locarno, Switzerland

16.30 hr – 17.00 hr  TEA BREAK

### Session IV : Patent & Business Development

Chairpersons : Dr. N. de' Souza and Mr. H. Subramaniam

17.00 hr Implications of the Changing Patent Regime and Patent Litigations in Pharma  
Mr. S. Majumdar, Patent Attorney, S. Majumdar & Company, Kolkata, India

17.45 hr Flexibility in Partnering, Becoming a Preferred Partner  
Dr. Esteban Pombo-Villar, Manager of External Collaborations, NS Research, Novartis Pharma AG

18.30 hr Concluding Session

18.50 – 21.00 hr  ZRC anniversary celebrations followed by dinner

# Session I : Medicinal Chemistry

## Introduction to the Chairpersons



**Dr. Rashmi H. Barbhैया**

Dr. Rashmi H. Barbhैया is President of Research and Development at Ranbaxy Research Laboratories, Delhi, India. Dr. Barbhैया was with Bristol-Myers Squibb for over 20 years. He obtained the Ph.D. degree in Clinical Pharmacology from the St. Bartholomew's Hospital Medical College, University of London. He continued his education through post-doctoral training at the University of Florida and University of Wisconsin.

Dr. Barbhैया started his industrial pharmaceutical career as a Research Scientist in the Department of Metabolism and Pharmacokinetics, Bristol-Myers Company. He has made remarkable contributions to drug development programs in several therapeutic areas such as AIDS and infectious diseases, cancer, depression, anxiety, hypertension, CHF, diabetes and mild to moderate pain, including migraine. While at Bristol-Myers Squibb, he also played a key role, working with drug discovery scientists, in introducing "developability" as a key criterion in lead optimization and selection of drug candidates for development.

His scientific contributions have resulted in over 150 publications. He is a member of several professional societies, among them are AAPS, ASCPT and ISSX. He has served on the Editorial Boards of Antimicrobial Agents and Chemotherapy and Biopharmaceutics and Drug Disposition journals. Dr. Barbhैया has received a number of awards for his scientific contributions. These include AAPS Fellow, AAPS Meritorious Manuscript Award, AAiPS Outstanding Achievement Award and Ranbaxy Award for Excellence in Pharmaceutical Research.



**Dr. Ramesh K. Goyal**

Dr. Ramesh Goyal presently is a Professor of Pharmacology, L.M. College of Pharmacy, Ahmedabad.

Dr. Goyal completed his Ph.D. in the year 1983. He was a Postdoctoral Fellow during 1984-85 in the University of British Columbia, Canada. He is a Fellow of Institution of Chemists (FIC), National Academy of Medical Sciences (FAMS), Indian Pharmacological Society (FIPS), International College of Nutrition (FICN), International Academy of Cardiovascular Sciences (FIACS). He was a Visiting Scientist at Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, Canada in year 1995. In year 1999 & 2001 he was also Visiting Professor, Institute of Cardiovascular Sciences, University Manitoba, Winnipeg, Canada.

He has over 136 research publications and 10 books to his credit. He has guided 98 M.Pharm students and 9 Ph.Ds. He has several Awards and Fellowships at the International, National and State Levels. He is the Life Member and Member in Editorial Board and Organising Secretary of several Professional Bodies. Currently He is General Secretary of Indian Pharmacological Society and Treasurer of International Academy of Cardiovascular Sciences (India).

# Speaker's profile

## **Prof. Walter Wahli**

Institut de Biologie Animale, Université de Lausanne,  
Switzerland.



Prof. Walter Wahli did his early education at Moutier and obtained his diploma in Biology from University of Berne in 1975. He was later a graduate student at the Department of Cell and Developmental Biology Zoology Institute and received his Ph. D. in 1977.

Prof. Wahli then moved to the United States of America as Postdoctoral Fellow at Carnegie Institute of Washington, Department of Embryology, Baltimore, Maryland. Prof. Wahli continued his research at National Institutes of Health, National Cancer Institute Laboratory at Maryland, USA as a Visiting Fellow and Visiting Associate.

Prof. Wahli then returned to Switzerland in 1980 as a Full Professor and Director of the Institute of Animal Biology, University of Lausanne. Since then Prof. Wahli has continued to work at this university. In 1999 he was promoted as Vice Rector of the University of Lausanne. He is also Director at the Center for Integrative Genomics, University of Lausanne.

Among the innumerable honours and awards Prof. Wahli has received, a few can be noted as; Elected Member of the Institut Jurassien des Sciences, des Lettres et des Arts, Elected Member of the European Molecular Biology Organization, Elected Member of the National Research Council of the Swiss National Science Foundation, Board of Trustees of the Roche Research Foundation, Otto Naegeli Award 2002, Euro Fed Lipid Science Award 2002.

He has been also serving as an Corresponding Editor of Proceedings of the Royal Society & in the Editorial Board of Journal of Molecular and Cellular Endocrinology, Molecular and Cellular Endocrinology, Molecular Endocrinology, Cellular and Molecular Life Sciences and has been also on the Advisory Board of European Journal of Biochemistry and Nuclear Receptor.

Dr. Walter Wahli has published more than 160 publications in well respected and peer reviewed journals and earned a respectable position in exploring mechanism of different diseases related to nuclear receptors.

For Notes :



# Topic

## **Role of PPARs in Metabolism and Cell Physiology**

Walter Wahli

Institut de Biologie animale, Université de Lausanne, CH-1015 Lausanne, Switzerland

Overweight rarely occurs in isolation but as part of a complex pattern of metabolic abnormalities that are risk factors for cardiovascular disease. These abnormalities are considerably influenced by genetic, behavioral and nutritional factors. A group of nuclear receptors, the peroxisome proliferator-activated receptors (PPARs), is involved in metabolic controls whose alteration can ultimately lead to the above-mentioned disorders. PPAR-alpha, -beta/delta and -gamma are ligand-activated transcription factors that have central roles in the storage and catabolism of fatty acids. All three are activated by naturally occurring fatty acids and fatty acid metabolites, indicating that they function as the fatty acid sensors of the body, each having a distinct physiological action. PPAR-alpha and PPAR-gamma control energy homeostasis and inflammatory responses. PPAR-alpha is involved in fatty acid catabolism and is the receptor for the fibrate drugs, which are widely used to lower triglycerides. PPAR-gamma plays a critical role in adipocyte differentiation and fatty acid storage and serves as the receptor for the glitazone class of insulin-sensitizing drugs used in the treatment of type 2 diabetes. PPAR-beta has been implicated in embryo implantation, tumorigenesis in the colon, reverse cholesterol transport, and recently in skin wound healing. During the past few years, the identification of PPARs, their ligands, both natural and synthetic, and PPAR target genes with their specific functions has been one of the most important achievements in the field of body lipid management and energy homeostasis. It underscores the potential therapeutic application of PPAR-specific compounds on the one side, and the crucial biological roles of fatty acids in the regulation of gene expression.

For Notes :

# Speaker's profile

## **Dr. Ranjan Mukherjee**

Senior Research Investigator, Bristol-Myers Squibb Co., Wilmington, USA



### **Dr. Ranjan Mukherjee**

Dr. Mukherjee completed his post graduation in Physics and Biophysics from the University of Calcutta. In 1987 he received his Ph.D degree from the University of Delaware in Biological Sciences. Thereafter, he continued his research work as a Post-doctoral fellow at Du Pont-Merck Pharmaceuticals Company. In 1992, Dr. Mukherjee joined Ligand Pharmaceuticals Inc. as a Research Scientist and was promoted to the position of Research Investigator. His accomplishments at Ligand Pharmaceuticals Inc in the field of PPAR & RXR in management of diabetes and related metabolic disorders are noteworthy. He Initiated the PPAR project at Ligand Pharmaceuticals leading to a collaboration with Eli Lilly to identify a PPAR  $\alpha/\mu$  coagonist for the treatment of diabetes. He also demonstrated that RXR agonists could be used for diabetes treatment. Dr. Mukherjee proposed and identified the first selective PPAR modulator for the treatment of obesity and syndrome X etc.

Dr. Mukherjee then moved to Bristol Myers Squibb formerly known as Dupont Pharmaceutical Company in 1999 and is presently continuing as a Senior Research Investigator II. He has worked extensively towards discovering the role of PPAR and RXR in various diseases including diabetes, dyslipidemia, hypercholesteremia and cardiovascular diseases.

He has published several research papers in prestigious journals including Nature, Journal of Biological Chemistry, Nucl. Acids Research, Journal of Steroid Biochem and Molecular Biology so on and so forth. He is the author of several reviews and chapters on PPARs in several books. He is the inventor/co-inventor of several US patents on PPARs /RXRs and their application in screening for novel therapeutics for metabolic diseases.

For Notes :

# Topic

## **RXRs, PPARs and Metabolic Diseases**

Ranjan Mukherjee  
Bristol Myers Squibb Company, USA

The retinoid X receptors (RXRs) and the peroxisome proliferator activated receptors (PPARs) are members of the intracellular receptor superfamily of ligand activated transcription factors. They bind to DNA as heterodimers of PPAR/RXR and as such modulate gene expression when bound to small molecule ligands. There are three subtypes for PPAR, PPAR $\alpha$ , PPAR $\beta$ (d) and PPAR $\gamma$ . The PPARs are targets for two widely used classes of drugs, the fibrates (PPAR $\alpha$ ) and thiazolidinediones (PPAR $\gamma$ ). The fibrates and thiazolidinediones are used in the treatment of dyslipidemias and type 2 diabetes respectively. The drugs presently in the clinic were developed before the molecular targets were known. In the last ten years we have made significant progress in understanding the mechanism of action of these receptors. This in turn has enabled us design the next generation of receptor modulators that preserve the efficacy without the adverse effects of the present drugs in treating cardiovascular diseases, diabetes and obesity.

For Notes :

# Speaker's profile

**Dr. Hiroaki Yanagisawa**

Director, Medicinal Chemistry Research Laboratories Sankyo Co., Ltd.



Dr. Yanagisawa had his earlier education in Applied Chemistry in Keio University, Japan and received his Ph.D degree in 1972 from the same university. Dr. Yanagisawa went for a postdoctoral research work at University of California, San Francisco and as a Research Associate at Princeton University. Since 1970 Dr. Yanagisawa has been leading a team of Medicinal Chemists at Sankyo Research Laboratories and has been promoted as a Director of Medicinal Chemistry Research in 1997. He has made immense contribution for the development of Sankyo virtually from its inception. Some of the products which came through his laboratory includes Cefmetazole, Cefpodoxime proxetil, Temocapril, Olmesartan medoxomil, antidiabetic agents and anti-atherosclerotic agents.

Dr. Yanagisawa has been a member of several professional bodies : Chemical Society of Japan, The Pharmaceutical Society of Japan, The Society of Synthetic Organic Chemistry and American Chemical Society. He had also been Councilor of Pharmaceutical Society of Japan, Medicinal Chemistry Division and Councilor of The Society of Synthetic Organic Chemistry, Japan.

For Notes :

# Topic

## **Research and Development of Medicines Controlling Renin-angiotensin System at Sankyo**

Hiroaki Yanagisawa

Medicinal Chemistry Research Laboratories

Renin-angiotensin system plays an important role in the control of blood pressure and electrolyte homeostasis. We have been studying the agents controlling this system, such as renin inhibitors, ACE inhibitors and All receptor antagonists (ARB), and succeeded in developing ACE inhibitor, temocapril, and ARB, olmesartan medoxomil. Research and development of these agents will be presented.

For Notes :



# Session I : Medicinal Chemistry

## Introduction to the Chairpersons



**Professor S. Chandrasekaran**

Prof. Chandrasekaran obtained his B.Sc., M.Sc. and Ph.D degree from Madras University. He worked as a Research Associate at Harvard University in the US during 1973-77 with Prof. E.J. Corey, a Nobel Laureate, 1990.

Dr. Chandrasekaran worked at Syntex Research at California for one year in 1975-76.

Prof. Chandrasekaran joined as a faculty at Indian Institute of Technology, Kanpur in 1978 and continued till 1986 when he was a full professor. In 1986, he moved to Indian Institute of Science, Bangalore and since then he is working at this prestigious institute as a Professor in Organic Chemistry and Chairman. Professor Chandrasekaran has contributed significantly to synthetic organic chemistry, new synthetic methodologies, reaction mechanisms. He has developed new reagents for organic synthesis involving inorganic selenium, molybdenum, tungsten and sulfur systems.

He has published a number of papers in international refereed journals and delivered more than 150 lectures in India and abroad. Prof. Chandrasekaran is a member and fellow of several Professional bodies including IUPAC and Indian academy of sciences, Indian national academy of sciences etc. He is a recipient of several distinctions and awards importantly, Basudev Banerji Medal and Prize, Indian Chemical Society, Shanti Swarup Bhatnagar Prize, CSIR, Honorary Professor, Jawaharlal Nehru Center for advanced scientific research, Silver medal Chemical Research Society of India, Amrut Mody Chair Professor of Chemistry, IISC, Bangalore etc. He has guided several students in their doctoral degrees in chemical sciences.



**Dr. Bansilal**

Dr. Bansilal hails from Kashmir. He obtained his Ph.D degree from Lucknow University while working in CDRI, Lucknow under the supervision of Dr. Nityanand. He was post-doctoral research associate at Stevens Institute of Technology, New Jersey; post-doctoral research fellow at Indiana University at Bloomington Indiana and at Rice University, Houston Texas, USA. He joined Hoechst Research Center as a research scientist in 1975 in chemistry department and became the Head in 1986. In 1997, he became the Vice President & Head of Research, Hoechst Marion Roussel Ltd. He has 30 years of rich experience in New Drug Discovery and since 1999 he is President and Head of Research, Quest Institute of Life Sciences, Nicholas Piramal India. Two drugs from his research team has reached the market namely - Trequinsin a vasodialator and Buqiterine which is an antiallergic & bronchodilator. Yet another drug Flavopiridol is in late Phase II clinical trials for cancer. He has published 50 papers in national and international journals and holds 45 patents. He is a member of several professional bodies.

# Speaker's profile

**Dr. Peter Lawrence Bullock**

Purdue Pharma LP, Ardsley, New York, USA



Dr. Peter Lawrence Bullock presently is a Director of Discovery Support Preformulation and Scientific & Technical Writing at Purdue Pharma LP, Ardsley, New York.

Dr. Bullock had his early education at the University of Toronto and obtained his Doctorate degree at the University of Kansas Medical Centre, Kansas City, USA in 1994. He joined as a postdoctoral fellow of Natural Sciences and Engineering Research Council at Institute of Ocean Sciences, Sidney, British Columbia, Canada in 1995. He was the principal investigator in a University Animal alternatives Research Program at Procter and Gamble, where he has worked on induction of liver cytochrome P450 enzymes in-vitro. Dr. Bullock has occupied several academic positions as well as industrial positions from 1983 onwards as Principal consultant at Bullock & Associates Ltd at Alberta, Head, In-vitro Metabolism at Phoenix International Life Sciences at Quebec, Principal Scientist at Cerep, Inc. at Redmond, WA, Scientific Director at Human Biologics International at Scottsdale, AZ. He joined Purdue Pharma as a Senior Principal Scientist in February 2000 and is continuing to work at Purdue Pharma as Assistant Director Discovery Support and then Director of Discovery Support. The research interests of Dr. Bullock is in drug metabolism and pharmacokinetics and he has significantly contributed to the development of high throughput metabolism screening supporting drug discovery.

Dr. Bullock has been an invited speaker at several academic institutions as well as pharma industries. He has published a large number of papers in peer reviewed journals.

For Notes :



# Topic

## **A New Paradigm for Drug Discovery in the 21st Century**

Peter L. Bullock, Ph.D.

Purdue Pharma LP

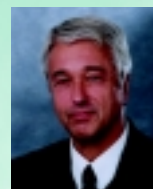
Historically, the rate of success of development candidates (DC) from nomination to first-in-man studies has been approximately 10%. Many failures have been associated with inadequate pharmacokinetic behavior in humans (e.g., variable bioavailability, poor dose-proportionality, rapid clearance) or a propensity for participating in drug interactions (e.g., cisapride). In addition, some new drugs have caused unexpected and unsafe side effects in the post-market period (e.g., terfenadine and torsade de pointes). Since this information began to be assimilated by the pharmaceutical industry during the late 1980s and early 1990s, the pharmaceutical industry has changed the way in which drugs are discovered. During the last two decades the discovery of medicines from new molecular entities (NME) has been made somewhat less risky and a little faster with the development of parallel and combinatorial organic synthesis, new robotic and analytical instruments (e.g., liquid micro-handlers, HT LC/MS, LC/MS/NMR), labware and new biological tools. In combination, these changes help scientists to discriminate more clearly between structurally and pharmacologically similar compounds (e.g., in lead selection). In fact, several processes which in the past have been carried out sequentially are now conducted in parallel, potentially saving resources and accelerating drug discovery (e.g., in lead optimization). Currently, chemical, pharmacological and pharmaceutical characterization occur nearly simultaneously. The nature and quantity of information available with which to select DC has changed substantially during this period. The objective of this new paradigm is to halt or slow the rise in discovery and development costs while reducing the time required to bring more 'drug-like' DC into non-clinical testing than in the past. Until 1998 Purdue Pharma was a generic/late-stage development company, relying on the reformulation of existing analgesics. However, since discovery efforts began in 1999, a rapid cycle of synthesis, purification and re-synthesis to prepare homologous series of NME has been integrated tightly with high-throughput evaluation of pharmacological activity (e.g., potency and efficacy) and moderate-throughput assessments of the pharmaceutical properties of these compounds that could be associated with developmental liabilities (e.g., aqueous solubility, metabolic clearance/inhibition, intestinal/CNS permeability, interaction with drug transporters, cytotoxicity, interaction with cardiac ion currents). Furthermore, it is now possible to investigate the pharmaceutical properties of NME with human-derived biological tools (e.g., cryopreserved cells, transfected cell lines, recombinant proteins), thus reducing our dependence on rodent-human extrapolations.

For Notes :

# Speaker's profile

**Dr. Volker Figala**

Vice President, Preclinical Development, Altana  
Pharma AG Byk-Gulden, Germany



Dr. Figala obtained his Master degree in Chemistry from the University of Munich in 1970. He joined in the research group of Prof. Dr. Gompper at the University of Munich for carrying out his Ph.D work in organic chemistry. After his Ph.D he joined Byk Gulden in 1974. Dr. Figala continued to give his best at Byk Gulden. He has developed a X-ray contrast agent, Osbil, which is in production since 1976. He was involved in the synthesis of Antiphlogistics. The product Eltenac was licensed to Schering Plough and is marketed in the veterinary market. He has also contributed in the field of selective Antimuscarinics. A product Telenzepine has proceeded to Phase III clinical trials. Dr. Figala's group was also one of the first to elucidate the mechanism of action of irreversible proton pump inhibitors. He has been the co-inventor of Pantoprazole. Since 1989 he has been heading the Group for Respiratory Diseases and is spearheading in the development of Phosphodiesterase Inhibitors. In 1991 he became the Director of Chemical Research and was honored as Honorary Professor at the University of Constance. Since 2002 he is serving as Vice President of pharmaceutical development of ALTANA Pharma, Germany.

For Notes :

# Topic

## **The control of acid secretion by Proton Pump Inhibitors - an ongoing success story of tailored molecules**

Volker Figala

AltanaPharma AG

Irreversible Proton Pump Inhibitors (PPIs) have dramatically changed the treatment of acid related diseases. In the beginning of the development of this class of compounds the lack of clear-cut structure activity relationships has hampered the design of potent and safe drugs. As common theme of structurally different compounds which all showed high biological activity, the instability towards acid was noticed. Based on this observation the straightforwardly the mechanism of action could be elucidated, which is presented in detail in the presentation.

Based on the insight of the mechanism of action of PPIs an economy of moving ideas could be developed which led to a better and faster selection of nearly ideal compounds with a well-balanced biological activity and the complete absence of side effects.

As the most promising compound Pantoprazole was further developed. The strategy for the synthesis of Pantoprazole and its building blocks is discussed. Recently the interest of medicinal chemistry especially in the area of PPIs focussed on the development of enantiomerically pure compounds. Conceivable differences between the individual enantiomers and the racemate are discussed; the routes the synthesis of enantiomerically pure compounds are compared.

For Notes :

# Speaker's profile

**Prof. Tamejiro Hiyama**  
Kyoto University, Japan



Prof. Hiyama did his early education under the supervision of Prof. Nozaki at Kyoto University, Japan and his postdoctoral research from Harvard University under the guidance of Prof. Yoshito Kishi. After his postdoctoral work Prof. Hiyama returned to Japan and worked at Sagami Chemical Research as Research Fellow where he rose to position of Group Leader. Prof. Hiyama moved to academics as a Professor, Research Lab. Resources Utilization, Tokyo Inst. Tech, Tokyo. Since 1997 he is Professor at Kyoto University. He has been publishing extensively in leading journals of Chemical Sciences. Prof. Hiyama is a well-respected scientist in Japan. He has been recognised by various Professional Societies in Japan and abroad. He has been editor of several prestigious journals like Bull. Chem. Soc. Japan, Quarterly Chemical Reviews, Synthetic Organic Chemistry, Japan etc. He has been Member of Royal Society of Chemistry, American Chemical Society, The Society of Silicon Chemistry Japan, The Chemical Society of Japan, The Kinki Chemical Society, The Japanese Liquid Crystal Society etc.

For Notes :

# Topic

## **Novel Synthetic Methods for Fluorine-containing Molecules**

Tamejiro Hiyama

Department of Material Chemistry, Kyoto University

Fluorine functionalities influence biological activity of many pharmaceutical agents. Some typical examples will be shown and synthetic methods of such compounds will be demonstrated using Flons or Halons in combination with metals. Oxidative desulfurization fluorination is also a powerful method for constructing various fluorine functionalities. Finally shown will be the use of fluoral and trifluorodichloroacetone, both giving trifluoromethylated target molecules.

For Notes :



# Session I : Medicinal Chemistry

## Introduction to the Chairpersons



**Prof. Bharat Chattoo**

Bharat Chattoo is a senior professor with the Department of Microbiology and Biotechnology Centre, M.S. University of Baroda. He has been the Head of the Department of Microbiology, M.S. University of Baroda, (1996-2001) and has been a professor since 1986. He is the Coordinator of Biotechnology Teaching Programme and the Director of Centre for Genome Research at M.S. University and is the founder Vice Chancellor of the Shri Mata Vaishno Devi University, Jammu.

He received his Ph.D. from the University of Delhi, in the field of Microbial Genetics. Subsequently, he worked at the University of Rochester Medical Centre in the area of yeast molecular genetics. He has been a Visiting Scientist/Professor, at the Weizmann Institute of Science, Israel, National Institute of Bioscience and Human Technology, Tsukuba, Japan, Rice Genome Programme, Tsukuba, Japan and United States Department of Agriculture, Beltsville, Maryland.

Dr. Chattoo is a fellow of the Indian National Science Academy. He is a member of the Gujarat Biotechnology Council. He received the national technology award for transfer of technology to industry. He has published extensively in the area of microbial and molecular genetics and genome analysis. His current interests are in the functional genomics of fungal pathogens, genomics and proteomics approaches to the study of host-pathogen interactions and in bioprocess development.



**Dr. Ranjan Mukherjee**

Dr. Mukherjee completed his post graduation in Physics and Biophysics from the University of Calcutta. In 1987 he received his Ph.D degree from the University of Delaware in Biological Sciences. Thereafter, he continued his research work as a Post-doctoral fellow at Du Pont-Merck Pharmaceuticals Company. In 1992, Dr. Mukherjee joined Ligand Pharmaceuticals Inc. as a Research Scientist and was promoted to the position of Research Investigator. His accomplishments at Ligand Pharmaceuticals Inc in the field of PPAR & RXR in management of diabetes and related metabolic disorders are noteworthy. He initiated the PPAR project at Ligand Pharmaceuticals leading to a collaboration with Eli Lilly to identify a PPAR alpha/mu agonist for the treatment of diabetes. He also demonstrated that RXR agonists could be used for diabetes treatment. Dr. Mukherjee proposed and identified the first selective PPAR modulator for the treatment of obesity and syndrome X etc.

Dr. Mukherjee then moved to Bristol Myers Squibb formerly known as Dupont Pharmaceutical Company in 1999 and is presently continuing as a Senior Research Investigator II. He has worked extensively towards discovering the role of PPAR and RXR in various diseases including diabetes, dyslipidemia, hypercholesteremia and cardiovascular diseases.

He has published several research papers in prestigious journals including Nature, Journal of Biological Chemistry, Nucl. Acids Research, Journal of Steroid Biochem and Molecular Biology so on and so forth. He is the author of several reviews and chapters on PPARs in several books. He is the inventor/co-inventor of several US patents on PPARs /RXRs and their application in screening for novel therapeutics for metabolic diseases.

# Speaker's profile

**Prof. C. Vijaya Kumar**

Professor of Chemistry, Physical and Biological  
Chemistry, University of Connecticut, USA



Prof. Challa Vijayakumar is presently Professor of Chemistry at the University of Connecticut, USA. Dr. Vijayakumar completed his postgraduation in India from Osmania University, Hyderabad and received his Ph.D from IIT, Kanpur in 1982 under the supervision of Prof. M.V. George. He worked as Postdoctoral fellow at University of Notre Dame and later as Research Associate at Columbia University under Prof. N.J. Turro who is known for his contributions in photochemistry. He joined University of Connecticut in 1988 as Assistant Professor in Chemistry and in 2000 he became a Professor in Chemistry in the same university. Prof. Vijaya Kumar was also Visiting Fellow of Princeton University. He has published nearly 100 papers in various journals including Journal of American Chemical Society, Journal of Phys. Chemistry, PNAS etc.

His research interest has been in Biological Chemistry, Photochemistry, Photochemical Protein Scissors, DNA Assisted Electron Transfer, Drug-DNA Interactions etc. Some of his work such as Photochemical Protein Scissors, Drug DNA Interactions etc. has been well cited in Chemical & Engineering News at various times. He has received several honors and awards, importantly, Faculty Development Award from Merck Sharp & Dohme in 1989-90 and 1988-89.

For Notes :



# Topic

## **Microcalorimetry : Drug-DNA and Drug-Protein Interactions**

Challa V. Kumar

University of Connecticut, USA

Our long term goal is to develop photochemical strategies to target biological macromolecules for therapeutic and other purposes. One approach has been to use molecular probes to snip proteins, or to cleave DNA at specific sites. The design of such reagents should be flexible to target distinct desired sites on the biomolecule. The design should also include sufficient information for the binding of the probe with a high selectivity or specificity to the target site. A modular, building block approach for the molecular design will be demonstrated. By changing the building blocks, desired sites on proteins or selected sites on the DNA have been targeted. The very first examples of protein cleavage by photochemical scissors will be demonstrated.

In addition to the photochemical strategies, we are also developing thermal /oxidative /hydrolytic methods. Multiple approaches will be presented to characterize the probe-target interactions. These methods will include spectroscopic, photochemical, biochemical, and biophysical methods. In summary, we have developed modular molecular probes that can cleave DNA with a high selectivity and snip proteins at a single site (specificity). Bovine serum albumin, for example, is snipped at residues 346-347, out of the 584 possible sites, while lysozyme is cleaved between residues 108-109, out of 128 possible sites. The resulting peptide products have been isolated, and identified by amino acid sequencing and from electrospray ionization mass spectrometry. Mechanistic studies, including flash photolysis studies, indicate that protein cleavage is mediated by initially generated radical cations. The very first examples of photochemical probes that can cleave proteins and DNA will be presented.

For Notes :

# Speaker's profile

**Dr. Pradeep Kumar Srivastava**  
CDRI, Lucknow, India



Dr. Pradeep Kumar Srivastava, is an Organic Chemist, working as a Senior Scientist (Assistant Director), in the chemical technology division of Central Drug Research Institute, Lucknow, India. He did his M.Sc. in Organic Chemistry in 1976 from Kanpur University. Further He joined research as Junior Research Fellow of Indian Council of Medical Research, New Delhi on topic "Synthesis and Biological Activity of Novel Anthelmintics" under Dr.A.K. Ramrakhyani, Feroze Gandhi Post Graduate College at Rae Bareli. He joined CDRI as Sr. Research fellow in 1980 and became a Scientist. In He has got more than 25 years of experience in the area of technology development. He was associated with the development of many products whose technology has been transferred to the industry for commercial production viz. Mefloquin, Acyclovir, Amoxycillin, Clofazimine, 2-Furoic acid and more. He also developed an improved method for the preparation of synthetic curcumin, a very important constituent of *Curcuma longa* (turmeric). Currently he is working on a technology development of a spermicidal compound, which has got anti-HIV activity.

He is the first person in the world to start a novel concept in science communication called "SCIENTOONS". Sciencetoons are the novel class of science cartoons, which are based on science. He has delivered more than 333 lectures so far in India, Thailand, Singapore, USA and Caribbean countries covering more than 18 different topics. Recipient of several National, Asian and International awards including "SILVER MEDAL" for the best lecture in the area of Pharmaceutical Sciences in an Asian Conference held at National University of Singapore, Singapore. He also won the most prestigious "THE OUTSTANDING YOUNG PERSON OF THE WORLD" award given by JUNIOR CHAMBER INTERNATIONAL (USA) to 10 selected persons of the world, after a competition among the 110 countries of the world, annually.

For Notes :

# Topic

## **Human Genome and DNA Technology : Key to the Better Future**

Pradeep K. Srivastava

Chemical Technology Division, Central Drug Research Institute, Lucknow-226001, India

Each cell nucleus contains chromosomes, which are composed of DNA. Enclosed in the DNA are genes but they represent 5% of the total DNA, remaining 95% of DNA is called 'junk' or 'extra' DNA. This extra DNA contains numerous repeated units, which show higher level of variation between individuals, and thus is exactly what it can offer in distinguishing one individual from other through profile. Initially DNA fingerprinting technique was used in the area of forensic sciences to solve the murder and rape cases, but now this technique has majority of uses starting from preservation of endangered species to mapping of the human genome.

American President Bill Clinton and British PM Tony Blair announced on June 26, 2000 that the Human Genome, a government funded project and Celera Genomic a private US company, have both produced a working draft of the 3.1 billion chemical letters that contain the entire biological secrets of the human life. Once the project cracks the final sequence, every physiological function, structural details and behavioural traits will have been explained in terms of genetic make up. It will explain that how diseases like cancer etc., occur. It will also be possible to know that if a newborn is vulnerable to certain diseases and thus prepare for preventive action. 20 year from now, life and death will be very much different from what we experience today.

This paper is an attempt to discuss about Human Genome project and DNA technology in detail that how knowing more about these will provide us better future the years to come.

For Notes :



# Session II : Separation Technology

## Introduction to the Chairpersons



**Dr. J. S. Yadav**

Dr. J.S.Yadav obtained his masters in 1972 and Doctorate in 1976 from India. He completed his Post Doctorate from Houston & Madison in USA. In 1981, he returned to India and joined National Chemical Laboratory (NCL) Pune and in 1986 he moved to Indian Institute of Chemical Technology (IICT) Hyderabad. In 1989 he was elevated as the Head of the Department of Organic Division-I and as Senior most Director grade Scientist at IICT. His research interests includes Synthetic Organic Chemistry, Natural Products, Agrochemicals-Pheromones and their utility in IPM, Molecular Modeling and Combinatorial Chemistry for drug discovery programmes.

Dr.Yadav's research group has successfully developed cost effective technologies for specialty chemicals like Diltiazem, Ondasetron, Pyrazinamide, Ketotifen, Mefloquin, Tamoxifen etc.

Dr.Yadav is a member of prestigious scientific bodies like Department of Science and Technology, Technical Advisory Board (TAB) and a National representative of International Union for Pure and Applied Chemistry (IUPAC).

He has received many academic and Industrial Awards viz., Shanti Swarup Bhatnagar Award (1991), Vasvik Award in Chemical Sciences & Technology (1999), Ranbaxy Research Award in Pharmaceutical Sciences (2000), Prof. Swaminathan 60<sup>th</sup> Birthday Commemoration Lecture Award (2002). He has to his credit more than 350 research publications in various reputed International journals. He has also 14 US Patents and 14 Indian Patents to his credit. Presently nearly 25 scientists and 60 research scholars are working under his supervision at IICT.



**Dr. J. M. Khanna**

Dr.J.M.Khanna is well-known as a successful scientist, manager and technocrat at the Ranbaxy Laboratories, India until July 2002. Dr. Khanna obtained his M.S. from Agra University and Ph.D from CDRI, Lucknow. Dr. Khanna was a research associate, 1968-70 at Ricker Lab. in California where he worked on non-stimulant anorexic agents and as a Visiting Scientist at Ohio State University during 1976-79. He worked as a Scientist in the Medicinal Chemistry Division at CDRI, Lucknow during 1970-76 where he was engaged in Synthesizing molecules in the field of anticancer, CMS/CVS, analgesics, antifilarial and antifertility drugs.

Dr. Khanna joined Ranbaxy Laboratories in 1979 as Chemical Research Manager. He steadily grew in his career along with the company and became the Vice President R&D & Technical Services in 1989.

He occupied the position of executive Vice President, R&D in 1993 and President in 1999. He was also Director, Member, Chairman of several councils and committees of Ranbaxy Laboratories.

Dr. Khanna has lead Ranbaxy at several fronts – ranging from Chemical Research, Biotechnology & Fermentation, Pharmaceutical Research, Oral controlled released systems, Drug discovery research, Clinical Research, Herbal drugs research, International Drug Regulations Affairs, Corporate QA etc. During his tenure, Ranbaxy has filed several patents, DMFs, ANDAs and also INDs.

He is recipient of several awards such as FICCI award, DSIR award, PC Ray Award etc. He holds 31 patents and has authored 59 publications. Presently he is Executive Director & President of Life Sciences, Jubilant Organosys Ltd. India.

# Speaker's profile

## **Professor Irving W. Wainer**

Director, Drug Discovery and Bioanalytical Chemistry Laboratory, Laboratory of Clinical Investigation, National Institute on Aging / National Institutes of Health, USA



Dr. Wainer graduated from Wayne State University in 1965 with a BS in chemistry and then received his PhD degree in chemistry from Cornell University in 1970. He then did postdoctoral doctoral studies in molecular biology (University of Oregon) and clinical pharmacology (Thomas Jefferson Medical School).

From 1978 to 1986 he worked for the US Food and Drug Administration as a Research Chemist. The foundations he laid at the FDA have lead to international regulations on the purity and content of new drug substances.

In 1986, Professor Wainer left the FDA to become Director of Analytical Chemistry, Clinical Pharmacokinetics Lab, and Associate Member, Pharmaceutical Division, St. Jude Children's Research Hospital, Memphis, TN. He stayed in Memphis until 1990 when he moved to Montreal, Quebec, Canada where he assumed the position of Professor and Head, Pharmacokinetics Laboratory, Department of Oncology, McGill University. In 1997, he moved back to Washington, DC as a Professor of Pharmacology at Georgetown University and this year he moved to his current position at the NIA/NIH. He is still an Adjunct Professor at McGill and Visiting Professor at the Universities of Pisa, Bologna, Kyoto and Sunderland.

Professor Wainer has published over 250 scientific papers and 8 books. He was founding editor of the journal Chirality and is currently Senior Editor of the Journal of Chromatography B: Biomedical Sciences and Applications. He holds ten patents including the development of the anti-cancer agent dex-ifosfamide. His awards include: co-recipient with Dr. John E. Stambaugh of the "Harry Gold Award" from the American College of Clinical Pharmacologists; "Sigma Xi Science Award", Food and Drug Administration Sigma Xi Club; "A.J.P. Martin Medal" presented by the Chromatographic Society for contributions to the development of chromatographic science; Elected Fellow of the American Academy of Pharmaceutical Sciences; Elected Member United States Pharmacopeial Convention Committee of Revision for 1995-2000. In addition, Professor Wainer was the recipient on an INSERM Fellowship (Post Jeune) at INSERM U7 Hopital Necker (Dr. Philippe Meyer), Paris, France 1983, 1984 and 1986. He still maintains a strong association with medical research in France.

In his current position at the Laboratory for Clinical Investigation at the National Institute on Aging/National Institutes of Health, Professor Wainer will continue his studies into treating the critically ill and terminal patients.

For Notes :

# Topic

## **Immobilized Drug Receptors and Transporters in Drug Discovery and Development**

Sharvil Patel, Ruin Moaddel, Krzysztof Jozwiak, Farideh Beigi, Fabio Leonessa, Irving W. Wainer  
Laboratory of Clinical Investigation, National Institute on Aging / National Institutes of Health, USA

A series of liquid chromatographic stationary phases have been developed for on-line screening for new drug candidates and for the characterization of these compounds. The stationary phases contain immobilized receptors such as nicotinic acetylcholine receptors and opioid receptors the drug transporter p-glycoprotein. Both frontal and zonal chromatographic techniques have been used as has a newly developed parallel screening liquid chromatographic system. Data from the chromatography of nicotinic acetylcholine receptor non-competitive inhibitors on the nicotinic acetylcholine receptor column have been used to construct quantitative structure - activity relationship to predict and describe interactions. The use of these columns in new drug discovery and in the ADMET stage of drug development will be discussed. In addition, the use of enantiomeric compounds to calibrate the immobilized receptor columns will be demonstrated.

For Notes :

# Speaker's profile

**Dr. William John Lough**

Institute of Pharmacy, Chemistry & Biomedical Sciences, University of Sunderland, UK.



Dr. William John Lough, is a Reader in Pharmaceutical Analysis Institute of Pharmacy, Chemistry & Biomedical Sciences, University of Sunderland, UK.

His research is in the general area of pharmaceutical and biomedical analysis with special interest in chiral resolution, low dispersion LC, determination of drugs in biological fluids and analysis of drugs for tropical disease therapy.

His interest in LC dates back to 1974 in the early days of the technique and his experience of chiral separations, much of which was gained in the UK pharmaceutical industry, dates almost as long. His early research in this field involved chiral ion-pair chromatography and the development of an immobilised chiral metal-diketonate catalyst and a hexahelicene chiral stationary phase for LC. His work as a Chromatography Section Leader and chiral separations specialist with Beecham Pharmaceuticals in the UK in the 1980's came at a time when breakthroughs were being made in LC chiral stationary phases that had a major impact on how chiral drugs were developed. His more recent interests are in chiral drug bioanalysis, screening strategies for chiral method development, and chiral CE. He has edited a book on "Chiral Liquid Chromatography" (1989), is a co-editor of "Chirality in the Natural & Applied Sciences" (2002) and in 1996 he was Chair of the 8th International Symposium on Chiral Discrimination. He has been a member of the Executive Committee of The Chromatographic Society for the past thirteen years and of the British Pharmacopoeia, Committee A (Medicinal Chemicals) for over five years.

For Notes :



# Topic

## **Chiral Resolution: Past, Present & Future**

W J Lough

Institute of Pharmacy, Chemistry & Biomedical Sciences, University of Sunderland

There are several accepted landmarks in the history of chiral resolution and its impact on pharmaceutical R&D. These include what is accepted to be the first chiral resolution by Pasteur reported in 1848 (involving hand-picking enantiomeric crystals of the sodium ammonium salt of racemic tartaric acid), at the end of the 19th century the recognition that different enantiomeric forms of a racemic drug ought to exert different pharmacological activity, and, in the late 1950's, the Thalidomide Tragedy. However, the major breakthroughs in the development and commercialisation of technology for chiral resolution did not come until the mid-1980's and at that time they had an immediate and important impact on pharmaceutical R&D. Only then was it possible for the pharmaceutical industry to properly address the many problems associated with the administration of racemic chiral drugs that the case of thalidomide had seemed to starkly illustrate. After the 1980's, subsequent developments were made rapidly and chiral resolution, at least on the analytical scale, very soon became a mature research area. In particular, the cross-fertilisation of ideas from different simple chiral selectors resulted in new chiral stationary phases for liquid chromatography, which, when used in parallel in automated screening systems, gave very high success rates for the development of chiral separations. However, even today, there is still scope for progress towards reducing the time from Discovery to Market in the pharmaceutical industry. For example, it would be useful to determine enantiomeric and other structurally-related drug impurities in one rather than two analytical methods.

For Notes :

# Speaker's profile

**Dr. David Lloyd**  
Bristol Myers Squibb, USA



Dr. David Lloyd is currently a group leader in the Analytical R&D Department of Bristol-Myers Squibb, New Brunswick, NJ, USA. He leads a team of analytical scientists providing separations and spectroscopy support throughout the drug development process.

Dr. Lloyd received B.Sc. (Physics) and Ph.D. (Chemistry) degrees from the University of York, UK, where he worked with his research advisor, Dr. David Goodall, on chiral detectors for fast reactions monitoring and for HPLC. His interest in capillary electrophoresis (CE) instrumentation developed whilst at York in the late 1980's, and he later turned to bioanalytical applications of CE during postdoctoral studies in the laboratory of Prof. Irving Wainer at St. Jude's Children's research hospital, Memphis, TN, USA. After moving to McGill University, Montreal, Canada, he was appointed as Assistant Professor in the Departments of Oncology and Experimental Medicine. One focus of his work was on the application of CE to solve bioanalytical problems, in particular the development of CE methods with direct injection of biofluids for the analysis of microscale biological compartments. Other research interests included chiral packed capillary electrochromatography, and CE determination of physical-chemical parameters, including stereoselective drug-protein binding and drug-drug interactions.

In a move from academia to industry, Dr. Lloyd joined DuPont Pharmaceuticals, now acquired by Bristol-Myers Squibb. His current CE research activities include non-aqueous CE separations for the analysis of poorly-water soluble compounds, and chiral separations by CE. Dr. Lloyd was previously Contributing Editor of Trends in Analytical Chemistry. He is currently Editor of the Journal of Chromatography B : Analytical Technologies in the Biomedical and Life Sciences.

For Notes :

# Topic

## **Capillary Electrophoresis Chiral Separations in Pharmaceutical Analysis**

David K. Lloyd

Analytical R&D, Bristol-Myers Squibb, POB 191, New Brunswick NJ 08903-0191, USA.

Despite its great impact in other fields such as analysis of the genome, capillary electrophoresis (CE) has generally achieved only modest acceptance in the analysis of small-molecule pharmaceuticals. A notable exception is the separation of chiral pharmaceuticals by CE. There are probably two main reasons for this: First, despite great advances, no chiral separation technique can be considered to be overwhelmingly superior, and so CE offers a competent alternative to HPLC, GC or SFC. Second, because of the high separation efficiency characteristic of the technique, CE is particularly suited to the separation of stereoisomers achieved via small differences in their binding to a chiral selector. In chiral CE or HPLC, for a given selector/selectand in an identical environment, the same interactions will occur. However, achieving resolution for a given peak pair requires the appropriate combination of selectivity and efficiency, and so other things being equal, CE will often be able to achieve resolution based on lesser differences in binding strength than HPLC. The breadth of application of chiral CE in the pharmaceutical industry will be discussed, with reference to the published literature and findings from a mini-symposium on the application of CE in the pharmaceutical industry held during the HPCE 2002 conference. Validation of chiral CE methods, and applications intended for regulatory submission will be highlighted. Method development techniques for chiral CE will be evaluated, ranging from basic screening strategies to the use of molecular modeling to develop an expert system for prediction of CE chiral separations.

For Notes :

# Speaker's profile

**Dr. Eric R. Francotte,**  
Novartis Pharma AG, Research Department,  
Central Technologies, Basel,  
Switzerland.



Dr. Eric Francotte is the Head Separation & Cold Metabolism, Novartis Pharma AG, Research Department, Central Technologies, Basel, Switzerland. Dr. Francotte gained his PhD in 1978 from the University of Louvain (Belgium) in Organic Chemistry in the group of Professor H. G. Viehe. He spent 2 years as postdoctoral fellow with Professor W. Oppolzer at Geneva University on the total synthesis of lysergic acid.

In 1980, he joined the Macromolecular Chemistry unit at Ciba-Geigy Central Research Laboratories in Basel, and was dealing with the development and application of chiral stationary phases for the chromatographic resolution of racemic compounds. In 1988 he became group leader and head of the research project on optically active polymers. In 1990 he was appointed as head of the Chromatography Laboratories in the Research Support Department within the Pharmaceutical Research of former Ciba, where he built up a center of expertise for the chromatographic separation of stereoisomers. Since 1997 he is Head of the Technology 'Separations' in Central Technologies at NOVARTIS Pharma and he is responsible for the research, development and application of analytical and preparative chromatographic processes.

He is the author or co-author of more than 70 publications, including several reviews and has contributed 3 book chapters on the topic of enantioselective separations. He is also inventor or co-inventor on more than a dozen patents. He has been Chairman of the international Symposium on Preparative Chromatography PREP'96 in 1996, and of the international Symposium on Biological & Pharmaceutical Analysis in 2000, and has been involved with the organisation at a number of international conferences in the fields of chromatography and chirality. Eric Francotte received several awards, including the Ciba Fellow Award in 1995, the "G. Jaubert 1998" Award given by the University of Geneva and the 'Novartis Distinguished Scientist' Award (Novartis 'Nobel Prize') in 2000. He is a member of the Editorial Board of several international journals (Chirality, Chromatographia, and Isolation & Purifications) and he is a permanent member of the International Scientific Committee of the International Symposium on Chirality (ISCD).

For Notes :

# Topic

## **Preparative Chromatographic Separation of Enantiomers**

Eric. R. Francotte

NOVARTIS Pharma AG, Research Department, Central Technologies, W KL-122.P25, Postfach, CH-4002 Basel (Switzerland)

Systematic investigation of the biological activity of the individual enantiomers has become the rule for all new racemic drug candidates and chiral considerations are now integral parts of drug research and development and of the regulatory process. To obtain the enantiomers of chiral drugs, several options are currently available and among them, enantioselective chromatography on a preparative scale is compelling increasing recognition. At the laboratory scale, the chromatographic technique has even become the method of choice, permitting to rapidly provide both enantiomers needed to perform the preliminary biological tests. The technology has now been applied up to production scale under economically competitive conditions. These achievements have been made possible thanks to the concomitant introduction of both, efficient chiral stationary phases and efficient separation techniques, such as simulated moving-bed (SMB) chromatography, which has opened up possibilities which were not conceivable some years ago in the field of chromatographic separations. However, even though preparative enantioselective chromatography already constitutes a powerful tool for the development of chiral drugs, several obstacles which prevent a broader and more intensive utilisation are still subsisting and will be addressed.

For Notes :



## Introduction to the Chairpersons



**Prof. H. L. Bhalla**

Prof. H.L. Bhalla, B. Pharm., M. Pharm., Ph.D. (Tech.), is senior most professor of Pharmaceutics & Pharmaceutical Technology in India. He is currently Advisor SciTech Centre, President, CRS-Indian Chapter, Emeritus Professor and Founder Director, B.V. Patel Pharmaceutical Education Research & Development Centre. He has over 100 research publications in National & International journals and guided 16 Ph.D. and over 30 M. Pharm. Scholars. He has coordinated many workshops/seminars as well as national and international conferences to promote Pharmaceutical Sciences and technology and interaction between industry and academic institutions.

Prof. Bhalla has been member of advisory boards of many journals in India and abroad. He was elected as President, Indian Pharmaceutical Congress Association (IPCA) for 1993 and President, Indian Local Chapter of Controlled Release Society in 1995. He is recently nominated to the Council of FAPA College of Pharmacy, Bangkok (Thailand); and European Association of Pharmaceutical Technology, Germany and Scientific Advisory Board of the 3<sup>rd</sup> World Congress on Emulsion, France. He is recipient of several Awards.

His services in social fields were recognized as Best President by Lions Club of India and Special Executive Magistrate for 2 years by State Government of Maharashtra in early 1980's. He is permanent invitee to the meetings of many trusts and associations.

**Prof. Mukesh Gohel**

Prof. Mukesh C. Gohel, M. Pharm., Ph. D. is working as a faculty member in L. M. College of Pharmacy since 1971. Presently, he is holding the position of Principal and Professor in the Department of Industrial Pharmacy. He has published 66 research papers in leading refereed national and international journals. He has 30 presentations to his credit in Indian Pharmaceutical Congress. He has successfully guided 66 M. Pharm. and 8 Ph. D. Students. He is a member of American Chemical Society since 1997 and life member of many scientific and professional bodies.



He has successfully completed several research projects funded by Ministry of Human Resource Development and All India Council for Technical Education. He is a recipient of three major research awards for his outstanding research publications. His areas of interest are use of semi-synthetic adjuvants in dosage form design, direct compression and dissolution enhancement. He is on the list of Advisory Board of Indian Journal of Pharmaceutical Sciences.

**Prof. Y. K. Gupta**



Professor Y.K. Gupta, MBBS, MD is a well-known Medical Scientist. He has been associated with All India Institute of Medical Sciences (AIIMS, New Delhi) for the past several years. His major research interests are neuropharmacology of vomiting and neurodegenerative disorders such as epilepsy, stroke, Parkinson's disease and Alzheimer's disease. He has evaluated several herbal drugs and antioxidants in animal models of neuropsychiatric disorders. He has published a number of excellent papers in International refereed journals, which are well cited. He has received several awards and prizes in recognition to his original contributions such as Science Academy medal for Young Scientists (Indian National Academy), Shakuntala Amir Chand Prize (Indian Council of Medical Research), Mangalore Southern Regional Conference Prize (Indian Pharmacological Society), G. Achari Oration Award (Indian Pharmacological Society), C.L. Malhotra Research Prize (Association of Physiologists and Pharmacologists of India), Major General S.L. Bhatia Oration Award (Association of Physiologists and Pharmacologists of India), Chandrakanta Dandiya Prize (P.C. Dandiya Trust), Fellow, Indian Pharmacological Society.

# Speaker's profile

**Dr. J. Angus Bell**

General Manager, Early Development & Laboratory Services, Quintiles Limited, Edinburgh, Scotland



Dr. Angus has over 30 years experience in pharmaceutical R&D. At Quintiles Angus is General Manager for business activities in Scotland. Additionally, he is accountable for preclinical business strategy world-wide, ensuring that innovative solutions are developed to meet the needs of customers in the face of an ever-changing regulatory and commercial environment. Previously Angus spent over 20 years at Glaxo gaining experience across a wide range of disciplines. Later he was responsible for the overall project management of R&D integration activities surrounding the GSK merger. Prior to this he was World-wide Director for New Product Delivery, a global process aligning development manufacturing and supply, regulatory and commercial functions in the development and delivery of the physical forms of Glaxo Wellcome's new medicines.

For Notes :



# Topic

## **Trends in New Medicine Development**

J Angus Bell

General Manager, Early Development & Laboratory Services, Quintiles Limited, Edinburgh, Scotland

Successful pharmaceutical and biotechnology companies seek to invest their R & D dollars in potential new medicines that have the best chance of approval and return on that investment. In an increasingly costly and highly regulated market place, companies must pick their winners early in the development process and take critical “go or no-go” decisions. Analysis of scientific, clinical, manufacturing and commercial activities must be integrated to achieve optimal success. These factors, together with emerging partnership roles will be discussed.

For Notes :

# Speaker's profile

**Dr. Subrahmanyam Vangala**

Site Head, Preclinical Pharmacokinetics  
Johnson and Johnson Pharmaceutical Research and  
Development, USA



Dr. Subrahmanyam had his early education in India. He is a Master of Science in Biochemistry from Andhra University. He did his Ph.D in 1986 in Biochemistry from Memorial University of Newfoundland, Canada.

From his days of Ph.D he has been interested in xenobiotics and he has gained expertise in Pharmacokinetics and Drug Metabolism. He was a post doctoral fellow at the school of Pharmacy at University of Colorado, Boulder in 1987 where he worked on in vitro drug metabolism and molecular toxicology utilizing hepatocytes.

During 1989-92 he was an Assistant Specialist Scientist at School of Public Health, University of California, Berkley, CA. He worked on in vitro and in vivo metabolism and molecular toxicology using isolated enzyme systems. He was a Senior Research Scientist at Wyeth-Ayerst Research, Princeton at New Jersey during 1992-97 where he worked on ADME, and established recombinant human CYP-isozyme banks for routine drug metabolism studies. He worked in Purdue Pharma, NY during 1998-2001 where he rose from Section Leader to Group Leader in Drug Metabolism. He contributed to drug discovery and pre-clinical programs and established several high throughput screening methods for discovery support such as fluorescence, cytotoxicity assays using hepatocytes and bDNA assay for cytochrome P450 induction in hepatocytes. He established several assays using microsomes, recombinant enzymes and hepatocytes.

Presently, he is the Site Head of Preclinical Pharmacokinetics at Johnson & Johnson Pharmaceuticals at NJ and managing several projects transitioning from Discovery to Development.

He has delivered several invited lectures in India, US and Canada and has published a number of research papers in International refereed journals. He has chaired several international conferences and is a member of several professional bodies.

For Notes :

# Topic

## **Evolving Paradigms of Preclinical Drug Development Processes: Bridging the Gap Between Discovery and Clinical Drug Development**

Vangala Subrahmanyam, Ph.D.

Division of Preclinical Drug Evaluation, Johnson & Johnson Pharmaceutical Research & Development, Raritan, New Jersey, USA

Drug development is very complex, lengthy and expensive process taking about 12 to 15 years and costing about half a billion dollars to successfully launch a drug into market place and it has been estimated that approximately one in 5,000 to 7,000 molecules makes into the market. In addition, approximately two to five per cent of marketed drugs have been withdrawn due to unforeseen idiosyncratic toxicities in humans costing huge losses of revenue due to accompanying lawsuits. The reasons for this is that the underlying properties of drug disposition are very complex and are very poorly understood. In addition the preclinical models used in drug development have many pitfalls and sometimes do not accurately represent humans. At least three types of major problems are evident during drug development that include chemical, pharmacokinetic and toxicological properties that effect the disposition of the drug. In addition, lack of good biomarkers to monitor safety and efficacy in the clinic is hindering the process of nominating the right candidates for clinical development. Recent advances in drug metabolism, "omics" technologies, PK/PD models, in silico models and biomarker programs are rapidly bridging these gaps and are revolutionizing the drug development processes. The goals of the evolving technological revolution is to enable the drug development process to be shorter (5 - 7 years) less expensive (< 250 million dollars) and perhaps to reach a stage of 1 in 1,000 molecules to be successfully launched without post-marketing idiosyncratic drug toxicity. This talk will particularly focus on how preclinical drug development processes has been evolving in the last decade and help discovery to nominate good candidates into PCD and also allow further to nominate good candidates into the clinical development. It appears that a combination of several in vitro (animals and human) and in vivo (animal) models are required with special emphasis on conducting mechanistic studies to discover "novel biomarkers" to help move compounds into clinic at much higher rate.

For Notes :

# Speaker's profile

**Prof. Dr. Monika Seibert-Grafe**

Head of Coordination Centre for Clinical Trials,  
University Hospital  
Heidelberg, Germany



Dr. Monika Grafe studied Medicine at the University of Mainz, Germany. She is a board certified Clinical Pharmacologist and an Anaesthesiologist. Prior to joining the University of Mainz, she worked for nearly 12 years in Hoechst AG/Hoechst Marion Roussel and finally Aventis.

Although the industry changed the names due to merger and acquisitions, Dr. Grafe greatly contributed to the growth of the industry as Head of Clinical Pharmacology. She has designed different clinical pharmacology studies, early clinical studies in patients including proof of concept studies in the target population. She is an expert in identification of relevant, clinically meaningful biomarkers and surrogates in clinical and preclinical studies. She has designed several early clinical development of compounds belonging to cardiovascular and metabolic diseases as well as inflammatory diseases.

Since July 2000, Dr. Grafe is Head of Co-ordination Center for clinical trials at the University Hospital Heidelberg at Germany. She is responsible for Scientific, clinical and operative support of clinical studies, Quality Assurance in Investigator Initiated Trials, Pharmacogenomics and Applied Clinical Genomic Research, Biomarker and Surrogates to allow measurement of drug effects in early stage of drug development.

Dr. Grafe has a love for teaching and she is a lecturer at the University Hospital at Heidelberg. She has published several papers and is a member of 8 scientific organizations.

For Notes :

# Topic

## **Optimising Drug Development in Phase I/IIa**

Monika Seibert-Grafe

Coordination Centre for Clinical Trials, University Hospital Heidelberg, Germany

The overall goal of exploratory clinical research is the fast selection of the best candidate for drug development in phase IIb/III, reduction of attrition rate and increase in probability of success. Therefore, the identification of key objectives as well as of important preclinical and clinical issues is necessary.

The following strategic tools can support to streamline the process of fast entry into man: Target product profile, preclinical and clinical decision trees including milestones, key success factors, GO/No GO criteria and a project plan containing a detailed schedule for requested activities. Worst case scenarios should be considered as well.

Use of biomarkers and surrogates in preclinical and clinical proof of concept studies help to identify whether the pharmacological/biological target is covered by the NCE which is an important milestone. The use of clinically meaningful surrogates reflecting the pathophysiology of the disease and the drug action makes the assessment of the potential therapeutic merits of an NCE more reliable. There are even surrogates which are accepted by authorities for approval of some drugs for certain diseases, e.g. HbA1c, blood pressure, eradication of *heliobacter pylori*. However, there are also examples of surrogates which are affected by drugs but which are not associated with clinical outcome, e.g. antiarrhythmics. Surrogate markers in early stages of drug development can be used as research tools, for better decision making and for drug selection. Demonstration of proof of concept in the target population is the important milestone in this early phase of drug development and might determine the fate of the NCE, step into phase IIb/III or discontinuation of development.

For Notes :

# Speaker's profile

**Dr. Heinz W. Radtke**

Executive Vice-President, Research and Development, Byk-Gulden StraBe2



Dr. Heinz Radtke was born 1943 in Bad Freienwalde and attended Medical schools in Kiel, Berlin, Zuerich and Goettingen between 1963 and 1969. He defended his MD thesis at the University of Zuerich in 1969. From 1969 to 1971 he did post doctoral research at the Max-Planck-Institute for biophysics in Frankfurt/Main. Between 1972 and 1978 he got his clinical training in internal medicine and nephrology at the Frankfurt University Hospital. In 1978 he completed his second thesis (habilitation) and received teaching permission in internal medicine at Frankfurt University. This was followed by a sabbatical year in pharmacological research at Tulane University New Orleans. 1983 Heinz Radtke changed from university into pharmaceutical industrial research at ALTANA. Since 1987 he is member of the board of management at ALTANA Pharma responsible for R&D. He published many scientific articles in physiology, renal disease and anemia.

For Notes :

# Topic

## **Project Management in Clinical Drug Development**

Prof. Dr. Heinz-Werner Radtke

ALTANA Pharma AG, Germany

For a fully integrated, research oriented pharmaceutical company nothing is more important than product candidates for the international prescription market.

To get product candidates through preclinical and especially through clinical development in a timely manner is the only way to safeguard the company's future. Therefore, much money is spent for research and even more for development. Every single day saved on time-to-market is several million dollars worth.

For regulatory approval a host of scientific data is necessary and very many disciplines are involved. Pure coordination of different tasks and activities is not sufficient and will end sooner or later in a disaster.

The only way to succeed is professional project management. This includes a well defined unambiguous goal to reach for, a passionate champion willing to fight for the goal as a project leader and a maximally motivated project team. The team comprises members from every department and discipline involved. Target oriented processes and suitable electronic tools are equally important as personal incentives for reaching important milestones and finally the prespecified goal.

The project leader being responsible for the success has all the freedom to search for alternative problem solving and trouble shooting by using all internal or external (contract research organisation) capabilities and capacities.

A steering committee reporting directly to the board of management is setting the stage and defining the corridor, wherein the project team may independently operate.

For Notes :

# Speaker's profile

**Dr. Fritz Erni**

Head Pharmaanalytica, Novartis quality Assurance  
Locarno, Pharmaceutical Operations, Switzerland



Dr. Fritz Erni had his education in Zurich, Switzerland. He obtained his Doctor of Science Degree in 1972 from ETH, Zurich under the supervision of Prof. Dr.W. Simon.

After his D.Sc., he worked in Hitachi Ltd., Japan in the application laboratory for Scientific & Analytical Instruments for 3 years. Since 1974, he has been associated with Sandoz and later with Novartis. Presently, he is Head of Novartis Pharmaanalytica at Locarno. During the last 30 years he has significantly contributed to Analytical Research and Development.

He has worked in Physico-chemical characterization of pharmaceutical products and drug substances. Dr. Erni has more than 20 years of experience in all CMC aspects including the preparation of CMC parts of all stages of registration documentation and global submissions. He has 7 years of experience in quality assurance and quality control starting from API upto fully finished product with full documentation for global submissions. His scientific interests are stability testing of pharmaceuticals, impurity testing and various aspects of chromatography as R&D/ QC tools in pharma industry.

For Notes :



# Topic

## **International Harmonisation - Impact of ICH on Impurity Testing**

Fritz Erni, Ph.D.

Novartis Pharma, Basel, Switzerland

The industry and the regulators of the US, Japan and Europe started more than 10 years ago to harmonize the requirements for the registration of new pharmaceutical products (International Conference on Harmonisation: ICH). As a result, new guidelines were developed with the participation of experts from industry and the regulators. The impact of these ICH guidelines is not limited to the involved regions (US, Japan and Europe). From the beginning of the harmonization process WHO was involved as observer in the ICH steering committee and in expert working groups. ICH has set global standards that are followed worldwide. Industry and Regulators have used these new sets of guidelines for several years. Some of the most important guidelines on Impurities in pharmaceutical drug substances and drug products were recently updated to eliminate some weakpoints. In this lecture the new updated ICH guidelines for the impurity testing in pharmaceuticals are discussed and the impact for the development of separation methods is presented.

The guidelines introduce the new concepts for the Assessments of impurities. It also give clear guidance above which level the impurities in drug substance and drug products have to be reported, identified and qualified. They make clear what limit of quantitation and limit of detection is needed for impurity tests.

Other ICH guidelines describe how to set specification limits, how to deal with chiral drugs and what is needed for the Validation of impurity test methods. Based on this, the goal of method development can be defined. This is needed for optimizing the chromatographic method with adequate strategies. The optimization is based on the needs for selectivity of the impurity guidelines, which is significantly different for drug substance and drug products. From the validation experiments and the systematic method optimization the System Suitability Test (SST) can be established.

For Notes :



# Session IV : Patent & Business Development

## Introduction to the Chairpersons



**Dr. Noel J de Souza**

Dr. Noel de Souza is associated with Drug Discovery and Development for over 30 years. He is currently Director, R&D at Wockhardt Limited.

During his tenure of 25 years with Hoechst, now amalgamated as Aventis, climaxed with two drugs among several attaining significant international attention. Flavopiridol, the first cyclin-dependent kinase inhibitor discovered under his leadership, is in Clinical Phase-II/III (Aventis) for the treatment of cancers. Secondly, the highly-acclaimed, unique adenylate cyclase activator, forskolin, led to the launch of Nippon Kayaku's semi-synthetic forskolin analog Adehl for congestive cardiomyopathy and to its use by different internationally renowned companies as an ingredient in cosmetic products. He has also been Director-R&D at SPARC, Sun Pharmaceuticals. Dr. de Souza is also well-known as an authority on Intellectual Property.

At Wockhardt Limited, the launch of India's first dermatological anti-infective product, NADOXIN, is a fruit of Wockhardt's Drug Discovery Team.



**Mr. Hariharan Subramaniam**

Hariharan Subramaniam is an attorney at law with a background in medicine. He has been in practice as an Intellectual Property Attorney for nearly 22 years. Presently, managing partner of Subramaniam, Nataraj and Associates, Attorneys-at-law, Patent and Trade mark Agents is specialised in the filed of Intellectual Property laws. Earlier he worked with Remfry & Sagar, Attorneys at law, one of the oldest law firms in the world for seventeen years with a substantial part thereof as the Head of its Intellectual Property Law Department. He has lectured at various workshops to prompt IP Literacy and Awareness Mission initiated by the Dept of Science & Technology, Confederation of Indian Industries (CII) and Council of Scientific and Industrial Research (CSIR). He has addressed many eminent gatherings on IP issues including FICCI, CII, and the WIPO in India and abroad. Expert witness before the Joint Parliamentary Commission for the amendment of Trade marks and Patents Laws in India.

He is a Council member of Asian Patent Attorneys Association, Japan and Vice President of Asian Patent Attorneys Association-Indian Chapter. He is one of the founder members of Anti Counterfeiting Group, Indian Chapter and a Iso a member of International Trademarks Association, New York and Association for the Protection of Intellectual Property, Geneva.

# Speaker's profile

**Mr. S. Majumdar**

Patent Attorney  
S. Majumdar & Company, Kolkata,  
India



Mr. Majumdar received his education at Calcutta, India. He holds a bachelor degree in Science and Law from University of Calcutta. He is enrolled with the Bar Council at Calcutta and is a Registered Patent Agent.

He has a diverse experience in the past nearly 20 years by handling over 5000 patent applications related to various fields of technology. He has a long experience in handling litigations in all branches of IPR. Mr. Majumdar has several publications in different fields of IPR. He is member of editorial board of "Journal of Intellectual Property Rights" published by NISC, CSIR, New Delhi. He is also a member of the National Committee for the harmonization of patent under International Patent Law Treaty. Mr. Majumdar is associated as a faculty to various organizations engaged in IPR promotion, including the Govt. of India.

He has handled a number of patent issues in India and abroad for various Corporates, departments of Govt. of India and undertakings, DST, DAE, MIT, SAIL and several others including pharmaceutical companies. He is representing several foreign companies in India, and offering consultancy services in relation to IPR protection and IPR management.

For Notes :

# Topic

## **Implications of the Changing Patent Regime & Patent Litigation Requirement**

S. Majumdar

S. Majumdar & Co., Kolkata

20th April, 1972 the independence day of Indian pharmaceutical industry. On this day the Indian Patents Act of 1970 took effect and excluded pharmaceutical products amongst others from patent protection. Such an amendment brought about major changes in the patenting and marketing policies in India by the multinational pharma companies. The patenting of pharma inventions by multinationals was slashed drastically. That led to thought process in the Indian pharma industry to market new generation molecules in India and in the process started reverse engineering new processes for producing known drugs. Over the years the Indian industry has successfully tapped the generic market and has been the shareholder of International Patents in the pharma field.

Increasing trends towards quality research have presently led to higher awareness. This has triggered a new patent regime in India including the product patents for pharma products. The cut-off date is January 1, 2005 when the product patent regime becomes operational leading to stiff patent issues for industry. The most important area being the identification of new ideas and protecting them adequately both in and outside the country.

The most threatful form of patents are those for new chemical entities and an insight into the strategies for their protection is thus essential. Emphasis should be given to drug delivery systems and various pharmaceutical uses of new compounds. In a product patent regime the industry has to carefully venture into new areas where others are protected and this needs greater understanding of the Indian and Foreign Patent Laws and its intricacies.

For Notes :

# Speaker's profile

**Dr. Esteban Pombo-Villar**

Manager of External Collaborations, NS Research,  
Novartis Pharma AG



Esteban Pombo-Villar was born in Bogotá, Colombia. He completed his education at Universidad Nacional (Bogotá), University of Warwick, (UK) and University of Newcastle upon Tyne (UK). He obtained his PhD in Organic Chemistry under the supervision of Professor BT Golding and completed his Postdoctoral work with Professor A Eschenmoser (ETH – Zurich, Switzerland). He has worked as a medicinal chemist in Sandoz Nervous System Research (Basel, Switzerland) since 1988. Currently he is serving Novartis Pharma, Basel in the capacity of Manager of External Collaborations, NS Research.

For Notes :

# Topic

## **Partnering for Value**

Esteban Pombo-Villar

Nervous System Research, Novartis Pharma Ltd, Basel, Switzerland

The presentation will illustrate the need for partnering and collaborating to increase value in the pharmaceutical industry. To respond to this need in an effective manner, structures and processes are established at Novartis Pharma which facilitate collaboration and partnering of both early research opportunities as well as late stage projects.

For Notes :

# Scientific Poster Presentations





**PS-1.****Synthesis and Evaluation of New DNA-Bis Intercalators as Potent Anti-Tumor Agents**

L.Venkateshwarlu &amp; V. Malla Reddy\*

Medicinal Chemistry Research Laboratory, University College of Pharmaceutical Sciences, Kakatiya University, Warangal-506 009 (AP) India

**Abstract :** Six New DNA Bis-Intercalators (2 sets) have been synthesized making use of three different linkers and anthranilic acid as the aromatic systems. The three linkers synthesized for the purpose are: N'(2-aminoethyl)glycinamide, bis N',N(2-aminoethyl)malamide, and 4-amino-N'(2-aminoethyl)benzamide. First these three linkers have been reacted with 2-aminobenzoyl chloride to get the 1st set of DNA bis-intercalators; viz: N[2-(2-aminobenzamido) ethyl]-N (2-aminobenzoyl) glycinamide, N,N'-bis-2[2-aminobenzamido)ethyl]malamide and 4-(2-aminobenzamido)-N[(2-aminobenzoyl)ethyl] benzamide. The 2nd set of three DNA bis-intercalators (N,N-bis dimethyltriazeno) derivatives have been obtained from the 1st set by the diazotisation of 2-amino group and then reacting with dimethyl amine. All the compounds including the intermediates have been purified and characterized by their physical, analytical and spectral (IR & NMR) properties.

These two sets of compounds have been evaluated for their In vitro and In vivo antitumor activity by four different models. Compound VI, 4-[2-(3,3-dimethyl triazeno)benzamido]-N[[2-(3,3-dimethyl triazeno)benzamidoethyl]benzamide was found to be relatively more potent in its antitumor activity. Dacarbazine has been used as the reference drug.

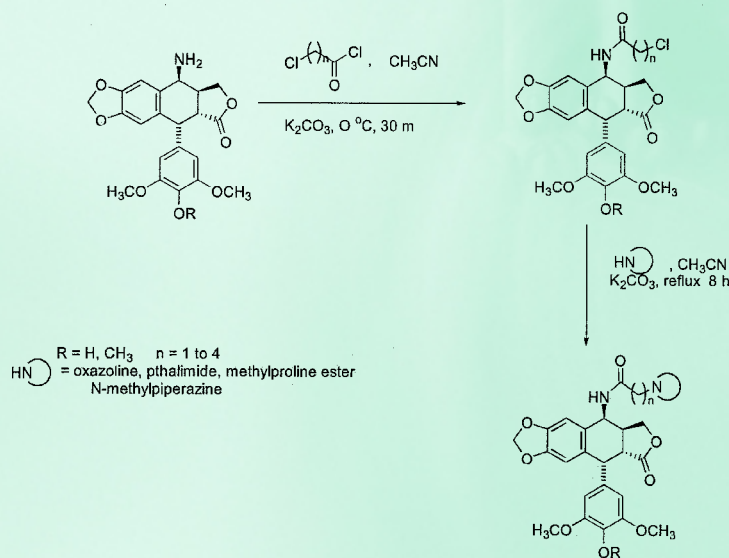
**PS-2.****Synthesis of new analogues of podophyllotoxin as topoisomerase II inhibitors**

B.Ashwini Kumar, M.Arifuddin and Ahmed Kamal

Biotransformation Laboratory, Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad-500 007, India

Podophyllotoxin is a bioactive lignan isolated from the plant sources of Podophyllum peltatum and Podophyllum emodi, and this compound has been the focus of extensive chemical modification leading to clinically useful anticancer drugs.

Etoposide a podophyllotoxin-derived glycoside is an important drug used in the treatment of a variety of cancers. This compound is known to inhibit the DNA-topoisomerase II. Although, it has been widely used in the clinic, the development of drug resistance, myelosuppression and poor bio-availability has prompted to develop new analogues of podophyllotoxin and 4'-demethylepipodophyllotoxin. In this endeavour a large number of podophyllotoxin congeners have been synthesized and evaluated for their cytotoxic potential.



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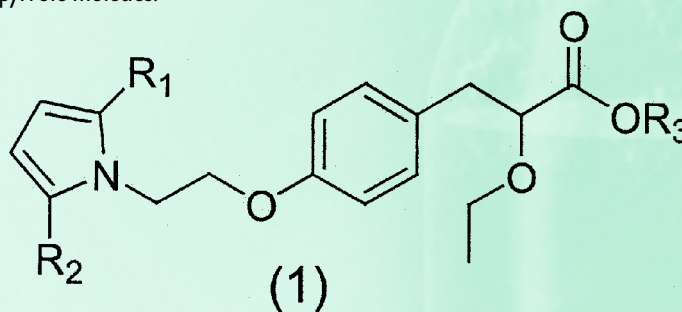
**PS-3. Novel alpha-alkoxy -beta -phenyl propanoic acid derivatives as potential hypolipidemic compounds having antidiabetic activity.**

Sujay Basu\*, Saurin Raval\*, Preeti Raval\*, H.M. Kothari\*, V.G. Barot\* and Vidya Bhusan Lohray\*, Archana Patel\*\*, Mukul Jain\*\*

\*Zydus Research Centre, Department of Medicinal Chemistry, Ahmedabad

\*\*Zydus Research Centre, Department of Pharmacology, Ahmedabad

Ever since the first report by the Pfizer scientists in 1990 alpha-alkoxy-beta-aryl propanoic acids have gained importance as potential hypolipidemic compounds having antidiabetic activities. The presence of pyrrole moieties in living organisms in various forms, such as chlorophyll or haemoglobin has prompted the scientists to use this heterocycle in man made drugs such as Atorvastatin which is a Billion Dollar hypocholesterolemic agent. The present study describes the synthesis and activity of a few alpha-alkoxy -beta-phenyl propanoic acid (1) derivative having alkyl pyrrole moieties.



**PS-4. Vilsmeier Haack reaction on quinaldines: The 4-chloro-3-formyl-2-(2-hydroxy-ethene-1-yl) quinolines, construction of diazepino quinoline system, their antimicrobial and cytogenetic studies**

Palathurai Subramaniam Mohan\*, Raju Nandha Kumar and Thangaraj Suresh

Department of Chemistry, Bharathiar University, Coimbatore - 641 046, India.

A literature search of the last decade reveals that there has been sustained interest in the application of Vilsmeier Haack reagent in organic synthesis. It has proved to be a mild and efficient reagent for the formylation of reactive aromatic and heteroaromatic substrates, as an activating agent for acylhalo addition, ring annulation etc. The classical Vilsmeier Haack reaction involves electrophilic substitution of an activated aromatic ring with a halomethyleniminium salt to yield the corresponding iminium species, which facilitates easy entry into large number of novel heterocyclic systems.

The study of Vilsmeier Haack reaction on 4-hydroxy quinaldines resulted in a potential intermediate 4-chloro-3-formyl-2-(2-hydroxy-ethene-1-yl)quinolines along with 3-formyl-4-hydroxy-quinaldines and 4-chloro quinaldines. The intermediate 4-chloro-3-formyl-2-(2-hydroxy-ethene-1-yl)quinolines is then utilized to prepare diazepino quinolines on treatment with phenylhydrazine hydrochloride.

All the above synthesized compounds have been screened for their antibacterial activities against *Aeromonas hydrophilla*, *Escherichia coli* and *Salmonella typhi* by Disc Diffusion method I using Streptomycin as standard.

They have also been studied for their antifungal activities against *Aspergillus flavus*, *Penicillium funiculosum* by Disc Diffusion method as Carbendazim as standard. The diazepino quinolines were then analyzed for Chromosomal aberrations in Human Peripheral blood leucocyte culture by Hungerford and Moor method.<sup>2</sup> The spectroscopic and analytical data supporting the structure of the synthesized compounds and the detailed results of the pharmacological studies will be highlighted during the presentation.

1 C.H. Collins and P.M. Lyne, *Microbial Methods*, University Park Press, Baltimore, 1970.

2 P.S. Moorhead, P.C. Novell, W.J. Mellman, D.N. Battips and D.A. Hungerford, *Exp. Cell. Res.*, 20 (1960) 613.

### PS-5. Syntheses and Evaluation of Novel Piperazinyl Phenyl Oxazolidinone Antimicrobial Agents

Brijesh Kumar Srivastava\*, Sunil V. Gupta\*, Manish Solanki\*, Prashant Kapadnis\*, Vijay Takale\*, Vidya Bhushan Lohray\*, Purvi Pandya+, K.S. Nand Kumar+

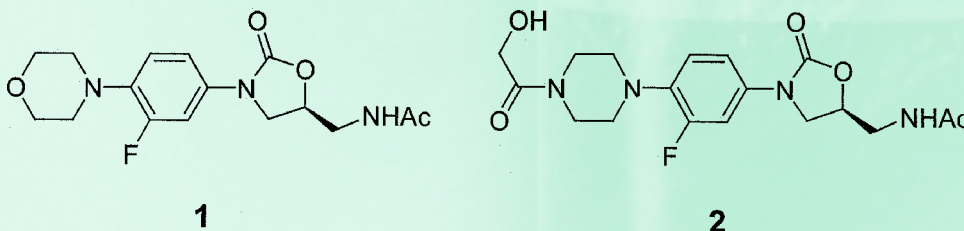
\**Medicinal Chemistry Division, ZRC, + Cell Biology Division, ZRC.*

*Zydus Research Center, Cadila Healthcare Ltd. Ahmedabad 382213*

**Abstract:** Oxazolidinones represent a novel class of antimicrobial agents, effective against Gram-positive pathogens, including vancomycin & methicillin resistant organisms. Linezolid 1 is the first drug launched in this class, almost after 30 years since the discovery of quinolone class of antibacterial. Eperezolid 2 is the follow up molecule which has not emerged out successfully as a drug.

We have prepared and evaluated the antibacterial properties of a number of N-phenyl piperazinyl derivatives of oxazolidinones in which the nitrogen at the 4-position of piperazinyl ring is substituted by different cinnamoyl groups.

Several compounds have inhibited the growth of Gram +ve bacteria used in the screening panel with MIC values 1 microgram/mL.



### PS-6. Synthesis of novel epoxy-bridged tetrahydropyranone frameworks

S. Muthusamy\*, S.A. Babu and C. Gunanathan

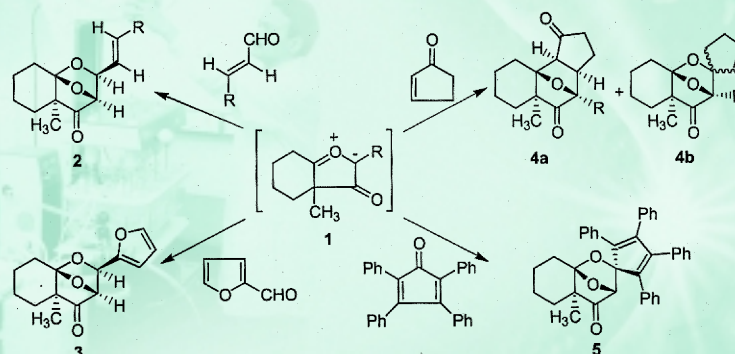
*Central Salt and Marine Chemicals Research Institute, Bhavnagar - 364 002, Gujarat*

Tandem-cyclization processes are superior methods for the stereocontrolled construction of numerous carbon-carbon bonds and/or ring systems in a single mode of operation. The 1,3-dipolar cycloaddition reactions offer a versatile route for the construction of a variety of complex molecules. The tandem cyclization-1,3-dipolar cycloaddition methodologies have well exploited to synthesize a variety of complex molecules and natural products in the area of terpenoids and alkaloids. The highly substituted dioxo-bridged polycyclic moieties are recognized as common structural units in naturally existing bioactive compounds, e.g. amberketal, austalide B, frontalin, levoglucosenone and zaragozic acid A. The epoxy-bridged tetrahydropyran skeleton is present in a wide range of natural products and exists as a part of polycyclic frameworks, e.g. loukacinols, xanthane epoxide, sporal and isogosterones. In continuation of our interest to explore the synthetic utility of alpha-diazo carbonyl compounds for the synthesis of highly substituted epoxy-bridged poly- or spirocyclic frameworks, herein we report our results on the reactivity profile of carbonyl ylides with carbonyl compounds.

It was envisaged that the reaction of alpha-diazo carbonyl compounds with rhodium(II) acetate could generate

metallocarbenoid based on our earlier work. The transient five- or six-membered-ring carbonyl ylides could be formed. For investigating the tandem intramolecular formation and intermolecular cycloaddition reactions of cyclic carbonyl ylides with carbonyl compounds, e.g. aromatic aldehydes, trans-cinnamaldehyde, trans-crotonaldehyde, 2-furancarboxaldehyde, chalcone, cycloalkenones and 2,3,4,5-tetraphenylcyclopenta-2,4-dienone as dipolarophiles (Scheme). The construction of poly- and spirocyclic frameworks incorporating the epoxy-bridged tetrahydropyranone moiety has been well demonstrated in the case of cyclic or acyclic alpha, beta-unsaturated ketones and aldehydes. Only C=O addition products were obtained in the case of alpha, beta-unsaturated aldehydes and 2,3,4,5-tetraphenylcyclopenta-2,4-dienone. These tandem cyclization-cycloaddition reactions were found to be highly chemo-, regio-, and stereoselective, giving the exo cycloadducts in good yields. The notable investigation of our results will be presented.

Scheme

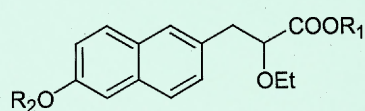


#### PS-7. Novel Alpha-alkoxy-beta-naphthyl- propanoic acid derivatives as hypolipidemic agents.

Hari Kishore Pingali\*, Mala Shah\*, Vidya Bhushan Lohray\*, Archana Patel+, Mukul R. Jain+.

\*Medicinal Chemistry Division, +Pharmacology Division, Zydus Research Center, Cadila Healthcare Ltd. Ahmedabad 382213.

Abstract: Alpha-alkoxy-beta-aryl propanoic acids are known to be excellent hypolipidemic and antihyper glycaemic agents. Although extensive work has been done and reported on this class of compounds with phenyl group at the beta position, focus has not been emphasised on synthesis and biological evaluation of compounds with naphthyl group in this position. Here in we report the synthesis and hypolipidemic activity of a few alpha-ethoxy-beta naphthyl propanoic acid derivatives of formula-1.



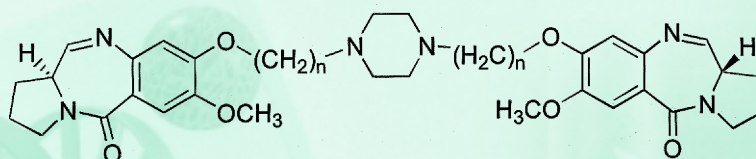
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#### PS-8. New pyrrolo[2,1-c][1,4]benzodiazepines useful as antitumour agents

P. S. M. M. Reddy, D. R. S. Reddy and Ahmed Kamal

Biotransformation Laboratory, Division of Organic Chemistry  
Indian Institute of Chemical Technology, Hyderabad-500 007, India

In the recent years there has been considerable interest in ring systems, such as the pyrrolo[2,1-c][1,4]benzodiazepines (PBD's). These are naturally occurring compounds and are isolated from various Streptomyces species. These compounds exhibit their biological activity by covalent binding in the minor groove of DNA in a sequence specific manner. A number of new dimers of PBD ring system have been prepared by linking with suitable spacers incorporating a piperazine ring with a view to examine their cross linking ability and their in vitro cytotoxicity. The newly prepared compounds has been further assayed against a panel of 60 human tumor cell lines in which several compounds exhibit promising biological activity.



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 Kamal, A.; Reddy, P. S. M. M.; Reddy, D. R. S. *Tetrahedron Lett.* 2002, 43, 6629.

### PS-9. 3-(5,10,15,20-TETRAKIS) CHROMEN-4-ONE PORPHYRINS AS POSSIBLE ANTICANCER AGENTS

B. RAJITHA\*, M. KANAKALINGESWARA RAO, M. AMARAVATHI AND P. NARSIMHA REDDY

*Department of Chemistry, National Institute of Technology, Warangal, India*  
*E.mail: rajitabhargavi@yahoo.com and penthala\_nr@yahoo.co.in*

Porphyrins reported to be photodynamic therapeutic agents (PDT). Flavone acetic acid (FAA) has been identified as a lead drug in the treatment of cancer. These observations prompted us to undertake the synthesis of 3-(5,10,15,20-tetrakis) chromen-4-one porphyrins, for the first time by adopting standard procedure. It is anticipated this novel compounds could be exploited as possible anti-cancer agents.

3-(5,10,15,20-tetrakis) chromen-4-one porphyrins (3 a-f) are prepared by the reaction of pyrrole (1) with simple and substituted chromen-3-aldehydes (2 a-f) in DCM under inert atmosphere. The purple colored porphyrins were characterized by UV, IR, <sup>1</sup>H NMR and FABS mass.

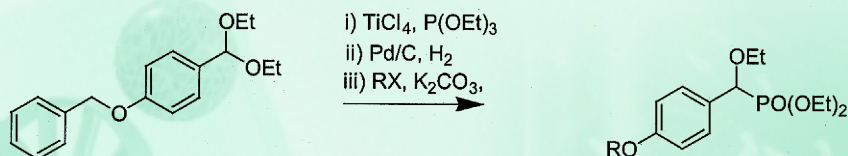
### PS-10. Novel alkoxy-phosphonate and carboxy-phosphonate derivatives as an anti-inflammatory agents.

P. S. Thombare\*, A. D. Argade\*, K. Y. Shah\* and V. B. Lohray\*  
 J. Mohapatra\*\*, V. M. Kanoje\*\*, B. R. Patel\*\* and M. R. Jain\*\*

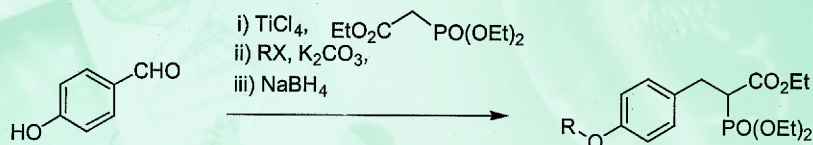
\*Zydus Research Centre, Department of Medicinal Chemistry, Ahmedabad

\*\*Zydus Research Centre, Department of Pharmacology, Ahmedabad.

Over the past few decades, phosphonates have played an ever increasing role in synthetic organic chemistry. Given the important biological functions of the phosphoryl group, its enhanced chemical and enzymic stability, organic phosphonates are among the most important classes of organophosphorous compounds. In the present study a number of alpha-alkoxy-phosphonate and alpha-carboxy-phosphonate analogues have been synthesized. Synthetic routes from inexpensive raw materials have been devised to get an access to a diverse library of compounds. These phosphonate analogues were tested for their anti-inflammatory activity. A few compounds have shown interesting anti-inflammatory activity in the in-vivo rat paw edema model. Further studies are underway to understand the mechanism of its anti-inflammatory activity.



SYNTHETIC SCHEME FOR CARBOXY-PHOSPHONATE



**PS-11. Isolation, Purification of tyrosinase (banana and brinjal species) and chemical modification of amino acid residues present at the catalytic site for the drug designing for various disorders and diseases.**

Sudha V.Amarapurkar\* Sarita J.Suryawanshi, P.J. Sudhakar, Anita P. Goswami

*Division of Biochemistry, Dept. Chemistry, University of Pune, Pune 411 007, INDIA*

Tyrosinase is key enzyme in many disorders and diseases like parkinsons, leucoderma vitilago melanoma and leprosy. Attempts were made to purify this enzyme from Musa species, using simple low priced with high resolution, unclogging column matrices like lignin and polysaccharides. The amino acid residues, which are involved in catalytic site, were found out by chemical modifiers. These residues can be used for drug designing for above disorders and diseases. Kinetic studies of pure enzyme is useful for management regime of doses particularly in parkinsons.

**PS-12. Synthesis of N-Hydroxyethyl-Piperidine and Pyrrolidine Homoazasugars and Evaluation of their Glycosidase Inhibitory Activity**

\$\$). Tarun Sharma , \$). Mohammed M. Matin , \$\$).. Sushma G. Sabharwal and \$). Dilip D. Dhavale \*

\$). *Department of Chemistry, Garware Research Centre, University of Pune, Pune 411 007, INDIA*

\$\$). *Department of Chemistry, Division of Biochemistry, University of Pune, Pune 411 007, INDIA*

Glycosidase inhibitors have great potential as drugs in the treatment of variety of carbohydrate mediated diseases. Azasugars like Nojirimycin and 1-Deoxy Nojirimycin are known to be potent glycosidase inhibitors. In the search for structure activity relationship, we have synthesised new analogues of polyhydroxylated piperidine and pyrrolidine alkaloids namely N-hydroxyethyl-D-gluco-1-deoxyhomonojirimycin, N-hydroxyethyl-L-ido-1-deoxy-homonojirimycin, 1,4,5-trideoxy-1,4-imino-N-hydroxyethyl-D-arabino-hexitol and 1,4,5-trideoxy-1,4-imino-N-hydroxyethyl-L-xyllo-hexitol. The glycosidase inhibitory activity of these compounds have been evaluated.

**PS-13. Design, Synthesis, Pharmacological evaluation of some novel 2-(substituted amino)-5-(substituted phenyl)-6-[(substituted aryl)amino]pyrimidine derivatives as potential second generation Histamine H1-receptor antagonists**

Mahesh Chhabria, Kombu Rajan, Vimal Patel, Mitesh Jani\*

*Department of Pharm. Chemistry, L. M. College of Pharmacy, P.O. Box 4011, Navrangpura, Ahmedabad - 380 009.*

Many potent H1-receptor antagonists are known today but major thrust in this area is synthesis of second generation antihistaminics, which should have potent histamine H1-receptor antagonistic activity with no or less

sedative and anticholinergic side effects. A series of 2-(substituted amino)-5-(substituted phenyl)-6-[(substituted aryl)amino]pyrimidine was designed on the basis of triangular pharmacophoric requirements for the histamine H<sub>1</sub>-receptor antagonist. The distances between the centroids of two aryl ring and tertiary nitrogen at C-2 position were found close to the specified distances. The presence of easily protonisable nitrogens will restrict the drug to cross blood brain barrier. This will reduce the CNS side effects.

Designed series was synthesised by cyclocondensation of the 2-cyano-3-(substituted aryl)amino-3-methylmercapto acrylonitrile with 2-(substituted)amidines in presence of strong base. All the compounds were obtained in good yields and characterised by UV, IR, <sup>1</sup>H NMR, Mass and elemental analysis.

All the synthesised compounds were screened for histamine H<sub>1</sub>-receptor antagonistic activity by in vitro method "Inhibition of isotonic contraction induced by histamine on isolated guinea pig ileum" using cetirizine as a standard drug. pA<sub>2</sub> values were calculated. All the compounds have exhibited significant H<sub>1</sub>-antagonistic activity with pA<sub>2</sub> value ranges from 8.2 - 9.5. The standard cetirizine has pA<sub>2</sub> value 9.4. Two compounds were found equipotent with cetirizine.

Antihistaminic drugs are known to have sedative and anticholinergic side effects. So the most potent compounds were screened for their sedative potential on albino mice using photoactometer. Both the compounds were found to have less sedation compared to standard drug cetirizine. The most potent compounds were also screened for anticholinergic activity on guinea pig ileum. None of the compounds has exhibited anticholinergic effect.

So the series of 2-(substituted amino)-5-(substituted phenyl)-6-[(substituted aryl)amino]pyrimidine has potential to be developed as potential second generation histamine H<sub>1</sub>-receptor antagonists.

#### **PS-14. Design, Synthesis and Pharmacological evaluation of some diarylpyrimidine derivatives as potential antiinflammatory agents with very low ulcerogenic potential**

Mahesh Chhabria, Prashant Modi and Jalpan Joshi\*

*Department of Pharm. Chemistry, L. M. College of Pharmacy, Navrangpura, Ahmedabad -380 009.*

Nonsteroidal antiinflammatory drugs (NSAIDs) are most widely used for the treatment of pain and inflammation, particularly arthritis. Most of the NSAIDs exhibit GIT side effects with their potent antiinflammatory activity. So there is always need of potent antiinflammatory agent with no or less GIT side effects. Presently COX-2 inhibitors are the drug of choice as they are reported to have very low ulcer index.

We have designed a series of diaryl pyrimidines on the basis of basic structural requirements for the COX-2 inhibitor. The structural similarity between known COX-2 inhibitor celecoxib and designed series was checked by indirect type of molecular modeling study, which suggested good 3D similarity between them (r m s d 0.164).

The designed series was synthesised by cyclocondensation of S,N-acetal and s-methyl di(substituted)arylisothiourea. All the compounds were characterised by UV, IR, <sup>1</sup>H NMR and Mass spectra.

All the synthesised compounds were screened for their antiinflammatory activity by in vivo model "Inhibition of carageenan induced rat paw edema". Celecoxib was used as standard drug. All the compounds have exhibited significant antiinflammatory activity. One derivative was found equipotent with the standard drug.

The most potent compound was also screened for its ulcerogenic potential on albino rats, which considered to be common side effect of the NSAIDs. Celecoxib and aspirin were used as standard drugs. Test compound has exhibited very low ulcer index at its therapeutic dose level (i.e. 50 mg/kg). At higher dose test compound has exhibited higher ulcer index than the celecoxib but was found four folds less than aspirin.

COX-1 inhibitory activity of the most potent compound was also evaluated by inhibition of gelatin induced RBC aggregation method. Aspirin and Celecoxib were used as standard drugs. Test compound exhibited very low and comparable COX-1 inhibitory activity to that of celecoxib.

**PS-15. Antimicrobial Activity of *Mappia foetida* Leaves and Stem**

Raju Nandha Kumara, Hutchan Vishwanathanb, Thangaraj Suresha and

Palathurai Subraminiam Mohana,\*

<sup>a</sup> Department of Chemistry, Bharathiar University, Coimbatore - 641 046, India

<sup>b</sup> Department of Environmental Sciences, Division of Genetics, Bharathiar University, Coimbatore - 641 046, India

*Mappia foetida* Miers, (*Nothapodytes foetida* Blume) (Icacinaceae) is an aromatic gregarious evergreen tree found in the Western Ghats of South India. The aqueous extracts of *Mappia foetida* have folkloric reputation for the treatment of a variety of ailments among the Toda Tribes of The Nilgiris. The biological screening of the species has proved its promising anticancer activities.

*Mappia foetida* leaves and stem were collected from the Nilgiri Hills of South India during September 2000. After sunshade dries of both leaves and stem, they were subjected to soxhlet extraction using three different solvents, Petroleum ether, Chloroform and Methanol.

The antibacterial and antifungal activities for the three extracts were then studied (in vitro) against various pathogens at different concentration by Agar Disc Diffusion Method. Streptomycin, Ampicillin and Carbendazim were used as standards. The Stem fractions showed significant zones than that of the leaf fractions. The detailed results obtained along with the zone of inhibition shown by each pathogen will be highlighted during the presentation.

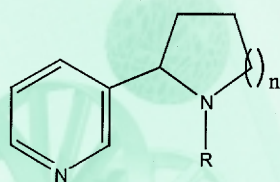
**PS-16. Development of a novel route to the synthesis of constrained nicotines and anabasines, useful drugs for the treatment of Parkinson's Disease and Pain.**

T.K. Sarkar\* and Sankar Basak

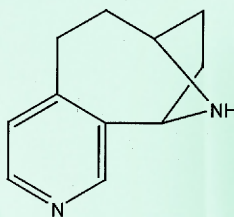
Department of Chemistry, Indian Institute of Technology, Kharangpur, 721 302, India

The nicotinic receptor has been a focus for a tremendous amount of effort for pharmacologists and chemists over several decades. The critical neurotransmission pathway is found in both mammals and insects and in humans, the nicotinic pathway is associated with pain and other chronic neurological disorders such as Alzheimer's disease, Parkinson's disease, Tourette's syndrome, schizophrenia, attention-deficit/hyperactivity disorder, and depression. Critical limitations for the potential use of nicotine as a therapeutic are peripheral side effects that are due to the non-selective profile of nicotine. The side effects are observed in the gastrointestinal system, in the cardio-vascular system, and body temperature and nicotine is a relatively toxic compound that is reinforcing and likely responsible for the addictive properties of tobacco. Compounds that target specific nAChR subtypes in the CNS may not induce these side effects and yet still retain the beneficial effects of nicotine. In light of this, a variety of conformationally restricted analogues of nicotine (1) and anabasine (2) has been synthesized by structural modification in such a way that original conformational mobility is severely limited to one particular conformation. Among these the bridged nicotinoid 3 was found to be very potent in binding as well as functional assays. Of the remaining analogues 4, 5, 6 were evaluated as agonists of neuronal acetylcholine receptors (nAChRs). In particular, compound 5 which activates human recombinant  $\alpha_2\beta_4$  and  $\alpha_4\beta_4$  nAChRs has been shown to be active in animal models of Parkinson's disease and pain. The long and circuitous synthetic route described for the ring systems does not appear to be viable for the synthesis of a large variety of bridged nictines and anabasines required to probe the conformations of (S)-nicotine which induces ion channel opening. Therefore, development of an alternative route which is easy, high-yielding and flexible was felt desirable. In this poster, our studies towards the development of a novel route to the synthesis of constrained nictines and anabasines 4-6 will be presented.

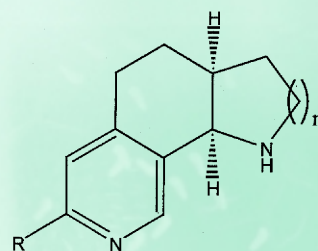




1: R = Me, n = 1  
2: R = H, n = 2



3



4: R = H, n = 1  
5: R = OMe, n = 1  
6: R = OMe, n = 2

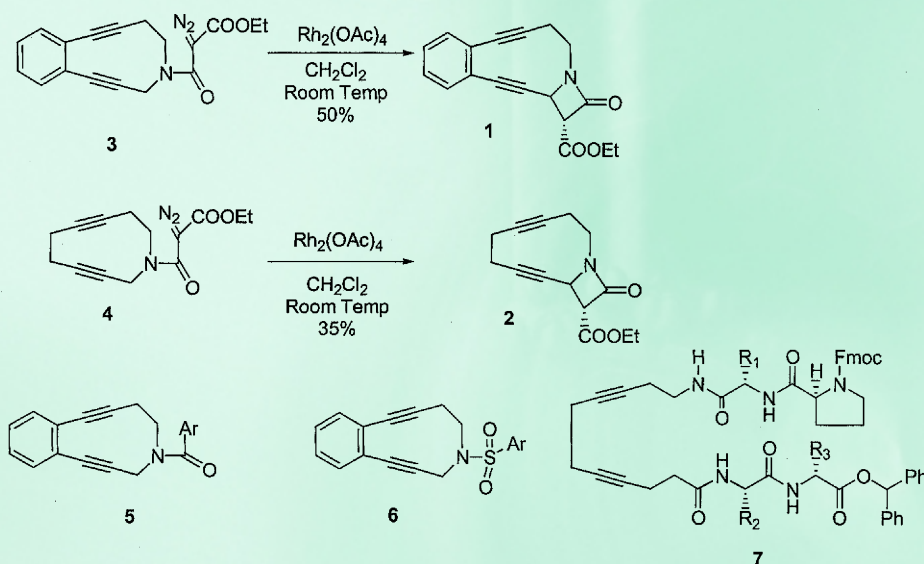
## PS-17.

### Search for DNA-Cleaving Agents: Synthesis and Reactivity of Novel Enediynes

Amit Basak\*, Subrata Mandal and Subhendu Sekhar Bag

Department of Chemistry, Indian Institute of Technology, Kharangpur 721 302, India

Functionalized enediynes, the well-known DNA-cleaving agents, are attractive targets because of the possibility to attach functionalities that serve the purpose of locking and selective binding. In this regard, nitrogen substituted enediynes stand above the other hetero atom substituted ones because of various advantages. Different strategies can be adapted to stabilize an otherwise reactive N-substituted enediyne which include fusion of small strained ring, perturbing the hybridization of the ring nitrogen, incorporation of weak interactions and ligation to metal ions. For example, Banfi and Guanti as well as our group have independently reported the synthesis of  $\beta$ -lactam fused enediynes (lactenediynes). The strained 4-membered lactam ring has been shown to prevent the enediynes from undergoing the Bergman Cyclization at room temperature and opening of the  $\beta$ -lactum ring caused the molecule to undergo the same under ambient conditions. We have also shown that the ambiently stable aryl-fused enediynyl amides, in sharp contrast to the corresponding sulphonamides, are potent DNA-cleaving agents. In the field of weak interactions, novel enediynyl peptides have been synthesized and their conformation and reactivity studied. Circular dichroism and variable temperature NMR measurements demonstrated that the enediyne backbone can be used as a template for nucleating b-sheets. This presentation will focus on a new approach to  $\beta$ -lactum fused enediynes by a novel carbene insertion route and discuss the synthesis and reactivity of profile including the interaction with plasmid DNA of various designed enediynes (1-7).



References: Basak, A.; Mandal, S. *Tetrahedron Lett.* 2002, 43, 000; Basak, A.; Mandal, S.; Das, A.K.; Bartolasi, V. *Bioorg. Med. Chem. Lett.* 2002, 12, 873; Banfi, L.; Guanti, G. *Angew. Chem. Int. Ed. Engl.* 1995, 34, 2393; Banfi, L.; Guanti, G. *Eur. J. Org. Chem.* 1998, 1543; Basak, A.; Khamrai, U.K.; Mallik, U. *Chem. Commun.* 1996, 749; Basak, A.; Shain, J.C.; Khamrai, U.K.; Rudra, K.R.; Basak, A. *J. Chem. Soc. Perkin Trans. L* 2000, 1955. Shain, J.C.; Khamrai, U.K.; Basak, A. *Tetrahedron Lett.* 1997, 38, 6067.

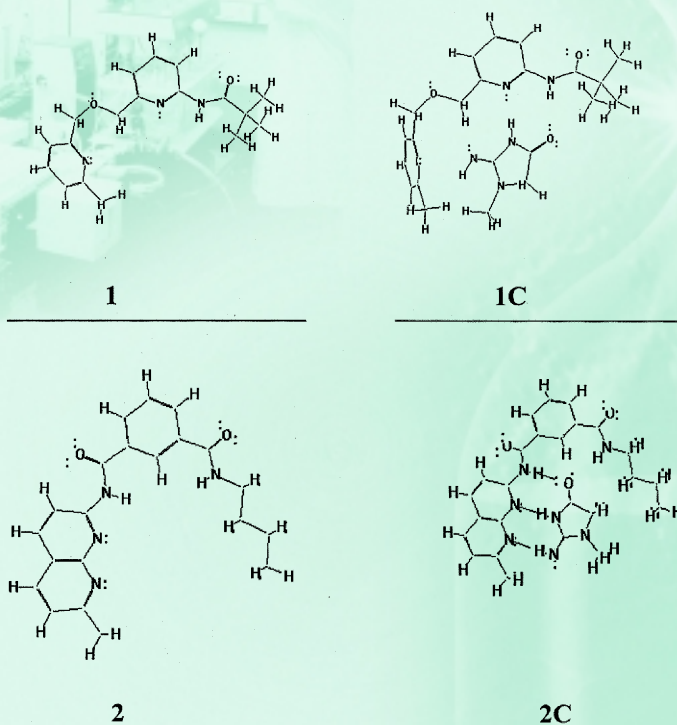
**PS-18.****Directed Molecular Recognition: Synthetic Receptors for Creatinine**

Shyamaprosad Goswami( and Subrata Jana

*Department of Chemistry, Bengal Engineering College (a Deemed University), Howrah 711 103, West Bengal, India.*

Creatinine is an important biological substrate as it is like urea, a blood metabolite and is thus of considerable significance in clinical diagnostic chemistry, particularly for evaluation of renal function. Creatinine is an end product of creatine catabolism and is a normal constituent of urine.

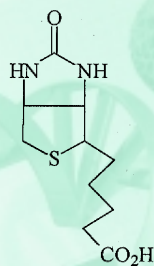
We have designed and synthesised simple artificial receptors (1 and 2) for the normal tautomer of creatinine. The synthesis and the binding studies will be discussed. Energy minimised structures for the creatinine complexes of 1 (1C) and 2 (2C) show the most favourable hydrogen bond formations between the receptors and creatinine suggesting complementarity of the hydrogen bond acceptor and donor groups in the respective receptor and the guest substrate. Development of fluorescent receptors for creatinine will also be presented.

**PS-19.****Directed Molecular recognition of Biotin: Design and Synthesis of Specific Receptors**

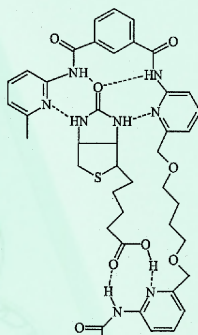
Shyamaprosad Goswami( and Swapan Dey

*Department of Chemistry, Bengal Engineering College (a Deemed University), Howrah 711 103, West Bengal, India.*

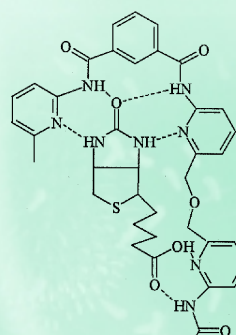
Biotin (I) is an essential vitamin (anti-egg white injury factor) that functions as an indispensable coenzyme in a range of biocarboxylations related to crucial physiological processes such as gluconeogenesis and fatty acid biosynthesis. Several elegant total syntheses of this important biological molecule have been reported. Biotin is mostly used in human nutrition and therapy, and in animal health. Like urea, it is an interesting molecule for recognition studies. We present here the design and synthesis of specific receptors for biotin where we intend to bind both the substituted urea part along with the free carboxyl group. The probable structures of the complexes having maximum number of hydrogen bonds are shown (Complexes A and B). Complex C shows the energy minimised structure of Complex B in favour of complexation of both the urea part as well as the more polar carboxyl group of biotin with the receptor.



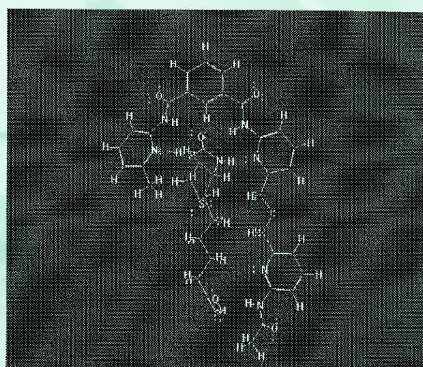
**1**



**Complex A**



**Complex B**



**Complex C**

**PS-20. Concise and practical synthesis of tetrahydroxy and trihydroxy Azepanes and evaluation of their Glycosidase Inhibitory Activity.**

<sup>a</sup> Vinod D. Chaudhari, <sup>a</sup> Jayant N. Tilekar, <sup>b</sup> Sushma G. Sabharwal and <sup>a</sup> Dilip D. Dhavale\*

<sup>a</sup> Department of Chemistry, Garware Research Centre, University of Pune, Pune 411 007, INDIA

<sup>b</sup> Department of Chemistry, Division of Biochemistry, University of Pune, Pune 411 007, INDIA

Preparation and evaluation of glycosidase inhibitory activities of various five, six and seven member iminosugars have gained lot of importance due to their potential use in cancer, obesity and AIDS. As a part of our recent work in this area, we have synthesised (2S, 3R, 4R, 5R) and (2S, 3R, 4R, 5S)-tetrahydroxy-azepane and (2S, 3R, 4R)-trideoxy-azepane from D-glucose and evaluated their glycosidase inhibition activity.

**PS-21. Synthesis and Evaluation of some novel thiazolopyrimidine derivatives as potential antifungal agents**

Ishwarsinh Rathod, Mahesh Chhabria\*, Tushar Mehta

Department of Pharm. Chemistry, L. M. College of Pharmacy, P.O. Box 4011, Navrangpura, Ahmedabad - 380 009.

Fungal infection has emerged out as a dreaded infection and in some cases fatal when observed with AIDS, Cancer and general aging process. There are very few antifungal drugs available in the market for the treatment of systemic fungal infection. So discovery of potent and safe antifungal drug is area of an active interest for medicinal chemist.

Potent antibacterial activity in some of the thiazolopyrimidine derivatives has been reported from our laboratory. Based on the reports available for antifungal drugs we have designed some novel thiazolopyrimidine derivatives as potential antifungal agents.

The designed compounds were synthesised by cyclocondensation of 4-amino-5-carbomethoxy-thiazole with s-methyl di(substituted)arylisothiourea. Fourteen compounds were synthesised. All the compounds were characterised by UV, IR, <sup>1</sup>H NMR and Mass spectra.

All the synthesised compounds were screened for their antifungal activity by Diffusion method using modified Sabourou's Agar as a medium. The organisms used were *A. Niger* and *G. Penicillium*. Griseofulvin and Fluconazole were used as standard drug. All the compounds have exhibited potent antifungal activity and were found to be more potent than the standard drug fluconazole. Three derivatives were found more potent than the standard drug Griseofulvin at same concentration ( $0.33 \times 10^{-6}$  M/ml) Except one all other derivatives were found to have comparable activity with Griseofulvin. The MIC of the most potent compound was found to be  $1.45 \times 10^{-5}$  mcg/ml on *G. Penicillium* and  $1.45 \times 10^{-4}$  mcg/ml on *A. Niger*.

So the results suggest that this series of thiazolopyrimidines has potential to be developed as potential antifungal agents.

## PS-22. Synthesis of Homologue of Irganox 1076 - Some Novel Observations

Jigar Desai\*<sup>+</sup> and K. B. Nair\*

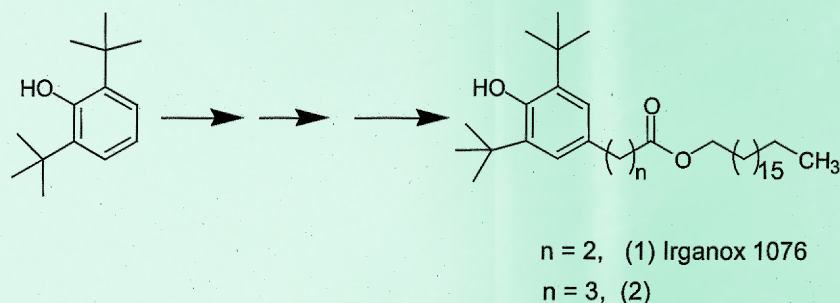
\*Department of Chemistry, Faculty of Science, M.S. University of Baroda, Baroda - 390002.

+ Present Address : Zydus Research Centre, Zydus Tower, Satellite Cross Roads. Ahmedabad - 380015

Octadecyl-3-(3',5'-di-tert-butyl-4'-hydroxyphenyl)propanoate [Irganox-1076] (1) is of great interest because of its extensive use in food packaging, polymer stabilization, pharmaceutical formulations and heat and UV stabilizers.

Literature data shows that introduction of a long aliphatic chain into alkylphenolic type of antioxidants decreases volatility and increases solubility of the material and hence improves their performance. It is reported that electron releasing group at the para position of hydroxyl group in 2,6-di-tert-butyl phenol would enhance the antioxidant activity, whereas an electron withdrawing group at the same position retard or completely eliminate such activity.

A convenient and high yielding synthesis of Irganox-1076 homologue (2) from 2,6-di-tert-butyl phenol is reported in the present study by introducing one additional methylene group in the alkyl chain between the aryl moiety and ester functional group. The formation of 4-tert-butyl phenol derivatives during the Friedel-Craft succinylation of 2,6-di-tert-butyl phenol has been rationalised.



## PS-23. A novel reaction of dimethylsulfonium methylide with Michael acceptors: application to the synthesis of difficultly accessible vinyl silanes and styrenes

Sunil K. Ghosh, Rekha Singh and Sonali M. Date  
B.A.R.C

Rather than the usual cyclopropanation and Peterson-type olefination, conditions for a novel elimination reaction from the adduct of dimethylsulfonium methylide and 2-silylalkylenes/ arylethenes malonate/cyanoacetate/ phosphonoacetate leading to geminally substituted vinyl silanes or styrenes, respectively, have been established. The important feature of this research work is that by varying conditions, the reactions can be tuned in either direction to give the vinylsilane or the cyclopropane exclusively. This study also documents that the loss of hydrogen overrides the loss of a silyl group in a situation where a Peterson type olefination is highly probable. Under the conditions of this study, dimethylsulphonium methylide acts as a synthetic equivalent of carbene anion. The olefinic products viz. vinyl silanes and styrenes are useful intermediates in organic syntheses which

otherwise are difficult to prepare. Details will be presented.

#### PS-24. Safety Profile of Aqueous Extract of Dried Leaves of "Gymnosporia Spinosa"

Dr. A.R. Kubavat, Dr. P.S. Karelia, Dr. B. K. Shah,

Shree M. P. Shah Medical College

**OBJECTIVE :** Leaves of G. Spinosa has been used by people for treatment of jaundice. No information is available regarding toxicity studies which prompted us to carry out this work.

**METHODS:** Acute and subacute toxicity study was carried out using aqueous extract of G. Spinosa leaves. For acute study 28 inbred Swiss albino mice of either sex were divided in to 4 equal groups. First group received distilled water (control). Second, third & fourth group received single dose of drug orally as 40, 120 & 240 mg/100 G. Bd. wt. respectively. Animals were observed for various sign and symptoms. After 72 hours blood was collected for blood counts and biochemical parameters. Liver, lungs and kidneys were subjected to histo-pathological studies. For subacute study 31 rats of either sex were divided in to 4 groups. First group received distilled water (control). Second, third & fourth group received single daily dose of the drug orally as 40, 120 & 240 mg/100 G. Bd. Wt. respectively. Various parameters mentioned for acute studies were used. The observation lasting for 3 weeks.

**RESULTS:** Throughout study there was no mortality. In acute toxicity except for degenerative changes in the liver, other organ showed no change. Analysis of biochemical data showed elevation of S. Alk. Phosphorus, Bl. urea, S. creatinine & R. B. S. Subacute study showed degeneration with fatty changes in the cytoarchitecture of the liver. No change in the other organ. Analysis of biochemical data showed elevation in Bl. urea, S. creatinine and R. B. S.

**CONCLUSION:** The data showed that there are chances of hepato-renal toxicity at higher dose level which is about 100x human therapeutic dose.

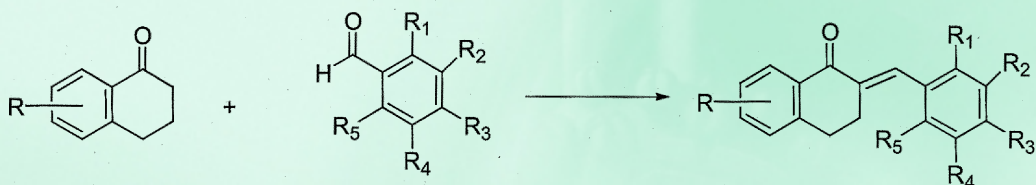
#### PS-25. Design, synthesis and cytotoxic activity of substituted 2-benzylidene-1-tetralones

V.A. Mahajan, P.D. Shinde, M.H. Bhure, H.B. Borate, M.K. Gurjar and R.D. Wakharkar\*

Division of Organic Chemistry: Technology, National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008

Various Mannich bases of Chalcones and related compounds are reported to display significant cytotoxicity against murine P388 and L1210 Leukemia cells as well as number of human tumor cell lines 1,2,3

Substituted 2-arylidene tetralones were synthesized with the aim of determining the relative orientation of two aryl rings for increased toxicity. The compounds in the present study were synthesized by the condensation of the appropriate aldehyde with the tetralones under either acidic or basic conditions.



R = H, 6-OMe

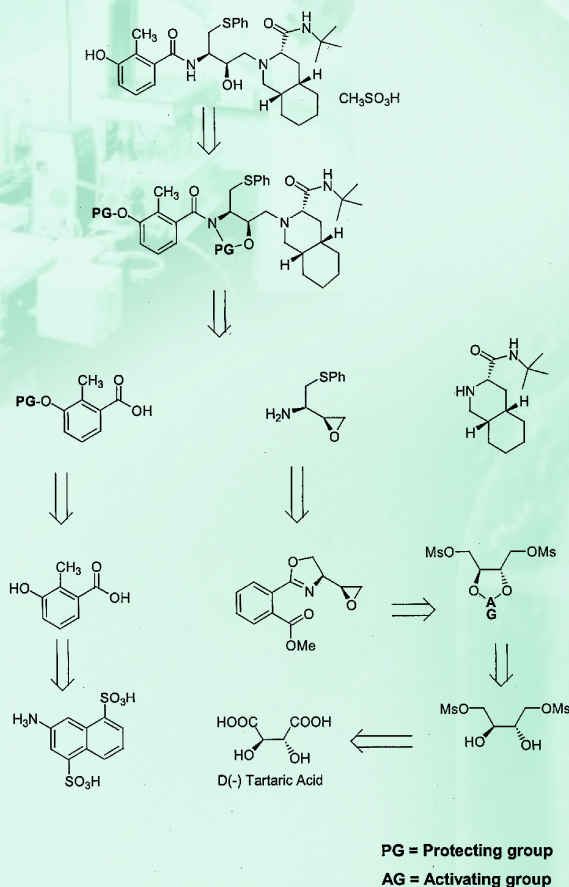
Stereochemical assignments for the products were made on the basis of NMR Spectra and X-ray crystallography. All the compounds were evaluated for cytotoxicity against various cell lines. Results of cytotoxic activity will be presented.

References:

1. H. Shih, L. Deng, C. J. Carrera, S. Adachi, H. B. Cottam and D. A. Carson; *Bio. Org and Med. Chem. Lett.* 2000, 10, 487
2. J. R. Dimmock et al. *J. Med. Chem.* 1999, 42, 1358
3. J. R. Dimmock et al. *J. Med. Chem.* 2002, 45, 3103



challenging problems in our society. Millions of people are suffering from this disease and its number is ever growing. Among various strategies to combat this epidemic, therapeutic inhibition of the virally encoded HIV protease has become an attractive target. The virally encoded enzymes are protease, reverse transcriptase and integrase, and are characterized as a homodimeric endo peptidase of the aspartyl protease family. Based on the transition state mimic concept utilizing various nonhydrolyzable hydroxy ethylene and hydroxy ethyl amine isosteres, a large number of potent and selective HIV protease inhibitors have been developed. Some of the common ones are Indinavir sulfate (Crivixan), Nelfinavir Mesylate (Viracept), Ritonavir (Norvir) and Saquinavir mesylate (Invirase). This study describes the various efforts towards developing an efficient process to manufacture Nelfinavir Mesylate, starting from D(-) Tartaric Acid. The retrosynthesis is described in the attached scheme. The main focus will be on identifying suitable protection/deprotection groups, reagents, reaction conditions etc required for operational simplicity and efficient scale up.



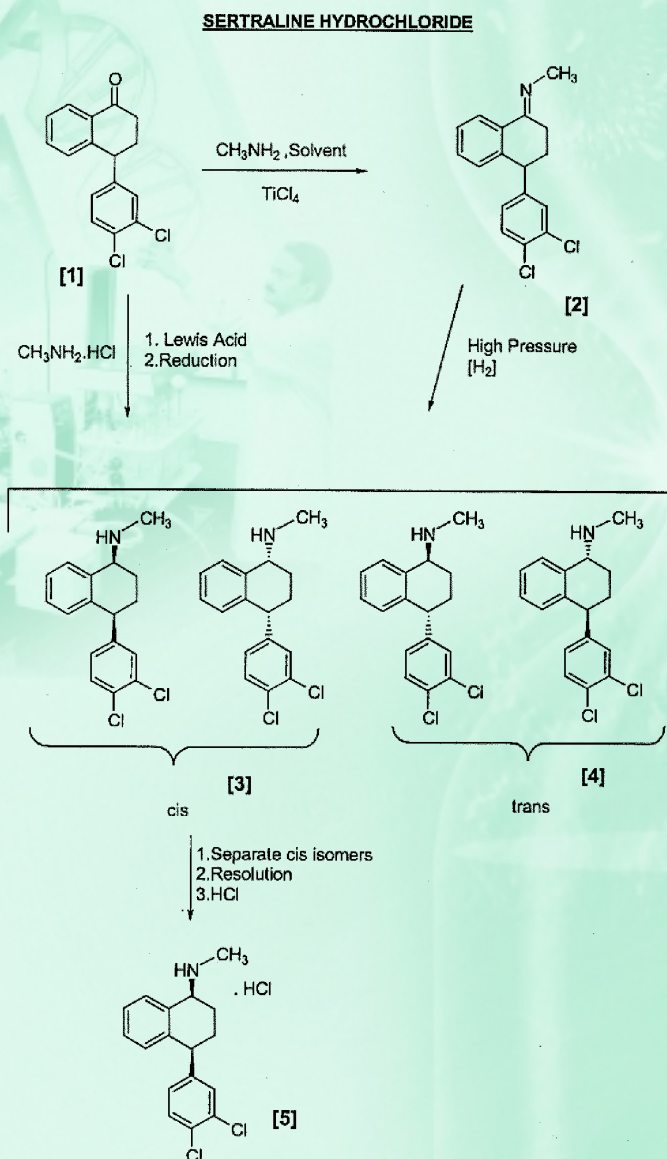
## PS-28. Novel Synthesis of Sertraline Hydrochloride

Anand.V.Daulatabad, Piyush.B.Limbad, B.Pandey, V.B.Lohray, B.B.Lohray

Non-Infringing Process Research (NIPR) Department  
Zydus Research Centre, Ahmedabad

Sertraline Hydrochloride, (+) (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride [5], currently being marketed as “Zoloft” by Pfizer is a selective serotonin reuptake inhibitor (SSRI). It is used for the treatment of depression, obsessive compulsive disorder, panic disorder, premature ejaculation and other anxiety related disorders. The typical method of manufacturing starts with 4-(3,4-dichlorophenyl)-3,4-dihydro-1-(2H)-Naphthalone [1], commonly known as tetralone, which is condensed with methyl amine in the presence of strong Lewis acid Titanium tetrachloride to give Imine [2], which is reduced to give racemic mixtures of cis amine [3] and trans amine [4]. Both of these steps involve low temperature, exothermic condensations, high dilutions to dissolve methyl amine gas, corrosive  $\text{TiCl}_4$ , a lot of solid waste and finally nonstereoselective high pressure reduction. An attempt has been made to address these issues by using one pot stereoselective reductive amination with solid methyl amine hydrochloride and using a milder Lewis acid at

ambient temperature, milder reduction atmosphere, to give the desired cis amine quantitatively. Separations of cis amines from the trans, its resolution with D(-)-Mandelic acid and subsequent HCl salt formation gives Sertraline Hydrochloride[5]. The various reaction conditions used for optimization of one pot stereoselective reductive aminations and their subsequent synthetic transformation will be described.



## PS-29. Novel Synthesis of S(+) Clopidogrel Bisulfate

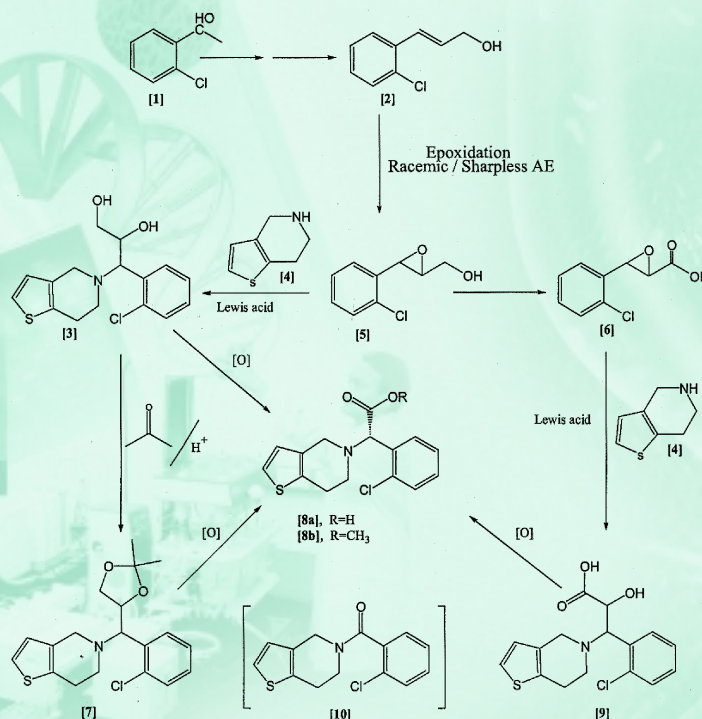
Vrajesh.B.Pandya, Piyush.A.Patel, B.Pandey, V.B.Lohray & B.B.Lohray

*Non-Infringing Process Research (NIPR) Department  
Zydus Research Centre, Ahmedabad*

S (+) Clopidogrel Bisulfate[8b], currently being marketed as 'Plavix', is a platelet aggregation inhibitor and used as antianginal agent, antiplatelet agent and is found to decrease morbid events in people with established atherosclerotic cardiovascular diseases and cerebrovascular diseases. A new and novel synthesis, applicable at racemic and chiral level, as depicted in Scheme, will be described. Thus, Sharpless Asymmetric Epoxidation (AE) gives required chiral epoxide [5], which on Lewis acid induced regioselective ring opening with nucleophile [4] gives [3]. Subsequent chemoselective oxidation of either [3] or [7] or [9] leads to chiral acid [8a], which can be esterified to give the desired product [8b]. (Scheme attached on next page). Surprisingly, however, one of the major degradation product in above oxidations was [10]. Mechanisms of above synthetic transformations, in the light of some of the latest literature observations, will also be described.



## Clopidogrel



### PS-30. Molecular Cloning, Expression and Characterization of Therapeutic Protein in Eukaryotic System

Sanjeev Gupta, Shyam Pagare, Dopal Patel and Rama S.Verma

*Biotechnology Department, Zydus Research Center, Moraiya Ahmdabad*

There are number of recombinant human cytokines and growth factors now a days used as a therapeutic protein. Most of them are potentially used to combat with various fatal diseases. Here we describe the cloning and high expression system of one of the cytokine, containing a single open reading frame and encoding a protein of 170-180 amino acids with a predicted molecular mass ranging from 19-25 kDa. Cloned cDNA has been expressed in yeast *Pichia pastoris*, a high expression system to express the protein in large quantity. To clone the desired gene total RNA was isolated from HEP-G2 cell lines and after cDNA synthesis PCR cloning was carried out in shuttle cloning vector followed by expression vector. After characterization of clone through sequencing, we transformed the gene construct into *Pichia* strain. Characterization of integrated gene has been done through PCR of the genomic DNA. After proper characterization, expression of protein has been carried out by employing different parameters. This glyco-protein has been expressed in large quantities by using a secretory vector containing the promoter and leader sequences. Characterization of secreted protein has been done by biological method using SDS -PAGE analysis and immuno-blotting.

### PS-31. Transactivation Studies of PPAR- $\alpha$ and PPAR- $\beta$ for the Analysis of New Drug Discovery Area.

Anindita Pal, Manju Sharma, Sathyashila Ahvad, Arun Singh and Rama S. Verma

*Bio-technology Department, Zydus Research Center, Morayia, Ahmedabad*

Peroxisome Proliferator Activated Receptors (PPARs) are ligand dependant transcriptional factors belonging to the nuclear receptor family. These receptors are critically involved in lipid, glucose, energy metabolism, control of cellular growth and differentiation by modulating the onset of certain important human metabolic diseases such as dyslipidaemia, obesity, Type II Diabetes and Atherosclerosis etc. PPARs, on dimerization with the 9-cis-retinoic acid receptor (RXR), bind to specific DNA motifs termed Peroxisome Proliferator response elements (PPRE), which are direct repeats with 1 bp spacing (DR-1) present in the regulatory region of the target genes thus regulating their expression. To date, three iso-forms of PPARs have been identified and named as PPAR alpha,

PPAR beta (delta) and PPAR gamma, each displaying a specific tissue distribution pattern. Both PPAR alpha and PPAR gamma have been shown to be involved in energy and lipid homeostasis and are activated by a wide variety of chemical compounds such as the synthetic thiazolidinediones (TZDs) and fibrates as well as the natural compounds such as prostaglandin-J2 derivatives and ecosinoids. The cloning and characterization of PPAR receptors resulted in development of sound knowledge of these receptor functions. Here, we report the development of a transactivation assay system and an expression assay system of PPAR alpha and PPAR gamma for screening of different compounds. In transactivation assay system, cloned PPAR (alpha or gamma) RXR and PPARE tagged with reporter genes are co-transfected into mammalian cell lines and the effect of the ligands (drug) on activation of regulated proteins is measured by the reporter gene assay. In expression assay system, the effect of these ligands on PPAR expression in mammalian cell lines was studied using PPAR alpha and PPAR gamma specific primers in a reverse transcriptional PCR based system.

**PS-32. High level production of recombinant thrombolytic proteins : Intracellular production of Streptokinase and Staphylokinase in E. coli**

Rajamohan G, Monika Dahiya and Kanak L. Dikshit

*Institute of Microbial Technology, 39 A, Chandigarh-160036*

Streptokinase (SK) and Staphylokinase (SAK) are clot-dissolving proteins of bacterial origin. While SK is routinely utilized as a thrombolytic agent, potential of fibrin-specific plasminogen activator activity of SAK has been identified very recently, suggesting its high potential as a thrombolytic agents for clinical purposes. In an attempt to produce SK and SAK in large quantity, we cloned genes encoding SK and SAK in E. coli and constructed expression plasmid vectors in which signal sequences of SK and SAK genes were replaced by an ATG start codon and engineered genes were placed under a strong promoter for the high level expression of intracellular recombinant thrombolytic proteins. Transfection of recombinant expression plasmids into E. coli resulted in high level expression of SK and SAK after IPTG induction that constituted 10-12% of total cellular proteins. Zymographic analysis of total cellular proteins of recombinant E. coli indicated the presence of high level of functionally active SK and SAK exhibiting PG-dependent proteolytic activity. Using two steps chromatographic steps, recombinant proteins were purified with yield of 50-60% that exhibited high specific activity that was very similar to the native protein. The procedure thus developed results 30-40 mg of highly purified preparations of SK and SAK from one liter of shake flask culture suggesting the viability of the process for the upscaling for the production of these thrombolytic agents. While thrombolytic potentiality of SK is already established in clinical medicine, availability of large amount of SAK preparation may facilitate detailed investigations on clinical and functional potentiality of SAK to develop it as a future thrombolytic agent of choice.

**PS-33. Pre-clinical efficacy of Tesaglitazar in various animal models of dyslipidemia or insulin resistance.**

Umrani R.D., Srinivasan M.R., Patel A.V., Sangle G.V., Pingali H.K.#, Lohray V.B.# and Jain M.R.

*Department of Pharmacology and Toxicology, Zydus Research Centre, Ahmedabad.*

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*Department of Medicinal Chemistry, Zydus Research Centre, Ahmedabad*

PPARs are known play an important role in the regulation of lipid and glucose homeostasis. PPAR alpha specific agonists such as fibrates have been shown to lower triglyceride and cholesterol levels in various animal models as well as humans, whereas PPAR gamma agonists such as thiazolidinediones improve insulin sensitivity and are useful as anti-hyperglycemic agents. In order to combine the beneficial effects of PPAR-alpha and PPAR-gamma agonists in one molecule in order to treat Metabolic Syndrome, various dual PPAR agonists have been developed. Tesaglitazar and Ragaglitazar represents NMEs belonging to this class and are undergoing clinical investigation (development of ragaglitazar is currently on hold due to incidences of bladder tumors in rodents). We have evaluated the efficacy of Tesaglitazar in various animal models of dyslipidemia, diabetes and obesity. The hypolipidemic effect was evaluated in Swiss Albino mice (6 day oral treatment with 0.01 to 10 mg/kg), hypocholesterolemic effects were investigated in Cholesterol-fed Sprague Dawley rats (4 day oral treatment with 0.01 to 10mg/kg), antiobesity effect was evaluated in High-fat fed Golden Syrian hamsters (14 days oral treatment with 10 mg/kg)

and high fat-fed C57BL/6J mice (14 weeks treatment with 1mg/kg) and antihyperglycemic effects were evaluated in genetic models of insulin resistance such as db/db mice (12 days treatment with 1mg/kg) and Zucker fa/fa rats (14 days treatment with 3mg/kg).

Tesaglitazar treatment produced a dose dependent reduction in circulating triglyceride levels (upto 79% reduction at 10 mg/kg; ID50= 0.08 mg/kg) in Swiss albino mice and total cholesterol (up to 62% reduction at 1 mg/kg) in hypercholesterolemic SD rats (ID50= 0.03 mg/kg). In hamsters, treatment with Tesaglitazar caused a reduction in body weight accompanied by a significant reduction in LDL cholesterol (79% at 10 mg/kg) as well as HDL cholesterol (45% at 10mg/kg). In db/db mice Tesaglitazar showed a reduction in serum glucose and triglyceride levels (72% and 43% respectively) with no significant effect on total cholesterol. However in C57BL/6J mice Tesaglitazar failed to prevent high fat diet induced dyslipidemia. On the contrary, we observed an alarming increase (145% at 1 mg/kg) in LDL cholesterol without any effect on the serum triglyceride and glucose levels. In Zucker fa/fa rats also, the drug failed to prevent body weight gain. Tesaglitazar did cause a reduction in triglycerides and free fatty acids (67% and 61% respectively) but elevated the fasted glucose levels (66% with 3 mg/kg).

The data indicates that although Tesaglitazar has an excellent profile in primary animal models of dyslipidemia like Swiss Albino mice and SD rats, the beneficial effects are not seen in other animal models such as fat-fed C57BL/6J mice which is considered as an excellent model for metabolic syndrome. Furthermore LDL elevation in C57BL/6J mice, HDL reduction in hamster, body weight gain and fasted hyperglycemia in Zucker fa/fa rats raises doubts about its versatility and as a molecule for Metabolic Syndrome.

#### **PS-34. Comparison of hypolipidemic effects of different PPAR agonists in male Swiss albino mice.**

Patel A.V., Umrani R.D., Srinivasan M.R., Sangle G.V., Majithiya J.B., Pingali H.K.#, Thombare P.S.#, Lohray V.B.# and Jain M.R.

*Department of Pharmacology and Toxicology, Zydus Research Centre, Ahmedabad.*

*# Department of Medicinal Chemistry, Zydus Research Centre, Ahmedabad*

Peroxisome proliferator activated receptors (PPARs) belong to a family of nuclear receptors, which forms a heterodimer with RXR and regulate expression of several other genes, which express PPARE. Three different isoforms of PPARs viz. PPAR-alpha, PPAR-beta/delta and PPAR-gamma, encoded by different genes regulate various aspects of lipid and carbohydrate metabolism. Fatty acids and eicosanoids have been identified as natural ligands for PPARs. Various synthetic ligands activate different PPAR subtypes to different extent. PPAR-alpha specific ligands including fibrates have been found to be effective in treatment of hyperlipidemia, whereas specific PPAR-gamma agonists such as pioglitazone & rosiglitazone are useful as anti-hyperglycemic agents. In order to find out the correlation between degree of PPAR-alpha activation and the hypolipidemic efficacy, we have studied the effects of Fenofibrate, GW9578, Wy14643 that are predominantly PPAR-alpha agonists and Ragaglitazar, Farglitazar and Tesaglitazar, which are dual agonists of PPAR-alpha & PPAR-gamma using Swiss albino mice, a model for screening for hypolipidemic compounds.

Male swiss albino mice of 6-8 week age were treated with PPAR agonists for 6 days. One hr after the last dose, 0.25 ml blood was collected from retroorbital plexus under light ether anesthesia and serum was analyzed for triglycerides and total cholesterol levels. Animals were sacrificed and liver weight recorded. GW9578 (10 mg/kg) was found to cause a significant reduction in triglyceride and cholesterol levels whereas Wy14643 (10 mg/kg) was found to reduce triglyceride alone. On the other hand fenofibrate (10 mg/kg) produced no effect on serum total cholesterol or triglyceride levels. Among the dual agonists, Tesaglitazar (3 mg/kg) produced highly significant reduction in both triglyceride & total cholesterol levels whereas ragaglitazar (3 mg/kg) reduced only serum triglyceride levels. On the other hand Farglitazar (3 mg/kg) did not reduce either parameters. Among all the compounds Tesaglitazar was found to be the most potent compound for triglyceride & cholesterol lowering effects. There was a significant increase in liver weight/body weight ratio in PPAR-alpha as well as dual PPAR-alpha & gamma agonists-treated groups. We have compared our results with the results of PPAR agonists in in-vitro transactivation assays (reported elsewhere). It was observed that in-vitro PPAR agonistic activity and in-vivo hypotriglyceridemic activity could be correlated for compounds having only PPAR-alpha activity. However,

this correlation does not exist if compounds have additional PPAR-gamma agonistic activity.

**PS-35. A simplified method for screening of anti-platelet aggregatory activity using microplate reader**

Shinde UA, Umrani, R.D. Kanoje V.M. and Jain MR

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Measurement of platelet aggregation is a fundamental tool in platelet studies. The technique for the measurement of platelet aggregation uses changes in light transmission of a suspension of individual platelets as it is converted into a suspension of aggregates with a spectrophotometer fitted with a magnetic stirrer beneath the cuvette, a temperature control device and a chart recorder. In the present investigation optimal conditions were developed for simultaneously measuring platelet aggregation in 96 samples using a microplate reader and anti-platelet aggregatory activity of different NSAIDs was evaluated.

The assay was performed using human as well as rodent blood. The Platelet rich plasma (PRP) fraction was collected from blood using centrifugation. The optimal platelet concentration in the PRP fraction was established for ADP and arachidonic acid-induced aggregation study. The concentration of ADP and arachidonic acid were fixed at 2 $\mu$ M and 1mM respectively. Microplate reader of Molecular Device make (Model Spectramax I 90) was used. The temperature of the assay was set at 37 C. The assay was performed with a volume of 100 $\mu$ l and agitation between the reads throughout the study using agitation mode were found to provide reproducible aggregation responses. Various NSAIDs were then investigated for their anti-platelet aggregatory activity under these conditions.

Microplate reader allows simultaneous measurement of a high number of samples with small assay volume and high degree of reproducibility. It also provides output data in the form that can be easily stored and ready for computer assisted analysis.

**PS-36. Anti-inflammatory, analgesic and ulcerogenic activity of various NSAIDs: comparison with their cyclooxygenase selectivity**

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Non Steroidal Anti-Inflammatory Drugs (NSAIDs) are the first line therapy for acute as well as chronic inflammatory pain conditions. The therapeutic utilities of NSAIDs is attributed to the inhibition of cyclooxygenase-2 (Cox-2) isoform, which is expressed in response to inflammatory stimuli. The major side effects of non-selective NSAID therapy is GI ulcer, which is attributed primarily to concomitant inhibition of Cox-1, the constitutive isoform involved in maintaining the mucosal integrity. Several selective Cox-2 inhibitors have been recently developed. In the present investigation, the effects of different Cox inhibitors on inflammation, pain & GI ulceration were compared with their Cox-1 and Cox-2 activity.

Anti-inflammatory activity was evaluated in female Wistar rats orally administered with the test compound one hr prior to sub-planter carrageenan injection (0.1 ml of 1%w/v). Percentage inhibition in paw swelling as compared to vehicle controls was taken as an index of anti-inflammatory activity. Analgesic effect was evaluated in female Swiss albino mice orally administered with the test compound one hr prior to intraperitoneal injection of acetic acid (10ml/kg of 0.06% v/v). Percentage inhibition in abdominal constrictions as compared to vehicle treated controls was taken as an index of analgesic activity. Ulcerogenic potential was investigated in 24hr fasted Swiss albino mice. Six hr after oral administration of the test substance, stomachs were resected out and the images were captured using flat bed scanner or stereozoom camera. Using Scion Image software ulcer area, length and total mucosal area was measured. Cox-1 and Cox-2 activities were estimated in human whole blood using ELISA-based estimation of TXB2 and LPS-induced PGE2 levels for Cox-1 and Cox-2 activity respectively.

Preferential (nimesulide) and selective (celecoxib and valdecoxib) Cox-2 inhibitors as well as non-selective Cox

inhibitor (ibuprofen) were found to possess good anti-inflammatory activity as compared to preferential Cox-I inhibitor (aspirin). Non-selective (ibuprofen), preferential Cox-I (aspirin) and Cox-2 inhibitors (nimesulide, ED50) were found to exhibit better analgesic activity than the selective Cox-2 inhibitors (celecoxib and valdecoxib). The incidence of gastric ulceration was higher in nonselective and preferential Cox-I inhibitors as compared to preferential and selective Cox-2 inhibitors. The incidence of ulceration in Cox-2 inhibitors was in the order: valdecoxib>nimesulide>celecoxib whereas the Cox-2 selectivity of these compounds were in the order of valdecoxib>nimesulide >celecoxib, which is contrary to the established hypothesis.

The present study suggests that Cox-2 inhibition may be essential for maximum anti-inflammatory activity, whereas Cox-I inhibition may be essential for maximum analgesic activity. The incidence of ulceration with Cox-2 inhibitors was found to be lower as compared to non-selective and Cox-I selective inhibitors, however, it could not be correlated with the Cox-2 selectivity of these agents. Therefore the exact mechanisms of GI ulceration caused by Cox inhibitors need to be established.

**PS-37. Cardiovascular effects of Pioglitazone in aged Zucker fatty (fa/fa) rats**

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Endothelial dysfunction is a common feature of Diabetes & Obesity, and may contribute to cardiovascular morbidity. Zucker Fatty rat, an animal model of obesity, insulin resistance and dyslipidemia shows age dependent alterations in the endothelial function accompanied by hypertension. We investigated the effects of pioglitazone, a PPAR-gamma agonist used in the treatment of NIDDM on various cardiovascular parameters using 10 months old Zucker fa/fa rats.

Zucker fa/fa rats and normal Wistar rats were treated with vehicle or pioglitazone (30mg/kg, p.o.) for 15 days. Their initial and post-treatment blood pressure was measured using non-invasive BP monitor. At the end of the treatment period the degree of thrombus formation on carotid artery in response to locally applied FeCl<sub>3</sub> was evaluated by measuring the blood flow using Laser Doppler Flow Meter and performing the histological investigation of the tissue. The thoracic aorta was isolated and the response of intact and endothelium denuded aorta to Acetylcholine and phenylephrine was recorded. The platelet aggregation in response to ADP was investigated using PRP from pioglitazone-treated and control rats as well as in-vitro incubation of PRP from normal Sprague Dawley rats with pioglitazone.

Pioglitazone treatment for 15 days significantly ( $p < 0.05$ ) reduced blood pressure in Zucker fa/fa but not in normal Wistar rats. Zucker fatty rats also showed increased thrombus formation in response to FeCl<sub>3</sub> as compared to Wistar rats, which was reduced by Pioglitazone treatment. In contrast to normal Wistar rats, intact aorta of untreated Zucker fatty rats was not fully relaxed with Ach. However, intact aorta of Pioglitazone treated Zucker fatty rats was fully relaxed with Ach. Pioglitazone treatment shifted the curve of Ach to left in intact but not the endothelium-denuded aorta. This response of Ach in Pioglitazone treated animals was blocked in presence of nitric oxide inhibitor L-NAME. In platelet aggregation study, as compared to the vehicle treated Zucker fatty rats the rate of ADP-induced platelet aggregation in pioglitazone treated group was significantly lower.

In conclusion, the present study showed that the treatment with pioglitazone improved cardiovascular profile of Zucker fatty rats by reducing hypertension, restoring the normal endothelial function, and protecting against thrombus formation due to platelet aggregation.

**PS-38. A comparative study of statin class of compounds in different models of dyslipidemia.**

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Effects of statins (HMG-CoA reductase inhibitors) such as Atorvastatin, Rosuvastatin, Itavastatin and Cerivastatin were studied in different animal models for its hypocholesterolemic effect. These compounds were evaluated using acute model of Triton-induced dyslipidemia in Swiss albino mice (SAM) and chronic models - diet-induced hypercholesterolemia in Sprague Dawley rats and diet-induced dyslipidemia in Golden-Syrian hamster. The effects of these statins were also studied in normal Wistar rats. The SAM were treated with single dose (100 mg/kg) of different statins in triton-induced dyslipidemic model, SD rats were treated for four days with 3 and 30 mg/kg, hamsters were treated for 7 days with 0.3, 1 and 3 mg/kg and normal Wistar rats were treated for 28 days with the dose equivalent to ten times the human therapeutic doses (calculated on body surface area basis) which was 30 mg/kg for atorvastatin, 7.7 mg/kg for Rosuvastatin, 24.64 mg/kg for Itavastatin and 0.56 mg/kg for Cerivastatin. At the end of the treatment period serum total cholesterol and triglycerides levels were estimated in all the animal models. In case of Hamsters and Wistar rats, various serum biochemical and hematological parameters were additionally studied.

In triton induced dyslipidemic mice Atorvastatin, Rosuvastatin and Cerivastatin produced a significant reduction in serum triglyceride and total cholesterol levels. However, in hypercholesterolemic SD rats and normal diet fed hamster statins significantly increased the serum total cholesterol as well as triglycerides levels. Whereas, in Wistar rats Atorvastatin and Itavastatin significantly decreased the serum triglycerides level. In contrast to the normal-diet fed hamsters, the high fat-fed hamsters were found to have significantly decreased the serum triglycerides and glucose levels in the animals treated with statins at 1 and 3mg/kg doses. Furthermore, the fat-fed hamsters showed signs of toxicity as evident in increased mortality and elevation in serum ALP, AST, ALT and bilirubin levels, which are indicators of liver toxicity. In order to investigate the reason for enhanced toxicity in fat-fed Hamsters, the plasma levels of these statins were estimated. Pharmacokinetic results did not show any significant difference in the plasma levels of the statins in normal diet-fed vs high fat-fed hamsters. Therefore, the reasons for enhanced toxicity of statins in high-fat fed hamsters and the exact mechanism of paradoxical effects of statins on serum cholesterol levels in different rodent species are not clear, which demand further investigations.

**PS-39. Comparison of Hematological, Biochemical and Organ weight changes in Sprague Dawley Rats after repeated administration of various PPAR agonists**

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PPAR modulators are currently used as insulin sensitizers and hypolipidemic drugs. Earlier studies have shown that marketed selective PPAR gamma agonists produce oedema, anaemia, cardiac hypertrophy and/or elevation of hepatic enzymes in humans and experimental animals.

In the present study we evaluated the potential of selective PPAR gamma agonist (Rosiglitazone) and dual PPAR alpha/gamma agonists (Tesaglitazar and Ragaglitazar) to cause such changes, attributed to PPAR gamma activation, in male Sprague Dawley Rats.

Groups of 6 rats received vehicle (5 % HPMC) or 30 mg/kg of Rosiglitazone, Ragaglitazar or Tesaglitazar daily by oral gavage for 14 days. Body weight and food consumption was monitored. On day 15, hematology and serum chemistry evaluations were carried out on overnight fasted animals. Animals were sacrificed with CO<sub>2</sub> and detailed necropsy examination was carried out. Vital organs were dissected free of fat and weighed.

The results of the present study revealed statistically significant reduction in total red blood cell count, Hemoglobin concentration by Tesaglitazar and Ragaglitazar and Hematocrit by Ragaglitazar when compared to concurrent controls. Serum analysis revealed significant increase in alkaline phosphatase levels only in Tesaglitazar treated group.

Grossly, cardiac enlargement was noticed in all treated groups, with maximum changes in Tesaglitazar treated

group and minimum in Rosiglitazone treated group. Tesaglitazar exposure also induced liver enlargement more than Ragaglitazar and no such changes noticed in Rosiglitazone treated animals.

**PS-40. Pharmacokinetic study of novel antihyperlipaemic agent LM-13765 in rabbits by employing High Performance Thin Layer Chromatography**

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A rapid, sensitive and specific high-performance thin-layer chromatographic method (HPTLC) has been developed for estimation of novel antihyperlipaemic agent LM 13765 in rabbit plasma and its use for pharmacokinetic study has been evaluated. A single stage extraction procedure was followed for extracting compound LM 13765 from plasma. Suitable volumes of the extract were spotted on precoated silica gel 60 F254 plates and the plates were developed using a mixture of benzene:methanol (8:2 v/v) as the mobile phase. The detection was carried out at 274 nm. The mean recovery of standard analytes added to plasma, at concentration levels 0.125 to 1.0 mcg/ml, was 97.3 % and limit of detection was found to be 12.5 ng/ml.

The proposed HPTLC method was employed to study the pharmacokinetics of LM 13675 in rabbits (n = 5). It was observed that LM 13675 metabolizes immediately after oral administration. The metabolite of LM 13675 was identified and characterised as a mineral derivative, LM 13765-C. Biological screening of LM 13765-C on hyperlipaemic rats indicated that it is less potent than the parent compound, LM 13675. This, in turn, suggests that LM 13765 acts as a prodrug which gets metabolized to active metabolite LM 13765-C immediately after oral administration.

**PS-41. Ragaglitazar: Pharmacokinetics in Fasted vs Non-fasted State, Male vs Female in Wistar Rat and Swiss Albino Mice**

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Ragaglitazar belongs to a new class of dual PPAR- $\alpha$  and  $\gamma$  agonist designed to restore insulin sensitivity and correct dyslipidemia. The present study was conducted in order to examine the effect of food as well as gender differences on single dose oral pharmacokinetics of Ragaglitazar across two species namely: Wistar Rat (WR) and Swiss Albino Mice (SAM) at the dose of 25 mg/kg body weight. Wistar Rat studies were conducted in four groups. Two male and two female groups (fasted and fed), comprising of three animals per group; were taken for kinetic studies in Wistar rat. Age of Wistar rat was between 8 to 10 weeks and body weight in the range of 200-250g. Studies in SAM were conducted in four groups; two male and two female groups each group comprising of 12 animals. SAM were 7 to 9 weeks old and had body weight in the range 25-30gm. For both the species one male and one female group of animals was subjected to 18 hours fasting prior to dosing and the other group of male and female was given feed ad libitum.

A comparison of fasted versus fed animals indicated that there was no significant effect of food on AUC(0-inf) in both Wistar Rat as well as Swiss Albino Mice. Similarly, no gender difference was observed in both WR and SAM. In conclusion, same dose administered to both male and female animals of either of the two species under fed or fasted condition would render similar level of drug exposure. Therefore, dosage adjustment, in Wistar rat and Swiss Albino Mice for conducting repeated dose toxicity studies so as to expose both male and female animals to the same extent would not be required.

**PS-42. Tesaglitazar: Effect of food and gender on single dose Pharmacokinetics in Swiss Albino Mice and Wistar Rat**

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Tesaglitazar, is being developed by Astra Zeneca under the trade name GALIDA(TM); to target glucose and lipid abnormalities associated with type 2 diabetes and other conditions related to insulin resistance. The effect of food and gender on pharmacokinetics of a single oral dose was investigated in Swiss albino mice (SAM) and Wistar rat (WR). Dose linearity was also established in fasted male and female WR. All studies for investigating the effect of food and gender in SAM were conducted at 30 mg/kg and those in WR at 100mg/kg of body weight. Dose linearity studies in WR were conducted upto 300 mg/kg in males and upto 200mg/kg dose in females. Studies to establish the effect of food and gender, in both the species; were conducted in four groups, two male and two female groups. WR were 8 to 10 weeks old and had a body weight of 200-250gm. SAM were between the age of 7 to 9 weeks and had a body weight of 25-30g. In both the species one male and one female group of animals were subjected to fasting for 18 hours prior dosing and food was supplied after 4 hours. The other group of male as well as female were given feed ad libitum.

It was observed that food significantly suppressed the AUC(0-inf) in fed animals when compared with that of fasted group of animals in both SAM and WR. Gender difference in pharmacokinetics was also observed in both the species when AUC (0-inf) was compared in fasted males versus fasted females and fed males with fed females. The AUC(0-inf) in females was greater than that of males. In order to give a similar drug exposure to both the genders, in both the species, dosage adjustment will be required i.e, males should be given a higher dose than females. In WR dose was proportional to AUC(0-inf) from 5mg/kg upto 300 mg/kg in males and upto 200mg/kg dose in females.

**43. Comparative Pharmacokinetics of Ragaglitazar, Tesaglitazar and Farglitazaar in male and female Wistar rat under fasted and non fasted condition**

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Ragaglitazar, Tesaglitazar and Farglitazar belong to a new class of dual PPAR- $\alpha$  and  $\gamma$  agonist designed to restore insulin sensitivity and correct dyslipidemia. The objective of the present study was to compare the oral Pharmacokinetics of all the three molecules in Wistar rat (WR) and to determine the effect of food and gender. Ragaglitazar was studied at a dose of 25mg/kg, Tesaglitazar at 100 mg/kg and Farglitazar at 30 mg/kg body weight. For comparison of oral availability of Ragaglitazar with Tesaglitazar, studies were also conducted with Ragaglitazar administered at a dose of 100 mg/kg in fasted male and female WR. Two male and two female groups were taken per molecule. Each group comprised of three animals. WR were 7 to 9 weeks old with body weight of around 200-250g. For all the three molecules, one male and one female group of animals was subjected to fasting for 18 hours prior to start of experiment and other group of male as well as female were given feed ad libitum.

A comparison of AUC(0-inf) was made in order to establish the effect of food and gender. Oral pharmacokinetics of Ragaglitazar was not affected by food or gender. On the contrary, the comparison of AUC(0-inf) between fasted and fed animals showed a drastic difference in Tesaglitazar and Farglitazar. Fasted animals (male and female) exhibited almost double AUC (0-inf) as compared to fed animals. Gender difference was also quite significant for both the molecules. A comparison of AUC (0-inf) in fasted males versus fasted females and fed males versus fed females exhibited a significant gender difference, with females exhibiting a higher AUC (0-inf) than males.

It may be concluded that although food and gender did not affect single dose oral pharmacokinetics of Ragaglitazar; the kinetics of Tesaglitazar and Farglitazar were significantly affected by both the variables. Food suppressed the absorption of both Tesaglitazar and Farglitazar and females exhibited a higher AUC than males. A comparison of oral availability of Ragaglitazar with Tesaglitazar at 100 mg/kg in both fasted males and females showed that Tesaglitazar had a greater AUC(0-inf) than Ragaglitazar in both the sexes. Oral availability of Farglitazar at 30 mg/



kg was very poor as compared to that of Ragaglitazar at a dose of 25 mg/kg. The oral availability of three molecules was in the order: Teasglitazar > Ragaglitazar > Farglitazar in Wistar rat.

**PS-44. Comparison of Macrodilution and Microdilution assays for In vitro susceptibility testing of Gatifloxacin and Ciprofloxacin against Gram positive and Gram negative strains**

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Determination of MIC can be done by various techniques such as broth dilution, disk diffusion, agar dilution assays and E-test. Amongst them macrobroth dilution technique is the most widely used. However, it was found that microdilution technique was more simple and less tedious to perform than macrobroth dilution technique. Hence, this study was aimed to compare microbroth dilution technique with macrobroth dilution technique, while determining MIC of two fluoroquinolones- Gatifloxacin and Ciprofloxacin against three Gram negative and three Gram positive bacteria. Bacteria were exposed to different concentrations of Gatifloxacin and Ciprofloxacin in both these techniques. Each experiment was performed three times (n=3). The results showed that the MIC values obtained from both these assays were comparable. Furthermore, it was also observed that Gatifloxacin and Ciprofloxacin both exhibited similar activity against Gram positive and Gram negative bacteria.

**PS-45. Basal cytotoxicity determination of Tesaglitazar ( Z- 242) in mammalian cells cultures**

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Mammalian cell culture model being one of the powerful biotechnological tools, we have set up cell culture models for determining the basal toxicity of compounds under the drug discovery program. For standardization and establishment of cell culture work, we decided to use tesaglitazar (AZ 242) drug which is at phase -II trail. Different cell lines were cultured for detecting the cytotoxicity of this compound. The compound was dissolved in DMSO at different con ranging from 0.1 - 1000ug/ml. Triton X100 was taken as standard compound. All incubation of the assay was done at 37°C + 5% CO<sub>2</sub> unless specified. The cytotoxicity of the compounds was determined by MTT assay. Percentage of toxicity was determined from the test values by considering positive and negative values. The experiments performed at different times with different cell lines showed that tesaglitazar did not induce cytotoxicity in these cell lines. This assay system developed in the department has been utilized to screen the cytotoxicity of many in house compounds against different mammalian cell types.

**PS-46. Dye uptake Assay to Determine the Viable Bacteria under Antibiotic Exposure**

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In many instances detection of viable bacteria by conventional methods is time consuming and laborious. In the present investigation, we decided to utilize 4 bacterial strains maintained in 96 -microwell plates used routinely for determining of MIC. These bacteria were exposed to linezolid and 11 unknown compounds. Before discarding the microplates, bacteria were exposed to MTT (methylthiazolotetrazolium) and the extracted formazone crystals were read at 540nm. The results indicate that MTT assay can detect the presence of bacteria in samples at higher values of MIC and at MIC values which could not be detected visually and spectrophotometrically. The assay also detected different bacterial con and had no interference of compounds. Further more, MTT uptake by the bacteria was abolished by heat killing of the bacteria suggesting the MTT uptake is a vital process. Taken together, these findings suggest that MTT assay can detect viable bacteria in many samples wherein conventional methods fail.

**PS-47. Antimicrobial use by obstetrics and gynaecology department of a tertiary care hospital : analysis for rationality and other aspects**

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**OBJECTIVES :** When a brief search was done on the use of antimicrobials in perioperative cases of obstetrics and gynaecology department of various institutions, it was found that irrational use of drugs in teaching hospital is common. Hence, we considered it necessary to study the perioperative prophylactic antimicrobial use in obstetrics and gynaecology department; also during and after labour.

**MATERIALS AND METHODS :** Case records of patients admitted to obstetrics and gynaecology department of G.G. Hospital, Jamnagar from 01/04/02 to 31/05/02 were collected from record section, out of which 25% cases were selected for the study of antimicrobial prescription and usage. Analysis of rationality was carried out by using the method of Phadke (1995) as modified by Gajjar (1999). For analysis of cost, a standard treatment protocol for each operative procedure was decided on the basis of recommendations of standard textbooks and cost for such treatment was worked out using lowest prices of a preparation as given in CIMS- April 2002. Cost of actual treatment was similarly worked out for comparison.

**OBSERVATIONS AND RESULTS :** 1. Antimicrobials were used in 95.14 % patients. 2. All cases of caesarean section and hysterectomy received antimicrobials. 3. Mean duration of antimicrobial therapy was 6.06 days. 4. Total cost of antimicrobials amounted to Rs. 57,501.55 with Rs. 41,412.88 of this being unnecessary. 5. Ciprofloxacin, ampicillin and metronidazole were most frequently prescribed antimicrobials. 6. Rationality scores indicated that antimicrobial use is semirational or irrational in majority of cases.

**CONCLUSION :** This study shows that postoperative and postpartum antimicrobial use in the hospital is excessive, not always rational and if modified appropriately can lead to substantial cost containment and possibly also reduce emergence of resistant organisms and their spread.

**PS-48. Color reduction by addition of adsorbent during r-HSA production by Pichia pastoris**

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The role of HSA in our body is that of a carrier of various proteins. It has been observed that during fermentation, as HSA is secreted in the medium, it readily binds with chromophore group of various coloring agents. This color is very difficult to remove even after purification. As a result the final purified protein has a very high color index, which is not desirable. To overcome this we developed a two-stage fermentation process using activated charcoal to obtain purified protein of pharmaceutically acceptable color.

**PS-49. Salmonella Pathogenicity Island 2 - Survival and Intracellular Replication of S. enterica in Infectious Model**

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Salmonella typhimurium causes an invasive disease in mice that has similarities to human typhoid. A type III protein secretion system encoded by Salmonella pathogenicity island 2 (SPI2) is essential for virulence in mice, as well as survival and multiplication within macrophages. Reactive nitrogen intermediates (RNI) synthesized by inducible nitric oxide synthase (iNOS) are involved in the control of intracellular pathogens, including S. typhimurium. We studied the effect of Salmonella infection on iNOS activity in macrophages. Immunofluorescence microscopy demonstrated efficient colocalization of iNOS with bacteria deficient in SPI2 but not wild-type Salmonella, and suggests that the SPI2 system interferes with the localization of iNOS and Salmonella. Furthermore,

localization of nitrotyrosine residues in the proximity was observed for SPI2 mutant strains but not wild-type Salmonella, indicating that peroxy-nitrite, a potent antimicrobial compound, is excluded from Salmonella-containing vacuoles by action of SPI2. Altered colocalization of iNOS with intracellular Salmonella required the function of the SPI2-encoded type III secretion system, but not of an individual "Salmonella translocated effector." Inhibition of iNOS increased intracellular proliferation of SPI2 mutant bacteria and, to a lesser extent, of wild-type Salmonella. The defect in systemic infection of a SPI2 mutant strain was partially restored in iNOS knock out mice. In addition to various strategies to detoxify RNI or repair damage due to RNI, avoidance of colocalization with RNI is important in adaptation of a pathogen to an intracellular life style.

**PS-50. Studies of the Behaviour of Aqueous Nonionic Surfactant Solutions**

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Surfactants are molecules which have both hydrophobic and hydrophilic regions and hence these molecules show interesting properties like micelle formation, surface activity in aqueous solutions. The nonionic surfactant solutions show cloud point where the solubility of the surfactant becomes minimum at a higher temperature. Ionic surfactants also show such properties in the presence of salts. The surfactants solubilize solute and also stabilize emulsion or form microemulsion. The micellar solution stability as a function of temperature or in presence of additives are therefore important for pharmaceutical preparations or in the drug delivery system. Similar is the case with the microemulsion.

In this presentation we will be presenting our work with mixed anionic-nonionic surfactants in the preparation of microemulsion, including phase diagrams as well as effect of various additives on the cloud points of nonionic surfactants like C12E6, C12E9 & C12E10. It was found that carboxy methyl cellulose and PEG 4000 molecules do probably enter the micelle. The microemulsions of water/mixed surfactants/n-alcohols/ cyclohexane show percolation behavior and the percolation threshold was found to be a function of surfactant composition. The mixed surfactants used were mixtures of anionic sodium dodecyl sulphate and nonionic Myrj 45 in various mole ratios. Various different alcohols (n-propanol, n-butanol, n-pentanol and n-hexanol) were used as cosurfactant in the microemulsion formation.

**PS-51. Development of Extended Release Dosage Form of Metformin for Once a Day administration.**

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Metformin HCl is an oral anti hyperglycemic agent. The drug has short half-life (about 3 hrs) necessitating two to three times a day administration for effective anti-hyperglycemic effect. To reduce the frequency of administration and to improve patient compliance, it is desirable to have a once daily formulation. Tablets were prepared using hydrophilic polymers in different concentration and evaluated for effective once a day administration. Drug release rate from the matrices was controlled either by using release rate enhancing excipients like microcrystalline cellulose and lactose or by using release retardants such as ethyl cellulose. The prepared matrices were evaluated in vitro for dissolution profile using USP apparatus I. Hydrophilic matrices using hypermellose were found to be superior in controlling the drug release rate. The optimized formulation was evaluated for bioequivalence in comparison with Glucophage<sub>XR</sub> tablets, Bristol-Myers Squibb, USA. Results showed that the developed formulation was bioequivalent when compared with the reference product.

**PS-52. Ultrasound: A Novel Strategy for Transdermal Drug Delivery**

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Ultrasound can enhance the transdermal delivery of drugs leading to better therapeutic or clinical efficacy. The present study examines the potential of ultrasound for enhancing the transdermal permeation of ketorolac tromethamine in vitro using rat skin. Ultrasound was applied in a continuous mode at an intensity of 1-3 Watt/cm<sup>2</sup> and a frequency of 1 MHz for 30 min. Significant increase in the percutaneous permeation of ketorolac through the rat skin was observed at 3 W/cm<sup>2</sup> when compared with treatment at 1 and 2 W/cm<sup>2</sup>. Enhanced ketorolac permeation can be explained by the mechanical and/or thermal action of ultrasound waves. The distance of ultrasound probe from the skin surface did not influence the flux of the drug significantly. Pretreatment of skin by 5% d-limonene in ethanol for 2 h followed by sonication at 3 W/cm<sup>2</sup> for 30 min, significantly enhanced the permeation of ketorolac when compared with passive flux with or without enhancer pretreatment. Combination of ultrasound and chemical enhancers can be best used for treatment of arthritis and other acute localized painful conditions in combination with medicated gels or ointments containing non-steroidal anti-inflammatory agents.

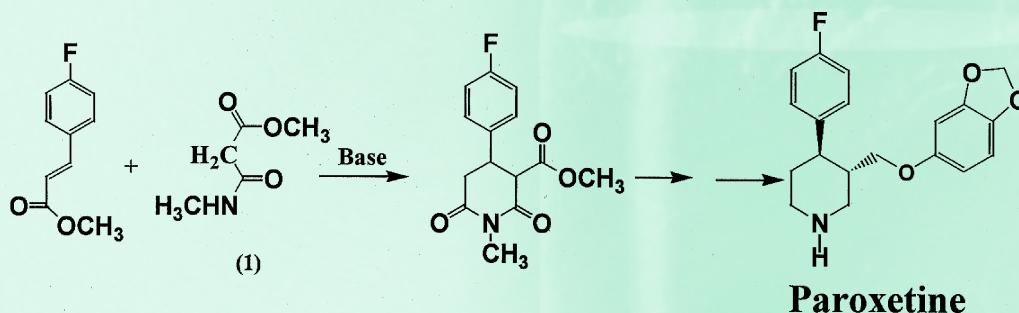
**PS-53. A Simple process for a key intermediate of Paroxetine.**

M. G. Dave, S. J. Patel

Department of Process Research, Zydus research Centre, Cadila Healthcare Ltd., Ahmedabad 382 213

Methyl-n- methyl amidomalonate 1, is a key intermediate in the synthesis of Paroxetine.

Reported process employs hazardous reagent like phosphorous pentachloride and condensation at -20 o C under anhydrous condition. We have developed an environment friendly process for its synthesis, which is suitable for scale up in multikilograms. The simplicity of the process is that the reaction can be performed at 30-35 o C and the esterification has been done in the presence of water.



**PS-54. A Simple Process for the Preparation of 4-methylcyclohexylamine: A Key intermediate in the synthesis of Antidiabetic drug Glimepiride.**

K. B. Sata#, H. B. Patel#, S. Sorathia\$, V. K. Agarwal\$

# Department of Process Research and Development, Zydus Research Centre, Cadila Healthcare Ltd., Ahmedabad - 382213, Gujarat (INDIA) \$API Division, Cadila Healthcare Ltd., 291, G.I.D.C. Industrial Estate, Ankleshwar - 393002, Gujarat (INDIA)

Trans-4-methyl cyclohexylamine 1 is a key intermediate in the preparation of antidiabetic drug Glimepiride 2. The reported process involves hydrogenation of 4-methyl-cyclohexanone oxime with sodium metal in absolute ethanol which is unsuitable for a large scale process. We have developed an alternate method using Raney nickel to get 4-methyl cyclohexylamine (cis + trans), which was purified to get pure trans-4-methyl cyclohexylamine.



1

**PS-55. Development of chiral HPLC methods for examining enzymatic resolution of racemic methyl 2-hydroxy-3-(4-benzyloxyphenyl)propionate**

Srinivas Kone, H.K.Jajoo, Manish Jain, Anil Argade#, S.K.Shah\$

*Department of Biopharmaceutics, # Department of Medicinal chemistry, \$ Department of Biotechnology, Zydus Research Center, Cadila Healthcare Ltd. Sarkhej Bavla, Moraiya, Ahmedabad-382213, Gujrat, India.*

Stereospecific conversion of chiral compounds by enzymes has been extensively used for the resolution of racemic mixtures. In order to examine the chiral purity of reactant and product, we need to develop chiral HPLC methods, which can separate the two enantiomers of the reactant and the product. In this report, we present the development of chiral RP-HPLC method for the resolution of enantiomers of methyl 2-hydroxy-3-(4-benzyloxyphenyl)propionate and the biotransformation product, methyl-2-acetoxy-3-(4-benzyloxyphenyl)propionate. The method uses a chiral-AGP column and phosphate buffer as mobile phase. The two enantiomers of methyl 2-hydroxy-3-(4-benzyloxyphenyl)propionate were resolved with retention times approx. 25 and 45 minutes. The enantiomers of methyl 2-acetoxy-3-(4-benzyloxyphenyl)propionate were resolved with retention times approx. 28 and 41 minutes.

**PS-56. Chiral chromatographic reverse phase and normal phase HPLC method development for enantiomers separation for Duloxetine final and its important process intermediates.**

Kailash C. Asati\*, H.K.Jajoo, Sandeep Vishnani, Hiten Shah, Anshumali Awasthi, Prakash M. Davadra.

*# Department of Biopharmaceutics, Zydus Research Centre, Cadila Healthcare Ltd. NH-8A Sarkhej Bavla, Moraiya, Ahmedabad-382213, Gujrat, India*

Duloxetine is a new age active pharmaceutical ingredient having anti-depressant activity. Which has one chiral center. The intermediate of duloxetine also having a chiral center. Therefore it is very essential to develop chiral HPLC method to determine the chiral purity of their intermediates while optimize the process. We have developed a reversed phase chiral HPLC method to assess the chiral purity of duloxetine final-I and an intermediate i.e. naphthalene derivative-2. Also a normal phase chiral HPLC method to assess the chiral purity of a duloxetine intermediate i.e. Alcohol derivative-3.

There are often pharmacodynamic, pharmacokinetic and / or Toxicological differences between enantiomers. For synthesis of drug it is important to monitor chiral purity and enantiomers excess of drug and also its intermediates during its synthesis. Resolving racemic mixture of two enantiomers has always been one of the most difficult problems in separation science.

**PS-57. Green Chemistry Approaches to the Synthesis of 5-Alkoxy carbonyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones by a Three-Component Coupling of One-Pot Condensation Reaction: Comparison of Ethanol, Water and Solvent-free conditions**

D Subhas Bose\* Liyakat Fatima and Hari Babu Mereyala

*Organic Chemistry Division III, Fine Chemicals Laboratory, Indian Institute of Chemical Technology, Hyderabad, 500 007, India.*

A general and practical green chemistry route to the synthesis of 5-alkoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones (Biginelli cyclocondensation reaction) using cerium(III) chloride as the catalyst (25% mol) is described under three different sets of reaction conditions. This method provides an efficient and much improved modification of original Biginelli reaction reported in 1893, in terms of high yields, short reaction times, simple work-up procedure and it has the ability to tolerate a wide variety of substitutions in all three components, which is lacking in existing procedures.

## **PS-58. Novel Approach in Drug Design**

Rajan Gupte, Jayant Deshpande and Kamlesh Ranbhan

*Kopran Research Laboratories Limited, Mumbai, India.*

Present day drug discovery research is encountered by several practical difficulties, such as, instability of chemical compounds, complexities in optical resolution, high level of toxicities exhibited by low molecular weight chemical moieties, etc. In order to overcome these difficulties of drug design, a novel technique of NCE generation is presented.

Biologically active lead compounds are covalently bound to a bifunctional polymer, such that the site of attachment of the lead molecule is different compared to the site of cleavage (in-vivo). Upon oral administration, the polymeric derivative of bioactive lead molecule undergoes chemo-enzymatic cleavage with the formation of chemically modified form of the lead molecule.

The advantages of NCEs generated by such novel approach are:

1. Enhanced physico-chemical stability 2. Formation of optically pure (enantiomeric) form 3. Development of safer NCEs

This novel technology when applied to lead molecules from antiulcer, antihypertensive, antibacterial, antiprotozoal therapeutic categories resulted in the generation of NCEs that have potential to address the issues of unmet medical needs. This technology can also be applied to the formation of known biologically active compound in-vivo from their polymeric precursors.

Based on above novel platform technology, several potentially useful NCEs have been developed. A novel antiulcer compound viz., KNC-6, with dual mode of action (clinically significant antisecretory and cytoprotective properties) developed using this technology, is poised to enter Phase I clinical trials.

## **PS-59. Bioequivalence study of Tramadol XL Tablests in Healthy Human Volunteers**

**Anshumali Awasthi**, S K. Goswami, Nimesh Patel, Sapna Gupta, Kamlesh Patel and Hemant Kumar Jajoo

*Department of Biopharmaceutics, Zydus Research Center, Zydus Cadila Healthcare Ltd., Ahmedabad. Gujarat. India*

Tramadol is an opiate-like analgesic agent used for management of moderate to severe pain. Objective of the study was to examine bioequivalence of Tramadol XL (extended release) tablets by comparing the single dose oral bioavailability of test and reference formulation (200-mg Tramadol extended release tablets) in healthy, adult, male, human subjects under fasted conditions. The determination of Tramadol in human plasma was performed using a selective and sensitive HPLC method with fluorescence detection after liquid-liquid extraction from plasma samples. Quantification of drug concentrations in plasma samples was achieved by the internal standard method using peak area ratio. The method was validated to establish linearity, range, LOQ, specificity, inter and intra-day precision and recovery. Stability of the analyte in plasma was established at room temperature, after freeze-thaw cycles and long term storage. All data indicated that the method meets established norms for validation of bioanalytical methods. The lower limit of quantification was 5 ng/mL. Human plasma samples were obtained after oral administration of preparations and analyzed for Tramadol. Pharmacokinetic parameters ( $C_{max}$ ,  $T_{max}$ ,  $AUC_{0-t}$  and  $AUC_{0-inf}$ ) were calculated using WinNonlin software and statistical analysis (two one sided 90% confidence intervals of log-transformed data) were carried out using WinNonlin software. The 90% confidence intervals of the log transformed parameters ( $C_{max}$ ,  $T_{max}$ ,  $AUC_{0-t}$  and  $AUC_{0-inf}$ ) were within the range of 80.00-125.00%. This indicated that the test formulation was bioequivalent to the reference formulation in terms of rate and extent of absorption.

**PS-60.**

**Validation of LC-MS/MS Method for the Estimation of Ziprasidone in Human Serum**

Sanjeev Mishra, Hiten Shah, Harshwardhan Patel and Hemant Kumar Jajoo

*Department of Biopharmaceutics, Zydus Research Center, Zydus Cadila Healthcare Ltd., Ahmedabad. Gujarat. India*

Ziprasidone is an antipsychotic agent used for treatment of patients with schizophrenia. Objective of the study was to develop and validate a sensitive method for analysis of Ziprasidone in serum samples for comparing the single dose oral bioavailability of test and reference formulation ( 80-mg Ziprasidone capsule) in healthy, adult, male, human subjects under fasted conditions. The determination of Ziprasidone in human serum was performed using a selective and sensitive LC-MS/MS (MRM) method after liquid-liquid extraction from serum samples. Internal standard selected was Risperidone. Quantification of drug concentrations in serum samples was achieved by the internal standard method using peak area ratio. The method was validated to establish linearity, range, LOQ, specificity, inter and intra-day precision and recovery. Stability of the analyte in serum was established at room temperature, after freeze-thaw cycles and long term storage. All data indicated that the method meets established norms for validation of bioanalytical methods. The lower limit of quantification was 5 ng/mL. Human serum samples were obtained after oral administration of preparations and analyzed for ziprasidone. Results of the bioequivalence study indicated that the formulation was bioequivalent to the reference formulation.

**PS-61.**

**Quantification of Polymorphs of Famotidine by Differential Scanning Calorimetry**

**Manish Srivastava**, Amrita Srivastava, Bhagirath Patel and Hemant Kumar Jajoo

*Department of Biopharmaceutics, Zydus Research Center, Zydus Cadila Healthcare Ltd., Ahmedabad. Gujarat. India*

Famotidine is a Histamine-H<sub>2</sub> receptor antagonist used for treatment of hyperacidity. It exists in two polymorphic forms A and B. Polymorphs of the drug can have different crystal structure and solubilities, which results in differences in their absorption. Hence, the differences in polymorphism can affect clinical efficacy of the product. Objective of the present study was to quantify the amount of polymorphic form A in Famotidine bulk drug samples (form B). Differential Scanning Calorimetry was used for these measurements. Calibration samples were prepared by mixing known amounts of two polymorphs and enthalpies for two polymorphs were measured using differential scanning calorimetry. Calibration curve was prepared between % of polymorph and enthalpy ((H) and was used to quantitate unknown samples. The lower limit of quantification was 2%. This method was used to quantitate the amount of two polymorphs in various samples of bulk drug Famotidine.

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04.	Lab India Instruments Pvt. Ltd I- Mangalam Apartments,52,Sampatrao Colony,Alkapuri,Baroda-390007	04 &05
05.	Niulab Equipment Company Pvt. Ltd Lab House,Plot No. F 13, Opp Seepz , M.i.d.c Andheri ( E) Mumbai-400093	06
06.	Agilent Technologies India Pvt. Ltd Unit No.3,Ground Floor, Enterprise Center, Nr.hotel Orchid, Off Western Express Highway,Villeparle ( E) Mumbai-400057	07
07.	Lcgc Chromatography Solution Pvt. Ltd B-3/10,3 <sup>rd</sup> Floor,Shanti Apartment, Near Ashish School, Bodakdev, Ahmedabd-380051	08
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11.	Electrolab 4,Ashoka Chambers, Nr.lion's Hall. Nr.mithakhali Six Road, Ellisbridge, Ahmedabd-380006	12
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22.	Gordhandas Desai Pvt. Ltd 2/1 , Arunodaya Society , Alkapuri, Vadodara-390007	23 & 24
23.	Researchco Book Centre 25-b/2, New Rohtak Road ( Near Libery Cinema) New Dehli-110005	25
24.	Citizen Industries Ltd. 308, Sarthak Complex, Swastik Char Rasta, Navarangpura, Ahmedabad-380009	26 To 29
25.	German Remedies, Worli, Mumbai	30 & 33
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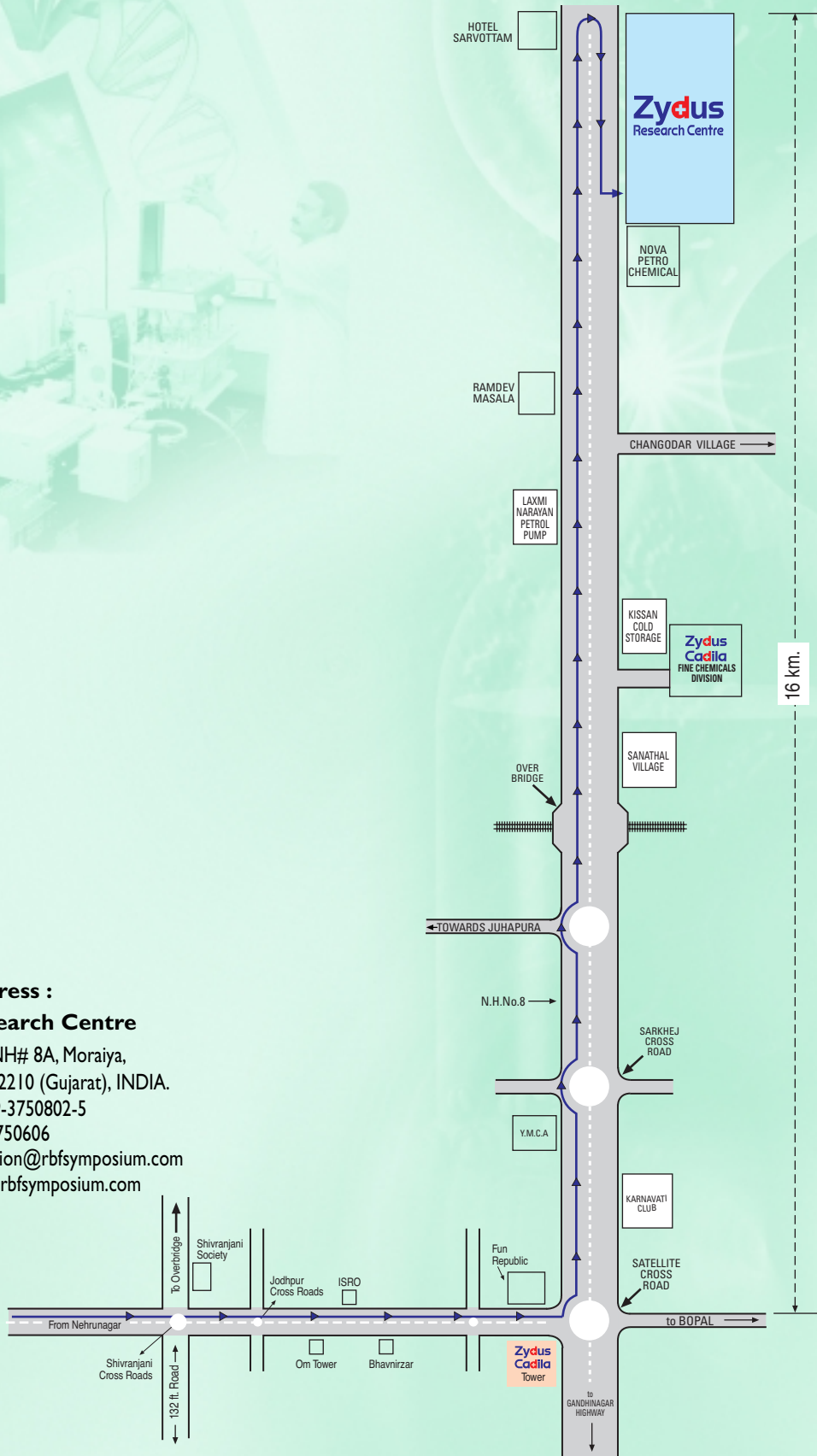
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