

**MUKUND S. CHORGHADE
VEENA M. CHORGHADE
MUKUND K. GURJAR
C. V. RAMANA
ASHOK V. KAMERKAR
HARRY ZAFRAN
RAGHUNATH A. MASHELKAR**

Building business based on pharma industry's interests: integration of basic and applied research

The Indian Government's economic liberalization program in the 1990s, announced by the then Prime Minister Narasimha Rao, has resulted in abandonment of the stifling protectionism of socialism. Trade barriers have been lowered, taxes cut, and bottlenecks for foreign investment have been removed. The Government of India has announced relaxation of drug price controls and the provision of fiscal incentives to promote collaboration with the Western World. New and comprehensive industrial policies have been formulated; foreign equity participation of 51% and above is now permissible. These facts allied with tremendous market opportunities in a vibrant, growing, middle class dominated consumer economy are expected to interest Western, Indian and Oriental companies.

India is described as a rich country, where poor people live. Its richness is due to our rich biodiversity and wisdom of traditional knowledgebase including traditional medicinal systems. As a part of the global innovation strategy, several companies world over are scouting for new ideas and patents. External technology acquisition i.e. the ability to assemble and manage an effective global knowledge network in a short time, rather than developing in-house capability is becoming the key determinant of competitiveness. Rather than being a perennial seeker of knowledge from the western world, India is emerging as an exporter of knowledge. India is well poised to become the global R&D platform of the 21st century mainly due to lower costs of doing research in India. It is remarkable that the entire S&T budget of India in a year, which included space, defense, atomic energy research, did not exceed 2.5 billion US dollars. The prevailing perception of the new post liberalization environment is an era in which Indian R&D institutes and industrial firms will operate with dramatically improved freedom and flexibility, better communication and IPR protection, enhanced consciousness about quality and time of delivery. What then are India's major strengths in technological innovation? India has the largest pool of qualified engineers in the world, the 7th largest pool of R&D personnel, and a large cadre of expatriate scientists, technologists, and entrepreneurs, who are increasingly engaged with their home country. On the institutional front, India's assets include numerous institutions of higher learning as well as an impressive array of research centers and laboratories that focus on a large range of scientific and technical problems. India has a huge domestic market, with

potential customers numbering a few hundred millions. It has an economy that has grown at almost 6% per year over the last decade. There are exceptional leaders within the government, academia, and the business domain who are promoting and catalyzing institutional transformation (both revolutionary and evolutionary) in a range of ways. There are increasing numbers of individuals, both within the country as well as outside it, who serve as role models for technology entrepreneurship.

THE PHARMACEUTICAL SECTOR IN INDIA

The Indian pharmaceutical sector has achieved global recognition as a low cost producer of bulk chemicals and formulation products. Leading Indian pharmaceutical companies have significant international marketing presence in nearly sixty countries; exports to the United States and Europe as continually on the rise.

Recently, Indian R&D contributions became significant and imports of bulk drug technologies reduced drastically. The industry is manufacturing practically the entire range of therapeutic groups; is nearly self-sufficient in raw materials for production from basic stage of a wide range of bulk drugs and formulations, and its level of operation is on par with international standards in production, technology and quality.

The Indian pharmaceutical industry is in its infancy regarding the development of internationally patentable New Chemical Entities. With the new IPR regime being implemented in 2005, all major pharmaceutical companies in India are experiencing a paradigm shift and are consolidating their efforts directed at creating new molecules and processes to retain competitiveness in the marketplace.

Numerous discovery research activities have begun. Dr. Reddy's Laboratories and Ranbaxy are leading the pack, have filed international patents. Other renowned companies such as Cadila Healthcare, Glenmark, Lupin, Nicholas Piramal Healthcare, Wockhardt, Zydus Cadila, Dabur, and Orchid have ambitious plans to be in the forefront of research; building of facilities and recruitment of personnel is proceeding rapidly. Indian companies have started soliciting strategic partnerships with Western companies to accelerate the introduction of new molecules for emerging markets, as well as selected global niche positions. To cite a few examples:

Ranbaxy has filed INDs for benign prostatic benign hyperplasia and anti-microbial. Dr Reddy's Research laboratories aim to develop robust compounds for cancer and COX 2 inhibition; additionally, anti cancer compounds are undergoing clinical studies in Europe. Torrent Pharmaceuticals have a compound in cardiovascular therapies. Glenmark Research Laboratory has developed a potent PDE-4 inhibitor for the treatment of inflammatory allergic disorders. Dabur Research Foundation has established a new drug discovery centre at Delhi with cancer as a focused area. The peptide based anti-cancer molecule is doing well in phase trials. The biotech companies are also emerging as formidable players. Shantha Biotech's DNA hepatitis B vaccine has captured 46% of the global market, co-marketing rights have been negotiated with Pfizer. Shantha Biotech has also developed a monoclonal antibody for lung cancer; clinical trials will be initiated in the near future.

THE COUNCIL OF SCIENTIFIC AND INDUSTRIAL RESEARCH

The Council of Scientific and Industrial Research is an umbrella organization for a network of forty laboratories around the country. This organization is gifted with 10,000 highly trained scientists and has rendered yeomen service to the cause of scientific research and training in India. Administratively, Dr. Raghunath A. Mashelkar, F. R. S., Director General (CSIR) and Secretary to the Ministry of Science and Technology heads the organization. A new vision resulted in the enunciation of a doctrine for the CSIR and formulation of plans for what the organization should be in the 21st century. These include goals for providing a global R & D platform providing competitive R & D and high quality science based technical services.

CSIR's R&D strengths encompass world class expertise for organic synthesis and facilities for isolation and structure elucidation, biological screening, toxicological testing and The essential complement of expertise of clinical medicine/pharmacology and infrastructure facilities for clinical/field trials is through strong institutional linkages built up with various medical institutes/hospitals, while industry participation in development ensures successful upscaling and implementation of technology. CSIR, a large publicly funded R&D system, is trying to make a cultural shift in its operations, by looking at research as a business, i.e. defining a new product and doing it in a business like manner, i.e. defining a new process. CSIR hopes that it will become an effective hub in the global knowledge network and also an innovation partner with industry in the long journey of mind to market place.

The R&D thrust, in the chemical/pharmaceutical sector is focused on development of new drugs, innovative/indigenous processes for known drugs (with special emphasis on drugs for tropical and other diseases endemic to the country) and development of plant based drugs through investigation of leads from the traditional systems of ayurvedic medicine. Technologies developed invariably involve indigenous substitutes for expensive imported raw materials, innovative modifications to optimization of conventional process routes and application of novel techniques for product quality/purity.

The National Chemical Laboratory, Pune is the "flagship" of the government laboratories in India under the auspices of the

Council for Scientific and Industrial Research. Over two hundred members of the staff have doctoral degrees. The following avenues of cooperation that have been exploited by various multinational pharmaceutical, biopharmaceutical companies are illustrative of the enormous worldwide benefits.

- 1) Synthesis of analogs for broad spectrum and high throughput screening
- 2) Lead optimization and analog design
- 3) Designed organic synthesis, scaffolds and building blocks for lead generation and development of synthetic methodologies
- 4) Route selection, Process Chemistry: preparation of 1-5 Kg. of drug candidates for pre-clinical and Phase I evaluation
- 5) Strategic in-licensing of compounds discovered in India: Several groups have advanced programs in the areas of anti-infective, anti-histamine, CNS drugs, cardiovascular natural product based drug discovery etc.

NCL's mission to "To Advance Knowledge and to Apply Chemical Sciences for the Good of People" is best exemplified by the following examples:

Pioneering research in carbohydrate chemistry led to the novel rearrangement (Figure 1) successful scale up at Cipla led to the commercial indigenous and overseas production and manufacturing of the popular anti-HIV drug AZT. Further, successful collaboration with Cipla resulted in cost effective processes for Stavudine and Lamivudine.

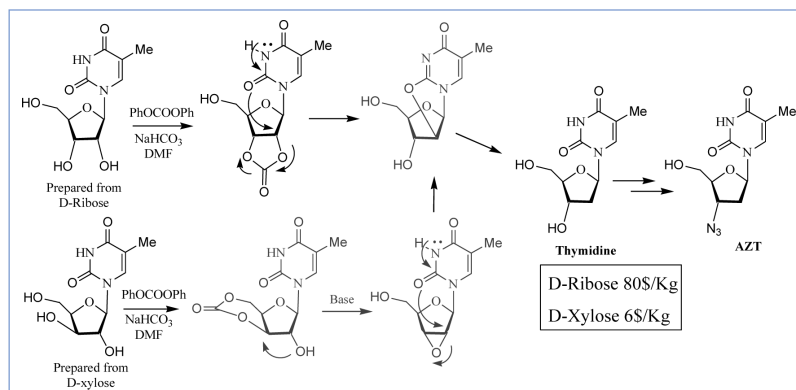


Figure 1. Key Rearrangement in the Preparation of Thymidine/AZT. Starting with D-Xylose

In 1996, a strategic move was undertaken to make the laboratory a performance driven organization funded by the export of knowledge and globally competitive technologies. During this renaissance period an aggressive effort led to process technologies for Etoposide, Etoposide Sulfate, Cytarabine, Taxotere side chain, Nevirapine, Mefloquin, Olanzapine, Atorvastatin, Donapezil, Venlafloxacin, Irinotecan, Cisapride, and Azithromycin. The NCL's process for Zidovudine (Figure 2) was a classic study wherein a comprehensive study of nucleophilic substitution on trichloronitrobenzenes resulted in uncovering of a novel di-decarboxylation of C2-arylmalonates. Amongst the various chiral pools available in nature, carbohydrates have occupied a special place in the armamentarium of the NCL; the allure of an abundantly available, enantiomerically pure and inexpensive material has been irresistible. We have been instrumental in developing carbohydrate based approaches for the stereoselective

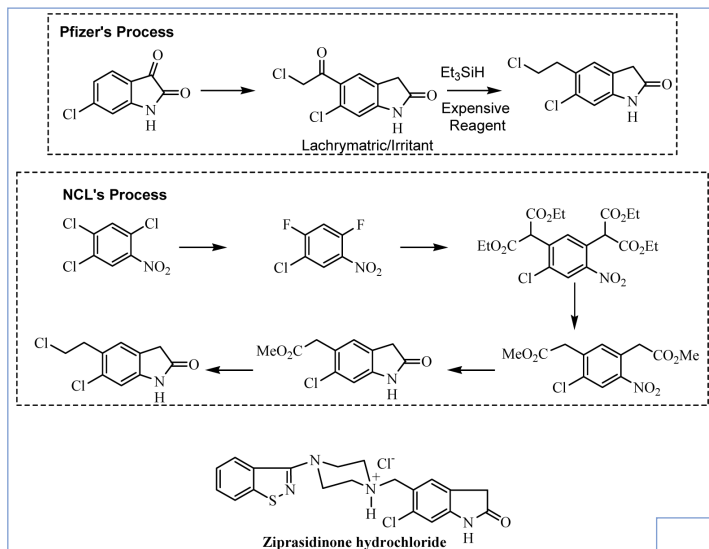


Figure 2. Key Steps in the NCL's Process for Ziprasidone.HCl

synthesis of several biologically active natural products such as Slagenin B, Slagenin C Microcarpalide. The easily available L-sugar, L-arabinose has been exploited as a suitable Chiron in their first total synthesis of naturally occurring slagenins B and C (Figure 3).

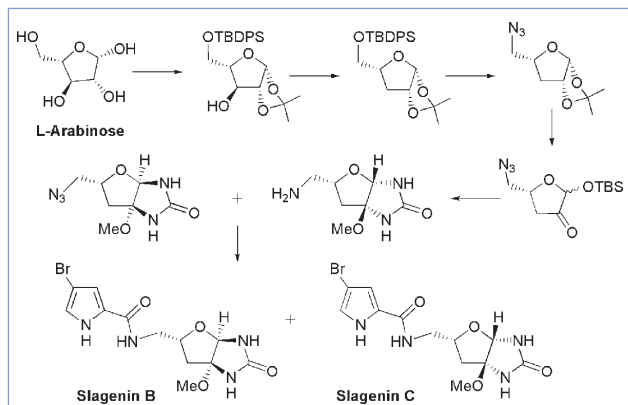


Figure 3. Chiral Pool Approach for the Synthesis of Naturally Occurring Slagenin B and Slagenin C

β-BLOCKERS & CMI-977

Drugs belonging to the class of aryloxypropanol amine are useful β-blockers. The β-blockers (β-adrenergic receptor blocking drugs) comprise a group of drugs prescribed for treating cardiovascular disorders such as cardiac arrhythmia or ischemic heart disease and hypertension. Such drugs include propranolol, atenolol, metoprolol, nadolol, carvedilol, Celiprolol etc (Figure 4). Amongst the above mentioned

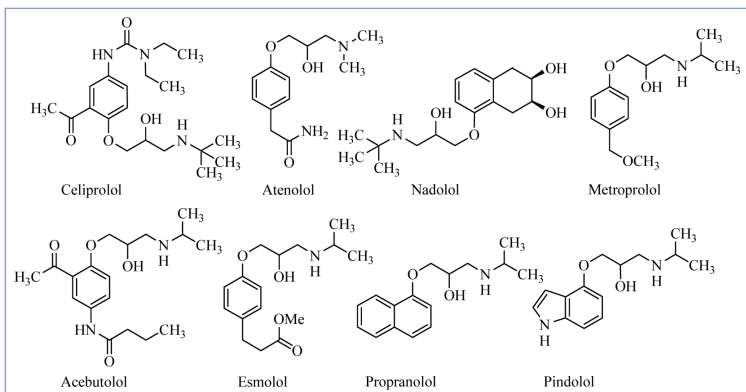


Figure 4. Commercial propanolamine β-Blockers

β-blockers, Celiprolol has an unique N,N-diethyl urea in its structural framework.

A turn key process for Celiprolol

The existing route starts with 4-ethoxy aniline which was treated with diethyl carbamoyl chloride in the presence of potassium bicarbonate to give N-p ethoxyphenylacetamide. Friedel-Crafts acylation using acetyl chloride and anhydrous aluminum chloride followed by acid hydrolysis furnished the acetophenone derivative. Reaction of the urea derivative with epichlorohydrin followed by treatment with hydrobromic acid gave bromohydrin. Celiprolol base was obtained by reaction of bromohydrin with tert-butyl-amine, in presence of triethylamine, and converted to the hydrochloride salt.

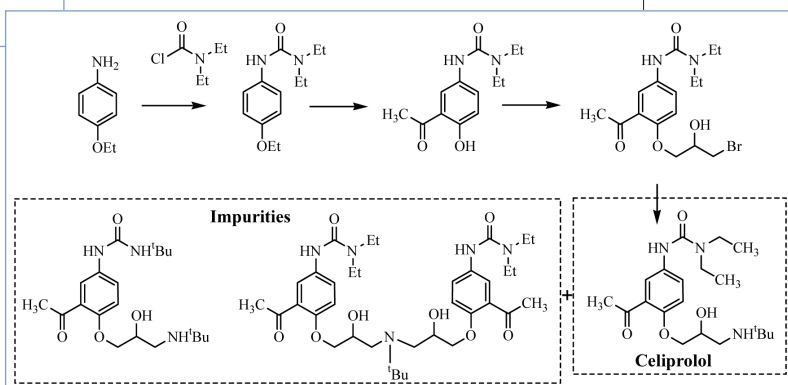


Figure 5. Commercial Route for Celiprolol.Hydrochloride

The introduction of N,N-diethyl urea is carried out at a fairly early stage of the process by using an expensive reagent, diethyl carbamoyl chloride (DECC). Being labile, this unit undergoes side-reactions resulting in two by-products that require extensive purification. We were alerted to the need for developing a new approach that could circumvent most of the above-mentioned difficulties. Introduction of the N, N-diethylurea segment as late as possible would be critical to our success. Concerning all the above issues we have devised a new approach starting with easily available 4-nitrophenol. One added advantage of the presence of the nitro group in the aromatic ring is, in majority of the case it provides crystalline intermediates, making their purification simple.

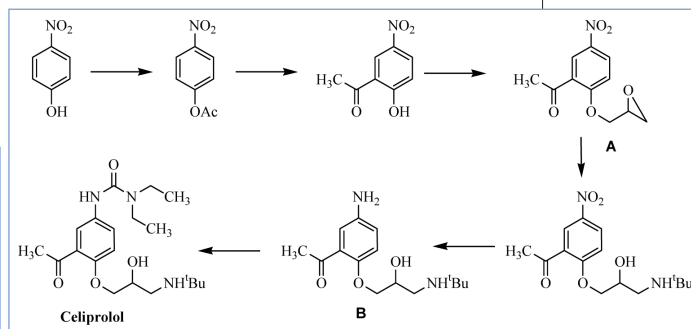


Figure 6. NCL's Route for Celiprolol. Hydrochloride

Our devised new process of Celiprolol. Hydrochloride starting with cheap 4-nitrophenol process is cost-effective and does not need any tedious separations. We are defining the resolution of intermediate aryl glycidol **A** in pursuit of a chiral process.

Innovative Approaches for chiral tetrahydrofurams

The alarming rise of asthma has led to a worldwide intensive search for safer and target-specific drugs. CMI-977 developed by Cytomed Inc. was under clinical evaluation, as a promising candidate for chronic asthma.

The inaugural synthetic route for CMI-977 (Figure 6), choosing (S)-(+)-hydroxymethyl- β -butyrolactone as a chiron, was plagued with several problems like poor selectivity and complicated separation of diastereomers which mitigated against efficient scale up and cost effective production of the target molecule.

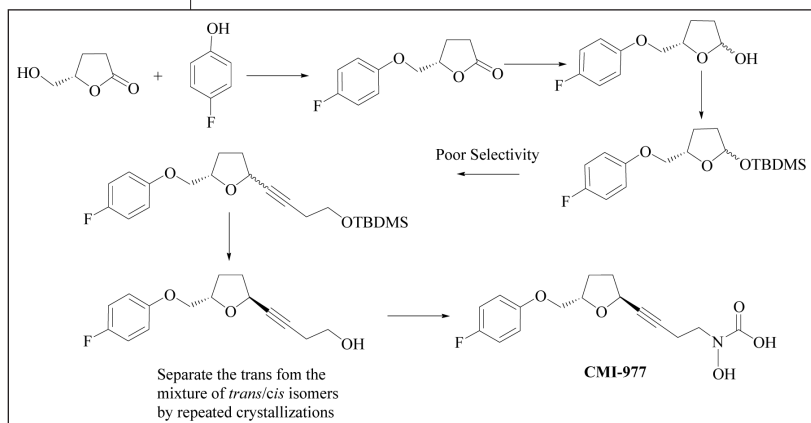


Figure 7. Inaugural Discovery Route for CMI-977

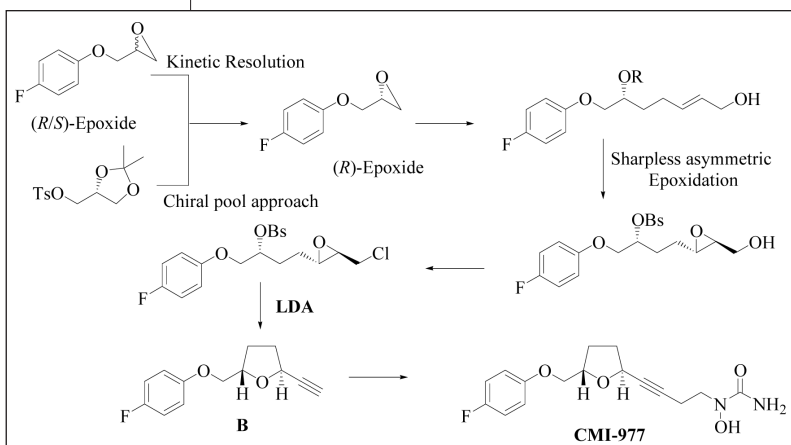


Figure 8. Some key transformations used in NCL's single enantiomer synthesis of chiral tetrahydrofurams

During the course of our efforts to solve the problems encountered in the reported approach, we devised and executed several novel routes simultaneously in our laboratory. The assembly of a tetrahydrofuran ring with suitable appendages of appropriate stereochemistry through the central transformation "double elimination-cum-intramolecular S_N2 ring closure" is unique.

Chiral Drugs and Chiral/Racemic Switches

Enantiomerically pure "Chiral Drugs" are of intense interest to the pharmaceutical industry; the USFDA has afforded particular emphasis to these. Chiral switches are chiral drugs that have been approved and marketed as racemates but have since been redeveloped as single enantiomers. There are distinct advantages for affecting a chiral switch such as (a) the dosage could be reduced, (b) the dose-response relationship would be simplified, (c) toxicity from the inactive stereoisomer would be minimized and (d) economics will be favorable.

Chiral Switch Scenario in India

A strategically beneficial chiral switch was effected by Emcure Pharmaceuticals in India. Using technology developed at the NCL, Ms. Emcure introduced (S)-Amlodipine as a single enantiomer drug with the trade name Asomex[®] in 2002. Amlodipine, a long-acting calcium channel blocker, is used for treatment of high blood pressure. It also increases the supply of blood and oxygen to the heart to control chest pain (angina). Asomex[®] contains only 2.5 mg of (S)-Amlodipine. Besylate and is as effective as 5 mg of racemic Amlodipine. Side effects with Asomex[®] are reduced very significantly; moreover a study of over ten thousand patients revealed a significant reduction in peripheral edema as compared to patients on racemic Amlodipine medication.

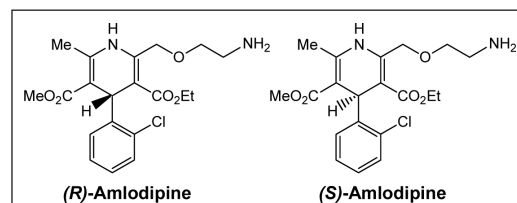


Figure 9.

A unique combination of innovative reactions/catalysts from academic researchers and invention of new technologies by process chemists at the NCL has contributed to intellectually stimulating and financially beneficial contributions to the pharmaceutical industry. The integration of basic research and process research development has played a crucial role in the strategic growth of the laboratory.

MUKUND S. CHORGHADÉ¹, VEENA M. CHORGHADÉ¹,
MUKUND K. GURJAR², C. V. RAMANA²,
ASHOK V. KAMERKAR³, HARRY ZAFRAN³
AND RAGHUNATH A. MASHELKAR⁴

1. Pharmaceutical Sciences Division, D & O Pharmachem, Inc., 14 Carlson Circle, Natick, Massachusetts 01760-4205
2. National Chemical Laboratory, Pune-411008, India
3. D & O Pharmachem, Inc., The Atrium, 80 East Route 4, Paramus, New Jersey 07652
4. Council of Scientific and Industrial research, New Delhi 110001, India