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MEDICINAL CHEMISTRY RESEARCH IN INDIA

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Abstract

The beginning of modern drug research in India can be traced to early part of the twentieth century. Dr Upendra Nath Brahmachari worked on drugs for kala-azar at the Campbell Medical College, Calcutta. Colonel Ram Nath Chopra organized an active centre of research on the Indian medicinal plants at the School of Tropical Medicine, Calcutta. The lead given by Chopra led to start of investigations on indigenous drug plants in various universities and colleges. By mid of the twentieth century, different institutions started getting organized for studies with systematic approach to design of new chemical entities. The credit goes to the Central Drug Research Institute, CSIR, for spreading the innovative drug research culture. The major discoveries made of the drugs through innovative drug research have been from the CDRI, Hindustan Ciba-Geigy Research Centre, and the University Institute of Pharmaceutical Sciences of the Panjab University. The other institution active was the Research Centre of the Hoechst Pharmaceuticals Limited. The Zydus Research Centre has come up of recent. There have emerged a good number of new drugs from Indian laboratories but only a few have been marketed.

Key words: Andhra University, Campbell Medical College, Central Drug Research Institute, Hindustan Antibiotics, Hindustan Ciba-Geigy Research Centre, Hoechst Pharmaceuticals Limited, Kuppuswamy Nagarajan, Lucknow University, Medicinal Chemistry, Nitya Anand, Panjab University, Ram Nath Chopra, Upendra Nath Brahmachari, Zydus Research Centre.

1. INTRODUCTION

The beginning of modern drug research in India can be traced to early part of the twentieth century. Dr Upendra Nath Brahmachari[1] worked on drugs for kala-azar at the Campbell Medical College, Calcutta. Colonel Ram Nath Chopra[2-4] organized an active centre of research on the Indian medicinal plants at the School of Tropical Medicine, Calcutta.

U. N. Brahmachari started working on treatment of the disease kala-azar in the second decade of the twentieth century. He examined organometallic compounds and concentrated his study on antimony derivatives. His idea of combining urea with stibanilic acid worked and led to discovery of the drug 'Urea Stibamine.' The drug was introduced for the treatment of kala-azar in 1922.

Upendra Nath Brahmachari (1873-1946)

Colonel Ram Nath Chopra is recognized as parent of pharmacology, pioneer of systematic studies of indigenous drugs, promoter of Indian systems of medicine, and patron of pharmacy. Through his work at the Calcutta School of Tropical Medicine for two decades (1921-41) he opened the largely neglected field of use of indigenous drugs in modern medicine, on which he carried out systematic studies. The enquiries

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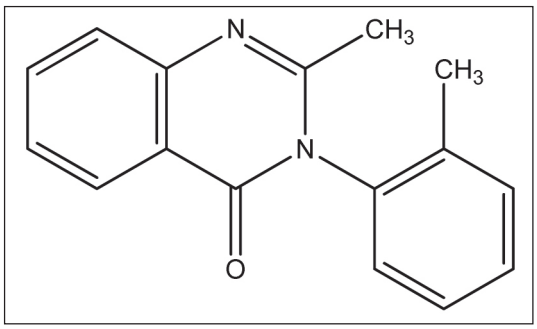
employing modern methods of chemical, pharmacological and therapeutic research, showed that certain drugs deserved pharmacopoeial recognitions and the examples cited included ispaghula, kurchi, rauwolfia, psorelea, cobra venom etc. In 1933, it was reported that an alkaloid obtained from *Rauwolfia serpentina*, on experimental studies in animals showed central depressant properties and lowered the blood pressure.[5] It was recorded that 'it should prove to be a valuable sedative drug' and 'if administered in proper dosage form should be of value as a remedy for hyperpiesis.'

Ram Nath Chopra (1882-1973)

The lead given by Chopra led to start of investigation on indigenous drug plants in various universities and colleges in centres such as at Calcutta, Bombay, Dacca, Patna, Allahabad, Lahore, Madras, Trivandrum etc. A particular mention may be made of the studies carried out by Dr Salimuzzaman Siddique (Tibbia College, Delhi).

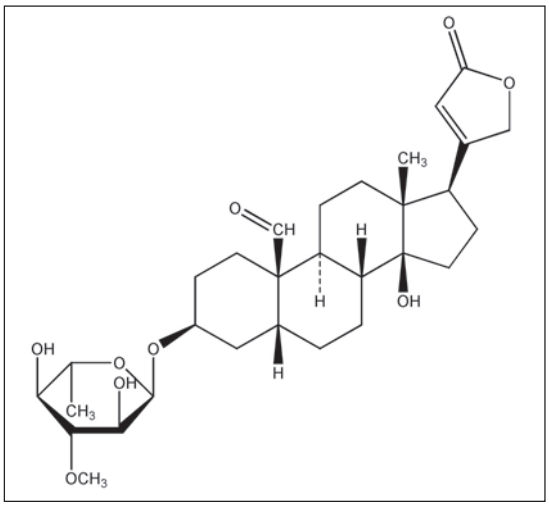
The earliest drug originating from India through modern drug research was the chemotherapeutic agent Urea Stibamine. Three other drug discoveries which came up later were methaqualone, peruvoside and hamycin. Out of the work initiated on the synthesis of quinazalones at the Department of Chemistry, Lucknow University, and later continued at the Regional Research Laboratory, now Indian Institute of Chemical Technology, Hyderabad, emerged the compound which was first screened at the K. G.'s Medical College, Lucknow,[6] and later designated



Methaqualone

as methaqualone. Methaqualone came up into wide spread use as hypnotic. It has been withdrawn from the market in many countries because of its abuse.

The cardiac glycoside peruvoside was isolated from *Thevetia peruviana* at the Pharmaceutical Laboratories of Andhra



Peruvoside

University,[7] and developed in Germany as a cardiotonic agent for use in therapy. It has been used in congestive heart failure.

Hamycin is an antifungal agent, an antibiotic discovered at the Research Laoratories of the Hindustan Antibiotics, Pimpri. It is a polyene produced by *Streptomyces pimprina*.[8] Hamycin has antifungal and antichromonal properties. It has been applied topically and given by mouth in a variety of fungal infections.

2. Medicinal Chemistry Research

The earlier two synthetic drugs discoveries were of urea stibamine and methaqualone. By mid of the twentieth century different institutions started getting organized for studies with systematic approach to design of new chemical entities which hopefully could lead to clinical examination of selected molecules and their becoming accepted as drugs by the Drugs Control Administration of the Government of India.

The first such institution which got established, in late 1950, was the Central Drug Research Institute at Lucknow, under the aegis of the Council of Scientific and Industrial Research. The idea for having an institution for collaborative drug research in India was first mooted by Dr Bishnupada Mukerji in his Presidential Address at the Section of Physiology of the Indian Science Congress (1945).[9] A short account of developments which led to CDRI creation is given in a biography of B. Mukerji.[10]

The Central Drug Research Institute emerged as an important centre of drug research in the country; where while doing commendable research it groomed high grade scientific manpower for staffing positions in the industry and elsewhere. The credit goes to the CDRI for initiating and spreading the innovative drug research culture. In doing this Dr Nitya Anand had a dominant role, and he stands out as the doyen of medicinal chemists of India of the twentieth century.

Later, the CSIR Regional Research Laboratories at Hyderabad and Jammu also engaged in medicinal chemistry research. The other public undertaking was the IDPL Research Centre, Indian Drugs and Pharmaceuticals Limited, Hyderabad.

Among the university departments which significantly contributed to drug research was the Department of Pharmaceutical Sciences, now University Institute of Pharmaceutical Sciences, of the Panjab University at Chandigarh.

The prominent private sector organization which made a mark in innovative drug research was the Hindustan Ciba-Geigy Research Centre, Bombay; Dr Kuppuswamy Nagarajan was the most distinguished among the medicinal chemists working at the Centre. The other private institution active was the Research Centre of the Hoechst Pharmaceuticals Limited, Bombay.

The above was the scene with regard to the institutions active in medicinal chemistry research when in 1982 Nagarajan and Arya took stock of the research developments of the preceding couple of decades.[11] We ourselves at the Panjab University were in the process of preparing book-length monograph on the subject which got published in 1985.[12] Based on the contents of the monograph a selective book-chapter was also brought out almost simultaneously.[13]

The three review publications contain a wealth of material on medicinal chemistry related research carried out in India. In the next section note is made of the new synthetic drugs discovered, followed by a section on drugs from natural sources leads, emerging from the Indian laboratories. Only those drugs have been taken into account which have been cleared for manufacture and marketing by the Drugs Control Administration, Government of India.

At this stage I may make a digression from main theme of the subject and refer to usage of the terms medicinal chemistry and pharmaceutical chemistry. In early 1970 the International Union of Pune and Applied Chemistry's Committee on International Education of Medicinal Chemists was established by the Organic Chemistry Division, Section of Medicinal Chemistry. Professor E. E. Smissman from the University of Kansas was made the chairman and I was taken as a member from India. Where I collected and

collated the information on medicinal chemistry education in the country, I also raised an issue of indiscriminate use in English language of the terms medicinal chemistry and pharmaceutical chemistry. Regarding this the recommendation of the Committee was "that in the interest of uniformity in the English language *Medicinal Chemistry* be adopted as the term to cover organic and biochemical aspects of drug action and design, and *Pharmaceutical Chemistry* to cover the training with physical and analytical chemical emphasis……; further, it was recommended that in languages other than English suitable corresponding terms be established.[14]

Presently the definition current for medicinal chemistry as per IUPAC recommendations[15] reads as below:

> "*Medicinal Chemistry* is a chemistry based discipline, also involving aspects of biological, medical and pharmaceutical sciences. It is concerned with the invention, discovery, design, identification and preparation of biologically active compounds, the study of their metabolism, interpretation of their mode of action at molecular level and construction of structure-activity relationships."

3. New Synthetic Drug Discoveries from Indian Laboratories

The major discoveries made of the drugs through innovative drug design have been from the Central Drug Research Institute, Hindustan Ciba-Geigy Research Centre, and the University Institute of Pharmaceutical Sciences of the Panjab University.

The new chemical entities designed at the CDRI which reached the stage of approval of the Drugs Control Administration, Government of India, as drugs for manufacture and marketing are Centimizone, Centbucridine, Centbutindole, Centchroman, Centpropazine, and Aablaquine. At a time the CDRI used to name the new discoveries with prefix 'cent.'

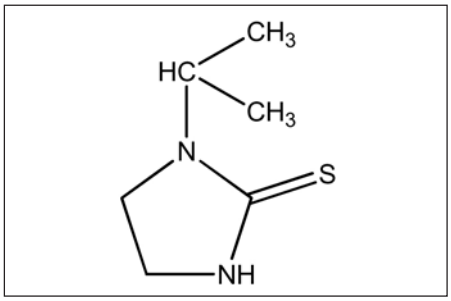
Now there is a good measure of systematization in devising generic names of drugs. Certain countries have their own setups for devising and selecting generic names, as are the systems for devising the names: BAN (British Approved Name), DCF (Denomination Commune Francaise), JAN (Japanese Approved Name), and USAN (United States Approved Name). The World Health Organization has assumed authority for the selection of generic or what they call International Nonproprietary Names (INNs).[16] They have laid principles for coining the INNs, and have published for the purpose the *Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances* and the *General Principles for Devising International Nonproprietary Names for Pharmaceutical Substances*. The INN programme of the WHO strives to provide one name for a drug. It is advised that one should not venture to self-create a generic name but use a code until the assignment of recommended INN. Here for the Indian drug discoveries the INN designations are mentioned wherever they have been obtained from the WHO.

The particulars provided next, for the CDRI and Ciba-Geigy Centre are largely based on what is contained in article by Nagarajan and Arya,[11] and book-monograph and book-chapter by Singh, Chawla and Kapoor,[12,13] or through correspondence with Anand[17] and Nagarajan,[18] respectively.

3.1 Mipnazole (INN) (Centimizone)

Mipnazole was the first notable drug discovery from the CDRI, which resulted from a number of 1-alkylimidazolidine-2-thiones examined for antithyroid activity.[19]

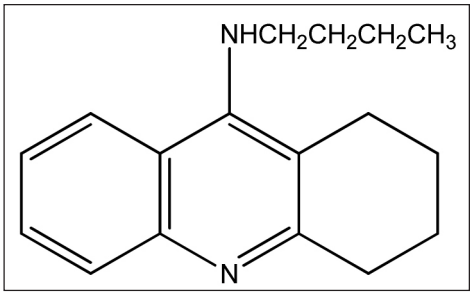
It was licensed to the Unichem Laboratories, Mumbai, in 1972.



Mipnazole (INN) (Centimizone)

3.2 Bucricaine (INN) (Centbucridine)

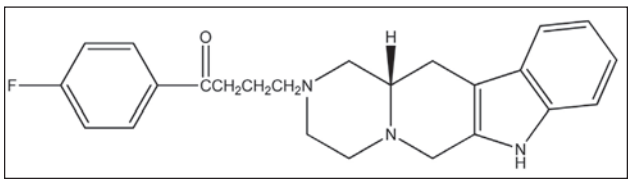
Bucricaine, chemically *N*-butyl-1,2,3,4-tetrahydro-9- acridinamine came out of the work on 4-substituted 2,3 polymethylenequinolines.[20] This is a local anaesthetic which was licensed to the Themis Medicare, Mumbai, in 1987.



Bucricaine (INN) (Centbucridine)

3.3 Buriperone (INN) (Centbutindole)

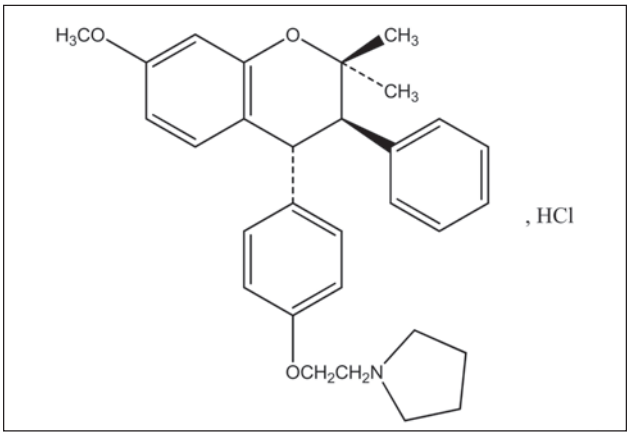
The drug belongs to the class of butyrophenones as is the prototype neuroleptic haloperidol. The related study yielded the new drug centbutindole.[21,22] This new drug was found to have distinct therapeutic advantages over known compounds like haloperidol as neuroleptic. Gruppo Lepetit, Milano, Italy, offered a very favourable licensing proposition but the Government delayed a decision for long and they withdrew the offer after 8 months; in India it was licensed to the Themis Medicare in 1987.[17]



Buriperone (INN) (Centbutindole)

3.4 Ormeloxifene (INN) (Centchroman)

In search of fertility regulating agents many compounds related to triphenylethylene structure were synthesized and biologically tested at the CDRI, out of which 3,4-diphenylchromenes and chromans proved to be of particular interest, leading to the discovery of centchroman.[23,24] The drug got to be of use as post-coital contraceptive and for dysfunctional uterine bleeding (DUB). It

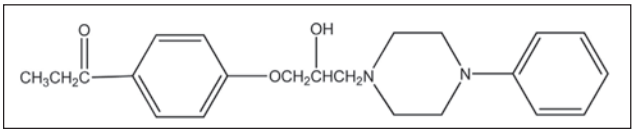


Ormeloxifene Hydrochloride (INN) (Centchroman Hydrochloride)

was licensed to Hindustan Latex, Trivandrum, in 1989 and is in the market[17] with the trade name SAHELI as oral contraceptive and NOVADEX for DUB. The drug was also licensed to Torrent, Ahmedabad, in 1990, for promotion for use in breast cancer, mastalgia and mastitis, breast pain, nodular breast and osteoporosis, it goes by CENTRON trade name.[17]

3.5 Centpropazine

Centpropazine belongs to a new class of noncyclic antidepressants discovered at the

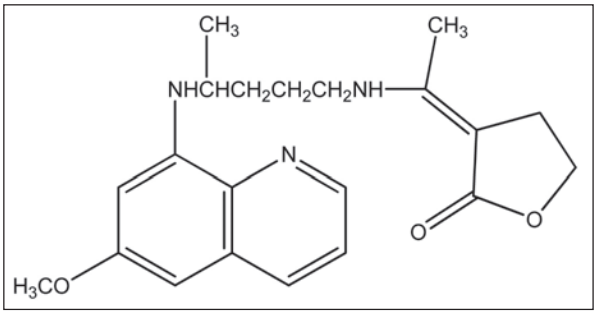


Centpropazine

CDRI.[25] The drug was licensed to Themis Medicare in 1996.

3.6 Aablaquine

Aablaquine is a prodrug of the antimalarial primaquine. Like primaquine it is useful for the treatment as well as the control of spread of malaria with significantly reduced toxic profile as compared with primaquine.[17,26] The prodrug was licensed by CDRI to Nicholas Piramal, Mumbai, in 1996.



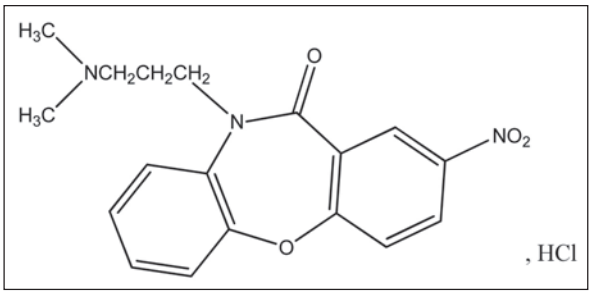
Aablaquine

The main marketable drug discoveries made at the Hindustan Giba-Geigy Research Centre were Nitroxazepine, Nonaperone, Amoscanate and Satranidzole.[11, 18]

The Ciba-Geigy Centre had interest in design and development of psychoactive agents. The antidepressant agent Nitroxazepine and neuroleptic Nonaperone were the major discoveries.

3.7 Nitroxazepine (INN)

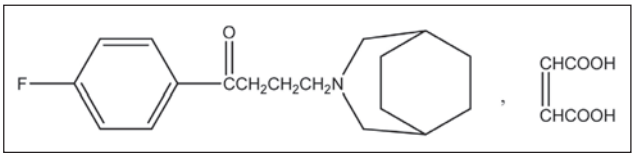
Nitroxazepine is a tricyclic antidepressant dibenzoxazepine structurally; Nitroxazepine Hydrochloride (SINTAMIL) was introduced by the Ciba Geigy in 1982 and is being sold by Navartis (formerly Ciba-Geigy)[11,18] It is indicated for the treatment of all grades and types of depression. It is also indicated for nocturnal enuresis.



Nitroxazepine Hydrochloride

3.8 Nonaperone (INN)

Nonaperone is a butyrophenone as the standard drug Haloperidol and CDRI product Buriperone. It was got ready as the maleate



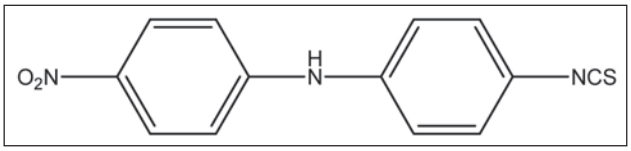
Nonaperone Maleate

(AZABIPERIDOL). It is antipsychotic in schizophrenics at doses which do not elicit extrapyridal side effects. The drug was allowed for marketing but it did not get commercialized.

The Ciba-Geigy Centre also engaged in studies on chemotherapeutic agents. The two drugs which got approval for marketing were Amoscanate and Satranidazole.

3.9 Amoscanate (INN)

Certain isocyanates have been studied at some laboratories for use as anthelmintics. The Ciba-Geigy prepared Amoscanate which is a broad spectrum anthelmintic, with activity against nematodes, cestodes and trematodes. It received registration as a drug for use in hookworm infections, but has not been marketed.



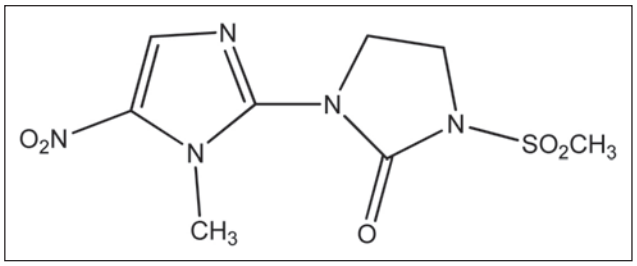
Amoscanate

Antiprotozoal agents have been the subject of investigations at different institutions. Mention has been made earlier of Urea Stibamine, and

Aablaquine. At the Ciba-Geigy antiprotozoal drug Satranidazole was successfully developed.

3.10 Satranidazole (INN)

Satranidazole is an imidazoly-limidazolidinone which is a potent amoebicide and trichomonacide. It has confirmed superiority over metronidazole. The drug was not marketed by the Ciba-Geigy. In 2000 Alkem Laboratories



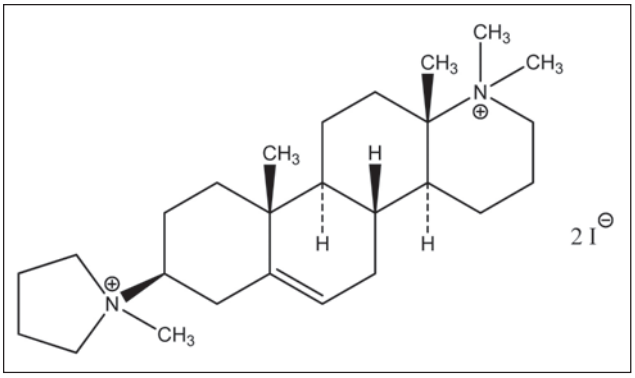
Satranidazole

manufactured this drug and prepared its formulation and marketed it as SATROGYL. This brand and its combination with ofloxacin (SATROGYL O) are in the market.

We at the Panjab University had our interest in heterosteroids and drug research.[27,28] The synthetic work which we carried out had focus on design of new chemical entities of medicinal interest. But it largely remained interesting organic chemistry because of want of appropriate facilities for biological testing. A part of the work aiming at design of quaternary ammonium steroids became medicinal chemistry as we were able to have collaboration with Department of Pharmacology of the University of Strathclyde, Glasgow, an institution known for its work on skeletal muscle relaxants. Through this liaison the drug chandonium iodide could be discovered and structure-activity relationship studies could be carried out.[29-31] The interorium distances feature was examined with the help of Department of Crystallography, Birkbeck College, University of London.

3.11 Candocuronium Iodide (INN) (Chandonium Iodide)

Out of several active compounds with varying interonium distances, chandonium iodide proved to be most active as neuromuscular blocker which also had an acceptable clinical profile.



Candocuronium Iodide (Chandonium Iodide) (HS-310)

Chandonium possesses a powerful non-depolarising neuromuscular blocking activity of short duration and rapid onset, being only slightly less active than the well known neuromuscular blocker pancuornium.[32,33] The interonium distance in chandonium iodide is 1.029 nm.[34] It has little or no ganglion blocking activity.

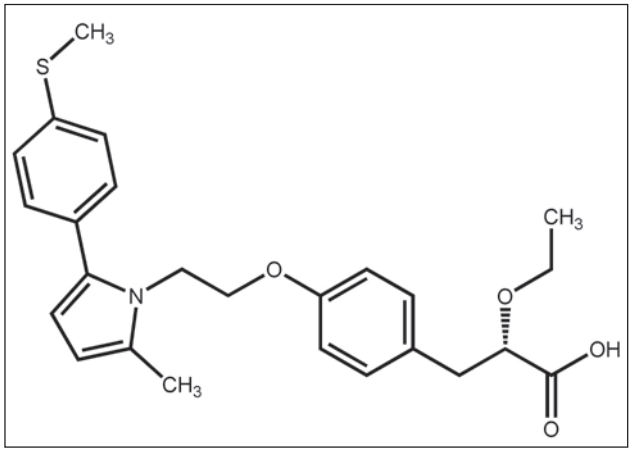
The developmental work and toxicity and clinical testing of chandonium was carried out through the Central Drug Research Institute; the personal interest taken by Dr Nitya Anand and Professor B. N. Dhawan was of great help. The results of clinical trials carried out at different centres were summed up in the Proceedings of the Symposium on the subject held at All India Institute of Medical Sciences, New Delhi, in April 1993. [35]

The CDRI arranged obtaining of the INN designation Candocuronium Iodide for Chandonium Iodide from the World Health Organization. The Drugs Control Administration cleared the drug for manufacture and marketing. The drug was licensed to the CIPLA, Mumbai, for commercialization in 1994.

The position regarding two of the drugs namely Saroglitazar and Alvocidib was not in my knowledge when the matter above was communicated. Now I am able to obtain authentic information and introductory noted about them are placed next.

3.12 Saroglitazar (INN)

During the last couple of decades there has been a continued interest in the design of peroxisome proliferator-activated receptor (PPARs) agonists. A category of drugs known as glitazones are PPAR gamma agonists and the other put as glitazars are dual alpha/gamma agonists.



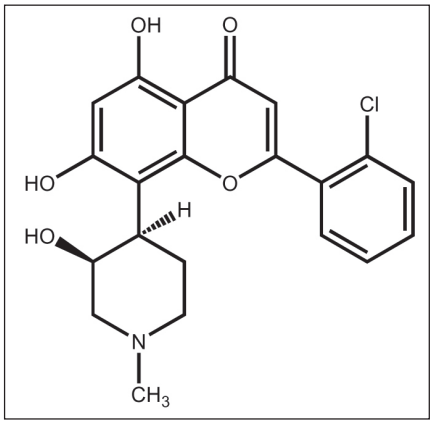
Saroglitazar

For the last several years the Zydus Research Centre of the Cadila Healthcare Limited, Ahmedabad, have directed their studies on glitazars. They have come up with the drug Saroglitazar (Lipaglyn), which has been approved by the Drugs Control Administration for manufacture and marketing (2013).[36] Its agonist action on PPAR alpha lowers the blood triglycerides and action on PPAR gamma improves insulin resistance and consequently lowers blood sugar.

The drug is predominantly PPAR alpha agonist with moderate PPAR gamma agonist profile. It improves hypertriglyceridemia in patients with type 2 diabetes mellitus. Saroglitazar showed good safety profile in preclinical and clinical studies and is indicated for the treatment of diabetic dyslipidemia and hypertriglyceridemia with Type 2 diabetes mellitus not controlled by statin therapy.

3.13 Alvocidib (INN) (Flavopiridol)

The discovery of this antineoplastic agent is another case of a molecule prepared in India and developed as a drug abroad. The basic idea for it came from observed anti-inflammatory activity of Rohitukine, an alkaloid isolated from the Indian plant *Desoxylum binectariferum*, which was toxic. Among the synthetic analogues was the molecule earlier designated as Flavopiridol and now bearing the WHO given International Nonproprietary Name Alvocidib. All of the related



Alvocidib

synthetic work was done at the Hoechst Research Centre at Bombay, but biological/clinical studies were carried out by the parent company at Frankfurt, Germany.[37] Alvocidib inhibits the cyclin-dependent kinase. The drug has been studied clinically for the treatment of chronic lymphocytic leukemia.

4. Drug from Natural Sources Leads

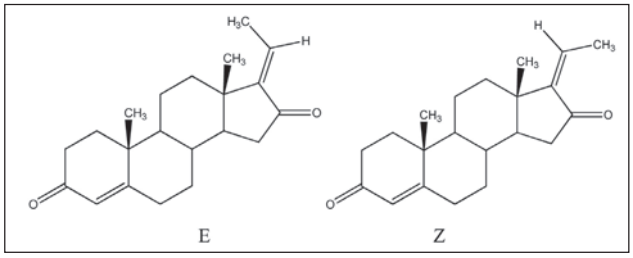
Some drugs have been generated from natural sources leads. Earlier, cardiotonic peruvoside and antifungal antibiotic hamycin have been listed. Here a mention is made of Gugulipid

and Consap. A reference is also made to diterpene colforsin which though did not become an approved drug but work pertaining to it is interesting.

4.1 Gugulipid

Guggal is the oleoresin exudation from *Commiphora weightii* (Arnott) Bhandari (*Commiphora mukul, Balasmodendron mukul* Hook. ex Stocks). Gugulipid is a fraction of guggal, which has been developed at the Central Drug Research Institute, Lucknow, in collaboration with Malti-Chem Research Centre, Baroda, for use as hypolipidaemic agent.

Gugulipid is mainly a mixture of sterols and steroids gugulosterones.



Gugulusterones

Gugulusterones which contribute 4-6 per cent of gugulipid, are *Z* and *E* 4,17(20) - pregnadiene-3,16-diones.

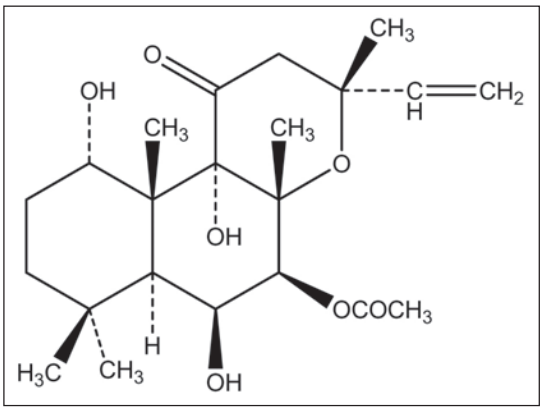
The CDRI licensed gugulipid to CIPLA, in 1988, which is marketing it under the patent name GUGLIP.

4.2 Consap

Several saponins have shown spermicidal activity.[38] Consap, a spermicidal cream containing saponins from *Sapindus mukorossi* prepared at the CDRI, after clinical testing and necessary approval was licensed to Hindustan Latex, in 2004, and has been marketed for use as local contraceptive.

4.3 Colforsin

The use of *Coleus* spp. in the treatement of heart diseases and other disorders has been



Colforsin

reported in Ayurvedic materia medica. A systematic study at the Central Drug Research Institute led to isolation of coleonol, a diterpenoid, from *Coleus forskohlii*. The principle isolated at the Research Centre, Hoechst Pharmaceuticals Limited, from the same plant was designated forskolin. There was a controversy about separate identities of coleonol and forskolin. Subsequentlly it was shown that both were identical.[39] The compound now goes by the name of colforsin.

Colforsin has positive inotropic effect, which is related to its ability to activate adenylate cyclase. It has bronchodilator activities and reduces intraocular pressure in glaucoma. It has been investigated for a number of conditions including glaucoma and impotence.

5. Fate of Indian Drug Discoveries

To summarize, the work on innovative design of new chemical entities which ultimately led to discovery of clinically usable products, there have been discovered thirteen drugs. The Central Drug Research Institute discoveries, six of the them, namely, are antithyroid mipnazole (centimizone), local anaesthetic bucricaine (centbucridine), antipsychotic buriperone (centbutindole), contraceptive ormeloxifene (centchroman), antidepresant centpropazine, and antimalarial aablaquine. Antidepressant nitroxazepine, antipsychotic nonaperone,

anthelmintic amoscanate, and amoebecide and trichomonacide satranidazole came from the Hindustan Ciba-Geigy Research Centre. The neuromuscular blocker candocuronium (chandonium) was designed at University Institute of Pharmaceutical Sciences of the Panjab University. Saroglitazar is from the Zydus Research Centre and Alvocidib systhesis was done at Hoechst Research Centre.

Out of the above thirteen drugs only three ormeloxifene (centchroman), nitroxazepine and satranidazole have been marketed. It is not known that what their status is commercially.

The discovery of new drugs in the country constitutes a respectable list. A huge lot of money and human resources have gone into the chemical work, pharmacological and other testing, toxicity studies in animals and carrying out of all phases of clinical trials. All drugs discovered in India are effective and safe and meet the international standards.

It is sad, however, that only a few of the drugs discovered in India have been commercially exploited. What comes in the way is diffidence on part of the Indian firms to risk marketing and the medical profession not coming forward to patronize home discoveries for unexplained reasons. The depressing state needs attention and examination by the policy makers.

Notes and References

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