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Two Decades of Medicinal Chemistry Research in India*†

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Although several traditional systems of medicine, e.g. Ayurveda, Siddha and Unani, have been in vogue in India for several centuries, internationally accepted norms of basic research towards developing new drugs are of relatively recent origin. There are many facets of the drug research carried out in the country and it would be a difficult task to summarize all the efforts and assess the results. This article is, therefore, restricted to a survey of the outcome of medicinal chemistry research in India, as understood in the modern context, in the last two decades, and is confined to significant researches in terms of new discoveries that have been made available to the Indian public or registered as well-recognized drugs. It also includes compounds that are in various stages of clinical trials and preparations with an interesting profile of biological activity. In a few instances even leads are mentioned. The review covers both synthetic preparations and natural products, although greater emphasis is laid on the former.

Contemporary drug development is a team effort, requiring a continuous interaction of scientists belonging to a wide spectrum of disciplines. As many as 80 different activities are involved in the process of drug development[1]. Thus, drug development is a time-consuming and costly process. On an average, it is found that at least 7-10 years are required after the discovery of a useful lead to take it successfully to the market, and international figures point to a cost of about $ 40,000,000 for the introduction of every new chemical entity. The current odds of a new preparation becoming a drug are as low as one in fifteen thousand, considering that fairly satisfactory therapy exists for many diseases and that drug regulatory authorities are enforcing increasingly stringent conditions with respect to the safety and efficacy of new drugs.

It is against this background that we wish to assess the outcome of medicinal chemistry research in India, taking also into account the fact that currently perhaps not more than Rs 100,000,000 ($ 12,000,000) are spent per annum in this area. It is also to be borne in mind that there are not many institutions in India which have the necessary minimal optimal multidisciplinary staff and infrastructural facilities for such research. Some of the important institutions with such facilities are listed below. Additionally, there may be a large number of places, like the pharmacology departments of many medical colleges, where a limited amount of work, often desultory in nature, is carried out. Among government run or funded institutions may be mentioned: (i) Central Drug Research Institute, Lucknow, (ii) Indian Drugs and Pharmaceuticals Ltd, Hyderabad, (iii) Regional Research Laboratories, Hyderabad and Jammu, (iv) Haffkine Institute, Bombay, (v) All India Institute of Medical Sciences, New Delhi, (vi) Indian Institute of Experimental Medicine, Calcutta (now known as the Indian Institute of Chemical Biology), and (vii) School of Tropical Medicine, Calcutta. The following institutions are run by private industry: (i) Ciba-Geigy Research Centre, Bombay, (ii) Hoechst Research Centre, Bombay, (iii) Sarabhai Research Centre, Baroda, (iv) Smith, Kline and French Ltd, Bangalore and (v) Boots.

For a better appreciation, the results of two decades of research in medicinal chemistry in the country have been categorized according to therapeutic areas, listing important compounds and their status.

Anthelmintics

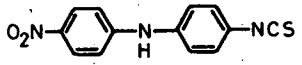
Gastro-intestinal Nematodes

Amoscanate, **1** (*Go.* 9333)—This is a broad spectrum anthelmintic[2] with activity against nematodes (hookworm, roundworm, filaria), cestodes (tapeworms) and trematodes (schistosomes). Having undergone successful clinical trials in hookworm patients, it is awaiting registration in India for this indication.

Ciba-Geigy Research Centre has also discovered a novel class of benzimidazole carbamates with a broad spectrum of anthelmintic activity, especially against nematodes, out of which one preparation is under clinical trials.

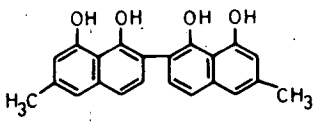
*Based on a talk given by K. Nagarajan at the 32nd Indian Pharmaceutical Congress held in Nagpur during 23-25 January 1981.

†Contribution No. 628 from CIBA-GEIGY Research Centre, Bombay 400063.



1 (CG)*

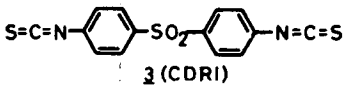
Diospyrol, **2** (*Go.* 7639)—Clinical reports on the activity of the juice of fresh *Diospyros mollis* fruits against hookworm prompted a study which led to the finding in an animal model that the activity resided in the polyphenolic binaphthyl, diospyrol[3]. However, the high susceptibility of diospyrol to aerial oxidation precluded development for the clinic.



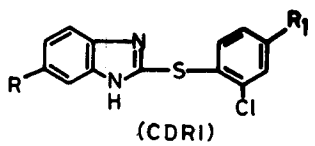
2 (CG)

Cestodes

Centsulphone (**3**)—This compound possesses good cestodicidal activity in animal models[4]. Useful leads in this area have also been obtained in compounds **4-7** related to **3**. Structures **8**, **9**[5] and **10**[6] represent other leads in this parameter.

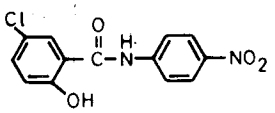


3 (CDRI)

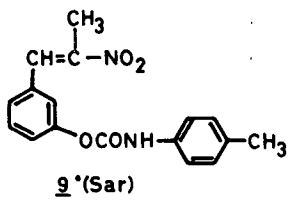


(CDRI)

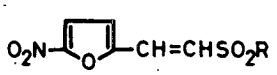
4 : R, Cl; R_1, NO_2
5 : R, H; R_1, NCS
6 : R, Cl; R_1, NCS
7 : R, NCS; R_1, NCS



8 (CDRI)



9 *(Sar)



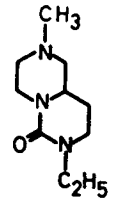
10 (IDPL)

*The following abbreviations are used throughout the paper to identify the Centres from which the preparations have originated:
CG—CIBA-GEIGY Research Centre, Bombay
CDRI—Central Drug Research Institute, Lucknow
IDPL—Indian Drugs & Pharmaceuticals Ltd, Hyderabad
Sar—Sarabhai Research Centre, Baroda
RRL—Regional Research Laboratory: H-Hyderabad; J-Jammu
Hoe—Hoechst Research Centre, Bombay

Filaria

Centperazine (**11**)—This compound exhibits high microfilaricidal activity when tested in cotton rats infected with *Litosomoides carinii*. In this test, it is five times more potent than diethylcarbamazine. Phase I clinical studies on centperazine have been completed[7].

The antifilarial activity of Go. 9333 (**1**) in experimental models has been mentioned earlier and is under detailed study.

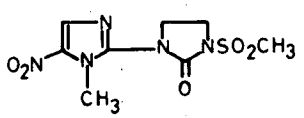


11 (CDRI)

Antiprotozoics

Amoeba, Giardia, Trichomonads

Go. 10213 (**12**)—This preparation has very potent amoebicidal activity in both hepatic and caecal infections in the hamster and also trichomonads, being several times more potent than metronidazole in these models. It is in advanced clinical trials which have confirmed its superiority over metronidazole, both in tolerability and efficacy[8]. It is also found to be active against giardial infections.

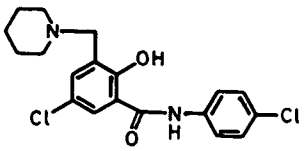


12 (CG)

Leads have been obtained at IDPL among furan haloacetamides and 3-[2-(heteroaryl)vinyl]-2*H*-1,4-benzoxazin-2-ones[6].

Malaria

The niclosamide analogue (**13**) has been found to be very active in experimental models[5]. Ciba-Geigy Research Centre has a limited programme on primaquine.



13 (Sar)

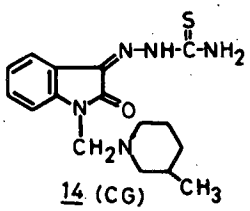
Antibacterials

Ciba-Geigy Research Centre had a broad programme for the synthesis of sulphasynergists. A combination is in clinical trials. Good *in vitro* antibacterial activity has been found in a series of 4-(2-heteroarylvinyl) coumarins[6].

Antivirals

Small Pox

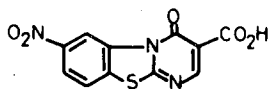
Go. 1428 (**14**)—It is an analogue of Marboran, very potent against neurovaccinial infections *in vivo*[9]. It is excellently tolerated in subacute toxicity studies. In view of the global elimination of small pox, clinical trials were not completed.



14 (CG)

Influenza

Go. 3016 (**15**)—It has considerable prophylactic activity in mice infected with influenza PR-8 virus. It also has a good activity against Sindbis and H-1 virus infections in hamsters[10].

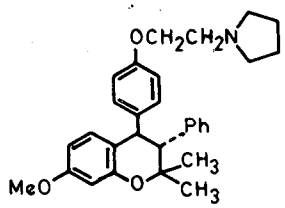


15 (CG)

However, the compound has not been developed further because of its poor activity against influenza and the treatment becomes complicated by the rapidity with which this virus mutates.

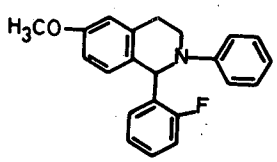
Antifertility

Centchroman (**16**)—It is a strong non-steroidal anti-estrogenic anti-implantation agent[11]. It is in Phase II clinical trials. In a recent clinical study, it has been found to be effective at a weekly dose of 15 mg.

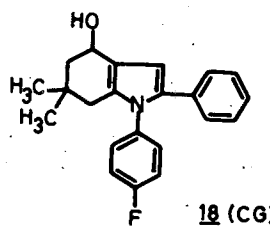


16 (CDRI)

Go. 5380 (**17**) *and Go.* 6924 (**18**)—These preparations are also potent inhibitors of implantation in rats[12]. Compound **17** is found to be teratogenic in rats but **18** is safe. Both are weak estrogens and antiestrogens. These have not been developed for the clinic, since the mechanism of action is considered to be unsuitable for use in humans.

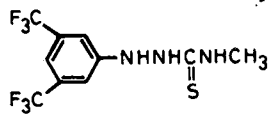


17 (CG)



18 (CG)

Go. 2696 (**19**)—It is a thiosemicarbazide and has potent anti-implantation activity in rats. The mechanism of action is nonhormonal and depends upon its antiestrogenic properties, thus rendering it novel for this parameter; however, its teratogenic potential in rats precluded development for the clinic[12].



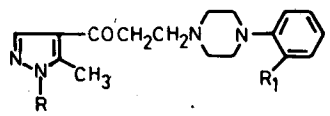
19 (CG)

Aristolic acid—It is a phenanthrene carboxylic acid, found to be an abortifacient[13]. Gossypol[14], a binaphthyl and the toxic principle of the cottonseed oil, has been found in China to be a potent spermatocidal agent. It has anti-fertility activity in rats and hamsters[14].

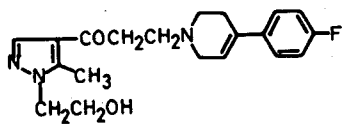
Cardiovascular System

Antihypertensives

Go. 1002 (**20**)[15], *Go.* 1507 (**21**) *and Go.* 4416 (**22**)[16]—These pyrazole derivatives are potent antihypertensives in rats. Their hypotensive properties are essentially due to marked peripheral vasodilatation. Clinical trials reveal that they are either insufficiently active or unable to control hypertension properly.

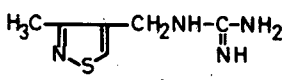


20: R, Ph; R_1, Me (CG)
21: R, CH_2CH_2OH; R_1, OMe (CG)



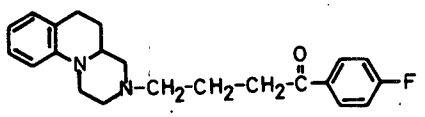
22 (CG)

Go. 8345 (**23**)—It is a guanidine derivative and a potent antihypertensive agent in rats[17]. Selective depletion of cardiac catecholamine levels by the preparation in the laboratory led to the hope that it may be of particular use in the clinic for angina. The hopes were, however, not realized.



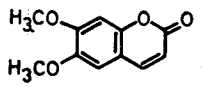
23 (CG)

Centpyraquin (**24**)—It is a potent antihypertensive agent with concomitant neuroleptic activity[18]. No clinical results for this compound have been reported so far.



24 (CDRI)

Scoparone (**25**)—It exhibits marked hypotensive and tranquillizing actions in experimental animals[19]. Clinical trials have, however, not given encouraging results.



25 (RRL, J)

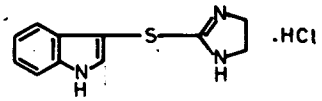
HT 725 (*Hoe*)—It is a peripheral vasodilator and antihypertensive and a potent cyclic AMP phosphodiesterase inhibitor and also an inhibitor of platelet aggregation. It is awaiting Phase I clinical trials in India.

Reserpine—The alkaloid reserpine from *Rauvolfia serpentina* may be mentioned in passing in this section. Although the isolation of the alkaloid in pure form is to be credited to Swiss workers, clinical reports of the efficacy of the plant in the treatment of hypertension emanated from Prof. Vakil in India. The medicinal properties of this plant have, of course, been known in this country for centuries.

Hayatin (*dl-bebeerine*)—It has been isolated from *Cissampelos pareira* at CDRI. It is identical with tubocurarine and has good ganglion blocking effects.

Vasoconstrictors

Go. 7996*B* (**26**)—It has been found to be a potent vasoconstrictor[20] and after having undergone successful clinical trials for nasal decongestion is awaiting registration. The base is known as 'tinazoline' generically. Varsyl® will be the registered name of the formulation in India.



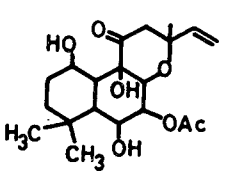
26 (CG)

Positive Ionotropic Agents

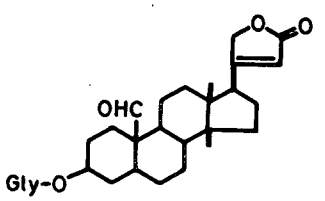
*Forskolin** (**27**)[21]—It has been isolated from *Coleus forskohlii*. It is a positive ionotropic agent with antihypertensive properties. It also acts as an activator of adenylate cyclase. It could be a potential substitute for digitalis and is scheduled to enter Phase I clinical trials. Peruvoside (**28**), isolated in India, has been developed into a cardiac glycoside[21a] and is sold as a drug in Germany.

*According to published reports, Colenol, isolated by CDRI from the same plant, differs from Forskolin in the stereochemistry of the acetoxyl group.

Asclepin, 3'-O-acetylcalotropin (CDRI), shows excellent cardiotonic activity and is undergoing preclinical toxicity studies[21b].



27 (Hoe, CDRI)



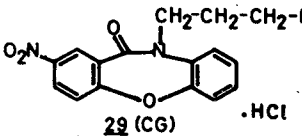
28 (Andhra University)

Central Nervous System

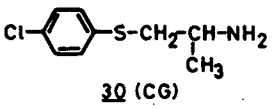
Antidepressants (Thymoleptics)

Go. 2330 (**29**) (*Nitroxazepine hydrochloride*)—It is registered as an antidepressant (Sintamil ®). It reverses reserpine and tetrabenazine induced depression and potentiates DOPA and amphetamine induced effects. It is a potent inhibitor of norepinephrine and 5-hydroxytryptamine uptake at the neuronal cell membrane. It antagonises mescaline induced stimulation and shows anti-aggressive and sedative properties in different systems in many animal species. It is much less anticholinergic than imipramine and is clinically a safe, efficacious and well-tolerated antidepressant. Extensive chemical, biological, metabolic, toxicological and clinical work has been published on this preparation[22].

Go. 2998 (**30**)—It is a novel nontricyclic and potent antidepressant[10], on which extensive preclinical and considerable clinical work has been carried out. It is found to be efficacious in clinical trials.

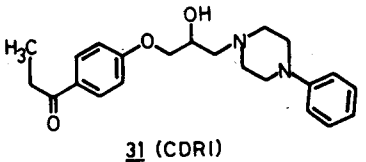


29 (CG)



30 (CG)

Centpropazine (**31**)—It is a potent antidepressant[23] and is undergoing clinical trials at present. Initial results are quite encouraging.

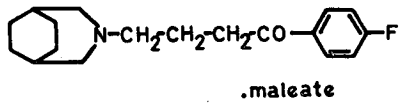


31 (CDRI)

Major Tranquillizers (Neuroleptics)

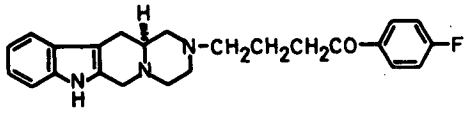
Go. 3315*A* (**32**) (*Nonaperone maleate*)—It is the active ingredient of Taomex ® and is a potent CNS depressant in animals[24] although it is weaker than haloperidol. The preparation is antipsychotic in schizophrenics at doses which do not elicit extrapyramidal side effects[24]. This confers a distinct advantage to it over other currently available

butyrophenones. Go. 3315A, which has recently obtained registration, has also anxiolytic properties at lower doses.



32 (CG)

Centbutindole (**33**)—It is a potent neuroleptic[25] and is undergoing detailed clinical studies.

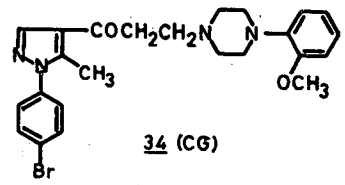


33 (CDRI)

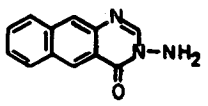
Tranquillosedative Activity

Go. 1076 (**34**)—It has been recognized as a potent tranquillizer in experimental animals[26]. Clinical trials, however, could not confirm its activity in humans.

Centazolone (**35**)—The tranquillosedative activity of **35** is comparable to that of chlordiazepoxide. It is undergoing extensive clinical trials in India and appears to be promising[27].



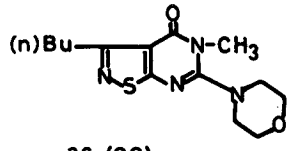
34 (CG)



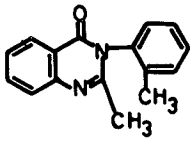
35 (CDRI)

Hypnotic Activity

Go. 6050 (**36**)—It was found to be a potent hypnotic in animal models[28], but has been abandoned in the clinic due to unsatisfactory performance. Methaqualone (**37**), a well-known hypnotic agent, was originally synthesized at RRL, Hyderabad. Sarabhai Research Centre's work shows that quinazolones still offer leads in this area[5].



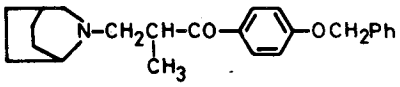
36 (CG)



37 (RRL, H)

Analgesic - Antitussive Activity

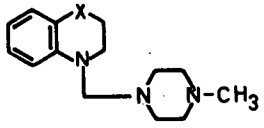
Go. 3572 (**38**)—This compound, with good analgesic-antitussive action, has been taken to the clinical stage, but unsatisfactory performance in humans has discouraged further development[29].



38 (CG)

Antihistaminic Activity

The group of compounds represented by the general formula **39** has offered interesting leads[5]. IDPL, Hyderabad is reported to have potent antihistaminics in animal experimentation[6].

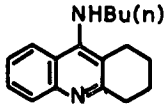


X = CH_2, O, S

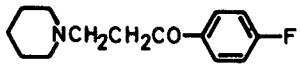
39 (Sar)

Local Anaesthetics

Centbucridine (**40**)—It is a local anaesthetic[30] and has been found to be very effective in the clinic. The compound is in Phase III clinical trials[31]. Similarly, **41** has been found to possess muscle relaxant properties[32].



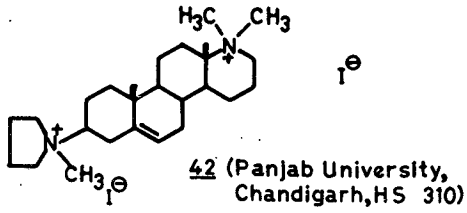
40 (CDRI)



41 (CDRI)

Neuromuscular Blocking Agent

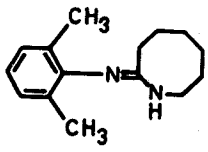
Chandonium iodide (**42**)—At the Department of Pharmaceutical Sciences, Panjab University, some azasteroids, in which one or two quaternary nitrogen groups are incorporated into the steroid nucleus, are being developed. So far, chandonium iodide (**42**) appears to be the most potent member of this series. It is a powerful non-depolarizing neuromuscular blocking agent and is undergoing toxicity trials[33]. A related compound HS-342 is also active[34].



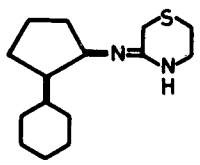
42 (Panjab University, Chandigarh, HS 310)

Antidiabetic Activity

Go. 8284 (**43**), *Go.* 11,111 (**44**)—Apart from the sulphonylureas and biguanides which are useful in the treatment of insulin dependent and independent diabetics respectively, there has been no breakthrough in this field at the international level. Two amidines, Go. 8284 (**43**) and Go. 11,111 (**44**), are unique in that they are highly active in both normal and diabetic rats[35]. However, chronic toxicity studies reveal an insufficient margin of safety precluding clinical trials. An amidino formamidine with an interesting biological profile is awaiting clinical trials.

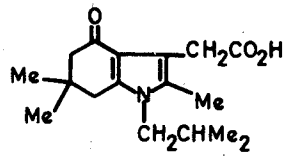


43 (CG)



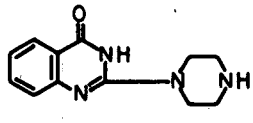
44 (CG)

Go. 9001 (**45**)—This formulation has shown promise not only because of its activity in both normal and diabetic rats, but also because, unlike indole-3-acetic acid and 5-methoxyindole-2-carboxylic acid, it does not inhibit gluconeogenesis. Extensive work on this group of compounds has failed to uncover a congener potent enough for development for clinical trials[36].



45 (CG)

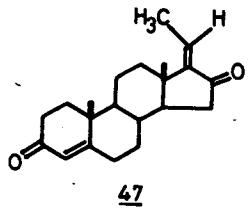
Centpiperalone (**46**)—It is a hypoglycaemic quinazolone derivative undergoing detailed clinical trials[37].



46 (CDRI)

Antihyperlipaemic Activity

Guggulipid (CDRI)—This composition from *Commiphora mukul*, mainly a mixture of sterols, has been found to be potent in this parameter. It is currently undergoing advanced clinical trials with favourable results. Chemical analysis has led to the isolation and structure elucidation of an interesting group of diterpenes. Compound **47** is one of the components of guggulipid[38]. Since none of the pure components offers advantages over the mixture, the latter continues to be developed in the clinic.

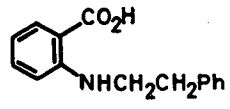


47

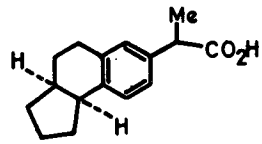
IDPL, Hyderabad has a few nitrogen heterocycles as leads in this area[6].

Anti-inflammatory Activity

Tromaril (**48**)—It is a potent anti-inflammatory, mild analgesic and antipyretic drug[39]. It offers some advantages over known anti-arthritic drugs and is a good example of a collaborative study between a national laboratory and industry.



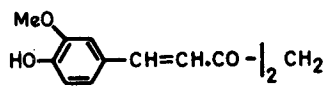
48 (RRL,H)



49 (Sar)

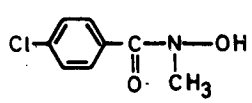
A complex α-phenylpropionic acid (**49**) is under development for the clinic[5].

Curcumin (**50**)—This compound, a constituent of *Curcuma longa* (turmeric), is known to possess local as well as systemic anti-inflammatory property. The anti-inflammatory activity of curcumin compares favourably with those of established agents[40].



50 (CDRI)

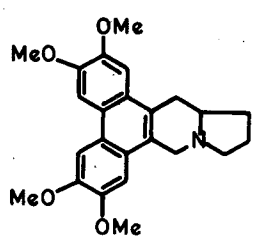
Go. 2624 (**51**)—This compound, a hydroxamic acid derivative, is very active in the turpentine pleurisy test in mice, a model for acute inflammation. However, activity in the chronic carrageenin oedema test does not justify further development[41]. IDPL, Hyderabad, has a few encouraging leads for this indication[6].



51 (CG)

Antiallergic Activity

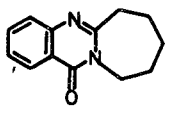
Tylophorine (**52**)—This compound, a phenanthraquinolizidine alkaloid of *Tylophora asthmatica*[42], has been claimed to be responsible for the antiasthmatic activity[43] of the leaves, on the basis of clinical trials conducted by Vallabhbhai Patel Chest



52

Institute, Delhi. The isomeric phenanthraindolizidine alkaloid, tylocrebrine, is known to have antitumour activity.

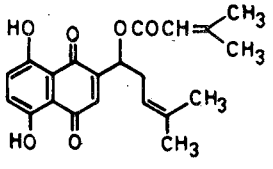
RLX (**53**)—This compound, an analogue of vasicinone, has been found to possess bronchodilatory activity. It is undergoing Phase I clinical trials[44]. Vasicine itself has abortifacient activity.



53 (RRL, J)

Antitumour Activity

Arnebin (**54**)—The compound, obtained from *Arnebia nobilis*, is reported to have good anticancer activity[45].

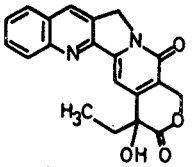


54 (CDRI)

Camptothecin (**55**)—This compound, isolated in USA, was a hot lead for some years in this field. The exceedingly minute quantities available from the only source available at that time, *Camptotheca acuminata*, rendered large scale clinical trials very difficult. Two groups of workers[46,47] have independently discovered a very rich source in a common tree, *Mappea foetida*. Subsequent exploitation, however, has been abandoned, since clinical findings on camptothecin are not encouraging.

The abundantly available Indian plant *Vinca rosea* is a source of two well-known anticancer alkaloids—vincristine and vincaleucoblastine.

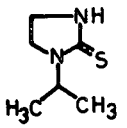
Magnesidin (*Hoe*)—It is a magnesium-containing antibiotic, isolated from marine natural sources. The potential of magnesidin or one of its analogues as an antitumour agent is under investigation[48].



55 (CDRI, CG)

Antithyroid Activity

Centimazole (**56**)—It is a potent goitrogen[49] and is available for this indication.



56 (CDRI)

Hepatoprotectives

*Picrorhiza kurroa**—It has been shown to have liver protective activity in animals[50] and beneficial effects in the treatment of human jaundice[51]. Picrosides I, II and III are constituents of this plant[52].

Summary

The two decades of medicinal chemistry research in India have been quite fruitful. Although spectacular breakthroughs like the β-blockers (propranolol, oxprenolol), the antiulcer agents (cimetidine) or antiallergics (sodium chromoglycate) have admittedly not resulted, the discovery of some drugs like Sintamil, Tromaril, Taomex and Centimazole and of several new chemical entities awaiting registration signifies that pessimism is unwarranted. Considering that such research is relatively young in this country and that the manpower and resources devoted to it are meagre compared to the global effort, the performance can be viewed with satisfaction.

Acknowledgement

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*For fairly exhaustive surveys of the chemistry of some biologically active Indian medicinal plants, *see* ref. 53 and 54.

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