Recent Developments in the Treatment of Infectious Diseases*

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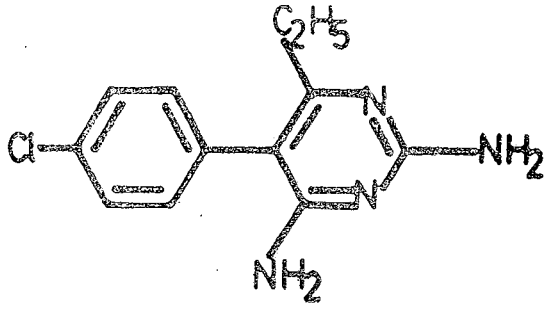
INTRODUCTION:

The developing countries have been facing major health hazards due to the prevalence of infectious diseases of various kinds. Poor standards of living and poorer standards of sanitation and personal and community hygiene have contributed in no small measure to the morbidity and mortality induced by such diseases with their attendant economic toll. The World Health Organization has identified 6 major tropical diseases (1) based upon their endemicity, lethality and inadequate availability of proper treatment. These are : Filariasis, Leishmaniasis, Leprosy, Malaria, Schistosomiasis and Trypanosomiasis. The first four diseases are prevalent in the country and will be taken up for discussion in this article. In addition, other diseases like helminthiasis, amoebiasis and infections due to bacteria, tuberculosis, fungi and viruses which also afflict the country's population to a large extent will be discussed. It must be mentioned at the outset that giant strides have been taken in the last decades in controlling if not conquering them. This has been possible due to several developments in the approaches to the design of drugs based upon (i) understanding the biochemistry of the organisms and disease pathology at the cellular, molecular and gene level; (ii) use of quantiative structure-activity relationships and molecular modelling; (iii) isolation of body's own defence mechanisms and their production by genetic engineering; (iv) elaboration of immunodiagnostics and vaccines by monoclonal antibody and recombinant DNA techniques; and (v) newer drug delivery systems.

MALARIA :

Malaria is endemic in more than 100 countries in Africa, Asia and Central and South America and in its socio economic impact is the most important of the transmissible parasitic diseases (2). It is estimated that over 90 million cases occur each year throughout the world with India accounting for a substantial percentage. Common forms of malaria are due to Plasmodium facliparum, P.vivax, P.ovale and P.malariae, all having mosquito as the vector. Hopes of eradicating or controlling malaria by use of insecticidal sprays have been abandoned due to mosquitos developing resistance, Biological controls using antilarval parasites such as Bacillus thuringiensis H 14 and B. sphaericus or larvivorous fish such as Gambusia and destruction of mosquito breeding sites by land drainage schemes have limited potential.

4-Aminoquinolines (chloroquine and amodiaquine) and the related amino alcohol, quinine have good blood schizontocidal properties, destroying the asexual blood forms but are not active against the intrahepatic forms. The parasites have already become resistant to the first two, and ominous signs portend that the third may also succumb. The same has been the fate of the antimetabolite synergistic combination, Fansidar of pyrimethamine 1 and sulphadoxine 2. (dl)-Mefloquine 3, a quinolyl alcohol is a good blood schizontozide for which resistance has been as yet unreported and is administered in combination with 1 and 2, but only in emergencies with a high prevalence of multidrug resistance. 3 exerts its action by inhibition of parasitic RNA and DNA synthesis. A phenanthryl methanol, halofantrine 4, with blood schizontocidal activity has been recently approved for the treatment of multidrug resistant malaria.



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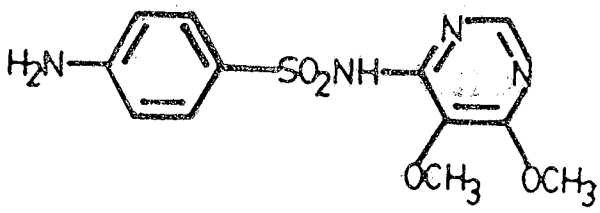
* Contribution No. 9 from Searle R & D Centre.



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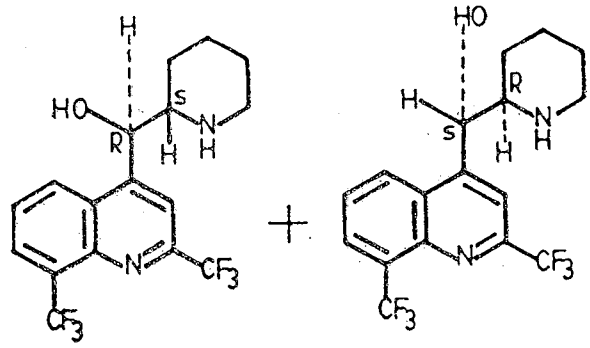

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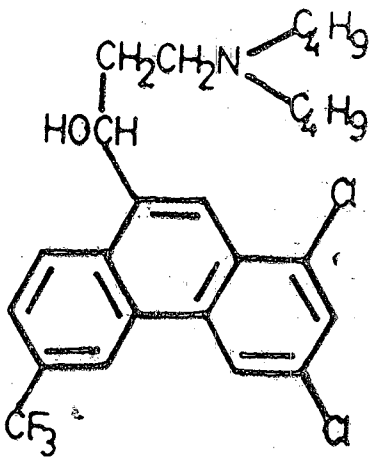

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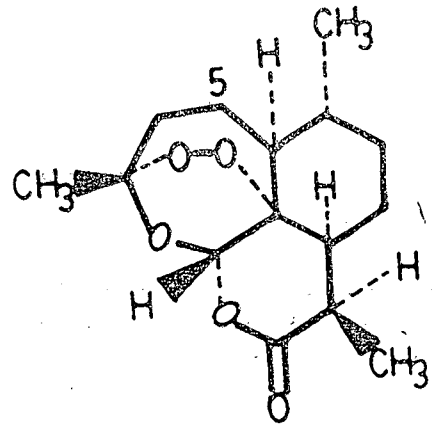
Artemisinin 5 (Qinghaosu), an unusual trioxane, occuring in a traditional Chinese herb, and its dihydro derivative 6 are also blood schizontozides, with a novel mechanism of action. The drugs affect the parasite plasma membrane first and then the nucleus. This is not the result of peroxidation of lipids. The primary mode of action may be inhibition of parasite protein synthesis. For galenical purposes, ethers of 6 such as 7 (3) or sodium artesunate 8 (4) are being developed clinically. These are expected to have important potential in the treatment of severe and complicated malaria.



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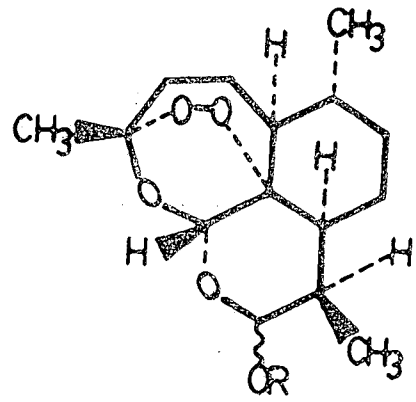
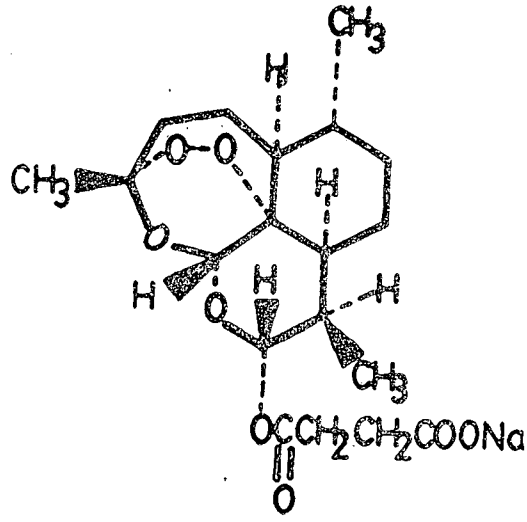


6 R=H

7 R=Alkyl



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Antimetabolites like proguanil, chlorproguanil and cycloguanil as well as the tetracyclines are active against both the erythrocitic and intra hepatic forms of P.falciparum, but not against other malarial parasites whereas primaquine is active against the intra hepatic forms of the latter parasites.

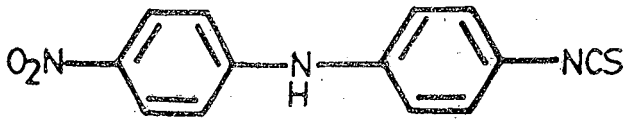
Chemoprophylaxis against malaria is unsatisfactory and depends upon chloroquine, proguanil, chlorproguanil, mefloquine and doxycyline.

Vigorous efforts are being deployed to develop immunodiagnostics and vaccines for malaria but no outstanding successes have been reported.

FILARIASIS :

This infestation comprises several diseases, mostly caused by filarial worms and transmitted by bloodsucking flies. (1) Lymphatic filariasis affects about 90 million people in Asia, Africa and South America and additionally 905 million are directly exposed to the risk of infection. The disease group is caused by the parasites Wucheria bancrofti and Brugia malayi and causes considerable disability and disfigurement and chronic lesions like elephantiasis and hydrocoele. Onchocerciasis or river blindness caused by Onchocerca volvulus is more deadly. It affects 40 million people mainly in tropical Africa but also in Central and South America and causes severe itching leading ultimately to blindness.

Lymphatic filariasis can be relatively safely and effectively treated with diethyl carbamazine (DEC). The drug is mainly microfilaricidal but in large doses also kills adult worms. Amoscanate, **9**, an aryl-isothiocyanate is an indigenously developed drug, with good activity against macrofilaria in experimental animals (5), but is not tolerated well by humans. Two benzothiazole isothiocyanate derivatives, **10**, (CGI 16343, developed in India) and **11** (CGP 20376) have good filaricidal properties and are currently in clinical trials in India.



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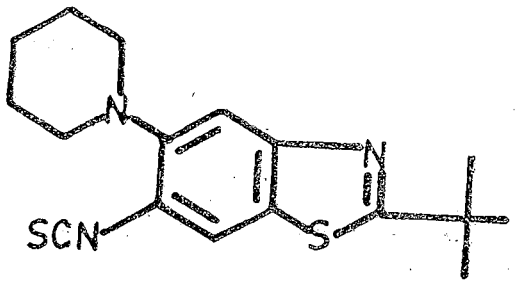

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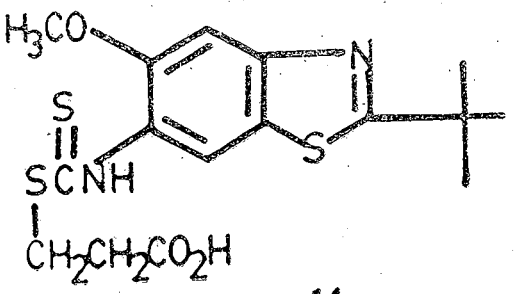

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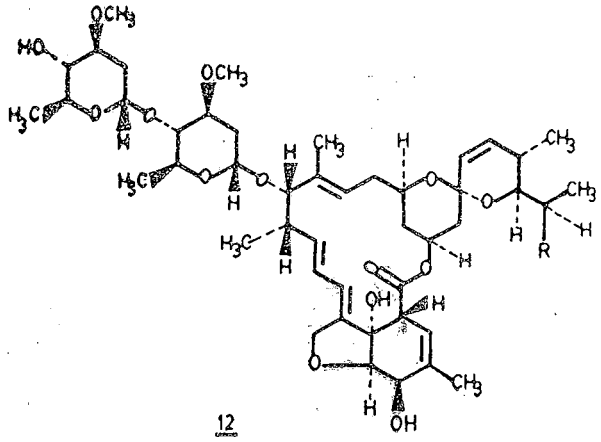
Treatment of onchocerciasis is less satisfactory. DEC kills the microfilaria of the parasite involved but causes intense undesirable side reactions. Suramin, a naphthalene sulphonic acid derivative, kills the adult worms but is exceedingly toxic. However, ivermectin **12**, a semisynthetic ionophore antibiotic of avermectin family has been a breakthrough in the treatment of onchocerciasis. This antibiotic is also a wonder drug for the treatment of exo and endo parasites in sheep, cattle and horses and exerts its activity in micrograms. Interestingly, the manufacturers have offered the drug free to the African patients. A derivative, CGI 6140 **13**, of amoscanate **9** has promising filaricidal activity and is undergoing clinical trials in Africa. Benzimidazole carbamates like mebendazole **(vide infra)** and flubendazole have parenteral activity against lymphatic filariasis and onchocerciasis.



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Attempts to have immuodiagnostics and prophylactic vaccines for filariasis have not yet resulted in commercial products.

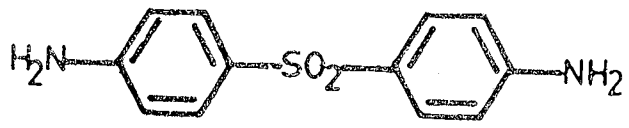
LEISHMANIASIS :

These are diseases caused by infection with the flagellatte protozoan parasite Leishmania donovani transmitted by the vector, sandfly. The diseases occur in three forms — the mucocutaneous form found mainly in South America, while the visceral and cutaneous forms are prevalent in the Indian subcontinent and several parts of Africa and South America. In visceral leishmaniasis, the parasite mounts an invasion of internal organs such as spleen and liver; the resulting kala-azar is lethal. Earlier spraying of DDT to control the malarial vector, mosquito, suppressed the propagation of sand flies, resulting in the checking of leishmaniasis. However, this effect wore out in course of time resulting in the recrudescenc of the disease in India. Thus in 1977, in Bihar over 100,000 people were affected. Unfortunately, there are no proper drugs to treat leishmaniasis; pentavalent antimonials like urea stibamine and stiboglucamine as well as bis-amidines like pentamidine involve painful parenteral application and cause severe toxic side effects (1). Pyrazolopyrimidine nucleosides like allopurinol are currently useful leads for developing the much needed newer drugs for this indication.

LEPROSY :

About 1.4 billion people or nearly a third of the world's population live in leprosy-endemic areas mostly in Africa and Asia, the figure 10.6 million representing the number of leprosy patients. India harbours a large percentage of this population. About a third face the threat of permanent, progressive physical debility often with the attendant threat of social rejection. (1).

The more well-known drugs for the treatment of leprosy are dapsone **14**, clofazimine **15** and rifampicin **16**. **14** is a folate antagonist, the activity of **15** has been related to the p-quiononimine system. Rifampicin **16** inhibits DNA directed RNA polymerase resulting in the inhibition of RNA. Earlier monotherapy demonstrated rapid development of resistance of the causative bacterium, Mycobacterium leprae to **14**, less with **16**, but rarely with **15**. Currently used multitherapy seems to give satisfactory results. Trials of antibacterial quinolones (vide infra) in the mouse foot pad test show that at least one quinolone derivative is active against M. leprae. Some β-lactam antibiotics and aminologycosides are also active.



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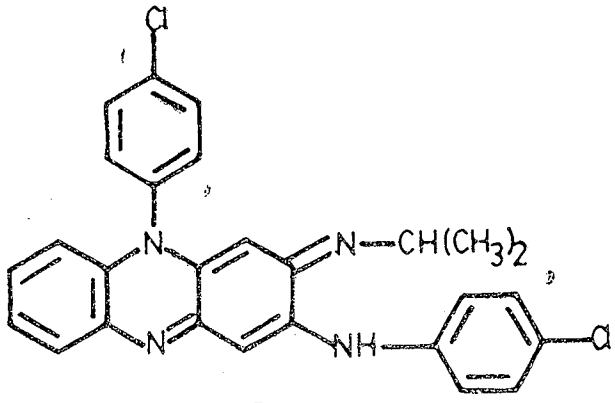

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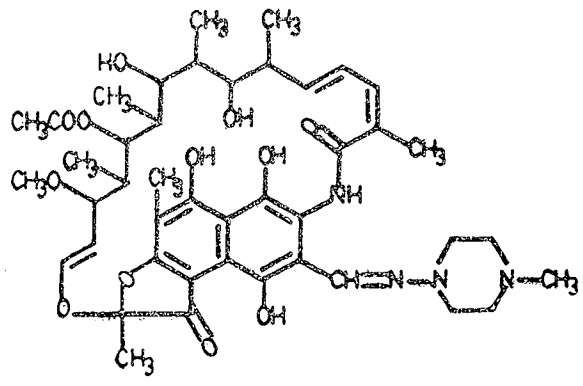

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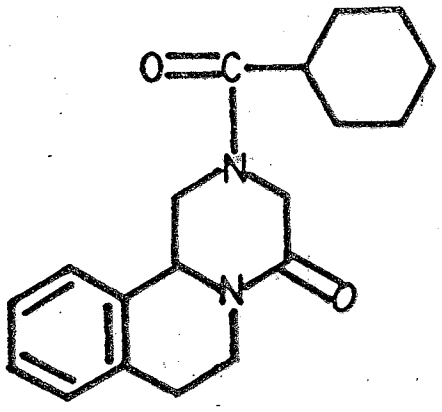
M. leprae specific monoclonal antibodies are now available and are being used to develop immunodiagnostics for leprosy. A few vaccines are also under clinical trials. (1).

GASTRO-INTESTINAL HELMINTHS :

Some of the common parasites that infest men are tapeworms, roundworms, hookworms,

pin worms and whipworms. Over 1 billion of the world's population is estimated to harbour roundworms; the book worms are more deadly in that they colonise the intestinal wall and suck blood continuously. The total daily **blood** consumption of these worms which parasitize at least 800 million humans is equivalent to the total exsanguination of 2 million people! (6).

For the treatment of tapeworm infections apart from niclosamide, a chlorosalicylanilide derivative, must be mentioned, a newer drug praziquantel **17** which is effective at a single dose. **17** is more known for its activity against all the three forms of schistosomiasis, viz. S. mansoni, S. haematobium and S. japanicum. Schistosomiasis is one of the 6 major tropical diseases and afflicts Africans and South Americans but is not endemic to India. Amoscanate **9** is also active against the three species while oxaminiquine **18**, a nitroquinoline derivative is a schistosomicide but only for infections due to S. mansoni.



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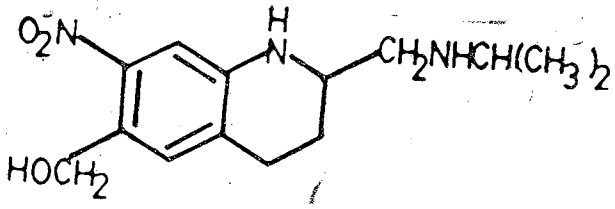

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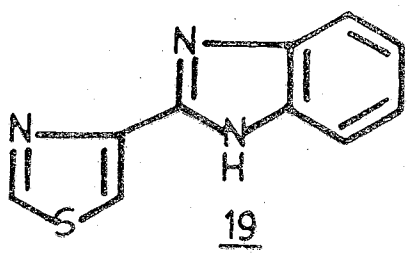
The benzimidazole, thiabendazole **19**, represented the first truly broadspectrum intestinal nematodicide, useful for the eradication of most intestinal nematodes with the possible exception of the whipworms. It appears to inhibit the fumarate reductase system of susceptible parasites. Benzimidazole-2-carbamates, represented by mebendazole **20**, are clear improvements over **19** and offer really effective treatment. The mechanism of action of **20** may be related to its parasitetubulin binding properties. Albendazole **(21)** and fenbendazole **(22)** are other popular carbamates, while the thiazolyl analogue, CGI 13866 **(23)** is a drug of indigenous development in clinical trials. Benzimidazole-2-carbamate itself is a plant antifungal agent.



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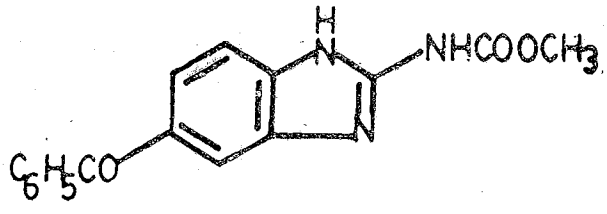

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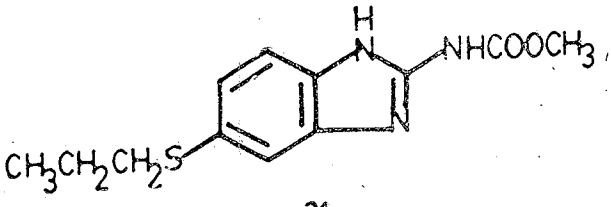

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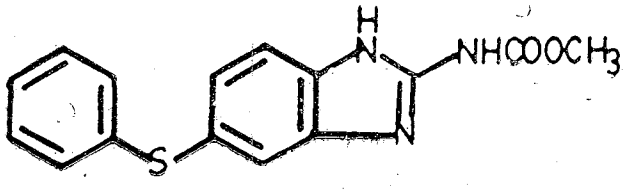

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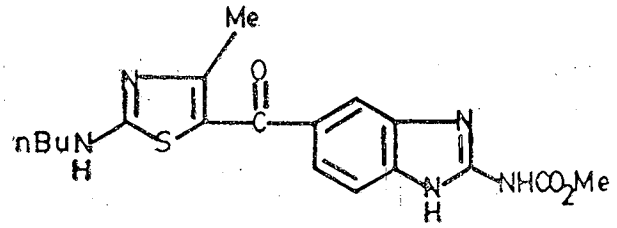

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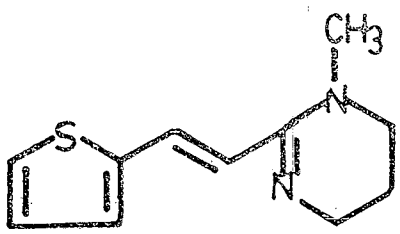
Other modern drugs with broad spectrum anthelmintic activity are the thienyl vinyl pyrimidine, pyrantel 24 and the imidazothiazole, tetramisole 25 in the racemic form; (the laevo rotary isomer, laevamisole is also active). The former is a parasite-neuromuscular depolarizing agent, while the latter is a fumarate reductase inhibitor. Incidentally, 25 has antidepressant, antiinflammatory and nonspecific immunostimulatory properties also! Amoscanate 9 was also developed and registered as an anthelmintic agent in India (5,7).



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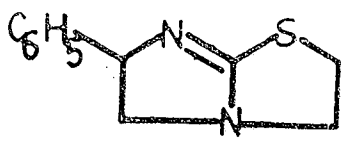

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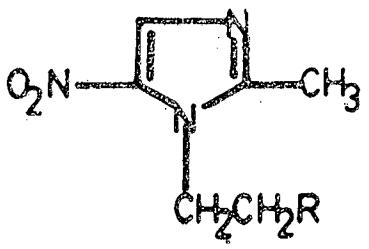
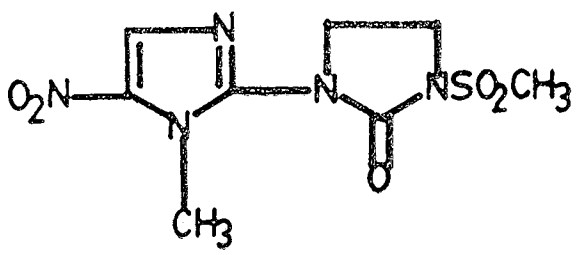
AMOEBIASIS :

Amoebiasis, a protozoal infection caused by Entamoeba histolytica is said to affect 10% of the world population with a high prevalence late in the tropics upto 100%. The main sites of infection are the intestine and to a lesser extent, the liver. (8) Current drugs of choice belong to the metronidazole group (9) represented by the wellknown metronidazole 26 and the sulphone, tinidazole 27 which are available in India. Satranidazole 28, developed locally and registered in India is a more potent amoebicide (10) but is unlikely to be marketed. The nitroimidazoles are particularly useful for the treatment of hepatic amoebiasis, but they have a wide spectrum of antimicrobial properties — activity against trichomonas, giardia, anaerobic bacteria, etc. etc. Satranidazole 28 is more potent than 26, in many of these indications esp. against anaerobes. (11) Metronidazole is selectively toxic to anaerobes and protozoa because it can accept electrons at the level of pyruvate metabolism at potentials which are incapable of being generated in aerobic cells. A transient nitro radical anion is formed which damages the parasite DNA by helix destabilization and strand breakage. (8)



26 R=OH

27 R=SO_2Et



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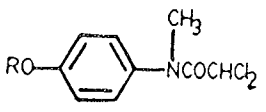
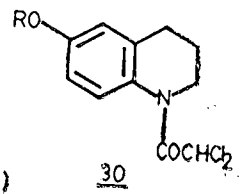
Dichloroacetanilides like diloxanide furoate 29 are particularly effective against lumen-dwelling amoeba. Juinfamide 30 is reported to be more potent (8). Inhibition of protein synthesis in the parasite by 29 may be the cause for its lethality. (8)



29 (R=2-Furoyl)



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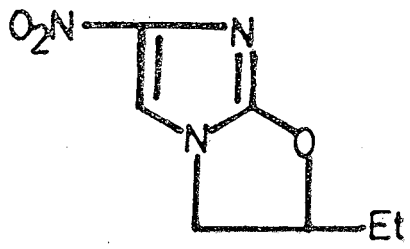
TUBERCULOSIS :

Rifampicin **16** has without doubt revolutionised the theapy of tuberculosis, helping in avoiding hospitalisation and promoting ambulatory treatment. As in the case of leprosy, multiple therapy is necessary to avoid development of resistance. A recommended combination is of **16** with isoniazide and ethambutol. Streptomycin, thiacetazone, thionamide and pyrazinamide are also in use (12). Uniquely among nitroimidazoles, the imidazooxazole derivative **31** has **in vivo** antitubercular activity in mouse experiments. (13)



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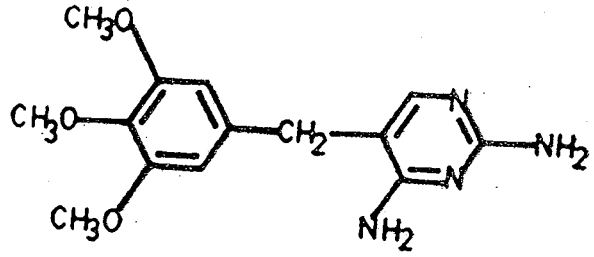
The quinolone antibacterials. esp. norfloxacin **(vide infra)** have clinically demonstrated antitubercular acitvity.

BACTERIAL INFECTIONS :

Not being confined to tropical countries, this area continues to see important developments. The sulpha synergistic combination cotrimoxazole of trimethoprim **32** and sulphamethoxazole **33** is still very popular in India. Cotrimoxazole exerts its antibacterial action by sequential blockade of bacterial folate synthesis. .



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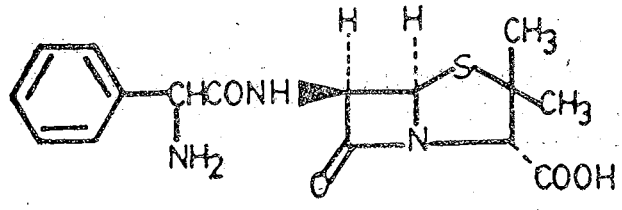
Ampicillin **34** and cephalexin **35** are representative examples of the penicillin and cephalosporin group respectively. Their activity is related to inhibition of bacterial cell wall biosynthesis. Rapid deactivation by the enzyme, beta-lactamase has been a persistent problem in this field. Inhibitors like clavulanic acid **37** and sulbactam are valuable discoveries in this respect. A combination, augmentin comprising amoxicillin **36** and **37** has been a major breakthrough; timentin is a similar combination of **37** with ticaricillin. (14) Current efforts in this field are devoted to discovery of cephalosporin antibiotics which are orally active and have a long half-life and broad spectrum, such as cefixime, cefetram pivoxil and cefpodoxime. The introduction of a formamido or methoxy group at position 7 on the cephalosporin framework imparts β-lactamase resistance to the drug.



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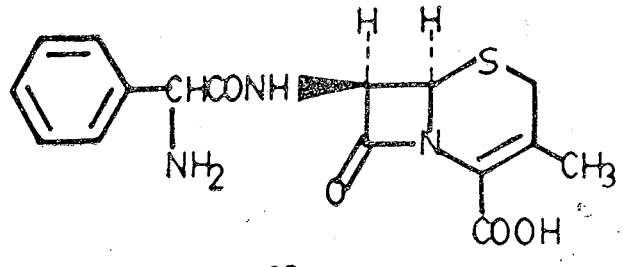

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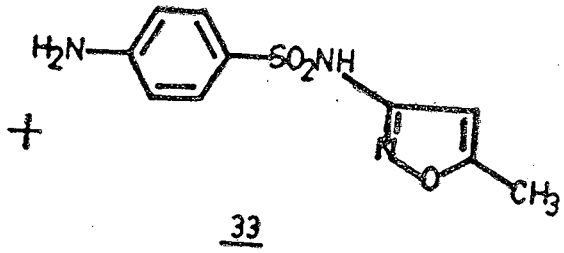

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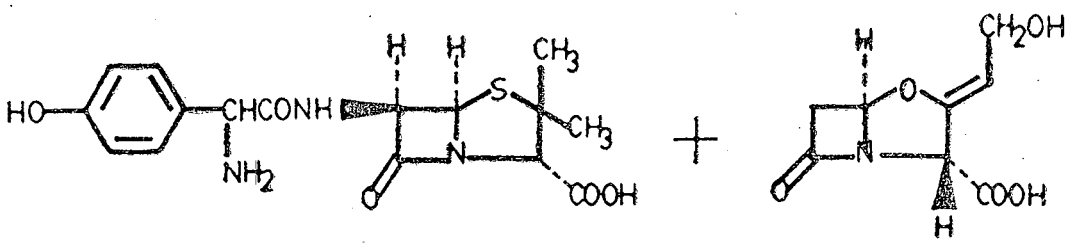
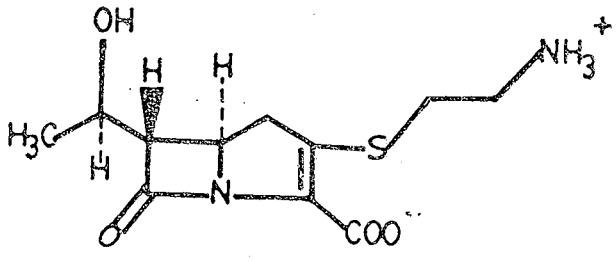


36 37

Thienamycin 38, a carbapenem has an extraordinarily broad spectrum of antibacterial activity, including recalcitrant bacteria like Pseudomonas aeruginasa and anaerobes but is beset with solubility problems. Several other carbapenems and carbacephems are under study. Aztreonam 39, belonging to the monobactam group is remarkable for its imperiviousness to beta-lactamase. (15) However, its activity is mainly only against gram negative bacteria. Nocardicin and tigemonam are other members of this group. The former is active against P. aeruginosa, Proteus species and Neisseria. In vitro it is not active against E. coli, but is so in vivo. Although it interferes with cell-wall synthesis, the mechanism is said to be different from that of penicillin.



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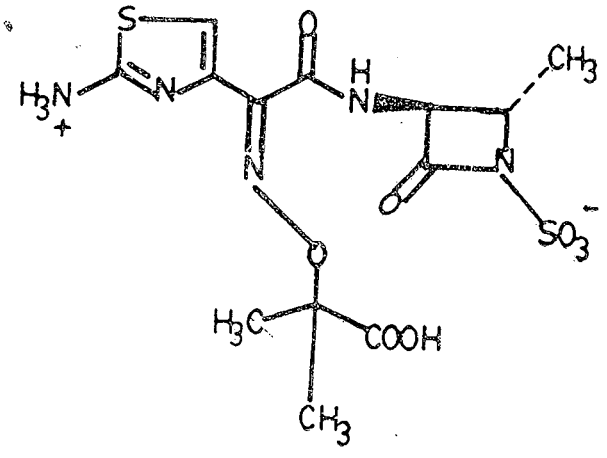
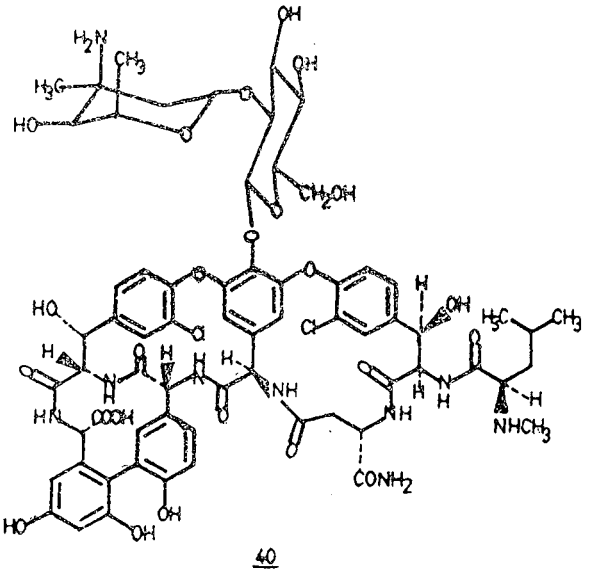


39

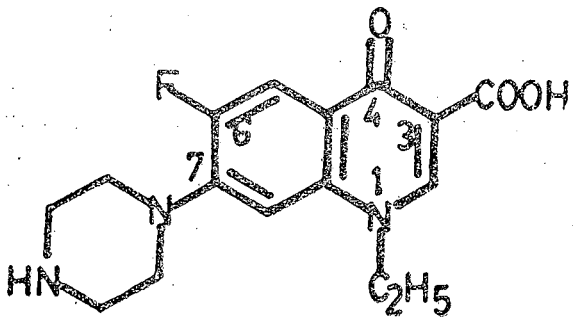
Vancomycin 40 is a glycopeptide antibiotic with marked activity against gram positive bacteria. Its combination with gentamycin or streptomycin is synergistic. Its use is reserved for life-threatening situations against resistant bacteria. 40 is also reported to have antitubercular activity. Teicoplanin is another such glycopeptide antibiotic with a longer half life than vancomycin. (16) Daptamycin is the first reported antibacterial lipopeptide.



40

The fluoroquinolone antibacterials (17) represent the most recent and major milestone in antibacterial chemotherapy, having their origin in nalidixic acid. Norfloxacin 41, ciprofloxacin 42 and pefloxacin 43 are some typical members, while ofloxacin is a tricyclic analogue. They have a wide range of activity — all bacterial pathogens of urogenital tract infections, diarrhoeal diseases, gonorrhoea, ophthalmological infections, etc. They are highly active against pseudomonas. Their activity in leprosy and tuberculosis has been noted eaalier. They have a good oral absorption and a long half-life. They are free from the risk of emergence of resistance atleast for the moment. Finally their mode of action is novel — potent and specific blocking of

bacterial DNA gyrase leading to inhibition of synthesis as well as functions of DNA resulting in rapid bacteriolysis. Norfloxacin is already available in the country.



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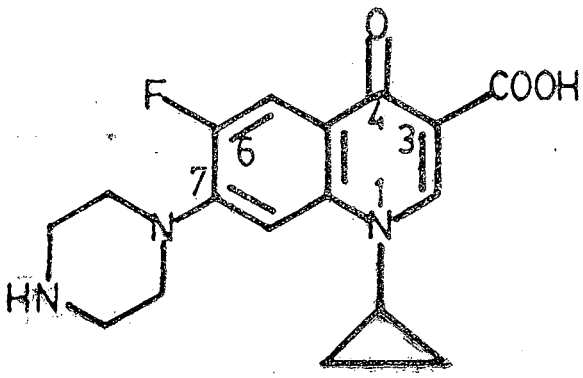

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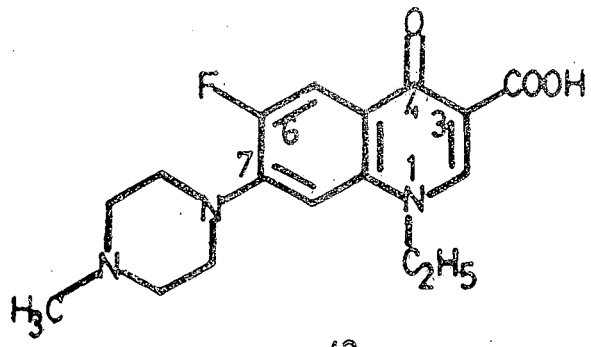
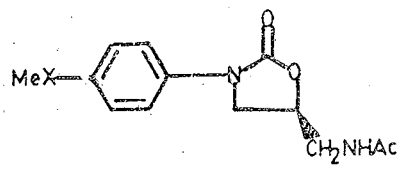


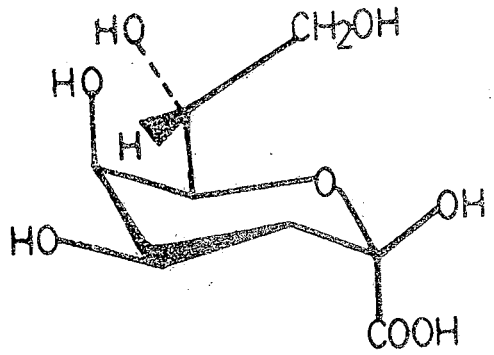
43

Finally in this section may be noted new leads. Oxazolidinones, DuP 721 44 and DuP 105 45 have wide spectrum activity against gram positive and negative bacteria and are highly potent in animal experiments. Activity is exerted by inhibition of protein biosynthesis before initiation of peptide chain formation (18). 3-Deoxy-β-manno-2-octulosonic acid 46 (β -KDO) is a constituent of the lipopolysaccharide of the outer membrane of gram-negative bacteria. Related compounds of the type 47 where R = L-alanyl-NH etc inhibit the enzyme involved and provide a different approach for antibacterial chemotherapy. (19) Bicyclic pyrazolidinones of general structure 48 (?) have been reported to have potent in vivo antibacterial activity. (20)



44 X=CO

45 X=SO



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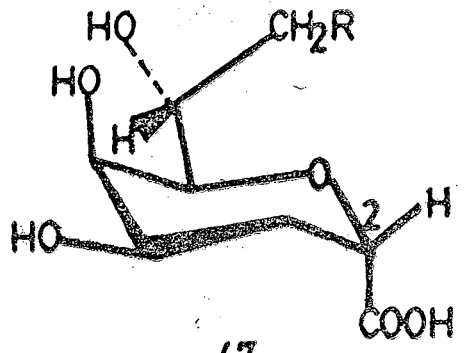

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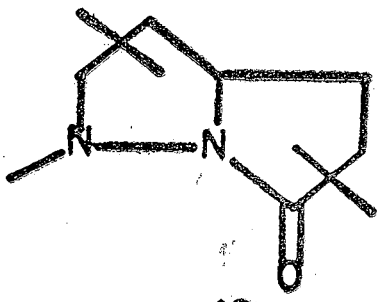

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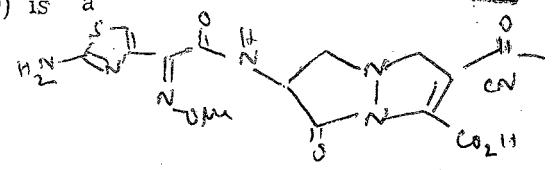

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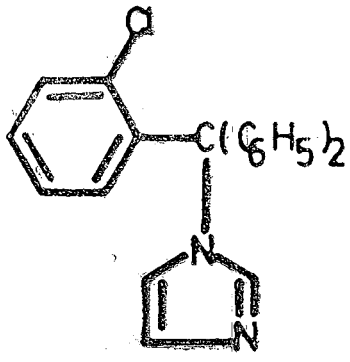
FUNGAL INFECTIONS :

The widespread use of immuosuppressants for the control of cancer and in other situations (eg organ-transplants) has given rise to an upsurge of opportunistic infections like those due to fungi which particularly in the West has assumed alarming, sometime life-threatening proportions (21). Imidazoles mark the beginnings of modern antifungal therapy. The prototype clotrimazole **49,** is used topically for infections due to the common fungus, Candida albicans; this was followed by miconozole **50.** Systematic activity is obtained in more complicated molecules like keticonazole **51.** The activity extends to triazole derivatives like itraconazole and fluconazole and fluconazole as well. Antifungal activity in this class of drugs is elicited primarily through inhibition of steroidogenesis. The newer triazoles offer greater selectivity and affect mammalian enzymes less.



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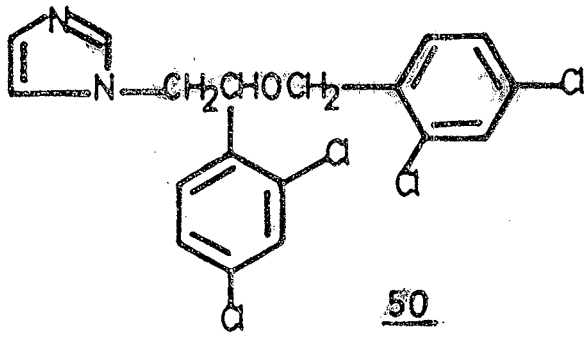

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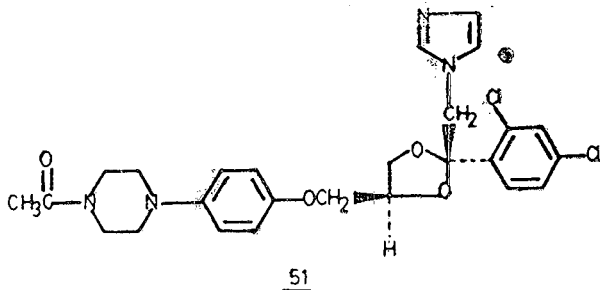
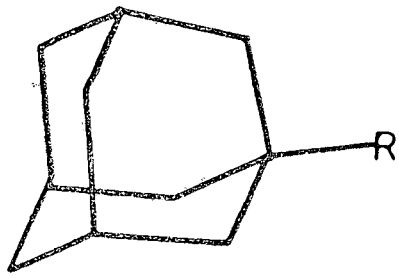


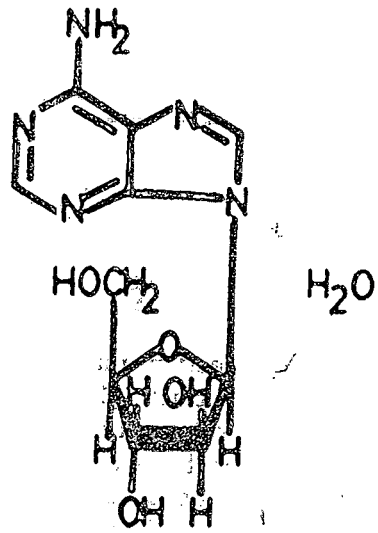
51

Vaccination against the small pox virus has been successful in total global eradication Genetically engineered vaccines using Υ-DNA technology are available for hepatitis. Vaccination against the influenza virus has not been very successful. Synthetic compounds like amantadine **52** and rimantadine **53** have limited applications. Nucleosides like vidarabine **54** and ribavirin **55** are somewhat successful in treating influenza A and B and other RNA, DNA viral infections, while acyclovir **56** represents the currently available drug for the treatment of painful infections due to genital herpes. Retrovir (AZT) **57** a pyrimidine nucleoside has become well-known as the only drug approved at the moment for treating the AIDS causing infection due to the retrovirus HIV. (22) **57** is known to be only a palliative.



52 R = NH_2

53 R = $-CH(NH_2)-CH_3$



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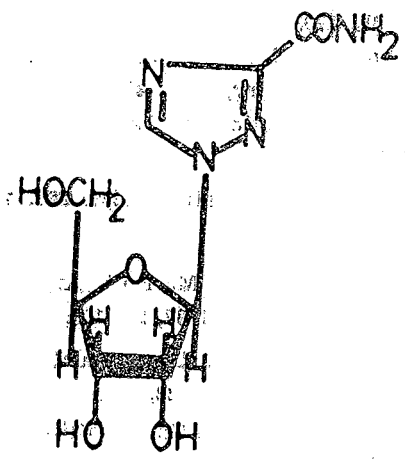

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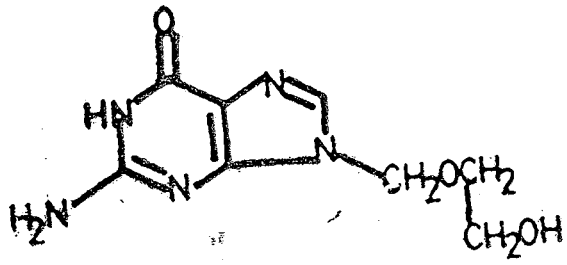

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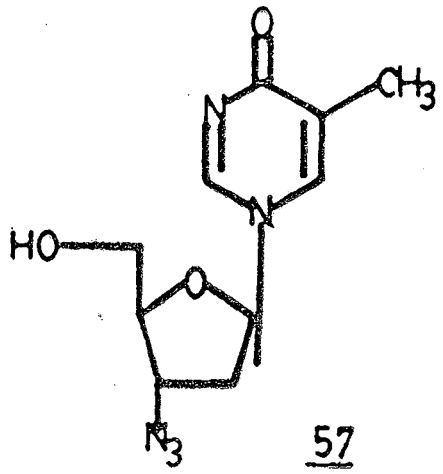

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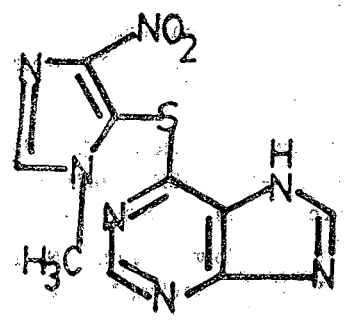
Azathioprine 58, a purine derivative, is used as an immunosuppressant in patients with kidney transplants. The life-saving drug has become available in India through a process developed in our laboratories. The cyclic polypeptide, cyclosporin 54 also has immunosuppressive properties. (23) It was originally isolated in Europe from the fungus Tolypocladium inflatum. An Indian source, Tolypocladium cylindrosporum has been announced. (24)



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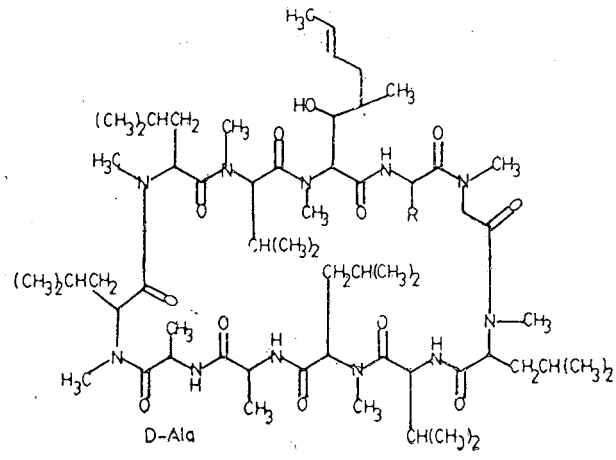

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