Chapter 14. Antiparasitic Agents

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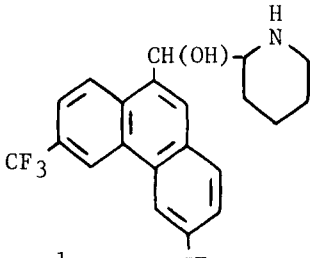
General - Chapters were published on drugs for intestinal parasitism[1] and current treatment of protozoan and helminth parasites.[2]

Malaria - Reviews appeared on antimalarial drugs.[3,4] A screening method was described using owl monkeys bearing human parasites.[5] Further evaluation of phenanthrene methanols showed WR 122,455 (1) to be effective against chloroquine-resistant *Plasmodium berghei* in mice[6] and chloroquine-resistant *Plasmodium falciparum* in man.[7] Activity differences among analogs of (1) were correlated with their conformation.[8] The active conformation of each structure was such that it allowed the formation of a hydrogen bond between the hydroxyl and protonated amine functions.



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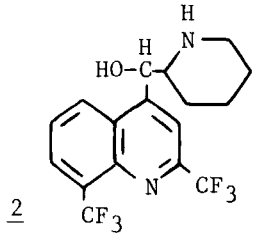

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The DNA binding of quinolinemethanols was studied.[9] Mefloquine (2), a potent antimalarial found clinically effective against chloroquine-resistant *P. falciparum*,[10] bound weakly compared to compounds such as quinacrine, ethidium or daunorubicin. The finding questions the role of DNA binding for the antimalarial activities of quinoline methanolamines. Similar doubts cast previously on the mode of antimalarial action of chloroquine and related compounds have led to the hypothesis[11] that these compounds possess just the right combination of lipid solubility and doubly protonated form to be concentrated into the trophozoite phagosomes of the parasites. As a result, the pH in the phagosomes increases, probably beyond the optimum range for the acid proteases which are responsible for digesting host hemoglobin. The net outcome is an acute amino acid deprivation of the parasites. Quinolinemethanolamines could act *via* a similar mechanism. But their inhibition of haemozoin clumping,[12] which follows exposure of the parasites to chloroquine or its active analogs,[13] suggests that the two classes of compounds do not act in exactly the same way. Primaquine, an 8-aminoquinoline antimalarial drug, was recently re-evaluated in rhesus monkeys.[14] It was found that the *d*-isomer had a therapeutic index at least twice that of the *dl*-isomer due to the much lower toxicity of the former. The finding may represent a separation between toxicity and antimalarial activity.

Smith *et al.*[15] noted that among many compounds tested, L-serine was the only methyl group donor for *Plasmodium knowlesi* in rhesus monkey erythrocytes. The observation agreed with a previous report by Platzer[16] that 10-formyltetrahydrofolate synthetase and 5,10-methylenetetrahydrofolate dehydrogenase were apparently absent in *P. lophurae*, whereas serine hydroxymethyl transferase was present in abundance in the cytosolic fraction of the parasite.[17]

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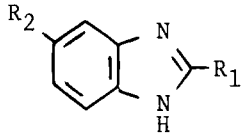
The methyl group from serine was about evenly distributed between methionine and thymidylate in *P. knowlesi*.[18] p-Aminobenzoate, dihydrofolate and tetrahydrofolate stimulated the incorporation, whereas pyrimethamine and 5-fluoroorotic acid inhibited it,[15] as one would expect. It will be interesting to see if specific inhibitors of plasmodial serine hydroxymethyl transferase can be found and if they will demonstrate *in vivo* antimalarial activity.

A quantitative structure-activity relationship of antimalarial activity and bacterial dihydrofolate reductase inhibition by quinazolines and 5-substituted benzyl-2,4-diaminopyrimidines was formulated.[19] Two fermentation products, erythromycin[20] and aplasmomycin,[21] a boron containing ionophore,[22] were active against *P. berghei* in mice.

Helminthiasis - Reviews were published on drugs used in the treatment of helminthiasis,[23,24,25] the control of parasites by drugs,[26] anticestodal and antinematodal drugs[27] and anthelmintics from laboratory animals to the target species.[28]



R_1

3, $-NHCOOCH_3$
4, $-NHCOOCH_3$
5, $-NHCOOCH_3$
6, $-NHCOOCH_3$
7, 
8, $-NHCOOCH_3$

R_2

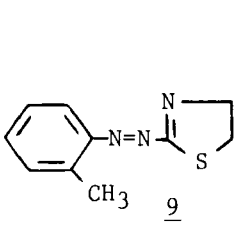
3, $-O-CH_2CH_2CH_3$
4, $-S-C_6H_5$
5, $-S-CH_2CH_2CH_3$
6, $-S-C_6H_5$
7, $-NHCOOCH(CH_3)_2$
8, $-C-C_6H_5$ (O)

Many efficacy studies were reported on the newer benzimidazole anthelmintics, oxibendazole (3), oxfendazole (4), albendazole (5), and fenbendazole (6), in papers presented at an international conference.[29] The compounds were generally effective against most important nematodes of sheep and cattle at oral doses of 2.5 to 10 mg/kg. Other studies further confirmed these observations for oxibendazole,[30] oxfendazole[31,32,33] and albendazole.[34,35,36,37] At higher doses albendazole eliminated adult *Fasciola hepatica* from sheep[38] and *Paragonimus kellicotti* from cats.[39] Cambendazole (7) was shown to be effective against *Dicrocoelium dendriticum*[40] and fenbendazole against *Moniezia expansa* infections.[41] Fenbendazole and mebendazole (8) were active against developing but not against mature *Trichinella spiralis* infections in mice.[42]

The existence of cross-resistance in *H. contortus* and *T. colubriformis* to all the benzimidazole anthelmintics has been well documented.[43] Because of the capability of thiabendazole in inhibiting embryonation of nematode eggs at very low concentrations,[44] suggestions were made by Le Jambre[45] and Coles and Simpkin[46] almost simultaneously that the ovicidal activity of benzimidazoles may be used to indicate cross-resistance among nematode eggs. Results presented in these two papers indicated that eggs from benzimidazole-resistant nematodes were also resistant to the ovicidal action of benzimidazoles. A test such as this could be used as a screen for detecting resistance to benzimidazoles.

Among other established anthelmintics, oxantel[47] was shown to be active against *Trichuris trichiura* in man and levamisole resinate[48] was active against *Dirofilaria immitis* microfilaria and partially effective against adult worms in dogs.

Newly described anthelmintic structures included 2-tolylazo-2-thiazoline (9),[49] dihydroquinoxalino[2,3-b]quinoxalines (10),[50] and isoxazoles, (11) and (12).[51] Ethyl-6-ethoxybenzothiazole-2-carbamate (13), a benzimidazole isostere, was a broadly effective anthelmintic in horses, pigs, chickens and sheep but was less potent than analogous benzimidazoles.[52] Methyl 6-(phenylsulfinyl)imidazo[1,2-a]pyridine-2-carbamate (14) was shown to be orally active against a broad range of helminths in sheep and cattle at 2.5 mg/kg and in swine and dogs at higher doses.[53]



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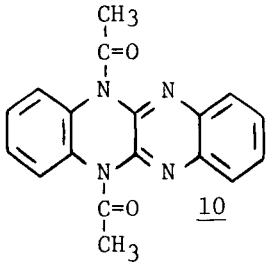

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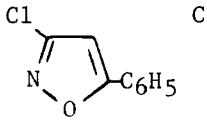

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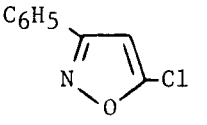

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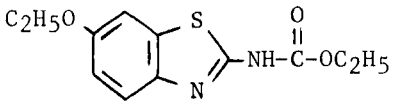

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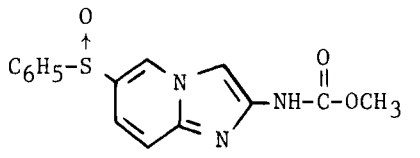

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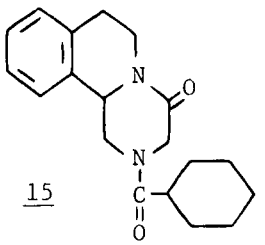
New tapeworm agents included praziquantel (EMBAY 8440, Droncit) (15), active against schistosomes and cestodes[54] in mice, rats[55] and dogs[56] by oral or parenteral administration. Uredofos (RH-565, diuredosan) (16), was shown to be effective against tapeworms, hookworms and whipworms in dogs.[57,58,59] Butamisole (17) was active against hookworms and whipworms in dogs but poorly effective against ascarid and tapeworm infections.[60] Nitroscanate (Lopatol) (18) was active against most nematodes and cestodes of dogs but inactive against whipworms.[61]



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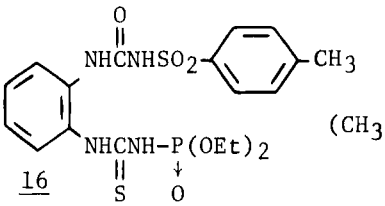

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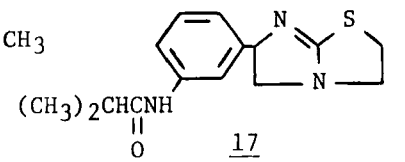

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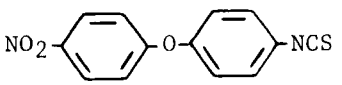

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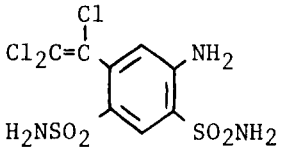
New drugs for the treatment of *Fasciola hepatica* in sheep and cattle included a benzenedisulfonamide (19)[62,63,64] active against mature flukes at 3.75 mg/kg, immature flukes at 10-15 mg/kg and possessing a wide margin of safety. Acemidophen (20), an analog of diamphenethide, showed expected superior activity against immature flukes.[65] Carbonyldicyanide phenylhydrazones exemplified by (21) were active but toxic.[66] 4-Isothiocyanato-4'-nitrodiphenylamine (C.9333-GO/CC1P 4540) (22) was active against human hookworm infections.[67,68]



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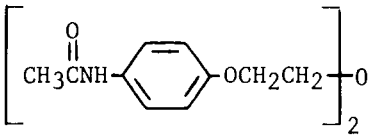

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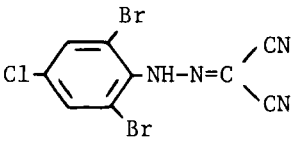

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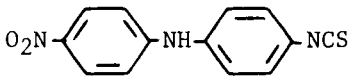

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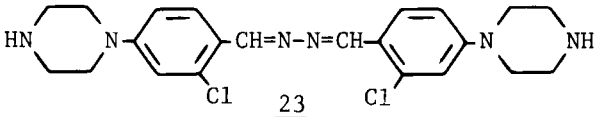

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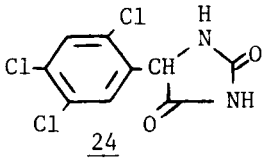
Schistosomiasis - Reviews were published on the chemotherapy of *Schistosoma mansoni*[69] and the chemistry of schistosomicides.[70] A series of papers[71,72,73,74,75] described the excellent activity of praziquantel, (15), against all species of schistosomes in mice, hamsters, monkeys and baboons by oral or parenteral administration. Studies on the antischistosomal drug 4-isothiocyanato-4'-nitrodiphenylamine (22) and its isocyanate analog[76] demonstrated that the latter compound was mutagenic and lacked activity against schistosomes. Several antischistosomal drugs including furapranidium, hycanthone, oxamniquine and metrifonate were shown to be mutagenic.[77,78] New structural types with reported antischistosomal activity were the benzalazine (23),[79] 5-(2,4,5-trichlorophenyl)hydantoin (24)[80] and N-acyl derivatives of N^4-(N-alkylglycyl)sulfanilamides (25).[81]



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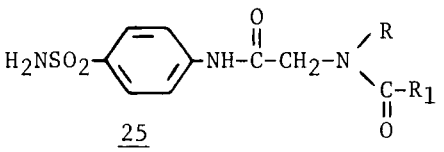

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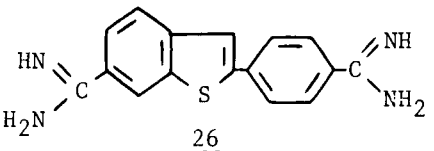

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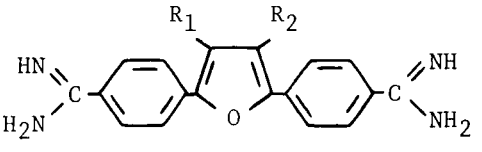

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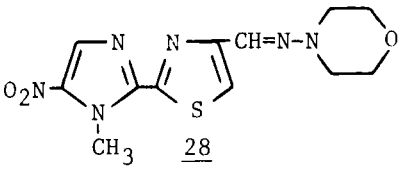

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Trypanosomiasis - A review of the biochemistry of *Trypanosoma cruzi* was published.[82] A session was organized to discuss the relevance of trypanosome biochemistry to control.[83] A novel approach to drug screening was proposed using African trypanosomes in the presence of SHAM or glycerol.[84] A mouse model was used to try to uncover new trypanosomiasis leads.[85] No entirely new antitrypanosomal structures were described. Variations of older types included the bisamidines 98/202 (26)[86] and (27)[87] and nitro heterocycles, the most potent of which was the nitroimidazole(28).[88]

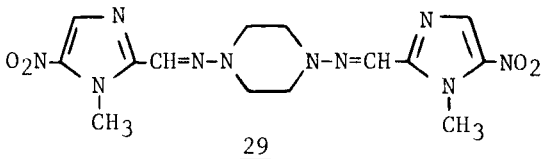
Thymidylate synthetase activities were detected in *Crithidia fasciculata, Crithidia oncopelti*, the bloodstream forms of *Trypanosoma brucei, T. congolense* and *T. lewisi* and the blood, intracellular and culture forms of

T. cruzi.[89] The trypanosomatid enzyme was inhibited by Mg^{++}, was much more sensitive to mercaptoethanol, had higher Km values for dUMP and tetrahydrofolate and had a higher molecular weight than the fetal rat liver enzyme. It is thus a possible target for chemotherapeutic attack. Among the antitrypanosomal drugs tested, suramin was a potent inhibitor of the trypanosomatid enzyme (ID_{50} ≈1.8 x 10^{-6}M) but not the mammalian enzyme (ID_{50} ≈1.1 x 10^{-3}M). However, since suramin also inhibits, at similar concentrations, the dihydrofolate reductases of *Onchocerca volvulus* and *T. rhodesiense*[90] and the L-α-glycerophosphate oxidase of *T. brucei*,[91] its mode of antitrypanosomal action still remains unknown.

Cross *et al.*[92] observed extensive breakdown of L-threonine to equimolar amounts of glycine and acetate during growth of *T. brucei* in culture. The pathway, which involves L-threonine dehydrogenase and aminoacetone synthetase and subsequent hydrolysis of acetyl-CoA, is most active in cultured trypanosomes but is also present in bloodstream forms.[93] The acetyl-CoA generated from threonine was apparently utilized by the parasite as a preferred source of carbon for lipid synthesis.[94] Antabuse was a strong inhibitor of threonine catabolism, probably due to its strong inhibition of L-threonine dehydrogenase (ID_{50} = 5.2 x 10^{-6}M).[92,93] It also blocked the growth of *T. brucei* in culture,[92] and inhibited O_2 uptake and motility of bloodstream *T. brucei*.[95] The drug was, however, unable to cure trypanosome infection in mice[92] which was attributed to probable inactivation or sequestering of the drug by blood cells.[95] The catabolism of threonine in trypanosomes, meanwhile, appears to be an attractive target for chemotherapy.

The successful *in vitro* cultivation of animal-infective *T. brucei* by Hirumi *et al.*[96] has opened the opportunity of evaluating new trypanocidal drugs *in vitro*.

Trichomoniasis - The only new drugs described were variations of nitroimidazoles, *e.g.*, HOE316 (29),[97] ornidazole (30),[98] pirinidazole (HOE088) (31)[99] and chloronizole (32).[100] A study was made of the antitrichomonal activity of nitropyridines and nitroimidazopyridines.[101]



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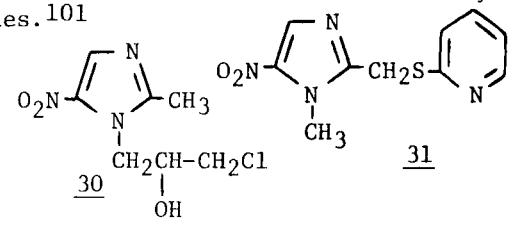

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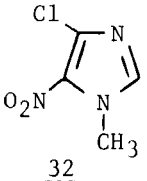

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Leishmaniasis - The nutritional requirements for the *in vitro* cultivation of *Leishmania donovani* and *Leishmania braziliensis* were described.[102] A number of antiparasitic agents were tested against *Leishmania mexicana* in tissue culture. Those which showed good activity were also active in mice.[103] Mycobacillin, a polypeptide antifungal, was active against *L. donovani*, presumably by disruption of the membrane.[104]

Amebiasis - Further studies were carried out on nitroimidazoles,[98] nitrobenzofurans,[105] nitropyridines and nitroimidazopyridines[101] and 4-alkylaminoquinolines and 4-alkylaminoquinaldines.[106,107]

Babesiosis - A comprehensive review of ovine babesiosis was published[108] covering most aspects of biology and chemotherapy. The first isolation of babesia in sheep in Great Britain was reported.[109] A potential *in vitro* screen was described, measuring the inhibition of hypoxanthine incorporation into *Babesia rodhaini*.[110]

Toxoplasmosis - Treatment of *Toxoplasma gondii* infected cats with 2-sulfamoyl-4,4'-diaminodiphenylsulfone and sulfadiazine reduced oocyst shedding but did not eliminate infection. Clindamycin appeared to have superior efficacy.[111] Robenidene and sulfamonomethoxine were effective in chicks, mice, rats and rabbits.[112]

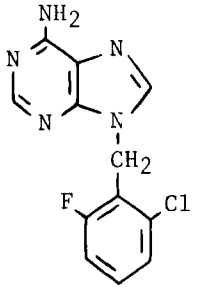
Cultivation of *T. gondii* in human fibroblast tissue cultures enabled the isolation of temperature-sensitive and drug-resistant mutants of the parasite by Pfefferkorn and Pfefferkorn.[113,114] An adenine-arabinoside resistant mutant was found deficient in adenosine kinase which could be the first successful step to convert the drug to its active form.[115] It was apparent that the parasite can grow without adenosine kinase. *T. gondii* was able to grow in Lesch-Nyhan cells and incorporate hypoxanthine or guanine from the culture medium.[116] The evidence suggests that the parasite depends mainly on the hypoxanthine-guanine phosphoribosyl transferase pathway for its purine supply.

Similar observations were made on pyrimidine metabolism by Pfefferkorn and Pfefferkorn.[117] Uracil was not significantly incorporated into the nucleic acids of human fibroblast cells but was extensively incorporated into the intracellular parasite. There was little or no uridine kinase but high levels of uridine and deoxyuridine phosphorylases and uracil phosphoribosyl transferases in the parasite.[118] A single-step mutant resistant to 5-fluorodeoxyuridine[119] was lacking the enzyme uracil phosphoribosyl transferase.[118] Apparently, uridine, deoxyuridine and 5-fluorodeoxyuridine all enter the parasite by the phosphorylase-phosphoribosyl transferase pathway. That the parasite could grow without uracil phosphoribosyl transferase suggests its ability to synthesize pyrimidines *de novo*.

Coccidiosis - Studies were reported distinguishing coccidiostatic from coccidiocidal effects,[120,121] isolation of oocysts,[122] and purification of schizonts,[123] sporocysts and sporozoites[124] and the development of resistance.[125,126,127,128] Arprinocid (MK-302) (33)[129,130] had excellent activity against several virulent field isolates of coccidia at 60 to 70 ppm. New 1-benzyl (34)[131] and 1-phenyl (35)[132] derivatives of 6-azauracil were reported to have high anticoccidial activity. Polyether ionophore antibiotics with reported anticoccidial activity included sephamycin,[133] salinomycin,[134,135] etheromycin[136] and glucopyranosylmonensin.[137]

Several types of riboflavin antagonists showed excellent anticoccidial activity.[138,139] The most potent compound in the group was 5-deazariboflavin (36). 1-Substituted-4(1H)-pyridinone hydrazones (37) were found to have broad anticoccidial activity. ^{13}C NMR spectroscopy and computer-assisted molecular modeling compared the conformation of (37) with robenedine (38).[140,141] Although the calculations did not permit an unambiguous assign-

ment of bioactive conformations, structural similarities were apparent in the low energy conformers of both compounds. The cross-resistance of (37) with (38) could be explained on this basis. Dithiosemicarbazones[142] showed activity against several *Eimeria* species whereas oxadiazoles, triazoles,[143] and 5-nitronicotinamide[144] and flutamide[145] were active only against *Eimeria tenella*.



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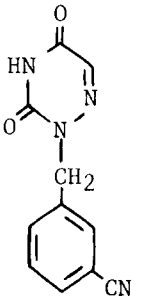

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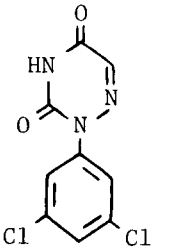

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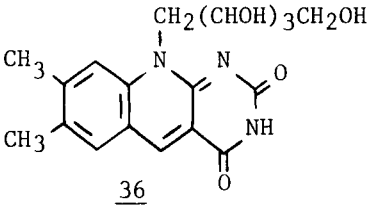
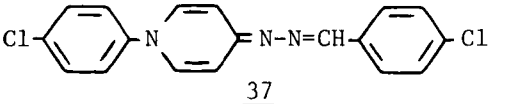
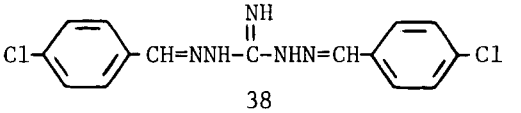


36



37



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