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Review

Treatment of Filariasis—Diethylcarbamazine and Its Congeners[1]

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Structural modifications of diethylcarbamazine (DEC), a drug of choice for treating different forms of human filariasis, are analyzed in order to delineate structure–activity relationships among various piperazine and nonpiperazine DEC analogues. The acyclic congeners of DEC do not possess any activity, probably because of their ability to exist in many conformations. On the other hand, many substituted piperazines display microfilaricidal activity, although they are less potent than DEC. A few rigid analogues of DEC have been found to possess promising antifilarial activity. This survey highlights the therapeutic potential of DEC against filariasis and trends in the design of better filaricidic drugs with DEC as a prototype molecule.

KEY WORDS: filariasis; diethylcarbomazine; piperazines; nonpiperazine compounds.

INTRODUCTION

Filariasis is one of the most prevalent and widespread parasitic diseases of the tropics, caused by slender, thread-like nematodes that invade different parts of the body of humans and animals (1,2). The main filarial parasites infecting humans are *Wuchereria bancrofti, Brugia malayi, Onchocerca volvulus, Loa loa, Dipetalonema perstans, D. streptocerca,* and *Mansonella ozzardi*. The disease is transmitted to humans by hematophagous arthropods, often mosquitoes and flies, which serve as the intermediate hosts and introduce infective larvae of filarial worms while feeding on the blood of humans.

After reaching the bloodstream, the first-stage larvae undergo several moltings and develop into adult male and female worms living in lymph nodes, lymphatic vessels, connective tissues, and other parts of the body. The females produce microfilariae which make their way to the blood circulation and subcutaneous tissues, whence they are taken up by the intermediate hosts to complete their life cycle (Fig. 1).

It is estimated that nearly 400 million people around the world are infected with different forms of filariasis (3). Lymphatic filariasis, caused by *W. bancrofti* and *B. malayi,* is the most common among all filarial infestations prevalent in tropical zones of Asia, Africa, South America, and some parts of the Australian continent. The filariases resulting from *O. volvulus, D. perstans,* and *D. streptocerca* infections are found mainly in different parts of Africa and South America, while infections by *L. loa* and *M. ozzardi* have been reported primarily from various regions of Africa and South America, respectively.

The clinical manifestations of *W. bancrofti* and *B. malayi* infections are characterized by three phases, *viz.* (a) inflammatory, leading to high fever, chills, enlargement of nodes, pain and swelling in the testes, and thickening of the spermatic cord; (b) obstructive, causing blockade of the lymphatic circulation, which leads to hydrocoel and chyluria in patients; and (c) elephantiasis, marked by massive enlargement of the legs, arms, scrotum, and breasts. The main clinical characteristic of *L. loa* infestations is the appearance of painful Calabar swellings on the face, limbs, head, wrist, and forearms. Occasionally the adult worm may wander into the eyeball, leading to nervous disorders and blindness.

The *O. volvulus* infection, also termed river blindness, poses a great threat in several parts of the African continent, causing loss of vision and blindness in a large number of patients every year. The early stage of occular onchocerciasis is marked by pain in the eyes, photophobia, lacrimation, and edema of the eyelids, which slowly leads to chronic conjunctivitis and, finally, loss of vision. Based on the high incidence of blindness caused by *O. volvulus,* some endemic areas of tropical Africa have been called the "Valley of Blinds" or "Blind Village."

The infestations by *M. ozzardi* and *Dipetalonema* spp. are nonpathogenic, but the former may cause hydrocoel or enlargement of the lymph nodes, while the latter may be associated with itching, abdominal pain, fever, edema of the scrotum, and high eosinophil counts. The last condition, also known as tropical eosinophilia, is usually due to the presence of *B. malayi, Dirofilaria* spp., and a number of other nematode parasites in humans.

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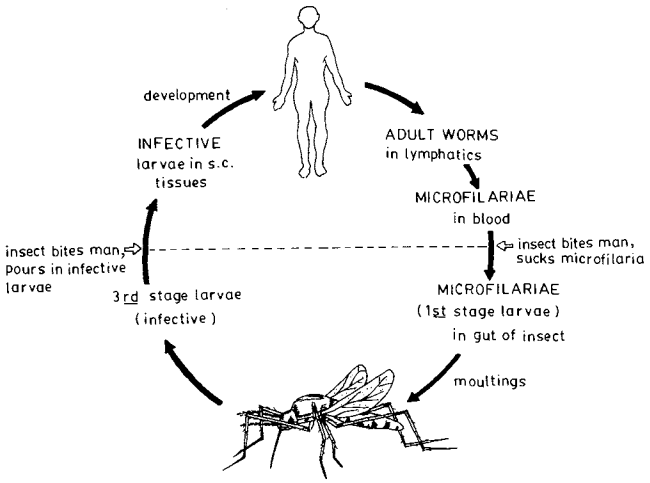


Fig. 1. Life cycle of a typical filarial parasite.

THE EFFICACY AND LIMITATIONS OF DIETHYLCARBAMAZINE

Despite enormous efforts by medicinal chemists, parasitologists, and clinicians, an ideal drug capable of providing a radical cure for filariasis is yet to be found. Diethylcarbamazine (DEC; compound 1, Fig. 2), a drug introduced more than three decades ago by the Lederle Laboratories of American Cyanamid Company (4), even today stands as the drug of choice in the treatment of human filariasis. A dose of 4–6 mg/kg of DEC given orally for a week results in a more than 90% clearance of circulating microfilariae of *W. bancrofti* and *B. malayi*. However, longer courses of treatment and higher doses are required to achieve complete eradication of both microfilariae and adult worms (5–7). The drug has also been used in the mass treatment of filariasis (8,9).

A DEC dose of 100–200 mg/adult has been found to be highly effective against the microfilariae of *O. volvulus* but has no action on adult worms (10–12). Attempts to use DEC in different formulations against cutaneous and occular onchocerciasis have yielded good results although not complete success (13–16). DEC also shows a marked efficacy against all stages of *L. loa* in humans (5) but does not cure *M. ozzardi* infection (17).

DEC is well tolerated by normal humans. However, in persons infected with filariasis, the drug produces moderate

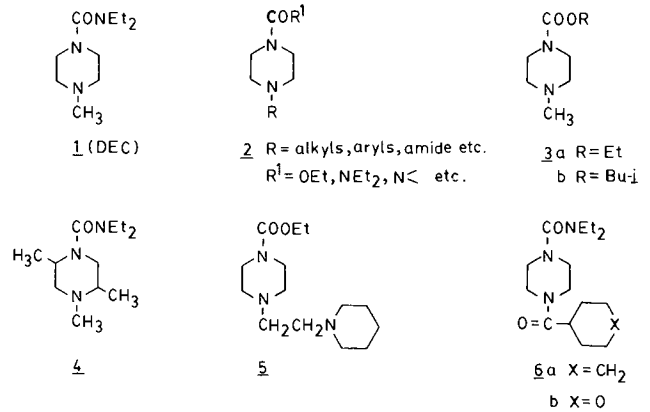


Fig. 2. Compounds 1–6.

to severe reactions such as fever, which depend upon the nature and intensity of the infection. This is thought to be due to the liberation of reactive substances resulting from the rapid destruction of circulating microfilariae. Several cases of collapse and death in *O. volvulus* patients and encephalitis in cases with *L. loa* infections have been reported (18,19). Visual loss during the oral administration of DEC in *O. volvulus* patients has also been observed (20). Recent studies have indicated that DEC interferes with some pharmacologically active agents such as SRS-A (slow-reacting substance of anaphylaxis) and histamine during inflammation and antigen–antibody reactions (21). The drug also inhibits the immediate type of hypersensitivity reaction of skin (22).

MOLECULAR MODIFICATIONS OF DEC

Although the efficacy of DEC in killing microfilariae and adult worms has been widely reported, its activity against the latter has not been unequivocally established. The severe allergic reactions resulting from the use of DEC in patients with heavy infection often restrict its use in mass therapy programs, especially in endemic areas where a high worm burden may be expected in the population. These limitations of DEC (23,24) amply justify the need for a better antifilarial drug (25).

The simplicity of the DEC molecule and the recognition of piperazine as a versatile pharmacophore in parasite chemotherapy resulted in the syntheses of a large variety of piperazine derivatives as possible filaricides. The structural modifications carried out in DEC in terms of ring size, the electronic nature of the nitrogen atoms, and the bulk of substituents can be described as follows.

1,4-Disubstituted Piperazines. A simple approach to search for a filaricide is to synthesize and screen various piperazines carrying substituents of varying electronic and steric natures at their 1 and 4 positions. However, one may doubt the productivity of such an approach, as DEC itself is the outcome of screening a large number of 1,4-disubstituted piperazines (4, 26, 27).

Following the discovery of DEC, a series of substituted piperazines (**2**) was synthesized, of which many showed moderate to good antifilarial activity (28–42). Thus, 1-carbethoxy-4-methylpiperazine (**3a**) (28, 31) and 1-*iso*-butoxycarbonyl-4-methylpiperazine (**3b**) (38, 39), next to DEC showed a manyfold better activity than the other piperazine derivatives. Compound (**3b**) reduced the microfilariae of *Litomosoides carinii* in cotton rats by 91% at an intraperitoneal or oral dose of 3 mg/kg × 5 and also killed 100% of the microfilariae and adult worms of *Dipetalonema viteae* in *Mastomys* at a subcutaneous dose of 50 mg/kg given for 5 days (39).

1-Diethylcarbamoyl-1,4,5-trimethylpiperazine (**4**) (40), a higher isoster of DEC, exhibited marked microfilaricidal activity. Some 1-carbethoxy-4-substituted piperazines have been found to possess antifilarial activity, of which **5** exhibited a high efficacy against *L. carinii* in albino rats at a dose of 100 mg/kg (41). Hoechst Laboratories have prepared 1-cyclohexylcarbonyl-4-methylpiperazine (**6a**; HOE-28637) and 1-(tetrahydropyran-4-carbonyl)-4-methylpiperazine (**6b**; HOE-29691), which exhibit a potent activity against *L. carinii* in *Mastomys natalensis*. A combination of **6a** and sura-

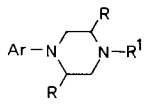
mine was found to possess better micro- and macrofilaricidal activity against *L. carinii* in *Mastomys* than the individual drugs (42).

In a slight variation of the above approach, the piperazines may be attached to other biologically active molecules. Thus, a number of 1-substituted piperazines carrying different heterocycles at their 4 positions (**7–9**, Fig. 3) were synthesized but none showed any noteworthy filaricidal activity (42–44).

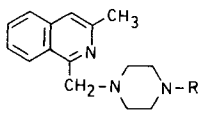
Fascinating examples of the preceding class of compounds are 4-[(7-chloro-4-quinolyl)amino]-α-(4-methyl and ethyl-1-piperazinyl)-*o*-cresols (**10**, Fig. 4) (45) and 2-[2-(4-hydroxyphenyl)-6-benzimidazolyl]-6-(1-methyl-4-piperazinyl) benzimidazole (**12**) (46–49), where 1-methylpiperazine is attached to substituted quinoline and benzimidazole heterocycles, respectively. The adult worms of *L. carinii* in gerbils are killed by **10** at a dose of 25 mg/kg given for 5 days. On the other hand, **12** exhibits a prolonged suppressive effect on the microfilariae of *L. carinii* at a sc dose of 4 mg/kg × 5 days (47, 48). Substitution of the alkyl groups in **10** by a diethylcarbamoyl chain gives rise to **11**, which when tested against *L. carinii* in *Mastomys natalensis* at a dose of 100 mg/kg × 5, could not improve the biological profile of the parent drug (50).

Ring-Cleft Analogues of Diethylcarbamazine. A number of ethylenediamine derivatives (**13**, Fig. 5) as the open-chain congeners of DEC have been prepared and shown to possess moderate (51) or no (52, 53) antifilarial activity. All these inactive acyclic compounds possess a high degree of conformational mobility, thereby indicating that the interatomic distances between the two nitrogen atoms of the piperazine ring and the spatial disposition of the groups are of much importance in governing their filaricidal activity. This hypothesis can be further tested by comparing the antifilarial efficacies of 1-methyl-4-diethylcarbamoylhomopiperazine (**14**) (54–56) and the 1,3-disubstituted imidazoline (**15**) (57) with DEC. Both **14** and **15** closely resemble DEC except that a methylene group has been either introduced or removed from the piperazine ring, which, in turn, changes the conformation as well as the interatomic distances in the resulting structures. The net result is that **14** shows one-fourth to one-half the activity of DEC, while **15** is completely inactive.

The Piperazine Heterocycles. The diethylcarbamoyl side chain of DEC, because of the free rotation across all its single bonds, may assume different conformations. It has been shown earlier that the acyclic compounds (**13**), having the highest conformational freedom do not possess any antifilarial activity. In this context, it is of interest to incorporate one of the ethyls of the diethylcarbamoyl chain of DEC into

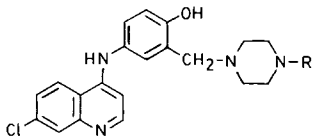


7 Ar = 2-pyrimidyl, 2-thiazolyl etc.
R = H, CH_3
R^1 = COOEt, $CONH_2$, $CSNH_2$

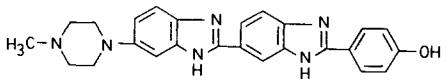


8 R = H
9 R = CO_2Et

Fig. 3. Compounds **7–9**.



10 R = CH_3, Et
11 R = $CONEt_2$

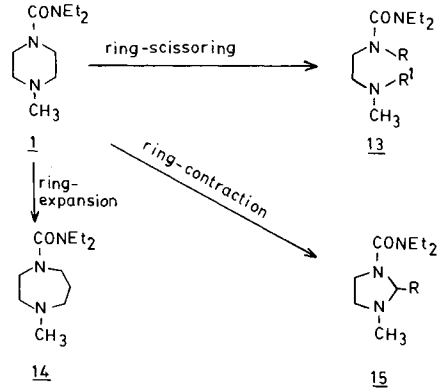


12 (HOE-33258)

Fig. 4. Compounds **10–12**.

a cyclic structure, which would considerably reduce its conformational mobility without altering the electronic and steric nature of the three nitrogen atoms. There are two facile ways to lock up the rotation of the diethylcarbamoyl group of DEC in a rigid framework. The C-4′-terminal of DEC may form a σ bond with either C-2 or C-3 of the piperazine ring, giving rise to 3-ethyl-8-methyl-1,3,8-triazabicyclo[4,4,0]decan-2-one (**16**, Fig. 6), (58, 59) or 6-ethyl-1-methyl-1,4,6-triazabicyclo[4,3,1]nonan-5-one (**17**) (60), respectively.

When tested against *L. carinii* infection in cotton rats, **16** showed more than 90% clearance of microfilariae from blood at an ip dose of 1 mg/kg given for 6 days, while **17** was inactive. Compound **16** (Centperazine) has also been found to be highly effective against *B. malayi* in gerbils and *W. bancrofti* in humans (61), and it is considered to be a potentially valuable drug against human filariasis (62). The marked activity of **16** may be attributed to its reduced conformational mobility, the planarity of all three nitrogen atoms, and the triazabicyclo ring system. Compound **17**, being unable to show a parallel resemblance to **16**, is devoid of the antifilarial activity. Further support for this observation comes from the synthesis of the piperazine heterocycles (**18–20**, Fig. 7) which were found to be inactive, as none of them displays the molecular geometry exhibited by **16** (63, 64). The structure–activity relationships for compounds of type **16** further show that the nature and bulk of the nitrogen substituents at positions 3 and 8 are also important in deter-



1 **13** **14** **15**

Fig. 5. Compounds **13–15**.

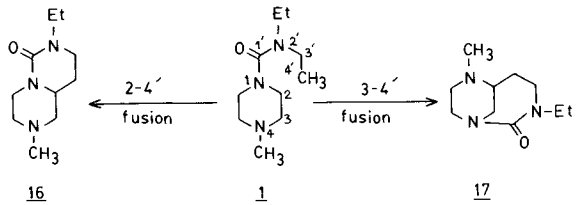


Fig. 6. Compounds 16 and 17.

mining the filaricidal activity (65). The optimal activity was associated with the congeners of **16** containing methyl and ethyl groups at positions 3 and 8 and the carbonyl chromophore at position 2 (65).

In a further probe of the evaluation of the filaricidal efficacy of piperazine heterocycles, the synthesis of bicyclopiperazine derivatives (**21–24**, Fig. 8), obtained by introducing one or two methylene bridges in the piperazine ring, has been carried out. Some of the compounds of this class exhibited potent antifilarial activity but none was superior to DEC (66). Later some other bicyclopiperazines (**25–28**) were also synthesized, all of which, except **28**, demonstrated a high reduction of blood microfilaremia in cotton rats or gerbils infected with *L. carinii* at a dose of 10 or 25–200 mg/kg (66–68).

The pharmacophoric groups, situated at the two nitrogens of the piperazine ring, are separated by 2.8 ± 0.1 Å in all these compounds. The piperazine rings of **22** and **23**, like DEC, are able to exist in chair and boat forms, while **21** and **24** are restricted to the boat conformation only. Thus, the activity of this class of compounds may be due to their conformational similarity to DEC at the carbonyl and nitrogen functions (67). However, the activity of **25–27** and inactivity of **28** may be explained on the basis of the preferred geometry of the 1-methyl group in DEC and these bicyclopiperazines (68).

Other Modifications. Encouraged by the promising antifilarial activity of **16**, some of its hexahydropyrimidine derivatives (**29** and **30**, Fig. 9) were also prepared (69), which may be regarded as the open-chain analogues of DEC obtained by cutting the piperazine ring from sides a and b and simultaneously connecting the 2 and 4′ carbon centers. When tested against *L. carinii* infection in cotton rats, **29** was found to be effective at a dose of 30 mg/kg, while **30** had no activity. Some other derivatives of **29** with more versatile pharmacophores were also prepared but none showed any appreciable filaricidal activity (70). The absence of filaricidal efficacy in **30** may point out the role of spatial disposition and the bulk around the three nitrogen atoms in governing the activity. The activity of **29**, on the other hand, may suggest that the piperarazine ring is not essential per se for antifilarial activity in the congeners of DEC.

The above rationale may be supported by the fact that

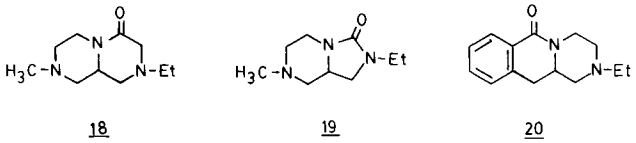


Fig. 7. Compounds 18–20.

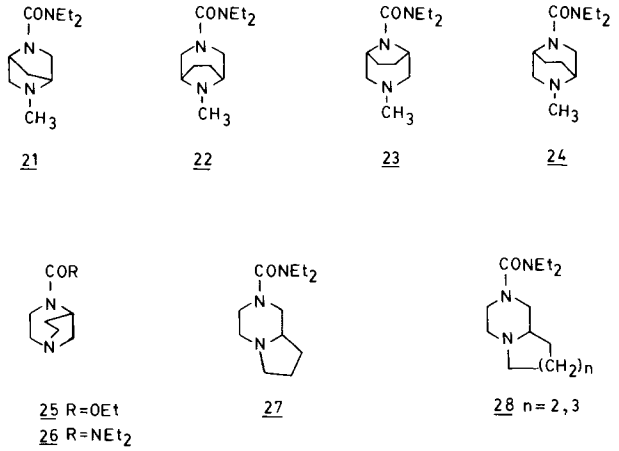


Fig. 8. Compounds 21–28.

various piperidine derivatives (**31–34**, Fig. 10) were demonstrated to be active against microfilariae of *L. carinii*, although none could exceed the potency of DEC (56). Some other nonpiperazine analogues (**35**, **36**) of DEC have also been shown to possess significant activity against *L. carinii* in gerbils (67, 71). However, the number of such examples is insufficient to conclude at present that the piperazine ring does not play a significant role in effecting antifilarial activity in the analogues of DEC.

CONCLUSION

Despite a large variety of molecular modifications carried out with DEC, definitive conclusions regarding the structural requirements for optimal filaricidal activity cannot yet be made. However, changes in the structural framework of DEC that do not alter much of its physical parameters are expected to yield a filaricide in most cases. Thus, compounds having two basic nitrogens enclosed in a five- or six-membered saturated carbon skeleton with groups such as methyl, ethyl, carbethoxy, and diethylcarbamoyl would usually display activity against microfilariae in the blood circulation.

The incorporation of DEC in rigid structures requires several points to be taken into consideration, the most important being the planarity of the molecule and the interatomic distances between component heteroatoms. The demonstration of antifilarial activity associated with compounds derived from hexahydropyrimidine indicates that this and other classes of nonpiperazine heterocycles should be explored for newer filaricides. Such studies could further clarify whether a piperazine ring is essential for antifilarial activity.

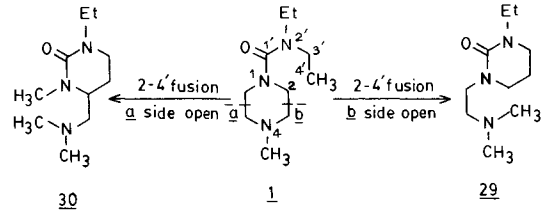


Fig. 9. Compounds 29 and 30.

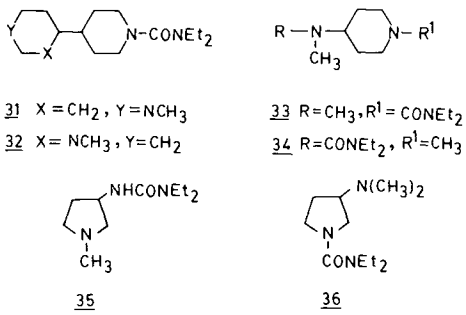


Fig. 10. Compounds 31–36.

The discovery of 12 by Hoechst may be regarded as a milestone in the chemotherapy of filariasis. Although this compound did not find its use in clinical practice due to its strong binding with the host's DNA (72–74), it gave a new direction in searching for better macrofilaricides. Thus, the attachment of piperazines with different bioactive pharmacophores requires a broader exploration for evolving drugs with action on adult worms or with depot microfilaricidal activity. Such drugs could serve to achieve a radical cure for, and eventual eradication of, filariasis. A modest effort in this direction involves the synthesis of methyl 5(6)-(4-substituted piperazin-1-yl)benzimidazole-2-carbamates (**37a** and **b**, Fig. 11) which show a 90–100% reduction of both microfilariae and adult worms of *L. carinii* in cotton rats at an intraperitoneal dose of 30 mg/kg × 5 days (75).

DEC will continue to be the drug of choice in the chemotherapy of human filariasis until the introduction of a new drug having great superiority over this drug. Its use in mass treatment programs will also continue but under more medical supervision. However, keeping in view the fact that DEC is primarily a microfilaricidal drug with selective action on adult filarial parasites, the search should continue for more effective drugs that kill both microfilariae and adult worms and are also safe in mass application. Thus the structural leads provided by some new candidate antifilarials such as mebendazole (**38**, Fig. 12), amoscanate (**40**), levamisole (**39**), clofazimine (**42**), and the nitrofurans (**41a–d**) (61, 76) should be fully explored.

Some of the logistic difficulties in developing a single drug effective against both microfilariae and adult worms are the morphology, physiological needs, and seats of predilection of microfilariae and adult worms. In such a situation, a combination of DEC and different anthelmintics (77) seems to provide a better prospect for chemotherapy of filariasis. The use of immunoregulators such as muramyl peptides along with DEC and/or other antifilarials may also help in developing better drugs for combating more resistant forms of filariasis. Finally, more information regarding the biochemistry and physiology of different stages of parasite development is required for a more rational approach to design an antifilarial agent. The development of *in vitro* correlates with *in vivo* screening would greatly help in testing a larger number of compounds for developing novel lead molecules in the chemotherapy of filarial infestations.

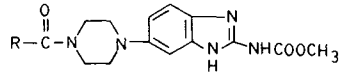


Fig. 11. Compound 37.

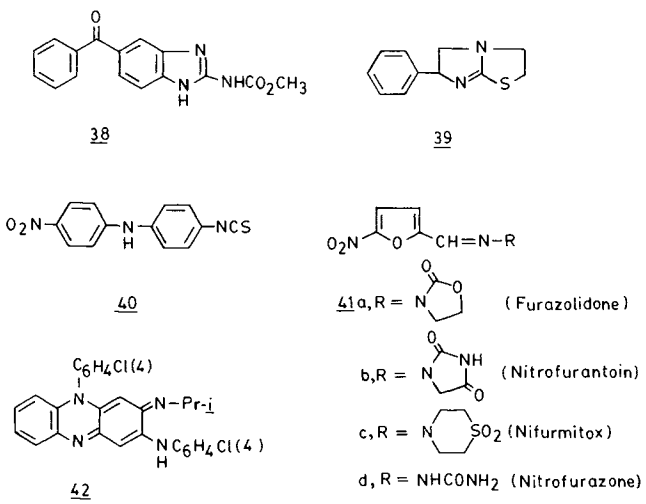


Fig. 12. Compounds 38–42.

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