Highly active nitro-aromatic antiparasitic drugs

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Die Pharmazie

Organ der Pharmazeutischen Gesellschaft der Deutschen Demokratischen Republik

ISSN 0031–7144 HEFT 6 JUNI 1982 37. JAHRGANG

■ ÜBERSICHT

Pharmazie 37, H. 6 (1982)

Highly Active Nitro-Aromatic Antiparasitic Drugs

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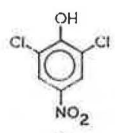
1. Introduction

Nitro-aromatic compounds comprise a vast family of organic compounds ranging from simple, substituted benzenes to complex, polyheteroatomic structures, many of which are agents of antihelmintic and antiparasitic chemotherapeutic value (for general reviews see [1, 17, 27, 34, 39, 51, 111]). This review concerns anti-helmintic agents which are nitro derivatives of benzene, furan, thiophene, thiazine, imidazole and fused polycyclic aromatic compounds. Therapeutic efficiencies and structure-activity relationships are examined in the light of the design of more efficient drugs potentially active against some of the major human parasitic afflictions, namely schistosomiasis, filariasis and trypanosomiasis.

2. Known Nitro-Aromatic and Heterocyclic Antiparasitic Drugs

2.1. Nitrobenzenes

Probably the simplest group of nitro compounds to exhibit anthelmintic activity are the substituted phenols. *Thorson* and co-workers [104] discovered that the dichloro nitrophenol (1) exhibited pronounced anthelmintic activity in domestic animals. Subsequent investigations have shown that the nitrophenol (2; disphenol) has anticestode activity [26] and is also efficient in eradicating the trematode Fasciola hepatica from sheep and cattle [117]. The cyano-iondonitrophenol (3), either as the free phenol or its N-methylglutamine salt (nitroxinil) is effective against liver flukes in domestic animals [13, 25, 26], the nematode Ancylostoma caninum in dogs [13] and Fasciola sp. in sheep, heifers and calves [28]. The amidine salts also show anthelmintic activity [12]. The chemotherapeutic activity



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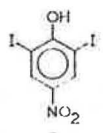

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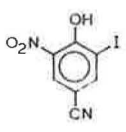

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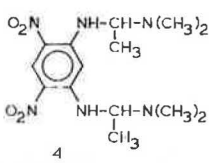

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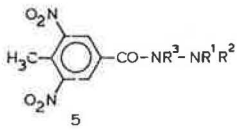
of a series of 201 different nitroanilines has been investigated by *Winkelmann* and co-workers [113] and it was found that the symmetric dinitroanilide **4** was effective against Schistosoma mansoni in mice. Unspecified anthelmintic activity has also been reported for some of the 3,5-dinitrotoluic acid hydrazides **5**, particularly for the 1,1-dimethyl ($R^1 = H$, $R^2 = CH_3$) and 1,2-dimethyl ($R^1 = CH_3$, $R^2 = H$) derivatives [45]. The nitrophenylacetamides **6** and **7** were found to possess anthelmintic activity against Enterobius vermicularis and oxyuris infections [72] and the thiourea (**8**) in low doses, was also shown to completely eradicate these parasites from mice [72].



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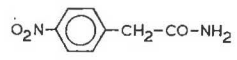

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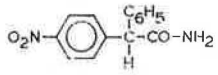

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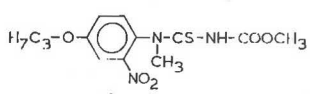

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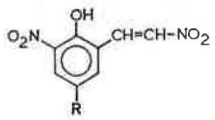
Nitrovinylnitrophenols **9** (R = H, Cl, OCH_3) were found to be active against Hymenolepis nana, Fasciola sp. and Metastrongylus apri [75] and in certain cases, nitrovinylphenols **10** without



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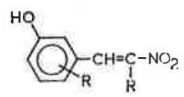

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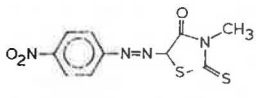
ring-nitro substituents were found to be active against H. nana in mice [19]. Other simple nitrobenzenes of known anthelmintic activity are the azorhodanine **11** (nitrodan; which eradicates nematodes such as Ascaris suum and the cestodes H. nana and Moniezia expansa) [64] and the hydrazone **12** (which eradicates the nematode Syphacia obvelata and the cestode H. nana in mice) [20].



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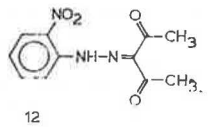

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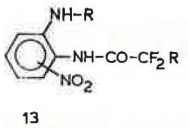

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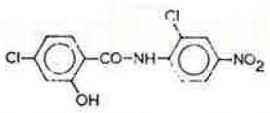

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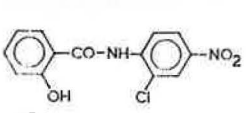

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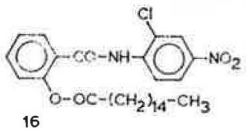

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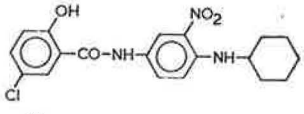
A large number of nitroanilides such as **13** [6] show anthelmintic properties and these are most pronounced for nitroanilides of halogenated benzoic acids. For instance, niclosamide (**14**) is the drug of choice for the treatment of tapeworm infections [17, 51], being effective agains Taenia saginata, T. solium, H. nana and Diphyllobothrium latum as well as the intestinal flukes Heterophyes heterophyes and Metagoniumus yokogawai [51]. It is interesting to note that the dechlorinated niclosamide (**15**) is quite inactive unless compounded with the surfactant, sodium dioctylsulphosuccinate, which gave it powerful anthelmintic activity against a large number of parasites with exceptional activity against H. nana [10]. Similarly, the introduction of a long-chain fatty acid ester group such as the palmitoyl derivative **16** greatly enhances its anthelmintic activity.

In an attempt to elucidate a structure/activity relationship in this large class, *Singh* and co-workers [96] synthesized a number of niclosamide analogues and found that the cyclohexylamino derivative **17** was the best cestodicidal agent with a particularly high therapeutic index (166.6) against H. nana. On the



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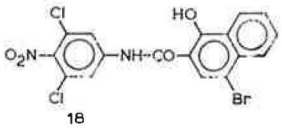
basis of further structural studies [97], he concluded that cestodicidal activity is not only dependent on the higher electron density of the un-nitrated ring, but is also related to the steric interactions between substituents at the 3- and 4-positions of that ring.

Other more profound structural modifications (eg. **18**) [32] are also found to increase anthelmintic activities in certain cases.

Heteroatom-bridged bi-aryls constitute another sub-class of anthelmintic nitrobenzenes. The best known N-bridged anthelmintic is the thiocyanate **19** (amoscanate: C 9333-Go/CGP-4540) which has activity against cestodes such as Hymenolepis diminuata in rats and H. nana in mice [68], nema-



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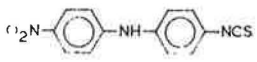
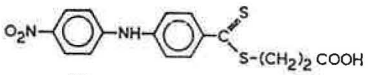


19

todes such as the hookworms Ancylostoma duodenale and Necator americanus [106], the whipworm Trichuris trichiura [106], the roundworm Ascaris lumbricoides [106] and Nematospiroides dubius [28, 92]. Schistosomicidal activity of this drug has been demonstrated against Schistosoma haematobium, S. mansoni in mice [99] and S. japonicum in dogs [99], mice [99, 118] and in rabbits and *in vitro* [118]. Furthermore, effective destruction of both micro- and macro-filariae (Litosomoides carinii [99, 100], Dipetalonema viteae [99, 100] and Brugia pahangi [89, 90]) has been reported in mongolian jirds. Preliminary studies of structural analogues of amoscanate (**19**) such as its thio-esters **20** indicate anthelmintic activity in mice [108].



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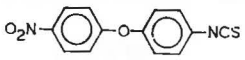

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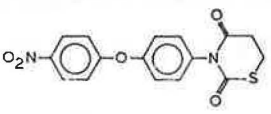
The O-bridged analogue of amoscanate is the thiocyanate ether **21** (nitroscanate) showing a broad spectrum of anthelmintic activity in domestic animals [16]. It is also used to eradicate nematodes and cestodes in dogs [15]. Recent reports [83] indicate that this drug eradicates the microfilariae of Brugia malayi and Dipetalonema viteae in the multimammate rat and the microfilariae of Litomosoides carinii in the cotton rat as well as both macro- and microfilariae of D. viteae (in jirds) and L. carinii (jirds and multimammate rats) [35]. Other O-bridged analogues **22** have shown anthelmintic properties [107] as have S-bridged dinitrophenols **23** [105].



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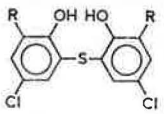

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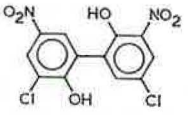
Directly linked bi-aryls are also known to have anthelmintic activity such as the cattle fasciolide niclofolan **24** [65]. Its isomer meniclopholan **25** eradicates trematodes especially Paragonimus



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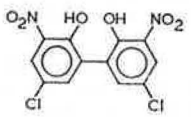

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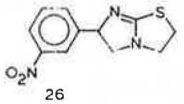
uterobilateralis from humans [111]. Some nitrobenzenes directly linked to heterocycles are also anthelmintic such as nitramisole (**26**) which is microfilaricidal to B. malayi, D. viteae and L. carinii in multimammate rats [83], the nitrophenylfuran **27** which eradicates S. obvelata from mice [78] and **28** which at 100 mg/kg b.i.d. results in 80—90% reduction of Ascaris serum in mice [112].



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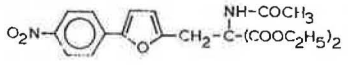

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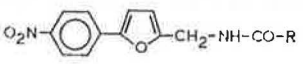

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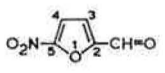
2.2. *Nitrofurans*

The second major class of anthelmintic nitro-aromatics comprises the nitrofurans. It is worthy of note that *without exception* the compounds investigated have always been derivatives of 5-nitrofuran-2-aldehyde (**29**). Of the various substitution



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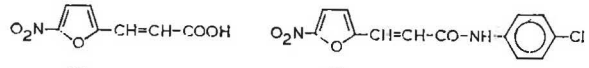
patterns possible, this 2,5-disubstitution is the most readily achieved by classical synthetic methods. (This may well be a major shortcoming of chemotherapeutic studies on the nitrofurans. Clearly, the synthesis of 3- and 4-substituted compounds, using recent methods, would provide at the very

least important insights into structure/activity relationships in this area.)

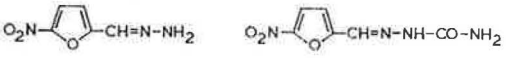
A much investigated sub-class of nitrofurans has been the derivatives of 5-nitro-2-furanacrylic acid (**30**) and an extensive study of the substituted amides, anilides and phthalides of this acid have shown that while these compounds are inactive *in vitro*, many exhibit good anthelmintic activity *in vivo* [58]. The most useful of these proved to be the chloroanilide **31**



30 31

which was active against Ancyclostoma duodenale and Tricophalus trichinous without undesirable side-effects [58]. A further 107 amides derived from **30** were synthesized and tested for their action against Schistosoma japonicum. Of the **33** compounds with activity, the two most active were the N-isopropyl and N-cyclohexyl derivatives [119]. Other amides have also been found to cure infections of Schistosoma mansoni in mice [50]. n-Alkyl esters of **30** have also shown exceptional anthelmintic activity and eradicate Syphacia obvelata from animals [87].

Perhaps the most commonly investigated types of nitrofuran are the derivatives of nitrofurfuralhydrazone (**32**). One of the simplest of these is nitrofural (**33**; nifurcin, furacin) which is active against the agent of Chagas' disease, Trypanosoma cruzi [91].



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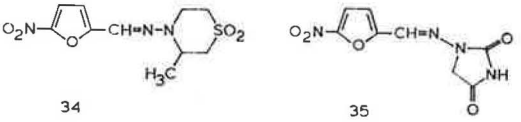
Another widely used hydrazone is nifurtimox (**34**; Lampit®) which shows promise as a trypanocide and filaricide [27, 111]. This drug eradicates T. cruzi [42] as well as offering protection against infection by this parasite [21] and is also active *in vitro*



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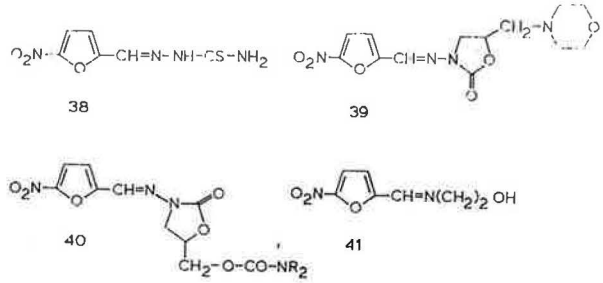
and *in vivo* against T. rhodesiense and T. lewisi [113]. It has been noted that nifurtimox decreased the number of parasites in the liver and spleen as well as the bloodstream of T. cruzi [110]. Both macro and microfilariae of Litmosoides carinii are destroyed by nifurtimox in the multimammate rat [27, 83], the chinese hamster [83] and cotton rats [83] as are both forms of Dipetalonema viteae in rodents [27], whereas only microfilariae of L. carinii are destroyed in the jird [83]. Nitrofurantoin (**35**) finds use as a veterinary anthelmintic [58] and shows promise as a filaricide [27] in destroying micro and macrofilariae of L. carinii in the multimammate rat [27, 83] and jird [83] but only macrofilariae of Brugia malayi and Dipetalonema viteae in multimammate rats [83]. Unfortunately, no activity is observed against either form of the agent of river blindness, Onchocerca volvulus [27]. Pyridoxine hydrochloride has been added to nitrofurantoin to increase the compatibility of the gastrointestinal tract for the latter [40].

An analogous hydrazone, furazolidone (**36**) also shows promising filaricidal activity by destroying microfilariae of B. malayi in the multimammate rat, macrofilariae of L. carinii in jirds as well as both forms of L. carinii and D. viteae in multi-

36 37

mammate rats and L. carinii in hamsters and cotton rats [83]. This drug also immobilizes the trypanosomes T. cruzi *in vitro* [38] and T. gambiense in mice [77]. Thiofuradene (**37**) has been found to be a useful veterinary anthelmintic against the roundworm Ascaridia galli [66]. Benazone VII (**38**) is effective against T. cruzi *in vivo* and *in vitro* [35] and the macrofilariae of L. carinii [83]. Furaltadone (**39**) and the related carbamate **40** [50] both display trypanocidal activity.



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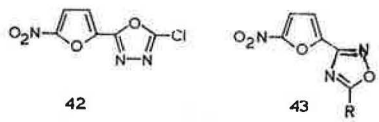
Another sub-class of active nitrofurans is formed by the Schiff-base derivatives of the aldehyde **29** of which **41** has known trypanocidal properties [38]. The same methylene-imino function is also shared by the more complicated heterocyclic anthelmintics **42** [44] and **43** [18].



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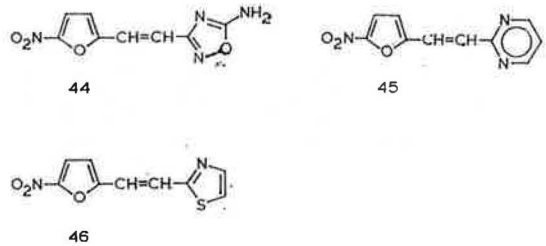
Nitrofurans linked to another heterocycle by a trans-vinyl bridge can also show anthelmintic activity and of these SQ 18,506 (**44**) has been the most studied, displaying proven activity against the blood fluke Schistosoma mansoni in mice [84] and Chagas' disease (T. cruzi) [94, 95]. The activity of **44** is superior to that of nifurtimox **34** against T. cruzi and to that of simplified analogues **45** and **46** [48].



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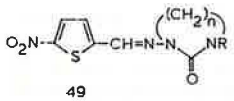
It is clear then that anthelmintic nitrofurans can possess a wide variety of side-chain structures. In all cases, however, the furfuryl carbon atom is always unsaturated and it has been suggested that the sp^2 (planar) nature of this carbon atom is critical for activity. It is found, in keeping with this prediction, that the acrylamides **47** show good anthelmintic activity, but their saturated analogues **48** are inactive [14].

47 48

2.3. Nitrothiophenes

By complete analogy with the nitrofurans, a wide range of nitrothiophenes has also shown anthelmintic activity. A number of heterocyclic hydrazones **49** have been examined for activity against Schistosoma mansoni in mice and in general the greatest activity has been found for side-chains containing a six-membered heterocycle (**49**: n = 3) with a small apolar N-substituent (**49**: R = H, C_2H_5, etc.) [49]. Similarly, studies with mice infected with Syphacia obvelata have shown that nitrothiophenes of quite diverse structure (eg. **50**—**53**) show high activity [22]. Nitrothiophenes with thiazole side-chains have also been examined for trypanocidal activity in mice [109].



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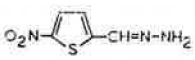

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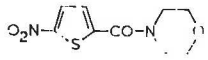

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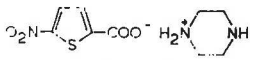

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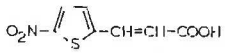

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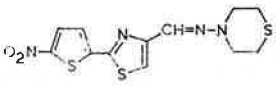

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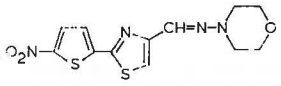

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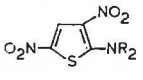

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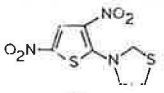

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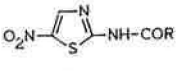
Strangely, the best agent against T. rhodensiense **54** was one of the worst against T. cruzi whereas the best against the latter trypanosome **55** was one of the worst against T. rhodensiense [109].

Dinitrothiophenes **56** have recently been shown to have schistosomicidal activity [47]. Hoffmann-La Roche have recently prepared one of these, Ro 11-0761 (**57**) which is claimed to be effective against the schistosomes S. mansoni, S. Haematobium and S. japonicum in a variety of laboratory animals [98].

2.4. Nitrothiazoles

Unlike the nitrofurans, most of the active nitrothiazoles have a nitrogen substituent in the 2-position and the simplest of these are the amides aminitrozale (**58**, R = CH_3), active against S. mansoni [5] and its aryl analogues (**58**: R = Ar) [23]. More complicated amides such as **59** ($R^1 = C_3H_7$, NH_2, $R^2 = CONH_2$, CH) [52] and **60** (R^1 = H, CH_3, $R^2 = CH_3$, C_2H_5, etc.) [53] are active against S. mansoni and Trichomonas vaginalis.



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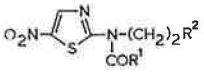

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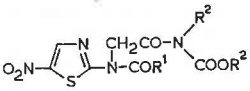

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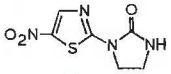

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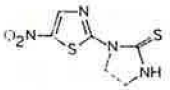
A large number of anthelmintic nitrothiazoles have a nitrogen heterocycle as 2-substituent. The best known of these is niridazole (**61**) which is of particular interest because of its microfilaricidal activity, especially against Onchocerca volvulus in humans [27, 102] and because of its utility as a schistosomicide [90] against S. haematobium and S. mansoni in humans [51]. It is also used to treat infections of guinea worm (Dracunculus medinensis) [51].

Several derivatives of niridazole (**61**) have been investigated and the thione **62** and thionamine **63** are also found to show activity in animals [102]. Condensation of niridazole with various reagents gives rise to **64** [3] and **65** [4] which have been found to show anthelmintic activity. The compound **66** which has a nitrogen substituent in the 2-position substituted by a nitrogen heterocycle has been shown to kill 80% of Schistosoma mansoni at a dose of 35 mg/kg per d [71].



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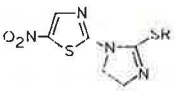

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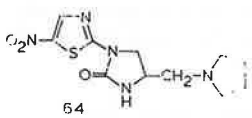

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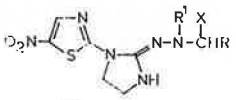

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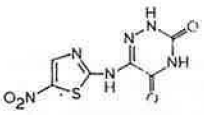

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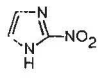
2.5. Nitroimidazoles

A large number of 5- and 2-nitroimidazoles have been developed as antitrichomonal and antiamoebic agents. These include azomycin (**67**), nimorazole (**68**), panidazole (**69**), pirinidazole (**70**), chloronidazole (**71**) and Hoe 316 (**72**). Unfortunately, they have not yet been closely examined for anthelmintic properties [34, 90, 111]. Those which demonstrate anthelmintic activity



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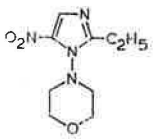

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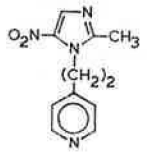

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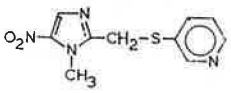

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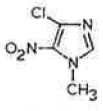

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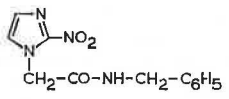
can be divided into two sub-classes depending on whether they bear the major substituent on N-1 or on C-2. Of the N-substituted nitroimidazoles, Ro 7-1051 (**73**) is effective against Chagas' disease (T. cruzi) in mice [2, 42, 80] and *in vitro* [42, 80]. Metronidazole (**74**) shows only limited trypanocidal activity against T. cruzi [42], but shows promise as macrofiliaricide against L. carinii [83] and B. pahangi [111]. Tinidazole (**75**) is active against B. pahangi [111] and ornidazole (**76**) is a possible microfiliaricide of L. carinii [83].



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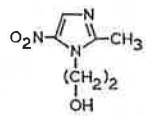

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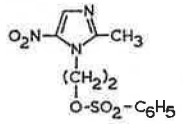

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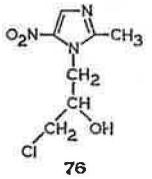

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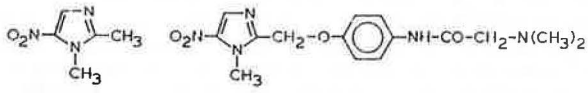
Dimetridazole (**77**) which is equally substituted in both positions, destroys macrofilariae of L. carinii in the multimammate rat [**83**]. Of the nitroimidazoles bearing their major substituent on C-2, the glycylamide (**78**) was found to be the most active



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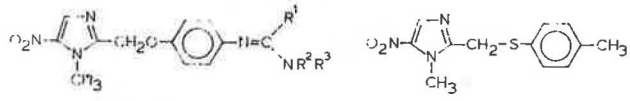
of 105 aryl ethers tested against Trypanosoma brucei in mice [**116**]. Anthelmintic activity has been claimed for an analogous ether (**79**) [7], while the thioether **80** has been shown to be markedly active against trypanomastigotes amastigotes of T. cruzi even during the manifest phase of Chagas' disease in mice [**81**]. In one case, **190** compounds of type **81** (X = N, S) were tested for nematocidal activity, but few showed any activity [**115**]. In another case, **135** derivatives of **81** were tested, but only a few showed an *in vitro* effect on Trypanosoma cruzi and T. brucei and there required high doses [**114**]. On



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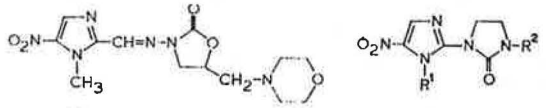
81 82

a more positive note, the hydrazones (**82**: X = O, SO_2, etc.) showed better activity against T. cruzi in mice than did the corresponding furans, thiophenes and thiazoles [**76**]. An analogous compound, moxnidazole (**83**) inactivates D. viteae and L. carinii in rats [**83**]. There have also been several reports of antischistosomal activity of the imidazolidinones (**84**) (R^1 = alkyl, alkoxy, R^2 = carboxy, carbothioxy or sulphoxy) [**57, 73, 74**]. Short term treatment with the isoxazolone (**85**) and analogues has been shown to be effective against acute and chronic infections induced with a wide range of T. cruzi substrains [**55, 69**]. Use of berenil and the isoxazolone (**86**; R = H or alkyl) at a dose of 40 mg/kg i.p. cured 10/10 mice which had been infected with T. brucei (TREU 66711) for 21 d [**54**].



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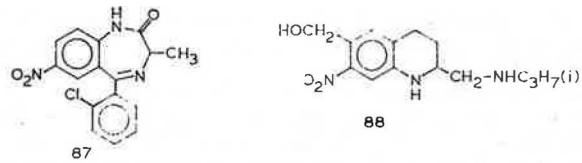
2.6. Polycyclic Nitro-aromatics

The most promising anthelmintics of this class of nitro-aromatics are the clonazepam (**87**; Ro 11-3128) which is schistosomicidal (S. mansoni, S. haematobium, but not S. japonicum) in various laboratory animals [**103**], and oxamniquine (**88**; Mansil®) which is the best current anthelmintic for Schistosoma mansoni [**1, 103**]. Other schistosomicides related to oxamniquine are the 6-methyl analogue **89** [**81, 37**] and the tricyclic analogue **90** [**9**]. The imidazole pyridines **91** and **92** are active against Trichostrongyles *in vitro* [**33**] and the benzimidazoles **93** and **94** show activity against Nematospiroides dubius in mice [**46**].



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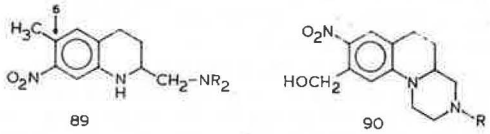

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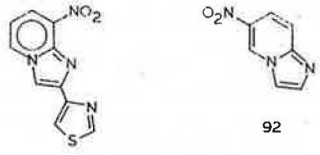

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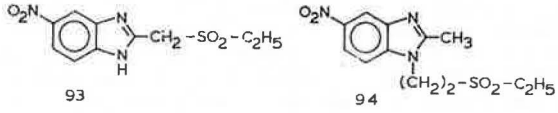

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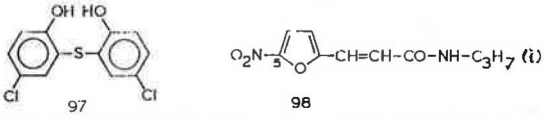
3. The Importance of the Nitro Group

Although there are exceptions [**59**], as a general rule the presence of a nitro substituent is the one immutable structural characteristic of nitro-aromatic anthelmintics that is required for activity. For instance, bithional (**97**) is a useful antimicrobial and fungicide, but shows only weak anthelmintic activity [**93**]. On the other hand, its dinitro derivative **23** is a powerful trematocide [**105**]. When other nitro-aromatic anthelmintics such as niclosamide (**14**) are reduced to their corresponding amino compounds, it is found that their activity is either diminished or lost entirely [**101**]. In other cases, analogues



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of nitro-aromatics, where the nitro group is replaced by another electron-withdrawing substituent (such as the 5-cyano and 5-carboxy analogues of the isopropylamide **98** [**85**] and the 5-chloro derivative of **93** [**46**]) are found to be inactive.

Other polycyclic nitro-aromatic anthelmintics are the phenothiazine **95** [**11**] and the benzofuran **96** [**82**].

There are, of course, many effective anthelmintics possessing no nitrosubstituent [**1, 17, 27, 34, 51, 90, 111**]. Nonetheless, it does appear that the nitro-aromatics constitute a special class in which the nitro group is essential for anthelmintic activity.

Very little is known of the mode of action of these drugs. It is evident that different anthelmintics produce diverse effects on different helminths. Niclosamide (**14**) for instance interferes with the respiration and blocks glucose uptake by tapeworms [**51**]. It appears to uncouple oxidative phosphorylation in both mammalian and taenoid mitochondria, but is therapeutically effective because the helminths depend on anaerobic metabolism of carbohydrates as their major source of energy [**51**].

The action of niridazole (**61**) on schistosomae is quite different. It appears to arrest egg-shell formation and to interfere with reproductive processes in the females. It also interferes with

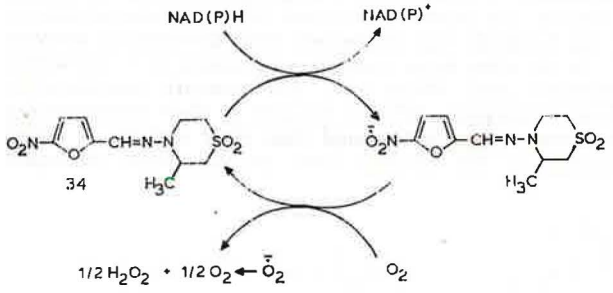
carbohydrate metabolism by inhibiting glucose adsorption and accelerating glycogen breakdown [27, 51]. On the other hand, the nitroimidazole **73** was found to inhibit protein and RNA synthesis in Trypanosoma cruzi, but had a negligible effect on DNA-synthesis or respiration [80]. In T. cruzi SQ 18506 (**44**) inhibited protein formation at the lowest effective concentration and may, therefore, be the primary mechanism of action [41]. Nitrophenolic anthelmintics are thought to interfere with phosphorylation processes in helminths [88].

It has been suggested that *in vivo* reduction of the nitro group to nitroso or hydroxylamino groups may be important [85] and the reduction potential of the nitro group should be an index for determining anthelmintic activity [60]. In character with anaerobic metabolic mechanisms, a key step in the uptake of nitro compounds could be their reduction by flavodoxins and ferrodoxins [70]. This would have the dual effect of generating a gradient that drives the selective uptake of these drugs by helminths, and may also create metabolites that are more cytotoxic than the unreduced nitro compounds [70]. Alternatively, the partially reduced nitro-aromatics could generate other toxic species by further reactions. It has been suggested that radical anions (one electron reduction products $RNO_2^{\cdot-}$) of nitro-aromatic and nitro-heterocyclic compounds are essential intermediates in the enzymatic reduction of these compounds to hydroxylamines or amines [61, 62, 63]. Oxygen inhibits nitroreductase activity in e. g. hepatic microsomal incubations and measurements of the rate of O_2 uptake have provided evidence [61] that the inhibition results from the electron transfer reaction [1]:

$$RNO_2^{\cdot-} + O_2 \rightarrow RNO_2 + O_2^{\cdot-}$$

Electron transfer to a nitro group and the consequent interference with the electron transport system has been postulated as the mechanism of action in nitrofurans [39]. The generation of superoxide ion has been postulated as the toxic principle in nitrofurans such as nitrofurantoin (**35**) [24, 79]. Addition of nifurtimox (**34**) to cultures of Trypanosoma cruzi has been shown to produce both superoxide ion and hydrogen peroxide (Scheme) [29].

Scheme



With NADH as reducing agent nifurtimox (**34**) induced release of superoxide anion, at a nifurtimox concentration closely parallel to the concentration reached in blood serum with a therapeutic dose of 15 mg/kg [30]. It is consistent with these theories of nitro reduction that enzyme preparations from cestodes catalyze the *in vitro* reduction of nitrophenol anthelmintics to the corresponding amino compounds [31].

4. Structure and Activity

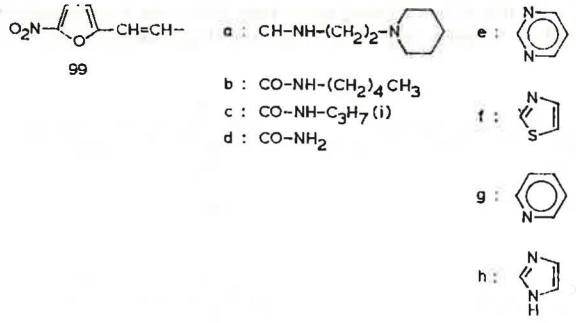
The interpretation of structure/activity relationships of the nitroaromatic anthelmintics is complicated by several factors. There are numerous cases where the activity of an anthelmintic varies enormously depending on the nature of the helminth. As yet, there is no anthelmintic which is therapeutically effective for the complete spectrum of helmintic afflictions. Indeed, most of the drugs examined in this review are only active against one class of helminth (eg. schistosomes) or just one species (eg. S. mansoni) or worse still, one strain (eg. S. mansoni — St. Lucia). This is further complicated by host specificity. For example, certain drugs are filaricidal in one type of laboratory animal, but not in others [83]. Finally, interpretation of the published structure/activity studies is complicated by incomplete and unsystematic structural variation and by technical problems prohibiting consistent dosages, etc.

In the case of nitro-heterocyclic compounds however, there appears to be one simplifying factor. There is good reason to believe that these compounds may be considered as having *firstly*, a nitro-heterocyclic nucleus to which is attributable the toxicity of the drug and *secondly*, a sidechain which may simply modify the physico-chemical parameters affecting the absorption of the drug by host and parasite [76]. In general, these two functions may be considered as distinct and independent, although there may be certain limitations such as the requirement for an unsaturated furfuryl carbon atom in the side-chain of nitrofurans which would effect the reduction potential of the nitro group [76]. We have therefore analyzed the relationships of anthelmintic activity of each structural component separately.

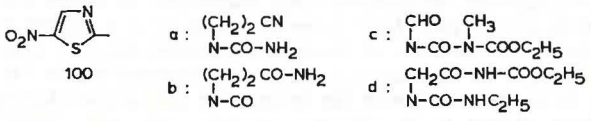
4.1. The Effect of the Structure of the Side Chain on Activity

4.1.1. Schistosomicides

Studies on S. mansoni in mice have shown that SQ 18,506 (**44**) shows the highest activity of the nitrofurans [85] while the related amides (**99**: **a–d**)[1] show decreasing activity as the N-

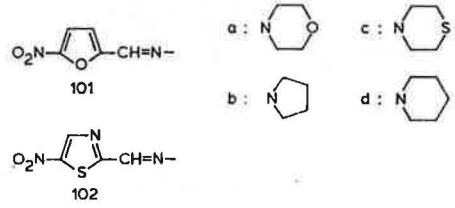


substituent becomes simpler (**a** → **d**) [50]. Heterocyclic analogues of SQ 18,506 (**99 e–h**) have schistosomicidal activity that decreases in the order **99e** = **99f** > **99g** > **99h** [48]. No thiazoles were as effective as niridazole (**61**) and the activity of open-chain analogues **100 a–d** against S. mansoni in mice decreases in alphabetical order **100 a** → **d** [52, 53].

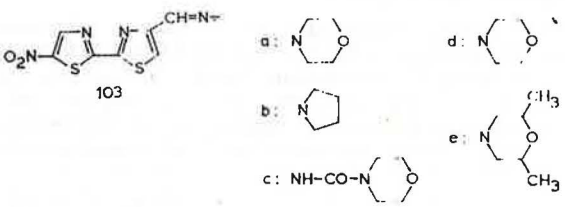


4.1.2. Trypanocides

SQ 18,506 (**44**) is also the best nitrofuran for eradicating T. cruzi in mice, being better than nifurtimox (**34**) [42, 56], which in turn is better than the series **101 a–d** which shows decreasing activity in alphabetical order [76]. Similarly, nitro-



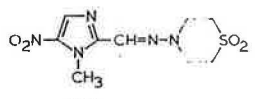
thiazines having the same side-chains (**102 a–d**) show decreasing activity in the order **102a** = **102c** → **102b** [76]. Trypanocidal activity of various nitrothiophene thiazoles **103**[2], however, depends on the species of protozoan tested. For example, in



[1] CO instead of CH in **99 a**.

[2] Nitrothiophen instead of nitrothiazol in **103**

mice infected with T. cruzi, activity declines in alphabetical order **103 a → e** whereas for T. rhodesiense the order is **103d > 103b > 103a > 103e > 103c** [109]. With nitroimidazoles, it was found that the aryl ether (**78**) was more effective against T. brucei in mice than Tinidazole (**75**) which in turn was more effective than Metronidazole (**74**) [116]. Against T. cruzi in mice, the sulphoxide **104** was superior to both its morpholine analogue **105** and nifurtimox (**34**) [76].



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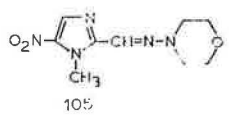

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4.1.3. Filaricides

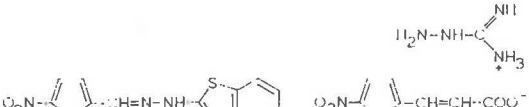
No quantitative or ranking studies have been undertaken. In the search for a macrofilaricide which has no effect on microfilariae, various nitro-heterocyclic compounds have been examined for their effect on Litomosoides carinii in a variety of laboratory animals [83], but no clear conclusions can be drawn as

— results depend on the nature of the experimental protocol and the type of laboratory animal and
— experimental screening with animal parasites is not always relevant to the treatment of human parasitic diseases.

Furazolidone (**36**) kills adult worms in cotton rats and mongolian jirds, but some tests reveal simultaneous microfilaricidal activity. The same drug kills both stages of L. carinii in multimammate rats and chinese hamsters. Similarly, nifurtimox (**34**) kills both forms in hamsters and rats although some experiments reveal only macrofilaricidal activity. Nitrofurantoin (**35**) proves to be both micro- and macrofilaricidal in all studies whereas nitrofural (**33**) and the nitroimidazoles metronidazole (**74**) and dimetridazole (**77**) kill only the adult forms in some animals but are completely inactive on other test animals [83].

4.1.4. Nematocides

Examination of the effect of nitrofurans and thiophenes on Syphacia obvelata in mice reveals different side-chain ranking for the two heterocyclic nuclei [22]. Of the compounds tested for both heterocycles, the following rankings were found: for **106** (X = O: best nitrofuran, X = S: inactive), **107** (X = O: second nitrofuran, X = S: eighth nitrothiophene), **108** (X = O: inactive, X = S: best nitrothiophene), **109** (X = O: third,



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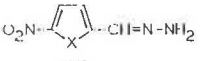

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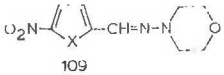

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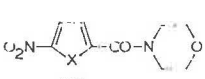

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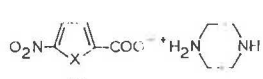

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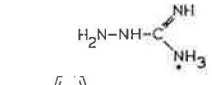

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113

X = S: inactive, **110** (X = O: inactive, X = S: second), **111** (X = O: sixth, X = S: third), **112** (X = O: fourth, X = S: seventh), **113** (X = O: fourth, X = S: inactive), etc.

4.2. The Effect of the Nitro-substituted Heterocycle on Activity

Only a few drug-screening studies have been performed in which different nitroheterocycles having the same side-chain have been compared (2-R): 5-Nitrofurans, 5-Nitrothiophenes, 5-Nitrothiazoles, 5-Nitroimidazoles, 2-Nitroimidazoles.

4.2.1. Schistosomicides

It has been reported that the antischistosomal activity of various nitrofuran acrylamides **47** is lost when the nitrofuran group is replaced by a nitrothiazine [60]. Other studies on mice infected with Schistosoma mansoni have shown that in general the nitrothiophenes are better than corresponding nitrofurans [59].

4.2.2. Trypanocides

Although one study has ranked the nitrofurans, SQ 18,606 (**44**) and nifurtimox (**34**) as being more active against T. cruzi than the N-substituted imidazoles Ro 7-1051 (**73**: 2-nitro) and metronidazole (**74**: 5-nitro) [52], the only study in which all compounds shared the same side-chains showed that 5-nitroimidazoles were better than nitrofurans, nitrothiophenes and nitrothiazines in that order [76]. In general, 5-nitroimidazoles are more effective when they bear the side-chain on C-2 rather than N-1. It also appears that 2-nitroimidazoles may be more effective than either type of 5-nitroimidazole. In any case, the 2-nitroimidazoles have a different physiological mode of action than their 5-nitro counterparts [80].

4.2.3. Nematocides

In general, nitrofurans have more effect than correspondingly substituted nitrothiophenes against Syphacia obvelata in mice [22].

Acknowledgement: One of us (D. P.) is grateful for financial support from the filariasis Scientific Working Group of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

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Received July 27, 1981

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