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Nitroimidazoles: Part XIX†—Structure-activity Relationships‡

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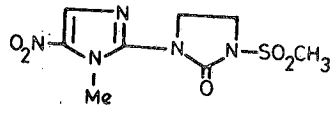
A variety of nitroimidazoles, mostly 1,2-disubstituted-5-nitroderivatives were examined for *in vitro* activity against *E. histolytica* and in early hepatic infection of infected golden hamsters. Many preparations carried a functionalised N atom at position 2. *In vivo* activity was found widely among 1-alkyl-5-nitroimidazoles carrying a substituted imidazolidinone (**1**) or imidazole (**2**). Out of these derivatives, 1-methyl-sulphonyl-3-(1-methyl-5-nitro-2-imidazolyl)-2-imidazolidinone (**1a**; C 10213-Go) was found to be the best and to be superior to marketed nitroimidazoles against hepatic and caecal infections of *E. histolytica* in the golden hamster and *T. foetus* infections in mice, and has been developed as a drug for treatment of amoebiasis, giardiasis and trichomoniasis.

Nitroimidazoles have a wide spectrum of chemotherapeutic properties[1]. Metronidazole, 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (**23a**), heralded a new era in the treatment of amoebiasis, being quite active against the invasive forms of the disease, both intestinal and hepatic, and spurred an enormous amount of chemical and biological work in the class of 5-nitroimidazoles[1]. We initiated our work in this area in 1972 and this involved the synthesis and evaluation of nearly 400 nitroimidazole derivatives and culminated in the development of 1-methylsulphonyl-3-(1-methyl-5-nitro-2-imidazolyl)-2-imidazolidinone (**1a**) (C 10213-Go) as a potent and well-tolerated antiamoebic-antitrichomonal agent[2-4]. The title investigation is an off-shoot of our comprehensive work in this area.



1a

Our initial efforts, guided by reports of antiamoebic properties for niridazole[5] and the high antiamoebic activity of 1-acetyl-3-(1-methyl-5-nitro-2-imidazolyl)-2-imidazolidinone (**1**, R = $COCH_3$)[6] in experimental models, were directed towards elaboration of various representatives of **1**. Subsequently, these were expanded to embrace nitroimidazole derivatives carrying variously functionalised nitrogen atom at position-2, in view of relatively fewer reports in the literature[δ] on such compounds and was followed by synthesis of derivatives carrying other heteroatoms, e.g. oxygen and sulphur at position-2. Many other 5-nitroimidazole derivatives having carbon substituents also at position-2 were synthesised and evaluated, the exercise being specially assisted by findings of facile acylation of 1-methyl-[9] and 1,2-dimethyl-5-nitroimidazoles[10,11]. A number of 4-nitroimidazoles became objects of our study in connection with delineation of structure-activity relations. A limited number of 2-nitroimidazoles were also prepared but found to be uninteresting as antiamoebic agents[12].

Chemistry

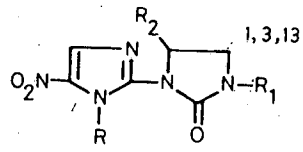
The synthesis of most of the new compounds mentioned in this paper has been already reported[3,9-11,13-25]. A few are known in the literature and the remaining were prepared by standard methods. 1-Substituted-5-nitroimidazoles (**1-16**) bonded to a nitrogen atom at position-2 are catalogued in Tables 1-16, while two 2-imino-5-nitroimidazolines (**17**) are listed in Table 17. Tables 18 and 19 are concerned with 1-methyl-5-nitro-2-imidazolyloxy derivatives (**18** and **19**) and Table 20 deals with some 2-mercapto compounds (**20**). Table 21 incorporates a few mono and dinitro alkylimidazoles (**21**). Tables 22-34 describe 1-substituted-5-nitroimidazoles (**22-34**) having a C–C bond at position-2 (or rarely an H atom), Table 23, in particular, incorporating a few clinically studied drugs like metronidazole, tinidazole etc. These were prepared for comparative evaluation. Table 35 lists four preparations belonging to the group of 1-methyl-5-nitro-4-substituted imidazoles (**35**), two of them being isomers of active compounds. Tables 36-38

†Part XVIII: *Indian J Chem*, 22B (1983) 157.

‡Contribution No. 656 from CIBA-GEIGY Research Centre.

δA few synthesised and tested by Winkleman *et al.*[7] have been shown to be 5-nitro-4-amino derivatives[8].

Table 1

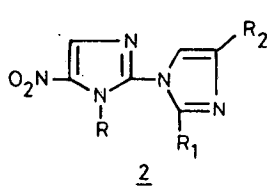


1

Compd	R_1	Antiamoebic activity	
		In vitro	*In vivo* (hepatic)
1a	SO_2Me	1	+ + + +
1b	SO_2Et	100	+ +
1c	SO_2Me	10	+ + + +
1d	SO_2NMe_2	0.1	+ + +
1e	SO_2NEt_2	0.1	+
1f	SO_2Me	100	+ +
1g	CONHMe	0.1	+ + + +
1h	CONHEt	0.1	+
1i	$CONHCH_2Ph$	0.1	+ + +
1j	$CONMe_2$	0.1	+ + + +
1k	$CONEt_2$	0.1	+ + + +
1l	CO(1-piperidinyl)	100	+
1m	CO(4-morpholinyl)	10	+ +
1n	COOEt	10	+ +
1o	CSNHMe	0.1	+ + + +
1p	CSNHEt	10	+ + +
1q	CSNH-cyclohexyl	100	+
1r	1-methyl-5-nitro-imidazolyl	10	—

R = Me for **1a** to **1e** and **1g** to **1r**; and R = CH_2CH_2OMe for **1f**.
R_2 = H for **1a**, **b** and **1d** to **1q**; and R_2 = Me for **1c** and **1r**.

Table 2*

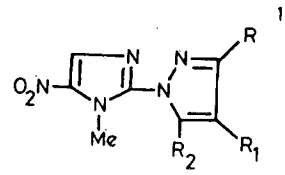


2

Compd	R_1	R_2	Antiamoebic activity	
			In vitro	*In vivo* (hepatic)
2a	H	H	1	+ + + +
2b	Me	H	100	+ + + +
2c	Et	H	100	+ + + +
2d	Pr(n)	H	100	+
2e	Me	Me	10	+ + +
2f	Et	Me	10	+ +
2g	H	Me	1	+ + + +
2h	H	Ph	10	—
2i	SMe	H	1	+ +
2j	SO_2Me	H	10	+ +
2k	H	NO_2	10	+
2l	Me	NO_2	10	+ + + +
2m	H	H	100	+ + + +

*2a-g, i and m as HNO_3 salts.
R = Me for **2a** to **2l**; and CH_2CH_2OMe for **2m**.

Table 3

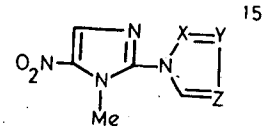


3

Compd	R_1	Antiamoebic activity	
		In vitro	*In vivo* (hepatic)
3a	H	100	+ + + +
3b	NO_2	100	—
3c	H	10	+ + +
3d	NO_2		+
3e	H		

R = R_2 = H for **3a**, **b**; R = NO_2; R_2 = H for **3c**; and R = R_2 = Me for **3d**, **e**.

Table 4

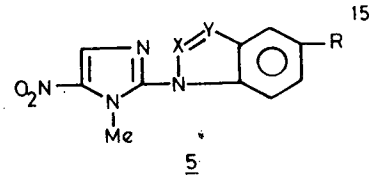


4

Compd	Y	Antiamoebic activity	
		In vitro	*In vivo* (hepatic)
4a	CH	10	+ +
4b	CH	100	+ + +
4c	N	10	—

X = Z = CH for **4a**; and X = Z = N for **4b** and **4c**

Table 5



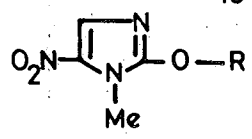
5

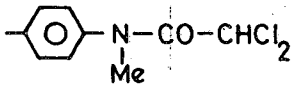
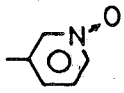
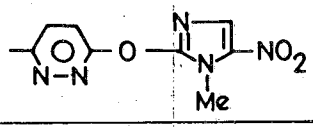
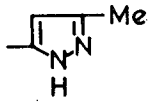
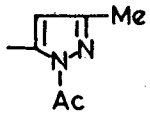
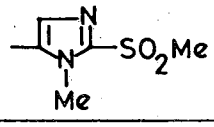
Compd	Y	R	Antiamoebic activity	
			In vitro	*In vivo* (hepatic)
5a	CH	H	10	—
5b	N	H	10	—
5c*	N	H	10	+ +
5d	CH	NO_2	0.1	—
5e	CH	Cl	10	—
5f	N	H	10	—
5g	N	NO_2	0.1	+ +

*Benztetrahydro
X = CH for **5a-c**; and X = N for **5d-g**

Table 18

18



Compd	R	Antiamœbic activity	
		in vitro	in vivo (hepatic)
18a	H	200	-
18b	OCH_2Ph	200	-
18c		<1	-
18d		1	-
18e		1	++
18f		1	-
18g		0.1	-
18h		10	-

In vivo activity against early hepatic infections of E. histolytica

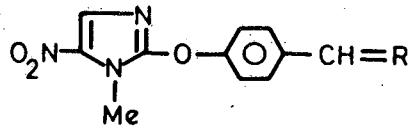
A perusal of Tables 1-43 reveals that there is little correlation between *in vitro* and *in vivo* activities. Thus **20g** with a MIC value of 0.01 γ/ml and several preparations with a MIC value of 0.1 γ/ml, e.g. **5d**, **11j**, **12b** etc. were inactive at screening doses, while some compounds which were less inhibitory *in vitro*, e.g. **2b**, **2e**, **2m** (MIC 100 γ/ml) had potent *in vivo* activity. Absorption and/or metabolism undoubtedly are some of the responsible factors.

It is evident from Tables 1-17 that among 1-substituted-5-nitroimidazoles carrying a N atom at position-2, *in vivo* activity is largely restricted to imidazolidinones (Table 1), imidazoles (Table 2) and pyrazoles (Table 3), to a lesser extent to other azoles and benzazoles especially triazole (Table 4) and the pyrrolidino derivative **10a** (Table 10). It is seen to some extent for oxazolidinones (Table 6) and bicyclic sulphamides (Table 9). Thiazolidones (Table 6), triazolidinediones (Table 7) and monocyclic sulphamides (Table 8) related to **1a** were inactive.

Most derivatives of 2-amino-1-methyl-5-nitroimidazole, such as alkyl and aryl derivatives (Table 11), amides and ureas (Table 12), schiff bases (Table 13), amidines (Tables 14 and 15) and guanidines (Table 16) were inactive or marginally active, **11d** and **11o** being exceptions. Dichloracetylimino-1,3-dimethyl-5-nitroimidazoline (**17a**; Table 17) with low *in vitro* activity was inactive *in vivo*. Three compounds, **18e** (Table 18)

Table 19

18



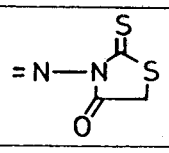
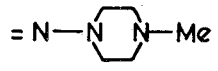
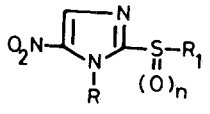
Compd	R	Antiamoebic activity	
		in vitro	in vivo (hepatic)
19a	O	1	–
19b	=NNHCOCONH$_2$	100	++
19c		10	–
19d		10	++

Table 20

18



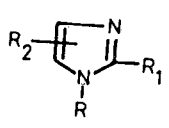
20

Compd	R_1	n	Antiamoebic activity	
			In vitro	*In vivo* (hepatic)
20a	Me	1	10	—
20b	Me	2	—	
20c	Me	2	100	—
20d	Et	0	1	
20e	CH_2Ph	0	0.1	—
20f	CH_2Ph	2	—	—
20g	$-CH_2-$(2-pyridyl)	0	0.01	—
20h	$-CH_2-$(3-pyridyl) (HCl)	0		—
20i	$-CH_2-$(4-pyridyl)	1	1	—
20j	$-CH_2-$(1-methyl-5-nitro-2-imidazolyl)	2	1	—
20k	$-(CH_2)_2$-thiamorpholine-1,1-dioxide-4-yl	0	10	—
20l	2-$CO_2Me.C_6H_4-$	0	10	—
20m	4-$NO_2-C_6H_4-$	0	0.1	—
20n	4-NHAc.C_6H_4-	0	1	—
20o	4-NHAc.C_6H_4-	2	100	—
20p	2,4-di(NO_2).C_6H_5	2	—	—

R = H for **20a**, **b**; R = CH_2CHOH for **20c**; and R = Me for **20d** to **20p**

Table 21

1,8

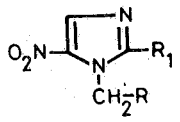


21

Compd	R	R_1	R_2	Antiamoebic activity	
				In vitro	*In vivo* (hepatic)
21a	H	NO_2	4-NO_2	300	—
21b	Me	NO_2	4-NO_2		—
21c	Et	NO_2	4-NO_2	300	—
21d	Me	NO_2	5-NO_2	1	—
21e	Et	NO_2	5-NO_2		—
21f	NO_2	H	4-NO_2	100	—
21g	NO_2	Me	4-NO_2	200	Toxic
21h	Me	N_3	5-NO_2	10	—
21i	Me	H	5-NO_2	10	+++
21j	Me	Me	5-NO_2	10	+++
21k	Me	H	4-NO_2	100	++
21l	Me	Me	4-NO_2	100	—
21m	C_6H_5CO	Me	5-NO_2	100	±
21n	CO.thienyl (2)	Me	5-NO_2	100	

and **19b** and **19d** (Table 19) representing 2-oxy-5-nitroimidazoles had moderate *in vivo* activity, while 2-mercapto derivatives or their sulphoxides or sulphones (Table 20) were inactive. Noteworthy is the fact that dichloracetamide **18c**, a nitroimidazole derivative of

Table 22



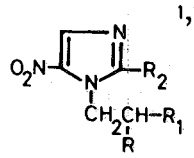
22

Compd	R	R_1	Antiamoebic activity	
			In vitro	*In vivo* (hepatic)
22a	CO_2H	Me	100	—
22b	2-CN.C_6H_4	H	10	+ +
22c	2-($CONH_2$).C_6H_4	H	—	
22d	2-CN.C_6H_4	Me	10	—
22e	2-($CONH_2$).C_6H_4	Me	100	—
22f	2-(CO_2Et).C_6H_4	H		—
22g	2-(CO_2Et).C_6H_4	Me		—

the known amoebicide, diloxanide[30] was bereft of *in vivo* activity against hepatic infection, even though *in vitro* potency was marked (Table 18).

Among simple 4 or 5-nitroimidazoles carrying an extra nitro group or one or two methyl groups (Table 21), as expected and reported[1], the known 5-nitroimidazoles (**21i**) and (**21j**) had a high degree of activity. Surprisingly, **21k**, the 4-nitro isomer of **21i** was also moderately active (ED_{100} 100 mg/kg × 2 p.o.). In the case of compounds derived mostly by manipulation of position-1, with a H atom or a methyl group at position-2, moderate to high activity was observed only for the known drugs. **23a-23d**, corresponding to metronidazole, secnidazole, ornidazole and tinidazole respectively (Tables 22 and 23). Nimorazole (**23e**) was weakly active and afforded 50% cure at 80 mg/kg × 2 p.o. It is to be noted particularly

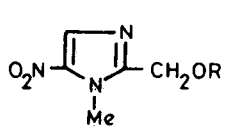
Table 23



23

Compd	R	R_1	R_2	Antiamoebic activity	
				In vitro	*In vivo* (hepatic)
23a	OH	H	Me	10	+ +
23b	OH	Me	Me	10	+ + +
23c	OH	CH_2Cl	Me	10	+ + + +
23d	H	SO_2Et	Me	10	+ + + +
23e	H	4-morpholinyl	H	10	+
23f	H	OEt	Et (4-methyl)	—	
23g	H	CH(OH)Ph	Me	100	±
23h	H	−C(=NOH)−Ph	Me	100	+
23i	H	CO_2H	Me	—	
23j	H	CH(Cl)Ph	Me	10	—
23k	H	CONHPh	Me	100	—
23l	H	$CONHN=CMe_2$	Me	100	±
23*m*	H	CH(OAc)Ph	Me	100	—
23n	H	OCONH.C_6H_4.CO_2Et (4)	Me	10	—
23o	H	1-imidazolyl	Me	10	—
23p	H	2-methyl-(1-imidazolyl)	Me	10	—
23q	OH	$-CH_2-$(1-pyrrolidinyl) (HCl)	Me	10	—
23r	OH	$-CH_2$(1-morpholinyl) methochloride	Me	—	
23s	H	5-nitro-1-phthalimido	H	—	—
23t	H	3-azabicyclo [3,2,2]-2-nonyl (HCl)	Me	10	—
23u	H	4-imino-1,4-dihydro-1-pyridyl (HCl)	Me	1	—
23v	H	2(2-hydroxyethyl)-1-piperidinyl	Me		—

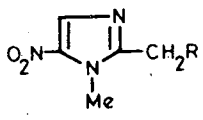
Table 24



24

Compd	R	Antiamoebic activity	
		In vitro	*In vivo* (hepatic)
24a	$-SO_2C_6H_4.Br(4)$	10	—
24b	$-CONHCOCl_3$	10	++++
24c	$-CONHCH_2CO_2Et$	10	—
24d	$-CONHC_6H_3.Cl_2(2,6)$	0.1	—
24e	$-CONH.C_6H_3Me_2(2,6)$	10	—
24f	$-CONH.C_6H_4.NO_2(2)$	0.1	—

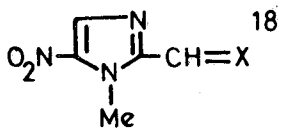
Table 25



25

Compd	R	Antiamoebic activity	
		In vitro	*In vivo* (hepatic)
25a	4-diethylcarbamoyl-1-piperazinyl (HCl)	100	±
25b	3-azabicyclo [3,2,2] nonyl (3)	0.1	—
25c	1,4-dihydro-4-imino-pyridyl (1)	—	
25d	1-imidazolyl	10	+++
25e	$CONHC_6H_5$	100	—

Table 26



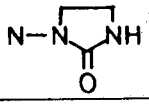
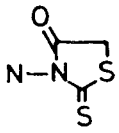
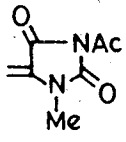
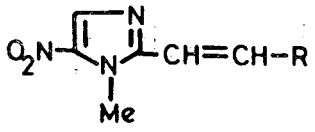
Compd	X	Antiamoebic activity	
		in vitro	in vivo (hepatic)
26a	$NNHCSNH_2$	100	-
26b	NNHCSNHMe	100	-
26c	$NNHCOCONH_2$	10	-
26d		10	-
26e		10	-
26f		100	-

Table 27

18



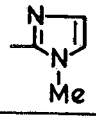
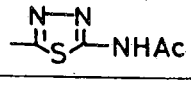
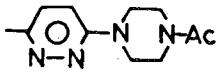
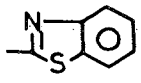
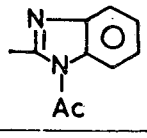
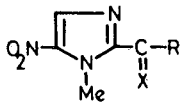
Compd	R	Antiamoebic activity	
		in vitro	in vivo (hepatic)
27a		1	-
27b		1	-
27c		1	±
27d		100	-
27e		0.1	-
27f		0.1	-
27g		10	

Table 28

9



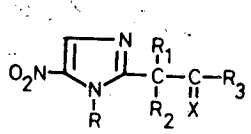
28

Compd	R	X	Antiamoebic activity	
			In vitro	*In vivo* (hepatic)
28a	C_6H_5	O	100	—
28b	4-Cl.C_6H_4	O	10	—
28c	4-NO_2.C_6H_4	O	10	—
28d	2-thienyl	O	10	—

Table 28—Contd.

Compd	R	X	Antiamoebic activity	
			In vitro	*In vivo* (hepatic)
28e	C_6H_5	NOH	1	—
28f	C_6H_5	$NNHC_6H_5$	10	—
28g	4-Cl.C_6H_4	NOH	0.1	—
28h	4-NO_2.C_6H_4	NOH	0.1	—
28i	NHC_6H_5	O	100	—
28j	NHC_6H_4-Cl(4)	O	—	—
28k	$NHC_6H_4.NO_2$(4)	O	100	—
28l	CO_2Et	O	10	—
28m	CO(1-methyl-5-nitro-2-imidazolyl)	O		—

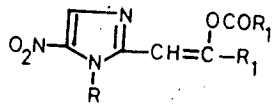
Table 29



29

Compd	R	R_1	R_2	R_3	X	Antiamoebic activity	
						In vitro	*In vivo* (hepatic)
29a	Me	H	H	2-thienyl		10	±
29b	CH_2CH_2OH	H	H	C_6H_5		10	+ +
20c	Me	H	H	C_6H_5	O	1	—
29d	Me	H	H	4-$NO_2C_6H_4$–	O	100	—
29e	CH_2CH_2O–$COC_6H_4.NO_2$ (4)	H	H	4-$NO_2C_6H_4$	O	10	—
29f	CH_2CH_2OH	H	H	4-$NO_2C_6H_4$	O	100	—
29g	$CH_2CH_2COC_6H_5$	H	H	4-$NO_2C_6H_4$	O	100	—
29h	Me	H	H	4-ClC_6H_4	O	10	—
29i	Me	H	H	2-thienyl	O	100	—
29j	CH_2CH_2O–CO–thienyl (2)	H	H	2-thienyl	O	10	—
29k	Me	Br	H	C_6H_5	O		+ +
29l	Me	Br	H	4-$NO_2C_6H_4$	O	100	—
29m	CH_2CH_2OH	Br	H	4-$NO_2C_6H_4$	O	10	—
29o	Me	H	H	3,4,5-$(OMe)_3$–C_6H_2	O	1	—
29p	Me	Br	H	2-thienyl	O		—
29q	Me	Cl	Cl	C_6H_5	O	10	+
29r	CH_2CH_2OH	Cl	Cl	4-$NO_2C_6H_4$	O	10	—
29s	Me	H	H	C_6H_5	NOH	10	—
29t	Me	H	H	4-$NO_2C_6H_4$	NOH	1	—
29u	Me	H	H	2-thienyl	NOH	10	±

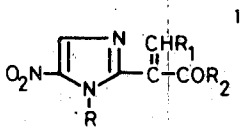
Table 30



30

Compd	R	R_1	Antiamoebic activity	
			In vitro	*In vivo* (hepatic)
30a	Me	C_6H_5	+	—
30b	Me	4-$NO_2.C_6H_4$	1	—
30c	CH_2CH_2O–$CO.C_6H_4.NO_2$ (4)	4-$NO_2.C_6H_4$	10	—
30d	Me	4-ClC_6H_4	10	—
30e	CH_2CH_2O–$CO.C_6H_4Cl$ (4)	4-$Cl.C_6H_4$	10	—
30f	CH_2CH_2OAc	4-$NO_2.C_6H_4$	100	—
30g	Me	3,4,5-$(MeO)_3-C_6H_2$	10	—
30h	Me	2-thienyl	10	—
30i	CH_2CH_2O–CO thienyl (2)	2-thienyl	10	—
30j	CH_2CH_2OAc	2-thienyl	10	—
30k	Me	4-thiazolyl	100	—

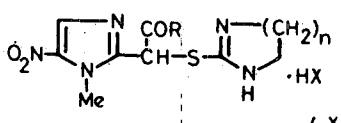
Table 31



31

Compd	R	R_1	R_2	Antiamoebic activity	
				In vitro	*In vivo* (hepatic)
31a	Me	OEt	C_6H_5	10	—
31b	Me	OEt	4-$NO_2C_6H_4$	100	+
31c	Me	NH_2	4-$NO_2C_6H_4$	10	—
31d	Me	4-morpholino	4-$NO_2C_6H_4$	100	—
31e	Me	4-morpholinylamino	4-$NO_2C_6H_4$	100	++
31f	CH_2CH_2OH	OH	4-$NO_2C_6H_4$	10	—
31g	Me	OEt	2-thienyl	10	—

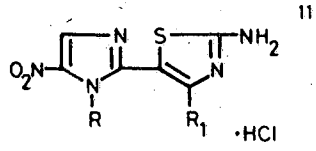
Table 32



32 (X = Cl or Br)

Compd	R	n	Antiamoebic activity	
			In vitro	*In vivo* (hepatic)
32a	C_6H_5	1	10	—
32b	C_6H_5	2	10	—
32c	4-$NO_2.C_6H_4$	2	10	—
32d	2-thienyl	2	10	—

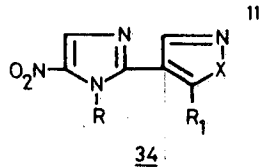
Table 33



33

Compd	R	R_1	Antiamoebic activity	
			In vitro	*In vivo* (hepatic)
33a	Me	C_6H_5	1	±
33b	Me	4-$NO_2.C_6H_4$	10	—
33c	Me	4-Cl.C_6H_4	10	—
33d	Me	2-thienyl	1	—
33e	CH_2CH_2OH	4-$NO_2.C_6H_4$	100	±

Table 34

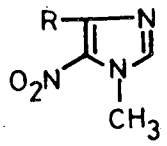


34

Compd	R	R_1	X	Antiamoebic activity	
				In vitro	*In vivo* (hepatic)
34a	Me	4-$NO_2.C_6H_4$	NH	10	±
34b	Me	4-$NO_2.C_6H_4$	O	10	—
34c*	Me	4-$NO_2.C_6H_4$	N-Me	0.1	—
34d*	Me	4-$NO_2.C_6H_5$	N-Ph	0.1	—
34e	Me	2-thienyl	O	10	—
34f	CH_2CH_2OH	4-$NO_2.C_6H_4$	O	10	±

*or isomer

Table 35



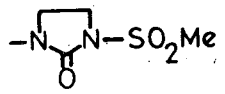
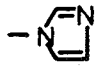
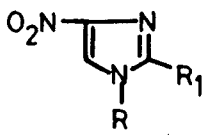
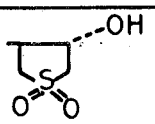
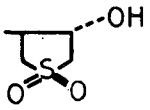
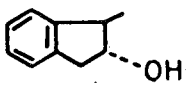
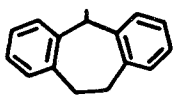
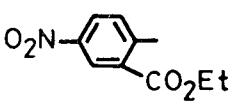
Compd	R	Antiamoebic Activity	
		in vitro	in vivo (hepatic)
35a	Me	10	++
35b	Cl	200	-
35c		200	++
35d		10	++++

Table 36

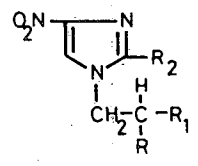


Compd	R	R_1	Antiamoebic Activity	
			in vitro	in vivo (hepatic)
36a		H	-	-
36b		Me	100	-
36c		Me	10	-
36d		Me	100	-
36e		Me	10	±
36f		Me	100	-

that **22a**, a metabolite[1] of metronidazole is inactive against hepatic infections up to 100 mg/kg × 2 p.o.

1-Substituted-5-nitroimidazoles carrying diverse carbon substituents at position-2 were inactive with a few exceptions (Tables 23-34) **24b** (Table 24), an analogue of ronidazole[1], was very potent, but unlike ronidazole had only marginal antibacterial activity. It was also unstable. The imidazole derivative, **25d** (Table 25), **29b** and **29k** (Table 29) were the other exceptions. **25d** is a homologue of **2a**, a highly active amoebicide. It

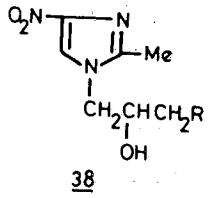
Table 37



37

Compd	R	R_1	R_2	Antiamoebic activity	
				In vitro	*In vivo* (hepatic)
37a	OH	H	Me	1	±
37b	OH	Me	Me	200	±
37c	OH	CH_2Cl	Me	100	—
37d	H	SO_2Et	Me	100	±
37e	H	1-morpholino (HCl)	H	1	±

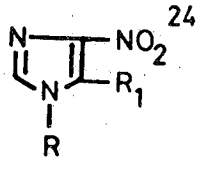
Table 38



38

Compd	R	Antiamoebic activity	
		In vitro	*In vivo* (hepatic)
38a	1-pyrrolidinyl (maleate)	—	—
38b	1-piperidinyl (maleate)	100	—
38c	3-methyl-1-piperidinyl (maleate)	100	—
38d	4-methyl-1-piperazinyl (maleate)	—	
38e	4-morpholinyl (maleate)	—	
38f	methochloride of above	—	

Table 39



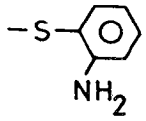
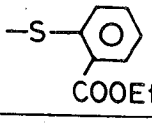
Compd	R	R_1	Antiamoebic activity	
			in vitro	in vivo (hepatic)
39a	Me	Me	100	-
39b	Me	Cl	--	-
39c	H	$CH_2CH_2NH_2$	100	-
39d	Me	$CH_2CH(NH_2)COOH$	-	
39e	Me	$-NH(CH_2)_2NEt_2$	-	-
39f	Me	$-NH(CH_2)_3N$ 	--	
39g	Me		100	-
39h	Me		100	
39i	Me		-	

Table 39 (Contd)

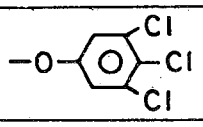
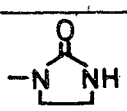
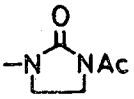
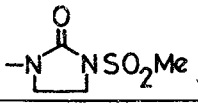
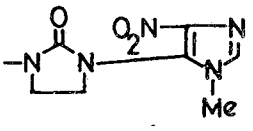
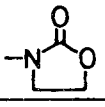
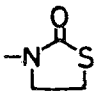
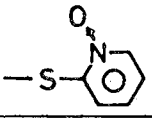
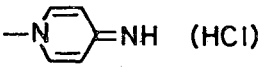
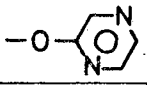
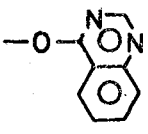
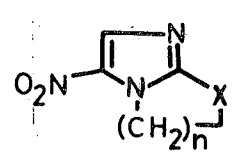
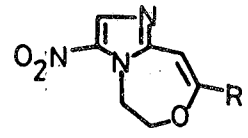
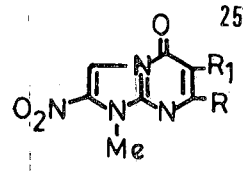
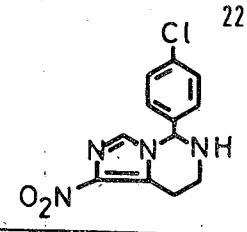
Compd	R	R_1	Antiamœbic activity	
			in vitro	in vivo (hepatic)
39j	Me			-
39k	Me		100	-
39l	Me		100	-
39m	Me		100	-
39n	Me		300	-
39o	Me		100	-
39p	Me		100	-
39q	Me		100	-
39r	Me		1	
39s	Me		-	
39t	Me		-	
39u	Me		100	-
39v	H	Me	10	-

Table 40 — Bicyclic nitroimidazoles

Compd	Structure	Antiamoebic activity	
		in vitro	in vivo (hepatic)
40a	 X = NMe n = 1	1	–
40b	X = NMe n = 2	100	+
40c	X = S n = 1	–	
40d	X = SO_2 n = 1		–
40e	 R = C_6H_5	10	–
40f	R = 4-$NO_2C_6H_4$	10	–
40g	R = 4-Cl.C_6H_4	10	–
40h	R = 2 Thienyl	1	–
40i	 R = CO_2Me; R_1 = H	100	–
40j	R = CO_2Et; R_1 = H	–	
40k	R = CO_2H; R_1 = H	–	
40l	R = H; R_1 = CO_2Et	10	–
40m		10	–

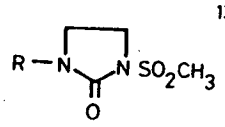
is interesting to note that the 'carbon-bound' pyrazole **34c** (Table 34) is inactive *in vivo*, while a 'nitrogen-bound' pyrazole **3a** (Table 3) is highly active. Curiously their *in vitro* activities are in the reverse order. The inactivity of nitroimidazolyl heterocycles (Tables 33 and 34) are in striking contrast to the properties of 1-methyl-2-(thiadiazolyl)-5-nitroimidazole (C.L. 64855[1]).

Three out of four 1-methyl-5-nitroimidazoles carrying substituents at position-4 rather than 2 were active *in vivo* also (Table 35). Compounds **35c** and **35d** are respectively analogues of **1a** and **2a**. 1-Substituted-4-nitroimidazoles carrying a H atom or a methyl substituent at position-2 (Tables 36-38) or a variety of substituents at position-5 (Table 39) are inactive or marginally active (e.g. **37a-37e**, isomers of clinically useful antiamoebic antitrichomonal drugs). Of the twelve bicyclic systems tested, which incorporate a 5-nitroimidazole (Table 40), only one (**40b**), showed weak activity, while a single example (**40m**) of a bicyclic system having a 4-nitroimidazole residue, was uninteresting. Of 10 examples of 1-methylsulphonyl

imidazolidinone carrying diverse substituents at position-3 (analogues of **1a**) and three of 1-substituted imidazoles (analogues of **2a**), eight were inactive *in vitro* and four *in vivo*. Only compound **42b** had some measure of activity in early hepatic infections. Other derivatives of imidazolidinone including **43f**, a metabolite of **1a**, included in Table 43 were uninteresting.

We can now consider very briefly structure-activity relationships in the groups of active compounds. Among the 3-(nitroimidazolyl)-2-imidazolidinones (Table 1), the substituent at position-1 could be widely varied with retention of activity. Thus this substituent can be the methylsulphonyl (**1a**), methylcarbamoyl

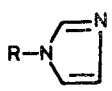
Table 41—



41

Compd	R	Antiamobic activity	
		In vitro	*In vivo* (hepatic)
41a	5-nitro-2-pyridyl	—	
41b	4-nitrophenyl	—	
41c	2-benzthiazolyl	—	
41d	2-benzoxazolyl	—	
41e	2-carbomethoxy-4-nitrophenyl	—	
41f	2-nitrophenyl		—
41g	2-aminophenyl	—	—
41h	5-nitro-2-thiazolyl		—
41i	3-chloro-6-pyridazinyl	—	
41j	$CONH_2$	—	

Table 42—



42

Compd	R	Antiamoebic activity	
		In vitro	*In vivo* (hepatic)
42a	5-nitro-2-thiazolyl	100	—
42b	3-chloro-6-pyridazinyl	1	++
42c	5-nitro-2-pyridyl	1	—

Table 43 - Miscellaneous Imidazoles, Imidazolidinones

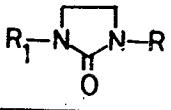
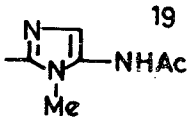
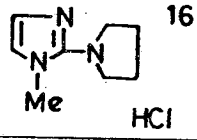
Compd	Structure			Antiamœbic activity	
		R	R_1	in vitro	in vivo (hepatic)
43a		SO_2Me	H	-	
43b		CSNHMe	H	1	±
43c		$CONMe_2$	H	100	
43d		SO_2NMe_2	H	10	
43f		SO_2Me	CONHMe		-
43g		SO_2Me	 19	--	
43h	 16			-	

Table 44—*In vivo* activity against caecal amoebiasis and *T. foetus* infections
mg/kg × 4 p.o. (% cure)

Compd	Caecal amoebiasis	*T. foetus*
1a	30 (100)	15 (100)
1c	40 (85)	15 (100)
1g		30 (100)
1j	30 (80)	30 (100)
1k	30 (95)	10 (100)
1o	40 (75)	10 (100)
1p		15 (100)
2a	40 (100)	20 (100)
2c	40 (90)	
2l	40 (60)	
3a	40 (100)	
6a		100 (100)
6c		100 (100)
6d		100 (100)
21i		40 (100)
21j		100 (0)
21k	120 (100)	
23a	40 (15)	40 (100)
23b	40 (85)	30 (70)
23c	30 (90)	20 (0)
23d	40 (40)	30 (100)
23e	40 (30)	100 (0)
25d		(100) (75)
39k		100 (0)

(**1g**), dimethylcarbamoyl (**1j**), methylthiocarbamoyl (**1o**) or a dimethylsulphamoyl (**1d**) group. In general, extension of a carbon chain in an active compound, e.g. by replacing a methyl with ethyl (**1a**→**1b**, **1d**→**1e**, **1g**→**1h**, **1o**→**1p**) or methoxyethyl (**1a**→**1f**) results in diminished activity. However, compound **1k** is an exception. Introduction of a methyl group in the imidazolidinone ring leaves the activity untouched (**1c**). The 5-nitro-4-substituted imidazole (**35c**) (Table 35), an isomer of **1a** is moderately active, while 1-methyl-4-nitroimidazole carrying the imidazolidinone residue at position-5 (**39n**; Table 39) is inactive at the screening dose. Replacement of the substituted N atom at position-1 in the imidazolidinone moiety of **1a** by O (as in **6d** and **6e**) increases the antiamoebic activity to some degree. Nitroimidazole derivatives of triazolidinediones (Table 7), monocyclic sulphamides (Table 8) and imides (Table 10; **10s-10u**) lack antiamoebic activity. Of the two active bicyclic sulphamide derivatives **9a** and **9b**, the latter with one more CH_2 group is less active. Compound (**41h**), a nitrothiazole analogue of **1a** and a derivative of niridazole is inactive at screening doses, despite the 'isosteric' change involved (N→S).

Compounds resulting from attachment of a nitrogenous aromatic heterocycle at position-2 of 1-substituted-5-nitroimidazoles through a N atom have generally good activity against early hepatic infection. In a series, where this heterocycle is varied from pyrrole (**4a**; 1 N atom) through imidazole (Table 2; 2 N atoms), pyrazole (Table 3; 2 N atoms) to triazole (**4b**; 3 N atoms) and tetrazole (**4c**; 4 N atoms), maximum activity is reached with compounds involving imidazole or pyrazole, the order of activities being **2a** ≒ **3a** > **4b** > **4e** > **4c** (see Tables 2-4). Titration of **2a** and **3a** shows the former to be superior (ED_{100} 25 mg × 2 for **2a** vs 45 mg × 2 for **3a**). Some activity persists with benzazole derivatives also, cf. **5c** and **5g** (Table 5).

Interestingly, good activity is seen to be widely prevalent in the group of 1-(1-substituted-5-nitro-2-imidazolyl) imidazoles (Table 2). The high antiamoebic activity obtained for the prototype **2a** of this series persists when the lipophilicity is increased by addition of up to two CH_2 groups (as two methyl groups or one ethyl) to the imidazole moiety (compounds **2b**, **2c**, **2e**, **2g**) or CH_2OMe group to the methyl group of the nitroimidazole (**2m**). High activity is seen also for the bis (nitroimidazole), (**2l**). However, addition of further methyl or methylene or mercapto groups results in attenuation of activity (**2d**, **2f**, **2h**, **2i**, **2j**).

Shifting of the imidazole residue in **2a** from position-2 to 4 affords the highly active isomer **35d** (Table 35), which is still inferior (ED_{100} 45 mg × 2) to **2a**. But interchange of groups at positions-4 and 5 as in **35d** and **39k** (Table 39) leaves the compound inactive at the dose at which it was tested. Interestingly, the interposition of CH_2 group between the nitroimidazole and imidazole groups in **2a** affords a compound (**25d**) with good activity, while a derivative of metronidazole (**23a**) with imidazole or 2-methylimidazole replacing the OH group (compounds **23o**, **23p**; Table 23) are inactive. Among three 1-heteryl imidazoles tested (Table 42), only the pyridazine derivative, **42c** had some measure of interest.

Among the pyrazoles (Table 3), the high activity of **3a** is diminished or lost by adding substituents like nitro and/or methyl groups to the pyrazole nucleus.

A class of 1-substituted-5-nitroimidazoles carrying a cyclic secondary amine function at position-2 (Table 10) was studied fairly extensively after the early observation of good activity for the pyrrolidine derivative **10a**. However, all the analogues presented in Table 10 obtained by systematic changes of the ring size or substituent at position-1 failed to give a better *in vivo* amoebicide. Indeed activity proved to be very specific for **10a**. The des-nitro derivative **43h** of **10a** was not even active *in vitro*.

Activity against caecal infection

A number of compounds listed in Tables 1-3 which showed very high degree of activity against early hepatic infection were examined in the caecal infection model and were all found to be curative, with small

differences in potency (Table 44). Of the five compounds chosen from Table 1, C 10213-Go (**1a**) was found to have an edge over others. **1a** was also superior to the imidazole (**2**) and pyrazole (**3**) derivatives. The metronidazole (**23a**) group of drugs listed in Table 23 showed varying degrees of efficacy, the most potent of them, ornidazole (**23c**) being less active than **1a**. 1-Methyl-4-nitroimidazole (**21k**) again presented a pleasant surprise by showing 100% cure at 120 mg/kg p.o. × 4. It would thus appear that nitroimidazoles active against hepatic infections in hamsters are consistently effective against caecal infections as well.

Antitrichomonal activity

Active antiamoebic compounds of general structure (**1**) showed 100% efficacy at doses of 10-30 mg/kg p.o., as also imidazole **2a** (Table 44). Among the compounds of general structure (**6**), **6d** with moderate antiamoebic activity in hepatic infections provided 100% cure in the *T. foetus* model at 100 mg/kg p.o. × 4. The thiazolidone (**6a**) and the pyrrolidone (**6c**) though inactive against hepatic amoebic infection at 45 mg × 2/kg p.o., again provided full cure at 100 mg/kg × 4 in *T. foetus* infected mice. Among the metronidazole group of compounds (**23a-23e**), ornidazole at 20 mg/kg × 4 p.o. and nimorazole at 100 mg/kg × 4 p.o. were ineffective while the other three were less active than **1a**. 1-Methyl-5-nitroimidazole (**21i**) was fully curative at 100 mg/kg p.o. × 4, while the 1,2-dimethyl analogue (**21j**), dimetridazole[1] was inactive. Members **37a-e** of the isomeric 4-nitro series were uniformly inactive even at 120 mg, as also the imidazole (**39k**) at 100 mg. Compound **25d**, a homologue of **2a** had moderate *in vivo* antitrichomonal activity; but **35c**, and more so, **35d**, which are respectively position isomers of **1a** and **2a** and which showed moderate and very good activity against hepatic amoebiasis, were inactive against *T. foetus* at 100 mg/kg × 4 p.o., thus indicating that dissociation of these two activities is possible in nitroimidazoles.

Conclusions

Among the various highly active new nitroimidazoles synthesised in our laboratories, we have chosen the methylsulphonylimidazolidinone **1a** for further development on the basis of considerations such as tolerability[30,31], stability and ease of synthesis. We have carried out extensive studies on **1a** in comparison with marketed nitroimidazoles such as **23a-e** in the following models:

(i) Golden hamsters, *Mesocricetus auratus*, infected in the liver or caecum or both with trophozoites of *E. histolytica*[32,33]; (ii) albino mice, *Mus musculus*, infected in the caecum with trophozoites of *E. histolytica*[34]; (iii) mice infected subcutaneously with *T. foetus* or various strains of *T. vaginalis*[35]; and (iv) mice infected with a resistant strain of *T. vaginalis*[36].

In all these models, **1a** was shown to have distinct advantages. **1a** was also found to be superior to metronidazole against a variety of anaerobes[37]. Pharmacokinetic and metabolic studies[38] have been carried out on **1a**, in animals and humans, using unlabelled as well as ^{14}C labelled (at position-2 of the nitroimidazole) substance[39]. Clinical tolerability and efficacy in patients suffering from amoebiasis or trichomoniasis have been established[4].

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