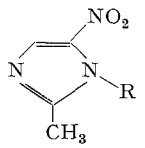
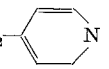
1-(2-(γ-Pyridyl)ethyl)-2-methyl-5-nitro-imidazole (Panidazole), A New Amoebicide

The antitrichomonal properties of 5-nitroimidazoles have been well substantiated in recent years and modification of the N_1-hydroxyethyl side chain of metronidazole (I) has received considerable attention[1,2]. We are now reporting the antiamoebic properties of a 5-nitroimidazole derivative with a basic side chain i.e. γ-pyridylethyl in the N_1 position. Panidazole, 1-(2-(γ-Pyridyl)ethyl)-2-methyl-5-nitroimidazole (II) displayed antitrichomonal



I, R = $-CH_2CH_2OH$

II, R = $-CH_2CH_2-$ 

activity in vivo, but more interestingly showed such activity against *Entamoeba histolytica* that it may well find a place in the chemotherapy of amoebiasis.

A culture of *E. histolytica* (B.W.) was grown on Dobell and Laidlaw's medium and subsequently maintained in LMS[4].

In vivo activity against amoebic hepatitis was investigated in the golden hamster (35–55 g). The liver was infected by means of the gelatin sponge method described by JARUMILINTA[5] under Nembutal anaesthesia. 24 h after infection the animals were divided into groups and treated with either panidazole, metronidazole, or emetine hydrochloride by stomach tube. The dose of emetine was restricted to single daily doses to avoid the toxic effects of the drug. Untreated controls were included in the experiment. 14 days after infection some of the hamsters from each group were killed and the livers examined macroscopically for amoebic abscesses and microscopically for *E. histolytica*.

The results are summarized in the Table. Seven days after infection only one control survived. Four hamsters from the emetine group that died on day 14 were found to have extensive amoebic liver abscesses. The remaining two died on day 17, both showed well developed liver abscesses with *E. histolytica* present.

In the panidazole group one died day 7 and a second on day 11; in the metronidazole group three died on day 5–7. Cause of death could not be established as they were cannabalised. No further deaths occurred and the survivors in both groups were killed and post-mortemed on day 21. Macroscopic examination showed normal livers and no *E. histolytica* could be detected microscopically. These experiments show that panidazole is a potent amoebicide.

The effect of panidazole, metronidazole and emetine on hepatic amoebiasis in golden hamsters

Compound	Dose mg/kg per os	No. of animals	Survivors (in days) 7	14	Observations
None	–	9	1	0	Liver amoebic abscesses in all the hamsters
Panidazole	100	10	9	8	3 killed day 14. No liver amoebic abscesses
Metronidazole	100	8	5	5	3 killed day 14. No liver amoebic abscesses
Emetine hydrochloride	5	8	8	4	2 killed day 14. One showed a liver amoebic abscess; other normal

Treatment started 24 h after infection. Panidazole and metronidazole twice daily for 4 days; emetine once daily for 4 days.

A 1% solution of panidazole in dimethyl sulphoxide (DMSO) was serially diluted with LMS to give a range of concentrations from 0.5 μg/ml to 100 μg/ml. In vitro activity was assessed by inoculating each tube with a 48 h culture of 50,000–100,000 trophozoites. After 48 h at 37 °C the tubes were examined microscopically for growth. Panidazole and metronidazole were amoebicidal at 1 μg/ml, and emetine at 1–3 μg/ml. DMSO had no activity against *E. histolytica*.

Zusammenfassung. Die Wirksamkeit des 1-(2-(γ-Pyridyl)-ethyl)-2-methyl-5-nitroimidazols (Panidazol) auf *Entamoeba histolytica* wurde mit derjenigen des Emetins und des Metronidazols verglichen. Panidazol erweist sich in vitro als ein starkes amöbezides Mittel und ist gegen die induzierte Leberamöbiasis des Goldhamsters hochwirksam.

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