2′-Chloro-1-hydroxy-2-naphthanilide-4′-isothiocyanate — a New Cestodicidal Agent [1]

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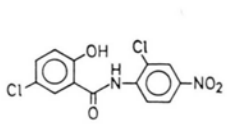
Cestodicidal Agent, *Hymenolepis nana*

2′-Chloro-1-hydroxy-2-naphthanilide-4′-isothiocyanate (**4**) has been synthesized as the structural analogue of yomesan (**1**) and was found to be active against experimental dwarf tapeworm *Hymenolepis nana* infection in rats at an oral dose of 7.5 mg/kg.

Despite the wide prevalence of cestode infections [2, 3], its chemotherapy has remained suprisingly backward during the past decade. Among the various compounds claimed to be effective against cestode parasites, 2′,5-dichloro-4′-nitrosalicylanilide (**1**, yomesan) has been reported to possess high taenicidal activity in a number of hosts [4] including humans [5]. In continuation of our earlier efforts [6, 7] in this laboratory to develop a better cestodicidal agent than **1**, a series of substituted-1-hydroxy-2-naphthanilides [9] were synthesized of which 2′-Chloro-1-hydroxy-2-naphthanilide-4′-isothiocyanate (**4**) was found to be highly effective



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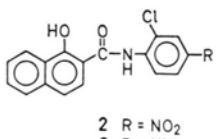

2 R = NO_2
3 R = NH_2
4 R = NCS

against *Hymenolepis nana* infection in rats. This communication reports the synthesis and cestodicidal activity of **4**.

1-Hydroxy-2-(2-chloro-4-nitro)naphthanilide (**2**), required as the starting material, was synthesized by treating 1-hydroxy-2-naphthoic acid with 2-chloro-4-nitro aniline in presence of phosphorus trichloride [10]. Hydrogenation of **2** using Raney-nickel as catalyst gave 82% yield of 1-hydroxy-2-(4-amino-2-chloro) naphthanilide (**3**) [11]. A solution of thiophosgene (1 ml) in chloroform (100 ml) was added dropwise to a stirred solution of **3** (3.2 g) in acetic acid (50 ml) and 4 N HCl (15 ml) and the reaction mixture stirred for 6 h at room temperature. Organic layer was separated, washed with water, dried (Na_2SO_4) and the residue, obtained on removal of solvent, was crystallised from acetone to give 3 g (85%) of **4** m.p. 180°, ν_{max} (KBr) $^{Cm-1}$ 3400 (OH), 2050 (NCS), 1640 (CONH). Anal. Calcd for $C_8H_{11}Cl\,N_2O_2S$: C, 60.93; H, 3.10; N, 7.89; Found: C, 60.83; H, 3.30; N, 7.98%.

The cestodicidal testing of **4** was carried out against experimental *H. nana* infection in rats using the technique of Steward [12] with slight modifications. Newly weaned male rats of University of Freiburg strain were infected by feeding them with 200 viable ova of *H. nana*. On day 15, after intubation of viable ova, rats which were found positive of *H. nana* ova in their faeces were treated after being starved overnight. Initially a single dose of 250 mg/kg of the compound was given orally to 3 animals and 3 were kept as control. All animals including the controls were again starved overnight before being sacrificed on day 3 post-treatment. The small intestine from individual animal was removed separately, washed and the worms collected and scored. Compound bringing down the worm load to 0–10% of the control was considered to be active in this test.

During the first investigation on the efficacy of **4** against *H. nana* in rats, **4** was given orally at dosages 250, 100, 50 and 10 mg/kg. The minimum effective dose giving 100% clearance of worm-load was found to be 7.5 mg/kg. In simultaneous controlled trials in rats, **4** exhibited ED_{100} and ED_{50} at 5 and 1.74 mg/kg given orally. Parallel experiments with yomesan (**1**) showed ED_{100} and ED_{50} at 50 and 14.5 mg/kg respectively. The relative potency of **4** with respect to **1** is calculated to be 8.3 (Table I).

Cestodicidal activity tests in mice infected with *H. nana* showed that **4** could achieve 100% removal of the worms at a dose of 14 mg/kg in comparison to 280 mg/kg dose of **1** for same order of activity.

The toxicity experiments carried on the normal and infected rats were highly encouraging. A single oral dose of 5 g/kg was tolerated well by normal rats without any mortality. Similarily, the young infected rats tolerated 1 g/kg of the compound (higher

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Table I. Comparative Efficacy of **4** and yomesan. (Probit Analysis — M. L. Method)

	4	Yomesan							
Dose (mg/kg)	5	2.5	1.75	1.25	50	25	17.5	12.5	8.75
No. of animals treated	6	4	5	6	4	5	7	9	5
No. of animals cleared	6	3	3	1	4	4	5	3	1
% Response	100	75	60	16.7	100	80	71.4	33.3	20
ED_{50}		1.74					14.5		
Fiducial limits		1.11—2.64				9.3—21.2			

Relative potency of **4** with respect to yomesan with fiducial limit — 8.3 (5.2—13.5).

dosages were not tried in view of the very low ED_{50}). The compound was found to be equally safe in mice, mastomys and dogs.

In further tests carried against *Hymenolepis diminuta* in rats and *Taenia* sp. in dogs, **4** proved to possess marked activity. The compound is currently in the advanced pharmacological and chronic toxicity studies in rats and monkeys in our laboratory.

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