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SYNTHESIS OF NEOEUDISTOMIN ANALOGS - AS POTENTIAL FILARICIDES[1]

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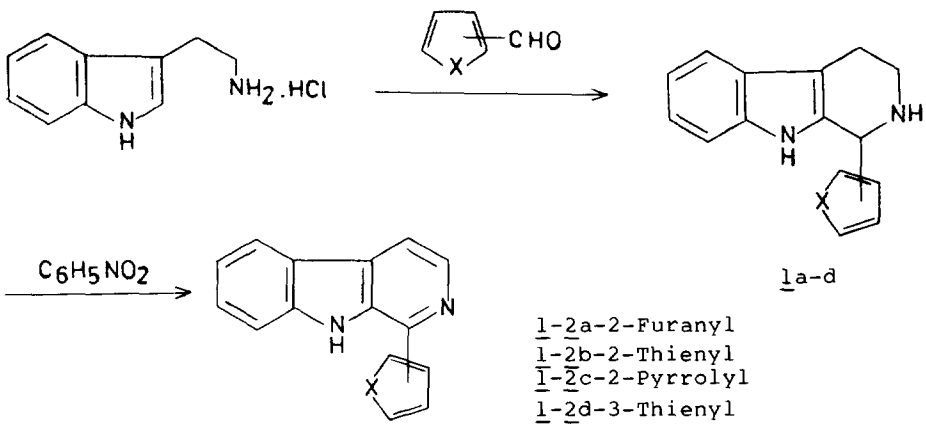
Abstract: Utilizing Pictet-spengler cyclisation, derivatives of neoeudistomin, 1-(furan-2-yl/thien-2-/3-yl/pyrrol-2-yl)-9H-pyrido[3,4-b]indoles have been synthesized. These compounds exhibited promising filaricidal activity, *in vivo* against *Litomosoides carinii* and *Acanthocheilonema viteae* in rodents.

Lymphatic filariasis, is one of the most prevalent, neglected tropical disease of this world. Morethan 900 million people are living in endemic areas and over 80 million people are infected with lymphatic filariasis. In India, approximately 25 million people are known to harbour circulating microfilariae (mf) and another 19 million people suffer from filarial manifestations caused by lymph dwelling filariids, *Wuchereria bancrofti* and *Brugia malayi*[2].

The successful treatment is jeoparadized, due to lack of suitable chemotherapeutic agents capable of eliminating both microfilariae and adult worms with least toxicity to the host[3]. Benzimidazole class of compounds possessing high order of activity against intestinal and to the extent against tissue dwelling helminths have several set backs[4,5] and thus there is need for search for new structural prototypes having macrofilaricidal (maf) activity.

In our recent studies[6], substituted 1-H/1-phenyl-9H-pyrido[3,4-b]indoles elicited interesting filaricidal activity against *L. carinii* and *A. viteae* in rodents. Eudistomin alkaloids containing 9H-pyrido[3,4-b]indoles nucleus, isolated from the caribbean tunicates *Eudistoma olivaceum* have been described to possess antiviral activity against herpes simplex virus (HSV-1)[7]. This has drawn our attention to synthesize neoeudistomin (**2c**) and its analogs and evaluate them for antifilarial activity.

The only reported synthesis of neoeudistomin (**2c**, x = NH) is by Rinehart *et. al*[8]. from 2-(1,3-dioxa-2-cyclohexyl)bromide and 1-cyano-9H-pyrido[3,4-b]indole, which was obtained in five steps from tryptamine. We now report a general two step synthesis of these class of compounds utilizing Pictel-spengler cyclisation reaction.



1a-d

1-2a-2-Furanyl
1-2b-2-Thienyl
1-2c-2-Pyrrolyl
1-2d-3-Thienyl

2a-d

Pictet-spengler cyclisation of tryptamine with pyrrole-2-carboxaldehyde in ethanol under inert atmosphere provided 1,2,3,4-tetrahydro-1-(pyrrol-2-yl)-9H-pyrido[3,4-b]indole (**1c**)[9] which on

Table 1: Physico-Chemical data and antifilarial activity of neoeudistomin analogs (1-2)

Compd.	Yield (%)	m.p. (°C)	Activity against *L. carinii* (30 mg/kg x 5 days, i.p.)		Activity against *A. viteae* (50 mg/kg x 5 days, i.p.)	
			mf	maf (sterl of ♀)	mf	maf
1a	52	160-1	0	0	0	22
1b	86	130-2	0	0	70	81
1c	84	168-9	-	-	75*	0
1d	93	180-3	0	0	73	100
2a	60	180 (Lit.[11] 179-80)	0	98	0	0
2b	76	165-8	0	0	0	0
2c	56	190-3 (Lit.[8] 192-5)	73	68(90)**	33	0
2d	51	150-2	-	-	20	44
DEC citrate	-	-	>90***	0	>90****	0

'0'- inactive; '-' not done; * at 200 mg/kg x 5 days (p.o)

** figures in parenthesis shows sterlization of ♀ worms. DEC - Diethyl carbamazine *** 6 mg/kg x 5 (i.p.) **** 350 mg/kg x 5 (i.p.)

dehydrogenation in refluxing nitrobenzene furnished neoeudistomin (**2c**)[10]. Similarly, the reaction was extended with furfural and thiophene-2-/3-carboxaldehyde gave the corresponding 1-(furan-2-yl)/(thien-2-/3-yl)-9H-pyrido[3,4-b]indoles (**2a-b, 2-d**; Table 1).

Antifilarial Activity

The micro- and macrofilaricidal activities of the synthesized compounds were evaluated against *L. carinii* in cotton rats (Sigmodon hispidus) and *A. viteae* in *Mastomys natalensis* as described earlier[6]. Compounds being insoluble in water were made fine suspensions with 1% Tween 80. Two to three animals were used for each dose level study and atleast two replicates were used for confirmation of activity.

Results and Discussion

Amongst the compound tested only compounds **2a** and **2c** showed significant filaricidal action (> 90% micro- and/or macrofilaricidal action or sterlization of female worms) against *L. carinii* at 30 mg/kg x 5 days (i.p.).

Ingeneral, all the substituted 9H-pyrido[3,4-b]indoles except **2a** and **2b** exhibited a wide range of activity against filarial parasite *A. viteae* in *Mastomys natalensis* at 50 mg/kg x 5 days (i.p.) or 200 mg/kg x 5 days (p.o.).

The tetrahydro derivatives **1** have better activity against *A. viteae* in *Mastomys natalensis* than *L. carinii* in cotton rats, whereas aromatized compounds **2** have better adulticidal activity against *L. carinii* than *A. viteae*. Compounds with thien-2-/3-yl substituent in tetrahydro series have more pronounced adulticidal effect against *A. viteae*, while compounds with furan-2-yl and pyrrol-2-yl substituent in aromatised series have pronounced effect against *L. carinii*. This would indicate that thienyl substituent at 1-position plays an important role in eliciting biological response in tetrahydro-ß-carbolines.

Accordingly, compound **1b** and **1d** are under further investigation *in vivo* against *Brugia malayi* and these results will be reported in due course else where.

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9. Pyrrole-2-carboxaldehyde (0.48g, 5.05 mmoles) was added in portions to a stirred solution of tryptaminehydrochloride (1g, 5.09 mmoles) in absolute ethanol (20 ml) in dark (to avoid the change of colour into black) under inert atmosphere over a period of 30 min. The reaction mixture was stirred for further 8 hr. and concentrated to dryness *in vacuo*. The residue thus obtained was neutralized with 10% aqueous Na_2CO_3 solution and extracted with chloroform (2 x 100 ml). The chloroform extract was washed with water, dried (Na_2SO_4) and concentrated to furnish a semisolid, which was purified over a florisil column, elute from a mixture of chloroform:hexane (9:1) gave orange colour crystals of 1c. Yield 1g; IR (KBr, cm^{-1}): 3397, 3214, 3180-2859, 1639, 1422, 827, 772, 744; ^{1}H-NMR-$CDCl_3$ (δ,ppm): 8.5 (bs, 1H, indole NH), 7.83 (s, 1H, NH), 7.56 (m, 1H, ArH), 7.2-6.93 (m, 4H, ArH), 6.7 (s, 1H, H-1), 6.4 (dd, 1H, H_3,, J=4Hz, J=2Hz), 6.17 (dd, 1H, H4', J=4Hz, J=2Hz), 3.76 (t, 2H, H_3, J=6Hz), 3.0 (t, 2H, H_4, J=6Hz); ms:(m/e) 237 (M^+, 54%).
10. Compound 1c (1g, 4.21 mmoles) was dissolved in $C_6H_5NO_2$ (40 ml) and refluxed for 4 hr. After cooling the excess of $C_6H_5NO_2$ was removed *in vacuo*. The obtained residue was purified over a silica column. elute from a mixture of hexane: chloroform (9:1) gave the light yellow crystals of 2c.
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