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Synthesis of 1-(N-Substituted-Carboxamido-2-Aminophenyl) 4-Methyl-Piperazines: D.E.C. Analogs and Their Antifilarial Activity-II

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A series of 1-(N-substituted-carboxamido-2-amino phenyl 4-methyl piperazines (**I–IX**) have been synthesized and tested for their antifilarial activity; compounds **III, V, VI** have exhibited 76.8 ,72.4 and 75% microfilaricidal activity respectively.

Key Words: 1-(N-Substituted-carboxamido-2-aminophenyl) 4-methyl-piperazines, D.E.C. analogs, Antifilarial activity.

INTRODUCTION

Filariasis or elephantiasis is a mosquito borne disease. It is one of the biggest and oldest known human malades affecting our 90 million people and exposing another 905 million at risk in the tropical countries. No suitable drug is available today which can act on adult filarials responsible for causing the disease manifestation. There is thus an urgent need to develop better microfilaricidal drugs. D.E.C. is the drug of choice for treating filariasis[1]. The drug kills 90% of the circulating microfilariae of *L. carinii* and mastomys but has poor or no activity against the adult worm of *L. carinii*. However, D.E.C. has severe side effects[2] and as such is not suitable for the eradication of filariasis. Molecular modifications[3] of D.E.C. led to centperazine which has greatly reduced conformational mobility of diethylcarbamoyl side chain and showed microfilaricidal activity superior to D.E.C. Keeping in view the enhanced activity of analogs of D.E.C. with rigid conformation, compounds **I–IX** have been prepared.

4-Chlorobenzoic acid on nitration[4] gave 4-chloro-3-nitrobenzoic acid. Nucleophilic displacement of chloro group in 4-chloro-3-nitrobenzoic acid with N-methyl piperazine followed by treatment with thionyl chloride yielded 4-(N-methylpiperazine)-3-nitrobenzoyl chloride; this upon reduction gave 4-(N-methyl piperazino)-3-aminobenzoyl chloride, which was treated with different heterocyclic and aromatic amines as well as with dimethyl amines to generate target compounds **I–IX (Scheme-1).** The synthesized compounds have been adequately characterised by spectral data (PMR) and by elemental analysis.

EXPERIMENTAL

Melting points were taken in open capillaries in a sulphuric acid bath and are uncorrected. PMR spectra were recorded on an R-32 Perkin-Elmer (90 MHz) instrument (chemical shift in δ-scale downfield from TMS internal standard).

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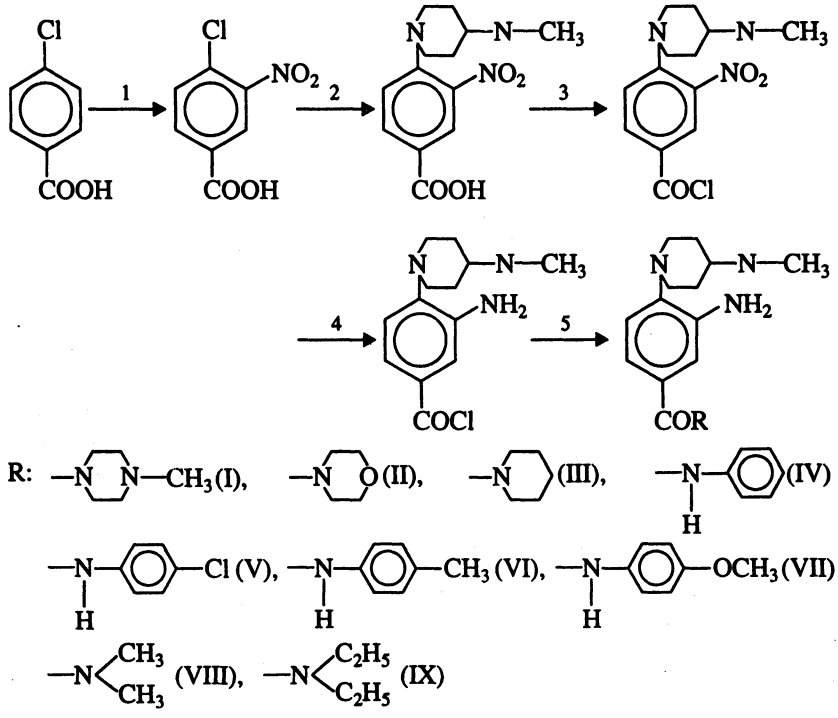
Preparation of 1-(N-substituted carboxamido-2-aminophenyl)-4-Methylplperazines (I–IX)

4-Chlorobenzoic acid (0.1 mol) was taken in a conical flask and to this was added 50 mL of fuming HNO_3. The reaction mixture was heated on a water bath for 1 h. The contents were allowed to cool and then poured into water when crystals of 4-chloro-3-nitrobenzoic acid separated out. These were filtered and recrystallized from methanol; m.p. 182°C; yield 85%.

4-Chloro-3-nitrobenzoic acid (0.1 mol) was dissolved in 30–40 mL of isopropyl alcohol and N-methyl piperazine (0.2 mol) was added to it. The reaction mixture was refluxed for 7–8 h. Excess solvent was evaporated; 4-(N-methyl piperazino)-3-nitrobenzoic acid thus separated was filtered and washed with methanol; m.p. 254–55°C; yield 65%.

To 4-(N-methyl piperazino)-3-nitrobenzoic acid (0.01 mol) was added chloroform (10 mL) and thionyl chloride (0.02 mol). The reaction mixture was allowed to reflux for 2–3 h. Excess thionyl chloride was removed by distillation. The product 4-(N-methyl piperazino)-3-nitrobenzoyl chloride (m.p 60°C) was highly unstable and immediately used up in further reaction.

4-(N-methyl piperazino)-3-nitrobenzoyl chloride (0.01 mol) was dissolved in methanol (15 mL); 0.1 g of Raney nickel was added. The contents were treated with 1 mL of hydrazine hydrate and the mixture refluxed for 4 h. The contents were filtered. The product was recrystallized from methanol; yield 60%; m.p. 70°C.



1. Fuming HNO_3, 2. N-Methyl piperazine 3. $SOCl_2$ 4. Raney Ni, Hydrazine hydrate 5. 10% NaOH solution of respective amine

4-(N-methyl piperazino)-3-aminobenzoyl chloride (0.01 mol) was treated with 1 mL of N-methyl piperazine in 8 mL of 10% sodium hydroxide.The reaction mixture was shaken vigorously for 30 min. Compound I was extracted as an oil in chloroform. Removal of chlorofom yielded I in 45% yield. Compound **II–IX** were prepared similarly by using different amines.

The physical data of compounds **I–IX** are recorded in Table-1, while PMR-spectral data are given in Table-2.

TABLE-1
PHYSICAL AND ANALYTICAL DATA OF SYNTHESIZED COMPOUNDS

Compound No.	Yield (%)	m.p. (°C)	m.f.	Analysis (%), Found (Calcd.)	
				C	H
I	42	Oil	$C_{17}H_{27}N_5O$	64.2 (64.3)	5.0 (5.0)
II	45	120	$C_{16}H_{24}N_4O_2$	63.1 (63.2)	7.8 (7.9)
III	48	Oil	$C_{17}H_{26}N_4O$	68.1 (68.2)	8.5 (8.6)
IV	76	110	$C_{18}H_{22}N_4O$	69.5 (69.8)	7.0 (7.1)
V	56	140	$C_{18}H_{21}N_4OCl$	62.5 (62.7)	6.1 (6.1)
VI	72	170	$C_{19}H_{24}N_4O$	70.2 (70.3)	7.02 (7.4)
VII	70	180	$C_{19}H_{24}N_4O_2$	67.0 (67.0)	7.0 (7.0)
VIII	52	Oil	$C_{14}H_{22}N_4O$	64.1 (64.2)	8.2 (8.3)
IX	50	Oil	$C_{16}H_{26}N_4O$	66.1 (66.2)	8.8 (8.9)

Antifilarial Activity: After the primary toxicity studies carried out in mice, the synthesized compounds were evaluated for antifilarial screening[5]. Cotton rats *(sigmadon hispidus)* infected with *L. carinii* used as primary screening models were injected intraperitoneally with 30 mg/kg dose of the test compound for 5 days. 5 mL of blood was taken from the tail of each animal before starting the treatment and thereafter at weekly intervals, *i.e.*, days 8, 14, 21, 28, 35 and 42. On day 42 treated and control animals were sacrificed to observe the condition of adult parasites.

Compounds **I, II** and **IV** showed mild microfilaricidal activity (17.2–35%) on day 8 but showed no activity against adult parasites. Compounds **III, V, VI** exhibited microfilaricidal activity 76.8, 72.4 and 75% respectively on day 8. However, the number of microfilariae increased and crossed the initial level in case of compound **III.** Compound **V** demonstrated comparatively prolonged suppression of microfilaraemia, *i.e.*, 84.2% fall in microfilariae till day 21.

Suppressed microfilaraemia was observed till day 42 with compound VI and 55–60% of surviving females were found sterilized. None of the compounds showed lethal effect on adult worms.

TABLE-2
PMR DATA OF-1-(N-SUBSTITUTED-CARBOXAMIDO-2-AMINOPHENYL)-4-METHYLPIPERAZINES

Compound No.	PMR δ ($CDCl_3$)
I.	δ 2.3 (N—CH_3 attached to aromatic ring, 3H, S) 2.34 (N—CH_3 attached to C=O group, 3H, S) 2.5 (CH_3—N , 8H, m) 3.15 (CH_2—N—CH_2) attached to aromatic ring (4H, t) 3.64 (CH_2—N—CH_2 attached to C=O group, 4H, t) 7.16 (Ar—5H, 1H, dj_0 = 8 Hz). 7.55 (Ar—6H, 1H, dj_0 = 8 Hz) 7.89 (Ar—2H, 1Hd, j_m = 2 Hz.)
II.	δ 2.37 (N—CH_3, 3H, S) 2.63, (CH_3—N , 4H, t) 3.18 (CH_2—O—CH_2, 4H, t) 3.69 (CH_2—N—CH_2, 8H, S) 7.12 (Ar—5H, 1H, Sj_0 = 8.5 Hz) 7.65 (Ar—6H, 1H, dj_0 = 8.5 Hz) 7.85 (Ar—2H, 1H, d, j_m = 2Hz)

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