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Synthesis of 1-Heterocyclic Aminomethyl-3-(4'-anilino-3'-nitrobenzoyl hydrazono)-2-indolinones as Antifilarial and CNS Active Agents

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A series of 1-heterocyclic aminomethyl-3-(4'-anilino-3'-nitrobenzoyl hydrazono)-2-indolinones (**VIa-VII**) have been synthesized and tested for their antifilarial and CNS activity. The compounds **VIa**, **VId**, **VIg** have exhibited 75.8, 78.2 and 70.5 % microfilaricidal activity respectively.

Key Words: 1-Heterocyclic aminomethyl-3-(4'-anilino-3'-nitrobenzoyl hydrazono)-2-indolinones, Antifilarial, CNS activity.

INTRODUCTION

The term "filariasis" (Sheel Pad) comprises a group of diseases caused by the invasion of lymphatic system or connective tissue by certain nematodes. Almost half a billion people are infected with the filariodea family of tissue nematodes mostly in tropical countries[1]. Filariasis is transmitted by the bite of blood sucking insects. During a blood meal the insect vector inject larvae into the definitive host (man). Adult male and female worms mate and the female releases microfilariae (M.F) which migrate through the blood or tissue. These larvae are picked up by the insect vector during a blood meal to complete the life cycle. No suitable drug is available today which can act on adult filarial responsible for causing the disease manifestation. There is an urgent need to develop better microfilaricidal drugs D.E.C. which is the drug of choice for treating filariasis[2]. The drug kills 90 % of the circulating microfilariae of *L. carinii* and mastomys but has poor or no activity against the adults worm of *L. carinii*. However, D.E.C. has severe side effects[3] and as such is not suitable for the eradication of filariasis. Molecular modification[4] of D.E.C. led to centperazine which has greatly reduced conformational mobility of diethyl carbamoyl side chain and showed microfilaricidal activity superior to D.E.C. keeping in view the enhanced activity of analogues of D.E.C. with rigid conformation, compounds **IIa-VII** have been proposed.

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 (90MHz) instrument (chemical shift in δ-scale downfield from TMS internal standard)

Synthesis of 1-heterocyclic aminomethyl-3-(4'-anilino-3'-nitrobenzoyl hydrazono)-2-indolinones (IIa-VII): The 4-chlorobenzoic acid was nitrated to furnish the nitro acid (**I**)[5] which under nucleophilic attack with aryl amines yielded **II** in reasonably good yields. Esterification of **II** resulted in the smooth formation of nitro esters **III** hydrazinolysis with 99 % hydrazine hydrate gave **IVa-d** in appreciate yields. Mild acid catalyzed condensation of **IVa-d** with indol-2,3- dione generated **Va-d**, respectively. Aminomethylation of **Va-d** with secondary heterocyclic amines morpholine, piperidine and N-methyl piperazine led to target compounds **VIa-I** (**Scheme-I**). All the newly synthesized compounds gave correct elemental analyses. Additional evidence in support of assigned structures was derived from their IR, PMR, ^{13}C NMR, mass spectral data.

4-Chloro-3-nitro benzoic acid (I): 4-Chloro benzoic acid (0.1 mol) was taken in a conical flask to which 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-nitro benzoic acid separated. These were filtered and recrystallized from methanol m.p. 182 °C, yield 85 %.

4-Arylamino 3-nitro benzoic acids (IIa): In a typical procedure 4-chloro-3-nitro benzoic acid (0.02 mol) and aniline (0.04 mol) in *n*-propanol (15 mL) were refluxed for 12 h. The separated solid (**IIa**) was filtered, washed with methanol and recrystallized from ethanol m.p. 248-50 °C; yield 80 % **IIb-d**

were prepared similarly using *p*-chloro aniline-*p*-toluidine and *p*-anisidine.

IIb: m.p. 274-275 °C, yield 64 %; **IIc:** m.p. 257 °C, yield 80 %; **IId:** m.p. 226 °C, yield 75 %. All the compounds **IIa-d** were characterized as their corresponding methyl esters (**IIIa-d**).

Methyl 4-anilino-3-nitrobenzoates (IIIa): IIa (0.01 mol) was taken in methanol (250 mL), thionyl chloride (1 mL) was added to it dropwise with cooling and shaking. The reaction mixture was heated on a water bath for 15 h. The contents were then neutralized with aqueous sodium carbonate, The product thus separated was filtered washed with water and recrystallized from methanol. **IIIa** thus obtained melted at 128-129 °C; yield 65 %. IR (KBr, ν_{max}, cm^{-1}): 1740 ($COOCH_3$); 3320 (NH); PMR ($CDCl_3$): 3.90 (s, 3H, CH_3); 7.15 (d, IH, Ar-5-H, *J* = 8 Hz), 7.2-7.5 (m, 5H, NH-C_6H_5); 7.95 (d, 1H, Ar-6-H, *J* = 8 Hz), 8.9 (s, 1H, Ar-2-H, J_m = 2 Hz), 9.78 (s, 1H, -NH-). (Found: C, 61.7; H, 3.3 $C_{14}H_{12}N_2O_4$ requires C, 61.3; H, 4.1 %).

IIIb: m.p. 145 °C, yield 68 %; IR (KBr, ν_{max}, cm^{-1}): 1720 ($COOCH_3$); 3300 (NH); PMR ($CDCl_3$): 3.9 (s-3H, CH_3), 7.14 (d, 1H, Ar-5-H, *J* = 8 Hz), 7.25 (d, 2H, Ar- 2'-6-H, *J* = 8 Hz), 7.43 (d, 2H, Ar-3'-5'-H, *J* = 8 Hz), 7.98 (d, 1H, Ar-6-H, *J* = 8 Hz), 8.88 (s, 1H, Ar-2-H, J_m = 2 Hz), 9.69 (s, IH, -NH-). (Found: C, 54.8; H, 3.6, $C_{14}H_{11}N_2O_4$ requires C,54.8; H, 3.5 %).

IIIc: m.p. 160-62 °C, yield 69 %; IR (KBr, ν_{max}, cm^{-1}): 1720 ($COOCH_3$); 3400 (NH); PMR ($CDCl_3$): 2.4 (S, 3H, Ar-CH_3), 3.9 (s, 3H, CH_3), 7.08 (d, 1H, Ar-H, *J* = 8 Hz), 7.1-7.3 (m, 4H, C_6H_4-CH_3), 7.92 (d, IH, Ar-6-H, *J* = 8 Hz), 8.75 (s, 1H, Ar-2-H, J_m =2 Hz), 9.7 (s, IH, -NH). (Found: C, 62.9; H, 4.9, $C_{15}H_{14}N_2O_4$ requires C, 62.7; H, 4.6 %).

IIId: m.p. 155 °C, yield 80 %; IR (KBr, ν_{max}, cm^{-1}): 1715 ($COOCH_3$); 3340 (NH); PMR ($CDCl_3$): 3.84 (s, 3H, $ArOCH_3$), 3.89 (s, 3H, CH_3), 6.95 (d, 1H, Ar-5-H, *J* = 8 Hz), 7.12 (d, 2H, Ar-2'-6'-H, *J* = 8 Hz), 7.21 (d, 2H, Ar-3'-5'-H, *J* = 8 Hz), 7.9 (d, 1H, Ar-6-H, *J* = 8 Hz), 8.87 (s, 1H, Ar-2-H, J_m = 2 Hz), 9.65 (s, 1H, -NH-1). (Found: C, 59.6; H, 4.6 $C_{15}H_{14}N_2O_5$ requires C, 59.3; H, 4.5 %).

4-Anilino-3-nitro benzoyl hydrazine (IVa): Compound **IIIa** (0.005 mol) and hydrazine hydrate 99 % (2 mol) in propanol-2 (20 mL) were refluxed for 6 h. The separated solid was filtered, washed with methanol and recrystallized from ethanol. m.p. 164-65 °C, yield 50 % (Found: C, 57.4; H, 4.4, $C_{13}H_{12}N_4O_5$ requires C, 57.2; H,4.6 %).

3-(4'-Anilino-3'-nitrobenzoyl hydrazono)-2-indolinone (Va): Compound **IVa** (0.005 mol) was dissolved in warm dimethyl formamide (5 mL). Containing 2-3 drops of glacetic acid. Isatin (0.005 mol) was added to it. The contents were heated for 0.5 h and allowed to stand at room temperature overnight. The solid was filtered, washed with methanol and recrystallized from dimethyl formamide.

Compounds **Vb-Vd** were prepared similarly, physical characteristics of the synthesized compounds are listed in Table-1.

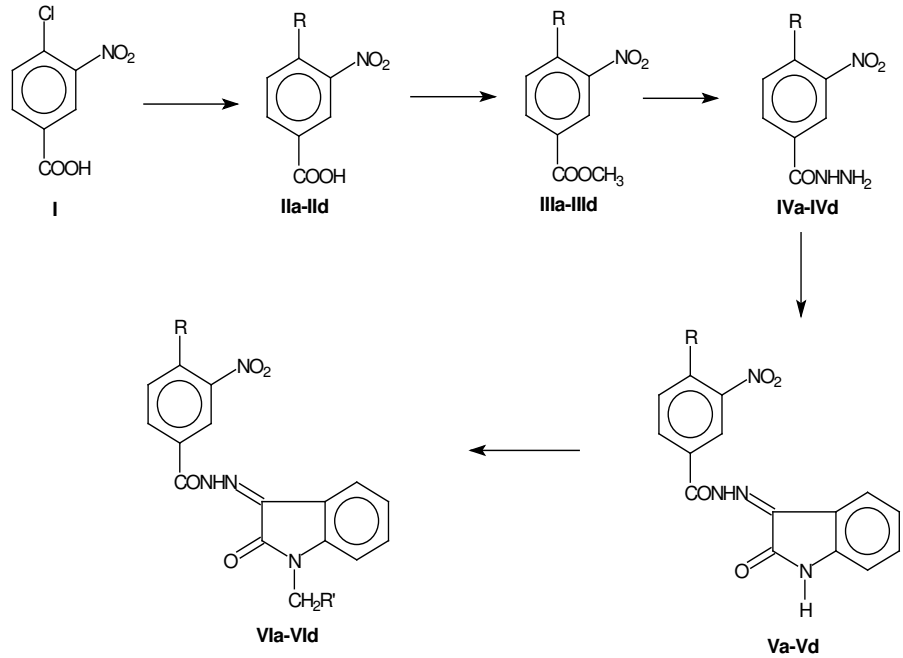
1-Heterocyclic aminomethyl-3-(4'-anilino-3'-nitro-benzoyl hydrazono)-2-indolinones (VIa): Compound **Va** (0.005 mol) was dissolved in hot dimethyl formamide (4 mL). To this solution aqueous formaldehyde (0.005 mol) and morpholine (0.005 mol) were added with vigorous stirring. The reaction mixture was heated for 5 min and allowed to stand at room temperature overnight. The product thus separated was filtered, washed with methanol and recrystallized from chloroform-petroleum ether (60-80 °C) (**Scheme-I**).

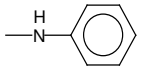
The same procedure was employed for synthesis of compounds **VIb-l**. Physical characteristics of the synthesized compounds are listed in Tables 1 and 2.

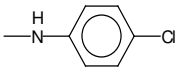
Antifilarial activity: After primary toxicity studies carried out in mice, the synthesized compounds were evaluated for antifilarial screening[5]. Cotton rats (*Sigmadon hispidius*) infected with *L. carinii* used as primary screening models were injected for 6 d intraperitonelly with 25 mg/kg dose of the test compound, a suspension of which was made in 1 % T-80 solution in sterides water 5 mL of blood was taken from the tail of each animal before starting the treatment and thereafter at weekly intervals *i.e.*, 8th, 15th, 22nd, 29th, 36th and 43rd day, on the 43rd day the treated and control animals were sacrificed to observe the condition of adult parasite.

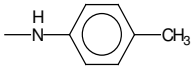
TABLE-L
CHARACTERIZATION DATA OF 3-(4'-ARYLAMINO-3'-NITRO BENZOYL HYDRAZONO)-2-INDOLINONES (**Va-Vd**) AND 1-HETEROCYCLIC AMINOMETHYL-3-(4'-ARYLAMINO-3'-NITROBENZOYL HYDRAZONO)-2-INDOLINONES (**VIa-VII**)

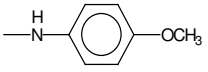
Compd.	R	m.p. (ºC)	Yield (%)	m.f.	Elemental analysis (%): Calcd. (found)	
					C	H
Va	H	274	53	$C_{21}H_{15}N_5O_4$	–	–
Vb	Cl	> 270	65	$C_{21}H_{14}N_5O_4Cl$	–	–
Vc	CH_3	> 270	70	$C_{22}H_{17}N_5O_4$	–	–
Vd	OCH_3	> 270	52	$C_{22}H_{17}N_5O_5$	–	–
VIa	H	226	65	$C_{26}H_{24}N_6O_5$	62.6 (62.3)	4.8 (5.0)
VIb	Cl	228	57	$C_{26}H_{23}N_6O_5Cl$	58.8 (58.4)	4.9 (4.8)
VIc	CH_3	237	81	$C_{27}H_{26}N_6O_5$	63.9 (63.8)	5.3 (5.1)
VId	OCH_3	224	64	$C_{27}H_{26}N_6O_6$	59.7 (59.5)	4.4 (4.2)
VIe	H	230d	70	$C_{27}H_{26}N_6O_4$	65.1 (65.0)	5.2 (5.0)
VIf	Cl	218	58	$C_{27}H_{25}N_6O_4Cl$	60.8 (60.8)	4.7 (4.9)
VIg	CH_3	211	67	$C_{28}H_{28}N_6O_4$	65.6 (65.4)	5.5 (5.5)
VIh	OCH_3	190	67	$C_{28}H_{28}N_6O_5$	63.6 (63.4)	5.3 (5.2)
VIi	H	212	75	$C_{27}H_{27}N_7O_4$	63.2 (63.1)	5.3 (5.1)
VIj	Cl	210	67	$C_{27}H_{26}N_7O_4Cl$	59.2 (59.0)	4.7 (4.5)
VIk	CH_3	198	68	$C_{28}H_{29}N_7O_4$	63.8 (63.8)	5.0 (5.4)
VIl	OCH_3	200	70	$C_{28}H_{29}N_5O_5$	61.9 (61.3)	5.3 (5.7)

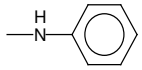


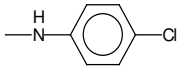
IIa R = 

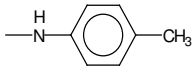
IIb R = 

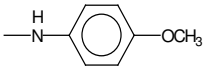
IIc R = 

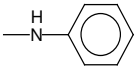
IId R = 

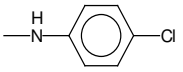
IIIa R = 

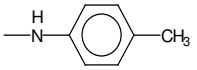
IIIb R = 

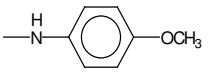
IIIc R = 

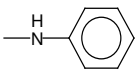
IIId R = 

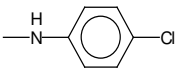
IVa R = 

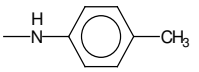
IVb R = 

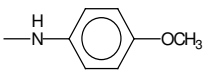
IVc R = 

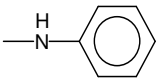
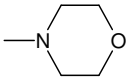
IVd R = 

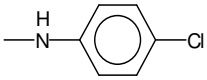
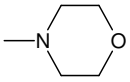
Va R = 

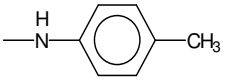
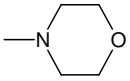
Vb R = 

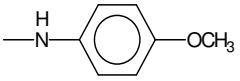
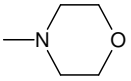
Vc R = 

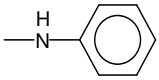
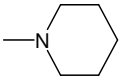
Vd R = 

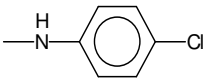
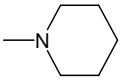
VIa R =  ; R' = 

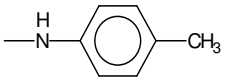
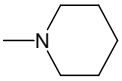
VIb R =  ; R' = 

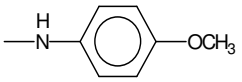
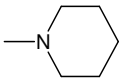
VIc R =  ; R' = 

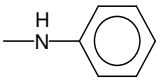
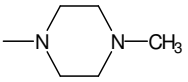
VId R =  ; R' = 

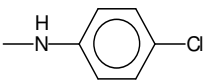
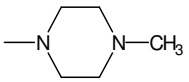
VIe R =  ; R' = 

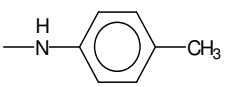
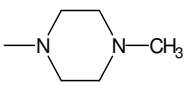
VIf R =  ; R' = 

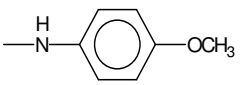
VIg R =  ; R' = 

VIh R =  ; R' = 

VIi R =  ; R' = 

VIj R =  ; R' = 

VIk R =  ; R' = 

VIl R =  ; R' =

Scheme-I

TABLE-2
PMR DATA OF 1-HETEROCYC1IC AMINO METHYL-3-(4'-ARYLAMINO-3'-NITROBENZOYL HYDRAZONO)-2-INDOLINONES

Compd.	PMR δ ($CDCl_3$)
VIa	2.6 (t, 4H, CH_2-N-CH_2), 3.65 (t, 4H, CH_2-O-CH_2), 4.43 (s, 2H, N-CH_2-N), 6.92-7.4 (m-9H-ArH), 7.94 (d, 1H, Ar-6-H), 8.9 (s, 1H, Ar-2-H), 9.7 (s, 1H, -NH Ar).
VIb	2.6 (t, 4H, CH_2-N-CH_2), 3.62 (t, 4H, CH_2-O-CH_2), 4.48 (s, 2H, NCH_2-N), 7.12 (d, 1H, Ar-5-1H), 7.1-7.8 (m, 8H, ArH), 7.92 (d, 1H Ar-6-H), 8.89 (s, 1H, Ar-2-H), 9.72 (s, 1H, -NH Ar).
VIc	2.46 (s, 3H, $ArCH_3$), 2.66 (t, 4H, CH_2-N-CH_2), 3.73 (t, 4H, CH_2-O-CH_2), 4.51 (s, 2H, N-CH_2-N), 7.1 (d, 1H, Ar-5-H), 7.17-7.8 (m, 8H ArH), 7.98 (d, 1H, Ar-6-H), 8.97 (s, 1H, Ar-2-H), 9.78 (s, 1H, NH Ar).
VId	2.62 (t, 4H, CH_2-N-CH_2), 3.7 (t, 4H, CRrO-CR_2), 4.6 (s, 2H, NCH_2-N), 6.84-7.43 (m, 8H, ArH), 7.78 (d, lR, Ar-6-R), 8.88 (s, 1 Ar-2-H), 9.62 (s, 1H, -NH Ar).
VIf	2.6 (t, 4H, CH_2-N-CH_2), 4.45 (s, 2H, N-CH_2-N), 6.9-7.9 (m, 8H, Ar-H), 7.98 (d, 1H, Ar-6H), 8.85 (s, 1H, Ar-2-H), 9.59 (s, 1H, NH Ar).
VIg	2.38 (s, 2H, $ArCH_3$), 2.58 (t, 4H, CH_2-N-CH_2), 4.3 (s, 2H, N-CH_2 -N), 7.0-7.9 (m, 8H, ArH), 7.92 (d, 1H, Ar-6-H), 8.91 (s, 1H, Ar- 2H), 9.69 (s, 1H, -NH Ar).
VIl	2.55 (t, 4H, CH_2-N-CH_2), 3.69 (s, 3H, $ArOCH_3$), 4.46 (s, 2H, NCH_2-N), 6.75-7.75 (m, 8H, ArH), 7.8 (d, 1H, Ar-6-H), 8.78 (s, 1H Ar-2-H), 9.52 (s, 1H, -NH Ar).

RESULTS AND DISCUSSION

Compounds **VIa**, **VId**, **VIg**, exhibited microfilaricidal activity to the extent of 75.8, 78.2 and 70.5 %, respectively on 8th day. However, the number of microfilaria increased and crossed the initial count by 22nd day compound **VId** showed an initial increase in microfilarial counts by 22nd day. The activity of compound **VId** when compared with D.E.C. the standard drug in use, showed a better antifilarial activity. Not withstanding > 90 % microfilaricidal activity of D.E.C. on 8th day, microfilaria reappeared subsequently and also no effect on adult worms was observed on the other hand compound **VId** showed sustained microfilaricidal action and also exhibited 58.6 % microfilaricidal effects.

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REFERENCES

1. R.S. Varma and A.P. Singh, *Indian J. Chem.*, **27B**, 482 (1988).
2. R.S. Varma and A.P. Singh, *Indian J. Chem.*, **29B**, 578 (1990).
3. CS. Marvel and O.S. Hiers, *Org. Synth.*, **5**, 71 (1925).
4. S. Sharma, *Pharm. Res.*, **3**, 75 (1986).
5. G. Harris, J.R.A. Pollock and R. Stevens, Dictionary of Organic Compounds, Eyre and Spottiswoode Publishers Ltd., London, Vol. 2, p. 662 (1965).