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Potent 1,3-Disubstituted-9*H*-pyrido[3,4-*b*]indoles as New Lead Compounds in Antifilarial Chemotherapy[†]

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Abstract—Substituted 9*H*-pyrido[3,4-*b*]indoles (β-carbolines) identified in our laboratory as potential pharmacophore for designing macrofilaricidal agents, have been explored further for identifying the pharmacophore responsible for high order of adulticidal activity. This has led to syntheses and macrofilaricidal evaluations of a number of 1-aryl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate derivatives (**3–7**). The macrofilarical activity was initially evaluated in vivo against *Acanthoeilonema viteae*. Amongst all the synthesized compounds, only twelve compounds namely **3a**, **3c**, **3d**, **3f**, **4c**, **4d**, **4f**, **5a**, **6f**, **6h**, **6i** and **7h** have exhibited either $>90\%$ micro- or macrofilaricidal activity or sterilization of female worms. These compounds have also been screened against *Litomosoides carinii* and of these only **3f** and **5a** have also been found to be active. Finally these two compounds have been evaluated against *Brugia malayi*. The structure activity relationship (SAR) associated with position-1 and 3 substituents in β-carbolines have been discussed. It has been observed that the presence of carbomethoxy at position-3 and an aryl substituent at position-1 in β-carbolines effectively enhance antifilarial activity particularly against *A. viteae*. Amongst the various compounds screened, methyl 1-(4-methylphenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (**4c**) has shown highest adulticidal activity and methyl 1-(4-chlorophenyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (**3a**) has shown highest microfilaricidal action against *A. viteae* at 50 mg/kg×5 days (ip). Another derivative of this compound namely 1-(4-chlorophenyl)-3-hydroxymethyl-9*H*-pyrido[3,4-*b*]indole (**5a**) exhibited highest activity against *L. carinii* at 30 mg/kg×5 days (ip) and against *B. malayi* at 50 mg/kg×5 days (ip) or at 200 mg/kg×5 days (po).

Introduction

The successful treatment of filariasis, a disease of many tropical and subtropical areas, is not possible because of the nonavailability of macrofilaricidal drugs.[1–3] The age old drug diethyl carbamazine (DEC) continues to be the mainstay of clinical practice despite its well known deficiencies.[4,5] Ivermectin, a semisynthetic macrocyclic lactone antibiotic, may take an impact as microfilaricide for onchocerciasis but it did not irreversibly damage the adult filarial worms.[6] Although organic arsenical compounds have long been known as good macrofilaricides,[7] their potential toxicity to the host has prevented their development as useful antifilarial drugs. Besides these antifilarials, a number of phenoxycyclohexane derivatives,[8] 2,4,6-substituted triazines,[9] 5-amino and 5,8-diaminoisoquinolines,[10] aplysinoposin derivatives[11] and 1,1′-dicyano-2-substituted ethylenes[12] were identified as potential filaricides but most of the compounds exhibited very poor adulticidal response. Benzimidazole group of anthelmintics exhibit high order of activity against intestinal helminths but have not found application for the treatment of tissue dwelling helminths.[13,14] Therefore the need arose to identify structural prototypes associated with macrofilaricidal activity.

In earlier communications,[15–24] the macrofilaricidal activities of 1-substituted and 1,5-/1,6-/1,7- and 1,8-disubstituted-9*H*-pyrido[3,4-*b*]indoles, (III-VII, Fig. 2) and representatives of pyrido[3,4-*b*]imidazo[1,2-*c*′]quinazolo[4,5-*e*] and [4,5-*g*]indoles (Fig. 1) were reported. These research activities did not reveal the optimal structural requirements to evoke very high order of macrofilaricidal activity. In continuation of this work, it was considered essential to evaluate 1,3-disubstituted-9*H*-pyrido[3,4-*b*]indoles (Fig. 3) because of the reasons stated later.

Centrally acting agents known to interact with benzodiazepine and γ-aminobutyric acid (GABA) receptors

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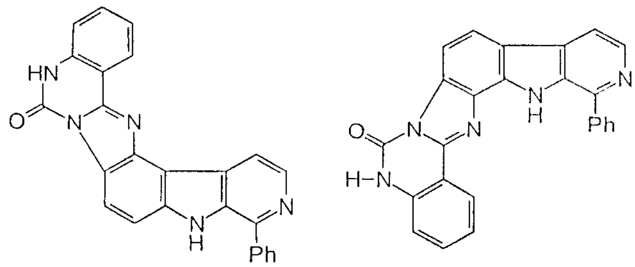

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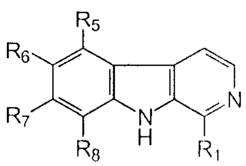
Figure 1.



III R_1 = H/Ph
IV R_5 = H/NO_2
V R_6 = H/NO_2/NH_2/NHAc
VI R_7 = H/NO_2
VII R_8 = H/NO_2/NH_2/NHAc

Figure 2.

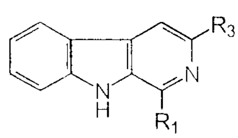


Figure 3.

also exhibit anthelmintic activity[25–28] and since 3-carboxy-β-carbolines (Fig. 4) also exhibit high order of affinity for benzodiazepine receptor,[29,30] it was considered desirable to evaluate the macrofilaricidal activities of esters of 1-substituted-3-carboxy-9*H*-pyrido-[3,4-*b*]indoles as macrofilaricidal agents. The details of this study are presented here. The design of 1,3-disubstituted-9*H*-pyrido[3,4-*b*]indoles (hereafter called β-carbolines for the sake of convenience) was based on the earlier experience.[15–24] It was observed that phenyl or thiophene ring at position-1 in β-carboline was necessary for evoking weak macrofilaricidal activity. The choice of substitutents at position-3 was limited to ester, amide and hydroxymethyl groups and for specific structure to activity relationship studies, the corresponding hydrazides were also prepared (Fig. 5).

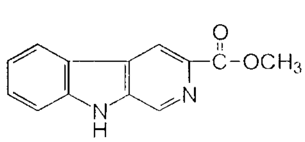


Figure 4.

Chemistry

Our synthetic approach was focused on the preparation of the key compounds 1-aryl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indoles (**3a–i**) in order to allow easy elaboration of the functional group attached to position 3. Pictet–Spengler cyclisation[31] of L-tryptophan methyl ester hydrochloride (**2**) in the presence of the appropriate aldehydes (R_1CHO) furnished the corresponding methyl-1-aryl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylates (**3a–i**). Dehydrogenation[32] of **3a–i** over sulphur in xylene yielded the respective methyl-1-aryl-9*H*-pyrido[3,4-*b*]indole-3-carboxylates (**4a–i**) as described in Scheme 1.

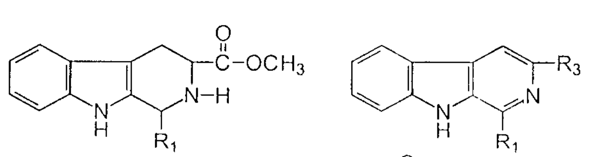
Methyl esters (**4a–i**), chosen as convenient intermediates, were elaborated in three ways (Scheme 2). In the first, the ester group at position-3 was reduced to its corresponding alcohol (**5a–i**) by lithium aluminium hydride ($LiAlH_4$) in dry THF;[33] in the second, the ester was reacted with aqueous ammonia in steel bomb to provide the respective amides[34] (**6a–i**) and in the third, compounds **4a**, **4c**, **4d**, **4f**, **4h** and **4i** were reacted with hydrazine hydrate in ethanol to furnish their corresponding carboxylic acid hydrazides[32] (**7a**, **7c**, **7d**, **7f**, **7h** and **7i**).

Antifilarial activity

The micro- and macrofilaricidal activities of the synthesized compounds (**3–7**) were evaluated against *L. carinii* in cotton rats (*Sigmodon hispidus*), *A. viteae* and *B. malayi* in *Mastomys coucha* as described earlier.[35,36] Compounds being insoluble in water were made fine suspensions within 1% Tween 80. Two to three animals were used for each dose level study and at least two replicates were used for confirmation of activity.

Results and Discussion

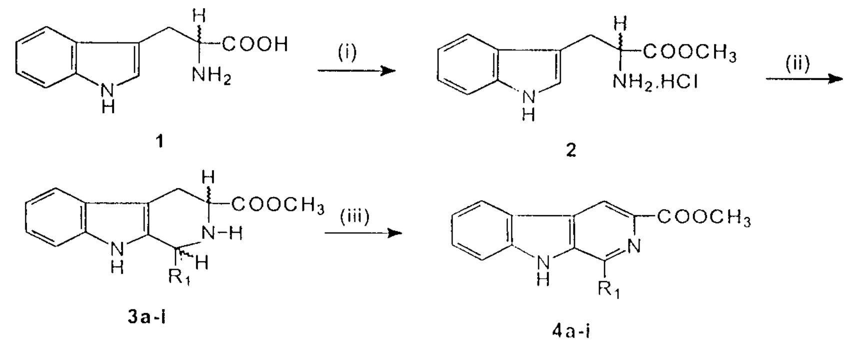
All the synthesized compounds (**3–7**) were evaluated for their antifilarial activity in vivo against *A. viteae* at 50 mg/kg×5 days by intraperitoneal (ip) route and/or 200 mg/kg×5 days through oral (po) route in *Mastomys coucha*. The antifilarial activity against *A. viteae* are given in Table 1. Compounds, which do not exhibit micro- or macrofilaricidal activity are not described in Table 1. During the course of discussion if the route of administration has not been described, the mode of



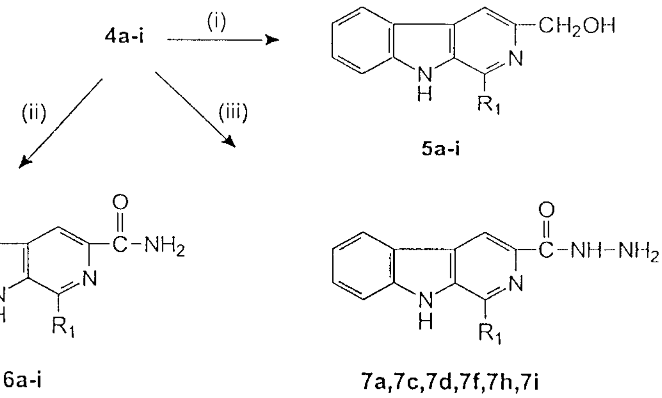
R_1 = See Table 1 and 2

R_3 = C(=O)-OCH_3; CH_2OH; C(=O)-NH_2; C(=O)—NH–NH_2

Figure 5.



Scheme 1. Reagents: (i) MeOH, $SOCl_2$; (ii) R_1CHO, MeOH, 10% aq Na_2CO_3; sulpher, xylene reflux.



Scheme 2. Reagents: (i) $LiAlH_4$ dry THF, reflux, 10% aq NaOH; (ii) aq ammonia, MeOH, 80 °C; (iii) hydrazine hydrate, EtOH, reflux.

administration of test compounds should be treated as intraperitoneal.

The other test models used in the present study for evaluation of antifilarial activity were *L. carinii* in cotton rats and *Brugia malayi* in *M. coucha*. *A. viteae* is metabolically similar to human filarial parasites which are anaerobic in nature and therefore, *A. viteae* in *Mastomys* was used for evaluation of efficacy for antifilarial activity of all newly synthesized compounds. This model has also been recommended by WHO for the experimental chemotherapy of filariasis.[37] *L. carinii*, a metabolically facultative filarial species maintained in cotton rats was earlier used for efficacy evaluation of diethylcarbamazine (DEC)[38] and was subsequently tested in human filarials with success. *B. malayi* is a target human filarial parasite and therefore, the use of an experimental model for evaluating efficacy of this parasite is obvious. Besides these reasons, the use of three different models was considered necessary because of the envisaged interactions of the synthesized compounds with GABA receptors. A precise comment on this subject is made later.

The micro and macrofilaricidal activities in compounds with various substituents at position-1 and position-3 in β-carbolines were monitored as follows: with a particular substituent at position-1, the effect of substituents such as ester, amide and hydroxymethyl group at position-3 was monitored. Along with this study the effect of the ester group at position-3 with and without a tetrahydro pyridine ring on the antifilarial activity was also monitored. In situations where the activity was significantly high, the effect of hydrazide at position-3 was also monitored. The active compounds (with at least 90% micro- and/or macrofilaricidal activity or sterilization of female worms) were short listed and were subjected for evaluation against *L. carinii* infection. The best compound from this short list was finally evaluated against *B. malayi* infection. The structure to activity relationship, therefore, relates to activity against *A. viteae* infection only.

Amongst the 4-halosubstituents at position-1 in β-carboline, 4-chlorophenyl substituent plays a significant role in eliciting antifilarial response and particularly, the tetrahydro pyridine ring along with the ester function at position-3 was found effective. For example, methyl 1-(4-chlorophenyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (**3a**) exhibited highest microfilaricidal (94%) and 39% macrofilaricidal activity along with the sterilization of all the surviving female worms but after its aromatization, the compound (**4a**) was found to be devoid of any filaricidal activity. The hydroxymethyl derivative (**5a**) of this compound showed a wide range of activity by different routes of administration. For example, it exhibited 76% micro- and 56% adulticidal activity along with sterilization of 75% of surviving female worms by ip administration but by po route it was predominantly macrofilaricidal (94%) without microfilaricidal activity. The amide and hydrazide functions (**6a** and **7a** respectively) at position-3 in β-carboline of this class of compound

Table 1. Antifilarial activity (in %) of 1-aryl-3-substituted-9*H*-pyrido[3,4-*b*]indoles (**3–7**) against *A. viteae* at 50 mg/kg×5 days ip[a]

Compound[b]	Antifilarial activity		
	mif	maf	Sterl. of ♀
3a	94	39	100
3b	0	25	0
3c	0	90	0
3d	90	0	0
3e	0	50	0
3f	0	93	0
3f[c]	91	0	0
3h	0	57	0
4b	0	56	67
4c	0	100	0
4d	0	84	100
4e	0	81	0
4f	0	94	0
4g	0	44	0
4h	0	60	0
4i	62	45	0
5a	76	56	75
5a[c]	0	94	0
5b	0	75	0
5c	0	0	40
6a	0	0	60
6d	0	69	0
6e	84	0	50
6f	44	86	100
6h	0	89	0
6i	93	0	0
7h	91	0	0
DEC[d] citrate[e]	90	0	0

[a]Intraperitoneal route.
[b]Compound numbers **3g**, **3i**, **4a**, **5d–5i**, **6b**, **6c**, **6g**, **7a**, **7c**, **7d**, **7f** and **7i** are inactive and are not described here; 'O'—inactive; '♀'—female worms; mif—microfilariae; maf—macrofilariae.
[c]At 200 mg/kg×5 days po.
[d]DEC—Diethylcarbamazine.
[e]At 350 mg/kg×5 days ip.

did not exert any significant role. For example, compound **6a** exhibited only sterilization of 60% female worms whereas **7a** failed to show any antifilarial response. On the other hand incorporation of 4-fluorophenyl substituent at position-1 in β-carboline, irrespective of the nature of group present at position-3 led to low order of antifilarial activity in comparison to compounds with 4-chlorophenyl substituent at position-1. The tetrahydro compound **3b** showed insignificant macrofilaricidal (25%) activity whereas its aromatised congener **4b** caused 56% adulticidal with 67% sterilization of the surviving female worms. The hydroxymethyl derivative (**5b**) exerted 75% adulticidal activity but the compound with an amide function at position-3 in β-carboline (**6b**) failed to show any response.

The ester group at position-3 with 4-methylphenyl substituent at position-1 in 9*H*-pyrido[3,4-*b*]indole, played a major role for evoking adulticidal activity against *A. viteae*. The most potent compound methyl 1-(4-methylphenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (**4c**) caused highest macrofilaricidal activity (100%) while its tetrahydro compound (**3c**) showed low but significant adulticidal response (90%). However, the antifilarial activity of the corresponding hydroxymethyl derivative (**5c**) was limited to sterilization of only 40% of the surviving female worms. Compared to these compounds, variations at position-3 in β-carboline with 4-halophenyl substituent at position-1 by incorporating amide (**6c**) or hydrazide (**7c**) group made the compounds ineffective against filarial infection.

Unlike 4-substituted phenyl substituents at position-1 in β-carbolines, compounds with 3-halophenyl substituent at position-1, exhibited distinct type of antifilarial action. In this class of compounds, it was interesting to note the effect of pyridine ring on antifilarial activity. For example, the tetrahydro compound **3d**, possessing 3-bromophenyl at position-1 in β-carboline, exhibited significant microfilaricidal activity (90%) which after aromatization (**4d**) led to enhanced adulticidal activity (84%) with complete loss of microfilaricidal activity and in addition made all the surviving female worms sterile. The adulticidal activity decreased up to 69% or completely disappeared after converting **4d** into its amide (**6d**) and to the hydrazide (**7d**) derivatives, respectively. The tetrahydro compound **3e**, having 3-fluorophenyl substituent at position-1 in β-carboline, exhibited only weak macrofilaricidal activity (50%) but unlike **3d**, adulticidal activity was not only retained but also increased to 81% after its aromatization to **4e**. The 3-chlorophenyl substituent at position-1 in β-carbolines, compounds in which the ester was reduced to the corresponding hydroxymethyl (**5e**) group led to complete loss of biological response while an amide function at position-3 (**6e**), unlike **6d**, predominantly evoked microfilaricidal activity (84%) with 50% sterilization of surviving female worms. However, none of the compounds, having 3-halosubstituent at position-1 in β-carboline exerted significant adulticidal response (>90%) against *A. viteae*.

Amongst the compounds with 2-halophenyl substituent at position-1 in β-carboline, the 2-chlorophenyl substituent at position-1 and an ester function at position-3 elicit interesting adulticidal response against *A. viteae* and was better than the one with 3-halophenyl substituent at position-1. In this group of compounds the role of pyridine ring in β-carboline was not very significant. For example methyl 1-(2-chlorophenyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (**3f**) showed significant adulticidal activity (93%) through ip route while, by po route, it was microfilaricidal (91%) with complete loss of adulticidal activity. Aromatisation of **3f** led to the compound **4f**, which exhibited 94% adulticidal activity and was equipotent to its parent compound **3f**. Its amide derivative, **6f**, showed 86% macro- and 44% microfilaricidal activities with 100% sterilization of survived female worms. The hydroxymethyl compound (**5f**) and the hydrazide (**7f**) were inactive as antifilarial agent. Compounds with 2-fluorophenyl substituent at position-1 were inactive except aromatised drivative **4g** which showed 44% adulticidal activity.

An overview of the activity data of compounds with thienyl substituent at position-1 in β-carboline clearly indicated that unlike the 1-halophenyl substituent, a thienyl group played a significant role for evoking microfilaricidal response. In general, it was interesting to note in this class of compounds the insignificant role of either pyridine ring or an ester function at position-3 in β-carboline for evoking antifilarial activity. The other derivatives such as hydrazide (**7h**) and amide (**6i**) exhibited interesting microfilaricidal response. The tetrahydro compound having thien-3-yl substituent at position-1 (**3h**) showed 57% adulticidal activity which remained almost equipotent (60%) after its aromatisation (**4h**) but the hydroxymethyl derivative (**5h**) did not evoke any antifilarial response. A major improvement in macrofilaricidal activity (89%) was recorded for the amide **6h** whereas the hydrazide derivative **7h** was only microfilaricidal (91%) without the adulticidal activity. Amongst the compounds with thien-2-yl substituent at position-1 in β-carboline, the tetrahydro compound (**3i**) was inactive while its aromatic congener **4i** exhibited 45% adulticidal and 62% microfilaricidal activity. The hydroxymethyl derivative (**5i**) of this series of compound failed to show any biological response but the amide (**6i**) exhibited significant microfilaricidal activity (93%). The hydrazide **7i** was devoid of any antifilarial activity.

Those compounds which showed significant filaricidal action ($>90\%$ micro- or macrofilaricidal response or sterilization of female worms), were next examined against *L. carinii* in *cotton rats* at 30 mg/kg×5 days ip. On the basis of this consideration compounds **3a**, **3c**, **3d**, **3f**, **4c**, **4d**, **4f**, **5a**, **6f**, **6h**, **6i** and **7h** were chosen for testing their antifilarial response against *L. carinii* and the results are summarized in Table 2.

Amongst all the twelve compounds screened, only **3f** and **5a** were found active and of the two **5a** exhibited more pronounced effect against *L. carinii* than **3f**. The compound **5a**, having hydroxymethyl at position-3 and 4-chlorophenyl at position-1 in β-carboline exhibited 95% adulticidal along with 29% microfilaricidal response and the tetrahydro compound **3f**, possessing 2-chlorophenyl substituent at position-1, showed insignifiant macrofilaricidal activity (20%) but caused sterilization of 88% surviving female worms.

Since, 1-(4-chlorophenyl)-3-hydroxymethyl-9*H*-pyrido-[3,4-*b*]indole (**5a**) and methyl 1-(2-chlorophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (**3f**) showed antifilarial activity against *L. carinii*, they were, therefore, evaluated for their efficacy against *B. malayi* by ip and po route of administrations (Table 3).

Compound **3f** failed to show any activity at 50 mg/kg×5 days ip against *B. malayi* whereas **5a** exhibited antifilarial activity by ip as well as by po route. At 50 mg/kg ×5 days ip, **5a** showed 62% adulticidal activity and 85% of the surviving female worms were found sterile while at 250 mg/kg×5 days po, activities of **5a** somewhat decreased since it exhibited only 56% macrofilaricidal activity and caused 69% sterilization of the surviving female worms.

Table 2. Antifilarial activity (in %) of **3f** and **5a** against *L. carinii* at 30 mg/kg×5 days ip

Compound	Antifilarial activity		
	mif	maf	Sterl. of ♀
3f	0	20	88
5a	29	95	0
DEC Citrate	90[a]	0	0

[a]At 75 mg/kg×5 days ip.

Table 3. Antifilarial activity (in %) of **5a** against *B. malayi*

Dose mg/kg×5 days	Route	Antifilarial activity		
		mif	maf	Sterl. of ♀
50	ip	0	62	85
250	po	0	56	69
DEC Citrate	ip	90[a]	50	0

[a]At 100 mg/kg×5 days ip.

A total analysis of the antifilarial activities of β-carboline derivatives reported earlier[15–24] and of the present study clearly indicate two results:

(i) β-carboline framework is a pharmacophore for macrofilaricidal activity; and
(ii) the nature of substituents specially at positions-1 and 3 significantly contribute towards the macrofilaricidal efficacy.

The present work also reveals that absorption, distribution and bioclearance of β-carboline derivatives by po of administration are substituent dependant. The results of parallel antifilarial evaluations in vivo against *A. viteae*, *L. carinii* and *B. malayi* evoke certain speculations which may provide a basis for future study. Adequate evidence[25,26] exists that β-carboline-3-carboxylic acid derivatives interact with GABA receptors and it is also known[27] that GABA receptor is a biochemical target site for antifilarial compounds. In the light of these observations, it would be reasonable to presume that compounds evaluated in the present study also interact with GABA receptors, which in *A. viteae*, *L. carinii* and *B. malayi* are either different or have significant difference in their population.

The logical next step of the future study would be to look into the GABA receptors of different human and experimental filarial worms. The experimental receptor model which will be very near to the human parasites (*Brugia malayi* and *Wuchereria bancrofti*) would be of great value for developing target sites of quick biological screening and the results of this study may give valuable inputs for high throughput screening.

Experimental

Chemistry

The compounds were routinely checked for their purity by thin layer chromatography (TLC) on silica gel G and column chromatography separations were carried out on Merck silica gel (230–400 mesh). Melting point (mp) were determined in capillary tubes on an electrothermal melting point Toshiniwal CL-03001 apparatus and are uncorrected. Infrared (IR) spectra were run on a Backman–Acculab-10 spectrophotometer (ν_{max} in cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker-400-FT instrument, and chemical shifts (δ in ppm) were reported relative to the solvent peak ($CHCl_3$ in $CDCl_3$ at 7.23 ppm CH_3OH in CD_3OD at 3.4 ppm and DMSO in DMSO-d_6 at 2.49 ppm) or TMS. Signals were designated as follows; s, singlet; bs, broad signal; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet. EI mass spectra were recorded on a Jeol-JMS-D-300 spectrometer. Chemical analyses were carried out on a Carlo–Erba EA 1108 elemental analyzer. Reagents and solvents were purchased from common commercial suppliers and used as received. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated with a Büchi rotary evaporator at low pressure. Yields were of purified product and were not optimized. The physical properties for compounds are sumarized in Tables 4 and 5.

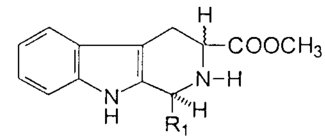
Methyl-1-(4-chlorophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4a): method A. A suspension of **3a** (1.56 g, 4.58 mmol) and sulphur (0.29 g, 9.16 mmol) in xylene (30 mL) was heated at reflux for 8 h; allowed to cool to room temperature, excess sulphur was filtered off and the filtrate was concentrated in vacuo. The residue was crystallized to afford **4a**, 0.36 g (37%). IR (KBr): 3236, 3010, 2822, 1716, 1600, 1362, 1250 cm^{-1}; MS: m/z (relative intensity) 338 (M, Cl^{37}, 14.8), 336 (M, Cl^{35}, 39.9), 278 (100), 214 (20); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.9 (s, 1H, H-4), 8.8(bs, 1H, indole NH), 8.25 (d, 1H, ArH, J = 8 Hz), 7.9 (d, 2H, ArH, J = 8 Hz), 7.64–7.50 (m, 4H, ArH), 7.4 (t, 1H, ArH, J = 8 Hz), 4.06 (s, 3H, OCH_3).

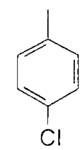
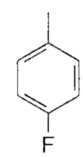
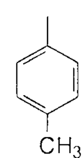
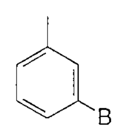
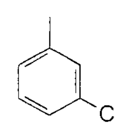
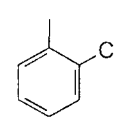
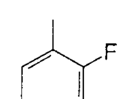
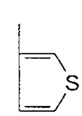
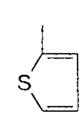
Methyl-1-(4-fluorophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4b). A suspension of **3b** (1.96 g, 6.06 mmol) and sulphur (0.39 g, 12.12 mmol) in xylene (35 mL) were reacted in a manner similar to that described for **4a** to afford **4b**, 1.16 g (81%). IR (KBr): 3320, 3040, 2960, 1720, 1620, 1350, 1250 cm^{-1}; MS: m/z (relative intensity): 320 (M, 1.2), 260 (100), 180 (23.7); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (s, 1H, H-4), 8.74 (bs, 1H, indole NH), 8.24 (d, 1H, ArH, J = 7 Hz), 8.0–7.9 (m, 2H, ArH), 7.82–7.52 (m, 2H, ArH), 7.4 (t, 1H, ArH, J = 6.67 Hz), 7.3–7.2 (m, 2H, ArH), 4.08 (s, 3H, OCH_3).

Methyl-1-(4-methylphenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4c). Compound (**4c**) was prepared from **3c** (4.0 g, 12.6 mmol) and sulphur (0.8 g, 25.2 mmol) in xylene (80 mL) by following the method described for **4a**, 3.53 g (97.1%), IR (KBr): 3220, 3040, 2980, 1720, 1620, 1340, 1240 cm^{-1}: MS m/z (relative intensity): 318 (M + 2, 4.0), 255 (37.4), 160 (53.3); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (s, 1H, H-4), 8.72 (bs, 1H, indole NH), 8.2 (d, 1H, ArH, J = 8 Hz), 7.86 (d, 2H, ArH, J = 8 Hz), 7.64–7.52 (m, 2H, ArH), 7.46–7.36 (m, 3H, ArH), 4.06 (s, 3H, OCH_3), 2.46 (s, 3H, CH_3).

Methyl-1-(3-bromophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4d). Compound **3d** (1.20 g, 3.12 mmol) and sulphur (0.20 g, 6.24 mmol) in xylene (25 mL) was reacted as described for **4a** to provide **4d**, 0.90 g (76%),

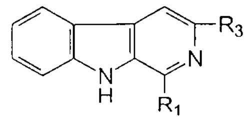
Table 4. Physico–chemical properties for the methyl 1-aryl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylates tested in this study

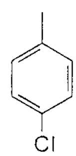
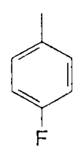
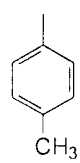
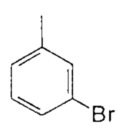
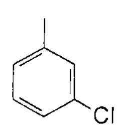
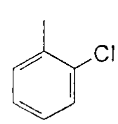
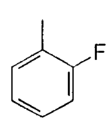
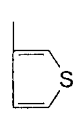
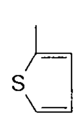
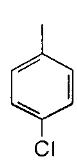


Compound[a]	R_1	% Yield[b]	mp °C	Solvent crystallization[c]	Formula[d]
3a		90	211	A	$C_{19}H_{17}N_2O_2Cl$
3b		78	152	B	$C_{19}H_{17}N_2O_2F$
3c		87	160	B	$C_{20}H_{20}N_2O_2$
3d		98	156	A	$C_{19}H_{17}N_2O_2Br$
3e		76	106	A	$C_{19}H_{17}N_2O_2Cl$
3f		32	209	A	$C_{19}H_{17}N_2O_2Cl$
3g		80	97	B	$C_{19}H_{17}N_2O_2F$
3h		75	140	C	$C_{17}H_{16}N_2O_2S$
3i		57	135	C	$C_{17}H_{16}N_2O_2S$

[a]See ref 9 for method.
[b]Yield is that obtained from neutralisation step as a final step.
[c]A = MeOH; B = EtOAc:hexane (7:3); C = EtOH:acetone (2:8).
[d]All compounds had elemental analyses within ±0.4% of theoretical values.

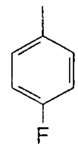
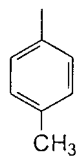
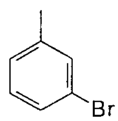
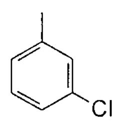
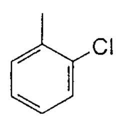
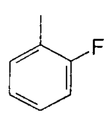
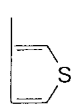
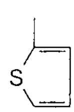
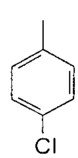
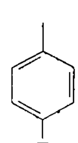
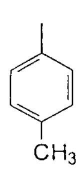
Table 5. Physico-chemical properties for the 1-aryl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate/hydroxymethyl/carboxamide/carboxylic acid hydrazide tested in this study



Compound[a]	R_1	R_3	% Yield[b]	mp °C	Solvent crystallization[c]	Formula[d]
4a		$-C(=O)-OCH_3$	37	270	A	$C_{19}H_{13}N_2O_2Cl$
4b		$-C(=O)-OCH_3$	81	271	B	$C_{19}H_{13}N_2O_2F$
4c		$-C(=O)-OCH_3$	97.1	> 300	B	$C_{20}H_{16}N_2O_2$
4d		$-C(=O)-OCH_3$	76	104	B	$C_{19}H_{13}N_2O_2Br$
4e		$-C(=O)-OCH_3$	80	285	A	$C_{19}H_{13}N_2O_2Cl$
4f		$-C(=O)-OCH_3$	99	249	A	$C_{19}H_{13}N_2O_2Cl$
4g		$-C(=O)-OCH_3$	75.1	262	B	$C_{19}H_{13}N_2O_2F$
4h		$-C(=O)-OCH_3$	95	210	A	$C_{17}H_{12}N_2O_2S$
4i		$-C(=O)-OCH_3$	85	195	A	$C_{17}H_{12}N_2O_2S$
5a		$-CH_2OH$	80	220	C	$C_{18}H_{13}N_2OCl$

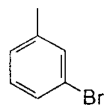
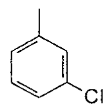
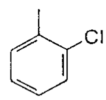
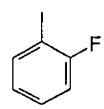
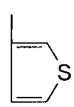
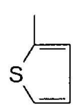
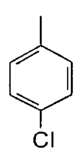
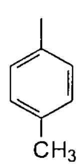
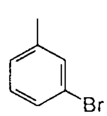
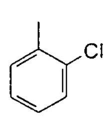
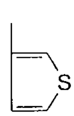
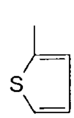
(continued)

Table 5—*contd*

Compound[a]	R_1	R_3	% Yield[b]	mp °C	Solvent crystallization[c]	Formula[d]
5b		$-CH_2OH$	46.8	218	D	$C_{18}H_{13}N_2OF$
5c		$-CH_2OH$	56.6	208	C	$C_{19}H_{16}N_2O$
5d		$-CH_2OH$	51.3	176	E	$C_{18}H_{13}N_2OBr$
5e		$-CH_2OH$	58.3	195	C	$C_{18}H_{13}N_2OCl$
5f		$-CH_2OH$	63.1	165	C	$C_{18}H_{13}N_2OCl$
5g		$-CH_2OH$	46.4	300	D	$C_{18}H_{13}N_2OF$
5h		$-CH_2OH$	56	102	E	$C_{16}H_{12}N_2OS$
5i		$-CH_2OH$	71	79	E	$C_{16}H_{12}N_2OS$
6a		$-\overset{O}{\overset{\|}{C}}-NH_2$	37	270	C	$C_{18}H_{12}N_3OCl$
6b		$-\overset{O}{\overset{\|}{C}}-NH_2$	70	246	F	$C_{18}H_{12}N_3OF$
6c		$-\overset{O}{\overset{\|}{C}}-NH_2$	38	285	B	$C_{19}H_{15}N_3O$

(continued)

Table 5—*contd*

6d		$-C(=O)-NH_2$	97	189		B	$C_{18}H_{12}N_3OBr$
6e		$-C(=O)-NH_2$	65	260		B	$C_{18}H_{12}N_3OCl$
6f		$-C(=O)-NH_2$	80	299		B	$C_{18}H_{12}N_3OCl$
6g		$-C(=O)-NH_2$	81	251		B	$C_{18}H_{12}N_3OF$
6h		$-C(=O)-NH_2$	49	300		A	$C_{16}H_{11}N_3OS$
6i		$-C(=O)-NH_2$	82	300		A	$C_{16}H_{11}N_3OS$
7a		$-C(=O)-NHNH_2$	72	235		G	$C_{18}H_{13}N_4OCl$
7c		$-C(=O)-NHNH_2$	40	242		H	$C_{19}H_{16}N_4O$
7d		$-C(=O)-NHNH_2$	70	135		G	$C_{18}H_{13}N_4OBr$
7f		$-C(=O)-NHNH_2$	86.6	193		H	$C_{18}H_{13}N_4OCl$
7h		$-C(=O)-NHNH_2$	52	250		H	$C_{16}H_{12}N_4OS$
7i		$-C(=O)-NHNH_2$	93.7	225	H		$C_{16}H_{12}N_4OS$

[a]See Experimental for method (A for **4a–i**; B for **5a–i**; C for **6a–i**; D for **7a–i**).
[b]Yield is referred to a final step.
[c]A = acetone:chloroform (8:2), B = hexane:ethanol (8:2), C = acetone, D = EtOAc:hexane (3:7), E = hexane:ethanol (1:9), F = acetone:hexane (5:5), G = ethanol, H = methanol.
[d]All compounds had elemental analyses within ±0.4% of theoretical values.

IR(KBr): 3320, 3082, 2940, 1740, 1620, 1340, 1240 cm^{-1}; MS m/z (relative intensity): 382 (M, Br^{81}, 6.1), 380 (M, Br^{79}, 5.2), 323(64.9), 241(58.4); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.9 (s, 1H, H-4), 8.72 (bs, 1H, indole NH), 8.24 (d, 1H, ArH, $J=8$ Hz), 8.12 (s, 1H, ArH), 7.9 (d, 1H, ArH, $J=8$ Hz), 7.68–7.56 (m, 3H, ArH), 7.48–7.38 (m, 2H, ArH), 4.08 (s, 3H, OCH_3).

Methyl-1-(3-chlorophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4e). Dehydrogenation of **3e** (0.86 g, 2.53 mmol) with sulphur (0.16 g, 5.06 mmol) in xylene (15 mL) using identical procedure as described for **4a** furnished **4e**, 0.79 g (80%). IR (KBr): 3340, 3082, 2940, 1760, 1640, 1350, 1250 cm^{-1}: MS: m/z (relative intensity): 338 (M, Cl^{37}, 1.6), 336(M, Cl^{35}, 5.4), 256(56), 64(100); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.9 (s, 1H, H-4), 8.72 (bs, 1H, indole NH), 8.24 (d, 1H, ArH, $J=8$ Hz), 8.1 (s, 1H, ArH), 7.88 (d, 1H, ArH, $J=8$ Hz), 7.68–7.56 (m, 3H, ArH), 7.5–7.38 (m, 2H, ArH), 4.08 (s, 3H, OCH_3).

Methyl-1-(2-chlorophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4f). Compound **4f** was synthesized from **3f** (1.0 g, 2.94 mmol) and sulphur (0.19 g, 5.88 mmol) in xylene (18 mL) as described for **4a**, 0.98 g (99%). IR (KBr): 3360, 3020, 2940, 1740, 1640, 1340, 1250 cm^{-1}; MS: m/z (relative intensity): 338 (M, Cl^{37}, 4.6), 336 (M, Cl^{35}, 3.1), 279(70.9), 217(100); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.9 (s, 1H, H-4), 8.84 (bs, 1H, indole NH), 8.24 (d, 1H, ArH, $J=7$ Hz), 7.94 (m, 1H, ArH), 7.8 (m, 1H, ArH), 7.7–7.56 (m, 2H, ArH), 7.52–7.38 (m, 3H, ArH), 4.06 (s, 3H, OCH_3).

Methyl-1-(2-fluorophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4g). A suspension of **3g** (1.45 g, 4.48 mmol) in xylene (25 mL) was reacted with sulphur (0.29 g, 8.96 mmol) as described for **4a** to afford **4g**, 1.07 g (75.1%). IR (KBr): 3300, 3040, 2960, 1740, 1660, 1360, 1260 cm^{-1}; MS: m/z (relative intensity): 320 (M, 1.5), 261 (100), 129 (10.9); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94 (s, 1H, H-4), 8.68 (bs, 1H, indole NH), 8.22 (d, 1H, ArH, $J=7.9$ Hz), 7.88 (t, 1H, ArH, $J=7.5$ Hz), 7.56–7.52 (m, 2H, ArH), 7.5–7.42 (m, 1H, ArH), 7.4–7.3 (m, 3H, ArH), 4.04 (s, 3H, OCH_3).

Methyl-1-(3-thienyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4h). By a similar procedure as described for **4a**, compound **4h** was obtained from **3h** (2.3 g, 7.37 mmol) in xylene (45 mL) and sulphur (0.47 g, 14.74 mmol), 1.8 g (95%). IR (KBr): 3320, 3080, 2980, 1720, 1440, 1340, 1290, 1080 cm^{-1}; MS: m/z (relative intensity): 308 (M, 1.8), 255(52.4), 160(54.9); ^{1}H NMR (400 Mhz, $CDCl_3$): δ 8.88 (m, 2H, H-4 indole and NH), 8.22 (d, 1H, ArH, $J=8$ Hz), 7.92 (m, 1H, ArH), 7.74 (d, 1H, ArH, $J=4.5$ Hz), 7.66–7.5 (m, 3H, ArH), 7.38 (t, 1H, ArH, $J=7$ Hz), 4.06 (s, 3H, OCH_3).

Methyl-1-(2-thienyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4i). Compound **3i** (1.9 g, 6.09 mmol) in xylene (35 mL) was dehydrogenated over sulphur (0.39 g, 12.18 mmol) to furnish **4i**, 1.6 g (85%). IR (KBr): 3340, 3100, 2980, 1740, 1420, 130, 1250, 1010 cm^{-1}; MS: m/z (relative intensity): 308 (M, 47.7), 250(100), 160(21.5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86 (m, 2H, H-4 indole and NH), 8.22 (d, 1H, ArH, $J=8$ Hz), 7.82 (d, 1H, ArH, $J=4.0$ MHz), 7.7–7.52 (m, 4H, ArH), 7.4 (m, 1H, ArH), 4.08 (s, 3H, OCH_3).

1-(4-Chlorophenyl)-3-hydroxymethyl-9*H*-pyrido[3,4-*b*]-indole (5a): method B. A solution of **4a** (0.4 g, 1.18 mmol) in dry THF (8 mL) was added dropwise to the stirred solution of $LiAlH_4$ (0.09 g, 2.37 mmol) in dry THF (20 mL) at ambient temperature. The reaction mixture was refluxed for 8 h and was allowed to maintain at room temperature. The complex was decomposed by 10% aq NaOH solution and solid separated was filterated, washed with water and then filterate was concentrated in vacuo. The residue thus obtained was filtered, washed with water and crystallized to provide the **5a**, 0.29 g (80%). IR (KBr): 3180, 3060, 2800, 1630, 1490, 1240, 1010, 720 cm^{-1}; MS: m/z (relative intensity): 310 (M, Cl^{37}, 4.5), 308(M, Cl^{35}, 54.9), 306(100), 278(47.5); ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 8.46 (bs, 1H, indole NH), 8.12 (d, 1H, ArH, $J=8$ Hz), 8.1–8.0 (m, 3H, ArH), 7.7–7.49 (m, 4H, ArH), 7.24 (t, 1H, ArH, $J=8$ Hz), 4.96 (s, 2H, CH_2), 3.7 (s, 1H, OH).

1-(4-Fluorophenyl)-3-hydroxymethyl-9*H*-pyrido[3,4-*b*]-indole (5b). Compound **4b** (0.38 g, 1.19 mmol) in dry THF (10 mL) and $LiAlH_4$ (0.09 g, 2.37 mmol) in dry THF (20 mL) were treated as for **5a** to provide **5b**, 0.16 g (46.8%). IR (KBr): 3220, 3040, 2780, 1610, 1500, 1400, 1220, 1040, 740 cm^{-1}; MS m/z (relative intensity): 293 (M+1, 100), 292 (M, 2.0), 122(34.6); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (bs, 1H, indole NH), 8.14 (d, 1H, ArH, $J=8$ Hz), 8.04–7.36 (m, 3H, ArH), 7.68–7.46 (m, 3H, ArH), 7.4–7.28 (m, 2H, ArH), 4.48 (s, 2H, CH_2), 3.78 (s, 1H, OH).

1-(4-Methylphenyl)-3-hydroxymethyl-9*H*-pyrido[3,4-*b*]-indole (5c). Compound **4c** (0.51 g, 1.62 mmol) in dry THF (10 mL) and $LiAlH_4$ (0.13 g, 3.23 mmol) in dry THF (25 mL) were reacted in a similar manner to that described for **5a** to afford **5c**, 0.26 g (56.6%). IR (KBr): 3160, 3040, 2770, 1620, 1500, 1240, 1010, 700 cm^{-1}; MS: m/z (relative intensity): 288(M, 100), 273(50.5), 133(65.3); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (bs, 1H, indole NH), 8.14 (d, 1H, ArH, $J=8$ Hz), 7.92–7.78 (m, 3H, ArH), 7.6–7.36 (m, 4H, ArH), 7.3 (t, 1H, ArH, $J=8$ Hz), 4.88 (d, 2H, CH_2, $J=5$ Hz), 3.92 (t, 1H, OH, $J=5$ Hz), 2.48 (s, 3H, CH_3).

1-(3-Bromophenyl)-3-hydroxymethyl-9*H*-pyrido[3,4-*b*]-indole (5d). In a manner similar to the preparation of **5a**, compound **5d** was obtained from **4d** (0.36 g, 0.95 mmol) in dry THF (10 mL) and $LiAlH_4$ (0.07 g, 1.89 mmol) in dry THF (20 mL) to 0.17 g (51.3%). IR (KBr): 3220, 3060, 2950, 1640, 1430, 1250, 1050, 730 cm^{-1}; MS m/z (relative intensity): 355 (M+2, 1.55), 276 (100), 245 (61.8); ^{1}H NMR (400 MHz, CD_3OD): (8.24–8.1 (m, 2H, indole NH and ArH), 7.9 (d, 2H, ArH, $J=6$ Hz), 7.68–7.46 (m, 4H, ArH), 7.24 (t, 1H, ArH, $J=6$ Hz), 3.56 (s, 1H, CH_2), 3.56 (s, 1H, OH), 3.3 (s, 2H, CH_2).

1-(3-Chlorophenyl)-3-hydroxymethyl-9*H*-pyrido[3,4-*b*]-indole (5e). Compound **5e** was prepared from **4e** (0.25 g, 0.74 mmol) in dry THF (12 mL) and $LiAlH_4$ (0.06 g, 1.48 mmol) in dry THF (15 mL) to 0.14 g (58.3%). IR (KBr): 3140, 3020, 2920, 1620, 1430, 1230, 1000, 710 cm^{-1}; MS *m*/*z* (relative intensity): 310 (M, Cl^{37}, 42.9), 308 (M, Cl^{35}, 100), 280(40.5), 243 (24.5); ^1H NMR (400 MHz, $CDCl_3$): δ 8.44 (bs, 1H, indole NH), 8.26 (d, 1H, ArH, J = 8 Hz), 8.0–7.86 (m, 3H, ArH), 7.62–7.46 (m, 4H, ArH), 7.34 (t, 1H, ArH, J = 8 Hz), 4.48 (d, 2H, CH_2, J = 5 Hz), 3.7 (t, 1H, OH, J = 5 Hz).

1-(2-Chlorophenyl)-3-hydroxymethyl-9*H*-pyrido[3,4-*b*]-indole (5f). In a manner similar to the preparation of **5a**, compound **5f** was obtained from **4f** (0.35 g, 1.04 mmol) in dry THF (15 mL) and $LiAlH_4$ (0.08 g, 2.08 mmol) in dry THF (20 mL) to 0.2 g (63.1%). IR (KBr): 3220, 3020, 2960, 1620, 1420, 1230, 1040, 710 cm^{-1}; MS *m*/*z* (relative intensity): 310 (M, Cl^{37}, 45.3), 308 (M, Cl^{35}, 100), 280(39), 243(27); ^1H NMR (400 MHz, $CDCl_3$): δ 8.52 (bs, 1H, indole NH), 8.48 (d, 1H, ArH, J = 8 Hz), 8.26–8.2 (m, 3H, ArH), 8.0–7.9 (m, 2H, ArH), 7.54–7.46 (m, 3H, ArH), 4.88 (s, 2H, CH_2), 3.88 (s, 1H, OH).

1-(2-Fluorophenyl)-3-hydroxymethyl-9*H*-pyrido[3,4-*b*]-indole (5g). Compound **4g** (0.20 g, 0.63 mmol) in dry THF (10 mL) were treated with LiAlH4 (0.05 g, 1.25 mmol) in dry THF (10 mL) as described for **5a** to furnish **5g**, 0.08 g (46.4%). IR (KBr): 3398, 2883, 1624, 1560, 1388, 1217, 1024, 748 cm^{-1}; MS *m*/*z* (rela-(relative intensity): 292 (M, 1.9), 242 (3.0), 55(100): ^1H NMR (400 MHz, $CDCl_3$): δ 8.4 (bs, 1H, indole NH), 8.14 (d, 1H, ArH, J = 8 Hz), 8.04–7.88 (m, 3H, ArH), 7.56–7.48 (m, 3H, ArH), 7.38–7.24 (m, 2H, ArH), 4.8 (s, 2H, CH_2), 3.74 (s, 1H, OH).

1-(3-Thienyl)-3-hydroxymethyl-9*H*-pyrido[3,4-*b*]indole (5h). A solution of **4h** (0.23 g, 0.75 mmol) in dry THF (15 mL) was reacted with $LiAlH_4$ (0.06 g, 1.49 mmol) in dry THF (15 mL) as for **5a** to afford **5h**, 0.12 g (56%). IR (KBr): 3240, 2923, 2862, 1625, 1452, 1244, 1645, 746 cm^{-1}; MS *m*/*z* (relative intensity): 280 (M, 32.1), 219 (77.4), 42(100); ^1H NMR (400 MHz, $CDCl_3$): δ 8.2–8.02 (m, 2H, indole NH and ArH), 7.9–7.8 (m, 2H, ArH), 7.7–7.44 (m, 5H, ArH), 4.88 (m, 2H, CH_2, J = 8 Hz), 3.8 (m, 1H, OH).

1-(2-Thienyl)-3-hydroxymethyl-9*H*-pyrido[3,4-*b*]indole (5i). In an analogous procedure as described for **5a**, compound **5h** was synthesized from **4i** (0.18 g, 0.60 mmol) in dry THF (8 mL) and $LiAlH_4$ (0.05 g, 1.20 mmol) in dry THF (15 mL) to 0.12 g (71%). IR (KBr) 3269, 2923, 2860, 1625, 1448, 1049, 744 cm^{-1}; MS *m*/*z* (relative intensity); 280 (M, 10.1), 266(100), 184(76.5); ^1H NMR (400 Mhz, $CDCl_3$): δ 8.18–8.0 (m, 2H, indole NH and ArH), 7.86–7.72 (m, 3H, ArH), 7.7–7.62 (m, 2H, ArH), 7.58–7.46 (m, 2H, ArH), 4.8 (m, 2H, CH_2), 3.7 (m, 1H, OH).

1-(4-Chlorophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxamide (6a): method C. A solution of **4a** (0.93 g, 2.75 mmol) in aq ammonia solution (8 mL) and methanol (10 mL) was heated 80 °C under pressure in steel bomb for 8 h. The reaction mixture was concentrated and separated solid was filtered and on crystallization gave **6a**, 0.33 g (37%). IR (KBr): 3442, 3366, 3220, 1664, 1386, 742 cm^{-1}; MS *m*/*z* (relative intensity): 323 (M, Cl^{37}, 9.5), 321 (M, Cl^{35}, 25.7), 278 (100), 242(51.1); ^1H NMR (400 Mhz, $CDCl_3$): δ 8.94 (s, 1H, H-4), 8.74 (bs, 1H, indole NH), 8.22 (d, 1H, ArH, J = 8 Hz), 8.04 (bs, 1H, NH of NH_2), 7.95 (d, 2H, ArH, J = 8 Hz), 7.7–7.5 (m, 4H, ArH), 7.38 (t, 1H, ArH, J = 8 Hz), 5.62 (bs, 1H, NH of NH_2).

1-(4-Fluorophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxamide (6b). Compound **4b** (1.4 g, 4.38 mmol) and aq ammonia (14 mL) in methanol (16 mL) were reacted in a manner similar to that described for **6a** to afford **6b**, 0.93 g (70%). IR (KBr): 3420, 3300, 1660, 1370, 720 cm^{-1}; MS *m*/*z* (relative intensity): 305 (M, 5.5), 256 (37), 64(100); ^1H NMR (400 MHz, $CDCl_3$): δ 8.96 (s, 1H, H-4), 8.66 (bs, 1H, indole NH), 8.22 (d, 1H, ArH, J = 8 Hz), 8.04 (bs, 1H, NH of NH_2), 8.02–7.94 (m, 2H, ArH), 7.88 (d, 1H, ArH, J = 8 Hz), 7.66–7.52 (m, 2H, ArH), 7.48–7.3 (m, 2H, ArH), 5.6 (bs, 1H, NH of NH_2).

1-(4-Methylphenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxamide (6c). By an analogous procedure as described for **6a**, compound **6c** was obtained from **4c** (1.0 g, 3.16 mmol) and aq ammonia (10 mL) in methanol (12 mL), 0.36 g (38%). IR (KBr): 3480, 3380, 3220, 1660, 1370, 740 cm^{-1}; MS *m*/*z* (relative intensity): 301 (M, 69.3), 270 (100), 181 (21.3); ^1H NMR (400 MHz, $CDCl_3$): δ 8.92 (s, 1H, H-4), 8.7 (bs, 1H, indole NH), 8.22 (d, 1H, ArH, J = 8 Hz), 8.1 (bs, 1H, NH of NH_2), 7.9 (d, 2H, ArH, J = 8 Hz), 7.66–7.52 (m, 2H, ArH), 7.48–7.42 (m, 2H, ArH), 7.38 (t, 1H, ArH, J = 8 Hz), 5.6 (bs, 1H, NH of NH_2), 2.5 (s, 3H, CH_3).

1-(3-Bromophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxamide (6d). In a manner similar to the preparation of **6a**, compound **6d** was synthesized from **4d** (1 g, 2.63 mmol) and aq ammonia (10 mL) in methanol (13 mL), 0.93 g, (97%). IR (KBr): 3496, 3253, 1678, 1369, 732 cm^{-1}; MS *m*/*z* (relative intensity): 368 (M, Br^{81}, 10.8), 366 (M, Br^{79}, 12.5), 323(100), 242(98.9); ^1H NMR (400 MHz, $CDCl_3 + CD_3OD$): δ 8.94 (s, 1H, H-4), 8.76 (bs, 1H, indole NH), 8.3–8.2 (m, 1H, ArH), 8.12 (d, 1H, ArH, J = 8 Hz), 8.04 (bs, 1H, NH of NH_2), 7.96–7.86 (m, 1H, ArH), 7.84–7.54 (m, 3H, ArH), 7.5 (t, 1H, ArH, J = 8 Hz), 7.46–7.36 (m, 1H, ArH), 5.62 (bs, 1H, NH of NH_2).

1-(3-Chlorophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxamide (6e). Compound **4e** (0.78 g, 2.32 mmol) and aq ammonia (8 mL) in methanol (10 mL) were treated as for **6a** to provide **6e**, 0.48 g (65%). IR (KBr): 3500, 3080, 3240, 1660, 1360, 710 cm^{-1}; MS *m*/*z* (relative intensity): 323 (M, Cl^{37}, 5.5), 321 (M, Cl^{35}, 15.1), 278 (36.4), 203 (68.2); ^1H NMR (400 MHz, $CDCl_3$): δ 8.97 (s, 1H, H-4), 8.72 (bs, 1H, indole NH), 8.3–8.2 (m, 1H, ArH), 8.05 (bs, 1H, NH of NH_2), 8.0–7.8 (m, 2H, ArH), 7.7–7.42 (m, 4H, ArH), 7.38 (t, 1H, ArH, J = 8 Hz), 5.65 (bs, 1H, NH of NH_2).

1-(2-Chlorophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxamide (6f). By a similar procedure as described for **6a**, compound **4f** (0.63 g, 1.87 mmol) and aq ammonia (6 mL) in methanol (8 mL) were reacted to furnish **6f**, 0.48 g (80%). IR (KBr): 3388, 3210, 1668, 1382, 748 cm^{-1}; MS *m/z* (relative intensity): 323 (M, Cl^{37}, 5.1), 321 (M, Cl^{35}, 12.3), 256 (30.9), 160 (46.6); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.04 (s, 1H, H-4), 8.38 (bs, 1H, indole NH), 8.26 (d, 1H, ArH, J = 8 Hz), 8.2 (bs, 1H, NH of NH_2), 7.7–7.58 (m, 3H, ArH), 7.56–7.46 (m, 3H, ArH), 7.38 (t, 1H, ArH, J = 8 Hz), 5.64 (bs, 1H, NH of NH_2).

1-(2-Fluorophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxamide (6g). By an analogous procedure as described for **6a**, compound **6g** was prepared from **4g** (0.87 g, 2.72 mmol) and aq ammonia (10 mL) in methanol (14 mL), 0.67 g (81%). IR (KBr): 3380, 3202, 1666, 1384, 748 cm^{-1}; MS *m/z* (relative intensity): 305 (M, 15.4), 262 (100), 139 (79.2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.9 (s, 1H, H-4), 8.62 (bs, 1H, indole NH), 8.22 (d, 1H, ArH, J = 8 Hz), 8.08 (bs, 1H, NH of NH_2), 7.88 (d, 2H, ArH, J = 8 Hz), 7.7–7.5 (m, 2H, ArH), 7.44 (m, 2H, ArH), 7.38 (t, 1H, ArH, J = 8 Hz), 5.58 (bs, 1H, NH of NH_2).

1-(3-Thienyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxamide (6h). In a manner similar to the preparation of **6a**, compound **6h** was prepared from **4h** (1.2 g, 3.89 mmol) and aq ammonia (11 mL) in methanol (15 mL) to 0.56 g (49%). IR (KBr): 3420, 3320, 1660, 1370, 730 cm^{-1}; MS *m/z* (relative intensity); 294 (M + 1, 21.9), 293 (M, 100), 250 (80.8); ^{1}H NMR (400 MHz, $CDCl_3 + CD_3OD$): δ 8.92 (s, 1H, H-4), 8.7 (bs, 1H, indole NH), 8.22 (d, 1H, ArH, J = 8 Hz), 8.06 (bs, 1H, NH of NH_2), 7.96–7.92 (m, 1H, ArH), 7.78 (d, 1H, ArH, J = 8 Hz), 7.66–7.54 (m, 3H, ArH), 7.38 (t, 1H, ArH, J = 8 Hz), 5.6 (bs, 1H, NH of NH_2).

1-(2-Thienyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxamide (6i). Compound **4i** (0.98 g, 3.18 mmol) and aq ammonia (10 mL) in methanol (13 mL) were treated in a manner similar to that described under **6a** to afford **6i**, 0.77 g (82%). IR (KBr): 3440, 3240, 1662, 1384, 746 cm^{-1}; MS *m/z* (relative intensity); 294 (M + 1, 19.1), 293 (M, 100), 250 (17.2); ^{1}H NMR (400 MH, $CDCl_3 + CD_3OD$): δ 8.85 (s, 1H, H-4), 8.79 (bs, 1H, indole NH), 8.22 (d, 1H, ArH, J = 8 Hz), 8.02 (bs, 1H, NH of NH_2), 7.84–7.74 (m, 2H, ArH), 7.68–7.58 (m, 2H, ArH), 7.56 (d, 1H, ArH, J = 8 Hz), 7.4 (m, 1H, ArH), 5.62 (bs, 1H, NH of NH_2).

1-(4-Chlorophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid hydrazide (7a): method D. Compound **4a** (1 g, 2.97 mmol) and hydrazine hydrate (1.5 mL, 48.2 mmol) was refluxed in ethanol (50 mL) for 4 h. The reaction mixture was concentrated and solid thus separated was filtered and on crystallization gave **7a**, 0.72 g (72%); IR (KBr): 3930, 3886, 2369, 1623, 1320, 836 cm^{-1}; MS *m/z* (relative intensity): 338 (M, Cl^{37}, 10.0), 336 (M, Cl^{35}, 26.9), 277 (29.3), 130 (100), ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 8.83 (s, 1H, H-4), 8.75 (bs, 1H, indole NH), 8.3–8.15 (m, 2H, ArH), 7.8–7.5 (m, 4H, ArH), 7.4–7.2 (m, 2H, ArH), 4.2–3.5 (bs, 3H, NH and NH_2).

1-(4-Methylphenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid hydrazide (7c). By a similar procedure as described for **7a**, compound **7c** was obtained from **4c** (1 g, 3.16 mmol) and hydrazine hydrate (2.8 mL, 84.6 mmol) in ethanol (20 mL), 0.4 g (40%). IR (KBr): 3279, 1666, 1618, 1557, 1347, 962 cm^{-1}; MS *m/z* (relative intensity): 316 (M 6.9), 257 (14.8), 64 (100). ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 8.6 (s, 1H, H-4), 8.01 (bs, 1H, indole NH), 7.91 (m, 1H, ArH), 7.81 (m, 1H, ArH), 7.55 (m, 2H, ArH), 7.35 (m, 2H, ArH), 7.17 (m, 2H, ArH), 3.7 (bs, 3H, NH and NH_2), 2.3 (s, 3H, CH_3).

1-(3-Bromophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid hydrazide (7d). In an analogous procedure as described for **7a**, compound **8d** was synthesized from **4d** (1 g, 2.62 mmol), hydrazine hydrate (1 mL, 32.1 mmol) in ethanol (5 mL) 0.7 g (70%). IR (KBr): 3350, 1643, 1278, 1074, 793 cm^{-1}, MS *m/z* (relative intensity), 381 (M, 1.2) 322 (1.9), 130 (100) ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 8.65 (s, 1H, H-4), 8.51 (bs, 1H, indole NH), 8.1–7.8 (m, 2H, ArH), 7.6–7.1 (m, 6H, ArH), 4.2–3.6 (bs, 3H, NH and NH_2).

1-(2-Chlorophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid hydrazide (7f). By a similar procedure as described for **7a**, compound **7f** was obtained from **4f** (1 g, 1.78 mmol) and hydrazine hydrate (1.5 mL, 48.2 mmol) in ethanol (50 mL), 0.52 g (86.6%), IR (KBr): 3940, 3780, 2360, 1630, 1320, 836 cm^{-1}, MS *m/z*: 338 (M, Cl^{37}, 15.3), 336 (M, Cl^{35}, 65.8), 279 (52.6), 278 (44.6), 242 (69.4); ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 9.25–9.12 (m, 2H, H-4 and indole NH), 8.56–8.2 (m, 4H, ArH), 8.18–7.7 (m, 4H, ArH), 4.2–3.25 (bs, 3H, NH and NH_2).

1-(3-Thienyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid hydrazide (7h). In a similar manner to the preparation of **7a** compound **7h** was obtained from **4h** (0.5 g, 1.62 mmol) and hydrazine hydrate (1.5 mL, 48.2 mmol) in ethanol (50 mL), 0.26 g (52%), IR (KBr): 3279, 3199, 1645, 1364, 828 cm^{-1}, MS *m/z*: 308 (M, 35.5), 277 (17.0), 255 (24.9), 249 (48.9); ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 8.85 (s, 1H, H-4), 8.4–8.1 (m, 2H, indole NH and ArH), 8.0 (m, 1H, ArH), 7.8 (m, 1H, ArH), 7.7–7.3 (m, 4H, ArH), 4.9–4.2 (bs, 3H, NH and NH_2).

1-(2-Thienyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid hydrazide (7i). A solution of **4i** (0.8 g, 2.59 mmol) and hydrazine hydrate (1.5 mL, 48.2 mmol) was refluxed in ethanol (50 mL) in a similar manner as described in **7a**, 0.75 g (93.7%); IR (KBr): 3945, 3906, 1630, 1357, 904 cm^{-1}; MS *m/z* (relative intensity): 308 (M, 35.5), 255 (24.9), 249 (48.9), 160 (28.9); ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 8.8 (s, 1H, H-4), 8.25–8.1 (m, 2H, indole NH and ArH), 7.8 (m, 1H, ArH), 7.6–7.4 (m, 5H, ArH), 4.8–4.3 (bs, 3H, NH and NH_2).

Materials and Methods for Biological Evaluation

1. *Acanthocheilonema viteae*: *A. viteae* infection was transmitted to 6 weeks old male *M. coucha* through the vector *Ornithodorus moubata* by the method as reported in literature.[39] The micro- and macrofilaricidal activities of the compounds were

assessed against *A. viteae* in *M. coucha* at 50 mg/kg ip and/or 200 mg/kg po for 5 consecutive days according to literature methods.[40,41]

2. *Litomosoides carinii*: The infection was transmitted to 6 weeks old *cotton rats* (*Sigmodon hispidus*) through the vector *Liponyssus bacoti* by the literature method.[42] Animals showing 250 or more microfilariae per 5 mm of blood were chosen for screening. Blood samples of experimental and control animals were examined for microfilariae before starting the treatment and thereafter at weekly interval until day 42. All the compounds were given 30 mg/kg ip for 5 consecutive days. On day 42, all the treated and control animals were sacrified and the condition of adult male and female worms observed. The micro- and macrofilaricidal action were assessed as described for *A. viteae*.
3. *Brugia malayi*: The 6 weeks old male mastomys were infected by inoculum of 50 infective larvae of *Brugia malayi* recovered from infected mosquitoes (*Aedes aegybti*).[36] Method of screening of compounds were similar to those of *A. viteae* except blood was examined up to day 92 post treatment. Animals were sacrificed on day 92 for adult worm recovery.

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References and Notes

1. National workshop on operational constrains and their feasible solutions for efficient functions of national filaria control program units in the country. December 1991, NICD, Delhi, India.
2. Ottesen, E. A.; Ramachandran, C. P. Lymphatic filariasis infection and disease: control strategies. *Parasitology Today* **1995**, *2*, 129–131.
3. Cao, W.; Ploeg, C. P. B.; Ren, Z.; Habbema, J. D. F. Success against lymphatic filariasis. *World Health Forum* **1997**, *18*, 17–20.
4. Sharma, S. Vector borne diseases. *Prog. Drug Res.* **1990**, *35*, 365–485.
5. Simonsen, P. E.; Meyrowitsch, D. W.; Makunde, W. H. Bancroftian filariasis: long-term effect of the DEC provocative day tool on microfilaraemia. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **1997**, *91*, 290–293.
6. Bennett, J. L.; Williams, J. F.; Dave, V. Pharmacology of Ivermectin. *Parasitology Today* **1988**, *4*, 226–228.
7. Ginger, C. D. Advances in Filarial Chemotherapy and Screening. *Parasitology Today* **1986**, *2*, 38–40.
8. Loiseau, P. M.; Depreux, P. In vitro antifilarial evaluation of phenoxycyclohexane derivatives. *Annals of Tropical Medicine and Parasitology* **1993**, *87*, 469–476.
9. Chauhan, P. M. S.; Chatterjee, R. K. Synthesis of 1,3-substituted pyrazoles as possible antifilarial agents. *Indian J. Chem.* **1994**, *33B*, 32–37.
10. Srivastava, S. K.; Chauhan, P. M. S.; Agarwal, S. K.; Bhaduri, A. P.; Singh, S. N.; Fatma, N.; Chatterjee, R. K.; Bose, C.; Srivastava, V. M. L. Syntheses and antifilarial profile of 5-amino and 5,8-diamino isoquinoline derivatives: a new class of antifilarial agents. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2623–2628.
11. Singh, S. N.; Bhatnagar, S.; Fatma, N.; Chauhan, P. M. S.; Chatterjee, R. K. Antifilarial activity of a synthetic marine alkaloid, aplysinopsin (CDRI Compound 92/138). *Tropical Medicine and International Health* **1997**, *2*, 535–543.
12. Tewari, S.; Chauhan, P. M. S.; Bhaduri, A. P.; Singh, S. N.; Fatma, N.; Chatterjee, R. K.; Srivastava, V. M. L. 1,1′-Dicyano-2-substituted ethylenes: A new class of glucose uptake inhibitors in antifilarial chemotherapy. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1891–1896.
13. Sharma, S. Design of new drugs for helminth diseases: lead optimization in benzimidozole. *Adv. Drug Res.* **1994**, *25*, 103–172.
14. Townsend, L. B.; Wise D. S. The synthesis and chemistry of certain anthelmintic benzimidazoles. *Parasitology Today* **1990**, *6*, 107–112.
15. Agarwal, A.; Agarwal, S. K.; Bhakuni, D. S.; Gupta, S.; Katiyar, J. C. Antiparasitic agents: Part VIII—Synthesis of 1,6- and 1,8-disubstituted-9*H*-pyrido[3,4-*b*]indoles and 2-substituted-1(3),10-dihydro-9-phenylpyrido[3,4-*b*]imidazo[4,5-b]-indoles and their anthelmintic activity. *Indian J. Chem.* **1989**, *28B*, 943–949.
16. Agarwal, A.; Agarwal, S. K.; Bhakuni, D. S. Antiparasitic agents: Part X—Synthesis of 2,7-disubstituted-1,6-dihydropyrido[3,4-*b*]imidazo[4,5-e]indoles as anthelmintic agents. *Indian J. Chem.* **1990**, *29B*, 843–847.
17. Agarwal, A.; Agarwal, S. K.; Bhakuni, D. S.; Gupta, S.; Katiyar, J. C. Antiparasitic agents: Part XIII—Synthesis and anthelmintic activity of 6- and 8-(2,4-dioxoquinazolin-3-yl)-1-substituted-9*H*-pyrido[3,4-*b*]indoles, 6- and 8-(2-methyl-5-acetamidobenzimidazol-1-yl)-1-substituted-9*H*-pyrido[3,4-*b*]-indoles and 6-[2-carbomethoxyamino-5-*N*,*N*′-dicarbo-methoxyquanidino)benzimidazol-1-yl]-1-phenyl-9*H*-pyrido[3,4-*b*]indole. *Indian J. Chem.* **1990**, *29B*, 848–854.
18. Kumar, P.; Agarwal, S. K.; Bhakuni, D. S. Antiparasitic agents: Part XI—Synthesis and anthelmintic activity of 6-/8-[(2-carbomethoxyamino)benzimidazole]-5-carbonylamino-1-substituted-9*H*-pyrido[3,4-*b*]indoles. *Indian J. Chem.* **1990**, *29B*, 1077–1088.
19. Agarwal, A.; Agarwal, S. K.; Bhakuni, D. S.; Singh, S. N.; Chatterjee, R. K. Antiparasitic agents: Part XVI—Synthesis of 5(6)-substituted benzimidazole-2-carbamates as anthelmintic agents. *Indian J. Chem.* **1993**, *32B*, 453–456.
20. Agarwal, A.; Agarwal, S. K.; Singh, S. N.; Fatma, N.; Murthy, P. K.; Chatterjee, R. K. Synthesis and antifilarial activity of pyrido[3,4-*b*]imidazo[1,2-c′]quinazolo[4,5-e]/[4,5-g]-indoles. *Med. Chem. Res.* **1994**, *3*, 523–530.
21. Bose, C.; Agarwal, S. K.; Chatterjee, R. K.; Srivastava, V. M. L. Carboline antifilarials: effects on carbohydrate metabolizing enzymes in *Litomosides carinii* female. *Indian J. Exp. Bio.* **1994**, *32*, 431–434.
22. Agarwal, A.; Agarwal, S. K.; Singh S. N.; Fatima N.; Chatterjee, R. K., Structure–antifilarial activity relationship of 5/6/7/8-mono or disubstituted 1H/1-phenyl-9H-pyrdo[3,4-*b*]-indoles—a new class of potential filaricides. *Z. Naturforsch* **1994**, *49c*, 526–529.
23. Agarwal A; Agarwal S. K. Antiparasitic agents: Part XVII. Synthesis of 2-methylmercapto-7-H/phenyl-1H,6H-pyrido[3,4-*b*]imidazo[4,5-e]indoles, 6-/8-(4-oxo-2-thioxoquinazoline-3-yl)-1-H/phenyl-9*H*-pyrido[3,4-*b*]indoles and 6-/8-(2,4-dioxo-1,3-benzoxazin-3-yl)-1-phenyl-9*H*-pyrido[3,4-*b*]indoles as anthelmintic agents. *Indian J. Chem.* **1995**, *34B*, 323.
24. Agarwal, A.; Agarwal, S. K.; Singh S. N.; Fatima N.; Chatterjee, R. K. Synthesis of neoeudistomin analogues—As potential filaricides. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1545–1548.

25. Moore, E. C.; Zedeck, M. S.; Agarwal, K. C.; Sartorelli, A. C. Inhibition of ribonucleoside diphosphate reductase by 1-formylisoquinoline thiosemicarbazone and related compounds. *Biochemistry* **1970**, *23*, 4492–4498.
26. Campbell, W. C.; Fisher, M. H.; Stapley, E. O.; Albers-Schonberg, G.; Jacob, T. A. Ivermetin: a potent new antiparasitic agent. *Science* **1983**, *221*, 823–828.
27. Johnston, G. A. R. In *GABA in Nervous System Function*; Roberts, E.; Chase, T. N.; Tower, D. B. Ed.; Raven Press, New York, 1978, 395.
28. Wang, C. C. Parastic enzymes as potential targets for antiparasitic chemotherpay. *J. Med. Chem.* **1984**, *27*, 1–9.
29. Braestrup, C.; Nielson, M.; Olsen, C. E. Urinary and brain β-carboline-3-carboxylates as potent inhibitors of brain benzodiazopine receptors. *Proc. Natl. Acad. Sci. USA* **1980**, *77*, 2288–2292.
30. Dodd, H. R.; Ovannes, C.; Robert G.; Potier P. Hybrid molecules: growth inhibition of *Leishmania donovani* promastigotes by thiosemicarbazones of 3-carboxy-β-carbolines. *J. Med. Chem.* **1989**, *32*, 1272–1276.
31. Cain, M.; Weber, R. W.; Guzman, F.; Cook, J. M.; Barker, S. A.; Rice, K. C.; Grawley, J. N.; Paul, S. M.; Skolnick, P. β-Carbolines: synthesis and neurochemical and pharmacological actions on brain benzodiazepine receptors. *J. Med. Chem.* **1982**, *25*, 1081–1091.
32. Agarwal, S. K.; Saxena, A. K.; Jain, P. C. Studies on β-carbolines: synthesis of 3-amino-9*H*-pyrido[3,4-*b*]indoles and its reaction with carbethoxy isothiocyanate and benzoyl isothiocyanate. *Indian J. Chem.* **1980**, *19B*, 45–47.
33. Meyer, M. D.; Kruse, L. I. Ergoline synthons: synthesis of 3,4-dihydro-6-methoxy-benz[cd]indol-5-(1H)-one(6-methoxy-uhle's ketone) and 3,4-dihydrobenz[cd]indol-5(1H)-one(uhle's ketone) via a novel decarboxylation of indole-2-carboxylates. *J. Org. Chem.* **1984**, *49*, 3195–3199.
34. Hicknbottom, W. J., *Reaction of Organic Compounds*. Longmans, London, 1959.
35. Kumar, S.; Seth M.; Bhaduri, A. P.; Visen, P. K. S.; Mishra, A.; Gupta S.; Fatima, N.; Katiyar, J. C.; Chatterjee, R. K.; Sen A. B. Syntheses and anthelmintic activity of alkyl 5(6)-(substituted-carbamoyl)- and 5(6)-(disubstituted-carbamoyl)benzimidazole-2-carbamates and related compounds. *J. Med. Chem.* **1984**, *27*, 1083–1089.
36. Murthy, P. K.; Tyagi, K.; Roy Chowdhury, T. K.; Sen, A. B. Susceptibility of *Mastomys natalensis* (GRA strain) to a subperiodic strain of human *Brugia malayai*. *Indian J. Med. Res.* **1983**, *77*, 623–630.
37. World Health Organisation. Report of the Seventh meeting of the Scientific Working Group on Filariasis: Filaricide screeners. TDR/Fil/SWG(7)82,3 Geneva: World Health Organisation, 1982.
38. Hewitt, R. I.; Kushner, S., Stewart, H., White, E., Wallace, W. S. Subbarow; Y., Experimental chemotherapy of filariasis III. Effect of 1-diethylcarbanyl 4-methylpiperazine hydrochloride against naturally acquired filarial infection in cotton rats and dogs. *J. Lab. Clin. Medicine* **1947**, *32*, 1314–1329.
39. Worms, M. J.; Terry, R. J.; Terry, A. *Dipetalonema witei*, filarial parasites of the jird, *Meriones libycus*, 1. Maintenance in the laboratory. *J. Parasit.* **1961**, *47*, 963–970.
40. Lammler, G.; Herzog, H.; Saupe E.; Schuetze, H. R. Chemotherapeutic studies on *Litomosoides carinii* infection of *Mastomys natalensis*. *Bull. Wld. Hlth. Org.* **1971**, *44*, 751–756.
41. Misra, S.; Chatterjee, R. K.; Sen, A. B. Antifilarial action of furazolidone. *Indian J. Med. Res.* **1981**, *73*, 725–728.
42. Howking, F.; Sewell, P. The maintenance of filarial infection (*Litomosoides carinii*) for chemotherapeutic investigations. *Br. J. Pharm. Chem.* **1948**, *3*, 285.