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Synthesis of novel β-carboline derivatives with potential antimicrobial and anti helminthic activities

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ABSTRACT

Synthesis of novel heterocyclic compounds containing the β-carboline moiety, which have a valuable biological activities, has been achieved through the nucleophilic substitution of tryptamine to N'-(2-(1H indo-3yl)ethyl) ethane1,2 diamine (**I)** followed by the cyclocondensation to the corresponding β-carboline derivatives (IV-IX). Isolated yields in the range of 50-80% were obtained. The structures of the newly synthesized compounds were elucidated by spectroscopic data. All the compounds were screened for the antibacterial and antihelminthic activities using streptomycin and albendazole as standard drugs.

Key words: Tryptamine, Beta-carbolines, Aldehydes, Antibacterial activity, Antihelminthic activity.

INTRODUCTION

β-carbolines(9H-pyrido[3,4-b]indoles) are a large group of natural and synthetic indole alkaloids with different degrees of aromaticity, some of which are widely distributed in nature, including various plants, foodstuffs, marine creatures, insects, mammalians as well as human tissues and body fluids[1]. β-carbolines includes the highly banned drugs such as LSD, Psilocybin, DMT, Bufotenin, and Ibogaine. Interestingly, the β-carbolines have never been scheduled as banned substances. However, the pharmacophore of the β-carbolines show anti-infective properties against a variety of opportunistic microorganisms including Bacillus subtilis, E.coli, Klebisella pneumoniae and several others. β-Carboline alkaloids were found in several medicinal plants and displayed a variety of action on the central nervous, muscular, and cardiovascular systems. It was discovered that β-carboline derivatives might possess anti-tumor activity through multiple mechanisms, such as targeting DNA [2], suppressing the activity of topoisomerase [3], CDK [4] and IjK [5]. Some β-carbolines such as N(9)-arylated alkyl substituted β-carbolines possess potent anti cancer activities[6-8] and DNA intercatalating potencies. Some β-carbolines, for example, ethyl β-carboline-3-carboxylated (beta-CCE), are known to bind with high affinity to the central benzodiazepine receptors (BzR) and show anti-convulsive and anxiolytic properties[9-11]. Also noteworthy is the anti tumor and antiviral activity of lavendamycin[12] and streptonigrin alkaloids[13]. They are potent reversible inhibitors of

MOA-A enzyme thereby facilitating the neuronal transmission of exogenous tryptamines. Some β-carboline derivatives bearing guanidinium group or amino group-terminated side chain, were known to exhibit inhibitory activities on Tat-TAR interaction as well as to HIV-1 in MT4 cells. Some of the derivatives are reported to possess antioxidant activity[14]. A β-carboline compound, flazin isolated from Suillus granulatus has been shown to possess weak anti-HIV-1 activity[15].

The seeds of Peganum harmal are the biological sources of beta carboline alkaloids like harmine, harmaline, and tetrahydroharmine. β-carbolines have since been identified in several more plants including Banisteriopsis caapi, Passionflower (Passiflora incarnata), Tobacco (Nicotiana rustica), and even within the human pineal gland. Beta carbolines are synthesized from tryptophans and tryptamines involving various reagents. These molecules have been subject to a lot of synthetic efforts due to their biological and pharmaceutical importance. Most approaches are based on Pictet-Spengler reaction of tryptamines and aldehyde[16],

Bischler-Napieralski reaction[17,18], Aza-witting reaction[19], [4+2] cyclo addition of electro deficient 1,2,4-triazines with enamines[20] intra molecular Michael addition[21], thermal electrocyclic reaction of 3-alkenylindole-2-aldoxime[22], and modified intra molecular Goldberg amide arylation[23]. Recently, β-carbolines have been reported to be synthesized by the Palladium-catalysed annulations[24,25]. Numerous novel tetrahydro-beta-carboline-carboxylic acids in food samples carbolines undergo degradation in the presence of nitrosating agents and results in the formation of the corresponding dihydro-beta-carbolines[26]. Aromatizations, reductions and alkylations and rearrangements of the heterocyclic system transform β-carbolines into other heterocyclic systems[27].

In this work we report a good yielding and simplest synthetic procedure for the preparation of novel class of beta carboline derivatives with potential antimicrobial and antihelminthic activity.

RESULTS AND DISCUSSION

Compounds IV-VII (Table-1) were prepared by condensation of tryptamine, bromoethyl amine hydrobromide and potassium carbonate. The condensation product was protected by pthalic anhydride and condensation with different aromatic aldehydes in the presence of toulene resulted in the cyclization. The cyclized product was deprotected with hydrazine hydrate and resulted in the formation of brown coloured powder with 50-80% yields (scheme-1). The synthesized compounds were analysed by ^{1}H NMR. The chemical shift of the condensed product was 2ppm due to NH protons. The protected compound has the chemical shift at 10ppm. The cyclized product has shown the chemical shift from 7.09 to 7.26ppm. The deprotected compound does not show chemical shift at 10ppm due to loss of protons in the pthalic anhydride ring. The compounds were analysed by IR spectra. The N-H stretching in aromatic ring is shown between 3369-3590 cm^{-1}. The C-N stretching is observed in the range of 1642-1660 and 1114-1369 cm^{-1} in aromatic and aliphatic rings respectively. The $–OCH_3$, C-F, C-Cl stretching is found at 1724 cm^{-1}, 1328 cm^{-1} and 762 cm^{-1} respectively.

Antibacterial activity: In the view of synthesizing new antimicrobials, we have synthesized newer β- Carboline derivatives E_1-E_4 and evaluated their efficacy as antimicrobials invitro by Cup Plate method against different strains. Tests were performed in triplicate and the results are reported as means of atleast three determinations. Inhibitory activity of compounds against bacterial strains was observed in the following order.

VIII > VI> IV> V> VII> IX

The presence of NO_2 and phenyl groups may be responsible for significant inhibitory activity than the standard drugs.

Anti-helminthic activity: The test compounds (**IV, V, VI, VII, VIII, IX)** exhibited interesting anti-helminthic activity, however with a degree of variation. Compounds (**VIII)** exhibited highly significant anti-helminthic activity. The activity of these compounds was comparable that of albendazole (Table-3). The activity may be contributed to the presence of Cl, F and NO_2 groups in their substituted derivatives.

EXPERIMENTAL

Melting points were determined and are uncorrected. IR spectra were recorded on Bruker (ν_{max} in cm^{-1}) and ^{1}H NMR spectra in DMSO/$CDCl_3$ as solvent. All tchemical shifts are reported in parts per million relative to tetramethylsilane. Coupling constants (J) are reported in Hz. Purity of compounds were checked on silica gel-G plates by TLC.

Synthesis of N-(2-(1H indo-3yl)ethyl) ethane1,2 diamine [I]

Tryptamine (1gm, 6.2 mmol) was taken in round bottom flask and was dissolved in acetone (7.5ml). Bromo ethylamine hydrobromide (0.8gm, 6.5 mmol) and potassium carbonate (2.35, 1.7 mmol) were dissolved in acetone in round bottom flask and placed on magnetic stirrer, after 5 minutes both the contents of round bottom flask were added together and refluxed for about 4 hours.The mixture was filtered and acetone was evaporated to give jelly mass, yield 70%, MP: 185^0C. IR: cm^{-1}, 3315 (NH), 1670 (aromatic ring), 1229 (aryl C-N), 1089 (alkyl C-N). ^{1}H NMR: δ, 2 (s, 3H, NH), 2.57-3.80 (m, 8H, CH_2), 7.15 (t, 2H, CH), 7.35 (d, 1H, CH), 7.47 (s, 1H, CH), 7.65 (d, 1H, CH), 10.90 (s, 1H, NH).

Synthesis of 2(2-(2-(1H indol-3yl)ethyl aminoethyl)isoindoline- 1,3dione [II]

The jelly mass of **I** (0.7gm, 3.4 mmol) and pthalic anhydride (0.3gm 2.0 mmol) in glacial acetic acid (5ml) was refluxed for 6 hours. It was extracted with ethyl acetate to give solid compound **II**, yield 36%, MP: 196^0C. IR: cm^{-1}, 3450 (NH), 1723 (C=O), 1670 (aromatic ring), 1075 (C-N). ^{1}H NMR: δ, 2 (s, 1H, NH), 2.58-3.60 (m, 8H, CH_2), 7.10 (t, 2H, CH), 7.40 (d, 1H, CH), 7.45 (s, 1H, CH), 7.62 (s, 1H, CH), 7.85-7.90 (d, 4H, CH).

Synthesis of 2(2(1substituted-3,4-dihydro-1H-pyrido [3,4-b]indol-2(9H)- yl) ethyl) isoindoline-1,3 dione [III]

To the solid compound of **II** (0.25gm, 0.7 mmol) toulene (5ml),1N sulphuric acid (0.25ml) and an substituted aromatic aldehydes (equimolar) were added and refluxed for about 3 hours. The resultant solid was washed with methanol to obtain brown coloured solid compound (yield 80%).

Synthesis of 2-(1-substituted-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)ethanamine[IV-VII]

The compound **III** (0.2gm, 0.4 mmol) in methanol (5 ml) and hydrazine hydrate (1.5ml) was stirred for 3 hrs on a magnetic stirrer. The resultant brown compound was filtered washed with methanol (yield 50%).

Synthesis of 2-(1-phenyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)ethanamine [IV]- Reaction time 3hrs. The product was washed with methanol and dried under vacuum. Yield 50% as brown fine powder MP: 216^oC. IR: cm^{-1}, 3369 (NH), 1195 (C-N), 1660 (aromatic ring).^{1}H NMR: δ, 2 (t, 2H, NH), 2.60-2.79 (m, 8h, CH_2), 5.2 (s, 1H, CH), 7.10-7.35 (t, 5H, Ar-H), 7.37-7.60 (d, 4H, Ar-H), 11.65 (s, 1H, NH).

Synthesis of 2-(1-(4-methoxyphenyl)-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl) ethanamine [V]

Reaction time :3hrs. The product was washed with methanol and dried under vacuum. Yield 65 % as brown fine powder, MP: 236^oC. IR: cm^{-1}, 3420 (NH), 1114 (C-N), 1642 (aromatic ring), 1727(OCH_3).^{1}H NMR: δ, 2 (t, 2H, NH), 2.62-2.76 (m, 8H, CH_2), 5.21(s, 1H, CH), 6.85 (d, 2H, CH), 7.05 (t, 2H, CH), 7.12 (d, 2H, CH), 7.44-7.58 (d, 2H, CH), 11.70 (s, 1H, NH).

Synthesis of 2-(1-(3-nitrophenyl)-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)ethanamine [VI]

Reaction time :3hrs. The product was washed with methanol and dried under vacuum. Yield 75% as brown powder, MP: 242^oC. IR: cm^{-1}, 3425 (NH), 1125 (N-C alkyl), 1031 (C-N), 1642 (aromatic ring), (OCH_3). ^{1}H NMR: δ, 2 (t, 2H, NH), 2.58-2.75 (m, 8H, CH_2), 5.19(s, 1H, CH), 7.10 (d, 2H, CH), 7.45-7.56 (d, 2H, CH), 7.61 (t, 1H, CH), 7.75-8.10 (d, 2H, CH), 8.15 (s, 1H, CH), 11.70 (s, 1H, NH).

Synthesis of 4-(2-(2-aminoethyl)-2, 3, 4, 9-tetrahydro-1H- pyrido [3,4-b]indol-1-yl)-N,N-dimethylaniline [VII]

Reaction time :3hrs. The product was washed with methanol and dried under vacuum. Yield 80% as brown powder, MP: 225^oC. IR: cm^{-1}, 3590 (NH), 1168 (C-N), 1642 (aromatic ring), 1345 (CH_3).^{1}H NMR: δ, 2 (t, 2H, NH), 2.60-2.77 (m, 8H, CH_2), 5.19(s, 1H, CH), 6.64 (d, 2H, CH), 7.01 (d, 2H, CH), 7.05 (d, 2H, CH), 7.50 (d, 1H, CH), 7.61 (d, 1H, CH), 11.62 (s, 1H, NH)

Synthesis of 2-(1-(4-chloro-3-fluorophenyl)-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)ethanamine [VIII]

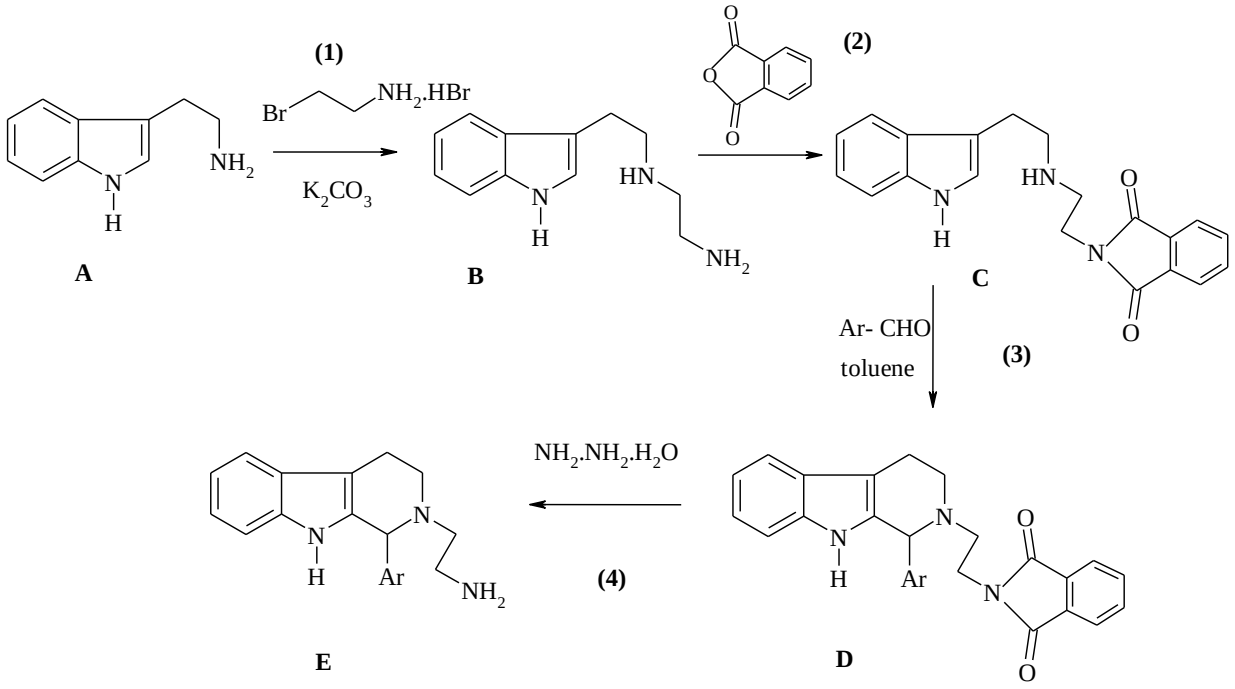
Reaction time :3hrs. The product was washed with methanol and dried under vacuum. Yield 60% as brown powder, MP: 231^oC. IR: cm^{-1}, 3310 (NH), 1677 (aromatic ring), 1328 (C-F), 1073 (N-C alkyl), 762(C-

Cl).^{1}H NMR: δ, 2 (t, 2H, NH), 2.60-2.75 (m, 8H, CH_2), 5.15(s, 1H, CH), 6.70 (s, 1H, CH), 6.90 (d, 1H, CH), 7.40 (d, 1H, Ch), 11.61 (s, 1H, NH).

Synthesis of 4-(2-(2-amino ethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-methoxyphenol [IX]

Reaction time :3hrs. The product was washed with methanol and dried under vacuum. Yield 55% as brown powder, MP: 247°C. IR: cm^{-1}, 3465 (OH), 3369 (NH), 1724 (OCH_3), 1660 (aromatic ring), 1195 (C-N).^{1}H NMR: δ, 2 (t, 2H, NH), 2.62-2.77 (m, 8H, CH2), 3.83 (s, 3H, CH), 5.20(s, 1H, CH), 6.65 (d, 1H, CH), 6.77 (d, 1H, CH), 6.87 (s, 1H, CH), 7.10 (t, 2H, CH), 7.50 (d, 1H, CH), 7.58(d, 1H, CH), 9.85 (s, 1H, OH), 11.62 (s, 1H, NH).

Scheme.1 : Scheme of Synthesis of β-carbolines derivatives.



B = I, C = II, D = III, E = IV; Ar = Aromatic benzaldehydes

(IV- IX)

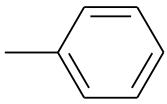
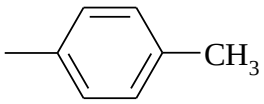
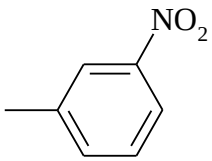
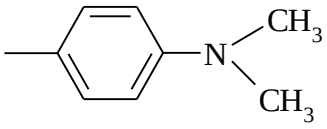
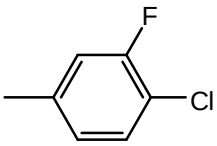
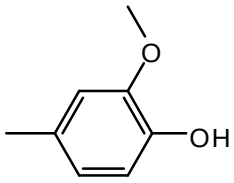
Compound	Yield(%)	M.P^{0}C	Mol.formula	Mol.weight
 **IV**	50	216^{o}C	$C_{19}H_{21}N_3$	291 gms
 **V**	65	236^{o}C	$C_{20}H_{23}ON_3$	321 gms
 **VI**	75	242^{o}C	$C_{19}H_{20}O_2N_4$	336 gms
 **VII**	80	225^{o}C	$C_{21}H_{26}O_3N_4$	382 gms
 **VIII**	60	231^{o}C	$C_{25}H_{21}O_2N_3FCl$	449.3 gms
 **IX**	55	247 ^{o}C	$C_{26}H_{25}\ O_4N_3$	443 gms

Table 2- Analytical data of compounds (IV- IX)

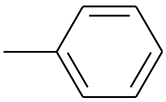
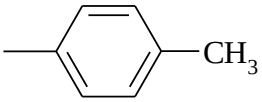
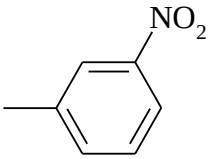
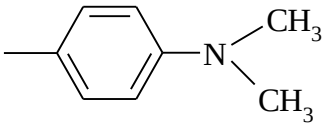
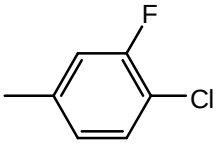
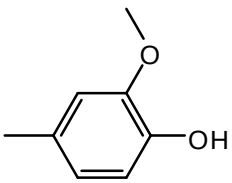
Compound	Structure	1H NMR spectra δ (ppm)	IR spectra (cm^{-1})
IV		2.1 (t, 2H, NH), 3.9-2.62 (m, 8H, CH_2), 5.01 (s, 1H, CH), 7 .95-7.5 (m , 6H, CH), 7.50-6.55(m, 3H, CH), 11.65 (s, 1H, NH).	3348, 3316.45 (NH), 3119 (aromatic CH), 1537 (C=C), 1264 (CN)
V		2.0 (t, 2H, NH), 2.62-3.5(m, 8H, CH_2), 3.83(s,3H,OCH_3), 5.19(s, 1H, CH), 6.70-7.2(m, 6H, CH), 7.2-7.32 (d, 1H, CH), 7.50-7.57 (d, 1H, CH)), 11.70 (s, 1H, NH).	3584, 3366.4 (NH), 3060 (aromatic CH), 1591 (C=C), 1197.2 (CN), 2972.9 (OCH_3)
VI		2.0 (t, 2H, NH), 2.5-2.95 (m, 8H, CH_2), 5.19(s, 1H, CH), 6.5-6.6 (t, 2H, CH), 6.6 (d, 1H, CH), 6.9-7.01 (m, 2H, CH), 7.4-7.35 (d, 1H, CH), 7.5 (s, 1H, CH), 7.9-7.6(d, 1H, CH), 11.50 (s, 1H, NH).	3425 (NH), 1125 (N-C alkyl), 1031 (C-N), 1642 (aromatic ring), (OCH_3)
VII		2.0 (t, 2H, NH), 2.50-2.85 (m, 8H, CH_2), 3.06(s, 6H,-CH_3), 5.01(s, 1H, CH), 6.64 (d, 2H, CH), 7.5-7.80 (m, 4H, CH), 7.85 (d, 2H, CH), 11.62 (s, 1H, NH)	3590 (NH), 1168 (C-N), 1642 (aromatic ring), 1345 (CH_3).
VIII		2 (t, 2H, NH_2), 2.4 (m, 6H, CH_2), 3.2 (t, 2H, CH_2), 3.9 (s, 3H, OCH_3), 5.1 (s, 2H, CH_2), 5.3 (s, 1H, CH), 6.6 (s, 1H, CH), 6.8 (t, 2H, CH), 7.1 (d, 2H, CH), 7.4 (d, 2H, CH), 7.6 (s, 1H, CH), 7.8 (t, 1H, CH), 7.9 (d, 1H, CH), 8.3 (d, 1H, CH)	3310 (NH), 1677 (aromatic ring), 1328 (C-F), 1073 (N-C alkyl), 762(C-Cl)
IX		2 (t, 2H, NH_2), 2.6 (m, 8H, CH_2), 4 (s, 6H, OCH_3), 5 (s, 2H, CH_2), 5.2 (s, 1H, CH), 6.6 (d,1H, CH), 6.7 (m, 5H, CH), 7.1 (d, 2H,CH), 7.4 (t, 1H, CH), 7.7 (d, 1H,CH), 8 (d, 1H,CH), 9.7 (s, 1H, OH).	3465 (OH), 3369 (NH), 1724 (OCH_3), 1660 (aromatic ring), 1195 (C-N)

Table 3- Anti-bacterial activity of the synthesized compounds (IV- IX)

Compound	Conc (µg/mL)	Zone of inhibition (mm)	
		Bacillus subtillus	Escherichia coli
Standard Streptomycin	100	7	6
	300	9	8
	500	10	9
	700	11	10
IV	100	12	12
	300	14	14
	500	15	15
	700	17	16
V	100	10	11
	300	11	12
	500	11	14
	700	13	16
VI	100	11	10
	300	12	10
	500	13	15
	700	16	17
VII	100	10	11
	300	11	14
	500	16	15
	700	18	16
VIII	100	12	11
	300	17	14
	500	19	15
	700	21	17
IX	100	9	8
	300	10	10
	500	12	12
	700	15	15

Table 4- Anti-helminthic activity of synthesized compound

Compound	Concentration (% w/v)	Starting Time (min.)	Paralysis Time (min.)	Death time (min.)
IV	0.1	0	37	55
	0.2	0	31	49
	0.5	0	22	40
V	0.1	0	29	52
	0.2	0	20	44
	0.5	0	13	26

	0.1	0	46	72
	0.2	0	42	68
VI	0.5	0	34	59
	0.1	0	25	50
	0.2	0	19	41
VII	0.5	0	12	20
	0.1	0	80	110
	0.2	0	62	95
VIII	0.5	0	31	60
	0.1	0	19	42
	0.2	0	21	42
IX	0.5	0	11	25
Standard	0.1	0	15	44
Albendazole	0.2	0	12	34
	0.5	0	5	20

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