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ORIGINAL ARTICLE

Synthesis, and Invitro Antihelmintic Activity of Beta - Carboline Derivatives

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Abstract

Beta-Carboline alkaloids are a heterogeneous group of indole alkaloids that can be either naturally occurring or artificially produced. They exhibit varying degrees of aromaticity and are commonly present in several taxa, including plants, marine organisms, insects, and animals. The main objective of this work is to synthesis and characterize the proposed beta – carboline derivatives and performed invitro Anthelmintic activity using earthworms. Compounds 3 [4-(9H-pyrido[3,4-b] indol-1-yl)phenol (3)] at a concentration of 0.1% exhibited the longest paralysis time of 6.26 ± 0.13 and death time of 8.28 ± 0.18. Further preparation and biological evaluation of these and some more derivatives may lead to the potent drug soon.

Keywords: Carboline, Anthelmintic, Molecular Docking, Beta tubulin

Introduction

Throughout history, humanity has suffered from a multitude of severe illnesses. Over the course of history, different medicinal plants have been used to treat illnesses. Calotropis gigantea (L) is an immensely important medicinal plant that possesses a multitude of therapeutic characteristics [1]. The root bark of this plant possesses efficacy in the treatment of various ailments including piles, tumours, wounds, parasite infections, and dysentery [2]. Helminthiasis is a disorder marked by the invasion of our internal organs by several species of worms. Helminthic diseases are spread by consuming eggs or larvae of worms found in contaminated food. They are highly common infections in humans, impacting a substantial proportion of the global population. It presents a multitude of harmful health hazards. As to the World Health Organisation (WHO), most drugs used to treat parasitic worms are artificial and have substantial adverse effects [3-6].

In modern times, helminthiasis has become a challenging issue. To address this problem, we need to explore other methods, such as traditional medicines that contain potent anti-helminthic chemicals [7]. In tropical developing nations, people heavily rely on herbal remedies due to their significant value for rural communities and potential contribution to the global community as a source of novel pharmaceuticals.

Beta - Carboline alkaloids are a diverse collection of indole alkaloids that can be found naturally or synthesised. They vary in their level of aromaticity and are commonly found in many creatures including plants, marine organisms, insects, and animals. In recent times, these compounds have garnered significant interest due to their intriguing biological and pharmacological characteristics. They have been found to interact with benzodiazepine receptors [8], intercalate into DNA [9], and inhibit CDK [10] and topoisomerase [11].

Due to anti-helminthic resistance, there is need of development of new moieties. The objective of the present study is to synthesize and evaluate anti-helminthic activity of Beta – Carboline

derivatives.

Experimental Method

General: The melting points were determined using an electrothermal digital instrument and were not adjusted for any corrections. NMR spectra were acquired using a Bruker Avance 500 MHz spectrometer, with a frequency of 500 MHz for 1H. The solvent used was DMSO-d6, and TMS was used as the internal standard. Pre-coated plates of silica gel were subjected to analytical Thin-Layer Chromatography (TLC).

The present work contains insilico docking studies, synthesis and invitro anthelmintic activity of 1-Substituted-9H-pyrido [3,4-b] indole (CARBOLINE DERIVATIVES) as –

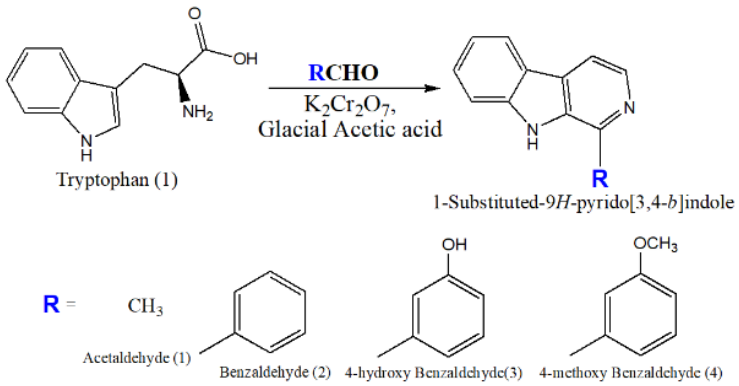

Figure 1 – Scheme for synthesis of Beta - carboline

General procedure for Synthesis of 1-Substituted-9H-pyrido[3,4-b] indole or Beta-carboline derivatives: [9] A mixture of L – tryptophan (2.0 gm, 10 mmol) and substituted aldehyde (acetaldehyde, Benzaldehyde, p-hydroxy benzaldehyde and p-methoxy benzaldehyde) 3 mL was added to 40 mL distilled water and in a loosely stoppered flask. The mixture was then stirred for 10 minutes at ambient temperature, then 1 mL 0.5 M sulphuric acid was added, and mixture was stirred overnight. Completion of reaction was monitored with TLC. Add 8 mL of glacial acetic acid and 5.88 g of potassium dichromate and refluxed the mixture for 10 minutes. Then sodium sulphite was added to remove the excess potassium dichromate and sodium carbonate was added to make the mixture neutral. Filtered the mixture and extracted with ethyl acetate (3 x 70 mL). The organic extracts were combined and then washed with water and then saturated with NaCl solution and dried over Sodium thiosulphate and concentrated under vacuum to obtain all four respective carboline derivatives. Physical Characteristics were discussed in Table 1.

Compound 1 [1-methyl-9H-pyrido[3,4-b] indole (1)]

IR: 3128.23 for N-H Stretching, 2846.74 C-H Stretching, 1461.94 C- N Stretching, 2611.44 C-H Stretching for aliphatic.

^1H *NMR* (400 MHz, DMSO) δ 8.28 (s, 1H, NH), 8.21 (s, 1H, Ar-H), 7.54 (s, 1H, Ar-H), 7.42 (s, 1H, Ar-H), 7.29 (s, 1H, Ar-H), 7.10 (s, 1H, Ar-H), 7.02 (s, 1H, Ar-H), 2.80 (s, 3H, CH).

Compound 2 [1-phenyl-9H-pyrido[3,4-b]indole (2)]

IR: 3384.84 for N – H Stretching, 2972.10 for C-H Stretching, 1305.72 for C – N Stretching.

^1H *NMR* (400 MHz, DMSO) δ 9.18 (s, 1H, NH), 8.48 (s, 1H, Ar-H), 8.02 – 7.87 (m, 2H, Ar-H), 7.64 (s, 1H, Ar-H), 7.46 (t, *J* = 17.6 Hz, 3H, Ar-H), 7.33 (d, *J* = 5.3 Hz, 2H, Ar-H), 7.18 (s, 1H, Ar - H), 7.09 (s, 1H, Ar – H).

Compound 3 [4-(9H-pyrido[3,4-b]indol-1-yl) phenol (3)]

IR: 3400.41 for O-H Stretching, 3328.12 for N – H Stretching, 2820.23 for C-H Stretching, 1656.74 for C – O Stretching.

^1H *NMR* (400 MHz, DMSO) δ 9.18 (s, 1H, NH), 8.48 (d, J = 31.3 Hz, 2H, Ar-H), 7.87 – 7.73 (m, 2H, Ar-H), 7.64 (s, 1H, Ar – H), 7.52 (s, 1H, Ar – H), 7.30 (s, 1H, Ar – H), 7.18 (s, 1H, Ar-H), 7.09 (s, 1H, OH), 7.01 – 6.83 (m, 2H).

Compound 4 [1-(4-methoxyphenyl)-9H-pyrido [3,4-b]indole (4)]

IR: 3157.25 for N _ H Stretching, 2854.45 for C-H Stretching, 1033.77 for C-O-C Stretching

^{1}H NMR (400 MHz, DMSO) δ 9.04 (s, 1H, NH), 8.56 (s, 1H, Ar – H), 8.01 – 7.83 (m, 2H, Ar – H), 7.66 (s, 1H, Ar – H), 7.53 (s, 1H, Ar – H), 7.34 (s, 1H, Ar – H), 7.19 (s, 1H, Ar – H), 7.10 (s, 1H, Ar – H), 7.07 – 6.96 (m, 2H), Ar – H, 3.77 (s, 3H, CH3).

Anti-helminthic Activity

The anthelmintic activity of all the synthesised compounds was evaluated using the method described by Ajayieoba et al. [12-13]

The anthelmintic activity of the Indian adult earthworm (Pheretima posthuma) was investigated. The earthworms, which were approximately 6±1 cm in size, were gathered from damp soil at Oriental University in Indore. They were then cleansed to eliminate any faecal matter and acclimated to laboratory settings prior to the start of the experiment. The earthworm bears a resemblance, both in terms of anatomy and physiology, to the intestinal roundworm parasites seen in humans.

Albendazole was used as standard and Normal saline was used as control. The earthworms were partitioned into five groups, with six earthworms in each group. The control group was prepared by diluting Albendazole with normal saline to achieve a concentration of 0.1% w/v. The synthesised compounds were suspended in normal saline and made at a concentration of 0.1% w/v for each compound.

The duration of total paralysis and mortality was recorded and analysed in Table 2. The Mean paralysis time and mean fatal time for each chemical were determined, with each reading being taken in triplicate. To determine death, each worm was regularly subjected to external stimuli that triggered and caused movement in earthworms, if they were still alive. [15]

The experimental data were presented as the mean value plus or minus the standard error of the mean for all synthesised substances. The means of the treatment groups were compared for significance using the student t-test.

Result & Discussion

The present work comprises of synthesis of β - carboline derivatives as an anthelmintic agent. It was reported in literature that presence of indole moiety increases the probability of anti-helminthic activity. With this consideration new β- carboline derivatives were synthesised by one pot reaction. L – tryptophan was reacted with different aldehyde such as acetaldehyde, Benzaldehyde, p-hydroxy benzaldehyde and p-methoxy benzaldehyde in presence of glacial acetic acid and potassium dichromate to obtain 1-Substituted-9H-pyrido[3,4-b] indole (Compound 1 to 4). The completion of Rection was monitored by TLC using Petroleum ether and ethyl acetate as eluent system in 8:2 ratio. All compounds physical properties such as melting point, yield, colours were observed and summarised in Table 1. Spectral data of all compounds were calculated and discussed in spectral interpretation. All compounds were characterized and confirmed their structure with IR and NMR.

Table 1 – Physical Characteristic data of all compounds (1-Substituted-9H-pyrido[3,4-b] indole)

S. No	Compound Name	Colour	M.P. (^{o}C)	% Yield	R_f
1	1-methyl-9H-pyrido[3,4-b]indole (1)	Pale yellow	226 - 228	22.20	0.32
2	1-phenyl-9H-pyrido[3,4-b]indole (2)	Pale brown	196-198	28.22	0.39
3	4-(9H-pyrido[3,4-b]indol-1-yl)phenol (3)	Brownish	190-192	32.36	0.48
4	1-(4-methoxyphenyl)-9H-pyrido[3,4-b]indole (4)	Cream	260-262	19.28	0.28

Anti-helminthic Activity

The in-vitro anthelmintic activity of all the synthesised carboline derivatives was tested against *Pheretima posthuma*, which closely resembles the intestinal roundworm parasite found

in humans. The findings were consolidated in Table 2, revealing that all drugs exhibit anthelmintic efficacy. Upon closer examination of Table 2 and Figure 2, it is evident that **Compounds 3** [4-(9H-pyrido[3,4-b]indol-1-yl)phenol (3)] at a concentration of 0.1% exhibited the longest paralysis time of 6.26 ± 0.13 and death time of 8.28 ± 0.18, surpassing the effects of albendazole (Standard) which had a paralysis time of 3.21 ± 0.08 and death time of 4.68 ± 0.12. Additionally, other compounds also possess anthelmintic action.

Table 2 Anti-helminthic potency of synthesised carboline derivatives

S. No	Compound Name	Time in Minutes (Mean ± SEM)	
		Paralysis (P)	Death (D)
1	Control	No paralysis was observed	No Death was observed
2	Standard (Albendazole)	3.21 ± 0.08	4.68 ± 0.12
3	1-methyl-9H-pyrido[3,4-b]indole (1)	9.23 ± 0.10	12.89 ± 0.05
4	1-phenyl-9H-pyrido[3,4-b]indole (2)	8.24 ± 0.19	11.01 ± 0.08
5	4-(9H-pyrido[3,4-b]indol-1-yl)phenol (3)	6.26 ± 0.13	8.28 ± 0.18
6	1-(4-methoxyphenyl)-9H-pyrido[3,4-b]indole (4)	8.67 ± 0.11	11.98 ± 0.08

All values represent in Mean ± SEM

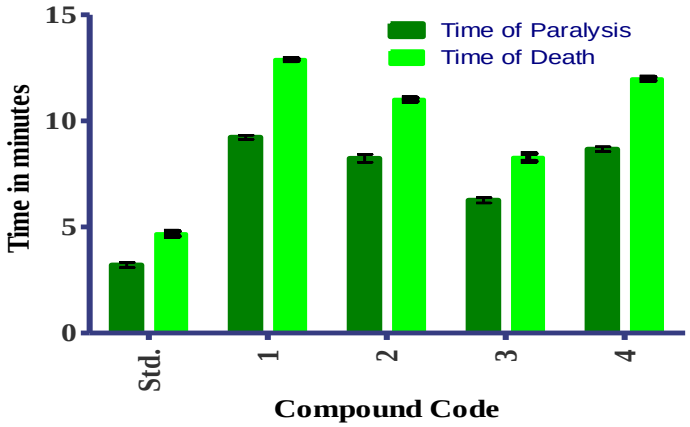

Figure 2: Graph represent Time of Paralysis & time of Death of synthesized carboline derivative.

Conclusion

After done all observation it may conclude that Compounds 3 [4-(9H-pyrido[3,4-b] indol-1-yl) phenol (3)] at a concentration of 0.1% exhibited best paralysis time of 6.26 ± 0.13 and death time of 8.28 ± 0.18, surpassing the effects of albendazole (Standard) which had a paralysis time of 3.21 ± 0.08 and death time of 4.68 ± 0.12. with this potential some more carboline derivatives will be prepared.

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