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AN OVERVIEW ON TETRAHYDRO-β-CARBOLINE DERIVATIVES AS PROMISING LEADS IN MODERN DRUG DEVELOPMENT

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ABSTRACT

Tetrahydro-β-carbolines (THβCs), also known as tryptolines, are structurally diverse heterocyclic alkaloids composed of a tricyclic pyrido [3,4-b] indole nucleus. They are naturally present in various plants such as Peganum harmala, marine organisms, and have emerged as privileged scaffolds in medicinal chemistry due to their interaction with multiple biological targets. The Pictet–Spengler condensation of tryptamine derivatives with aldehydes or ketones represents the principal synthetic route to THβCs, enabling the generation of structurally diverse analogues including cis and trans isomers. Numerous synthetic modifications, including asymmetric catalysis, metal-mediated cyclization's, and microwave- assisted protocols, have been developed to improve reaction efficiency and stereoselectivity. THβCs exhibit a broad range of biological activities such as anticancer, antimicrobial, antileishmanial, antimalarial, antioxidant, neuroprotective, and antiinflammatory effects. They modulate critical enzymes and receptors, including monoamine oxidase and serotonin pathways, underscoring their potential in treating neurodegenerative and psychiatric disorders. This comprehensive review highlights advances in THβC synthesis, biological evaluation, and therapeutic applications, emphasizing for future research directions for drug development.

KEYWORDS: Tetrahydro-β-carbolines (THβCs), Pictet–Spengler reactions, Microwave-assisted methods, structure–activity relationship.

INTRODUCTION

β-Carbolines are a special group of natural and synthetic compounds containing an indolebased three- ring structure.[1] They are found in many plants (for example, *Peganum harmala*), microorganisms, marine animals, insects, foods, tobacco smoke, and even in human tissues.[2] These compounds have a wide range of biological activities, including anti-inflammatory, anticonvulsant, antiparasitic, antitumor, anti- microbial, antiviral, and neurological effects. The activity of β-carbolines depends on the type and position of chemical groups attached to their core structure.[3]

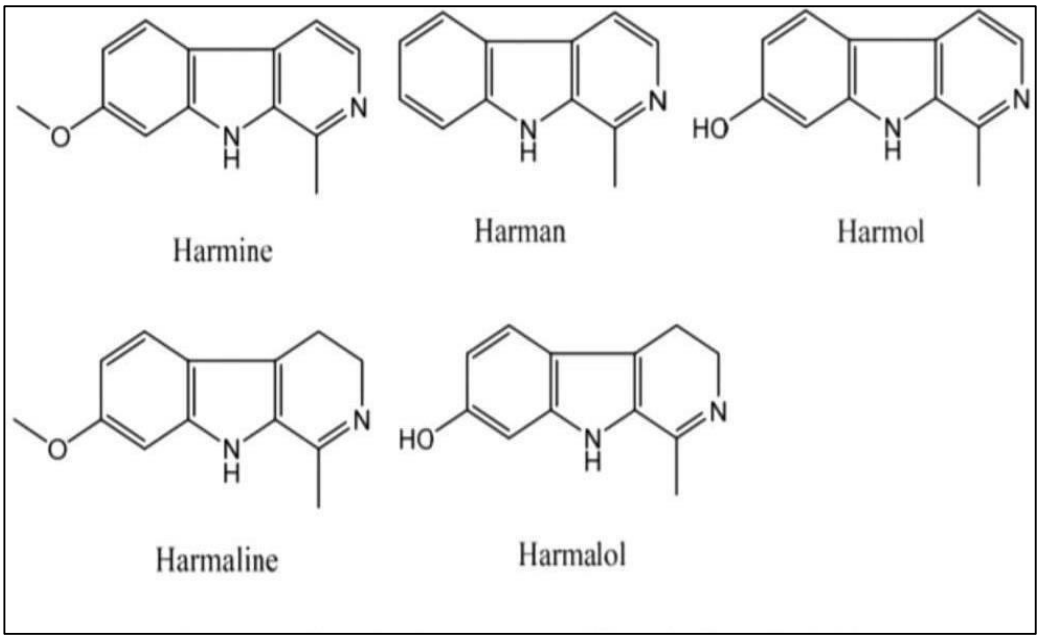


Figure 1: Chemical structure of β – carboline alkaloids.

Some β-carbolines, such as N2-bivalent and N9-bivalent types, are known to block certain enzymes (AChE, BChE) and NMDA receptors, which makes them promising for treating neurological disorders.[20] They have also shown potential against diseases like leishmaniasis and are part of some existing medicines (e.g., tadalafil, vinpocetine, reserpine).[1]

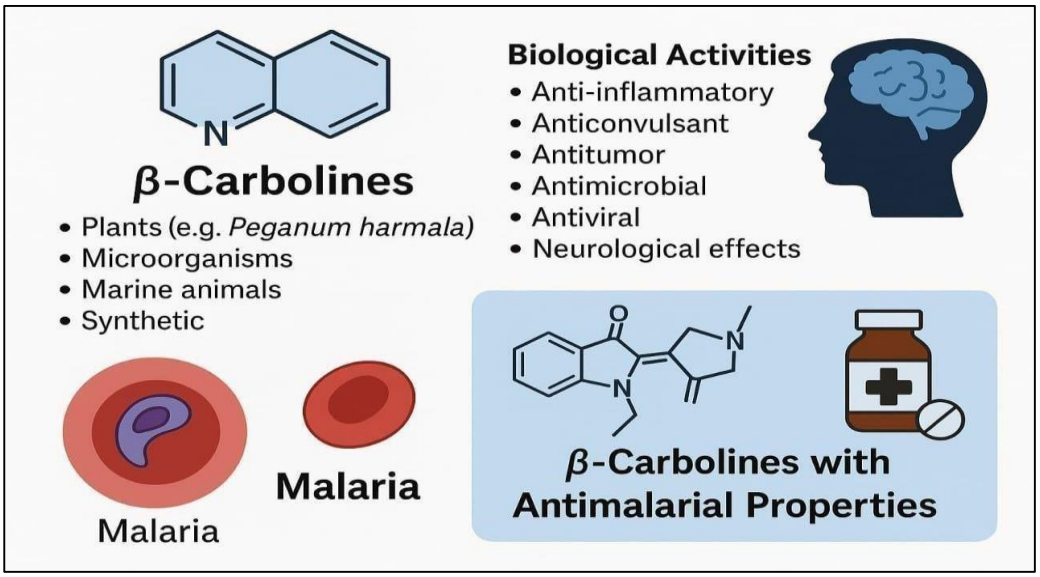


Figure 2: β –carbolines and its activities.

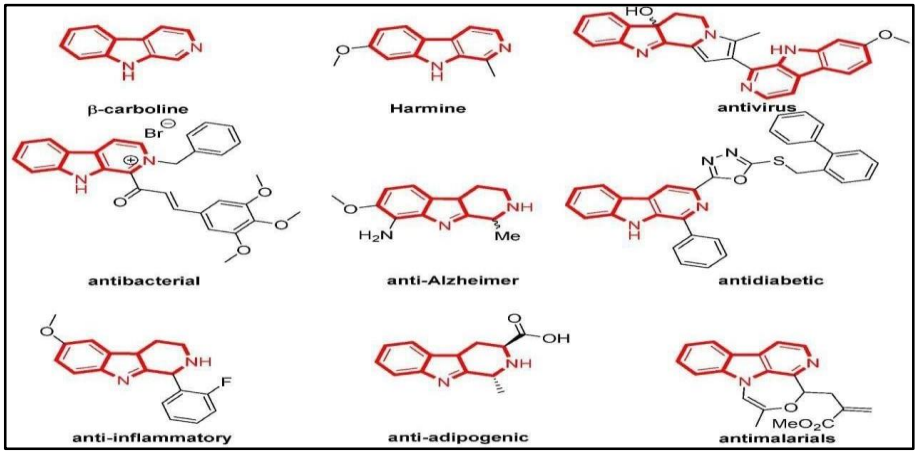


Figure 3: Examples structures of β – carbolines.

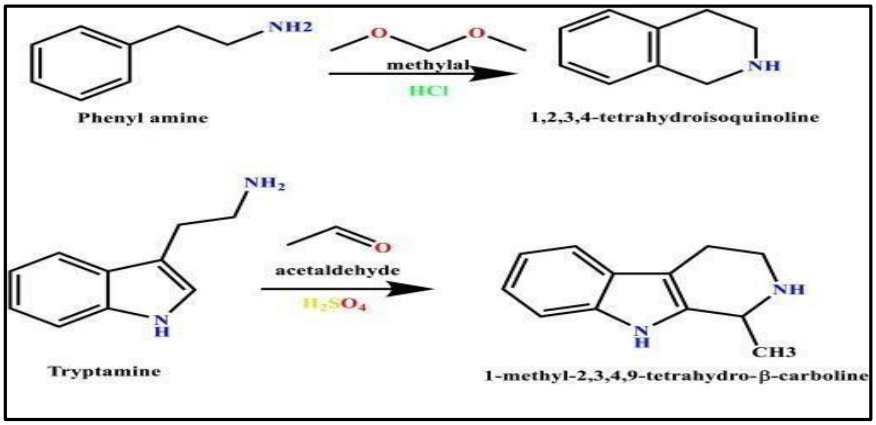
This study focuses on β-carbolines with antimalarial properties. Malaria is a serious infectious disease caused by Plasmodium parasites, mainly *P. falciparum* and *P. vivax*, which kill over half a million people every year, mostly children.[5] Resistance to current drugs (such as chloroquine and artemisinin-based combination's) is a growing problem. This creates an urgent need for new drugs, especially those with nitrogen- containing ring systems like β-carbolines both natural and synthetic β-carbolines have shown strong activity against malaria parasites.[5]

Examples include harmine and harmaline from *P. harmala*, *manzamine* derivatives from marine sponges, and bis- indole alkaloids from *Strychnos* plants.[1] Synthetic β-carbolines have also led to new antimalarial classes such as spiroindolones, with cipargamin being a promising candidate currently in clinical trials.[11]

SYNTHESIS OF TETRA HYDRO BETA CARBOLINE

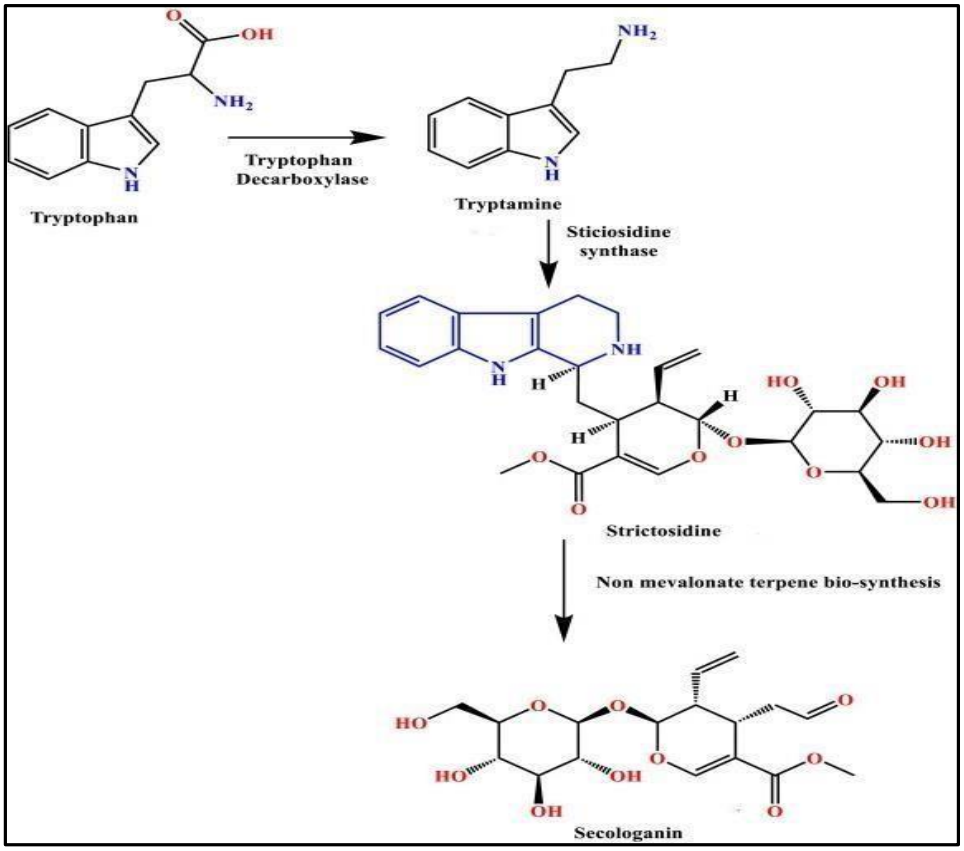
1. Tetrahydro-β-carboline (THBC) and β-carboline (β-C) ring system

Tetrahydro-β-carboline (THBC) and β-carboline are key structural motifs in medicinal chemistry, found in many pharmacologically active alkaloids. (Cao et al., 2007).[1] The Pictet– Spengler condensation, discovered in 1911 by Pictet and Spengler, condenses β-arylamines with aldehydes or ketones to form tetrahydro – isoquinolines.[2] The reaction occurs in two steps: first, a Schiff base (imine) is formed, then it undergoes 6-endo-trig cyclization to produce the THBC scaffold.[2] In 1928, Tatsui synthesized 1-methyl – 1,2,3,4-tetrahydro-β-carboline from tryptamine and acetaldehyde (Ascic et al., 2012; Calcaterra et al., 2020), as shown in Scheme 1.



Scheme 1: First reported Pictet – Splengler synthesis.

The enzyme-catalyzed Pictet – Spengler condensation of tryptamine with Strictosidine synthases produces Strictosidine. Secologanin biosynthesis follows Strictosidine formation and involves multiple steps, including non-mevalonate terpene pathways.[5] This step is crucial in the biogenetic pathway of monoterpene indole alkaloid formation. Most indole alkaloids are biosynthesized from tryptophan via tryptophan decarboxylase, a pyridoxal- dependent enzyme.[5] The pathway has been well-studied and summarized in Scheme 2 (O'Connor and Maresh, 2006; Battersby et al., 1968).

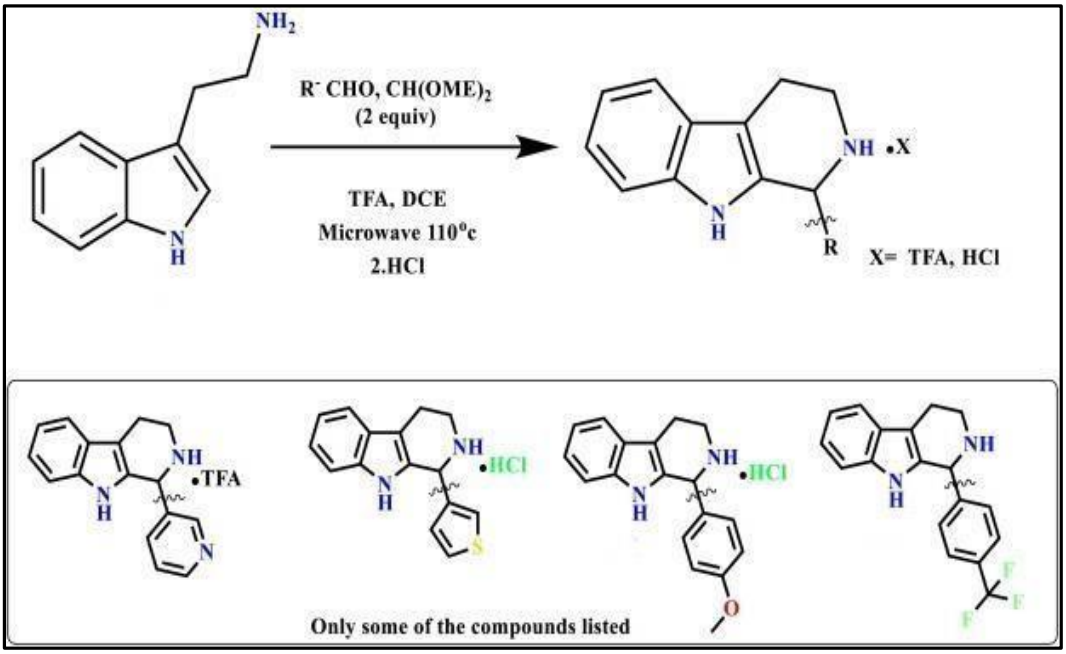


Scheme 2: Bio-Synthetic pathway of indole alkaloids.

In recent years, the THBCs and β-carbolines were extensively studied, and still, many more studies are in progress. The synthetic tactics were altered, which resulted in good yields of THBCs, β – carboline, and its derivatives that were tested against various pharmacological activities like anticancer (Yao et al., 2019), anti-Alzheimer's (Horton et al., 2017), etc.[4]

2. Microwave-assisted synthesis

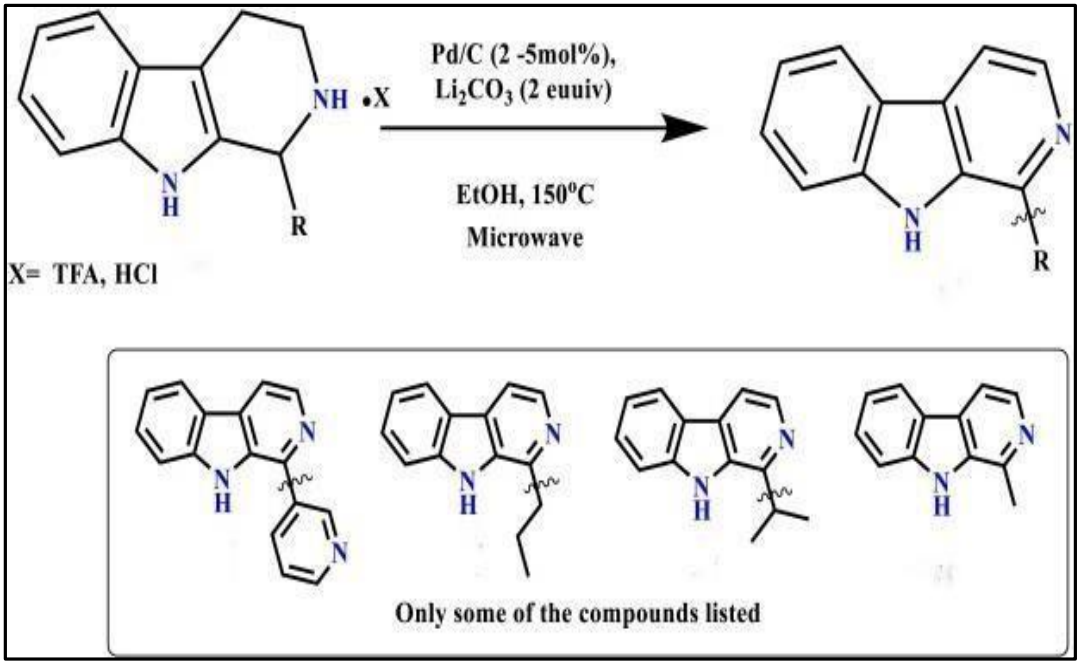
The Pictet–Spengler reaction usually requires long reflux times, but microwave radiation greatly accelerates it.[7] Scott Eagon and Marc O. Anderson reported microwave-assisted synthesis of tetrahydro-β- carboline (THBC) and β-carboline in just 20 minutes. The reaction used tryptamine as the starting material with 1,2-dichloroethane (DCE) and trifluoroacetic acid (TFA) as solvents, achieving up to 99% yield (Scheme 3).[7] After THBC formation, aromatization of tetrahydro-β – carboline salts with Pd/C in ethanol under microwave conditions produced β-carboline salts (Scheme 4). This method is rapid, efficient, and highly.[7]



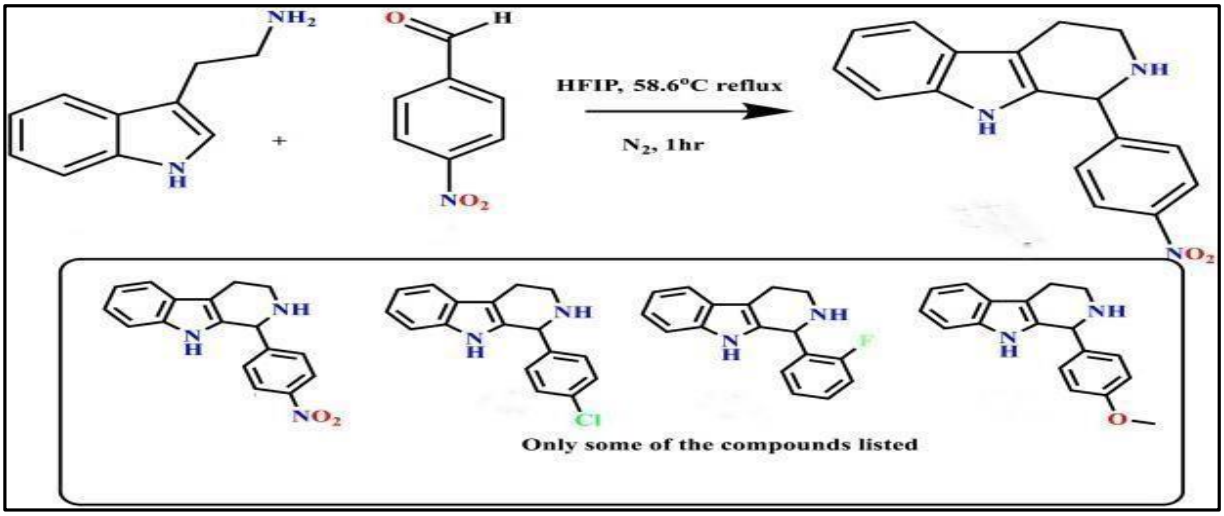
Scheme 3: Microwave-assisted synthesis of THBC derivatives.

3. Microwave assisted synthesis of β-carboline derivatives

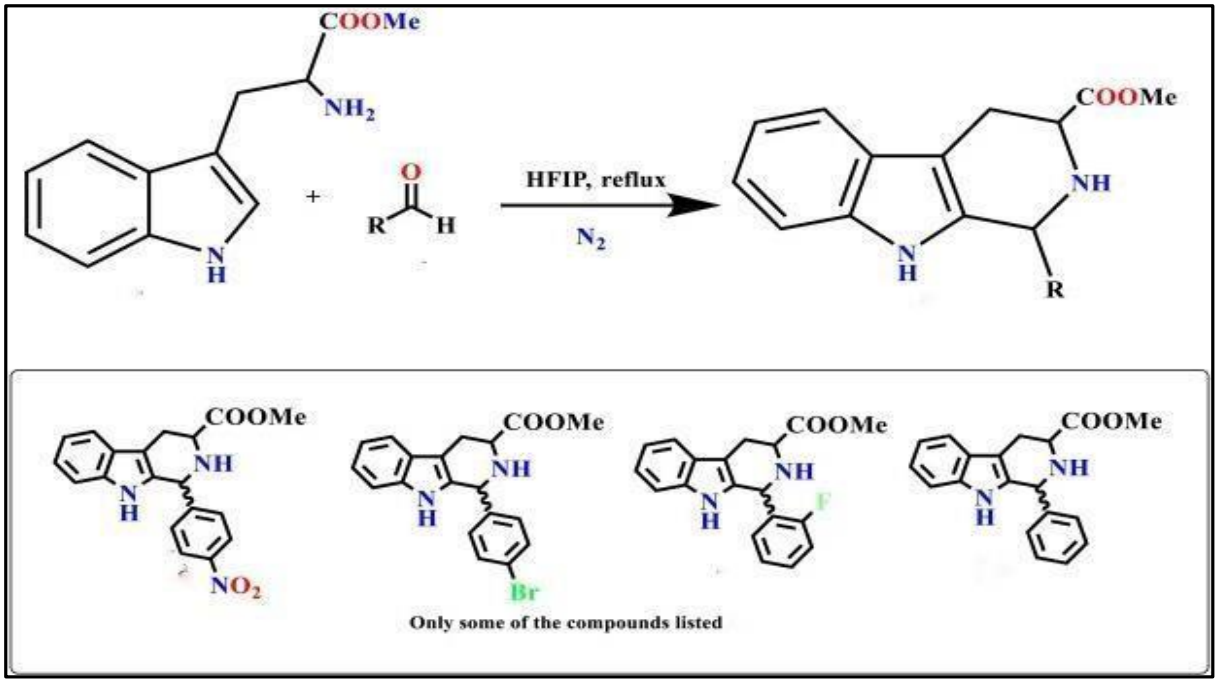
Wang et al. reported the synthesis of 1-substituted-1,2,3,4-tetrahydro-β-carboline in the presence of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as solvent and Li–Na as catalyst under anhydrous conditions.[2] Pictet-Spengler reactions between tryptamine derivatives and aldehydes, or activated ketones with HFIP, could accelerated the tetrahydro-β-carbolines in high yields (99 %) upon reaction for one hour under nitro- gen atmosphere at 58.6 °C (Scheme 5). The same research group also reported the synthesis of L-tryptophan methyl ester derived by THBC (Wang et al., 2014) (see Scheme 6).[2]



Scheme 4: Microwave-assisted synthesis of β – carboline derivatives.



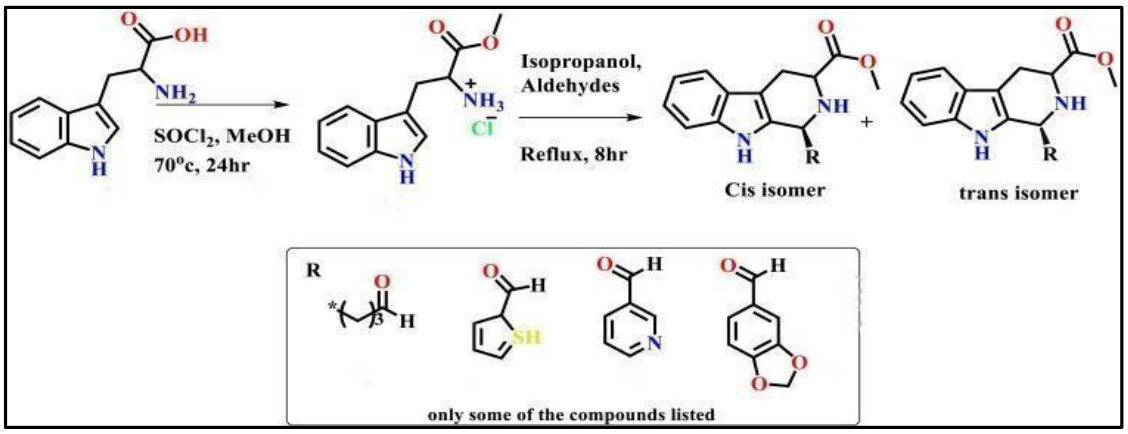
Scheme 5: Synthesis of THBC derivatives with HFIP and N2.



Scheme 6: Synthesis of THBC methyl ester derivatives with HFIP and N2.

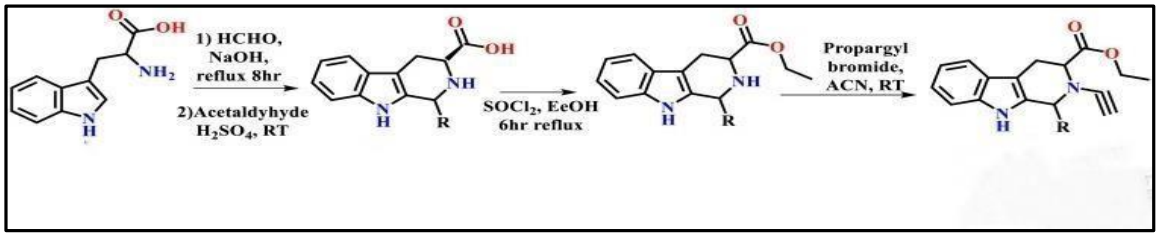
VARIOUS SYNTHETIC APPROACHES

Apart from microwave-assisted synthesis, several alternative methods for β-carboline derivatives have been explored, including Ru (II)-catalyzed C–H arylation and hydroxy methylation, Cu (II)-mediated C–H hydroxylation, metal-free one-pot synthesis using NMethyl-2-pyrrolidone, and iodine-catalyzed aromatization. These approaches generally provide moderate to good yields and allow investigation of C–H functionalization and regioselectivity.[9] For generalized THBC and β – carboline synthesis, L- or DL- tryptophan is first esterified with thionyl chloride to give methyl/ethyl esters. Subsequent reaction with aromatic or aliphatic aldehydes forms THBC esters (cis/trans – isomers), which are then oxidized to yield the final β- carboline compounds.[10] Singh and co – workers reported antifungal activity of these THBC ester derivatives (Scheme 7).[16]



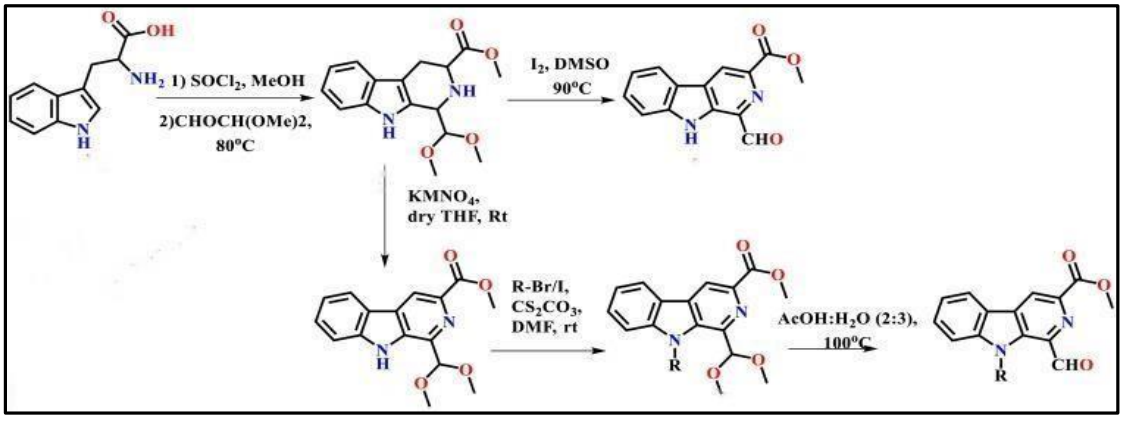
Scheme 7: Synthesis of THBC esters by R. Singh and co-workers.

Sharma et al. reported the anti-plasmodial activity of N-substituted THBC derivatives using a distinct synthetic strategy from Singh et al. Initially, THBC carboxylic acid was prepared by refluxing L – tryptophan, formaldehyde, and sodium hydroxide for 8 hours. The carboxylic acid was then esterified with thionyl chloride for 6 hours, followed by conjugation with alkynyl bromide to yield the final N- substituted THBC analogs (Scheme 8).[6]



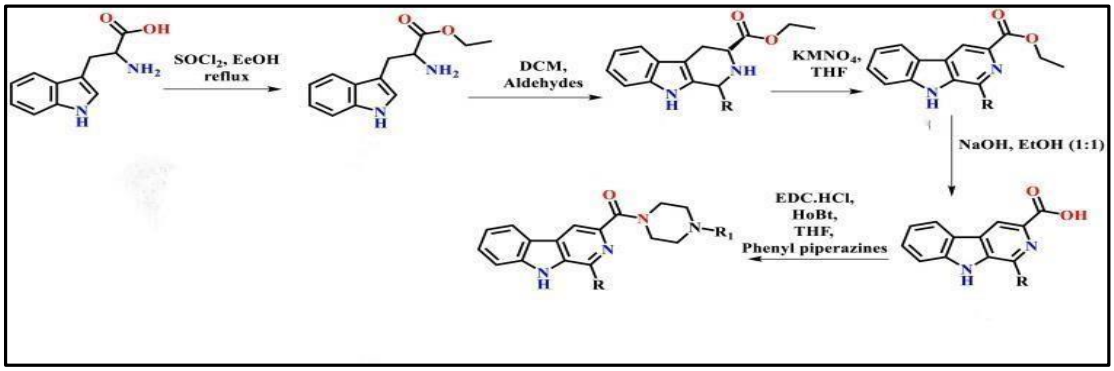
Scheme 8: Synthesis of THBC derivatives by Sharma and co-workers.

A convenient and highly efficient iodine-catalyzed method has been applied to synthesize fluorescent β- carboline derivatives, including C-1(3)-tethered thiazolo[4,5-c]carbazoles, naphtho[2,1-d]thiazoles, and benzothiazoles.[16] Virender Singh's group studied their photophysical and fluorescent properties. Oxidation of THBC esters using iodine or potassium permanganate yielded 1-substituted β-carboline esters up to 98% starting from L-tryptophan.[16] Various solvents were tested, including DMF, THF, and DMSO, with DMSO in the presence of catalytic iodine giving the highest yield. (Scheme 9).[10]

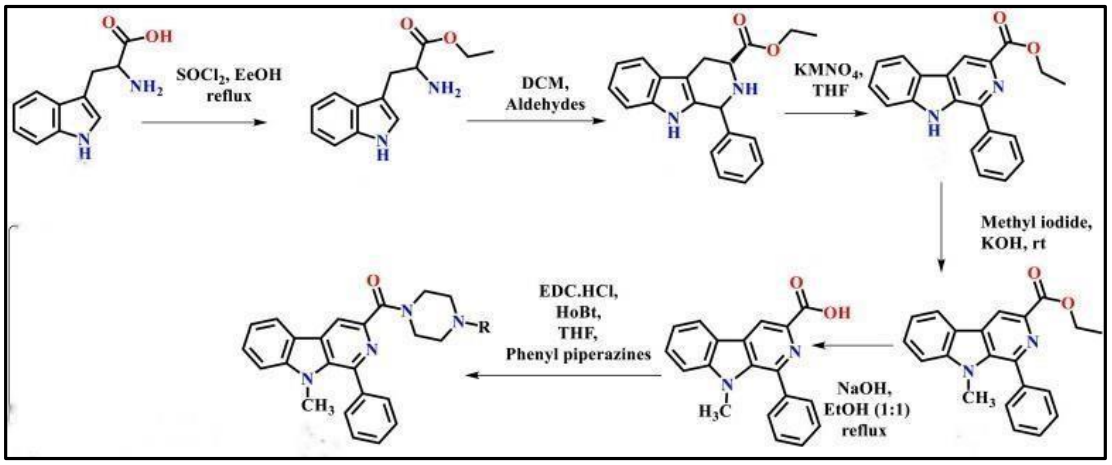


Scheme 9: Synthesis of 1-formayl β-carboline by Virender Singh and co-workers.

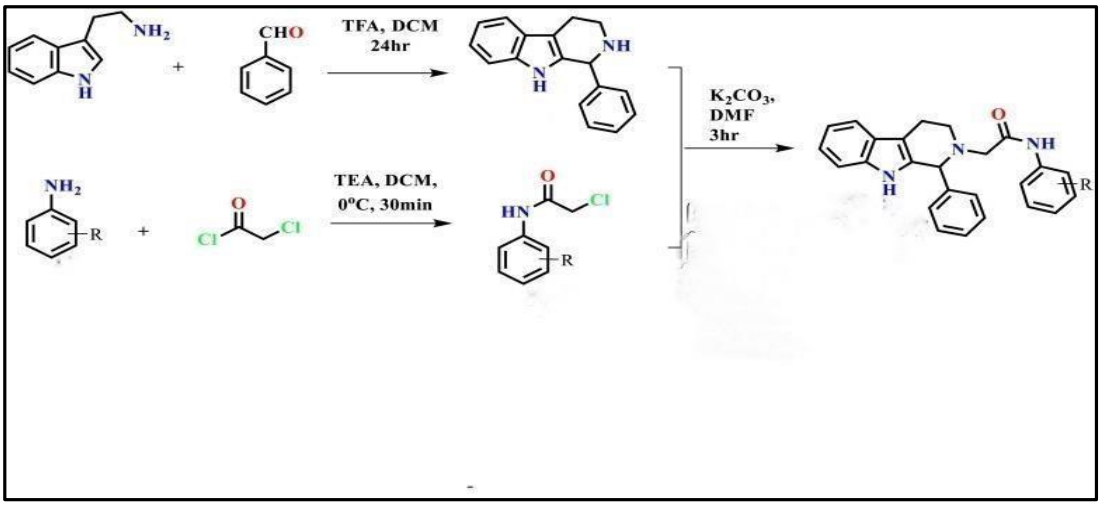
Murugesan et al. synthesized β-carboline phenyl piperazine derivatives from DL-tryptophan. THBC esters were prepared via esterification and aldehyde conjugation, then oxidized to βcarboline esters. Hydrolysis yielded β-carboline carboxylic acids, which were coupled with substituted phenyl piperazines using EDC·HCl/HOBt (Scheme 10), and NH methylation at the 9-position was achieved with methyl iodide (Scheme 11).[10] Additionally, 1-phenyl THBC derivatives from tryptamine were coupled with acetamides using K_2CO_3/DMF giving up to 80% yields (Scheme 12).[19]



Scheme 10: Synthesis of β – Carboline phenyl piperazines.



Scheme 11: Synthesis of 9-methyl β-carboline phenyl piperazines.



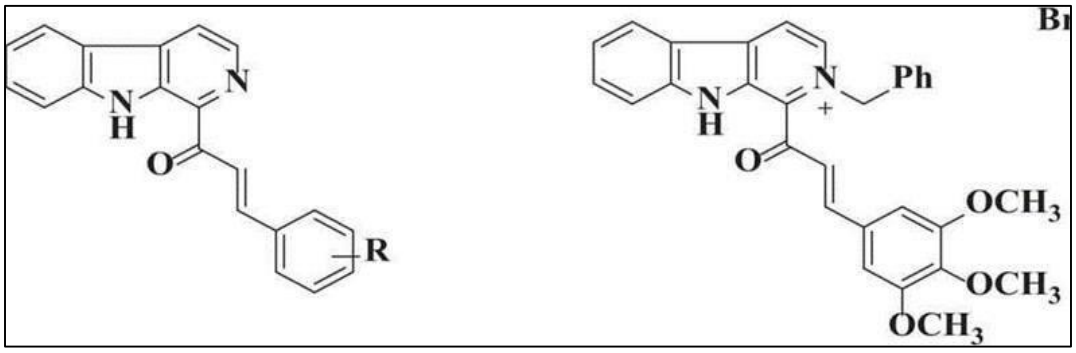
Scheme 12: Synthesis of 1,2,3,4-tetrahydro-β-carboline acetamide derivatives.

REVIEW OF LITERATURE

1. ANTI-CANCER ACTIVITY

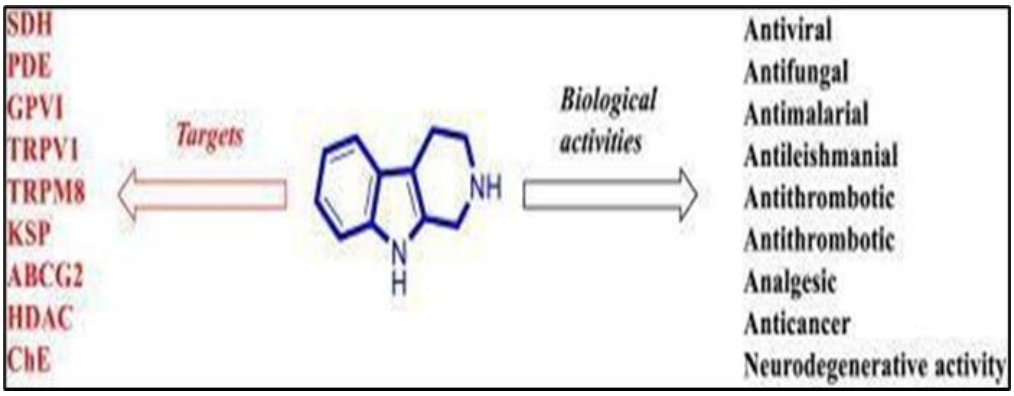
Tetrahydro-β-carboline (THβC) derivatives have shown notable anti-cancer activity. Anna Jaromin et al., reported that certain THβC compounds inhibit the kinesin spindle protein (Eg5), which plays a crucial role in mitosis, thereby suppressing cancer cell migration and reducing colony formation. These derivatives further induce apoptosis through the Bax/Bcl-2/caspase pathway and may intercalate with DNA to inhibit topoisomerases I and II, affecting cancer cell proliferation. Additionally, THβCs can inhibit aminopeptidase N(APN), target cancer stem cells and improving chemotherapy sensitivity by reducing tumor growth.[1]

Tetrahydro-β-carboline (THβC) derivatives exhibit strong anticancer activity against several human cancer cell lines, including MCF-7, A549, HT-29 and K562. They exert their effects mainly through DNA intercalation and inhibition of topoisomerase I/II, which disrupts DNA replication and cell division. Many derivatives also induce mitochondrial-mediated apoptosis by promoting cytochrome-c release and activating caspase pathways. In addition, THβCs are known to cause cell-cycle arrest at either the G1/S or G2/M checkpoint depending on the substitution pattern.



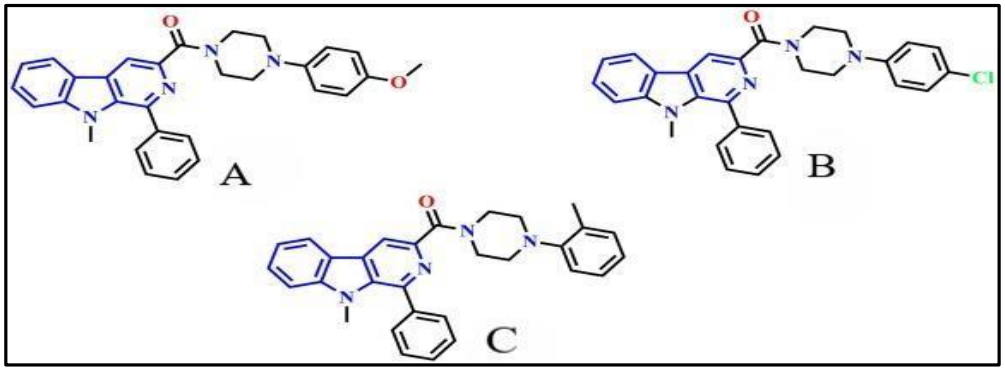
2. ANTIMICROBIAL ACTIVITY

Devi Nidana S.S[1], Hima C.S[2], and Dr. Shaiju S Dharan[3] report that tetrahydro-β-carbolines (THβCs) are naturally occurring alkaloids with a tricyclic pyrido[3,4-b] indole structure, present in foods, plants (Peganum harmala, Pausinystalia yohimbe), and cigarette smoke. They possess pharmacological properties including monoamine oxidase inhibition, antioxidant action, and antimicrobial activity. Dietary THβCs such as MTCA and THCA form during food processing, acting as free-radical scavengers but sometimes showing neurotoxic or genotoxic effects. Owing to their low concentrations, high- performance chromato- graphic methods with fluorescence or MS detection are preferred for accurate identification.[2]

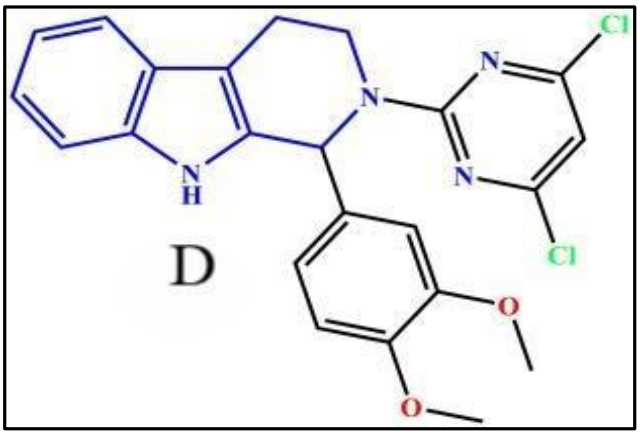


3. ANTI-LEISHMANIAL ACTIVITY

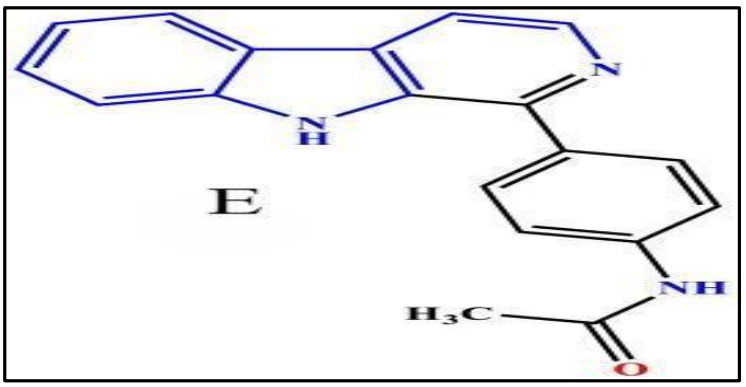
Penta Ashok et al. reported the synthesis of piperazinyl-β-carboline-3-carboxamide derivatives and evaluated their anti-leishmanial activity against Leishmania infantum and Leishmania donovani. Among the reported derivatives, compounds A ,B and C exhibited potent inhibition of promastigotes (EC50 1.59, 1.47, and 3.73 μM, respectively) and amastigotes (EC50 1.4, 1.9 and 2.6 μM respectively) of L. infantum (Ashok et al., 2019).[3]



Ravi Kumar et al. reported the synthesis of 2-(pyrimidine-2-yl)-1-phenyl-2,3,4,9- tetrahydro1H-β-carbo- line derivatives and evaluated for anti-leishmanial activity against L. donovani. Compound D. exhibited significant anti-leishmanial activity with an IC50 value of 1.93 mg/ml against amastigotes (Kumar et al., 2010).[4]

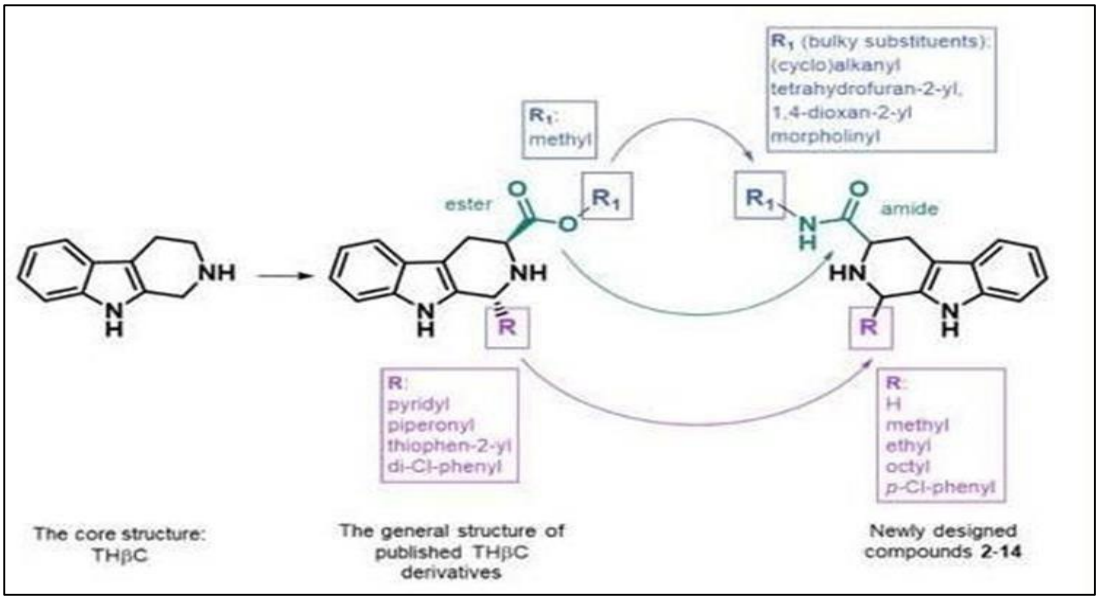


Vikrant Singh M. Gohil et al. reported the anti-leishmanial activity of 1-aryl-β-carboline derivatives against L. donovani. Compound E. (IC50 2.16 ± 0.26 μM) showed notable activity than the standard drug miltefosine (IC50 12.07 ± 0.82 μM) (Gohil et al., 2012).[5]



4. ANTIPLASMODIAL ACTIVITY

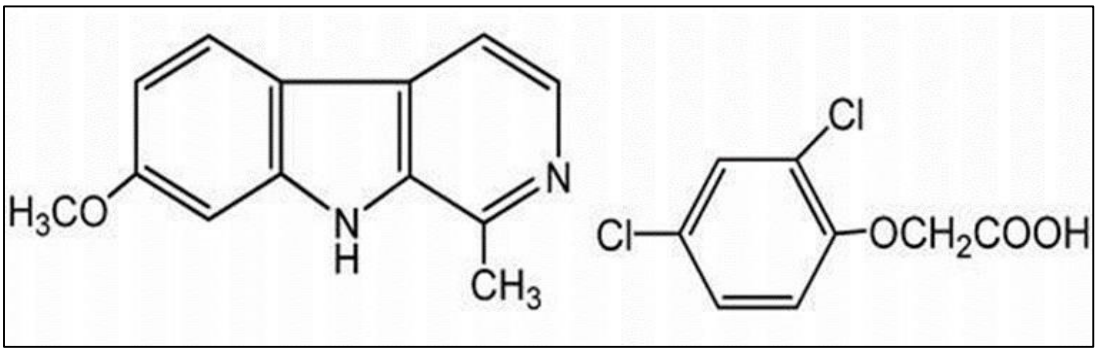
Anna Jaromin[1], Beata Gryzło[2], Marek Jamrozik[2], Silvia Parapini[3], Nicoletta Basilico[4], Marek Cegła[2], Donatella Taramelli[5], and Agnieszka Zagórska[2]* reported that synthesized tetrahydroβ- carboline derivatives were tested for anti – plasmodial activity against two P. falciparum strains: D10 (chloroquine- sensitive) and W2 (chloroquine-resistant).[6] IC_{50} values ranged from 4.00 ± 0.53 to 35.36 ± 4.86 µM, with compound 7 showing the highest potency and a high Log D value. Most compounds had similar inhibitory effects on both strains, and except for compound 6 were more effective against the CQ- resistant strain, suggesting superior sensitivity toward resistant parasites. These results are promising in the context of increasing resistance to artemisinin derivatives, although the structure–activity relationship appears not to be solely dependent on Log D or substituent type +



5. HERBICIDAL ACTIVITY

Qunfang Weng, Jingfei Huang, Yong Zeng, Yueye Deng, and Meiying Hu evaluated βcarboline derivatives for herbicidal activity against rape and barnyard grass. Fully aromatic βcarbolines showed stronger activity than tetrahydro-β-carbolines, with electron-withdrawing substituents at positions 1 and 3enhancing efficacy.[7]

Some seeds failed to germinate at 100 µg/mL, and roots treated with 2,4-D were inhibited. Compounds c2 and d2 exhibited the highest activity and were selected for further EC50 analysis.[18]



MATERIALS AND METHODS

Table 1: Materials Used for Microwave-Assisted Synthesis and Anticancer Evaluation.

MATERIAL	PURPOSE
Substituted Tryptamine	Key starting amine for THβC core
Aromatic/heteroaromatic aldehyde	Condensation component
Glacial acetic acid	Catalyst & reaction medium
Ethanol / Methanol	Solvent
Microwave reactor (controlled)	Accelerated synthesis
Silica gel	Product purification
Cancer cell lines (e.g., MCF-7, A549)	Cytotoxic assay
MTT reagent	Cell viability testing
DMSO	Sample preparation

METHOD

Tryptamine + Aromatic aldehyde mixing → Addition of acetic acid catalyst → Transfer to microwave tube → Microwave irradiation at controlled temperature (100–140°C) for 5–15 min → Cooling & pouring over crushed ice → Filtration & purification through silica column → Structural confirmation by FT-IR, NMR → Preparation of sample in DMSO → Treatment of cancer cells → Incubation & MTT addition → Absorbance reading for cytotoxicity.[21,22,23]

Table 2: **Materials Used for Microwave-Assisted Synthesis and Antileishmanial Evaluation.**

MATERIAL	PURPOSE
Tryptamine derivative	Starting material
Aldehyde substitute	For THβC formation
Ethanol	Reaction solvent
Acetic acid	Catalyst
Microwave reactor	Synthesis acceleration
Mueller-Hinton agar	Antibacterial assay medium
Potato dextrose agar	Antifungal assay medium
Bacterial strains (*E. coli, S. aureus*)	Test organisms
Fungal strains (*Candida spp.*)	Test organisms
Standard drug (Ciprofloxacin/Fluconazole)	Positive control

METHOD

Tryptamine + Aldehyde mixing → Addition of solvent & acid → Sealing in microwave vessel → Microwave heating at optimized settings → Cooling & crystallization → Column purification → Preparation of dilutions → Inoculation of agar plates → Well diffusion method → Incubation → Measurement of inhibition zones.[24,25,26]

Table 3: Materials Used for Microwave-Assisted Synthesis and Antiplasmodial Evaluation.

MATERIAL	PURPOSE
Tryptamine Starting amine	Starting amine
Aromatic aldehyde	Condensation partner
Acetic acid	Catalyst
Microwave synthesis vessel	Reaction container
Ethanol	Solvent
Weed seeds (e.g., Echinochloa crus-galli)	Bioassay plant
Soil trays	Growth study
Distilled water	Control
Standard herbicide (atrazine)	Reference comparison

METHOD

Tryptamine + Aldehyde → Addition of ethanol & acetic acid → Microwave heating for 5–10 min → Cooling & purification → Dissolution to prepare test concentrations → Soil tray preparation → Seed sowing → Application of synthesized compound solution → Observation of germination, shoot & root inhibition → Comparison with standard herbicide.[27,28,29]

Table 4: Materials Used for Microwave-Assisted Synthesis and Antimicrobial Evaluation.

MATERIAL	PURPOSE
Tryptamine derivative	Starting material
Aldehyde component	Manniche-type reaction
Acetic acid	Catalyst
Microwave reactor	Rapid synthesis
RPMI-1640 medium	Parasite culture
Plasmodium falciparum strain	Test organism
SYBR Green I	Fluorescence assay
Haematocrit blood	Parasite maintenance
Standard drug (Chloroquine)	Positive control

METHOD

Tryptamine + Aldehyde → Microwave irradiation with catalyst → Rapid formation of THβC derivative → Cooling & purification → Preparation of compound dilutions → Parasite culture maintenance → Compound treatment in 96-well plates → Incubation period (48 h) → SYBR Green addition → Fluorescence measurement for parasite inhibition.[30,31,32]

Table 5: Materials Used for Microwave-Assisted Synthesis and Herbicidal Evaluation.

MATERIAL	PURPOSE
Tryptamine	Base compound
Aromatic aldehyde	Condensation reagent
Glacial acetic acid	Catalyst
Microwave reactor	Reaction acceleration
RPMI-1640 medium + FBS	Culture medium
Leishmania donovani promastigotes	Test parasite
MTT / Alamar Blue dye	Viability assay
Standard drug (Amphotericin B)	Positive control

METHOD

Tryptamine + Aldehyde combination → Microwave-assisted condensation in acidic medium → Rapid cyclization to THβC → Cooling & extraction → Column purification → Preparation of test concentrations → Parasite culture inoculation → Addition of compound solutions → Incubation for 48–72 h → Dye addition (MTT/Alamar Blue) → Absorbance/fluorescence measurement for viability reduction.[33,34,35]

CONCLUSION AND OUTCOMES

The foregoing literature survey clearly indicates that tetrahydro-β-carbolines (THβCs) can be efficiently synthesized through a variety of synthetic strategies, with microwave-assisted methods offering significant advantages in terms of reaction rate and yield. Owing to their diverse biological activities and pharmacological relevance, THβCs represent highly valuable molecular scaffolds.

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