International Journal of Research and Review
Vol. 9; Issue: 12; December 2022
Website: www.ijrrjournal.com
Review Paper *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Characterization, Chemistry, Structural Activity Relationship and Antimicrobial Activities of Tetrahydro-β-carboline

Devi Nidana S.S[1], Hima C.S[2], Dr. Shaiju S Dharan[3]

[1,2,3]Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Neyyattinkara, Kerala 695124, India

Corresponding Author: Devi Nidana S.S

DOI: https://doi.org/10.52403/ijrr.20221201

ABSTRACT

Tetrahydro-β-carboline, a derivative of β-carboline alkaloid, is found in a variety of plants, animals, insects, mammals, and human tissues and body fluids. It is found abundantly in nature and includes both natural and synthetic forms. Tetrahydro-β-carboline and their derivatives have been proven to exhibit important biological features, which makes it easier to build novel synthetic techniques for the alteration of Tetrahydro-β-carboline core to create high potential medications.
Tetrahydro-β-carboline was proven to exhibit various pharmacological activities such as antiviral, antileishmanial, anticancer, antifungal, HDAC inhibitor, antithrombotic, antimalarial, analgesic, and anti-AD inhibitor action. The characterization, chemistry, structure activity relationship, and antimicrobial activities of tetrahydro-β-carboline derivatives are highlighted in this review along with recent research and developments in these areas.

KEYWORDS: Tetrahydro-β-carboline, Tetrahydro-pyrido[3,4-b]-indole, Heterocycle, Alkaloid, Structure, Activity, Derivative, Antimicrobial activity, Occurrence.

INTRODUCTION

Tetrahydro-β-carbolines are a class of organic and synthetic alkaloids with a Tricyclic pyrido[3,4-b]-indole ring structure. They are a member of β-carboline family with a partially saturated ring exhibits broad range of pharmacological and biological activities[1].

Tetrahydro-β-carboline also known as Tryptoline, Tetrahydronorharmane or Tetrahydro-pyrido[3,4-b]-indole.
Tetrahydro-β-carbolines are found in plants (Peganum harmala and Pausinystalia yohimbe), fruits, and vegetables such as Tomato, Kiwi, Banana, Pineapple and foods such as wine, vinegar, soy souce, chocolate etc. Consumption of foods containing THβCs cause it to accumulate in human biological tissue, fluids and brain and produce Antioxidant and free radical scavenging activities. THβC which is produced in the human body is pinoline (5-methoxy tryptoline) a metabolite of melatonin in the pineal gland. Tadalafil is an example of a drug that is commercially available and contains the THβC structure that is used to treat male erectile dysfunction and pulmonary arterial hypertension [1-4]. In this overview, the occurrence, structural modifications, antimicrobial activities of the synthetic THβC derivatives are briefly discussed.

1.PHYSICO-CHEMICAL PROPERTIES

1.1. EXPERIMENTAL PHYSICO-CHEMICAL PROPERTIES

Molecular weight	172.226
Melting point	206-208 °C
Boiling point	351.6 °C
Appearance	Solid
Solubility	>25.8 [ug/mL]
LogP	0.746
Safety	Irritant

Fig 1. Experimental physico-chemical properties of Tetrahydro-β-carboline [5,6].

1.2. COMPUTED PHYSICO-CHEMICAL PROPERTIES

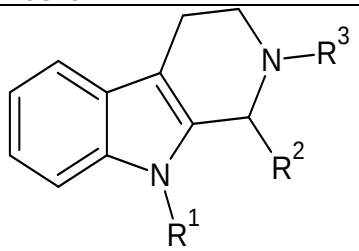
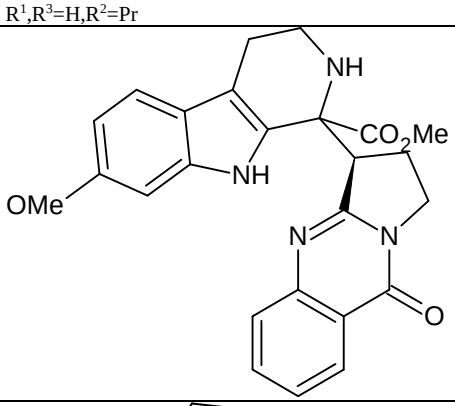
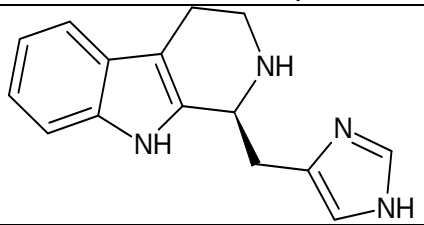
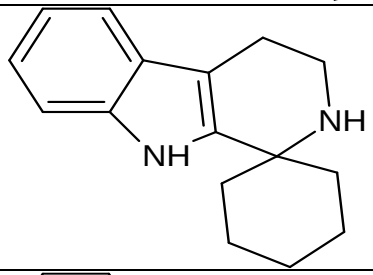
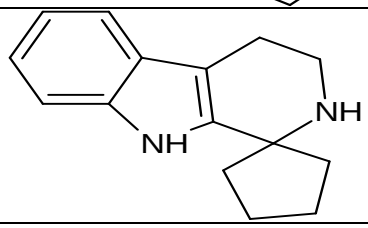
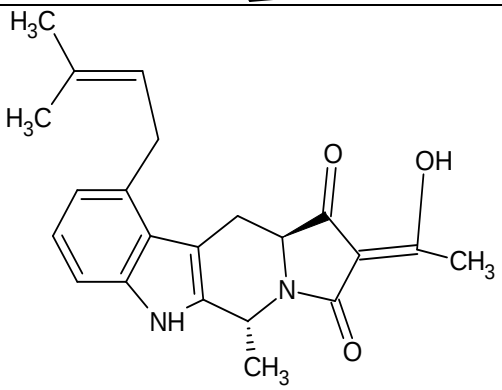
Molecular Weight	172.23
Monoisotopic Mass	172.1000484
XLogP3-AA	1.5
Hydrogen Bond Donor Count	2
Hydrogen Bond Acceptor Count	1
Rotatable Bond Count	0
Heavy Atom Count	13
Topological Polar Surface Area	27.8 Å²
Heavy Atom Count	13
Isotope Atom Count	0
Formal Charge	0
Complexity	193
Isotope Atom Count	0
Defined Atom Stereocenter Count	0
Undefined Atom Stereocenter Count	0
Defined Bond Stereocenter Count	0
Undefined Bond Stereocenter Count	0
Covalently-Bonded Unit Count	1

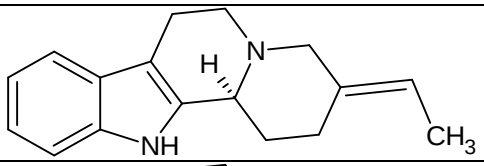
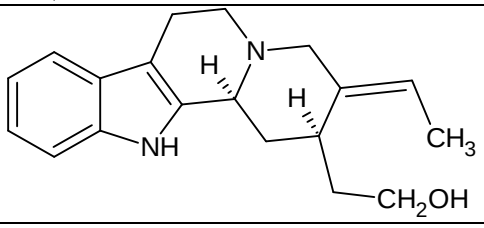
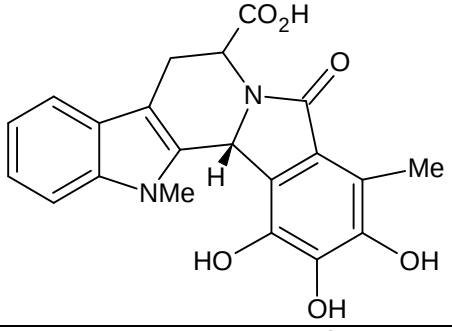
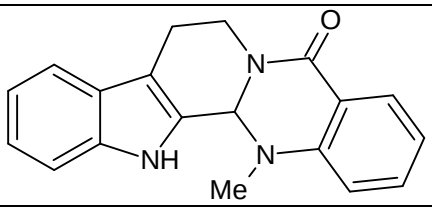
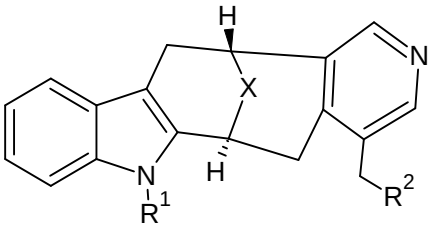
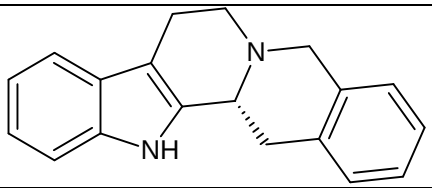
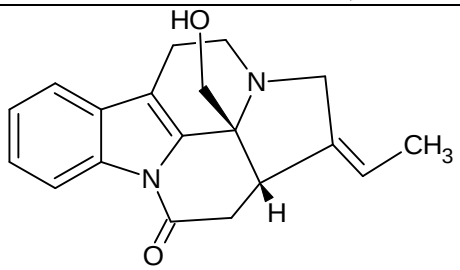
Fig 2. Computed physico-chemical properties of Tetrahydro-β-carboline [5,6].

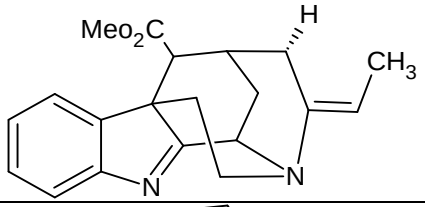
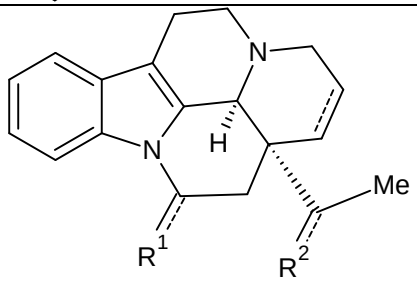
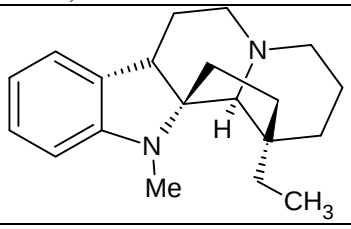
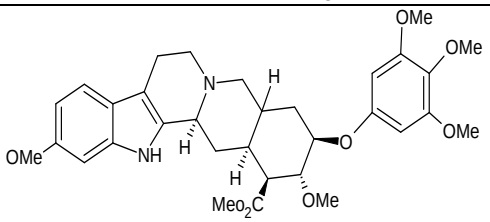
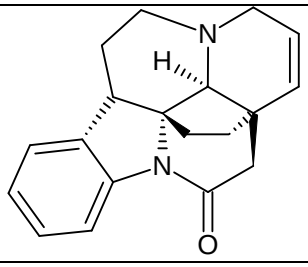
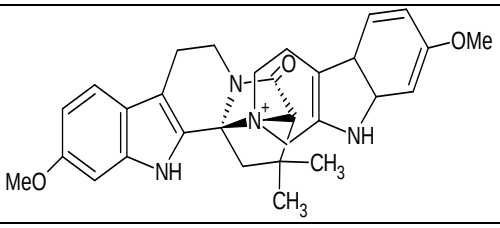
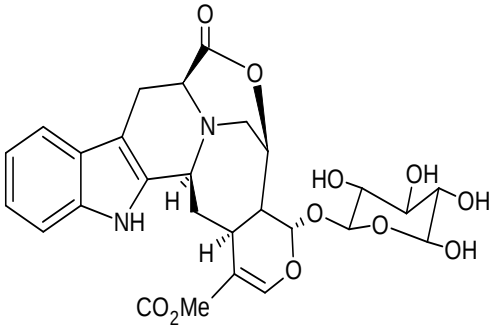
2. OCCURRENCE AND BIOLOGICAL ACTIVITIES

THβCs are group of naturally occurring alkaloids that possess a tricyclic pyrido[3,4-b]indole ring structure. THβCs are often referred to as 'mammalian alkaloids'. They are found in common staple foods such as grains and nuts, coffee, processed foods like roasted sugar beets, roasted chokeberries, alcoholic beverages, natural products like banana, tomato juice, fish, meat, and even in cigarette smoke. THβCs have been also found in plant systems. The best-known natural THβCs have been identified from Peganum harmala and Pausinystalia yohimbe (formerly Corynathe yohimbe). Yohimbe alkaloids include pharmacologically intriguing natural compounds contain yohimbine and its isomers, reserpine, and ajmalicine the latter two are being used as antihypertensive medications at the moment. Ayahuasca, also known as yaje, is a hallucinogenic beverage made from the Amazonian plant Banisteriopsis caapi. Harmala alkaloids contain a variety of β-carbolines, such as tetrahydroharmine, Tryptoline, Harmicine, and Pinoline (a melatonin metabolite produced in the pineal gland). They bind to benzodiazepine receptor and produce their pharmacological activity and act as inhibitor of monoamine oxidase (MAO). Tryptophan derived THβCs appear in many commercial foods for example 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (MTCA) and 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (THCA). They occur naturally during food production, processing and storing of food. Therefore the consumption of these dietary sources cause accumulation of THβC in the biological tissue and fluids and act as free radical scavenger and produce antioxidant activity. Food smoking is a traditional preservation technique used to improve the organoleptic qualities of food. It offers a range of volatile chemicals, including carbonyls that can produce THβCs. According to Collins and his Co-workers N-methylated THβC are endogenous neurotoxins. 1-Methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (MTCA), a tryptophan-acetaldehyde condensation THβC, exhibits cytogenetic effects and may result in the death of neuronal cells in vitro. Additionally, βCs created during food preparation may exhibit genotoxic and comutagenic potential[7-9].

The analysis of THβCs is a complex process involving their isolation and identification prior to quantitative analysis due to its low concentration in the foods and biological samples it is necessary to clean up before purification and trace enrichment. High performance analytical techniques with increased selectivity are used such as Capillary gas chromatography (GC) and high performance liquid chromatography (HPLC). These are necessary to prevent coeluting and interfering peaks. Although electrochemical and UV absorption detection technologies are both useful, fluorescence and mass spectrometry are chosen because to their selective and sensitive detection. Due to its great selectivity and specificity, mass spectrometry (MS) in combination with high-performance chromatographic method is one of the best on-line systems for the identification of THβCs[10].

ID	NAME	STRUCTURE	OCCURENCE	BIOACTIVITY
1	(+)-1-ethyl-9-methyl-tetrahydro-β-carboline (−)-tetrahydroharman/ (S)-eleagnine +)-N-acetyl-komarodine (−)-komaroidine N-(+)-methyltetrahydro-harman	 R^1=Me,R^2=Et,R^3=H R^1,R^3=H R^2=Me R^1=H, R^2=Pr,R^3=Ac R^1,R^3=H,R^2=Pr	1.Analogues of natural products 2.Albizia polyphylla 3,4. N. komarovii and N.schoberi 5.Petalostyles labicheoides	Not reported
2	(±)-peharmaline A		Peganum harmala	Cytotoxic activity (HL-60, PC-3, SGC-7901)
3	Haploscleridamine		Sponge of the order Haplosclerida	Inhibitor of cathepsin K
4	komavine		Nitraria komarorii, Nitraria schoberi	Not reported
5	Harmicine		Kopsia griffithii	Not reported
6	Griseofamine A		Penicillium griseofulvum	Antibacterial activity

7	(+)-deplancheine		Alstonia deplanchei	Not reported
8	(−)-geissoschizol		Tabernaemontana bufalina, Hunteria zeylanica	Not reported
9	Chaetogline E		Modified Epinephelus drummondhayi with a silent fungal gene from Chaetomium globosum	Not reported
10	Evodiamine		Evodia rutaecarpa	Anticancer anti-inflammatory antimicrobial and many others
11	Marcophylline Norsuaveoline Suaveoline	 R^1=H, R^2=CH^2OH, X=NMe R^1=H, R^2=CH^2, X=NH R^1=Me, R^2=CH^2, X=NH	Rauwolfia macrophylla Rauvolfia caffra Rauwolfia suaveolens S. Moore (apocynaceae)	Not reported Not reported Acetylcholinesterase inhibitor
12	(S)-(−)-decarbo-methoxy-dihydrogambirtannine		Enantiomer of 12 was isolated from Hunteria zeylanica	Not reported
13	(±)-arbornamine		Kopsia arborea	Not reported

14	(+)-strictamine		Alstonis scholaris Rhazya strictu	Antitumor, antiviral anti-inflammatory antibiosis activities
15	19-(S)-hydroxy-Δ^{14}-vincamone (−)-19-hydroxy-Δ^{14}-eburnamonine (+)-19-oxoeburnamine (+)-19-OH-eburnamine	 R^1=O,R^2=OH,Δ^{14} R^1=O, R^2=OH R^1=OH,R^2=O R^1=OH,R^2=OH	Kopsia jasminiflora, Kopsia pauciflora	Not reported closely related analogues show antitumor activity.
16	(+)-vallesamidine		Vallesia dichotoma	Not reported
17	reserpine		Rauwolfia serpentina	Commercially available drug for the treatment of high blood pressure
18	(+)-14,15-dehydro-strempeliopine		Schizozygia caffaeoides	Not reported
19	+)-peganumine A		Peganum harmala L	Cytotoxic activity (MCF-70, PC-3, HepG2, HL-60)
20	(−)-rubenine		Adina rubescens	Not reported

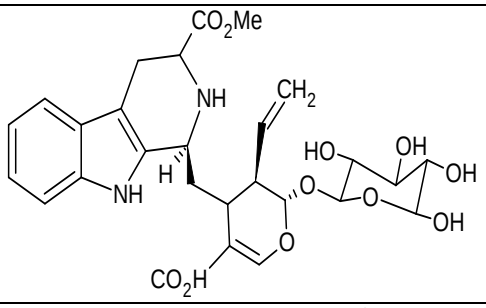
21	(−)-5-carboxystrictosidine		Rhazya orientalis, Guenttarda platypoda, Uncaria tomentosa, Ophiorrhiza nutans,	Not reported

FIGURE 3. Natural occurrence and bioactivity of synthesized Tetrahydro-β-carbolines [11].

3.CHEMISTRY

THβC (Tetrahydro-9H-pyrido-[3,4-b]indole) is a tricyclic heteroaromatic compound composed of an indole fused to pyrimidine ring. This indole ring system is ortho - fused to C-3 and C-4 of a pyrimidine ring. Two nitrogen atoms are present in C-2 and C-9. THβC have a pyrido nitrogen in the 2nd position compared to α, γ or δ-carbolines which have nitrogen in the position C-1, C-3 and C-4 respectively [10].

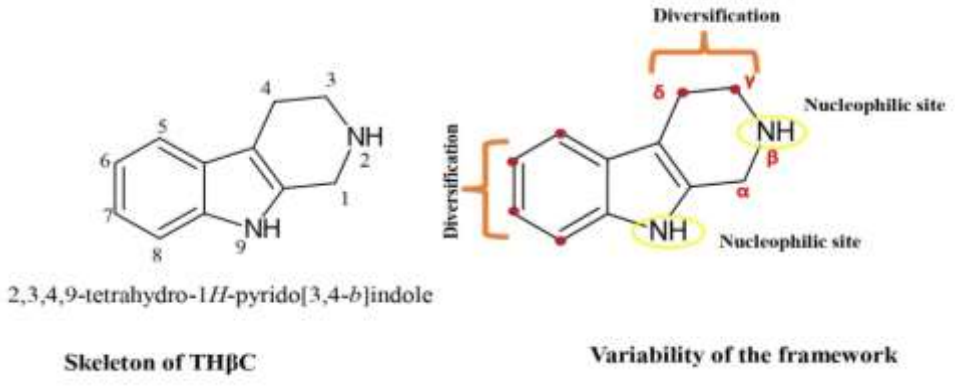
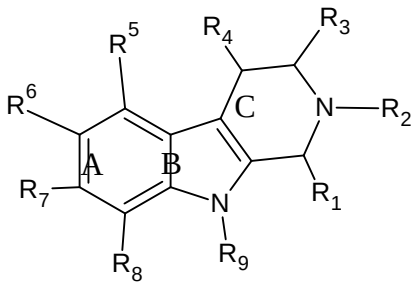


Fig 4. Structure of Tetrahydro β-carboline [11].

Since it has a semi-rigid form, i.e., rigid indole ring and flexible pyrimidine structural motif, it shows preferrable affinity for various receptors and act as both H-bond donor and H-bond acceptor in drug design. The Pictet-Spengler reaction between indoleethylamines and aldehydes or ketoacids is one of the most effective and well-established methods for the production of THβCs. An iminium cation intermediate is formed during this reaction eventually undergo cyclisation in presence of an acid gives rise to THβC. This reaction occurs naturally in a food environment and is dependent on temperature and pH. When THβCs are synthesised using an aldehyde other than formaldehyde, they have a chiral carbon C-1 and two enantiomers. The oxidation of the pyrido ring produces the fully aromatic β-carbolines. Another option is the Bischeler-Napieralski process, a tryptamide cyclized usually to replace the lost carbonyl oxygen, dehydrating reagents like PCl_5, $POCl_3$, $SOCl_2$, or $ZnCl_2$ are used. The result of the Bischeler-Napieralski reaction is DHβC, which, when further reduced, becomes THβC. Because of the extremely sterioselective character of the reaction, chirality can be imparted using asymmetric transfer hydrogenation (ATH), which uses Noyori-type catalysts. The traditional Nyori reaction reduces a chemical to the corresponding chiral THβC using an azeotropic combination of Et3N and HCOOH as the hydrogen supply. While the selectivity is flipped to the cis-product under kinetic control, the trans-product is mostly created under thermodynamic control. The overall management of the cis/trans selectivity is highly challenging,

though; in addition to the reaction temperature, the selectivity is significantly impacted by the pattern of substitution as well as the size and electrical properties of the substituents [2,3,10,12,13].



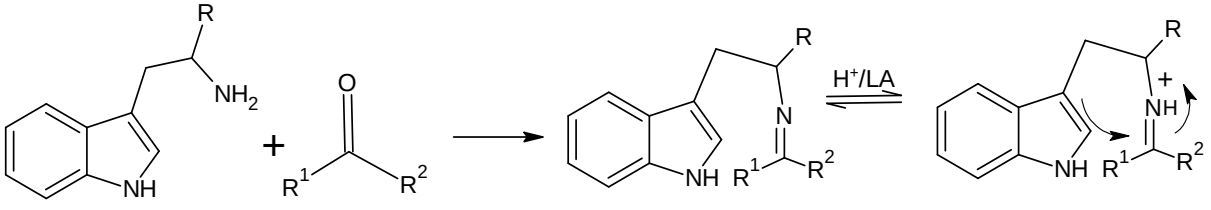
4.STRUCTURAL ACTIVITY RELATIONSHIP

POSITIONS	SAR
R_1	• Fully saturated C-ring analogues appear to lack selectivity for I_2 versus I_1 sites. • Substitution with methyl group is not tolerated. • Ring extension to an azepinonindole lowers affinity.
R_2	• Replacing 'H' with methyl lower I_2 affinity with no change in I_1. • A cationic center is preferred. • Substitution of N^+ Br^- salts, Aromatic and aliphatic N substitution, Quinazoline moiety will increases Anti-TB potency. • Insertion of an electron rich groups like Benzyl, Pentafluorobenzyl increase cytotoxic activity. • N-oxides, amides and small carbon chains may increase anti-leishmanial activity • Alkyl substitution enhances antitumor activity.
R_3	• A key site for binding to the Bz site of the $GABA_{A1}$ receptor. • Substitution of ester group increases affinity. While amino, alkoxy, were detrimental. • The introduction of a carboxylic acid group (COOH) abolishes the affinity of the tetrahydroβcarboline system.
R_4	• Planarity of the molecule is favourable to the cytotoxic activity.
R_5	• Strong affinity is usually expected from the unsubstituted ring. -OH, -OCH_3 groups increases Anti-TB potency
R_6	• Substitution at this position, antileishmanial activity may be detrimental. • Introduction of hydroxy group at position-6 is tolerated for affinity to BzR. • 6-bromo substitution increases cytotoxic activity. • -OH, OCH_3 groups increases Anti-TB potency
R_7	• Substitution with methoxy group favours affinity to imidazoline site. • Introducing alkoxy substituent led to increased cytotoxic activity. • -OH, OCH_3 groups increases Anti-TB potency. • Insertion of polar groups like • Alkoxy,Phenyl alkoxy increase cytotoxic activity
R_8	• Strong affinity is usually expected from the unsubstituted ring. • Substitution with bromo group favours affinity to imidazoline site. • -OH, OCH_3 groups increases Anti-TB potency
R_9	• Substitution of N- methyl group is tolerated with imidazoline site. • Good for binding to BzR. • Simple methyl group increases antileishmanial activity. • N9-alkyl substituted dramatically decreased BzR affinity. • Phenyl, alkyl substitution increases Anti-Tb potency. • Insertion of small apolar groups like Ethyl,propyl,isobutyl increase cytotoxic activity.

FIGURE 5. Structural activity relationship of Tetrahydro-β-carboline [8,14-17].

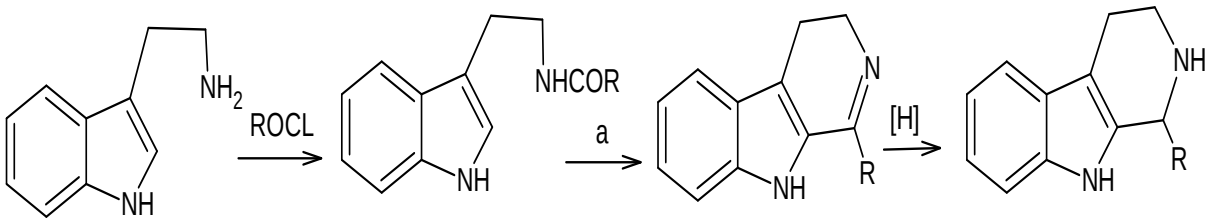
5. SYNTHESIS

One of the most popular processes for creating the tetrahydro-β-carboline ring system is the Pictet-Spengler (PS) reaction. Ame Pictet and Theodor Spengler, two chemists, made the initial discovery of this traditional reaction in 1911.The reaction takes place in two steps in the first step Tryptophan or Tryptamine and aldehyde or ketone undergo condensation reaction to form imine. In the second step the imine undergo cyclization in presence of bronsted acid or lewis acid to form tetrahydro-β-carboline[18].



Tryptamine (R= H)
Tryptophan (R= COOH)

Bischler-Napieralski cyclization is another mostly used facile method for the synthesis of THβC. It involve the acylation of exocyclic amine and dehydration of this amine to amide by use of various dehydrating agents such as PCl_5, $SOCl_2$, $ZnCl_2$, BF_3,OEt_2, P_2O_5 etc are used to promote loss of the carbonyl oxygen. The product formed is DHβC which is reduced to synthesize THβC [18].



a=PCl_5, $POCl_3$, $ZnCl_2$, BF_3, P_2O_5, OEt_2

6. PHARMACOLOGICAL ACTIVITIES

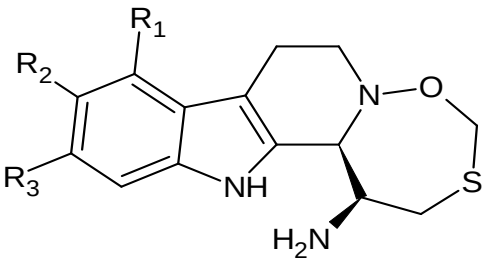
6.1. ANTIMICROBIAL ACTIVITIES

6.1.1 ANTI- HERPES SIMPLEX VIRUS-1

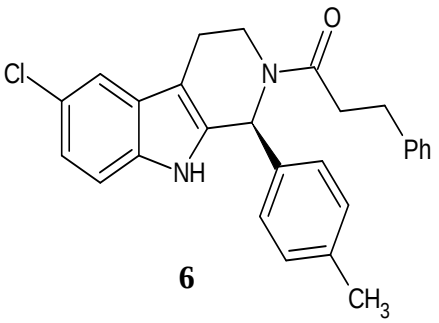
A member of the Alphaherpesvirinae subfamily, herpes simplex virus type 1 (HSV-1) is a linear dsDNA virus. HSV-1 causes primary and recurrent vesicular eruptions, particularly in the vaginal and orolabial mucosa.

It is known that THβCs are antiviral agents. Since Rinehart et al in 1984's investigation into the effectiveness of eudistomins against herpes simplex virus-1. Four Eudistomins carrying the scaffold for THβC (1-5, Figure 1). They were discovered in the colonial tunicate Eudistoma olivaceum and are marine alkaloids[19,20].

Eudistomins C, E, K, and L have a condensed oxathiazepine ring system in addition to the fundamental THβC structure, which has only been described in these particular compounds. According to reports, these four eudistomins have between 25 and 250 ng/12.5 mm disc of in vitro activity against Herpes simplex virus-1 (HSV-1)[20]. Later, it was asserted that eudistomin K had activity against the polio vaccine type-1 virus[21]. Eudistomins C and E have also been shown to have antiviral activity against RNA viruses, such as the Coxsachie A-21 virus and the equine rhinovirus[21]. When influenza A and B were tested in Madin-Darby canine kidney (MDCK) cells in 1992, (-)debromoeudistomin K (5) and its structural analogues demonstrated substantial antiviral efficacy. Additionally, activities have been discovered against the poliovirus type-1, vesicular stomatitis virus, respiratory cyncytial virus, and Coxsachie virus B4[22].



1 Eudistomin C R_1=H,R_2=OH,R_3=Br
2 Eudistomin E R_1=Br,R_2=OH,R_3=H
3 Eudistomin K R_1=H, R_2=H,R_3=Br
4 Eudistomin L R_1=H,R_2=Br, R_3=H
5 (-)-debromoeudistomin K R_1=H,R_2=H,R_3=H

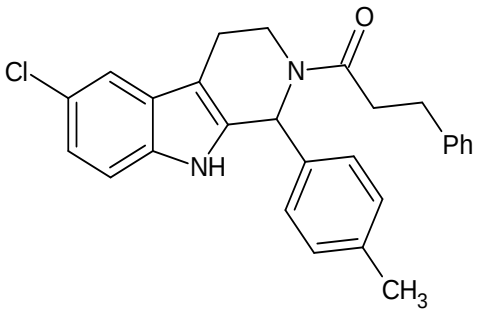


6

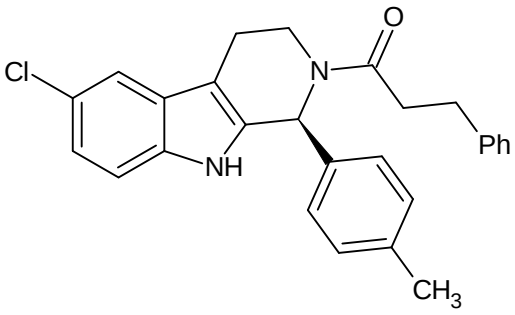
However, recent studies on a novel family of THβCs have focused on its ability to combat the human papilloma virus. There has never been any additional research or development on these eudistomin antiviral properties. Researchers at GlaxoSmithKline developed a compound (6) with nanomolar activity against HPV after optimising a series of 1-substituted THβC derivatives. The substance's activity was IC50 = 23 nm after optimization. GlaxoSmithKline has obtained a patent for employing this type of THβCs to treat HPV[23].

6.1.2. ANTI-HPV ACTIVITY

The human papillomaviruses (HPVs), which have double-stranded DNA, are the most common cause of cervical cancer. They are also thought to play a part in the development of head and neck cancer (HNC), non-melanoma skin cancers, and other anogenital malignancies, according to recent research. Currently, HPV infection is believed to be the most prevalent sexually transmitted disease in the world[24].



7

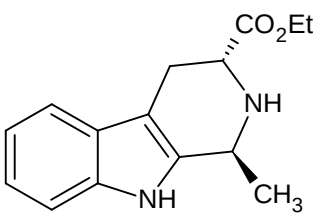


8

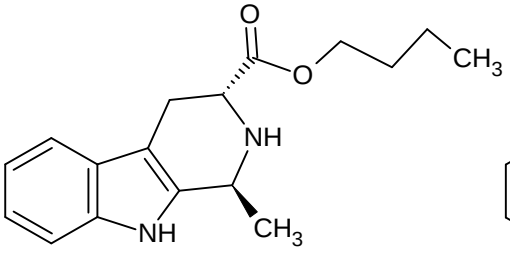
Miller and his coworkers have synthesised and developed a number of 1, 2-disubstituted THβCs. Racemic compound (**7**) among them demonstrated a 62 nM anti-HPV IC50 and has p-tolyl and phenylpropionyl groups at the C1 and N3 positions, respectively. When the two isomers were further separated enantiomerically, the S-isomer (**8**) showed strong anti-HPV action (IC50 = 23 nM), but the R-isomer is only 7.7 mM[23] . When administered intravenously to rats at a dose of 1 mg/kg, the pharmacokinetic experiment revealed that (**8**) had a 6.2-hour half-life and 3.6-mL/min/kg clearance value. Furthermore, (**8**) demonstrated a 5 mg/kg dose-related oral bioavailability of 73% in mice. In subsequent testing against a panel of enzymes and receptors, no undesirable off-target action was found. Additionally, (**8**) had no harmful cytochrome-P450 activity[3] .

6.1.3. ANTI-TMV ACTIVITY

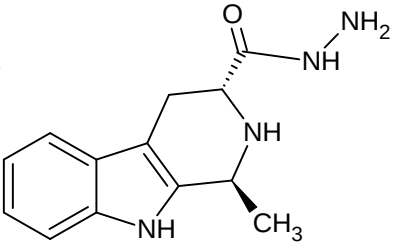
TMV(Tobacco Mosaic Virus) is a positive-sense single-stranded RNA virus that belongs to the Tobamovirus genus. It is primarily produced in plants, and because it is an RNA virus, it is quite vulnerable to natural mutations that could change its characteristics.



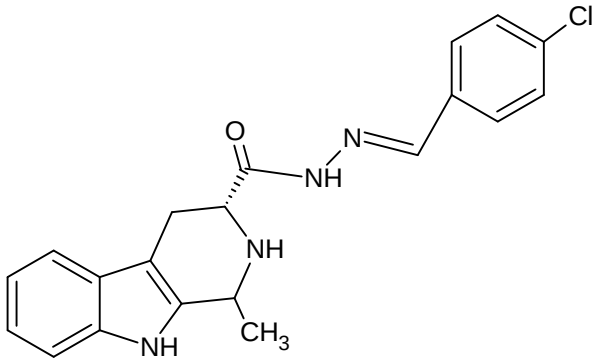
9



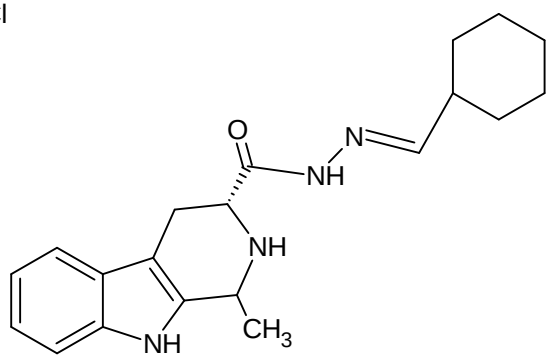
10



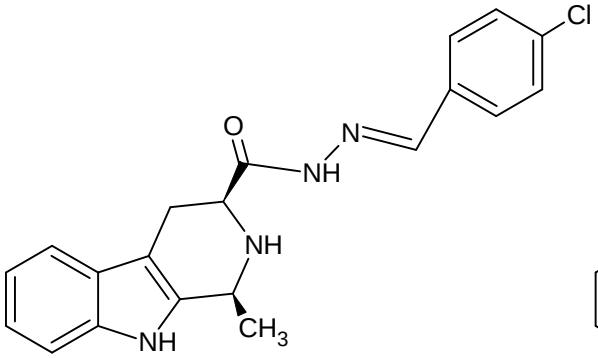
11



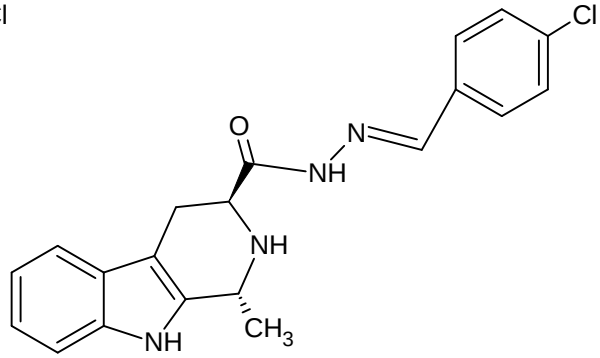
12



13



14



15

A number of THβCs compounds with anti-TMV and fungicidal properties were synthesised and produced by Wang et al. In preliminary testing, it was shown that compound (**9**) had greater anti-TMV action than the widely used antiviral drug ribavirin, both in vitro and in vivo. Compound 8 has an ethyl ester group on the C3 position of the THβC. At 500 mg/mL in vivo, the inactivation, curative, and protective activities of (**9**) were respectively 50.4, 43.9, and 47.3 percent[25]. On the ester group, structural optimization was carried out. Better antiviral activity was demonstrated by compound (**10**) and (**11**) with butyl ester and hydrazide in vitro than by compound (**9**). The activities of compounds (**10**) (51.3 percent, 42.2 percent, and 43.2 percent at 500 mg/mL) and (**11**) (64.2 percent, 57.2 percent, and 59.5 percent at 500 mg/mL) were significantly greater than those of ribavirin (37.3 percent, 36.2 percent, and 38.5 percent at 500 mg/mL). Additionally, (**19**) shown fungicidal effects against *Cercospora arachidicola Hori, Alternaria solani, Bipolaris maydis*, and *Rhizoctonia solani*[28] . On the basis of compound (**11**), further compounds (**12**) and (**13**) having an acylhydrazone moiety were developed. Compounds (**12**) (70.4 percent, 71.5 percent, and 64.2 percent at 500 mg/mL) and (**13**) (75.8 percent, 62.8 percent, and 69.2 percent at 500 mg/mL) showed better in vivo inactivation, curative, and protective actions. When TMV was tested in the field for antiviral efficacy, compound (**13**) outperformed the control plant virus inhibitors in terms of activity. Wang et al. described NK0209 in 2020 as a highly effective drug for the prevention and management of plant virus-related illnesses. Naturally, NK0209 was derived from compound (**12**), but it was a mixture of the isomers (**14**) (1S, 3S) and (**15**) (1R, 3S) at a ratio of 10:1. The in vivo inactivation, cure, and protection activities of NK0209 were greater than those of the reference drug ningnanmycin at a concentration of 500

mg/mL (66.7, 63.2, and 68.1 percent vs. 57.3, 54.2, and 55.0 percent, respectively). For the total prevention and control of TMV viral disease in the field, NK0209 was the first drug to be successful[27].

6.1.4. ANTI-LEISHMANIAL ACTIVITY

Leishmaniasis is a neglected tropical disease (NTD) that is widespread throughout 98 nations. Leishmaniasis is a vector-borne illness brought on by the flagellated protozoans of the genus Leishmania. An intracellular parasite that infects people and is spread to them by the biting of sand flies, primarily Phlebotomus and Lutzomyia, causes the tropical and subtropical disease leishmaniasis.

A number of antileishmanial scaffolds, including N-methylpiperazine[28], benzoyl[29], piperazinoyl, furyl[30], and naphthyl, were connected to the N-2 site of THβC by Manda et al . The most effective antileishmanial drugs had IC_{50} values against promastigotes of 9.1 and 22.1 mM for the thiophen-2-yl linked analogue (**19**) and naphthyl linked analogue (**20**), respectively.

Additionally, (**19**) and (**20**) showed promising antitrypanosomal action against T. brucei[31] .

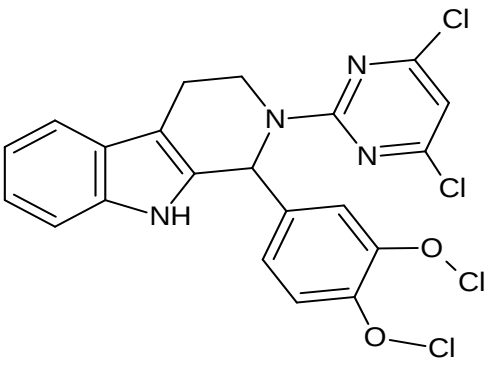
Ashok et al. also discovered novel 1, 2-disubstituted THβCs with antileishmanial properties. Compounds (**17**) and (**18**) demonstrated selective and strong suppression of amastigotes with IC50 values of 0.67 and 0.87 mM, respectively, which were comparable to amphotericin B[32].

Kumar et al. developed and synthesised THβC compounds with the 2-aminopyrimidines group, a key pharmacophore in antileishmanial agents [33,34].

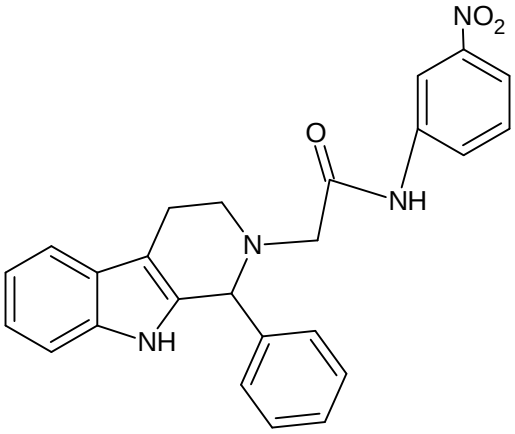
Gellis et al. evaluated the antileishmanial activity of their antimalarial compounds with the general structure (**18**). The most promising chemical for inhibiting L. Donovani has an IC50 value of 6.1 M (compared to 6.3 M for pentamidine) [35].

With IC50 values of 3.79 M and 5.17 M for the ortho-bromosubstituted and para-ethylated compounds, respectively, Chauhan et al. synthesised a series of indolylglyoxylamides with the general structure (**21**) in 2010 and found good antileishmanial activity. These results were significantly better than the typical pharmacological activities (IC50 for pentamidine: 20.43 M) [36].

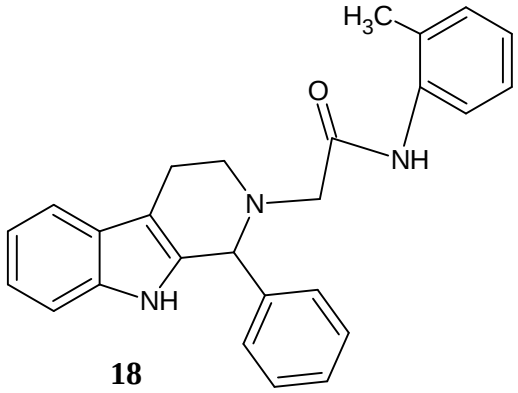
Triazine derivatives (**22**) and other related compounds (**23**) have been identified by Kumar et al. as leishmanicidals. The triazino derivatives have also been examined in live animals [37,38].



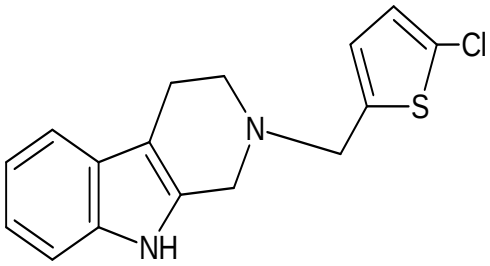
16



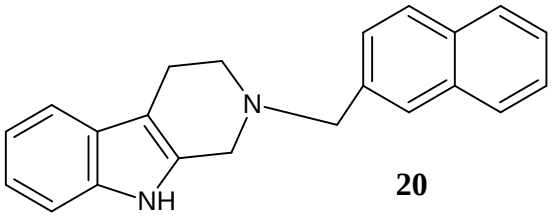
17



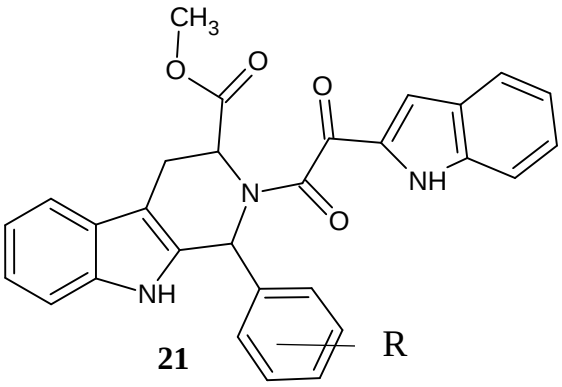
18



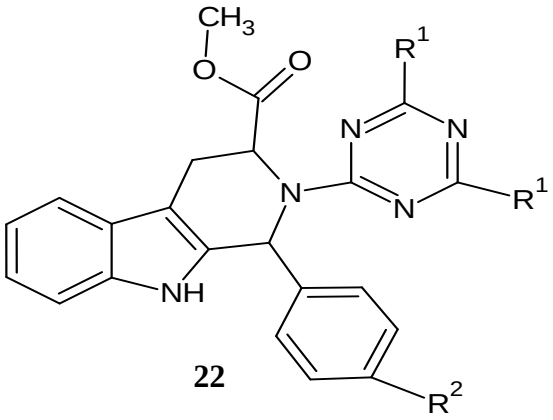
19



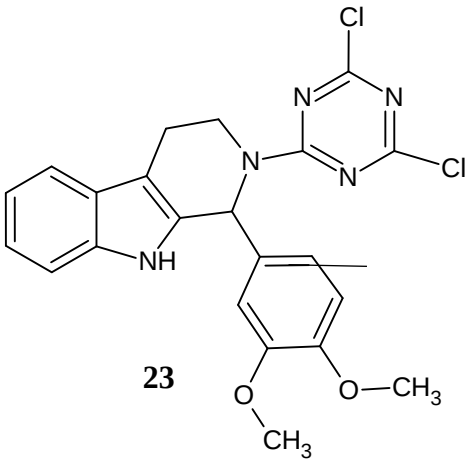
20



21



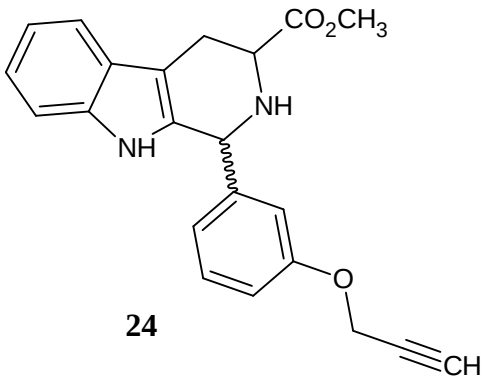
22



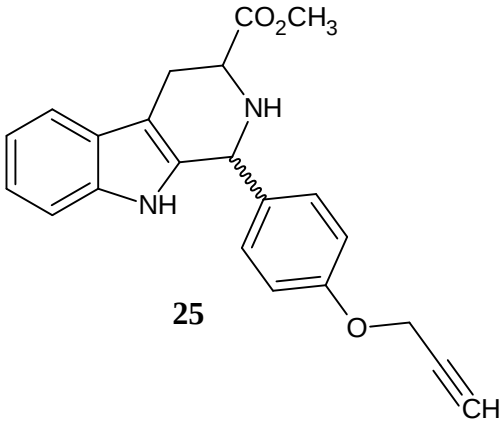
23

6.1.5. ANTIBACTERIAL ACTIVITY

Salehi P, et al. studied the antibacterial properties of the produced tetrahydro-β-carboline derivatives were evaluated against Staphylococcus aureus, an Enterococcus faecalis strain that is vancomycin resistant, Bacillus cereus, and one strain of Escherichia coli that is a Gram-negative bacterium. Compounds 4b, 4c showed a moderate antibacterial activity (MIC64 g/mL) against E. faecium. All chemicals, with the exception of (24), (25), suppressed E. faecium growth more effectively than vancomycin. All synthesised substances had little efficacy against S. aureus, E. coli, and B. cereus (MIC 4 64 g/mL)[39] .



24



25

CONCLUSION

Tetrahydro-β-Carbolines are thought to be a potential class of bioactive heterocyclic compounds that display a variety of biological properties. The facile rapid synthesis and wide range of pharmaceutical activities made THβC receive great attention from pharmaceutical chemists, which resulted in the development of various therapeutic medications. This review discusses the characteristics, occurrence, method of synthesis, and antimicrobial properties of synthetic THβCs. We could anticipate many more triumphs of this framework in drug discovery when more active THβC NPs are found.

Declaration by Authors

Ethical Approval: Not Applicable
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. Herraiz T, Galisteo J. Tetrahydro-β-carboline alkaloids occur in fruits and fruit juices. activity as antioxidants and radical scavengers. Journal of Agricultural and Food Chemistry. 2003;51(24):7156–61.
2. Laine A, Lood C, Koskinen A. Pharmacological importance of optically active tetrahydro-β-carbolines and synthetic approaches to create the C1 stereocenter. Molecules. 2014;19(2):1544–67.
3. Wang J, Gong F, Liang T, Xie Z, Yang Y, Cao C, et al. A review of synthetic bioactive tetrahydro-β-carbolines: A medicinal chemistry perspective. European Journal of Medicinal Chemistry. 2021;225:113815.
4. Daugan A, Grondin P, Ruault C, Le Monnier de Gouville A-C, Coste H, Kirilovsky J, et al. The discovery of Tadalafil: A novel and highly selective PDE5 inhibitor. 1: 5,6,11,11a-tetrahydro-1*h*-imidazo[1‘,5‘:1,6]pyrido[3,4-*b*]indole-1,3(2*h*)-dione analogues. Journal of Medicinal Chemistry. 2003;46(21):4525–32.
5. Tryptoline [Internet]. ChemSpider. [cited 2022Nov8]. Available from: https://www.chemspider.com/Chemical-Structure.96979.html/
6. Tryptoline [Internet]. National Center for Biotechnology Information. PubChem Compound Database. U.S. National Library of Medicine; [cited 2022Nov8]. Available from:

https://pubchem.ncbi.nlm.nih.gov/compound/Tryptoline
7. Herraiz T, Galisteo J. Tetrahydro-β-carboline alkaloids that occur in foods and biological systems act as radical scavengers and antioxidants in the Abts Assay. Free Radical Research. 2002;36(8):923–8.
8. Cao R, Peng W, Wang Z, Xu A. β-carboline alkaloids: Biochemical and pharmacological functions. Current Medicinal Chemistry. 2007;14(4):479–500.
9. Herraiz T. Tetrahydro-β-carbolines, potential neuroactive alkaloids, in chocolate and Cocoa. Journal of Agricultural and Food Chemistry. 2000;48(10):4900–4.
10. Herraiz T. Analysis of the bioactive alkaloids tetrahydro-β-carboline and β-carboline in food. Journal of Chromatography A. 2000;881(1-2):483–99.
11. Szabó T, Volk B, Milen M. Recent advances in the synthesis of β-carboline alkaloids. Molecules. 2021;26(3):663.
12. Han Y, Dong W, Guo Q, Li X, Huang L. The importance of indole and Azaindole Scaffold in the development of antitumor agents. European Journal of Medicinal Chemistry. 2020;203:112506.
13. Dvořák Z, Poulíková K, Mani S. Indole scaffolds as a promising class of the aryl hydrocarbon receptor ligands. European Journal of Medicinal Chemistry. 2021;215: 113231.
14. Akabli T, Toufik H, Yasri A, Bih H, Lamchouri F. Combining ligand-based and structure-based drug design approaches to study the structure-activity relationships of a β-carboline derivative series. Structural Chemistry. 2018;29(6):1637–45.
15. Devi N, Kumar S, Pandey SK, Singh V. 1(3)-formyl-β-carbolines: Potential Aldo-X precursors for the synthesis of β-carboline-based molecular architectures. Asian Journal of Organic Chemistry. 2017;7(1):6–36.
16. Tewari U, Sharma D, Srivastava S, Kumar BK, Faheem, Murugesan S. Anti-tubercular insights of carbolines – a decade critique. ChemistrySelect. 2021;6(9):2428–45.
17. Khodair R, Da'aboul I. Synthesis of novel compounds from Harmine (β-carboline derivatives) isolated from Syrian Peganum Harmala L. Seeds. International Journal of Academic Scientific Research.2017;5(2):57-76
18. Maity P, Adhikari D, Jana AK. An overview on synthetic entries to tetrahydro-β-carbolines. Tetrahedron. 2019:75(8):965–1028.
19. Rinehart KL, Kobayashi J, Harbour GC, Hughes RGJr, Mizsak SA, Scahill TA. Eudistomins C, E, K, and L, potent antiviral compounds containing a novel oxathiazepine ring from the Caribbean tunicate Eudistoma olivaceum. J Am Chem Soc. 1984;106(5):1524–6.
20. Rinehart KLJr, Kobayashi J, Harbour GC, Gilmore J, Mascal M, Holt TG. Eudistomins A-Q, .beta.-carbolines from the antiviral Caribbean tunicate Eudistoma olivaceum. J Am Chem Soc. 1987;109(11):3378–87.
21. Menna M, Fattorusso E, Imperatore C. Alkaloids from Marine Ascidians. Molecules. 2011;16(10):8694–732.
22. Van Maarseveen JH, Hermkens PHH, De Clercq E, Balzarini J, Scheeren HW, Kruse CG. Antiviral and antitumor structure-activity relationship studies on tetracyclic eudistomines. J Med Chem. 1992;35(17): 3223–30.
23. Miller JF, Turner EM, Sherrill RG, Gudmundsson K, Spaltenstein A, Sethna P. Substituted tetrahydro-β-carbolines as potential agents for the treatment of human papillomavirus infection. Bioorganic & Medicinal Chemistry Letters. 2010;20(1): 256–9.
24. Zur Hausen H. Papillomaviruses in the causation of human cancers - a brief historical account. Virology. 2009;384(2): 260–5.
25. Song H jian, Liu Y xian, Liu Y xiu, Huang Y qiong, Li Y qiang, Wang Q min. Design, synthesis, anti-TMV, fungicidal, and insecticidal activity evaluation of 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid derivatives based on virus inhibitors of plant sources. Bioorg Med Chem Lett. 2014;24(22):5228–33.
26. Song H jian, Liu Y xian, Liu Y xiu, Huang Y qiong, Li Y qiang, Wang Q min. Design, synthesis, anti-TMV, fungicidal, and insecticidal activity evaluation of 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid derivatives based on virus inhibitors of plant sources. Bioorg Med Chem Lett. 2014;24(22):5228–33.
27. Wang H, Song H. Synthesis of Four Optical Isomers of Antiviral Agent NK0209 and Determination of Their Configurations and

Activities against a Plant Virus. J Agric Food Chem. 2020;68(9):2631–8.
28. Silva CMBL, Garcia FP, Rodrigues JH da S, Nakamura CV, Ueda-Nakamura T, Meyer E. Synthesis, Antitumor, Antitrypanosomal and Antileishmanial Activities of Benzo[4,5]canthin-6-ones Bearing the *N*′-(Substituted benzylidene)-carbohydrazide and *N*-Alkylcarboxamide Groups at C-2. Chemical and Pharmaceutical Bulletin. 2012;60(11):1372–9.
29. Germonprez N, Maes L, Van Puyvelde L, Van Tri M, Tuan DA, De Kimpe N. In Vitro and in Vivo Anti-Leishmanial Activity of Triterpenoid Saponins Isolated from Maesa balansae and Some Chemical Derivatives. J Med Chem. 2005;48(1):32–7.
30. Boeck P, Bandeira Falcão CA, Leal PC, Yunes RA, Filho VC, Torres-Santos EC, et al. Synthesis of chalcone analogues with increased antileishmanial activity. Bioorganic & Medicinal Chemistry. 2006; 14(5):1538–45.
31. Manda S, Khan SI, Jain SK, Mohammed S, Tekwani BL, Khan IA. Synthesis, antileishmanial and antitrypanosomal activities of N-substituted tetrahydro-β-carbolines. Bioorganic & Medicinal Chemistry Letters. 2014;24(15):3247–50.
32. Ashok P, Chander S, Tejería A, García-Calvo L, Balaña-Fouce R, Murugesan S. Synthesis and anti-leishmanial evaluation of 1-phenyl-2,3,4,9-tetrahydro-1H-β-carboline derivatives against Leishmania infantum. European Journal of Medicinal Chemistry. 2016;123:814–21.
33. Chandra N, Ramesh, Ashutosh, Goyal N, Suryawanshi SN, Gupta S. Antileishmanial agents part-IV: synthesis and antileishmanial activity of novel terpenyl pyrimidines. Eur J Med Chem. 2005; 40(6):552–6.
34. Suryawanshi SN, Bhat BA, Pandey S, Chandra N, Gupta S. Chemotherapy of leishmaniasis. Part VII: Synthesis and bioevaluation of substituted terpenyl pyrimidines. European Journal of Medicinal Chemistry. 2007;42(9):1211–7.
35. Gellis, A.; Dumètre, A.; Lanzada, G.; Hutter, S.; Ollivier, E.; Vanelle, P.; Azas, N. Preparation and antiprotozoal evaluation of promising β-carboline alkaloids. Biomed. Pharmacother. 2012;66:339–347.
36. Gellis A, Dumètre A, Lanzada G, Hutter S, Ollivier E, Vanelle P. Preparation and antiprotozoal evaluation of promising β-carboline alkaloids. Biomed Pharmacother. 2012;66(5):339–47.
37. Kumar, A.; Katiyar, S.B.; Gupta, S.; Chauhan, P.M.S. Syntheses of new substituted triazino tetrahydroisoquinolines and β-carbolines as novel antileishmanial agents. Eur. J. Med. Chem. 2006, 41, 106–113.
38. Kumar R, Khan S, Verma A, Srivastava S, Viswakarma P, Gupta S. Synthesis of 2-(pyrimidin-2-yl)-1-phenyl-2,3,4,9-tetrahydro-1H-β-carbolines as antileishmanial agents. European Journal of Medicinal Chemistry. 2010;45(8):3274–80.
39. Salehi P, Babanezhad-Harikandei K, Bararjanian M, Al-Harrasi A, Esmaeili MA, Aliahmadi A. Synthesis of novel 1,2,3-triazole tethered 1,3-disubstituted β-carboline derivatives and their cytotoxic and antibacterial activities. Med Chem Res. 2016;25(9):1895–907.

How to cite this article: Devi Nidana S.S, Hima C.S, Shaiju S Dharan. Characterization, chemistry, structural activity relationship and antimicrobial activities of tetrahydro-β-carboline. *International Journal of Research and Review*. 2022; 9(12): 1-15. DOI: *https://doi.org/10.52403/ijrr.20221201*

******