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Review Paper

Recent developments in the Synthesis and Biological Activities of THβ-carboline and Its Analogs: Review

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Abstract

1,2,3,4-Tetrahydro-β-carbolines (THβCs) are a large group of natural and synthetic indole alkaloids that possess a common tricyclic pyrido[3,4-b] indole scaffold that are widely distributed in nature. The scaffold and its derivatives are of great interest due to their diverse biological activities and applied in medicine as therapeutic agents. These days, the importance of these compounds in inspiring drug discovery programs is proven and, therefore, their continued synthesis is of great interest. Therefore, this review summarizes the development in synthetic methods of THβCs and their comprehensive biological activities over the past decades. The review on β-carbolines might serve as a good reference to promote its inclusion in the planning and synthesis of future drugs.

1. Introduction

The β-carboline are indole alkaloids that possess a common tricyclic pyrido[3,4-b] indole ring structure. Some examples are β-carboline 1, tryptoline 2, and dihydro-β-carbolines 3 (Figure 1) (Zhibin *et al*., 2015). β-carbolines can be categorized according to the saturation of their nitrogen containing, six-membered ring. Unsaturated members are named as fully aromatic β-carbolines (βCs), whereas the partially or completely saturated ones are dihydro-β-carbolines (DHβCs) and tetrahydro-β-carbolines (THβCs), respectively (Rihui *et al*., 2007; Dai *et al*., 2018).

Although *β*-carboline is fully aromatic, the members with partially saturated rings (3,4-dihydro- *β*-carbolines **3** and 1,2,3,4-tetrahydro-*β*-carbolines **2** are also well-known (Figure 1). 1,2,3,4-Tetrahydro-*β*-carbolines are a class of compounds, existing in a large number of both simple and complex, natural and synthetic compounds (Hess. M, 2003). The three rings in TH*β*C are referred to as A,B (pyrrole ring), and C-ring (piperidine moiety) (Figure 1). Since the first time in 1961, McIsaac identified endogenous pinoline, 6-methoxy-tetrahydro-*β*-carboline **7**, from an extract of pineal gland tissue (Arrell and McIsaac, 1961). The most representative *β*-carboline such as harmine **4**, harmaline **5**, and harman **6**, the tricyclic 1,2,3,4-tetrahydro-*β*-carboline (TH*β*C) ring system is a key structural element in a range of biologically important alkaloids (Erhad *et al*., 2012).These compounds are isolated from *Peganum harmala* (Zygophillaceae), which is being used as a traditional herbal drug as an emmenagogue and abortifacient, as hallucinogenic drinks in Amazon basin, and to treat the alimentary tract cancers and malaria in Northwest China (Hamid *et al*., 2008; Shengkun *et al*., 2010). The TH*β*Cs alkaloids continue to be promising lead compounds for discovering and developing novel clinical drugs. The SAR studies have demonstrated that the introduction of

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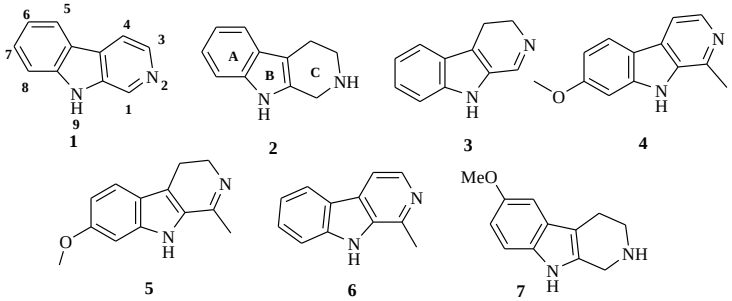


Figure 1: Chemical structure of β-carboline.

appropriate substituents into the positions -1, -2, -3 and -9 of the *β*-carboline nucleus play a crucial role in determining their multiple pharmacological function (Franciele C., *et al*., 2012). Tadalalif **15**, yohimbine **16**, ajmalicine **17**, and reserpine **18** are the representative analogs of the carboline alkaloids with a range of pharmacological activities (Scheme 1) (Chun-Xiang Z., *et al*., 2013).

2. Source and Biosynthesis of TH*β*s

2.1. Source of TH*β*s

Tetrahydro-*β*-carboline (TH*β*Cs) alkaloids are naturally occurring tricyclic indole derivatives produced in biological tissues (Gitte *et al*., 1999), plants (Nagatoshi, et al., 2002; Donatus and Ephraim, 2011), red alga (Herraize, 2000) and meat-derived products (Ekaterini and Tomas, 2003; Idowu *et al*., 2006) such as juices, jams and sausages (Herraiz, 1998), and also in alcoholic beverages (Herraiz, 1999) from indolethylamines and/or tryptophan and aldehydes or *α*-ketoacids during the production, processing and storage of food products through a Pictet-Spengler condensation (Biswajit, 2007). *Peganum harmala* L (Zygohpyllaceae) is widely studied plant species which is abundant in *β*-carbolines and TH*β*Cs (Mehdi and Hadi, 2016). *P. harmala* are traditionally used as emmenagogues, narcotics, abortifacients and in treatment of fever, rheumatism and asthma as well for recreation and as a stimulant of the central nervous system (Tomas *et al*., 2010; Kai-Bo *et al*., 2016). This plant is also reported to have antimicrobial (Lingam, *et al*., 2008; Kianfe *et al*., 2020), antifungal, anticancer (Samundeeswari *et al*., 2017), and antioxidant (Fariza *et al*., 2011) properties.

2.2. Biosynthesis of TH*β*s

In the use of enzyme-mediated synthesis of TH*β*Cs, in the indole alkaloid field, the most prominent and best characterized members of the highly substrate-specific Pictet-Spenglerases, the norcoclaurine synthases (NCS) (Benjamin *et al*., 2017) and the strictosidine synthases (STRs) (Eva *et al*., 2014) have been applied effectively in *vivo* and in *vitro* to catalyze Pictet-Spengler reaction (PSR) (Fangrui *et al*., 2012). The STR condenses tryptamine **12** and secologanin **13** to generate an intermediate Schiff base that cyclizates to give the (S)-configured 1,2,3,4-tetrahydro-*ß*-carboline (S)-strictosidine **14** which is the key intermediate of indole alkaloid biosynthesis in plants (Scheme 1) (Tomás and Juan, 2014; Desiree *et al*., 2018). The first Strictosidine synthase (STS), "Pictet-Spenglerase,", originally isolated from cell cultures of *Catharanthus roseus* and *Rauvolfia serpentine* plants for the biosynthesis of the alkaloid ajmalicine, is the central enzyme that catalyze PSR to yield **14** (Eva-Maria *et al*., 2016). Since then, the TH*β*C strictosidine has become a common precursor for a number of TH*β*C alkaloids and quinoline such as **15**, **16**, **17**, **18**, quinine **19**, vincamine **20** and are found in a wide variety of plant species (Justin *et al*., 2017; Peter *et al*., 2010). In contrast to *β*Cs alkaloid synthesis in plants, the biosynthesis in microorganisms remains poorly understood. The recently reported McbB from Marinactinospora thermotolerans is a novel enzyme proposed to catalyze the PSR (Takahiro *et al*., 2015).

Flower **Seed capsule** **Seed**

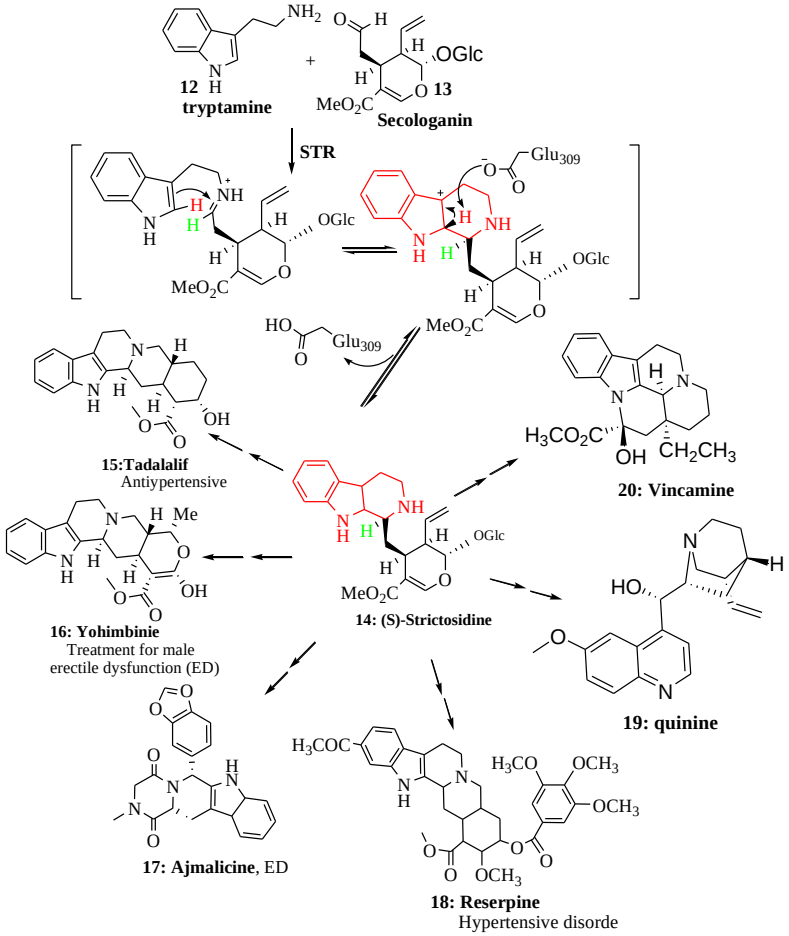
Figure 2: Picture of Peganum harmala.

3. Synthetic Approaches towards THβC Derivatives

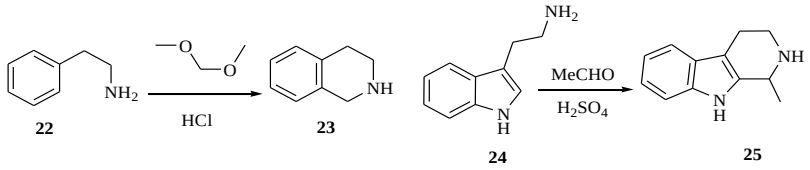
There are numerous methods that have been developed for the synthesis of THβC and their derivatives. Since the discovery of Pictet-Spengler reaction (PSR), 119 years ago, remarkable results have been obtained. In the meantime, many approaches have been developed for the synthesis of THβCs and their derivatives, which has been reviewed in several publications. Generally, conventional method (Laura *et a*l., 2004; Pooja et al., 2017), biocatalytic methods (Peter B., et al., 2010), transition metal catalyzed, ionic-liquid methods (Muthukrishnan et al., 2006), microwave assisted methods (Christophe *et al*., 2005) have been employed. The most well-known and straightforward route for the construction of THβC moiety is Pictet-Spengler reaction (PSR) (Pooja et al., 201. Another classical protocol is Bischler-Napieralski cyclization (BN) where the product is a DHβC, which can then be further reduced to form the corresponding THβC (Hongjian *et al*., 2014). These classical reactions are well established as a method of choice for construction of THβC frameworks (Bojan P. and Peter E., 2008). Several other methods such as Fischer-indole reaction (Byeong-Yun et al., 2014), Friedl-Craft indole alkylation reaction (Raquel et al., 2005), intramolecular allylic alkylation of indole (Marco et al., 2004), and Simultaneous ring B and ring C closing methods (Ana *et al*., 2004) were reported.

3.1. Pictet-Spengler reaction (PSR)

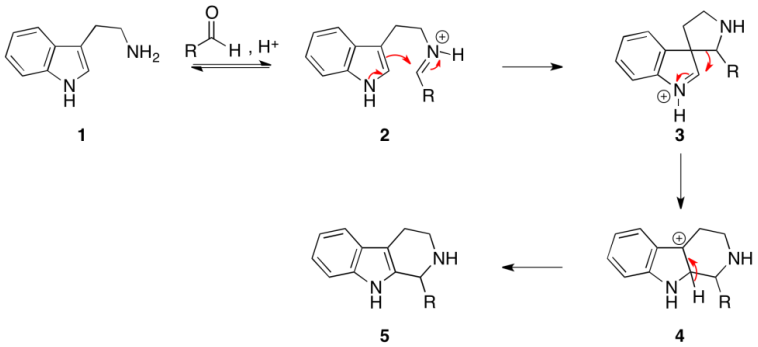
The Pictet-Spengler reaction was first discovered by Pictet and Spengler in 1911 where they synthesized 1,2,3,4-tetrahydroisoquinoline (THIQ) 23 from β-phenylethylamine 22 and formaldehyde dimethylacetal under heating in the presence of hydrochloric acid. After the discovery of the PSR it took nearly 20 years before Tatsui used tryptamine 24 as the amine component, which paved the way for the first synthetic creation of the 1-Methyl-1,2,3,4-tetrahydro-β-carboline 25 skeleton in the year 1928 (Vemu et al., 2016) (Scheme 2).



Scheme 1: Strictosidine-synthase-catalyzed natural PS condensation of tryptamine **12** and secologanin **13**



Scheme 2: The first PSR; the synthesis of THIQ **23** and TH*β*C **25**.



Scheme 3: The general reaction mechanism of Pictet-Spengler reaction.

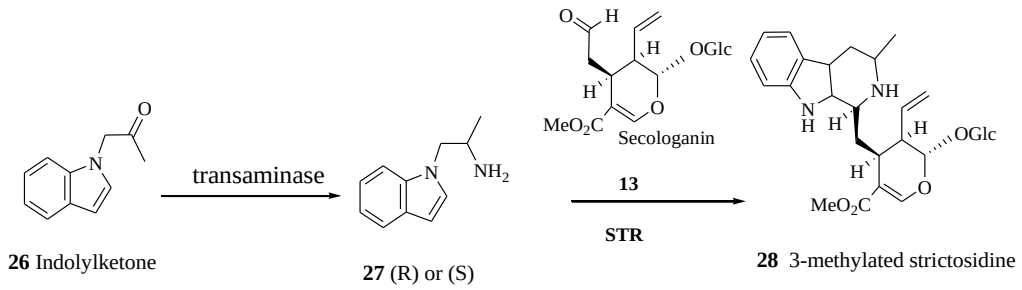
A typical PSR reaction is a two-step process that involves the condensation of an aliphatic amine with aldehyde or ketone to form an imine or iminium ion. Final intramolecular cyclization between a sufficiently reactive, electron-rich aromatic ring and the activated iminium ion results in a N-heterocyclic ring via a new C-C bond (So-Won, 2006). From the mechanistic view, it is well recognized that an acidic catalyst (usually an excess of a Brønsted acid/Lewis acids ranging from catalytic to stoichiometric amounts, in the presence of non-aqueous protic or aprotic solvent activates the imine intermediate before cyclization into the tetrahydro-β-carboline (Matthieu *et al*., 2013; Mouhamad *et a*l., 2012) (Scheme 3). According to Fu-Ming et al., though intrinsically slow in reaction rates, ketones reactions (instead of aldehydes) can be accelerated (from days to minutes) using microwaves in open vessels with high isolated yields (Fu-Ming et al., 2004). Although the reactions in water require large excess of strong Brønsted acid (Akio et al., 2007).

A variety of efficient catalytic systems were used for the synthesis of TH*β*Cs including conventional catalysts using TFA (Fu-Ming *et al*., 2004), conc. H_2SO_4 (Vikrantsinh *et al*., 2012), AcOH, *p*-TsOH (Vemu N., 2016) and Lewis acids (Radhika *et al*. 2008) have been reported as catalysts for the PSR.

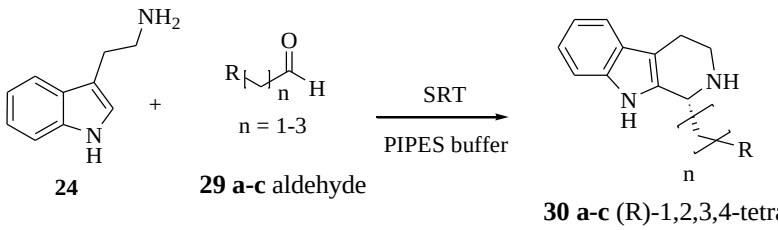
3.1.1. Biocatalytic PSR

Various biomimetic approaches has been developed on the basis of the first known enzyme-catalyzed pathway of PSR leading to TH*β*Cs. In this regard, in 2016, Fischereder and his co-workers synthesized diastereomerically pure TH*β*C derivatives **28** via two enzymatic steps in a one-pot method (Eva et al., 2014). This was achieved by the amination of the prochiral indolylketones **26** catalyzed by transaminase enzyme followed by condensation of tryptamine **27** with secologanin **13** via a Pictet-Spengler reaction catalyzed by strictosidine synthase. Peter *et al*. reported that strictosidine synthase from *Ophiorrhiza pumila* utilizes a range of simple achiral aliphatic and aromatic aldehydes and substituted tryptamines to form highly enantioenriched (ee >98%) tetrahydro-*β*-carbolines via a Pictet-Spengler reaction (Peter *et al*., 2006).

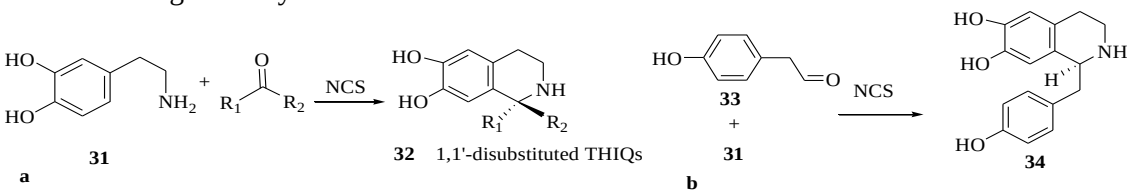
Although in the natural reaction, the STR condenses tryptamine **12** and secologanin **13** to generate the (S)-configured 1,2,3,4-tetrahydro-ß-carboline (S)-strictosidine (Scheme 1), a study made by Desiree *et al*., revealed that the biocatalytic Pictet–Spengler reaction of tryptamine with aliphatic aldehydes **29a-c** give unexpectedly access to the (R)-configured 1,2,3,4-tetrahydro-*ß*-carboline **30a-c** giving the products with up to >98% ee (Scheme 5)(Desiree *et al*., 2018). The crystal structure of STR from *Rauvolfia serpentina* revealed the catalytic reaction mechanism of STR, including the role of the catalytic residue Glu309 is depicted in Scheme 1 (Xueyan *et al*., 2006). Benjamin group have described that not only STR but also norcoclaurine synthase (NCS) from *Thalictrum flavum* (TfNCS) can catalyze the PSR between dopamine **31** and unactivated ketones for the first-time, thus facilitating the facile biocatalytic generation of 1,1'-disubstituted THIQs **32** (Scheme 6a). The mechanistic studies on Norcoclaurine Synthase is



Scheme 4: Biomimetic synthesis of 3-methylated THβC strictosidine via PSR.



Scheme 5: Strictosidine synthase catalyzed Pictet-Spengler reaction between tryptamine and aliphatic low-molecular-weight aldehydes.



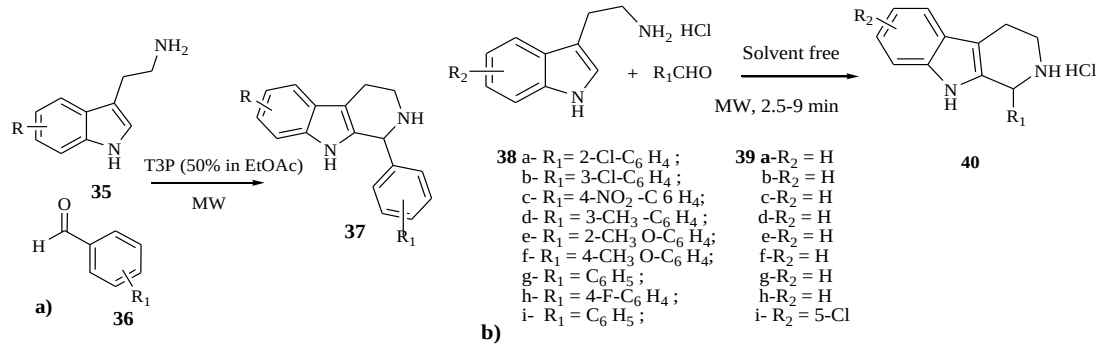
Scheme 6: a) Biocatalytic route to 1,1'-disubstituted THIQs, from dopamine and ketones, via a PSR, catalysed by NCS. b) The PSR catalyzed by norcoclaurine synthase to give (S)-norcoclaurine **34**.

discussed in detail by Louis where NCS catalyzes an asymmetric PS condensation of dopamine and 4-hydroxyphenylacetaldehyde **33** to give (S)-norcoclaurine **34** (Scheme 6b) (Louis *et al*., 2007).

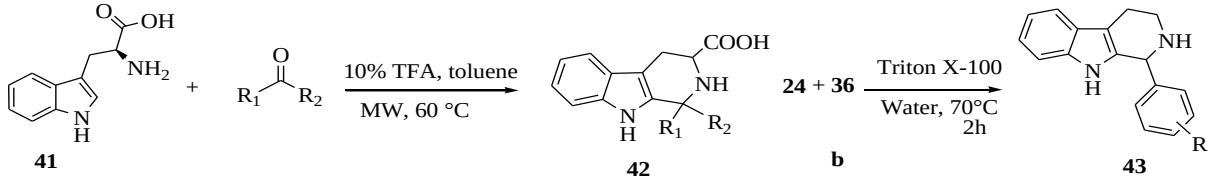
3.1.2. Micro-wave/Ultrasound assisted PSR

In recent years, an efficient and environmentally friendly synthesis of tetrahydro-*β*-carboline via PSR employing micro-wave (MW)/ultrasonic (US) irradiation has tremendously increased due to its simplicity, short reaction time, high yield and green nature of the reactions (Venkata *et al.*, 2016), and several studies had been reported (Wu and Sun, 2012; Bikash et al., 2003; Campiglia *et al*., 2004; Scott *et al*., 2014). In 2013, Matthieu *et al*., synthesized and reported various tetrahydro-*β*-carbolines **37** from a mixture of substituted tryptamine **35** and a variety of substituted aldehydes **36** in the presence of Propane phosphonic acid anhydride (T3P®) using microwave irradiation (Scheme 7a) (Matthieu *et al*., 2013). T3P® was required for this cyclization and ketones are often problematic in the Pictet-Spengler reaction. Under neat reaction system, without additional catalyst Fei and Qi-Dong developed the synthesis of 1,6,7-substitiuted-1,2,3,4-Tetrahydro-*β*-carbolines **40** from tryptamine hydrochlorides **38** and different aldehydes (Scheme 7b). The study used to compare the reaction result between conventional heating (90 min, 100°C, AcOH, and 80% max) and microwave irradiation (2-3 min, < 100°C, neat, and 95%) where dramatic reduction in the reaction time and higher product yield was achieved (Fei et al., 2007).

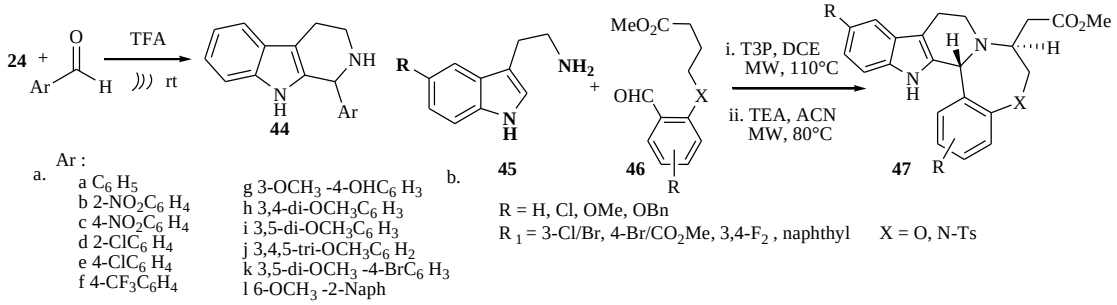
In 2004, Fu-Ming *et al*., demonstrated that though intrinsically slow in reaction rates (which had taken 13h to 15.5 days via conventional method at rt; 74-84% yield), ketone reactions (specifically cyclic ketones such as cyclohexanone and cyclopentanone) with tryptophan **41** can be accelerated (hours to minutes) using microwaves (60°C and 150 W) in an open vessels with high isolated yields of 1,3-disubstituted-1,2,3,4-tetrahydro-*β*-carboline **42** (67–99%) (Scheme 8a) (Matthieu *et al*., 2013). By using non-ionic surfactant catalyst Triton X-100 (10mol%) in aqueous media under ultrasound irradiation, Venkata group reported a highly efficient procedure for the preparation of tetrahydro-*β*-carbolines in good yields (89-94%; 2-4 hrs.) compared to conventional heating methods (65-75%; 9-12 hrs.) by the condensation of tryptamine **24** and aryl/ heteroaryl aldehydes **36** having both ED and EW substituents to furnish tetrahydro-*β*-carbolines **43** via PSR (Scheme 8b)(Venkata P., *et al*., 2016).



Scheme 7: a) T3P® catalyzed microwave-assisted PSR; b) Synthesis of tetrahydro-*β*-carboline.



Scheme 8: a) Synthesis of 1,3-disubstituted-1,2,3,4-tetrahydro-*β*-carboline 42. b) Ultrasound irradiation promoted PSR to give **43**.



Scheme 9: a). Synthesis of 1-aryl-TH*β*Cs by US-assisted method. b). T3P catalyzed microwave-assisted formation of TH*β*C-benzoxazepine system **47**.

In 2016, Gisela *et al*., also synthesized a series of twelve tetrahydro-*β*-carboline derivatives **44** (Scheme 9a) via one-pot US-assisted PSR from tryptamine **24** and a variety of arylaldehydes under US irradiation in methylene chloride and TFA catalysis at rt in good to excellent yields (1-2h; 43-87% yield) compared to conventional method (12-48h; 12-70% yield) (Gisela *et al*., 2016). In 2017, Srinivasulu group reported an efficient microwave-associated PS cyclization of substituted tryptamine **45** with (E)-methyl 4-(2-formylphenoxy) but-2-enoates **46** having various functional groups. Here, the formation of THBC-benzoxazepine systems **47** was achieved by using a diastereoselective one-pot MW-irradiated reaction T3P/TEA mediated PS/aza-Michael addition/cyclization cascade (Scheme 9b) with 61 % yield (Srinivasulu *et al*., 2017).

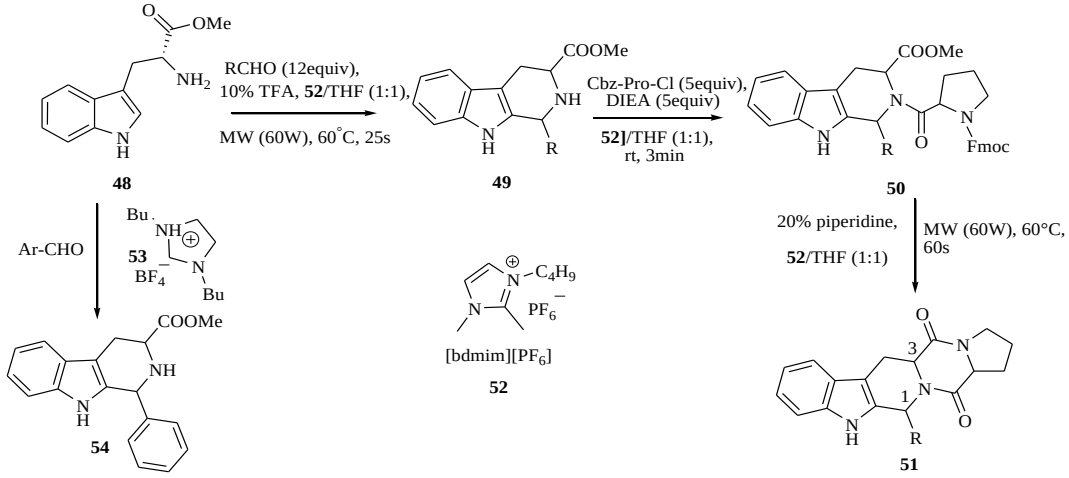
3.1.3. Ionic-liquid catalyzed PSR

Nowadays, ionic liquids are used as catalysts as well as ecofriendly solvents in organic synthesis due to unique physical and chemical properties (non-volatile, recyclable, non-explosive) which can also be applied in the synthesis of TH*β*Cs via PSR (Barnali et al., 2009). In 2004, Ya-Hew and Yen-Ho synthesized tetrahydro-*β*-carbolinediketopiperazines **50** from tryptophan methyl ester **48** and various aldehyde all with higher total isolated yields under microwaves (49–69%; 60 min) than at rt (20–41%; 2h) in the 1-Butyl-3-methylimidazolium hexafluorophosphate **52** ([bdmim][PF_6]) [bdmim][PF_6]/THF solvent system with temperature controlled at 60°C (Scheme 10a)(Ya-Hew Y. and Yen-Ho C., 2004). In 2006, Muthukrishnan *et al*. also reported an ionic liquid promoted Pictet-spengler reaction of D-tryptophan ester **48** with different aldehydes in different imidazolium based ionic liquids like [bbim]BF_4, [bbim]PF_6, and [bbim]Br in the presence of trifluoroacetic acid (TFA) as an acid catalyst. Here, [bbim]BF_4 **53** was found to be superior in terms of yield, reaction time and easy isolation of products as compared with other ionic liquids at 100 °C for 2 h to afford the corresponding 1,3-disubstituted

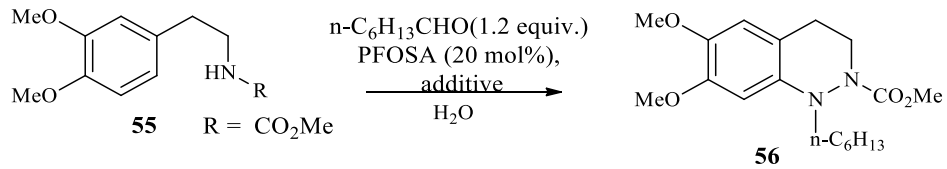
1,2,3,4-tetrahydro-*β*-carboline **54** between 70-90% yield (Scheme 10b) (Muthukrishnan *et al*., 2006).

3.1.4. Bronsted and Lewis acid catalyzed PSR

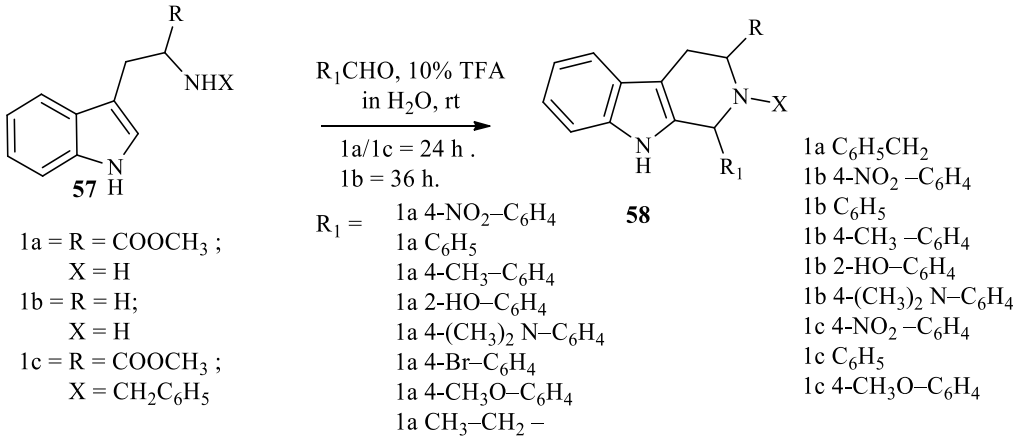
Bronsted acids and Lewis acids are also reported to assist cyclization in PSR. Brønsted acids such as trifluoroacetic acid [TFA] (Rodrigo *et al*., 2009), p-toluenesulfonic acid [TsOH] [69], acetic acid [AcOH] [70], and sulfuric acid [H_2SO_4] [8] have been reported to be good catalysts for the Pictet–Spengler reactions in organic solvents. According to Akio *et al*., although Brønsted acids such as TFA, trifluoromethanesulfonic acid (TfOH), and (TsOH) have been known to be good catalysts for the PSR in organic solvents, they were not effective catalysts in water. However, the addition of n-Perfluorooctanesulfonic acid (PFOSA) significantly accelerated the cyclization of **55** giving rise to **56** in 90% yield (Akio *et al*., 2007). In the same year, unlike the traditional Pictet-Spengler protocol involving aprotic solvent, Biswajit group demonstrated that the PSR in 10% TFA in water, proceeded smoothly and afforded the desired compound **58** in 82% isolated yield. Nevertheless, reduction in the concentration of TFA from 10 to 5 or 2% produced cyclized products in diminished yields (Scheme 12).



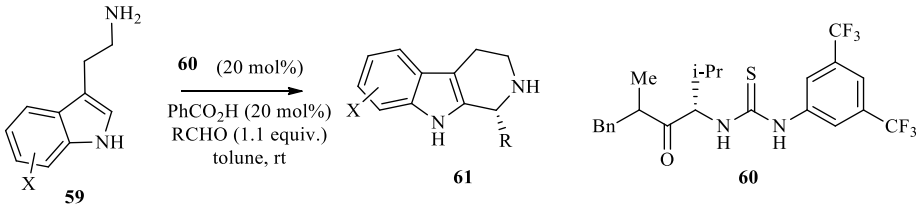
Scheme 10: [bdmim][PF6] promoted synthesis of tetrahydro-*β*-carbolinediketopiperazines **51**.



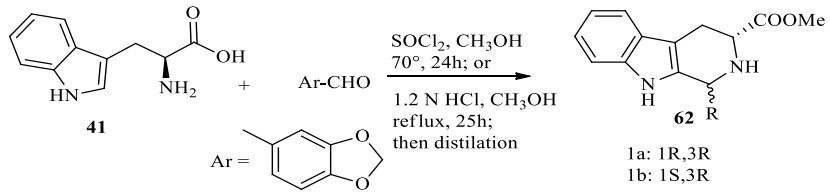
Scheme 11. PFOSA catalyzed PSR in water.



Scheme 12. Water mediated Bronsted acid catalyzed PSR.



Scheme 13. Enantioselectivity (Thio)urea Catalyzed PSR.



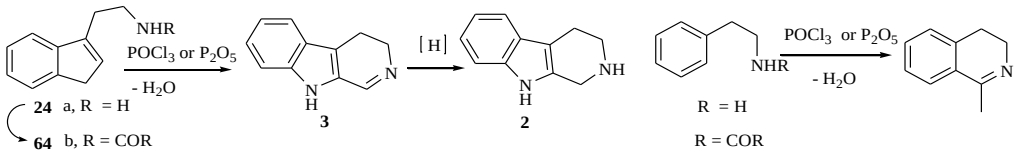
Scheme 14. Acids catalyzed PSR to afford **62**.

In addition to the Brønsted acids, several Lewis acids are used in the cyclization methods of PSR to give TH*β*Cs. In 2009, Rebekka and Eric developed an enantioselective catalytic PSR with a broad substrate scope for tryptamine derivatives **59** with a catalytic cycle in which imine protonation is induced by a thiourea catalyst **60** associated via H-bonding to the conjugate base of a weak Brønsted acid (benzoic acid) additive (Scheme 13) promote catalytic asymmetric PSR providing unprotected TH*β*Cs **61** in high ee and yield. Here, cyclization of the highly reactive protioiminium ion followed by rearomatization would regenerate the Brønsted acid cocatalyst (Rebekka and Eric, 2009). Dina *et al*., prepared 2,3,4,9-tetrahydro-1H-*β*-carboline-3-carboxylic acid methyl ester **62**, a key intermediate in the synthesis of Tadalafil **15** where the PSR occurs concomitantly with the esterification of the carboxylic moiety, with further advantage in using the less expensive D-Trp-OH **41** instead of its methyl ester using an inorganic acid (HCl) which is easily available, low cost, industrially applicable and easily handling (Scheme 14) (Dina *et al*., 2010).

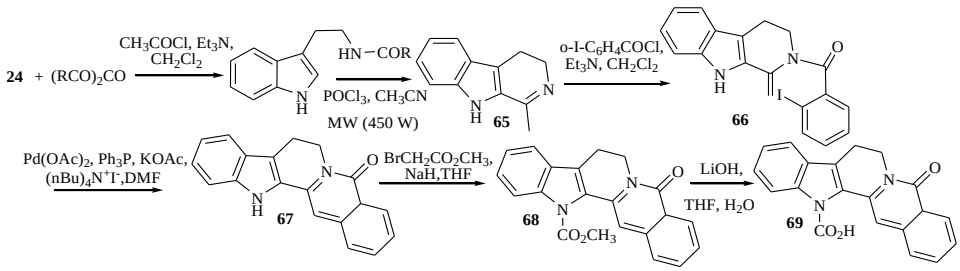
3.2. Bischler-Napieralski Cyclization Reaction

Bischler-Napieralski reaction/cyclization (BNR) is another plausible and classical reaction for TH*β*Cs formation from *β*-indolylamides **64** after the acylation of tryptamine **24** where the cyclization starts from tryptamides **64** (Scheme 15) and usually requires reagents that are harsh, dangerous and difficult to handle, for example $POCl_3$ (Kayed *et al*., 2002) and/or P_2O_5 (Chen *et al*., 2010) in benzene or toluene at high temperature. The first product of the BNR is a DH*β*C **3**, followed by reduction to form the corresponding TH*β*C **2**. However it is an established classical protocol, the synthetic methods of TH*β*Cs using BNR have been reported very rarely since the reaction involves multi steps, results in poor yields (Thokchom and Okram *et al*., 2016), often-long reaction times, harmful and toxic catalysts, tedious workup, and production of great amount of wastewater (Adrienn *et al*., 2006).

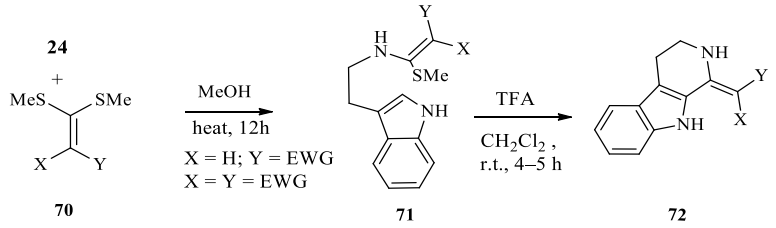
In order to overcome these problems, researches have been conducting using a modified reaction conditions either by using different dehydrating reagents, microwave irradiation (Bikash et al., 2004), and suitable catalysts such as T3P® reagent (Peter *et al*., 2016), zeolites (Adrienn *et al*., 2006). In 2000, Francisco *et al*., disclosed the first report on MW accelerated Bischler-Napieralski reaction which have been used in the syntheses of heterocycles **67** and **69**. Here, the acylation of the imine **65** with *o*-iodobenzoyl chloride produce the enamide **66**, which was submitted to a Heck reaction to furnish the target heterocycle **67** (Scheme 16)(Francisco *et al*., 2000). In addition, Sriparna *et al*., (2005) have developed a synthesis of novel functionalized enamines **72**. The desired N,S-acetals **71** were easily accessible in high yields via direct displacement on the appropriate polarized ketene dithioacetals **70** with tryptamine **24** in refluxing ethanol (Scheme 15 a). However, attempted Bischler-Napieralski type intramolecular cyclization of the N,S-acetals **71** in the presence of various Lewis/protic acids ($SnCl_4$, H_3PO_4 or PTSA) under varying conditions furnished only complex mixtures of products. Here, the TFA/CH_2Cl_2 combination was found to be the best in terms of yields, cleaner work-up and isolation procedure (Scheme 17) (Sriparna *et al*., 2015). Similarly, Thokchom and Okram reported a novel 1-substituted tetrahydro-*β*-carbolines by cyclocondensation of ketene S,S-acetals **73** with tryptamine **24** in $InCl_3$ and TFA by Bischler-Napieralski cyclization. Based on the established classical mechanism of Bischler-Napieralaski, the electron rich nitrogen atom of tryptamine attack the electrophilic carbon of ketene S,S-acetal, thereby forming a new C-N bond initially. Finally, the elimination of one molecule of methanethiol may generate



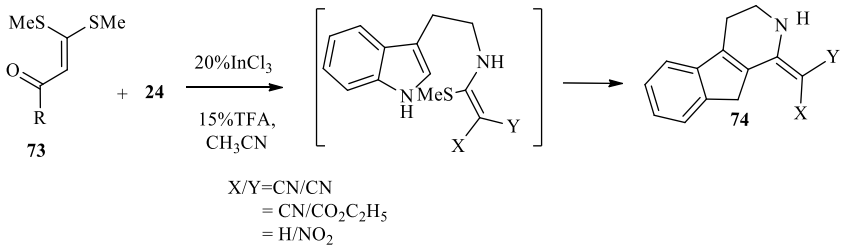
Scheme 15: The general reaction scheme for Bischler-Napieralski reaction/cyclization.



Scheme 16: Microwave-accelerated Bischler-Napieralski reaction to afford **69**.



Scheme 17: Synthesis of **71**.



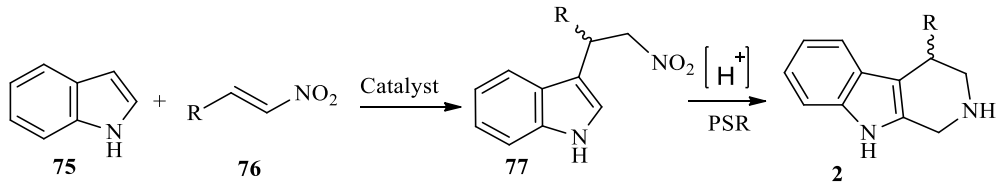
Scheme 18: Synthesis of **74**.

an iminium intermediate and a subsequent intramolecular electrophilic elimination of one more molecule of methanethiol gives the final desired product **74** (Scheme 18) (hokchom and Okram, 2016).

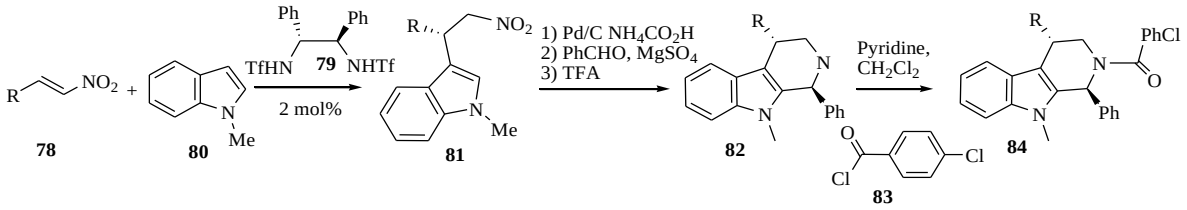
3.3. Micheal addition: Friedele-Crafts allylation of indoles with nitroalkene

The Friedel-Crafts (FC) reaction of aromatic compounds with electron-deficient alkenes is used widely in synthetic organic chemistry (Prashant *et al.*, 2016; Ren-Jin *et al*., 2018). Particularly, FC reaction of indoles **75** with various electrophiles is one of the most straightforward methods to afford indole derivatives and much effort has been expended. In this regard, the FC alkylation between indoles (nucleophiles) and *β*-nitroalkenes **76** (electrophile) being promoted by metal complex ligands (Pradeep *et al*., 2007), Lewis acids (Xiang *et al*., 2011) and/or organcatalysts is significant as it gives access to indole-based alkaloids such as TH*β*Cs **2** (Keiji *et al*., 2014). FC adduct **77** is further reduced to amine to give a cyclized product **2** (Scheme 19).

However, the construction of TH*β*Cs with substitution at positions 1 and 3 can be conveniently obtained by using the PS cyclization from tryptamine **24** and tryptophan **41** respectively, obtaining 4-functionalized TH*β*Cs remains more challenging. One merit of Friedel-Crafts alkylation of indoles with nitroalkene is to give 4-substitiuted TH*β*Cs. In 2005, the enantioselective Friedel-Crafts addition of indoles to nitro-olefins using chiral hydrogen-bonding bis-sulfonamides as the catalysts has been developed by Wei and his co-workers (Wei *et al*., 2005). It was showed that without catalyst no reaction was observed between *β*-nitrostyrene **78** and N-methyl indole **80** and proceeded with good yield and moderate enantioselectivity for nitrostyrene having electron-withdrawing groups (R= *p*-Br-Ph, *o*-NO_2-Ph). However, introduction of electron-rich substituents on the phenyl group in the nitrostyrene resulted in lower enantioselectivity (R= *o*-OMe-Ph) (Scheme 20).



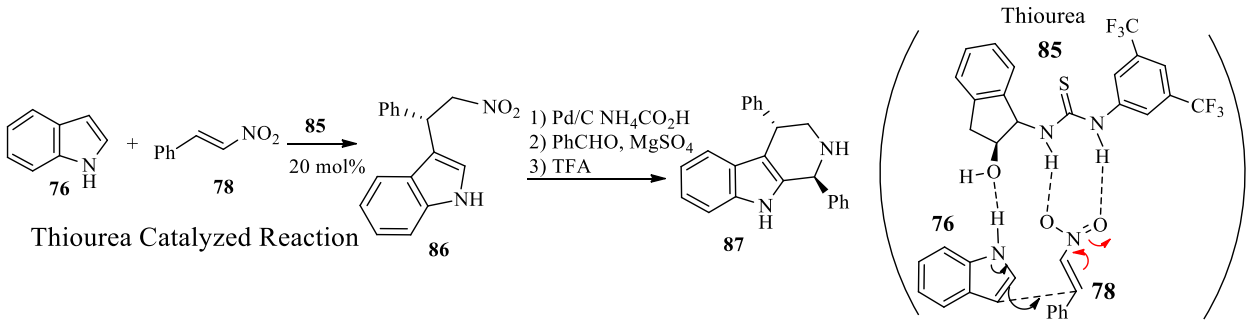
Scheme 19: Friedel-Crafts alkylation of indoles with nitroalkene to give tetrahydro-*β*-carboline **2**.



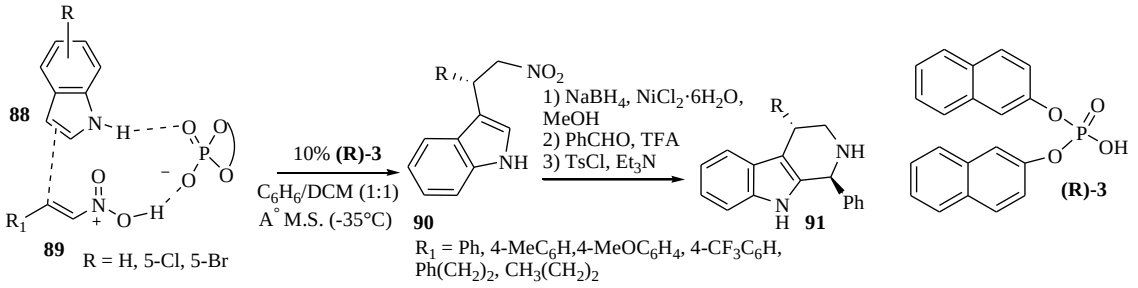
Scheme 20: 1,2-diphenyltrifluoromethanesulfonamide **79** catalyzed FC reaction to afford **84**.

In the same year, Raquel *et al*., synthesized previously unreported 1,4-diphenyl-substituted TH*β*C using thiourea **85** catalyzed FC alkylation. The study revealed that thiourea promote the FC additions of indoles **76** to nitroalkenes **78** by forming a reversible complex involving a double hydrogen bond between the thiourea hydrogen atoms and the two oxygen atoms of the nitroalkene (Scheme 21). Recently, the detailed reaction mechanism of aminoindanol based thiourea derivative containing bifunctional organocatalyst **85** was reviewed by Isaac group in 2016 to develop organocatalytic enantioselective FC alkylation of indoles, employing nitroalkenes as versatile electrophile (Isaac *et al*., 2016).

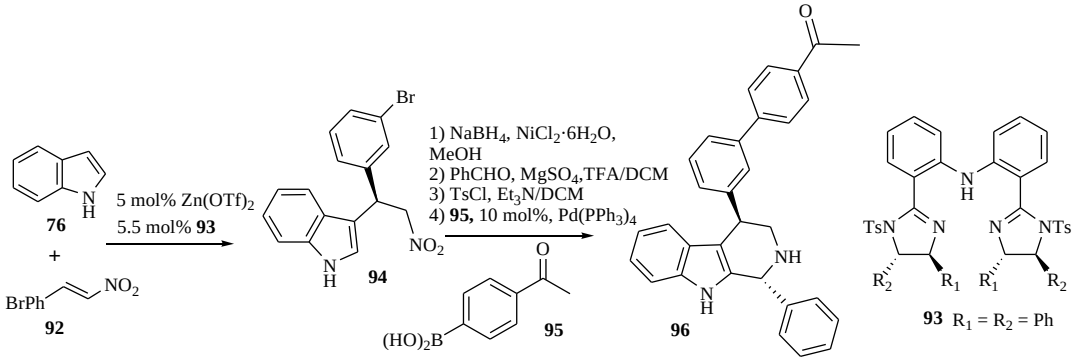
The first Chiral phosphoric acid (R)-3 reported by Junji *et al*., to provide the best enantioselectivity in the Friedel-Crafts alkylation of indole **88** with nitroalkene **89** (2equiv) bearing electron-donating, electron-withdrawing, and hetero-aromatic groups underwent the Friedel-Crafts alkylation reaction to afford Friedel-Crafts adducts **90** with excellent enantioselectivitie in benzene/DCM (1:1) at -35°C transforming into amine and 1,2,3,4-tetrahydro-*β*-carboline derivative **91** (Junji *et al*., 2008). In this catalysis, the phosphoric acid activates the nitro moiety and at the same time the phosphoryl oxygen atom forms a hydrogen bond with the hydrogen atom of the indole N-H moiety wherein the phosphoric acid worked as a bifunctional catalyst (Scheme 22). The detailed reaction mechanism of chiral Bronsted acid catalyzed FC type reactions of indole and its derivatives with various carbon-centered electrophiles (electron deficient olefins, carbonyls, and imine) was briefly reviewed (Pinaki *et al*., 2014).



Scheme 21: Friedel-Crafts alkylation of indoles **76** with nitroalkenes **78** catalyzed by thiourea **85** to provide TH*β*C **87**.



Scheme 22: Chiral Brønsted acid catalyzed FC alkylation of indoles with nitroalkenes.



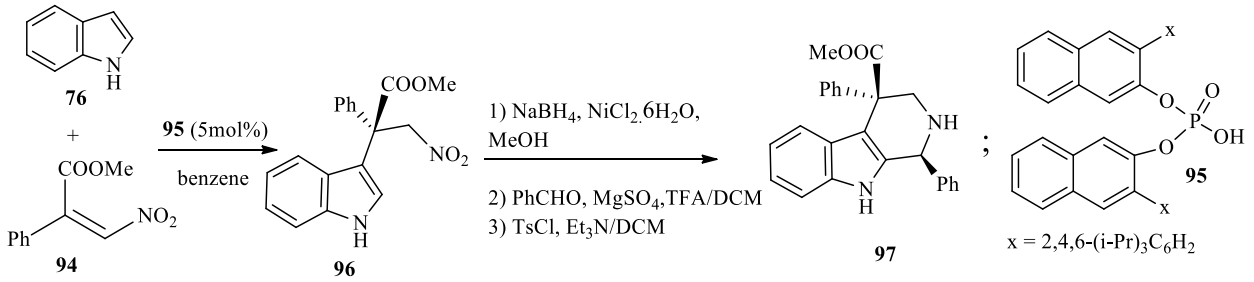
Scheme 23: Asymmetric FC alkylation of indole **76** with nitroalkenes **92** to give tetrahydro-*β*-beta carboline product **96**.

In additions, novel ligands were used as a promoter in the asymmetric Friedel-Crafts alkylation of indole derivatives with nitroalkenes to afford TH*β*Cs. For example, in 2010, Han and Da-Ming designed and tested for the asymmetric Friedel-Crafts method thus provides a way for the construction of a chiral 1,2,3,4-tetrahydro-*β*-carboline **96** library (Han *et al*., 2010). In the asymmetric Friedel–Crafts alkylation of indole **76** with nitroalkenes **92**, the complex of ligand **93** with Zn $(OTf)_2$ gave good reactivity and excellent enantioselectivity. The chiral adduct **94** derived from 3-Br-substituted nitrostyrene **92** was transformed to chiral TH*β*C (Scheme 23). The tosylated Pictet-Spengler product further undergo Suzuki-Miyaura coupling with 4-acetylphenylboronic acid **95** gave the desired product 70% yield (97% ee). Interestingly, in 2014, Keiji and his co-workers reported the first example of a chiral phosphoric acid **95** catalyzed enantioselective FC reaction of indoles **76** with *β,β*-disubstituted nitroalkenes **94** (other possible electrophile) proceeded via a 12-membered-ring transition state in which concomitant activation of the indole N-H moiety by phosphoryl oxygen and the nitro group by a Brønsted acidic site is involved. An employment of a nitroalkene having an ester group (electron-withdrawing moiety) at the *β*-position, and the desired products of TH*β*C **97** (Scheme 24) with all-carbon quaternary centers were attained with good to excellent selectivities (up to 97% ee).

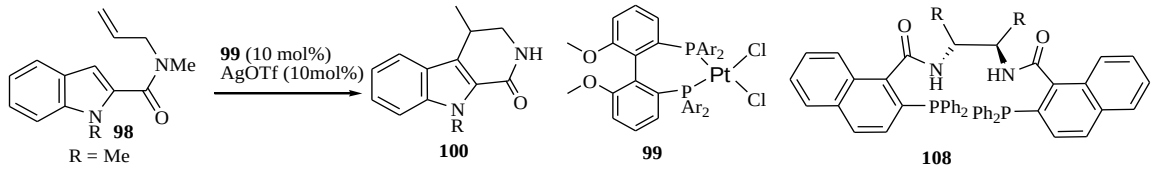
Transition-metal catalyzed Friedel-Crafts-type allylic alkylation reactions of indoles have been proved to be efficient and successful strategies for the synthesis of structurally diverse indolines in good yields (Run-Duo *et al*., 2016). Specially, Friedel-Crafts-type intramolecular allylic alkylation of indole also has been explored as an efficient alternative to the PSR for the synthesis of 4- and 1-substitiuted TH*β*Cs (Marianna *et al*., 2003). The Marco's group extensively described the catalytic and enantioselective Friedel-Crafts allylic alkylation reaction of indoles in the presence of chiral transition metal complexes.

In 2003, Cong *et al*., have developed a mild and effective platinum-catalyzed procedure for the intramolecular alkylation of indoles with unactuated olefins where alkylation of alkenyl indoles involves nucleophilic attack of the indole on a platinum-complexed olefin. For example, reaction of **98** with a catalytic 1:1 mixture of **99** and AgOTf led to the isolation of **100** in 80% yield (Scheme 25) (Cong *et al*., 2003). In another work, Marco *et al*., produced Pd-catalyzed intramolecular cyclized TH*β*C **105** through the formation of intermediate **104** and the synthesis of the key intermediate **103** which was readily accomplished starting from 2-carboxy aldehyde **101** in five steps (Marco *et al*., 2004). Initial attempts of cyclization were performed by treatment of the intermediate **103** with $[PdCl(\pi\text{-allyl})]_2$ /PPh_3 in the presence of Li_2CO_2 /BSA as the base (Scheme 26).

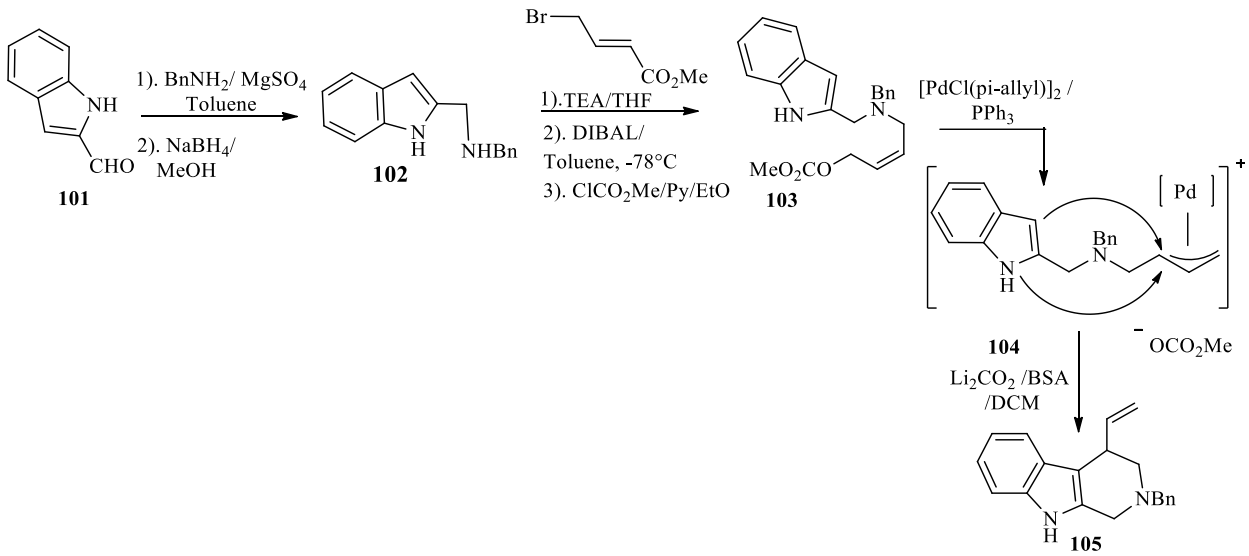
Remarkably, the desired cyclized TH*β*C **105** was isolated, by selective C-alkylation, in 91% yield after 4h at room temperature. Notably, compound **103** underwent Pd-cyclization with exclusive formation of the six-membered ring, stressing the regioselective attack to the internal more hindered position of the η^3-Pd intermediate **104**.



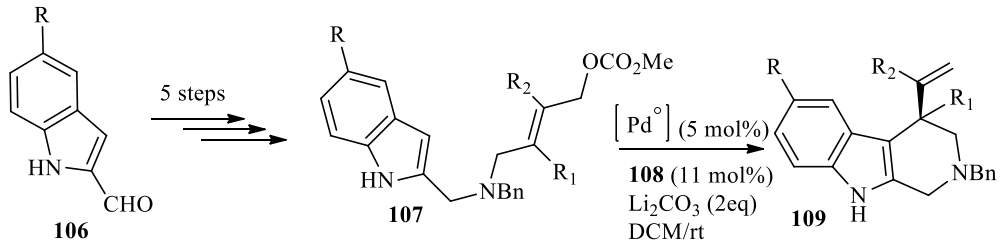
Scheme 24: Enantioselective FC reaction of indoles with β-alkoxycarbonyl-*β*-disubstituted nitroalkenes.



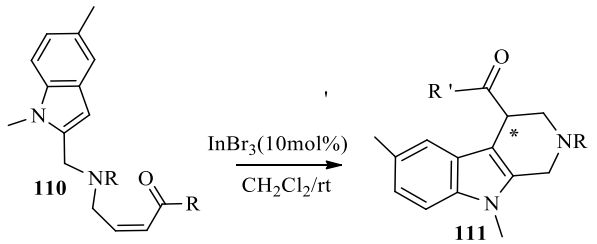
Scheme 25: Pt-Catalyzed intramolecular allylic alkylation of indoles with un-activated olefin.



Scheme 26: Pd-catalyzed intramolecular TH*β*C **105**.



Scheme 27: a) Synthesis of 4-Vinyl-TH*β*Cs **109**.



Scheme 28: $InBr_3$ catalyzed intramolecular FC allylic alkylation.

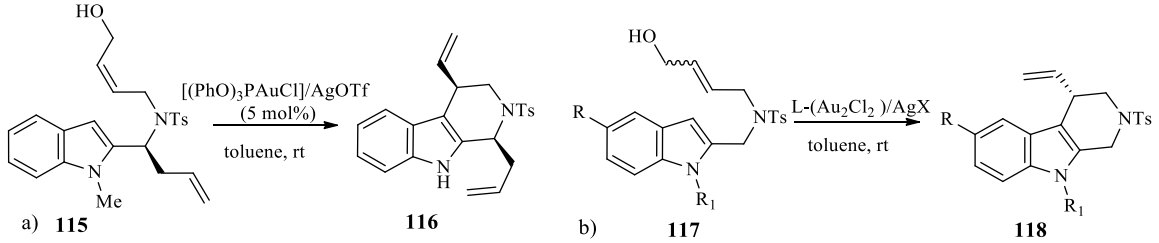
Later, in 2006, Marco and his coworkers investigated a general and mild Pd-catalyzed alkylation of indoles through nucleophilic substitution with allylic carbonates based on the use of intramolecular Pd-catalyzed asymmetric allylic alkylation for the synthesis of 4-vinyl-TH*β*Cs. The precursor (E)-5-substituted indolyl carbonates **107** were prepared from the corresponding aldehydes **106** in five steps. The Pd-catalyzed cyclization of **107** in the presence of ligand **108** provided 4-vinyl-TH*β*Cs **109** (Scheme 27) (Marco *et al*., 2006). In addition to the transition metal catalyzed cyclization, several Lewis acids (LA) are found to be useful in different cyclization methods. In 2006, Marco's group, reported on the effectiveness of $InBr_3$ in promoting intramolecular FC-type Michael conjugate addition of indole to enones (*α,β*-unsaturated ketones) **110**. Thus, $InBr_3$ proved to be tolerant for several protecting groups and substitution patterns in the cyclized 4-substituted TH*β*Cs **111** products by furnishing excellent yields (70–98%) within a few minutes' reaction time. (Scheme 28) (Marco *et al*., 2006).

Although the synthesis of 4-vinyltetrahydro-*β*-carbolines have been already addressed with carbonate precursors. In 2010, Macro *et al*., extended their scope and apply (Z)-allylic alcohols **115**, which is suitable precursors for the synthesis of *α,γ*-disubstituted-TH*β*C **116** by diastereoselective gold-catalyzed allylic alkylation in the presence of the catalytic system $[(PhO)_3PAuCl]/AgOTf$ (5 mol%) (Scheme 25a). Here, the presence of the free OH group assumed promoted a chelating arrangement with allylic framework over the di-nuclear gold complex by means of linking counterion effect (-OH···X···Au) which was crucial for the accomplishment of the cyclization (Marco *et al*., 2010).

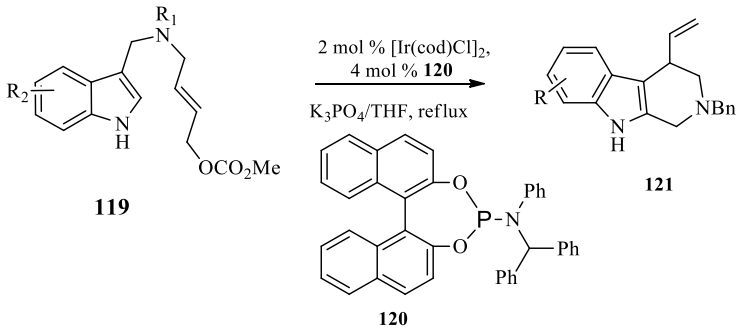
To verify the assumption Macro *et al*., proceeded with the extension of their protocol to the preparation of analogous TH*β*Cs using chiral gold(I) π-Lewis acids for the enantioselective synthesis of vinyl-tetrahydro-*β*-carbolines **118** from **117** by means of direct alkylation of indoles with allylic alcohols. Evidences emphasized the importance of the free OH function in controlling both the chemical and stereochemical courses of the process (Scheme 29) (Marco *et al*., 2011).

In another example, Chun-Xiang *et al*., reported an oxidative addition reaction of **119** to generate an Ir(III)-π-allyl complex **122**. The Ir(III)-π-allyl moiety undergoes nucleophilic attack by the indole C-3 with the assistance of a base, leading to the formation of dearomatized spiroindolenine intermediate **123**, which is converted to the corresponding product **121** after aromatization (Scheme 30) (Chun-Xiang *et al*., 2013). Here, the study of the reaction mechanism led to a successful discovery of an unprecedented dearomatized spiro intermediate and an *in-situ* migration pathway (Scheme 31, path a). Indeed, however 6-*endo-trig* cyclisation (Scheme 31, path b) might seem more probable for the Pictet-Spengler cyclisation producing TH*β*Cs (Semenov *et al*., 2005), spiroindolenine compounds were proposed as the intermediates in some cases (Xiao *et al*., 2013).

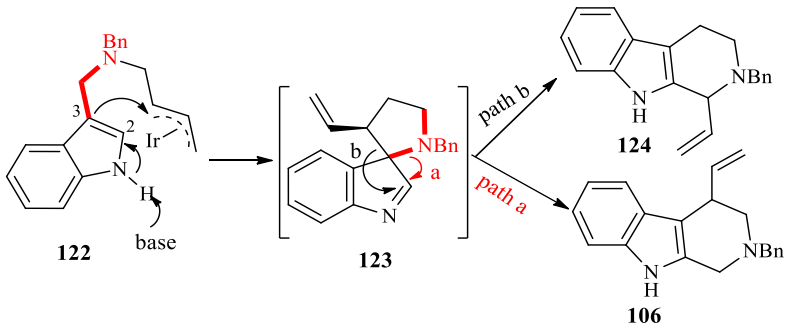
In support of this fact, Ze-Peng *et al*. describe a ruthenium **126**-catalyzed intramolecular allylic dearomatization/migration reaction of indoles and the isolation of a 5-membered spiroindoline **127** to support the dearomatization/migration pathway to afford 4-substitiuted TH*β*C **128** in good to excellent yields (Scheme **32**) (Ze-Peng *et al*., 2014).



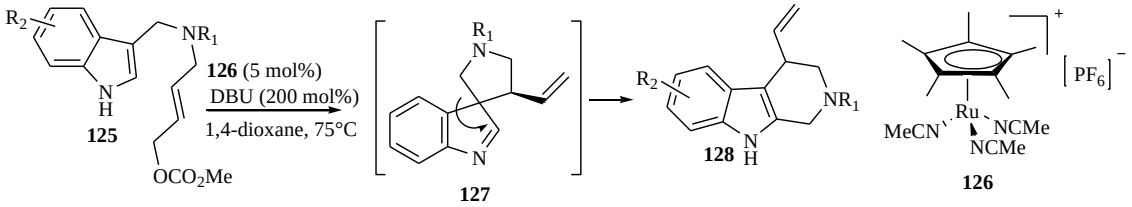
Scheme 29: a) Gold-catalyzed diastereoselective synthesis of TH*β*Cs **116** by intramolecular allylic alkylation. b) Intramolecular asymmetric allylic alkylation of **117** to afford TH*β*Cs **118**.



Scheme 30: Ir-catalyzed intramolecular asymmetric allylic alkylation reaction.



Scheme 31: Plausible Reaction Pathway.



Scheme 32: Synthesis of 4-substitiuted TH*β*Cs **128**.

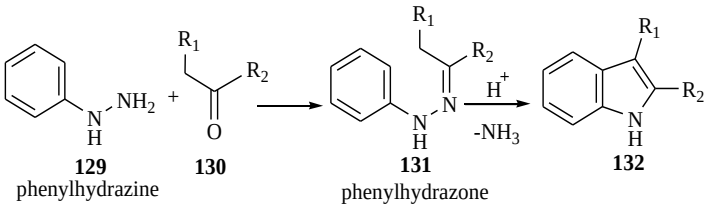
3.5. Fischer-indole reaction

The Fischer indole synthesis (FIS) is a classical and the most widely used method for indole scaffolds based natural and synthetic products. David, and Majid *et al*., extensively reviewed the reaction protocol and the total synthetic products using FIS (David 1993; Majid *et al*., 2017). From the various indole-based products, TH*β*Cs (via the formation of fused pyrrole moiety, ring B, Fig. 1) has been reported well (Nauzer *et al*., 2006; Berthold *et al*., 2007). Previously discussed approaches involve cyclization of tryptamine, tryptophan, or allylic indole (fused ring A and ring B together) whereas FIS involves late-stage indole introduction. The FIS converts ayrlhydrazones **131** of aldehydes or ketones **130** into indoles **132** in the presence of an acid catalyst (Jie *et al*., 2006; Khara and Mukherjee, 2015).

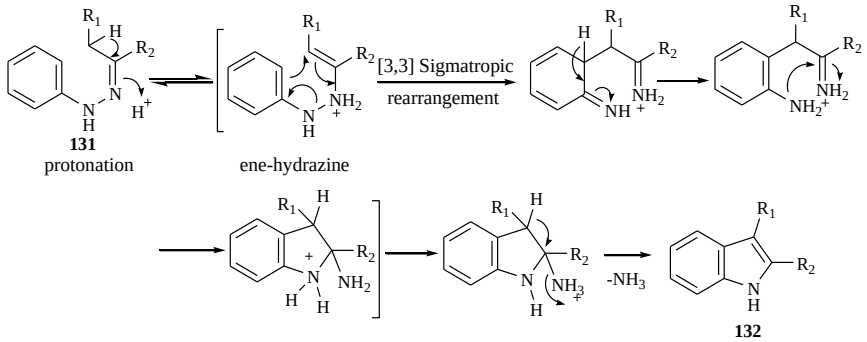
In a very early report by Richard *et al*., Fischer indole cyclization was employed for the synthesis of tetracyclic TH*β*C **134**. It was accomplished based on HCl-catalyzed Fischer indole reaction with phenyl hydrazine **129** which cleanly afforded deformyl-isogeissoschizine **134** in 64% isolated yield from ketone **133** (Scheme 35) (Richard *et al*., 2002

Two years later, Bipul *and* his co-workers described the synthesis of a novel fused TH*β*Cs, quinazolino-*β*-carboline-5-one derivatives **138** using FIS as shown in Scheme 36. The main intermediate, the formation of substituted TH*β*C **136** was prepared from substituted hydrazone **135** by using formic acid as acidic catalyst (Bipul *et al*., 2004). The TH*β*C was then treated with substituted anthranilic acid derivatives **137** in the presence of $POCl_3$ in toluene under reflux to provide the products **138** in almost 80-90% yield.

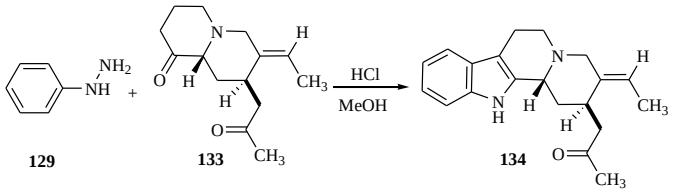
Another report on the synthesis of a series of tetrahydro-β-carboline-1-one 142 was accomplished based on Fischer indole reaction starting from substituted aniline 139 by Jiang-Ping group. Here, compound 140 was reacted with a diazonium intermediate derived from substituted aniline 139 to generate hydrazone 141, which was refluxed in formic acid to provide a β-carboline analog 142 (Scheme 37) (Jiang-Ping et al., 2007).



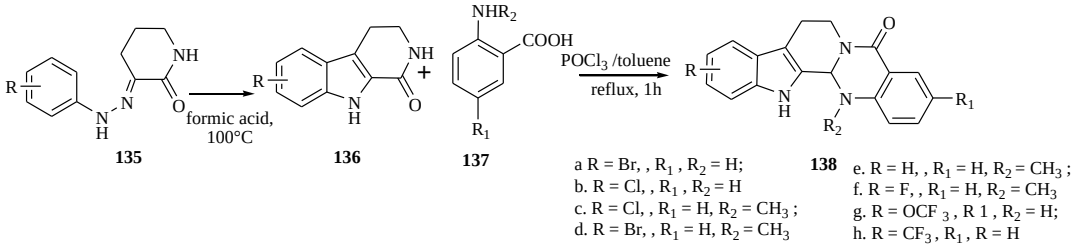
Scheme 33: General reaction for Fischer indole synthesis.



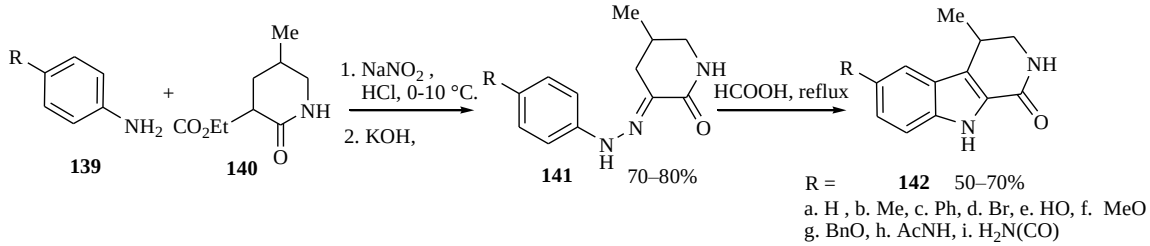
Scheme 34: The reaction mechanism for Fischer indole synthesis.



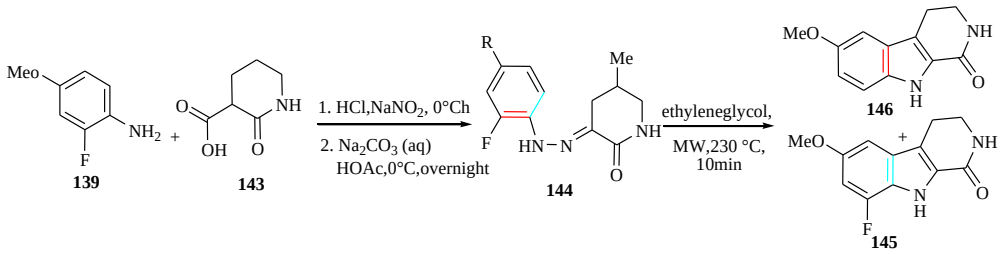
Scheme 35: HCl-catalyzed Fischer indole synthesis to afford tetracyclic THβC **134**.



Scheme 36: Synthesis of novel quinazolino-β-carboline-5-one derivatives **138** using FIS.

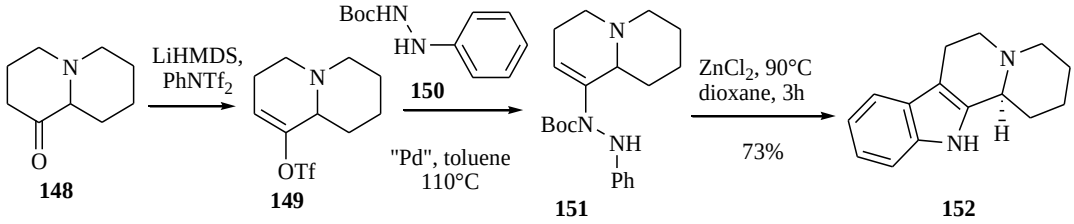


Scheme 37: 6-substitiuted-4-methyl-1-oxo-1,2,3,4-terahydro-β-carboline.

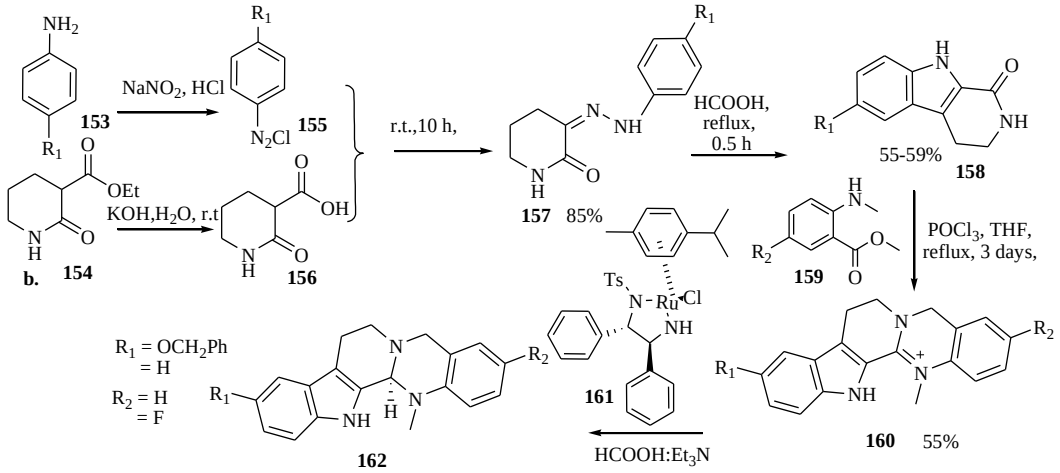


Scheme 38: MW-assisted synthesis of fluorinated and non-fluorinated TH*β*Cs using FIS.

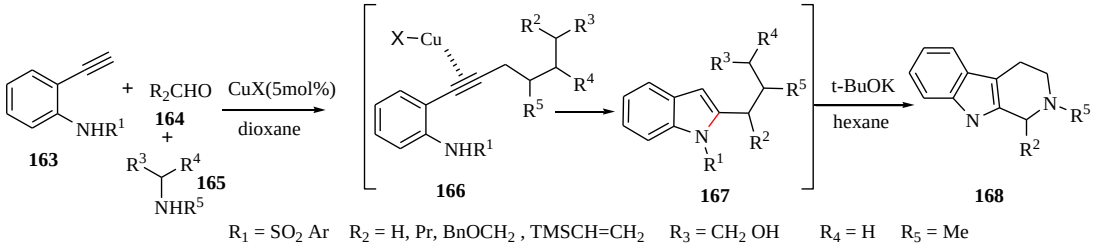
In 2006, Jorge *et al*. reported two possible sites for new carbon-carbon bond formation by FIS during cyclization of fluorinated hydrazone. Here, under MW conditions, Fischer cyclization of hydrazone **144** from 2-fluoro-4-methoxy aniline **139** via diazonium intermediate produces 8-fluoro-6-methoxy-1-oxo-1,2,3,4-terahydro-*β*-carboline **145** (yield, 34%). But, unexpected and comparable amount of non-fluorinated carboline 6-methoxy-1-oxo-1-4-terahydro-*β*-carboline **146** (yield, 32%) was accompanied. Thus, the cyclization also occurred on the fluorine-substituted position, with loss of fluorine (Scheme 38) (Jorge *et al*., 2006). In another work, Byeong-Yun *et al*. have demonstrated that enol triflate **149** prepared from the corresponding bicyclic ketone was readily coupled with aryl hydrazide **150** to give ene-hydrazide **151** in good yield. Here, the resulting ene-hydrazide undergoes the Fischer indolization reaction, affording the corresponding natural product desbromoarborescidine A **152** in 73%. According to the study, among the Lewis acids used, $ZnCl_2$ provided the best results when heated in 1,4-dioxane under reflux (Scheme 39). Recently, Zhen-Gang group reported the total synthesis of Evodiamine derivatives (multi-targeting antitumor lead compound) using FIS. The key TH*β*-carboline intermediates **158** were synthesized by reacting **155** with **156** under Fischer indole synthesis protocol, followed by treating with HCOOH at reflux. In the presence of $POCl_3$, intermediates **158** were reacted with methyl 2-(methylamino) benzoate **159** to afford the dehydroevodiamine derivatives **160**. Finally, asymmetric catalytic hydrogenation of **160** by catalytic RuCl[(S,S)Tsdpen](p-cymene) **161** gives Evodiamine derivatives **162** (Scheme 40) (Zhen-Gang *et al*., 2015).



Scheme 39: $ZnCl_2$-catalyzed Fischer indolization reaction to **152** from enol triflate **149**.



Scheme 40: Synthesis of evodiamine derivatives **162** via FIS.



Scheme 41: One-pot three synthesis of tetrahydro-*β*-carbolines using t-BuOK.

3.6. Simultaneous pyrido[2,3-b]indole ring formation

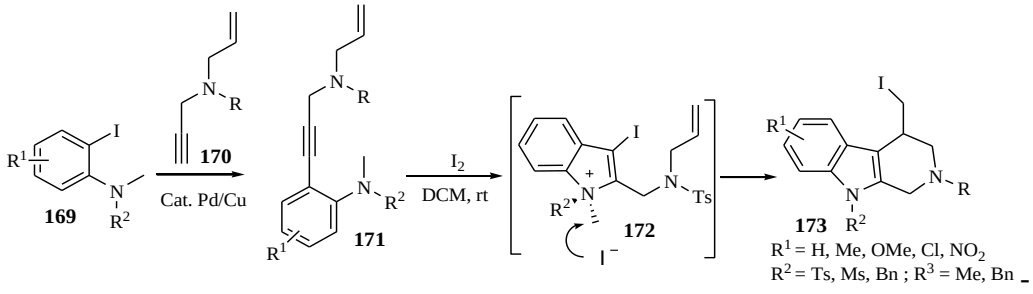
The simultaneous construction of the three rings of the The simultaneous construction of the three rings of the TH*β*C core is difficult to achieve efficiently from a naked scaffold. This reaction follows *via* catalytic cascade reactions to form concurrently fused indole-pyridines rings, pyrido[2,3-b]indole (Veerababurao *et al*., 2018; Kimio et al., 2010; Daisuke *et* al., 2012; Jonathan *et al*., 2015). In 2011, Ohta *et al*., generated by copper-catalyzed indole formation TH*β*Cs **168** *via* a Cu-catalyzed domino three-component coupling-cyclization reaction using ethynylanilines **163**, aldehydes **164** and secondary amines **165**. This was achieved by a second cyclization at the C-3 position followed by t-BuOK/hexane mediated cyclization of intermediate 2-(aminomethyl)indole **167** (Scheme 41) (Ohta *et al*., 2011).

Hongjian *et al.*, described an iodine-mediated domino electrophilic cyclization reaction of substituted 2-(3-(Allylamino)prop-1-ynyl)anilines **171** for the preparation of 4-iodomethyl substituted tetrahydro-*β*-carbolines **173** (yield, 90-95%). First, compound **171** was readily prepared by Sonogashira coupling of the **169** and corresponding alkyne **170.** Here, the iodine served as a Lewis acid, coordinates to the triple bond to promote cyclization which produces the intermediate **172** followed by the removal of the alkyl group by iodide via an S_N2 reaction and final cyclization (Scheme 42) (Hongjian *et al*., 2013).

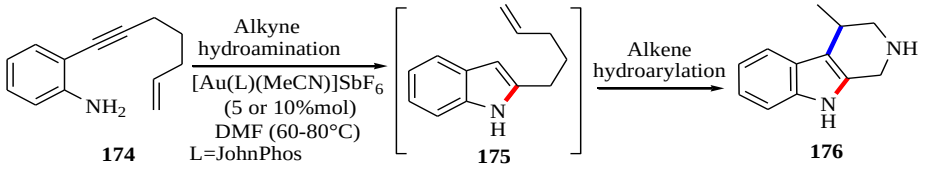
Recently, in 2015, Ana and his co-workers explored the gold-catalysed hydroaminative/arylative cascade cyclization of 2-aminoaryl-1,7-enyne **174** as an expeditious route to 2,3-fused indole rings **176** via unactivated alkene and 1,3-unsubstituted indole intermediates **175** (Scheme 43)

4. Biological Activities of TH*β*Cs

β-Carboline alkaloid and its saturated analogue (DH*β*Cs and TH*β*Cs) are common structural motifs in natural products and pharmaceuticals originally isolated from *P. harmala* L. and found to exhibit various biological activities. Specifically, TH*β*Cs derivatives have attracted attention because of their biological and pharmaceutical properties such as antimicrobial (Ida *et al*., 2016; Bruno *et al*., 2019), antioxidant (Gerard et al., 2017), anticancer, antimalarial (Kurzawa *et al*., 2015), anti-inflammatory (Maria *et al*., 2012), and anti-leishmanial activities (Sudhakar *et al*., 2014). Therefore, in view of growing importance of various THβC derivatives, this review has attempted to present brief



Scheme 42: Iodine-mediated domino electrophilic cyclization to tetrahydro-*β*-carbolines **175**.



Scheme 43: Gold(I)-catalyzed synthesis of 2,3-fused indole derivatives **176**.

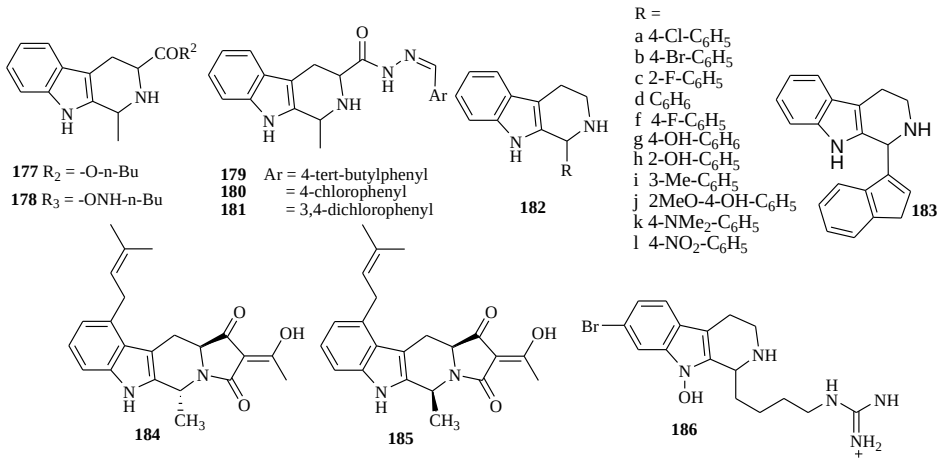


Figure 3: Chemical structure of active antimicrobial tetrahydro-*β*-carboline derivatives.

account of recently reported TH*β*C alkaloids and their bioactivities mainly over the period of 2014-2020.

4.1. Antibacterial Activity

In 2014, Hong-jian group reported the activity of a series of tetrahydro-*β*-carboline-3-carboxylic acid derivatives and the compound **177** exhibited more than 70% fungicidal activities against 14 kinds of phytopathogens at 50 mg/kg. The study showed that, the compound containing butyl ester **163** on 3-position was much higher than that of compound containing N-butylamide **178** on 3-position. In the same year, this group reported the fungicidal activities of tetrahydro-*β*-carboline derivatives containing acylhydrazone moiety (−CONHN=CH−) by adopting the tactics of active fragment stitching and using compound **177** as the lead compound. The result revealed that the derivatives showed good fungicidal activities against 14 kinds of phytopathogens; especially compounds **179**, **180**, and **181** exhibited desirable fungicidal activities against each of the phytopathogens. Additionally, tetrahydro-*β*-carboline derivatives exhibited higher activities than analogues *β*-carboline derivatives (Yongxian *et al*., 2014). In another work, recently reported series of 1-aryl-2,3,4,9-tetrahydro-1H-*β*-carbolines compared the substitution effect on microbial effect on a simple tryptoline **2**. Hence, compounds **182a**, **182f** , **182g**, **182i**, **182j** and **182k** are found to effectively inhibit the growth of microbial cultures of *E. coli, S. aureus, A. niger, and H. oryzae* in good comparison to the standard drug Penicillin and they have successfully improved the activity of basic 2,3,4,9-tetrahydro-1H-*β*-carboline scaffold (Fig. 3)(Gajjala *et al*., 2020).In 2018, Alexandra and Olga, described a more detailed biological profile of the eudistomin U **183** (indole scaffold linked to *β*-carboline; orginally isolated from *Caribbean Lissoclinum* fragile). Hence, it was shown that the Gram-positive bacteria (*S. pyogenes, S. aureus, and M. smegmatis*) were most susceptible to the treatment with the compound **183**. Accordingly, the corresponding IC_{50} values (3.4-6.4 μg/mL) were nearly two-fold more potent than Gram-negative bacteria (*E. coli and P. aeruginosa*; 12.3-27.7 μg/mL) (Alexandra A., *et al*., 2018). Recently, Xuan and Zhanzhu disclosed antibacterial activities of naturally occurring Griseofamine A **184** and its diastereomer 16-epi-griseofamine A **185** for the first time. Griseofamine A **184** exhibited in vitro activities against a panel of drug-resistant Gram-positive bacteria (*S. aureus, S. epidermidis, E. faecalis, and E. faecium*) with MIC values of 8-16 μg/mL. while 16-epi-griseofamine A **185** was 2-3 times more potent than griseofamine A with MIC values of 2-8 μg/mL. The result suggests the crucial role of the stereochemistry in the antibacterial activity (Xuan P. and Zhanzhu L. 2019). Furthermore, Jiayi *et al*. reported the methanol extract of N-hydroxylated 1,2,3,4-tetrahydro-*β*-carboline **186** constituents of the New Zealand ascidian *Pseudodistoma opacum* and tested against a chloroquine-resistant strain (FcB1-Colombia) of Plasmodium falciparum and found to exhibit an IC_{50} value of 3.8 μM (±0.2, n = 3) (Figure 3) (Jiayi W., *et al*., 2015). Currently, however, only a few studies have been published on the antimicrobial activities of *β*-carboline alkaloids in general.

4.2. Anticancer Activity

Since a few years, *β*-carboline alkaloid (*β*C and TH*β*C) ring system has attracted significant attention due to their effective anticancer activities [131-134]. In 2014, Nagula *et al*., synthesized a series of TH*β*C-hydantoin hybrids **173a-173h 186a-h** and evaluated for their anticancer activity against lung (A549), cervical (ME180, HeLa), prostate (PC-3) and breast (MCF-7) cancer cell lines by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Given that

most of tetrahydro-*β*-carboline/hydantoin hybrids showed strong anticancer activities (IC_{50} <20 l M) among which compound **173b 186b** (R_1= OH, R_2= H) displays the highest cytotoxicity (IC_{50} = 6.08 ± 0.2 μM) (Nagula *et al*., 2014). Another study by Ying group in, tetrahydro-*β*-carboline/hydroxylcinnamic acid hybrids linked with different substituted nitrogen-containing heterocycles at the positions-N9 **187** were synthesized and screened for their antitumor activities against six human cancer cells including hepatoma cells (30.08-5.93μM), gastric cancer cells (32.09-6.63μM), colon carcinoma cells (28.36-9.32μM), breast adenocarcinoma cells (24.37-7.76μM), ovarian cancer cells (35.91-8.21μM), and SMMC-7721(31.69-6.45μM). Here, the analysis of SAR revealed that the antiproliferative activities suggested the ED substitutions (OCH_3) on the ferulic acid derivatives were able to confer antitumor activities to these molecules (Ying *et al*, 2014). In the same year, Cong *et al*. reported various 2-benzoyl-1,3,4,9-tetrahydro-*β*-carboline **175a-e** through substitution at different positions to define the SAR resulted in the discovery of potent inhibitors of the transforming growth factor-β (TGFβ) signaling pathway (pivotal oncogenic pathways in most advanced cancers). Among them, compound **188d** (n=1, Ar= phenyl), one of the tested compounds, not only showed potent inhibition of lung cancer cell proliferation in vitro but also strongly suppressed growth of lung cancer and breast cancer in vivo (Cong *et al*., 2014).

Furthermore, novel N-substituted tetrahydro-*β*-carboline-imidazolium salt derivatives **189** were evaluated for their *in vitro* antitumor activity against a panel of human tumor cells lines (HL-60, SMMC-7721, A-549, MCF-7, SW480) and proved to be potent antitumor agents. The imidazolium salt derivatives bearing a 2-ethyl-imidazole (12.81-2.77μM), benzimidazole (15.03-3.24μM) or 5,6-dimethyl-benzimidazole ring and a 3-naphthylmethyl or 1-(naphthalen-2-yl)ethan-1-one at position-3 (17-13-2.61μM) of the imidazole ring, were found to be the most potent compounds (Bei *et al*., 2016).

Additionally, in 2016, Samundeeswari group reported C_6- and C_7-substitiuted coumarin TH*β*Cs 190a-g on coumarin moiety and only **190e** (C_7-CH_3**)** and **190f** showed appreciable activity screened for their growth inhibitory activity against 60 human cancer cell lines. Here, C_7-CH_3 substituted coumarin **190e** showed moderate activity with < 50% Growth inhibition (GI) for all human cell lines, whereas, compound **190f** (R= 5,6-Benzo) exhibited better activity with > 50% GI for nearly 15 cell lines which included renal cancer cell lines. The study concluded that substituent at C_6 and C_7 positions on coumarin enhances the anticancer activity (Samundeeswari S., *et al*., 2016). Recently, this Samundeeswari group again comes up with a promising anticancer TH*β*C-hybrid due to their inhibition of DNA topoisomerase or CDK. Among these phenyl-1,4-bis-TH*β*Cs the racemic mixture **191** which shows a broad spectrum of growth inhibition with GI_{50} values ranges from 1.0 μM to 4.5 μM against most of the cancer cell lines (45 cell lines out of 60) (Figure 4).

4.3. Antioxidant Activity

Oxidative stress (which cause the generation of Reactive Oxygen Species, ROS), *β*-amyloid (A*β*) deposits, mitochondrial dysfunction, and low levels of acetylcholine has been implicated as a core contributor

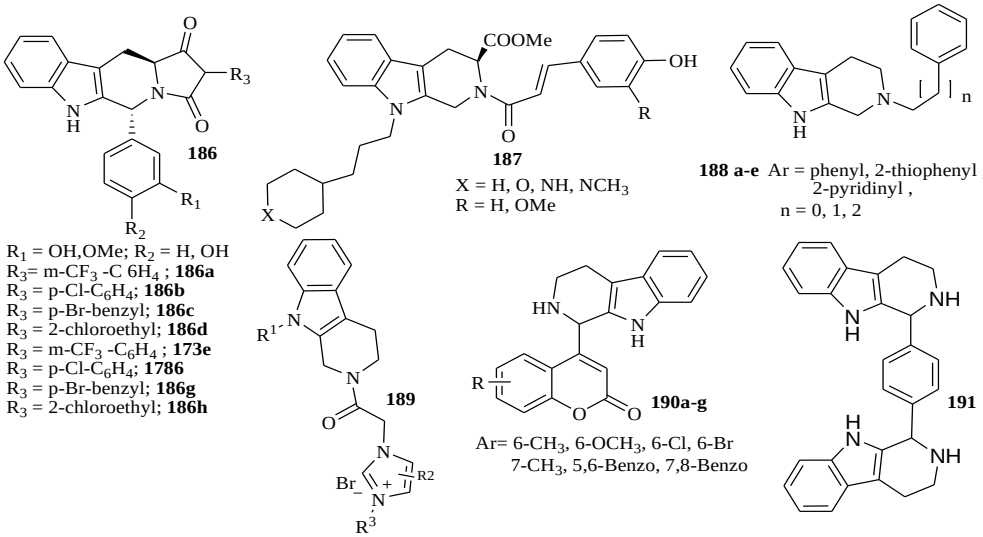


Figure 4: The chemical structure of active anticancer compounds.

to the initiation and progression of multiple neurodegenerative diseases including Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson disease (PD), multiple sclerosis (MS) and stroke (Jonica *et al*., 2016; William *et al*., 2017). Here, the pathogenesis of several neurodegenerative diseases, including PD, AD, and MS involving the generation of reactive oxygen species and the properties of antioxidants are extensively reviewed (Miguel *et al*., 2015; Grace *et al*., 2017) Studies have also shown that natural and synthetic TH*β*Cs possess a wide range of antioxidant activity (Il *et al*., 2016; Teik *et al*., 2015; Hui-Fang *et al*, 2017; Xiaoming *et al*., 2017).

In 2016, Nicole *et al*., evaluated TH*β*Cs for their radical scavenging activity by monitoring their interaction with 2,2-diphenyl-1-picrylhydrazyl (DPPH). Here, compounds **192a-e** (EC_{50} = 9.17-3.17), **f** (EC_{50} = 1.83) and **g** (EC_{50} = 1.82) revealed radical scavenging activity, ranging from 50% to 74% compared to that of *α*-tocopherol (Nicole *et al*., 2015). Based on the topology of the active site of cholinesterases and other target proteins involved in the pathogenesis of AD, Gerard *et al*., have synthesized tacrine-trolox and tacrine-tryptoline hybrids with various linker chain lengths. The result discovered that free radical scavenging activities (studied using 1,1-diphenyl-2-picrylhydrazyl, DPPH) were not significantly affected by varying linker chain lengths and the hybrid compound containing the tryptoline moiety linked with a 7 carbon spacer to tacrine **193** displayed the best AChE and BuChE inhibitory activity (IC_{50} = 17.37 and 3.16nM). With same concept, Yifan *et al*., synthesized bivalent *β*-carboline derivatives modified by several series of hydrophobic moieties as potential neuroprotective agents for AD. The result showed **194** (R_1=CH_3, n=2) and (R_1=CH_3, n=3) exhibited the good selectivity potency on butyrylcholinesterase (BuChE) inhibition (IC_{50} =1.7 and 2.7 μM, respectively) and resulted in a marked decrease in cell viability (57.2%) due to the neuroprotective potential of the compounds on H_2O_2-induced oxidative stress on neuronal cell line SH-SY5Y (Yifan *et al*., 2018). Recently, Yihang and his co-workers reported the first *in vivo* (into the striatum of Wistar rats) evaluation of the neurotoxic effects of TaClo **195** causing aggressive PD from the perspective of mitochondrial dysfunction. When the changes in the mitochondrial membrane potential were measured by incubating the tissues with 5,5′6,6′-tetrachloro-1,1′3,3′-tetraethylbenzimidazole-carbocyanine iodide (JC-1 stain), TaClo impairs the function of mitochondrial complex by causing oxidative stress which is known to occur at the early stage of cell apoptosis (Figure 5) (Yihang *et al*., 2019).

Very recently, Ahmad *et al*., described novel TH*β*C, 2-benzoyl-6-methoxy-9-methyl-1-phenyl-1,2,3,4-tetrahydro-*β*-carboline **196**, and evaluated for *in vitro* acetylcholinesterase (AChE) inhibitory activity which showed potential AChE inhibitor with an IC_{50} value of 26.52 ± 0.79 mM (Figure 5) (Ahmad et al., 2020).

4.4. Anti-leishmanial Activity

Leishmaniasis is caused by intracellular protozoan *Leishmania* spp parasites and is considered as one of the most neglected tropical diseases. Due to no effective vaccines, the treatment of leishmaniasis relies on the chemotherapy approach (Dandugudumula *et al*., 2017; Penta *et al*., 2019; Renata *et al*., 2019). From the literature quest, it was revealed that several natural and synthetic product scaffolds, including the class of *β*-carbolines have shown potential anti-leishmanial agents (Shikha *et al*., 2015; Nitin *et al*., 2016).

In 2014, Sudhakar *et al*., identified tetrahydro-*β*-carboline analogs **197a-f** possessing significant antileishmanial activity against *Leishmania donovani* promastigotes. The thiophen-2-yl linked analog **197e** and naphthyl linked analog **197f** were most promising antileishmanial agents, exhibiting IC_{50} values of 9.1 and 22.1 μM, respectively. Similarly, Penta *et al*. screened for 1-phenyl-N2-substitiuted tetrahydro-*β*-carboline derivatives **1981a-p** against both promastigote and amastigote forms of *L. infantum.* Here, the two analogues (R = H, R_1 = CH_3) and (R = *m*-NO_2, R_1 = H) exhibited selective and potent inhibition of amastigotes with IC_{50} values 0.67 and 0.87 mM respectively and potency was comparable with amphotericin B. Here, the SAR study suggested that, substitution on *meta, ortho* positions showed favorable effect, while replacement with bulkier group had minimal effect on activity and *para* substitution was not desirable (Penta *et al*., 2016). In another study, N2-substitiuted tetrazole hybrids 1,2,3,4,9-tetrahydro-*β*-carboline **199a-u** identified as potential antileishmanial chemotypes. From the analogues, compound with (R = 3,4,5 tri-OMe, R_1 = Cyclohexyl) was found to be the most active in the series having IC_{50} = 1.57 ± 0.12 μM. However, in this study, no obvious trend of activity with respect to the substituent was observed. Surprisingly, results obtained from examination of anti-leishmanial potential of tetrahydro-*β*-carbolines-peptide hybrid **200** showed represent a new structural lead for anti-leishmanial chemotherapy. Most of the screened derivatives exhibited significant *in vitro* anti-leishmanial activity against promastigote and intracellular amastigotes (IC_{50} ranging from 2.43 to 7.61 μM) than the control, miltefosine (IC_{50} = 8.2 μM), with less cytotoxicity (Figure 6) (Irfan et al., 2019).

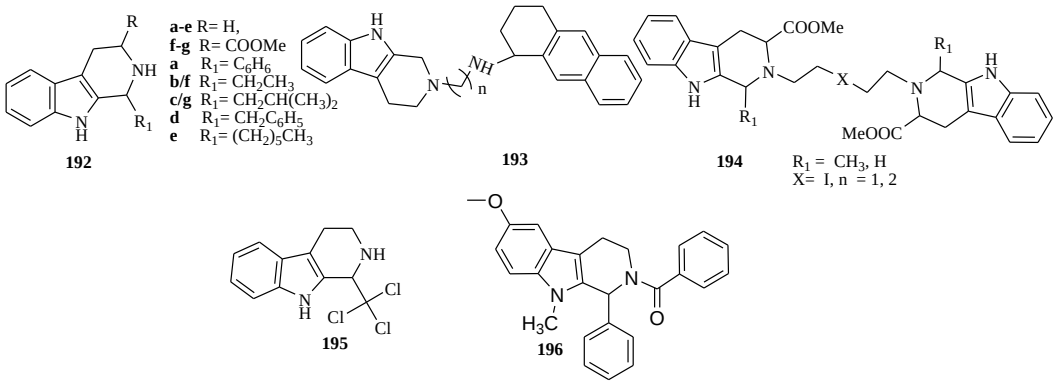


Figure 5: The chemical structure of active antioxidant compounds.

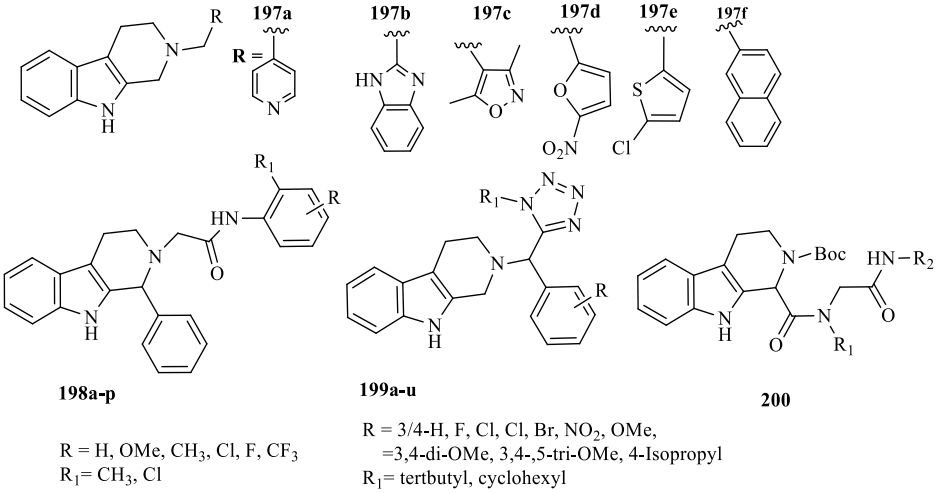


Figure 6: The structure of active antileishmanial compounds.

4.5. Anti-malarial Activity

The *β*-carbolines and TH*β*Cs are also reported to have a very significant anti-malarial activity (Zhong-Ke *et al*., 2015; Haifeng *et al*., 2015; Chalerm *et al*., 2016; Abebe *et al*., 2016). In 2014, Lydia *et al*., evaluated for antimalarial activity of 1,2,3,4-tetrahydro-*β*-carboline analogues against a chloroquine-resistant strain of *P. falciparum*. Amongst the analogues **201a** (9.6 μM) and **201b** (17.2 μM) exhibited either comparable or enhanced antimalarial activity versus the corresponding fully aromatic *β*-carboline structure (Lydia *et al*., 2014). Varun and his co-workers reported *in vivo* antimalarial potency of two novel TH*β*Cs **202a** and **202b** (5 μg/mL) against *Plasmodium berghei*. Based on the results, the compounds were categorized as highly active against the chloroquine (CQ) sensitive (NK-65) strain of rodent malaria parasite *P. berghei* with IC_{50} = 5 μg/mL, a comparable inhibitory activity with the standard drug CQ (10 μM) and leucovorin (5μg/mL) exhibited (Varun *et al*., 2018). Scott *et al*. evaluated a library of tetrahydro-*β*-carboline derivatives **203** by appending various aromatic substitutions in order to make additional SAR study against *P. falciparum*. Among the series, a 5-chloro-TH*β*C derivative (R = Me), displayed modest activity against human cells. According to the SAR study, replacing the methyl group of the lead compound with a phenyl ring (R = C_1-Ph) allows for additional hydrophobic interactions, giving products with improved activity (Scott *et al*., 2010). In additions, Bharvi *et al.* investigated anti-malarial activity of TH*β*C-Quinoline conjugates linked via either 1H-1,2,3-triazole **204a-b** (which has a favorable influence on the anti-plasmodial activity) or a substituted acyl hydrazide-core **205a-b** for their *in vitro* anti-plasmodial evaluation on CQ resistant W2 strain of *P. falciparum*. However, the introduction of hydrazine core not only diminished the activities but also resulted in increased cytotoxicity against mammalian Vero cells (Figure 7) (Bharvi *et al*., 2010).

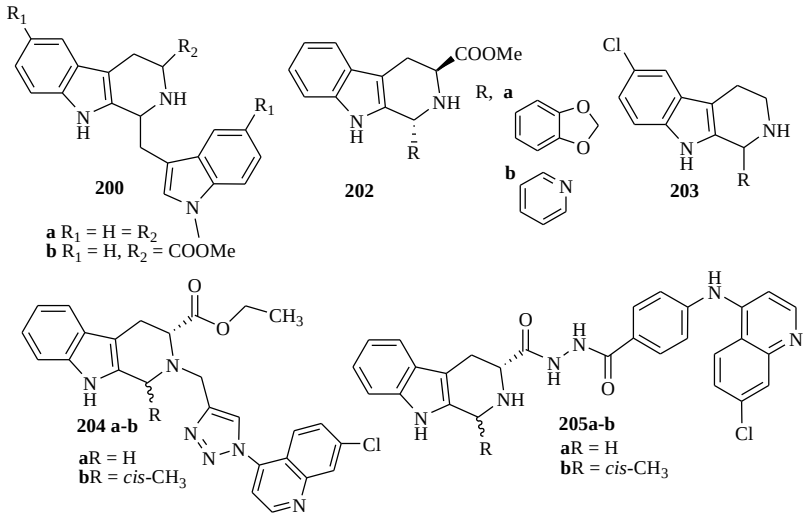


Figure 7: The structure of some anti-malarial compounds.

5. Conclusion

In conclusion, impressive results have been obtained since the discovery of Pictet-Spengler reaction as a route for TH*β*C synthesis, and the scope of the reaction has been greatly extended and over the years, a wide range of synthetic methods have been reported to improve its synthetic efficiency, applying new reaction promoters, a variety of substrates, and position of substitutions etc. Specially, researchers are focusing on the advancement of synthetic design to achieve greener chemistry applying solvent-free, ionic-liquid, and micro-wave assisted syntheses. Besides, new natural and synthetic TH*β*Cs products are continued to be discovered, and the biological activity of candidate TH*β*Cs is likewise being explored. TH*β*Cs and its derivatives have exhibited actually a wide range of biological activities including antimicrobial, anticancer, antioxidant, antileishmanial, and antimalarial which revealed that TH*β*Cs are a candidate drug scaffold in treating diseases.

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