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(REVIEW ARTICLE)

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Tetrahydrocarbazoles as potential therapeutic agents: A review of their synthesis and biological activities

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Abstract

Tetrahydrocarbazoles (THCs) are a remarkable class of compounds characterized by a privileged structural scaffold centered around the natural indole moiety. This extraordinary framework appears in a multitude of naturally occurring pharmacological compounds and alkaloids, demonstrating significant inhibitory activities such as antibacterial effects, protein kinase inhibition, and tumor growth suppression. Given its versatile biological properties, THC consistently the attention of the scientific community.The primary objective of this review is to create a comprehensive reference on the synthesis and biological properties of THCs. In simpler terms, we aim to provide a detailed assessment of various catalysts, including their reaction conditions , synthesis and biological activity This review targets a broad audience interested in understanding the fascinating world of tetrahydrocarbazoles and their impact on medicine and biology .

Keywords: Tetrahydrocarbazole (THcz);substituted 1,2,3,4-Tetrahydrocarbazole ;Structure ;Compound; Biological and Pharmacological Activity; Synthesis

1. Introduction

1,2,3,4-Tetrahydrocarbazole [THCz] is a tricyclic aromatic structure consisting of a five membered pyrrole ring fused with one side benzene ring and other side cyclohexane ring respectively [1-3]. Tetrahydrocarbazole (THCz) structure is majorly present in natural products and biologically active compounds[4-7] (Fig.1). Carbazole itself and 1,2,3,4 – tetrahydrocarbazole 1,2,3,4 – Tetrahydrocarbazole [THCz] derivatives are well known for their pharmacological activities several search for newer physiologically active compounds. They are used in the synthesis of antibacterial and antifungal [4], cytotoxic against cancer cells [5] , Screend for antinociceptive activity[6], antiobestic[7], antidiabetic (type IIdiabeties), antipsychotic activity, and anti-emetic medicine.

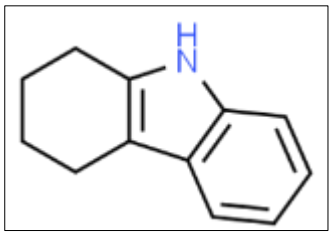

Figure 1 2D Structure of 1,2,3,4-Tetrahydrocarbazole

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A lot of strategy available for the preparation of 1,2,3,4-tetrahydrocarabzole scaffold in literature. However, Fischer indole synthesis approach is most common synthetic method used for the preparation of tetrahydrocarbazole scaffold and also play important role in preparation of various natural products [8,9].

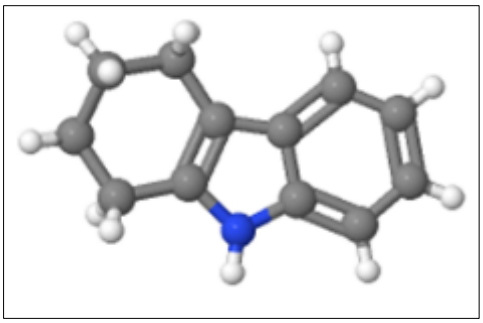

Figure 2 3D Structure of 1,2,3,4-Tetrahydrocarbazole

Various research groups synthesized tetrahydrocarbazoles based on Fischer indole method using starting material phenyl hydrazine and cyclohexanone using conventional, microwave and catalyst approach. In this review article, we covered synthetic methods of 1,2,3,4- tetrahydrocarbazoles based on conventional or microwave or catalyst based on reported review literature.and also mention their pharmacological activity. In 2020, Ajit Nangare et al. and co-workers published the review article on topic synthetic derivatives of aromatic carbazole [10]. TY Chaudhari et al. published in detail on topic various synthetic methods to the preparation of tetrahydrocarbazoles . This review will give researchers to idea in short way to find out the preparation of 1,2,3,4-tetrahydrocarbazoles from conventional approach or microwave method or use of catalyst and mention it pharmacological activity.

2. Synthetic methods to prepare substituted or unsubstituted tricyclic 1,2,3,4-tetrahydrocarbazoles

2.1. Fischer-Borsche reaction for the synthesis of substituted 1,2,3,4-tetrahydrocarbazole

The method involves the condensation reaction of 4-methoxy phenyl hydrazine with substituted cyclohexanone with to form arylhydrazone based on Fischer indole synthesis method which further undergoes sigmatropic rearrangement in the presence of acetic acid/HCl gave substituted 1,2,3,4-tetrahydrocarbazole. [11]

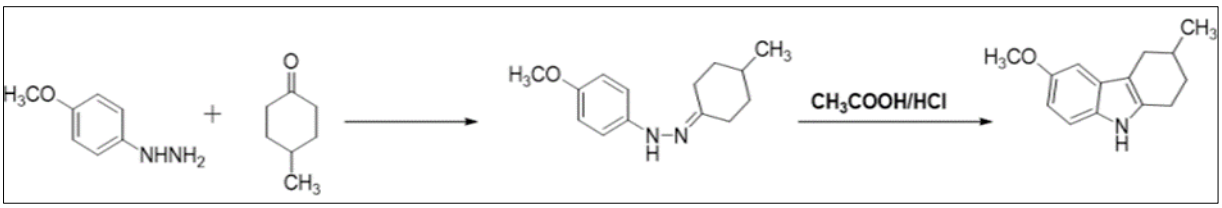

Figure 3 Synthesis of substituted 1,2,3,4-tetrahydrocarbzole

2.2. Borsche-Drechsel cyclization reaction for the synthesis of 1,2,3,4-tetrahydrocarbazole

The acid-catalyzed rearrangement of cyclohexanone phenylhydrazone gives 1,2,3,4-tetrahydrocarbazole [11]

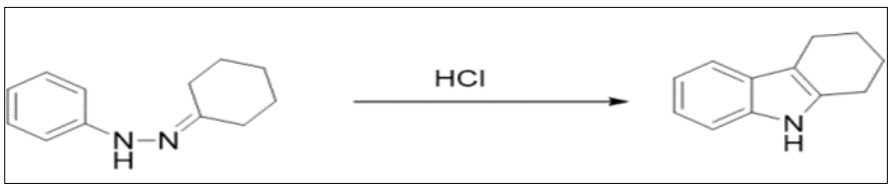

Figure 4 Synthesis of 1,2,3,4-tetrahydrocarbazole

2.3. A Loffler and D. Ginsburg prepared 1,2,3,4-tetrahydrocarbazole from thermal cyclization of the oxime of 2-phenylcyclohexanone

Heating the starting material oxime of 2-phenylcyclohexanone in aqueous ethanol give 1,2,3,4-tetrahydrocarbazole [12]

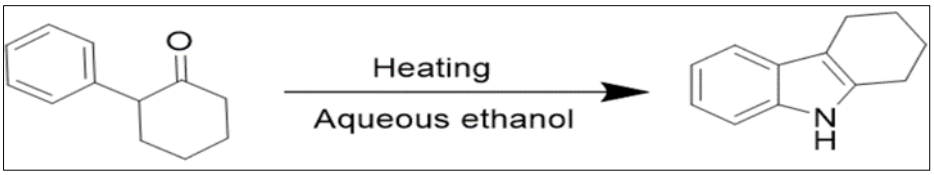

Figure 5 Synthesis of 1,2,3,4-tetrahydrocarbazole

2.4. CU Rogers et al. reported aqueous alcohol- mineral acid method for the preparation of 1,2,3,4-tetrahydrocarbazole

A mixture of 108 g. phenylhydrazine and 1.5 moles of hydrochloric acid was stirred and refluxed while 98 g. of cyclohexanone was added during one hour gave 1,2,3,4-tetrahydrocarbazole. The yield of the reaction was found 95 %.[13]

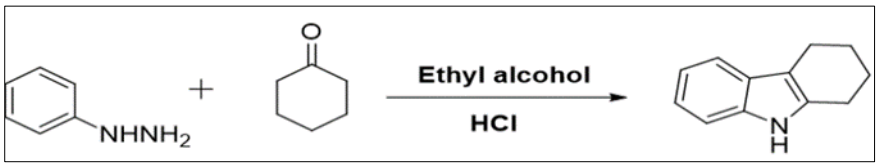

Figure 6 Synthesis of 1,2,3,4-tetrahydrocarbazole

2.5. Vera Barbieri and Maria Grazia Ferlin reported MW assisted synthesis of substituted 1,2,3,4-tetrahydrocarbazoles

Reaction of 2-methoxy-4-nitro-phenylhydrazine with cyclohexanone in the presence of acetic acid was MW irradiation at 100 W at the temperature 1400 C give 6-nitro, 8-methoxy 1,2,3,4-tetrahydrocarbazole. The yield of the product was found 80 %.[14]

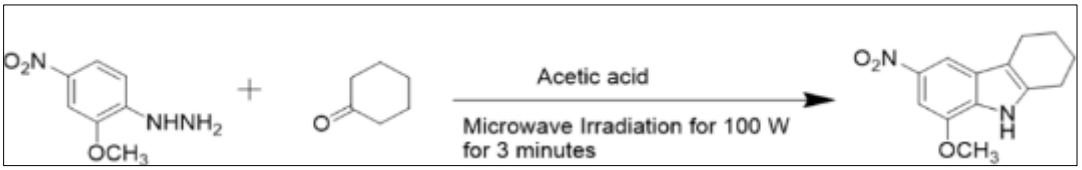

Figure 7 Synthesis of substituted 1,2,3,4-tetrahydrocarbazole

3. Chemistry Of Tetrahydrocarbazole

Tetrahydrocarbazole, a fused heterocyclic compound composed of a carbazole ring system with four saturated hydrocarbon rings, exhibits intriguing reactivity that stems from its unique molecular structure. The carbazole moiety, a tricyclic aromatic system, imparts both aromatic and basic characteristics to tetrahydrocarbazole, influencing its interactions in various chemical environments. The presence of four saturated hydrocarbon rings further contributes to the molecule's versatility. In terms of electrophilic aromatic substitution reactions, tetrahydrocarbazole displays reactivity typical of carbazole derivatives. The aromaticity of the carbazole ring system allows for electrophile attack at positions ortho and para to nitrogen atoms, leading to regioselective substitution. The saturated hydrocarbon rings, although not directly participating in these reactions, provide steric hindrance and affect the overall reactivity by influencing the accessibility of the carbazole ring.[15]

Tetrahydrocarbazole's nitrogen atoms, acting as Lewis bases, make it susceptible to reactions with various electrophiles. This reactivity is particularly evident in Friedel-Crafts acylation and alkylation reactions, where electrophiles attack the nitrogen atoms to form stable carbocation intermediates. The presence of four hydrocarbon rings surrounding the carbazole core influences the regioselectivity of these reactions, often leading to complex product

mixtures. In nucleophilic substitution reactions, the saturated hydrocarbon rings can act as leaving groups under certain conditions, facilitating substitution reactions at these positions. Additionally, the nitrogen atoms in the carbazole ring can undergo nucleophilic attack, leading to the formation of diverse substitution products. The interplay between the carbazole and hydrocarbon components contributes to the overall reactivity in these nucleophilic substitution processes.

The saturated hydrocarbon rings in tetrahydrocarbazole also play a crucial role in hydrogenation reactions. The presence of multiple double bonds in the carbazole ring system allows for selective hydrogenation, providing access to saturated derivatives. This controlled hydrogenation can be influenced by the steric hindrance introduced by the surrounding hydrocarbon rings, resulting in unique hydrogenation patterns.Furthermore, the reactivity of tetrahydrocarbazole extends to oxidative processes. The electron-rich nature of the carbazole ring makes it susceptible to oxidation, leading to the formation of various oxidation products. The presence of the hydrocarbon rings can modulate the oxidation potential of tetrahydrocarbazole, affecting the overall reaction kinetics and product distribution.[16]

In summary, the reactivity of tetrahydrocarbazole is a complex interplay of its carbazole aromatic core and the surrounding saturated hydrocarbon rings. This molecule exhibits versatility in electrophilic aromatic substitution, nucleophilic substitution, hydrogenation, and oxidation reactions. The unique combination of aromatic and aliphatic characteristics renders tetrahydrocarbazole a valuable building block in the synthesis of diverse chemical compounds, making it a subject of interest in organic chemistry research and applications.[17]

4. Pharmacological Activity of Tetrahydrocarbazole

4.1. Pharmacological activities of tetrahydro carbazole derivatives anticonvulsant activity

Anticonvulsant activity can be performed by MES (maximal electroshock method). In the MES method, adult male and female Albino rats (Wistar strain) weighing 100-200 g were used. The animals were divided into three groups (control, standard and test) and each group comprising of three rats. The test compound was suspended in 1% aqueous CMC suspension and was injected i.p. in doses ranging from 15, 30 and 60 mg/kg body weight. Phenytoin sodium was used as a standard drug which was given in the dose of 30 mg/kg by I.P. which was observed to protect 100% against the induced convulsions. The control group received only 1% aqueous CMC suspension. The seizures were induced by electroconvulsiometer.

The animals were subjected to electroshock by delivering the current of 150 ma through the corneal electrodes for a period of 0.2 seconds. The animals were observed for 30 min convulsive responses. Different stages of convulsions i.e. the tonic flexion (towards the upper extremities), tonic extensor phase (extension of the lower extremities), clonic convulsions (intermediate jerking of limbs), stupor (unconsciousness) and recovery or death were observed for each animal. The anticonvulsant effect of newly synthesized compound was assessed by absence or reduction of hind limb tonic extensor phase.

Each value represents the mean SEM (standard error mean) of three rats significantly different from standard drug phenytoin. N-substituted tetrahydrocarbazole derivatives shows potent anticonvulsant activity. Various derivatives like N (4 –Amino Benzoyl) 1,2,3,4-Tetrhydroacabazole has better results.[18,19]

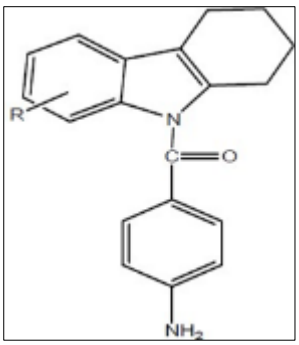

Figure 8 Tetrahydro carbazole derivatives

4.2. Antimicrobial activity Agar well diffusion method

Antimicrobial analysis was followed using standard agar well diffusion method to study the antibacterial activity of compounds. Each bacterial isolate was suspended in Brain Heart Infusion (BHI) broth and diluted to approximately 105 colony forming unit (CFU) per ml. The test organisms were flood-inoculated onto the surface of BHI agar and then dried. Five- millimeter diameter wells were cut from the agar using a sterile cork-borer and 30µL (50µg compound in 1 ml of solvent-Ethanol) of the sample solution were poured into the wells. The plates were incubated for 18 hours at 37ºC for bacteria. Antibacterial activity was evaluated by measuring the diameter of the zone inhibition in mm against the test microorganisms. DMSO was used as solvent control. Ciprofloxacin was used as reference antibacterial agent. The tests were carried out in triplicate.[20]

Bromo derivatives of carbazole have been synthesized by simple and easier Fischer indole synthesis with suitable solvent followed by bromination. Dibromo 1,2,3,4 tetrahydrocarbazole (compound 9a) shows antimicrobial activity.

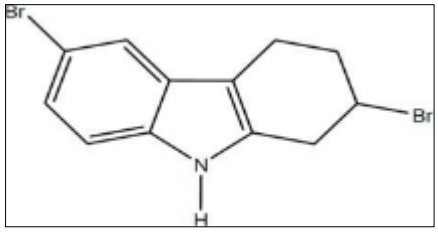

Figure 9 Compound 9a

4.2.1. Anticancer activity

The anticancer activity of the synthesized compounds was carried out on cancer cell lines namely HT-29 (Colon cancer). The inhibition of the growth of cell lines, *i.e.*, Cytotoxicity was considered as anticancer activity. Toxicity of test compound in cells was determined by MTT assay based on mitochondrial reduction of yellow MTT tetrazolium dye to a highly coloured blue formazan product which was measured as absorbance at 492 nm on a spectrophotometer (spectra max, Molecular devices) and the IC50 values were determined by plotting % inhibition (from control) versus concentration[21]

The following novel compounds shows anti-cancer activity: 3-nitro phenyl-*N*-[2-oxo- 2- (1,2,3,4-tetrahydro-9*H*-carbazol-9-yl)ethyl] thio semicarbazone (compound 10a), 2-nitro phenyl-*N*-[2-oxo-2- (1,2,3,4-tetrahydro-9*H*-carbazol-9-yl)ethyl] thio semicarbazone (Compound 10b), 4-methoxy phenyl -*N*-[2- oxo-2-(1,2,3,4-tetrahydro- 9*H*-carbazol-9-yl)ethyl] thio semicarbazone (compound 10c), 2-chloro phenyl -*N*-[2-oxo- 2-(1,2,3,4-tetrahydro-9*H*- carbazol-9-yl)ethyl] thio semicarbazone (compound 10d), 4-dimethyl cinnamaldehyde-*N*-[2- oxo- 2-(1,2,3,4- tetrahydro-9*H*-carbazol-9-yl)ethyl] thio semicarbazone (compound 10e)[22,23]

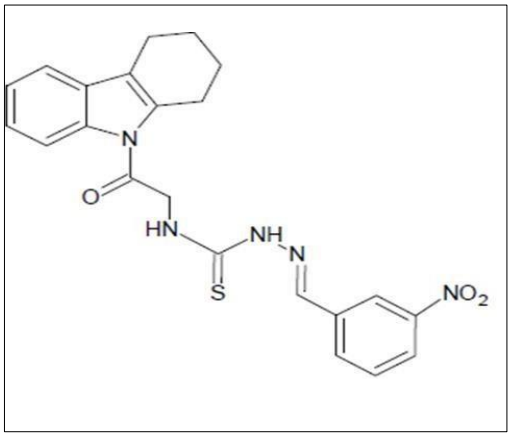

Figure 10a Compound 10a

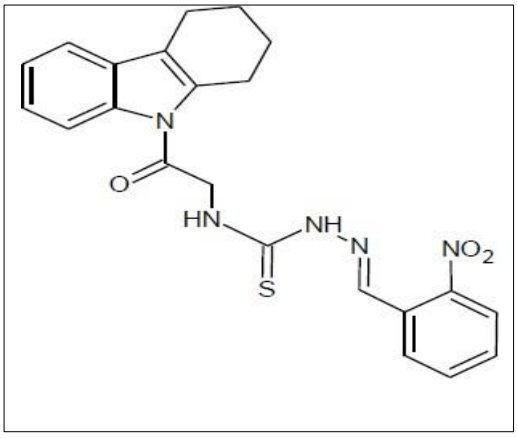

Figure 10b Compound 10b

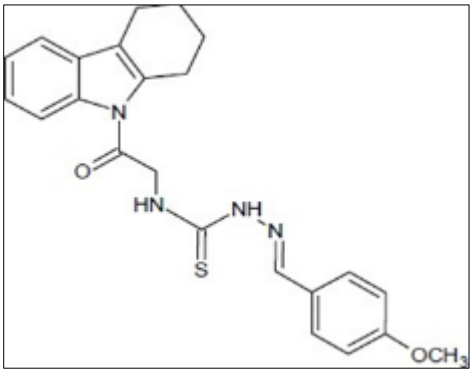

Figure 10c Compound 10c

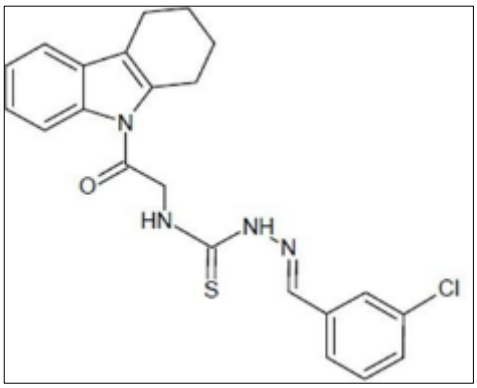

Figure 10d Compound 10d

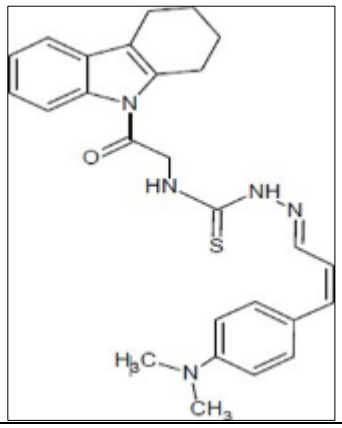

Figure 10e Compound 10e

4.2.2. Neuroprotective activity

New tetrahydrocarbazole benzyl pyridine hybrids (compound 11a). The compounds were tested for in-vitro neuroprotective activity against Butyryl cholinesterase (BuChE) inhibitors by Ellman's method using Donepezil as a standard drug. The result shows that compound 4a (IC50 = 0.088±0.0009μM) exhibit the most potent BuChE inhibitor[24]

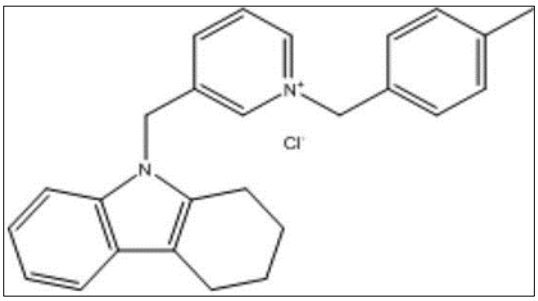

Figure 11 Compound 11a

4.2.3. Anti-inflammatory activity

The compounds isoxazolinyl and pyrazolinyl-1,2,3,4-tetrhydrocarbazoles were individually prepared by using chalconyl-1,2,3,4-tetrahydrocarbazoles (compound 12a, b) with condensation of hydroxylamine hydrate and hydrazine hydrate respectively. compounds shows anti-inflammatory activities by using carrageenan induced edema model in rates.[25,26]

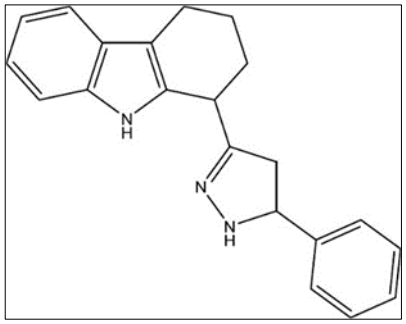

Figure 12 Compound 12a

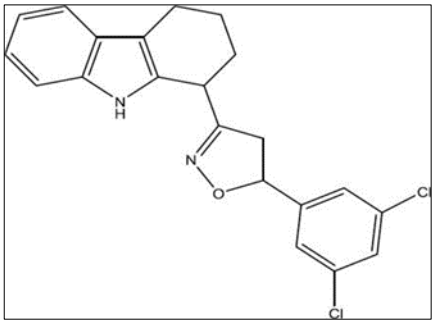

Figure 12 Compound 12b

4.2.4. Hypoglycemic and Hypolipemic activities

A series of tetrahydrocarbazole derivatives was designed and synthesized on the basis of the AMP-activated protein kinase activator GY3. All the synthesized compounds were screened in HepG2 cell lines for glucose consumption activity and several of them showed potent glucose decreasing activity. *In vivo* evaluation of the hypoglycemic and hypolipemic effects indicated that compound 13a exhibited comparable activity with pioglitazone, but with a weaker body-weight increasing effect. [27]

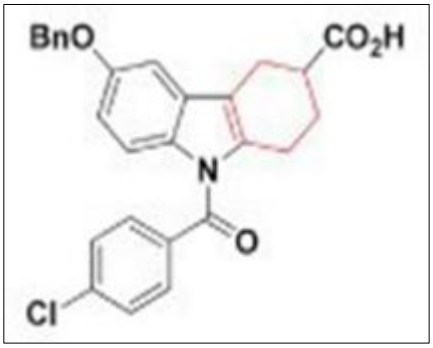

Figure 13 Compound 13a

Using scaffold migration and structure-based design, a series of tetrahydrocarbazole-3- carboxylic acids was derived from GY3. The compounds 6a prepared from (4-(benzyloxy) phenyl) hydrazine hydrochloride over 5 steps, which included the Fischer indole synthesis, hydrolysis, benzylation, benzoylation and catalytic hydrogenation to give the key intermediate. Subsequent reaction of intermediate with arylmethyl bromides gave the compound 13a[28]

5. Conclusion

In this review article, we covered various synthetic method for the preparation of 1,2,3,4-tetrahydrocarabzoles based on conventional, microwave and catalyst approach And covered their therapeutic activity against various disease . Now day's use of catalyst is become popular and it is very useful in the synthesis of complex natural products. Catalyst gives a short way to prepare complex or multistep molecule. However, availability and cost of catalyst is very important to synthetic and medicinal chemist. Generally, most of the preparation of 1,2,3,4-tetrahydrocarabzoles based on Fischer indole synthesis method in review literature. Substitution like hydrogen and electron donating or electron withdrawing group due to inductive or mesomeric effect plays a major role for the preparation of 1,2,3,4-tetrahydrocarabzoles in good yield and less time in review literature. This review gives a detail idea of availability and selection of various synthetic method available for preparation of 1,2,3,4-tetrahydrocarabzoles based on conventional, microwave and catalyst approach with percentage yield. 1,2,3,4 – Tetrahydrocarbazole [THCz] derivatives are also review for their pharmacological activities several search for newer physiologically active compounds show activity against antibacterial and antifungal, cytotoxic against cancer cells , Screend for antinociceptive activity, antiobestic, antidiabetic (type IIdiabeties), antipsychotic activity, and anti-emetic medicine.

Compliance with ethical standards

Acknowledgement

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Thank you all for being part of this endeavor.

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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