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CHEMISTRY AND SYNTHESIS OF CHIPPIINE-DIPPININE GROUP OF ALKALOIDS FOUND IN *TABERNAEMONTANA* SPECIES

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ABSTRACT

The chippiine/dippinine/tronocarpine alkaloids are a group of indole alkaloids that are found in *Tabernaemontana* plants. They all have pentacyclic backbone structure. To date 14 alkaloids belonging to this group have been isolated. They are produced in extremely low concentrations in stem, bark and root of the plant. The chemical structure of the chippiine-dippinine alkaloids has been widely studied and various strategies for the synthesis of these alkaloids have been proposed in the past 20 years.

KEYWORDS: Chippine, Dippinine, Tronocarpine, *Tabernaemontana*, Indole alkaloids, Synthesis.

INTRODUCTION

Alkaloids are important plant secondary metabolites that were initially discovered and used as early as 4000 years ago and are well recognized for their rich therapeutic potential. Alkaloids are structures that have at least one nitrogen atom in their backbone. They may also contain some neutral or weakly acidic compounds. Apart from carbon, nitrogen, or hydrogen, alkaloids may comprise sulfur and rarely bromine, phosphorus, or chlorine. Because of their vast array of pharmacological actions (anticancer, antimalarial, anesthetic, stimulant), they are purified from the crude extract by acid-base extraction. Alkaloids are low-molecular-weight structures and form approximately 20% of plant-based secondary metabolites So far, approximately 12,000 alkaloids are isolated from various genera of the plant kingdom.

There are three central types of alkaloids: true alkaloids, proto-alkaloids, and pseudo-alkaloids. The N atom of true alkaloids are obtained from amino acids and they are a part of the heterocyclic ring of the alkaloid backbone. They are mostly salts and crystalline in nature. They are usually solid and are highly reactive. Various amino acids like L-Phenylalanine, L-lysine, L-tyrosine and L-tyrosine provide the N atom to these alkaloids. The most common examples are Nicotine, Morphine, Cocaine and so on. In proto-alkaloids the N atom is obtained from amino acid but is not a part of the heterocyclic backbone structure. These are a minor group of alkaloids obtained from L-tryptophan and L-tyrosine. They are used as a medicine in various disorders like mental illness and pains. The Nitrogen in the heterocyclic ring of pseudo-alkaloids is not derived from amino acids instead they are formed from the intermediates of amino acid pathways. Sometimes non amino acids can also produce these types of alkaloids for example Caffeine. Alkaloids can also be classified on the basis of the type of heterocyclic ring structure they possess like a purine ring or an imidazole ring and so on.[1]

Indole alkaloids are the largest group of alkaloids that are derived from tryptophan. Important sub groups of indole alkaloids include Tryptamine derivatives and carbazoles. Apart from these there are various other types like Bis-indole alkaloids, Ergot alkaloids, mono and diterpenoid indole alkaloids and so on. They are found in fungi and plants. Polyhalogenation is a common feature of these alkaloids.[2] The *Tabernaemontana* plants have been used in various traditional medicines like Chinese medicine and Ayurveda to cure sore throat, hypertension, toothache and inflammation.[12] The flower of the plant is used to prepare Kajal in India and also as an antidote for snake venom. It also has anti-cancerous, anti-malarial, anti-arrhythmic effects.[3] Majority of alkaloids in *Tabernaemontana* plants are monoterpene alkaloids, it also contains bis-indole and Iboga type of type of alkaloids among others. The chippiine/dippinine/tronocarpine class of alkaloids are sometimes classified under the Iboga type of alkaloids.[13]

Figure 1: Crepe Jasmine flower of *Tabernaemontana divaricata.*

Isolation and Characterisation: The chippiine /dippinine /tronocarpine group of metabolites presently consists of 14 indole alkaloids isolated from *Tabernaemontana* plants. Tabernaemontana plants are spread throughput the African, South American and South Asian continents.[11] These alkaloids all possess pentacyclic ring-systems. The first member of this family was isolated in 1985 by Van Beek *et al*. from the root of the African tree. This pentacyclic alkaloid, chippiine, was named after the species from which it was isolated, *T. chippii*. Two structural analogs of alkaloid have subsequently been isolated, (-)-10,11-demethoxychippiine, from the South American tree *T. markgrafiana* by Torssell *et al*. in 1994 and (-)-16-O-methyl-10,11-demethoxychippiine from the roots of the Thai plant *T. pandacaqui* by Takayama et al. in 2019. In 1999, Kam and Sim isolated two novel chippiine-related indole alkaloids, (+)-dippinines A and C from the leaf and stem-bark extracts of Malaysian flowering plant *T. corymbose*. The following year, this group isolated another member of this family from the bark of the same plant, (+) tronocarpine, which possesses a modified seven membered lactam C-ring and an unsaturated cyclohexene E-ring. Kam *et al*. later isolated (-)-dippinines B and D in 2001 from the stem and leaf extracts of this plant, respectively. In 2014, Kong *et al*. isolated 10 new indole alkaloids from the leaves of *T. corymbosa*. These metabolites included (+)-tabercarpamines A–J, of which two dimeric bisindoles (A–B) and four monomeric indole alkaloids (G–J) contain chippiine-type skeletons. The characterization was performed using the data from NMR studies.

Chippiine- It is characterized by a bond between N1 and C16, indicating a six-membered hemiaminal D-ring. Consequently, the orientations of H15α and H20 revealed that the cyclohexane E-ring adopts a boat conformation.

Tronocarpine- A three-bond correlation from C2 to H6 indicated that the C6-C5-N4 unit is attached to C7 of the indole ring, while correlation between C3 and N(4)H implied that C3 is bonded to C2. This evidence elucidated the seven membered lactam C-ring in tronocarpine, which differs from a cyclic amine C-ring present in the previously-isolated chippiine/dippinine alkaloids.

Dippinine- Dippinine has 4 isoforms. Dippinine A possesses a pentacyclic chippiine-like skeleton. A major difference in the structures of the chippiines and dippinine A is that the six-membered E-ring in alkaloid adopts a chair conformation. Dippinine B was also found to possess an acetyl group in place of the corresponding C20-hydroxyethyl moiety found in alkaloid.[4]

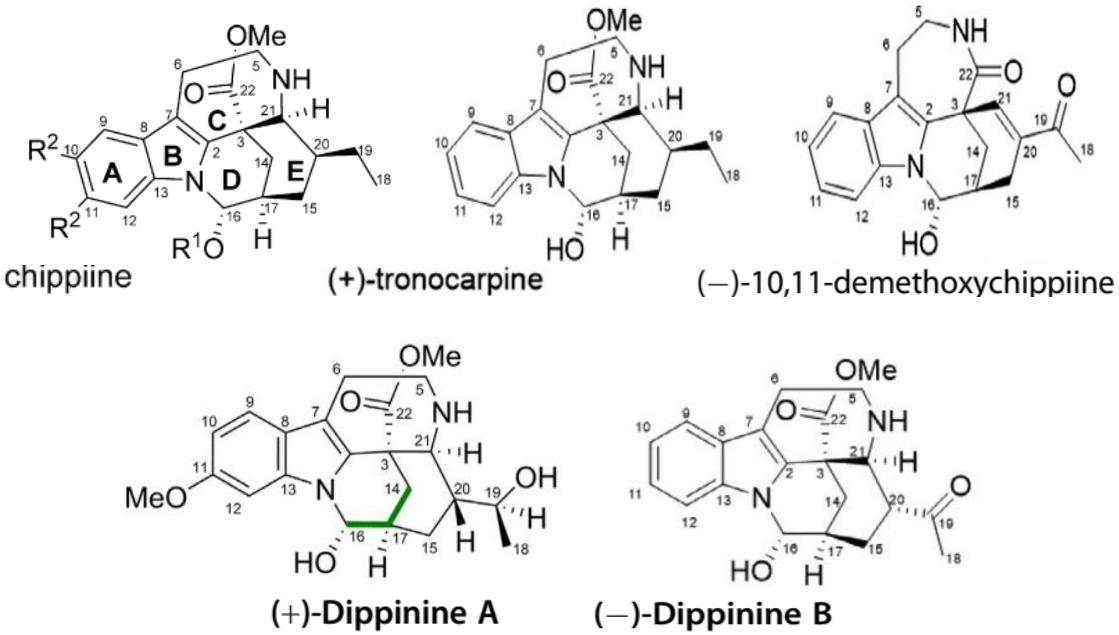

Fig. 2: Basic structure of the chippiine type alkaloids.

Chemical Synthesis: 1) Synthesis of Chippiine**:** Chippiine-type alkaloids most likely arise biogenetically from an Iboga-class alkaloid, such as (-)-catharanthine, which is derived via a well-known pathway from tryptophan. Bryan Landschoot in 2014 suggested and proved that the use of manganese (III) acetate appears to have many applications toward oxidative cyclizations of N containing heterocycles. Application of this oxidative cyclization chemistry was proven to be effective in the synthesis of a variety of pyrido-indole compounds. Regardless of complexity and ring size, the reliable success of this reagent in functionalizing the indole ring paved a way to synthesize tronocarpine, chippiine, and dippinine B.[5]

S C Taylor in 2020 suggested the putative biogenesis of chippine-type alkaloids, oxidation of (-)-catharanthine at C16, along with C19–C20 alkene reduction, would give aminal, which is the di-demethoxylated analog of the known alkaloid 16-hydroxyconopharyngine. Subsequent cyclization of the indole nitrogen onto the aldehyde carbonyl (C16) would result in a hemiaminal switch and afford (-)-10,11- demethoxychippiine. C10 and C11 methoxylation of (-)-10,11- demethoxychippiine would then yield chippiine.[4]

J Zhou *et al.*, in 2021 first synthesized two 10,11 dimethoxy analogs and two C20 epimers from tryptamine via LLS (Long Linear Steps). The challenging pentacyclic core was efficiently constructed by the sequential use of an asymmetric Michael/aldol cascade reaction and an intramolecular SN2'–type reaction. Additional highlights of synthesis included a Pd catalyzed Ag aided α, β-dehydrogenation of the highly compact cyclohexanone, a Pd-catalyzed Stille cross-coupling, and a catalyst-controlled highly stereoselective hydrogenation to install the side-chain at C20 in a highly selective manner.[6]

2) Synthesis of Dippinine: Seok Kam and Mow Sim in 1999 reported that dippinine A possesses a similar carbon skeleton. In addition, Dippinine A differs from the previous compound in having an oxidized ethyl side chain, the C(20) side chain now being a hydroxyethyl group.[7]

Seong *et al.*, in 2019 showed that treatment of lactam with Schwartz reagent followed by a simple addition of methanol and potassium carbonate provided a chemically unstable hemiaminal derivative. The hemiaminal derivative underwent the most efficient rearrangement to (+)-dippinine B at pH 6.6. This was therefore known as pH desired conversion. However, it is important to note that (+)-dippinine B readily decomposed in the presence of strong acid.[8]

S C Taylor in 2020 suggested that Oxidation of the ethyl group of (-)-10,11-demethoxychippiine to the corresponding methyl ketone, followed by stereochemical inversion at C20 to the more stable α-configuration and subsequent ketone reduction, would afford (+)-dippinine A. Concomitant oxidation of the hemiaminal moiety to the corresponding lactam would then yield (-)-dippinine D. A similar sequence beginning from (-)-10,11-demethoxychippiine would afford (+)-dippinine C lacking a C11 methoxyl group. Starting from (-)-10,11-demethoxychippiine, oxidation of the ethyl moiety and subsequent epimerization at C20 would afford (-)-dippinine B.[4]

3) Synthesis of Tronocarpine: Fu She-Han *et al.*, 2019 presented the first asymmetric total synthesis and absolute configuration determination of (+)-tronocarpine. The synthesis of enantiopure (+)-tronocarpine was achieved within a 20-step longest linear sequence from tryptamine. The [6.5.7.6.6]-pentacyclic core was constructed at early stage by using a sequential cyclization strategy via a newly developed catalytic asymmetric Michael/aldol cascade and tandem reduction/hemiamidation procedure to assemble the seven-membered lactam. The side-chain functionalities were incorporated at a late stage by several appropriately orchestrated manipulations under mild conditions.[9]

Atsushi *et al.*, 2020 reported a concise total synthesis of tronocarpine, a chippiine-type indole alkaloid. The key feature of this total synthesis is a one-pot construction of the pentacyclic skeleton containing an azabicyclo [3.3.1] nonane core by tandem cyclization from an indole derivative with all carbon side chains and functional groups. The stereochemical outcome in this tandem cyclization is controlled by the stereocenter at the C14 position. This strategy can be utilized to synthesize other chippiine-type alkaloids with azabicyclo [3.3.1] nonane skeletons.[10]

CONCLUSIONS

The genus *Tabernaemontana* is comprised of about 110 types of plants, which are found in tropical and some subtropical regions of South America, Sub-Saharan Africa, and Asia. Extracts of these plants have been utilized in traditional medicine for a variety of purposes. The chippiine/dippinine/tronocarpine group of metabolites presently consists of 14 indole alkaloids (1–14) isolated from *Tabernaemontana* plants. These alkaloids all possess pentacyclic ring-systems and are biogenetically related.

These alkaloids are found at extremely low concentrations therefore various strategies for synthesis of these group of alkaloids have been practised from last 2 decades. In India the plant *Tabernaemontana divaricata* called as Chandani (Common name) contains 10,11-Demethoxychippiine in the stem and bark. Uses of these alkaloids is not yet reported as they are obtained in little quantity and the total synthesis is quite tedious and expensive. However, the plant has been known for its potent acetylcholinesterase inhibitory activity.

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