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Review on asymmetric synthetic methodologies for chiral isoquinuclidines; 2008 to date

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ABSTRACT

Isoquinuclidines constitute the central structural nucleus of numerous biologically active natural products, for example, iboga alkaloids such as ibogamine and catharanthine as well as non-indole-containing alkaloids such as the dioscorine and the cannivonines. Furthermore, in medicinal and pharmaceutical chemistry, the isoquinuclidine core is commonly employed as a rigid azabicyclic scaffold, thus providing significant precursors in the synthesis of numerous valuable alkaloids. Summarizing well-organized approaches to access the chiral isoquinuclidine structural centerpiece signifies a significant endeavor not only for developing biologically active natural products but also enhancing biological researches that can lead to possible drug discovery. Over time, the values and methodologies for the asymmetric synthesis of chiral isoquinuclidines are increasing; hence to advance asymmetric synthesis, this review combines and discusses the pros and cons of each synthesis techniques from 2008. This review should be helpful for promoting further developments of asymmetric synthetic methodologies and for medicinal chemistry.

Contents

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1. Introduction

Attributed to a broad spectrum of biological properties, the six-numbered nitrogen-containing heterocycles have attracted great attention.[1] The chiral isoquinuclidines (also known as 2-azabicyclo[2.2.2]octane) core **1**, a six-numbered nitrogen-containing heterocycle, occurs in numerous natural products such as the iboga alkaloids and non-indole containing alkaloids (Fig. 1).

These alkaloids contain impressive biological properties.[2] (+)-Catharanthine **2** (also known as (+)-3,4-didehydrocoronaridine), a prototypical structure iboga-alkaloid, is an important synthetic intermediate of monomeric and dimeric vinca alkaloids, for example, (+)-vinblastine **3a** and vincristine **3b** (also known as (2′β)-22-oxovincaleukoblastine), which possess anti-tumor property and are used extensively for the treatment of human cancer (Fig. 1).[3] *Daphniphyllum* alkaloids, for example, (±)-caldaphnidine D **4**, display various biological and pharmacological properties such as anti-oxidative and cytotoxicity (Fig. 2).[4]

Xestocyclamine A **5**, a polycyclic alkaloid isolated first from the Papua New Guinea marine, is an anti-cancer drug and displays strong inhibitory activity towards protein kinase C beta (abbreviated as PKCβ) (Fig. 2).[5] (+)-Ibogamine **6** is a significant iboga alkaloids, which occurs in Tabernanthe iboga or simply iboga (Fig. 3).

In rats, (+)-Ibogamine **6** (also called epiibogamine) persistently decreased the self-administration (also known as SAM) of morphine and cocaine (Fig. 4).[7] Chiral isoquinuclidines are also present in non-indole containing alkaloids such as the cannivonines **7** and (−)-dioscorine **8** (Fig. 4).[8]

Alkaloids of *Dioscorea hispida* (Fig. 3) (a member of the Dioscoreaceae), are also known as 'ubi gadong', exemplified by dioscorine display depressant actions and anti-diuretic activities. Dioscorine **8** also demonstrates the character of modulation of nicotinic acetylcholine receptors (abbreviated as AChR).[9] Further, the chiral isoquinuclidines are also important precursors for the asymmetric synthesis of various significant pharmaceutical and biological active compounds such as oseltamivir phosphate (also called as Tamiflu) **10** which is a popular anti-influenza medicine (Fig. 5).

Tamiflu **10** is also a novel neuraminidase (abbreviated as NA) inhibitor.[10] It is recently shown that, by boosting the level of the growth factor called glial cell line-derived neurotrophic factor (abbreviated as GDNF), ibogaine **9** decreases alcohol cravings.[11] Moreover, chiral isoquinuclidines are receptors of numerous agonists and antagonists.[12–14] The chiral isoquinuclidines have a lot of applications in inhibitory enzymatic effect and are valuable precursors in medicinal chemistry.[15–18] Owing to diverse applications

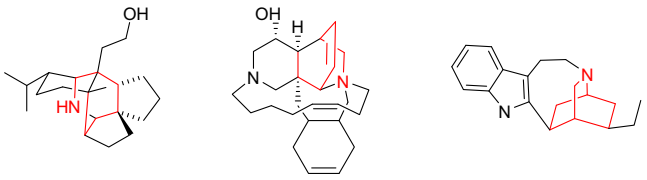

Figure 2. Structure of caldaphnidine D, xestocyclamine A and ibogamine.

in agrochemical and pharmaceuticals, isoquinuclidines has of interest to synthetic organic chemists. The construction of efficient and well-organized routes to isoquinuclidines signifies a significant and continuing task in organic chemistry. Aza-Diels–Alder protocols have been a vital contribution to develop chiral isoquinuclidines.[19] Since, the first asymmetric synthesis of chiral isoquinuclidines from aza-Diels–Alder reactions of imines was disclosed in 1943. Initially, for aza-Diels–Alder cycloaddition reactions, electron-rich diolefins for example Danishefsky's diene (Kitahara diene) were used.[20] In recent years, for aza-Diels–Alder cycloaddition reactions, the diolefins used have been substituted with derivatives of cyclohexanone. The resulting synthesized isoquinuclidines have displayed potent inhibition activity against acetylcholinesterase (abbreviated as AChE) and amyloid β fibrillogeneis (abbreviated as (Aβ).[21] Commonly, the Brønsted acids and Lewis acids ($TiCl_4$, $ZrCl_4$ and $HfCl_4$) and derivatives of proline are involved in reaction activation.[22,23] More recently, some other catalysts, for example [Emim][Pro] and 1,1′-bi-2-naphthol (abbreviated as BINOL) derivatives have been utilized in the aza-Diels–Alder adduction, resulting high enantioselectivity and productivity.[24,25] The literature, related to the asymmetric synthesis of chiral isoquinuclidines derivatives, from 1943 to 2008 has been reviewed by Khan et al.[26] This review covers the asymmetric synthetic approaches during the period 2008 to date towards chiral isoquinuclidines derivatives.

2. Asymmetric synthesis of iboga-like isoquinuclidine *via* Sonogashira coupling

Banerjee et al. synthesized iboga-like isoquinuclidines. These units consist of benzofuran entity and dehydroisoquinuclidine ring which is linked with $-CH_2-$, $-(CH_2)_2-$ and $-(CH_2)_3-$ groups.[27] These units display antinociceptive properties. The moieties **11** and **12**

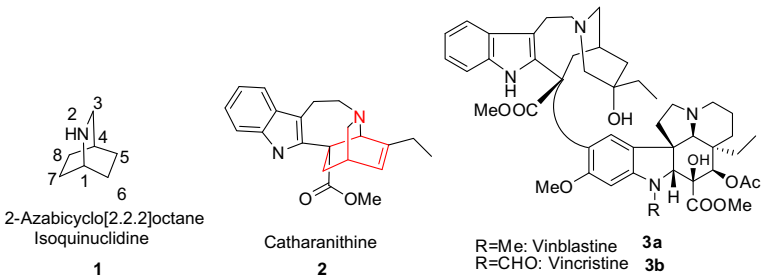

Figure 1. Structure of catharanthine, vinblastine and vincristine.