BISBENZYLISOQUINOLINE ALKALOIDS: BIOLOGICAL SIGNIFICANCE AND SYNTHETIC ADVANCES

Tursunov Firdavsi Hamzaevich
Samarqand state university named after Sharof Rashidov
E-mail: firdavsazi@yahoo.com

Abstract: Bisbenzylisoquinoline alkaloids (bisBIAs) represent a diverse and pharmacologically rich class of natural products derived primarily from plants of the Berberidaceae, Menispermaceae and related families. These compounds exhibit a broad spectrum of biological activities, including anti-inflammatory, anticancer, and neuroactive effects, making them valuable leads in drug discovery. Their complex architectures—characterized by multiple chiral centers and distinctive diaryl ether or biphenyl linkages—pose significant challenges for chemical synthesis. Recent progress in total synthesis, encompassing oxidative couplings, enantioselective Pictet–Spengler reactions, and modern cross-coupling strategies, has enabled access to both acyclic and cyclic bisBIAs. This article highlights the biosynthetic origins, structural diversity, and synthetic methodologies of bisBIAs, emphasizing advances that facilitate the preparation of enantioenriched derivatives and their potential therapeutic applications.

Keywords: Bisbenzylisoquinoline alkaloids, Benzylisoquinoline alkaloids, Biosynthesis, Total synthesis, Pictet–Spengler reaction

Annotatsiya: Bisbenzilizoxinolin alkaloidlari (bisBIA) asosan Berberidaceae, Menispermaceae va unga yaqin oilalarga mansub o’simliklardan olingan turli xil va farmakologik jihatdan boy tabiiy mahsulotlar sinfini ifodalaydi. Ushbu birikmalar yallig’lanishga qarshi, saratonga qarshi va neyroaktiv ta'sirlarni o’z ichiga olgan keng ko’lamli biologik faollikni namoyish etadi, bu ularni dori vositalarini kashf etishda qimmatli yo’nalishga aylantiradi. Ularning bir nechta xiral markazlari va o’ziga xos diaril efir yoki bifenil bog’lanishlari bilan tavsiflangan murakkab arxitekturasi kimyoviy sintez uchun jiddiy qiyinchiliklar tug’diradi. Oksidlovchi birikmalar, enantioselektiv Pictet-Spengler reaksiyalari va zamonaviy o’zaro bog’lanish strategiyalarini o’z ichiga olgan to’liq sintezdagi so’nggi yutuqlar ham asiklik, ham siklik bisBIAlarga kirish imkonini berdi. Ushbu sharhda bisBIAlarning biosintetik kelib chiqishi, strukturaviy xilma-xilligi va sintetik metodologiyalari ta’kidlangan, enantioenrifiklangan hosilalarni tayyorlashni osonlashtiradigan yutuqlar va ularning potentsial terapevtik qo’llanilishini ta’kidlaydi.

Kalit so‘zlar: Bisbenzilizoxinolin alkaloidlari, Benzilizoxinolin alkaloidlari Biosintez, To'liq sintez, Pictet-Spengler reaksiyasi

Аннотация: Бисбензилизохинолиновые алкалоиды (бисБИА) представляют собой разнообразный и фармакологически богатый класс природных продуктов, получаемых преимущественно из растений семейств Berberidaceae, Menispermaceae и родственных им семейств. Эти соединения

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обладают широким спектром биологической активности, включая противовоспалительное, противораковое и нейроактивное действие, что делает их ценными лидерами в поиске новых лекарственных средств. Их сложная структура, характеризующаяся множественными хиральными центрами и характерными диарилэфирными или бифенильными связями, представляет значительные трудности для химического синтеза. Недавний прогресс в области полного синтеза, включающий окислительные реакции сочетания, энантиоселективные реакции Pictet–Spengler и современные стратегии кросс-сочетания, открыл доступ к как ациклическим, так и циклическим бисБИА. В данном обзоре рассматриваются биосинтетическое происхождение, структурное разнообразие и синтетические методологии бисБИА с акцентом на достижениях, облегчающих получение энантиообогащенных производных и их потенциальное терапевтическое применение.

Ключевые слова: Бисбензилизохинолиновые алкалоиды, Бензилизохинолиновые алкалоиды, Биосинтез, Полный синтез, Реакция Пикте–Шпенглера.

Introduction

Benzylisoquinoline alkaloids (BIAs) are a large family of over 2,500 plant-derived compounds long used as analgesics and disinfectants. Several members, including morphine, colchicine and noscapine, remain important in modern medicine[1]. Recently, interest has grown in bisBIAs—molecules containing two BIA units—found in plant families such as Berberidaceae, Ranunculaceae, Lauraceae, and Menispermaceae. These compounds show diverse biological activities and are mainly formed by the condensation of coclaurine or reticuline units, resulting in three main classes: bisreticulines, coclaurine-reticulines and biscoclaurines. The two benzylisoquinoline units are typically linked through biphenyl, diphenyl ether or benzyl phenyl ether bonds with varied substitution patterns and chirality leading to structural diversity[2]. Over 500 bisBIAs have been identified and this review discusses their biosynthesis, medicinal relevance and synthetic approaches.

BIOSYNTHESIS

Bisbenzylisoquinoline alkaloids (bisBIAs) arise from a highly conserved biosynthetic pathway starting with the amino acid (S)-tyrosine. Through the action of tyrosine decarboxylase, tyrosine is converted into 4-hydroxyphenylacetaldehyde and dopamine. These intermediates then undergo a Pictet–Spengler condensation, catalyzed by norcoclaurine synthase, to form (S)-norcoclaurine, the central precursor of all BIAs[3]. Subsequent O- and N-methylation steps generate N-

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methylcoclaurine, a key biosynthetic intermediate that serves as the foundation for many structurally diverse alkaloids.

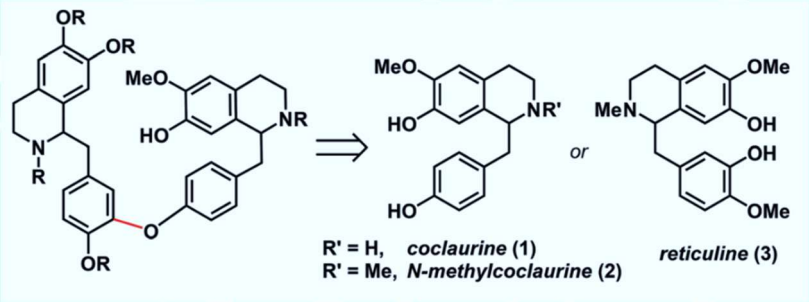


Fig-1. Coclaurine (1 and 2) and/or reticuline (3) are the biosynthetic building blocks of the majority of bisBIAs.

Formation of simple bisBIAs occurs through oxidative dimerization of two N-methylcoclaurine units, catalyzed by the P450 enzyme CYP80A1. More complex cyclic bisBIAs result from additional enzymatic modifications that introduce further functional groups and ring closures. Despite major advances, gaps remain in understanding this pathway[5]. Notably, the enzymes responsible for creating the sterically crowded and electron-rich diaryl ether linkages in cyclic bisBIAs—such as tetrandrine and berbamine—have yet to be identified, underscoring the complexity of bisBIA biosynthesis.

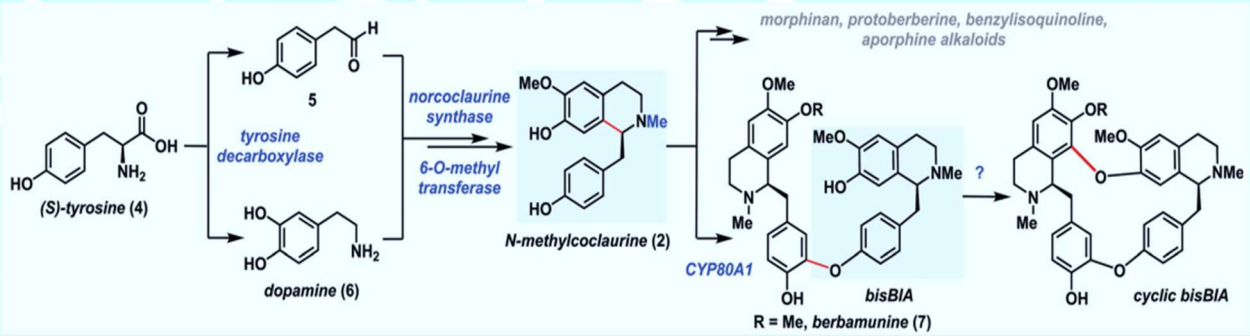


Fig-2. Present insights into the biosynthetic pathway of bisBIAs.

BIOLOGICAL ACTIVITY

Bisbenzylisoquinoline alkaloids (bisBIAs) exhibit broad pharmacological activities, including anti-inflammatory, antiviral, antitumor, analgesic and antiplasmodial effects. Traditionally used in India, China, Africa and Southeast Asia some bisBIAs were even employed as muscle relaxants and arrow poisons in South America. Their diverse bioactivities have attracted increasing research attention. Studies have reported antimicrobial, antiallergenic and antiparasitic effects including activity against Trypanosoma brucei and Leishmania donovani, as well as synergism with cefazolin against methicillin-resistant Staphylococcus aureus[6]. Recent findings highlight their ability to inhibit calcium influx in neurons and glial cells, thereby reducing neuroinflammation and apoptosis. For

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example, curine induces vasorelaxation by blocking L-type calcium channels in smooth muscle.

Of particular interest is the antiviral potential of bisBIAs against SARS-CoV-2. Several compounds isolated from Menispermaceae plants have shown strong inhibitory effects on viral entry and replication. Tetrandrine suppresses coronavirus protein expression, while cepharanthine, an approved drug, effectively inhibits SARS-CoV-2 replication (EC_{50} = 0.35 μM) by modulating NF-κB signaling and increasing plasma membrane rigidity.

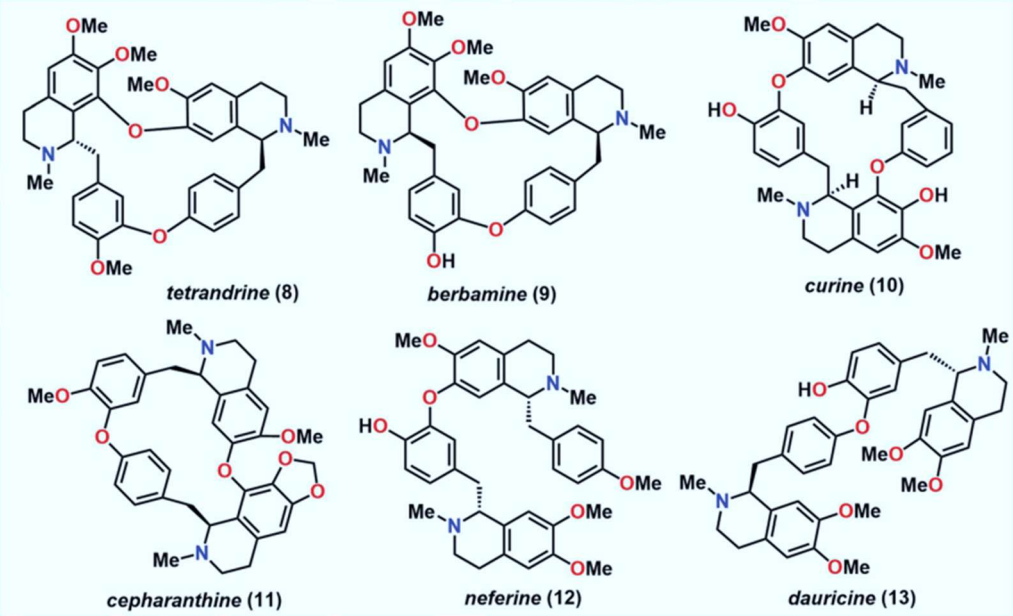


Fig-3. Selected bioactive bisBIAs

Among the most studied bisBIAs are tetrandrine (8), berbamine (9), neferine (12) and dauricine (13). Tetrandrine, the principal alkaloid of Stephania tetrandra-shows potent immunomodulatory, vasodilatory, anticancer and antiviral activities. It inhibits NF-κB, Ca^{2+}/calmodulin-dependent kinase II and two-pore calcium channels, impeding cancer progression and Ebola virus entry. Tetrandrine also acts as a P-glycoprotein inhibitor, reversing multidrug resistance and currently being developed clinically as CBT-1 for combination cancer therapy. However, its toxic metabolites may cause pulmonary and hepatic damage.

Berbamine, from Berberis amurensis, has long been used to treat inflammation and cancer. It targets multiple signaling pathways (e.g., p53, Fas, CaMKIIγ, STAT3) and enhances the efficacy of drugs like sorafenib, gefitinib and paclitaxel in resistant tumors.

Neferine, found in Nelumbo nucifera, exhibits antioxidant, antidepressant, antidiabetic and anticancer properties[7]. It induces autophagy, promotes apoptosis and reverses epithelial–mesenchymal transition to combat chemoresistance.

Dauricine, from Menispermum dauricum, demonstrates cardioprotective, neuroprotective and anti-inflammatory effects. It reduces amyloid-β secretion and

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oxidative stress, suggesting potential in Alzheimer's disease, though high doses can be cytotoxic to liver, kidney and lung cells.

Together, these studies emphasize the rich therapeutic promise of bisBIAs and their value as leads for developing new antiviral, anticancer and neuroprotective agents.

TOTAL SYNTHESES OF bisBIAs

Synthesis of Coclaurine and its Derivatives

Coclaurine and its analogues serve as essential building blocks and precursors in bisBIA synthesis. The earliest route involved condensation of 4-benzyloxy-3-methoxyphenylethylamine with (4-ethoxycarbonyloxyphenyl)acetyl chloride, followed by Bischler–Napieralski cyclization, PtO_2 reduction and acidic deprotection to afford coclaurine. Variants of this sequence, including Arndt–Eistert homologation and $LiAlH_4$ reductions[8], have been used to prepare N-methylcoclaurine and other derivatives.

Modern strategies favor N-acyl Pictet–Spengler reactions over the classical Bischler–Napieralski method to improve efficiency and enantioselectivity. In 2015, Hiemstra et al. developed an enantio- and regioselective Pictet–Spengler condensation between arylacetaldehydes and NPS-protected arylethylamines using (R)-TRIP as a chiral catalyst, yielding (R)-coclaurine, (R)-reticuline and related alkaloids in up to 92% . Subsequent O-methylation and deprotection steps proceeded smoothly, producing hydrochloride salts in 71–89% yields with optical purity largely maintained.

Synthesis of Acyclic bisBIAs

Two general strategies exist for bisBIA construction: Formation of diaryl ether bonds connecting partially built fragments and Prefunctionalization of both isoquinoline units followed by ether bond coupling.

Historically, most syntheses have relied on Cu-catalyzed Ullmann couplings, despite their harsh conditions, low yields and long reaction times. Improved variants using Ni or Pd catalysis or modern couplings like Chan–Evans–Lam and Buchwald–Hartwig reactions have broadened substrate scope but still show variable efficiency in forming C–O bonds.

Early synthetic milestones include the 1955 Ullmann coupling of (–)-armepavine derivatives to give O-methyldauricine (24% yield), followed by Kametani and Fukumoto's 1960s total synthesis of (±)-dauricine, integrating Arndt–Eistert and Bischler–Napieralski steps. Related protocols produced magnolamine, berbamunine and neferine analogues in 34–45% yields[9].

Subsequent modular and enantioselective approaches emerged. For instance, (+)-O-methylthalibrine was synthesized from tetrahydroisoquinoline-1-carbonitrile via Noyori transfer hydrogenation, reductive N-methylation and a final

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Ullmann coupling, yielding 51% overall. This route was later adapted for (+)-tetramethylmagnolamine, (+)-laudanosine and (+)-armepavine.

Beyond cross-coupling, oxidative C–O bond formations have provided greener alternatives. Bobbitt and Hallcher (1971) achieved the first electrochemical dimerization of an N-carbethoxy armepavine derivative to yield racemic dauricine. Nishiyama et al. later optimized electrolytic phenol coupling to generate (+)-O-methylthalibrine and related dimers through asymmetric Bischler–Napieralski reactions, giving 29% overall yield[10].

A recent highlight is the catalytic aerobic desymmetrization used by Opatz (2020) in the concise synthesis of (S,S)-tetramethylmagnolamine. Starting from Boc-protected tetrahydroisoquinoline intermediates, a $CuPF_6$/DBED-catalyzed oxidative coupling under O_2 established the key C–O bond. Following methylation and Boc deprotection, the natural product was obtained in 21% overall yield over seven steps, a significant improvement over the previous 16-step route.

Synthesis of Cyclic bisBIAs

Cyclic bisbenzylisoquinoline alkaloids represent the most structurally complex members of the BIA family, mainly due to the challenge of forming precise diaryl ether linkages.

In 2017, Opatz and co-workers achieved the racemic synthesis of (±)-curine (10) and (±)-tubocurine (55) through two sequential Ullmann-type couplings. The dihalogenated intermediate (51) was prepared by coupling phenylethylamine (47) with phenylacetic acid (48), followed by Bischler–Napieralski cyclization, reduction and N-methylation[11]. A second MOM-protected benzylisoquinoline fragment (53) was obtained from aminonitrile (52) using an umpolung–alkylation–reduction sequence. The challenging double C–O bond formation between 51 and 53 produced the desired dimers and final benzyl deprotection yielded (±)-curine and (±)-tubocurine in a 2:1 diastereomeric ratio, also constituting a formal synthesis of (±)-tubocurarine (56).

A similar dual Ullmann approach was later applied in a twelve-step modular synthesis of (±)-tetrandrine (8) and (±)-isotetrandrine (58) Each of four outlined routes combined N-acyl Pictet–Spengler reactions to construct the 1-benzyltetrahydroisoquinoline units with Cu-mediated intramolecular diaryl ether couplings to close the macrocycle[12]. Variations included different sequences of inter- and intramolecular Pictet–Spengler cyclizations and assembly of either aromatic subunit first (A–C or A′–C′). Final $LiAlH_4$ reduction of carbamates in macrocycle 57 produced racemic mixtures of (R,R)/(S,S)-tetrandrine and (S,R)/(R,S)-isotetrandrine in 3–19% overall yields. Computational studies revealed that the C-1 stereocenter of the macrocyclic intermediate influences formation of the second chiral center, dictating the product's diastereomeric outcome.

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CONCLUSIONS

Current strategies for the total synthesis of bisbenzylisoquinoline alkaloids (bisBIAs) highlight both the **remarkable structural diversity** of these molecules and the **limitations of existing synthetic methodologies**. Their complex architectures continue to inspire the development of more efficient, selective and sustainable synthetic approaches. Beyond their synthetic appeal, the **broad therapeutic potential** of bisBIAs has driven extensive research into structural analogs and bioactive derivatives. As interest in these natural products grows, further progress in **enantioselective and modular synthesis** will be essential to enable broader biological exploration and facilitate the discovery of **clinically relevant bisBIA-based therapeutics.**

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