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Review Article

Recent Advances in Isoquinoline Chemistry, Synthetic Strategies, Functionalization, And Applications

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ABSTRACT

Isoquinolines (C_9H_7N)[1] are a broadly important class of nitrogen-containing heterocycles found in numerous natural alkaloids[21] and synthetic drug leads. Their structural diversity (isoquinolines, tetrahydroisoquinolines[2], benzylisoquinolines, protoberberines[3,4,22], aporphines, benzophenanthridines[5,6,7,23] underpins varied biological activities — anticancer[5,6,7,23,30], antimicrobial[20,22], CNS-modulating[24], and cardiovascular actions[3,4,22] — and has motivated intense synthetic-method development (classic annulations, Bischler–Napieralski[14,15,16], Pictet-type, and modern transition-metal-catalyzed C–H activation[8,9,10,25,29]/annulations). This review summarizes structural features, natural product families and biosynthesis[17,18], major synthetic strategies, SAR highlights[27,28], pharmacological applications, recent advances (2019–2024), and future directions. Key statements about natural-product importance, THIQ prevalence, and modern C–H strategies are supported by current literature.

INTRODUCTION

Introduction And Structural Overview:

Isoquinoline consists of a fused benzene and pyridine ring (2,3-fusion)[1] and is isomeric with quinoline. The nitrogen's position determines electronic distribution and reactivity, making isoquinoline-based scaffolds highly versatile in medicinal chemistry and natural-product frameworks[21]. Reduced variants such as tetrahydroisoquinolines[2] (THIQs) are major natural-product subfamilies with distinct stereochemical complexity and bioactivity[17,18].

Types Of Isoquinoline Alkaloids:

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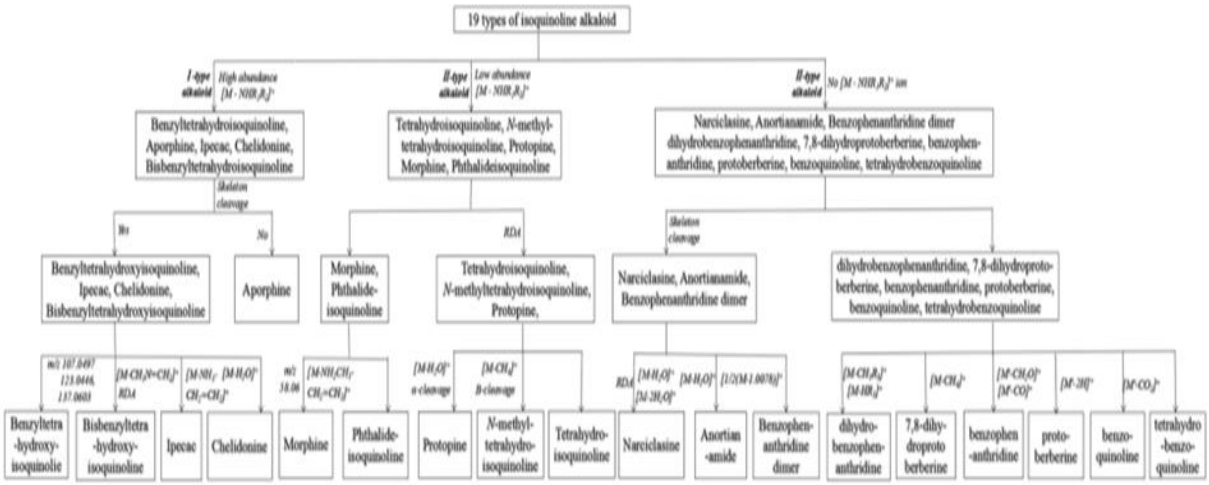


The diagram splits isoquinoline alkaloids into three main types:

1. I-type alkaloids

High abundance (presence of $[M - NHR_2]^+$ ion in mass spectrometry)

Examples:

- Benzyl-tetrahydroisoquinoline
- Aporphine
- Ipecac
- Chelidonine
- Bisbenzyl-tetrahydroisoquinoline

Skeleton cleavage leads to further subtypes.

2. II-type alkaloids

Low abundance ($[M - NHR_2]^+$ ion is low)

Examples:

- Tetrahydroisoquinoline
- N-methyl-tetrahydroisoquinoline
- Protopine
- Morphine
- Phthalideisoquinoline

RDA (Retro-Diels–Alder) cleavage or nitrogen/skeleton rearrangement is seen.

3. III-type alkaloids

No $[M - NHR_2]^+$ ion

Examples:

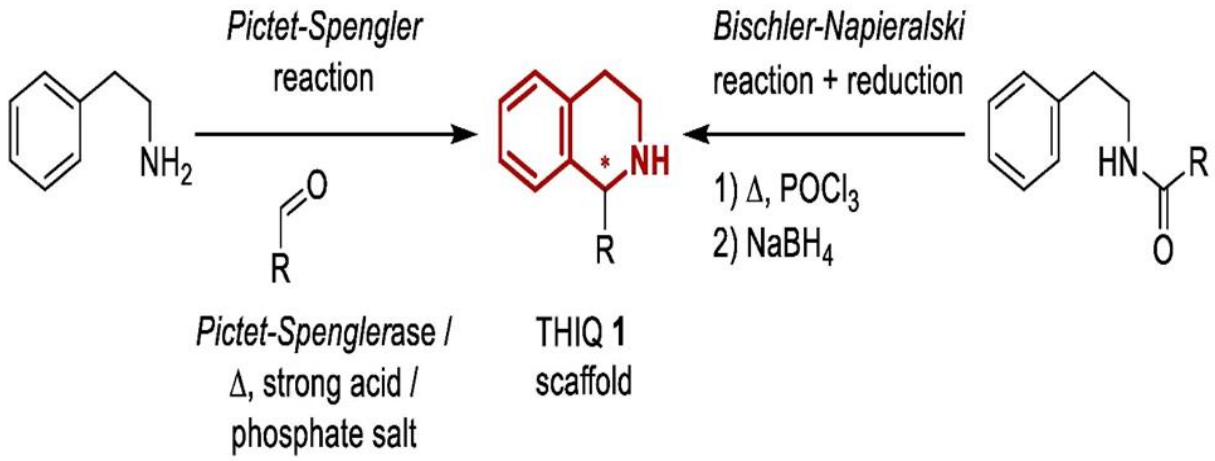
- Narciclasine
- Anortianamide
- Benzophenanthridine dimer
- Dihydrobenzo-phenanthridine
- 7,8dihydroproto-berberine
- Benzophenanthridine
- Proto-berberine
- Benzoquinoline
- Tetrahydro-benzoquinoline

Biosynthetically[17,18], THIQs commonly derive from dopamine- and phenylalanine-derived building blocks via Pictet–Spengler and oxidative coupling sequences; enzymatic tailoring (P450s, methyltransferases) yields structural complexity. Recent reviews and biosynthetic studies have mapped many pathways and enzymatic steps for THIQ and protoberberine formation. Representative bioactivities: berberine[3,4,22] (metabolic, antimicrobial, anticancer effects), sanguinarine[5,6,7,23] (anticancer, enzyme inhibition), and multiple THIQ alkaloids[2,17,18] (CNS, cardiovascular, antimicrobial roles). Comprehensive updates surveying isolates and activities from 2019–2023 reinforce the continued discovery of novel isoquinoline alkaloids and bioactivities.

Synthetic Strategies:

A. Classical Methods:

Bischler–Napieralski[14,15,16] and Pictet–Gams/Pictet–Spengler strategies remain foundational for assembling THIQ cores and substituted isoquinolines; they are widely used in natural-product syntheses and analog development.



B. Modern Annulation & C–H Activation Methods:

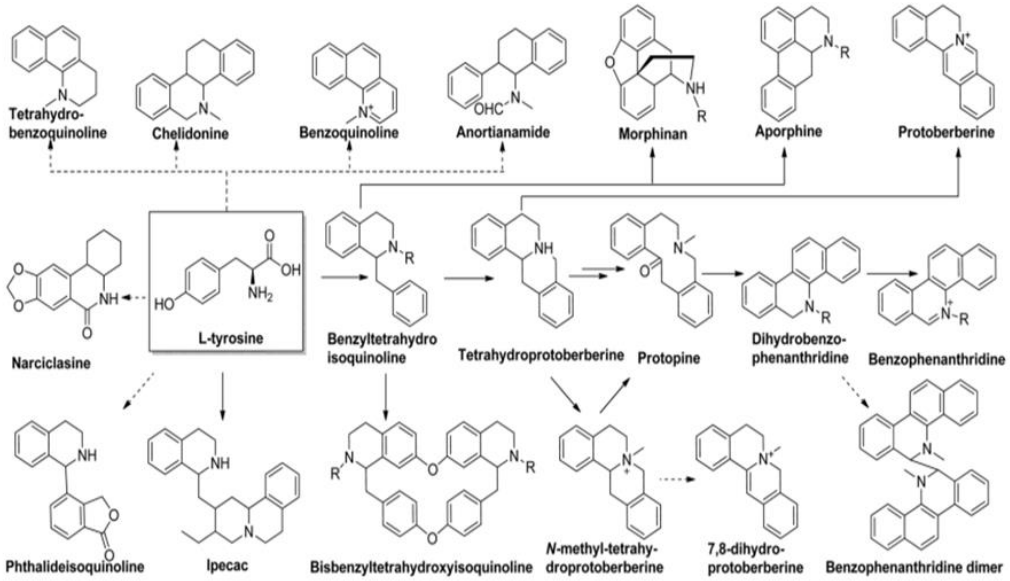
Transition-metal-catalyzed C–H activation/annulation[8,9,10,25,29] and alkyne annulations[8] have become powerful, atom-economical routes to substituted isoquinolines and fused frameworks; these methods enable late-stage diversification and tolerance of functional groups. Recent thematic reviews summarize Rh(III)-/Pd-/Co-catalyzed annulations and alkyne-based isoquinoline constructions.

C. Oxidative, Hypervalent Iodine, And Radical Approaches:

Oxidative annulations, photoredox[12,19]-mediated C–H functionalizations, and hypervalent iodine[26]-mediated oxidations provide alternative, milder conditions for functionalizing isoquinoline precursors and building N-oxides or N-functionalized derivatives. Photochemical C–H alkylations of heterocycles have expanded substrate scope.

D. Total Synthesis & Complex Manipulations:

Recent total syntheses of complex THIQ alkaloids have integrated modern catalytic steps with classic cyclizations[17,18,30], enabling shorter, more efficient routes to natural products and analogs.

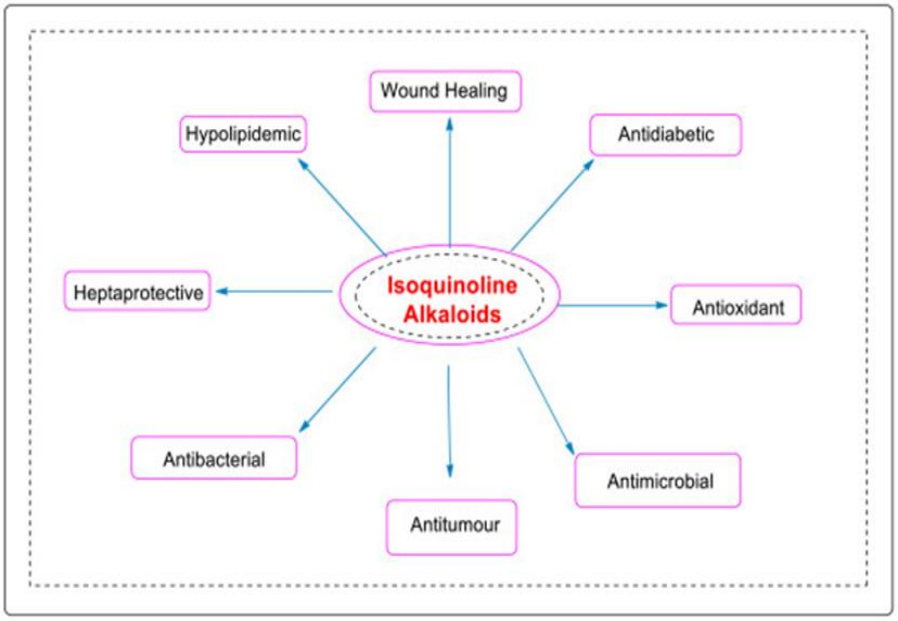


Structure–Activity Relationship (SAR) Insights:

General SAR trends observed across classes:

- Planar, cationic protoberberine cores (e.g., berberine) interact with nucleic acids and proteins; quaternization and charged states influence cell uptake and DNA intercalation.
- Substitution on the benzene portion (electron-withdrawing vs donating groups) modulates lipophilicity and target engagement (kinases, topoisomerases).
- Fused and polycyclic isoquinolines increase π-surface area and often improve potency against DNA-processing enzymes or tubulin.
- N-oxide formation is used to tune polarity and to serve as synthetic handles for further derivatization. These SAR principles come from multiple medicinal chemistry optimization studies and review articles.

Pharmacological Applications & Notable Molecules:



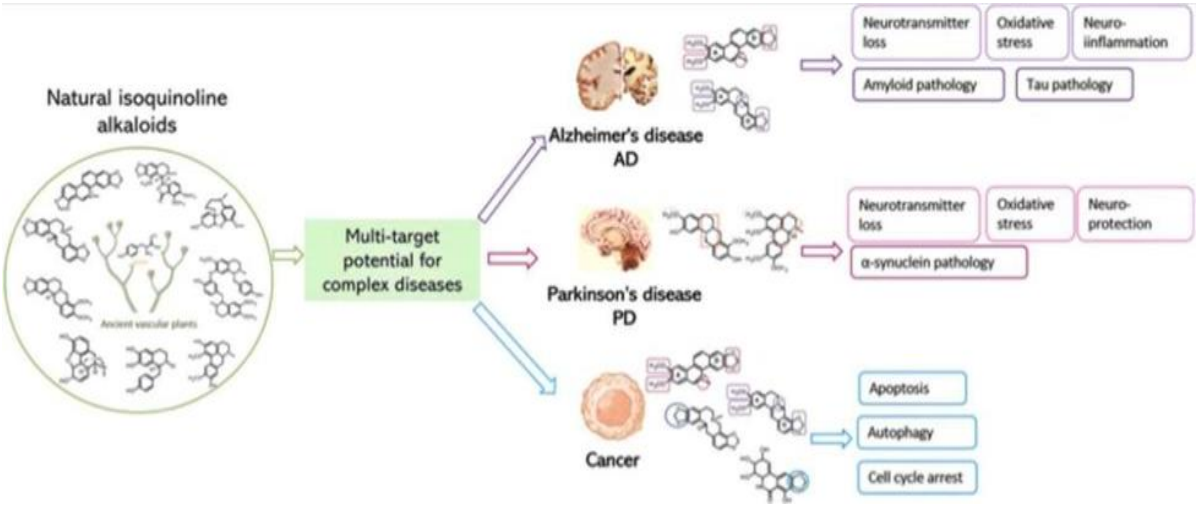
A. Anticancer:

Isoquinoline alkaloids such as sanguinarine[5,6,7,23], chelerythrine, and berberine[3,4,22] show anticancer activities by inducing apoptosis, arresting cell cycle, inhibiting topoisomerase, or modulating signaling pathways. Many synthetic isoquinoline derivatives (pyrrolo-/indolo- fused variants) were developed as kinase or tubulin inhibitors. Recent profiling identifies sanguinarine as an inhibitor of aurora kinases and stemness pathways in select cancers.

B. Antimicrobial & antiparasitic:

Berberine[3,4,22] and related protoberberines show strong antibacterial[20], antifungal, and antiparasitic effects; structural modification (alkylation/quaternization) often enhances potency and membrane interactions. Systematic reviews of berberine's broad bioactivity and clinical meta-analyses support therapeutic potential in metabolic and infectious conditions.

C.CNS & neurodegenerative targets



THIQ derivatives[2] and certain isoquinoline scaffolds have been studied for acetylcholinesterase inhibition[24], MAO inhibition, and neuroprotective activities relevant to Alzheimer's and related disorders. Reviews focused on THIQ derivatives for Alzheimer's summarize progress and translational challenges.

D. Cardiovascular, metabolic action:

Berberine's effects on AMPK activation and lipid/glucose regulation have generated interest in metabolic syndrome and cardiometabolic indications; meta-analyses and clinical systematic reviews summarize these effects.

Recent Advances (2019–2024) — Highlights:

- Comprehensive surveys of newly isolated isoquinoline alkaloids (2019–2023) catalog new scaffolds and activities.
- Methodological growth in C–H activation annulations [8,9,10,25,29] and alkyne-based syntheses enabling fast access to diverse substituted isoquinolines.
- Biosynthetic and enzymatic studies[17,18] have elucidated THIQ pathways and opened routes to microbial/biotechnological production.
- Clinical/systematic evidence for berberine across metabolic endpoints (diabetes, lipids) has accumulated, expanding translational interest[4,22].

Challenges And Future Directions:

- Toxicity & selectivity tradeoffs[27]: Many isoquinoline alkaloids are bioactive but may be cytotoxic — medicinal chemistry must optimize therapeutic window.

- Drug-likeness & ADME challenges: Berberine's low oral bioavailability is a prototypical ADME issue[3,4,22]; formulation and prodrug strategies are active areas of research.

- Sustainable synthesis & scalability[25,29,19]: Broader adoption of 3d-metal catalysis, photocatalysis, and biocatalysis will improve sustainability for complex isoquinoline derivatives.

- Translational gap[30]: Many leads exist in vitro/in vivo; more rigorous preclinical ADME/Tox and mechanism-of-action studies are needed for clinical progression.

CONCLUSION:

Isoquinoline chemistry spans rich natural-product diversity and cutting-edge synthetic methodology. The scaffold remains a privileged structural motif in medicinal chemistry — progress in C–H activation, biosynthesis elucidation, and translational pharmacology (notably berberine research) suggests significant potential for new therapeutics, provided selectivity and ADME hurdles are carefully addressed.

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