Function-Driven Strategies for the Total Synthesis of Ibogaine and Related Indole Alkaloids for Neurotherapeutic Development

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In recent years, the opioid epidemic has devastated families and communities across the globe. Millions of people struggle with addiction to opiates. These are substances that hijack the brain's reward system fuelling a rampant and difficult to conquer addiction. To recover is not as simple as going to the doctor and getting a prescription, it requires a battle that so many people struggle through. Traditional treatments like methadone or buprenorphine can reduce cravings, but relapse rates remain high. This has pushed scientists to search for something new, something that doesn't just dull withdrawal symptoms but helps the brain repair the systems destroyed by the opiates.[22]

One unexpected lead came not from a pharmaceutical lab, but from Central Africa. There, the roots of the Tabernanthe iboga shrub have been used for centuries in spiritual ceremonies. Its active compound, ibogaine (IBG), has long intrigued researchers for one astonishing reason. In some studies, a single dose seemed to dramatically reduce opioid cravings and withdrawal symptoms. But ibogaine also had a darker side, intense hallucinations and life-threatening effects on heart and muscle health.[23]

Ibogaine's discovery as an anti-addictive agent sparked a wave of interest in the 1960s and '70s . Patients described feeling "reset," freed from the obsessive pull of drugs after one experience. Yet the same compound that seemed to "rewire" the brain and help with opiate addiction did not come without its negative side effects, those being an effect on the heart. These severe cardiac arrhythmias, often due to ibogaine's interaction with ion channels in the heart, made it too dangerous for clinical use . The compound was soon outlawed in the United States and many other countries.[24, 3]

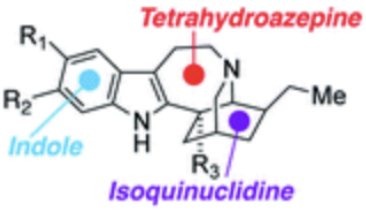
For decades, that ban reflected a broader stigma surrounding psychedelics in medicine . Despite mounting evidence that psychedelic compounds could promote neuroplasticity, something directly tied to the ability to recover from addiction, researchers were largely prevented from studying them. The result was a scientific stalemate: everyone could see ibogaine's potential, but no one could safely unlock it. [25]

This puzzle set the stage for a new era of chemistry-driven discovery. If ibogaine could not be safely used, perhaps it could be *redesigned*. How can chemists reshape a molecule's structure to preserve its benefits while removing its risks?

Enter Dr. David Olson and his team at UC Davis, who decided to treat ibogaine not as a dead end but as a blueprint. Their goal was to identify which parts of its molecular structure caused toxicity and which parts prompted neuroplasticity, and then re-engineer the molecule into something safer with a potential clinical future. To accomplish this, they harnessed the power of a biochemical tool, function-oriented synthesis. The idea of thinking about what makes each part of a molecule biochemically active and then deriving exact function from each functional group opened the door for Dr. Olson and his lab to create a molecule that takes the best of IBG while bypassing the negative side effects that yield IBG as clinically unviable.[7]

At the heart of ibogaine lies a polycyclic scaffold made of several interlocking carbon rings. Within this intricate structure are two key functional groups that caught the attention of Dr. David Olson: a

tetrahydroazepine and an isoquinuclidine. Think of these functional groups, as two distinct rooms in ibogaine's molecular house, each with its own role in shaping how the molecule behaves.



Iboga Alkaloids	R_1	R_2	R_3
(–)-Ibogaine	OMe	H	H
(–)-Noribogaine	OH	H	H
(–)-Voacangine	OMe	H	CO_2Me
(–)-Coronaridine	H	H	CO_2Me
(–)-Tabernanthine	H	OMe	H
(–)-Ibogaline	OMe	OMe	H

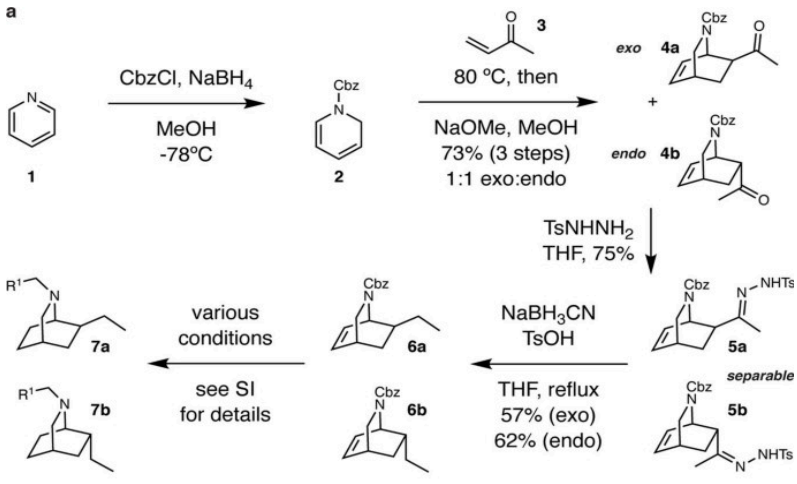
Source: https://doi.org/10.1039/D0NP00033G

The challenge was to figure out which room was responsible for ibogaine's unwanted effects and which it wanted. Was it actually only one specific part of the structure that triggered hallucinations or cardiac risks, or to have any benefit from the drug did it have to come with these negative side effects? To answer that, Olson's team built each room on its own as two model molecules, each missing one of the key features, and compared how they behave. These became Scaffold 1 and Scaffold 2, chemically cousins of ibogaine designed to isolate the effects of individual functional groups.

Despite their shared goal, the synthesis of the two scaffolds told very different stories, one of multi-step craftsmanship and the other of elegant simplicity.

The creation of Scaffold 1, which contained the indole and isoquinuclidine groups, was a process full of clever maneuvers that highlight fundamental organic principles.

Chemists first reacted a pyridine with CbzCl (carbobenzyloxy chloride), in what's essentially a substitution-like reaction: the nitrogen "attacks" a carbonyl carbon that's made extremely attractive (or electrophilic) to the electron dense nitrogen because it sits next to both a carbonyl group and a chlorine atom. The result is a carbobenzyloxy-protected dihydropyridine, a molecule that's temporarily lost its aromatic stability but is perfectly primed for the following steps.



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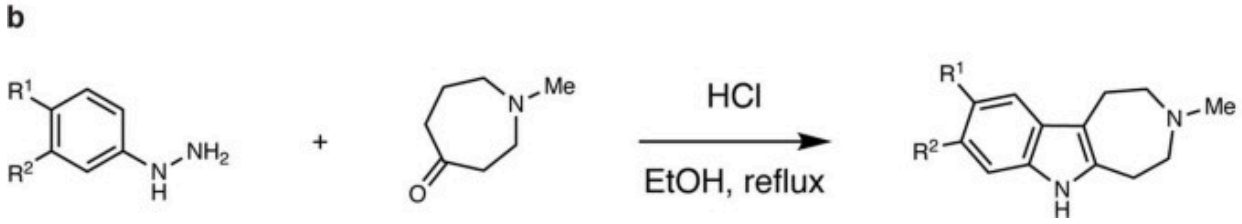
The dihydropyridine has four π electrons in a conjugated system (in this case two double bonds that are separated by one bond), setting it up perfectly for a Diels–Alder reaction, one of the most famous reactions in organic chemistry. The dihydropyridine (representing the traditional “diene”) meets methyl vinyl ketone (the “dienophile”), and together they snap into a new bicyclic structure, a molecule with two connected rings.

At this point, the structure carries a ketone group (a carbon double-bonded to oxygen), which contains another electrophilic carbon. This is taken advantage of by a tosylhydrazide molecule that attacks the carbonyl carbon (a classic nucleophilic attack), leading through a proton rearrangement and an elimination to form a hydrazone. Finally, the chemists perform a reduction of the hydrazone (the equivalent of just replacing the hydrazone with hydrogens,, which strips away the tosyl group and leaves behind a clean bicyclic bridge with an ethyl substituent.

Each of these steps not only transforms the molecule but also demonstrates different core ideas in organic chemistry, ranging from electrophilicity, aromaticity, electron delocalization, nucleophilicity, orbital overlapping, and so much more. The result, Scaffold 1, preserved the indole and isoquinuclidine pieces of ibogaine while removing the tetrahydroazepine ring, allowing researchers to observe how isoquinuclidine affected the functionality of IBG.

Still, to truly complete the comparison, the team needed the inverse image, a molecule with the tetrahydroazepine but without the isoquinuclidine. Scaffold 2, containing the indole and tetrahydroazepine, was synthesized in just one reaction: the Fischer indole cyclization.

It starts with a substituted phenylhydrazine, which seeks out and attacks a carbonyl carbon, forming a tetrahedral intermediate, the equivalent of the two molecules doing a quick handshake where electrons shift and rearrange positions. A few proton shuffles later, water leaves the molecule, and a hydrazone takes its place.



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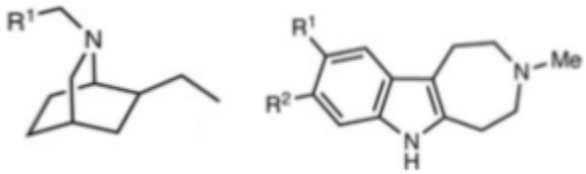
Next, under acidic conditions, the hydrazone undergoes a dramatic internal rearrangement known as a 3,3-sigmatropic (Cope) rearrangement. It’s like the molecule momentarily turns itself inside out, rearranging bonds to form a diimine structure. A final touch of acid protonates the nitrogen, setting off a semi–E2

elimination that closes the ring and forms the beautifully stable aromatic indole, this same functional group being found in serotonin and tryptophan, and a hallmark of many biologically active molecules.

Biochemical Consequences of Structural Editing

Though beauty lies in the elegance of complex syntheses and intricate molecular architectures, the true practicality of these compounds emerges in their biochemical and medical applications. Now that they had both scaffolds, representing the core functional groups of the molecule, they had to apply them to the actual drug-like functions of ibogaine to determine which functionalities were responsible for its adverse effects. By selectively modifying and isolating functional groups across a series of ibogaine analogs, Olson's group systematically correlated structural changes with functional outcomes. Traditionally, ibogaine has been avoided clinically because of two major liabilities: its adverse effects on hERG channels and its psychedelic activity.

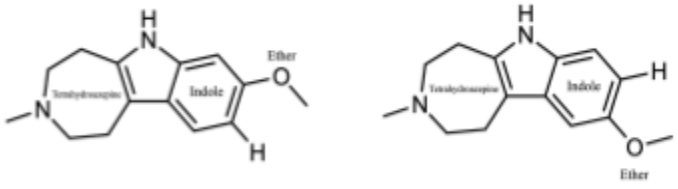
Ibogaine is highly nonpolar and lipophilic, promoting strong association with hydrophobic environments such as cell membranes and increases ibogaine's local concentration near membrane-embedded proteins such as hERG. hERG is a membrane-spanning potassium channel involved in cardiac repolarization, and ibogaine's lipophilicity contributes to unintentional hERG blockade. So evaluating functional group polarity gives insight into which moieties may be contributing to adverse effects. This led to Dr. Olsen isolating isoquinuclidine as the adverse functional group eliminating Scaffold 1 as a candidate.



Scaffold 1 Scaffold 2

Leaving Scaffold 2, with the tetrahydroazepine as a potential safe drug. Scaffold 2 lacks an isoquinuclidine ring therefore increasing polarity and reducing lipophilicity. With this change in polarity Dr. Olsen and his group found, an approximate 100-fold reduction in hERG inhibition in tabernanthalog (TBG, the drug made from scaffold 2). With the establishment of which parts of Ibogaine were causing the adverse effect to hERG, there were still other important biochemical aspects of the use of TBG that had to be inspected. [78]

Biased 5-HT$_2$A Signaling and Mitigation of Psychedelic Liability



Tabernanthalog (TBG) Ibogaminalog (IBG)

Source:https://www.nature.com/articles/s41586-020-3008-z

Secondly, Ibogaine's *primary psychoactive effect* arises from its activity at the serotonin 5-HT$_2$A receptor, a G-protein–coupled receptor (GPCR). Like many GPCRs, 5-HT$_2$A can adopt multiple

conformations depending on which ligand is bound; endogenous serotonin and psychedelics stabilize distinct signaling states. Olson's group identified the substructures responsible for hallucinogenic 5-HT_2A signaling and demonstrated that subtle modifications—such as shifting an ester from the C5 (IBG) to the C6 position (TBG)—can dramatically reduce or eliminate hallucinogenic signaling while preserving therapeutic pathways.[4],[5],[6] These results illustrate how small structural edits *can* bias GPCR signaling with high functional selectivity.

Does TBG Retain Ibogaine's Benefits?

CNS Pharmacokinetic Advantages

A key question then emerges: with so many structural changes, is TBG as effective as ibogaine?

The answer is that it retains many of ibogaine's beneficial properties and may even exceed them in certain aspects. One metric for evaluating CNS-active compounds is the CNS MPO (Central Nervous System Multi-Parameter Optimization) score, which integrates physicochemical parameters—logP, logD, molecular weight, topological polar surface area, hydrogen-bond donors, and pKa—into a 0–6 scale. Higher scores (≥4) correlate with improved brain penetration and reduced toxicity.[9],[10]

Ibogaine scores modestly (~3.8), IBG scores higher (~5.2), and although TBG's exact value has not been published, its physicochemical profile closely resembles IBG, supporting the hypothesis that TBG *may* demonstrate a similarly favorable CNS MPO.

Receptor Selectivity and Therapeutic Mechanism

Beyond safety improvements, TBG's receptor profile is central to its therapeutic value. A major design goal was the elimination of opioid receptor agonism to reduce abuse liability. Preclinical results show that TBG has negligible affinity for opioid receptors and does not produce conditioned place preference in rodents.[11],[12]

In contrast, TBG retains engagement at serotonin receptors, acting as a 5-HT_2A agonist with minimal or functionally antagonistic activity at 5-HT_2B.[13],[14] This selectivity is crucial because 5-HT_2B activation is associated with valvular heart disease; minimizing 5-HT_2B activity while preserving 5-HT_2A-mediated therapeutic effects greatly improves safety.

Interestingly, 5-HT_2A shows stereoselective preference for the (–)-ibogaine enantiomer, while the opposite enantiomer is largely inactive—highlighting the importance of chirality in receptor binding.

Neuroplasticity

Functionally, TBG and IBG both activate the neural-plasticity pathways associated with 5-HT_2A. Chronic stress, trauma, and depression reduce dendritic spine density and arbor complexity in the prefrontal cortex and hippocampus. Psychedelics counteract this by activating a cascade in which 5-HT_2A stimulation triggers glutamate release, which activates AMPA receptors, driving brain-derived neurotrophic factor (BDNF) secretion. BDNF then activates TrkB, initiating mTOR signaling—a central regulator of growth and protein synthesis. Once mTOR is stimulated, neurons begin forming new dendritic spines and strengthening synaptic connections.

This cascade (5-HT_2A → glutamate → AMPA → BDNF → TrkB → mTOR) drives psychedelic-induced structural plasticity and underlies TBG's ability to promote long-lasting therapeutic effects.[4],[14],[15]

Mechanistic Basis for Anti-Addictive Effects and SERT Modulation

In rodent models, TBG reduces alcohol- and heroin-seeking behavior.[11],[12]

Ibogaine's ability to reduce opioid withdrawal arises from two key pharmacological actions:

1. Partial κ-opioid receptor agonism, which reduces dysphoria and stress during withdrawal.

2. NMDA receptor antagonism, which decreases the glutamatergic hyperexcitability characteristic of withdrawal.[20],[21]

Ibogaine and its analogs also modulate the serotonin transporter (SERT) in a mechanistically unique way. Rather than acting as competitive reuptake inhibitors, they bind noncompetitively and stabilize SERT in an inward-open conformation, preventing serotonin reuptake.[16],[17]

TBG and related analogs similarly act as conformationally selective SERT inhibitors, suggesting they may function as antidepressants and psychoplastogens simultaneously.[18],[19]

Conclusion

Together, these structure–function insights—from hERG interactions and ester placement to stereochemistry, SERT modulation, and psychoplastogenic signaling—demonstrate how rational design can transform ibogaine from a risky psychedelic into safer, more effective analogs such as IBG and TBG.

In summary, the story of ibogaine and its modern analogs demonstrates how fundamental principles of organic chemistry—functional group transformations, stereoelectronic effects, ring modifications, and structure–activity relationships—directly translate into therapeutic innovation. The synthetic campaigns discussed throughout this paper reveal how subtle but intentional changes in molecular architecture, such

as relocating an ester substituent or removing the isoquinuclidine core, can dramatically alter polarity, receptor bias, metabolism, and cardiotoxic liability.[4],[5],[6],[7],[8]

These transformations reflect core concepts taught in undergraduate organic chemistry: how resonance, electronics, sterics, and conformational constraints dictate reactivity and biological function. By applying these principles, medicinal chemists were able to "de-risk" ibogaine's scaffold, separating its therapeutic psychoplastogenic effects from hallucinogenic signaling and hERG channel blockade.

At the biological level, ibogaine and its analogs display a uniquely polypharmacological profile: noncompetitive inhibition of SERT that stabilizes the transporter in its inward-open conformation[16],[17], rapid activation of the neuroplasticity cascade that restores dendritic complexity[14],[15], and modulation of withdrawal-associated circuits through κ-opioid and NMDA receptor mechanisms.[20],[21] This mechanistic convergence suggests a broader therapeutic potential compared with traditional monoamine-based antidepressants or single-target addiction treatments.

Future Directions

Notably, this mechanistic promise is reflected in human evidence. Observational studies and clinical reports conducted in New Zealand, Mexico, and Brazil report that a single ibogaine session can substantially reduce opioid withdrawal symptoms, decrease cravings, and maintain abstinence for weeks to months in a subset of patients. In one cohort, individuals with opioid dependence experienced rapid resolution of acute withdrawal within 24 hours and significant reductions in drug use for months afterward without additional dosing.[26] Other longitudinal studies have reported marked decreases in craving intensity, improved psychosocial functioning, and reduced relapse rates compared with baseline behavior.

While these studies are limited by their non-randomized designs, together they provide compelling early evidence that ibogaine's molecular mechanisms translate into meaningful clinical outcomes.

Ultimately, ibogaine and its rationally redesigned analogs stand as powerful examples of how organic chemistry enables therapeutic breakthroughs. The same principles students learn when studying stereochemistry, protecting groups, conformational analysis, or nucleophilic reactivity are the tools that allowed chemists to transform a complex natural product into safer, more selective, and more effective psychoplastogens. In this way, the ibogaine scaffold bridges organic with translational neuroscience—showing how mastering fundamental chemical logic empowers the development of next-generation neuropsychiatric treatments capable of addressing addiction, depression, and trauma through both molecular and behavioral mechanisms.

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