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Review

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# DARK Classics in Chemical Neuroscience: Ibogaine

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**Abstract**

The West African iboga plant has been used for centuries by the Bwiti and Mbiri tribes to induce hallucinations during religious ceremonies. Ibogaine, the principal alkaloid responsible for iboga's psychedelic properties, was isolated and sold as an antidepressant in France for decades before its adverse effects precipitated its removal from the market. An ibogaine resurgence in the 1960s was driven by U.S. heroin addicts who claimed that ibogaine cured their opiate addictions. Behavioral pharmacologic studies in animal models provided evidence that ibogaine could blunt self-administration of not only opiates but cocaine, amphetamines, and nicotine. Ibogaine displays moderate-to-weak affinities for a wide spectrum of receptor and transporter proteins; recent work suggests that its actions at nicotinic acetylcholine receptor subtypes may underlie its reputed anti-opiate effects. At micromolar levels, ibogaine is neurotoxic and cardiotoxic, and has been linked to several deaths by cardiac arrest. Structure-activity studies led to the isolation of the ibogaine analog 18-methoxycoronaridine (18-MC), a α3β4 nicotinic receptor modulator that retains ibogaine's anti-craving properties with few or no adverse effects. Clinical trials of 18-MC treatment of nicotine addiction are pending. Ibogaine analogs may also hold promise for treating anxiety and depression via the "psychedelic-assisted therapy" approach that employs hallucinogens including psilocybin and methylenedioxymethamphetamine ("ecstasy").

## Introduction

As science and medicine advanced, a pharmaceutical revolution began during the first half of the 20th century and led to the creation of many drugs that greatly improved general health.[1] Unintended consequences through the misuse and abuse of medications, however, are now a significant societal burden.[2] The opioid drug class contains the most potent and effective FDA-approved analgesics, functioning as mu, delta or kappa opioid receptor agonists.[3] The wide availability of prescription opioids such as fentanyl and oxycodone coupled with their tremendous potency trap many individuals in a lifelong addiction.[4] Cheaper street drugs such as heroin and methadone may be sought out by physically dependent individuals who cannot acquire prescriptions for licit analgesics. The current opioid abuse epidemic led the U.S. government to declare a "public health emergency" in 2017.[2] Nevertheless, the public perception of drug addiction is as a weakness, even a character flaw, rather than as the disease it actually is and that requires treatment and compassion.[5]

The Schedule I drug ibogaine has been touted as a cure for opiate addiction. Ibogaine is one of many alkaloid compounds from the root of the *Tabernanthe iboga* plant (**Figure 1**).[6,7] Iboga plays dual roles in the lives of the population of West Africa. Low doses are used as a stimulant to prevent fatigue on hunting excursions and to dull hunger and thirst; high doses are used for hallucinogenic properties during initiation rites and religious rituals.[8,9] The Bwiti and the Mbiri religious ceremonies involve extensive use of iboga (**Figure 2**).[10,11] The plant was brought to France in the mid-nineteenth century, and its primary psychoactive compound, the indole alkaloid 10-methoxyibogamine better known as ibogaine, was isolated in 1901.[12] Ibogaine was marketed in France under the trade name Lambarene for over 40 years. This purified ibogaine hydrochloride was prescribed as an antidepressant and sometimes used as a

stimulant.[13] Even though the hallucinogenic nature of ibogaine itself was documented in the early 1900s, the drug was administered to detoxified morphine addicts at the Addiction Research Center federal facility in Lexington, Kentucky in 1955,[12] and soon after exploited illicitly in the U.S.

Interest in ibogaine for its potential anti-addictive properties gained momentum with Howard Lotsof, a teenage New York City heroin addict who encountered the drug in 1962.[6,14] Lotsof reported taking ibogaine and experiencing several hours of vivid hallucinations and a panoramic life review, complete with interpretations of the meaning behind what he was seeing. Afterwards, his usual heroin withdrawal symptoms were reputedly absent. Lotsof claimed that ibogaine-generated insights into his motivation for abusing heroin contributed to his immediately abstaining from the opiate.[15] The loss of the impulse to abuse opiates transformed Lotsof into the leading advocate for ibogaine as an FDA-approved medical treatment for opiate addiction (**Figure 3**).[16] Anecdotal accounts from heroin users suggested that one treatment with ibogaine provided up to six months of relief, while a series of treatments was beneficial for up to three years.[11] There were ibogaine-associated deaths, however, leading to its Schedule 1 classification in 1970 and removal from the French market.[8] Lotsof continued his ibogaine research, receiving two patents in 1985 for using the drug to facilitate opiate withdrawal in patients.[12,17] Lotsof persuaded Stanley Glick, a behavioral pharmacologist at Albany Medical College, to test ibogaine in morphine-dependent rats. The results were promising enough to spur Glick to team with Martin Kuehne at the University of Vermont to create potent and effective but less toxic ibogaine analogs, leading to 18-methoxycoronaridine (18-MC), currently being prepared for clinical trials to treat nicotine addiction.[6]

## Chemical synthesis

Ibogaine (10-methoxyibogamine, CAS No: 83-74-9; **Figure 4**) has a molecular weight of 310, one hydrogen bond donor, three hydrogen bond acceptors, and a logP value = 3.65. The crystal structure of this natural product was published almost 60 years ago.[18] A total synthesis of ibogaine (**Scheme 1**) was first achieved by Büchi and coworkers in 1966 , beginning with initial reduction of N-benzyl-3-cyanopyridinum bromide (**S1-1**) using aqueous $NaBH_4$.[19] This reduction reaction provided a mixture of dihydropyridines (**S1-2** and **S1-3**) that was then condensed with methyl vinyl ketone (MVK) via Diels-Alder cycloaddition to yield isoquinuclidine **S1-4**. Subsequent hydrolysis with concentrated HCl then provided 1˚ amide **S1-5**, whose ketone was reduced with $NaBH_4$ to form a mixture of alcohol **S1-6** and acetate **S1-7**. Either of these compounds could then be oxidized with NaOCl to yield tricyclic urethane **S1-8** via a variation of the Hofmann rearrangement. Next, hydrolysis with 6N $H_2SO_4$, followed by acetylation with acetic anhydride, produced acetoxy ketone **S1-9**, which was then subjected to hydrogenolysis to provide the HCl salt of 2˚ amine **S1-10**. In turn, this 2˚ amine was condensed with 3-(5-methoxyindolyl)-acetyl chloride to provide 3˚ amide **S1-11**. An acetic acid solution containing *p*-toluenesulfonic acid was then used to cyclize **S1-11** to lactam **S1-12**, which was globally reduced with $LiAlH_4$, then subsequently oxidized and dehydrated to provide α,β-unsaturated ketone **S1-14**. Finally, the alkene in intermediate **S1-14** was first reduced with zinc in acetic acid, followed by Wolff-Kishner reduction of the requisite unsaturated ketone, provided a readily separable mixture of ibogaine (**1**) and its C4 epimer, **S1-15**.[19] It was noted by the authors that the structures synthesized were inconsistent with the configuration of the ethyl group found in the published crystal structures.[18,19]

A simplified total synthesis of ibogaine in 2012 (**Scheme 2**) started with 4-methoxy-2-iodaniline (**S2-1)**, which upon heteroannulation with a disilylated alkyne yielded **S2-2** and **S2-3**. Compound **S2-3** was converted into **S2-2** using triethylchlorosilane (TESCI) and imidazole, followed by silyl deprotection with TBAF to yield the 5-methyoxy-2-iodotryptol **S2-4** and subsequent iodination to form **S2-5**. Attachment of the tropane moiety was achieved with $CS_2CO_3$, providing **S2-6** and **S2-7**. Compound **S2-6** underwent a reductive Heck coupling in DMF to yield ibogaine at a 9.8% overall yield.[20]

**Manufacturing information**

As a compound classified as Schedule I by the Drug Enforcement Administration (DEA), the U.S. recognizes no therapeutic use for ibogaine and its analogs; its synthesis is for research purposes only. A Schedule I DEA license is required for a researcher to obtain the drug. Those with an active NIH grant are eligible to acquire radiolabeled and nonradioactive ibogaine and certain of its analogs from the National Institute on Drug Abuse (NIDA) Drug Supply Program (DSP). Compounds are synthesized-to-order via the NIDA DSP by the Research Triangle Institute (RTI; Research Triangle Park, NC). Sigma-Aldrich also provides ibogaine HCl in the U.S. Ibogaine is either Schedule I or illegal in the UK, Norway, Sweden, Denmark and France, but surprisingly unregulated in most countries. It has been legalized for prescription use in Brazil and New Zealand.[21,22] Ibogaine manufacturers or suppliers are listed in Cameroon, Canada, India and South Africa.[23]

**Drug metabolism**

Ibogaine subcutaneously or intraperitoneally administered to rats was found at 100-fold higher levels in adipose tissue compared to plasma after one hour, in keeping with the drug's lipophilicity. Intraperitoneal ibogaine levels dropped over 10-fold after 12 hours, suggesting first-pass metabolism by the liver.[24] The short half-life of ibogaine (two hours in rats, seven hours in humans)[24,25] is inconsistent with behavioral effects lasting 24 hours or more after its administration in animals.[8,26,27] Speculation about an active metabolite was confirmed with the identification of 12-hydroxyibogaine, commonly referred to as noribogaine.[28] Experiments with human liver microsomes showed that ibogaine undergoes demethylation at C-12, catalyzed primarily by CYP2D6 and to a lesser extent by CYP2C19 and CYP3A4 (**Figure 5**).[29] This was confirmed in a clinical study of orally-dosed ibogaine (20 mg) in healthy volunteers.[30] The half-life of noribogaine in humans varied between dosing groups from 27.6 - 49.7 hours.[31] The synthetic, less toxic ibogaine analog 18-methoxycoronaridine (18-MC; **Figure 4**) is metabolized to 18-hydroxycoronaridine (18-HC) by CYP2C19.[32] Pharmacokinetic data of orally administered ibogaine (500 – 800 mg dose) in humans showed that peak whole blood concentrations ranged from 700-1000 (ng/ml).[33] Intravenous infusion of ibogaine (20 mg/kg) in rats yielded a plasma concentration of 373 mg/ml after infusion and a brain concentration of 143-170 ng/g three hours after infusion.[34] Plasma levels ($C_{max}$) of noribogaine were reported for healthy volunteers when orally dosed at 3 mg (5.2 ng/ml), 10 mg (14.5 ng/ml), 30 mg (55.9 ng/ml), and 60 mg (116 ng/ml), with peak values appearing within 2-3 hours.[31] Brain concentrations of noribogaine after oral administration in rats were reported two hours after administration for 10 mg/kg (1727 ng/g), 30 mg/kg (5795 ng/g), 56 mg/kg (15117 ng/g), and 100 mg/kg (17067 ng/g) doses, representing high brain penetration for noribogaine.[35]

## Structure-activity relationships (SAR)

Ibogaine is the most abundant of approximately 80 structurally similar alkaloids found in the *Tabernanthe iboga* plant.[20,36] Most of these compounds have the ibogamine backbone, but also include variations of catharanthine (methyl(2α,5β,6α)-3,4-didehydroibogamine-18-beta-carboxylate), iboluteine (pseudoindoxylibogaine), and kisantine.[19] The adverse effects of ibogaine led to the synthesis and pharmacologic screening of chemical congeners in hopes of identifying less toxic anti-addictive compounds. The coronaridine scaffold was identified as a potential lead due to its lack of the development of tumors associated with ibogaine treatment.[37] The albifloranine structure (18-hydroxycoronaridine), originally isolated from the *tabernaemontana albifloria* plant, was chosen for synthetic manipulations and led to the development of 18-methoxycoronaridine (18-MC).[37] This analog retained efficacy in rodent models of inhibiting morphine and cocaine administration, while lacking the tremors and neurotoxicity associated with ibogaine.[38] Thirteen 18-MC analogs were evaluated for inhibition of binding at the opioid receptors and the α3β4 nicotinic acetylcholine receptor. A majority of the 18-MC analogs displayed marked inhibition (> 85%) of the α3β4 nACh receptor at 18 - 20 μM concentration.[39] Inhibition of this receptor has been proposed as the mechanism behind the anti-addictive properties of 18-MC.[40]

## Pharmacology

How exactly ibogaine triggers at the molecular level its curious effects remains a mystery. There is no clear receptor preference; ibogaine and most of its analogs bind with weak (micromolar) affinities to many target proteins (**Table 1**).

Unlike LSD, mescaline and psilocybin, the hallucinogenic properties of ibogaine cannot be ascribed to 5-$HT_{2A}$ receptor activation. Its active metabolite noribogaine does, however, display sub-micromolar kappa opioid receptor (KOP) affinity (0.61 μM; **Table 1**) and partial agonism ($E_{max}$ 72% of dynorphin A, and 18% activity in an arrestin recruitment assay).[41] This profile is reminiscent of the KOP-selective agonist and hallucinogen salvinorin A, although this natural product possesses considerably higher KOP affinity and potency.[42] Similarly, ibogaine's inhibition of binding of the noncompetitive, NMDA-selective antagonist [$^3$H]MK-801 ($IC_{50}$ = 5.2 μM in human caudate, 9.8 μM in human cerebellum)[43] may explain the dissociative effects of ibogaine shared with the NMDA channel blockers ketamine and phencyclidine.[44]

Ibogaine and noribogaine were effective in decreasing morphine self-administration in rats.[8,9] Consistent with this, ibogaine and noribogaine bind to the mu opioid receptor (MOP) in the low- and sub-μM range, respectively. [11,45] Noribogaine is a MOP partial agonist; its efficacy is dependent on the assay and model in which it is tested. The analog 18-MC also served as a MOP partial agonist relative to the full agonist and synthetic met-enkephalin derivative DAMGO.[46] In this way, ibogaine treatment of opiate physical dependence would mirror the current use of "maintenance" opiates such as methadone and buprenorphine, alleviating withdrawal symptoms while minimizing addiction risk.[47]

Ibogaine is also reported to curtail psychostimulant use.[48–50] The 2 μM Ki value for both ibogaine and noribogaine at the dopamine transporter (DAT; **Table 1**) essentially matches that of the amphetamines,[51,52] although the latter's abuse potential lies in its function as a DAT substrate and stimulator of dopamine *efflux* from neuron to synapse via the DAT.[53,54] Ibogaine, in contrast, is unusual among DAT (and SERT) inhibitors in that it binds to and stabilizes the *inward*-facing transporter conformation in the "alternating-access" mechanism responsible for

shunting the neurotransmitter substrate and ion cofactors into the neuron.[55,56] It is unclear how or if the preference for a DAT conformation different from that of amphetamine and cocaine could explain the observed behavioral differences. Ibogaine does differ from these more notorious drugs of abuse in that its DAT and SERT inhibition is noncompetitive.[56] Unlike the amphetamines, ibogaine and its analogs have not been reported to induce substrate efflux; presumably, the drug antagonizes amphetamine's ability to do so. The DAT affinity of cocaine, a DAT blocker that cannot induce substrate efflux, is approximately 20-fold higher than that of ibogaine and noribogaine.[51,57] Conceivably, ibogaine's mild interference with synaptic dopamine uptake is inadequate for eliciting euphoria, yet appreciable to the point of blunting cocaine self-administration in animals. Ibogaine and analogs also show the unusual property of serving as DAT and SERT "pharmacochaperones": binding of the drug stabilizes the tertiary structure of the transporter, even allowing misfolded mutant versions to refold into functional transporters.[51,58,59] It remains to be seen if this property is relevant to ibogaine's behavioral profile; however, it may explain ibogaine's effects on mood and psychological performance and noribogaine's anxiolytic effects in zebrafish.[60,61]

The adjuvant analgesic and anti-reinforcing actions of ibogaine may also be attributed to its actions at NMDA receptors. Given that glutamate is a principal pain neurotransmitter,[62] ibogaine's inhibition of NMDA receptors could contribute to the drug's potentiation of morphine analgesia.[63,64] Given that NMDA receptors are involved in the regulation of long-term memory formation,[65] modulation of NMDA signaling could contribute to the anti-addictive properties of ibogaine.[66] Interestingly, 18-MC has little or no NMDA receptor activity.[67]

Perhaps the most likely accounting for the alleged anti-addictive property of ibogaine is via its actions at the nicotinic acetylcholine receptor. Ibogaine is a non-competitive antagonist at

several nicotinic acetylcholine receptors including the α1β1 and α3β4 subtypes.[68,69] The α3β4 receptor is expressed within the habenulointerpeduncular cholinergic pathway of the brain, considered a second drug reward pathway.[68] Ibogaine displays binding affinities in the nM – μM range depending on the assay and model system.[70] For example, ibogaine binds to the human α3β4 receptor with $K_d$ = 460 nM in saturation binding assays, but a $K_i$ value of 56 μM is obtained when ibogaine displaces [$^3$H]-imipramine.[68,71] The ibogaine derivative 18-MC displays even weaker affinity ($K_i$ = 400 μM) in displacing [$^3$H]-imipramine.[71] Functionally, ibogaine is most potent with an $IC_{50}$ of 0.95 μM, with noribogaine and 18-MC respective $IC_{50}$ values at 6.2 μM and 1.47 μM as measured by the inhibition of (±)-epibatidine-induced $Ca^{2+}$ influx.[71] The anti-addictive properties of 18-MC have been connected to inhibition of the α3β4 receptor, as injection of 18-MC into the habenulointerpeduncular pathway inhibited nicotine administration in rodent models.[40] Intracranial injections of 18-MC within the medial habenula blocked dopamine release in rats sensitized to nicotine.[72]

**Adverse effects and dosage**

Although ibogaine appears promising in animal models of addiction, it has remained controversial due to life-threatening, dose-dependent adverse effects. In rodents, the median lethal doses ($LD_{50}$ values) for ibogaine and noribogaine are 263 mg/kg and 630 mg/kg body weight, respectively.[73] Preclinical studies with rats registered the development of tremors with ibogaine, not seen with noribogaine or 18-MC.[26,38] While 100 mg/kg ibogaine and 300 mg/kg noribogaine elicited no adverse effects in mice, higher doses (above 400 mg/kg with ibogaine and 500 mg/kg for noribogaine) produced convulsions, nervous behavior, and limb paralysis.[73] Ibogaine has been associated with neurotoxicity in rodents,[38] and death of Purkinje cells in the

cerebellar vermis due to excitotoxic glutamate release via activation of glia and astrocytes.[74] The neurotoxicity was replicated in rats, but not in mice [75]. In any event, the dose of ibogaine used clinically is well below the doses used to cause neuronal toxicity in preclinical settings.[76]

In clinical studies, nausea and ataxia have been reported from ibogaine administration at four times the recommended dose of 25 mg/kg.[76] A Phase 1 clinical study of 36 males taking noribogaine reported headache and nosebleed as adverse events;[31] seizures are reported with very high ibogaine doses.[77,78] Cardiovascular problems, specifically prolongation of the QTc interval, have contributed to fatalities associated with ibogaine ingestion.[13,76,79–81] This may be due to ibogaine's action at the human ether-a-go-go–related gene (hERG) channel—a potassium channel important for repolarization of cardiac neuromuscular junctions.[82] Ibogaine inhibited hERG potassium channels expressed in TSA-201 cells with an $IC_{50}$ value of 4 μM;[83] the inhibition was proposed to occur via hERG interactions in the cytosol.[84,85] A review of 19 ibogaine fatalities from 1990-2008 concluded that pre-existing heart conditions contributed to ibogaine's lethality in 12 of the 14 cases with sufficient autopsy data.[76] A thorough examination of the ibogaine – cardiac arrest relationship can be found in Reference 93.

High doses of ibogaine trigger hallucinations of 24 hours or more.[33,50,74] Use of the iboga plant is purported to stimulate a retrospective viewpoint of traumatic childhood events and experiences, also permitting the drug addict to perceive the addiction.[86] The experience has been described as a dissociative, dream-like state, and is attributed to ibogaine's cholinergic effects.[77] Recently, 22 ibogaine users in Brazil compartmentalized their ibogaine "highs" into three phases. The first phase of 4-8 hours consisted of intense emotional, cognitive, and perceptual feelings. The effects gradually decreased during the following 8-20 hours (second phase). An additional

1-3 days were needed before the subjects perceived a full return to normal consciousness (third phase).[87]

**History and importance in neuroscience**

Beginning in 1962, Howard Lotsof advocated for ibogaine's use in treating opiate addiction, first based on his personal experience and later from controlled experiments. He published many accounts of addicts who used ibogaine to treat their addictions, usually successfully.[14,49,50,88] His findings and proselytizing persuaded pharmaceutical scientists in academia and industry to seriously consider and experimentally address the possibility that ibogaine or its derivatives possessed useful anti-addictive properties.[6] Lotsof's prodding led Stanley Glick and colleagues to intraperitoneally inject 2.5 – 80 mg/kg doses of ibogaine into rats, employing a morphine self-administration model. Indeed, ibogaine pretreatment at doses above 10 mg/kg was effective in decreasing morphine self-administration, an effect lasting weeks in some animals.[8] In support of the premise that anti-addictive drugs decrease dopamine signaling within the nucleus accumbens and/or the prefrontal cortex, *in vivo* microdialysis showed that pretreatment with ibogaine (40 mg/kg) 19 hours before a morphine challenge (5 mg/kg) blunted the release of dopamine in both the nucleus accumbens and the prefrontal cortex.[9] This effect was seen long after ibogaine was eliminated from the body, foreshadowing the discovery of an active metabolite identified as noribogaine.[26,28,89] Similar to ibogaine, noribogaine was shown to decrease morphine and cocaine self-administration, water bar presses, and dopamine release in the nucleus accumbens in Sprague-Dawley rats.[90] Noribogaine has been shown to dose-dependently inhibit self-administered intravenous nicotine consumption by rats,[91]

likely due to its modulation of α3β4 nACh receptors.[71,92] It is worth noting that the smoking cessation drug varenicline (Chantix) is a α4β2 nACh receptor partial agonist.[93] Moreover, noribogaine demonstrated a 23% depression in food intake in rats,[91] providing the rationale for assessing the efficacy of 18-MC as an anti-obesity candidate.[94]

## Conclusion

The natural alkaloid and legendary street drug ibogaine belongs in the DARK Classic category in that it is a double-edged sword, evoking fascination with its hallucinogenic properties and promise as an anti-addiction magic bullet and at the same time dread of its unpredictable lethality. Ibogaine, and to some extent its chief metabolite noribogaine, may exhibit properties that mitigate the physical dependence on opiates and other drugs of abuse, but for many self-experimenters there is a heavy price to pay in the form of cardiovascular damage, neurotoxicity, and even death. The search for analogs that retain the positive aspects of ibogaine and lack its adverse effects led to the discovery of 18-methoxycoronaridine (18-MC), a compound that inhibits morphine, cocaine, methamphetamine, ethanol and nicotine self-administration and/or drug-seeking behavior in rodents[95-96] without displaying ibogaine-like tremors or cerebellar toxicity at therapeutic doses.[38]

Ibogaine, noribogaine, 18-MC and other analogs bind to multiple receptor and transporter proteins, but recent findings suggest that nicotinic acetylcholine receptor subtypes could be the target in blocking the craving for drugs of abuse. The anti-addictive properties of 18-MC, now in preparation for clinical trials as a smoking cessation therapeutic, appear to be mediated in part at the level of the α3β4 nACh receptor.[67,71,92] In the view of the authors, the notion that a nicotinic receptor subtype is by itself the target that wholly mediates anti-addiction or anti-

dependence properties of ibogaine or its analogs is unconvincing. Nor is the idea palatable that the primary biological target of the iboga alkaloids remains undiscovered. More attractive is the possibility that ibogaine's simultaneous actions at multiple receptors creates the observed behavioral profile.

While ibogaine was once used and then discarded as an antidepressant in Europe[13], its analogs may hold promise for treating anxiety and depression today via the "psychedelic-assisted therapy" approach in vogue.[98] Ketamine, also a dissociative anesthetic, is effective in treating depression that is otherwise medication-resistant[99] and should soon be FDA-approved. Psilocybin, LSD and MDMA ("ecstasy") are also psychedelics currently under investigation regarding treating depression and severe anxiety disorders.[98,100]

Remarkably, the curiosity and tenacity of a 19-year-old New York City addict lacking formal medical training or political power launched a worldwide fascination with a hallucinogen that reputedly cured him of his opiate addiction. Decades later and after countless NIH-funded investigations and global clinical trials, a structural analog of Howard Lotsof's wonder drug may one day serve as a true pharmacotherapeutic for addiction and other CNS disorders.

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**Legends to figures, schemes and tables**

**Figure 1**: *Tabernanthe iboga* bush (reproduced with permission from www.triptowellness.net)

**Figure 2:** Bwiti tribesman during iboga ceremony (reproduced with permission from www.buyiboga.com)

**Figure 3:** Lotsof's Elixir (www.pinterest.com – image in the public domain)

**Figure 4:** Chemical structures of ibogaine, noribogaine, and 18-methoxycoronaridine (18-MC)

**Figure 5:** Metabolic pathway of ibogaine

**Figure 6:** Development pathway from ibogaine to 18-MC

**Scheme 1:** Original total synthesis of ibogaine (Büchi et al., 1966)

**Scheme 2:** Revised total synthesis of ibogaine (Jana and Sinha, 2012)

**Table 1:** Ibogaine, noribogaine and 18-MC affinities for biological targets

Reported binding affinity ($K_i$ values) for ibogaine, noribogaine, and 18-MC. Functional data is reported as follows: * antagonistic properties, ** partial agonist properties, *** full agonist properties, # pharmacochaperone, $ missing value.

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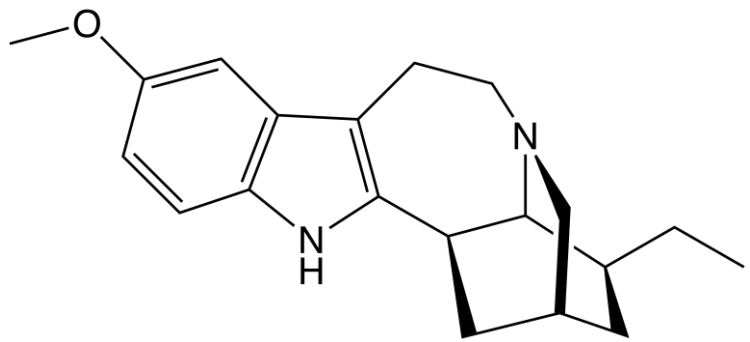
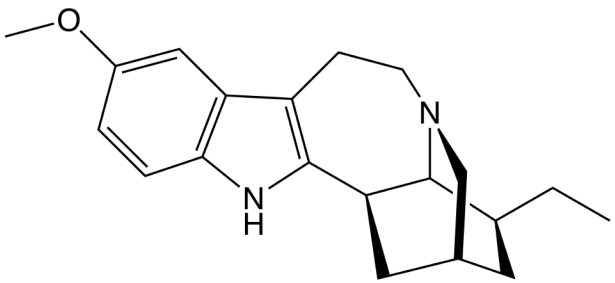
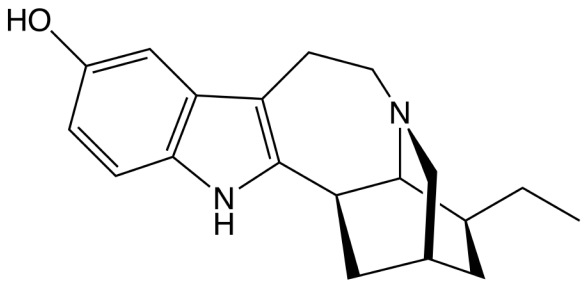



Ibogaine

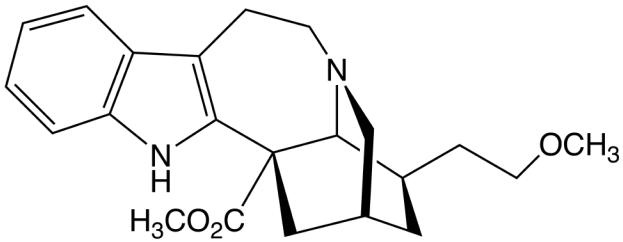
Ibogaine

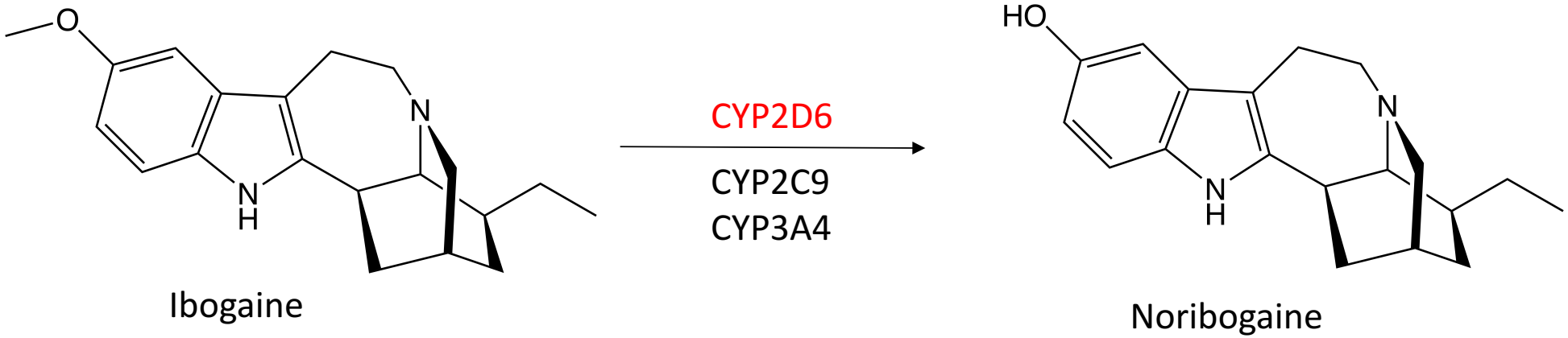



Noribogaine




18-MC



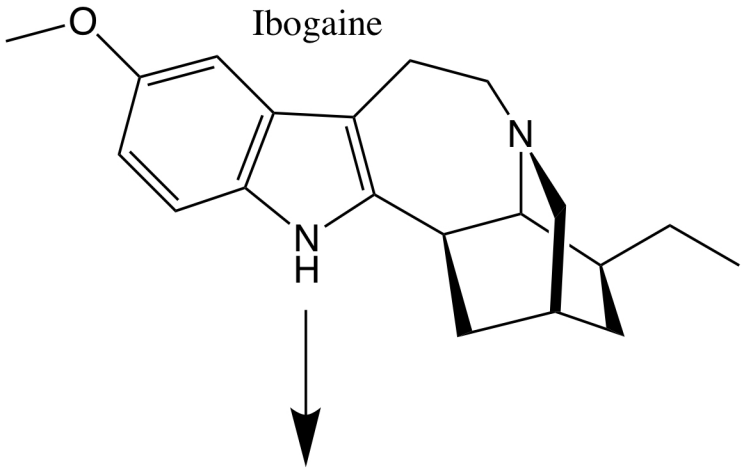


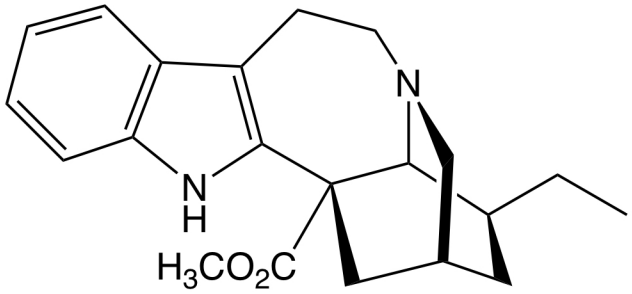

Ibogaine

Noribogaine

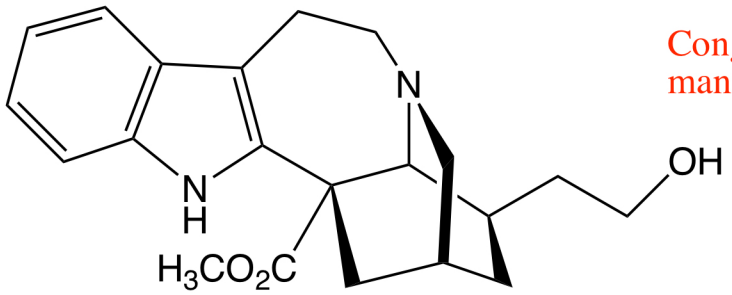
Major Pathway

Minor Pathway

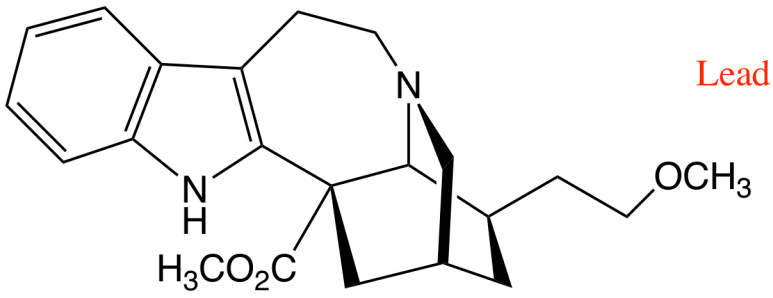


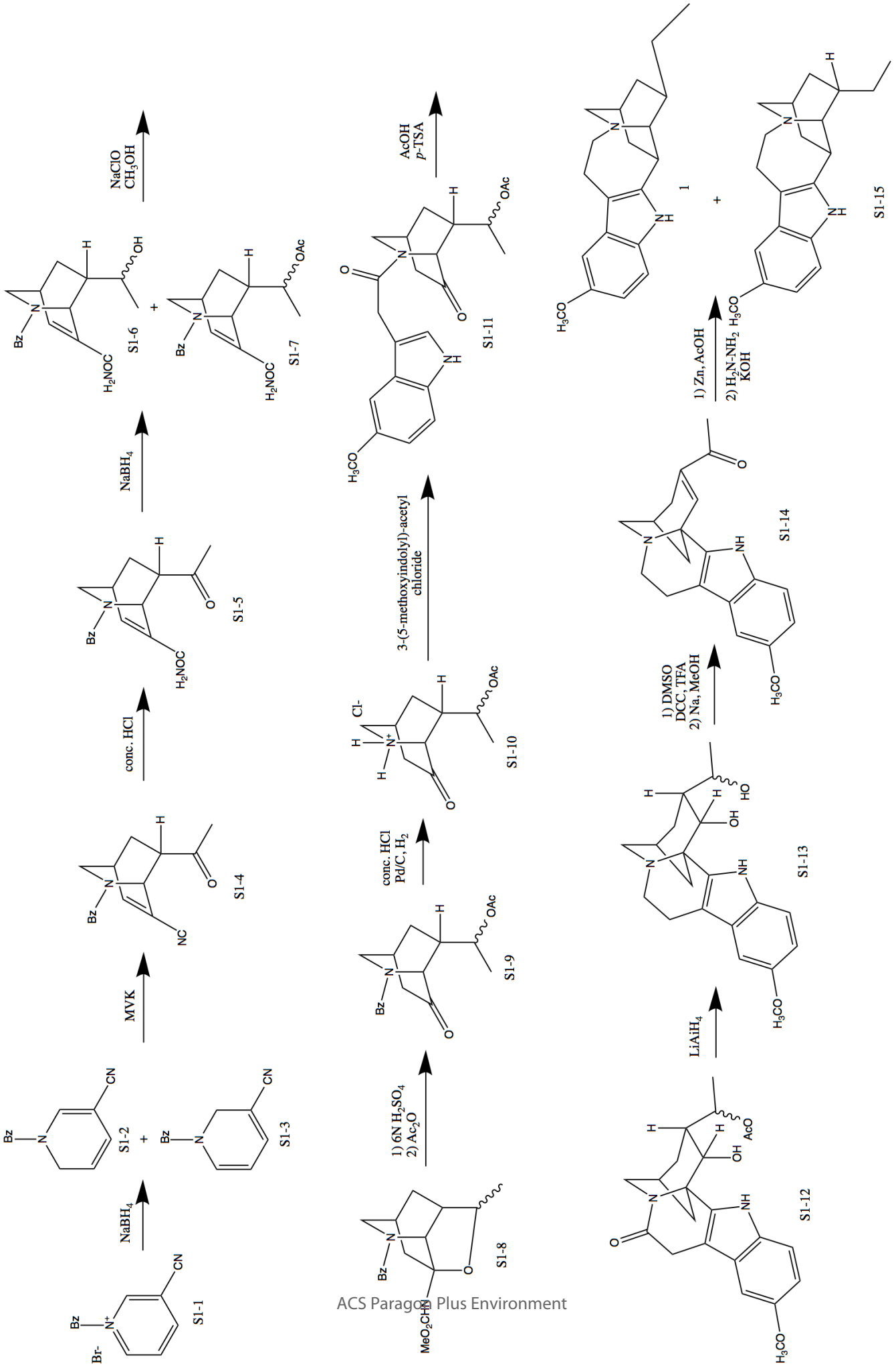

Scaffold lacking the tremorigenic effects seen in ibogaine




Congener suitable for synthetic manipulations




Lead compound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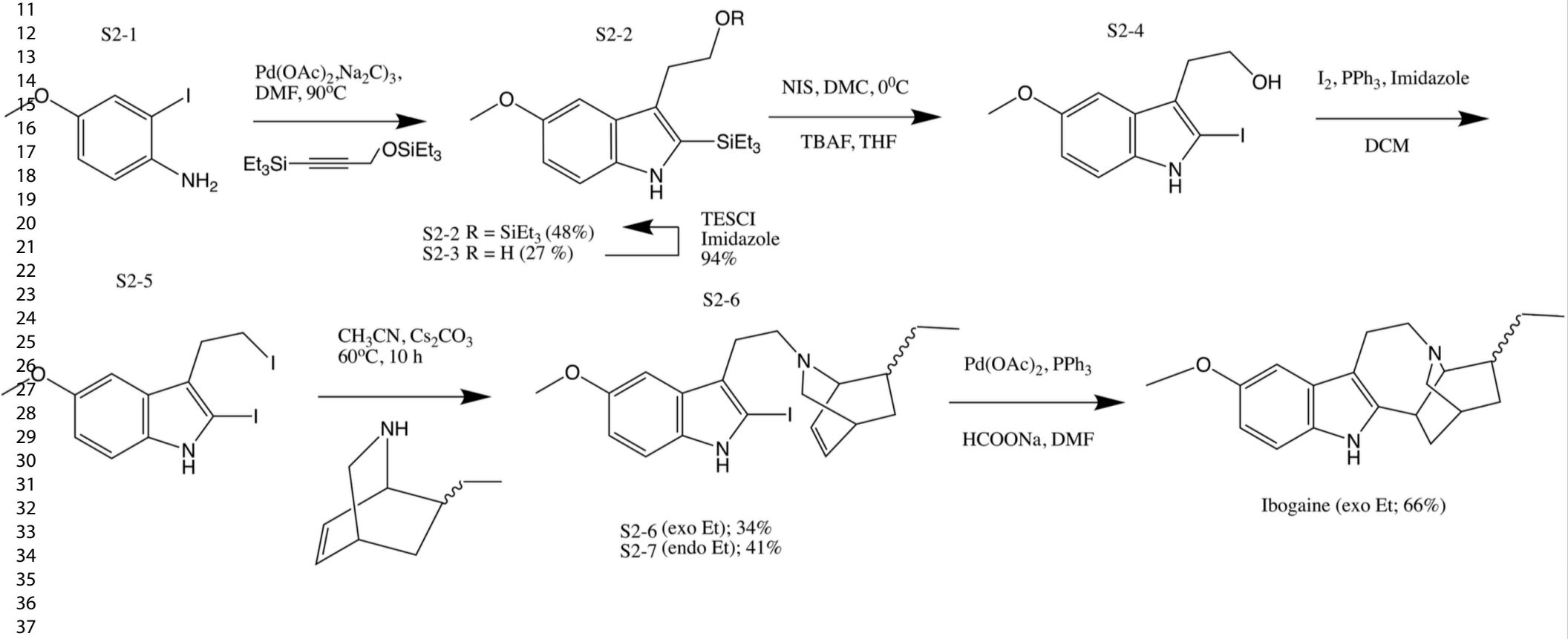
MVK
conc. HCl
NaBH4
NaClO
CH3OH
1) 6N H2SO4
2) Ac2O
conc. HCl
Pd/C, H2
3-(5-methoxyindolyl)-acetyl chloride
AcOH
p-TSA
LiAlH4
1) DMSO
DCC, TFA
2) Na, MeOH
1) Zn, AcOH
2) H2N-NH2 H3CO
KOH
S1-1
S1-2
S1-3
S1-4
S1-5
S1-6
S1-7
S1-8
S1-9
S1-10
S1-11
S1-12
S1-13
S1-14
S1-15
1


S2-1
Pd(OAc)2,Na2C)3,
DMF, 90°C
Et3Si
OSiEt3
S2-2
OR
SiEt3
NIS, DMC, 0°C
TBAF, THF
S2-4
OH
I2, PPh3, Imidazole
DCM
S2-2 R = SiEt3 (48%)
S2-3 R = H (27 %)
TESCI
Imidazole
94%
S2-5
CH3CN, Cs2CO3
60°C, 10 h
S2-6
S2-6 (exo Et); 34%
S2-7 (endo Et); 41%
Pd(OAc)2, PPh3
HCOONa, DMF
Ibogaine (exo Et; 66%)

| Receptor | Affinity (Ki, μM) | | | Reference |
|---|---|---|---|---|
| | Ibogaine | Noribogaine | 18-MC | |
| KOP | 2.2 ** | 0.61 ** | 5.1 | 41, 45 |
| MOP | 2.0 * | 0.68 ** | 1.1 ** | 45, 46 |
| DOP | >10 | 5.2 | 3.5 | 45 |
| | >100 | 25 | | 89 |
| $5\text{-HT}_{1A}$ | >100 | >100 | 46 | 45 |
| $5\text{-HT}_{1D}$ | >100 | >100 | >10 | 45 |
| $5\text{-HT}_{2A}$ | 16 | >100 | 40 | 45 |
| $5\text{-HT}_{3}$ | 2.6 | >100 | 3.8 | 45 |
| $D_1$ | >10 | >10 | >100 | 45 |
| $D_2$ | >10 | >10 | >16 | 45 |
| $D_3$ | 70 | >100 | 25 | 45 |
| NMDA | 3.1 | 15 | > 100 | 45 |
| | 5.2 | 31 | | 43 |
| | 9.8 | 38 | | 43 |
| $M_1$ | 16 | 15 | 32 | 45 |
| $M_2$ | 32 | 36 | >100 | 45 |
| nAChα3β4 | 56 * | * $ | 400 * | 69, 71 |
| | (Kd = 0.46) | | | 68 |
| | 1.1, 9.5, 17 | | | 68 |
| Na channel | 3.6 | 17 | 6.4 | 45 |
| σ1 | 2.5 | 11 | >100 | 45 |
| | 8.5 | 15 | | 97 |
| σ2 | 0.40 | 19 | 13 | 45 |
| | 0.19 | 5.2 | | 97 |
| SERT | 4.1 # | 0.57 | >10 | 28, 45, 58 |
| DAT | 2.0 | 2.0 # | $ | 51 |
| NET | >100 | 39 | > 10 | 45 |