Yohimbine

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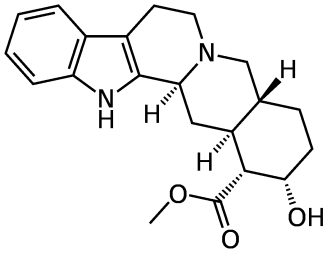
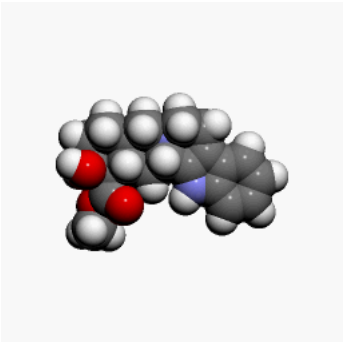




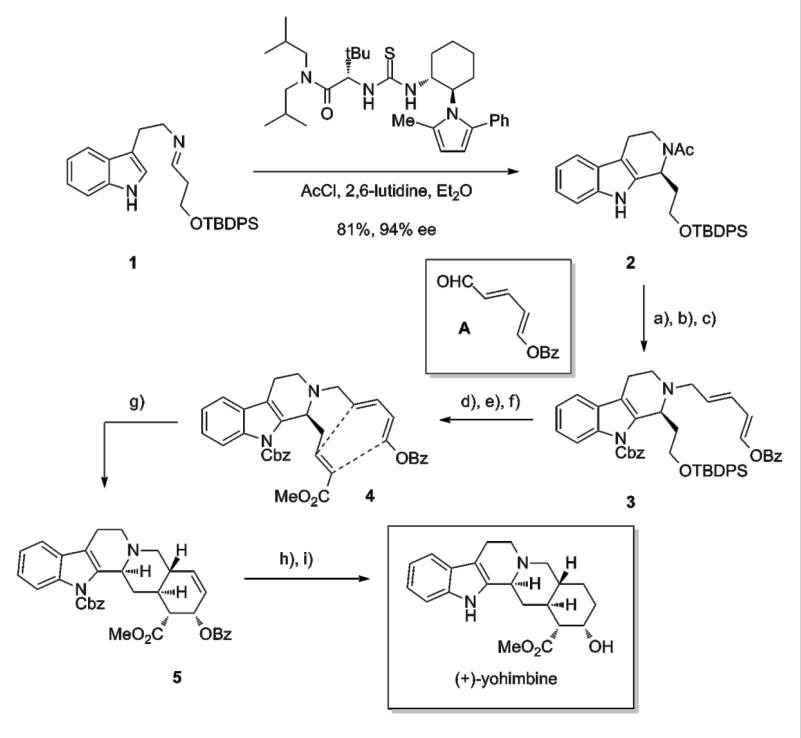
Systematic (IUPAC) name	
17α-hydroxy-yohimban-16α-carboxylic acid methyl ester	
Clinical data	
Trade names	Actibine, Erex, Testomar, Yocon, Yohimar, Yohimbe
Legal status	Prescription Only (S4) (AU) OTC supplement (US)
Routes	Oral
Pharmacokinetic data	
Half-life	0.25-2.5 hours
Excretion	Urine (as metabolites)
Identifiers	
CAS number	146-48-5 [1] ✓
ATC code	G04BE04 [2] QV03AB93 [3]
PubChem	CID 8969 [4]
IUPHAR ligand	102 [5]
DrugBank	DB01392 [6]
ChemSpider	8622 [7] ✓
UNII	2Y49VWD90Q [8] ✓
ChEBI	CHEBI:10093 [9] ✓
ChEMBL	CHEMBL15245 [10] ✓

Chemical data	
Formula	$C_{21}H_{26}N_2O_3$
Mol. mass	354.44 g/mol (base) 390.90 g/mol (hydrochloride)
✓ **(what is this?) (verify)** [11]	

Yohimbine is a mild MAOI with stimulant and aphrodisiac effects. It is sold as prescription medicine in pure form for the treatment of sexual dysfunction. Yohimbine was explored as a remedy for type 2 diabetes in animal and human models carrying polymorphisms of the α_{2A}-adrenergic receptor gene.

Common brand names for Yohimbine are: Erex, Testomar, Yocon, Yohimar, Yohimbe.

Synthesis



Research

Yohimbine primarily acts as an antagonist of α_2 receptors. Additionally, it inhibits the function of monoamine oxidase enzymes, although it is not clear if it is a RIMA, MAOA, or MAOB inhibitor.

RIMAs, like moclobemide (an antidepressant), do not require dietary restrictions. Many people have been supplementing with yohimbine on normal diets (containing tyramine and phenylalanine, found in most cheeses and fish respectively) with no adverse effects. MAOIs are normally contraindicated for use with tyrosine-rich food,[*citation needed*] but recently, numerous[*citation needed*] companies have begun combining yohimbine with tyrosine in their energy products. However, tyrosine failed to potentiate the effect of yohimbine except for somewhat augmenting the increase in DHPG.

When yohimbine are used in pharmahuasca it does not have any MAOI effects on tryptamines, e.g. DMT keeps being orally inactive. This suggest that yohimbine is a MAOB inhibitor. A range of cacti contain tyramine, including the *Echinopsis pachanoi* (syn. *Trichocereus pachanoi*), known as the San Pedro cactus which also contain the phenylethylamine mescaline. Multiple drug use with yohimbine and mescaline cactus are inconclusive.[*citation needed*]

Overdoses of yohimbine can cause priapism. Normally priapism is treated with pseudoephedrine, but in combination with MAOIs like yohimbine it can lead to hypertensive reactions. The first step in management may be blood exchange transfusion.[*citation needed*]

Medical uses

Indications

SSRI side-effects

MAOI and SSRI are normally never mixed as a rule of thumb. However, yohimbine, with its weak MAOI activity, has safely been used to treat sexual side-effects caused by some SSRI antidepressants (see below for more information about sexual dysfunction).[*medical citation needed*] Also, 14 mg yohimbine increases salivation, so yohimbine could have a potential interest in the treatment of dry mouths, another common side-effect caused by SSRIs. In fact, doctors believe that heartburn, another common SSRI side-effect, is caused by dry mouth because it reduces the amount of saliva running down the esophagus (saliva is known to neutralize excess acid in the stomach).[12]

Sexual dysfunction

The NIH states that yohimbine hydrochloride is the standardized form of yohimbine that is available as a prescription medicine in the United States, and that it has been shown in human studies to be effective in the treatment of male impotence. Yohimbine has been shown to be effective in the treatment of orgasmic dysfunction in men. Yohimbine has also been used to treat hypoactive sexual desire disorder (reduced libido) in women.[13]

Large doses of yohimbe have caused priapism. However, controlled studies suggest that it is not always an effective treatment for impotence, and evidence of increased sex drive (libido) is anecdotal only.

> It cannot be excluded that orally administered yohimbine can have a beneficial effect in some patients with ED. The conflicting results available may be attributed to differences in drug design, patient selection, and definitions of positive response. Generally, however, available results of treatment are not impressive.

Yohimbine blocks the pre- and post-synaptic α_2 receptors. Blockade of post-synaptic α_2 receptors causes minor corpus cavernosum smooth muscle relaxation. In fact, the majority of adrenoceptors in the corpus cavernosum are of the α_1 type. Blockade of pre-synaptic α_2 receptors facilitates the release of several neurotransmitters in the central and peripheral nervous system — thus in the corpus cavernosum — such as nitric oxide and norepinephrine. Whereas nitric oxide released in the corpus cavernosum is the major vasodilator contributing to the erectile process, norepinephrine is the major vasoconstrictor through stimulation of α_1 receptors on the corpus cavernosum smooth muscle. Under physiologic conditions, nitric oxide attenuates norepinephrine vasoconstriction. Continuous administration of yohimbine, as opposed to on-demand administration, might result in less norepinephrine output due to increased turnover, or α_1 receptors down regulation via a feedback mechanism, not causing the vasoconstriction due to excessive norepinephrine release which can be seen often with on-demand administration. α_1 blockers prevent vasoconstriction caused by norepinephrine as well.

Dosage

- Anorgasmia or reduced libido: 5.4-16.2 mg a day 1–2 hours before sexual activity. or 5.4 mg three times a day
- Erectile dysfunction: A suggested first line treatment for mild to moderate ED are a combination of 6 mg yohimbine hydrochloride and 6000 mg arginine glutamate (50% arginine, 50% glutamic acid). Other doses of yohimbine alone to treat ED are 15 to 30 mg a day 1–2 hours before sexual activity.

Fat loss

There is no conclusive evidence for Yohimbine to be of benefit in bodybuilding or weight loss.

Other uses

Yohimbine has also been used for xerostomia, as a blood pressure boosting agent in autonomic failure, and as a probe for noradrenergic activity. Wikipedia:Identifying reliable sources (medicine)

The addition of yohimbine to fluoxetine or venlafaxine has also been found to potentiate the antidepressant action of both of these agents.

Yohimbine has been used to facilitate recall of traumatic memories in the treatment of post traumatic stress disorder (PTSD). Use of yohimbine outside of therapeutic settings may not be appropriate for persons suffering from PTSD. In pharmacology, yohimbine is used as a probe for α_2-adrenoceptor. In veterinary medicine, yohimbine is used to reverse anesthesia from the drug xylazine in small and large animals.

Adverse effects

Depending on dosage, yohimbine can either lower or increase systemic blood pressure, known as vasodilation and vasoconstriction respectively; small amounts of yohimbine can increase blood pressure, while large amounts can dangerously lower blood pressure.

The therapeutic index of yohimbine is quite low; the range between an effective dose and a dangerous dose is very narrow. A typical dose for sexual dysfunction would be 15–30 mg, whereas 100 mg would be considered dangerous. This may also lead to the precipitation of panic disorder type reactions, heart attack, and possibly death.

Hallucinations or paralysis may occur with doses greater than 40 mg. Higher doses of oral yohimbine may create numerous side effects, such as rapid heart rate, overstimulation, insomnia and/or sleeplessness. Some effects in rare cases were panic attacks, hallucinations, headaches, dizziness, and skin flushing.[]

More serious adverse effects may include seizures and renal failure. Yohimbine should not be consumed by anyone with liver, kidney, heart disease, or a psychological disorder.

Precautions and contraindications

Yohimbe bark is on the FDA list of dangerous supplements. The levels of yohimbine that are present in yohimbe bark extract are variable and often very low. Therefore, although yohimbe bark has been used traditionally to reduce male erectile dysfunction, there is not enough scientific evidence to form a definitive conclusion in this area.

In Africa, yohimbe has traditionally been used as an aphrodisiac.[14] However, it is important to note that while the terms *yohimbine*, *yohimbine hydrochloride*, and *yohimbe bark extract* are related, they are not interchangeable.

Yohimbine is an alkaloid naturally found, along with several other active alkaloids, in *Pausinystalia yohimbe* (Yohimbe), *Rauwolfia serpentina* (Indian Snakeroot), and *Alchornea floribunda* (Niando). Yohimbine has been used as an over-the-counter dietary supplement in herbal extract form.

In addition to the main active chemical, yohimbine, *Pausinystalia yohimbe* contains approximately 55 other alkaloids, of which yohimbine accounts for 1% to 20% of total alkaloids. Among them, corynanthine is an α_1 receptor blocker. Hence the use of yohimbe extract in sufficient dosages may provide concomitant α_1 and α_2 receptors blockade and thus may better enhance erections than yohimbine alone.

Pausinystalia yohimbe is currently threatened with extinction in its native habitat due to international demand.[*citation needed*] Its conservation is difficult because the bioactivity of the tree has led many Western governments to declare it a proscribed species.

Interactions

MAOIs

At least 14 days should elapse between discontinuation of MAOI therapy and initiation of treatment with yohimbine.

NRIs

Yohimbine in combination with norepinephrine reuptake inhibitor such as dextromethorphan, tramadol, some antidepressants, and central nervous system stimulants used to treat ADHD, can cause a hypertensive crises. This is due to those drugs in combination with an α_2 receptor antagonist leads to too much norepinephrine in the brain, which causes blood pressure to spike to dangerous levels.

Yohimbine in combination with modafinil is frequently associated with nausea, dangerous acute rapid heart beat, and acute increased blood pressure. Yohimbine exhibits some degree of MAOI activity, while modafinil has been shown to increase levels of various monamines and therefore could result in severe risk of dangerous side effects.

Stimulants

Research on cats suggests that yohimbine increases the effects of catecholaminergic stimulants, namely amphetamine and modafinil.

Sports

Sport supplements with yohimbine as the main ingredient are sold as purported energy boosters.[*citation needed*]

Pharmacology

Yohimbine has high affinity for the α_2-adrenergic receptor, moderate affinity for the α_1 receptor, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1F}, 5-HT_{2B}, and D_2 receptors, and weak affinity for the 5-HT_{1E}, 5-HT_{2A}, 5-HT_{5A}, 5-HT_7, and D_3 receptors. It behaves as an antagonist at α_1-adrenergic, α_2-adrenergic, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2B}, and D_2, and as a partial agonist at 5-HT_{1A}. Its intrinsic activities at the other sites listed are unclear/unknown, but it is probably mostly antagonistic at them.[*citation needed*] Yohimbine interacts with serotonin and dopamine receptors in high concentrations.

Pharmacologic Profile of Yohimbine

Molecular Target	Binding Affinity (K_i in nM)	Pharmacologic Action	Species	Source
SERT	1,000	Inhibitor	Human	Frontal Cortex
DAT	1,000	Inhibitor	Rat	Brain
5-HT_{1A}	346	Partial Agonist	Human	Cloned
5-HT_{1B}	19.9	Antagonist	Human	Cloned
5-HT_{1D}	44.3	Antagonist	Human	Cloned
5-HT_{1E}	1,264	Unknown	Human	Cloned
5-HT_{1F}	91.6	Unknown	Human	Cloned
5-HT_{2A}	1,822	Antagonist	Human	Cloned
5-HT_{2B}	143.7	Antagonist	Human	Cloned
5-HT_{2C}	>10,000	Unknown	Human	Cloned
5-HT_3	>10,000	Unknown	Rat and Mouse	Cloned, Cortex & NG108-15
5-HT_{5A}	1,000	Unknown	Rat and Mouse	Cloned

5-HT_7	2,850	Unknown	Human	Cloned
α_{1A}	1,680	Antagonist	Human	Cloned
α_{1B}	1,280	Antagonist	Human	Cloned
α_{1C}	770	Antagonist	Human	Cloned
α_{1D}	557	Antagonist	Human	Cloned
α_{2A}	1.05	Antagonist	Human	Cloned
α_{2B}	1.19	Antagonist	Human	Cloned
α_{2C}	1.19	Antagonist	Human	Cloned
D_1	>10,000	Unknown	Human	Cloned
D_2	339	Unknown	Human	Cloned
D_3	3,235	Unknown	Human	Cloned

References

[1] http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?term=146-48-5&rn=1
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