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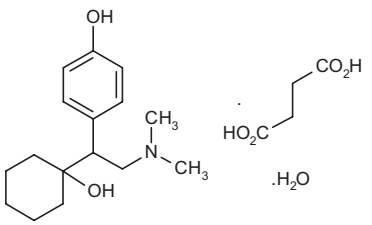
Desvenlafaxine Succinate

Prop INNM; USAN

Antidepressant
Treatment of Postmenopausal Syndrome
5-HT and Norepinephrine Reuptake Inhibitor

O-Desmethylvenlafaxine
DVS-233
WY-45233 (as free base)

4-[2-(Dimethylamino)-1-(hydroxycyclohexyl)ethyl]phenol succinate hydrate



$C_{20}H_{33}NO_7$
Mol wt: 399.4786

CAS: 386750-22-7

CAS: 093413-62-8 (as free base, anhydrous)

EN: 326260

Abstract

There are three major classes of drugs available for the pharmacotherapy of depression: tricyclic antidepressants, monoamine oxidase (MAO) inhibitors and selective serotonin reuptake inhibitors (SSRIs). Venlafaxine, a tricyclic compound which was launched in 1994, was the first serotonin and norepinephrine reuptake inhibitor (SNRI) and exhibited particular efficacy as a first-line treatment for major depression, being devoid of the anticholinergic, sedative and cardiovascular adverse events common to many antidepressants. In an effort to further improve the efficacy and safety profile of this agent, several oxidative metabolites of venlafaxine were identified. Of these metabolites, *O*-desmethylvenlafaxine (desvenlafaxine, DVS-233, WY-45233) displayed the greatest preclinical antidepressant activity and tolerability and was chosen for further development. Preclinical studies also indicated that desvenlafaxine may be effective in relieving vasomotor symptoms associated with menopause (*i.e.*, hot flashes and night sweats). The succinate salt is preregistered for the treatment of major depression and continues to undergo testing for the relief of vasomotor symptoms associated with menopause.

Synthesis

Desvenlafaxine succinate can be obtained by *O*-dealkylation of venlafaxine (I) using several different reagents. Demethylation of (I) has been reported by treatment with sodium dodecanethiolate in either polyethylene glycol (PEG) 400 at 190 ºC or in EtOH at 150 ºC in a sealed tube, or by treatment with sodium thiophenolate in PEG 400 at 160 ºC (1-3). An alternative reagent reported for the demethylation of (I) is lithium tri(*sec*-butyl)borohydride (L-selectride) in hot 1,2-dimethoxyethane (1, 2). The desvenlafaxine base (II) obtained can be converted to the succinate salt by treatment with succinic acid in aqueous acetone (1). Scheme 1.

In an alternative method, the fumarate salt of desvenlafaxine can be prepared. Treatment of 4-benzyloxyphenylacetic acid (III) with oxalyl chloride in the presence of a catalytic amount of DMF gives the acid chloride (IV), which is condensed with dimethylamine in CH_2Cl_2 to produce the corresponding amide (V). Deprotonation of amide (V) using butyl lithium in cold THF, followed by condensation with cyclohexanone (VI), gives the hydroxycyclohexyl acetamide (VII), which is subsequently reduced to the amine (VIII) by means of alane, generated *in situ* from $LiAlH_4$ and H_2SO_4. Debenzylation of (VIII) is then effected by transfer hydrogenolysis in the presence of Pd/C and 1,4-cyclohexadiene to produce desvenlafaxine, which is finally isolated as the corresponding fumarate salt (4, 5). Scheme 2.

Background

Depression is a psychiatric disorder that can be a primary condition or may co-exist with other mental, psychiatric or physical illnesses. Many subtypes of depression have been described, including major depressive disorder (or unipolar major depression), bipolar disorder (or manic-depressive illness), dysthymic disorder, adjust-

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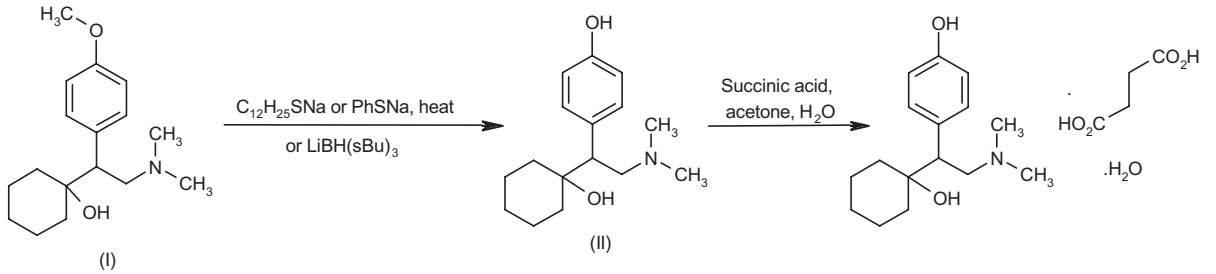
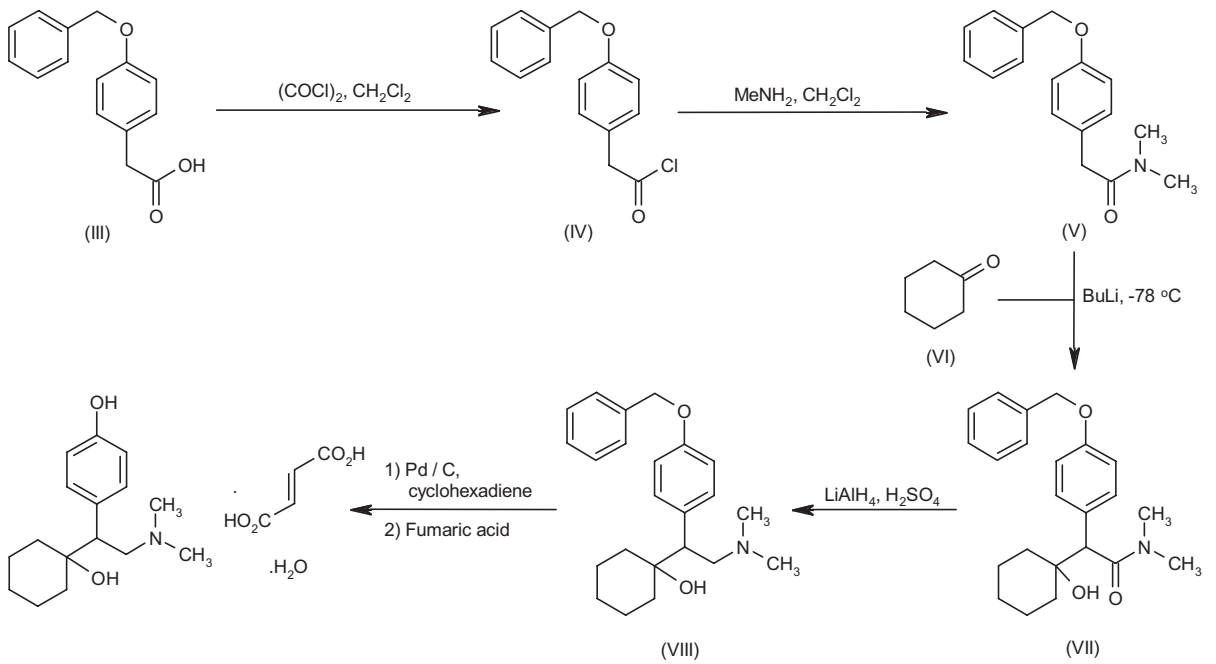
Scheme 1: Synthesis of Desvenlafaxine Succinate



Scheme 2: Synthesis of Desvenlafaxine Fumarate



ment disorder, seasonal affective disorder, premenstrual dysphoric disorder, postpartum depression, psychotic depression and atypical depression, among others. In general, these disorders are characterized by depressed mood, loss of interest or pleasure, feelings of guilt or low self-esteem, disturbances in sleep and/or appetite, low energy and poor concentration. Depressive disorders are very common, affecting an estimated 121 million people worldwide, including more than 19 million adults in the U.S. alone. According to the World Health Organization (WHO), depression is the leading cause of disability in the world when measured as YLDs (years lived with disease). It is the fourth most important contributor to the global burden of disease as measured by DALYs (disability-adjusted life years) and is predicted to become the second most important by the year 2020 (6-8).

Clinical depression is thought to be caused by an imbalance in the brain neurotransmitters serotonin (5-HT) and norepinephrine (NE). The indolamine hypothesis was first proposed some 30 years ago to explain major depression, the most common subtype. Individuals with major depression were speculated to have a deficiency in available 5-HT or subnormal 5-HT receptor function. Impaired serotonergic transmission in the brains of untreated patients with moderate to severe depression was finally demonstrated in 1996. The catecholamine hypothesis was subsequently described in the 1960s and suggested that depression is the result of abnormally low levels of NE in the brain. More recent studies have shown that not all individuals respond in a similar manner to NE. However, imbalances in this transmitter continue to be considered an important factor mediating depression (6, 9, 10).

The treatment of depression includes psychotherapy alone or in combination with pharmacotherapy, and can result in improvement within a few weeks in up to 80% of those affected and treated. To date, three major classes of drugs constitute available antidepressive pharmacotherapy. These are the tricyclic antidepressants, which alter the balance of brain 5-HT and NE, the monoamine oxidase (MAO) inhibitors, which slow the breakdown of these neurotransmitters in the brain, and the selective serotonin reuptake inhibitors (SSRIs), which enhance the activity of 5-HT but do not affect other neurotransmitters (6, 11-15).

Among the tricyclic antidepressants, three dual serotonin and NE reuptake inhibitors (SNRIs) are available for the treatment of depression, *i.e.*, venlafaxine hydrochloride, milnacipran hydrochloride and duloxetine hydrochloride. These agents also weakly inhibit dopamine reuptake and vary in selectivity, tolerability and toxicity (6, 16, 17). Several SNRIs are also under active development for the treatment of depression, as shown in Table I.

Investigators involved in antidepressant drug development continue to improve on known drug classes, searching for agents with greater specificity, fewer unwanted adverse events and a more rapid onset of antidepressant action. Venlafaxine, launched in 1994 and the first antidepressant in the SNRI drug class, has shown particular efficacy as a first-line treatment for major depression, in addition to anxiety, melancholia and agitation. The agent has shown efficacy and is devoid of the anticholinergic, sedative and cardiovascular adverse events common to many antidepressants. In an effort to further improve the efficacy and safety profile of this agent, several oxidative metabolites of venlafaxine were identified. The major metabolite in humans, *O*-desmethylvenlafaxine (desvenlafaxine, DVS-233, WY-45233), exhibited the greatest preclinical activity and tolerability and the succinate salt was chosen for further development as a treatment for depression (6, 14, 18).

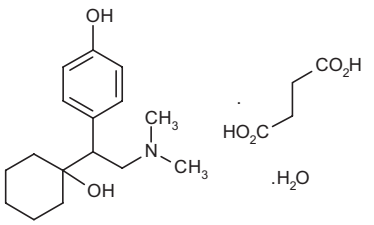
In addition to antidepressant activity, researchers have speculated that SNRIs and SSRIs may be effective in relieving vasomotor symptoms associated with menopause (*e.g.*, hot flashes, night sweats). The standard treatment for menopausal vasomotor symptoms is estrogen treatment, but there are many safety concerns associated with estrogen therapy. Researchers have therefore initiated a search for nonhormonal therapies for this indication. Results from preclinical and placebo-controlled clinical trials suggest that SSRIs and/or SNRIs may represent an alternative nonhormonal treatment for relieving vasomotor symptoms associated with menopause. Improvement in hot flashes seen with these agents may be associated with improvements in mental health, vitality and sleep. Desvenlafaxine in particular exhibited potent preclinical activity and is being investigated as the first nonhormonal agent for this indication (19).

Preclinical Pharmacology

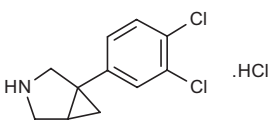
Receptor binding studies in rat brain *in vitro* showed that desvenlafaxine (1 μM or greater) possessed no significant affinity for dopamine D2, muscarinic, α_1-adrenergic, histamine H_1, mu-opioid, 5-HT_2 or 5-HT_1 receptors, but displayed potent NE and 5-HT uptake inhibition (IC_{50} = 1.16 and 0.18 μM, respectively). Activity was similar to that of the parent compound venlafaxine (IC_{50} = 0.64 and 0.21 μM, respectively), although desvenlafaxine was less active in inhibiting dopamine uptake (IC_{50} = 13.4 μM *vs.* 2.8 μM) (18).

Table I: SNRIs under active development for depression (from Prous Science Integrity®)

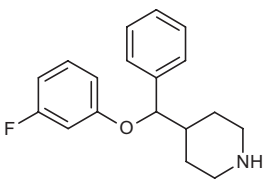
Drug	Source	Phase
1. Desvenlafaxine succinate	Wyeth Pharmaceuticals	Prereg.
2. NS-2359 (372475)[1,2]	NeuroSearch	II
3. DOV-216303[1]	DOV Pharmaceutical/Merck & Co.	II
4. DOV-21947[1]	DOV Pharmaceutical/Merck & Co.	I
5. SEP-225289[1,2]	Sepracor	I
6. Flufenoxine	FAES	Preclinical
7. SEP-227162[2]	Sepracor	Preclinical



(**1**)



3 (racemic)
4 ([+]-isomer)



(**6**)

[1]Also has dopamine reuptake-inhibitory activity. [2]Structure not available.

Another *in vitro* study demonstrated that desvenlafaxine exhibited activity only at 5-HT and NE transporters after profiling over 100 targets. Competitive binding studies revealed that the agent had the highest activity at the rat 5-HT transporter (SERT; IC_{50} = 80.8 ± 5.4 nM), modest activity at the human NE transporter (hNET; IC_{50} = 893.4 ± 194.5 nM) and weak activity at the human dopamine transporter (DAT). Likewise, desvenlafaxine potently inhibited [^{3}H]-5-HT uptake (EC_{50} = 47.3 ± 19.4 nM) in a choriocarcinoma cell line (JAR) stimulated with staurosporine to induce hSERT expression, and modestly inhibited [^{3}H]-NE uptake in MDCK epithelial cells which overexpress hNET (EC_{50} = 531 ± 113 nM) (20).

Desvenlafaxine was demonstrated to have a good antidepressant profile *in vivo*. The agent, like venlafaxine, significantly reversed reserpine-induced hypothermia in mice (minimum effective dose [MED] = 3 mg/kg i.p. *vs.* 10 mg/kg i.p. for venlafaxine) and induced pineal β-adrenergic subsensitivity (10 mg/kg i.p. as single or multiple doses). Desvenlafaxine was less active than the parent compound in inhibiting the firing of dorsal raphe 5-HT neurons (ID_{50} = 2.2 mg/kg i.v. *vs.* 0.28 mg/kg i.v. for venlafaxine) and NE neurons in the locus coeruleus (18).

A study in rats demonstrated that desvenlafaxine (30 mg/kg p.o.) rapidly penetrates the blood-brain barrier and increases 5-HT and NE levels. Desvenlafaxine was detected in the brain ($t_{1/2}$ = 2.1 h) and hypothalamus ($t_{1/2}$ = 2.2 and 2.5 h for males and females, respectively) in both male and female rats. However, levels of the agent in the brain were significantly lower in males (C_{max} = 771 ± 290 ng/g *vs.* 2835 ± 961 ng/g in females). The agent also increased preoptic hypothalamic extracellular NE levels by 116%. When given in combination with a 5-HT_{1A} receptor antagonist, both NE (97%) and 5-HT (78%) were increased. Dopamine levels were unaffected by desvenlafaxine treatment (21).

Preclinical data suggest that desvenlafaxine may be effective as a treatment for hot flashes and night sweats associated with menopause. The effect of desvenlafaxine was examined *in vivo* using two rat models of ovariectomy-induced thermoregulatory dysfunction. Both acute (30 and 60 mg/kg s.c.) and repeated doses (60 mg/kg s.c. for 9 days) of desvenlafaxine attenuated naloxone-induced tail skin temperature elevations by 62%, 72% and 66%, respectively. Desvenlafaxine (10, 30 and 60 mg/kg s.c. 30 min prior to dark phase) also restored cycling of tail skin temperature during the active dark phase, which is impaired in ovariectomized animals (22). Similar efficacy in alleviating vasomotor instability was observed with orally administered desvenlafaxine. Dose-dependent (10-100 mg/kg p.o.) attenuation of naloxone-induced flush was reported within 1 h of acute administration of the agent in morphine-dependent rats; the efficacy of the agent was maintained even following chronic (8-9 days) administration. The agent also acutely and transiently decreased tail skin temperature elevations in an ovariectomy-induced telemetry model. The effects observed were similar to those seen with chronic systemic ethinylestradiol administration (23).

Pharmacokinetics and Metabolism

A sustained-release tablet formulation of desvenlafaxine exhibited good oral bioavailability (80.5%) in an open-label, randomized, single-dose (100 mg p.o. or 50 mg by 1-h i.v. infusion), crossover study in 14 healthy subjects. The agent was generally well tolerated, with no clinically significant changes in vital signs, ECGs or laboratory parameters reported. A higher C_{max} was obtained with i.v. infusion (232 ng/ml *vs.*160 ng/ml), although $t_{1/2}$ values were comparable (14-15 h) for both routes of administration. A higher overall exposure was observed with oral dosing (AUC = 3996 ng.h/ml *vs.* 2443 ng.h/ml). An equally balanced enantiomeric ratio was obtained following both i.v. and oral formulations (24).

The pharmacokinetics of an oral sustained-release tablet formulation of desvenlafaxine were examined in a randomized, single-dose (100, 300 and 600 mg after a medium-fat breakfast), crossover study conducted in 24 healthy male subjects. All doses were generally well tolerated, with no significant changes in ECG or laboratory parameters. Nausea and dizziness were the most common adverse events observed. Desvenlafaxine was slowly absorbed (mean t_{max} = 7-8 h) and eliminated (mean $t_{1/2}$ = 11 h) and its pharmacokinetics were linear and dose-proportional over the doses tested. Low intersubject variability was seen (25).

A randomized, single-dose (75 and 100 mg after a medium-fat breakfast), crossover study in 35 healthy male and female subjects compared the relative bioavailability of oral sustained-release desvenlafaxine and oral extended-release venlafaxine. Good absorption and drug availability were observed with desvenlafaxine, with higher C_{max} values compared to venlafaxine. In addition, nausea intensity was less severe with desvenlafaxine compared to venlafaxine (26).

The safety, tolerability and pharmacokinetics of oral single-dose sustained-release desvenlafaxine (150, 225, 300, 450, 750 and 900 mg once daily after a medium-fat breakfast or 750 mg in the fasted state) and oral extended-release venlafaxine (150 mg once daily) were examined in a randomized, placebo-controlled study in 79 healthy male subjects. No significant changes in blood pressure, ECG intervals, laboratory parameters, psychomotor performance or memory were observed with treatment. Desvenlafaxine was concluded to be safe at doses up to 750 mg, with less severe nausea observed at theses doses as compared to venlafaxine. In the desvenlafaxine groups, vomiting was experienced by 2 of 6 subjects and 4 of 6 subjects receiving the 750 and 900 mg doses, respectively. The mean t_{max} and $t_{1/2}$ values for desvenlafaxine were 6-8 and 9-11 h, respectively, and C_{max} and AUC values increased in an approximately linear manner over the dose range. Slightly higher C_{max} and AUC values were obtained when desvenlafaxine was administered with food, although the slow release profile was not significantly altered (27, 28).

The safety and pharmacokinetics of sustained-release desvenlafaxine were examined in a randomized,

placebo-controlled, ascending-multiple-dose (300, 450 and 600 mg once daily after a medium-fat breakfast for 14 days) trial conducted in 36 healthy male subjects. The agent was generally well tolerated, nausea being the most common adverse event; no significant changes in ECG and laboratory parameters were observed. The 450-mg dose was concluded to be the maximum tolerated multiple dose; of the 9 subjects in the highest dose group, 6 experienced orthostatic hypotension. The agent was slowly absorbed (mean t_{max} = 5-8 h), and C_{max} and AUC values increased proportionally over single doses of 300-600 mg and multiple doses of 300 and 450 mg. Single-dose $AUC_{0-\infty}$ and steady-state $AUC_{0-24\ h}$ values were similar for all doses (29).

Clinical Studies

Desvenlafaxine is undergoing phase III clinical trials for the treatment of major depression and vasomotor symptoms associated with menopause. Several randomized, double-blind, placebo-controlled trials are planned or have been initiated to examine the safety, efficacy and tolerability of fixed and flexible doses of sustained-release formulations of desvenlafaxine (50, 100, 200 or 400 mg p.o. once daily) in adult patients with major depressive disorder (30-35). Another randomized, double-blind, placebo-controlled, parallel phase III trial is examining the efficacy and safety of the sustained-release formulation in reducing relapse rates in adult outpatients with major depressive disorder (36). The antidepressant efficacy and safety of this formulation is being compared to extended-release venlafaxine in a randomized, double-blind, placebo-controlled, parallel phase III trial involving adult outpatients with major depressive disorder (37, 38), and a 6-month, open-label, randomized, uncontrolled trial is also under way to determine the long-term safety of sustained desvenlafaxine in elderly outpatients (65 years and older) with major depressive disorder (39). Finally, two randomized, double-blind, placebo- and active-controlled (*i.e.*, tibolone) phase III trials in healthy postmenopausal women are examining the safety and efficacy of sustained-release desvenlafaxine as a treatment for vasomotor symptoms associated with menopause. The studies are also assessing the effects of the agent on sleep parameters, changes in weight, breast pain and health outcome indicators (40, 41).

Wyeth submitted an NDA in December 2005 for an extended-release formulation of desvenlafaxine succinate for the treatment of major depressive disorder in patients with both emotional and somatic symptoms. Submission of an NDA for desvenlafaxine for the treatment of vasomotor symptoms associated with menopause is expected soon (42, 43).

Source

Wyeth Pharmaceuticals (US).

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