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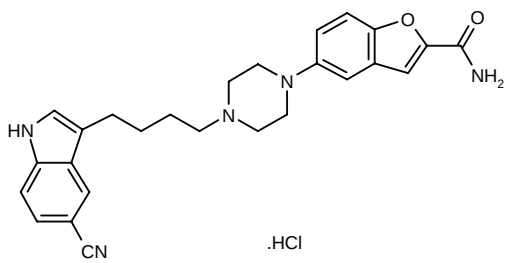
Vilazodone Hydrochloride

Prop INNM

Antidepressant
5-HT$_{1A}$ Partial Agonist
5-HT Reuptake Inhibitor

EMD-68843
SB-659746A

5-[4-[4-(5-Cyanoindol-3-yl)butyl]piperazin-1-yl]benzofuran-2-carboxamide hydrochloride



C26 H27 N5 O2 . Cl H Mol wt: 477.9932

CAS: 163521-12-8 (as free base)
CAS: 163521-08-2

EN: 226940

Synthesis

Vilazodone can be prepared by two related ways:

1) The condensation of indole-5-carbonitrile (I) with 4-chlorobutyryl chloride (II) gives 3-(4-chlorobutyryl)-1*H*-indole-5-carbonitrile (III), which is reduced with diborane, yielding 3-(4-chlorobutyl)-1*H*-indole-5-carbonitrile (IV) (1). Reaction of compound (IV) with 5-(1-piperazinyl)benzofuran-2-carboxylic acid (V) affords the expected 1,4-disubstituted piperazine (VI). Finally, the carboxy group of (VI) is converted into the target carboxamide by reaction with 2-chloro-1-methylpyridinium methanesulfonate (CMPM) and ammonia gas (2). 5-(1-Piperazinyl)benzofuran-2-carboxylic acid (V) is obtained by cyclization of 5-aminobenzofuran-2-carboxylic acid (VII) with bis(2-chloroethyl)-amine (VIII) (2). Scheme 1.

2) The hydrogenation of 5-nitrobenzofuran-2-carboxylic acid ethyl ester (IX) with H_2 and Raney nickel in MeOH gives the corresponding 5-aminobenzofuran compound (X), which is cyclized with bis(2-chloroethyl)amine (VIII) in dichloromethane to afford 5-(1-piperazinyl)benzofuran-2-carboxylic acid ethyl ester (XI). Reaction of compound (XI) with di-*tert*-butyl dicarbonate in THF provides the protected amine compound 5-[4-(*tert*-butoxycarbonyl)-1-piperazinyl]benzofuran-2-carboxylic acid ethyl ester (XII), which first is reacted with formamide and sodium alkoxide in *N*-methylpyrrolidone to provide the corresponding amide (XIII) and then is deprotected by treatment with HCl/MeOH to give 5-(1-piperazinyl)benzofuran-2-carboxamide (XIV). Finally, amide (XIV) is condensed with 3-(4-chlorobutyl)-1*H*-indole-5-carbonitrile (IV) (3). Scheme 1.

Description

Hydrochloride, m.p. 269-72 °C (2).

Introduction

Depressive disorders include several conditions such as two major forms of unipolar depression (*i.e.*, major depression and dysthymia), adjustment disorder, subsyndromal depression (or minor depression), seasonal affective disorder (SAD), premenstrual dysphoric disorder (PMDD), postpartum depression, atypical depression and bipolar disorder. In general, depression or feelings of unhappiness or disappointment is quite common, affecting up to one-third of all people at some time. However, when these types of feelings become exaggerated, pervasive and interfere with everyday life, they are considered pathological depression. More than 19 million adults in the U.S. each year suffer from some type of depressive disorder and the World Health Organization predicts that by the year 2020 depression will be the second leading cause of disability worldwide (4, 5).

Men and women of all ages suffer from depression and the incidence increases with age. The disorder can alter emotions, cognition, physical functioning and/or behavior. An individual suffering from a depressive disorder may only experience a single depressive episode or

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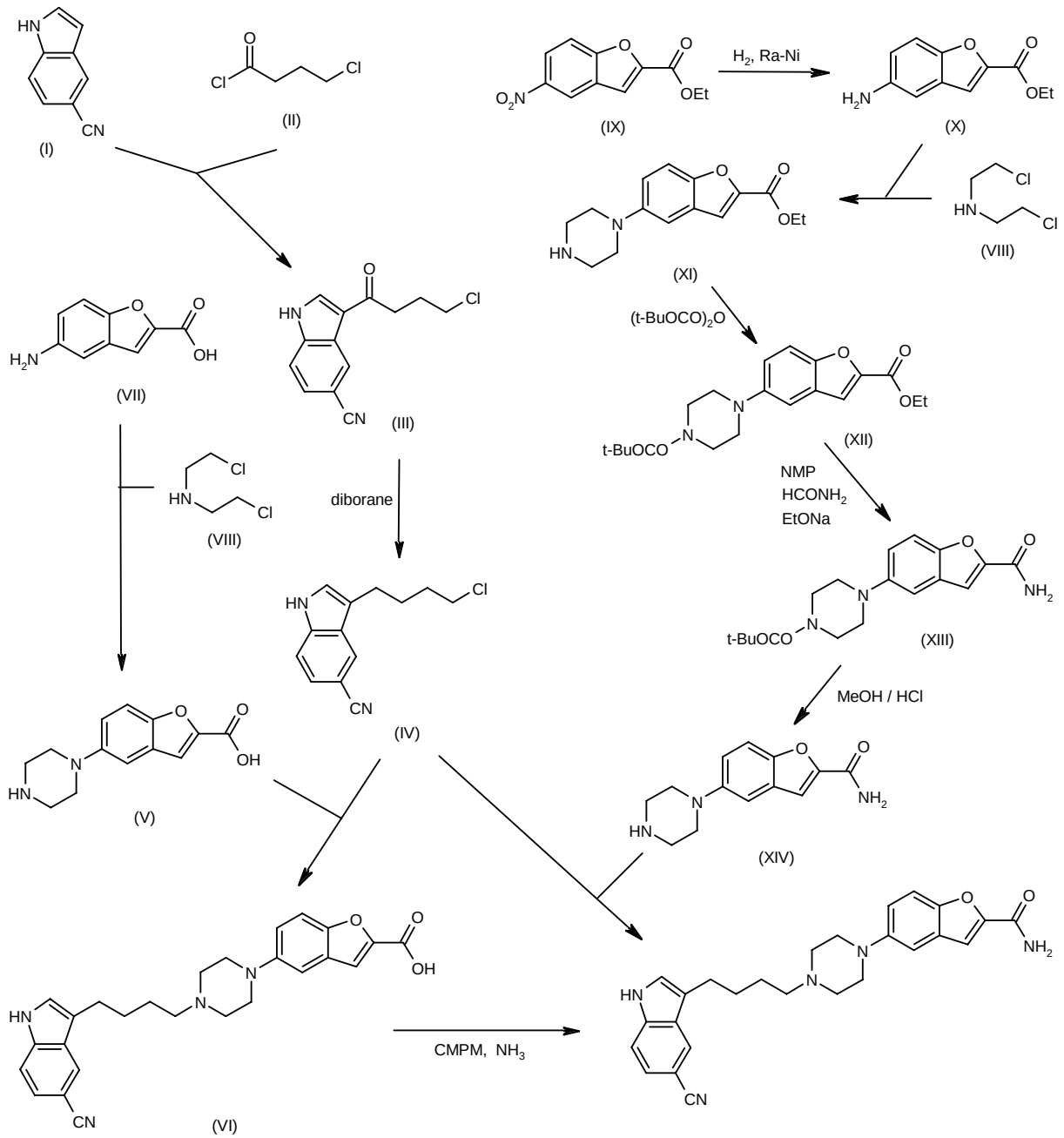
Scheme 1: Synthesis of Vilazodone hydrochloride



can suffer from a chronic condition. The causes of depression are usually multifactorial. Heredity and childhood environment may predispose an individual to depression or a traumatic event may trigger a depressive episode. It is generally accepted that neurochemical abnormalities are ultimately responsible for the emergence of depressive symptoms (4).

Although depression can represent an extreme disability, up to 80% of all individuals affected can improve and return to their normal daily life activities with appropriate treatment. In addition to nonpharmacological treatment (*e.g.*, cognitive, behavioral and psychodynamic therapies), there are currently 3 major classes of drugs available for the treatment of depression. Tricyclic

Table I: Comparative activities of vilazodone and other antidepressant drugs on 5-HT$_{1A}$ receptor and 5-HT reuptake in rat brain. (Prous Science MFline database).

Drug	5-HT$_{1A}$ receptor affinity IC$_{50}$ (nM)	5-HT reuptake inhibition IC$_{50}$ (nM)	Ref.
Amitriptyline		106	17
Amoxapine		563	18
Anpirtoline	570		19
Brofaromine		525	20
Citalopram		17.5 (7-28)	21
Clomipramine	28000	1.5	22
Desipramine		483	23, 24
Duloxetine	2750	17.7 (11.3-24.1)	17, 25-27
Fluoxetine	79000	57.5 (32.9-82.1)	22, 28-30
Fluvoxamine		27	29
Imipramine	18000	211.2 (152.4-270.0)	18, 20, 22-24, 29, 31
Ipsapirone	18.8 (10.7-26.9)		32, 33
MKC-242	0.4		34
Napamezole		887	35
Paroxetine		6.4	35
Ru-24969	14		36
Siramesine	21000	190	37, 38
Vilazodone	0.5	0.2	11

antidepressants (TCAs) which act by altering the balance of norepinephrine and serotonin in the brain, were first introduced in the late 1950s and have been the standard treatment for depression for many years despite their slow onset of action and unpleasant and often serious (*e.g.*, cardiac toxicity in overdose) side effects. A second class of compounds are the monoamine oxidase (MAO) inhibitors which slow the breakdown of norepinephrine and serotonin (5-HT) in the brain, allowing for prolonged activity of these neurotransmitters. Since the late 1980s, selective serotonin reuptake inhibitors (SSRIs) have overtaken TCAs in the market due to their excellent safety profiles. SSRIs enhance the activity of 5-HT via inhibition of its reuptake without affecting other neurotransmitter systems. The result is considerably less side effects as compared to TCAs and MAO inhibitors. Other antidepressants include reversible MAO inhibitors (RIMAs) and noradrenergic reuptake inhibitors which also lack the anticholinergic and cardiovascular adverse effects associated with TCAs. However, with regard to broader efficacy and reductions in the latency prior to the onset of antidepressant effects, all these newer types of compounds are not superior to the older antidepressants. In fact, SSRIs are considered less effective than TCAs as a treatment for the more severe forms of depression and they may also cause new adverse effects related to nonelective stimulation of postsynaptic 5-HT receptors (6, 7).

As a result, the search for new generation antidepressants continues. Researchers are attempting to identify compounds that have a shorter latency before the onset of clinical effects, broader efficacy and fewer side effects. One such strategy to achieve a more rapid onset of antidepressant effects is the selective agonism of postsynaptic 5-HT$_{1A}$ receptors. Agents possessing this property would theoretically not suppress initial firing activity of 5-HT neurons and therefore cause a rapid net increase in neurotransmission (8). Although no selective postsynaptic 5-HT$_{1A}$ receptor agonists are available to date, antagonists at the postsynaptic 5-HT$_{1A}$ receptor agonist and agonists at the presynaptic 5-HT$_{1A}$ receptor have been found. Some benzodioxopiperazines do show both postsynaptic 5-HT$_{1A}$ activity and agonist activity at presynaptic 5-HT$_{1A}$ autoreceptors (9). Vilazodone hydrochloride (EMD-68843, SB-659746A), another SSRI that is a partial agonist at the 5-HT$_{1A}$ receptor, may be more effective and tolerable than agents currently available for the treatment of depression (10).

Pharmacological Actions

The IC$_{50}$ values observed for vilazodone for the 5-HT$_{1A}$ and σ receptors *in vitro* were 0.5 and 17 nM, respectively. Higher IC$_{50}$ values of 100 nM or greater were obtained for the agent for the 5-HT$_{1D}$, 5HT$_{2A/C}$, 5-HT$_4$, dopamine D$_{1/2/3/4}$, BZD/GABA, $\alpha_{1/2}$, histamine H$_{1/2}$, muscarinic M$_{1/2}$, opioid, NMDA, AMPA, kainate and glycine receptors. Reuptake of 5-HT, norepinephrine and dopamine *in vitro* was inhibited by vilazodone with IC$_{50}$ values of 0.2, 60 and 90 nM, respectively. 5-HT reuptake was also inhibited *in vivo* in rats with ED$_{50}$ values of 0.7 mg/kg s.c. and 3.8 mg/kg p.o. (11).

Results from *in vivo* studies in rats showed that following administration of 10 mg/kg p.o., 5-HTP accumulation in the striatum was inhibited by 40%; dopamine levels were not affected by vilazodone treatment (11).

Further *in vivo* studies in rats showed that acute systemic treatment with vilazodone resulted in a larger maximal increase in extracellular 5-HT in the ventral hippocampus and the frontal cortex than that observed with

Box 1: Effects of vilazodone on sleep EEG (15) [Prous Science CSline database].

Design	Randomized, double-blind, placebo-controlled, crossover clinical study
Population	Young healthy subjects (n = 10)
Treatments	Vilazodone, 20 mg p.o. s.d.
Results	Rapid eye movement sleep duration: P > EMD [p <0.001] Suppression of rapid eye movement sleep duration: EMD > P [p <0.001] Rapid eye movement density: P > EMD [p <0.001] Suppression of rapid eye movement density: EMD > P [p <0.001] Increase in slow wave sleep @ the first third of the night: EMD > P [p <0.05]; @ the third third of the night: EMD > P [p <0.01] Increase in wake after sleep onset @ the second third of the night: EMD > P [p <0.01]; @ the third third of the night: EMD > P [p <0.05] Increase in delta power: EMD > P Decrease in sigma power: EMD > P
Conclusions	Vilazodone appears to have a strong effect, which is in agreement with postsynaptic 5-HT_{1A} receptor agonistic activity

fluoxetine. The frontal cortex appeared to be more responsive to high doses of fluoxetine and slightly less responsive to vilazodone (12).

The efficacy of vilazodone was also examined in behavioral animal models. A study in mice showed that vilazodone (30-55 mg/kg p.o.) decreased immobility in both the behavioral despair and tail suspension tests. Results from another study in rats demonstrated that the agent inhibited ultrasonic vocalizations in rats with ED_{50} values of 3.8 mg/kg s.c. and 12.8 mg/kg p.o.; fluoxetine had no effect on ultrasonic vocalizations (100 mg/kg p.o.). The inhibitory action of the agent was maintained for a long period of time and could be blocked by administration of the 5-HT_{1A} antagonist, WAY-100635 (1 mg/kg s.c.). In contrast to 8-OH-DPAT (0.55 mg/kg s.c.) which reduced the body temperature of rats, vilazodone neither altered body temperature nor interacted with 8-OH-DPAT. Fluoxetine had no effect on body temperature (11, 13).

Clinical Studies

A study involving 2 open-label [carbonyl-^{11}C]-WAY-100635 positron emission tomography (PET) scans performed in 10 healthy male volunteers (24-54 years old) has confirmed that vilazodone displays occupancy at the 5-HT_{1A} receptor site. One PET scan was performed at baseline while the second was performed at a median of 13 days later following a single oral dose of vilazodone (20 or 40 mg), pindolol (5, 10 or 20 mg), penbutolol (40 or 80 mg), S-15535 (20 mg) or buspirone (20 mg); scans were performed to coincide with the plasma Tmax of the particular agent administered. All agents except buspirone displayed occupancy at the 5-HT_{1A} receptor site. Following single-dose vilazodone, occupancy at the 5-HT_{1A} receptor site was ensured if plasma levels of the agent were > 50 ng/ml (14).

A randomized, double-blind, placebo-controlled crossover study conducted in 10 young healthy male subjects (20-30 years old) examined the effects of vilazodone (20 mg at 21:00 h) on sleep EEGs (at 22:00-7:00 h). Results from EEG spectral analysis revealed a significant global effect on conventional sleep EEG parameters due to a marked and significant suppression of rapid eye movement (REM) sleep duration and density. An increase in slow wave sleep (SWS) and in wakefulness after sleep onset was observed (WASO) and treatment with the agent also significantly increased and decreased delta and sigma powers, respectively. The effects elicited by vilazodone were found to occur in distinct time intervals in that alterations in SWS were observed during the first third of the night while the increase in wakefulness was noted in the second third of the night. From the results obtained, it was concluded that vilazodone may have induced desensitization of presynaptic 5-HT_{1A} receptors and postsynaptic 5-HT_2 receptors without significantly affecting the function of postsynaptic 5-HT_{1A} receptors (15) (Box 1).

Vilazodone continues to undergo phase II clinical development and is expected to be available in 4 years (10, 16).

Manufacturer

Merck KGaA (DE); licensed to GlaxoSmithKline plc (GB).

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