Drugs of the Future 2004, 29(12): 1201-1205

CCC: 0377-8282/2004

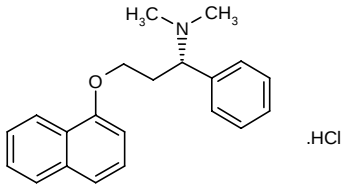
Dapoxetine Hydrochloride

Rec INNM; USAN

Treatment of Premature Ejaculation
5-HT Reuptake Inhibitor

LY-210448

(*S*)-(+)-*N*,*N*-Dimethyl-3-(1-naphthyloxy)-1-phenylpropylamine hydrochloride
(+)-(*S*)-*N*,*N*-Dimethyl-α-[2-(1-naphthyloxy)ethyl]benzylamine hydrochloride



$C_{21}H_{23}NO.HCl$
Mol wt: 341.8796
CAS: 129938-20-1
CAS: 119356-77-3 (as free base)
CAS: 119356-78-4 (as tartrate)
EN: 148608

Abstract

Premature ejaculation is the most common form of ejaculatory dysfunction, affecting up to 39% of the general male population. Behavioral therapy is an effective treatment in the majority of cases. However, pharmacotherapy is required in those cases of lifelong premature ejaculation. Tricyclic antidepressants and clomipramine are the most extensively studied agents for this indication, in addition to α-adrenoceptor antagonists, benzodiazepines and gabapentin. However, these agents are associated with a variety of adverse events. Selective serotonin reuptake inhibitors (SSRIs) may be less effective than clomipramine, but they are also associated with fewer side effects. The most advanced agent under clinical development for premature ejaculation is the potent SSRI dapoxetine, a compound structurally related to the antidepressant fluoxetine (Prozac®). Dapoxetine has shown favorable distribution and pharmacokinetics, and the safety and efficacy of the agent have been demonstrated in a phase II trial. Dapoxetine is presently in phase III development for the treatment of premature ejaculation.

Synthesis

Dapoxetine can be prepared by several ways:

1) Knoevenagel condensation of benzaldehyde (I) with malonic acid (II) in the presence of ammonium acetate results in the β-amino acid (III), which by reductive alkylation of its amino group with formaldehyde produces 3-(dimethylamino)-3-phenylpropionic acid (IV). Then, Fischer esterification of acid (IV) with ethanolic HCl furnishes the intermediate amino ester (V), which is alternatively obtained by Michael addition of dimethylamine to ethyl cinnamate (VI). Reduction of the ester function of compound (V) with bis(2-methoxyethoxy)aluminum hydride or lithium aluminum hydride provides the amino alcohol (VII). Compound (VII) is then coupled with 1-fluoronaphthalene (VIII) by means of NaH in dimethylacetamide to give racemic dapoxetine, which is finally resolved into enantiomers by means of tartaric acid (1, 2). Scheme 1.

2) Reduction of the chiral precursor *N*-Boc-(*R*)-phenylglycine (IX) with borane in THF provides the *N*-Boc-amino alcohol (X), which is activated as the mesylate (XI) by reaction with methanesulfonyl chloride in pyridine. Displacement of the mesylate group of compound (XI) with NaCN in DMF furnishes the Boc-amino nitrile (XII), which is submitted to hydrolysis of the nitrile group with concomitant *N*-Boc group cleavage under acidic conditions to give amino acid (XIII). Reduction of compound (XIII) using borane in THF yields amino alcohol (XIV), which by Eschweiler-Clarke methylation affords the dimethylamine (XV). Finally, dimethylamine (XV) is condensed with 1-fluoronaphthalene (VIII) by means of NaH in DMA (1). Scheme 2. [^{14}C]-Labeled dapoxetine can be similarly prepared employing [^{14}C]-sodium cyanide.

3) Selective tosylation of (*R*)-1-phenyl-1,3-propanediol (XVI) at the primary hydroxy group with *p*-toluenesulfonyl chloride, TEA and poly-DMAP in CH_2Cl_2 gives tosylate (XVII), which is condensed with 1-naphthol (XVIII) by means of NaOH, LiOH or *t*-BuOK in DMF to yield (*R*)-3-(1-naphthyloxy)-1-phenylpropanol (XIX). Compound (XIX) can also be obtained by condensation of

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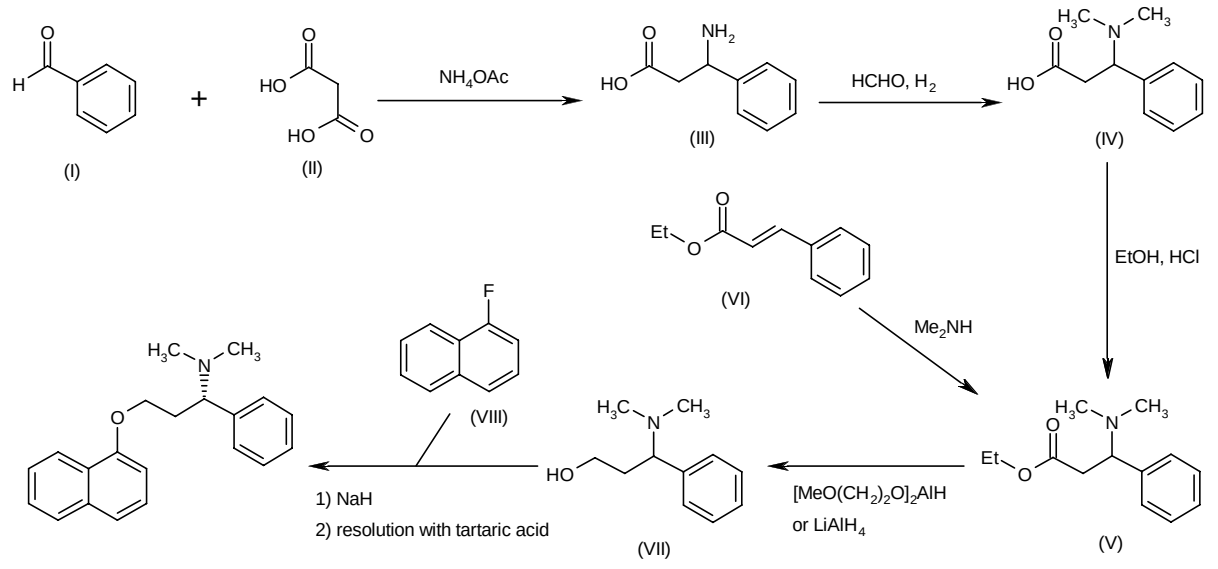
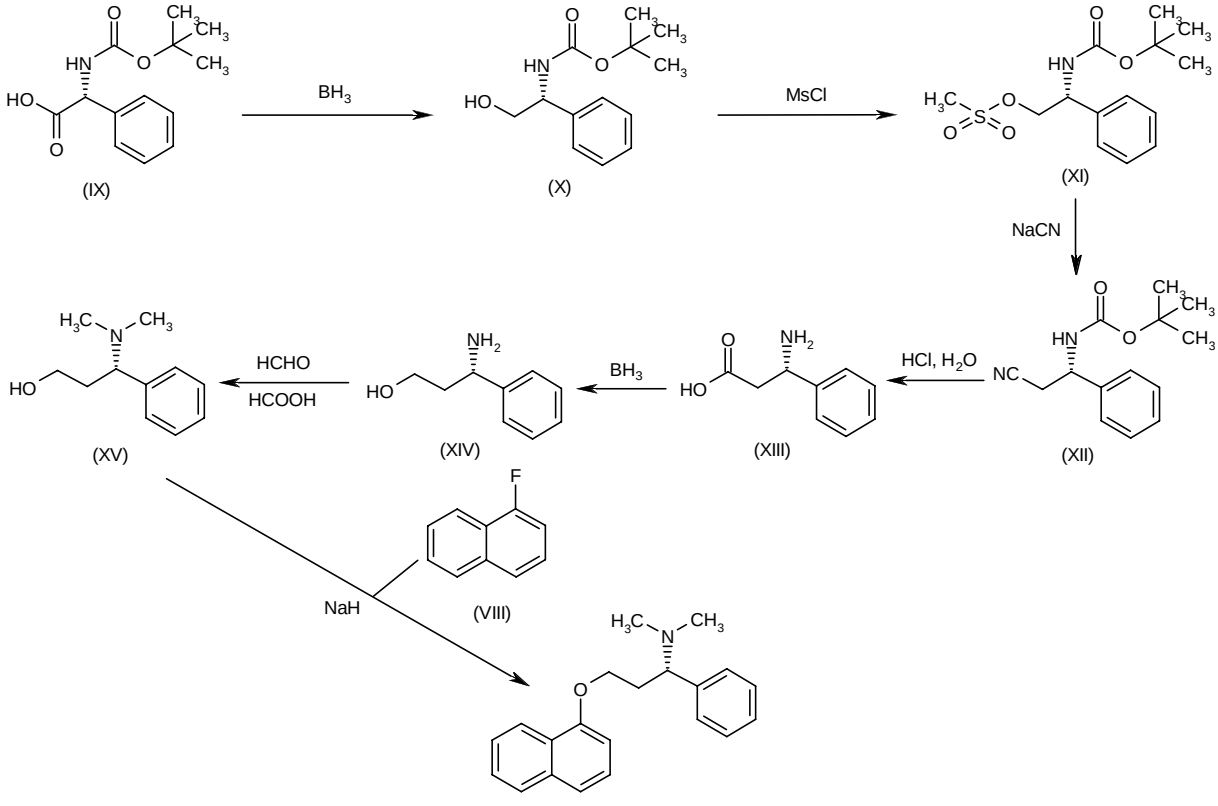
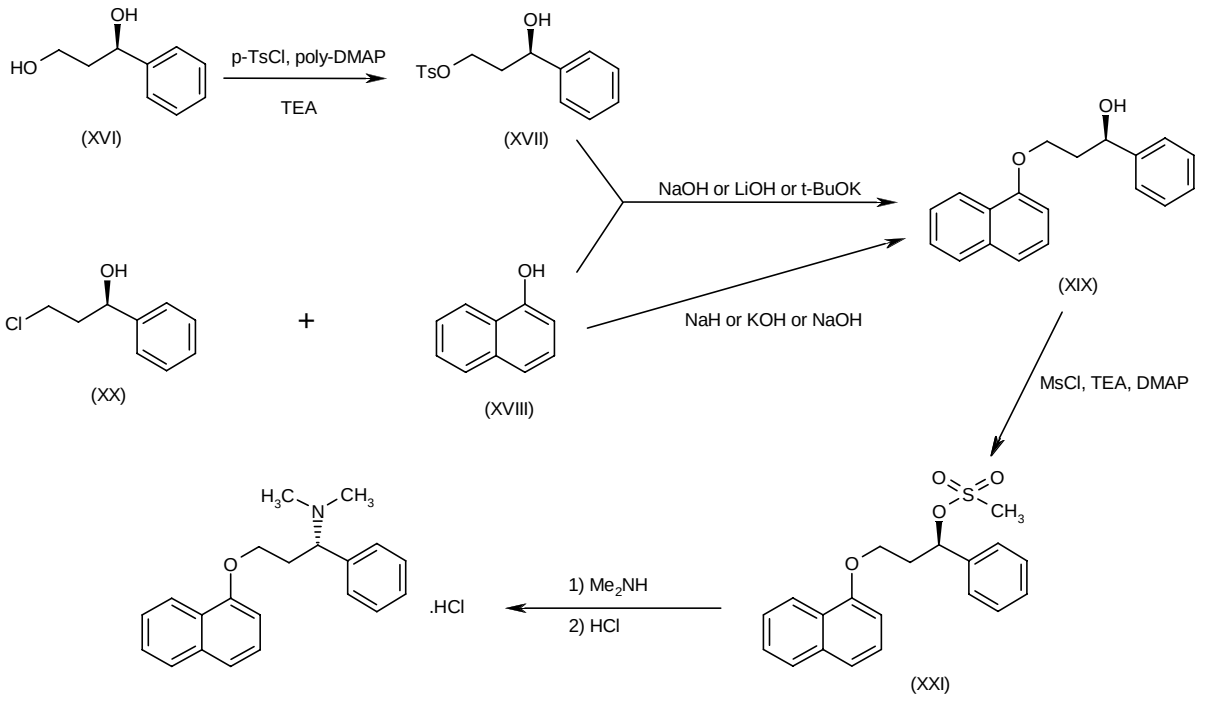
Scheme 1: Synthesis of Dapoxetine



Scheme 2: Synthesis of Dapoxetine



Scheme 3: Synthesis of Dapoxetine



(*R*)-3-chloro-1-phenylpropanol (XX) with 1-naphthol (XVIII) by means of NaH, KOH or NaOH in DMF or DMSO. Reaction of alcohol (XIX) with methanesulfonyl chloride, TEA, DMAP in THF provides the mesylate (XXI), which is finally treated with dimethylamine in the same solvent and acidified with HCl (3). Scheme 3.

Introduction

At some point in their lives, up to 70% of all men suffer from ejaculatory dysfunction, ranging from premature or rapid ejaculation through retarded ejaculation to the complete inability to ejaculate. Premature ejaculation, which is by far the most common form of ejaculatory dysfunction, affecting up to 39% of the general male population, is defined in "The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition" (DSM-IV) as "...persistent or recurrent ejaculation with minimal sexual stimulation before, on or shortly after penetration and before the person wishes it." Premature ejaculation is associated with a negative impact on the quality of life, sexual performance and enjoyment of sex. At present, there are no standardized methods to assess premature ejaculation. Research criteria include measuring and examining the latency to ejaculation after intromission or reduced intravaginal latency time (IELT), limited control over the occurrence of ejaculation, concern about ejaculating too soon, dissatisfaction with the inability to select the moment of ejaculation and the occurrence of antiportal ejaculation (4-6).

Premature ejaculation is a complex physiological process. In general, it is thought to be psychogenic in nature, with anxiety playing a significant contributing role. Accordingly, behavioral therapy is the gold standard of treatment in the majority of cases, with an estimated 60-95% success rate. However, lifelong premature ejaculation is postulated to be a neurobiological phenomenon and not an acquired disorder due to learned behavior. It is thought to be due to normal biological variability in IELT of individuals with possible familial genetic vulnerability, since a greater incidence of the disorder is observed in first-degree male relatives of men presenting premature ejaculation. The physiological dysfunctions responsible for lifelong premature ejaculation are speculated to be related to a reduction in serotonergic neurotransmission, 5-HT_{2C} receptor hyposensitivity and/or 5-HT_{1A} receptor hypersensitivity, in addition to malfunction in other central inputs and neurotransmitters, including dopamine and α_1-adrenoceptor- and cholinergic-dependent autonomic and somatic reflexes (4-11).

In those cases of premature ejaculation which are lifelong or not corrected with behavioral therapy, pharmacotherapy is required. Numerous agents that affect different receptors have been shown to delay ejaculation. Compounds such as tricyclic antidepressants and

clomipramine, in particular, are the most extensively studied agents for this indication. In addition, α-adrenoceptor antagonists (*e.g.*, prazosin), benzodiazepines (*e.g.*, clonazepam) and the anticonvulsant gabapentin have also displayed efficacy in delaying ejaculation. However, these agents are also associated with adverse events. On the other hand, selective serotonin reuptake inhibitors (SSRIs) may be less effective as compared to clomipramine, for example, but they are also associated with fewer side effects. Thus, SSRIs represent a promising class for the treatment of premature ejaculation (4, 12, 13).

The most advanced agent under clinical development for premature ejaculation is the potent SSRI dapoxetine, a compound that is structurally related to the antidepressant fluoxetine (Prozac®). Dapoxetine has shown favorable distribution and pharmacokinetics and was chosen for further development (11, 14).

Pharmacokinetics

The biodistribution of dapoxetine was examined in rats at 5, 30 and 60 min following i.v. administration of 10 μCi of [^{11}C]-dapoxetine (about 25 pmol). The highest concentration of the agent was detected in the lung (% injected dose/g = 4.56 ± 0.27, 1.28 ± 0.18 and 0.67 ± 0.04, respectively, at these time points). Accumulation values in brain were 0.76 ± 0.02, 0.46 ± 0.04 and 0.27 ± 0.01 % injected dose/g, respectively. PET imaging studies were also performed in a rhesus monkey administered [^{11}C]-dapoxetine (500 mCi/μmol followed by 5 mCi coinjected with 2.5 mg/kg of the unlabeled drug). Results revealed significant displaceable binding in the cerebral cortex and subcortical gray matter (14).

The biodistribution of dapoxetine was also examined using whole-body autoradiography and organ dissection following oral administration of [^{14}C]-dapoxetine (10 μCi, 25 mg/kg). The parent drug and *N*-demethyl metabolite (nordapoxetine) were detected in the organs examined, although the majority of the radioactivity measured was not identified. The highest concentration of the agent was detected in organs involved in absorption and elimination, including the ileum, cecum, stomach, duodenum, liver, colon and kidney; the lung, preputial and Harderian glands also exhibited higher concentrations. Levels of the agent in the majority of examined tissues returned to baseline values at 72 h postdosing, except for in the preputial gland and liver where radiocarbon levels were still detectable at 1 week postdosing (15).

The NADPH-dependent metabolism of [^{14}C]-dapoxetine was examined in a study using mouse, rat, dog, monkey and human liver microsomes. All microsomes metabolized the agent to its monodesmethyl metabolite, although human microsomes were less efficient as compared to other species. In addition, *N*-oxide and *N*,*N*-didesmethyl metabolites were formed in lesser amounts. It appears that the metabolites detected *in vitro* are further metabolized, since none were detected in animal urine up to 48 h following oral administration (16).

The metabolism and disposition of oral dapoxetine were examined in mice (25 mg/kg), rats (25 mg/kg) and beagle dogs (15 mg/kg). The plasma concentrations of dapoxetine and its *N*-dealkylated metabolites were lower in all species as compared to plasma radioactivity. The $t_{1/2}$ values for dapoxetine in rats and dogs were 3.2 and 2.2 h, respectively, and the $t_{1/2}$ values for radioactivity in mice, rats and dogs were 29.5, 59 and 4.7 h, respectively. Extensive metabolism to additional metabolites was indicated since the plasma AUC values for the parent compound and its 2 metabolites only accounted for 0.9-3.6% of the plasma AUC for radioactivity. The bioavailability of dapoxetine in rats was 11%. Radioactivity was excreted mainly in the urine (56%) in mice and in feces in rats and dogs (65% and 70%, respectively); biliary excretion was observed in rats. Neither the parent compound nor the dealkylated metabolites could be detected in the urine of any species (17).

A column-switching HPLC method was reported for determining dapoxetine and its mono- and didesmethyl metabolites in human plasma. The limit of quantitation was 20 ng/ml and responses were linear from 20 to 200 ng/ml. The method was validated in a phase I study of single oral doses in fed/fasted humans. Endogenous plasma components were found not to interfere with dapoxetine determinations (18).

The pharmacokinetics of single oral doses of dapoxetine (20, 40, 60, 80 and 120 mg) were determined in a phase I study in 4 healthy adults. The pharmacokinetics of dapoxetine and its *N*-monodesmethyl metabolite were linear. The mean C_{max} (124, 290, 480 and 548 ng/ml, respectively) and $AUC_{(0-\infty)}$ (723, 1565, 2280 and 2907 ng·h/ml, respectively) values for dapoxetine obtained for doses of 20, 40, 60 and 80 mg were dose-proportional. The *N*-monodesmethyl metabolite was detectable in some samples, but levels were too low to assess all pharmacokinetic parameters. C_{max} values for this metabolite at the 40-, 60- and 80-mg doses were 5.5, 8.0 and 13.7 ng/ml, respectively, and $AUC_{(0-t)}$ values were 38.8, 44.3 and 96.9 ng·h/ml, respectively (19).

A randomized, double-blind, placebo-controlled trial in 77 healthy male volunteers assessed the pharmacokinetics of single (60, 100, 140 and 160 mg) or multiple doses (80, 100 or 100 mg once daily for 6 days) of dapoxetine. The pharmacokinetics, as determined using noncompartmental methods, were similar for both single and multiple doses. The agent was rapidly absorbed, with C_{max} values achieved by approximately 1.5 h postdosing. A proportional increase in C_{max} and AUC values was observed for doses up to 100 mg. The $t_{1/2}$ value was about 18 h. No serious adverse events or significant changes in laboratory tests, vital signs or ECG were observed with treatment. The most common adverse event was mild to moderate nausea (20).

Clinical Studies

The efficacy and safety of dapoxetine (60 and 100 mg p.o.) were examined in a multicenter, double-blind, ran-

domized, placebo-controlled, crossover phase I study including 166 patients suffering from premature ejaculation (mean baseline IELT = 1.01 min). Ten patients (9 in the 100-mg dose group) discontinued due to adverse events and 130 patients completed the study. The tolerability of the agent was concluded to be acceptable. The most common adverse event was nausea (5.6% and 16.1%, respectively, *vs.* 0.7% on placebo). Significant increases in IELT as compared to placebo were observed posttreatment (IELT = 2.94 and 3.20 min, respectively, *vs.* 2.05 min on placebo). The 60-mg dose was selected for further clinical evaluation (21).

Dapoxetine is currently undergoing phase III studies involving more than 2,400 patients for the treatment of premature ejaculation (22).

Sources

Alza Corp. (US); Johnson & Johnson Pharmaceutical Research & Development (US). Dapoxetine was originally developed by Lilly and subsequently licensed to PPD, which then outlicensed it to Alza, a wholly owned subsidiary of Johnson & Johnson. The product will be marketed in the U.S. by Ortho-McNeil Pharmaceutical, in Canada by Janssen-Ortho, Inc. and around the world by Janssen-Cilag companies.

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