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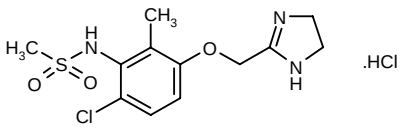
Dabuzalgron Hydrochloride

Prop INNM

Treatment of Urinary Incontinence
$\alpha_{1A/1L}$-Adrenoceptor Partial Agonist

R-450
Ro-115-1240

N-[6-Chloro-3-(4,5-dihydro-1*H*-imidazol-2-ylmethoxy)-2-methylphenyl]methanesulfonamide hydrochloride



$C_{12}H_{16}ClN_3O_3S.HCl$
Mol wt: 354.2563

CAS: 219311-43-0

CAS: 219311-44-1 (as free base)

EN: 324230

Abstract

Stress urinary incontinence is the most common form of urinary incontinence. Adrenergic receptors have been the focus of research to develop effective agents to manage the disorder. The α_{1A}-adrenoceptor subtype in particular is found in abundance in the bladder neck and proximal urethra and is recognized as playing an important role in the sympathetic neuronal control of urinary outlet tissue smooth muscle tone. However, selective α_{1A}-adrenoceptor agonists which have been shown to be effective in relieving symptoms of urinary incontinence are associated with unwanted hemodynamic effects such as elevation of blood pressure. The α_{1L}-adrenoceptor is a fourth adrenoceptor subtype identified and found to mediate contraction of urinary outlet smooth muscle. Evidence suggests that this subtype is actually a pharmacological form of the α_{1A}-adrenoceptor gene product. The α_{1A}- and α_{1L}-adrenoceptors together have therefore become attractive targets for the development of agents with improved safety profiles for the treatment of stress urinary incontinence. Dabuzalgron (Ro-115-1240, R-450) is a novel $\alpha_{1A/1L}$-adrenoceptor partial agonist that has been shown to control urethral smooth muscle *in vitro* and *in vivo*. Moreover, the agent emerged as safe and effective as a treatment for stress urinary incontinence from a randomized trial.

Synthesis

Dabuzalgron can be synthesized by two related methods:

1) Reaction of 2,6-dinitrotoluene (I) with hydroxylamine and KOH in ethanol provides 2,4-dinitro-3-methylaniline (II), which by Sandmeyer reaction with *tert*-butyl nitrite and $CuCl_2$ in acetonitrile leads to the aryl chloride (III). Selective reduction of one nitro group of compound (III) by transfer hydrogenation with cyclohexene and Pd/C in ethanol affords the nitro aniline (IV), which is then submitted to diazotization, followed by hydrolysis of the resultant diazonium fluoroborate in aqueous H_2SO_4 to yield 4-chloro-2-methyl-3-nitrophenol (V). This chlorophenol (V) can also be prepared by chlorination of 2-methyl-3-nitrophenol (VI) with *N*-chlorosuccinimide in the presence of triflic acid in acetonitrile. Alkylation of phenol (V) with bromoacetonitrile by means of K_2CO_3 in 2-butanone produces the aryloxyacetonitrile (VII), which by reduction of the nitro group with Zn/AcOH, followed by acylation of the resultant aniline (VIII) with mesyl chloride in pyridine gives the sulfonamide (IX). Finally, Me_3Al-catalyzed addition of ethylenediamine to nitrile (IX) in toluene gives dabuzalgron, which is isolated as the hydrochloride salt (1). Scheme 1.

2) Reduction of 2-methyl-3-nitrophenol (VI) by catalytic hydrogenation over Pd/C in ethanol gives 3-amino-2-methylphenol (X), which is alkylated with bromoacetonitrile by means of Cs_2CO_3 in 2-butanone to provide the aryloxyacetonitrile (XI). Then, acylacion of the amino group of compound (XI) with mesyl chloride in pyridine/CH_2Cl_2 produces the sulfonamide (XII), which by subsequent chlorination using *tert*-butyl hypochlorite in *t*-BuOH/CCl_4 at –4 °C leads to the aryl chloride (IX). Treatment of nitrile (IX) with HCl gas and EtOH in CH_2Cl_2 affords imidate (XIII), which is finally condensed with ethylenediamine in MeOH (1). Scheme 2.

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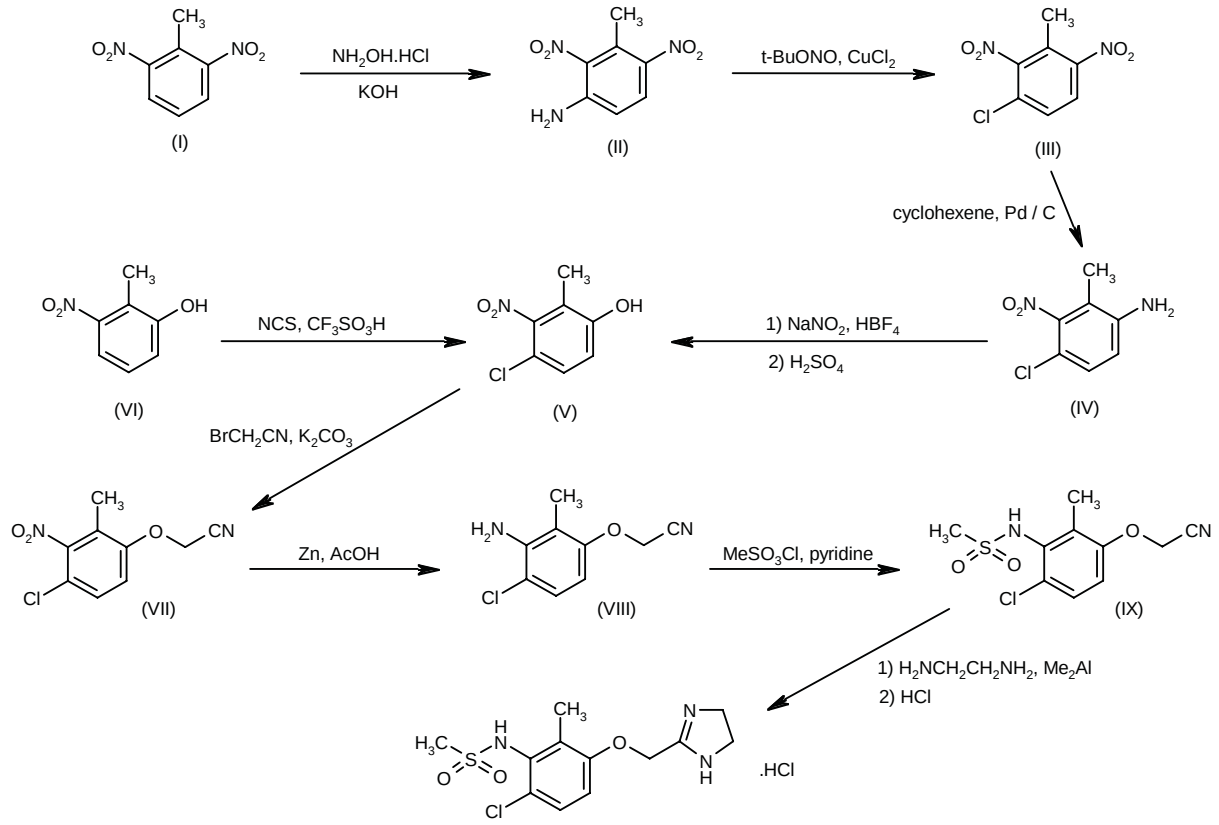
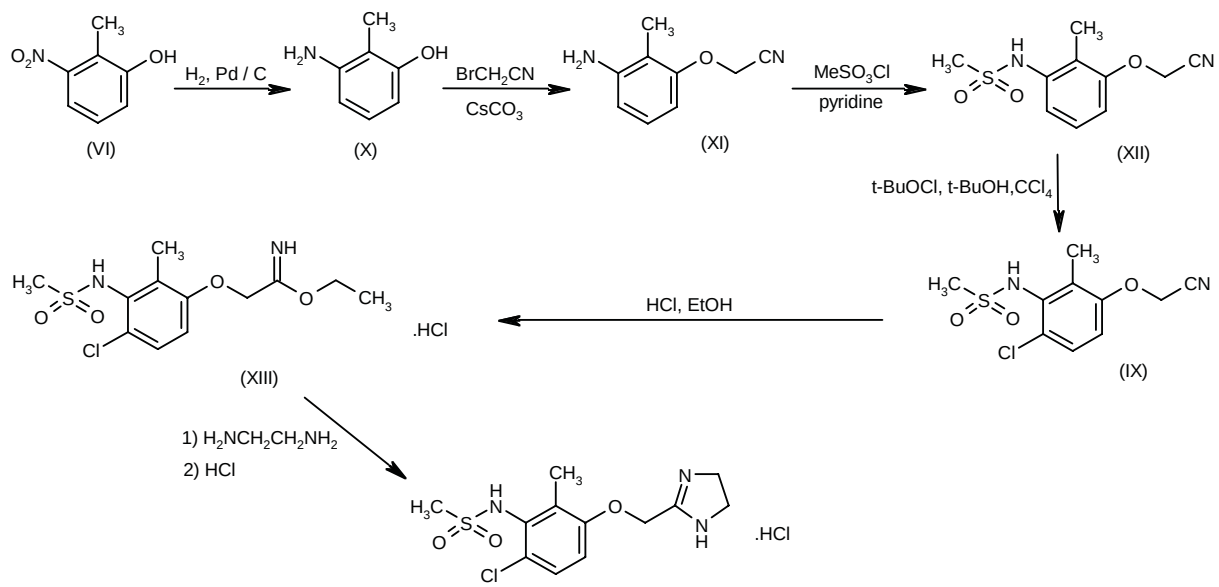
Scheme 1: Synthesis of Dabuzalgron Hydrochloride



Scheme 2: Synthesis of Dabuzalgron Hydrochloride



Introduction

Urinary incontinence is an extremely common disorder, affecting up to 12 million adults in the U.S. alone. It is classified into several subtypes: urge, stress, functional, overflow, mixed and transient incontinence. Stress urinary incontinence (SUI) in particular is the most common form of the disorder and is defined as involuntary leakage of urine on effort, exertion, sneezing or coughing. It is estimated that up to 50% of women over the age of 18 experience at least a mild form of the disorder. Pregnancy and childbirth resulting in weakening of the pelvic floor structures that support the bladder are the major causes of SUI. Other factors which increase risk are obesity, smoking, constipation and lung disease (2-5).

Pharmacotherapy for urinary incontinence can be classified into peripherally and centrally acting agents. Researchers have focused on adrenergic receptors as a potentially valuable target for developing agents to manage urinary incontinence. The β_3-adrenoceptor has been identified as controlling detrusor relaxation without inducing cardiovascular effects. α-Adrenoceptors, 3 subtypes of which have been cloned (α_{1A}, α_{1B} and α_{1D}), are found in abundance in the bladder neck and proximal urethra. The α_{1A}-adrenoceptor subtype is especially abundant and is recognized as an important neurotransmitter receptor implicated in the sympathetic neuronal control of urinary outlet tissue smooth muscle tone. A fourth adrenoceptor subtype has also been reported, the α_{1L}-adrenoceptor. This subtype has been shown to mediate contraction of rabbit and human urinary outlet smooth muscle. However, because a distinct gene product has not been identified, it is thought that this subtype is the pharmacological form of the α_{1A}-adrenoceptor gene product. This fourth adrenoceptor subtype is therefore referred to as the $\alpha_{1A/1L}$-adrenoceptor. Thus, the α_{1A}- and α_{1L}-adrenoceptors combined are attractive targets for the treatment of SUI (2, 6-15).

Early clinical experience with selective α_1-adrenoceptor agonists such as midodrine and methoxamine demonstrated efficacy in relieving symptoms of urinary incontinence. However, these agents were associated with dose-dependent hemodynamic adverse events including elevation of blood pressure (16-18). Thus, the search for novel agents with improved safety profiles continues. Dabuzalgron (Ro-115-1240, R-450) is a novel $\alpha_{1A/1L}$-adrenoceptor partial agonist that has been shown to control urethral smooth muscle *in vitro* and *in vivo*. Moreover, the agent has been shown to have minimal effects on hemodynamic variables. Dabuzalgron was thus selected for further development as a treatment for SUI (19, 20).

Pharmacological Actions

In competition binding studies examining [^{3}H]-prazosin binding to CHO-K1 membranes prepared from cells expressing human recombinant α_{1A}-, α_{1B}- and α_{1D}-adrenoceptors, dabuzalgron was shown to be approximately 30-fold selective for the α_{1A}-adrenoceptor subtype. The pK_i values obtained for the receptor subtypes were 7.39 ± 0.07, 5.8 ± 0.10 and 5.19 ± 0.07, respectively (19, 20).

Dabuzalgron exhibited selective α_{1A}-adrenoceptor-agonist properties in functional assays of inositol phosphate (InsP) accumulation and stimulation of calcium fluxes (FLIPR) using CHO-K1 cells transfected with human recombinant α_{1A}-, α_{1B}- and α_{1D}-adrenoceptors. The pEC_{50} values for InsP accumulation in α_{1A}-adrenoceptor-transfected cells for the free base and the hydrochloride salt were 6.79 ± 0.04 and 6.69 ± 0.05, respectively; whereas pEC_{50} values in α_{1B}- and α_{1D}-adrenoceptor-transfected cells were < 4.0. The values obtained for the hydrochloride salt in FLIPR assays were 7.47 ± 0.09 for the α_{1A}-adrenoceptor and < 5.0 for the other receptor subtypes (19, 20).

Dabuzalgron was also examined *in vivo* in experiments using anesthetized micropigs and rabbits. The agent (0.03-1000 μg/kg i.v.) caused nonselective, dose-dependent increases in intraurethral pressure (ED_{50} = 41 ± 5.1 μg/kg; maximum increase of 21 ± 3.2 cmH_2O) and diastolic arterial blood pressure (ED_{50} = 36 ± 6.1 μg/kg; maximum increase of 33 ± 4.6 mmHg) in anesthetized micropigs. However, although the potency of these effects was similar to that of the full $\alpha_{1A/1L}$-adrenoceptor agonist amidephrine, differences in their magnitude were seen. The increase in intraurethral pressure on dabuzalgron was less than half that seen following administration of amidephrine (ED_{50} = 40 ± 8.1 μg/kg; maximum increase of 51 ± 3.3 cmH_2O), and the increase in blood pressure observed with dabuzalgron was only one-third of that observed with amidephrine (ED_{50} = 39 ± 4.5 μg/kg; maximum increase of 95 ± 8.1 mmHg). Similar results were obtained in experiments using anesthetized rabbits where both dabuzalgron and amidephrine dose-dependently increased intraurethral (ED_{50} = 70 and 51 μg/kg, respectively) and mean arterial (ED_{50} = 77 and 30 μg/kg, respectively) pressures. These results indicate that dabuzalgron acts as a partial agonist relative to amidephrine in these models (19, 20).

In contrast to results obtained in anesthetized animals, dabuzalgron (1-300 μg/kg i.v.) had only minimal effects on blood pressure in conscious micropigs. The agent significantly and dose-dependently increased urethral tension, while it had no effect on diastolic arterial pressure or heart rate at a dose (300 μg/kg) which elicited maximum effects on urethral tension; an increase of 12 ± 2 mmHg in diastolic arterial pressure unrelated to changes in heart rate was observed with the higher dose of 1000 μg/kg. In contrast, amidephrine (1-300 μg/kg i.v.) produced dose-dependent increases in urethral tension, diastolic arterial pressure and heart rate that were greater than dabuzalgron (19, 20).

Clinical Studies

A multicenter, randomized, placebo-controlled, crossover study conducted in 37 women with mild to

moderate SUI examined the efficacy and safety of dabuzalgron (1.5 mg b.i.d. for 2 or 4 weeks). The treatment was well tolerated. Adverse events were generally transient and mild to moderate. One or more adverse events were reported by 72% and 83% of the patients in the placebo and dabuzalgron treatment groups, respectively. The most frequent treatment-related adverse events were those associated with α-adrenoceptor agonism and included paresthesia (*i.e.*, scalp tingling), headache, rigors, piloerection and pruritus. Two patients receiving dabuzalgron discontinued due to adverse events unrelated to treatment. No significant differences were observed in mean systolic or diastolic blood pressure between placebo and active treatment groups and no clinically significant changes in ECG or laboratory parameters were noted with treatment. Mean sitting heart rate was slightly lower in patients receiving dabuzalgron as compared to placebo. The number of weekly SUI episodes reported was significantly lower in the group administered dabuzalgron (8.4 *vs.* 6), representing a 28% improvement over placebo. The mean number of pads used and wet pads changed/week was also significantly lower in the active treatment group. It was concluded that more randomized controlled trials involving larger patient populations are warranted to confirm the results obtained in this study (21), and the compound continues in phase I/II development for this indication (22).

Sources

Chugai Pharmaceutical Co., Ltd. (JP); F. Hoffmann-La Roche, Ltd. (CH).

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