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CCC: 0377-8282/2003

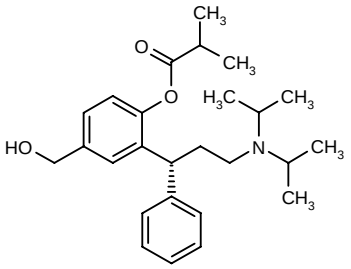
Fesoterodine

Prop INN

Treatment of Urinary Incontinence
Muscarinic M_3 Antagonist

SPM-907

2-Methylpropionic acid 2-[3-(*N*,*N*-diisopropylamino)-1(*R*)-phenylpropyl]-4-(hydroxymethyl)phenyl ester
Isobutyric acid 2-[3-(diisopropylamino)-1(*R*)-phenylpropyl]-4-(hydroxymethyl)phenyl ester



$C_{26}H_{37}NO_3$

Mol wt: 411.5823

CAS: 286930-02-7

CAS: 286930-03-8 (as maleate)

CAS: 345663-07-2 (as hydrochloride)

CAS: 286930-04-9 (as hydrochloride hydrate)

EN: 299639

Abstract

Urinary incontinence and overactive bladder are extremely common disorders affecting up to 12 and 20 million adults in the U.S., respectively. Current pharmacotherapy includes peripherally acting compounds which modulate bladder smooth muscle contraction or centrally acting agents which modulate the neurological control of urination. Anticholinergic agents inhibit bladder smooth muscle contraction through interference with acetylcholine action on muscarinic receptors on detrusor smooth muscle. However, the first anticholinergic agents were associated with a high rate of adverse events due to nonselectivity and targeting of several muscarinic subtypes and thus other organs. The search for novel, more bladder-selective antimuscarinic agents with better tolerability was initiated. Fesoterodine is a novel selective muscarinic M_3 receptor antagonist that has shown potent antimuscarinic activity *in vitro* and *in vivo* and has been selected for further development as a treatment for urinary incontinence and overactive bladder.

Synthesis

Esterification of the benzoic acid derivative (I) with $MeOH/H_2SO_4$ gives the methyl ester (II), which is debenzylated with H_2 over Ra-Ni in methanol to yield the 4-hydroxybenzoate derivative (III). Reduction of compound (III) by means of $LiAlH_4$ in THF affords the 4-(hydroxymethyl)phenol derivative (IV), which is finally esterified with isobutyryl chloride (VI) and TEA in dichloromethane (1). Scheme 1.

Alternatively, the methyl ester (II) can be reduced with $LiAlH_4$ in ethyl ether to give the 4-(benzyloxy)benzyl alcohol derivative (V), which is debenzylated by hydrogenation with H_2 over Ra-Ni in methanol to yield the already reported 4-(hydroxymethyl)phenol derivative (IV) (1). Scheme 1.

Introduction

Urinary incontinence and overactive bladder are extremely common disorders, affecting up to 12 and 20 million adults in the U.S., respectively. Urinary incontinence is characterized by a strong need to urinate followed by involuntary leaking and complete voiding and can occur at any age, although its prevalence is estimated to be 40% and 90% higher in geriatric and psychogeriatric populations, respectively. The incidence is also higher in women as compared to men over the age of 75 years. In addition, children can be afflicted with both daytime and nighttime urinary incontinence. It is estimated that 10-20% of all 5-year-olds and 5-7% of all 10-year-olds suffer from nighttime incontinence. Overactive bladder is due to spastic contractions of the detrusor muscle of the bladder resulting in sustained, high bladder pressure and the urgent need to urinate. Symptoms include frequent urination, urgency and urge incontinence and can be caused by nerve damage due to abdominal trauma, pelvic trauma or surgery, bladder stones, adverse

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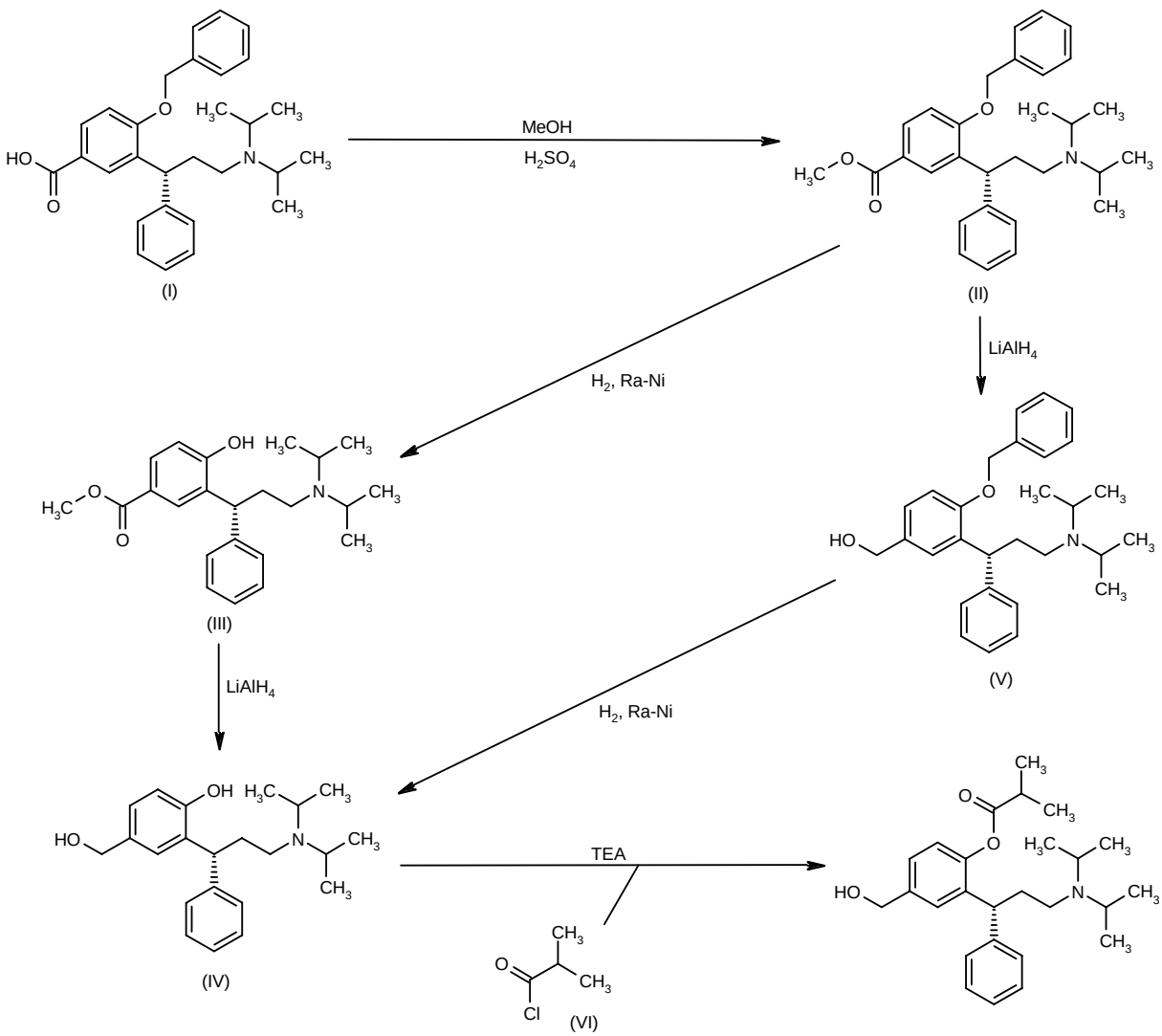
Scheme 1: Synthesis of Fesoterodine

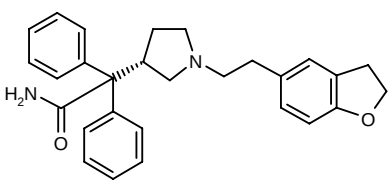


effects of drugs or neurological disease (*e.g.*, spinal cord lesions, multiple sclerosis, Parkinson's disease) (2).

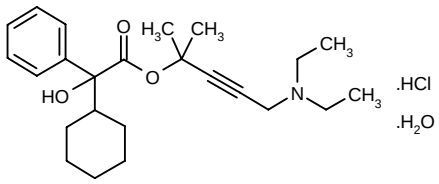
Urinary incontinence is classified into several subtypes: urge, stress, functional, overflow, mixed and transient incontinence. Urge urinary incontinence accounts for 65% of all cases and is characterized by abnormal spontaneous bladder smooth muscle contraction leading to urine leakage that can be unrelated to bladder urinary volume. It is caused by neurogenic instability due to spinal cord injury, multiple sclerosis or excessive neurotransmitter release in the bladder or myogenic instability due to bladder hypertrophy caused by outlet obstruction or urinary tract infection. Stress incontinence is also common and results from physical changes such as weakening of the pelvic floor muscles that support the bladder. Functional incontinence is generally age-related and due to the inability of an individual to move, think and/or communicate properly, thus preventing them from reaching the toilet in time. Overflow incontinence is more common in men and is due to weakened bladder muscles or blockage of the urethra by a urinary stone or benign prostatic hyperplasia. This form is associated with increased volume of residual urine and impaired ability of the bladder to contract. Mixed incontinence is the coexistence of more than one type of incontinence and is usually a combination of stress and urge urinary incontinence in women. Transient incontinence is temporary and can be caused by medications, urinary tract infections, tumors, severe constipation, restricted mobility or mental impairment (2).

Table I: Anticholinergic agents under development (from Prous Science Integrity®).

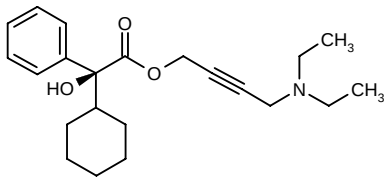
Drug name	Source	Condition	Phase
1. Darifenacin	Novartis	Incontinence, urinary	II
		Overactive bladder	Prereg.
2. Temiverine Hydrochloride Hydrate	Nippon Shinyaku	Incontinence, urinary urge	Prereg.
3. (*S*)-Oxybytynin	Sepracor	Incontinence, urinary	III
		Overactive bladder	III
		Urinary frequency	III
4. Solifenacin Succinate	Yamanouchi	Incontinence, urinary urge	Prereg.
		Urinary frequency	Prereg.
5. KRP-197	Kyorin/Ono	Incontinence, urinary	II
6. Fesoterodine	Schwarz	Incontinence, urinary urge	III
		Overactive bladder	III



(1)



(2)



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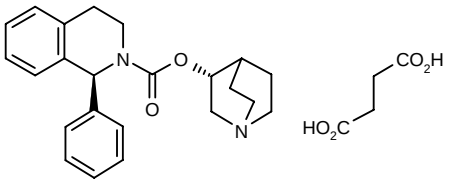

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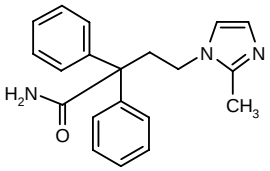

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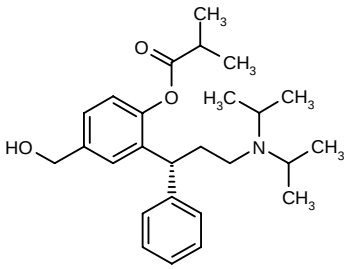

(6)

In some cases, urinary incontinence and overactive bladder can be managed without pharmacotherapy, using exercise, pessaries, implants, biofeedback or behavioral therapy. In other cases, pharmacotherapy is the better option. Agents to treat this disorder include both peripherally acting compounds which modulate bladder smooth muscle contraction or centrally acting agents which modulate the neurological control of urination. Anticholinergic agents have been found to be particularly effective for treating urge urinary incontinence and overactive bladder. During normal micturition, acetylcholine released from postganglionic parasympathetic neurons acts on muscarinic receptors on detrusor smooth muscle in the bladder to stimulate contraction. Anticholinergic agents interfere with this action, thus reducing detrusor contractions. However, the first anticholinergic agents described for this disorder were not selective, acting at all muscarinic receptor subtypes and thus on other organs. They were associated with a high incidence of adverse events, including dry mouth, blurred vision, nausea and tachycardia, and were contraindicated in patients with bladder obstruction. Thus, the search for novel, more selective agents less likely to induce adverse events was initiated. Those novel anticholinergic agents currently under development are shown in Table I (2-6).

One attractive target for the treatment of urinary incontinence and overactive bladder is the M_3 muscarinic receptor, which is present primarily on the bladder and appears to mediate contractile activity. Researchers have focused on designing agents that selectively antagonize the M_3 receptor and thus are bladder-selective. Fesoterodine is one such novel selective muscarinic M_3 receptor antagonist that has shown potent antimuscarinic activity *in vitro* and *in vivo* and has been selected for further development as a treatment for urinary incontinence and overactive bladder.

Pharmacological Actions

The pharmacodynamic effects of fesoterodine and its active metabolite, SPM-7605, were examined *in vitro* on carbachol- and electrical field stimulation-induced contractions of rat bladder strips and after i.v. administration

Table II: Pharmacokinetics and safety of fesoterodine (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized, double-blind	Fesoterodine, 4 mg p.o. o.d. x 3 d Fesoterodine, 8 mg p.o. o.d. x 3 d Fesoterodine, 12 mg p.o. o.d. x 3 d Fesoterodine, 20 mg p.o. o.d. x 3 d Fesoterodine, 28 mg p.o. o.d. x 3 d Placebo	40	Fesoterodine appeared to be safe in healthy volunteers at all doses studied. At higher doses, an increase in residual urinary volume and a reduction of salivary secretion were observed	10
Healthy volunteers	Randomized, double-blind	Fesoterodine, 4 mg p.o. o.d. x 3 d Fesoterodine, 8 mg p.o. o.d. x 3 d Fesoterodine, 12 mg p.o. o.d. x 3 d Fesoterodine, 20 mg p.o. o.d. x 3 d Fesoterodine, 28 mg p.o. o.d. x 3 d Placebo	40	Fesoterodine was well tolerated and at daily doses equal to or higher than 12 mg/day it increased residual urinary volume. The higher doses were also associated with a lower saliva production and mild to moderate increases in heart rate	11
Healthy volunteers	Randomized, double-blind	Fesoterodine, 8 mg o.d. Placebo	48	A single oral dose of 8 mg fesoterodine was safe and well tolerated in young males as well as elderly males and females	8

(0.01, 0.1 and 1 mg/kg) to healthy rats *in vivo*. Fesoterodine and SPM-7605 (1 μM-1 mM) shifted the concentration-response curve for carbachol to the right, with no significant depression of the maximum, suggesting competitive antagonism. The pA_2 values were 8.7 ± 0.3 and 8.8 ± 0.3, respectively, and the slopes of the Schild plot were 1 and 1.3, respectively. Similar pA_2 values were obtained for oxybutynin and atropine, 8.4 ± 0.1 and 9.0 ± 0.3, respectively. Both agents concentration-dependently inhibited electrical field stimulation-induced contractions with maximum inhibition (60 ± 15.3 and 43.6 ± 13.1%, respectively) observed at a concentration of 0.1 μM; in contrast, the maximum inhibition observed with 0.1 μM of oxybutynin and atropine was 33.7 ± 14 and 39.7 ± 27.1%, respectively. Administration of fesoterodine and SPM-7605 (0.01 mg/kg i.v.) to healthy rats resulted in an increase in bladder capacity (0.99 ± 0.1 *vs.* 0.83 ± 0.1 ml for fesoterodine; 1.08 ± 0.1 *vs.* 0.98 ± 0.1 ml for SPM-7605) and intercontraction intervals (5.48 ± 0.7 *vs.* 4.61 ± 0.5 min for fesoterodine; 6.04 ± 0.7 *vs.* 5.44 ± 0.8 min for SPM-7605) at 90-120 min postdosing; micturition volume only slightly increased at this dose. Significant reductions in micturition pressure were observed for both agents at this dose, indicating that the threshold dose was less than 0.01 mg/kg (7).

Pharmacokinetics and Safety

The pharmacokinetics of single oral doses of fesoterodine (8 mg) and its active metabolite SPM-7605 were examined in a randomized, double-blind, placebo-controlled, parallel-group study involving 16 healthy young (18-45 years) males, 16 healthy elderly (> 65 years) males and 16 healthy elderly females. Fesoterodine was well tolerated with no serious adverse events or significant changes in physical exams, heart rate, blood pressure, ECG parameters or laboratory parameters reported in any group. The mild adverse events observed were similar in all 3 population groups and no differences were observed in the pharmacokinetics among the 3 subject populations. Mean maximum plasma levels of SPM-7605 were detected about 5 h postdosing. C_{max} and AUC values were similar in the 3 populations following normalization for body weight. Renal clearance was lower in elderly as compared to younger subjects. The mean terminal $t_{1/2}$ value for all 3 groups ranged from 7-9.4 h and the mean residence time for SPM-7605 for all 3 groups was 11 h. It was concluded that fesoterodine is safe for elderly subjects and no dose adjustments are required in this population (8) (Table II).

The pharmacokinetics of ascending single oral doses of fesoterodine (4, 8 and 12 mg) and SPM-7605 were examined in 24 healthy male subjects. SPM-7605 pharmacokinetics were found to be dose-proportional. Maximum plasma levels of SPM-7605 were seen about 5 h postdosing and the mean terminal $t_{1/2}$ value ranged from 7.3-8.9 h. The median half-value duration for the doses tested ranged from 7.7-8.7 h. Renal clearance values ranged from 249-264 ml/min and the cumulative excretion of SPM-7605 increased with dose (9).

A randomized, double-blind, placebo-controlled, group-comparison study examined the pharmacokinetics of multiple ascending oral doses (4, 8, 12, 20 and 28 mg once daily for 3 days) of fesoterodine and SPM-7605 in 40 healthy male subjects. Fesoterodine was concluded to be safe at all doses examined. No significant changes in physical exams, blood pressure, ECG parameters or laboratory parameters were observed with treatment. The most common adverse events reported were dry mouth and voiding difficulties at the higher doses; these adverse effects were consistent with antimuscarinic action and were confirmed by decreases seen in salivary production and increases in residual urinary volume in the 12-, 20- and 28-mg dose groups. The increases in residual urinary volumes suggest that the agent is effectively relaxing the

bladder detrusor muscle in these healthy subjects. Mild to moderate increases in heart rate were observed with the ascending doses, also reflecting the antimuscarinic effects of the agent. Due to rapid metabolism, fesoterodine was not detected in plasma. Maximum SPM-7605 plasma levels were detected 4-6 h postdosing and mean $t_{1/2}$ values and mean residence time were 5-7 h and 11-13 h, respectively. SPM-7605 plasma levels, AUC values and cumulative renal clearance increased linearly with fesoterodine dose (10, 11) (Table II).

Clinical Studies

Results from a phase IIb trial in patients with overactive bladder/urge urinary incontinence showed that fesoterodine significantly and dose-dependently reduced symptoms. The compound was well tolerated and exhibited a favorable efficacy:safety ratio (12).

Fesoterodine is now moving into phase III clinical studies (13).

Source

Schwarz Pharma AG (DE).

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