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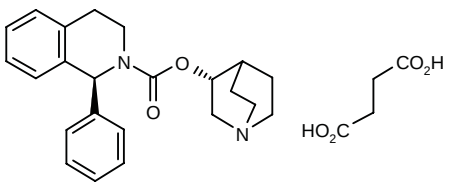
YM-905

Treatment of Urinary Incontinence
Muscarinic M_3 Antagonist

YM-53705 (as monohydrochloride)

1(*S*)-Phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylic acid 3(*R*)-quinuclidinyl ester monosuccinate



$C_{23}H_{26}N_2O_2.C_4H_6O_4$ Mol wt: 480.5660

CAS: 180272-14-4 (undefined isomer, free base)
CAS: 180272-15-5 (undefined isomer, oxalate)
CAS: 180272-16-6 (undefined isomer, monohydrochloride)
CAS: 180468-39-7 (as monohydrochloride)

EN: 249699

Synthesis

YM-905 has been obtained by two related ways: Scheme 1.

1) The benzoylation of 2-phenylethylamine (I) with benzoyl chloride (II) and triethylamine in chloroform, or with benzoic acid (III), DPPA and triethylamine in DMF, gives the corresponding benzamide (IV), which is cyclized by means of $POCl_3$ and P_2O_5 in refluxing xylene and reduced with $NaBH_4$ in ethanol, yielding racemic 1-phenyl-1,2,3,4-tetrahydroisoquinoline (V). The reaction of (V) with ethyl chloroformate by means of K_2CO_3 in chloroform affords racemic 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylic acid ethyl ester (VI), which is transesterified with quinuclidine-3(*R*)-ol (VII) by means of NaH in refluxing toluene to provide the quinuclidinyl ester (VIII) as a diastereomeric mixture. This mixture is resolved by chiral HPLC, giving the target compound as a pure enantiomer (1).

2) The racemic 1-phenyl-1,2,3,4-tetrahydroisoquinoline (V) can also be submitted to optical resolution with (+)-tartaric acid to give 1(*S*)-phenyl-1,2,3,4-tetrahydroisoquinoline (IX) (1), which is condensed with ethyl chloroformate by means of K_2CO_3 in chloroform to afford 1(*S*)-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylic acid ethyl ester (VI). This compound is transesterified with quinuclidine-3(*R*)-ol (VII) by means of NaH in refluxing toluene to directly provide the pure enantiomer (1, 2).

Introduction

Urinary incontinence is uncontrolable and can be caused by various factors such as neurologic disease (*e.g.*, Alzheimer's disease) or weak pelvic muscles. Approximately 800,000 older Americans living at home are incontinent, which limits their daily activities. Several anticholinergic drugs are available for the treatment of urinary incontinence, including oxybutinin, propiverine and tolterodine. These drugs act by blocking the action of acetylcholine at postganglionic cholinergic sites, thereby increasing bladder capacity by reducing the number of motor impulses reaching the detrusor muscle. New therapeutic approaches under study for the treatment of urinary incontinence are shown in Table I.

In an attempt to develop more bladder-selective muscarinic M_3 receptor antagonists for use in the therapy of urinary incontinence, researchers at Yamanouchi prepared a series of 1,2,3,4-tetrahydro-2-isoquinolinecarboxylate derivatives. One compound in the series, YM-53705, exhibited high affinity for this receptor and good selectivity for inhibition of rhythmic bladder contractions versus salivary secretion (1). Pharmacological studies were subsequently conducted with the monosuccinate YM-905.

Pharmacological Actions

YM-905 exhibits high affinity for human muscarinic m_1, m_2 and m_3 receptors, with respective K_i values of 25, 120 and 10 nM. The M_3 receptor-mediated, carbachol-induced increase in intracellular Ca^{2+} levels in mouse salivary gland cells was antagonized by YM-905, tolterodine,

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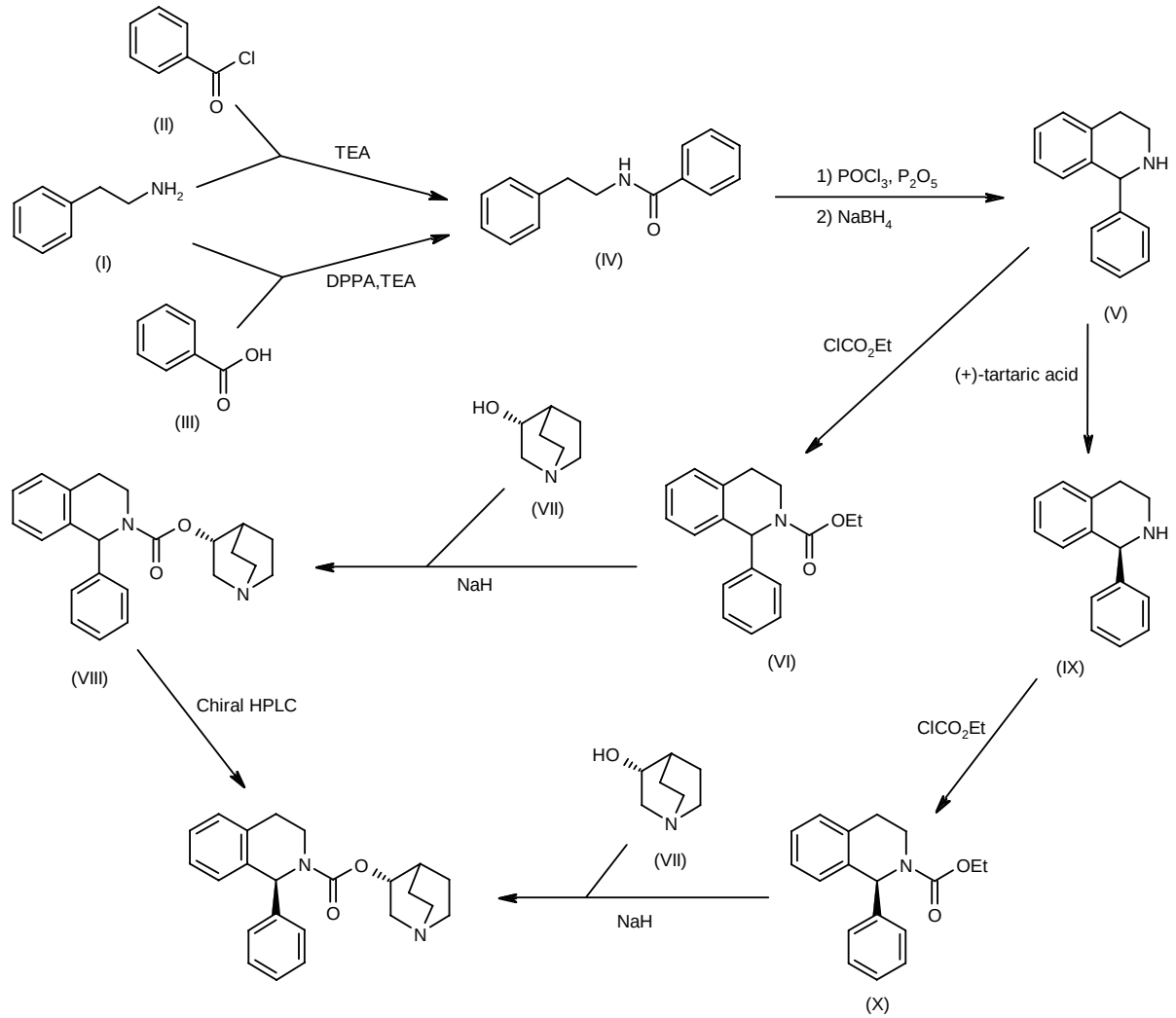
Scheme 1: Synthesis of YM-905



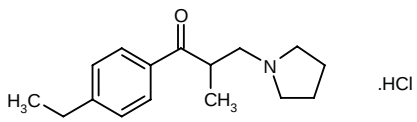
oxybutynin and atropine, with pK_B values of 7.4, 9.3, 9.0 and 9.9, respectively, whereas the responses in guinea pig detrusor muscle cells were antagonized by YM-905, tolterodine and oxybutynin with pK_B values of 8.5, 8.9 and 8.6, respectively. Also, carbachol-evoked contractions of guinea pig detrusor muscle cells were antagonized by YM-905, tolterodine, oxybutynin and atropine with pA_2 values of 7.1, 8.1, 7.4 and 8.4, respectively. When tested in anesthetized mice, both YM-905 and oxybutynin potently inhibited carbachol-induced increases in baldder pressure at doses of 0.1-1 mg/kg i.v. In contrast, only oxybutynin was associated with potent inhibition of carbachol-stimulated salivation at these doses (3, 4).

The effects of YM-905 on colonic function have also been investigated *in vitro* and *in vivo*. The compound potently inhibited carbachol-induced guinea pig colon contractions in a competitive manner (pA_2 = 7.5). Inhibition of defecation induced by bethanechol, neostigmine and nicotine in rats was observed at oral doses of YM-905 of 1-30 mg/kg. Title compound was also able to inhibit restraint stress-induced defecation (ED_{50} = 4.0 mg/kg p.o.) and diarrhea, a model of irritable bowel syndrome (IBS). As above (3, 4), YM-905 was shown to inhibit M_3 receptor-mediated intracellular Ca^{2+} mobilization in guinea pig colonic longitudinal muscle cells (pK_B = 8.4) to a significantly greater extent than in mouse salivary gland cells (pK_B = 7.4). The results from these latter studies indicate that YM-905 may also be useful in the treatment of colonic motor dysfunction such as in IBS (5, 6).

YM-905 is currently in phase II trials in the U.S. and Europe for the treatment of urinary incontinence (7).

Table I: Drugs in clinical trials for urinary incontinence (Prous Science Ensemble database).

Compound	Manufacturer	Phase	Mechanism of Action
1. Inaperisone HCl . (*Riran*, *Inapen*)	Hokuriku; Yamanouchi	Preregistered	Muscle relaxant
2. Temiverine HCl (*Urespan*)	Nippon Shinyaku	Preregistered	Anticholinergic; calcium antagonist
3. Darifenacin	Pfizer	Phase III	Muscarinic M_3 antagonist
4. Duloxetine oxalate	Lilly, Shionogi	Phase III	5-HT and NE reuptake inhibitor
5. (S)-Oxybutynin	Sepracor	Phase II/III	Anticholinergic
6. KRP-197	Kyorin	Phase II	Muscarinic M_1 and M_3 antagonist
7. NC-1800	Nippon Chemiphar	Phase II	Centrally acting agent
9. NS-49	Nippon Shinyaku; Sanofi Synthélabo; Abbott	Phase II	α_{1A}- adrenoceptor agonist
9. YM-905	Yamanouchi	Phase II	Muscarinic M_3 antagonist
10. ZD-6169	AstraZeneca	Phase II	Potassium channel activator
11. Resiniferatoxin	Afferon; Mundipharma	Phase II	Vanilloid compound*
12. Saredutant	Sanofi Synthélabo	Phase II	Tachykinin NK_2 antagonist
13. HCT-1026	NicOx	Phase I/II	Nitric oxide donor



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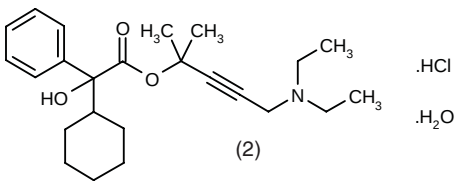

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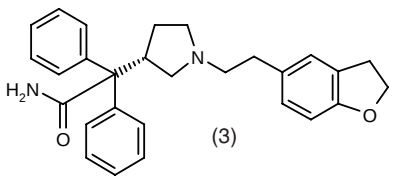

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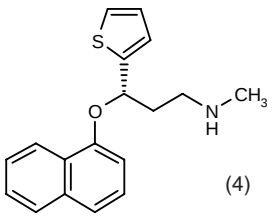

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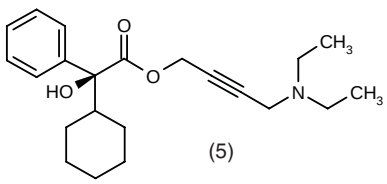

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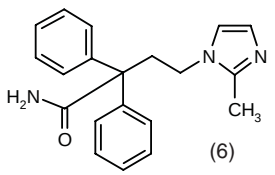

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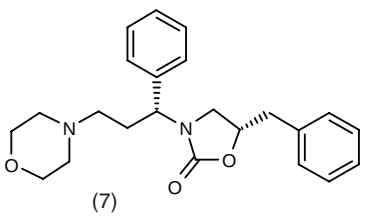

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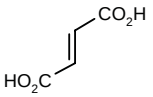

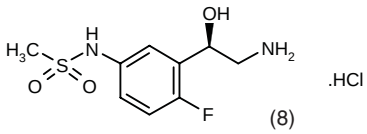

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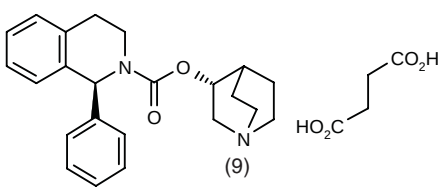

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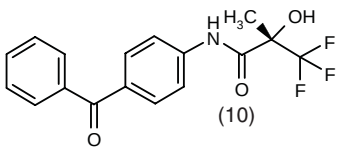

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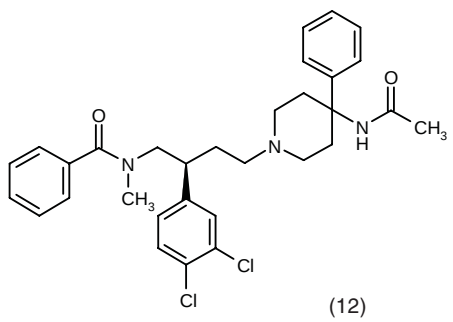

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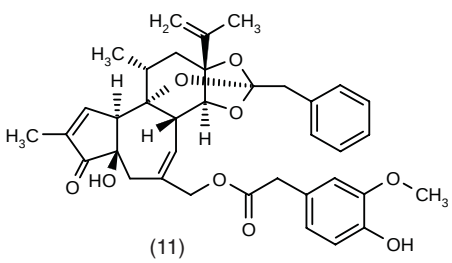

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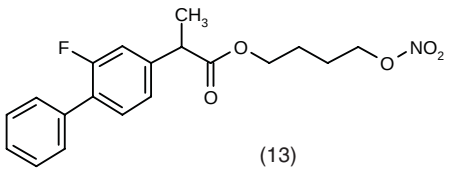

(13)

*Desensitizer of overactive afferent neurones

Manufacturer

Yamanouchi Pharmaceutical Co., Ltd. (JP).

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