drugs and drug candidates

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Review

Repositioning Oxybutynin Hydrochloride: State of the Art in Synthesis, Mode of Action, Metabolism, and Formulations

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Abstract: For decades, oxybutynin hydrochloride has been prescribed to improve bladder control in cases of incontinence and excessive urination frequency. This review summarizes synthetic methods enabling the preparation of the racemic drug and, in a detailed manner, preparation of (*S*)-2-cyclohexyl-2-hydroxy-2-phenylacetic acid, a key intermediate in the synthesis of (*S*)-oxybutynin. The mode of action and metabolism are briefly addressed in order to explain the main adverse effects associated with its use and to justify the evolution observed in the diverse commercial formulations. Repositioning opportunities are discussed in terms of clinical trials for the management of hyperhidrosis, hot flashes, and obstructive sleep apnea.

Keywords: bladder; breast cancer; hot flashes; hyperhidrosis; obstructive sleep apnea; oxybutynin; prostate cancer

Citation: Vanden Eynde, J.J. Repositioning Oxybutynin Hydrochloride: State of the Art in Synthesis, Mode of Action, Metabolism, and Formulations. *Drugs Drug Candidates* **2023**, *2*, 865–882. https://doi.org/10.3390/ddc2040043

Academic Editor: George Mihai Nitulescu

Received: 17 September 2023
Revised: 15 October 2023
Accepted: 20 October 2023
Published: 24 October 2023

1. Introduction

Better knowledge of signaling pathways and therapeutic targets allows us to find novel applications for marketed drugs or drug candidates failing in late stages of clinical trials. The so-called "drug repositioning" or "drug repurposing" concept was introduced in 2004 by Ashburn and Thor [1]. It enables pharmaceutical companies to save time and money because efficient procedures of preparation at laboratory and pilot scales have already been developed. In addition, results of most pre-clinical and clinical assays have already been accumulated. Drug repositioning also provides new tools to physicians, giving them the opportunity of proposing innovative, but sometimes experimental, medications to their patients. Examples of successfully repositioned drugs (Figure 1) include acetylsalicylic acid (**1**), sildenafil (**2**), and thalidomide (**3**). Acetylsalycilic acid, well-known for its antipyretic and analgesic effects, eases blood circulation [2] and could exhibit beneficial effects in some cancers [3]. Sildenafil was initially developed to treat cardiovascular problems but it failed in the corresponding clinical trials. The molecule is now prescribed in the case of erectile dysfunction [4] and extensively studied for its antitumoral activities [5]. Thalidomide [6], on the other hand, was commercialized to relieve nausea in pregnant women but was soon abandoned due to its teratogenic consequences. Thalidomide is now manufactured as an effective agent against erythema *nodosum leprosum* and multiple myeloma.

Many other approved drugs have been screened or are still screened in order to find them new applications for the treatment of, among other things, Alzheimer's disease [7], asthma [8], and more recently, COVID-19 [9].

The racemic oxybutynin (**4**, Figure 2) is an antimuscarinic agent clinically that has been used, in its hydrochloride form (**4.HCl**), in the therapy of overactive bladder for almost five decades. Interestingly, a series of reports indicated that it could emerge as a promising medication for managing hyperhidrosis, hot flashes, and, hopefully, obstructive sleep apnea. Therefore, we thought it useful to summarize, for the first time in a single paper, the knowledge acquired on the syntheses, mode of action, metabolism, and formulations of this substance. Repositioning opportunities are highlighted.

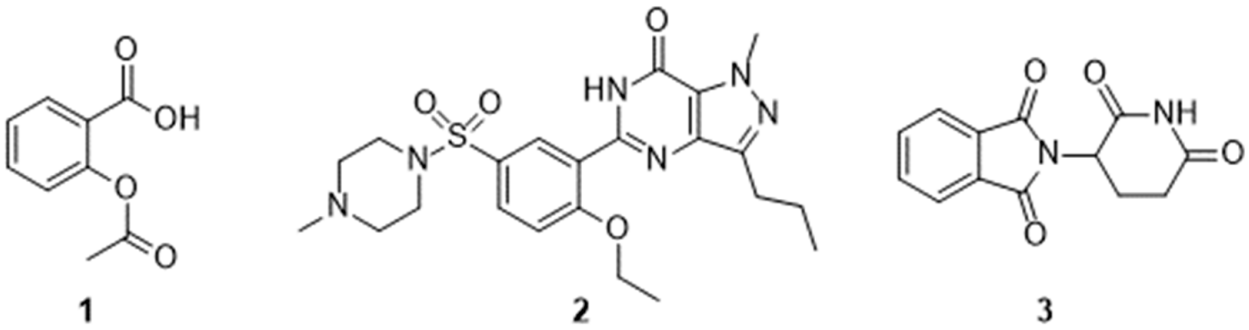


Figure 1. Structure of acetylsalicylic acid (**1**), sildenafil (**2**), and thalidomide (**3**).

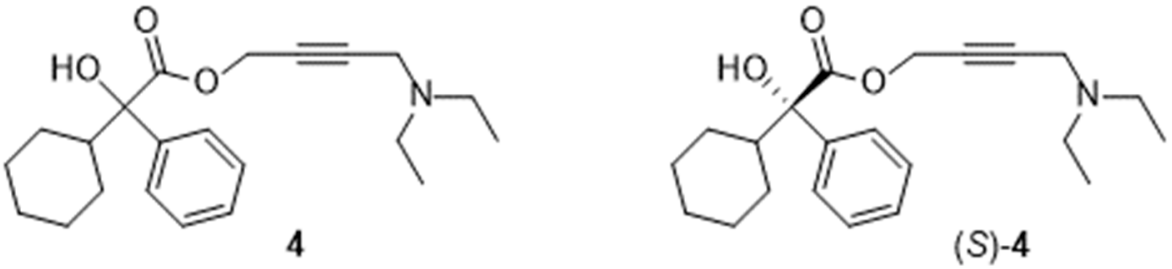


Figure 2. Structure of oxybutynin (**4**) and its (*S*)-enantiomer.

2. Chemical Names

The Chemical Abstracts registry numbers of the racemate of oxybutynin and its hydrochloride are 5633-20-5 and 1508-65-2, respectively. Its index name is benzeneacetic acid, α-cyclohexyl-α-hydroxy-, 4-(diethylamino)-2-butynyl ester. Registry numbers of the (*R*)- and (*S*)-enantiomers (Figure 2) are 119618-21-2 and 119618-22-3, respectively. The corresponding registry numbers for the hydrochlorides are 1207344-05-5 and 230949-16-3. The denominations aroxybutynin [10] for the (*R*)-enantiomer and esoxybutynin [11] for the (*S*)-enantiomer can also be found in the literature.

The IUPAC name is 4-diethylaminobut-2-ynyl 2-cyclohexyl-2-hydroxy-2-phenylethanoate. Sometimes, oxybutynin is considered as a derivative of the following:

- glycolic acid: 4-diethylamino-2-butynyl phenylcyclohexylglycolate;
- acetic acid: 4-diethylamino-2-butynyl 2-cyclohexyl-2-hydroxy-2-phenylacetate.

The name oxybutynin is often used, indifferently, to designate the free base as well as its hydrochloride. Therefore, in order to stay consistent and to lighten the text of the review, we shall distinguish both species by numbering them **4** and **4.HCl**, respectively.

3. Syntheses

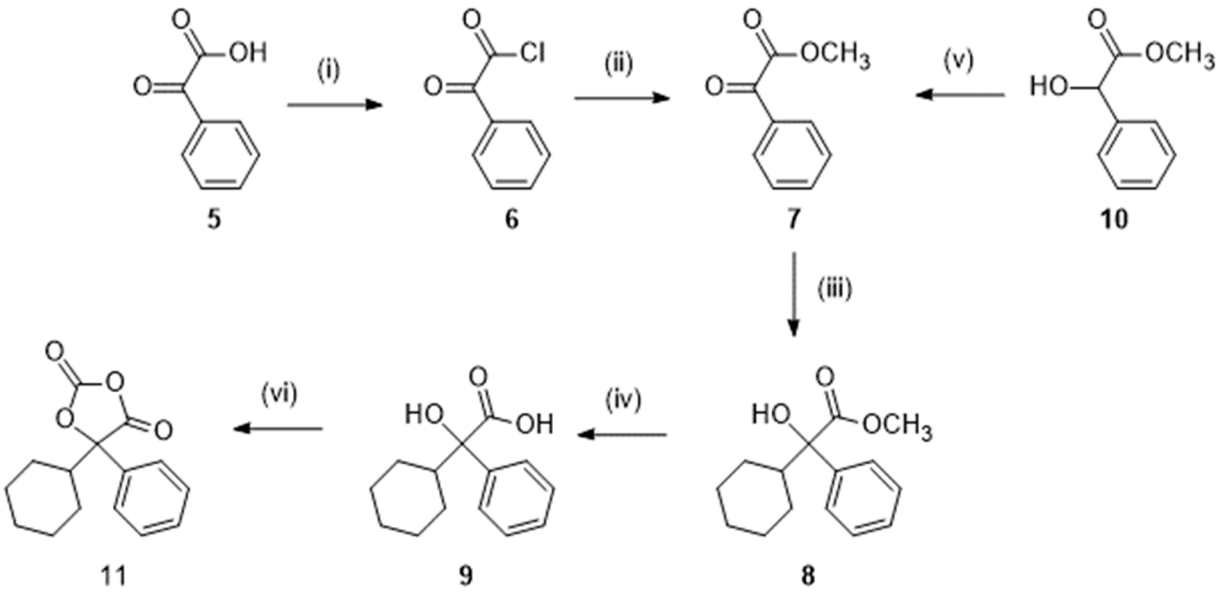
3.1. Syntheses of the Racemic Mixture

Practically, oxybutynin can be prepared by a convergent synthesis requiring two key reagents, namely 2-cyclohexyl-2-hydroxy-2-phenylacetic acid (**9**, Scheme 1) or a corresponding ester (usually the methyl ester **8**, Scheme 1) and 2-propyn-1-ol (propargyl alcohol; **12**, Scheme 2) or a derivative, which are coupled in an esterification or transesterification reaction.

3.1.1. Preparation of Methyl 2-Cyclohexyl-2-Hydroxy-2-Phenylacetate (**8**) and the Corresponding Acid (**9**)

There are two routes (Scheme 1) to obtain reagents **8** and **9**. One route starts from 2-oxo-2-phenylacetic acid (phenylglyoxylic acid; **5**), which is first converted into the acid chloride **6** by treatment with thionyl chloride. Further reaction with methanol produced the ester **7**. Action of bromocyclohexane under conditions of a Grignard reaction afforded methyl 2-cyclohexyl-2-hydroxy-2-phenylacetate **8**, which could be hydrolyzed to the corresponding

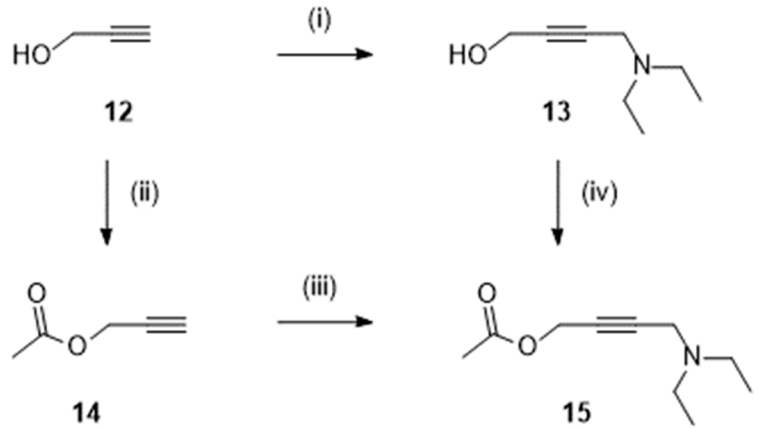
acid **9** [12,13]. In the alternative route, methyl 2-hydroxy-2-phenylacetate (methyl mandelate; **10**) was the starting material that could readily be oxidized into **7** before the Grignard reaction [13]. Optionally, activation of acid **9** under the form of 5-cyclohexyl-5-phenyl-1,3-dioxolane-2,4-dione **11** (Scheme 1) by reaction with trichloromethylchloroformate has been reported [14].



Scheme 1. Preparation of the intermediates **8**, **9**, and **11**. Reagent(s); catalyst; solvent(s); yield(s). (i) $SOCl_2$; toluene; 92% [12]. (ii) CH_3OH; 87% [12]. (iii) Bromocyclohexane, Mg; I_2; tetrahydrofuran; 65% [12], 57% [13]. (iv) NaOH; H_2O, CH_3OH; 77% [13]. (v) Pyridinium chlorochromate; CH_2Cl_2; 76% [13]. (vi) *N*-methylpiperidine, trichloromethylchloroformate; tetrahydrofuran; 79% [14].

3.1.2. Preparation of Derivatives of 2-Propyn-1-ol

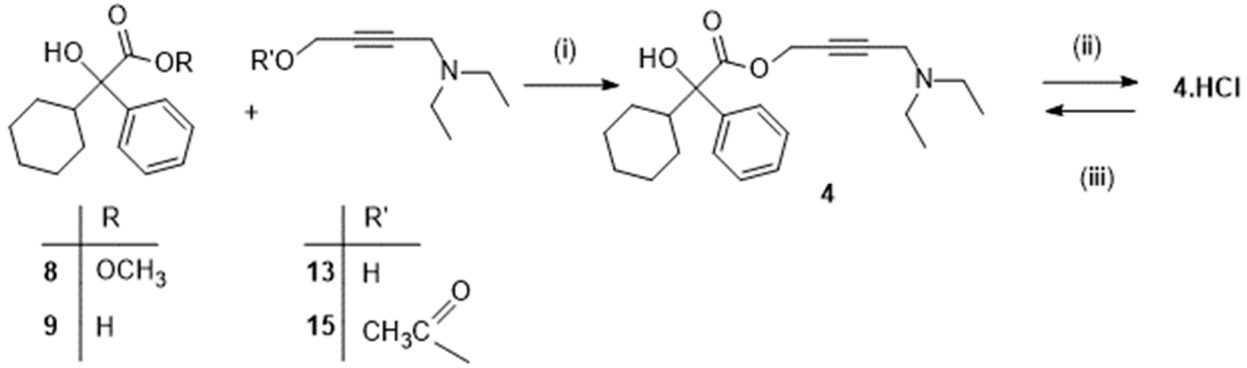
In most procedures, the butynyl alcohol **13** (Scheme 2) was prepared by a Mannich reaction involving 2-propyn-1-ol **12** [13], formadehyde, and diethylamine. In some works, **12** [12] was esterified with acetyl chloride (to give **14**) before the Mannich reaction to finally afford acetate **15** [12,14]. The later could also be obtained from **13** and a mixture of acetic acid and acetic anhydride [15].



Scheme 2. Preparation of derivatives **13**–**15**. Reagent(s); catalyst; solvent(s); yield(s). (i) HCHO, $(C_2H_5)_2NH$; $CuSO_4$; H_2O; 23% [13]; (ii) CH_3COCl, $(C_2H_5)_3N$; CH_2Cl_2; 91% [12]. (iii) HCHO, $(C_2H_5)_2NH$; CuCl; 1,4-dioxane; 89% [12]. (iii) HCHO, $(C_2H_5)_2NH$; $(CH_3CO_2)_2Cu$; 1,4-dioxane; 84% [15]. (iv) $(CH_3CO)_2O$; H_2SO_4; CH_3CO_2H; 81% [15].

3.1.3. Final Step

Ultimately, oxybutynin **4** and its hydrochloride **4.HCl** were synthesized (Scheme 3) by coupling ester **8** or acid **9** and alcohol **13** or ester **15**. Details on published sequences, experimental conditions, and yields can be found in Table 1. Overall yields, calculated from commercially available precursors 2-oxo-2-phenylacetic acid **5** [12] or methyl 2-hydroxy-2-phenylacetate **10** [13] and 2-propyn-1-ol **12**, ranged from a modest 23% [12] to a poor 6% [13].

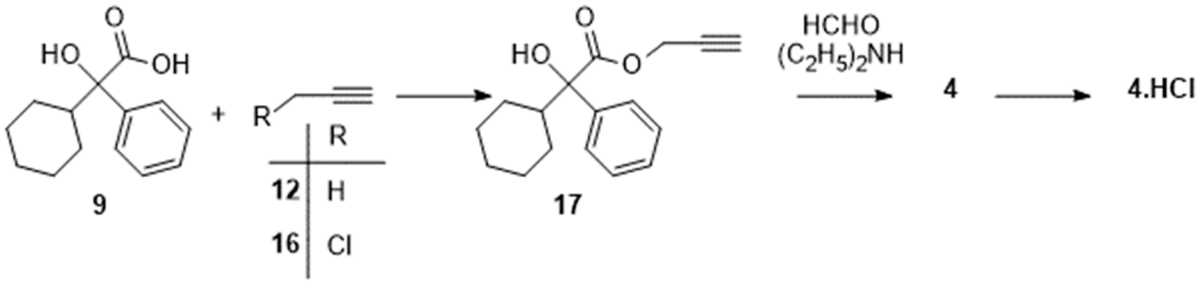


Scheme 3. Final steps in the preparation of oxybutynin **4**.

Table 1. Published sequences for the final step affording oxybutynin, experimental conditions, and yields.

Sequence	Experimental Conditions	Yield [Reference]
8 + **15** -> [4] -> **4.HCl**	(i) CH_3ONa; n-heptane, then (ii) HCl_{aq}; H_2O	86% [12]; 51% [16]
8 + **15** -> **4**	(i) CH_3ONa; n-heptane	73% [16]
8 + **13** -> **4**	(i) NaOH; H_2O	91% [17]
9 +**13** -> [4] -> **4.HCl**	(i) 1-Hydroxybenzotriazole hydrate, N-methylmorpholine, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; CH_2Cl_2, then (ii) HCl_g; CH_3OH	27% [13]
4.HCl -> **4**	(iii) NaOH; H_2O, n-heptane	96% [16]
4.HCl -> **4**	(iii) NaOH; H_2O	95% [18,19]

Yes, it is a compound number; brackets indicate. Additionally, a recent Chinese patent [20] mentioned, as illustrated in Scheme 4, the possibility of preparing ester **17** from **9** and 3-chloroprop-1-yne **16**. The Mannich reaction was then performed in the last reaction of the sequence yielding **4.HCl**. A sequence allowing access to ester **17** from **9** and 2-propyn-1-ol **12** has also been adapted to synthesize some deuterated derivatives of oxybutynin [13,21,22]. However, experimental details were not clearly disclosed in any of those four references.



Scheme 4. Alternative route yielding oxybutynin **4**.

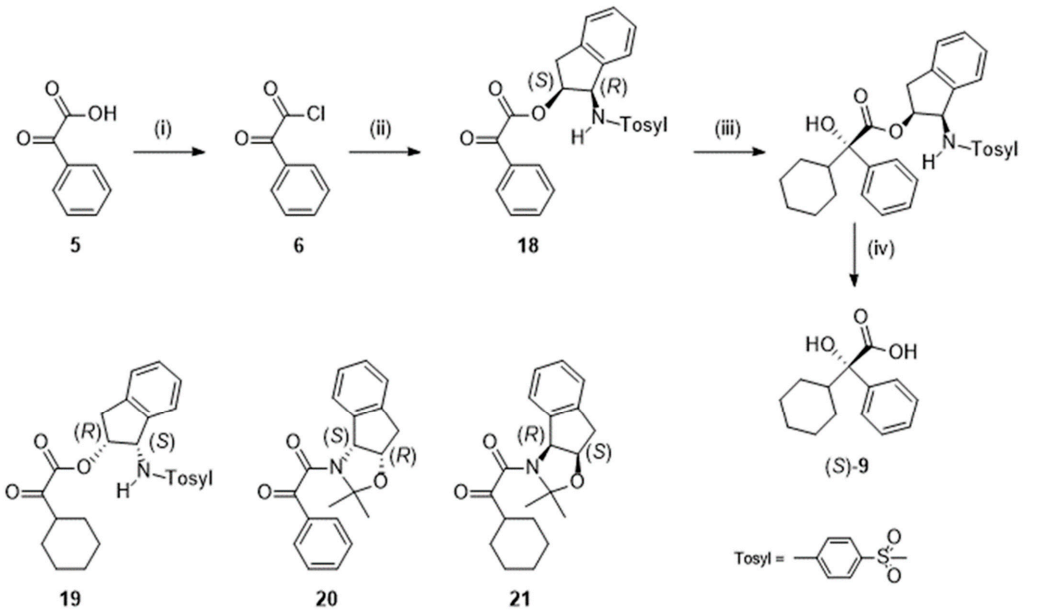
3.2. Preparation of (S)-Oxybutynin

Because the (*S*)-enantiomer of oxybutynin exhibits a better tolerability than the (*R*)-enantiomer (see Section 4), its preparation has attracted much interest, essentially during the first decade of this century. In fact, all efforts were dedicated to the obtention of the key intermediate, namely the (*S*)-enantiomer of 2-cyclohexyl-2-hydroxy-2-phenylacetic acid **9**. The simplest way to isolate it was to treat, as described in the patent of Bakale et al. [23], the racemic mixture with L-tyrosine methyl ester in order to afford the expected (*S*)-oxybutynin in 42% yield.

Besides the separation of diastereoisomers, more sophisticated methods have been described to prepare (*S*)-**9**, and they are summarized hereafter. Evidently, those protocols can be adapted to afford the (*R*)-enantiomer of **9**.

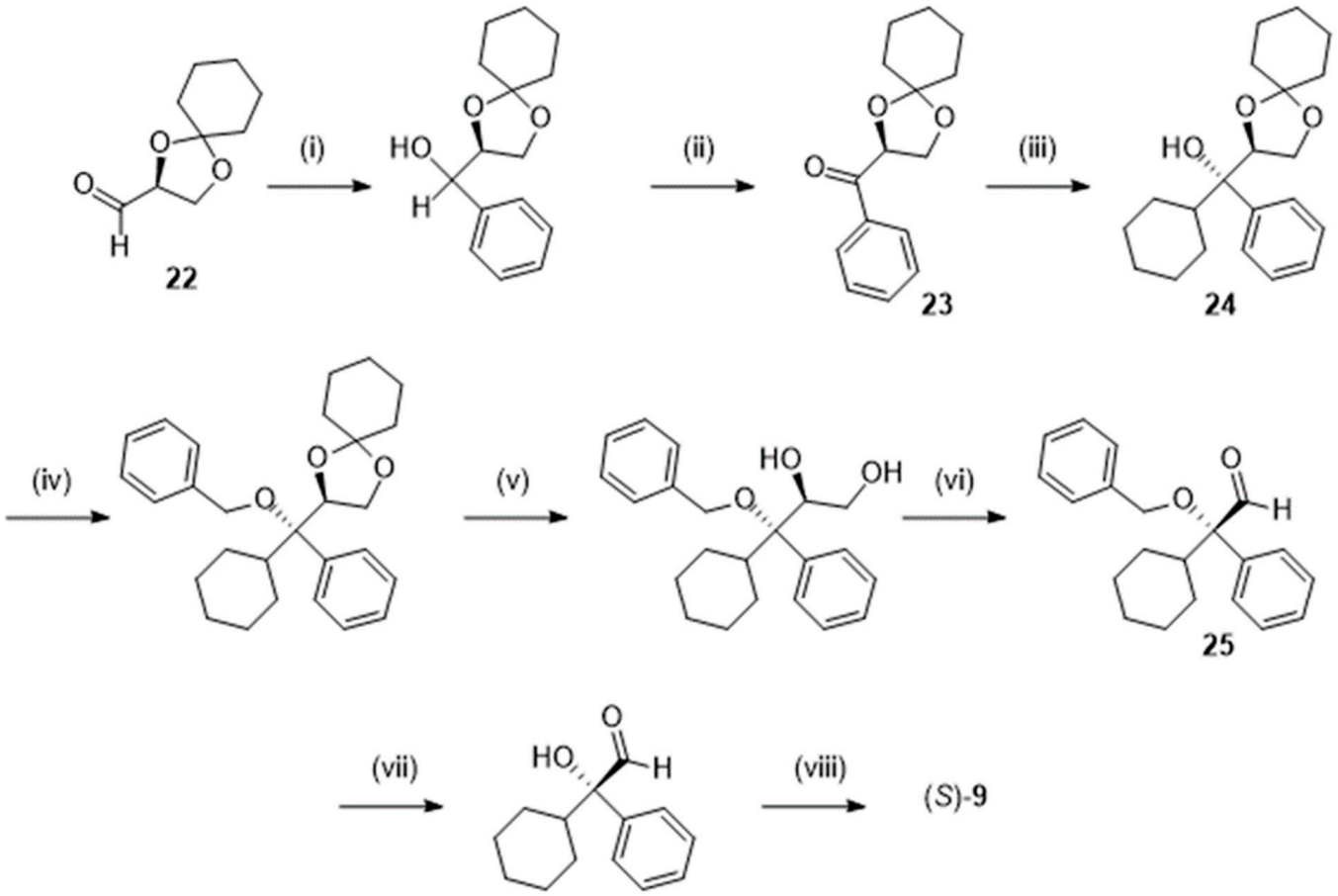
For example, Senanayake et al. [24] obtained (*S*)-2-cyclohexyl-2-hydroxy-2-phenylacetic acid in enantiomeric excesses higher than 98% by forcing a Grignard reagent to preferentially attack the less hindered face of 2-oxo-2-phenylacetic acid or 2-oxo-cyclohexylacetic acid derivatives. To achieve that goal, the authors used bulky chiral auxiliaries based on substituted *cis*-1-amino-2-indanol moieties (1-*para*-tolylsulfonyl group and acetonide). One representative case is depicted in Scheme 5. Thus, 2-oxo-2-phenylacetic acid (**5**) was converted into its acyl chloride and then reacted with *cis*-(1*S*,2*R*)-2-*para*-tolylsulfonamidoindanol to afford ester **18**. Subsequent Grignard reaction and hydrolysis of the ester yielded the targeted (*S*)-2-cyclohexyl-2-hydroxy-2-phenylacetic acid (*S*)-**9**. Other structurally related chiral intermediates (**19**–**21**) evaluated in the study are represented in Scheme 4. The best yields were obtained from esters **18** and **19** bearing the *N*-*para*-tolylsulfonamidoindanyl group.

Sequence	Overall Yield
18 -> (*S*)-**9**	81%
19 -> (*S*)-**9**	80%
20 -> (*S*)-**9**	30%
21 -> (*S*)-**9**	42%



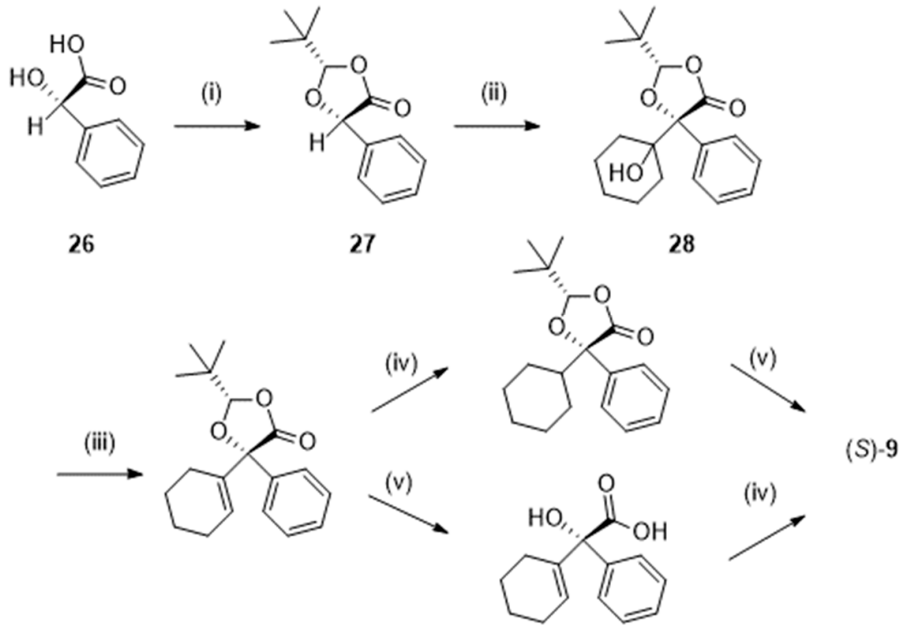
Scheme 5. Preparation of (*S*)-2-cyclohexyl-2-hydroxy-2-phenylacetic acid (*S*)-**9** following [24]. Reagent(s); catalyst; solvent(s); yield(s). (i) $(COCl)_2$; $HCON(CH_3)_2$; CH_2Cl_2; 95%. (ii) *Cis*-(1*S*,2*R*)-2-*para*-tolylsulfonamidoindanol; $(C_2H_5)_3N$; tetrahydrofuran; yield not mentioned. (iii) Bromocyclohexane, Mg; $ZnCl_2$; tetrahydrofuran; 55%; (iv) NaOHaq; CH_3OH; >95%.

Later, Chattopadhyay et al. [25] described another stereocontrolled Grignard reaction (Scheme 6) by addition of cyclohexylmagnesium bromide on phenyl ketone **23**, obtained from (*R*)-2,3-*O*-cyclohexylydene-D-glyceraldehyde **22**. The first attempts to hydrolyze acetal **24** and subsequent oxidation led to decomposition or poor yields. Better results were obtained by protecting the alcohol function of **24** by reaction with benzylbromide. That expanded the sequence but enabled isolation of the expected (*S*)-**9** with an acceptable overall yield (eight steps) of 25%, with an enantiomeric excess of 98%.



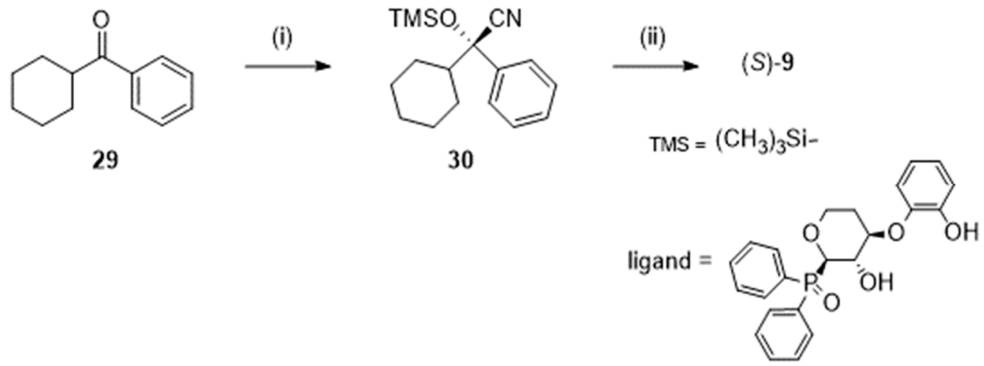
Scheme 6. Preparation of (*S*)-2-cyclohexyl-2-hydroxy-2-phenylacetic acid (*S*)-**9** following [25]. Reagent(s); catalyst; solvent(s); yield(s). (i) Phenylmagnesium bromide; tetrahydrofuran; 88%. (ii) Pyridinium chlorochromate, CH_3CO_2Na; CH_2Cl_2; 84%. (iii) Cyclohexylmagnesium bromide; tetrahydrofuran; 87%; (iv) NaH, $C_6H_5CH_2Br$; tetrahydrofuran; 88%; (v) HClaq; CH_3OH; 92%. (vi) $NaIO_4$; CH_3CN, H_2O; 81%. (vii) Dichlorodicyanobenzoquinone; CH_2Cl_2; 88%. (vii) $NaClO_2$; 68%.

In another approach (Scheme 7), trimethylacetaldehyde (pivaldehyde) was acetalized with (*S*)-2-hydroxy-2-phenylacetic acid (**26**; (*S*)- mandelic acid). The resulting dioxolone (**27**) was deprotonated and stereoselectively coupled with cyclohexanone at −78 °C. Dehydration of the so-formed alcohol (**28**) followed by hydrolysis and hydrogenation (or the inverse sequence) yielded (*S*)-**9** in excellent enantiomeric excess (>99.9%) and an overall yield of 66% [26].



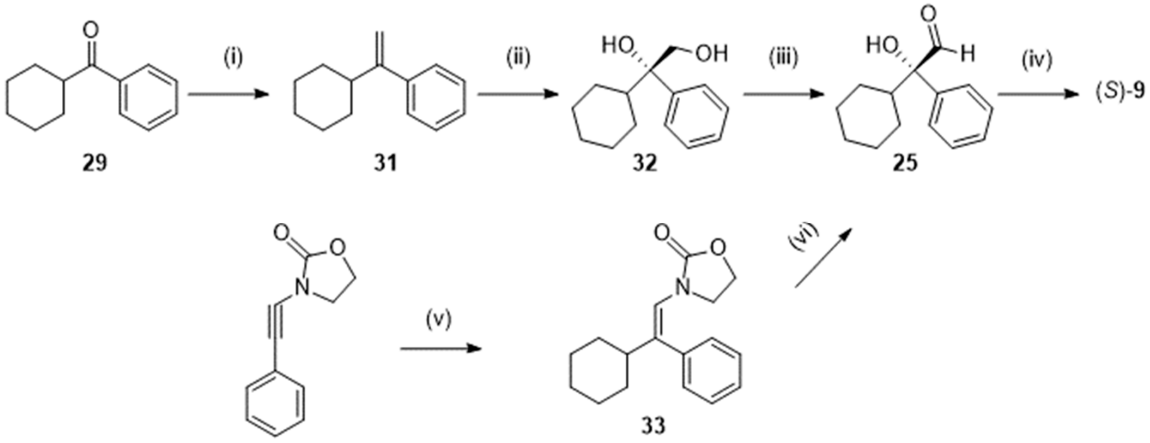
Scheme 7. Preparation of *S*-2-cyclohexyl-2-hydroxy-2-phenylacetic acid (*S*)-**9** following [26]. Reagent(s); catalyst; solvent(s); yield(s). (i) $(CH_3)_3CHO$; trifluoromethylmethanesulfonic acid; pentane; 96%. (ii) Lithium bis(trimethylsilyl)amide; cyclohexanone, tetrahydrofuran; 76%. (iii) $SOCl_2$, pyridine; tetrahydrofuran; >98%. (iv) H_2; Pd/C; CH_3OH; 95%. (v) KOH; CH_3OH; then HCl; 96%.

Catalytic enantioselective cyanosilylation of cyclohexyl phenyl ketone **29** (Scheme 8) with a chiral gadolinium complex was the first step of the procedure reported by Shibasaki et al. [27]. Subsequent reduction, desilylation, and oxidation afforded the expected (*S*)-**9** in an overall yield of 80% with an enantiomeric excess higher than 99.5%. Interestingly, enzymatic resolution of racemic mixtures of cyanohydrins structurally related to **30** has been the subject of a study by Gotor et al. [28].



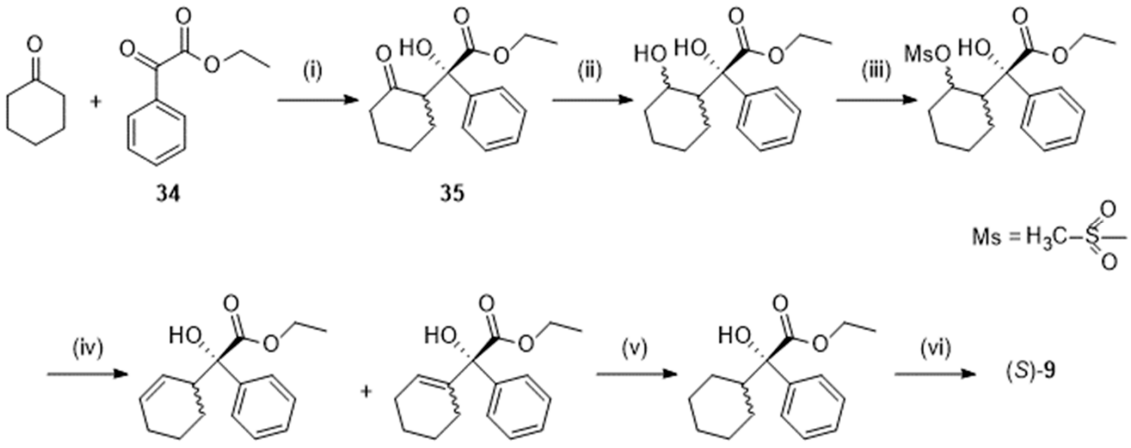
Scheme 8. Preparation of *S*-2-cyclohexyl-2-hydroxy-2-phenylacetic acid (*S*)-**9** following [27]. Reagent(s); catalyst; solvent(s); yield(s). (i) Trimethylsilyl cyanide; gadolinium (*O*-isopropyl)$_3$, ligand; C_2H_5CN; 100%. (ii) Diisobutylaluminium hydride; toluene then HClaq; tetrahydrofuran then $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene; H_2O, *tert*-butanol; 80%.

Alternatively (Scheme 9), ketone **29** was introduced in a Wittig reaction with methylenetriphenylphosphorane yielding alkene **31**. Asymmetric dihydroxylation with osmium tetraoxide under Sharpless conditions gave **32** in an enantiomeric excess of 92%. Then, a Swern reaction oxidized the terminal alcohol into the corresponding aldehyde **25**, which could be further oxidized to acid (*S*)-**9** with an overall yield of 45% [29]. Notice that aldehyde **25** has also been obtained, in an enantiomeric excess of 84%, from 3-[(*Z*)-2-phenyl-2-cyclohexylvinyl]oxazolidin-2-one **33** (Scheme 9), as proposed by Gourdet and Lam [30].



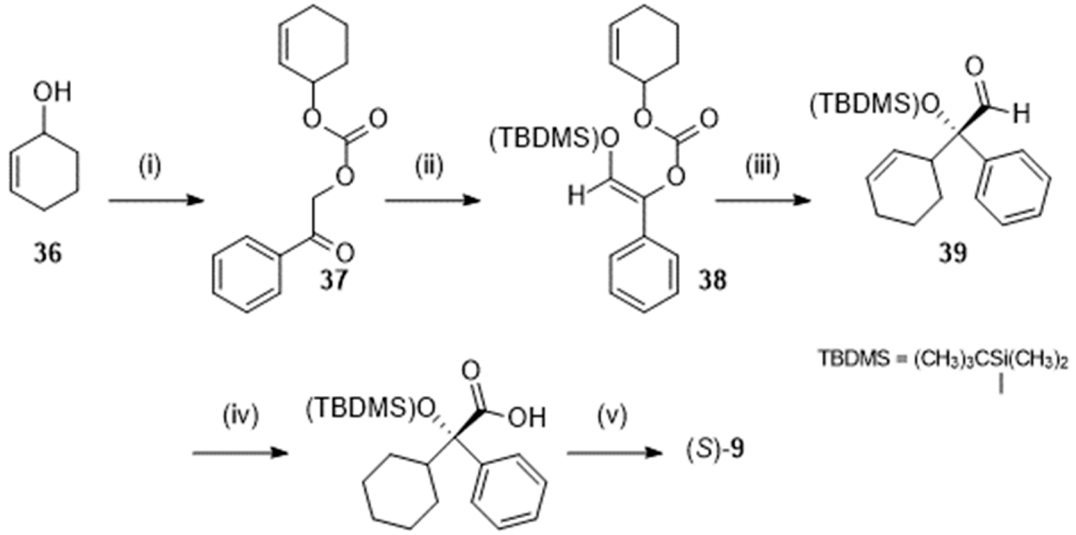
Scheme 9. Preparation of (*S*)-2-cyclohexyl-2-hydroxy-2-phenylacetic acid (*S*)-**9** following [29,30]. Reagent(s); catalyst; solvent(s); yield(s). (i) $Ph_3P^+CH_3I^-$, n-C_4H_9Li; tetrahydrofuran; 92%. (ii) OsO_4, $K_3Fe(CN)_6$, hydroquinine 1,4-phthalazinediylether; *tert*-ButOH, H_2O; 70%. (iii) $(COCl)_2$, $(C_2H_5N)_3$; dimethylsulfoxide, CH_2Cl_2; not isolated. (iv) $NaClO_2$, $NaHPO_4.2H_2O$, 2-methyl-2-butene; *tert*-ButOH; 70%. (v) Cyclohexylmagnesium bromide, $(CH_3CO)_2Cu$; tetrahydrofuran; 74%. (vi) $K_2OsO_2(OH)_2$, $K_3Fe(CN)_6$, hydroquinine 1,4-phthalazinediylether; *tert*-butanol; 80%.

Following Maruoka et al. [31], (*S*)-**9** could be prepared through a *L*-proline-catalyzed asymmetric aldol reaction between cyclohexanone (in 10-fold excess) and ethyl 2-oxo-2-phenylacetate (**34**, Scheme 10). That reaction yielded ester **35** in good yield (79%), good diastereoselectivity (dr $\geq$ 20:1), and good enantiomeric excess (96%). However, synthesis of the pure corresponding acid (*S*)-**9** was not straightforward, so that the authors had to design a tedious five-step sequence starting from **35**. The overall yield, calculated on **34**, fell to 40%.



Scheme 10. Preparation of (*S*)-2-cyclohexyl-2-hydroxy-2-phenylacetic acid (*S*)-**9** following [31]. Reagent(s); catalyst; solvent(s); yield(s). (i) L-proline; dimethylsulfoxide; 79%; (ii) BH_3-$(CH_3)_2S$; tetrahydrofuran, CH_3OH; not purified. (iii) Methanesulfonyl chloride, $(C_2H_5N)_3$; CH_2Cl_2; 80% (iv) LiCl; hexamethylphosphoramide; 81%. (v) H_2; Pd/C; C_2H_5OH; 94%. (vi) NaOH; CH_3OH; 93%.

In the work of Trost et al. [32], the initial precursor of (*S*)-**9** was the commercially available cyclohex-2-en-1-ol **36** (Scheme 11), which was converted in a basic medium by treatment with carbon dioxide and then 2-bromoacetophenone, into ketocarbonate **37**. Deprotonation of **37** and protection of the enol by *tert*-butyldimethylsilyl chloride was accompanied by an intramolecular rearrangement affording **38**. In the subsequent step, an internal allylic alkylation involving a chiral palladium catalyst gave aldehyde **39**. Reduction of the cyclohexenyl ring, oxidation, and deprotection afforded the expected (*S*)-acid **9** with an enantiomeric excess higher than 99% but an overall yield of 22%.



Scheme 11. Preparation of (*S*)-2-cyclohexyl-2-hydroxy-2-phenylacetic acid (*S*)-**9** following [32]. Reagent(s); catalyst; solvent(s); yield(s). (i) NaH, CO_2; then $C_6H_5COCH_2Br$; $HCON(CH_3)_2$; 42%. (ii) Sodium bis(trimethylsilyl)amide, *tert*-butyldimethylsilyl chloride; tetrahydrofuran; 83%. (iii) Tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct; ligand; 1,4-dioxane; 94%. (iv) H_2; Pd/C; C_2H_5OH; 94%. (v) $NaClO_2$, $NaHPO_4.2H_2O$, 2-methyl-2-butene; *tert*-butanol, H_2O; 95%.

Having in hand (*S*)-2-cyclohexyl-2-hydroxy-2-phenylacetic acid **9** (or the (*R*) enantiomer), optically active oxybutynin (hydrochloride) could be synthesized using one of the procedures described in Schemes 3 and 4. The activated (*S*)-acid **11** has been involved, with butynyl alcohol **13**, in the multigram preparation of (*S*)-oxybutynin hydrochloride [14].

3.3. Resolution of the Racemic Mixture

Although high-performance thin-layer chromatography has been cited [33], enantiomers of oxybutynin have been generally separated by high-performance liquid chromatography. The silica-based support of the columns was covalently bonded to ovomucoid [34] or, more often, coated with polysaccharides such as amylose-tris(3,5-dimethylphenylcarbamate) [35,36] or cellulose-tris(4-methylbenzoate) [37]. Also reported and noteworthy is the use of β-cyclodextrin derivatives, essentially hydroxypropyl-β-cyclodextrin, as chiral selectors for the separation by high-performance liquid chromatography [38] as well as by electrophoresis [39], liquid–liquid reactive extraction [40], and recycling high-speed counter-current chromatography [41].

Astonishingly, preparation of diastereoisomers was seldom described. One example could be found in the patents of Molnar and Johnston [18,19]. The inventors treated the racemic mixture under its free base form, with D-malic acid in 2-propanol, and isolated the D-malate salt of (*R*)-oxybutynin in 41% yield. In the most recent patent [19], the same inventors claimed that "eleven other chiral acids were tested for production of (*R*)-oxybutynin salt from racemic oxybutynin: L-tartric acid, D-tartric acid, L-(+)-lactic acid, D-glucuronic acid, *D*-gluconic acid, *L*-malic acid, (1*R*,3*S*)-(+)-camphoric acid, (*S*)-(+)-mandelic acid, (1*R*)-(-)-10-camphorsulfonic acid, L-pyroglutamic acid, and D-(-)-quinic acid. None of the other eleven chiral acids were successful in chiral resolution to produce an (*R*)-oxybutynin salt from racemic oxybutynin".

4. Mode of Action and Metabolism

Micturition is mainly controlled by coordinated actions of the detrusor muscle and the bladder neck muscle. During bladder filling, the detrusor muscle is relaxed, whereas the neck muscle is contracted. The situation is reversed during urine elimination. Too frequent urinary urgencies, which are caused by abnormal contractions of the detrusor muscle, are manifestations of the so-called overactive bladder condition. Those contractions occur, in

brief, when acetylcholine, released from parasympathetic nerves, binds to M_3 muscarinic receptors located on the detrusor muscle. Therefore, blockade of those M_3 muscarinic receptors emerged as a strategy of choice for treating overactive bladder [42,43].

Oxybutynin is one of the most popular antagonists of muscarinic receptors and it has been widely prescribed in the therapy of overactive bladder for decades. However, muscarinic receptors are present in many parts of the body, including salivary glands, gut smooth muscle, eyes, heart, and brain [42,44]. That explains the series of side-effects observed after administration of the drug, among which are dry mouth, the most common and frequent side-effect, decreased sweating, constipation, blurred vision, tachycardia, and nausea. Impairments of cognitive function have also been reported and should be linked to the ability of the drug to cross the blood–brain barrier, due to its lipophilic character [43,45–47]. That adverse effect is observed in elderly patients especially, since permeability of the barrier increases with aging, as evidenced by magnetic resonance imaging [48]. Narrowing and degradation of endothelial cells, alterations of tight junction proteins, and dysregulations of transport mechanisms are among the factors contributing to blood–brain barrier deterioration [49].

Interestingly, it was demonstrated that, when orally absorbed, oxybutynin had a bioavailability as low as 6% [50]. Indeed, in the gut and the liver, the drug is rapidly metabolized by cytochrome P450 isozyme 3A4 into *N*-desethyloxybutynin (**40**; Figure 3), giving rise to concentrations of *N*-desethyloxybutynin in serum 4 to 10 times higher than those of the initial drug (additional data can be found under Section 5). However, that first metabolite also exhibits high affinity for the M_3 muscarinic receptors and especially for those located in the parotid gland. *N*-desethyloxybutynin is thought to be the main agent responsible for the dry mouth side-effect associated with the oral administration of oxybutynin [42,51,52].

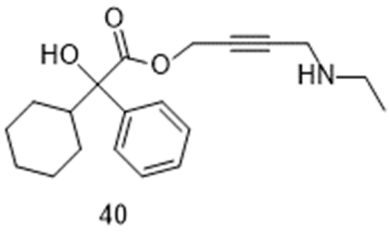


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Figure 3. Chemical structure of *N*-desethyloxybutynin **40**.

It is important to note that oxybutynin also exerts spasmolytic and local anesthetic effects on the bladder smooth muscle. However, those effects are far weaker than the antimuscarinic activity. Nevertheless, the efficacy of each enantiomer in both pathways has been studied. There were conflicting reports on the spasmolytic effects. The (*S*)-enantiomer has been claimed to exhibit higher [42,53] or similar [54–56] spasmolytic action when compared with the (*R*)-enantiomer. On the other hand, all studies underlined the lower antimuscarinic activity of the (*S*)-enantiomer when compared with the (*R*)-enantiomer, thus explaining the better tolerability of former [51,54,57]. However, up to now, those characteristics did not justify the marketing of any single enantiomer.

5. Formulations and Brand Names

Usually, physicians prescribe 5 to 20 mg of oxybutynin daily for the treatment of overactive bladder. Tablets of Ditropan® were approved by the U.S. Food and Drug Administration (FDA, Silver Spring, MD, USA) on 16 July 1975. Ditropan® syrup was FDA-approved on 29 November 1979.

As mentioned earlier, oxybutynin is rapidly converted into *N*-desethyloxybutynin upon gastric and hepatic metabolism and that first metabolite could be responsible for the well-known dry mouth side-effect. Therefore, it is not surprising that the original formulations of the racemic drug have successfully evolved to extended-release systems and transdermal administrations.

The Ditropan XL® tablet (FDA-approved on 16 December 1998), an extended-release formulation of the drug, was commercialized by Janssen Pharmaceuticals Inc. (Raritan, NJ, USA). It consisted of a core containing a layer of the drug and excipients and a second layer made of osmotic agents. The drug layer was surrounded by a drilled semipermeable membrane enabling controlled entry of water and release of oxybutynin [58].

Ditropan® and Ditropan XL® have now given way to more than 200 generics [59].

The first transdermal formulations of oxybutynin were the Oxytrol® patches marketed by Allergan USA Inc. (Madison, NJ, USA), further to the FDA approval published on 26 February 2003. Oxytrol® patches, which should be applied on the abdomen, hip, or buttock, are diffusion-controlled delivery systems (5.7 × 7.6 cm^2) dispensing 3.9 mg of oxybutynin per day [60]. The product was approved on 15 June 2004 by the European Medicines Agency (EMA) under the brand name Kentera® (Teva B.V., Haarlem, The Netherlands) [61].

Gelnique® is a 10% oxybutynin gel available in sachets of 1 g. It was FDA-approved on 27 January 2009 and is manufactured by Allergan USA Inc. [62]. On 8 December 2011, FDA approved a 3% oxybutynin gel supplied in a metered-dose pump dispenser, sold by Antares Pharma Inc. (Ewing, NJ, USA) [63]. A gel preparation of a nanosuspension of oxybutynin is currently under study in order to minimize skin irritation and improve the permeation efficiency [64].

Advantages, efficacy, and safety of the transdermal administration of oxybutynin were the subject of several clinical trials discussed in the works of Cohn [65] and Vozmediano-Chicharro [52]. The original pharmacokinetic parameters for different oral and transdermal formulations can be found in the study of Kennelly [51]. Roughly [42], the oxybutynin tablet (5 mg PO bid-qid) achieved a maximum concentration in serum of 12 ng/mL within 1 h with a half-life time of 2–3 h, whereas the extended-release formulation (5–30 mg PO qd) enabled the concentration to reach a maximum of 4 ng/mL within 5 h and exhibited a half-life time of 13 h. Few differences between the pharmacokinetic parameters of each enantiomer, when orally administered as the racemate, have been detected [66]. Table 2 summarizes the maximum plasma concentrations of the enantiomers of oxybutynin and desethyloxybutynin, at steady state, after administration of Ditropan® [50] and Ditropan XL® [58] in children aged 5–15.

Table 2. Maximum plasma concentrations of the enantiomers of oxybutynin and desethyloxybutynin, at steady state, after administration of Ditropan® and Ditropan XL® in children aged 5–15.

	C_{max} in ng/mL (t_{max} in h)		
	Oxybutynin Tablets [a]	**Oxybutynin Syrup** [a]	**Oxybutynin Extended-Release** [b]
(*R*)-oxybutynin	6.1 ± 3.2 (1)	5.7 ± 6.2 (1)	0.7 ± 0.4 (1)
(*S*)-oxybutynin	10.1 ± 7.5 (1)	7.3 ± 7.3 (1)	1.3 ± 0.8 (1)
(*R*)-desethyloxybutynin	55.4 ± 17.9 (1)	54.2 ± 34.0 (1)	7.8 ± 3.7 (1)
(*S*)-desethyloxybutynin	28.2 ± 10.0 (1)	27.8 ± 20.7 (1)	4.2 ± 2.3 (1)

[a]: data normalized to an equivalent of Ditropan® tablets 5 mg BID or TID [50]; [b]: data normalized to an equivalent of Ditropan XL® 5 mg daily [58].

Other alternatives enabling a decrease in the plasma concentration of *N*-desethyloxybutynin, and consequently to reduce side-effects, have been studied and include rectal, intravesical, as well as vaginal administrations.

Although still not commercially available, suppositories of oxybutynin were the subject of several clinical trials, the first report appearing in 1998 [67]. The daily dose was similar to that used in oral administration and varied between 5 and 20 mg. Suppositories administered in the study of Winkler [67] contained 5 mg of oxybutynin for 1.25 g of fat. It is noteworthy that the topic remains of interest, since suppositories loaded with oxybutynin microparticles were recently described and evaluated by Bedse et al. [68].

Intravesical solutions were initially obtained by dissolving oxybutynin tablets (5 mg) in distilled water (10 mL) and were instilled in the bladder by means of a catheter twice

a day [69]. Discomfort associated with such a daily treatment led to the development of a delivery system (UROS™, Situs Corp., San Diego, CA, USA) constituted by a reservoir allowing the release of the drug over the period of a month that can be removed by cystoscopy [70,71]. The device saw, however, little success. Improved systems of instillation still attract attention, as evidenced by the recent patent literature [72,73].

Intravaginal gels containing oxybutynin [74,75] have been the subject of several in vivo studies on an animal model (rabbits), but to the best of our knowledge, there has been no clinical trial involving such gels. A preliminary determination of the efficacy of an insert releasing oxybutynin in the vagina of rabbits was performed by the group of Levin in 2000 [76]. Other vaginal rings have been designed and some were successfully evaluated in humans but still not commercialized [77–79].

Intravesical and intravaginal drug delivery systems for the treatment of bladder diseases have been reviewed by Cerea [80] and Srikrishna [81], respectively.

6. Repositioning Opportunities

To date, 69 registered clinical trials can be retrieved in the database [82] of the U.S. National Library of Medicine, when using "oxybutynin" as a search term. The majority of them (50 trials) are studies on the safety and/or efficacy of oxybutynin for the treatment of dysregulations of bladder activity and, anecdotally (one trial; NCT03877289), for the treatment of cystitis in children. A Phase 2 trial analyzed the effects of a combination of oxybutynin and desloratadine (**41**; Figure 4) in cases of seasonal allergic rhinitis (NCT00816972; started in 2005) and another Phase 2 trial studied the potential of a combination of oxybutynin and clonidine (**42**; Figure 4) in reducing excessive salivation (sialorrhea) in patients with Parkinson's disease (NCT01370811; started in 2011).

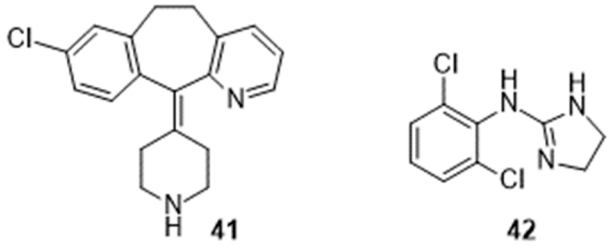

Figure 4. Chemical structures of desloratadine **41** and clonidine **42**.

As detailed below, the remaining trials provided repositioning opportunities for the management of hyperhidrosis (nine trials, but one, NCT02099695, has been withdrawn) and hot flashes (four trials). More recently, there was an increase in interest for the use of oxybutynin in combination (see Section 6.3) as a pharmacotherapy for obstructive sleep apnea (four trials).

6.1. Hyperhidrosis

Hyperhidrosis [83–85] is the term used to define an excessive sweating without any link with a normal response of the body to heat or effort. Armpits, soles of the feet, palms of the hands, and face are the body regions that are the most frequently affected by hyperhidrosis. Because stimulation of cholinergic receptors on eccrine sweat glands is responsible for perspiration, hyperfunctioning of those glands could be controlled by the use of anticholinergic agents [86]. That approach has been evaluated in the absence of sympathetomy or after such a surgical intervention.

The first registered clinical trial dedicated to the efficacy of oxybutynin in the treatment of axillary hyperhidrosis was launched in Brazil in 2007 (NCT01118429). Positive results were published in 2011 [87] since the authors claimed that "more than 80% of the patients experienced an improvement in axillary hyperhidrosis. . . . The side effects were minor, dry mouth being the most frequent (73.5%)".

Among the other clinical trials, let us mention one Phase 3 trial (NCT01855256), which started in 2013, and one Phase 4 trial (NCT01310712), which started in 2010 [88]). Today, oxybutynin may be prescribed by physicians for the treatment of hyperhidrosis (e.g., [89–93]).

6.2. Hot Flashes (Vasomotor Symptoms)

Hot flashes are sudden episodes of sensation of excessive heat of the body, often accompanied by uncontrolled sweating and the appearance of red blotches on the face, the chest, and the neck [94–96]. Those episodes can be associated, at least in part, with a decrease in the level of estrogen and they involve numerous neurotransmitters, among which are norepinephrine, serotonin, and acetylcholine. Frequent in healthy peri- and post-menopausal women, vasomotor symptoms are also observed in patients under hormone suppression therapies, among which are women having been diagnosed with some breast cancers and men under treatment for prostate cancer [97,98].

Amid various drugs prescribed to decrease the frequency and/or intensity of hot flashes [99], antimuscarinic agents, including oxybutynin, had been patented as early as 2007 [100]. The inventor (K.D. LaGuardia) had been involved in the first registered clinical trial (Phase 2) on the subject, entitled "The effect of extended-release oxybutynin chloride on vasomotor symptoms in healthy post-menopausal women" (NCT00990886; started in 2004). Results were published in a conference paper in 2007 [101] and in a manuscript much later [102]. More recently, a Phase 3 trial (NCT02961790; started in 2016) successfully evaluated the efficacy of lower doses of oxybutynin in the management of hot flashes in women under hormonotherapy or not [103]. Further to those promising results, oxybutynin, even if not FDA-approved for that application, is suggested as an alternative medication by some oncologists and gynecologists [104–106]. Two more trials are still recruiting, one (Phase 2) for the study of the efficacy of oxybutynin in men treated for prostate cancer (NCT04600336; started in 2021). The second (Phase 3) will compare oxybutynin and paroxetine (**43**; Figure 5), an antidepressant, in women with hormone-dependent breast cancer (NCT05637671; started in 2022).

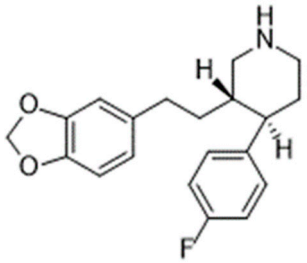

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Figure 5. Chemical structure of paroxetine **43**.

6.3. Obstructive Sleep Apnea

Reduction in the activity of the upper airway dilator muscles is a normal phenomenon during sleep. However, in the situation of obstructive sleep apnea, the reduction reaches such an extent that it obstructs the flow of air into the lungs and temporarily blocks breathing, perturbing oxygenation of the blood.

The possibility of restoring the activity of pharyngeal muscles under the influence of a noradrenergic agent [107] and an antimuscarinic agent [108] had been highlighted years ago. However, it is only recently that combinations of such drugs [109–111] emerged as a challenging opportunity for the treatment of obstructive sleep apnea. More specifically, the combination of oxybutynin and atomoxetine (**44**, Figure 6) was the subject of two Phase 2 registered clinical trials, which started in 2016 (NCT02908529; [110]) and 2020 (NCT04115878). Two other Phase 2 trials (NCT05550246; NCT05944965) should start in the

second half of 2023, as part of the Sleep Disorders Research Program of the Brigham and Women's Hospital at Boston (Boston, MA, USA).

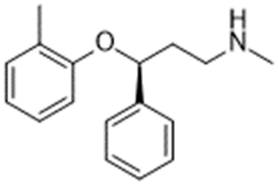

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Figure 6. Chemical structure of atomoxetine **44**.

Two additional Phase 2 trials, sponsored by Apnimed (Cambridge, MA, USA), can be retrieved in the database [82] of the U.S. National Library of Medicine, but, surprisingly, they did not appear with the search term "oxybutynin". In one trial (NCT 04445688), a combination of oxybutynin (5 mg) and atomoxetine (80 mg) was defined under the code name AD036. The conclusion of the evaluation was that "AD036 significantly improved obstructive sleep apnea severity in patients with moderate pharyngeal collapsibility. Atomoxetine may account for the majority of improvement in obstructive sleep apnea severity, while the addition of oxybutynin may mitigate the disruptive effect of atomoxetine on sleep and further improve ventilation" [112]. Soon after, the company sponsored another Phase 2 trial (NCT04631107) with the combination of the (*R*)-enantiomer of oxybutynin and atomoxetine, in poorly defined proportions and under the code name AD109. In the published results [10], it was intriguingly reported that "the current study is with aroxybutynin (AD109), a new enantiomerically pure form of oxybutynin. . .". Anyway, the authors concluded that "this study provides additional support that a pharmacological intervention for obstructive sleep apnea, namely the combination of atomoxetine and aroxybutynin, offers promising results. Additional development of this compound and others is warranted".

7. Conclusions

Oxybutynin improves bladder control in cases of incontinence and excessive urination frequency by blocking M_3 muscarinic receptors on the detrusor muscle. The drug, also named 4-diethylamino-2-butynyl 2-cyclohexyl-2-hydroxy-2-phenylacetate, possesses a chiral center and is commercialized under the form of the racemate. Its synthesis requires three key reactions, namely (i) a Grignard reaction; (ii) a Mannich reaction; and (iii) an esterification or a transesterification in order to bound an acidic segment containing the chiral center and the chain containing the triple bond. Despite the fact that enantiomerically pure isomers are not in clinical use, there was, in the years 2000–2010, a marked interest in the preparation of (*S*)-oxybutynin and more specifically in the design of protocols yielding essential intermediates required to afford it, namely (*S*)-2-cyclohexyl-2-hydroxy-2-phenylacetic acid and analogs. Very recently, the (*R*)-enantiomer of oxybutynin attracted attention because of a potential efficacy, in combination with atomoxetine, in the treatment of obstructive sleep apnea.

In the gut and the liver, oxybutynin is rapidly converted into the active *N*-desethyloxybutynin metabolite, which is thought to be responsible for the most frequent dry mouth side-effect observed when taking the drug. That observation gave rise to intense efforts in order to find a means of bypassing the first metabolic step. That led to successful and extensively prescribed extended-release and transdermal formulations, among other things.

A number of clinical trials also indicated that oxybutynin could help manage hyperhidrosis, hot flashes, and, in combination with atomoxetine, obstructive sleep apnea. This represents a new hope to ease the daily life of many persons, and among them patients under hormonotherapy.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are contained within the article.

Conflicts of Interest: The author declares no conflict of interest.

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