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Dedicated to Professor Alexandru T. BALABAN on the occasion of his 90th anniversary

THE FIRST 40 YEARS OF SOFT ANTICHOLINERGIC AGENTS

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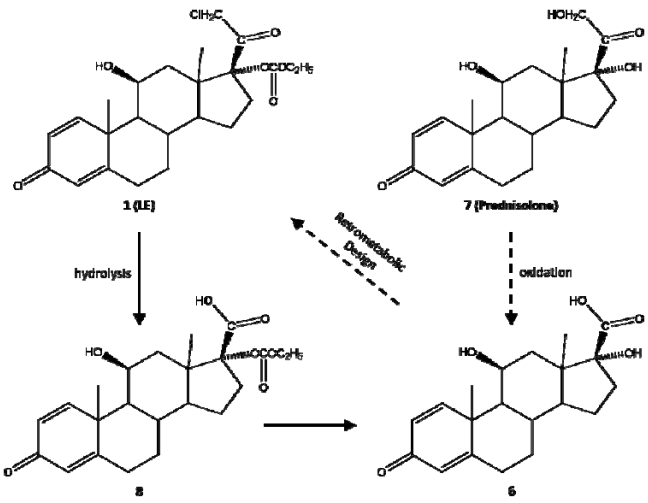
Retrometabolic drug design approaches (RMDD) combine quantitative structure-activity and structure-metabolism relations (QSAR and QSMR) to improve the therapeutic index (ratio of toxic and effective dose, TI = TD50/ED50), of newly designed drugs. Soft drug (SD) design approaches, a subclass of RMDD, have been successfully employed in the development of safer drugs. The combination of "soft analog" and "inactive metabolite" techniques in drug development was first exemplified by the highly successful and safe soft corticosteroid, Loteprednol Etabonate. Similar techniques have been used to design safe topically active anticholinergic drugs with much reduced side effects. The "soft analog" and some of the "inactive metabolite" approaches have led to improved antimuscarinic drug candidates, which all (n = 76) can be fit with a bilinear exponential equation of activity vs molecular descriptors. The "remote inactive metabolite" approach was the most successful, having resulted in the new and very safe drug Sofpironium Bromide, which received regulatory approval to treat hyperhidrosis, a debilitating idiopathic disease and an unmet need.



INTRODUCTION

Anticholinergic drugs inhibit the effects of acetylcholine by blocking its binding to the widely distributed muscarinic cholinergic receptors; therefore, they are used or are of therapeutic interest for a variety of applications including COPD, asthma, motion sickness prevention, mydriasis, Alzheimer's disease, Parkinson's disease, intestinal motility, cardiac function, and urinary bladder function, among others. Cholinergic (muscarinic) receptors are ubiquitous as they are present in most cells.[1] There are five receptor subtypes, M_1-M_5; however, there are no subtype-specific agonists or antagonists known, consequently the desired pharmacological effect is always accompanied with numerous receptor-mediated side effects, such as dry mouth, photophobia, blurred vision, drowsiness, dizziness, restlessness, urinary incontinence and retention, irritability, disorientation, hallucinations, tachycardia, cardiac arrythmias, nausea, constipation, and severe allergic reactions, all of which often inhibit their clinical use. Topical administration of antimuscarinic agents to targeted areas, such as sweat

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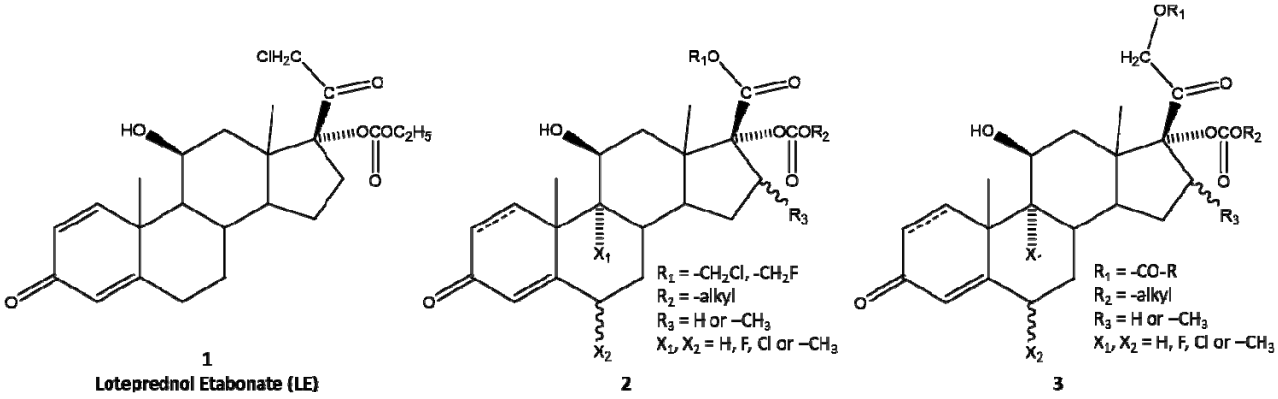
glands, where the localized blockage of muscarinic receptors would be of clinical benefit to treat hyperhidrosis, an unmet medical need, would be a desirable strategy. The currently used oral and topical anticholinergics exhibit unwanted side effects from the absorbed drug, which limits the effectiveness as only limited dosages can be safely administered.[2-5] To develop anticholinergics with maximum local therapeutic benefits and minimal systemic side effects, the soft drug subclass of retrometabolic drug design approaches promises the desired separation of local versus systemic activates.[6-7] Soft drugs are designed based on a combination of structure-activity (SAR) and structure-metabolism (SMR) relationships. The soft drugs have potent local therapeutic effects while subsequently undergoing predictable, designed-in metabolism. The designed-in metabolism is preferably hydrolytic, avoiding oxidative transformations. The predicated metabolite is inactive; thus, the overall result is a significant improvement in the therapeutic index (a ratio of the toxic vs active doses).

There are several strategies to design soft drugs,[6-7] the most successful ones are the "soft analog" and the "inactive metabolite" approaches, as demonstrated by the various design approaches used for the soft anticholinergics.

A good example of the soft analog/inactive metabolite design is provided by the highly successful soft corticosteroid, Loteprednol Etabonate **1 (LE)**, a member of the novel class of soft corticosteroids,[8] as represented by the general formulas **2**, compared to the "classical" corticosteroids **3**.



1
Loteprednol Etabonate (LE)

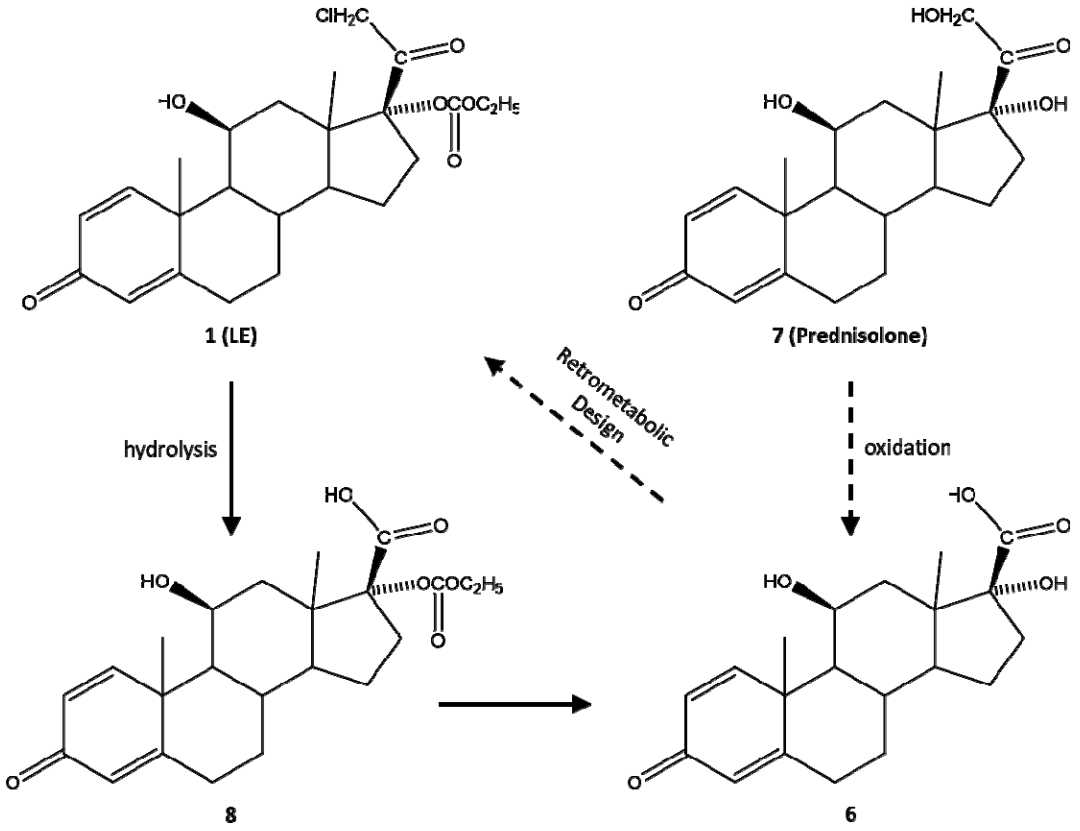
2

3

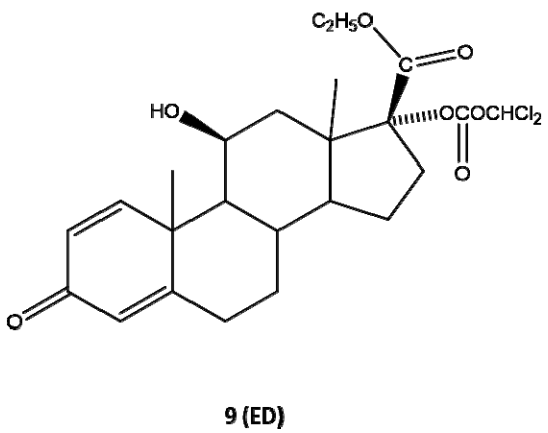
In the design process, the metabolism of the natural basic corticosteroid, hydrocortisone **4**, was first considered. Through its metabolism, **4** is converted to sixteen metabolites [9], primarily via oxidative metabolism. Consistent with the soft drug design principles,[6,7,10] the focus is on the oxidative metabolites of the important pharmacophore, the C_{17}-dihydroxy acetone sidechain, which is oxidized to an acidic metabolite, among which the cortienic acid **5** seemed the most promising starting structure for a potential soft steroid. The specific "inactive metabolite" selected was the Δ^1-cortienic acid (prednienic acid) **6**, one of the inactive metabolites of prednisolone **7**. Isosteric/isoelectronic considerations resulted in the new 17β-chloromethyl ester pharmacophore of the acid replacing the 17β-dihydroxyacetone group. The 17α- position was converted to a carbonate function, novel in corticosteroids, which is much more stable than the 17α-esters as it would prevent reactive mixed anhydride formation. The novel chloromethyl ester was expected to undergo hydrolytic metabolism to the already inactive acid **8**, which eventually would be hydrolyzed to the inactive metabolite **6**, the starting structure in the design process.

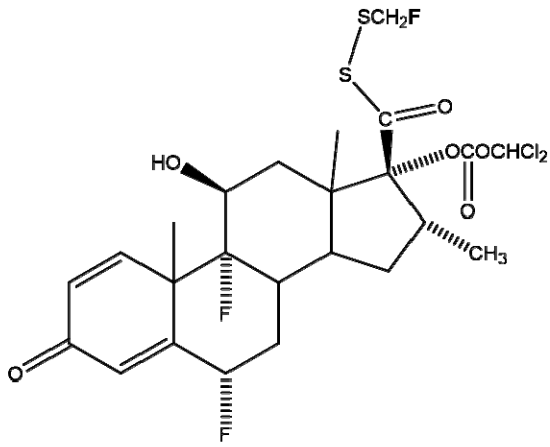
The therapeutic index (TI = TD50/ED50 or toxic dose/effective dose) for all marketed corticosteroids is, by convention, normalized to approximately 1.0, where if a corticosteroid has an increased potency, the toxicity also increases virtually parallel. On the other hand, the TI for LE is a dramatically improved 24.0.[6,10]

The soft drug LE was developed, and ultimately received market approval in 1998, gaining FDA approval for four different inflammatory and allergic eye conditions. LE became a highly successful drug, as presented by a comprehensive review "20 Years of Clinical Experience with a Retrometabolically Designed Corticosteroid"[11] where at that time, some 90 million prescriptions were generated. In addition to the originally approved four ophthalmic diseases, it has also been used in corneal transplant and most recently (2019) approved to treat dry eye disease.



The class of the above soft steroids, including LE, is based on hydrolytic metabolism of the pharmacophore containing the 17β- sidechain. An alternate soft steroid class was also developed, focusing on the 17α- group. The frequently used activity enhancing 17α-esters do not hydrolyze, thus could not be considered for soft drug design. It was found, however, that a 17α-dichloroacetate group provides the necessary heteroatom pharmacophore (one of the chlorine atoms is always in the right position[6]), but also unexpectedly is hydrolyzed very easily *in vivo*, thus providing the soft property. The simplest structure, derived again from Δ^1-cortienic acid **6**, Etiprednol Dichloroacetate **9** (**ED**), demonstrated good activity and easy hydrolytic metabolism.[12,13] The corresponding 17α-dichloroacetyl derivative **10** of fluticasone demonstrated very high potency and unexpected "soft" properties.[14]



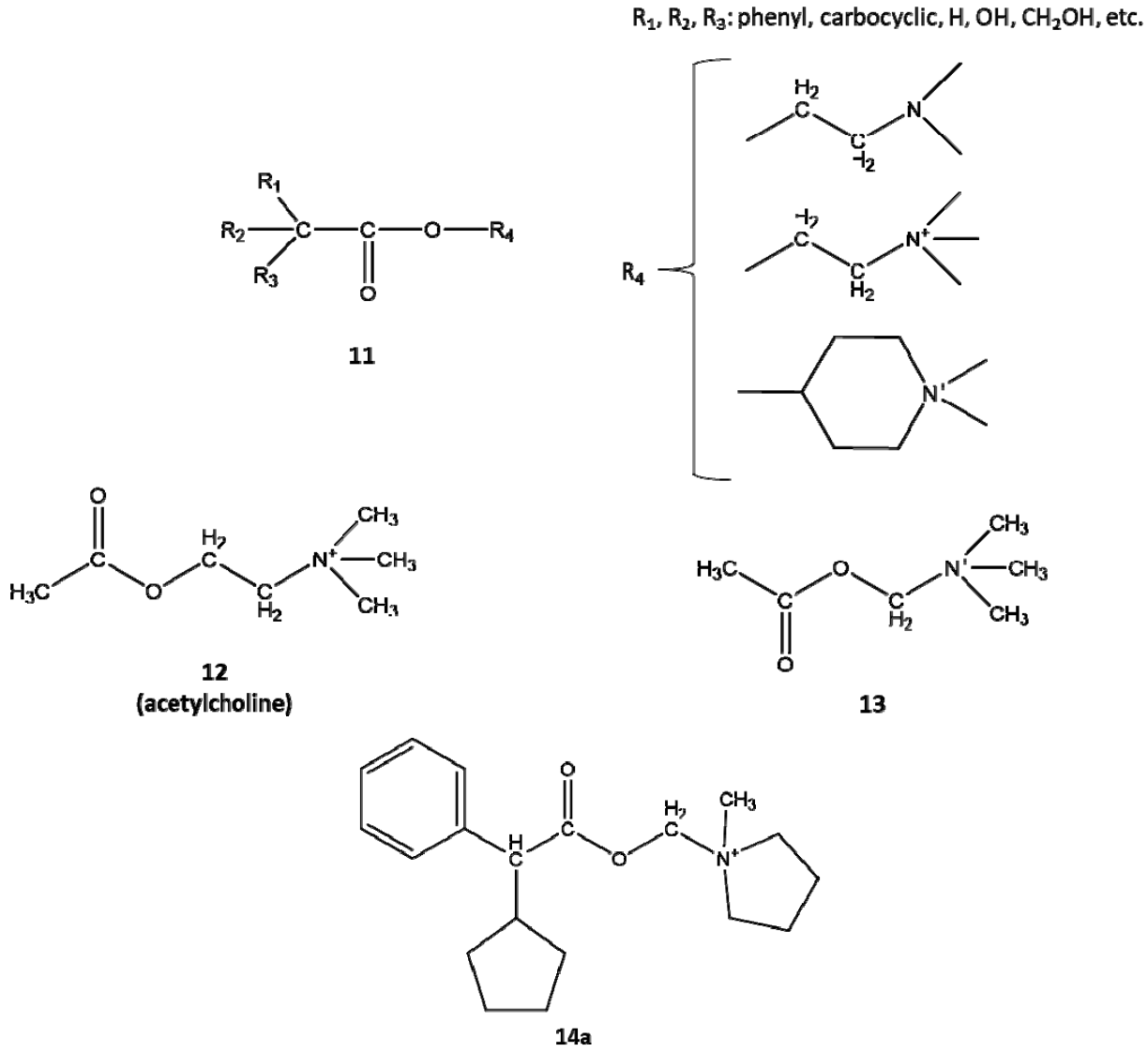


The above examples clearly demonstrate the "inactive metabolite" design approach to soft drugs. Interestingly, recent studies have shown that all of these soft corticosteroids (**2, 9, 10**) are hydrolyzed by Paraoxonase 1, an enzyme connected to HDL.[15]

RESULTS AND DISCUSSION

As stated above, the cholinergic receptors are ubiquitous, widely distributed similarly to the corticosteroid receptors. Thus, in order to separate local, topical activity from systemic toxicity, similar approaches were explored for the design of soft anticholinergics as to the soft corticosteroids. The first approach utilized focused on the soft analog of some antimuscarinic agents.

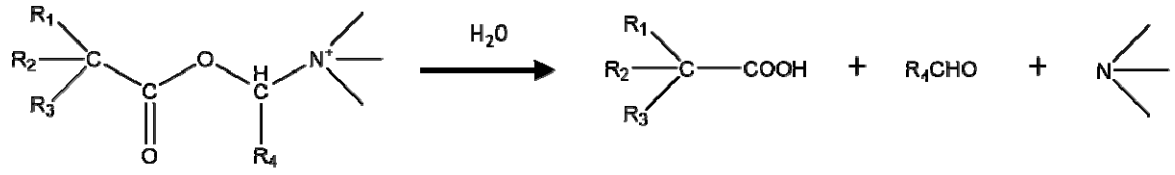
The antimuscarinic pharmacophore **11** is generally considered as the bulky carboxylate esters of tertiary or quaternary amino alcohols, having 2 or 3 carbon atoms separating the ester oxygen and the amine nitrogen, like in acetylcholine **12**. Although esters, these molecules are not easily hydrolyzed. Analogs of acetylnorcholine **13** were thus synthesized based on a unique chemistry,[16] since norcholine (formocholine) is highly unstable. Since acetylnorcholine is 5,000 times less active than acetylcholine,[17] it was surprising to find that some of the new, soft antimuscarinic analogs like **14a** were as, if not more potent than atropine **15**.



Indeed, **14a** has an antimuscarinic pA_2 of 8.4, while in the same conditions, atropine is 8.5.

However, it was found that these compounds undergo non-enzymatic, chemical hydrolysis,

which is too slow to be used as soft anticholinergics (hydrolysis t/2 of **14a** at pH 7.4, 37°C is 20 hours, in plasma is 6.5 hours, while at pH 9.4 only 5 minutes). The hydrolysis, consistent with the soft drug design principles, destroys the pharmacophore as these esters fall apart, albeit too slowly, to an acid, aldehyde and tertiary amine:



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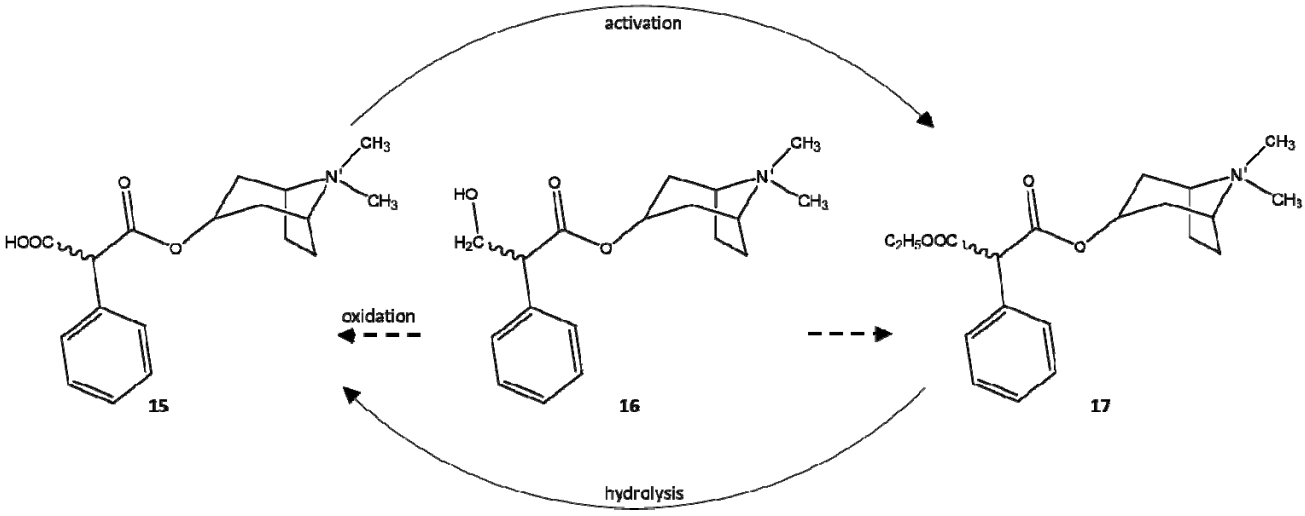
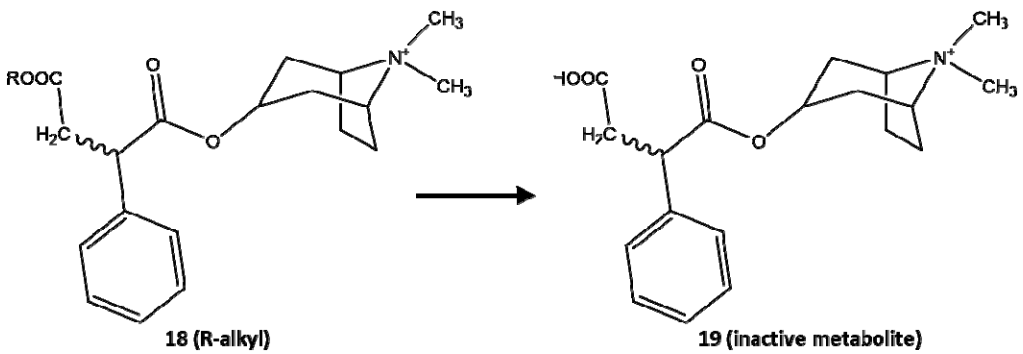
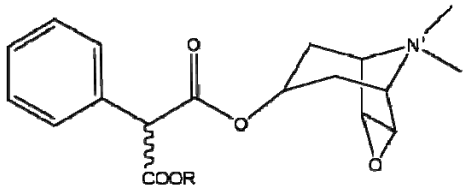
Subsequently, the "inactive metabolite" approach was explored for designing safer, locally active antimuscarinic agents. A hypothetical inactive metabolite **15** of metatropine was chemically modified to a presumably "soft" ester **17**, which resembles metatropine **16**, but undergoes hydrolytic deactivating metabolism to the starting inactive metabolite **15**.



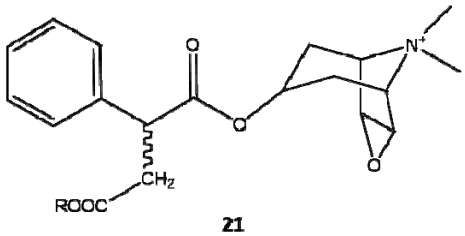
The soft metatropine analog **17** demonstrated good antimuscarinic activity (pA_2 of 7.85 vs atropine of 8.5) and facile hydrolytic de-activation *in vivo*. It was clinically developed (USAN name Tematropium Methyl Sulfate) as a short acting mydriatic agent and antiperspirant, but its development was halted after better soft antimuscarinic candidates were found. Structure **17** is essentially a malonic acid diester. Analogous phenylsuccinic esters **18** were also synthesized and studied by introducing another methylene group into the initial inactive metabolite **15**.



The analogous soft malonic ester **20** and succinyl **21** ester analogs of metscopolamine **22** were also synthesized and studied.



20 (R-alkyl)



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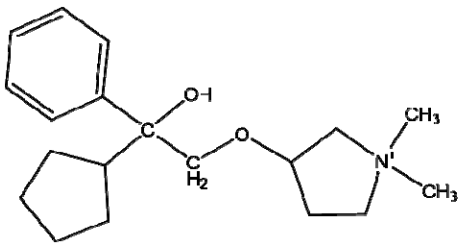
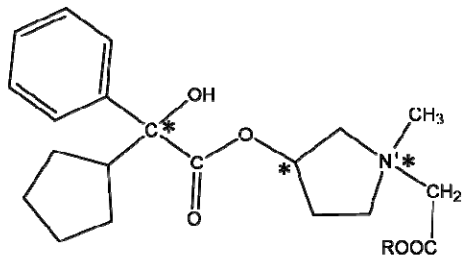
It turned out that all the above soft analogs fulfilled the expected facile *in vivo* hydrolysis criteria, as they are short acting mydriatic agents, but all are less potent than the corresponding "hard" analogs. Longer alkyl esters did not help. A quantitative structure-activity relationship between activity (antimuscarinic pA_2) and molecular descriptors (volume V, partition coefficient Log P, dipole measurement D) revealed [22] that molecular volume is the most important property. The best correlation was obtained including all three parameters: V, Log P and D (r = 0.915). It appears though that introducing the hydrolytically sensitive ester function in the close vicinity of the pharmacophore, while "soft", did negatively affect the needed isoelectronic environment.

In order to develop a clinically useful soft anticholinergic, a new design strategy was needed. The idea was to leave the antimuscarinic pharmacophore and its surrounding space intact, and place the metabolizable, hydrolytically sensitive function in a remote "nonessential" part of the molecule. Glycopyrrolate (GP) **23**, an antimuscarinic used as an oral antiperspirant drug[23] and most recently, topically [24], was the start for the design target. While used very carefully topically, controlling the dose with wiping the target area using a specially saturated cloth, the usual anticholinergic side effects are still present. There was clearly a need for a well-functioning soft analog.



23 (glycopyrrolate (GP))



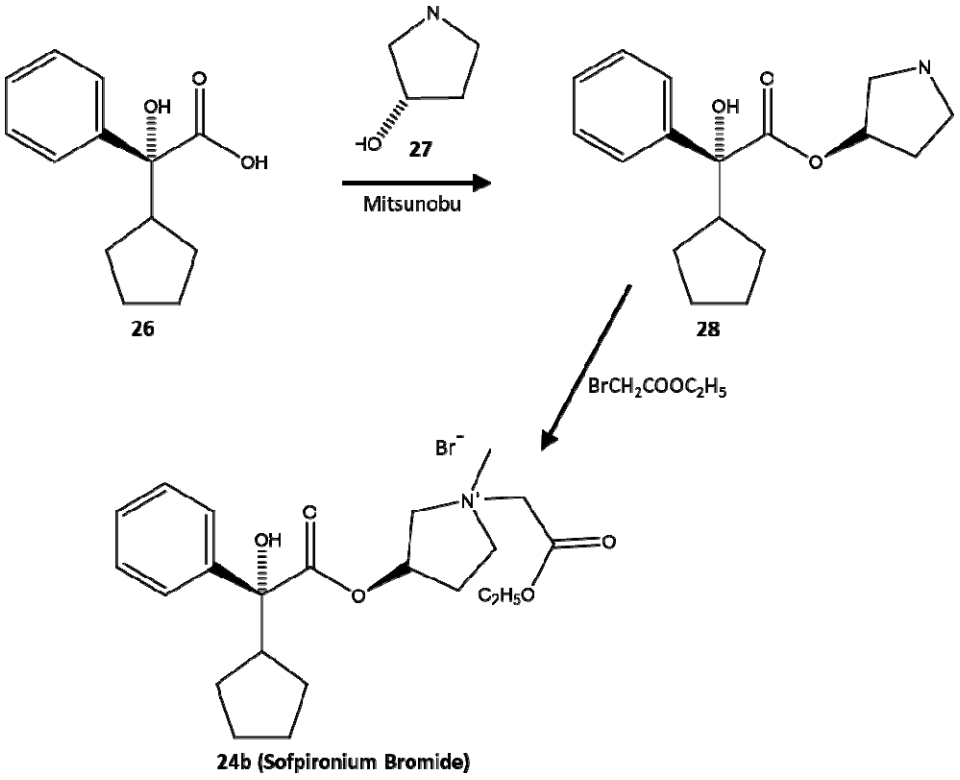
24 Soft analogs

R-alkyl
a – Me
b – Et

25 R = H

In this design approach, formally, one of the methyl groups in **23** was replaced with an ester function [25,26], subject to easy deactivation. The corresponding hydrolysis product, the acid (zwitterion **25**) was expected to be void of significant activity and to be eliminated quickly from the body. Molecule **24** has three optically active centers, consequently there are eight stereoisomers possible, which were all synthesized and studied.[27,28] It became evident that the 2R stereoisomers are more potent than the 2S, as **24a** (2R-methyl ester) M_3 binding is 9.00 (pA_2 – 8.31), while the racemic **24** (methyl) binding was 7.80 with a pA_2 of 7.90. Furthermore, it became clear that for the stereoisomers of the 3'-position, the 3'R is also more potent (M_3 binding for **24b** 2R3R' is 9.06 while 2R3'S is 8.60). On the other hand, the stereoisomerism of the N- does not affect the activity.[29] Accordingly, the 2R,3'R-ethyl ester was selected for development. The synthetic method[28,29] previously used was the basis for the industrial[30] production method. (R)-α-cyclopentylmandelic (**26**) was reacted with (S)-1-methyl-3-pyrrolidinol (**27**) under Mitsunobu[31]

conditions to provide 3'(R)-N-methyl-3-pyrrodidnyl-2(R)-cyclopentyl-mandelate (**28**), which is alkylated with ethyl bromoacetate to provide 3'(R)-[2(R) cyclopentylphenyl-hydroxyanetoxyacetoxy]-1'-methyl-1'-ethoxycarbonylmethyl-pyrrolidirium bromide (**24b**).



EXPERIMENTAL

The previously reported[28] and further developed[30] methods were adapted. Melting points were determined in open glass capillaries. All chemicals used were reagents grade. (S)-1-methyl-3-hydroxypyrrolidine was purchased from a supplier such as Accela ChemBio, San Diego, CA. Ethyl bromoacetate was purchased from a supplier such as Sigma-Aldrich, St. Louis, MO. Elemental analysis was determined by Atlantic Microlab, Norcross, GA. ^{1}H-NMR was recorded on a Brucker 400-1 Spectrometer. ^{13}C-NMR was recorded on a Varian INOVA Spectrometer. Mass spectra were recorded on a Thermo Finnigan LCQ with electrospray ionization (ESI).

3'(R)-N-Methyl-3-pyrrolidinyl-2(R)-cyclopentylmandelate[26]

To a stirred solution of (R)-α-cyclopentylmandelic acid (175 g, 0.80 mol), triphenylphosphine (208 g), and (S)-1-methyl-3-pyrrolidinol in anhydrous THF was added at 5°C over 1.5 hours a solution of diisopropyl azodicarboxylate (DIAD) (161 g) in anhydrous THF. After stirring at ambient temperature for 20 hours, the mixture was concentrated to dryness, the residue was dissolved in methyl t-butyl ether (MTBE) and filtered. The filtrate was extracted with dilute sulfuric acid. The aqueous phase was extracted with MTBE to remove triphenylphosphine oxide, and neutralized with aqueous potassium carbonate. The mixture was extracted with MTBE, the MTBE phase was dried over magnesium sulfate and concentrated to 211 g (97.5% yield) of 3'-(R)-N-methyl-3-pyrrolidinyl-2-(R)-cycopentylmandelate as a yellow oil. Inversion of the 3'-chiral center of 1-methyl-pyrrolidin-3-ol was complete; no racemization was detected. ^{1}H-NMR (400 MHz, $CDCl_3$): Δ 7.28-7.65 (five phenyl H), 5.22 (pyrrolidine CHOH), 3.82 (OH), 2.93 (cyclopentyl CH), 2.48-2.73 (six pyrrolidine CH_2), 2.33 (three N-CH_3), 1.19-1.82 (eight cyclopentyl CH_2).

3'(R)-(2(R)-Cyclopentylphenylhydroxyacetoxyl)-1'methyl-3'-ethoxycarbonyl methyl pyrrolidinium bromide **24b** (Sofpironium Bromide).

To a stirred solution of 3'(R)-N-methyl-3-pyrrolidinyl-2(R)-cyclopentylmandelate (211 g, 0.70 mol) in anhydrous MTBE was added ethyl bromoacetate (348 g, 3 equiv) at room temperature. The mixture was refluxed for 4.5 hours and cooled to room temperature. The solid which formed was collected on a filter, washed with MTBE, and suspended in ethyl acetate. The mixture was stirred at reflux for 1 hour, cooled to ambient temperature, and filtered to provide 265 g (83.6% yield) of 3'-(R)-(2-R)-cyclopentylphenylacetoxy)-1'-methyl-1'-ethoxycarbonylmethyl-pyrrolidinium bromide as a white crystalline powder, mp 144-146°C, purity 9.85% by HPLC. ^{1}H-NMR (400 MHz, $CDCl_3$): Δ 7.22-7.56 (five phenyl H), 5.55 (pyrrolidinyl CH), 4.69, 5.21 (two NCH_2COOEt H, 4.69 (70%) major isomer 2R3R'1'R, 5.21 (30%) minor isomer 2R3'R1'S), 3.82-4.48 (seven H, pyrrolidine CH_2, OH), 3.11,3.67, 3.11, 3.67 (NCH_3 three H, 3.67 (70%), 3.11 (30%), 2.89 (two H $COOCH_2Me$), 2.22 (cyclopentyl CH), 1.31-1.78 (eight H cyclopentyl CH_2), 1.26-1.32 (three H C-CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$/TMS): Δ 174.4,174.0, 165.0, 164.8, 141.3, 141.0, 128.5, 127.9, 127.7, 126.0, 125.7, 79.9, 79.6, 73.4, 70.0, 65.2, 63.7, 63.0, 62.9, 62.6, 51.8, 50.7, 48.1, 47.1, 30.1, 29.7, 27.2, 26.8, 26.7, 26.2,14.2. MS (ESI/MS/MS)

parent m/z 390.23 (theoretical 390.23) and expected fragments m/z 362, 188, and 160 ions. C,H,N calc. for C22H32NO5Br, 56.17, 6.86, 2.98, found 56.23, 6.97, 3.04.

CONCLUSIONS

The soft antimuscarinic agent **24b** presents numerous potential uses as a drug, mainly by the topical route, such as inhalation (COPD), intestinal motility, sialorrhea, etc, but was first developed to treat hyperhidrosis,[32] an idiopathic pathological sweating disorder and "unmet need", where approximately 3- 5% of the population suffers from it.

The official USAN name for the selected 2R,3'R-**24b** is Sofpironium Bromide (SB). It was developed by Brickell Biotech Inc. in the USA and Kaken Pharmaceutical Co. in Japan. SB was found to be well tolerated, demonstrating uniquely low system toxicity, due to the designed-in facile metabolism. SB demonstrated effective treatment [33] in clinically meaningful end points in subjects with hyperhidrosis. Two Phase 2b studies resulted in excellent statistically significant and clinically meaningful results, as reported recently.[34] It was found that SB is effectively hydrolyzed in the blood, with a t/2 of just 12-15 minutes, by the HDL linked Paraoxonase 1,[35] which explains the successful separation of local vs systemic activity. Development in Japan was faster advancing; in March 2020 it was reported to have completed the pivotal Phase 3 study,[36] securing approval in Japan.

The above short review of quaternary soft anticholinergic compounds can be closed with a comprehensive quantitative structure-activity relationship (QSAR) with a linearized biexponential (LinBiExp) model.[37] Contrary to Hansch-type parabolic models, LinBiExp represents a natural extension of the linear models earlier established. The correlation covers 76 structures, where the model can fit activity data that show a maximum around a given parameter value but shows linearity away from this turning point. The main parameter, as shown before,[22] is the molecular volume, while stereospecificity is also important. The maximum is indicative of the size limitations at the boundary site.

Application of the various soft drug design approaches finally led to a new drug, Sofpironium Bromide, which successfully fulfills the separation of the desired local activity versus systemic activity/toxicity. It received marketing approval in Japan very recently.[38]

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