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Synthesis of scopolamine as an effective medication

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Abstract. Scopolamine used to be notorious for its alkaloid toxicity, but now it is also well-known as an effective treatment of nausea and vomiting and it can achieve good therapeutic effects. It is important to understand how and why it works to optimize preparation methods and therapeutic effects. This research is going to explain mechanisms of actions and extraction and synthesis methods of scopolamine through reviewing various case studies. Scopolamine is found to work as muscarinic receptors antagonist, competitively binding to them against acetylcholine. There are numerous extraction methods of scopolamine, including water extraction, organic extraction, and hybrid extraction of both. Other than that, scopolamine can also be synthesized from cheap starting materials though this method is not yet mature. As a result, scopolamine is valuable for its therapeutic effects, and development of its synthesis still requires further study. In addition, this can also provide a new approach for designing and synthesizing new drug routes.

Keywords: Muscarinic Receptors Antagonist, Synthesis, Scopolamine.

1. Introduction

A common annual plant called datura stramonium belongs to the Solanaceae family [1]. It is a commonly utilized herbal remedy with a rich history in traditional medicine [1]. The plant serves as a local reservoir of tropane alkaloids, such as atropine and scopolamine, which are anti-cholinergic drugs containing a methylated nitrogen atom [1]. The plant's tropane alkaloids have anticholinergic effects that may impact both the central and peripheral nervous systems if consumed [2]. The severe toxicity can lead to delirium, restlessness, seizures, elevated body temperature, muscle breakdown, and potentially fatal outcomes at higher doses [2]. Historically, tropane alkaloids derived from botanical sources have been implicated in foodborne illness outbreaks, including incidents associated with adulterated flour, alkaloid-containing berries, and other food products contaminated by plant components containing these alkaloids [2].

Surprisingly, this life-threatening plant is found to have tremendous therapeutic effect. The compound scopolamine, derived from DS, is a potent muscarinic antagonist with high affinity, primarily employed for the management of motion sickness and post-operative gastrointestinal symptoms [3]. The majority of the inhibitory and excitatory actions of acetylcholine (ACh) on central neurons and the majority of ACh's peripheral effects are mediated by muscarinic receptors [4]. The antiulcer medication pirenzepine, in example, showed tissue-specific changes in its affinity in radioligand-binding experiments, indicating the existence of at least two receptor subtypes, M1 and M2. M3, M4, and M5 subtypes were later identified [4].

As a potent antagonist of muscarinic receptors, scopolamine competitively inhibits acetylcholine at these receptors, which serves various functions in the brain and other organ systems [5]. Acetylcholine

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is a neurotransmitter produced by neurons to facilitate chemical communication with specialized cells such as myocytes and glandular tissues [5]. Without the neurotransmitter due to the blockage of acetylcholine at muscarinic receptors, the muscles are unable to operate appropriately [6]. Hence, scopolamine is helpful in situations where there should be less parasympathetic activity [7]. Scopolamine has central sedative, antiemetic, and amnestic actions in addition to peripheral antimuscarinic activities [7]. Although over-excitement and restlessness can take place at larger doses, scopolamine mainly causes sedation [7].

Scopolamine was the 382nd most prescribed medication in 2017 in United States, which the number of total prescriptions was 525017 in specific [8]. In addition, the cost per day of therapy was no more than $10.00 in the US between 2014 and 2017 [8]. The currently predominant sources of scopolamine are extraction, but the foliage of Datura plants only contains 0.25%–0.7% alkaloids [9]. Hence, this research is going to evaluate extraction and synthesis methods of scopolamine.

2. Mechanisms of action

As shown in Figure 1, scopolamine and atropine are found to be structurally similar to acetylcholine, which all contains ester moiety [10, 11]. The tropic acid portion of the structures of both medicines contains a single asymmetric carbon atom (chiral center) [11]. The main difference between the scopine moiety and the tropine substructure in the atropine chemical is that the epoxy function is bridged over the C-C bond [11]. Besides, scopolamine has a good lipid solubility and a weak basic character [11]. Hence, scopolamine and atropine are potential competitive inhibitors against acetylcholine at muscarinic receptors. The administration of these two substances blocks the neurotransmissions for muscle contraction, resulting in muscle dysfunction.

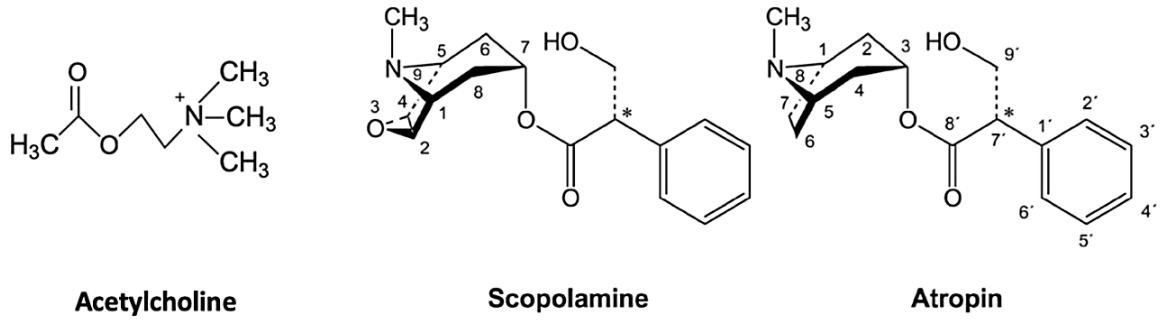

Figure 1. Structures of acetylcholine, scopolamine and atropine [10, 11].

Two following experiments were conducted to confirm the binding affinity of scopolamine at muscarinic receptors. The ligand affinities for M1-M5 muscarinic receptors were assessed in the initial experiment using membranes from recombinant Chinese hamster ovary cells expressing a specific receptor and radio-labelled N-methyl scopolamine [11]. The 5 major subtypes of muscarinic receptors were expressed by membranes from recombinant Chinese hamster ovary cells [11]. The experiment results are presented in terms of Ki value, which is a type of equilibrium dissociation constant. Less ligand is needed to inhibit the activity of a binding partner when Ki is smaller, indicating a higher binding affinity.

As shown in Table 1, scopolamine has the lowest Ki value of 0.83 among all five M1 receptors antagonists. Similarly, it has the lowest Ki values of 5.3, 0.34, 0.38, 0.34 respectively to hM2, hM3, hM4, and hM5. However, in the last column, SCH226206 has the lowest Ki value to M2/M1. But the difference in Ki value of scopolamine and SCH226206 is small enough to be neglected, thus scopolamine is the most potent muscarinic receptors antagonist.

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Table 1. Ki values of five muscarinic receptors antagonists (Scopolamine, Biperiden, Pirenzepine, VU0255035, SCH2262006) [11].

Compound	hM_1	hM_2	hM_3	hM_4	hM_5	M_2/M_1
Scopolamine	0.83 (0.05)	5.3 (1.4)	0.34 (0.06)	0.38 (0.07)	0.34 (0.11)	6.4
Biperiden	2.2 (0.23)	102 (24)	5.3 (1.3)	3.1 (0.8)	4.4 (1.4)	46
Pirenzepine	43 (14)	4200 (1370)	468 (172)	148 (53)	237 (122)	98
VU0255035	124 (62)	8530 (4000)	2000 (628)	2430 (854)	4970 (1390)	69
SCH226206	1240 (255)	30 (11)	529 (194)	76 (20)	128 (14)	0.02

In the second experiment, the affinities were evaluated by measurements of the release of acetylcholine (ACh) after administration of scopolamine. ACh measurements were carried out using Damsma adjustments [12].

From frontal cortex, the initial dialysate level of ACh is at around 0.16 (Figure 2). After 15 minutes of administration of scopolamine, the level starts to increase sharply. It reaches the maximum the level of approximately 1.27 after 45 minutes. Subsequently, the levels gradually dropped and reached the level of about 0.22 after 120 minutes. As a control set, the dialysate levels of Ach treated with saline solution generally remains constant around 0.155 throughout the experiment.

From hippocampus, the initial dialysate level of ACh is constant at around 0.11 (Figure 3). It immediately starts to increase right after the administration of scopolamine. After 45 minutes, the level peaks at 2.4, and then gradually declines to 0.5. Meanwhile, the dialysate level of ACh unstably fluctuates between 0.1 and 0.9, and eventually stops at 0.95.

The difference in magnitudes of increase in the release of ACh is probably due to different sensitivity of scopolamine to different regions of the brain [12]. The phenomenon is primarily due to scopolamine's muscarinic receptor inhibition. By blocking presynaptic muscarinic auto receptors, scopolamine promotes the release of acetylcholine (ACh) [12].

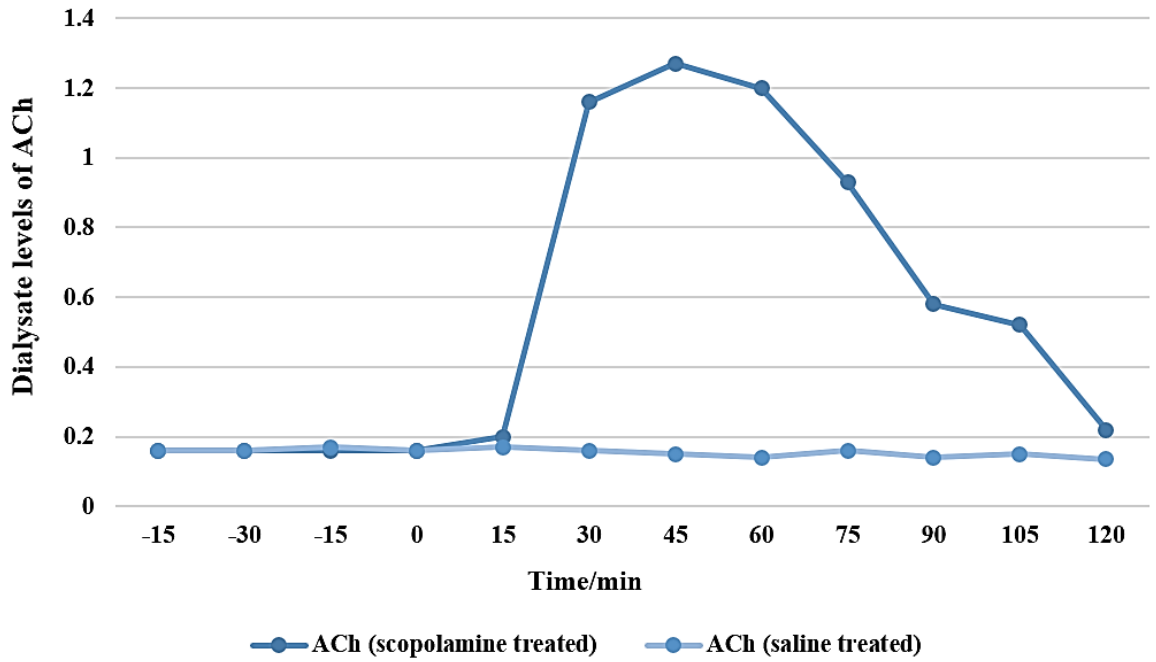

Figure 2. Dialysate levels of ACh from frontal cortex treated with scopolamine and saline [12].

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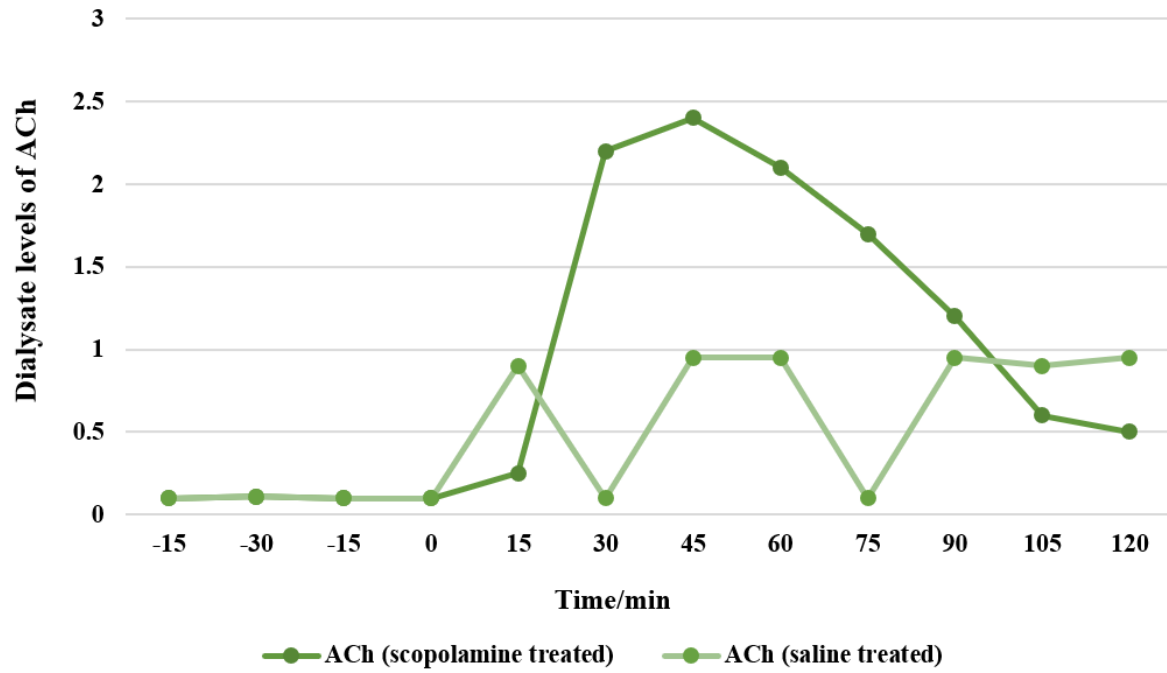

Figure 3. Dialysate levels of ACh from hippocampus treated with scopolamine and saline [12].

3. Extraction and synthesis

The primary source of scopolamine is the extraction from Datura plants, where it is derived from. With advancements in technology, there has been a proliferation of extraction methods (Table 2) [13].

Table 2. Datura extraction methods [13].

Water extraction methods	Organic extraction methods	Hybrid extraction methods
Boiling water leaching	Immersion ultrasonic extraction	Soaking centrifugal extraction
Dry water powder immersion	Ethanol extraction	
Direct leaching	Solicitation	
	Total alkali extraction	
	Methanol extraction	
	Cold dipping	
	Petroleum ether extraction	

The datura genus, despite being one of the most abundant sources of alkaloids in nature, typically contains only 0.2–0.8% of the total alkaloid content [14]. Hence, synthesis of scopolamine is also critical. 6,7-dehydrotropine (1) is found to be a key intermediate to synthesize scopolamine, and other tropane alkaloids as well (Figure 4) [14].

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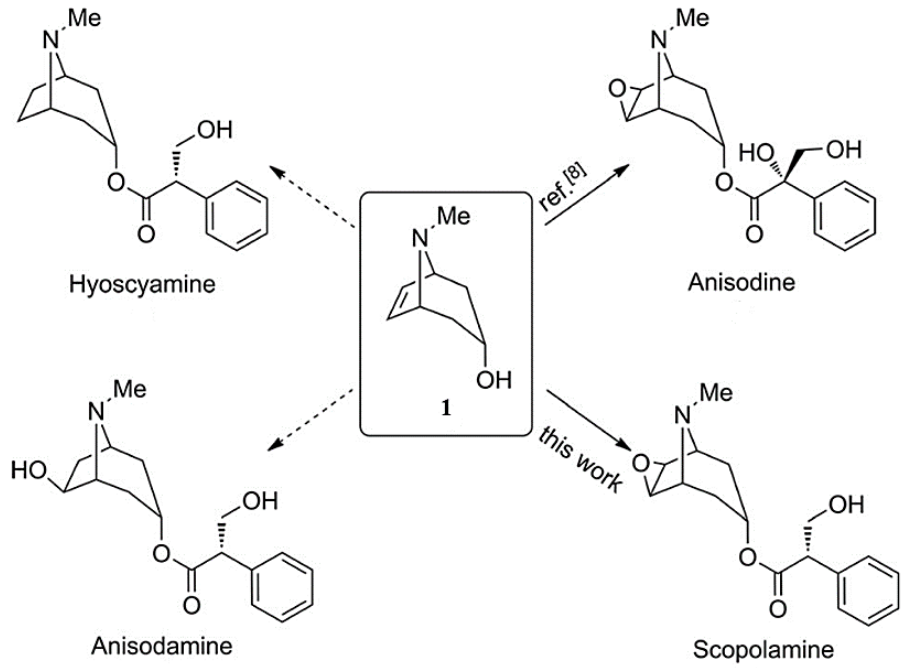

Figure 4. 6,7-dehydrotropine (1) as a synthetic precursor for various tropanes [14].

Subsequently, various methods for synthesis of 1 has been investigated. The process with highest yielding is described as follows. Utilizing commercially available 2,5-dimethoxy-2,5-dihydrofuran (2) as the hydroxysuccinaldehyde precursor in a modified Robinson reaction, 6-hydroxytropinone (4) was produced with a 30% yield [14]. Despite the moderate yield of compound 4, this reaction is performed in water at ambient temperature and utilizes inexpensive starting materials [14]. 4 was then converted to ethylene glycol ketal 5 with a high yield of 90 % [14]. Tosylation of alcohol 5 provided sulfonate 6, which upon treatment with tBuOK and subsequent elimination yielded the desired olefin 7 in an excellent yield of 82% [14]. In two processes, deprotection of the acetal and reduction with produced 6,7-dehydrotropine 1 in 53% yield.

The introduction of the tropic acid moiety was achieved through esterification between acetyltropic acid chloride and alcohol9 using Čeković's procedure [14]. Over the two phases, the target ester 10 was produced in a 56% yield. The desired scopolamine 12 was subsequently produced in a yield of just 16% by epoxidizing alkene 10 with H_2O_2 [14]. As shown in Figure 5, it's interesting to note that epoxidation of 10 produced the desired product 11 in 39% yield when the main alcohol was TBS protected. However, attempts to eliminate the TBS group resulted in the breakdown of the initial substance 13. It should be noted that better yields have been reported for similar substrates and that the final step yields up to step 13 were not optimized.

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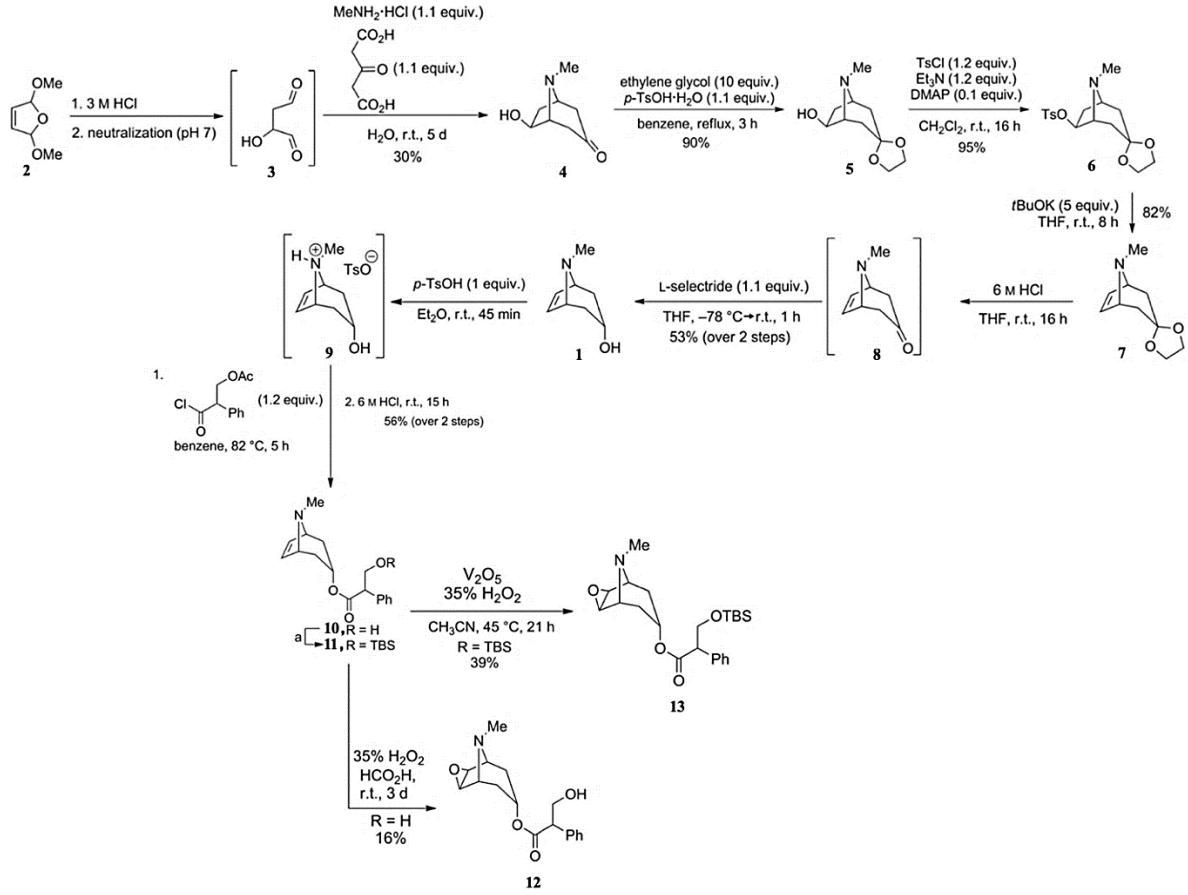

Figure 5. Synthesis of scopolamine [14].

4. Conclusion

With the help of two experiment results, it is clear that scopolamine has a high binding affinity to muscarinic receptors and functions as a potent competitive inhibitor. It is widely used across the world as an effect treatment of nausea and vomiting. Therefore, it is important to produce it at low costs as possible. Compared with tiny amount of scopolamine within datura plants, scopolamine can be made from inexpensive starting materials. However, the process is still in its infancy. For the time being, the main source of scopolamine is still extraction methods. It's possible that once the synthesis techniques become sufficiently sophisticated, they will serve as a reliable and affordable source of scopolamine.

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