A Comprehensive Review of Ephedrine Analogues: Varieties, Abuse and Synthesis Methodologies

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Abstract: Ephedrine analogues include ephedrine and its derivatives, which can be categorized into natural and synthetic types depending on their sources. Natural analogues primarily originate from Ephedra plants such as ephedrine, pseudoephedrine, norephedrine, norpseudoephedrine, methylephedrine and methylpseudoephedrine. Synthetic analogues are obtained through chemical modifications to achieve specific purposes. The review delves into the abuse issues and potential hazards associated with ephedrine analogues, introduces various methods ranging from traditional extraction techniques of ephedrine analogues to modern chemical and biosynthesis technologies. This aids researchers, regulatory bodies, and the public in better understanding the sources and applications of ephedrine and its analogues, providing an important reference for subsequent research and regulation of ephedrine analogues.

Keywords: Ephedrine; Ephedrine Analogues; Abuse; Synthesis Methodologies

1. Introduction

Ephedrine analogues consist of ephedrine and its derivatives, which are amine substances commonly used in the treatment of respiratory diseases, possessing significant medicinal value. Simultaneously, due to their primary structure of 1-hydroxy-1-phenylethylamine, they typically exhibit certain psychoactive effects. Ephedrine analogues were initially discovered in the Ephedra plant, a traditional Chinese medicine used for inducing sweat and alleviating asthma. In 1887, Japanese scientist Nagai first isolated ephedrine from the Chinese Ephedra plant[1]. There are numerous types of ephedrine analogues; besides ephedrine, other bioactive ephedrine alkaloids have been subsequently isolated and purified from the Ephedra plant. Beyond their application in the pharmaceutical field, with the development of drug abuse issues, ephedrine analogues, being precursor substances, are often illicitly misused for the manufacture of methamphetamine and other amphetamine-type stimulants, posing significant challenges to public health safety and legal enforcement. Through a systematic review of the extensive domain of ephedrine and its derivatives, this review aims to serve as a valuable resource for the academic community, medical professionals, and regulatory authorities.

2. Varieties of Ephedrine Analogues

Ephedrine analogues are amine substances composed of ephedrine and its derivatives, including both naturally occurring alkaloids in ephedra plants and chemically synthesized ephedrine derivatives. Accordingly, ephedrine analogues be categorized into natural and synthetic types depending on sources.

2.1 Ephedrine and Pseudoephedrine

Ephedrine and pseudoephedrine(Fig. 1) are two structurally similar compounds, both of which are the main components of ephedra and isomers of each other. Both of them are adrenergic drugs. There are more than 300 preparations with ephedrine as the main component, and more than 200 preparations with pseudoephedrine as the main component[2]. Ephedrine has a strong excitatory effect, similar to the sympathetic nervous excitement of epinephrine, which can excite the central nervous system. Compared to ephedrine, pseudoephedrine has vasoconstrictive effects and smaller effects on the central nervous system (CNS). Clinically, (1S, 2S)-pseudoephedrine is widely employed in treating colds, allergies (like hay fever), and asthma-related

conditions (such as bronchial asthma, whooping cough). Conversely, (1R,2S)-ephedrine is commonly promoted for its decongestant properties, and as a weight-loss supplement and performance-enhancing substance[3].

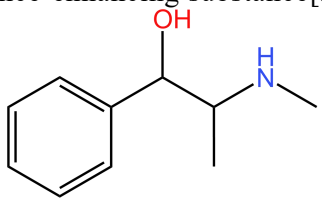

Figure 1. Chemical Structures of Ephedrine and Pseudoephedrine

2.2 Natural Ephedrine Derivatives

Natural ephedrine derivatives refer to those derivatives of ephedrine naturally occurring in ephedra, primarily encompassing norephedrine, norpseudoephedrine(Fig. 2), methylephedrine, and methylpseudoephedrine(Fig. 3).

Norephedrine is a chiral amine compound with diverse applications, which can be utilized in the synthesis of novel thiourea and thiazolidine anticancer drugs. Additionally, it serves as a chiral ligand in the field of pharmaceutical synthesis[4]. Commonly known as phenylpropanolamine(PPA), it is a key component in asthma medication and was previously a primary ingredient in cold remedies. Its pharmacological effects are similar to ephedrine, belonging to the sympathomimetic drugs. It stimulates the alpha receptors, leading to vasoconstriction, reducing neuronal uptake of norepinephrine, and enhancing bodily excitability. However, due to its numerous adverse reactions and drug risks, it has been globally banned[5]. On the other hand, norpseudoephedrine is a psychotropic drug. Both nor-ephedrine and norpseudoephedrine can also be detected in khat[6].

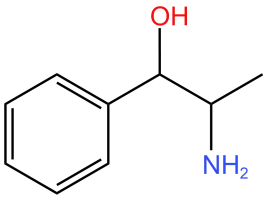

Figure 2. Chemical Structures of Norephedrine and Norpseudoephedrine

Methylephedrine and methylpseudoephedrine are methyl derivatives of ephedrine and constitute one of the primary components in ephedra. There are relatively few pharmacological reports regarding these compounds. Generally, they are believed to possess similar pharmacological effects to ephedrine, but methyl ephedrine exhibits fewer side effects compared to ephedrine. Their pharmacological actions include relaxing smooth muscles, vasoconstriction, anti-inflammatory effects, diaphoresis and antipyretic activity, antibacterial and antiviral properties, antitussive and antiasthmatic effects, as well as central nervous system stimulation[7]. Due to its stimulatory effects, methyl ephedrine has been classified as a banned substance by the International Olympic Committee[8].

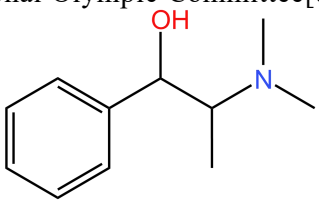

Figure 3. Chemical Structures of Methylephedrine and Methylpseudoephedrine

2.3 Synthetic Ephedrine Analogues

Synthetic ephedrine analogues refer to modified ephedrine analogues synthesized artificially through chemical means for specific purposes. These substances are commonly referred to as substituted ephedrine, such as chloroephedrine(Fig. 3). However, it is worth noting that chloroephedrine is an important intermediate for the illicit preparation of methamphetamine, and its legitimate use has not yet been identified[9].

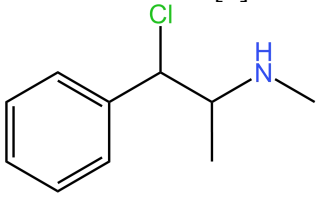

Figure 4. Chemical Structures of Chloroephedrine

Due to the different substituents, there are many types of chemically synthesized ephedrine derivatives, and their chemical structure general formula can be summarized as Fig 5.

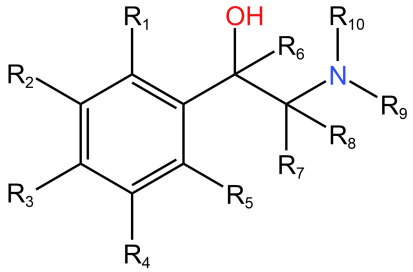

Figure 5. General Formula of Chemical Structure of Ephedrine Analogues

3. Abuse of Ephedrine Analogues

Ephedrine is an amphetamine-like stimulant that functions similarly to adrenaline by constricting blood vessels and stimulating the heart to raise blood pressure. It also dilates pupils, bronchia, and suppresses intestinal activity while increasing blood sugar levels[10]. The effects of ephedrine are thought to result from its actions, including raising intracellular calcium levels and facilitating calcium entry via voltage-gated calcium channels[11]. Research has shown that ephedrine produces a distinct set of subjective effects and is less effective as a reinforcer compared to amphetamine[12].

The abuse of ephedrine analogues is becoming increasingly severe, and the main reasons can be attributed to two aspects. Firstly, ephedrine substances possess psychoactive effects, which prompt some individuals to consume them as drugs or mix them with other substances in pursuit of temporary mental stimulation and pleasure. Some criminal elements even adulterate ephedrine with caffeine for sale[13]. Research indicates that consuming ephedrine, by itself or when paired with caffeine, notably boosts the repetition count[14]. Secondly, ephedrine analogues are also crucial precursors for the production of amphetamine-type stimulants such as methamphetamine[15]. These amphetamine-type stimulants possess stronger excitatory effects than ephedrine analogues and have thus become significant targets in illegal drug trafficking. Acquiring ephedrine analogues through illegal channels and subsequently manufacturing amphetamine-type stimulants has become a profitable means for some criminal elements. The abuse of these stimulants poses great harm to abusers and society, including damage to physical health, disruption of social order, and threats to public safety. In East and South-East Asia, the bulk of methamphetamine and amphetamine is produced with ephedrine and pseudoephedrine production[16]. The illegal synthesis and use of ephedrine analogues should be given sufficient attention.

4. Synthesis of Ephedrine Analogues

4.1Extraction of Ephedrine from Ma Huang

Ephedra has traditionally served as the primary source for extracting ephedrine analogues. There are three main traditional methods for extracting ephedrine[17]: The first is the toluene method. After extracting the ephedrine alkaloids from ephedra, toluene is used to extract pseudoephedrine and ephedrine. An improved method involves cancelling the water extraction step, converting the alkaloid salt into an alkaloid under alkaline conditions, and directly extracting it with xylene due to its solubility in xylene[18]. The second method is steam distillation, specifically by soaking in hydrochloric acid solution to extract ephedrine from ephedra. The third technique utilizes ion exchange, which includes immersing ephedra in hydrochloric acid. This process exploits the alkalinity variance of pseudoephedrine and ephedrine for resin adsorption, followed by their separation through a robust acid cation exchange column. Due to the fact that the main ephedrine analogues in the ephedra plant are ephedrine and pseudoephedrine, and the contents of other types of ephedrine analogues are relatively low, the extraction methods for ephedra are primarily used to extract ephedrine and pseudoephedrine.

4.2 Chemical Synthesis

There are several classical chemical synthesis methods for ephedrine analogues include the following: using styrene as the raw material, a dibrominated compound is generated, which is then heated with methanol and reacted with methylamine to obtain racemic ephedrine. Another method starts with propionaldehyde, which is first brominated and then reacted with hydrobromic acid and methanol to synthesize racemic ephedrine. Starting from benzene, ephedrine hydrochloride and pseudoephedrine hydrochloride can be synthesized through acylation, bromination, monomethylation, reduction, and

resolution[19]. The chemical synthesis of ephedrine analogues offers multiple approaches. At present, the field of its chemical synthesis mainly focuses on more efficient, environmentally friendly, and cost-effective synthesis techniques.

4.3 Biosynthetic Methods

In the field of ephedrine analogues synthesis, microbial synthesis technology is the frontier of research. In the biosynthesis of ephedrine analogues, microbial semi-synthesis and microbial direct synthesis are the two primary methods. In microbial semi-synthesis, specific enzymes from microorganisms are employed to transform precursor substances into the target product. Microbial pyruvate decarboxylase (PDC), with the assistance of TTP and magnesium ions, catalyzes the decarboxylation of pyruvate, which then undergoes condensation with benzaldehyde to yield R-PAC (phenylacetylcarbinol)[20]. R-PAC can then be converted into ephedrine and other ephedrine analogues through reductive amination. In microbial direct synthesis, the direct production of ephedrine analogues is achieved by optimizing the metabolic pathways of microorganisms and regulating gene expression. Based on the principle of genetic transformation of large foreign DNA molecules mediated by low-energy ion injection, recombinant yeast strains can be utilized to synthesize ephedrine, pseudoephedrine, and other ephedrine analogs[21]. However, no reports of the specific genes responsible for the synthesis of ephedrine analogues have been documented as of yet. Additionally, multiple microbial synthesis processes can be utilized to generate the target product. Lee et al[22]. firstly used recombinant Escherichia coli (pQE-AHAS I) to prepare 1-phenylacetylcarbinol (l-PAC) from benzaldehyde and pyruvate, then used recombinant Escherichia coli (pQE-CvTA) to couple the purified l-PAC to 1-propylamine, producing (1R, 2S)-NE through a two-step microbial synthesis process.

5. Conclusions

It serves as a reference for researchers in related fields. In order to ensure public health and safety, future research should focus on developing safer and more efficient synthetic methods for ephedrine analogues, as well as enhancing regulations and prevention efforts to curb their illegal production and abuse.

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