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Review Article

A Review of 20 Years Research Progression on Prodrug Technology in Inhaled Medications

Lijuan Liu[1], Jinghang Chen[2]*, Min Wang[3] and Wei Li[4]

[1]*Department of Pharmacy and Examination, Henan Vocational College of Nursing, Anyang, 455000, China.*
[2]*Department of Respiratory and Critical Care Medicine, The People's Hospital of Anyang City, China.*
[3]*Department of Nursing, Henan Vocational College of Nursing, Anyang, 455000, China.*
[4]*Department of Medical Technology, Henan Vocational College of Nursing, Anyang, 455000, China.*

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ABSTRACT

In contrast to systemic administration methods such as oral or injection, inhaled medications are directly administered to the respiratory tract to exert a therapeutic impact, which has clear benefits in the treatment of respiratory illnesses. However, existing inhaled medications are difficult to fulfill clinical prescription demands, and the research and development of novel inhaled pharmaceuticals has significant hurdles due to a lack of comprehensive theoretical and practical experience guidance. Personalized customization of candidate pharmaceuticals to fulfill the needs of inhalation treatment using prodrug technology is now an alternate method of inhalation drug development. This article examines the use of prodrug technology in inhalation administration throughout the last 20 years. These studies discovered that: esterification modification or prodrug technology combined with macromolecular compounds can extend drug pulmonary residence; mannose modification or acid-sensitive bond linkage can achieve drug release in alveolar macrophages; and personalized modified prodrugs can achieve drug release in alveolar macrophages. It is possible to produce physicochemical qualities suited for inhalation administration while reducing medication toxicity. Overall, using prodrug technology may be able to meet the different needs of inhaled drug development and give ideas for how to make new inhaled drugs.

INTORDUCTION

The three oldest modes of administration are oral, topical, and inhalation. In comparison to systemic administration methods such as oral or injection, pulmonary inhalation drugs enter the respiratory tract directly through special drug delivery devices to exert therapeutic effects and have demonstrated clear advantages in the treatment of asthma and chronic obstructive pulmonary disease (COPD). Tropthronium bromide is a derivative of atropine, the active ingredient in Datura and Chinese ginseng (Williams and Rubin, 2018). Tropthronium bromide was the first commercialized M choline receptor antagonist. Tropthronium bromide was the first beta-agonist inhaled medication. By the 1970s, short-acting beta-receptor agonists (SABA), short-acting M-choline receptor antagonists (SAMA), and inhaled corticosteroids (ICS) had all achieved significant advances in the treatment of asthma and COPD. Albuterol, ipratropium bromide, and beclomethasone dipropionate are examples of sexual medications. These inhaled medications, which were created in the 1960s and 1970s, are known as first-generation inhaled drugs because they have a shorter duration of effect and require 4 to 6 doses per day. By the 1990s, pharmaceutical companies had produced the second generation of long-acting inhaled medicines, which could be taken twice daily. Formoterol, chromotropium bromide, fluticasone propionate, and budesonide are examples of representative medications. Second-generation inhalation therapies are the current gold standard for inhaled treatment. Inhaled medicines have progressed to the third generation since 2012, and the combined therapy of ICS,

* Corresponding author: cjh16637232627@163.com
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long-acting beta-receptor agonists (LABA), and long-acting M-choline receptor antagonists (LAMA) allows for once-daily ultra-long treatment. Effective inhalers are now on the market, such as fluticasone furoate, vilanterol, umeclidinium bromide, and others (Strong *et al*., 2018).

The primary advancement from first-generation to third-generation inhaled medications for asthma and COPD has been in lengthening the action period of inhaled therapies, although the mechanism of action has not altered considerably. The effect of medications is to manage symptoms, not to postpone them. Disease progression and the fact that COPD patients are not responsive to ICS make it challenging to address clinical medication demands with existing inhaled medicines (Chu and Drazen, 2015). Other lung disorders, in addition to asthma and COPD, have treatment issues. Although inhalation administration can maintain a high local drug concentration at the site of respiratory infection, reducing the risk of drug resistance, current anti-infective inhalation preparations are based on marketed systemic drugs to change the route of administration, typically from the lungs after administration. It is rapidly absorbed into the systemic circulation and requires high-dose administration; existing pulmonary arterial hypertension drugs can only regulate blood vessels, and the drugs are difficult to accumulate in lesions, preventing effective treatment. It is currently used to treat pulmonary fibrosis and lung cancer. The medications utilized in the system are all supplied systemically, resulting in significant toxic and side effects as well as poor patient compliance. Inhalation medications that are effective have yet to be produced.

Many hurdles face the development of inhaled medications. In addition to examining its pulmonary safety and efficacy in drug design, it is also vital to comprehensively assess its pulmonary biopharmaceutical characteristics to guarantee that inhaled medications can sustain effective concentrations in lung tissue for an extended period of time. To satisfy the needs of biopharmaceutical features, new oral drug discovery can follow the Lipinski five principles (Lipinski, 2004), in conjunction with the biopharmaceutical categorization system and supporting in vitro and in vivo assessment methodologies. In contrast, there are currently no systematic theoretical or practical guidelines for the creation of inhaled medications. Inhaled medications undergo a complicated process in the lungs, requiring optimum physicochemical qualities to balance their dissolution, penetration, absorption, metabolism, and lung tissue retention. As a result, for the development of inhaled medications, personalized structural alteration addressing the faults of candidate pharmaceuticals to suit the requirements of inhalation treatment is now a possibility. The second and third generations of inhaled medications are mostly created by personalized structural alteration of the initial molecule.

Through alteration of the medication's molecular structure, prodrug technology endows the drug with greater solubility, enhanced stability, and permeability change. The active component is released by enzymatic or chemical activity after entering the human body, and the drug effect is exerted, which can alleviate the problem of absorption and distribution of the original medicine. Long-acting release, drug release site selectivity, and toxicity are all factors to consider. As indicated in Table I, a number of inhalation prodrug products have been approved for commercialization. Laninamivir octanoate (4 in Table I), for example, is hydrolyzed in lung tissue by S-formylglutathione hydrolase and acylprotein thioesterase 1 to the active form lanimirvir, which has anti-influenza virus properties. The local antiviral activity of a single dose of inhalation may be sustained in the lungs for at least 5 days, achieving a single dose for the treatment of influenza (Yamashita, 2010). The goal of this study is to look at the research on pre-drug technology in the field of pulmonary inhalation administration over the last 20 years and come up with new ideas for making medicines.

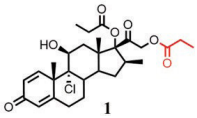
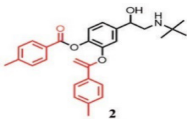
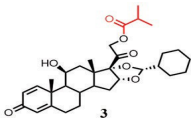
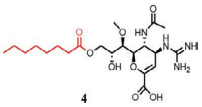
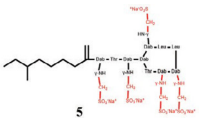
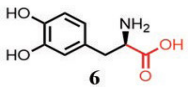
PULMONARYMETABOLSIMANDINHALED MEDICATIONS

The lung has 40 distinct cell types, each with a unique spectrum of enzymatic activity. Endogenous chemicals are usually metabolized in endothelial cells, whereas external metabolic systems are mostly found in lung epithelial cells. Clara cells (non-ciliated bronchiolar cells) and alveolar type II cells are involved in most of the external metabolic activities. These cells have a wide range of metabolic enzymes and are the first line of defense against inhaled foreign materials.

The enzymes present in the lungs are not the same as those found in the liver. In the lung, the most common cytochrome P450 (CYP) isoforms are CYP1B1, CYP2B6, CYP2E1, CYP2J2, CYP3A5, and CYP1A1. The most abundant hepatic CYP3A4 enzyme is expressed to a lesser extent in the lung tissue, and the CYP3A5 isoform is thought to be in the lung tissue (Hukkanen *et al*., 2002). Aside from the CYP family, the lung also expresses sulfotransferase, uridine diphosphate (UDP) glucuronyltransferase, glutathione S-transferase, esterase, peptidase, cyclase oxygenase, and flavin monooxygenase. A vast variety of bio converting enzymes may metabolize various substrates.

The metabolic features of the lungs have a substantial influence on medication efficacy and duration of action. After being breathed, the medication aerosol comes

Table I. Marketed inhalation prodrugs.

Prodrug	Active form	Metabolic enzyme	Pharmacological activity	Indication	Time to market	Product name	Structural formula
Beclomethasone dipropionate	17 Beclamethasone monopropionate	Esterases	Glucocorticoids, antiinflammator, anti-allergic	Asthma, allergic rhinitis, etc.	1976	Qnasl, QVAR, etc.	 1
Bitolterol	Colterol	Esterases	β2 adrenergic receptor agonist, dilates the bronchus	Bronchial asthma, chronic bronchitis	Listed in 1984; withdrawn in 2001	-	 2
Ciclesonide	Desmethyl-propionyl ciclesonide	Esterases	Glucocorticoids, anti-inflammatory	Asthma and allergic rhinitis, etc.	2004	Alvesco, Wei Feining, etc.	 3
Laninamivir octanoate	Laninamivir	S-Formylglutathione hydrolase and acyl-protein thioesterase 1	Neuraminidase inhibitor, anti-influenza virus	Influenza virus infection	2010	INAVIR	 4
Colistin metha-nesulfonate	Colistin	Hydrolase	Antibiotic, effective against Gram-negative bacteria	Pseudomonas aeruginosa infection associated with cystic fibrosis	2012	Colobreathe	 5
Levodopa	Dopamine	Dopa decar-boxylase	Replenish the deficiency of dopamine in the striatum	OFF episodes in patients with parkinson's disease	2018	Inbrija ®	 6

into contact with the airway mucus in the lungs, where the drug's local disintegration influences its following pulmonary processes. The medication will quickly diffuse to lung epithelial cells or be phagocytosed and removed by macrophages. After entering lung epithelial cells, it may undergo drug processing, be kept in certain organelles, or bind to its target receptors, influencing drug affinity and retention period in lung tissue (Cooper *et al*., 2012). Esterified drugs or protein drugs can easily undergo hydrolysis due to the abundance of pulmonary esterases, some drugs, such as budesonide, can also undergo an esterification-hydrolysis cycle with fatty acids in cells. Metabolic processes can guide the development of inhaled drugs, including the design of inhaled prodrugs.

CONCEPT AND CLASSIFICATION OF PRODRUGS

The pre-body medication is often referred to as the pre-medicine. The first ALBERT proposed that pre-medicine is a substance that has pharmacological activity after biological change. It is roughly separated into two categories front medicine and biopharm of the carrier link. The active ingredient (mother medication) is covalently linked to the carrier component of the preceding drug connected by the carrier. This carrier group can enhance physical chemistry or pharmacokinetics and is often easier to remove by hydrolysis. Small molecular groups (ester, amide, amine), macromolecular polymers [polyethylene glycol (PEG)], or targeted (antibody) are examples of carriers. The carrier group, which is activated by metabolic alteration of its own official group, is not included in the pre-biological drug.

The application of pre-medicine can be divided into three categories based on the functions and purpose of the pre-medicine design: first, from the perspective of improving the physical nature of the medicine, through drug modification stability, reducing the local stimuli and pain caused by the drug to the human body; second, from the perspective of improving efficacy, the active activation ingredients in the body can reduce the toxicity o Starting with learning features, pre-drug design can increase drug absorption, control drug metabolism, or lengthen the period of drug action. It can also target specific organs, tissue delivery, etc. (Abet *et al*., 2017).

MEDICATIONS FOR PULMONARY INHALATION

The application of previous drug technology in inhalation drugs is summarized based on the functions of pre-medicine and the needs of the development of lung inhalation drugs, which primarily include four categories: improving the nature of physical and chemical poisoning, long-acting, and targeting. It is worth mentioning that the design and synthesis of each pre-medicine can enhance a number of functions simultaneously. A shift in nature can result in a range of functional changes.

Enhance the physical and chemical qualities

Some medications' dissolving properties make them unsuitable for lung inhalation. Using the pre-medicine approach can alter the drug's original physical and chemical characteristics (Fig. 1) to fit the preparation requirements of inhalation preparations, facilitating lung delivery and improving patient compliance. The liquid ventilation approach, which uses the full fluoromy carbonized substance as the medium, is a means of directly giving the medicine to severely wounded lungs. To create a series of nicotinate (7) anterior medications, the lively hydrogen of niacin was replaced with a fluoride carbon chain, which considerably increased drug solubility in the whole fluoroprobrine (Hsu *et al*., 2003). Smoose acid is esterase sensitive, and the mother medicines are rapidly liberated during hydrolysis. Oxolin is a potent anticonvulsant. Large-dose abdominal injections can have severe toxic consequences; therefore, lung administration is an option. Isopylol, on the other hand, is a viscous and insoluble oil that is not suitable for inhalation. It is prepared to be prepared to make an aqueous solution following the preparation of the drug. When dripping into the lungs, it has high tolerance and quick outcomes; it causes equal seizures in the lungs with lower dosages without acute toxicity (Dhir *et al*., 2011). Water solution is an essential feature in medication development. It has the potential to increase the solubility of medicines and water-soluble polymers such as PEG. PEG has been used in the creation of many ppilids, including powerful pine dragons, paclitaxel, etc. (Bayard *et al*., 2013).

Low drug capacity is a key issue in the development of inhalable drug carriers. Nanoprocinomy can be dramatically increased by lipopymal medication. In pure pharmaceuticals, the hyperlinate palmate (9, 10) and methamphetamicin are employed to create polymal-hydroxyl polymer nanoprocols or nano-nanoprocols. The load capacity ranges from 14% to 34% (the amount of nanoprocinomy in the original medication is approximately 1% to 5%). Furthermore, the polymer's polymer, PEG-modified antibody fragments, and others have achieved a large drug load by pre-medicine methods.

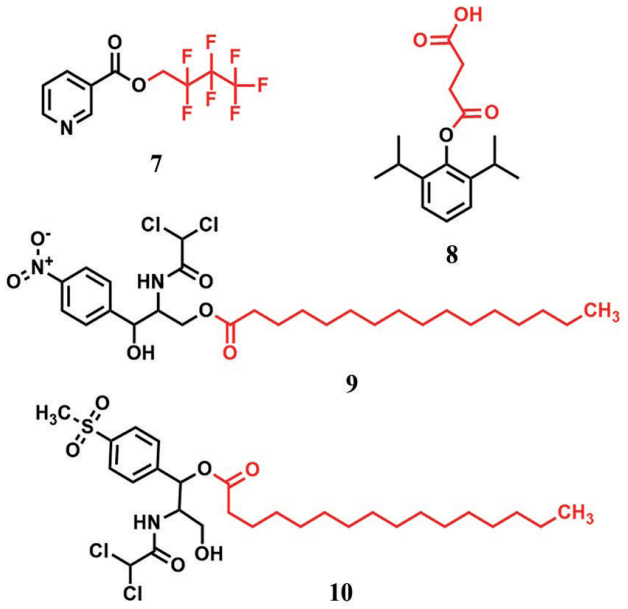


Fig. 1. Prodrugs to improve physicochemical properties.

The poisonous impact

Some pharmaceuticals have significant toxic and side effects when taken in numerous or high dosages, causing organ damage. Therefore, decreasing drug toxic side effects is the key to drug delivery. One potential technique for overcoming the unfavorable effects of lung disorders is to minimize overall body absorption by breathing local delivery active chemicals, and the pre-drug can further reduce drug toxicity by altering the medication (Fig. 2). Combining the two methods can achieve a good goal of medication reduction and efficiency.

Because oral or inhaled administration causes toxicity, multi-viscosin E, which is used to treat Gram-negative bacterial infection, is generally utilized as a non-active pre-body medication (sodium sulfonate) (5) (Boisson *et al*., 2013). CMS is produced by coating the pupamine on the beamononin portion of the beamonon sulfon. In the body, it swiftly hydrolyzes it into a succession of methane sulfide derivatives, which finally produces viscosin. CMS dry powder inhalation agents have been approved for listing in Europe. Furthermore, atomication has been used in the treatment of cystic fibrosis and ventilator related lung infections both at home and abroad, although its clinical safety and dose must be confirmed.

A cationic peptide with broad spectrum antibacterial action is known as an antibacterial peptide (AMPS). The contact with the bacterial cell membrane is what gives

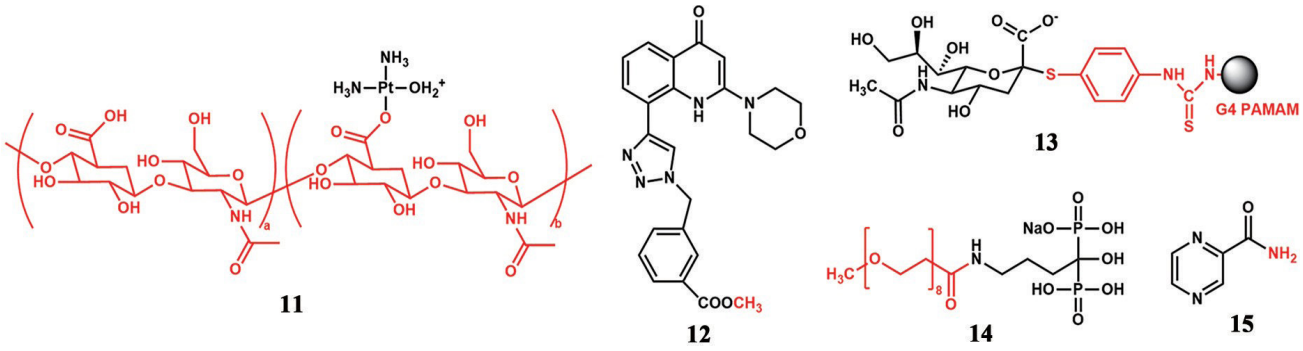


Fig. 2. Prodrugs to reduce local and systemic toxicity. G4 PAMAM, Generation 4 polyamidoamine.

it antibacterial activity. AMPS, on the other hand, has a low selectivity for human biofilms, which can easily lead to host toxicity. The preliminary medicine pro-AMPS decrease static charges by incorporating hypoligida pre-bodies, lowering antibacterial activity and cytotoxicity. After inhaling the atomization, it could be activated by the NE of the bronchial tube, reducing the potential toxicity of AMPS in the bronchial space for treating cystic fibrous lesions (Forde *et al*., 2019).

Cisplatin has broad-spectrum anticancer action, but intravenous use causes severe nephrotoxicity and persistent neurotoxicity. The lung drip hyaluronic acid (HA) -ciser compound (11) may make the medication widely disseminated in the lung tissue, and the content in other organs is exceedingly extraordinarily content. low, with a considerable reduction in the incidence of inflammation. Paclitaxel injections throughout the body can result in systemic toxicity of the digestive and immunological systems. The impact of mouse trachea injection (L-glutamic acid)-paclitaxel on the original non-small cell lung cancer has been greatly increased, and the effect of anti-tumor effectiveness has been increased. In the first study of PEG-paclitaxel, the amount of paclitaxel that could be taken safely was increased by 100 times (20).

Phosphate 3-kinase (PI3K) is involved in the aberrant activation of immune cells and lung fibroblasts. It might be used to treat severe asthma and pulmonary fibrosis. However, the systemic aim of PI3K inhibitors has limited their widespread usage. CL27C (12) is an anterior cell permeability medication (Campa *et al*., 2018). When model mice inhale CL27C, inflammation goes down, lung function gets better, and death rates go down. Systemic toxicity can be avoided.

The combination of hemagglutinin on the viral envelope and cell membrane saliva initiates type A flu virus infection. Due to its strong cytotoxicity, free saliva monomer cannot prevent hemoglobin attachment in the body. The nasal application of polyamide-pagamine (PAMAM) branches-like macromolecular (13) pre-drug inhibitory action on the virus may be significantly enhanced, allowing influenza virus infection to be successfully avoided.

Mucosal damage results from Allen phosphate having a structure comparable to phospholipidal alkaline, which is competitively replaced by mucosal phospholipidal alkaline. It has mucosal damage features, causing respiratory system damage and making it unsuitable for lung administration. For example, low molecular weight glycol (510 da) (14) can reduce lung mucosa toxicity after lung delivery.

Anti-tuberculosis medications (15) are an earlier treatment that is converted in the liver into the active substance pyrium acid after being taken orally. However, pyrdinamide's hepatic toxicity has resulted in a restricted amount of administration, and it is being attempted to administer it straight to the lungs by inhalation. For example, the shell glycogen nanoscale dried powder inhalation preparations for albumramamide and pyrdinamide, or the inhaled trio combination of benamine, Moxishaxin, and pyrdinamide made by spraying the dry methods powder, etc. According to studies, inhaled dry powder is safe and non-toxic, and it aids in the delivery of high-dose medications to the respiratory tract to treat TB (Eedara *et al*., 2016).

Furthermore, atomization inhalation of non-active pre-active medications, such as Huan Sonal (3), might lower the occurrence of local adverse effects in the oropharynx because non-active pharmaceuticals deposited in the region are eaten before activation.

Long-term impact

Local drug concentration directly impacts the curative efficacy of medications with local actions in the lungs. The tiny molecules that are free and simple to dissolve after the medications pass through the respiratory mucus can spread fast in the epidermal cells and infiltrate

the blood within a few minutes. The lungs remain short. Some medications have a high lung affinity and have lingered in the lungs for a long time because they dissolve slowly with target molecules and target cells or are easier to interact with non-target lung tissue. Long-term drug residency in the lungs is advantageous for maintaining greater lung drug concentrations, achieving long-term benefits, lowering administration frequency, and boosting patient compliance. The drug's absorption process results in the drug's clearance and effectiveness in the lungs, as well as the start of the overall unfavorable reaction (Loira-Pastoriza *et al*., 2014). Delaying absorption, increasing lung stay duration, and enhancing pharmacokinetics of medicines in the lungs are therefore critical to boosting pulmonary effectiveness.

Ester

Esterization prior to medication is a frequently used approach for prolonging drug lungs (Fig. 3), which may improve the lipophytic of the drug by slowing the dissolving rate and transmission rate of transmissions, delaying absorption and removal, and promoting pharmaceuticals and fatty acids. Reverse combination, increased drug affinity, and extended lung residency. Huan Sonald (3) and diopenonic acid perbalotamone (1) are anti-inflammatory sugar cortical hormones. Monitoring of metabolites is effective. These active metabolites have high lipophilicity and can be coupled with fatty acids. By keeping these medicines in the airway longer, the esterification in the cells extends how long they work.

Dicemethonate (DXP) (16) is a dexamethasone pre-lipid medication. Spray dry DXP, 1, 2-two palm-SN-glycerin 3-choline (DPPC), and hyaluronic acid to obtain big porous particles. The palmate section allows DXP to insert a double-layer DPPC and regulate the discharge of porous particles. DXP also slows down the release of the lipophilic After administering DXP powder to the rats' bronchi, a significant quantity may be observed in the 24-h lung lining fluids.

The rosary's prefront (TRE) is cut in half and must be constantly injected or supplied numerous times each day. Short-term high-drug concentrations following inhalation will result in both systemic and local adverse effects. The carboxyl carboxyl hydrogen of the main chiral is substituted with a range of alkyl chains of varying lengths, resulting in a series of alkyl-based drugs (C2TR–C16TR).

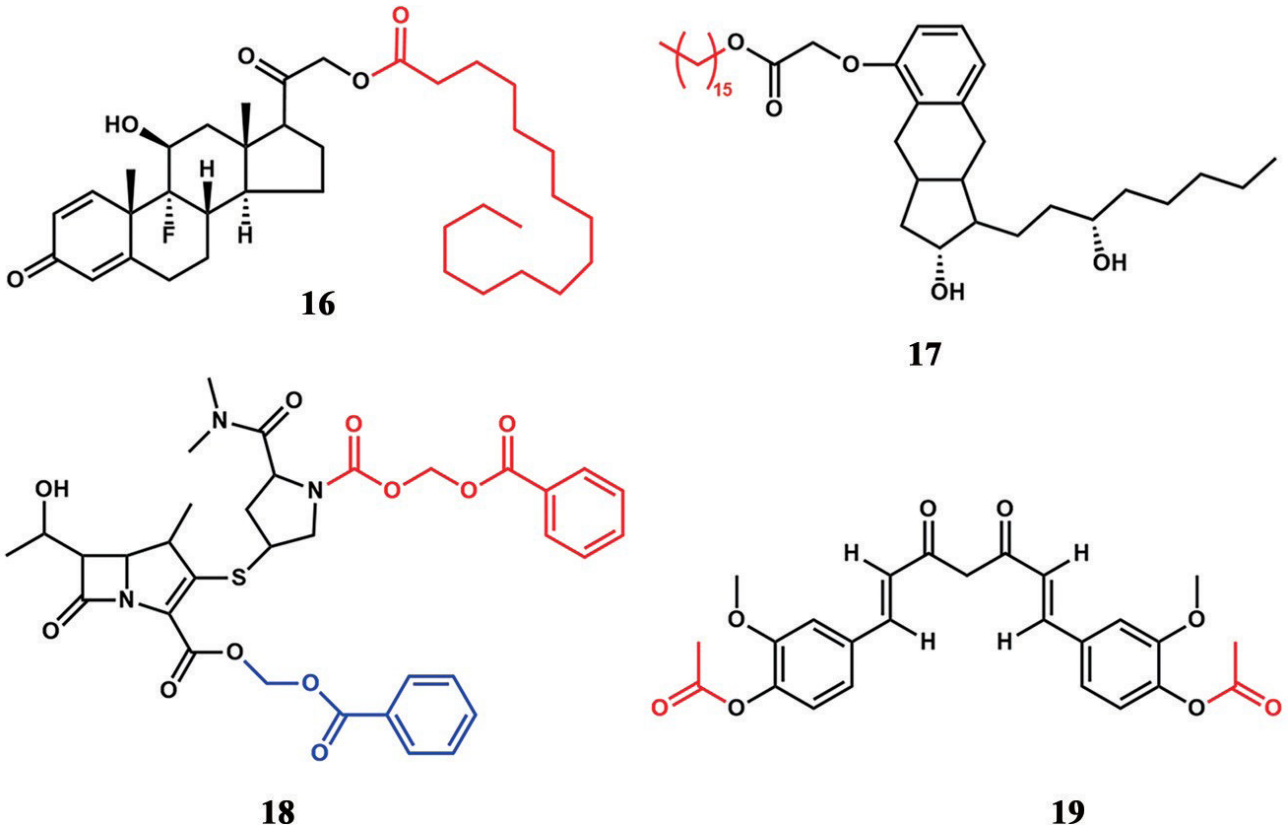


Fig. 3. Esterified prodrugs to prolong lung retention.

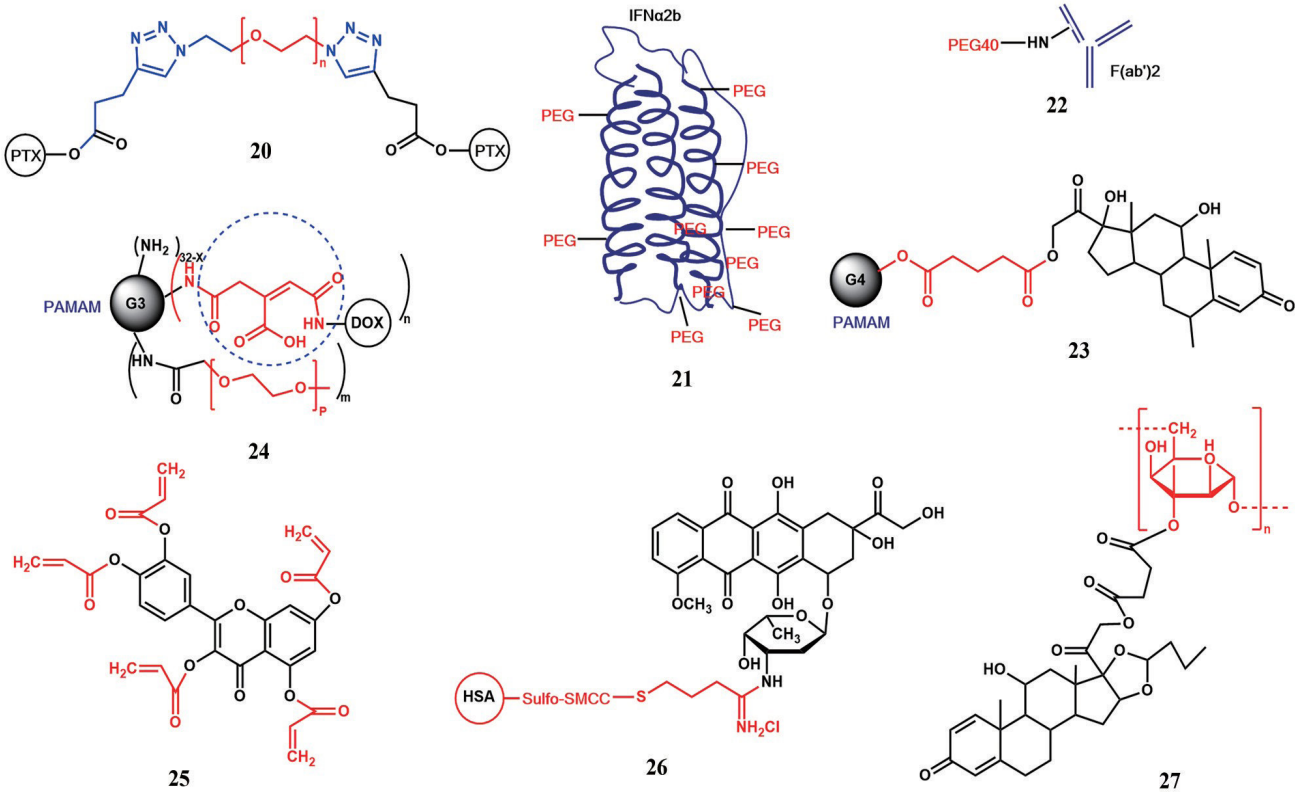


Fig. 4. Macromolecular prodrugs to prolong lung retention. PTX, Paclitaxel; IFN, Interferon; PEG, Polyethylene glycol; HSA, Human serum albumin; Sulfo-SMCC, Sulfosuccinimidyl 4-(N-maleimidomethyl)-cyclo-hexane-1-carboxylate.

In animal studies, TPD lipid nanoparticles, as compared to pre-inhaled cyclopan solution, have the effect of enlarging blood vessels, particularly the front cyclopan (C16TR) of the hexishnecelasses (C16TR). There are fewer dosages and fewer side effects (Leifer *et al*., 2018). C16TR, also called front cycloonate (17), is a drug that widens the blood vessels in the lungs for a long time. Due to its low molecular weight and ease of dissolution, Moro Peinan will swiftly absorb the whole-body cycle through the lung epithelium after administration, and the lung stays will be brief. Cover Mei Luopenan's hydrophilic carboxylic acid and amines with hydrophilic benzetal and formaldehyde bridge chemistry to create a novel type of insoluble pre-medicine MRPD (18). According to previous studies, the tracheal injection produces MRPD mucus penetrating crystals that can generate a high amount of Moro peinan in the lungs of guinea pigs. Furthermore, as compared to cowantin, cowantin acetate (19), previous medications were extended by 7.2 times after the lungs were delivered (Hu *et al*., 2017). Effect Laumi Mi (4), who is cited in the preamble, is also evidence that esterification before the drug lengthens the lungs.

Hyper molecular medicine

Pharmaceuticals and macromolecular substances are another popular technique for increasing the residence time of inhaled small molecules in the lungs (Fig. 4). The common price of medications is linked to big molecules, such as synthetic polymers, albumin, or cells, in the drug delivery system of macromolecules. This strategy's potential

The benefit is that the medication's distribution is determined by the macromolecular carrier rather than the drug itself. In general, macromolecular penetration is poor, vascular endothelium speed is sluggish, or it may be associated with lung tissue, causing it to slow down from the lungs to the blood, stay in the lung tissue, and gap for longer. According to research, the residence duration of macromolecules in lung tissue is proportional to their molecular weight. The bigger the molecular weight within a given range, the longer the staying duration (Ryan *et al*., 2013).

The most popular pre-medicine approach for lung administration is PEG. The pine-polyethylene glycol hydrolysis (2 KDA) conjugate is about 4 times and 8 times greater than the free drug solution. Paclitaxel and PEG (20

kDa and 6 kDa) conjugate (20) both have an anti-tumor action in the lungs and veins. Furthermore, due to the longer duration of the 20 KDA combination, the anti-tumor impact in the mouse lung cancer model's medium-dose dose is significantly stronger than 6 KDA. PEGization is frequently utilized to treat pulmonary disorders, such as enhancing interferon 2 (21) retention. PEG (40 kda) and anti-white agglose (IL)-17A and IL-13 fragments are used in both arms.

Pentisic acid connects the pine dragon of the methyl-powered pine to PAMAM branch-like macromolecules. The binding (23), which can remain in the lungs for 7 days, increases the therapeutic impact of allergic pneumonia in mice. The lungs continue to release branches that have a greater anti-tumor therapeutic impact. *In vitro* cisplatin release by a hyaluronic acid-cisplatin complex (11). When compared to intravenous injection, the lung exposure of rats after 24 and 96 h rose by 5.7 and 1.2 times, respectively. The compound's dry powder inhalation agent is effective in lung cancer in the mouse bronchus. Corticin polyethylene (25) interacts with bell amine to form nanoholin (-aurette) nanogelry, which may be inhaled. Under physiological circumstances, the ester is consistently released in 48 h, and there is continuing antioxidant action. Human serum albumin (HSA), Dornbarie, and aldehyde even couplets (26) and adsorb caused apoptotic trails, making it possible to inhale nanoparticles after atomization. It is consistently deposited in the lungs of mice, and the drug is released for an extended period of time. Dorrioxing and Trail's synchronized apoptotic impact have boosted anti-tumor efficacy. Due to the presence of Bu Di Neida in the lungs, Chinese vineytose can serve as a slow-release substitute repository for covalent and combination medicines.

Others

Other nitric oxide (NO) is a powerful vascular dilatation agent. Pulmonary hypertension and acute respiratory distress syndrome can be reduced by vitality inhalation. Excess NO will be swiftly cleared from the pulmonary arteries by hemoglobin, and the clinical impact will be short. Periphetic acid can be utilized in the preparation of hydrophilic minor molecule pre-drugs (Fig. 5). Encapsulate Proli/No in a polyethylene oxide-lactic acid cluster to obtain a stable inhaled form of NO (Jeh *et al*., 2004).

It is important to note that long-term medication release in the lungs is not the same as gradual release. Slow medication release may be ineffective because it may not reach effective drug concentrations. As a result, the lung release dynamics of the active components are also important to consider when the medicine is left in the lungs. Active pharmaceuticals are coupled to the main chain of the polymer by two distinct ester linkages alkyl ester (29) and phenolone (30), resulting in diverse chemical bonding in an inhaulable cycloopenic meta-molecular anterior medicine. Dynamics of medium hydrolyzed medium (Fig. 5). The fast released phenolin medication creates higher effective drug levels in the lungs than the slowly released alkyl-based therapy. The drug's 24-h release is usually modest, and it must be delivered frequently, therefore no antibacterial action is shown (Das *et al*., 2017).

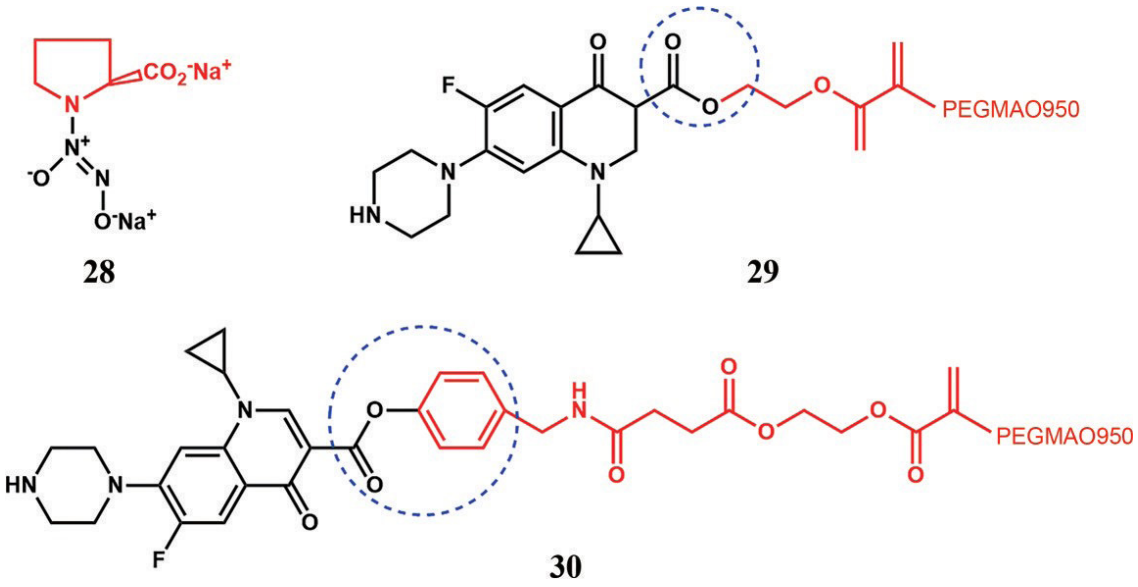


Fig. 5. Other prodrugs to prolong lung retention. PEGMAO950, Polyethylene glycol methacrylate.

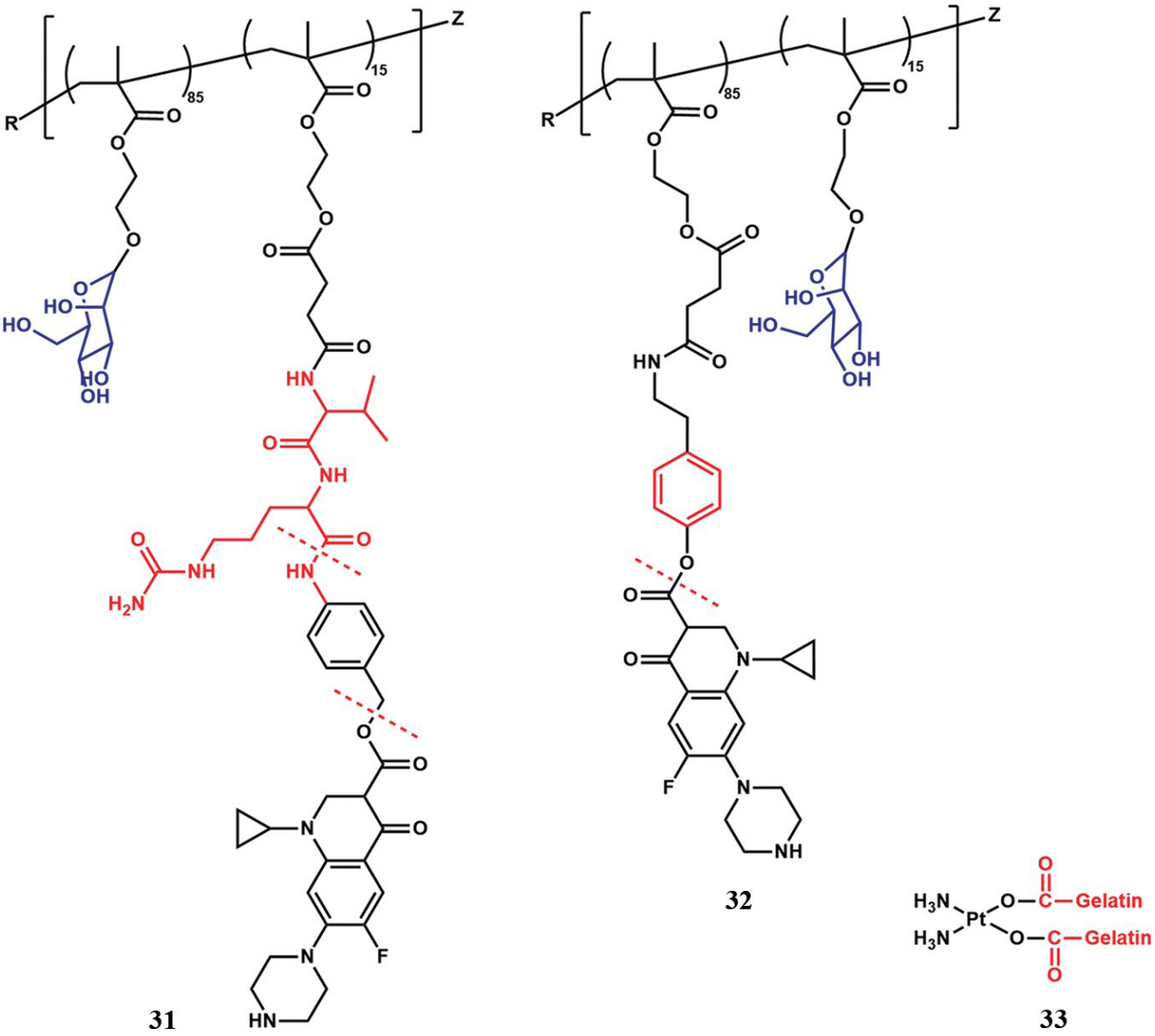


Fig. 6. Prodrugs for actively targeted delivery.

A focused influence

Targeted releases can limit the drug's release and potency to certain areas or settings, boosting delivery efficiency and decreasing unwanted responses. Lung administration is a drug delivery method that targets the lung organs, and pre-drug technology can further accomplish a targeted function through active or fixed-point biological activation. Drugs for active targeting medications are often linked to a carrier that can recognize targeted particular markings (such as antigens or receptors) and transmit them on to its action components via specialized binding reactions. Pre-body medications can be broadly dispersed but only activated at the appropriate parts in the activation of particular parts. In general, this fixed-point creature activation may be accomplished by utilizing the target site's specific physiological circumstances or endogenous enzymes.

Medicine with active targeting

Mannose receptors are abundant on the surface of macrophages. In the design of the drug or preparation of the preparation or preparation, you might include mannose to tar*get al*veolar macrophages (Fig. 6). Cydaliax and intracellular proteases that can hydrolyze phenolacene joint formation before synthetic drug monomer and

manicoprotic monosorbiated bonus-fractured chain transfer (RAFT) drugamers (31: two peptide joints, 32: phenolacene joints). The hydrophilic glycotic residue can improve drug solubility, target and improve macrophage uptake and intracellular delivery, and generate high amounts of continuous release in cells via enzymatic or hydrolytic processes. Drugamers have good lung delivery and can be administered in a single dosage to maintain an effective bacteriostatic concentration in the alveolar macrophage region (79). The ionizing Circa-Plancetestone has a substantially greater therapeutic impact on pneumonia fever, Francis infection, and pulmonary gangrene.

Tumor sites can target specific receptors on the surface of tumor cells. In human malignancies, the epidermal growth factor receptor (EGFR) is overexpressed. The gelatin nanoprocone's cisplatin reaction load is employed to change the surface of the gelatin-cisplatin (GP-PT) nano composite (33) with a biomotenne epidermal growth factor (BEGF). Inhaling GP-PT-BEGF can target cells with high epidermal growth factor receptor expression, resulting in high cisplane dosages in the lung tumor portion (Tseng *et al*., 2009).

Biological activation preoperative medication

Fixed-point biological activation interpretations can be produced for particular physiological circumstances in the target location that differ from other tissues (Fig. 7). Use acid-sensitive linkages to limit medication release in an acidic environment, such as a tumor microenvironment or macrophages. Dorriobixing via acid-sensitive bonds (34), cashmere ionotide (24/35), or the 4-(radio sulfamyl) benzoic acid joint (36). They join together using polymer macromolecules. Under the acidic circumstances of in vitro, the conjunction is immediately released. It has a greater anti-tumor impact after lung administration than free medicines. To induce pH-sensitive release of various tobacco crickets in macrophages, the acid-sensitive oxylic acid cinkinyl (37) is loaded into solid lipid nanoparticles coated in dew glycogen. It has stronger intracellular antibiotic effects after atomization than the lungs, and it is predicted to be employed to treat latent TB infection. Migrate cancers have high quantities of active oxygen, like hydrogen peroxide, and the pre-drug can be activated in tumor cells by hydrogen peroxide, resulting in possible anti-rotor tumor therapy. Prodrug 7 (38) is a hydrogen peroxide treatment medication that uses borate as a trigger unit and fragrant beanin as a fluorescent group to monitor the release of active hydroxyl tree alkali components. The animal model has potent anti-tumor efficacy (Kim *et al*., 2014).

Additional functions

Polypeptide and protein pulmonary delivery

Because the lungs metabolic activity is relatively poor, polypeptide and protein medication hydrolysis can be decreased. In recent years, lung administration has also been employed to treat polypeptides and vaccinations systemically. Drugs absorb blood into the body to exert systemic effects, and the absorption of the lungs influences the drug's therapeutic impact. PAMAM-like macromolecules are an effective absorption promoter. The promotion impact on absorption grows from 0 to 3 generations,

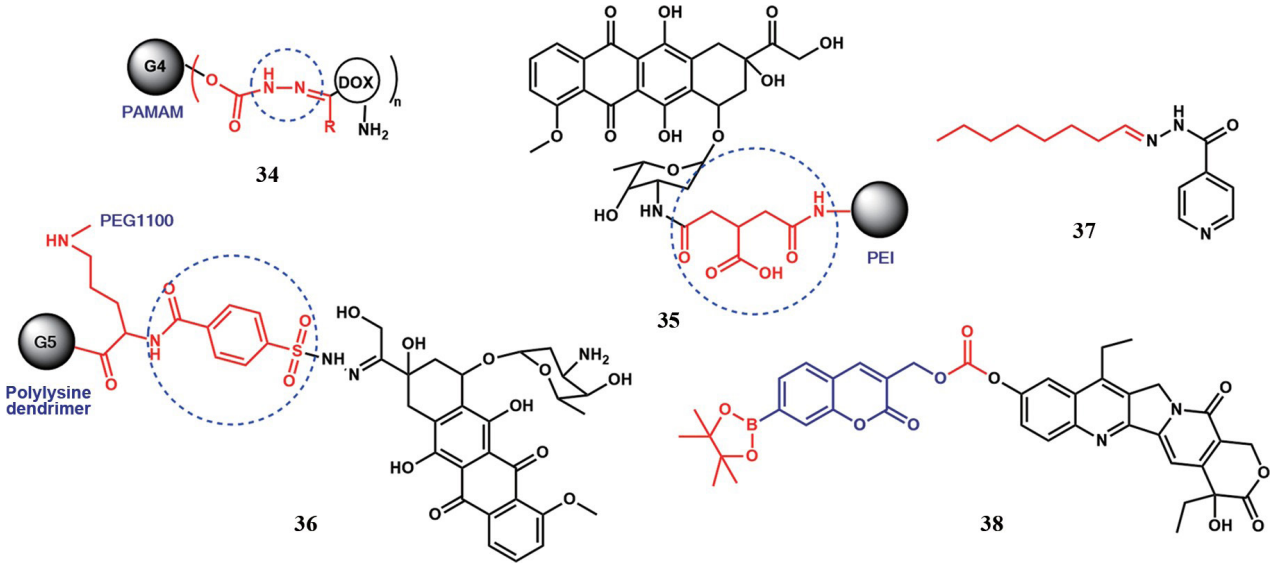


Fig. 7. Biologically activated prodrugs for targeted drug release. DOX, Doxorubicin; PEI, Polyethylenimine.

which may considerably boost insulin and calcium absorption in mouse lungs without producing any respiratory tissue damage. Membrane damage. PEGization is utilized to shield the polypeptide from local protein hydrolysis, enhancing system absorption of the whole molecular system following lung injection (Fig. 8). Specific PEG modification (39) of the 18-bit lysine of calcium (39) can boost the polypeptide's stability in rat uniform pulp. Per lyricine specific alteration (40), perfecting the lysine of the 34th bit of pancreatic hyperglycemid peptide can make it more stable in the protein hydrolysis of the lungs and better enter the body circulation (Lee *et al*., 2009).

PEGization according to research on the effects of insulin lung absorption, once the blood enters the circulation, PEG's protein provides a constant plasma protein concentration. However, PEGization and the usage of high molecular weight PEG on the polyport sites will limit the system's absorption. This might be linked to the previously described PEG alteration of the higher molecular weight.

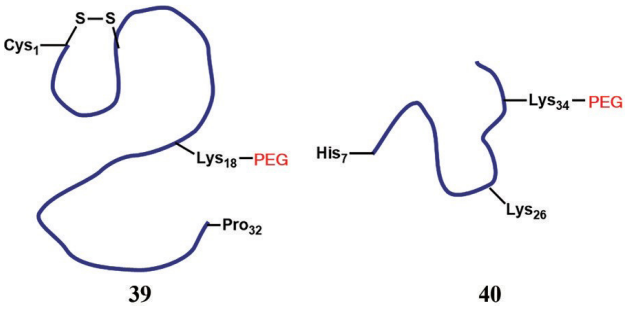


Fig. 8. Prodrugs for pulmonary delivery of peptides and pro- teins. Cys, Cysteine; Lys, Lysine; Pro, Proline; His, Histidine.

Pre-biological drug inhalation

Geshabinnia (Fig. 9) must be converted into an active form by phosphorylation in the nucleus in order to have a cytotoxic role. Body studies have demonstrated Garcitabin's safety and anti-tumor benefits in primary or metastatic lung cancer animal models. After human body atomization, the concentration of lung medicines might be (42) (16%). Schinotic acid enters the human body as an active sulfide, and inhaling phosphoric acid sulfide (42) can block 75% of lung cancer and enhance mouse longevity (91). Rob Fluste (43) is a once-daily selective phosphate 4 (PDE-4) inhibitor authorized for the treatment of chronic obstructive pulmonary disease. Robluste is converted to its active metabolites, Rob Flint N-oxides, via cytossence CYP1A2 and CYP3A4. The presence of CYP1A2 in the lungs has been shown. Although there is little evidence for CYP3A4, there is a homogenous enzyme for CYP3A5. According to this, Rob Fluste has the ability to be breathed in, transported to the lungs, and activated. In the mouse model, Rob Flint inhalation has been shown to treat asthma in moderation, and the Rob Fluste formula for lung delivery is being investigated. Dopamine precursor medication Levba Dabka (6). The European Union has authorized laosoba inhalation powder (Inbrija) for intermittent treatment of Parkinson's disease. It can be taken using a breathing inhalation device, which allows the levota to bypass the gastrointestinal tract and swiftly enter the bloodstream via the lung system and reach the brain.

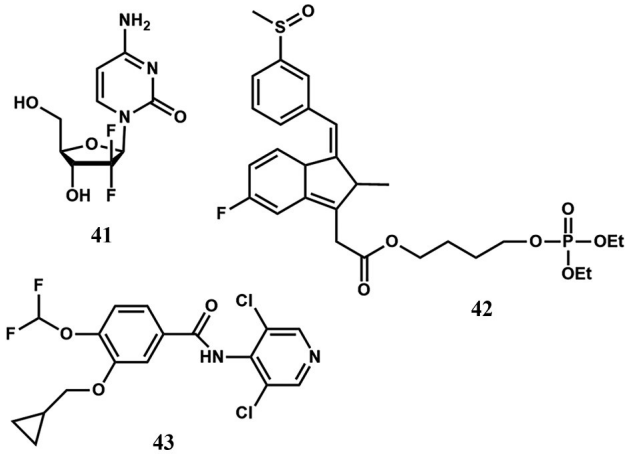


Fig. 9. Inhaled bioprecursors.

SUMMARY, CONCLUSION, AND PROSPECTS

Pre-drug technology is a method of preventing drug molecule flaws and has become an essential aspect of the drug research and development process. Modifying a drug lets it get its ideal and chemical properties as well as its biochemical properties faster. This speed up the process of preclinical optimization.

Pre-medicine design can suit the various criteria of novel inhalation medication development. It can delay medication absorption from the lungs and increase the period of lung residency by estering modification or coupling with macromolecular compounds; exploit the specific structure or physiological circumstances of the target portion, Through the modification of the target head or a specific chemical bond, one can achieve active targeting or fixed biological response interpretation of the lungs; through personalized modification, one can obtain physical and chemical properties suitable for lung administration and reduce the drug's overall and lung toxicity. Table II outlines the use of pre-drug technologies

Table II. The applications of prodrug design in inhaled medicines.

Active form	Prodrug	Modification method	Indication
Improve the physical and chemical properties of medicine			
Nicotinic acid	Fluorinated nicotinic acid	Esterification, enhancing the solubility in the	Not mentioned
Propofol	Esters, Propofol hemisuccinate	Fluorocarbon, Esterification, turning oil to aqueous solution	Seizures
Prednisolone/ paclitaxel	Polyethylene glycol (PEG)-	PEGylation, improving water solubility	Pharmacokinetics
Chloramphenicol or thiamphenicol	drug conjugates Chloramphenicol palmitate	Esterification, increasing drug loading	only/lung cancer Respiratory tract
Reduce toxicity			
Colistin	or thiamphenicol palmitate Colistin methanesulfonate	Modification of amino group with methane	infection Cystic fibrosis
Antimicrobial peptides (AMPs)	Pro-AMPs	sulfonic acid, Elongation with the AAAG linker, tetragluta	Cystic fibrosis
Cisplatin	Cisplatin-hyaluronan (HA)	mate motif and *N*-terminal acetylation Conjugation with HA	Lung cancer
Paclitaxel	Conjugates poly (*L*-glutamic acid)-	Conjugation with poly (*L*-glutamic acid)	Lung cancer
CL27e	Paclitaxel CL27c	Esterification	Asthma and
Sialic acid (SA)	SA-conjugated polyamidoamine	Conjugation with PAMAM	pulmonary fibrosis Influenza pneumonia
Alendronate	(PAMAM) dendrimer PEG-alendronate	PEGylation	Hypercalcemia and
Pyrazinic acid	Pyrazinamide	Bioprodrug	Osteoporosis tuberculosis
Long-lasting effect			
Desmethylpropionyl-ciclesonide	Ciclesonide	Esterification	Asthma and allergic
17-Beclamethasone monopropionate	Beclomethasone dipropionate	Esterification	Rhinitis asthma, allergic
Dexamethasone	Dexamethasone palmitate	Esterification	Rhinitis respiratory tract
Treprostinil	Hexadecyl-treprostinil	Esterification	Infection pulmonary arterial
Meropenem	Insoluble prodrug (MRPD)	Modification of the hydrophilic carboxylic	Hypertension lung inflammatory
Curcumin	Curcumin acetate	acid and amine functional groups Esterification	Pulmonary arterial
Laninamivir	Laninamivir octanoate	Esterification	Hypertension influenza virus infection
Prednisolone	PEG-prednisolone conjugates	PEGylation	Pharmacokinetics only
Paclitaxel	PEG-paclitaxel	PEGylation	Lung cancer
Interferon (IFN) α2	PEGylated IFNα	PEGylation	Lung-resident
Anti-interleukin-17A (IL-17A) F(ab')2 and anti-IL-13 Fab'	PEG40-F(ab')2 and PEG40-Fab'	PEGylation	Lung inflammatory
Methylprednisolone (MP)	MP-PAMAM dendrimer conjugate	Conjugation with PAMAM	Lung inflammatory
Doxorubicin (Dox)	Dendrimer-Dox conjugate	Conjugation with PAMAM or polylysine dendrimer	Lung cancer

Table continued on next page.....

Active form	Prodrug	Modification method	Indication
Cisplatin	Cisplatin-hyaluronan (HA) conjugates	Conjugation with HA	Lung cancer
Quercetin	Quercetin conjugated poly (*β*-amino esters)	Reaction of acrylated quercetin with a secondary diamine	Cellular oxidative stress
Dox and apoptotic TRAIL protein	TRAIL/Dox human serum albumin (HSA)	Conjugation with HSA	Lung cancer
Budesonide	Dextran-budesonide	Conjugation with dextran	Asthma and its related inflammation
Nitric oxide	$C_5H_7N_3O_4Na_2 \cdot CH_3OH$ (PROLI/NO)	*L*-Proline	Pulmonary arterial hypertension, thrombus
Ciprofloxacin	Drugamers	Reversible addition-fragmentation chain transfer (RAFT) polymerization of polyethylene glycol methacrylate comonomer and prodrug monomer	Pneumonia
Targeted drug delivery			
Ciprofloxacin	Drugamers	Mannose modification for macrophage targeting	Bacterial infection in alveolar macrophages
Cisplatin	Cisplatin-incorporated in gelatin with biotinylated-EGF modification	Biotinylated-EGF modification for tumor targeting	Lung cancer
Dox	Dendrimer-Dox conjugate	Conjugation with PAMAM *via* acid-sensitive hydrazone bond	Lung cancer
Dox	PEGylated PAMAM dendrimer-based Dox	Conjugation with PAMAM *via* acid-sensitive *cis*-aconitic anhydride (CA) bond	Lung cancer
Dox and siRNA	Polyethylenimine (PEI)- CA-Dox/siRNA	Conjugation with PEI *via* acid-sensitive CA anhydride bond	Lung cancer
Dox	Dox-conjugated dendrimer	Conjugation with PEGylated polylysine dendrimer *via* acid labile 4-(hydrazinosulfonyl) benzoic acid linker	Lung cancer
Isoniazid	Isonicotinic acid octylidene-hydrazide	Mannose modification for macrophage targeting	Intracellular tuberculosis infection
Pulmonary delivery of peptides and proteins			
SN-38 Insulin/calcitonin	ProDrug 7 PAMAM-insulin/calcitonin conjugate	Modification with H_2O_2 activated groups Conjugation with PAMAM	Lung cancer Pharmacokinetics only
Salmon calcitonin	PEGylated salmon calcitonin	PEGylation, improving chemical stability	Hypercalcemia
Glucagon-like pep- tide-1 (GLP-1)	PEGylated GLP-1	PEGylation, improving chemical stability	Diabetes
Insulin	PEGylated insulin	PEGylation	Pharmacokinetics only
Gemcitabine phos- phate	Gemcitabine	-	Lung cancer
Bioprecursors			
Sulindac sulfide	Phospho-sulindac	-	Lung cancer
Roflumilast *N*-oxide	Roflumilast	-	Chronic obstructive pulmonary disease
Dopamine	Levodopa	-	Parkinson's disease

in medication development for the lungs. The most prevalent inhalation medication modification procedures are esterification modification and coupling with macromolecular carriers. The esterification modification can increase drug lipopia, improve drug-lung affinity, and the ester linkages are readily hydrolyzed in the lung content

and release the drug, assisting the medication to perform the effect. Because the lung distribution characteristics of a drug with macromolecules are primarily determined by the macromolecular carrier rather than the drug itself, the body behavior of the drug can be controlled by the design of the macromolecular carrier, thereby protecting unstable drugs and regulating lung drugs. The properties of dynamics lengthen the lung retention time. Polyethylene glycol, polyamide-amine, polyethylene amine, polylerate, hyaluronic acid, and shell polycosan are examples of commonly used carrier macromolecules. Furthermore, alveolar macrophages may be utilized to change alveolar macrophages using mannose, and a targeted release of tumors or macrophages can be accomplished by acid-sensitive bonds, such as pyrine bonds, such as cricket or cashmere octa.

However, there are several issues and uncertainties associated with the use of pre-drug technology in the administration of inhaled medications. To begin with, inhaling pre-inhaled medication necessitates the activation of metabolic enzymes in the lungs. However, as compared to the gut and liver, lung enzyme expression is typically low, and the expression mode of drug metabolic enzymes is also different. The pulmonary tissue defects will impair the enzyme activity of the lung and the pre-metabolic medicine's capabilities. Second, the buildup and evacuation of the macromolecular carrier in the lungs is an issue that should be addressed in the creation of significant molecular medications. It is important to examine any undesirable responses that may occur as a result of the supplemental substance. Polyethylene glycol, for example, may trigger an immunological reaction as a toxin, and its non-biological breakdown is normally eliminated by the kidney, although it takes a long time and may create hazardous by-products. Finally, there are technological hurdles in evaluating drugs prior to inhalation. The association between pre-clinical animal tests and clinical trials of pre-clinical trials that can be breathed into the preceding drug is not evident due to species variations in lung metabolism. Tofimilast, AWD-12-281, and UK-500001, for example, are PDE-4 inhibitors. Although clinical assessments show promising benefits, clinical trial data is invalid.

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IRB approval ethical statement

This article does not contain any studies with human participants performed by any of the authors.

Statement of conflict of interest

The authors have declared no conflict of interest.

REFERENCES

Abet, V., Filace, F., Recio, J., Alvarez-Builla, J. and Burgos, C., 2017. Prodrug approach: An overview of recent cases. *Eur. J. med. Chem.*, **127**: 810-827. https://doi.org/10.1016/j.ejmech.2016.10.061

Bayard, F.J.C., Thielemans, W., Pritchard, D.I., Paine, S.W., Young, S.S., Bäckman, P., Ewing, P. and Bosquillon, C., 2013. Polyethylene glycol-drug ester conjugates for prolonged retention of small inhaled drugs in the lung. *J. Contr. Release*, **171**: 234-240. https://doi.org/10.1016/j.jconrel.2013.07.023

Boisson, M., Gregoire, N., Couet, W., and Mimoz, O., 2012. Colistin in critically ill patients. *Minerva. Anestesiol.*, **79**: 200-208.

Campa, C.C., Silva, R.L., Margaria, J.P., Pirali, T., Mattos, M.S., Kraemer, L.R., Reis, D.C., Grosa, G., Copperi, F., Dalmarco, E.M. and Lima-Júnior, R.C., 2018. Inhalation of the prodrug PI3K inhibitor CL27c improves lung function in asthma and fibrosis. *Nat. Commun.*, **9**: 1-16. https://doi.org/10.1038/s41467-018-07698-6

Chu, E.K., and Drazen, J.M., 2005. Asthma: One hundred years of treatment and onward. *Am. J. Respir. Crit. Care Med.*, **171**: 1202-1208. https://doi.org/10.1164/rccm.200502-257OE

Das, D., Chen, J., Srinivasan, S., Kelly, A.M., Lee, B., Son, H.N., Radella, F., West, T.E., Ratner, D.M., Convertine, A.J., and Skerrett, S.J., 2017. Synthetic macromolecular antibiotic platform for inhalable therapy against aerosolized intracellular alveolar infections. *Mol. Pharm.*, **14**: 1988-1997. https://doi.org/10.1021/acs.molpharmaceut.7b00093

Dhir, A., Zolkowska, D., Murphy, R.B. and Rogawski, M.A., 2011. Seizure protection by intrapulmonary delivery of propofol hemisuccinate. *J. Pharmacol. exp. Ther.*, **336**: 215-222. https://doi.org/10.1124/jpet.110.173591

Cooper, A., Ferguson, D. and Grime, K., 2012. Optimisation of DMPK by the inhaled route: Challenges and approaches. *Curr. Drug Metab.*, **13**: 457-473. https://doi.org/10.2174/138920012800166571

Eedara, B.B., Tucker, I.G. and Das, S.C., 2016. Phospholipid-based pyrazinamide spray-dried

inhalable powders for treating tuberculosis. *Int. J. Pharm.*, **506**: 174-183. https://doi.org/10.1016/j.ijpharm.2016.04.038

Forde, É., Kelly, G., Sweeney, L., Fitzgerald-Hughes, D., MacLoughlin, R., and Devocelle, M., 2019. Vibrating mesh nebulisation of pro-antimicrobial peptides for use in cystic fibrosis. *Pharmaceutics*, **11**: 239. https://doi.org/10.3390/pharmaceutics11050239

Hsu, C.H., Jay, M., Bummer, P.M. and Lehmler, H.J., 2003. Chemical stability of esters of nicotinic acid intended for pulmonary administration by liquid ventilation. *Pharm. Res.*, **20**: 918-925. https://doi.org/10.1023/A:1023899505837

Hu, X., Yang, F.F., Wei, X.L., Yao, G.Y., Liu, C.Y., Zheng, Y. and Liao, Y.H., 2017. Curcumin acetate nanocrystals for sustained pulmonary delivery: Preparation, characterization and *in vivo* evaluation. *J. Biomed. Nanotechnol.*, **13**: 99-109. https://doi.org/10.1166/jbn.2017.2326

Hukkanen, J., Pelkonen, O., Hakkola, J. and Raunio, H., 2002. Expression and regulation of xenobiotic-metabolizing cytochrome P450 (CYP) enzymes in human lung. *Crit. Rev. Toxicol.*, **32**: 391-411. https://doi.org/10.1080/20024091064273

Jeh, H.S., Lu, S. and George, S.C., 2004. Encapsulation of PROLI/NO in biodegradable microparticles. *J. Microencapsul.*, **21**: 3-13. https://doi.org/10.1080/02652040310001619767

Kim, E.J., Bhuniya, S., Lee, H., Kim, H.M., Cheong, C., Maiti, S., Hong, K.S. and Kim, J.S., 2014. An activatable prodrug for the treatment of metastatic tumors. *J. Am. chem. Soc.*, **136**: 13888-13894. https://doi.org/10.1021/ja5077684

Lee, K.C., Chae, S.Y., Kim, T.H., Lee, S., Lee, E.S. and Youn, Y.S., 2009. Intrapulmonary potential of polyethylene glycol-modified glucagon-like peptide-1s as a type 2 anti-diabetic agent. *Regul. Pept.*, **152**: 101-107. https://doi.org/10.1016/j.regpep.2008.09.008

Leifer, F.G., Konicek, D.M., Chen, K.J., Plaunt, A.J., Salvail, D., Laurent, C.E., Corboz, M.R., Li, Z., Chapman, R.W., Perkins, W.R., and Malinin, V.S., 2018. Inhaled treprostinil prodrug lipid nanoparticle formulations provide long-acting pulmonary vasodilation. *Drug Res.*, **68**: 605-614. https://doi.org/10.1055/s-0044-100374

Lipinski, C.A., 2004. Lead-and drug-like compounds: The rule-of-five revolution. *Drug Discov. Today Technol.*, **1**: 337-341. https://doi.org/10.1016/j.ddtec.2004.11.007

Loira-Pastoriza, C., Todoroff, J. and Vanbever, R., 2014. Delivery strategies for sustained drug release in the lungs. *Adv. Drug Deliv. Rev.*, **75**: 81-91. https://doi.org/10.1016/j.addr.2014.05.017

Olsson, B., Bondesson, E., Borgström, L., Edsbäcker, S., Eirefelt, S., Ekelund, K., Gustavsson, L. and Hegelund-Myrbäck, T., 2011. Pulmonary drug metabolism, clearance, and absorption. In: *Controlled pulmonary drug delivery*. Springer, New York, NY. pp. 21-50. https://doi.org/10.1007/978-1-4419-9745-6_2

Ryan, G.M., Kaminskas, L.M., Kelly, B.D., Owen, D.J., McIntosh, M.P. and Porter, C.J., 2013. Pulmonary administration of PEGylated polylysine dendrimers: Absorption from the lung versus retention within the lung is highly size-dependent. *Mol. Pharm.*, **10**: 2986-2995. https://doi.org/10.1021/mp400091n

Strong, P., Ito, K., Murray, J. and Rapeport, G., 2018. Current approaches to the discovery of novel inhaled medicines. *Drug Discov. Today*, **23**: 1705-1717. https://doi.org/10.1016/j.drudis.2018.05.017

Tian, C., Liu, Y., Li, Z., Zhu, P. and Zhao, M., 2022. Mitochondria related cell death modalities and disease. *Front. Cell Dev. Biol.*, **10**: **Pages?** https://doi.org/10.3389/fcell.2022.832356

Tseng, C.L., Su, W.Y., Yen, K.C., Yang, K.C. and Lin, F.H., 2009. The use of biotinylated-EGF-modified gelatin nanoparticle carrier to enhance cisplatin accumulation in cancerous lungs via inhalation. *Biomaterials*, **30**: 3476-3485. https://doi.org/10.1016/j.biomaterials.2009.03.010

Wedzicha, J.A., Calverley, P.M. and Rabe, K.F., 2016. Roflumilast: A review of its use in the treatment of COPD. *Int. J. Chron. Obstruct. Pulmon. Dis.*, **11**: 81. https://doi.org/10.2147/COPD.S89849

Williams, D.M. and Rubin, B.K., 2018. Clinical pharmacology of bronchodilator medications. *Respir. Care*, **63**: 641-654. https://doi.org/10.4187/respcare.06051

Yamashita, M., 2010. Laninamivir and its prodrug, CS-8958: Long acting neuraminidase inhibitors for the treatment of influenza. *Antivir. Chem. Chemother.*, **21**: 71-84. https://doi.org/10.3851/IMP1688