Article @ Virology

Medical Treatment of Condyloma Acuminatum, a Review on the Chemistry of Therapeutic Drugs

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ABSTRACT

Condyloma acuminatum is a venereal disease caused by human papillomavirus. In recent years, the prevalence of condyloma acuminatum has increased significantly in China, making it become a high-risk veneral disease. Condyloma acuminatum which is highly infectious, has a certain incubation period, and is prone to relapse after treatment. The article discusses the methods of drug therapies for condyloma acuminatum and the chemistry of these drugs.

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Key Words: Condyloma acuminatum; Human papillomavirus; Drug therapies

Abbreviations: CA, Condyloma Acuminatum; HPV, Human Papillomavirus; STD, Sexually Transmitted Diseases; IC_{50}, 50% Inhibitory Concerntration; PMEG, 9-[(2-Phosphonomethoxy)ethyl]guanine.

Condyloma Acuminatum(CA) which is also known as Genital Wart or Anogenital Wart, is one of the most common sexually transmitted diseases (STD). The disease is transmitted from one to another through direct sexual contact with an infected partner. CA is caused by the human papilloma virus (HPV) type 6 or less commonly by HPV type 11. HPV is a double-stranded DNA virus belonging to the genus Papillomavirus of the family Papillomavirus, of which over

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170 types are known. HPV only affects humans.

In recent years, medical treatment of CA has made progress, but all these therapies may cause considerable side-effects, such as erythema and oedema. Recurrence rates are often high. New and improved treatments for CA are therefore essential. Prophylactic drugs are mainly based on vaccines, and they are mostly biomacromolecules such as polysaccharide or protein. Here, the author introduces some low-molecular-weight therapeutic drugs in order to provide more and better choices for the treatment. Due to the complex biological activities of these compounds, some can be used to treat other diseases. Herein, we only discuss something about HPV as references for pharmaceutical chemists.

1. Podophyllotoxin

Podophyllotoxin Tincture is an extremely common topical drug. The main ingredient of the drug is the podophyllotoxin which is extracted from the medicinal plant of *Berberidaceae* family. The tests in vitro and in vivo demonstrated that Podophyllotoxin Tincture had the activity of antitumor, as potential tubulin inhibitors[1].

It inhibited the microtubule polymeriza--tion and cell nucleus mitosis in metaphase. The chemotherapic action of podophyllo--toxin in external treatment of CA is assumed to be due to inhibit the growth of epithelial cell infected by HPV. Modern pharmacological studies have demonstrated that the cytotoxicity of podophyllotoxin is associated with inhibiting DNA topoiso--merase II by stabilizing the covalent topo II DNA cleavable complex[2].

The first catalytic enantioselective total synthesis of (−)-podophyllotoxin is accomplished by a challenging organo--catalytic cross-aldol Heck cyclization and distal stereocontrolled transfer hydrogena--tion in five steps from three aldehydes[3].

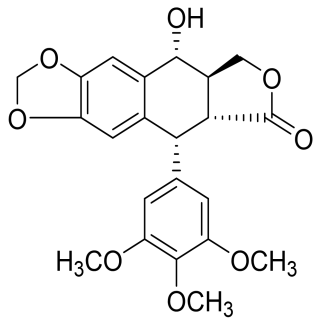


Figure 1:Structure of podophyllotoxin

Because of the scarcity of plant resources and the difficulties in organic synthesis, podophyllotoxin isolated from the secondary metabolites of plant endophytes may be a new drug source. As is reported, two endophyte fungi, both strains of *Phialocephala fortinii*, from rhizomes of the plant *Podophyllum peltatum*, could produce Podophyllo--toxin[4].

The solubility of a compound is a very important parameter whether isolated from plants or endophyte fungi. Six organic solvents were tested by HPLC and

UV detector, and the order is acetone>ethyl acetate>ethanol> propan-2-ol > butan-1-ol > methanol[5]. Among these solvents, the solubility of podophyllotoxin in acetone increased most significantly with the increasing temperature. Podophyllotoxin dissolved more easily in acetone and ethyl acetate than lower alcohols, which can be explained by the structure similarity between the solvent and solute due to the carbonyl group, corresponding to the empirical rule 'like dissolves like' to some extent. The experimental solubility and the modified Apelblat equation with the parameters might be used as essential data in purification and crystallization of podophyllotoxin.

2. Green tea catechins

Polyphenon E is a standardized extract of green tea leaves from *Camellia sinensis (L.) Kuntze*, a species of the Theaceae family, containing mainly tea polyphenols with immunostimulatory, antiproliferative and antitumour properties[6].

Polyphenon E(structure see figure 3) is a powerful antioxidant, which has a protective effect on erythrocyte membrane ATPase, inhibiting enzymes and kinases involved in the production of inflammatory mediators. The mechanism of Polyphenon E inhibiting the proliferation of HPV-infected cells lies in inducing cell apoptosis and mediating cell cycle aberration, which may contribute to the removal of skin damage of condyloma acuminatum.

It is worth mentioning that, compared with the specific interactions with the target, the antioxidant effect of phenolic hydroxyl groups is often the main reason for their activities.

3. Imiquimod

It has been determined that the in vivo antiviral activity of Imiquimod (1-isobutyl -1H-imidazo[4,5-c]quinolin-4-amine, see figure 4) can be attributed to the ability to induce the production of cytokines, especially interferon (IFN). The FDA approved imiquimod in 1997 for the treatment of external and perianal warts. Imiquimod upregulates tumor necrosis factor-α, interferon-α, -β, and -γ, leading to decreased HPV DNA/mRNA production and regression of warts[7].

Imiquimod could be synthesized by 4-hydroxy-3-nitro-1H-quinolin-2-one[8], see figure 5.

4. Ammonium trichloro (dioxoethylene--O,O') tellurate

Ammonium trichloro (dioxoethylene--O,O') tellurate (AS101, see figure 6) is an organotellurium (IV) compound that exhibits immunomodulation activity. Although no inhibitory activity of serine-, metallo-, or aspartic proteases was observed, AS101 exhibited time- and concentration-dependent inactivation of cysteine proteases.

Similar to cisplatin, an anticancer drug, AS101 is a complex. The possible

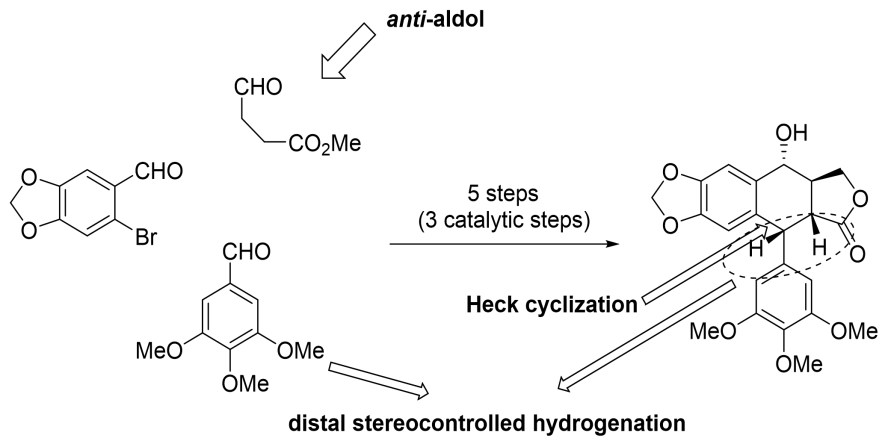


Figure 2: Synthesis of podophyllotoxin

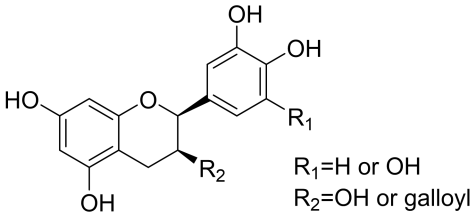


Figure 3: Structure of Polyphenon E

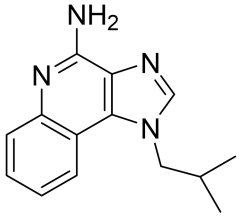


Figure4: Structure of Imiquimod

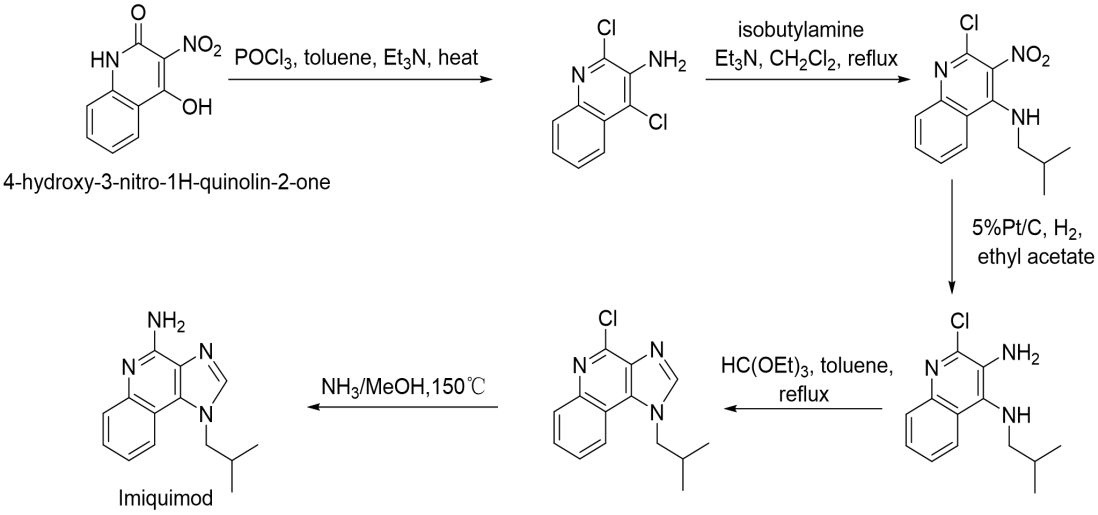


Figure 5: Synthesis of imiquimod

mechanism of action of such similar compounds is that metal ions form specific adducts with the target and destroy the original structure, thus inhibiting the action.

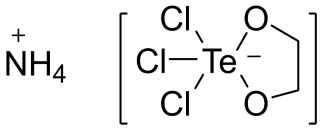


Figure 6: Structure of AS101

Research shows that AS101 15% w/w cream is an effective topical therapy for genital warts requiring relatively short duration of treatment (459±360 days), with minimal side-effects (mild--tomoderate burning and itching in 42% of patients) and low recurrence rate (4%). These results should be strengthened in a placebo-controlled trial as it is known that some genital warts may clear without treatment[9].

AS101 can be conveniently prepared by refluxing tellurium(IV) chloride with dry ethylene glycol in acetonitrile[10](See figure 7).

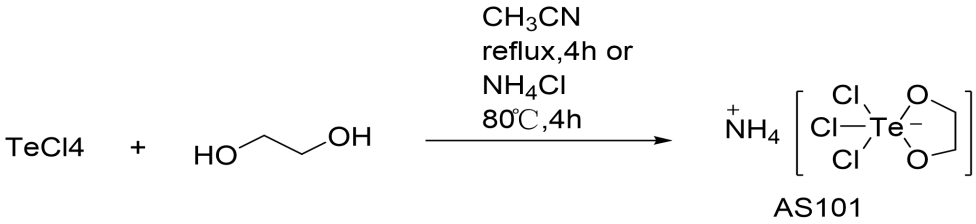


Figure 7: Synthesis of AS101

The following pathway is suggested for this reaction:

1. $TeCl_4+2HOCH_2CH2OH \rightarrow HOCH_2CH_2Cl+HOCH_2CH_2OTeCl_3+H_2O$
2. $CH_3CN+HOCH_2CH_2Cl \rightarrow CH_3C(=NH)OCH_2CH_2Cl$
3. $CH_3C(=NH)OCH_2CH_2Cl+HCl+H_2O \rightarrow CH_3CO_2CH_2CH_2Cl+NH_4Cl$
4. $HOCH_2CH_2OTeCl_3+NH_4Cl \rightarrow [(-OCH_2CH_2O-)TeCl_3]^- NH_4^+ + HCl$

5. Other small molecule inhibitors

Drug screening based on compound library is the main source of new drug development, including natural product library and synthetic compound library.

Since ancient times, human beings have recorded the use of natural products for disease treatment. Although the methods represented by combinatorial chemistry, high-throughput screening, targeted drug design have occupied the main position in the research and development of new drugs in the past decades, but they have far failed to achieve the expected results.

Natural products have diverse structures and novel mechanisms, so the search for drug lead compounds from plants and microorganisms still has excellent potential.

As is reported, caffeic acid exhibited highly potent antiviral activities against infection by three HPV subtypes (6, 16 and 18), with half-maximal inhibitory concerntration (IC_{50}) values of 12.1--16.5μg/mL[11].

Presumably because HPV-6 and-11 causing CA are low-risk viruses, there are very few reports on the screening of natural products based on such viruses compared with high-risk diseases such as AIDS. However, there are some Chinese herbs that are recognized to have the effect of treating CA and may be the source of drug leading compounds, which are worth further study, such as *Coix lacryma-jobi*, *Bletilla striata*, *Prunus mume*, *Radix Tricho--santhis*, *Maifanshi*, *Equisetum hiemale*, *Lithospermum erythrorhizon*, *Houttuynia cordata*, and *Isatis indigotica*[12].

Since a series of compounds containing the same parent nucleus can be rapidly synthesized by organic synthesis, which is convenient to study the structure-activity relationship, the activity test of related compounds has been reported more frequently.

Alkoxyalkyl acyclic nucleoside phos--phonate diesters were synthesized and some compounds show the anti-virus activities. EC_{50} of ODE-Bn-PMEG against HPV-11 is 0.18μM[13].

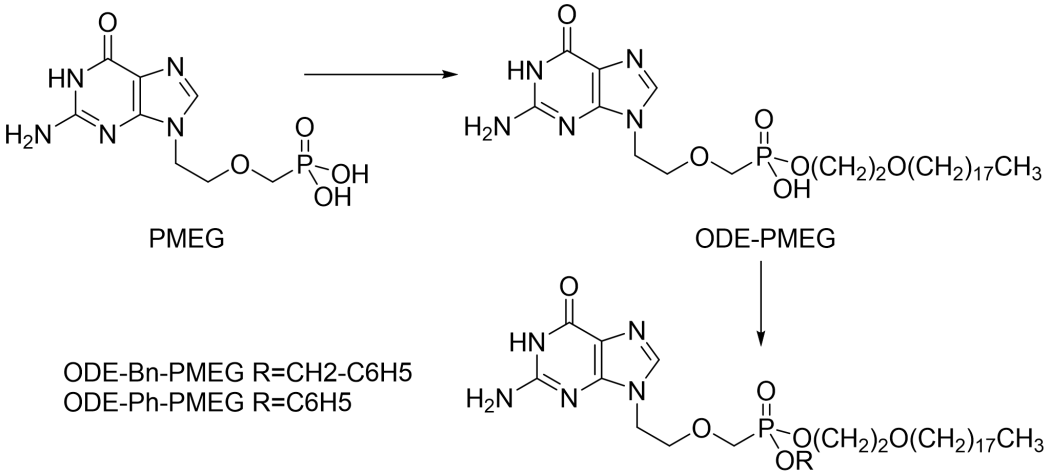
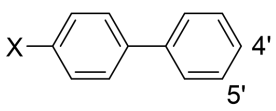
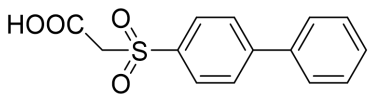


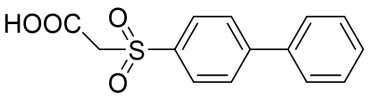
Figure 8: Structures of PMEG and its derivatives



biphenyl skeleton



(biphenyl-4-sulfonyl)acetic acid **1**



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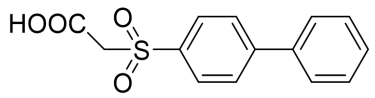

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Figure 9: Structures of biphenyl derivatives.

Biphenyl derivatives(See figure 9) were synthesized and measured with the ATPase activity of recombinant HPV6 E1 helicase. By changing the substituents X of the biphenyl skeleton, (biphenyl-4-sulfonyl) acetic acid 1 shows the best inhibiting capacity with IC50 of 2.0μM. While changing the aromatic groups, 4'-OMe 2 and 4',5'-(1,3-dioxolane) 3 show the better capacity with IC50 of 1.3μM[14].

Conclusions

In conclusion, the drugs of condyloma acuminatum treatments are multifarious, and each drug has a certain effect. We need to be patient through comprehensive treatment to thoroughly remove the virus, and to achieve the level of clinical cure. Drug developers should also speed up the development of new drugs, while screening based on the compound library to obtain drug lead compounds is an excellent method.

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