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The Design of Oxamniquine

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ABSTRACT: *Oxamniquine is a drug which developed to treat with schistosomiasis, an pandemic disease caused by flatworm which resulted in nearly 500,000 death every year.[1] The design of oxamniquine begin with the lead compound lucanthone. Through modifications on pharmacophores, the less toxic, orally active and more effective drug oxamniquine is obtained. The synthesis of oxamniquine begin with a molecule with quinoline structure. Currently, the synthesis of oxamniquine needs to undergo different kinds of reactions, including substitution and reduction.*

KEYWORDS: *Schistosomiasis; oxamniquine; drug design; synthesis; side effects*

Main content

Oxamniquine, called [7-nitro-2-[(propan-2-ylamino) methyl] -1, 2, 3, 4-tetrahydroquinolin-6-yl]methanol in its IUPAC name. It contains several functional groups, including hydroxyl, alkene and amine.

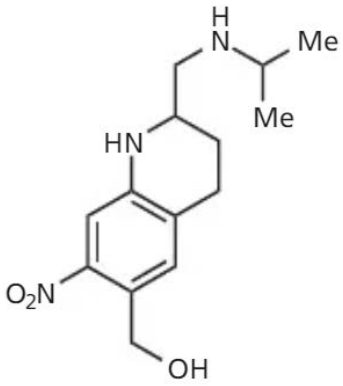

Figure 1: The structure of Oxamniquine

Oxamniquine is designed as a medicine to treat with schistosomiasis. In early 1960s, the only drug for schistosomiasis is lucanthone and stibocaptate. However,

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for lucanthone, it has to be regularly taken and will lead to side effects such as nausea and vomiting, and it cannot effectively kill all three pathogenic strains. For stibocaptate, it cannot be orally taken, which contribute to inconvenience in treatment. Besides, both of drug have toxic effect on human body and require frequent dosing regimens.[2] These drawbacks push Pfizer to initiate a project that aimed at developing an orally active, non-toxic agent that would be effective as a single dose against all pathogenic strains in 1964.

Synthesis

The overall synthesis process is shown in figure 2.

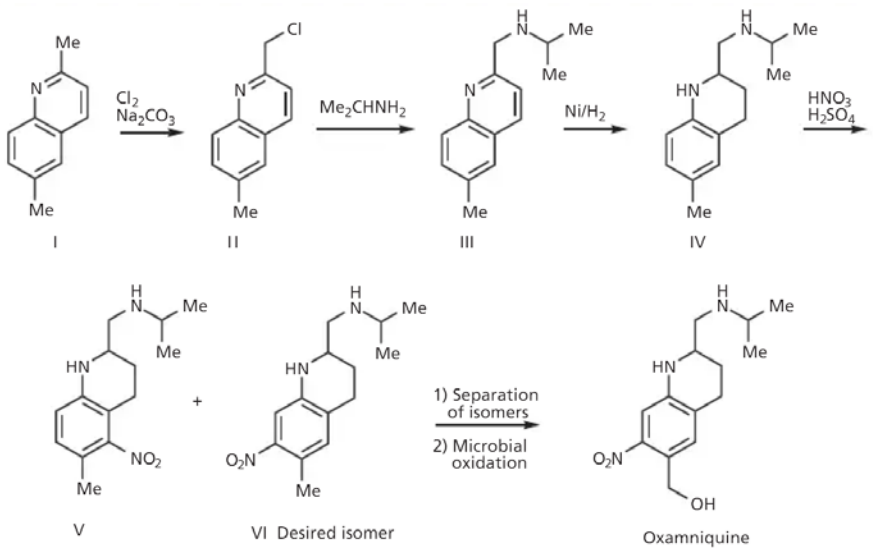

Figure 2: The synthesis process of Oxamniquine

To begin with, molecule I undergoes reaction substitution and use Na2CO3 to activate the reaction to obtain structure II. Then, as the chlorine is contacted to a primary carbon, molecule II undergoes SN2 (bimolecular nucleophilic substitution) reaction. As SN2 is a stereospecific reaction, no isomer is generated during the reaction.

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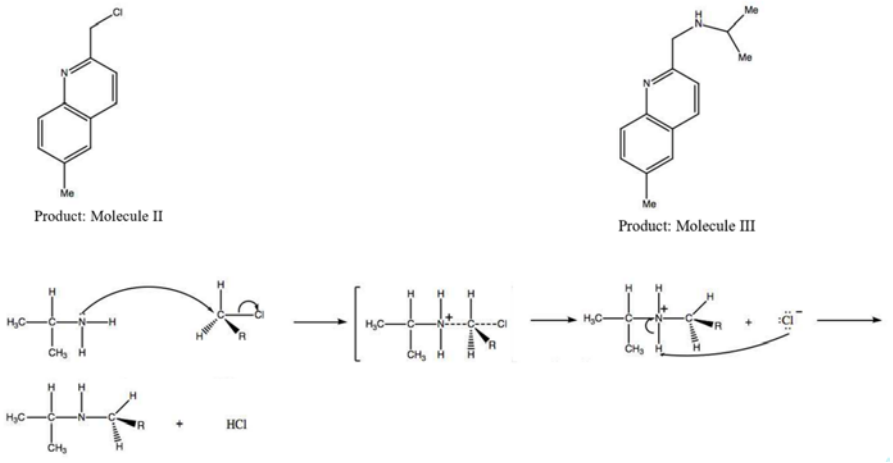

Figure 3: The SN2 reaction during the conversion of molecule II to molecule III

After that, molecule III undergoes hydrogenation, with nickel acts as a catalyst to obtain structure IV. Then, concentrated nitric and concentrated sulfuric acids react to form nucleophile NO2+. The nucleophile then attack the double bond para to the methyl side chain. As there are two possible attack positions, the reaction will generate two structural isomers. By separating the isomers, molecule with structure VI can be selected and undergo microbial oxidation to obtain the final product, Oxamniquine.

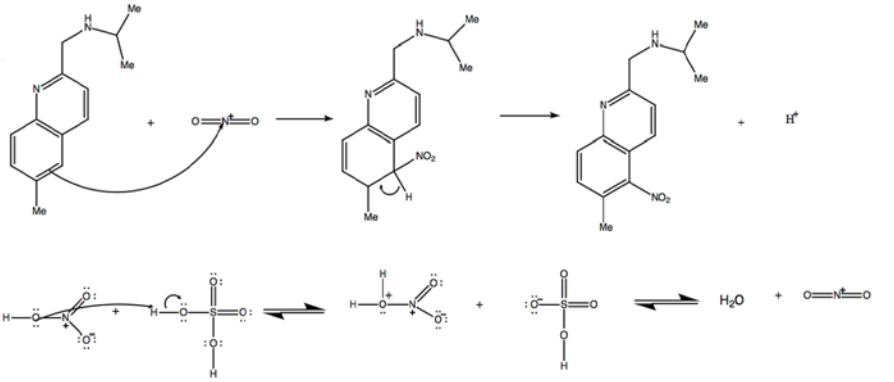

Figure 3: The reaction mechanism when molecule IV converts to molecule V and VI

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Mechanism of action

Oxamniquine targets at the nucleic acid synthesis in schistosomal cells. When oxamniquine is bound to the active to the active site of schitosomal enzyme, which is specific in parasites. The hydroxyl group is converted into an ester group, which is much easier to leave and enable the dissociation of molecule. When its binds to DNA, which is rich in electron, the molecule will acts as an alkylating agent and therefore prevents DNA replication.[3]

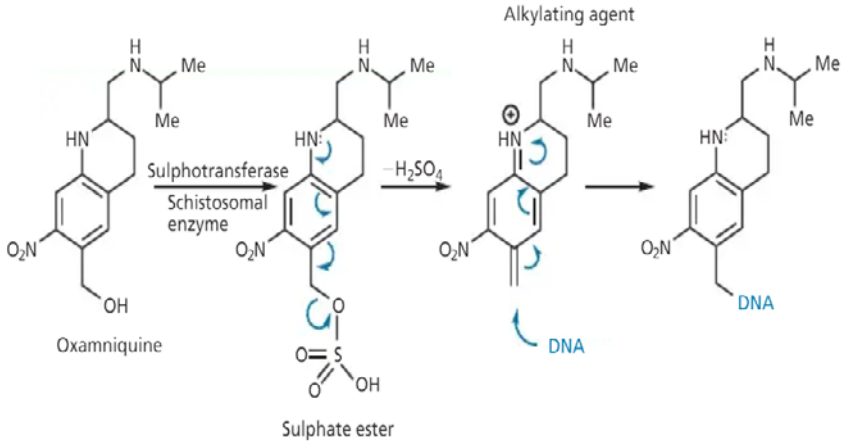

Figure 4: The inhibition of DNA replication of parasites cells

Drug design (modifications on pharmacophores)

The drug design began with the lucanthone, which acts as the lead compound. With two rings in the left of lucanthone being removed and substitute sulfur atom into chlorine atom, lucanthone is converted into mirasan. As chlorine is more electronegative than sulfur, it contributes to the reactivity of the drug.[4] The success of drug binding with the enzyme in mice indicates that the β-aminoethylamino side chain contributes to the enzyme-substrate specificity. Nevertheless, mirasan was active in mice instead of human.

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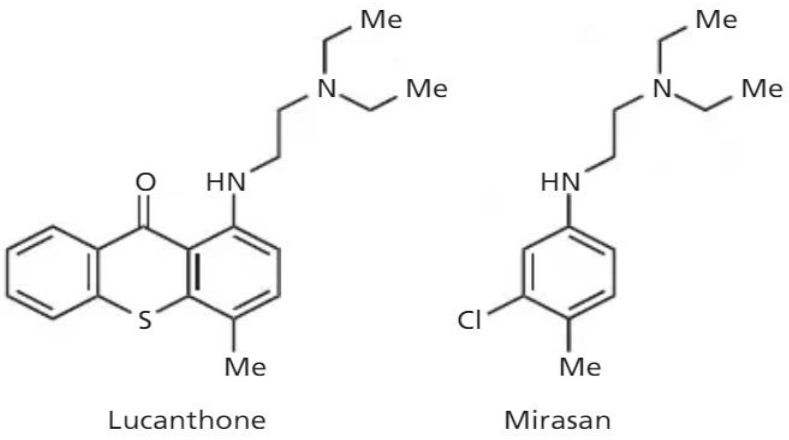

Figure 5: The structure of Lucanthone and Mirasan

Therefore, further modification is set up. By forming a cyclic structure, bonds are restricted at their position, indicating by the blue color. Thus, the probability of exhibiting active conformation increases, and also it is active in monkey, which has a closer relationship with human than mice.

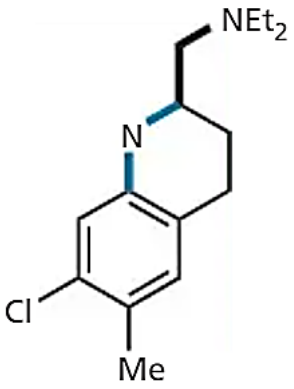

Figure 6: The bicyclic structure resulted from modification on mirasan

By substituting the chlorine atom with a less electronegative NO2 group, proton become less easier to leave. The basicity of the molecule is increased, which indicates that it's harder for the molecule to dissociate in water and the molecule is less ionized.[5] As the cell membrane is made of phospholipid, a nonpolar material,

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it will be easier for the molecule to pass through the cell membrane of gut and target cells. Through several tests, it indicates that a secondary nitrogen will have the greatest reactivity. Also, the more branched the alkyl group, the increased contact area with binding sites and the stronger the van der Waal's force between the molecule and the hydrophobic area of binding sites, which allows the molecule to pass through the membrane in a easier way. However, actions should avoid adding a methyl group on or extending the length of the side chain as these will eliminate the activity.[6] By compromising these conclusions, a optimum structure is obtained, which is an intermediate product during the synthesis process. By oxidizing the methyl group into hydroxymethylene, oxamniquine is obtained as the final drug, The hydrogen bond formed results in stronger interaction with binding sites, indicating a strong activity.

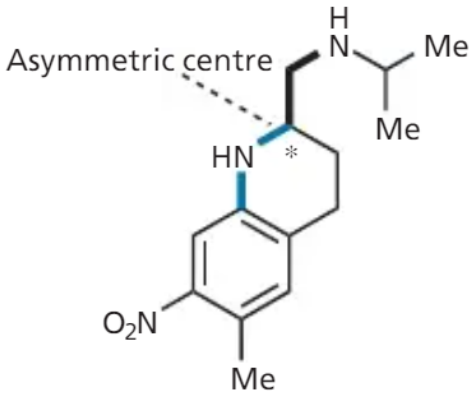

Figure 7: The optimum structure

Side effects

The adverse effect of oxamniquine is milder than previous drugs, commonly including headache, dizziness, somnolence, and abdominal pain. Within the liver, a study shows that for 79% of patients, 36% have raised alkaline phosphatase and 52% have a raised eosinophil count. Also, there are some rare side effects on cardiovascular, such as electrocardiographic and electroencephalographic changes.[7]

Conclusion

Overall, the article introduces the history of drugs used to deal with schistosomiasis, the design and synthesis process of oxamniquine and the way it

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functions. Also, the side effects of oxamniquine in therapeutic treatment is mentioned.

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