

Study on the Oxamniquine

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ABSTRACT. This paper mentions what is *Schistosoma* and schistosomiasis and the development and mechanism of action of the medicine—Oxamniquine.

KEYWORDS: *Schistosoma*, schistosomiasis, and Oxamniquine.

1. Schistosoma and schistosomiasis

Schistosoma is a parasite causing the schistosomiasis. There are mainly three species of *Schistosoma* “*S. mansoni*, *S. haematobium*, and *S. japonicum* cause intestinal schistosomiasis (Sm and Sj) and urogenital (Sh) schistosomiasis.”(Rugel 2). Schistosomiasis is widespread in tropical regions. (case study 4). The larval forms of this parasite can enter the human body, by penetrating human skin, through contaminated water. (case study 4). Then, they grow into adult form within the bloodstream and reproduce themselves. (case study 4). A large number of people are infected with the disease every year, and this disease can cause organ damaging or even leading to death. (case study 4)

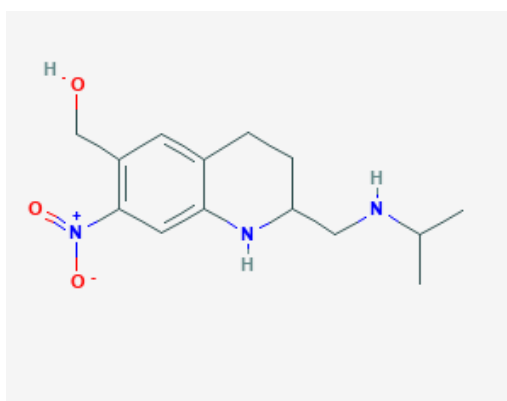


Figure1. Image adapted from Figure 1. *Schistosoma*

2.. Oxamniquine (OXA)

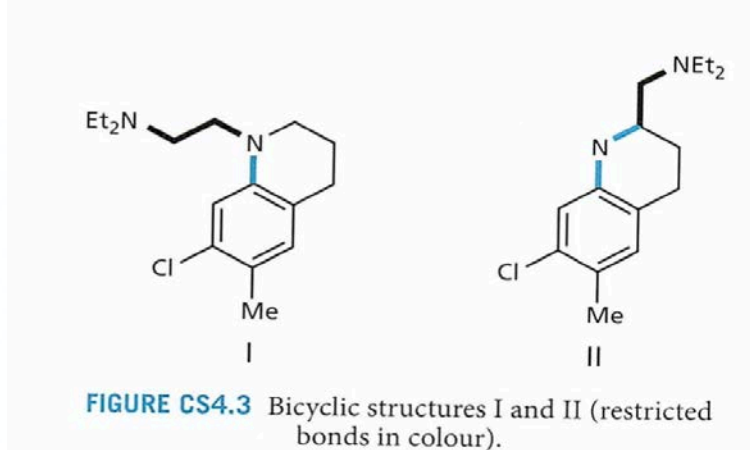
Oxamniquine (OXA), 1,2,3,4-tetrahydro-2-[(isopropylamino) methyl]-7- nitro-6-quinolinemethanol (Ahmad, Iqbal, et al. 603), is an antischistosomal prodrug used for the treatment of schistosomiasis and it was being admitted to market in 1975. (case study 4). It was designed to be cheap and infrequent oral administration. Nevertheless, “OXA operates only against the *S. mansoni*, and the adult male worms are more vulnerable to the action of the drug than the female parasites.”(Silva et al. 3274). OXA side effects include temporary dizziness, drowsiness, and headache. (case study 4)



Figure2.Oxamniquine 2D structure

3. The design and development of Oxamniquine (OXA)

Before the OXA was designed, the drugs available for the disease, schistosomiasis, were Lucanthone and Sibocaptate. (case study 4). However, both of Lucanthone and Sibocaptate have serious side effects and need to be taken



frequently. (case study 4). Thus, there raises the demand for a new drug which need to be more efficient and have a milder side effect which is the Oxamniquine.

Figure 3. OXA Mechanism of Action

When designing a new drug, there are a few stages that need to be done. Scientists need to identify target diseases and drug targets. These two stages were done when designing Lucanthone and Sibocaptate. The next step is that they need a lead compound as a starting point. In this case, Lucanthone was chosen to be the lead compound because it was orally active. (case study 4). After several tries, Mirasan was made. Mirasan has an electronegative chloro substituent which successfully improves the activity. (case study 4). This finding suggests that more electronegative substituents lead to more activity. However, Mirasan was only able to against the parasite in mice. (case study 4). Then, “a side chain bonds were fixed in a ring to prevent rotation around that bond.” (case study 4). This change improves more on the activity, but it was only active in monkeys. (case study 4). Afterwards, “two of the side chain bonds were constrained”(case study 4). The result is that this compound became even more active on mice. (case study 4). This finding suggests that changing the substitution pattern may change the position of their binding regions and therefore change the activity. (case study 4).

After that, several trends were discovered. To understand these discoveries, we have to know that there are three types of binding forces which are ionic bond, hydrogen bond, and London force. Ionic bond happens when there are oppositely charged ions. Because oppositely charged ions cause attraction toward each other and form force. Hydrogen interacts with Fluorine, nitrogen, and oxygen and forms a hydrogen bond. The London force happens on every molecule. At any moment, since the electron within a molecule distributes unevenly, two molecules will have

forces act on each other. Now we can go over the discoveries. The discoveries are list below.

1. “Longer chains led to the reduction activity.” (case study 4). Because if the substituents are too large, it may stop the drug bind into the binding site. (case study 4).

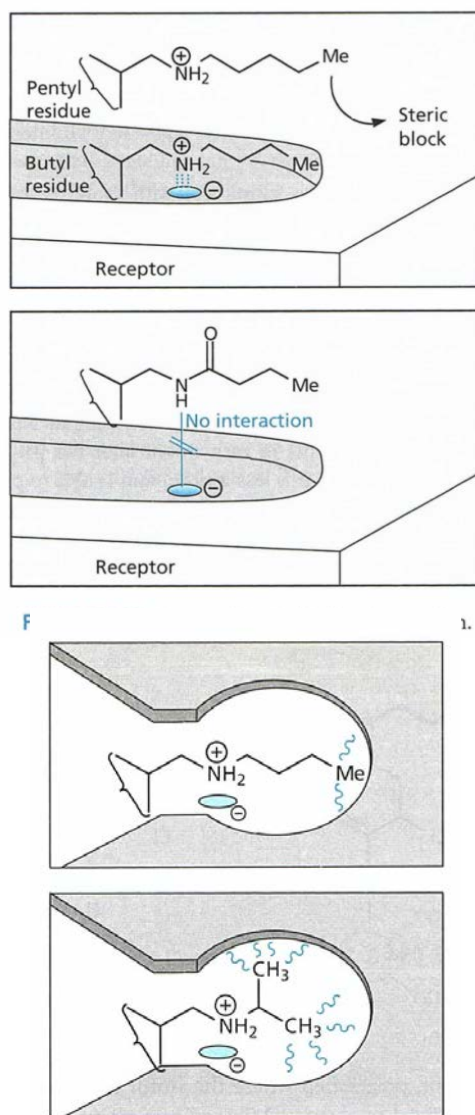


FIGURE CS4.7 Branching of the alkyl chain.

2. “An electron-deficient aromatic ring is beneficial to activity.” (case study 4). Since a strong electron-deficient aromatic ring can pull the cyclic nitrogen’s electrons pairs into the ring, thus reduces the basicity and lets the drug pass through more easily. (case study 4).

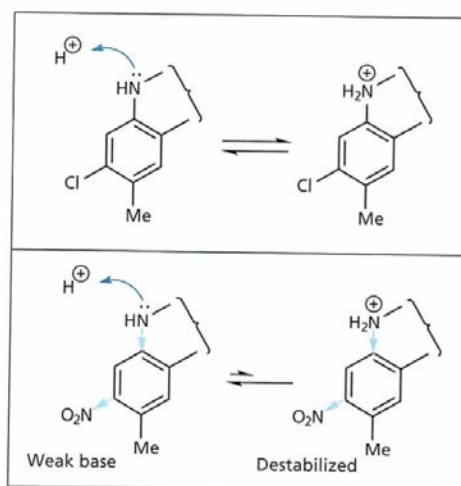


FIGURE CS4.4 Effect of aromatic substituents on pK_a .

3. A secondary amino group on the side chain is best for activities. (case study 4).

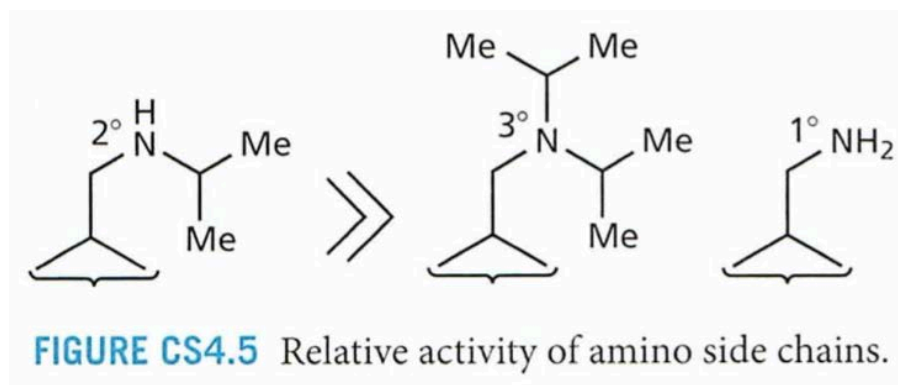
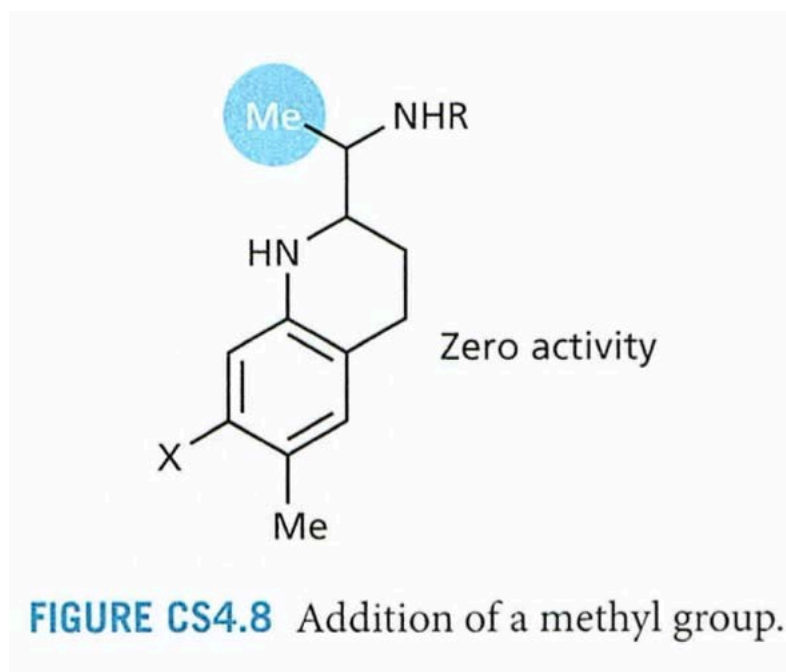


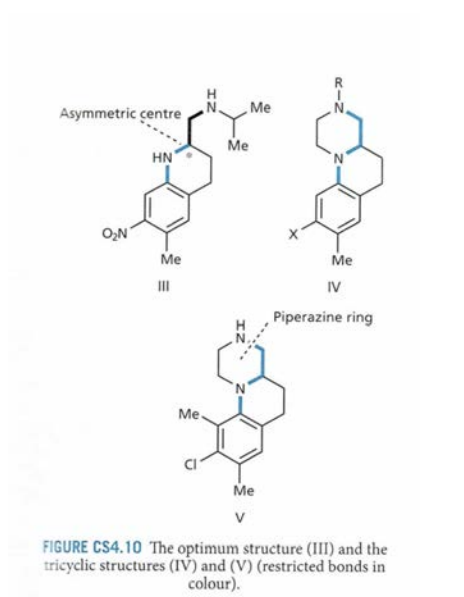
FIGURE CS4.5 Relative activity of amino side chains.

4. “Branching of the alkyl chain increased activity”(case study 4). This is because that branching led to more molecules and thus more London force interactions. (case study 4).

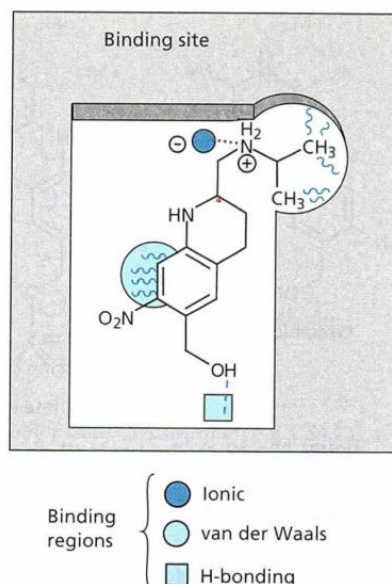
5. Methyl group on the side chain disable activity. (case study 4). A methyl group is too large so that it hinders the correct conformational blocking. (case study 4).



After these trends were discovered, three structures were made, shown as III, IV, and V. Even though structure V was three times more active than III, structure III was selected for further modification on account of cheap, simple, and easy to synthesize. (case study 4). A deeper level of research shows that a hydroxymethylene group is a more active group. Thus, methyl group on III was changed into hydroxymethylene group, and this alteration finalized the oxamniquine structure. (case study 4). a hydroxymethylene group is more active than the methyl group; thus methyl group on III was changed into hydroxymethylene group, and this change finalized the Oxamniquine structure. (case study 4).



The right side is the proposed binding interaction for OXA to a binding site. This structure involves all the three types of binding forces, and it can bind into the binding site as the graph shown below. These forces and the structure of OXA do help for the OXA to better bind into the binding site.



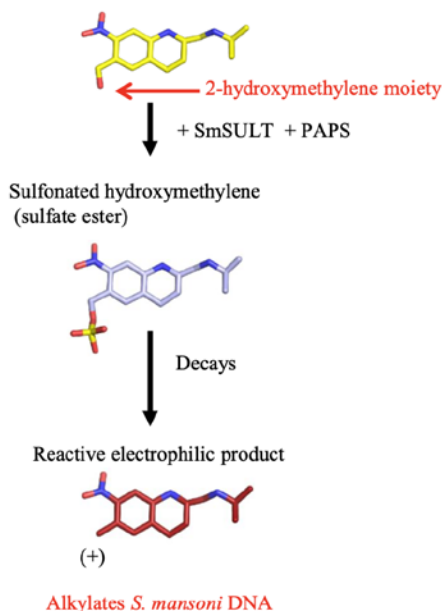
All the figures are adapted from Case Study 4

4. Oxamniquine Mechanism of Action.

Enzymes are proteins that can act as a catalyst to speed up the chemical reaction. Most of the reactions that occur in our body need enzymes in order to proceed. The way an enzyme works is that a substrate which is a reactant fits into an enzyme active site. When the substrate and the enzyme fit together, chemical reactions happen at the enzyme active site and then form products. Then, products are released from enzymes, and enzymes can be reused with substrates to form products.

Some drugs are an enzyme inhibitor that can stop the enzyme from functioning by preventing the substrate from entering the active site. In this case, OXA is an enzyme inhibitor, but it is more complicating than only preventing the substrate from entering; It reacts with the enzyme that presents in the parasite. In this way, the OXA "inhibits nucleic acid synthesis in *Schistosoma* cells" (case study 4). By "binds to a specific *S. mansoni* sulfotransferase, known as SmSULT, where it is transiently sulfonated. Activated OXA binds to DNA, and other macromolecules" (Rugel et al. 9) and therefore disable the enzyme and leads to the death of *Schistosoma*. The enzyme inhibitor only operates for the target enzyme.

Thus, the OXA targets the sulfotransferase enzyme that only present in the parasite cell but not in humans' cells so that the OXA won't affect the human's enzyme. (case study 4).



References

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