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# Docking studies of different derivatives of Penicillin in the treatment of the disease Syphilis

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**Abstract**
Syphilis is a chronic, persistent, and multi-stage infection primarily transmitted via sexual contact with active lesions or from an infected mother to her foetus. With no vaccine available to prevent syphilis, effective control depends heavily on the prompt identification and treatment of infected individuals and their contacts. **Penicillin G** remains the first-line treatment across all stages of syphilis, proving highly effective against the causative agent, Treponema pallidum. Apart from arsenical, bismuth, and mercurial compounds, penicillin and a few other antibiotics including fumigacin, gliotoxin, aspergillic acid, and bromo aspergillic acid are the only chemotherapeutic medicines that work against Treponema pallidum. There are different types of classes of penicillin which show the activity to inhibit PBPs (Penicillin-Binding Proteins) and causes cell lysis and cell death. They target the microorganisms such as gram positive and gram-negative aerobes and certain anaerobes. Later, we study in brief about the significance of 1RT2 protein in molecular docking techniques. Penicillin G remains the first-line treatment across all stages of syphilis, proving highly effective against the causative agent, Treponema pallidum. If we consider all the penicillin derivatives and done their docking studies against the protein 1RT2, we observe different types of docking output.

**Keywords:** Treponema Pallidum, Anti syphilitic effect, Spirocheticidal, RhoGTPase- activating protein, docking scores.

## 1.1 Introduction

Syphilis is a chronic, multi-stage infectious disease predominantly spread through sexual contact with active lesions or transmitted from an infected mother to her foetus[1]. While the disease remains endemic in many developing regions, there has been a concerning resurgence in several developed nations[2]. This resurgence presents serious global public health challenges, particularly because syphilis lesions significantly increase the risk of HIV acquisition and transmission. Since no vaccine exists to prevent syphilis, effective control relies on the timely diagnosis and treatment of infected individuals and their contacts[3-4].

Penicillin G continues to be the primary treatment for syphilis at all stages, demonstrating high efficacy against the causative organism, *Treponema pallidum*[5]. However, the growing resistance of *T. pallidum* to azithromycin has diminished the reliability of this alternative antibiotic, complicating treatment strategies. Research highlights the critical role of maintaining adequate penicillin levels to effectively treat syphilis. For early-stage syphilis, successful treatment requires maintaining a minimum serum concentration of 0.03 IU/mL (0.018 µg/mL) for 7–10 days, without interruptions exceeding 24 hours[6-8]. This regimen aligns with the bacterium's slow doubling time of 30–33 hours in early disease stages[9].

Animal studies have further shown that both the duration of therapy and serum penicillin concentration play a synergistic role in eliminating the pathogen[10]. Concentrations as low as 0.01 µg/mL have been found sufficient to eradicate *T. pallidum* in rabbit models and in vitro experiments. These findings underscore the necessity of sustained and appropriate dosing to achieve successful treatment outcomes[11-12].

### 1.2 Competitive study of penicillin on Treponema pallidum

The most effective, nontoxic, and antibacterial drug used to treat clinical illness is penicillin. In dilutions of roughly 1:50,000, the purest penicillin on the market prevents the growth of the most susceptible organisms, including staphylococcus and gonococcus[13]. 200 million organisms can be killed with just 0.04 units of penicillin per cubic centimetre, or roughly 0.02 micrograms of the pure drug. The fact that its activity is comparable to that of highly active enzymes implies that penicillin either stimulates an enzymatic system or is a component of an enzyme. Dunham and Rake's observations, which show that crystalline penicillin G did not immobilize Treponema pallidum at the same concentration as the partly purified form, support this likelihood. A partially purified penicillin preparation, capable of being concentrated through adsorption on alumina, exhibited significant antispirochaetal activity[14-16]. Although crystalline penicillin G did not immobilize spirochetes in vitro, it showed some anti-syphilitic effects when administered in high doses, as indicated by its ability to influence the rabbit's response to *Treponema pallidum* infection. Laboratory studies on animal models demonstrated that the purification process enhanced penicillin's antispirochaetal efficacy. Penicillin is effective against bacteria during their active multiplication phase but is less effective when the bacteria are in a resting state. At very low concentrations (0.04–0.1 units per cubic centimeter), penicillin significantly inhibited oxygen consumption, ultimately halting the process. This suggests that penicillin can eliminate bacteria during the early lag phase of growth, likely by disrupting a metabolic pathway essential for the initial stages of bacterial development [17]. (Figure 1)

In addition to compounds such as arsenical, bismuth, and mercurial agents, penicillin, and a few other antibiotics—such as fumigacin, gliotoxin, aspergillic acid, and bromo-aspergillic acid—are among the limited chemotherapeutic options effective against *Treponema pallidum*[18]. Research by Eagle and Musselman demonstrated that penicillin, at a threshold concentration of 0.01 unit per cubic centimeter, exhibited spirocheticidal activity in vitro using the Reiter strain of spirochetes. The rate and effectiveness of its action increased with concentration, peaking at approximately 0.1–0.25 units per cubic centimeter. (Table 1) [19]

### 1.3 Mechanism of penicillin on Treponema pallidum

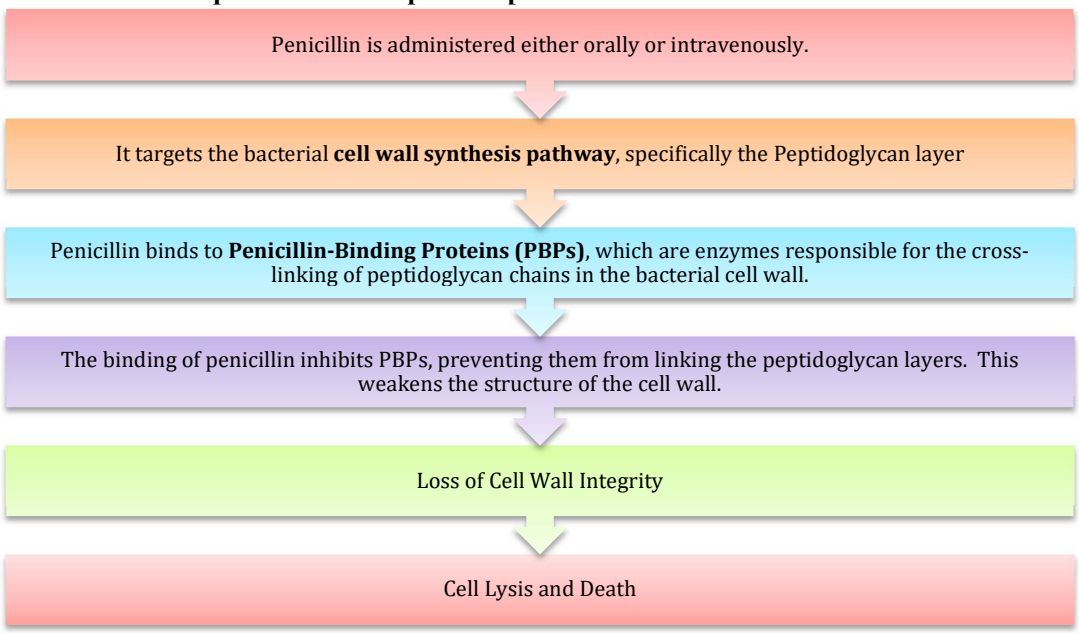
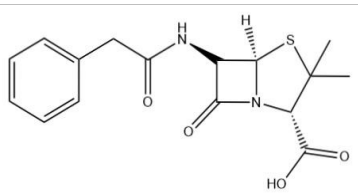
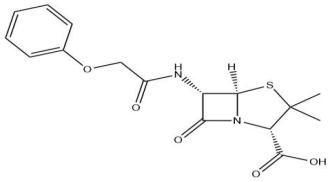
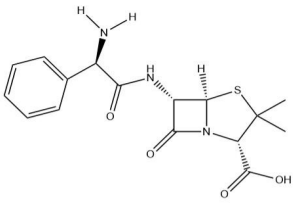
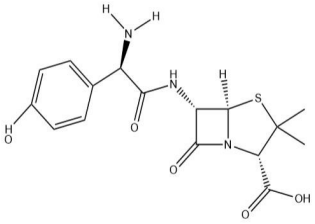
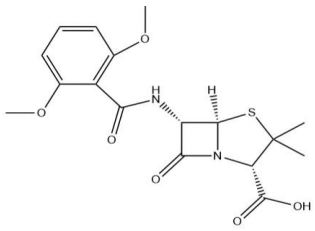



**Figure 1 Mechanism of penicillin on Treponema pallidum**

**Table 1 Classification of Penicillin**

| Types | Drug Structure | Targeted Microorganisms | Uses | References |
|---|---|---|---|---|
| **Penicillin G** |  | Gram positive aerobic Organism such as Streptococci | Diphtheria pneumonia, gonorrhoea, syphilis | **6** |
| **Penicillin V** |  | gram positive staphylococcal And enterococcus species Gram negative anaerobic Organisms and certain spirochetes. | Scarlet fever, Pneumonia and other respiratory disease. | **10** |
| **Ampicillin** |  | Non penicillinase producing gram-negative organism such as Neisseria meningitides, Haemophilus influenza Neisseria gonorrhoea | Respiratory, GI, Urinary Tract infection, Meningitis. | **13** |
| **Amoxicillin** |  | Gram positive cocci, including nonpenicillin resistant streptococcal, staphylococcal and enterococcus species Gram positive anaerobic organism, and Gram negative anaerobic organism. | Skin, nose, throat, and. Lower respiratory tract infection. | **15** |
| **Methicillin** |  | Organism such as staphylococcus Aureus, staphylococcus pneumoniae and streptococcus pyogenes. | Skin and skin structure Infections, osteomyelitis and endocarditis. | **21** |

## 1.4 Significance of 1RT2 protein in molecular docking technique

1RT2 refers to a protein structure identified in the Protein Data Bank (PDB) with the PDB ID "1RT2." This structure represents a **protein-ligand complex**, specifically the **RhoGTPase-activating protein** (GAP) complex with a small molecule inhibitor. The RhoGTPases are a family of signaling proteins that play a critical role in regulating the cytoskeleton, cell division, and other important cellular processes. (Figure 2) [20-23]

**Key details about 1RT2:**

**PDB ID**: 1RT2

**Organism**: The protein in the structure is derived from humans, specifically the **RhoGTPase-activating protein**.

**Ligand**: The structure includes a small molecule inhibitor, which binds to the GAP domain, influencing the RhoGTPase signaling pathway. (Table 2)

**Function**: The GAP domain of this protein negatively regulates Rho GTPases by stimulating their GTP ase activity, which helps control various cellular functions, including cell movement and division.

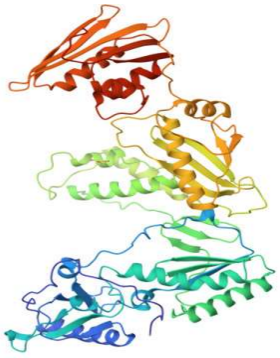
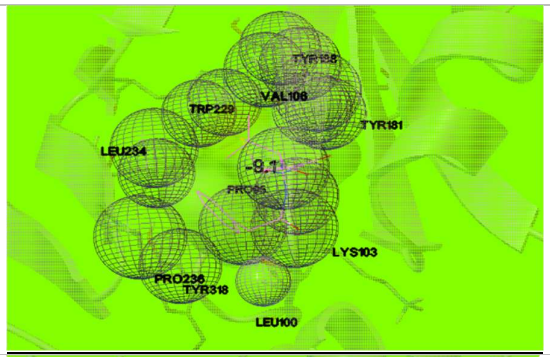
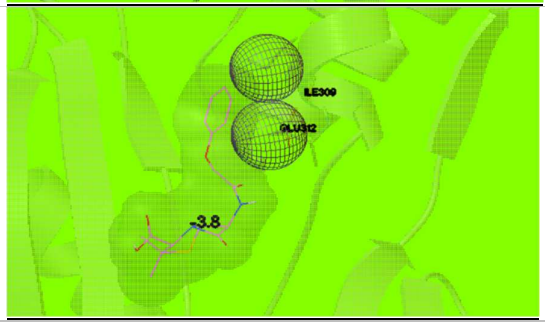
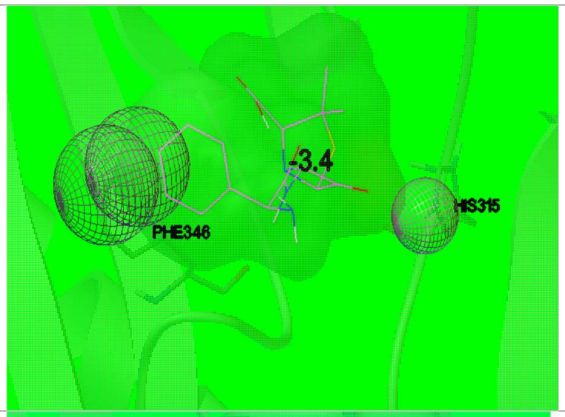
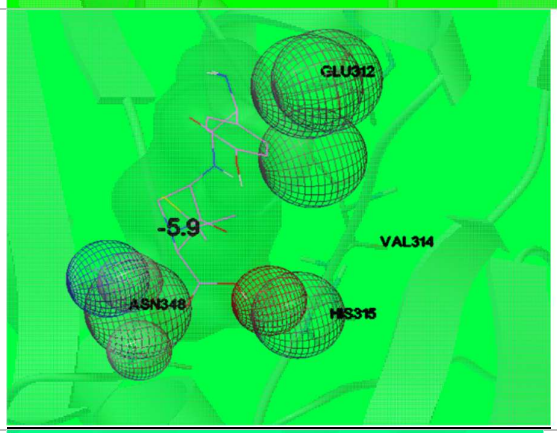
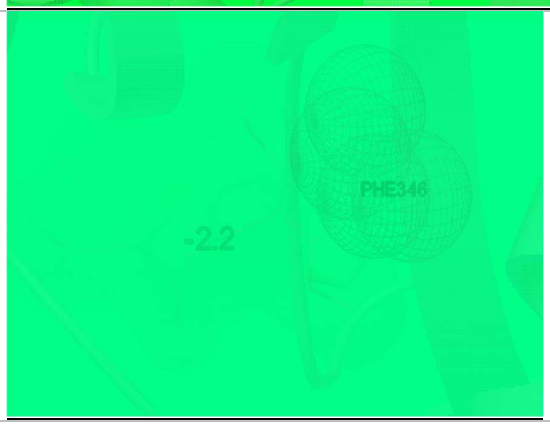


**Figure 2 Diagram of 1RT2 protein**

**Table 2 Protein-ligand interaction**

| Sl No. | Ligand Name | Protein-Ligand interaction | Docking Score |
|---|---|---|---|
| 1 | Penicillin G |  | -9.1 |
| 2 | Penicillin V |  | -3.8 |

| | | | |
|---|---|---|---|
| 3 | Ampicillin |  | -3.4 |
| 4 | Amoxicillin |  | -5.9 |
| 5 | Methicillin |  | -2.2 |

### 1.5 Docking Scores for Antimicrobial Activity

Docking scores represent the predicted binding affinity of a ligand (e.g., a drug) to a target protein. A lower docking score typically indicates a stronger predicted interaction.

Drugs with lower docking scores are often predicted to bind more strongly to the target protein, which could correlate with higher antimalarial activity. So, from the all above mentioned compounds **Penicillin G** shows the docking output **-9.1**, so it has the most antimicrobial and antifungal activity from all the penicillin derivatives.

### 1.6 Docking Scores for Binding Affinity

Binding affinity is the strength of the interaction between the drug and its target protein. This is often expressed in terms of Gibbs free energy **(ΔG\Delta GΔG)**, with more negative values indicating stronger

binding.

### 1.7 Docking output

The docking output often provides a measure of binding affinity, which helps predict how well the drug might inhibit the target protein. Effective antimalarial agents should ideally show high binding affinity to key targets in the malaria parasite.

### 1.8 Validation and Experimental Correlation of Docking Study

Validation involves confirming that the docking predictions align with actual biological activity. While docking provides useful predictions, experimental validation is crucial. In vitro and in vivo tests are required to confirm that the predicted binding translates to actual antimalarial efficacy. Docking results are often used to prioritize compounds for further testing. In summary, while docking output provides valuable insights into the potential binding affinity and interaction of antimicrobial drugs with their targets, the ultimate measure of antimicrobial activity comes from experimental testing. Docking helps guide the selection of promising candidates for further development and testing.

### 1.9 Conclusion:

Syphilis is a chronic, persistent, and multi-stage infection primarily transmitted via sexual contact with active lesions or from an infected mother to her foetus. Although the disease remains indigenous and native in many developing regions, it has seen a troubling resurgence in several developed countries. Penicillin G remains the first-line treatment across all stages of syphilis, proving highly effective against the causative agent, *Treponema pallidum*. If we consider all the penicillin derivatives and done their docking studies against the protein 1RT2, we observe different types of docking outputs [Penicillin G-9.1, Penicillin V-3.8, Ampicillin-3.4, Amoxicillin -5.9, Methicillin-2.2], so penicillin G has the most effective docking output that is -9.1, So Penicillin G has the most antimicrobial and anti-fungal activity and hence proved that Penicillin G is most effective against the *Treponema pallidum* and use in the treatment of Syphilis.

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**Conflict of Interest:** None
**Funding:** Not applicable

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