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| **30S Protein Synthesis Inhibitors** | | |
| **Drug** | **Aminoglycosides** | **Tetracyclines** |
| SAR | IMAGE  Polycationic at physiological pH   * Poor oral absorption   **Ring I**   * Crucial for broad-spectrum activity. * First target of inactivating enzymes. * The 2-, 3-, 4- hydroxyl groups are not essential for activity * Methylation of the amine will retain activity and will lower susceptibility to transferases. * All substitutions must be equatorial.   **Ring II**   * Many modifications are possible, for example the 3- amine can be substituted or acylated   **Ring III:**   * The amine can be methylated or changed to a hydroxyl group, but its removal will abolish activity | IMAGE  **Positions 1, 10, 11, 12 and 12a:** any changes will completely abolish activity, even changes in the stereochemical configuration.   * Resonance between position 10 and 11 needed for activity   **Position 2:** any changes leads to decreased activity, even substitution to the amide  **Position 4:** amine in the α-position is essential, but monosubstitution is also active.  **Position 5:** R4 can be a hydroxyl, keto group or a hydrogen, and all are active  **Position 6:** both substitutions (R2 and R3) are not necessary.  **Position 7:** Cl, F, Br, NO2 and a tertiary amine are all active.  **Position 8:** any electron withdrawing or donating group is still active.  **Position 9:** bulky substitution decreases resistance  **Warhead:** Resonance between 11 and 12 |
| Mechanism of Action (MOA) & Target | * Binds irreversibly to the 30S ribosomal subunit and changes to the “A” site * Enters cell by binding negatively charged phospholipids and entering via electron transport linked system 🡪 method can be antagonized by divalent cations * Bactericidal   Target: 30S | * Binds reversibly to **30S** ribosomal subunit at the A site, preventing attachment of tRNA – leading to termination of translation * Bacteriostatic   Target: 30S |
| Mechanism of Resistance (MOR) | 1. Decreased permeation of aminoglycosides (loss of porin) 2. Bacteria produce enzymes that acetylate or phosphorylate aminoglycosides’ hydroxyl groups to make aminoglycoside inactive 3. Ribosomal mutations | 1. Develops efflux pumps 2. Genes for tet-resistance transmitted by plasmids 3. Enzymatic modification of antibiotic preventing binding to 30S |
| Indication/Spectrum | * Very broad spectrum, but better against G- * Used mainly against G- bacilli AEROBES | Broad spectrum: G+, G-, aerobic and anaerobic |
| Toxicity/ DDI | Nephrotoxicity, Ototoxicity, Neuromuscular blockade (muscular paralysis) | Phototoxicity, Inhibition of bone growth, nephrotoxic, hepatotoxic , stains teeth  DDI: chelation with cations (dairy products, antacids, supplements) |