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| **FOLIC ACID SYNTHESIS INHIBITORS** | | |
| **Drug Class**  **(examples)** | **Sulfonamides**  (Sulfamethoxazole, Sulfacetamide, Silver Sulfadiazine) | **Trimethoprim**  **(Related Compound: Pyrimethamine)** |
| **SAR** | Essential components   * Benzene ring * Un-substituted amine para to sulfonamide * Sulfonamide para to amine * Sulfonamide must be un-ionized to cross bacterial cell membrane * Sulfonamide must be ionized to interact with DHPS active site * Di-substitution of sulfonamide abolishes activity (acidic hydrogen required) * Mono-substituted sulfonamide may increase activity (EWG & heterocycles favorable) | * Removal of primary amine results in complete inactivity * Removal of one or more methoxy groups on trimethoprim results in loss of activity to varying degrees |
| **Target** | Dihydropteroate Synthase  (DHPS) | Dihydrofolate Reductase (DHFR) |
| **Mechanism of Action (MOA)** | PABA mimic that competitively inhibits the synthesis of dihydrofolic acid from PABA  Bacteriostatic | Inhibits a step of the recycling of the folate cofactor (dihydrofolate to tetrahydrofolate) for purine and thymidine biosynthesis. Binds with ~300x more affinity to bacteria vs. human DHFR  Bacteriostatic |
| **Mechanism of Resistance (MOR)** | 1. Decreased drug uptake (most common)  2. Overexpression of DHPS  3. Increase PABA in bacteria  4. Decrease affinity for sulfonamide by DHPS | 1. Overexpression of DHFR  2. Decrease affinity for sulfonamide due to mutated enzyme |
| **Spectrum** | Broad Spectrum but use as monotherapy is rare | Broad Spectrum  Used in synergy with sulfonamides because of resistance |
| **Toxicity** | Nephrotoxicity; Crystalluria, Rash, Photosensitivity, Stevens-Johnson Syndrome | Hypersensitivity rash, Hyperkalemia, Hematologic effects |